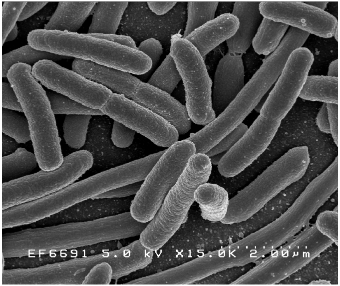
Modelling and statistics of branching processes

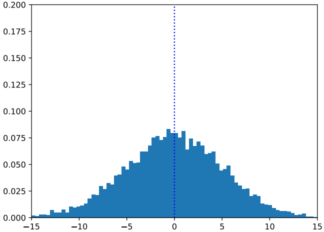
Aline Marguet, *Inria Grenoble – Rhône-Alpes*

Modelling the dynamics of a cellular population

Recent technological development: microfluidics, videomicroscopy, etc.

➥ Single-cell measurements: heterogeneity of cellular populations
➥ Individual-based models to capture this heterogeneity





Development of structured individual-based models

- Study of complex cellular mechanisms (division, ageing, inheritance)
- Inference of division rate, gene expression parameters

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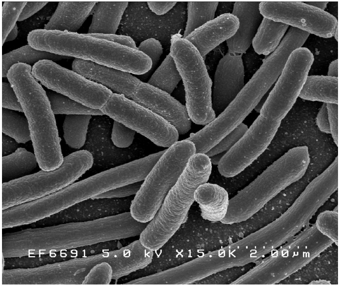

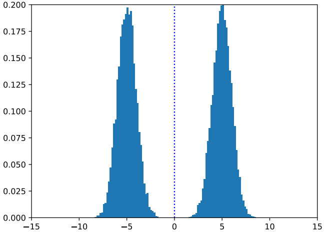

Development of structured individual-based models

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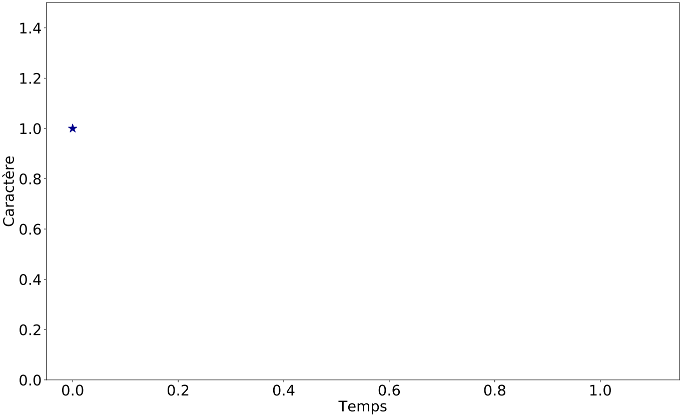
- ♦ Inference of division rate, gene expression parameters

Structured branching processes

Model description



1. The trait $(X_t^u)_{t\geq 0}$ of each individual u follows a Markov process.

$$\text{Ex: } dX_t = r(X_t)dt + \sigma(X_t)dW_t, \quad X_0 = x.$$

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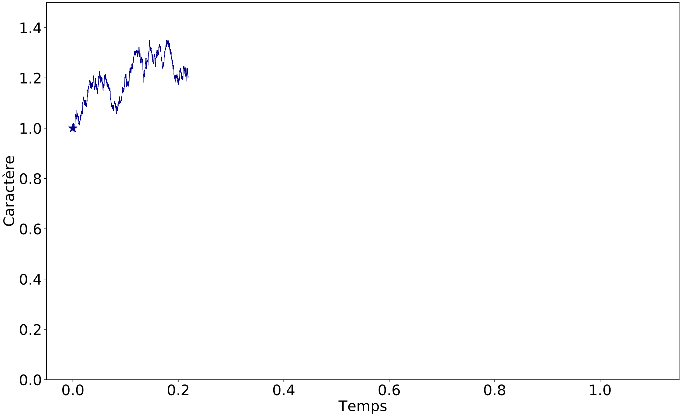

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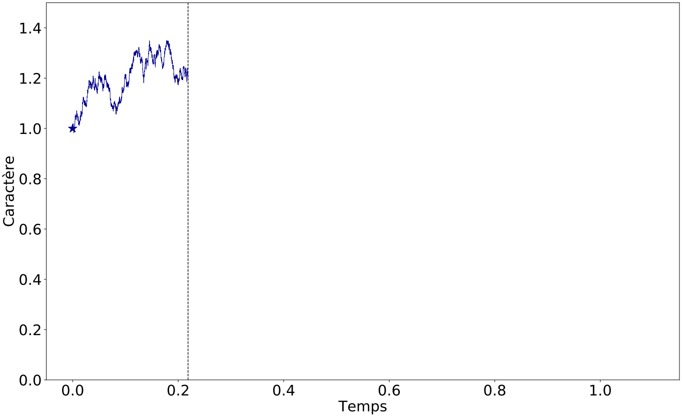
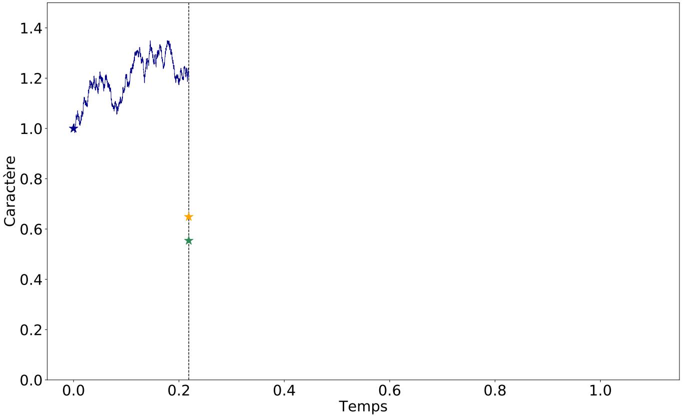


2. A cell u divides at time t at rate $B(X_t^u)$, i.e.

$$\mathbb{P}\left(\beta(u) > t | \alpha(u),\ (X_s^u, \alpha(u) \leq s \leq t)\right) = \exp\left(-\int_{\alpha(u)}^{t} B(X_s^u) ds\right)$$

where $\beta(u)$ denotes the lifetime of u and $\alpha(u)$ its time of birth.

Model description

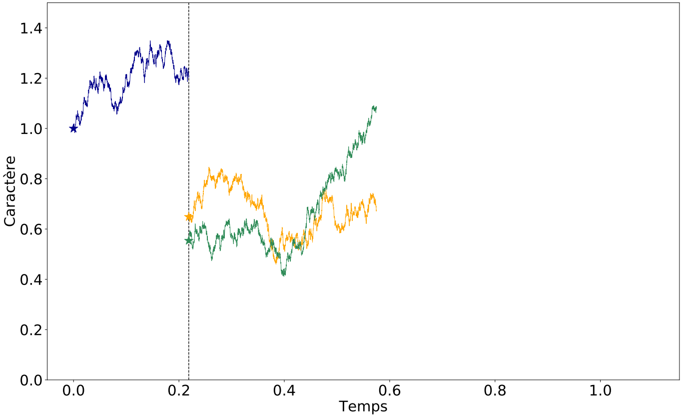


3.- At division, a cell with trait x is replaced by k daughter cells with probability $p_k(x)$.

- The traits at birth are given for the ith descendant by $F_i(x, \theta)$.

Ex: $F_1(x, \theta) = \theta x, F_2(x, \theta) = (1 - \theta)x,$ where $\theta \sim \kappa(d\theta)$.

Model description



4. Conditionally to the trait of their ancestor, the daughter cells evolves independently following the same dynamics.

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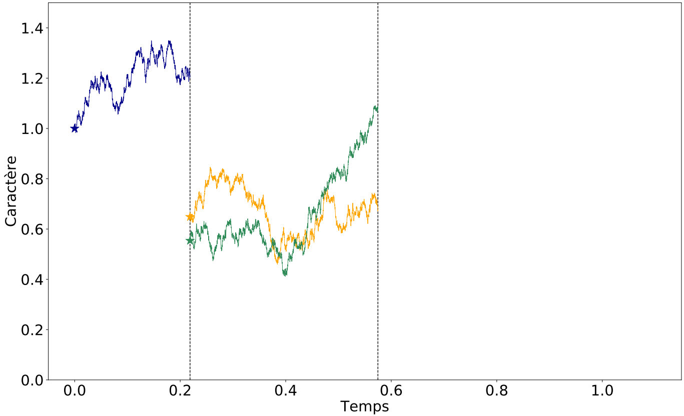

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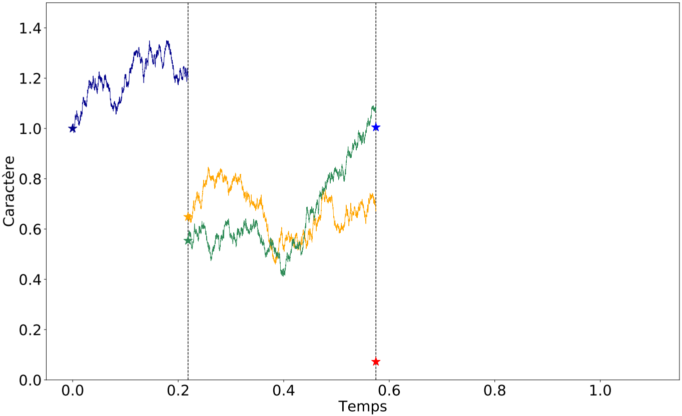

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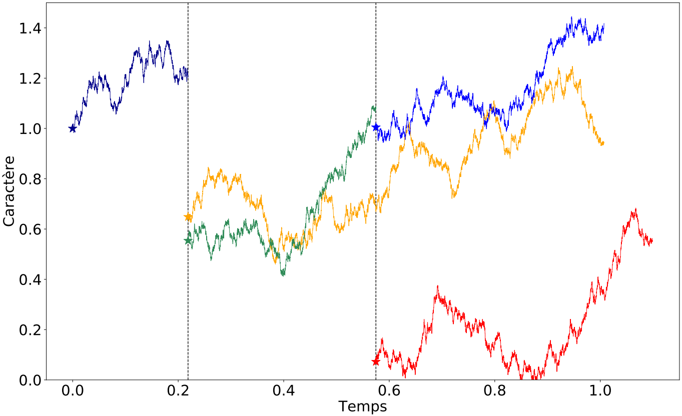

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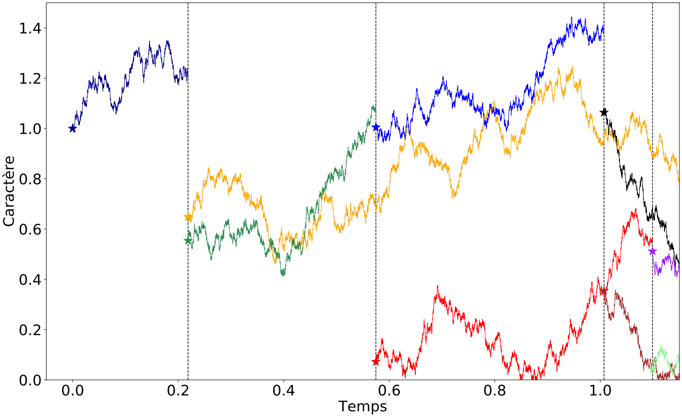

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Examples

- Study of ageing: age-structured populations
- Study of the division mechanism: asymmetry, size-dependency, heritability
- Switching dynamics: different division rate for different subpopulations (dormant cells, etc.)

Example: study of the proliferation of an infection in a cellular population

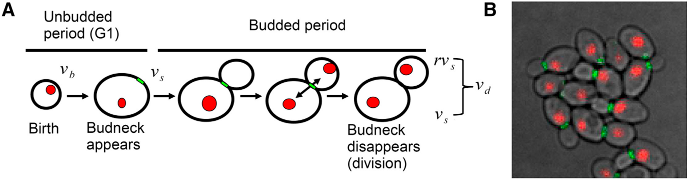

Figure: Image : Soifer, Robert & Amir, 2016.

- Asymmetric division : asymmetric sharing of the parasites in the daughter cells
- Strategy to eliminate the infection?

A. Marguet, C. Smadi, Long time behaviour of a general class of branching Markov processes, Preprint, 2019.

Inference in branching processes

Inference of the division rate

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- Piecewise Deterministic branching processes

- Stochastic flow

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  - Genealogical time, Size-structured population:

    M. Doumic, M. Hoffmann, N. Krell, L. Roberts, Statistical estimation of a growth-fragmentation model observed on a genealogical tree, 2015 (generalization to any flow along a branch, N. Krell, 2018).
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  - Continuous time ?

Genealogical time

Bifurcating Markov chains

We consider Ulam-Harris-Neveu notations: for $n, m \geq 0$, let

$$\mathbb{T} = \bigcup_{m \in \mathbb{N}} \{0,1\}^m, \quad \mathbb{T}_n = \bigcup_{m=0}^{n} \{0,1\}^m, \quad \mathbb{T}_n^\star = \mathbb{T}_n \setminus \{\emptyset\}.$$

Let X_u be the trait at birth of cell $u \in \mathbb{T}$. Assume that we are given observations

$$\mathbb{X}^n = (X_u)_{u \in \mathbb{T}_n}.$$

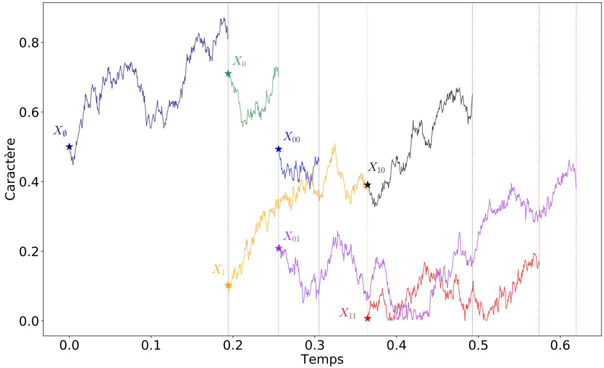
The process $(X_u, u \in \mathbb{T})$ is a bifurcating Markov chain with transition kernel $\mathcal{P}$ from $\mathbb{R}$ into $\mathbb{R} \times \mathbb{R}$ such that:

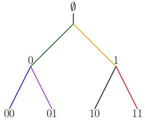
$$\mathbb{E}\Big[\prod_{u \in \mathbb{G}_m} \psi_u(X_u, X_{u0}, X_{u1}) \,\Big|\, \mathcal{F}_m \Big] = \prod_{u \in \mathbb{G}_m} \mathcal{P}\psi_u(X_u),$$

for all $m \geq 0$.

Guyon 2007.

Example of trajectory





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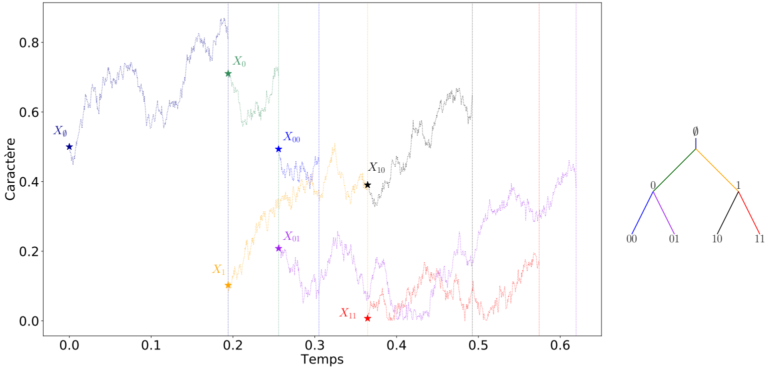

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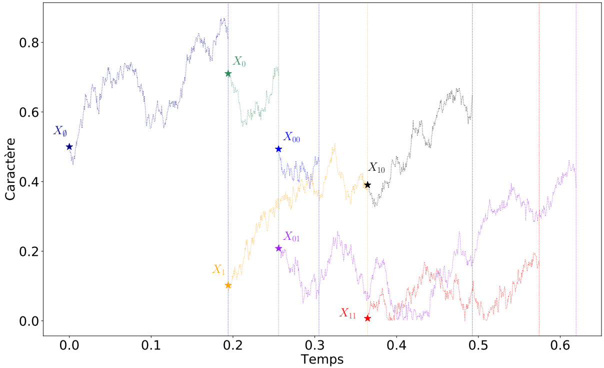
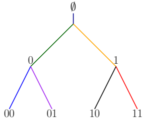
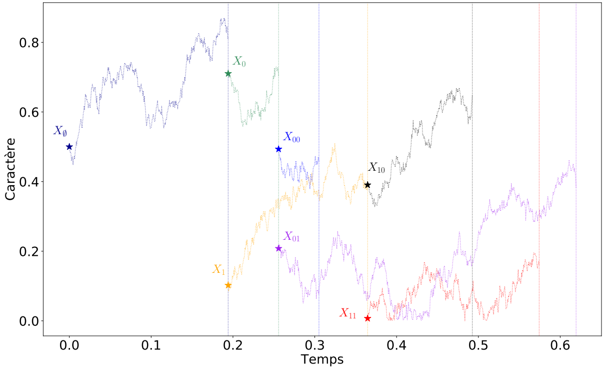
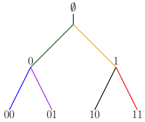




♦ Deterministic dynamic: as if we observed trajectories.

Example of trajectory





- Deterministic dynamic: as if we observed trajectories.
- Stochastic dynamic: unknown trajectories.

Kernel estimation

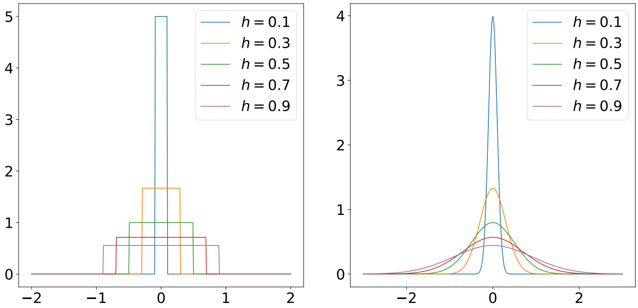
Kernel estimation

A function $G : \mathbb{R} \to \mathbb{R}$ is a kernel of order k if for all $i = 0, \dots, k$.

$$\int_{\mathbb{R}} x^i G(x) dx = \mathbf{1}_{\{i=0\}}$$

For $h > 0$, we define

$$G_h(y) = h^{-1} G(h^{-1} y), \quad \forall y \in \mathbb{R}.$$



Kernel estimator of the invariant measure

Consider the empirical measure

$$\mathcal{M}_n(\varphi) = \frac{1}{|\mathbb{T}_n^\star|} \sum_{u \in \mathbb{T}_n^\star} \varphi(X_u).$$

If $\mathcal{M}_n(\varphi)$ converges towards $\nu(\varphi)$, we have

$$\mathcal{M}_n(G_h(\cdot - x_0)) \xrightarrow[n \to \infty]{} \int_{\mathbb{R}} G_h(x - x_0)\nu(x)dx.$$

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An estimator of $\nu(x_0)$, for $x_0 \in \mathbb{R}$ is then given by

$$\widehat{\nu}_n(x_0) = \mathcal{M}_n(G_h(\cdot - x_0)).$$

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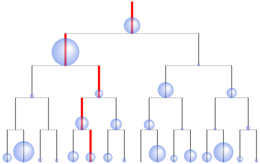
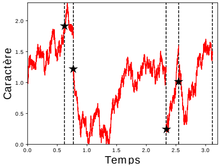
➥How *good* is this estimator?

Convergence of the empirical measure

Process of the tagged cell

Let Y be the Markov chain corresponding to the trait of the tagged cell.





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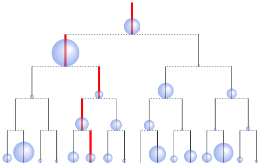

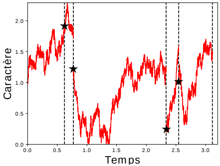

The transition operator of Y is given by $\mathcal{Q} = (\mathcal{P}_1 + \mathcal{P}_2)/2$, where

$$\mathcal{P}_1(x, dy) = \int_{\mathbb{R}} \mathcal{P}(x, dy dy_2) \quad \mathcal{P}_2(x, dy) = \int_{\mathbb{R}} \mathcal{P}(x, dy_1 dy).$$

Convergence of the tagged chain

Theorem

Under assumptions, $\mathcal{Q}$ admits an invariant measure ν. Moreover, there exist $C > 0$ and $\rho \in (0,1)$ such that for all $m \in \mathbb{N}$:

$$\left|\mathcal{Q}^m \varphi - \nu(\varphi)\right|_\infty \leq C\rho^m \left|\varphi - \nu(\varphi)\right|_\infty$$

Convergence of the tagged chain

Let

$$|\varphi|_V = \sup_{x\in\mathbb{R}} \frac{|\varphi(x)|}{1+V(x)}.$$

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$$\left|\mathcal{Q}^m\varphi-\nu(\varphi)\right|_V \le C\rho^m\left|\varphi-\nu(\varphi)\right|_V$$

for all measurable function $\varphi:\mathbb{R}\to\mathbb{R}$ such that $|\varphi|_V<\infty$, where $V(x)=x^2$.

Convergence of estimator

Let $\beta > 0$ and let G be a kernel of order $k > \beta$. Let us set

$$h = |\mathbb{T}_n|^{\frac{-1}{2\beta+1}}$$

Theorem

Under assumptions ensuring the ergodicity of the tagged chain Y, we have

$$\Big(\mathbb{E}\big[\big(\widehat{\nu}_n(x_0) - \nu(x_0)\big)^2\big]\Big)^{1/2} \lesssim |\mathbb{T}_n|^{-\beta/(2\beta+1)},$$

uniformly in $\mathcal{Q}$ for $\mathcal{Q}$ in a given Hölder regularity class depending on β.

Estimation of the division rate

Size-structured population

Assume that the cells grow exponentially at rate a, and divide in two equal parts. Then, the transition kernel of the chain of successive size at birth along a branch is given by

$$\mathcal{Q}_B(x, dy) = \mathbf{1}_{2y \geq x} \frac{B(2y)}{ay} e^{-\int_{\frac{x}{2}}^{y} \frac{B(z)}{az} dz} dy.$$

Moreover, if ν_B is the invariant measure of the chain, we have

$$\nu_B(x) = \frac{B(2x)}{ax} \mathbb{E}_{\nu_B} \left[\mathbf{1}_{\{X_u \geq x,\ X_{u^-} \leq 2x\}} \right],$$

where X_u denotes the size at birth of cell u and u^- is the ancestor of u. Then, an estimator of B is given by

$$\widehat{B}(x) = a \frac{x}{2} \frac{n^{-1} \sum_{u \in \mathcal{U}_n} G_h(X_u - x/2)}{n^{-1} \sum_{u \in \mathcal{U}_n} \mathbf{1}_{\{X_u \geq x,\ X_{u^-} \leq 2x\}}}$$

M. Doumic, M. Hoffmann, N. Krell, L. Roberts, Statistical estimation of a growth-fragmentation model observed on a genealogical tree, 2015.

Randomly structured population

Assume that the dynamic of the trait follows

$$d\phi_x(t) = r(\phi_x(t))dt + \sigma(\phi_x(t))dW_t, \quad \phi_x(0) = x.$$

The dependency in B of the transition function is complex but explicit:

$$q(x,y) = \int_0^1 \frac{\kappa(z)}{z} B(y/z)\sigma(y/z)^{-2}\mathbb{E}\Big[\int_0^\infty e^{-\int_0^t B(\phi_x(s))ds} dL_t^{y/z}(\phi_x)\Big]dz,$$

where $L_t^y(\phi_x)$ is the local time at time t at position y of ϕ_x and

$$Q(x,dy) = q(x,y)dy$$

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M. Hoffmann, A. Marguet. Statistical estimation in a randomly structured population, 2018.

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➥ Likelihood contrast in a parametric framework with (r,σ,κ) known.

M. Hoffmann, A. Marguet. Statistical estimation in a randomly structured population, 2018.

Parametric model

Assume that the division rate B belongs to a class

$$\mathcal{B} = \big\{ B : [0, L] \to \mathbb{R}, B(x) = B_0(\vartheta, x), x \in [0, L], \vartheta \in \Theta \big\},$$

where $x \mapsto B_0(x, \vartheta)$ is known up to a parameter $\vartheta \in \Theta$, and $\Theta \subset \mathbb{R}^d$ is a compact set.

Aim

Estimate ϑ from $(X_u, u \in \mathbb{T}_n)$.

Likelihood contrast

A likelihood contrast is given by:

$$\mathcal{L}_n\big(\vartheta, (X_u, u \in \mathbb{T}_n)\big) = \prod_{u \in \mathbb{T}_n^\star} q_\vartheta(X_{u^-}, X_u),$$

where X_{u^-} is the trait of the ancestor of u. We consider the estimator of ϑ given by:

$$\widehat{\vartheta}_n \in \operatorname*{argmax}_{\vartheta \in \Theta} \left\{ \frac{1}{\mathbb{T}_n^\star} \sum_{u \in \mathbb{T}_n^\star} \log\left(q_\vartheta\left(X_{u^-}, X_u\right)\right) \right\}.$$

M. Hoffmann, A. Marguet. Statistical estimation in a randomly structured population, 2018.

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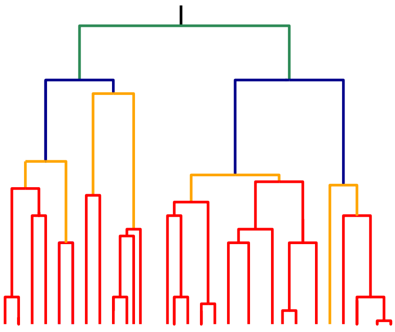
Under regularity assumptions on B, we prove that

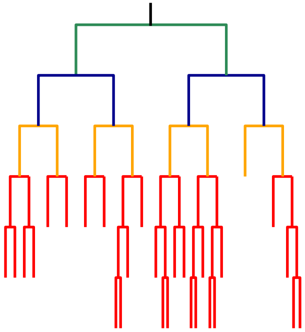
- $\widehat{\vartheta}_n$ converges in probability to ϑ when n tends to infinity.
- $\widehat{\vartheta}_n$ is asymptotically efficient.

M. Hoffmann, A. Marguet. Statistical estimation in a randomly structured population, 2018.

Continuous time

Data : continuous time vs genealogical time





- Random size of the population
- Sampling bias: more cells coming from fertile lineages
- Censored data: the cells at the bottom of the tree have not divided yet

Behavior of a typical individual

For all $t > 0$, $x_0 \in \mathcal{X}$, for all measurable positive function $F : \mathbb{D}([0,t], \mathcal{X}) \to \mathbb{R}$, we have:

$$\mathbb{E}_{\delta_{x_0}}\left[\sum_{u \in V_t} F\left(X_s^u, s \leq t\right)\right] = \mathbb{E}_{\delta_{x_0}}(N_t)\mathbb{E}_{x_0}\left[F\left(Y_s^{(t)}, s \leq t\right)\right],$$

with $\left(Y_s^{(t)}\right)_{s \leq t}$ a time-inhomogeneous Markov process.

- Tool: First moment semigroup transformation (Del Moral 2004, Bansaye 2013, Champagnat et Villemonais 2016, Cloez 2017)
- Interest : A unique process to summarize the dynamic of the whole population

A. Marguet, Uniform sampling in a structured branching population, 2019.

Estimation of the division rate: age-structured population

- Many-to-One formula

$$\mathbb{E}\left[\sum_{u\in V_t} g(X_t^u)\right] = \frac{e^{\lambda_B t}}{m}\mathbb{E}\left[g(\chi_t)B(\chi_t)^{-1}H_B(\chi_t)\right],$$

where χ is an auxiliary process.

- Convergence of the empirical measure: using the geometric ergodicity of χ.
- Representation of B: combining

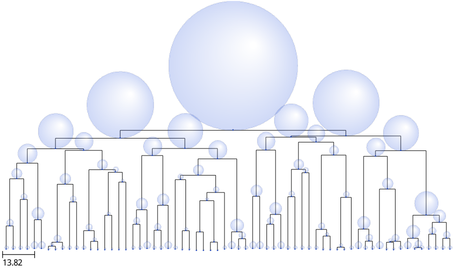
$$B(x) = \frac{B(x)e^{-\int_0^x B(z)dz}}{1-\int_0^x B(y)e^{-\int_0^y B(z)dz}dy}$$

and the invariant measure of χ.

M. Hoffmann, A. Olivier Non-parametric estimation of the division rate of an age-dependent branching process, 2016.

Perspectives

- estimation of B continuous time & stochastic flow
- study of asymmetry in division
- dependency of the division mechanism in some trait



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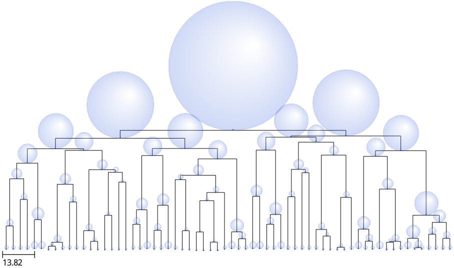

Thank you for your attention!

Asymptotic normality

Let us define $\Psi(\vartheta)$ the Fisher information matrix which coefficients are given for all $1 \leq i, j \leq d$ by:

$$\Psi(\vartheta)_{i,j} = \nu_\vartheta \mathcal{Q}(\vartheta) \left(\frac{\partial_{\vartheta_i} q_\vartheta \partial_{\vartheta_j} q_\vartheta}{q_\vartheta^2} \right).$$

Theorem

Under regularity assumptions and if $\Psi(\vartheta)$ is invertible, for all ϑ in the interior of Θ, we have:

$$|\mathbb{T}_n|^{1/2} \left(\widehat{\vartheta}_n - \vartheta \right) \to \mathcal{N}\left(0, \Psi(\vartheta)^{-1}\right),$$

in law when n tends to infinity, where $\mathcal{N}\left(0, \Psi(\vartheta)^{-1}\right)$ is the d-dimensional normal law with mean 0 and the inverse of the Fisher information matrix $\psi(\vartheta)$ as covariance matrix.