Statistical estimation of the division rate of a size-structured population

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1 The problem

1. The problem
2. Goldenshluger and Lepski's method

The informal problem and the PDE translation for size-structured population

- A cell grows.
- Depending on its size x, the cell has a certain chance to divide itself in 2 offsprings, ie 2 cells of size $x/2$.
- We are interesting by the evolution of the whole population of cells, each of them having this behavior.

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Size-Structured Population Equation (finite time)

$$\begin{cases} \dfrac{\partial}{\partial t}(n(t,x)) + \kappa \dfrac{\partial}{\partial x}(g(x)n(t,x)) + B(x)n(t,x) = 4B(2x)n(t,2x), \\ n(t,x=0) = 0, \quad t > 0 \\ n(0,x) = n_0(x), \quad x \geq 0. \end{cases}$$

- $n(t,x)$ the "amount" of cells with size x ($\neq$ density),
- g the "qualitative" growth rate of one cell: linear is $g = 1$ ...
- B is the division rate, which depends on the size

Asymptotics of the PDE

It can be shown (Perthame Ryzhik 2005 for instance) that

- $n(t,.)$ grows exponentially fast ie $I_t = \int n(t,x)dx$ asymptotically proportional to $e^{\lambda t}$,
- the renormalized $n(t,x)/I_t$ tends to a density N, which satisfies

Size-Structured Population Equation (asymptotics)

$$\begin{cases} \kappa \dfrac{\partial}{\partial x}\big(g(x)N(x)\big) + \lambda N(x) = \mathcal{L}\big(BN\big)(x), \\ B(0)N(0) = 0, \qquad \int N(x)dx = 1, \end{cases}$$

where N step D step κ step L step H step B step

- for any real-valued function $x \rightsquigarrow \varphi(x)$, $\mathcal{L}\big(\varphi\big)(x) := 4\varphi(2x) - \varphi(x)$.
- $\kappa = \lambda \dfrac{\int_{\mathbb{R}_+} xN(x)dx}{\int_{\mathbb{R}_+} g(x)N(x)dx}$.

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- Statistical point of view: we observe a n-sample $X_1, ..., X_n$ of iid variables with density N.

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Assumptions

1. For the considered nonnegative functions g and B and for $\kappa > 0$, there exists a unique solution (λ, N) of SSPS
2. This solution satisfies, for all $p \geq 0$, $\int x^p N(x)dx < \infty$ and $0 < \int g(x)N(x)dx < \infty$.
3. The functions N and gN belong to $\mathcal{W}^{s+1}$ with $s \geq 1$
   $\mathcal{W}^{s+1}$ denotes the Sobolev space of regularity $s+1$ measured in $\mathbb{L}^2$-norm.
4. We have $g \in \mathbb{L}^\infty(\mathbb{R}_+)$ with $\mathbb{R}_+ = [0, \infty)$.

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The statistical methodology is based on kernel rules. Classical assumptions on kernels are made (not specified in the sequel).

Estimation of N

Given K a kernel, we set $K_h(x) = \frac{1}{h}K\left(\frac{x}{h}\right)$ and

$$\hat{N}_h(x) := \frac{1}{n}\sum_{i=1}^{n} K_h(x - X_i)$$

Bias-Variance decomposition

$$\mathbb{E}\left[\left\|N - \hat{N}_h\right\|_2\right] \leq \|N - K_h \star N\|_2 + \frac{1}{\sqrt{nh}}\|K\|_2,$$

where $K_h \star N = \mathbb{E}(\hat{N}_h)$

For $\mathcal{H}$ a family of bandwidths, the "best choice" is the oracle:

$$\bar{h} := \mathrm{argmin}_{h\in\mathcal{H}}\left\{\|N - K_h \star N\|_2 + \frac{1}{\sqrt{nh}}\|K\|_2\right\}.$$

How to select the bandwidth h only based on data?

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How to select the bandwidth h only based on data? Recent work of Goldenshluger and Lepski (2009, 2010)!!! Here just a "toy" version, but that's exactly what we needed.

Bandwidth selection by the GL method

SSPE Set for any x and any $h, h' > 0$,

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"Estimator" of the bias term

$$A(h) := \sup_{h' \in \mathcal{H}} \left\{ \|\hat{N}_{h,h'} - \hat{N}_{h'}\|_2 - \frac{\chi}{\sqrt{nh'}}\|K\|_2 \right\}_+$$

where, given $\varepsilon > 0$, $\chi := (1+\varepsilon)(1+\|K\|_1)$.

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$$\hat{h} := \arg\min_{h \in \mathcal{H}} \left\{ A(h) + \frac{\chi}{\sqrt{nh}}\|K\|_2 \right\} \quad \text{and} \quad \hat{N} := \hat{N}_{\hat{h}}.$$

Some explanations for this choice ...

$$
\begin{aligned}
A(h) &= \sup_{h' \in \mathcal{H}} \left\{ \|\hat{N}_{h,h'} - \hat{N}_{h'}\|_2 - \frac{\chi}{\sqrt{nh'}} \|K\|_2 \right\}_+ \\
&\leq \sup_{h' \in \mathcal{H}} \left\{ \|\mathbb{E}(\hat{N}_{h,h'}) - \mathbb{E}(\hat{N}_{h'})\|_2 \right\} + \zeta
\end{aligned}
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\zeta = \sup_{h' \in \mathcal{H}} \left\{ \|\hat{N}_{h,h'} - \mathbb{E}(\hat{N}_{h,h'}) - \left(\hat{N}_{h'} - \mathbb{E}(\hat{N}_{h'})\right)\|_2 - \frac{\chi}{\sqrt{nh'}} \|K\|_2 \right\}_+ .
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- $\|\mathbb{E}(\hat{N}_{h,h'}) - \mathbb{E}(\hat{N}_{h'})\|_2 \leq \|K\|_1 \|K_h \star N - N\|_2$
- ζ is a residual controlled by "Uniform bounds". It is small (n^{-1}) if χ is large enough.

First result

Oracle inequality

If $\mathcal{H} = \{1/\ell \;/\; \ell = 1, ..., \ell_{max}\}$ and if $\ell_{max} = \delta n$, if moreover $\|N\|_\infty < \infty$,
then for any $q \geq 1$,

$$\mathbb{E}\left(\|\hat{N} - N\|_2^{2q}\right) \leq \square_q \chi^{2q} \inf_{h \in \mathcal{H}} \left\{ \|K_h \star N - N\|_2^{2q} + \frac{\|K\|_2^{2q}}{(hn)^q} \right\} + \square_{q,\varepsilon,\delta,\|K\|_2,\|K\|_1,\|N\|_\infty} \frac{1}{n^q}.$$

Estimation of $D = \frac{\partial}{\partial x}\big(g(x)N(x)\big)$

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$\hat{D}_{h,h'}(x) := \frac{1}{n}\sum_{i=1}^{n} g(X_i)(K_h \star K_{h'})'(x - X_i)$,

$$\tilde{A}(h) := \sup_{h' \in \tilde{\mathcal{H}}} \left\{ \|\hat{D}_{h,h'} - \hat{D}_{h'}\|_2 - \frac{\tilde{\chi}}{\sqrt{nh'^3}}\|g\|_\infty \|K'\|_2 \right\}_+ ,$$

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where, given $\tilde{\varepsilon} > 0$, $\tilde{\chi} := (1 + \tilde{\varepsilon})(1 + \|K\|_1)$.

Finally, we estimate D by using $\hat{D} := \hat{D}_{\tilde{h}}$ with

$$\tilde{h} := \mathrm{argmin}_{h \in \tilde{\mathcal{H}}} \left\{ \tilde{A}(h) + \frac{\tilde{\chi}}{\sqrt{nh^3}}\|g\|_\infty \|K'\|_2 \right\}.$$

Result for the derivative D

Oracle inequality for D

If $\tilde{\mathcal{H}} = \{1/\ell \;/\; \ell = 1, \ldots, \ell_{max}\}$ and if $\ell_{max} = \sqrt{\delta' n}$, if moreover $\|N\|_\infty$ and $\|g\|_\infty < \infty$, then for any $q \geq 1$,

$$\mathbb{E}\left(\|\hat{D} - D\|_2^{2q}\right) \leq \square_q \tilde{\chi}^{2q} \inf_{h \in \tilde{\mathcal{H}}} \left\{ \|K_h \star D - D\|_2^{2q} + \left[\frac{\|g\|_\infty \|K'\|_2}{\sqrt{nh^3}}\right]^{2q} \right\}$$

$$+ \square_{q, \tilde{\varepsilon}, \delta', \|K'\|_2, \|K\|_1, \|K'\|_1, \|N\|_\infty, \|g\|_\infty} \frac{1}{n^q}.$$

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There exist some $q > 1$ such that

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Let $c > 0$,

$$\hat{\kappa} = \hat{\lambda} \frac{\sum_{i=1}^n X_i}{\sum_{i=1}^n g(X_i) + c}.$$

The inversion of $\mathcal{L}$

In SSPE, it remains to (approximately) invert $\mathcal{L}$. (see Perthame, Zubelli, Doumic (2009))

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Define $T > 0$, an integer $k \geq 1$ and the regular grid on $[0, T]$ with mesh $k^{-1}T$ defined by

$0 = x_{0,k} < x_{1,k} < \cdots < x_{i,k} := \frac{i}{k}T < \ldots < x_{k,k} = T.$

Set $\varphi_{i,k} =: \frac{k}{T}\int_{x_{i,k}}^{x_{i+1,k}} \varphi(x)dx$ for $i = 0, \ldots, k-1$, and define by induction the sequence

$$H_{i,k}(\varphi) := \frac{1}{4}(H_{i/2,k}(\varphi) + \varphi_{i/2,k}) \text{ with } \begin{cases} H_0(\varphi) := & \frac{1}{3}\varphi_{1,k}, \\ H_1(\varphi) := & \frac{4}{21}\varphi_{0,k} + \frac{1}{7}\varphi_{1,k} \end{cases}$$

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for any sequence $u_i, i = 1, 2, \ldots,$

$$u_{i/2} := \begin{cases} u_{i/2} & \text{if } i \text{ is even} \\ \frac{1}{2}(u_{(i-1)/2} + u_{(i+1)/2}) & \text{otherwise.} \end{cases}$$

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$$H_{i,k}(\varphi) := \frac{1}{4}(H_{i/2,k}(\varphi) + \varphi_{i/2,k}) \text{ with } \begin{cases} H_0(\varphi) := & \frac{1}{3}\varphi_{1,k}, \\ H_1(\varphi) := & \frac{4}{21}\varphi_{0,k} + \frac{1}{7}\varphi_{1,k} \end{cases}$$

Finally, we define

$$\mathcal{L}_k^{-1}(\varphi)(x) := \sum_{i=0}^{k-1} H_{i,k}(\varphi) 1_{[x_{i,k}, x_{i+1,k})}(x).$$

The inversion of $\mathcal{L}$

In SSPE, it remains to (approximately) invert $\mathcal{L}$. (see Perthame, Zubelli, Doumic (2009))

Define $T > 0$, an integer $k \geq 1$ and the regular grid on $[0, T]$ with mesh $k^{-1}T$ defined by

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The (approximative) inversion of $\mathcal{L}$

Finally, we define

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Proposition

- $\mathcal{L}_k^{-1} : \mathbb{L}^2[0,T] \mapsto \mathbb{L}^2[0,T]$ is continuous
- $\|\mathcal{L}_k^{-1}(\varphi) - \mathcal{L}^{-1}(\varphi)\|_{2,T} \leq C \frac{T}{\sqrt{k}} \|\varphi\|_{\mathcal{W}^1}$, with $C < \frac{1}{\sqrt{6}}$.

We estimate $H = BN$ by

$$\hat{H} = \mathcal{L}_k^{-1}(\hat{\kappa}\hat{D} + \hat{\lambda}\hat{N}).$$

Oracle inequality for the estimation of $H = BN$

We establish an oracle inequality for $H = BN$ which is true under all previous assumptions.

Theorem

$$\mathbb{E}\left[\left\|\hat{H} - H\right\|_{2,T}^{q}\right] \leq C\left\{E_D + E_N + E_\lambda + E_{\mathcal{L}} + n^{-\frac{q}{2}}\right\}$$

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- $E_D = \sqrt{R_\lambda}\,\inf_{h\in\tilde{\mathcal{H}}}\left\{\|K_h \star D - D\|_2^q + \left(\frac{\|g\|_\infty \|K'\|_2}{\sqrt{nh^3}}\right)^q\right\}$

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- $E_\lambda = \varepsilon_\lambda n^{-\frac{q}{2}}$
- $E_{\mathcal{L}} = \left((\|N\|_{\mathcal{W}^1} + \|gN\|_{\mathcal{W}^2})\frac{T}{\sqrt{k}}\right)^q$

Rate of convergence for the estimation of B

here We finally set $\hat{B} = \hat{H}/\hat{N}$ and $\tilde{B} = \max(\min(\hat{B}, \sqrt{n}), -\sqrt{n})$.

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Theorem

one can choose a family of $\mathcal{H}$ and $\mathcal{H}'$ independent of s such that for any compact $[a, b]$ of $[0, T]$ (under technical assumptions),

$$\mathbb{E}\left[\left\|(\tilde{B} - B)1_{[a,b]}\right\|_2^q\right] = O\left(n^{-\frac{qs}{2s+3}}\right).$$

Why is it the good rate?(1)

In the deterministic set-up

- we observe $N_\epsilon = N + \epsilon\zeta$, with $\|\zeta\|_2 \leq 1$ and

$$BN = \mathcal{L}^{-1}\left(\kappa\partial_x\big(g(x)N(x)\big) + \lambda N(x)\right).$$

- Since $\mathcal{L}^{-1}$ is continuous and the recovery of $\partial_x N$ is a more difficult inverse problem than the recovery of N, hence the ill-posedness is only due to ∂N (degree of ill-posedness $=1$)
- Hence if $N \in \mathcal{W}^s$, error in $\epsilon^{\frac{s}{s+1}}$.

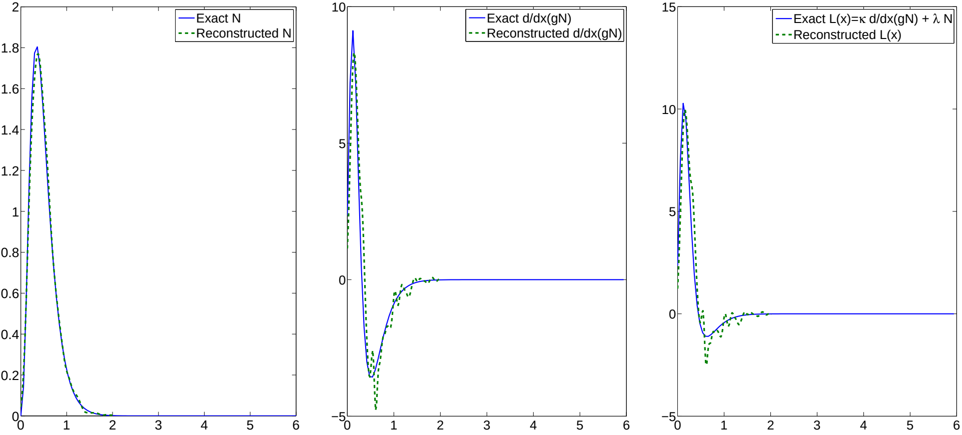
Why is it the good rate?(2)

In the n-sample set-up

- problem well approximated by $N_\epsilon = N + \epsilon\mathbb{B}$ with $\mathbb{B}$ Gaussian white noise and $\epsilon = n^{-1/2}$.
- $\mathbb{B}$ is not in $\mathbb{L}_2$ but in $\mathcal{W}^{-1/2}$,
- Hence one needs to integrate ie $Z_\epsilon = \mathcal{I}^{1/2}N + \epsilon\mathcal{I}^{1/2}\mathbb{B}$ to have a noise in $\mathbb{L}_2$.
- Hence $Z_\epsilon = \mathcal{I}^{3/2}(\partial N) + \epsilon\mathcal{I}^{1/2}\mathbb{B}$ is of degree of ill-posedness 3/2.
- Hence if $N \in \mathcal{W}^s$, error in $\epsilon^{\frac{s}{s+3/2}} = n^{-\frac{s}{2s+3}}$.

Simulations

n=5000, Gaussian kernel, $B = 3\sqrt{x}$, $g = 1$.



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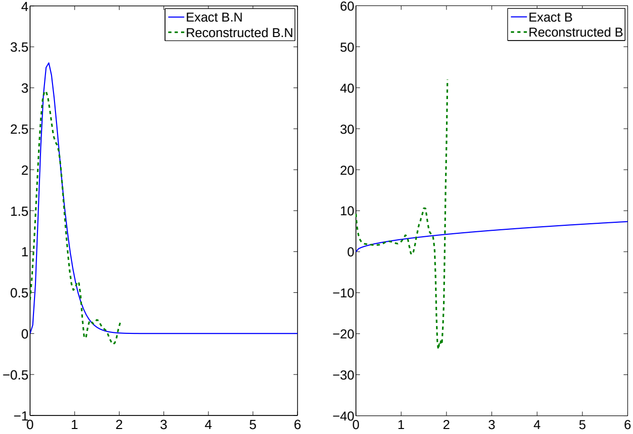

Perspectives

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$$... = 2 \int_x^\infty B(y)k(x,y)n(t,y)dy - B(x)n(t,x),$$

Division of the cell of size y into 2 cells of size x and $y - x$ with probability density$=k(x, y)$. Equal mitosis: $k(x,y) = \delta_{x=\frac{y}{2}}$, so $2\int_x^\infty B(y)k(x,y)n(t,y)dy = 4B(2x)n(t,2x)$

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  - Construct a microscopic stochastic system that matches with the PDE's approximation and that take advantage of richer observation schemes (Probabilistic works in progress studied by B. Cloez, V. Bansaye, M. Doumic, M. Hoffmann, N. Krell, T. Lepoutre, L. Robert,...)

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Simulation study with Gaussian kernel

$n = 50\,000$, $\kappa = 1$, $g(x) = 1$ and 3 different functions B:

- $B_1(x) = 1$
- $B_2(x) = 1_{x \leq 1.5} + \text{affine part} + 5 \times 1_{x \geq 1.7}$ (B_2 continuous)
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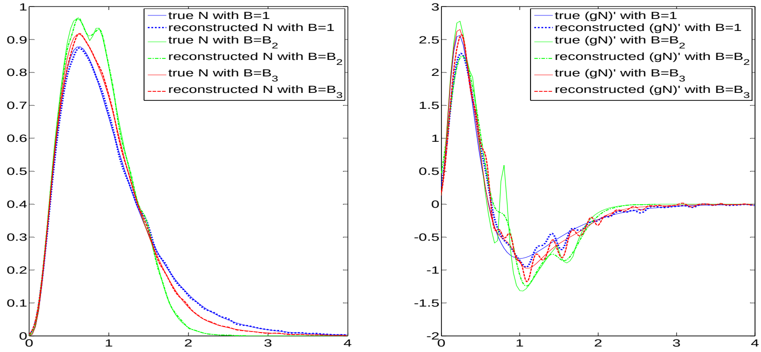

Figure: Reconstruction of N (left) and of D (right)

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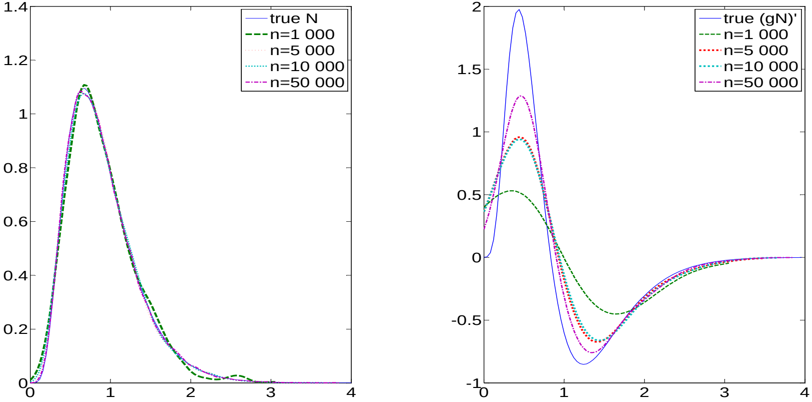
SSPS



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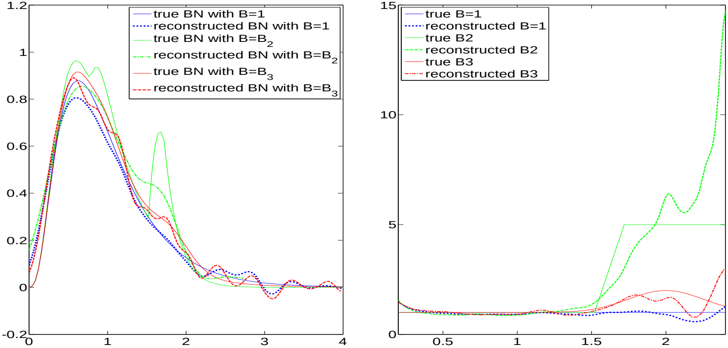

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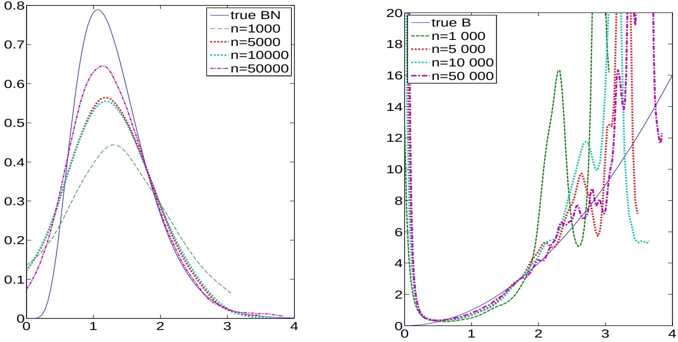

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