Statistical inference in transport-fragmentation equations

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Context

- We consider (simple) particle systems $\approx$ toy models for the evolution of cells or bacteria.
  - Each particle grows by ingesting a common nutrient.
  - After some time, each particle gives rise to two offsprings by cell division.
- We structure the model by state variables like size, growth rate and so on.
  - Deterministically, the density of structured state variables evolves according to a fragmentation-transport PDE.
  - Stochastically, the particles evolve according to a PDMP that evolves along a branching tree.

Toy model : size-structured populations

- $n(t, x)$: density of cells of size x.
- Parameter of interest : Division rate $B(x)$.
- 1 cell of size x gives birth to 2 cells of size $x/2$.
- The growth of the cell size by nutrient uptake is given by a growth rate $g(x) = \tau x$ (for simplicity).

Structured populations (cont.)

- Transport-fragmentation equation

$$\partial_t n(t,x) + \partial_x\big(\tau x n(t,x)\big) + B(x)n(t,x) = 4B(2x)n(t,2x)$$

with $n(t,x=0)=0,\ t>0$ and $n(0,x)=n^{(0)}(x),\ x\geq 0.$

- obtained by mass conservation law :
  - LHS : density evolution + growth by nutrient + division of cells of size x.
  - RHS : division of cells of size $2x$.
- Several extensions...

Objectives

- Main goal : estimate non-parametrically B from genealogical data of a cell population of size N living on a binary tree.
- Avoid an inverse problem (cp. Doumic, Perthame, Zubelli, 2009 & Doumic, H., Reynaud, Rivoirard, 2012) thanks to richer data set.
- Reconcile the deterministic approach with a rigorous statistical analysis (relaxing the steady-state approximation).

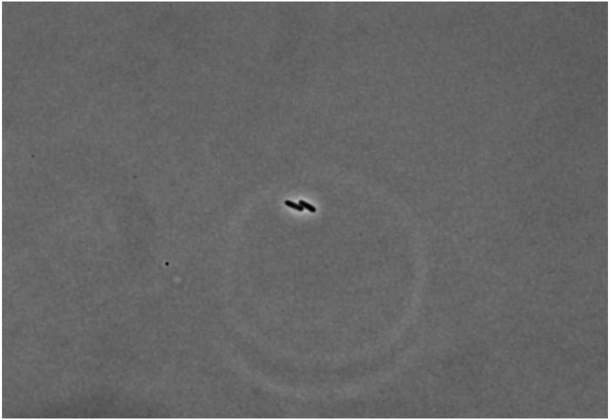
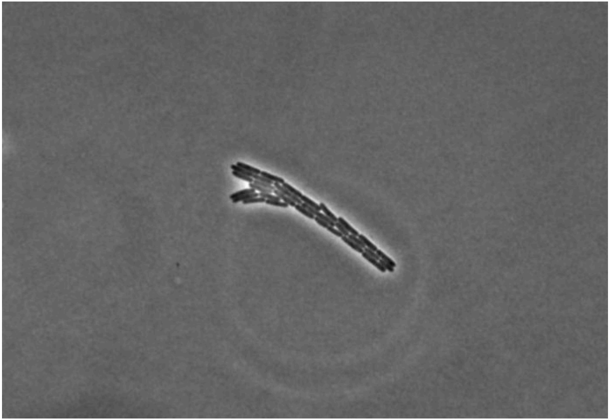


FIGURE : Evolution of a *E. Coli* population.



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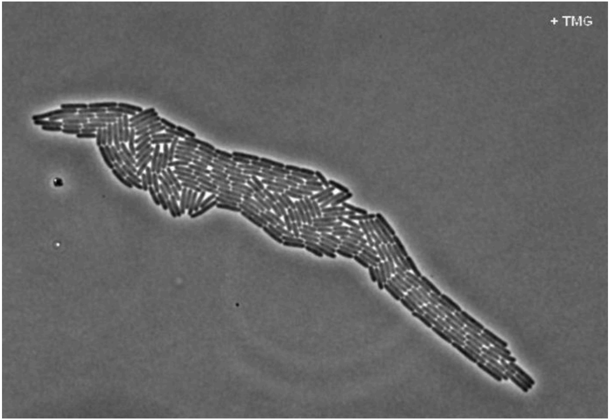

FIGURE : Evolution of a *E. Coli* population.

Strategy

- Construct a stochastic model accounting for the stochastic dependence structure on a tree for which the empirical measure of N particles solves the fragmentation-transport equation (in a weak sense).
- Develop appropriate statistical tools to estimate B.
- Additional difficulty & goal : incorporate growth variability (each cell has a stochastic growth rate inherited from its parent).

Result 1

- We construct a Markov process on a binary tree

$$(X_t, V_t) \in \Big(\bigcup_{k \geq 0} [0, \infty)^k \Big)^2,$$

where X_t=size and V_t=growth rate of living cells at time t (inherited from their parent according to a kernel ρ).

- $n(t, \cdot) := \mathbb{E}\left[\sum_{i=1}^{\infty} \delta_{X_i(t), V_i(t)} \right]$ is a (weak)-solution of an extension of the transport-fragmentation equation :

$$\partial_t n(t,x,v) + v\,\partial_x\big(x\,n(t,x,v)\big) + B(x)n(t,x,v)$$

$$= \quad 4 \int \rho(v', dv) n(t, 2x, dv').$$

- The initial framework $g(x) = \tau x$ is retrieved as soon as $\rho(dv) = \delta_\tau(dv)$

Result 2

- Genealogical data : we observe size+variability $(\xi_u, \tau_u)_{u \in \mathcal{U}_N}$, where $\mathcal{U}_N$ is a (connected) subset of size N of the binary tree $\mathcal{U} = \cup_{k \geq 0} \{0,1\}^k$.
- Main result : We can construct an estimator $(\widehat{B}_N(x), x > 0)$ of the s-regular division rate $B(x)$ s.t.

$$\boxed{\mathbb{E}\left[\|\widehat{B}_N - B\|^2_{L^2_{\text{loc}}}\right]^{1/2} \lesssim (\log N) N^{-s/(2s+1)}}$$

Numerical implementation and effect of variability

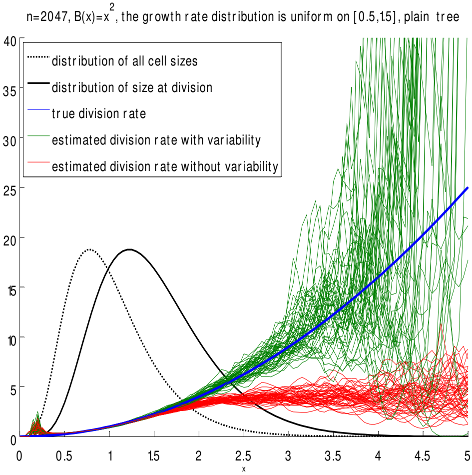

FIGURE : Simulated data

Comparison with the inverse problem approach

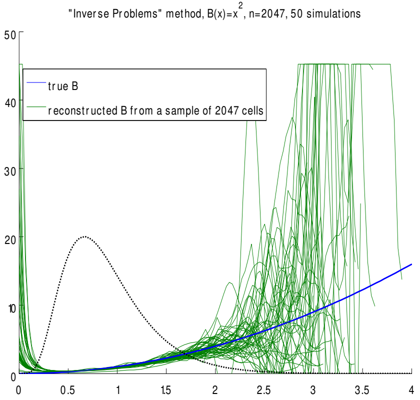

FIGURE : Exploration on simulated data via the global approach (inverse problem), $N \approx 3000$.

Numerical implementation

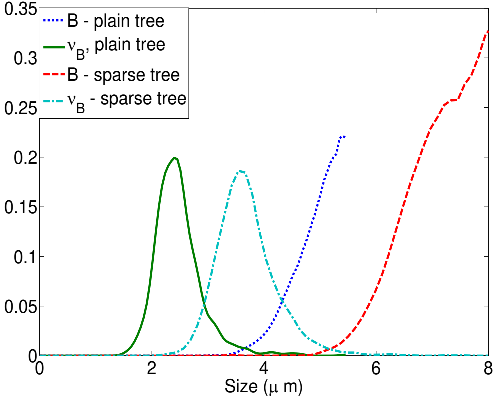

FIGURE : Exploration on real-data. Sparse tree, $N \approx 3000$.

Statistical estimation

- Given a pair ξ_{u^-}, ζ_{u^-} and ξ_u, we can identify τ_{u^-} through

$$2\,\xi_u = \xi_{u^-}\, e^{\tau_{u^-}\zeta_{u^-}}.$$

- We have

$$\mathbb{P}(\zeta_u \in [t, t+dt]\,|\zeta_u \geq t, \xi_u = x) = B(xe^{\tau t})dt$$

from which we obtain the density of the lifetime ζ_{u^-} (lifetime of the parent u^-) conditional on $\xi_{u^-} = x$ and $\tau_{u^-} = v$:

$$\boxed{t \rightsquigarrow B(xe^{vt})\exp\Big(-\int_0^t B(xe^{vs})ds\Big).}$$

Toward a Markov kernel

- Using $2\,\xi_u = \xi_{u^-} \exp\big(\tau_{u^-}\zeta_{u^-}\big)$, we further infer

$$\mathbb{P}\left(\xi_u \in dx' \,\middle|\, \xi_{u^-} = x, \tau_{u^-} = v\right)$$
$$= \frac{B(2x')}{vx'} \mathbf{1}_{\{x' \geq x/2\}} \exp\Big(- \int_{x/2}^{x'} \tfrac{B(2s)}{vs} ds\Big) dx'.$$

- We obtain a simple an explicit representation for the transition kernel on $\mathcal{S} = [0, \infty) \times \mathcal{E}$,

$$\boxed{\mathcal{P}_B(\mathbf{x}, d\mathbf{x'}) = \mathcal{P}_B\big((x, v), x', dv'\big)dx'}$$

The explicit transition

- The formula is given by

$$\mathcal{P}_B\big((x,v),x',dv'\big)dx'$$
$$=\frac{B(2x')}{vx'}\mathbf{1}_{\{x'\geq x/2\}}\exp\Big(-\int_{x/2}^{x'}\frac{B(2s)}{vs}ds\Big)\rho(v,dv').$$

- $\rho(a,da')$: appropriate Markov kernel on $\mathcal{E}$.
- Under appropriate conditions on B, the Markov chain on $\mathcal{S}=[0,\infty)\times\mathcal{E}$ is geometrically ergodic. (It is however not reversible.)

Identifying B through the invariant measure

- Under appropriate assumptions, we have existence (and uniqueness) of an invariant measure on $\mathcal{S}$

$$\nu_B(d\mathbf{x}) = \nu_B(x, dv)dx$$

i.e. such that $\nu_B \mathcal{P}_B = \nu_B$.

- More precisely, we have a contraction property

$$\sup_{|g| \leq V} \left| \mathcal{P}_B^k g(\mathbf{x}) - \int_{\mathcal{S}} g(\mathbf{z}) \nu_B(d\mathbf{z}) \right| \leq RV(\mathbf{x})\gamma^k$$

for some $\gamma < 1$ locally uniformly in B for an appropriate Lyapunov function V.

Identifying B through the invariant measure

$$\begin{aligned}
&\nu_B(y, dv') \\
&= \int_{\mathcal{S}} \nu_B(x, dv) dx\, \mathcal{P}_B\big((x,v), y, dv'\big) \\
&\quad = \frac{B(2y)}{y} \int_{\mathcal{E}} \int_0^{2y} \nu_B(x, dv) dx \exp\Big(- \int_{x/2}^{y} \frac{B(2s)}{vs} ds\Big) \frac{\rho(v, dv')}{v}.
\end{aligned}$$

"Survival analysis trick"

$$\exp\Big(- \int_{x/2}^{y} \frac{B(2s)}{vs} ds\Big) = \int_y^{\infty} \frac{B(2s)}{vs} \exp\Big(- \int_{x/2}^{v} \frac{B(2s')}{vs'} ds'\Big) ds$$

and $\mathcal{P}_B$ is involved in the RHS again...

Identifying B through the invariant measure

- We obtain

$$\nu_B(y, dv') = \frac{B(2y)}{y} \int_{\mathcal{E}} \int_0^{2y} \nu_B(x, dv) dx$$
$$\int_y^{\infty} \tfrac{B(2s)}{vs} \exp\big(- \int_{x/2}^{s} \tfrac{B(2s')}{vs'} ds' \big) ds \frac{\rho(v, dv')}{v}$$
$$= \frac{B(2y)}{y} \int_{\mathcal{S}} \int_{[0,\infty)} \mathbf{1}_{\{x \leq 2y,\, s \geq y\}} v^{-1}$$
$$\nu_B(x, dv) dx\, \mathcal{P}_B\big((x, v), s, dv'\big) ds.$$

and integrate in dv'.

Key representation

- We obtain the key representation

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

- We conclude

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

Final estimator

- Introduce a kernel function $K : [0,\infty) \to \mathbb{R}$, $\int_{[0,\infty)} K(y)dy = 1$ and set $K_h(y) = h^{-1}K\big(h^{-1}y\big)$ for $y \in [0,\infty)$ and $h > 0$.
- Final estimator

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

- The estimator $\widehat{B}_n(y)$ is specified by K, the bandwidth h and the threshold ϖ.

Some references

- Doumic, M., H. M., Reynaud-Bouret, P. and Rivoirard, V. (2012) *Nonparametric estimation of the division rate of a size-structured population*. SIAM Journal on Numerical Analysis. **50**, 925-950
- Doumic, M., H.,M., Krell, N. and Robert, L. (2012) *Statistical estimation of a growth-fragmentation model observed on a genealogical tree. arXiv :1210.3240*
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