Estimating the distribution of fitness effects in a structured population of cells

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Introduction and Data

- All organisms are subject to mutations
- These new traits can change the selective value (fitness) of an individual
  We call *Fitness* the ability of an individual with a certain genome to survive and reproduce
- **How these mutations affect the selective value is a central question in evolutionary biology**
- The density of the distribution of these effects is called the **Distribution of Fitness Effect (DFE)**

- **Probabilistic Model** :
  1. Z_t^j represents the noisy measure of the fitness of the cell in channel $j \in J$ at time t.
  2. N_t^j represents the number of times the cell in channel j has mutated.
     $(N_j(t), j \geq 1)$ are *i.i.d* Poisson processes with intensity $\lambda \in (0, \infty)$.
  3. X_k^j represents the effect of the k-th mutation on the cell in channel j. $(X_i^j)_{i,j\geq 0}$ are *i.i.d* with density $f \in L^1(\mathbb{R}) \cap L^2(\mathbb{R})$.
  4. ε_t^j represents the measurement noise at time t for channel j.
     $(\varepsilon_t^j)_{j\geq 0}$ are *i.i.d* and that $\mathbb{E}(\varepsilon_t^j) = 0$.
- We consider a noisy compound Poisson process:

$$Z_t^j = \left(\sum_{k=1}^{N_t^j} X_k^j\right) + \varepsilon_t^j,\ t \geq 0.$$

Statement of the problem: Estimate the density of X_i from observations of Z_t on each channel $j \in J$

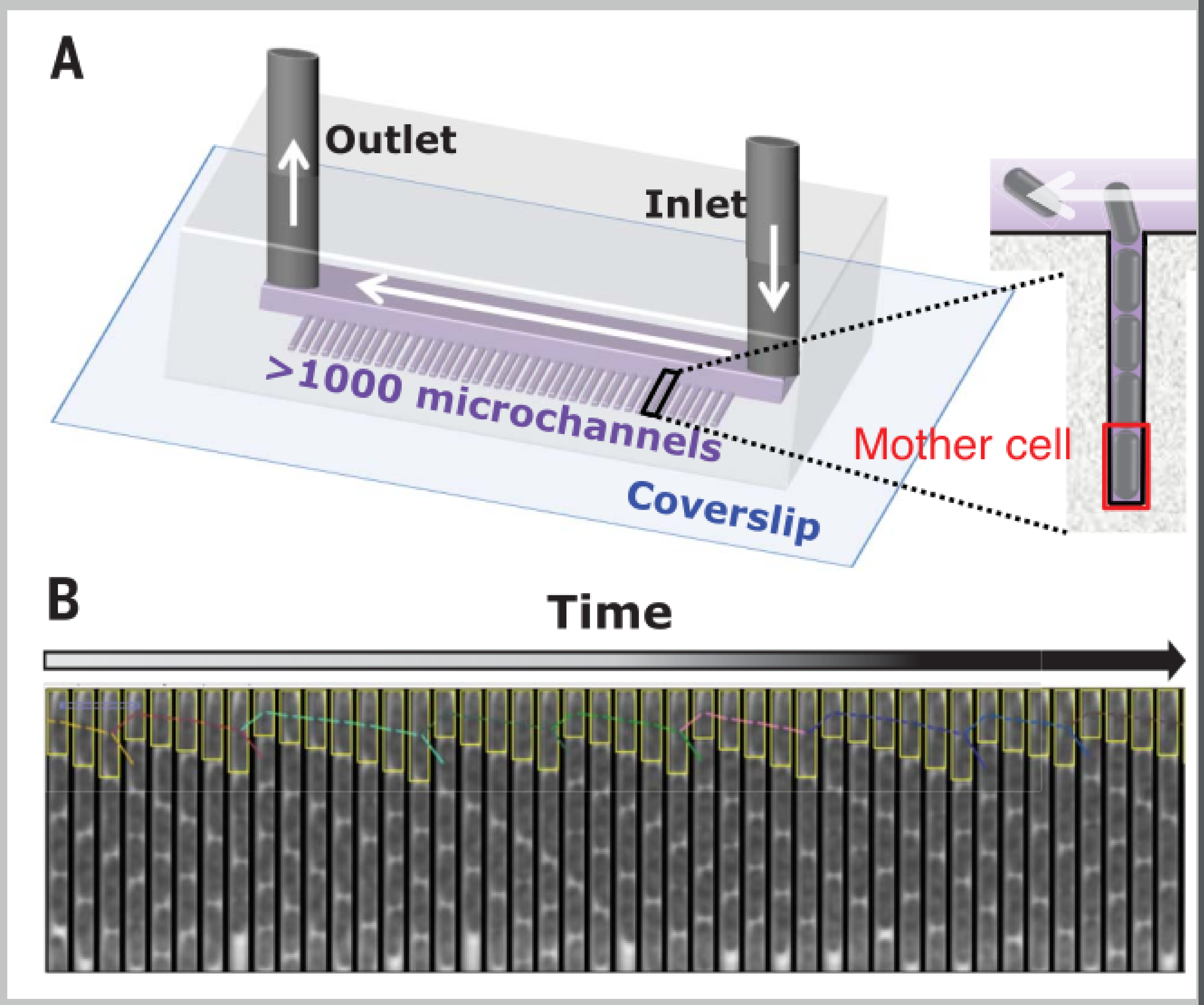

Figure 1:Measurement of the evolution of the fitness of several cell lines over time

Robert et al., 2018

Combine two classical problems in non-parametric inference.

- Deconvolution
- Decompounding

Statistical Strategy and statistical Results

- **Strategy:** Estimate the characteristic function of X :
  (heuristic) If $\varphi_X(\xi) \simeq \widehat{\varphi}_X(\xi)$, then $f(x) \simeq \widehat{f}(x)$
- Indeed, the characteristic function $\varphi_X \longrightarrow$ Density f of X:

$$f(x) = \frac{1}{2\pi}\int_{\mathbb{R}} \varphi_X(\xi) e^{-ix\xi} d\xi$$

- **Theorem :** For all reals $0 < t_1 < t_2$ such that $t_2 \leq \frac{1}{4}\log(Jt_2)$
  $Jt_1 \to \infty$, $Jt_2 \to \infty$ as $J \to \infty$ and for any $m < C^J_{t_1,t_2}$, the following inequality holds

$$\mathbb{E}\left(||\widehat{f}_{m,J} - f||^2\right) \leq ||f_m - f||^2 + \sum_{i=1}^{2} \frac{4e^{4t_i}}{J(t_2-t_1)^2}\int_{-m}^{m}\frac{du}{|\varphi_\varepsilon(u)|^2} + \frac{4K_{J,t_1,t_2}}{(t_2-t_1)^2}\cdot\left(\frac{\mathbb{E}[X_i^2]}{Jt_i} + \frac{\mathbb{E}[\varepsilon^2]}{Jt_i^2} + 4\frac{m}{(Jt_i)^2}\right).$$

where K_{J,t_1,t_2} and $C^J_{t_1,t_2}$ depends on m, t_1, t_2 and $\log\varphi_\varepsilon(\cdot)$.
Futhermore, **m can be chosen in an optimal way from data**

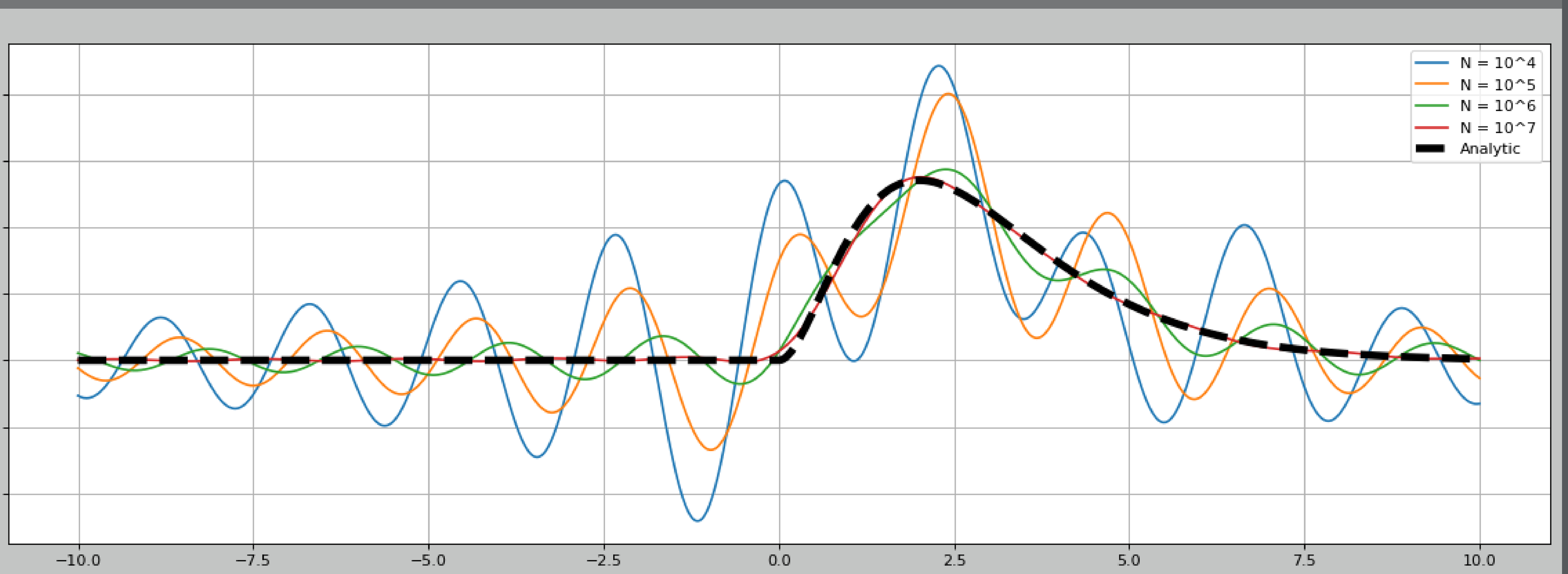

Figure 2:Reconstruction of the Gamma $\Gamma(3)$ distribution with J channels, corrupted by a Gaussian noise $\mathcal{J}(0,1)$ with $J \in 10^4, 10^5, 10^6, 10^7$ and $t_1 = 0.1, t_2 = 1, m = 3$

The estimator converges to f when $J \to \infty$.

A link with PDEs

The evolution of the stochastic process can also be described with PDEs.

- **Step 1a:** If every mutation is deleterious

$$\partial u(t,x) = -\lambda u(t,x) + \int_x^\infty k\left(\frac{x}{y}\right)u(t,y)\frac{dy}{y}.$$

  Where $K(1) = 1$ when $K(s) = \int_0^\infty x^{s-1}k(x)dx$
- **Step 1b:** If mutations can have some beneficial effects

$$\partial u(t,x) = -\lambda u(t,x) + \int_0^\infty k\left(\frac{x}{y}\right)u(t,y)\frac{dy}{y}.$$

  Where $K(1) = 1$. Here, K can be non-monotonous.

ex. If $k_0(dx) = (1-\alpha)\delta_{1-\varepsilon} + \alpha\partial_{1+\eta}$, then

$$K(s;\alpha,\varepsilon,\eta) = (1-\alpha)(1-\varepsilon)^{s-1} + \alpha(1+\eta)^{s-1}$$

Step 2. Add a terme of growth ?

$$\partial u(t,x) = -\lambda u(t,x) + \int_0^\infty k\left(\frac{x}{y}\right)u(t,y)\frac{dy}{y} + xu(t,x).$$

Step 3. How to modify Step 2 to have

$$u(t,x) \to U(x)e^{\alpha t}$$

Why do that ?
Our goal is to understand the diversity of mutation in a stable population.

References

[1] Lydia Robert, Jean Ollion, Jérôme Robert, and al.
Mutation dynamics and fitness effects followed in single cells.
Science, 359(6381):1283–1286, 2018.

[2] Marie Doumic and Miguel Escobedo.
Time asymptotics for a critical case in fragmentation and growth-fragmentation equations.
Kinetic and Related Models, 9(2):251–297, 2016.

[3] Céline Duval and Johanna Kappus.
Nonparametric adaptive estimation for grouped data.
Journal of Statistical Planning and Inference, 182:12–28, 2017.

[4] Céline Duval and Johanna Kappus.
Adaptive procedure for fourier estimators : application to deconvolution and decompounding.
Electronic Journal of Statistics, 13(2):3424–3452, 2019.

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