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:

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

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

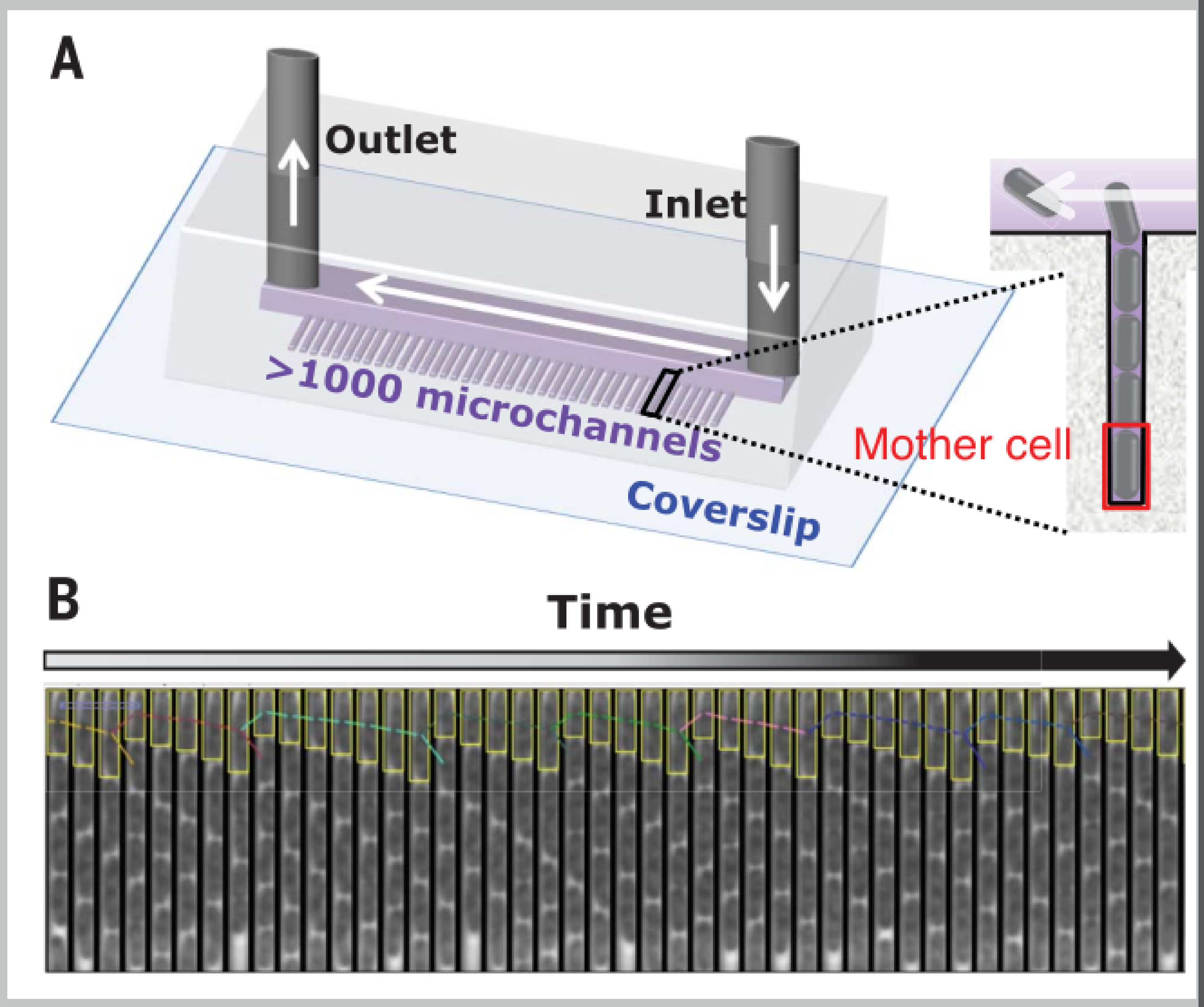

Figure 1:Measurement of the evolution of the fitness of several cell lines over time

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

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

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**

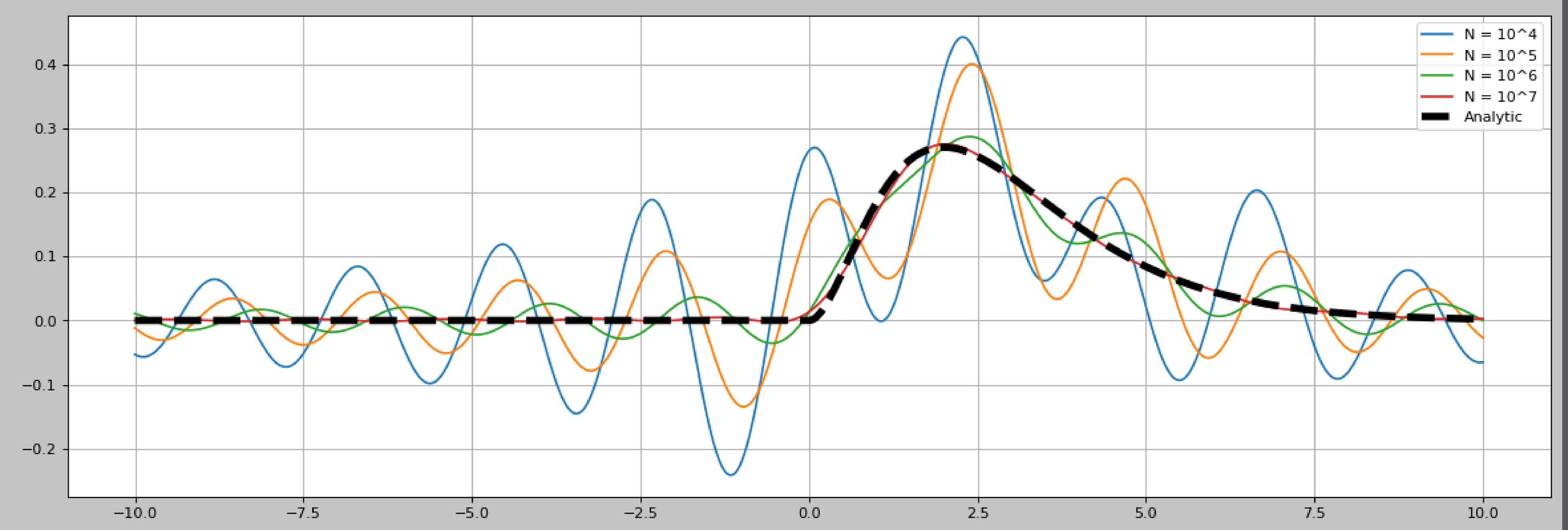

Figure 2:Reconstruction of the Gamma $\Gamma(3)$ distribution with J channels, corrupted by a Gaussian noise $\mathcal{J}(0,1)$ with $J \in 10^4, 10^5, 10^6, 10^7$.
$t_1 = 0.1, t_2 = 1, m = 3$

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

- Perspectives:
  1. Is this estimator minimax? (*i.e the "best" estimator among all estimators)*

A Structured Deterministic Equation

- If $u(t,x)$ is the probability distribution of the fitness x at time t:

$$\frac{\partial}{\partial t}u(t,x) = -\lambda u(t,x) + \lambda\int_0^\infty \frac{1}{z}k_0\left(\frac{x}{z}\right)u(t,z)dz; \quad u(0,x) = u_0(x)$$

- **The asymptotic-behavior of solution can be determine using Mellin transform. It strongly depends on the initial condition.**
- **Theorem :** If u_0 satisfies *"good" hypothesis*, then, for all $\delta > 0$

$$\boxed{u(t,x) = a_0 x^{-q_0} e^{(K(q_0)-1)t}\left(1 + \left(e^{K(r-\delta)-K(q_0))t}\right)\right)}$$

as $t \to \infty$, uniformly for all $x \geq 1$, where K is the Mellin transform of k_0.
- A similar result can be obtain if $0 < x < 1$.

- Perspectives:
  1. Reconstruct the mutation kernel from data.
  2. If the mutation rate depends on the fitness ?
  $$\frac{\partial}{\partial t}u(t,x) = -\lambda B(x)u(t,x) + \lambda\int_0^\infty \frac{1}{z}k_0\left(\frac{x}{z}\right)B(z)u(t,z)dz$$
  3. Equation in population ? Add a term for the cell's division.
  4. Asymptotic behavior of the solution?
  5. Conditions on the kernel of mutations to obtain a stationnary distribution.

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