

Estimer l'effet des mutations sur la fitness d'une population de bactéries

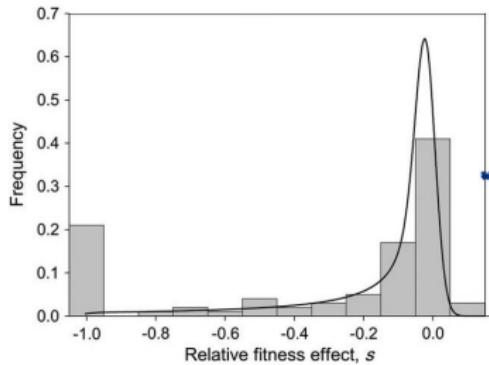
Jérémy Andréoletti et Nathanaël Boutillon

Encadrantes : Marie Doumic et Lydia Robert

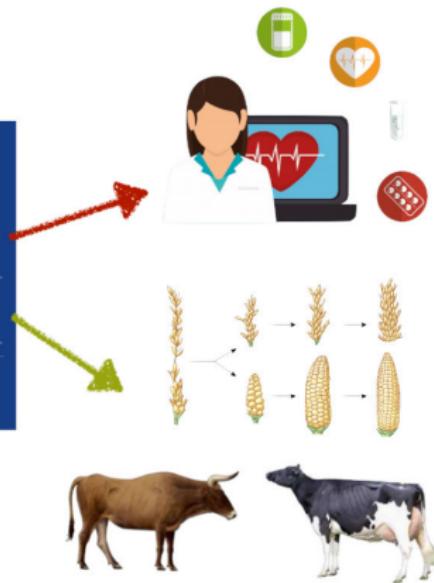
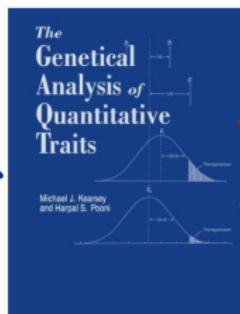
Objectifs

- Comprendre la dynamique d'apparition des mutations, chez *E. coli*
- Estimer la **DFE = Distribution des Effets des mutations sur la Fitness**

Distribution of fitness effects
caused by single-nucleotide
substitutions in bacteriophage f1



Peris et al., Genetics, 2010



Modèle

On pose

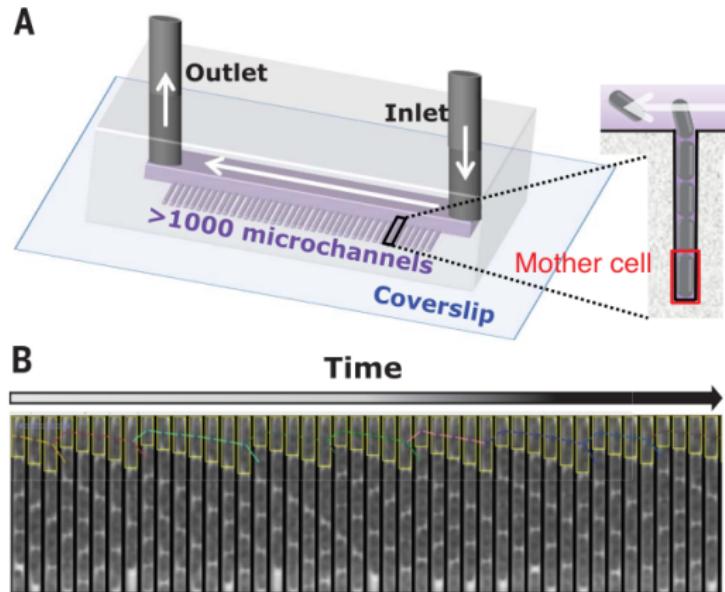
W_t	fitness (taux de croissance) au temps t
$s_i = \frac{W_{t_{i-1}} - W_{t_i}}{W_{t_{i-1}}}$	effet <i>relatif</i> de la mutation i
N_t	nombre de mutations avant le temps t

d'où :

$$\frac{W_t}{W_0} = \prod_{i=1}^{N_t} (1 - s_i)$$

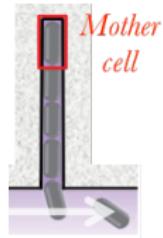
→ But = trouver la loi des s_i .

Experience μ -MA (mutation accumulation)



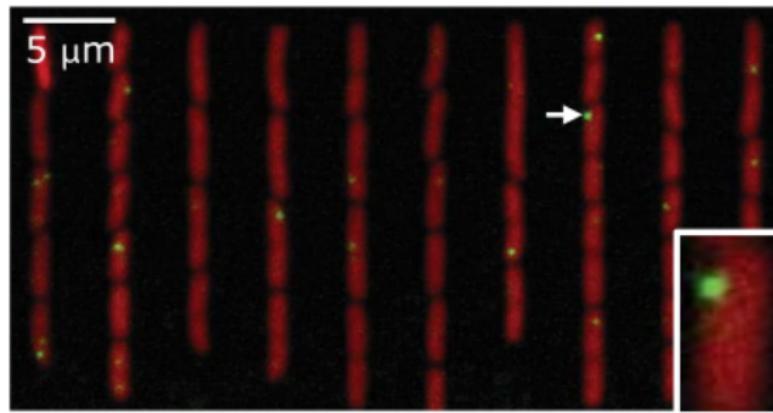
Robert et al.

Experience μ -MA (mutation accumulation)



Robert et al.

Experience MV (mutation visualization)



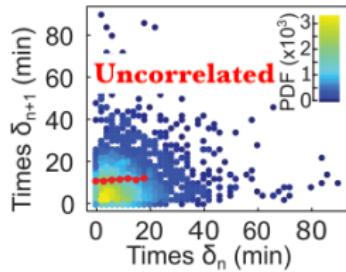
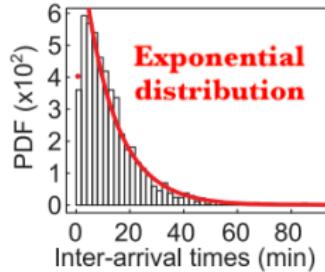
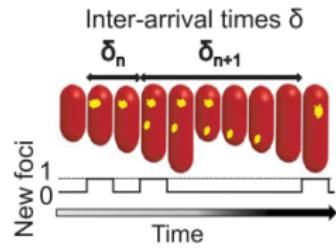
Robert et al.

Experience MV (mutation visualization)

Robert et al.

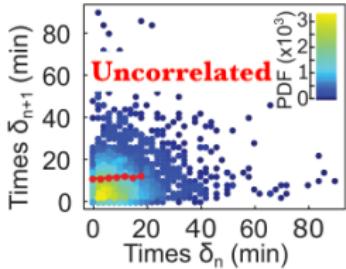
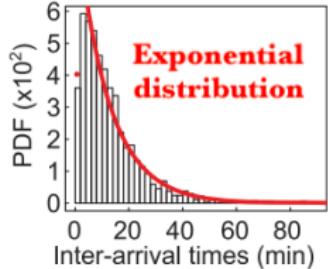
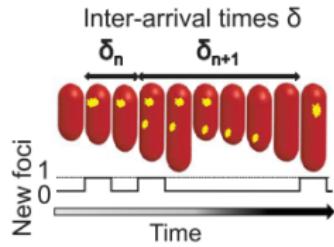
Résultats de l'article

- les mutations apparaissent selon un **processus de Poisson** ;

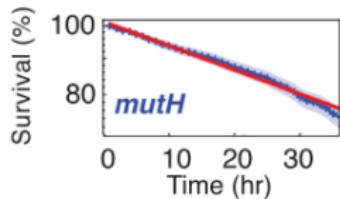
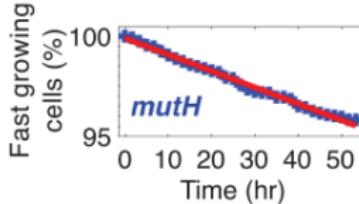
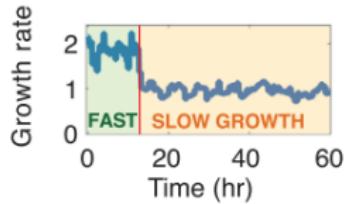


Résultats de l'article

- les mutations apparaissent selon un **processus de Poisson** ;



- 0,3% des mutations sont fortement délétères ; 1% sont létale ; leurs effets sont **indépendants** ;



Résultats de l'article

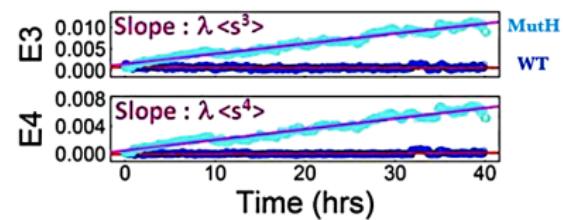
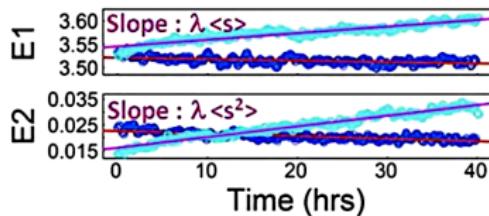
- estimation des **premiers moments** de la loi des effets des mutations ;

$$E_n(t) := \sum_{k=1}^n \binom{k}{n} (-1)^k \ln \left(\mathbb{E} [W_t^k] \right) = (\lambda \mathbb{E}[s^n]) t$$

Résultats de l'article

- estimation des **premiers moments** de la loi des effets des mutations ;

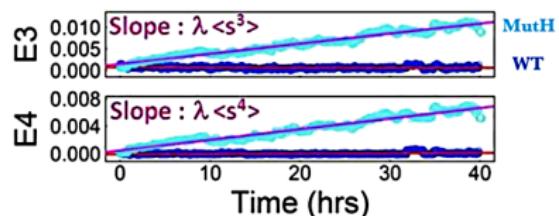
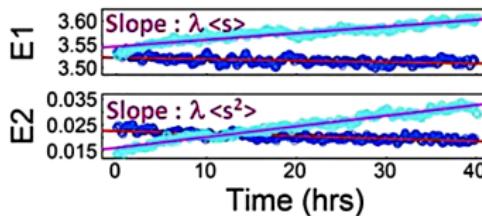
$$E_n(t) := \sum_{k=1}^n \binom{k}{n} (-1)^k \ln \left(\mathbb{E} [W_t^k] \right) = (\lambda \mathbb{E}[s^n]) t$$



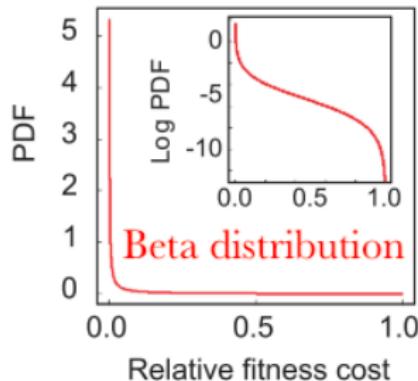
Résultats de l'article

- estimation des **premiers moments** de la loi des effets des mutations ;

$$E_n(t) := \sum_{k=1}^n \binom{k}{n} (-1)^k \ln \left(\mathbb{E} [W_t^k] \right) = (\lambda \mathbb{E}[s^n]) t$$

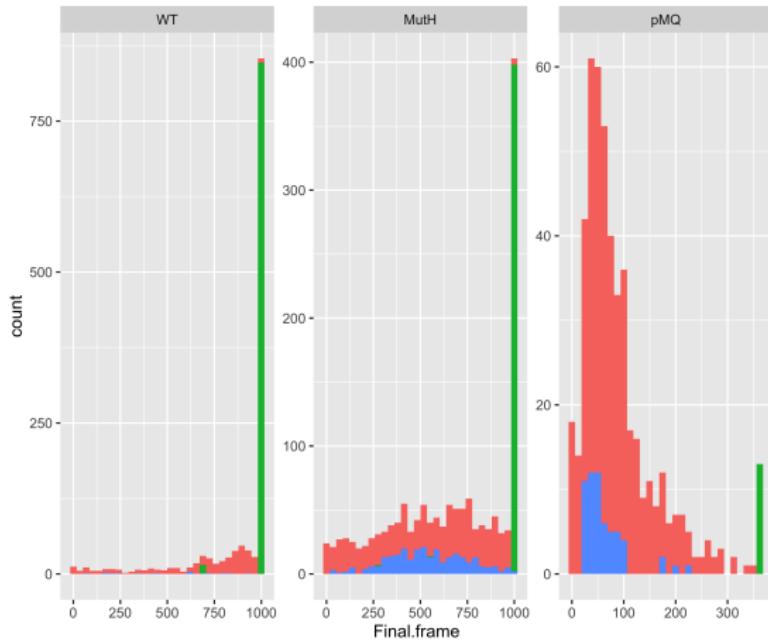


Non-parametric DFE characterization			
Mean	$3.1 \times 10^{-3} \pm 0.4 \times 10^{-3}$	Skewness	16.6 ± 0.7
CV	9.5 ± 1.2	Kurtosis	360 ± 90

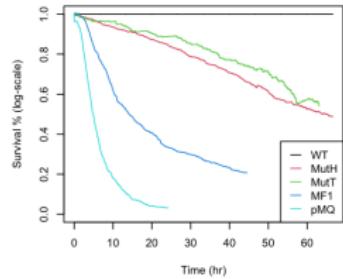


Analyses préliminaires - Survie

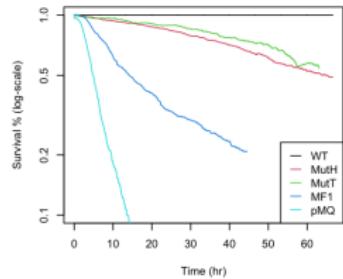
Cells' final states through the experiments



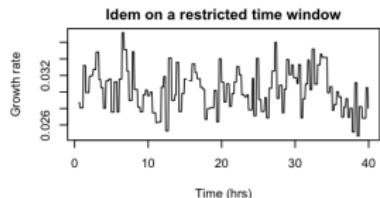
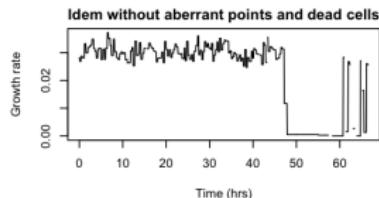
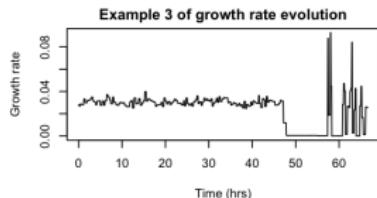
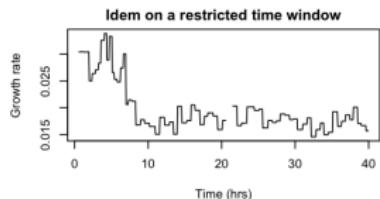
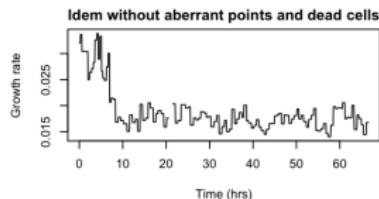
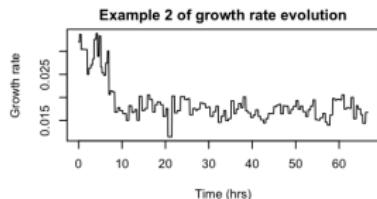
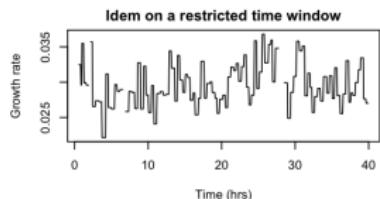
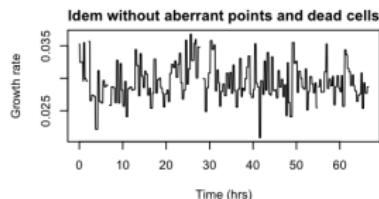
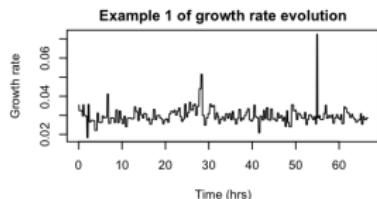
Survival of the 5 cell lines over time, no escape, no senescence



Log-survival of the 5 cell lines over time, no escape, no senescence

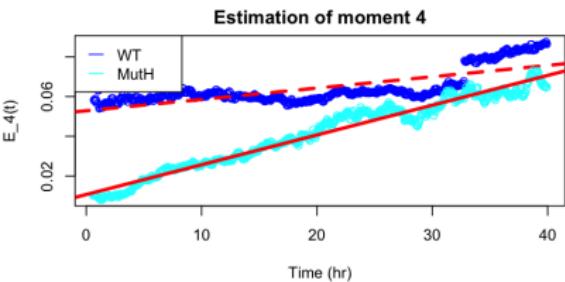
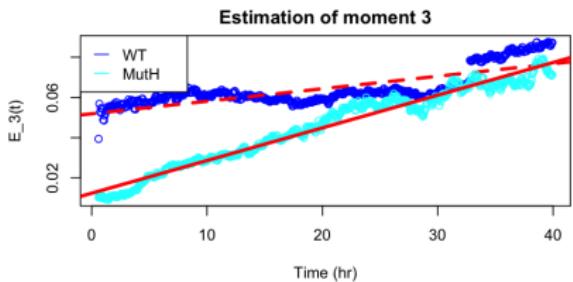
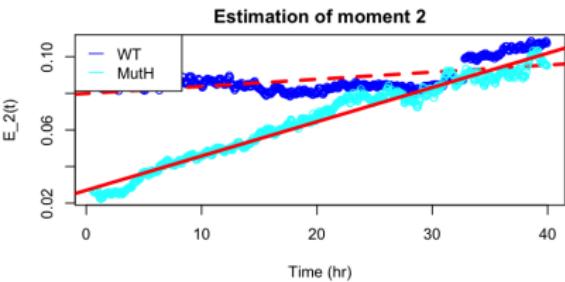
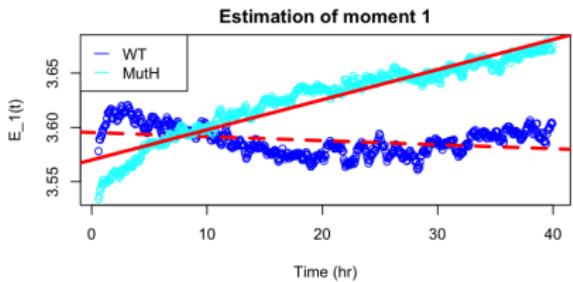


Analyses préliminaires - Taux de croissance



Analyses préliminaires - Taux de croissance

$$E_n(t) := \sum_{k=1}^n \binom{k}{n} (-1)^k \ln \left(\mathbb{E} [W_t^k] \right) = (\lambda \mathbb{E}[s^n]) t$$



Choses à faire

Énoncé du problème : estimer la loi des s_i (qui sont iid) sachant que l'on sait estimer la loi des W_t et N_t ($t \geq 0$), et sachant que

$$\frac{W_t}{W_0} = \prod_{i=1}^{N_t} (1 - s_i)$$

Choses à faire

Énoncé du problème : estimer la loi des s_i (qui sont iid) sachant que l'on sait estimer la loi des W_t et N_t ($t \geq 0$), et sachant que

$$\frac{W_t}{W_0} = \prod_{i=1}^{N_t} (1 - s_i)$$

- Trouver la loi de s à partir des $\mathbb{E}[s^n]$: semble délicat dans notre cas : on n'obtient qu'une approximation très grossière.
- Faire un programme en Python pour tester les résultats que l'on obtiendra en partant d'une distribution fixée pour les s_i ;
- Utiliser le fait que $\ln W_t$ est une somme de variables aléatoires iid pour trouver la loi de ces variables.

Références

-  Robert et al., *Mutation dynamics and fitness effects followed in single cells*, Science 359, 1283–1286, 16 March 2018
-  Peris et al., *Distribution of fitness effects caused by single-nucleotide substitutions in bacteriophage f1*, Genetics, 2010
-  Eyre-Walker Keightley, *The distribution of fitness effects of new mutations*, Nat Rev Genet 8, 610–618, 2007