Modèles de croissance-fragmentation pour la dynamique des populations bactériennes

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Rencontre chaire MMB

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"Populations microbiennes et microbiote"

Structured population models

The individuals (cells) are characterized by one or more traits (age, size, size-increment, etc.).

Model: partial differential equation that prescribes the time evolution of a population density with respect to the trait.

The unknown: a function $u_t(x) = u(t, x)$

- $\triangleright$ $t \geqslant 0$ is the time
- $\triangleright$ x is the trait

Ref. [Webb '85], [Metz, Diekmann '86], [Perthame '07], [Bansaye, Méléard '15], etc.

Age-structured model

Consider a population of cells that are characterized by their age $a \geqslant 0$.

The age pyramidal $u_t(a)$ of the population at time $t \geqslant 0$ evolves according to the renewal equation

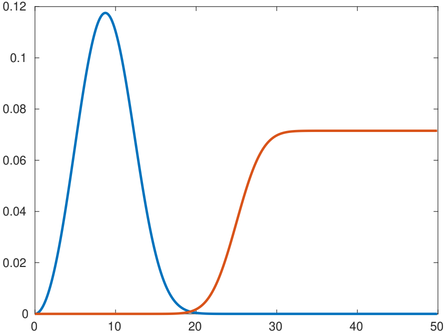
$$\begin{cases} \partial_t u_t(a) + \partial_a u_t(a) + B(a) u_t(a) = 0, \\ u_t(0) = 2 \int_0^\infty B(a) u_t(a)\, da. \end{cases}$$

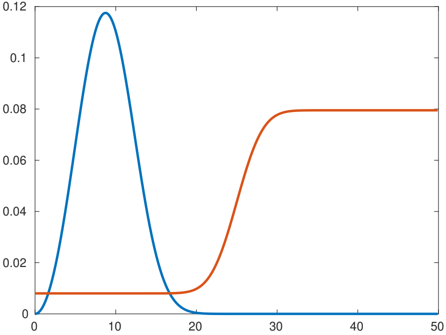
$B(a)$: division rate at age a, *i.e.*

the probability of not dividing by age a is: $\exp\left(- \int_0^a B(a')\, da' \right)$

Ref. [Sharpe & Lotka, 1911], [McKendrick, 1926], [Von Foerster, 1959], etc.

Numerical simulations





Blue: $u_0(a)$, Red: B(a)

Stationary distribution and convergence

Particular solutions with stable age distribution and time exponential growth:

$$\hat{u}_t(a) = \mathcal{U}(a)e^{\lambda t}.$$

The Malthus parameter λ is the unique solution to

$$1 = 2\int_0^\infty B(a)e^{-\int_0^a(\lambda+B(a'))da'}da$$

and the stable age pyramidal is given by

$$\mathcal{U}(a) = \mathcal{U}(0)e^{-\int_0^a(\lambda+B(a'))da'}.$$

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Convergence: for all initial distribution u_0

$$u_t(a) \sim \langle u_0, \phi\rangle\, \mathcal{U}(a)e^{\lambda t} \qquad \text{as } t \to +\infty.$$

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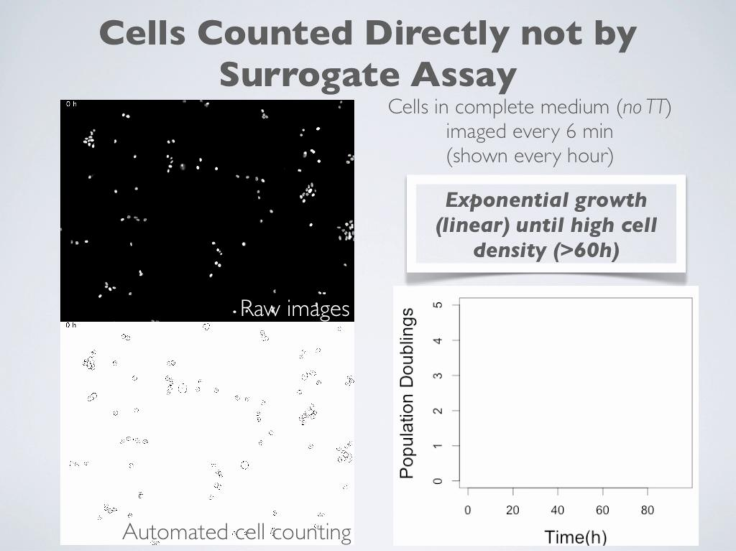
Convergence: exist $C, \alpha > 0$ s.t. for all initial distribution u_0 and all $t \geqslant 0$

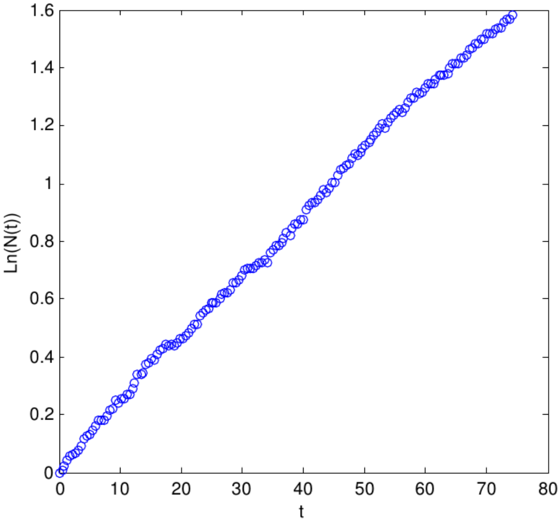
$$\|e^{-\lambda t}u_t - \langle u_0, \phi\rangle \mathcal{U}\| \leqslant Ce^{-\alpha t}\|u_0\|.$$

Ref. [Sharpe & Lotka, 1911], [Feller, 1941], [Greiner, 1984], [Webb, 1984], [Michel, Mischler, Perthame, 2005], [Gwiazda & Perthame, 2006], [Bansaye, Cloez, G., 2020], etc.

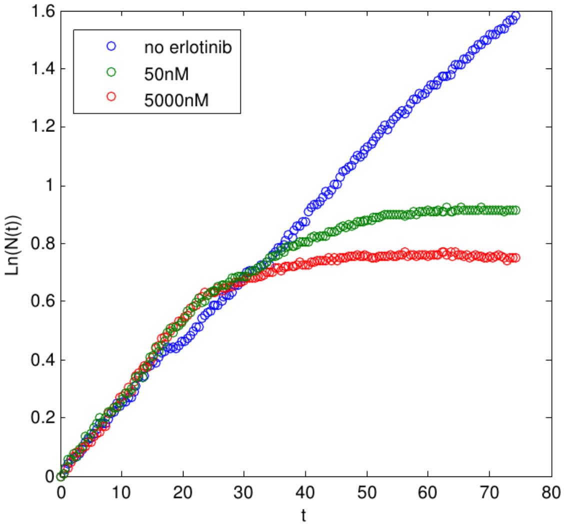
Application to experimental data



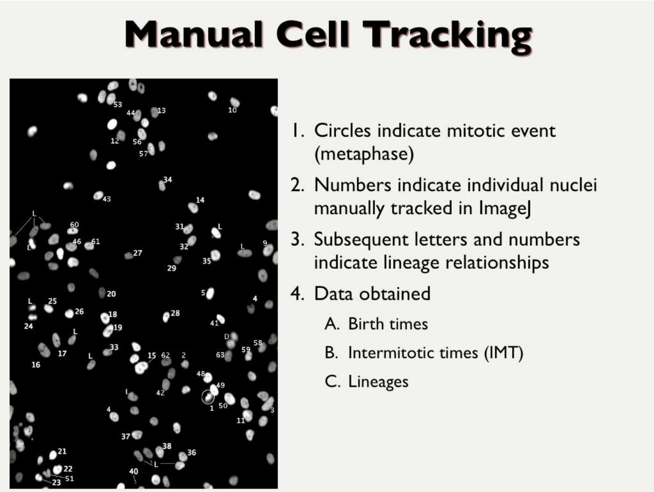
Exponential growth of the cell population



PC9 cancer cells with Erlotinib treatment

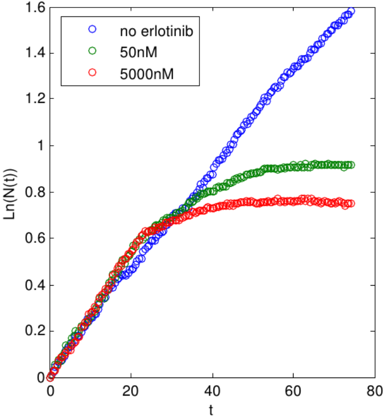


Estimating $B(a)$



$$\mathcal{U}(a) = e^{-\int_0^a (\lambda + B(a'))da'} \rightsquigarrow B(a)$$

Result



Ref. [G., Garbett, Quaranta, Tyson, Webb, 2012]

Size-structured model

Consider a population of cells that are characterized by their size $x > 0$.

The size distribution $u_t(x)$ of the population at time $t \geqslant 0$ evolves according to the growth-fragmentation equation

$$\partial_t u_t(x) + \partial_x\big(g(x)u_t(x)\big) + B(x)u_t(x) = 2\int_0^1 B\Big(\frac{x}{z}\Big)u_t\Big(\frac{x}{z}\Big)\frac{\wp(dz)}{z}$$

$g(x)$: growth rate at size x

$B(x)$: division rate at size x

at division: $x \;\rightarrow\; zx \,+\, (1-z)x$

z distributed according to the kernel $\wp$ (example: $\wp = \delta_{\frac{1}{2}}$)

Ref. [Bell & Anderson, 1967], [Fredrickson, Ramkrishna, Tsuchiya, 1967], [Sinko & Streifer, 1967], etc.

Stationary distribution and convergence

Particular solutions with stable size distribution and time exponential growth:

$$\hat{u}_t(x) = \mathcal{U}(x)e^{\lambda t}.$$

Under biologically relevant assumptions, such solutions exist but λ and $\mathcal{U}$ are not given explicitly in terms of g, B and $\wp$.

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Except in critical cases, we have convergence: for all initial distribution u_0

$$u_t(x) \sim \langle u_0, \phi \rangle \, \mathcal{U}(x)e^{\lambda t} \qquad \text{as } t \to +\infty.$$

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Except in critical cases, we have convergence: $\exists C, \alpha > 0,\ \forall u_0, \forall t \geqslant 0$

$$\|e^{-\lambda t}u_t - \langle u_0, \phi\rangle\, \mathcal{U}\| \leqslant Ce^{-\alpha t}\|u_0\|.$$

Ref. [Diekmann, Heijmans, Thieme ‘84], [Perthame, Ryhzik ‘05], [Michel, Mischler, Perthame ‘05], [Doumic, G. ‘10], [Cáceres, Cañizo, Mischler ‘11], [Balagué, Cañizo, G. ‘15], [Zaidi, van Brunt, Wake ‘15], [Mischler, Scher ‘16], [Bertoin, Watson ‘18], [Bernard, G. ‘20], [Bansaye, Cloez, G., Marguet ‘20], [Banasiak, Mokhtar-Kharroubi ‘21], etc.

Inverse problem

Can we recover $g, B, \wp$ from $\lambda, \mathcal{U}$?

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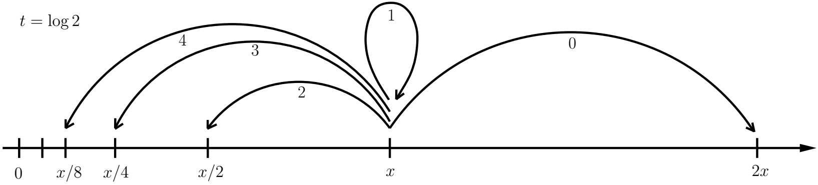
Yet, it is still a challenging issue.

Ref. [Perthame, Zubelli, 2007], [Doumic, Perthame, Zubelli, 2009], [Doumic, Hoffmann, Reynaud-Bouret, Rivoirard, 2012], [Doumic, Tine, 2013], [Bourgeron, Doumic, Escobedo, 2014], [Doumic, Hoffmann, Krell, Robert, 2015], [Doumic, Escobedo, Tournus, 2018], [Doumic, Olivier, Robert, 2020], etc.

The case $g(x) = x$ and $\wp = \delta_{\frac{1}{2}}$

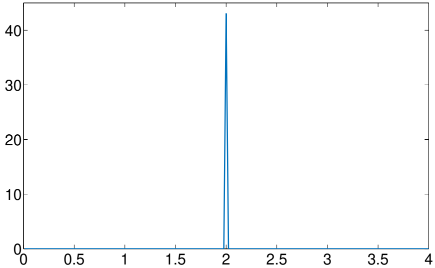
$$\partial_t u_t(x) + \partial_x\big(x u_t(x)\big) + B(x)u_t(x) = 4B(2x)u_t(2x)$$

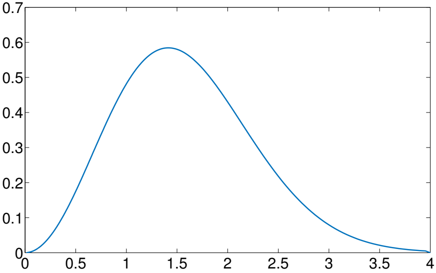


For any initial size $x > 0$ and any $n \in \mathbb{N}$, the size at time $t = n \log 2$ belongs to the set

$$\mathsf{X}_x = \{y > 0 : \exists k \in \mathbb{Z}, y = 2^k x\}.$$

Numerical simulations





Boundary spectrum and oscillating behavior

There is a family of complex dominant eigenvalues

$$\lambda_k = 1 + \frac{2ik\pi}{\log 2}, \quad \mathcal{U}_k(x) = x^{1-\lambda_k}\mathcal{U}(x), \quad \phi_k(x) = x^{\lambda_k}, \quad k \in \mathbb{Z}.$$

Convergence: for all initial distribution u_0 we have

$$u_t(x) \sim \sum_{k=-\infty}^{+\infty} \langle u_0, \phi_k \rangle e^{\lambda_k t}\,\mathcal{U}_k(x) \qquad \text{as } t \to +\infty.$$

Ref. [Diekmann, Heijmans, Thieme, 1984], [Greiner, Nagel, 1988], [van Brunt, Almalki, Lynch, Zaidi, 2018], [Bernard, Doumic, G., 2019], [Martin, G., 2021]

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Convergence: $\exists C, \alpha > 0, \ \forall u_0, \forall t \geqslant 0$

$$\left\| e^{-t} u_t - \sum_{k=-\infty}^{+\infty} \langle u_0, \phi_k \rangle e^{(\lambda_k - 1)t} \mathcal{U}_k \right\| \leqslant C e^{-\alpha t} \|u_0\|.$$

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$$\left\| e^{-t}u_t - \sum_{k=-\infty}^{+\infty} \langle u_0, \phi_k \rangle e^{(\lambda_k - 1)t}\mathcal{U}_k \right\| \leqslant Ce^{-\alpha t}\|u_0\|.$$

Mean convergence: $\exists C, \alpha > 0, \ \forall u_0, \forall t \geqslant 0$

$$\left\| \frac{1}{\log 2}\int_t^{t+\log 2} e^{-s}u_s - \langle u_0, \phi_0 \rangle \mathcal{U} \right\| \leqslant Ce^{-\alpha t}\|u_0\|.$$

Ref. [Diekmann, Heijmans, Thieme, 1984], [Greiner, Nagel, 1988], [van Brunt, Almalki, Lynch, Zaidi, 2018], [Bernard, Doumic, G., 2019], [Martin, G., 2021]

Age or size?

Size structure is more relevant than age structure for *E. coli*,
see [Robert, Hoffmann, Krell, Aymerich, Robert, Doumic, 2014].

Age or size? → size-increment

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see [Robert, Hoffmann, Krell, Aymerich, Robert, Doumic, 2014].

An even more relevant structure is the increment of size since division $y \geqslant 0$, leading to the *adder* or *incremental* model:

$$\begin{cases} \partial_t u_t(x,y) + \partial_x\big(xu_t(x,y)\big) + \partial_y\big(xu_t(x,y)\big) + xB(y)u_t(x,y) = 0, \\ xu_t(x,0) = 4\displaystyle\int_0^\infty 2xB(y)u_t(2x,y)\,dy. \end{cases}$$

Ref. [Hall, Wake, Gandar '91], [Amir '14], [Taheri-Araghi, Bradde, Sauls, Hill, Levin, Paulsson, Vergassola, Sun '15], [Sauls, Li, Sun '16], [Martin, G. '19], [Doumic, Olivier, Robert '19], [Xia, Greenman, Chou '20], [Doumic, Hoffman '21], [Fermanian, Doucet, Hoffmann, Robert, Doumic: Celldivision plateform] etc.

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An even more relevant structure is the increment of size since division $y \geqslant 0$, leading to the *adder* or *incremental* model:

$$\begin{cases} \partial_t u_t(x,y) + \partial_x\big(g(x)u_t(x,y)\big) + \partial_y\big(g(x)u_t(x,y)\big) + g(x)B(x,y)u_t(x,y) = 0, \\ g(x)u_t(x,0) = 2\int_0^\infty \int_0^1 g\left(\frac{x}{z}\right)B\left(\frac{x}{z},y\right)u_t\left(\frac{x}{z},y\right)\frac{\wp(dz)}{z}dy. \end{cases}$$

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Future work

There remain open questions about the convergence for models with two (or more) variables.

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→ part of the objectives of the ANR project NOLO

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Thank you for your attention!