Deterministic models and statistical aspects to model growth and division

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Outline of the deterministic part (Marie!)

- A little bit on Structured Population Models and our motivation
- The Direct Problem
- The asymptotic behaviour
- The Inverse Problem in a deterministic setting
  - Case of Mitosis (division into 2 equal cells)
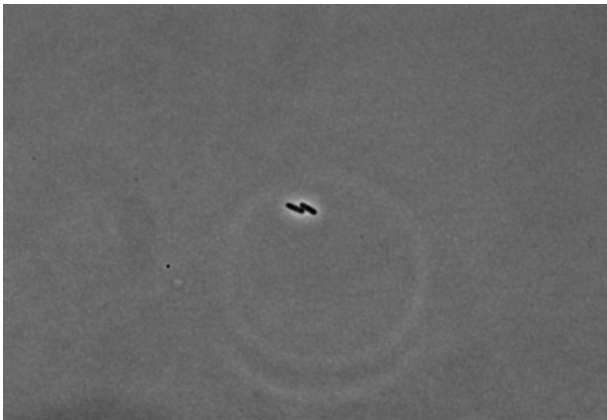 - General fragmentation kernel
- deterministic perspectives

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

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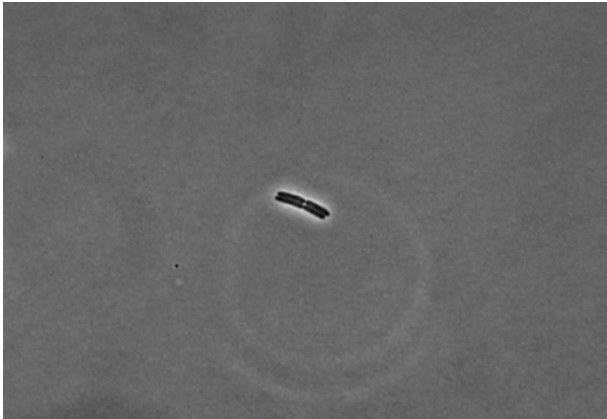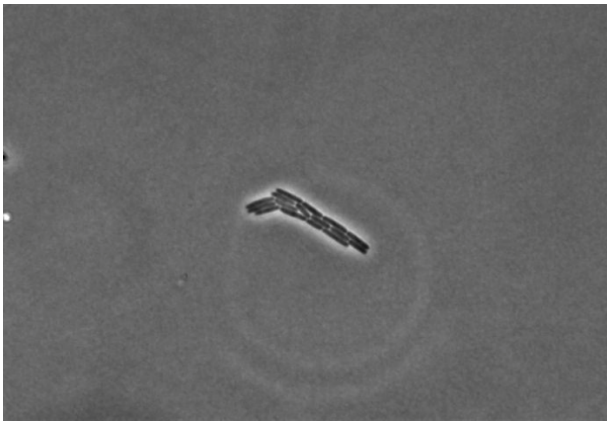
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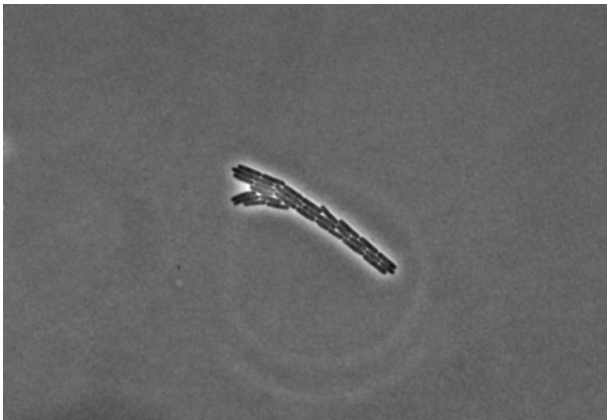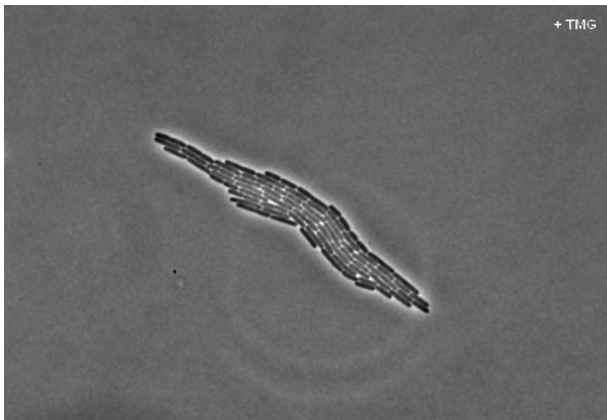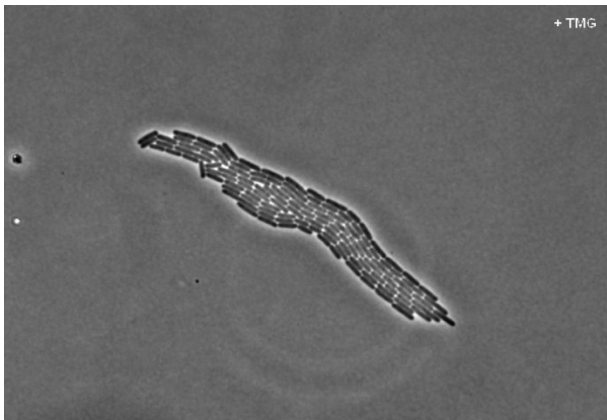
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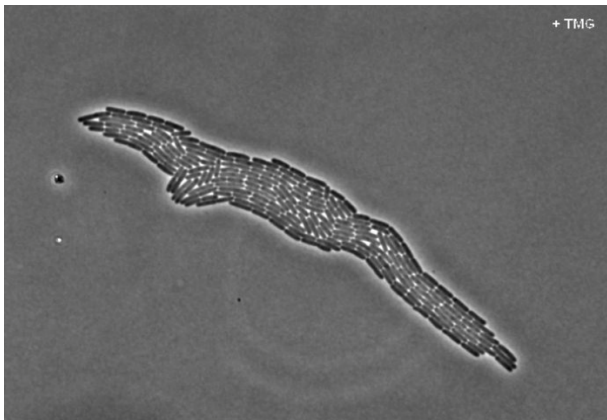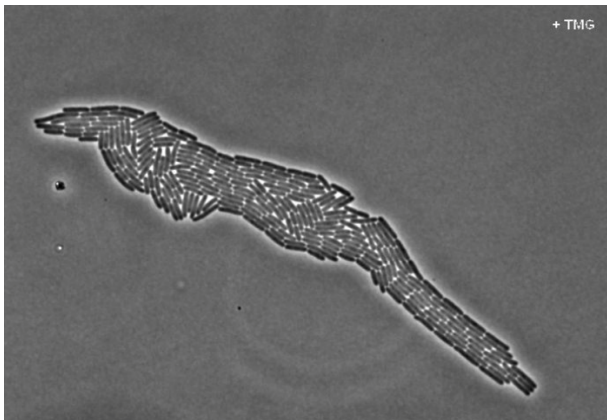Figure: Evolution of a *E. Coli* population.

To model this: PDMP ? Yes...
And also Structured Populations...

Population density: $n(t, x)$
can also be viewed as the law of the empirical measure of a PDMP: ask Nathalie Krell...

x is the "structuring variable", *e.g.* it may be

- for unicellular organisms: the mass / volume of the cell
- for polymers: the number of monomers inside
- the DNA content of the cell
- the cell age (age-structured populations)
- a protein content: cyclin, cyclin-dependent kinases etc
- a fluorescent label like CFSE
- a parasite growing inside the individuals
- for stem cells: the maturity

Recent reference: B. Perthame, *Transport Equations in Biology,* 2007.

Some examples of structured populations
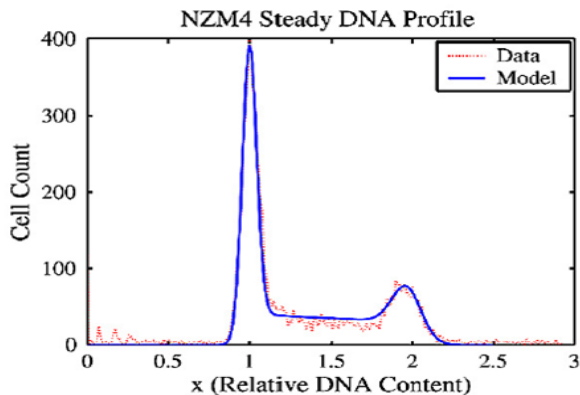
Figure: From B. Basse et al, Modeling the flow of cytometric data obtained from unperturbed human tumor cell lines: parameter fitting and comparison. of Math. Bio., 2005

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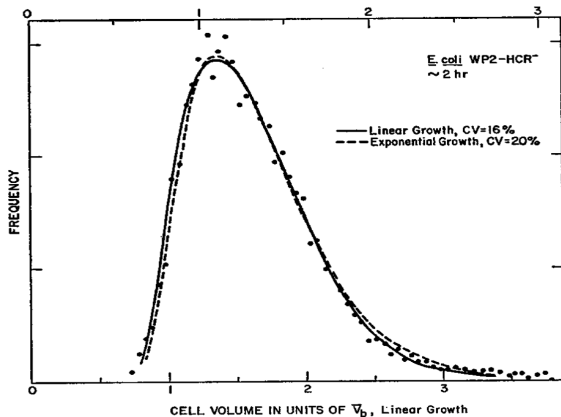
Figure: Cell volumes distribution for E. Coli THU in a glucose minimal medium at a doubling time of 2 hrs. H.E. Kubitschek, Biophysical J. 9:792-809 (1969)

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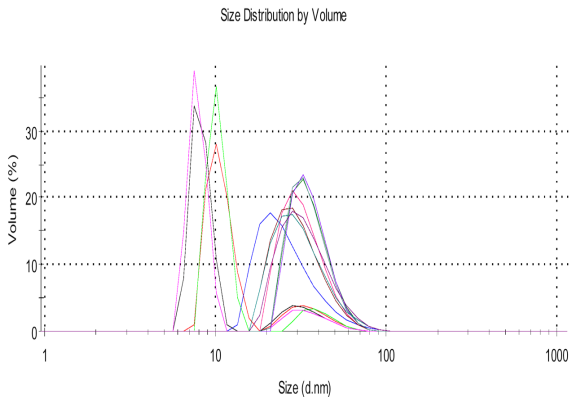
Figure: Size distribution kinetic of PrP polymerization in physico-chemical condition leading to the formation of amyloid fibrils monitored by MWSLS technique (taken from ANR TOPPAZ, INRA/BPCP data courtesy of H. Rezaei).

The Size-Structured Population equation (or transport-fragmentation equation)

We consider a populations of "individuals" such that

- each particle of size x grows with a growth rate $g(x)$,
- a particle of size y may divide with a division rate $B(y)$

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- for a given dividing particle of size y, the probability to give rise to two offsprings of respective size x and $y - x$ is given by a probability law $k(x, y) = k(y - x, y)$, so that
  $\int\limits_0^y k(x,y)dx = 1$ and due to symetry $\int\limits_0^y xk(x,y)dx = \frac{y}{2}$

First and probably most studied case: "equal mitosis" :
$k(x, y) = \delta_{x=\frac{y}{2}}$.

The Size-Structured Population equation (or transport-fragmentation equation)

The deterministic model is obtained by a mass conservation law:

$$\frac{\partial}{\partial t}n(t,x) + \frac{\partial}{\partial x}\big(g(x)n(t,x)\big) =$$

$$-B(x)n(t,x) + 2\int_x^\infty B(y)k(x,y)n(t,y)dy$$

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

- LHS: density evolution + growth (*e.g.* by nutrient uptake).
- RHS: exchanges by division:
  loss by the division of cells of size x, income by the division of cells of size $y > x$ according the division law $k(x,y)$.

  For $k = \delta_{x=\frac{y}{2}}$: $2\int_x^\infty B(y)k(x,y)n(t,y)dy = 4B(2x)$.

The Size-Structured Population equation
2 major relations, Direct vs Inverse Problem

The number of individuals only evolves by fragmentation:

$$\frac{d}{dt} \int n(t, x) dx = \int B(x) n(t, x) dx.$$

The total mass only evolves by growth:

$$\frac{d}{dt} \int x n(t, x) dx = \int g(x) n(t, x) dx.$$

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Our Inverse Problem: we suppose k known, $g = cg_0$ with g_0 a known function,
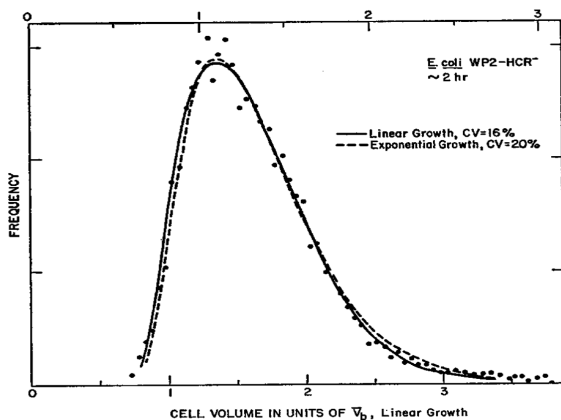$c > 0$ a constant and B are to be estimated.

The Size-Structured Population equation
Direct vs Inverse Problem

What is really observed ? Remember:

We do not observe $n(t, x)$ but rather a DOUBLING TIME and a
STEADY DISTRIBUTION.

The Size-Structured Population equation
Long-time asymptotics

This motivated the method proposed by Perthame & Zubelli (*Inverse Problems*, 2007): **Use the asymptotic behaviour.**

2 Seminal references on the asymptotics obtained *via* the *General Relative Entropy* (GRE) principle:

- for the mitotic case: Perthame, Ryzhik, J. Diff. Equ., 2004
- for GRE in general: Michel, Mischler, Perthame, JMPA, 2004,

If we look at a solution under the form $n(t, x) = e^{\lambda t} N(x)$, $x \geq 0$:

$$
\begin{cases}
\frac{\partial}{\partial x}(g(x)N(x)) + \lambda N(x) = -B(x)N(x) + 2 \int_x^\infty B(y)k(x, y)N(y)dy, , \\[2mm]
gN(x = 0) = 0, \qquad N(x) \geq 0, \qquad \int_0^\infty N(x)dx = 1, \\[2mm]
-g(x)\frac{\partial}{\partial x}(\phi(x)) + \lambda\phi(x) = B(x)(-\phi(x) + 2 \int_0^x k(y, x)\phi(y)dy), , \\[2mm]
\phi(x) \geq 0, \qquad \int_0^\infty \phi(x)N(x)dx = 1.
\end{cases}
\tag{1}
$$

The Size-Structured Population equation
Long-time asymptotics

Theorem (MD, P. Gabriel, M3AS, 2010)

Under some technical assumptions on g, B and k, there exists a unique triplet (λ, N, ϕ) with $\lambda > 0$, solution of the eigenproblem (1)

and then we have, by the GRE principle (ref. above)

$$\int_{\mathbb{R}_+} \left| n(t,x)e^{-\lambda t} - \langle n^{(0)}, \phi \rangle N(x) \right| \phi(x) dx \to 0 \text{ as } t \to \infty$$

(generalizes previous results by Michel, M3AS, 2004. Under some extra assumptions, the convergence is exponential: last work M.J. Càceres, J.A. Cañizo, S. Mischler, JMPA, 2011)

The Direct Problem

The direct mapping is $\Gamma : (c, B) \to (\lambda, N)$.
The space of interest is $L^2(\mathbb{R}_+)$: general framework for inverse problems
(see Engl, Hanke, Neubauer, *Regularization of Inverse Problems*, 1995)

In (Perthame, Zubelli, 2007):
results for mitotic division and $0 < B_m \le B \le B_M < +\infty$.
Extension to the general case:

Theorem (MD, L.M. Tine, submitted, 2011)

Under the previous T.A. (and one other), if $B \in L^2(\mathbb{R}_+)$, the map Γ is injective and Lipschitz-continuous (and even Fréchet derivable) from a proper definition domain to $\mathbb{R}_+^* \times L^2$, under the strong topology of L^2.

Moreover, for g and k regular enough, if $B \in H^s$, then $N \in H^{s+1}$.

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- We measure N and λ with an error term modeled by

$$\|N_\varepsilon - N\|_{L^2} \leq \varepsilon \ \text{ and } \ |\lambda_\varepsilon - \lambda| \leq \varepsilon.$$

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$$\|N_\varepsilon - N\|_{L^2} \leq \varepsilon \ \text{ and } \ |\lambda_\varepsilon - \lambda| \leq \varepsilon.$$

- We seek c and B such that

$$c\frac{\partial}{\partial x}(g_0(x)N(x)) + \lambda N(x) = -B(x)N(x) + 2\int_x^\infty B(y)k(x,y)N(y)dy$$

Estimate B through

$$L(N, \lambda) = \mathfrak{L}(BN),$$

with

$$L(N,\lambda)(x) = c\partial_x(g(x)N(x)) + \lambda N(x),$$

$$\mathfrak{L}(f)(x) = 2\int_x^\infty f(y)k(x,y)dy - f(x).$$

If we forget about c and λ : the problem $N \to H = BN$ is linear.

The Inverse Problem
The deterministic approach

$$c \int g_0(x) N(x) dx = \lambda \int x N(x) dx,$$

so the following definition (or slight variants) gives good results:

$$c_\varepsilon := \lambda_\varepsilon \frac{\int x N_\varepsilon(x) dx}{\int g_0(x) N_\varepsilon(x) dx}.$$

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$$c_\varepsilon := \lambda_\varepsilon \frac{\int x N_\varepsilon(x) dx}{\int g_0(x) N_\varepsilon(x) dx}.$$

Our problem is reduced to a linear one ($+$ some work) which writes: find B solution of

$$L(N, \lambda) = \mathfrak{L}(BN),$$

with

$$L(N, \lambda)(x) = c \partial_x \big(g(x) N(x) \big) + \lambda N(x),$$

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1. solve the dilation problem: for L in a proper space, find H such that

$$2 \int_x^\infty H(y)k(x,y)dy - H(x) = L(x),$$

and H in a proper space - ideally, the "proper space" is L^2. For mitosis, the equation becomes:

$$4H(2x) - H(x) = L(x).$$

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2. solve the derivative inverse problem: estimate $L(N, \lambda) = c_\varepsilon \partial_x \big(g_0(x)N(x)\big) + \lambda N(x)$ from a measure $N_\varepsilon \in L^2$. Classical inverse problem of *degree of ill-posedness* 1 for a L^2-noise: use your favorite regularization method to treat the derivative & gain 1 degree of regularity.

The Inverse Problem
the Dilation Equation: Equal Mitosis

Proposition (MD, B. Perthame, J.P. Zubelli, 2009)

Let $L \in L^2(\mathbb{R}_+, x^p dx)$, with $p \neq 3$, then there exists a unique solution $H \in L^2(\mathbb{R}_+, x^p dx)$ to

$$4H(2x) - H(x) = L(x).$$

For $p < 3$, this solution is given explicitly by $H^{(1)}$ below, and for $p > 3$, by $H^{(2)}$:

$$H^{(1)}(x) = \sum_{n=1}^{+\infty} 2^{-2n} L(2^{-n} x), \qquad H^{(2)}(x) = -\sum_{n=0}^{+\infty} 2^{2n} L(2^n x).$$

The solutions with $L = 0$ in $\mathcal{D}'(0, \infty)$ have the form $\frac{f(\log(x))}{x^2}$ with $f \in \mathcal{D}'(\mathbb{R})$ a $\log(2)-$ periodic distribution.

The general case: nonlocal fragmentation kernel

$$H(x) - 2 \int_x^\infty H(y) k(x,y) dy = F, \qquad (2)$$

Proposition (MD, L.M. Tine, submitted)

Let k a fragmentation kernel and $p \in \mathbb{R}$ satisfying:

$$C_p = \sup_x \int_x^\infty \frac{x^p}{y^p} k(x,y) dy < \frac{1}{4}. \qquad (3)$$

$\forall \ F \in L^2(\mathbb{R}_+, x^p dx), \ \exists! \ u \in L^2(x^p dx)$ to (2), and

$$\|H\|_{L^2(x^p dx)} \leq \frac{1}{1 - 2\sqrt{C_p}} \|F\|_{L^2(x^p dx)}.$$

2nd step: Regularizing the derivative term
1st method: Quasi-Reversibility

(in Perthame, Zubelli, 2006) Add a small derivative for BN : we obtain the following well-posed problem:

$$
\begin{cases}
\alpha \frac{\partial}{\partial y}(B_{\varepsilon,\alpha}N_\varepsilon)(y) + 4B_{\varepsilon,\alpha}(y)N_\varepsilon(y) - B_{\varepsilon,\alpha}\left(\frac{y}{2}\right)N_\varepsilon\left(\frac{y}{2}\right) = \\
+\lambda_{\varepsilon,\alpha}N_\varepsilon\left(\frac{y}{2}\right) + 2\frac{\partial}{\partial y}\left(N_\varepsilon\left(\frac{y}{2}\right)\right), \qquad y > 0, \\
\\
(B_{\varepsilon,\alpha}N_\varepsilon)(0) = 0.
\end{cases}
$$

Theorem (Perthame, Zubelli, 2006)
We have the error estimate, optimal for $\alpha = O(\sqrt{\varepsilon})$:

$$
\|B_{\varepsilon,\alpha}N_{\varepsilon,\alpha} - B\,N\|^2_{L^2(dx)} \leqslant C\left(1 + \frac{1}{\alpha^2}\right)\|N_\varepsilon - N\|^2_{L^2(dx)} + C\alpha^2\|N\|^2_{H^2(\mathbb{R}_+)} ,
$$

Regularization step
2nd method: Filtering

(in MD, B. Perthame, J.P. Zubelli, Inv. Prob., 2009)
Filter the derivative with a mollifier kernel ρ_α, $\alpha > 0$:

$$\begin{cases} 4B_{\varepsilon,\alpha}(y)N_\varepsilon(y) - B_{\varepsilon,\alpha}\left(\frac{y}{2}\right)N_\varepsilon\left(\frac{y}{2}\right) = {\color{red}\rho_\alpha *}\left(\lambda_{\varepsilon,\alpha}N_\varepsilon\left(\frac{y}{2}\right) + 2\frac{\partial}{\partial y}\left(N_\varepsilon\left(\frac{y}{2}\right)\right)\right), \\ \\ (B_{\varepsilon,\alpha}N_\varepsilon)(0) = 0, \end{cases}$$

with
$$\rho_\alpha(x) = \frac{1}{\alpha}\rho\left(\frac{x}{\alpha}\right), \qquad \rho \in \mathcal{C}_c^\infty(\mathbb{R}), \quad \int_0^\infty \rho(x)\,dx = 1, \quad \rho \geqslant 0.$$

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$$||B_{\varepsilon,\alpha}N_{\varepsilon,\alpha} - B\,N||_{L^2(dx)}^2 \leqslant C\left(1 + \frac{1}{\alpha^2}\right)||N_\varepsilon - N||_{L^2(dx)}^2 + C\alpha^2||N||_{H^2(\mathbb{R}_+)}^2 \ ,$$

Numerical Scheme
Mitotic Case

General requirements:

- avoid instability
- conserve main properties of the continuous model: laws for the increase
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1 question (possible only for the mitotic case): in

$$4H(2x) - H(x) = L(x),$$

shall we begin from the left, deducing B(2x) from B(x) or from the right, deducing B(x) from B(2x) ?

Numerical Scheme
Mitotic Case

Recall the identity:

$$H^{(1)}(x) = \sum_{n=1}^{+\infty} 2^{-2n} L(2^{-n}x), \qquad H^{(2)}(x) = -\sum_{n=0}^{+\infty} 2^{2n} L(2^n x).$$

Departing from large x : choose $H^{(2)}$
Departing from 0 : choose $H^{(1)}$
$H^{(1)}$ is "more regular" (in L^p for $1 \leq p \leq \infty$ if L is in L^p)

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BEST CHOICE: departing from 0.

Numerical Scheme
Mitotic Case (with B. Perthame, J.P. Zubelli)

- departs from zero (mimics $H^{(1)}$)
- mass and number of cells balance laws preserved:
- stability: $4H(2x)$ is approximated by $4H_{2i}$

$$4H_i^f = H_{\frac{i}{2}}^f + L_{\frac{i}{2}}^f, \qquad \forall\, 0 \leqslant i \leqslant I,$$

and we need to define the quantities $G_{\frac{i}{2}}$. We choose

$$G_{\frac{i}{2}} = \begin{cases} G_{\frac{i}{2}} & \text{when } i \text{ is even,} \\ \frac{1}{2}\big(G_{\frac{i-1}{2}} + G_{\frac{i+1}{2}}\big) & \text{when } i \text{ is odd.} \end{cases}$$

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- add an artificial noise to $N(x)$ to get a noisy data $N_\varepsilon(x)$

- Run the numerical scheme for the inverse problem to get a birth rate $B_{\varepsilon,\alpha}(x)N_\varepsilon(x)$ and compare it with the initial data $B(x)$ - look for the best α for a given error ε.

Numerical Results - Mitosis
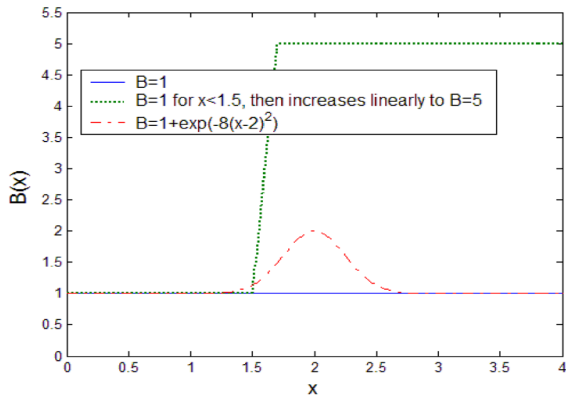
Three tested division rates B

Numerical Results - Mitosis
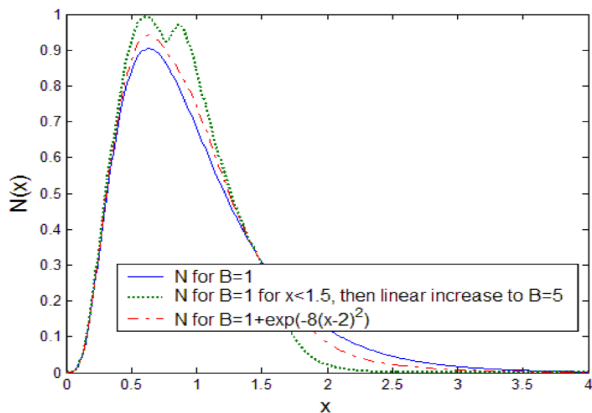
Three related asymptotic distributions N
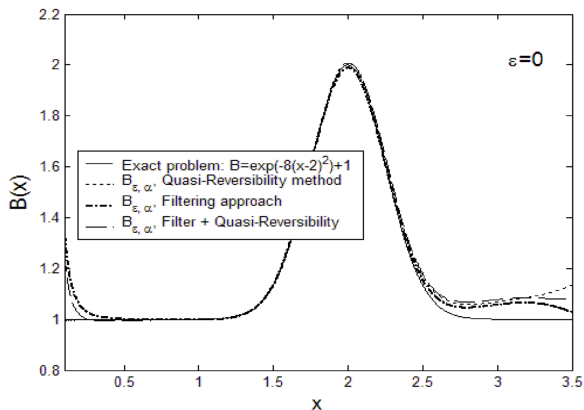
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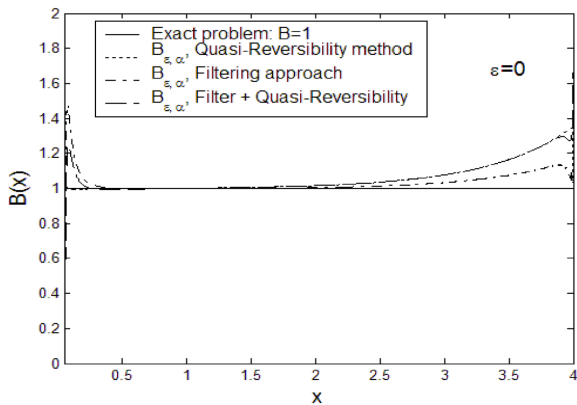
Results with no noise - constant B

Numerical Results - Mitosis
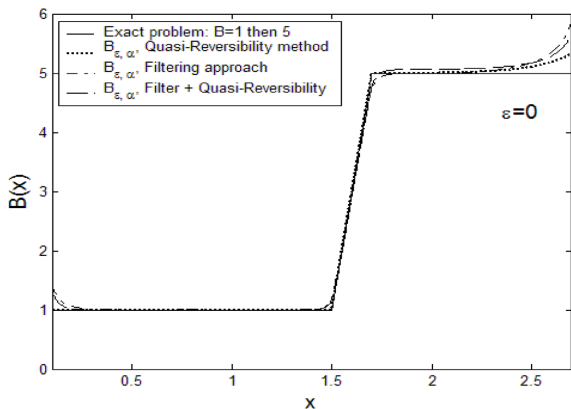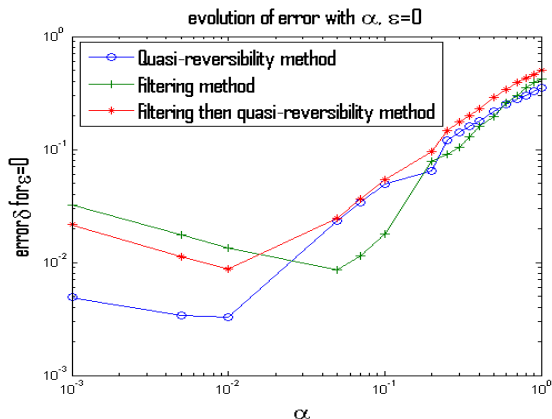

Results with no noise - step B

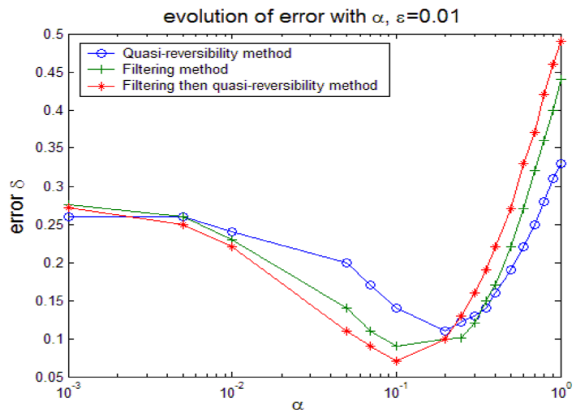# Numerical Results - Mitosis

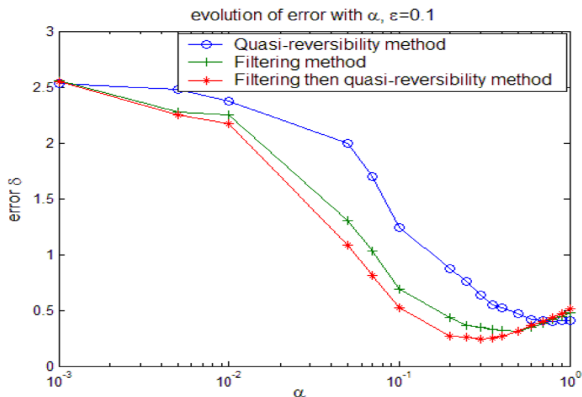Results with no noise - varying B

Numerical Results - Mitosis

Results with no noise - Error with respect to the regularization parameter α
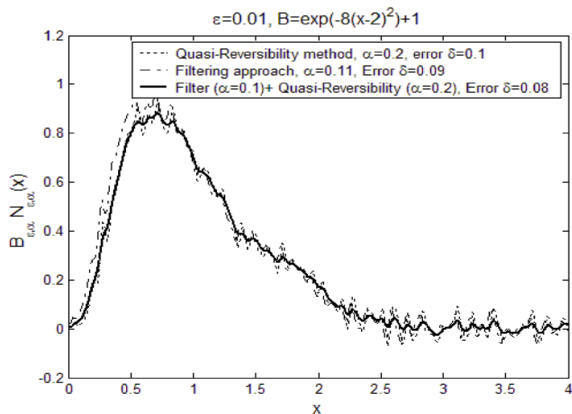
Numerical Results - Mitosis

evolution of error with α, $\varepsilon=0.01$

- Quasi-reversibility method
- Filtering method
- Filtering then quasi-reversibility method

Results with noise $\varepsilon = 0.01$ - Error with respect to the regularization parameter α

Numerical Results - Mitosis

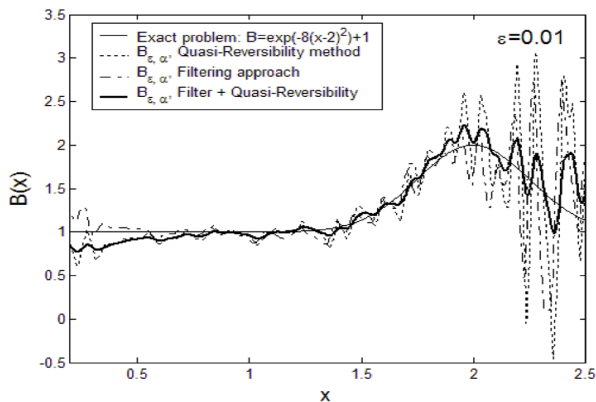evolution of error with α, ε=0.1

- Quasi-reversibility method
- Filtering method
- Filtering then quasi-reversibility method

Results with noise $\varepsilon = 0.1$ - Error with respect to the regularization parameter α

Numerical Results - Mitosis

$\varepsilon=0.01$, B=exp(-8(x-2)^2)+1

Legend:
- Quasi-Reversibility method, α=0.2, error δ=0.1
- Filtering approach, α=0.11, Error δ=0.09
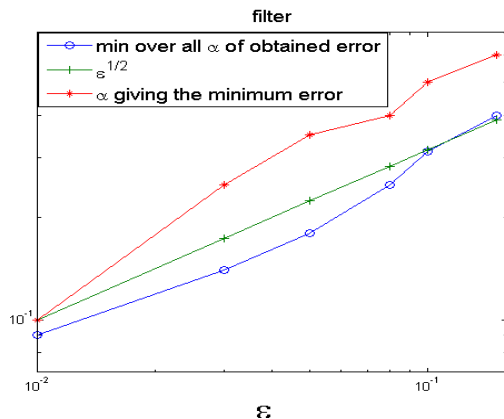- Filter (α=0.1)+ Quasi-Reversibility (α=0.2), Error δ=0.08

Results with noise $\varepsilon = 0.01$ - *BN*
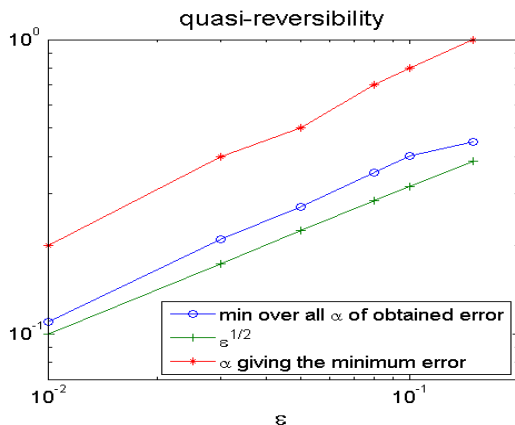
Numerical Results - Mitosis

Results with noise $\varepsilon = 0.01$ - B

Numerical Results - Mitosis

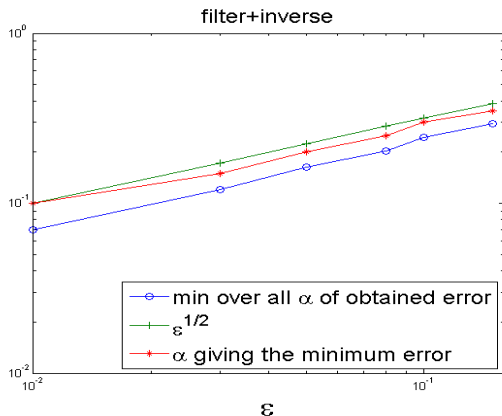

Optimal α with respect to ε, compared to $\sqrt{\varepsilon}$ and the optimal error

Numerical Results - Mitosis

Optimal α with respect to ε, compared to $\sqrt{\varepsilon}$ and the optimal error

Numerical Results - Mitosis

Optimal α with respect to ε, compared to $\sqrt{\varepsilon}$ and the optimal error

The Kubitschek data
(with P. Maia, J.P. Zubelli)

- An approximate doubling time T_ε is observed (which yields an estimator λ_ε of λ_0 through $T_0 = \log(2)/\lambda_0$).
- Measurements of densities of cells of size x are given for a given irregular grid $\{x_i, i = 1, \ldots\}$.
- By spline interpolation, the curve N_ε is obtained.
- The growth rate is postulated to be of the form $g(x) = \lambda x$

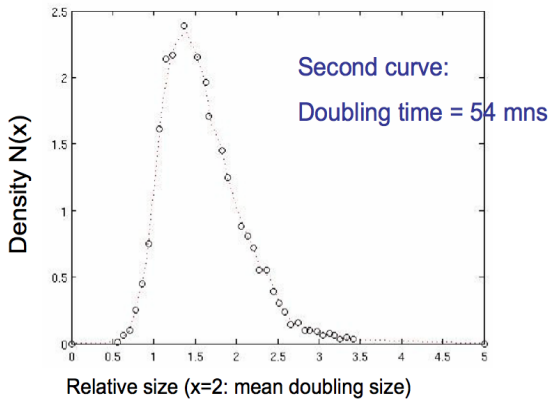Figure: The construction of N_ε for a given λ_ε
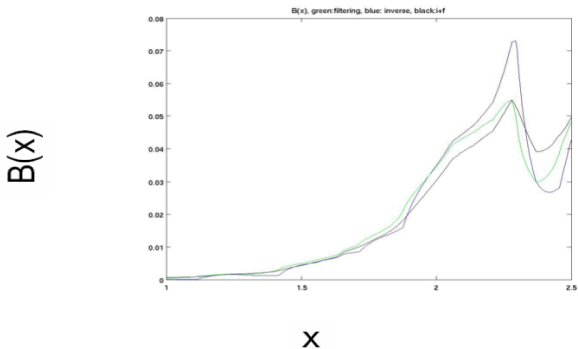
Figure: Estimation of $B(x)$ for a given λ_ε by numerical regularisation.

Numerical Scheme: general fragmentation kernel (with L.M. Tine)

Quasi-Reversibility Method:

$$
\begin{cases}
-\alpha x_i^{-m}\left(\dfrac{x_{i+1}^{m+1}H_{i+1}-x_i^{m+1}H_i}{\Delta x}\right) + H_i - 2\sum_{j=i}^{ka} H_j \kappa_{i,j}\Delta x = L_i \\[3mm]
\text{with } L_i = -\lambda_0 N_i - c\left(\dfrac{g_{i+1}N_{i+1}-g_i N_i}{\Delta x}\right), \quad \forall\, i = 1,...,ka \\[3mm]
H_0 = 0 \text{ and } H_l = 0, \quad \forall\, l > ka.
\end{cases}
$$

what gives (scheme has to depart from the upper bound):

$$
\begin{cases}
H_{ka} = \dfrac{L_{ka}}{A_{ka,ka}}; \\[3mm]
H_i = \dfrac{1}{A_{i,i}}\left(L_i - \sum_{j=i+1}^{ka} A_{i,j}H_j\right); \quad \forall\, i = ka-1,...,1
\end{cases}
$$

Since $A_{ij} > 0$ for $j \geq i+1$, we choose Δx small enough so that $A_{ii} = 1 + \alpha i - 2\kappa_{i,i}\Delta x > 0$ for all i. This guarantees that no oscillations (should) appear.

Introduction to Patricia's talk: the statistical approach (joint with M. Hoffmann, P. Reynaud-Bouret & V. Rivoirard)

Till now: we have supposed

$$||N - N_\varepsilon||_{L^2} \leq \varepsilon$$

But why an L^2 norm ? What about real data ?
Kubitschek: pre-processed data. Our will: global approach to incorporate a more realistic model for the noise.

Perspectives (coming soon...)

- Further investigation of the solution for the general fragmentation kernel (with T. Bourgeron and M. Escobedo)

- Construct a PDMP that matches with the PDE's approximation and that takes advantage of richer observation schemes (with M. Hoffmann, N. Krell, L. Robert).

- Extend this framework to a more realistic biological framework, that encompasses in particular variability in cell growth.

- What is the real structuring variable, age, size, else ?