Deterministic models and statistical aspects to model growth and division

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PDMP Days, 26-28 March 2012, Marne-la-Vallée
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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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

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
Some examples of structured populations

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)
Some examples of structured populations

**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 population 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 $B(y)$.
The Size-Structured Population equation
(or transport-fragmentation equation)

We consider a population 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 $B(y)$,
- 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
  \[ \int_0^y k(x, y)dx = 1 \] and due to symmetry
  \[ \int_0^y xk(x, y)dx = \frac{y}{2} \]

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:

\[
\frac{\partial}{\partial t} n(t, x) + \frac{\partial}{\partial x} \left( g(x) n(t, x) \right) = -B(x) n(t, x) + 2 \int_x^{\infty} B(y) k(x, y) n(t, y) dy
\]

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:

$$\frac{d}{dt} \int xn(t, x) dx = \int g(x)n(t, x)dx.$$
The Size-Structured Population equation

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Direct Problem: \((g, k, B)\) given, what is the solution \(n\)? Which asymptotic behaviour? How does it depend on the coefficients?
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**Inverse Problem:** estimate \((g, k, B)\) from (partial) measures of \(n\).
The Size-Structured Population equation
2 major relations, Direct vs Inverse Problem

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**Inverse Problem:** estimate \((g, k, B)\) from (partial) measures of \(n\).

**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 \( n(t, x) = e^{\lambda t} N(x), x \geq 0 \):

\[
\begin{align*}
\frac{\partial}{\partial x} (g(x) N(x)) + \lambda N(x) &= -B(x) N(x) + 2 \int_x^\infty B(y) k(x, y) N(y) dy, \\
g N(x = 0) &= 0, \quad N(x) \geq 0, \quad \int_0^\infty N(x) dx = 1, \\
-g(x) \frac{\partial}{\partial x} (\phi(x)) + \lambda \phi(x) &= B(x)(-\phi(x) + 2 \int_0^x k(y, x) \phi(y) dy), \\
\phi(x) \geq 0, \quad \int_0^\infty \phi(x) N(x) dx &= 1.
\end{align*}
\] (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 \( (\lambda, N, \phi) \) with \( \lambda > 0 \), solution of the eigenproblem (1)*

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

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

(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 $\Gamma : (c, B) \rightarrow (\lambda, N)$.
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 $0 < B_m \leq B \leq B_M < +\infty$.
Extension to the general case:

Under the previous T.A. (and one other), if $B \in L^2(\mathbb{R}_+)$, the map
$\Gamma$ 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 $N \in H^{s+1}$. 
The Inverse Problem
The deterministic approach

We postulate \( k(x, y) \) and some \( g_0(x) \) with \( g = cg_0 \).

We measure \( N \) and \( \lambda \) with an error term modeled by
\[
\|N_\varepsilon - N\|_{L^2} \leq \varepsilon \quad \text{and} \quad |\lambda_\varepsilon - \lambda| \leq \varepsilon.
\]

We seek \( c \) and \( B \) such that
\[
c \frac{\partial}{\partial x} (g_0(x) N(x)) + \lambda N(x) = -B(x) N(x) + 2 \int_\infty^x B(y) k(x, y) N(y) \, dy.
\]

Estimate \( B \) through \( L(N, \lambda) = L(BN) \),
\[
L(f)(x) = 2 \int_\infty^x f(y) k(x, y) \, dy - f(x).
\]

If we forget about \( c \) and \( \lambda \): the problem \( N \rightarrow H = BN \) is linear.
The Inverse Problem
The deterministic approach

- We postulate $k(x, y)$ and some $g_0(x)$ with $g = cg_0$. 

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The Inverse Problem
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The Inverse Problem
The deterministic approach

- We postulate $k(x, y)$ and some $g_0(x)$ with $g = cg_0$.
- We measure $N$ and $\lambda$ with an error term modeled by
  \[ \| N_\varepsilon - N \|_{L^2} \leq \varepsilon \text{ and } |\lambda_\varepsilon - \lambda| \leq \varepsilon. \]

- 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

\[ L(N, \lambda) = \mathcal{L}(BN), \]

with

\[ L(N, \lambda)(x) = c \frac{\partial}{\partial x} (g(x)N(x)) + \lambda N(x), \]
\[ \mathcal{L}(f)(x) = 2 \int_x^\infty f(y)k(x, y)\,dy - f(x). \]

If we forget about $c$ and $\lambda$: 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:

\[ c_\varepsilon := \lambda \varepsilon \frac{\int x N_\varepsilon(x) \, dx}{\int g_0(x) N_\varepsilon(x) \, dx}. \]
The Inverse Problem
The deterministic approach

\[ c \int g_0(x)N(x)dx = \lambda \int xN(x)dx, \]

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

\[ c_\varepsilon := \lambda \varepsilon \frac{\int xN_\varepsilon(x)dx}{\int g_0(x)N_\varepsilon(x)dx}. \]

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

\[ L(N, \lambda) = \mathcal{L}(BN), \]

with

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

\[ \mathcal{L}(f)(x) = 2 \int_x^{\infty} f(y)k(x, y)dy - f(x). \]
The Inverse Problem

The deterministic approach

2 main steps:

1. solve the dilation problem: for \( L \) in a proper space, find \( H \) such that
   \[
   2 \int_{\infty}^{\infty} x \, H(y) \, k(x, y) \, dy - H(x) = L(x),
   \]
   and \( H \) in a proper space - ideally, the "proper space" is \( L^2 \).

   For mitosis, the equation becomes:
   \[
   4 H(2x) - H(x) = L(x).
   \]

2. solve the derivative inverse problem: estimate \( L(N, \lambda) = c \varepsilon \partial_x (g_0(x) N(x)) + \lambda N(x) \) from a measure \( N \in L^2 \).

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 deterministic approach

2 main steps:

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:

$$4H(2x) - H(x) = L(x).$$
The Inverse Problem
The deterministic approach

2 main steps:

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

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

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

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

2. solve the derivative inverse problem: estimate $L(N, \lambda) = c_\varepsilon \partial_x (g_0(x)N(x)) + \lambda N(x)$ 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 $H^{(2)}$:

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

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

\[ H(x) - 2 \int_{x}^{\infty} H(y) k(x, y) dy = F, \quad (2) \]

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

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

\[ C_p = \sup_{x} \int_{x}^{\infty} \frac{x^p}{y^p} k(x, y) dy < \frac{1}{4}. \quad (3) \]

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

\[
\begin{aligned}
\alpha \frac{\partial}{\partial y} (B_{\epsilon, \alpha} N_{\epsilon})(y) + 4 B_{\epsilon, \alpha}(y) N_{\epsilon}(y) - B_{\epsilon, \alpha}(\frac{y}{2}) N_{\epsilon}(\frac{y}{2}) = \\
+ \lambda_{\epsilon, \alpha} N_{\epsilon}(\frac{y}{2}) + 2 \frac{\partial}{\partial y} \left( N_{\epsilon}(\frac{y}{2}) \right), \quad y > 0,
\end{aligned}
\]

\[
(B_{\epsilon, \alpha} N_{\epsilon})(0) = 0.
\]

**Theorem (Perthame, Zubelli, 2006)**

*We have the error estimate, optimal for $\alpha = O(\sqrt{\epsilon})$ :*

\[
\| B_{\epsilon, \alpha} N_{\epsilon, \alpha} - B_N \|^2_{L^2(dx)} \leq C \left( 1 + \frac{1}{\alpha^2} \right) \| N_{\epsilon} - N \|^2_{L^2(dx)} + C \alpha^2 \| N \|^2_{H^2(\mathbb{R}_+)} ,
\]
Regularization step
2nd method: Filtering

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

\[
\begin{aligned}
4B_{\varepsilon,\alpha}(y)N_\varepsilon(y) - B_{\varepsilon,\alpha}(\frac{y}{2})N_\varepsilon(\frac{y}{2}) &= \rho_\alpha^*(\lambda_{\varepsilon,\alpha}N_\varepsilon(\frac{y}{2}) + 2 \frac{\partial}{\partial y}(N_\varepsilon(\frac{y}{2}))) , \\
(B_{\varepsilon,\alpha}N_\varepsilon)(0) &= 0,
\end{aligned}
\]

with
\[
\rho_\alpha(x) = \frac{1}{\alpha} \rho(\frac{x}{\alpha}), \quad \rho \in C_c^\infty(\mathbb{R}), \quad \int_0^\infty \rho(x) \, dx = 1, \quad \rho \geq 0.
\]

Proposition (MD, Perthame, Zubelli, 2009)
We have the error estimate, optimal for \( \alpha = O(\sqrt{\varepsilon}) \):

\[
||B_{\varepsilon,\alpha}N_\varepsilon,\alpha-BN||_{L^2(dx)}^2 \leq C \left(1 + \frac{1}{\alpha^2}\right) ||N_\varepsilon-N||_{L^2(dx)}^2 + C\alpha^2 ||N||_{H^2(\mathbb{R}^+)}^2,
\]
Numerical Scheme
Mitotic Case

General requirements:
- avoid instability
- conserve main properties of the continuous model: laws for the increase
  - of biomass
  - of number of cells, e.g. for the quasi-reversibility method:

\[ H(2x) - H(x) = L(x), \]

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

- avoid instability
- conserve main properties of the continuous model: laws for the increase
  - of biomass
  - of number of cells, e.g. for the quasi-reversibility method:

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 \( B(2x) \) ?
Recall the identity:

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

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 \(L^p\))
Recall the identity:

\[
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\]

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 \(L^p\))

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 $4H_{2i}$

$$4H_i^f = \frac{H_i^f}{2} + \frac{L_i^f}{2}, \quad \forall \ 0 \leq i \leq I,$$

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

$$G_{\frac{i}{2}} = \begin{cases} 
G_i \quad & \text{when } i \text{ is even,} \\
\frac{1}{2} (G_{\frac{i-1}{2}} + G_{\frac{i+1}{2}}) & \text{when } i \text{ is odd.}
\end{cases}$$
Numerical schemes: steps
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- solve the direct problem for a given $B(x)$ Method: use of the exponential convergence of $n(t,x)$ to $N(x)$: Finite volume scheme to solve the time-dependent problem.
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- Then renormalization at each time-step to reach the asymptotic distribution.
Numerical schemes: steps

- solve the direct problem for a given $B(x)$ Method: use of the exponential convergence of $n(t,x)$ to $N(x)$: Finite volume scheme to solve the time-dependent problem.
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- add an artificial noise to $N(x)$ to get a noisy data $N_\varepsilon(x)$
Numerical schemes: steps

- solve the direct problem for a given \( B(x) \) Method: use of the exponential convergence of \( n(t,x) \) to \( N(x) \): Finite volume scheme to solve the time-dependent problem.
- Then renormalization at each time-step to reach the asymptotic distribution
- 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 \( \alpha \) for a given error \( \varepsilon \).
Numerical Results - Mitosis

Three tested division rates $B$

- $B=1$ for $x<1.5$, then increases linearly to $B=5$
- $B=1+\exp(-8(x-2)^2)$
Numerical Results - Mitosis

Three related asymptotic distributions $N$
Numerical Results - Mitosis

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 $\alpha$
Numerical Results - Mitosis

Results with noise $\varepsilon = 0.01$ - Error with respect to the regularization parameter $\alpha$
Numerical Results - Mitosis

Results with noise $\varepsilon = 0.1$ - Error with respect to the regularization parameter $\alpha$
Numerical Results - Mitosis

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

Results with noise $\varepsilon = 0.01 - B$
Numerical Results - Mitosis

Optimal $\alpha$ with respect to $\varepsilon$, compared to $\sqrt{\varepsilon}$ and the optimal error
Optimal $\alpha$ with respect to $\varepsilon$, compared to $\sqrt{\varepsilon}$ and the optimal error
Numerical Results - Mitosis

Optimal $\alpha$ with respect to $\varepsilon$, compared to $\sqrt{\varepsilon}$ and the optimal error
An approximate doubling time $T_\varepsilon$ is observed (which yields an estimator $\lambda_\varepsilon$ of $\lambda_0$ 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 $N_\varepsilon$ is obtained.

The growth rate is postulated to be of the form $g(x) = \lambda x$. 
Figure: The construction of $N_\varepsilon$ for a given $\lambda_\varepsilon$

Second curve:
Doubling time = 54 mns
Doubling Time: 54 minutes

Figure: Estimation of $B(x)$ for a given $\lambda_\varepsilon$ by numerical regularisation.
Numerical Scheme: general fragmentation kernel (with L.M. Tine)

Quasi-Reversibility Method:

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

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

\[
\begin{align*}
H_{ka} &= \frac{L_{ka}}{A_{ka,ka}}; \\
H_i &= \frac{1}{A_{i,i}} \left( L_i - \sum_{j=i+1}^{ka} A_{i,j} H_j \right); \quad \forall \ i = ka - 1, \ldots, 1
\end{align*}
\]

Since \( A_{ij} > 0 \) for \( j \geq i + 1 \), we choose \( \Delta x \) 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.
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?