Couplage entre algorithme SAEM et précalcul pour la paramétrisation populationnelle d'équations de réaction diffusion

Emmanuel Grenier, Violaine Louvet, Paul Vigneaux

Equipe NUMED, Lyon

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Outline

1. Motivations
2. Mixed effects model
3. SAEM
4. Extension to PDE
5. Application : KPP
6. Conclusions

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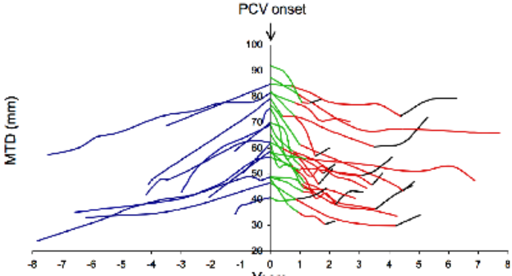
Motivations

Low-grade gliomas

- Progressive brain tumors characterized radiologically by slow and continuous growth preceding anaplastic transformation
- Their treatment includes surgery, radiotherapy and chemotherapy but remains controversial
- Develop model and simulation tool to conceive potentially more effective treatment schedules and to predict treatment efficacy in LGG patients on the basis of pre-treatment time-course tumor size observations.

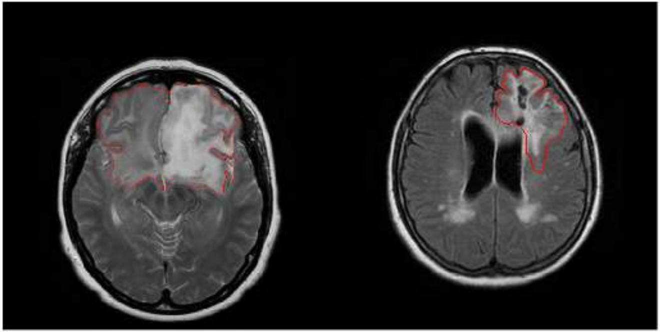


Issues

ODE Model

- Development in Numed Team of a tumor growth inhibition model for LGG based on ODEs
- Interesting results : correct description of tumor growth and response to treatments

But ...



Issues

EDP Model

- Significant contributions from the group of Kristin Swanson (University of Washington) toward modeling the time and space evolution of gliomas.
- Models based on partial differential equations, describe the spatiotemporal evolution patterns of tumor cells in the brain as "traveling waves" (based on KPP equations) driven by 2 processes : uncontrolled proliferation and tissue invasion

$$\frac{\partial c}{\partial t} = \rho c(1 - c) + \nabla.(D\nabla c)$$

c = tumor cells concentration
Tumor's volume (which is the observed clinical data) :

$$V(t) = \int_{\Omega} c(t, x) dx$$

Model Parameters Estimation

We have :

- a PDE model
- some clinical datas for a few individuals

and we want to adjust the model taking into account the individual variability

Some existing works :

- Inverse problem approaches : huge literature.
  - essentially done indiv. by indiv.
- Another viewpoint : use knowledge from all the population
  - and adopt a statistical approach.
  - Again : huge literature

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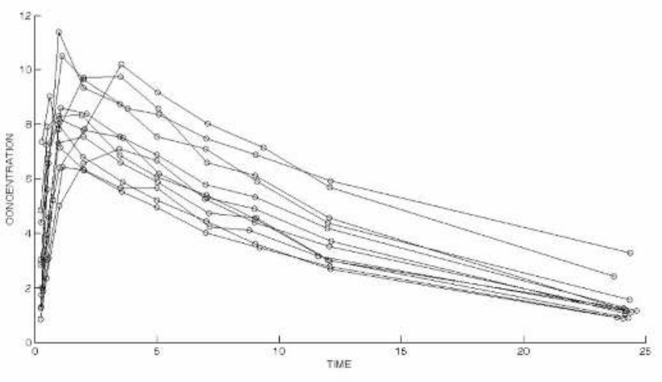
Focusing on : (nonlinear) mixed effects model

Population of 12 individuals :



- each curve described by the same parametric model
- with its own individual parameters (inter-subject variability)

Focusing on : (nonlinear) mixed effects model

$$y_{ij} = f(x_{ij}, \psi_i) + \varepsilon_{ij}, 1 \leq i \leq N, 1 \leq j \leq n_i \quad (1)$$

- $y_{ij} \in \mathbb{R}$: j^{th} observation of individual i
- N : number of individuals
- n_i : number of observations of individual i
- $x_{ij} \in \mathbb{R}^{n_x}$: **known** design variables (usually observation times)
- ψ_i : vector of the n_ψ **unknown individual parameters**
- ε_{ij} : residual errors (including measurement errors for example)

Focusing on : (nonlinear) mixed effects model

$$y_{ij} = f(x_{ij}, \psi_i) + \varepsilon_{ij}, 1 \leq i \leq N, 1 \leq j \leq n_i$$
$$\psi_i = h(c_i, \mu, \eta_i) \quad (2)$$

- c_i : known vector of M covariates
- μ : unknown vector of **fixed effects** (size p)
- $\eta_i \sim_{i.i.d.} \mathcal{N}(0, \Omega)$: unkn. vect. of **random effects** (size q)

  Ω is the $q \times q$ var.– covariance matrix of the rand. eff.
- $\varepsilon_{ij} \sim_{i.i.d.} \mathcal{N}(0, \sigma^2)$: residual errors

Parameters of the model to be determined : $\theta = (\mu, \Omega, \sigma^2)$

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The Expectation-Maximization algorithm

(Dempster, Laird & Rubin, 1977)

Goal : Maximum Likelihood Estimation

Since ψ is not observed, $\log p(y,\psi;\theta)$ can not be directly used to estimate θ. An option :

Iterative algorithm : at step k

- E step : evaluate

$$Q_k(\theta) = \mathbb{E}[\log p(y,\psi;\theta)|y;\theta_{k-1}]$$

- M step : update the estimation of θ

$$\theta_k = \text{Argmax} \quad Q_k(\theta)$$

Some practical drawbacks :

- CV depends on the initial guess
- Slow CV of EM
- Evaluation of $Q_k(\theta)$

The SAEM algorithm (Stocha. Approx. of EM)

(Delyon, Lavielle & Moulines, 1999)
Improvement of the EM algorithm implemented in the Monolix software

SAEM : what's done ?

To our knowledge, the following is working with MONOLIX :

- ODE's
- Systems of ODE's and Chains of ODE's
- Stochastic DE's
- Numerous validation on real applications :
  - PK/PD (1 or more compart.), viral dynamics models ...

but the **integration of PDE's remains an open problem**.
Some attempts here and there but essentially done by transforming the PDE into a set of ODE's.

Due to the computational cost

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The primitive idea ...

Assume you don't want to simplify the model

and want to keep the PDE to have the solution

- decouple PDE resolution and SAEM evaluation :
- **precompute** solutions (as functions of parameters)
- store them and call them when SAEM need them

This is the classical **Offline**/**Online** concept

- Offline step : very long computational time (who cares ?)
- Online step : "instantaneous" $\Rightarrow$ SAEM doable

Rk : there is still the problem of storage ... (balance v.s. cpu)

Precomputation

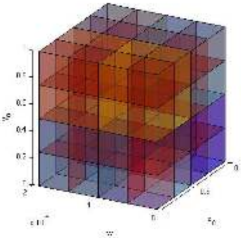
To evaluate quickly a function f, ...

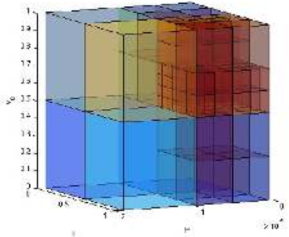
... interpolate from precomputed values on a grid

Start with an hyper-rectangle (let's say a "cube") :

$$C_{init} = \Pi_{i=1}^{N} [x_{min,i}, x_{max,i}]$$

- Divide the "cube" and compute weigths of children
- Choose a child (e.g. highest weight) and divide it
- Iterate as needed





Examples of weights

Let $\{f_k\}_{k=1,2^N}$: values of f at the summits of C_i.

- Simplest : volume of cube $C_i \rightarrow$ regular mesh
- L^1 weight :

$$f_m := \frac{1}{2^N} \sum_{k=1}^{2^N} f_k \quad \text{and} \quad \omega_i^1 = \frac{1}{2^N} \sum_{k=1}^{2^N} |f_k - f_m|.$$

- L^∞ weight :

$$\omega_i^\infty = \sup_{1 \leq k \leq 2^N} |f_k - f_m|.$$

- BV weight : avoid excessive ref near discontinuities

$$\omega_i^{BV} = vol(C_i) \sup_{1 \leq k \leq 2^N} |f_k - f_m|$$

Remarks

Errors :

- With this approach the **global error** ε
- decomposes as : **numerical error** ε^{num} (PDE)
- and an **interpolation error** ε^{interp} (Database,DB)
- Given a level of admissible ε, one can derive the optimal choice of the computational cost needed to solve the PDE.

Feasibility : for a $\mathcal{C}^1$ function, building database is doable if there are no more than

- 5-6 parameters for a 4 levels DB
- 4-5 parameters for a 5 levels DB

$\rightarrow$ **for more parameters, additional ideas are needed**

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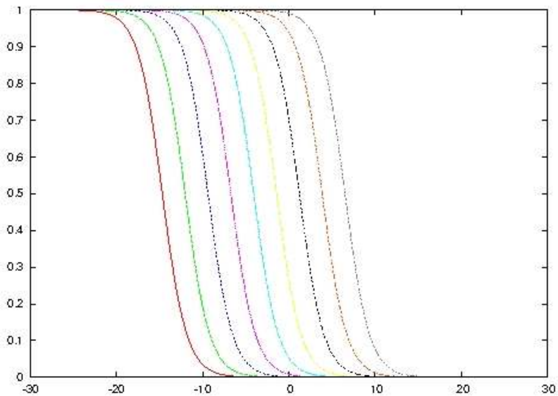
Description of the KPP model

We consider the classical reaction-diffusion PDE named after Kolmogoroff, Petrovsky and Piscounoff (1937) :

$$\partial_t u - \nabla.(D\nabla u) = Ru(1-u), \forall t > 0, \forall x \in \Delta \quad (3)$$

$$u(T_0, x) = \alpha 1_{|x-x_0|\leq\varepsilon}, \text{ and Neumann B.C. on } \Delta \quad (4)$$



Properties of the KPP model

- Maximum principle : $\forall t > 0, \quad 0 \leq u(t,.) \leq 1$
- Good model for front propagation
- Speed $= 2\sqrt{RD}$, Front width $\propto \sqrt{\frac{D}{R}}$
- Define the “volume” of the invaded zone :

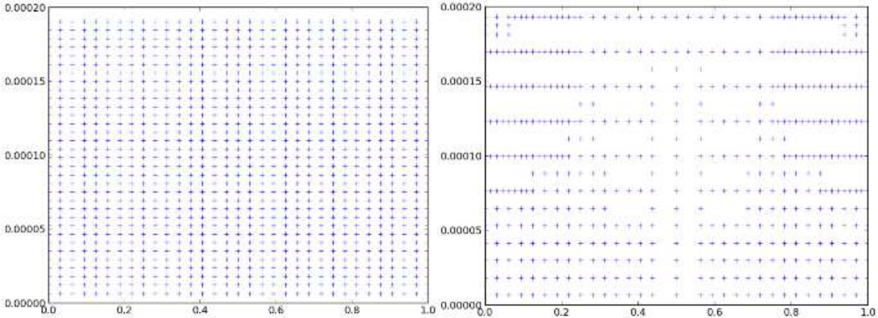
$$V(t) = \int_{\Delta} u(t,x)dx \tag{5}$$

- Parameters :
  - R (reaction coefficient),
  - D (diffusion coefficient),
  - x_0 (localisation of the initial “invaded zone”).
- Can be applied to numerous fields with propagation phenomena (flame propagation, tumour growth [Swanson], etc) : existence of particular solutions called "*travelling waves*".

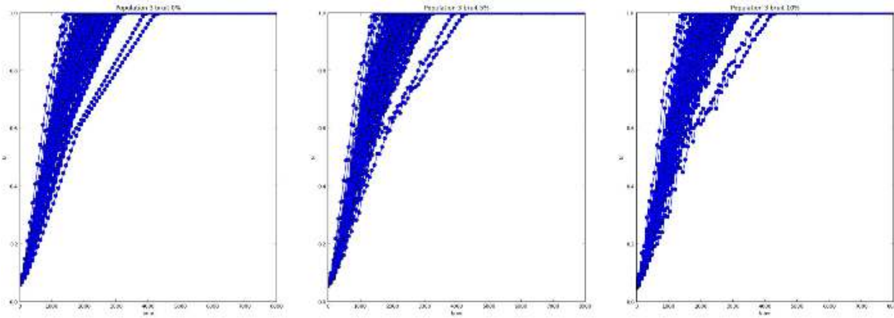
Technical details

Build 2 databases :

- homogeneous : 1089 summits
- heterogeneous : 500 summits



Technical details - Populations



100 to 1000 individuals in each population. Noise : 0%, 5%, 10%
Lognormal distribution of parameters.
101 points in time.

Results : individual and population errors

Goal : estimation of the population and individual parameters (R, D and x_0) with Monolix using the virtual population as observed data

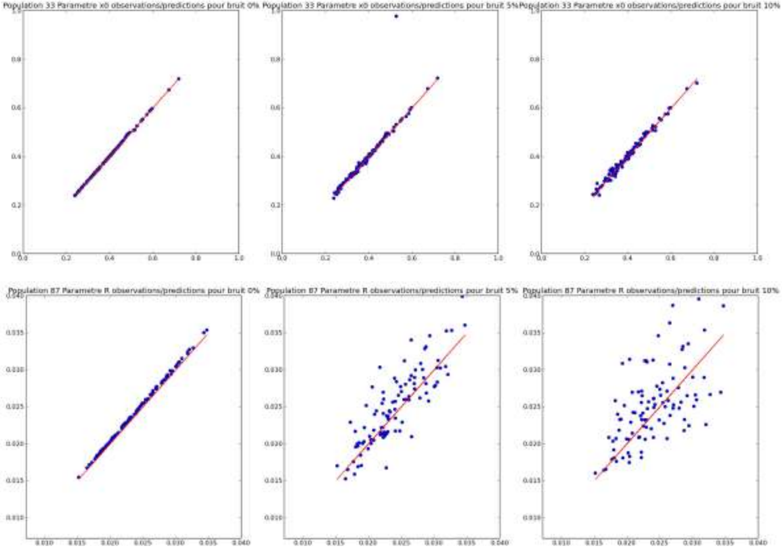
Population errors for 150 populations with 100 individuals

	noise 0%	noise 5%	noise 10%
x_0	2.8	3.2	4.0
R	2.26	9.9	15.9
D	9.0	15.6	20.9

Individual errors for 150 populations with 100 individuals

	noise 0%	noise 5%	noise 10%
x_0	20.9	19.2	17.0
R	58.6	46.1	47.5
D	26.5	22.5	23.5

Results : pred vs obs indiv params (100 ind)



Results : same quality with a lower cost

	"Exact" case	Interpolation with homogeneous mesh	Interpolation with heterogeneous mesh
Offline	No offline computation	Mesh with n segmentations, $(2^n+1)^2$ points. For 5 segmentations, 1089 points	Mesh with n points. Example with 500 points
Unit average CPU	-	$2.12s$	$2.12s$
Offline total CPU	-	$38mn28s$	$17mn40s$
Online	SAEM, 10^6 KPP evaluations	SAEM, 10^6 interpolations	SAEM, 10^6 interpolations
Unit average CPU	$2s$	$4.5\times10^{-4}s$	$5.1\times10^{-4}s$
Online total Cost	$\sim$ 23 *days* 3 *h*	$7mn30s$	$8mn30s$
Total cost	$\sim$ 23 *days* 3 *h*	$45mn58s$	$26mn10s$

The number of calls of the solver in SAEM is about 10^6 for this case. Note that this is sequential CPU time. The mesh generation can be easily parallelize on many cores with an excellent scalability.

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Conclusions

Summary

- Coupling of SAEM and PDE's
- Doable but limited to 5–6 parameters (in basic mode)
- Reasonable quality of param. estimation
- Need a case by case study for each PDE

Perspectives

- Explore various way to reach higher # of params
  - optimized sparsity of the DB–mesh
  - “dynamic” adaptivity
  - Kriging, experimental design
- Application to other models (some done, other in progress)

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