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

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Outline

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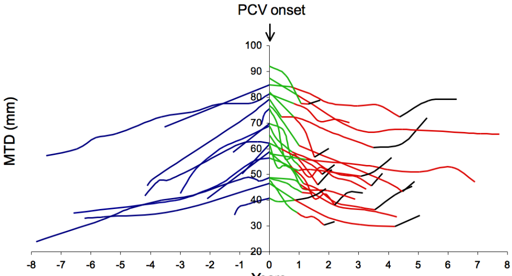
Motivations

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.

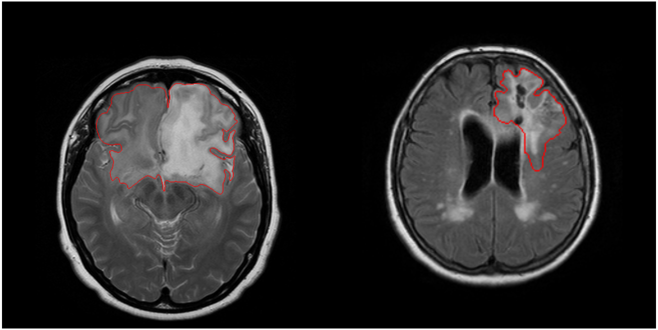


Issues

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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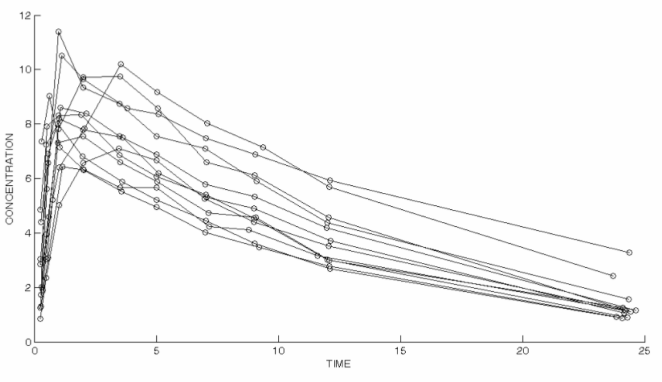
Focusing on : (nonlinear) mixed effects model

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

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

- $y_{ij} \in \mathbb{R}$: 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

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

- 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

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

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

Outline

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

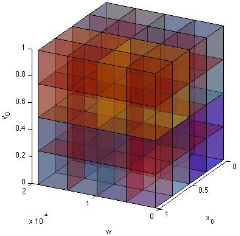
To evaluate quickly a function f, ...

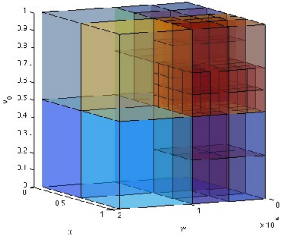
... interpolate from precomputed values on a grid

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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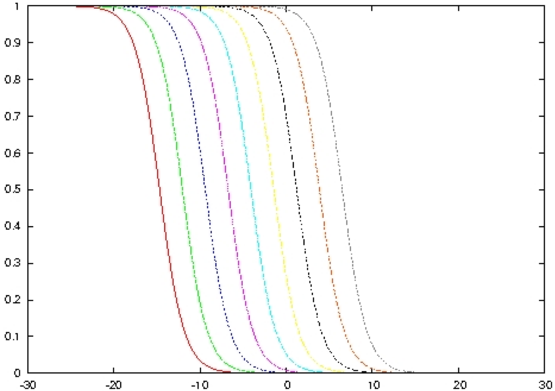
Description of the KPP model

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 :

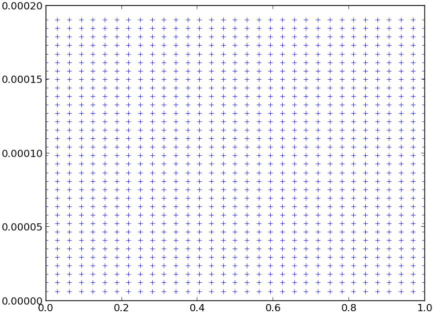
$$V(t) = \int_{\Delta} u(t,x)dx \tag{5}$$

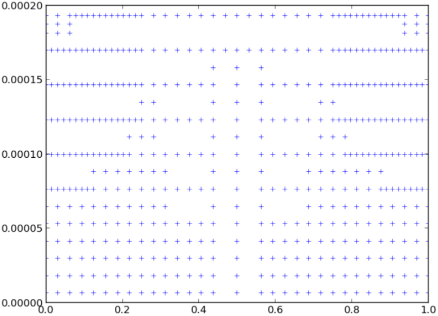
- Parameters :
  - R (reaction coefficient),
  - D (diffusion coefficient),
  - x_0 (localisation of the initial “invaded zone”).
- Can be applied to numerous fields with propagation phenomena (flame propagation, tumour growth [Swanson], etc) : existence of particular solutions called "*travelling waves*".

Technical details

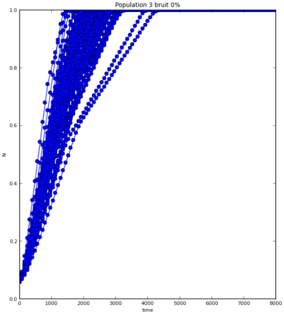
Build 2 databases :

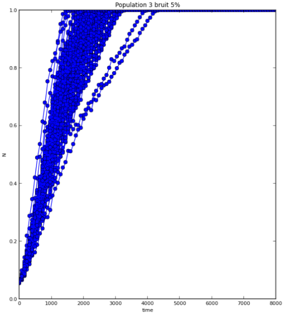
- homogeneous : 1089 summits
- heterogeneous : 500 summits

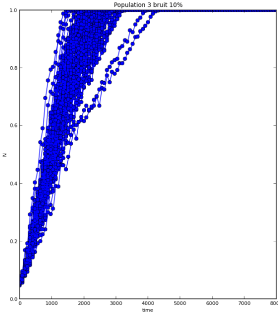




Technical details - Populations







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

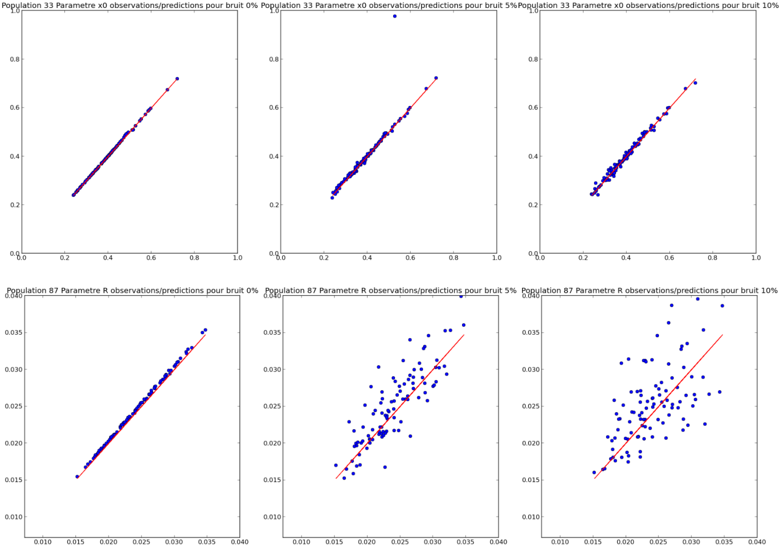
Population errors for 150 populations with 100 individuals

	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	$2s$	$4.5 \times 10^{-4}s$	$5.1 \times 10^{-4}s$
Online total Cost	~ 23 *days* 3 *h*	$7mn30s$	$8mn30s$
Total cost	~ 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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