New methods for complex models defined by a large number of ODEs. Application to a Glucose/Insulin model

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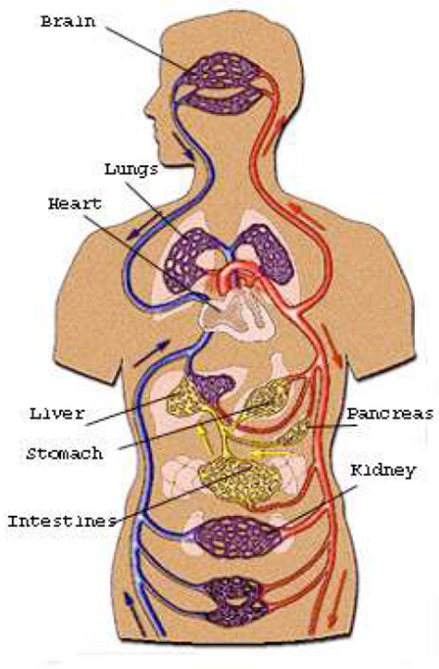
Model description

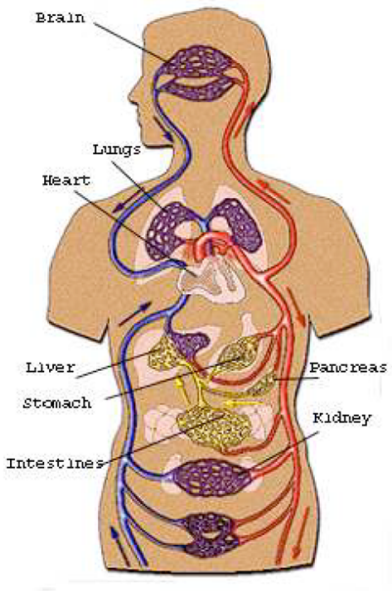
The model used is the model developed by Karin Alvehag in her Master thesis *Glucose Regulation* (2006)

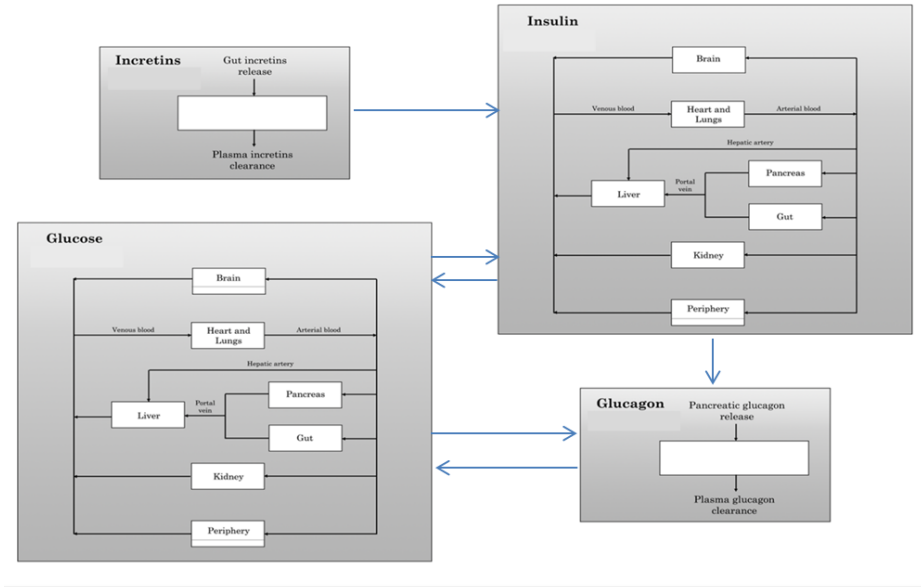


The model describes the change and feed-back interactions between glucose and insulin after an add of glucose in healthy patients.

Model description

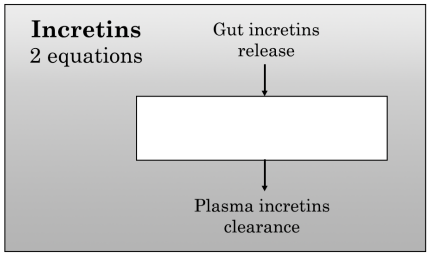
- 4 agents : glucose and 3 hormones, insulin, glucagon and incretins, are assumed to have an effect on glucose metabolism.
- Each anatomical organ is represented by a compartment.

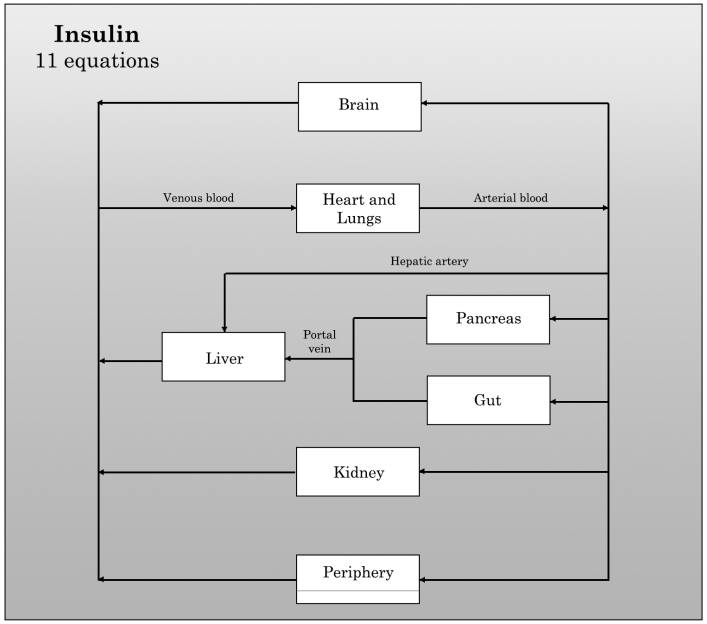


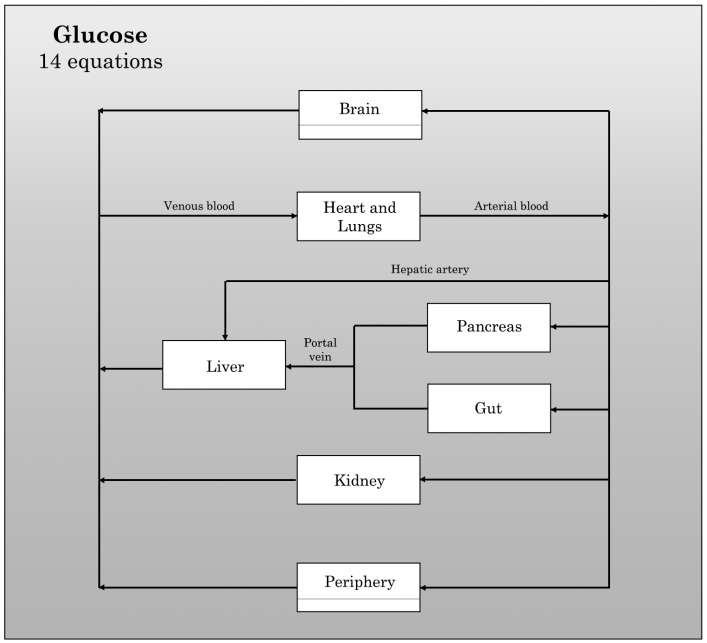


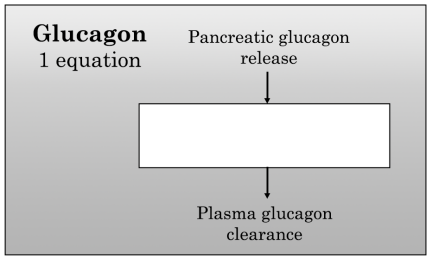
Modular structure of the model

Model
28 equations



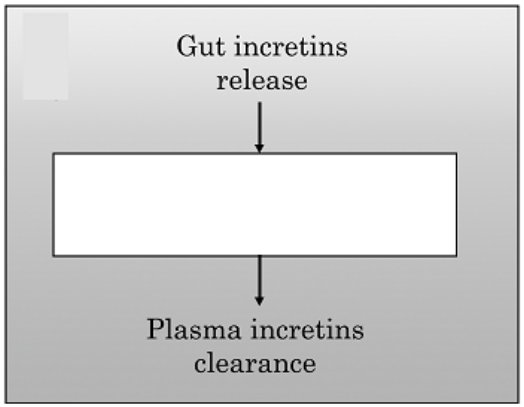






Submodels implementation

Description of the model



Mathematical representation

$$
\begin{aligned}
VI &= 9.930 \\
r &= 0.14 \\
TI &= 25 \\
IG_0 &= 0 \\
AI_0 &= 0 \\
I(t) &= \frac{AI(t)}{VI} \\
\frac{dIG(t)}{dt} &= -\frac{IG(t)}{TI} \\
\frac{dAI(t)}{dt} &= \frac{IG(t)}{TI} - r \times I(t)
\end{aligned}
$$

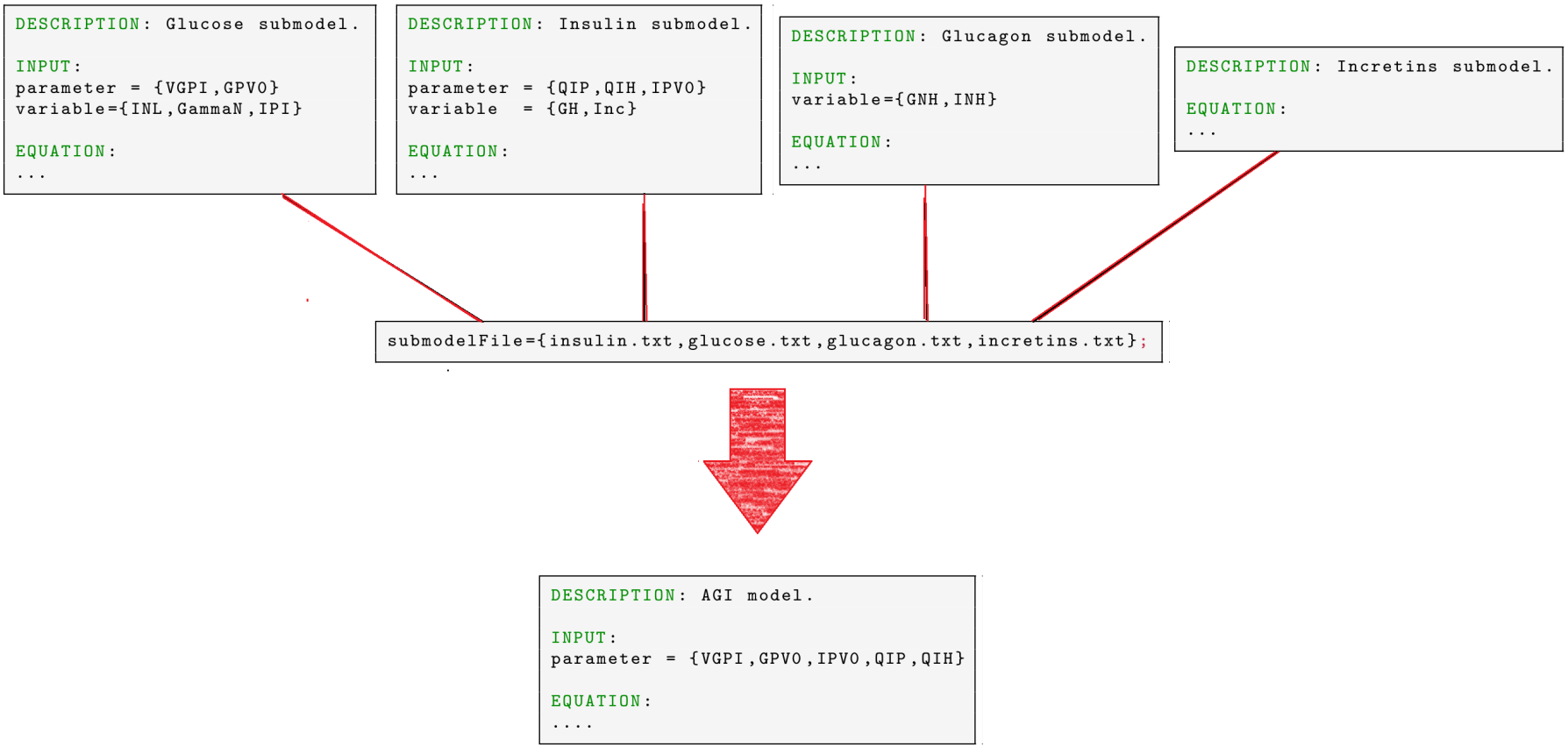
Implementation in Mlxtran

```
DESCRIPTION: Incretins submodel.

EQUATION:
VInc=9.930
rMIncC=0.14
TauInc=25

IncG_0=0
AInc_0=0
Inc=AInc/VInc
ddt_IncG=-IncG/TauInc
ddt_AInc=IncG/TauInc-rMIncC*Inc
```

Creation of the complete model from submodel implementations



Dynamical system

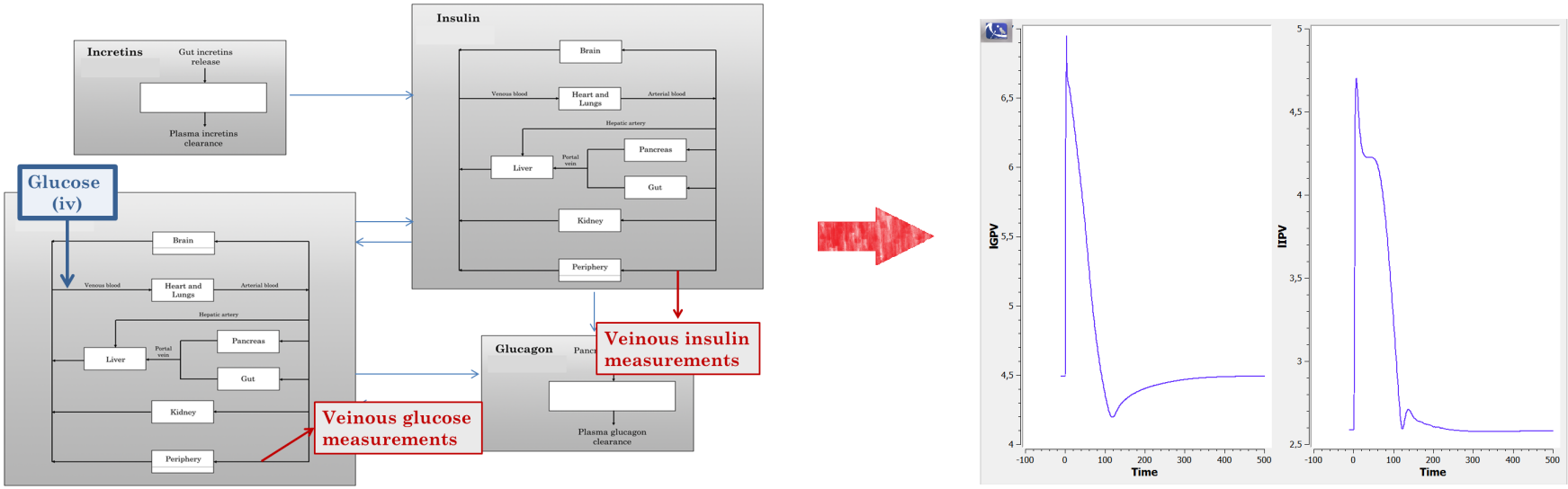


FIGURE : 2 kinds of observations : peripheral venous glucose and insulin log-concentration.

Statistical model

Statistical model for continuous data :

For $1 \leq i \leq 50$ and $1 \leq j \leq 20$,

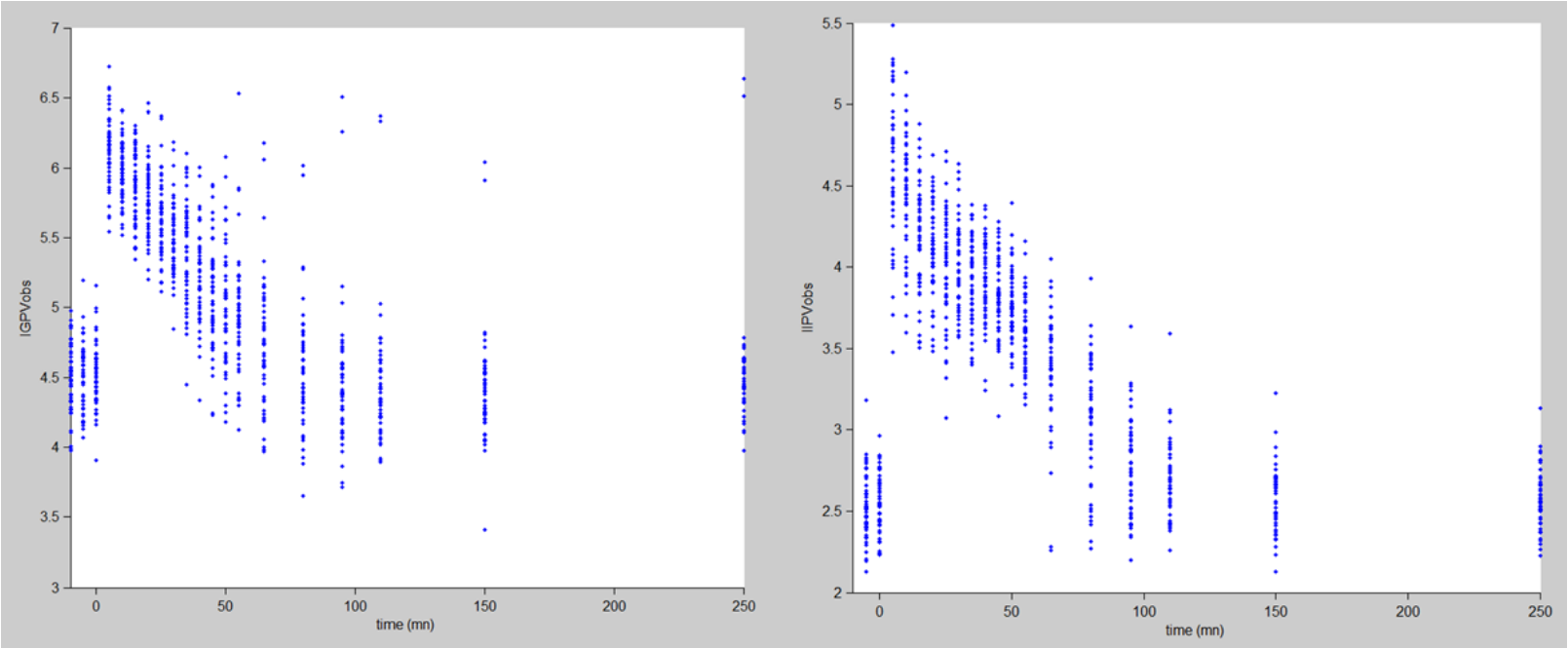
$$\begin{aligned} y_{ij} &= f(t_{ij}, \psi_i) + a\,\varepsilon_{ij} \\ \log(\psi_i) &\sim \mathcal{N}(\psi_{pop},\ 0.1\,\mathbb{I}_5) \\ \psi_{pop,k} &\in [0.9, 1.1] \end{aligned}$$

We consider **5 normalized parameters** :

$$\psi_i = (GPV0_i, IPV0_i, VGPI_i, QIH_i, QIP_i)$$

Data-set simulations

- 1 input : intravenous (100g of Glucose)
- 2 kinds of observations : peripheral venous glucose and insulin log-concentration.



The simulations were made using *simulmlx*, a MIxtran interpretor for R and Matlab.

Parameters estimation

Model for continuous data :

$$y_{ij} = f(t_{ij}, \psi_i) + a\,\varepsilon_{ij}$$

where f is the structural model.

The algorithms implemented in MONOLIX : SAEM, MCMC, Importance sampling, require to **compute f a large number of times**.

$\Longrightarrow$ **Time consuming** if f is solution of a large system of ODEs.

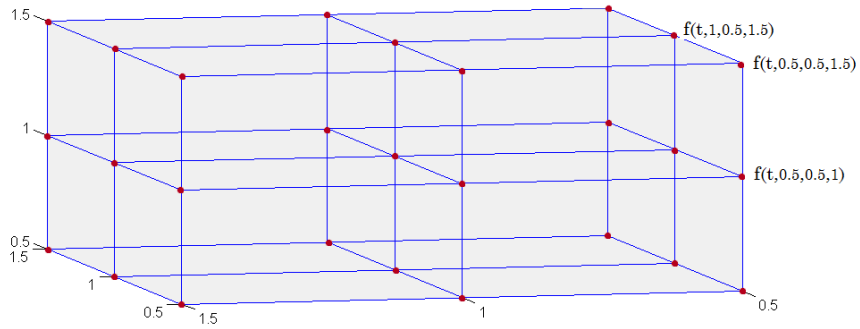
Proposed method

The proposed method is an extension of these algorithms that limits the total number of times the ODE system need to be solved.

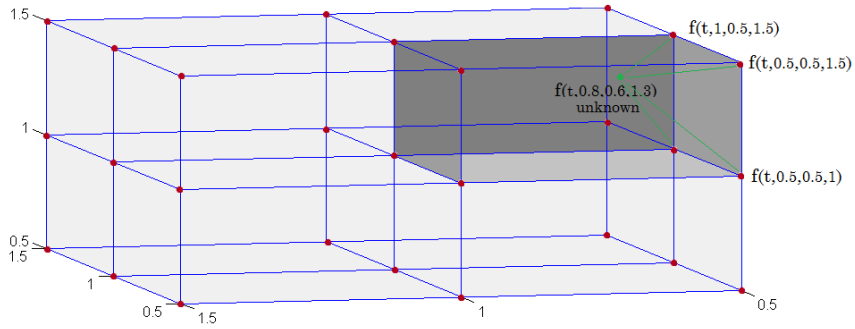
Principle :

- Evaluate the structural model f on a well-defined grid of parameters of sampling step h
- Approximate the original model f by interpolating these isolated values

Proposed method



Step 1: Grid calculation



Step 2: Approximation

For any time t_{ij}, we define $f_h(t_{ij}, \cdot)$ as an interpolation of $f(t_{ij}, \cdot)$ computed on a discrete grid of parameters.

$$y_{ij} = f_h(t_{ij}, \psi_i) + \varepsilon_{ij}$$

$$f_h \underset{h \to 0}{\longrightarrow} f$$

Results with the Glucose/Insulin model

Numerical experiment :

- f solution of a system of 28 ODEs
- Estimation of 5 population parameters with their IIV.
- $h = 0.1$ *i.e.* 21^5 points on the grid

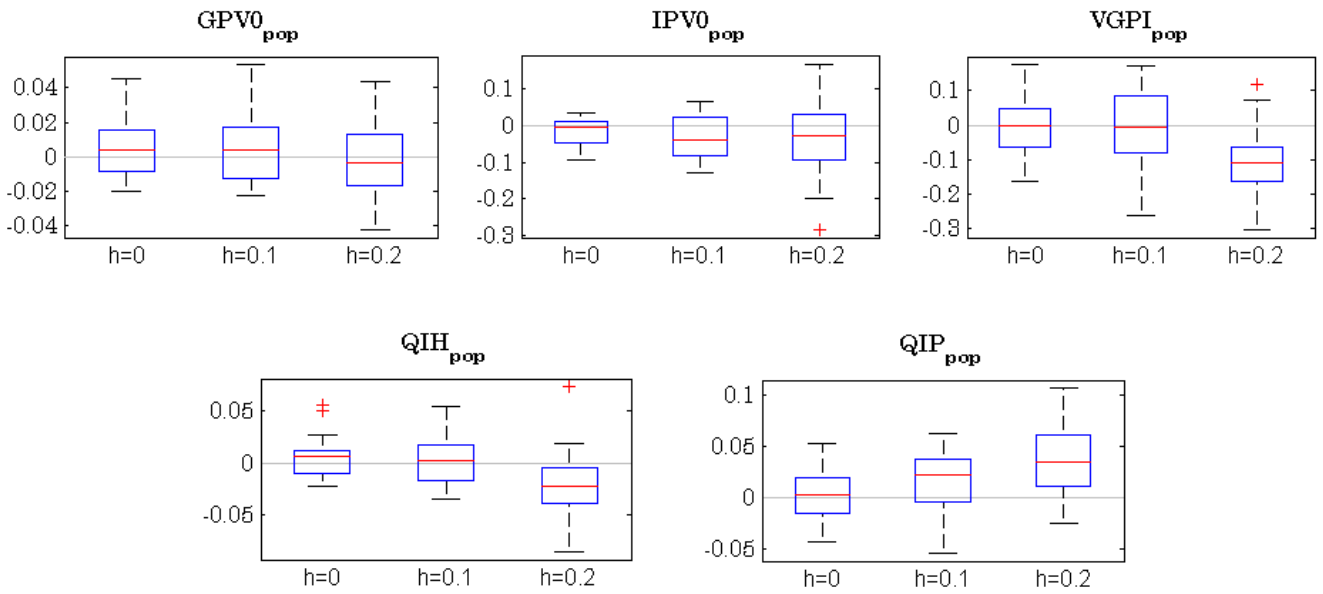
Time in seconds

	SAEM	**F.I.M**	**MCMC**
f	1004	153	290
$\mathbf{f_h}$	45	7	16

Time for 100 runs :

- 40h with classical algorithms
- 4h with this approach (including 2h of grid calculation on a laptop).

Results with the Glucose/Insulin model



Relative Root Mean Square Error (%) in function of the sampling step :

	$GPV0_{pop}$	$IPV0_{pop}$	$VGPI_{pop}$	QIH_{pop}	QIP_{pop}
$h = 0$	1.9	4.1	8.8	2.0	2.2
$h = 0.1$	2.3	6.5	10.5	2.1	3.1
$h = 0.2$	2.3	9.9	15.0	3.4	4.8

Advantages and limitations of the proposed method

Advantages

- f is computed only once on each point of the grid (easy to parallelize)
- The same grid can be used for different tasks and different algorithms, for different covariate models, for different error models,..

Limitation

- This method is efficient for very complex models with a small number of parameters to estimate (5 or 6)

Conclusion and perspectives

- Good results with a small number of parameters (5) : time divided by 10 for a RMSE raise of less than 5%.
- To improve the quality of the estimators, we could refine the grid in areas of interest.
- The same idea can be applied to PDE (Partial Differential Equations) models. See the poster from Paul Vigneaux et al. (I-49).

Thank you for your attention !

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