Compartmental model identification based on an empirical Bayesian approach: the case of thiamine kinetics in rats

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Abstract—*Compartmental models are a very popular tool for the analysis of experiments in living systems. There are three main aspects that have to be taken into account: the degree of detail of the model, its a priori identifiability and the* a posteriori *(numerical) identifiability. In some cases, where standard approaches are adopted, the models can be either* a priori *or* a posteriori *unidentifiable. The paper proposes model identification within a Bayesian framework, to solve* a posteriori *unidentifiability problems. In particular, a stochastic simulation algorithm is proposed to perform a Bayesian identification of compartmental models, and an empirical Bayesian technique is proposed to propagate information among multiple experiments. The power of this methodology was demonstrated by evaluating the kinetics of thiamine under several experimental conditions. The complexity of the existing model (nine parameters) and limited experimental data (8/12 for each model) caused* a posteriori *identifiability problems when standard approaches were adopted. The application of the methodology identifies all 28 models (four tissues under seven different conditions).*

Keywords—*Thiamine, Compartmental model, Bayes estimate, Empirical Bayes, Markov chain Monte Carlo, Nervous tissue*

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1 Introduction

COMPARTMENTAL MODELS are a very popular tool for the analysis of experiments in living systems, with applications in many branches of biology (CARSON *et al.*, 1983; JACQUEZ, 1996). The complexity of the models depends both on the available knowledge of the specific problem and on the available experimental data. For example, very detailed models can be exploited in pharmacology and physiology under tightly controlled experimental conditions.

However, there are three common aspects that have to be taken into account when managing compartmental models. First, the degree of detail of the model has to be defined in accordance with the goal of the study. Secondly, its *a priori* identifiability should be checked: it should be evaluated if, given the experimental design under ideal hypotheses (both model and data are supposed to be error-free), it is possible, from a theoretical point of view, to identify unambiguously the model parameters (COBELLI and DISTEFANO, 1980; GODFREY and DISTEFANO, 1987). If the system is not *a priori* identifiable, it is crucial to establish what parameters should be fixed to known values so that the *a priori* identifiability can be obtained.

A priori identifiability is a necessary condition for the identifiability of the compartmental model: it guarantees a good structural design of the experiment (CARSON *et al.*, 1983). Therefore the third issue that must be considered is the so called *a posteriori* identifiability. In practice, given real data and a particular identification procedure, it is necessary to verify whether the estimates of the model parameters are unique and, in this case, if they are obtained with sufficient precision. In general, this step is performed using standard software tools for the analysis of compartmental models that implement non-linear identification algorithms.

Unfortunately, in some cases, it is not possible to satisfy these three requirements at the same time. In fact, on the one hand, it would be necessary to build a 'sufficiently' detailed model and, on the other hand, it is impossible/unseemly to perform a 'sufficiently' rich experiment. Thus the model may be either *a priori* or *a posteriori* unidentifiable. In both these cases, a Bayesian approach to model identification can represent a suitable solution. When the model is *a priori* unidentifiable, it is possible to add some information to it, introducing (if possible) the *a priori* knowledge (as prior distribution), in particular of the unidentifiable parameters. This allows us to identify the model without fixing unidentifiable parameters to arbitrary values or without forcing model simplification or, finally, without performing more complex and costly experi-

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ments. This solution is suitable when the information about the unidentifiable parameters is sufficiently detailed.

Even when the model presents an *a posteriori* unidentifiability, a Bayesian approach to the model identification can be an interesting solution. In fact, in this case also, it is possible to solve the problem in a satisfactory way by implementing powerful optimisation algorithms that are able to take into account the prior knowledge of the model parameters.

This paper proposes a Bayesian formulation for compartmental model identification. Moreover, in the Appendix, its possible implementation through a simulation algorithm is discussed, together with some technical details. A second issue focused on in this paper is the combined use of multiple experiments (when they are available) as a further strategy to deal with compartmental model *a posteriori* unidentifiability. As a matter of fact, in biomedical science, several experiments are carried out to evaluate the differences in a substance's kinetics between a reference group (the controls) and one or more 'treated' groups. The basic hypothesis for such a study is that the kinetic parameters in the treated groups have moved away from those of the controls. In other words, the kinetic parameters of the treated subjects are modifications of the corresponding parameters of the controls. Such an assumption can be easily encoded into a Bayesian model. A standard method consists in resorting to a hierarchical structure for the probability densities of the kinetic parameter that can be used to propagate information among different experiments and then among different groups.

In this paper, we propose a more efficient computational strategy, based on the so-called empirical Bayes approach, that allows us to estimate the model parameters from the data of the control group and then to propagate such information among different groups through a prior distribution specification, without building a complex population model.

We apply our method to a study characterised by *a posteriori* identifiability problems, involving the assessment of the thiamine (Th) kinetics in rats under different conditions.

2 Bayesian approach to compartmental model identification

Given a generic compartmental model M, denoting with $\{t_1, t_2, \ldots, t_N\}$ the N instants at which the measurements are collected and assuming that each measurement is affected by noise, we can write the output equation in its input/output form as

$$\boldsymbol{m}_i = M(\theta, \boldsymbol{u}, t_i) + \boldsymbol{v}_i \tag{1}$$

where $\boldsymbol{m}_i$ is the vector of the measurements taken at time t_i, $\boldsymbol{v}_i$ is the vector of measurement errors at time t_i, $\boldsymbol{u}$ are the input variables, and θ are the compartmental model parameters.

The stochastic approach to such an identification problem considers all variables (i.e. experimental data, model parameters, measurement errors) as stochastic variables, described through their probability distributions. In particular, a common assumption is that measurement errors are independently and normally distributed, and that their standard errors are proportional to the measurement values. Therefore we can write

$$\boldsymbol{v}_i \sim N(0, \Sigma_{v_i}) \tag{2}$$

where $\Sigma_{v_i} = \text{diag}((CV^2 \cdot [m_{1_i}^2, m_{2_i}^2, \ldots]))$, diag is the diagonal matrix, and CV is the so-called coefficient of variation. Thus

$$p(\boldsymbol{m}_i|\theta) = N(M(\theta, \boldsymbol{u}, t_i), \Sigma_{v_i})$$

To describe exhaustively the stochastic model, an assumption about the *a priori* distribution of the unknown-parameter vector has to be made. A usual choice leads us to consider the compartmental model parameters θ_i as *a priori* independent and normally distributed, so that

$$\theta_i \sim N(\tilde{\theta}_i, \tilde{\sigma}_i^2) \tag{3}$$

where $\tilde{\theta}_i$, $\tilde{\sigma}_i^2$ are fixed parameters, embedding prior knowledge of the model parameters.

Having defined the probabilistic model, the goal of the Bayesian approach is to obtain the posterior distribution of the compartmental model parameters θ. It is easy to see that

$$\begin{aligned} p(\theta|\boldsymbol{m}_1, \boldsymbol{m}_2, \ldots, \boldsymbol{m}_N) &\propto p(\theta)p(\boldsymbol{m}_1, \boldsymbol{m}_2, \ldots, \boldsymbol{m}_N|\theta) \\ = \prod_{i=1}^{h} p(\theta_i) \prod_{i=1}^{N} p(\boldsymbol{m}_i|\theta) &\propto \prod_{i=1}^{h} \exp\left(-\frac{(\theta_i - \tilde{\theta}_i)^2}{2\tilde{\sigma}_i^2}\right) \\ \times \prod_{i=1}^{N} \exp\left(-\frac{(\boldsymbol{m}_i - M(\theta, \boldsymbol{u}, t_i))^T \Sigma_{v_i}^{-1} (\boldsymbol{m}_i - M(\theta, \boldsymbol{u}, t_i))}{2}\right) \end{aligned} \tag{4}$$

where h is the number of parameters in θ.

Unfortunately, in this case, the posterior distribution of θ cannot be derived in closed form, so that it is necessary to resort to an iterative strategy based on simulations, known as the Markov chain Monte Carlo (MCMC) (GILKS *et al.*, 1996). The MCMC allows us to derive the desired sample posterior distribution and therefore to compute the posterior moments using sample statistics. Details of the computational procedure applied in this paper are reported in the Appendix.

2.1 *Multiple experiments: an empirical Bayes approach*

As discussed in Section 1, let us suppose that K different experiments (denoted by $e_0, \ldots, e_{k-1}$) are available and that e_0 is the experiment carried out on the control group. Generally, there are two possible ways to estimate the compartmental models: either considering each experiment independently or considering all the data 'together'. In the first case, adopting the Bayesian model discussed above, the parameters $\tilde{\theta}_i$ and $\tilde{\sigma}_i^2$ in eqn 3 can be fixed for each experiment at different values in accordance with the prior knowledge.

On the other hand, supposing that the experiments are carried out on a common underlying population, following standard Bayesian statistics, all the experiments are considered jointly, and the parameters $\tilde{\theta}_i$ (and $\tilde{\sigma}_i^2$) are treated as stochastic variables too, drawn from a common probability distribution depending on other hyperparameters (WAKEFIELD *et al.*, 1994). More specifically, a hierarchical model should be built in which $\tilde{\theta}_i$ (and $\tilde{\sigma}_i^2$) are drawn, for example, from a normal distribution with hyperparameters μ and τ. The resulting hierarchical stochastic model allows an information flow from one experiment to the others, without pooling the data together directly. Unfortunately, such an approach turns out to be highly demanding from a computational viewpoint. Thus, in this paper, we propose a more efficient approach based on an empirical Bayes framework (CARLIN and LOUIS, 1996), in which experiments are considered separately, but their θ prior distribution (i.e. the values of $\tilde{\theta}_i$ and $\tilde{\sigma}_i^2$) is chosen in accordance with the θ estimate obtained from another experiment.

In particular, we propose the following strategy:

(*a*) Assuming that the experiment on the control group e_0 can be more easily repeated and that its data set is more complete, choose for e_0 a flat *a priori* distribution (large variance), so that the Bayesian estimate is mainly data driven.

(*b*) Use as prior distribution for the models $e_1, \ldots, e_{k-1}$ the estimate obtained from e_0. In particular, fix $\tilde{\theta}_i$ equal to the point estimate obtained in e_0, and $\tilde{\sigma}_i$ equal to its standard deviation increased, for example, by two times. These

choices express the *a priori* assumption that each model parameter in the treated subjects is close to that of the control group (same mean value), but, as the standard deviation is doubled, that some differences may exist.

(*c*) When the experiments follow a particular design for which a partial order can be derived (i.e. increasing dosages of a drug), it is possible to use a chain scheme for assessing priors, in which the parameter estimates of e_i are used as priors for e_{i+1} instead of using the estimates of e_0 as reference values for all the experiments.

3 Case study: thiamine kinetics

Th, also known as vitamin B_1, is a vitamin that is involved in cellular metabolism in different phosphorylated forms (COOPER and PINCUS, 1979; BETTENDORFF, 1994; RINDI, 1996). In plasma, there are only two forms of this vitamin: Th itself and thiamine monophosphate (ThMP) (RINDI *et al.*, 1968; REGGIANI *et al.*, 1984). Such forms pass through the cell wall with different mechanisms, which can be active or not. Within the cell, they are transformed mainly by reactions of phosphorylation and dephosphorylation. ThPP, the co-enzymatic form, cannot cross the cytoplasmatic membrane and is totally confined inside the cell.

In the present study, we investigated *in vivo* the alterations of Th metabolism induced in rat nervous tissue by three different structural analogues of Th (amprolium, oxythiamine, pyrithiamine) used at different dosages. We explored the sciatic nerve and three brain regions (cerebellum, brainstem and cerebral cortex) characterised by different Th kinetic parameters.

3.1 *Experiment*

The study involved 240 adult Wistar albino rats divided into seven groups (one group of 48 rats for control and a group of 32 rats for each of the six treatments). At appropriate times, a single dose of 30 μg of labelled Th (thiazole-[2^{14}C]Thiamine,^{14}C-Th), corresponding to 1.25 μCi, dissolved in 0.5 ml saline, was given through intraperitoneal injection to rats starved overnight with water ad libitum. Th analogues were administered together with labelled Th to the rats of six treated groups. In particular,

(i) groups 1 and 2 received amprolium in doses, respectively, 100 and 1000 times higher than that of ^{14}C-Th
(ii) groups 3 and 4 received oxythiamine in doses, respectively, 100 and 1000 times higher than that of ^{14}C-Th
(iii) groups 5 and 6 received pyrithiamine in doses, respectively, 10 and 100 times higher than that of ^{14}C-Th.

All the rats, during the day of the injection, received a Th-deficient diet.

The rats were killed by decapitation at fixed time intervals: {0.25, 0.5, 1, 2, 6, 12, 24, 48, 96, 144, 192, 240} h after ^{14}C-Th administration for the control group and {0.25, 0.5, 1, 2, 6,12, 24, 48} h for the treated groups. Blood was collected, and plasma was separated according to RINDI *et al.* (1984). After decapitation, the cerebral cortex, brainstem (medulla and pons), cerebellum and sciatic nerve were dissected according to RINDI *et al.* (1980) and utilised immediately for Th compound determinations.

The number of sampling times for the treated rats was limited owing to the belief, before experiment, that the Th dynamics in rats undergoing analogue treatment was fast enough to be described completely by data collected over 48 h. From an *a posteriori* analysis, it was clear that this hypothesis was wrong and that the slowest time constant was difficult to derive from the collected data. However, because of cost problems, it was decided not to repeat the experiment.

At each scheduled time, four rats from each group were killed, and measurements were taken. Then, following the *naive pooled data* approach (a method of estimating mean (population) pharmacokinetic parameters from data collected in a population, by first averaging the concentration at each time point and then fitting a model to the averaged data), at each time point, the mean value of the four measurements was computed and then the set of all the mean values was considered as coming from a single (mean) subject to fit a (mean) Th kinetic model. Obviously, this approach neglects the intra-individual variability, which, in any case, was limited by the fact that the rats were genetically similar.

3.2 *Compartmental model of thiamine kinetics*

A compartmental model for Th kinetics in nervous tissue has been already proposed and widely discussed (RINDI *et al.*, 1984; 1987; PATRINI *et al.*, 1993; NAUTI *et al.*, 1997) and is reported in Fig. 1.

This model uses three compartments to represent the intracellular pools of Th (pool 1), ThPP (pool 2), ThMP (pool 3) and two compartments to describe Th (pool 6) and ThMP (pool 7) in plasma. It assumes that ThPP is produced only by pyrophosphorylation and that ThPP is dephosphorylated in two steps: the first one produces ThMP, and the second produces Th. The intracellular biochemical reactions involving Th phospho-esters are

$$Th \overset{ThPk}{\Rightarrow} ThPP \overset{ThPPase}{\Rightarrow} ThMP \overset{ThMPase}{\Rightarrow} Th$$

Moreover, the compartmental model includes two delay compartments (pools 4 and 5) to describe the plasmatic Th and ThMP flow into the cells (REGGIANI *et al.*, 1984). Finally, a loss in the Th and ThMP compartments models the Th and ThMP exit from the tissues by their release into the plasma or by their metabolism to molecular forms not recognisable as Th or its phospho-esters.

3.2.1 *Mathematical formulation of the compartment model:* In our tracer experiment, in accordance with RINDI *et al.* (1984), PATRINI *et al.* (1993) and NAUTI *et al.* (1997), we can assume

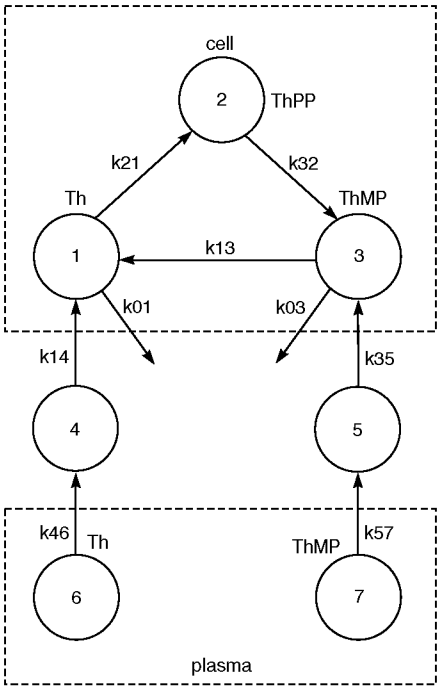

Fig. 1 *Compartmental model of thiamine kinetics in nervous tissues (from RINDI et al. (1984))*

that all transfer processes between different compartments are linear. In fact, although in general these transfer processes can also be intrinsically non-linear, in our case the (local) linearity assumption is allowed, the concentration of the labelled compounds being very low. Then, the compartmental model of Fig. 1 is described by the following system of differential equations:

$$\frac{dq_1(t)}{dt} = k_{14}q_4(t) + k_{13}q_3(t) - (k_{21} + k_{01})q_1(t) \quad (5)$$

$$\frac{dq_2(t)}{dt} = k_{21}q_1(t) + k_{32}q_2(t) \quad (6)$$

$$\frac{dq_3(t)}{dt} = k_{35}q_5(t) + k_{32}q_2(t) - (k_{13} + k_{03})q_3(t) \quad (7)$$

$$\frac{dq_4(t)}{dt} = k_{46}q_6(t) - k_{14}q_4(t) \quad (8)$$

$$\frac{dq_5(t)}{dt} = k_{57}q_7(t) - k_{35}q_5(t) \quad (9)$$

where t is the time (h), and q_i is the concentration (nCi ml^{-1} in plasma and nCi g^{-1} in cells) of the labelled Th in the ith compartment. As, in our experimental setting, pools 1, 2, 3, 6, 7 are sampled, whereas pools 4 and 5 are not measurable, the dynamic system of eqns 5–9 can be rewritten in a more synthetic way

$$\boldsymbol{y}(t) = M(\theta, \boldsymbol{u}, t) \quad (10)$$

where $\boldsymbol{y}(t) = [q_1(t), q_2(t), q_3(t)]^T$ (i.e. the quantity of intracellular ^{14}C-Th, ^{14}C-ThPP and ^{14}C-ThMP for unit mass of tissue), $\boldsymbol{u}(t) = [q_6(t), q_7(t)]^T$ (i.e. the plasma concentration of ^{14}C-Th and ^{14}C-ThMP), M is the Th kinetic model expressed by eqns 5–9, and $\theta = [k_{01}, k_{03}, k_{21}, k_{32}, k_{13}, k_{14}, k_{46}, k_{35}, k_{57}]^T$ is the vector of the model parameters.

3.3 *Identification of thiamine kinetic model*

Given the compartmental model of Fig. 1 and the data set, the goal of our analysis was to investigate how, for each of the four nervous tissues, the compartmental parameters (and then the Th kinetics) change in the seven different groups of rats.

First of all, we checked successfully the *a priori* identifiability of the compartmental model of Fig. 1 with respect to our experimental setting using a software tool called global identifiability (GLOBI) (AUDOLY *et al.*, 1998).

After this preliminary step, we tried to identify the compartmental model using standard methods (e.g. non-linear least squares or maximum likelihood) implemented in commercial software packages, as SAAM II (SAAM INSTITUTE, INC., 1997). Unfortunately, because of the complexity of the model (nine parameters) and the limited number of experimental data available in analogue treated rats (eight data), these algorithms were not able to find satisfactory solutions. In fact, in a large number of cases, the minimisation algorithm was not able to converge to a solution, or, in some cases, it proposed a solution that unfortunately represented only a local minimum of the cost function and not the global one; this problem was identified by obtaining different solutions starting from different points in the parameter space. These reasons prompted us to adopt the methodology proposed in Section 2.

3.4 *Results*

All 28 compartmental models (four nervous tissues in seven groups of rats) have been identified successfully with the procedure proposed in the paper. In particular, in accordance with the empirical Bayesian approach presented here, the *a priori* distribution for θ in the control group was assumed to be 'not informative' (i.e. a very large variance was adopted: $\tilde{\theta}_i = 0.5$ and $\tilde{\sigma}_i = 10$), so that the estimation procedure was completely driven by data. The *a priori* distribution for θ in the groups treated with analogues at the lowest dosage (groups 1, 3 and 5) was set on the basis of the estimates obtained in the controls, whereas the distribution in the groups treated with analogues at the highest dosage (groups 2, 4 and 6) was set on the basis of the estimates obtained in the corresponding low-dosage groups.

By using the MCMC algorithm reported in the Appendix, after 40 000 runs we obtained the joint sample posterior distributions of the parameters, and we computed the first and second moments and the 95% confidence intervals for each kinetic parameter. For example, Fig. 2 shows the posterior distributions of the model parameters related to phosphorylation (k_{21}) and dephosphorylation (k_{32}, k_{13}) in the cerebellum of control rats (group 7).

Interesting information can be derived about the action of the analogues on phosphorylation and dephosphorylation (k_{21}, k_{32}, k_{13}) and on the uptake of Th.

To extract, from all these data (252 marginal posterior distributions), some physiological information about the action of the analogues on phosphorylation and dephosphorylation (k_{21}, k_{32}, k_{13}) and on the uptake of Th, a number of analyses have been performed. To illustrate the discussion, we report the results related to the control (group 7) and oxythiamine groups (3 and 4) in the brainstem (see Table 1).

(*a*) The effect of the analogue on a parameter is considered statistically significant if the confidence intervals of the parameter estimate before and after the treatment do not overlap. Using this approach, we can say that, for example, oxythiamine certainly increases the dephosphorylation rate from ThPP to ThMP (k_{32}), and that progressively higher doses induce a corresponding increase in the rate. However, the dephosphorylation rate from ThMP to Th (k_{13}) and the phosphorylation rate (k_{21}) do not increase significantly in the treated rats.

(*b*) To evaluate the effect of the analogue on the uptake of Th, it is necessary to recall the meaning of the variation of the two compartmental parameters k_{14} and k_{46}

  (i) pool 4 (see Fig. 1) is introduced to model the transport through the cellular membrane. In particular, the transfer function from pool 6 and pool 1 is a low-pass filter

$$H(s) = \frac{k_{46}k_{14}}{s + k_{14}}$$

  (ii) k_{14} is the pole of the low-pass filter
  (iii) k_{46} is the static gain that describes the low-frequency spectral characteristics
  (iv) $k_{46}k_{14}$ is the transfer constant of the system that can be viewed as an instant gain at high frequencies.

In the light of the remarks mentioned above, we can observe in Table 1 that, under oxythiamine treatment at high doses, k_{14} increases, so that the transport rate of Th from plasma into cells increases too. However, k_{46} decreases considerably, so that the total amount of Th going into the cerebellar cells after a low-frequency input of Th in plasma, for example after a meal, is reduced with respect to that of the control rats. Finally, the transfer constant is decreased: this means that lower quantities of Th flow instantaneously into the brainstem cells after a high-frequency variation in Th plasma concentration. Of course, similar considerations can be addressed to the ThMP uptake mechanism. However, in the following, we consider only Th, its uptake being the most relevant input in the cell.

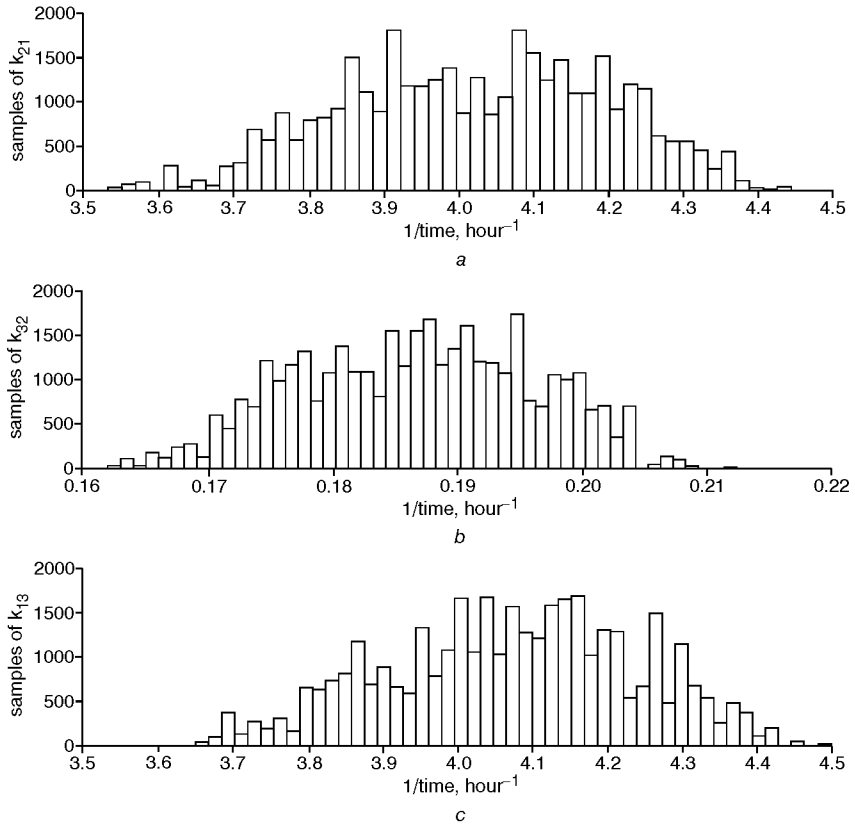

Fig. 2 *Posterior distribution of intracellular phosphorylation and dephosphorylation parameters in cerebellum of control rats. (a) Phosphorylation; (b) dephosphorylation: first step; (c) dephosphorylation: second step*

Table 1 Parameter estimates of Th compartmental model Fig. 1 in brainstem tissue for group 7 (control), group 3 (treated with low oxythiamine dosage) and group 4 (treated with high oxythiamine dosage). For each parameter, mean, standard deviation and lower and upper bound of 95% confidence intervals (respectively the 2.5 and 97.5 percentile of the posterior distribution) are reported

	k_{01}	k_{03}	k_{21}	k_{32}	k_{13}	k_{14}	k_{46}	k_{35}	k_{57}	$k_{14} \cdot k_{46}$	$k_{35} \cdot k_{57}$
Group 7											
Mean	0.0422	0.315	7.82	0.233	1.72	0.513	0.606	0.21	0.271	0.311	0.0563
Standard deviation	0.0538	0.0173	0.336	0.0119	0.0859	0.0221	0.0208	0.022	0.0281	0.0108	0.00318
Median	0.0186	0.314	7.83	0.233	1.71	0.512	0.606	0.209	0.269	0.311	0.0563
2.5%	0.000983	0.28	7.12	0.209	1.54	0.468	0.566	0.17	0.219	0.289	0.0503
97.5%	0.193	0.348	8.45	0.256	1.88	0.556	0.65	0.256	0.333	0.333	0.0626
Group 3											
Mean	0.0209	0.223	8.18	0.42	1.95	0.466	0.61	0.439	0.611	0.283	0.268
Standard deviation	0.0236	0.0112	0.263	0.0151	0.0735	0.0265	0.0286	0.0217	0.0255	0.0121	0.0103
Median	0.0119	0.224	8.18	0.42	1.94	0.466	0.609	0.438	0.61	0.283	0.268
2.5%	0.000712	0.2	7.7	0.392	1.8	0.416	0.552	0.399	0.562	0.259	0.249
97.5%	0.0908	0.246	8.68	0.448	2.08	0.519	0.664	0.483	0.664	0.306	0.288
Group 4											
Normal	0.0367	0.22	7.27	0.551	1.74	0.656	0.369	0.583	0.414	0.242	0.241
Standard deviation	0.0319	0.0116	0.193	0.0166	0.0553	0.039	0.0182	0.0303	0.0197	0.0106	0.00885
Median	0.0266	0.222	7.27	0.551	1.74	0.656	0.37	0.582	0.414	0.241	0.241
2.5%	0.0013	0.193	6.87	0.518	1.62	0.581	0.336	0.524	0.378	0.222	0.224
97.5%	0.111	0.239	7.64	0.583	1.85	0.734	0.403	0.643	0.452	0.264	0.259

From this analysis, the following general conclusions can be drawn.

Phosphorylation and dephosphorylation: As is apparent from the value of the labelled Th compounds in the cell, the effect of all the analogues is to create a cellular Th deficiency. However, different analogues have different effects on the phophorylation/dephosphorylation reactions: oxythiamine causes, in every tissue, an increase in the transfer rate from ThPP to ThMP (k_{32}) and, in almost all regions (excluding the brainstem), an increase from Th to ThPP (k_{21}); amprolium decreases k_{21} and increases k_{32} in all the regions apart from the sciatic nerve, where k_{32} is also decreased; finally, pyrithiamine decreases all the transfer constant values.

Thiamine uptake: In rats treated with oxythiamine, the high-frequency gain $k_{14} \cdot k_{46}$ is unchanged after analogue administration. In contrast, in amprolium-treated rats, the static gain k_{46} and the product $k_{14} \cdot k_{46}$ are decreased with respect to those of normal rats. Pyrithiamine has the same effect as amprolium; the only difference is related to the sciatic nerve, in which the product $k_{14} \cdot k_{46}$ is maintained nearly constant.

Overall thiamine metabolism: The reduction in Th contents in tissues, induced by oxythiamine administration, is partially compensated by an increase in the rate of Th intracellular metabolism. Its mild effect is confirmed by the value of the product $k_{14} \cdot k_{46}$, which is unchanged or only slightly changed after analogue administration. Amprolium and pyrithiamine have stronger effects on Th metabolism, with a decrease in the static gain of Th uptake (k_{46}) and a consequent reduction in the product $k_{14} \cdot k_{46}$. The strongest effect was found in pyrithiamine-treated rats. The velocity of intracellular biochemical reactions is progressively lowered, regardless of the analogue administered. Finally, the sciatic nerve shows a slightly different behaviour compared with the other tissues. In fact, the Th metabolism is progressively decreased with the increase in the analogue dose, even in oxythiamine-treated rats. Moreover, the sciatic nerve seems to maintain the same capability of taking up Th, even in pyrithiamine-treated rats. However, this fact may be due to the relatively low content of (labelled and unlabelled) Th present in the sciatic nerve, even in normal rats, or to the different role of this tissue, which is part of the peripheral nervous system.

Finally, as an example, Fig. 3 shows the data fitting for the concentrations of labelled Th, ThPP and ThMP in the brainstem for groups 7, 3 and 4. It highlights clearly some problems related with the model identification: the slowest time constants of the dynamics in treated rats are not easily derivable from the data, because of the reduced sample size. Although not shown, for simplicity, the reconstructed curves are always provided with their posterior distributions that allow us to derive soundly the reliability of the estimates.

4 Conclusions

In this paper, we have proposed a methodology for the identification of compartmental models within a Bayesian framework. It allows us to cope successfully with identification problems in particularly critical contexts. It offers three main advantages

(*a*) the possibility of including *a priori* information about model parameters (this solution is particularly interesting when the data set is poor and/or *a posteriori* identifiability problems occur)
(*b*) ability to derive the correct (also asymmetric) confidence intervals for the estimated parameters of the model
(*c*) the necessity of making explicit all the statistical hypotheses under which the obtained results are valid.

Moreover, for what concerns point (*a*) in this paper, we have suggested an interesting strategy to propagate the information between different experiments following an empirical Bayesian approach. This solution is particularly appealing when, to limit the computational time in a reasonable way, we cannot build a full population model considering all the experiments together.

The methodology presented here can be applied to a variety of areas of medicine, where problems with model identification could be found. In this paper, we have applied our methodology to a complex identification problem, concerning Th kinetics, that was affected mainly by two different difficulties: first, few measurements were available in each pool for analogue-treated subjects; in particular, the lower dynamics components were missed in the treated rats. Secondly, data came from 'destructive experiments' and therefore from different subjects; this is a source of variability embedded in the experimental data. In this particularly difficult context, the application of classical approaches to compartmental model identification did not allow us to obtain useful results. Thanks to our proposed Bayesian approach, it was possible to overcome all the identifiability problems and to address physiologically relevant conclusions by comparing the results obtained for a large number of Th kinetic models related to the different nervous tissues.

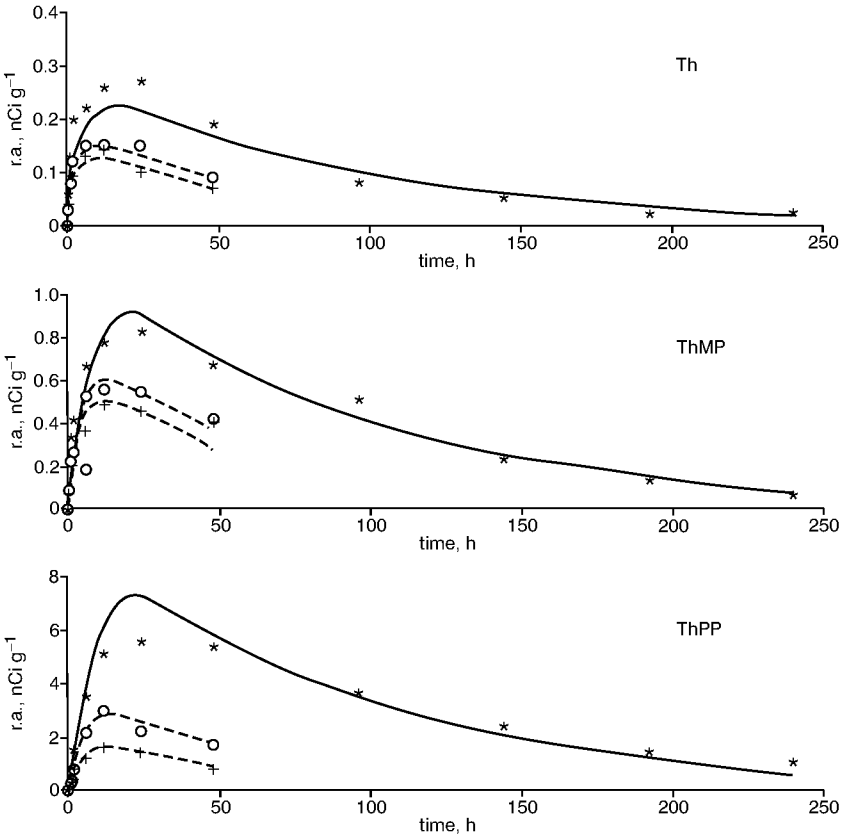

Fig. 3 *Measured and estimated (a) Th, (b) ThMP and (c) ThPP concentrations in brainstem after intraperitoneal injection of bolus of ^{14}C-Th in (*–*–*) control rats, (○ ○ ○) rats treated with low dosage of oxythiamine and (+–+–+) rats treated with high dosage*

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Appendix

MCMC algorithms are based on two fundamental steps: the generation of a Markov chain and a subsequent Monte-Carlo integration. The first step is performed thanks to a theorem that allows us to generate a Markov chain that converges in distribution to a 'target' distribution (e.g. the posterior distribution) by sampling from a convenient probability distribution. The second step uses Monte-Carlo integrations of the Markov chain to derive the desired posterior moments. The MCMC methods differ from each other in the way the Markov chain is created.

In this paper, we adopted a single-component Metropolis–Hastings (BELLAZZI *et al.*, 1997; MAGNI *et al.*, 1998). In particular, the scheme proposed for the Th study generates the Markov chain drawing samples iteratively for the compartmental parameters θ_i, as follows:

(i) a candidate sample $\hat{\Theta}_i$ is extracted from a proposed distribution q

$$q(\hat{\Theta}_i|\Theta_i^{(cur)}) = N(\Theta_i^{(cur)}, \max(0.6\Theta_i^{(cur)}, 0.005))$$

where $\Theta_i^{(cur)}$ is the current sample of the chain for the ith element of θ

(ii) the vector $\hat{\Theta}$ is built by updating the ith element of current sample $\Theta^{(cur)}$with the proposed sample $\hat{\Theta}_i$

(iii) the proposed sample is accepted with probabilities

$$\alpha = \min\left(1, \frac{f(\hat{\Theta})q(\Theta_i^{(cur)}|\hat{\Theta}_i)}{f(\Theta^{(cur)})q(\hat{\Theta}_i|\Theta_i^{(cur)})}\right)$$

where the function f is

$$f(\beta) = \exp\left(-\frac{(\beta_i - \tilde{\theta}_i)^2}{2\tilde{\sigma}_i^2}\right) \times \prod_{i=1}^{N} \exp\left(-\frac{(\boldsymbol{m}_i - M(\beta, \boldsymbol{u}, t_i))^T \Sigma_{v_i}^{-1} (\boldsymbol{m}_i - M(\beta, \boldsymbol{u}, t_i))}{2}\right)$$

where β_i is the ith component of β

(iv) if the candidate is accepted, it becomes the ith component of the new sample of the chain ($\Theta_i^{(new)} = \hat{\Theta}_i$), otherwise the ith component of the new sample of the chain is like the old one ($\Theta_i^{(new)} = \Theta_i^{(cur)}$).

This procedure has to be repeated for each θ_i to generate a whole sample of the Markov chain; of course, a suitable number of samples are required to ensure the convergence of the chain and a good description of the target distribution. To determine this number, we applied the criterion proposed by RAFTERY and LEWIS (1996). It is important to note that the step (iii) of the algorithm requires us to solve the differential eqns 5–9 several times for each run of the MCMC scheme. This is obviously very expensive in terms of the computational efforts required by the algorithm.

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