Using QR to solve quantitative modeling problems: an application to intracellular thiamine kinetics

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Abstract

Recent works carried out within the Qualitative Reasoning (QR) research framework are centred on the exploitation of QR techniques to address the problem of quantitative System Identification (SI) with the goal to enhance the overall process, namely the selection of a proper model identifier and the parameter estimation procedure. Traditional SI, both parametric and non-parametric, may be really problematic for those application domains, such as the medical/physiological one, of which either the available knowledge is incomplete or the structural model is not identifiable or the observed data are poor in number and in quality. This paper deals with the application of an hybrid method, which builds a fuzzy system identifier upon a qualitative structural model, to solve identification problems of the intracellular kinetics of Thiamine (vitamin B_1). The model obtained is not as much informative as a purely structural one but robust enough to be used as a simulator, and then to provide physiologists with a deeper understanding of the Thiamine metabolism in the cells.

Introduction

The identification of quantitative structural models of the dynamics of complex real-world systems offers potential benefits to the deep comprehension of the system at study as well as to the performance of certain tasks. If we focus our attention on physiology and medicine, such models provide a concise description of complex dynamics, allow for the calculation of physiological quantities that can not be directly measured, allow the physiologist to formulate hypotheses dealing with the physiological and biochemical structure of the system, help the clinician to formulate and test diagnostic hypotheses as well as to plan therapeutical treatments. Unfortunately, structural modeling of a large number of patho-physiological mechanisms may be hampered by the incompleteness of the available knowledge of the underlying nonlinear dynamics. In such cases, the system dynamics is often studied under the hypothesis that minimal perturbations affect the system, that is under the linearity assumption. Although the resulting model captures limited aspects of the system dynamics, it may give useful information; nevertheless, also the linear formulation may be prohibitive as identifiability problems may occur.

In theory, a valid alternative to structural modeling, although potentially less informative, could be represented by non-parametric black-box modeling approaches to SI (Jang 1993; Khannah 1990; Wang 1994). But, in practice, such models, which learn the nonlinear dynamics of the system from input-output data, result to be very inefficient and not robust when the available experimental data are poor either in number or in quality. Such a situation is not rare in the fields of physiology and medicine.

Motivated by these considerations, we started a project which aims at the design and implementation of an efficient and robust method capable to make the most of both the available structural knowledge and the observed data. The method, that we call FS-QM, is domain-independent and results from the integration of qualitative models, namely QSIM models, and fuzzy systems (Bellazzi et al. 1998; Bellazzi, Guglielmann & Ironi 1999). As both frameworks have been introduced to cope with the complexity of real-world systems, their combination should benefit from the analytical power of the former one as well as from the approximation properties of the latter.

In outline, the method exploits the incomplete structural knowledge to build a QSIM model of the system dynamics, and then it infers, through simulation, all of its possible behaviors. The set of behaviors is mapped, in accordance with the a priori expert knowledge, into a fuzzy rule-base, where each rule may be seen as a measure of the possible transition from states to the next ones. The mathematical interpretation of such a rule-base properly defines and initializes a nonlinear functional approximator, which is then tuned to the experimental data. The emphasis of this paper is rather on applicative aspects than on methodological issues. We discuss the identification problems which arise from modeling a system in the physiological domain, the intracellular thiamine kinetics, and the solutions given by the application of our method (Bellazzi et al. 1998; Bellazzi, Guglielmann & Ironi 1999). The comparison of our results with those obtained by means of a traditional application of fuzzy systems to SI (Wang 1994) highlights the good performance of our method when applied to derive a simulator of the thiamine kinetics in the intestine cells. The significant improvement in terms of efficiency and robustness of FS-QM over traditional methods is due to the good initialization of both the structure of the fuzzy identifier and its parameters built by

encoding the system dynamics captured by its qualitative behaviors (Bellazzi, Guglielmann & Ironi 2000).

For the sake of completeness, let us remark that the idea of exploiting QR techniques for SI is not new within the QR community. Most of the work done addresses the problem of the automation of the traditional process of SI, that is the automation of both structural identification and the choice of the most appropriate numerical techniques for parameter estimation and their initialization (Bradley, Stolle 1996; Bradley, O'Gallagher & Rogers 1997; Easley, Bradley 1999; Capelo, Ironi & Tentoni 1996; Capelo, Ironi & Tentoni 1998; Ironi, Tentoni 1998). Another piece of work deals with a method for SI capable to deal with states of incomplete knowledge (Kay, Rinner & Kuipers 1999) in which both the candidate model space and the stream of observations are defined semi-quantitatively. What distinguishes this piece of work from the other ones is its capability to deal with systems characterized by both incomplete structural knowledge and poor stream of data.

Modeling problems in the physiological/medical domain

The application of mathematical modeling techniques to the study of a wide spectrum of metabolic and endocrine processes has been largely described in the literature (Carson, Cobelli & Finkenstein 1983). A metabolic system may be essentially viewed as a system of chemical reactions and transport processes controlled by substances produced by the endocrine system. The description of the dynamics of such systems, even in the most simple cases, is a really complex task, and it has been made tractable by the compartmental modeling methodology (Atkins 1974; Jacquez 1972). Within this framework, a system is decomposed into a finite set of subsystems, called *compartments*, and the compartments interact either with each others or with the environment [1] by exchanging material.

A compartment is fundamentally an idealized store of a substance, which may often be adequately assumed homogeneously distributed. The transfer of material through the system that occurs by physical transport or chemical reactions is represented as transfer from one compartment to another. The model equations are expressed by Ordinary Differential Equations (ODE) in terms of the state variables of the system, denoted by $x_i(t)$, that represent the concentration or amount of substance in the $i-$th compartment which exchanges matter with other compartments at time t. Then, the rate of change of each $x_i(t)$ is based on the mass balance law:

$$\dot{x}_i = f_{i0} + \sum_{\substack{j=1 \\ j\neq i}}^{n} f_{ij}(x_j) - \sum_{\substack{j=1 \\ j\neq i}}^{n} f_{ji}(x_i) - f_{0i}(x_i) \quad (1)$$

where $\dot{x}_i$ denotes the time derivative of x_i; f_{ij} denotes the rate of mass transfer into the $i-th$ compartment from the $j-th$ compartment. In general, the transfer of material depends on the quantity or concentration of material in the source compartment and may also be dependent on the quantity or concentration in some other compartments, that is:

$$f_{ij} = f_{ij}(x_j; x_l, x_m, ...) \quad (2)$$

where x_j denotes the state variable of the source compartment, whereas x_l, x_m, .. indicate the variables controlling f_{ij}. The mathematical model of a compartmental structure then consists of a set of ODE's which are fully defined when the functional relations (2) are explicitly stated. Mostly, given the complexity of the processes dealt with, such relations are naturally nonlinear, and their definition may very often be intractable due to the incompleteness of the available knowledge. However, for systems intrinsically nonlinear, a linearity assumption ($f_{ij}(x_j) = k_{ij}x_j$) may be reasonably adopted when the observed dynamics is obtained in response to a small-signal perturbation around the system steady-state condition produced by the administration of a tracer material. The next step in the system identification process deals with the estimation of the unknown parameters from data. Also in the linear case, this step may be critical if the *a priori* identifiability condition is not satisfied, that is, if from the ideal data that the experiment would generate it is not possible to determine uniquely the theoretical estimate of the unknown parameters. However, as real data are not noise-free, theoretical identifiability does not guarantee that the estimation results are accurate enough to identify a good model of the system dynamics, i.e. *a posteriori identifiability*. A model can be considered valid, and then give useful information if the identifiability conditions are satisfied. Methods for testing both a priori and a posteriori identifiability are discussed in the literature (Cobelli, DiStefano III 1980, Ljung 1987).

The intracellular thiamine kinetics: Identification problems and solutions

Thiamine (Th), also known as vitamin B_1, is one of the basic micronutrients present in food and essential for health. In particular, Th is contained in dried yeast, meat, nuts, legumes and potatoes. Within the cells, Th participates in the carbohydrate metabolism, in the central and peripheral nerve cell function and in the myocardial function. Deficiency of Th causes beriberi with peripheral neurologic, cerebral and cardiovascular manifestations (Merck Sharp and Dohme 1987). More in detail, after its absorption in the intestinal mucosa, Th is released into plasma for the distribution to the other tissues, either in its original chemical form (Th) or in a mono-phosphorilated one (ThMP). Th is transported through the cell membrane by means of an enzyme-mediated mechanism, and is then directly transformed into a higher energy compound, Thiamine Piro-Phosphate (ThPP); ThPP is dephosphorylated into ThMP, and it is in equilibrium with Thiamine Tri-Phosphate (ThTP). ThPP is the active element that participates in the carbohydrate metabolism. The chemical reactions occurring within the cells are described in Fig. 1.

Identification of the structural model

Since early 80's several studies have been carried out to quantitatively assess the Th metabolism in the cells (Rindi

[1] indicated as compartment 0

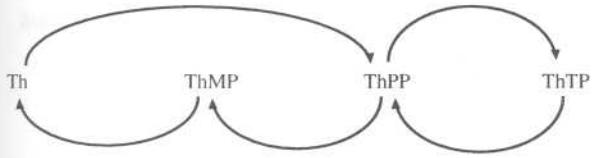

Figure 1: The chemical pathway of Th within cells. Th transforms into ThPP; ThPP transforms into ThMP, that is transformed back into Th. ThPP also transforms in a reversible way into ThTP.

et al. 1980; Rindi et al. 1992). All these studies were performed on rats, and had the basic goal to quantitatively define the normal and pathological conditions underlying Th chemical transformations and cellular uptake and release. Since the Th metabolism is intrinsically nonlinear, the first exploratory approach to its quantitative characterization consists in its analysis around the steady state conditions. Therefore, from an experimental viewpoint, all these studies were based on tracer experiments, in which a small amount of labeled (radio-active) Th was injected in plasma or in peritoneum; the specific activity (radioactivity per gram) of labeled Th was subsequently measured in plasma and in the cells. From a modeling viewpoint, a linear compartmental model has been used to study the Th kinetics in several organ tissues, with particular reference to the nervous ones. Let us observe that the ThTP form can be neglected in the model. As a matter of fact, the fast chemical pathway between ThPP and ThTP and the relatively low concentration of ThTP allows us to consider ThTP in equilibrium with ThPP. Then, the model, whose structure is shown in Fig. 2, is described by the following ODE's:

$$\dot{x}_1 = k_{14}x_4 + k_{13}x_3 - (k_{01} + k_{21})x_1 \quad (3)$$

$$\dot{x}_2 = k_{21}x_1 - k_{32}x_2 \quad (4)$$

$$\dot{x}_3 = k_{32}x_2 + k_{35}x_5 - (k_{03} + k_{13})x_3 \quad (5)$$

$$\dot{x}_4 = k_{40}u_1 - k_{14}x_4 \quad (6)$$

$$\dot{x}_5 = k_{50}u_2 - k_{35}x_5 \quad (7)$$

where x_1 is the intracellular Th, x_2 is the intracellular ThPP, x_3 is the intracellular ThMP, x_4 is the quantity of Th in the cell membrane while x_5 is the quantity of ThMP in the cell membrane; u_1 is the plasmatic Th and u_2 is the plasmatic ThMP. Finally, the parameters k_{ij} are the transfer coefficients to be estimated from data. As a matter of fact, the compartments denoted by 4 and 5 are fictitious as they do not correspond to any chemical form of Th, but they are just used to model the absorption process of Th in the cells. The model (3-7) proved to satisfy a priori identifiability conditions when a bolus injection in plasma is delivered.

The same model and the same experimental setting were applied to study the intestine tissue metabolism in normal subjects and in subjects suffering from diabetes (one of the main disfunctions of carbohydrate metabolism), both treated and non treated rats. In this case, the main purpose of the study was to quantitatively evaluate the differences in the transfer constants and turnover rates in the three different classes of subjects; on the basis of this evaluation it would also be possible to understand if insulin treatment is able

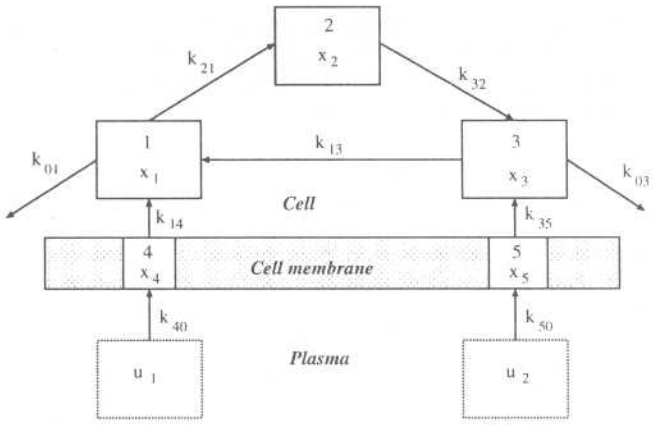

Figure 2: The compartmental model of the Th metabolism within cells. The inputs of the system are the quantity in plasma of Th and ThMP (measured as the concentrations u_1 and u_2, respectively). The flows between the quantity x_1 (Th), x_2 (ThPP) and x_3 reflects the chemical pathway described in Figure 1.

to re-establish quasi-normal conditions in Th metabolism. Unfortunately, the compartmental model identification was unsuccessful, even using different optimization techniques, ranging from standard nonlinear estimation procedures to Bayesian ones. This results in an a posteriori unidentifiability of the model. The main reason of this failure may be explained by the intrinsical problems related to the experimental setting: as mentioned before, the intracellular labeled Th is measured after a bolus in plasma. However, the physiological Th pathway in the intestine tissue presents a Th *absorption* way directly from the intestinal mucosa and a subsequent *release* into the plasma tissue. On the contrary, it is completely unknown how the Th quantity is physiologically absorbed by intestine cells from plasma, and also how such absorption is regulated. Therefore, the linearity assumption for the transport process from plasma into cells results to be completely inadequate. This problem hampers the use of compartmental modeling techniques for analyzing the data, and, at a first glance, the use of the data themselves. This is particularly dramatic for this kind of experiments: at each sampling time four rats are sacrificed, and a single measurement is derived as the mean of the four subjects. The efforts and costs of the experimental setting motivate the exploitation of other techniques for data modeling.

The need for a novel approach

An alternative solution to structural identification is to resort to the so-called "non-parametric" modeling methods. This term is somehow misleading, since the models are always characterized by a set of equations and parameters; however, such parameters do not have a precise physical meaning, and this gives the reason for the "non-parametric" wording. The non-parametric methods aim at reproducing the functional relationships between the observable variables only on the basis of the available data, without requiring knowledge on the physiological system at hand. In our case, due to the complexity of the problem, a natural choice is to exploit

nonlinear dynamic discrete models, known as Nonlinear AutoRegressive models with eXogenous inputs (NARX). In such a framework the system dynamics of an output variable y is described by the input-output equation[2]:

$$y_{k+1} = f(y_k, \ldots, y_{k-l}, \underline{u}_k, \ldots, \underline{u}_{k-h}) \qquad (8)$$

where $\underline{u} \in \Re^{n-1}$ and $y \in \Re$ are discrete-time sequences, l and h are known observability indexes, and the function $f(\cdot)$ is in general unknown. Assuming $l = h = 0$, equation (8) may be written as follows:

$$y_{k+1} = f(\underline{x}_k), \quad \text{where } \underline{x}_k = \{y_k, \underline{u}_k\}$$

In this context, methods recently proposed to find a function approximator of f are Feed-forward Neural Networks, Radial Basis Functions, Wavelet Functions, Fuzzy Systems. However, to build f with the desired accuracy only from the observations, all these approximation schemes usually require sufficiently large data sets . As far as our application is concerned, such schemes cannot be applied, since no more than 17 measurements are available for each Th chemical form. Moreover, the identification problem is a nonlinear one: the treatment of nonlinear problems is not straightforward and demands some prior information to properly state a reasonable initial guess on the parameter values, and then to get convergence to their optimal estimate. The methods mentioned above, except Fuzzy Systems (FS), are not capable to embed prior knowledge, and therefore the initial values of the parameters are randomly chosen. In this setting, the adoption of a non-parametric model able to exploit also the available structural knowledge seems the natural solution for effectively coping with the problems mentioned above. As a matter of fact, FS's are able to embed the a priori knowledge of the domain under the form of inferential linguistic information, called Fuzzy Rules (FR), but in practice, the information in the linguistic form about a complex system is often poor or unavailable, and then the function f is usually inferred only from the data.

This paper deals with the application of an hybrid method (Bellazzi, Guglielmann & Ironi 2000), based on the integration of QSIM models (Kuipers 1994) and FS's (Wang 1994), called FS-QM, which builds a fuzzy identifier upon the available a priori knowledge. The idea underlying our method is simple: the set of behaviors $\{B_1, .., B_m\}$ generated by the simulation of a QSIM model of the system at study is mapped into M FR's which, as a whole, capture the structural and behavioral knowledge of the system dynamics. As a matter of fact, such a mapping is possible whenever the available knowledge allows us to define a bijective mapping between the quantity-space Q_L, in the QSIM representation, and the fuzzy-quantity space Q_F, whose elements are fuzzy sets. In outline, the main steps of the method are sketched in Fig. 3.

The mathematical interpretation of the generated rules, through suitable fuzzy operators, such as the *singleton fuzzifier*, the *product inference rule*, the *center average defuzzifier*, and the characterization of fuzzy sets by *Gaussian membership functions*, allows us to initialize the approximator $\tilde{f}_0$

[2] Without loss of generality we consider here nonlinear Multiple Input-Single Output systems

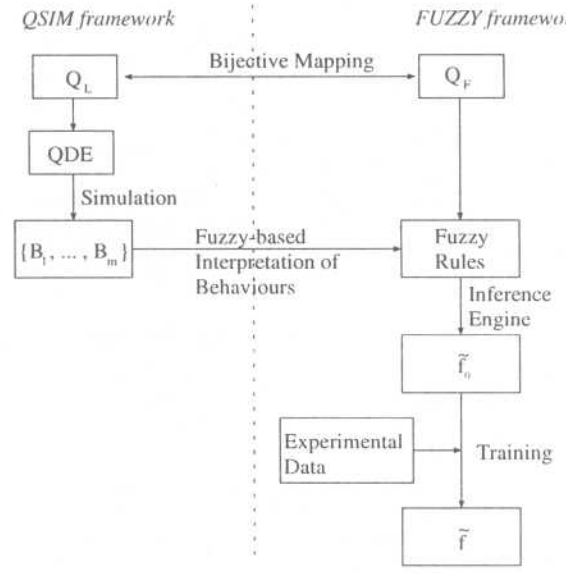

Figure 3: Main step of FS-QM.

of f:

$$\tilde{f}_0(\underline{x}) = \frac{\sum_{j=1}^{M} \hat{y}^j [\prod_{i=1}^{n} exp(-(\frac{x_i - \hat{x}_i^j}{\sigma_i^j})^2)]}{\sum_{j=1}^{M} [\prod_{i=1}^{n} exp(-(\frac{x_i - \hat{x}_i^j}{\sigma_i^j})^2)]} \qquad (9)$$

where: $\{\hat{x}_i^j\}$ and $\{\sigma_i^j\}$ are the parameters characterizing the Gaussian membership function which is related to the input variable x_i and appears in the j-th rule, $\hat{y}^j$ is the point where the membership function of the output, or equivalently of the consequent, in the j-th rule reaches its maximum value. Such an expression allows us to interpret the nonlinear function approximation problem with a FS as the process of tuning on a set of data the vector of parameters $\underline{\theta} = \{\underline{\hat{y}}, \underline{\hat{x}}, \underline{\sigma}\}$, initialized by the vector $\underline{\theta}_0$ in equation (9). The approximator derived in equation (9) is known to possess the universal approximation property, i.e. the capability of approximating any continuous function with an arbitrary degree of accuracy (Wang 1994).

A non-parametric model of Thiamine kinetics

Although a complete knowledge on the mechanism of Th transport in the intestine cells from plasma is not known, the overall structure of the model in Fig. 2 still remains valid: the fluxes and the compartments in plasma and in the cells reflect the available information on the system. On the contrary, the number of compartments that model the membrane and the functional relationships describing the cellular absorption are not completely known. Therefore, we can ignore the compartments 4 and 5, and consequently the equations (6-7), and directly model the plasmatic Th absorption process.

As data sets for all the state variables are available, a non-parametric model of the overall system can be obtained (i) by splitting it into three decoupled subsystems, related to the

Variables	Q_L	Q_F		
			$\hat{x}$ (nCi/g)	σ (nCi/g)
x_1	0	Low	0	13
	$(0\ Th^*)$	Medium	30	13
	Th^*	High	60	13
x_2	0	Low	5	30
	$(0\ ThPP^*)$	Medium	80	30
	$ThPP^*$	High	165	35
x_3	0	Low	0	22
	$(0\ ThMP^*)$	Medium	50	20
	$ThMP^*$	High	130	44
u_1	0	Low	20	400
	$(0\ U1S)$	Medium	1000	400
	$U1S$	High	2000	400
	$(U1S\ inf)$	Very High	3000	400
u_2	0	Low	70	140
	$(0\ U2S)$	Medium	330	70
	$U2S$	High	470	50
	$(U2S\ inf)$	Very High	600	60

Table 1: Mapping between Q_L and Q_F related to each variable. The last two columns report, respectively, the values of $\hat{x}$ and σ.

three Th chemical forms (Th, ThPP and ThMP) obtained in response to the tracer input signals, namely plasmatic Th (u_1) and ThMP (u_2), and (ii) by formulating a NARX model for each of them. Such models can be written as follows:

$$x_{1_{k+1}} = f_1(x_{1_k}, x_{3_k}, u_{1_k}) \quad (10)$$

$$x_{2_{k+1}} = f_2(x_{2_k}, x_{1_k}) \quad (11)$$

$$x_{3_{k+1}} = f_3(x_{3_k}, x_{2_k}, u_{2_k}) \quad (12)$$

The first step consists in the identification of f_1, f_2, f_3 in normal subjects. Our final goal deals with the construction of a *simulator* of the overall nonlinear intracellular Th kinetics. Such a simulator will allow us to understand the discrepancies in the Th metabolism between the different classes of subjects, namely normal, diabetic either treated or not, by comparing the results obtained by the simulator against the actual data.

Construction of the fuzzy identifiers

The construction of each f_i proceeds as sketched in Fig. 3, and starts with the construction of the QSIM models of each decoupled subsystem. Each model is described by a single Qualitative Differential Equation (QDE).

1 - *Th subsystem*: The Th dynamics is described by the QDE:

$$\dot{x}_1 = S^+(u_1) + M^+(x_3) - M^+(x_1) \quad (13)$$

– S^+ and M^+ have the usual QSIM meaning;
– $S^+(u_1)$ models the nonlinear absorption process which governs the transfer of Th from plasma. The saturable functional relation is justified by the limited quantity of the mediating enzyme in the time unit;
– $M^+(x_3)$ models the chemical reaction of ThMP into Th. Let us observe that x_3 is modeled as a triangular shaped function: this modeling assumption is based on the knowledge of the tracer qualitative behavior in the cells.
– $M^+(x_1)$ models the chemical reaction of Th into ThPP.

2 - *ThPP subsystem*: The dynamics of ThPP is modeled by:

$$\dot{x}_2 = M^+(x_1) - M^+(x_2) \quad (14)$$

– $M^+(x_2)$ models the reaction of ThPP into ThMP. x_1 is analogously modeled as x_3, and $M^+(x_1)$ has the same meaning as above.

3 - *ThMP subsystem*: The equation modelling the dynamics of ThMP is:

$$\dot{x}_3 = S^+(u_2) + M^+(x_2) - M^+(x_3) \quad (15)$$

The functional constraints are analogously defined as in the other subsystems.

The input-output variables in (10-12) assume values in R^+, and their qualitative representations in both QSIM and FS frameworks are defined by their respective Q_L's and Q_F's. Table 1 summarizes the Q_L's and Q_F's of each x_i and u_i, and highlights the one-to-one correspondence between each Q_L and the respective Q_F. Let us observe that the elements of Q_F are represented in the linguistic form as well as through the values of the parameters which characterize the related membership functions. In our context, such parameters are the mean values ($\hat{x}$) and standard deviations (σ) and have been derived on the basis of the available physiological knowledge. Since the data used for SI come from tracer experiments, each subsystem is simulated starting from $x_i(0) = 0$, $i = 1, 2, 3$. For the same reason, among all of the generated behaviors we consider only those ones that reach the system quiescent state. The translation of the generated Quiescent Qualitative Behaviors (QQB) into fuzzy rules is preceded by their analysis with the aim of (i) aggregating those behaviors that do not present any differences with respect to the variables of interest, (ii) filtering those

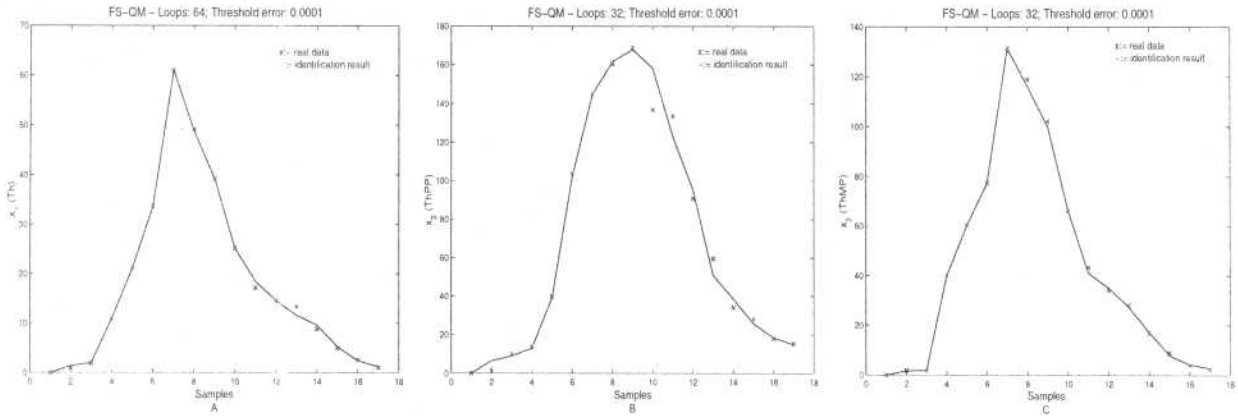

Figure 4: FS-QM identification results related to x_1 (A), x_2 (B), x_3 (C). The results have been obtained with a threshold error equal to 0.0001.

behaviors which are inconsistent with physiological constraints not explicitely embedded in the model. The remaining Admissible Behaviors (AQB) are automatically mapped into FR's. Table 2 summarizes, for each model, the number of QQB's, of AQB's, and of the generated IF-THEN rules. Let us remark that the set of AQB's does not include spurious behaviors, which, on the other hand, would have been easily filtered on the basis of the a priori knowledge of the admissible experimental profiles. Generally, the absence of any spurious behavior in the AQB set is not guaranteed: in such a case, a reduction in FS-QM efficiency might be caused.

Subsystem	# QQB's	# AQB's	# FR's
1	20	2	11
2	6	6	9
3	42	7	12

Table 2: Results of the qualitative simulation of the 3 models, in terms of the number of the generated QQB's, and of the AQB's. The number of the generated IF-THEN rules from the translation of the AQB's into the fuzzy framework is also reported.

The mathematical interpretation of each set of rules, in accordance with the choices underlying equation (9), allows us to derive a good initialization of each approximator $\tilde{f}_{i_0}$, and then the system is described by:

$$\tilde{f}_{1_0}(x_1, x_3, u_1) = \frac{\sum_{j=1}^{11} \hat{X}_1^j [e^{-(\frac{x_1-\hat{x}_1^j}{\sigma_1^j})^2} e^{-(\frac{x_3-\hat{x}_3^j}{\sigma_3^j})^2} e^{-(\frac{u_1-\hat{u}_1^j}{\sigma_{u_1}^j})^2}]}{\sum_{j=1}^{11} [e^{-(\frac{x_1-\hat{x}_1^j}{\sigma_1^j})^2} e^{-(\frac{x_3-\hat{x}_3^j}{\sigma_3^j})^2} e^{-(\frac{u_1-\hat{u}_1^j}{\sigma_{u_1}^j})^2}]} \quad (16)$$

$$\tilde{f}_{2_0}(x_2, x_1) = \frac{\sum_{j=1}^{9} \hat{X}_2^j [e^{-(\frac{x_2-\hat{x}_2^j}{\sigma_2^j})^2} e^{-(\frac{x_1-\hat{x}_1^j}{\sigma_3^j})^2}]}{\sum_{j=1}^{9} [e^{-(\frac{x_2-\hat{x}_2^j}{\sigma_2^j})^2} e^{-(\frac{x_1-\hat{x}_1^j}{\sigma_3^j})^2}]} \quad (17)$$

$$\tilde{f}_{3_0}(x_3, x_2, u_2) = \frac{\sum_{j=1}^{12} \hat{X}_3^j [e^{-(\frac{x_3-\hat{x}_3^j}{\sigma_3^j})^2} e^{-(\frac{x_2-\hat{x}_2^j}{\sigma_2^j})^2} e^{-(\frac{u_2-\hat{u}_2^j}{\sigma_{u_2}^j})^2}]}{\sum_{j=1}^{12} [e^{-(\frac{x_3-\hat{x}_3^j}{\sigma_3^j})^2} e^{-(\frac{x_2-\hat{x}_2^j}{\sigma_2^j})^2} e^{-(\frac{u_2-\hat{u}_2^j}{\sigma_{u_2}^j})^2}]} \quad (18)$$

$\hat{X}_i^j$ denotes the mean value of the membership function which belongs to Q_F of x_i, and appears in the consequent part of the j-th rule. The vector of parameters in each approximator, initialized in accordance with the values in Table 1, provides a good initial guess for the optimization procedure for parameter estimation from data.

Results

In order to make significant the comparison of the performance of our method with a data-driven approach , we look at each equation in (16-18) as a three-layer feedforward neural network, and exploit the Back Propagation algorithm (BP) for parameter estimation. As data-driven approach, we consider fuzzy-neural identifiers (FS-DD) whose structures are dimensionally fixed equal to the instantiated values of M in (16-18) but built from the numerical evidence. Let us observe that, since we exploit information derived from the qualitative simulation to fix the dimension, the performance of FS-DD is here improved with respect to its traditional application where also its structural dimension has to be derived from the data.

The application of our method to identify the system for simulation purposes follows a three-steps scheme:

1. *identification*: for each $\tilde{f}_{i_0}$, the values of parameters are tuned on a set of real data by using the BP algorithm in order to get an estimate $\tilde{\underline{\theta}}$ of $\underline{\theta}$, starting from the initial guess $\underline{\theta}_0$ provided as explained above;
2. *validation*: the accuracy of $\tilde{f}_i$, derived at step 1, is tested in accordance with a *parallel scheme* [3] on a new data set;

[3] In a parallel scheme, the next value of the output variable is calculated given the current measurements of the input variables and the simulated value of the current output: $\tilde{y}_{k+1} = \tilde{f}(\tilde{y}_k, \underline{u}_k)$

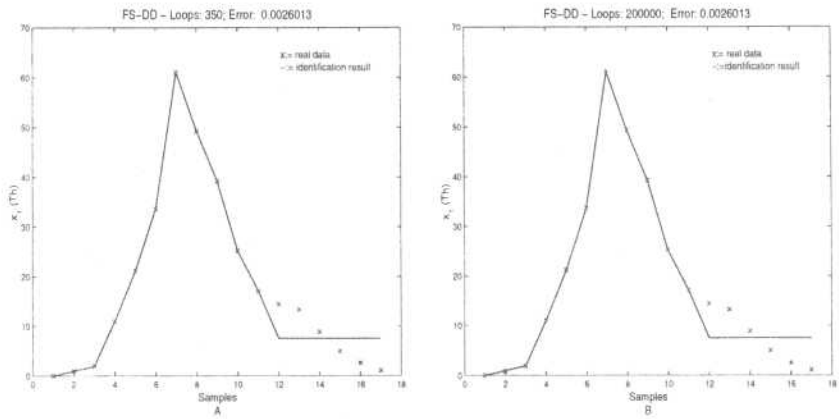

Figure 5: FS-DD identification results related to x_1: (A) - number of BP loops equal to 350; (B) - number of BP loops equal to 200000. The training errors do not change.

3. *simulation*: the accuracy of all of the three $\tilde{f}_i$ as a whole model is tested on a new data set in accordance with a *parallel scheme* where only the current inputs to the overall system (u_1, u_2) are measured data whereas the current output and input to each subsystem are simulated values.

Identification. Figure 4 shows the results we obtained with the application of our method in the identification phase of each x_i with a threshold error equal to 0.0001 by using a data set observed in normal subjects. Although the problem is ill-posed due to the small number of data, FS-QM performs quite well: this can be explained by the goodness of the initialization of both the identifier structures and the guesses of parameters. On the contrary, FS-DD, initialized by exploiting only the data, does not converge to the solution but it gets trapped in a local minimum. Let us fix our attention on the results of FS-DD identification of x_1: Fig. 5 highlights that, although the number of BP loops is highly increased from 350 (Fig. 5A) to 200000 (Fig. 5B), the training error remains constant, and there is no way to reach the fixed threshold error. Moreover, we can observe a perfect fit on the first 11 data. Such a fit does not derive from identification but is rather imputable to the construction of the requested 11 rules.

Validation and simulation. Each identified $\tilde{f}_i$ has been validated on a new set of data collected in an independent experiment, still on normal subjects.

Our final goal is the construction of a simulator of the overall system dynamics that is capable to reproduce the system behavior in response to any input signals, at least in the range of the experimental settings previously defined. Such a simulator is defined through the equations:

$$\begin{aligned} \tilde{x}_{1_{k+1}} &= \tilde{f}_1(\tilde{x}_{1_k}, \tilde{x}_{3_k}, u_{1_k}) \\ \tilde{x}_{2_{k+1}} &= \tilde{f}_2(\tilde{x}_{2_k}, \tilde{x}_{1_k}) \\ \tilde{x}_{3_{k+1}} &= \tilde{f}_3(\tilde{x}_{3_k}, \tilde{x}_{2_k}, u_{2_k}) \end{aligned} \tag{19}$$

where $\tilde{x}_{i_0} = x_{i_0}$, and $u_{i_k}, \forall k$, are the input data to the system. The simulation results on the new data set (Fig. 6) clearly show the robustness and validity of FS-QM as an alternative methodology to identify nonlinear systems.

Remark. Clearly, within this approach the possibility of identifying parameters with a precise meaning is lost, but the reliable simulator at our disposal makes possible to enrich the knowledge of Th kinetics and to provide diagnostic and therapeutic information to physiologist: in particular, it will be possible to fit the main goal of the study, that is the understanding of insulin action on the Th metabolism in the cell. An indirect evaluation of the effects of diabetes on Th metabolism may be obtained by comparing the profiles simulated by (19) against the data of pathological subjects either treated or not. From a preliminary analysis of the results obtained, we can reasonably affirm that ThPP exhibits the same behavior both in normal and treated subjects.

Discussion

Mathematical modeling is often used in biomedical sciences to obtain a quantitative description of the (patho-)physiology underlying a physical system. Compartmental models represent a powerful class of such approaches: they are able to describe the mechanisms of release and uptake of a certain physiological substrate by contemporaneously expressing the system dynamics through a set of ODE's and quantifying the fluxes of substrate between compartments through a set of parameters. When the available data do not allow to identify the model parameters, due to measurement errors, inaccurate sampling time or, more simply, to inadequacy of some model assumptions, the model itself is revised or discarded. An alternative solution is to resort to non-parametric modeling, that describes the dynamics of the system at hand relying on very general nonlinear functions, moulded by the available data. In this context, the structural assumptions made by compartmental models are relaxed, and only a descriptive quantitative knowledge may be derived.

Unfortunately, it may happen that also non-parametric approaches are likely to fail: as a matter of fact, since a posteriori unidentifiability may be also due to the lack of either a sufficient number or a sufficient quality of data, the search

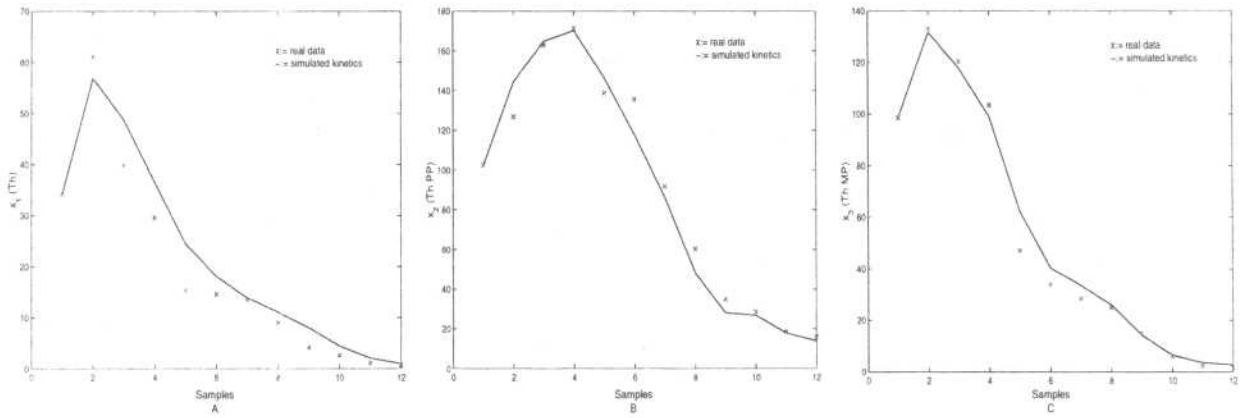

Figure 6: FS-QM simulation results related to x_1 (A), x_2 (B), x_3 (C).

for a robust non-parametric description turns out to be unfeasible in most cases.

In this paper we have described the successful application of a novel methodology that aims at filling the gap between the parametric (compartmental) and non-parametric modeling. Thanks to the application of QR techniques, the structural assumptions on the relationships between the problem variables are retained; moreover, thanks to the application of FS's, such assumptions are translated into a non-parametric model, whose parameters are properly initialized on the basis of a priori knowledge. Finally, the approximator of the system dynamics derived is robust enough for the purposes of the study.

From the application viewpoint, our proposed approach enabled us to draw physiologically sound conclusions from a set of data, that revealed to be unexploitable by classical compartmental modeling.

In conclusion, the results presented in this paper confirm our belief in the potential usefulness of our methodology for several classes of domains, among which medicine represents a prominent field: the presence of structural knowledge and the availability of costly data set, poor in number and in quality, motivate the development of approaches able to combine qualitative and quantitative information. The marriage of QR and fuzzy-based methods allows us to smooth down the distinction between mathematical models identification and Data Mining approaches, moving towards new approaches able to intelligently analyze the available data. In our future work, our aim will be to better systematize FS-QM in order to allow for its broader application in different areas.

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