Qualitative models and fuzzy systems: an integrated approach for learning from data

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Abstract

This paper presents a method for the identification of the dynamics of non-linear systems by learning from data. The key idea which underlies our approach consists in the integration of qualitative modeling techniques with fuzzy logic systems. The resulting hybrid method exploits the a priori structural knowledge on the system to initialize a fuzzy inference procedure which determines, from the available experimental data, a functional approximation of the system dynamics that can be used as a reasonable predictor of the patient's future state. The major advantage which results from such an integrated framework lies in a significant improvement of both efficiency and robustness of identification methods based on fuzzy models which learn an input-output relation from data. As benchmark of our method, we have considered the problem of identifying the response to the insulin therapy from insulin-dependent diabetic patients: the results obtained are presented and discussed in the paper.
Keywords: fuzzy logic system, non-linear dynamical system identification, qualitative modeling, qualitative simulation.

1 Introduction

The prediction of the evolution over time of the patient's state plays a crucial role both in a diagnostic and therapeutic medical context. A traditional way to approach such a problem deals with both the formulation of mathematical models of the dynamics of patho-physiological systems and the simulation of their behaviour [3]. Such models, which are generally described by Ordinary Differential Equations (ODE), are computationally tractable with classical methods which allow us to derive, either analytically or numerically, meaningful predictions of the behaviour of the considered system. But, for the medical domain as for many other physical domains, quantitative model formulation may be not successfully applicable due to the incompleteness of the available knowledge about either the functional relationships between variables or the numerical values of model parameters, which could be non identifiable both for the lack of adequate experimental settings and for the impossibility of measuring 'in vivo' the values of a few variables. Approaches recently proposed to coping with difficulties in model building in presence of incomplete knowledge are represented by qualitative modeling methods [10]. Such methods allow us to describe the dynamics of a system through Qualitative Differential Equations (QDE), where functional relationships and numeric values are respectively defined in terms of regions of monotonicity and of their ordinal relations with landmark values. Given a set of QDEs which model a dynamical system and an initial state, i.e. the qualitative magnitude of variables along with their direction of change, qualitative descriptions of the behaviours of the system are derived through qualitative simulation.

Whereas qualitative predictions of a patho-physiological system behaviour may be properly exploited in the testing phase of diagnostic reasoning [6], they are almost always inadequate to be used in a therapy planning context as the effects of different therapies are requested to be deeply investigated at a quantitative level.

As alternative to conventional mathematical modeling frameworks, the so-called non-parametric approaches, that are able to describe the dynamics of a real system from input-output data, have been proposed. Neural networks, multi-variate splines and fuzzy logic systems are the best known approximation schemes used for learning an input-output relation from data [7, 8, 17]. Although these approaches are successfully applied to a variety of domains, they are affected by two main drawbacks that are particularly serious in medicine: first, the identification result, a non-linear function, does not capture any structural knowledge; second, the model identification procedure usually requires a large amount of data and is often extremely inefficient.

This paper deals with a method which integrates both mathematical and non-parametric modeling frameworks with the goal to preserve the advantages which come from the application of both of them and, at the same time, to overcome their respective drawbacks. Therefore, our goal is the definition of a robust and efficient method for non-linear dynamical system identification, which exploits both the available a priori knowledge, namely the structural and human expert knowledge, and the experimental one. The structural knowledge is properly represented by qualitative models, whereas the human expert knowledge by rules which describe linguistic information. As qualitative modeling formalism we have chosen QSIM [10] because of both its expressive power to represent differential equations in case of incomplete knowledge and its reasonable predictive capacity. Among the non-parametric approaches, fuzzy logic systems seem to be the most suitable ones as they are capable of conjugating experimental data analysis and prior knowledge representation through rules, and, moreover, they can be proved to be universal approximators [17], i.e. they can approximate at any degree of accuracy any non-linear function. In general, fuzzy logic methods are based on fuzzy inference procedures which are initialized with a rule-base predefined by the human expert. When such a base is not available or poorly defined, also the fuzzy inference may become extremely inefficient. Our method aims at solving the problem of the construction of a meaningful rule-base: fuzzy rules are automatically generated by encoding the knowledge of the system dynamics captured by its qualitative simulated behaviours. The basic steps of our method may be summarized as follows:

- formulation and simulation of a qualitative model of the patho-physiological system at study;
- automatic generation of the initial set of Fuzzy Rules (FR) from the outcomes of the qualitative simulations;
- generation of the Fuzzy System (FS) which corresponds to the FR;
- parameter estimation of the FS from a set of experimental data.

We have applied our method to the identification of the dynamics of the Blood Glucose metabolism in insulin dependent diabetic patients. In particular we addressed the problem of predicting the Blood Glucose Level (BGL) time course in response to different perturbations, such as meals and conventional insulin therapies. In such a clinical context the experimental data usually come from the home-monitoring of patients: their low-quality and the high complexity of the system motivate the use of the approach we have implemented. The assessment of a tool able to derive reliable and accurate predictions may allow us to achieve the ultimate goal of improving the control of BGL in diabetes therapy.

2 Background

This section recalls the basic concepts and definitions of both QSIM and fuzzy logic systems which are relevant to a clear and formal description of our method. A more extensive treatment can be found in [10, 17].

2.1 Basic concepts of QSIM

The central inference within QSIM is qualitative simulation: given a set of QDEs which model a system and an initial state, a qualitative description of all of its possible behaviours (QBs) is provided. A *system* S is modeled by a set $\{x_i,\ i = 1, \ldots, m\}$ of state *variables*, real-valued continuously differentiable functions of time, and a set of *constraints* that relate them.

The QSIM constraint notation has a clear correspondence with ODEs by making explicit all the functions and operators in the equation. Therefore, constraints which express arithmetic and time derivative operators are defined. The functional relationships between variables are not explicitly specified but just described in terms of monotonicity regions. For example, the M^-/M^+ constraints express a relation of strict decreasing and increasing monotonicity, respectively; whereas the S^-/S^+ constraints describe functions which are monotonic decreasing/increasing over an interval and take on constant values outside that interval.

The qualitative magnitude of each $x_i(t)$ is defined with respect to a finite ordered set $L := \{l_j,\ j = 1, k\}$, called *quantity space*, whose elements l_j are landmark values that represent real qualitative distinctions for the behaviour of $x_i(t)$. Each set L_i is associated with the set of distinguished time-points T_i, which represents the set of instants where x_i takes on a landmark value.

Definition 1. The qualitative magnitude of $x_i(t),\ qmag(x_i, t)$, is defined by either a landmark value or an open interval between two landmarks:

$$qmag(x_i, t) \ := \begin{cases} l_j & \text{if } x_i(t) = l_j \\ (l_j, l_{j+1}) & \text{if } x_i(t) \in (l_j, l_{j+1}) \end{cases}$$

Definition 2. The direction of change of $x_i(t),\ qdir(x_i, t)$, is the sign of its time derivative and can be either increasing, steady or decreasing, i.e. $qdir \in \{+, 0, -\}$.

Definition 3. The qualitative value of $x_i(t),\ QV(x_i, t)$, is defined by the pair $< qmag,\ qdir >$.

Definition 4. The qualitative state of S at time $t,\ QS(S, t)$, is the set of the qualitative values at time t of all the system's variables, which are consistent with the constraints.

Definition 5. A qualitative behaviour of S over the time set $T = \cup_i^m T_i = [t_0, t_n]$ is defined by the sequence:

$$QS(S, t_0), QS(S, t_0, t_1), QS(S, t_1), ..., QS(S, t_{n-1}, t_n), QS(S, t_n),$$

where $QS(S, t_{n-1}, t_n)$ is the qualitative state of S at (t_{n-1}, t_n).

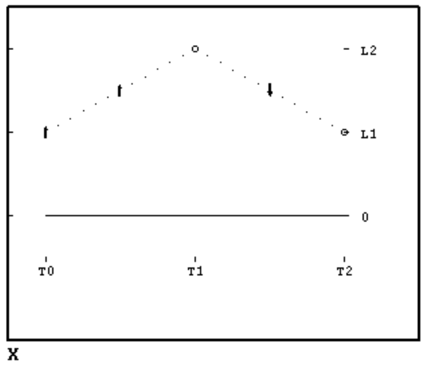


Figure 1: Plot of a qualitative behaviour

The plot of the qualitative behaviour of an individual variable given in Fig. 1 exemplifies the definitions given above: the qualitative behaviour of the variable x is defined on the time set $T = \{t_0,\ (t_0, t_1),\ t_1,\ (t_1, t_2),\ t_2\}$, which is represented along the horizontal axis, by the sequence of qualitative values in $t \in T$: $< l_1, \uparrow>,\ < (l_1, l_2), \uparrow>,\ < l_2, \circ >,\ < (l_1, l_2), \downarrow>$, $< l_1, \circ >$, where $l_1,\ l_2$, arranged on the vertical axis, are the landmark values in the quantity space L, and the symbols $\uparrow$, $\circ$, $\downarrow$ denote the direction of change increasing, steady and decreasing, respectively.

2.2 Basic concepts of Fuzzy Systems

A Fuzzy System (FS) is a system which exploits fuzzy concepts for reasoning about a set of objects. Although the theory on fuzzy sets is quite complex, for the purposes of this paper we will define FS through some simple ingredients.

The *Universe of discourse* (U) is the collection of objects that we would like to reason about. A *Fuzzy set* F in U is a generalization of the concept of ordinary set. F is characterized by a membership function $\mu_F : U \rightarrow [0, 1]$; $\mu_F(u)$ represents the degree of membership of $u \in U$ to the set F.

A *Linguistic Variable* is a variable whose values are words in natural language, and that can be represented through a collection of fuzzy sets. For example, the continuous variable Blood

Glucose Level (BGL) may be described with the linguistic terms Low, Normal, High, Very High. Each value of its universe of discourse may be hence assigned a degree of membership to a fuzzy set corresponding to such linguistic terms.

A *Fuzzy Rule Base* (FRB) is the knowledge base that we use to reason about the objects in U. In particular, a FRB is a collection of rules of the kind:

$$\text{IF } x_1 \text{ is } F_1 \text{ and ... and } x_n \text{ is } F_n \text{ THEN y is } G$$

where $F_1, \ldots, F_n$ and G are fuzzy sets, and $x_1, \ldots, x_n$ and y are linguistic variables. For example, if we want to express a rule that forecasts the value of the linguistic variable BGL, using the linguistic level of the variable insulin, we may write:

$$\text{IF } insulin \text{ is } high \text{ THEN BGL is } Low$$

The most popular FSs proposed in the literature basically differ in the way they map input (antecedents) and output (consequents) information in a rule [17]. Herein, we will restrict to the class of FSs that are useful for function approximation. In particular, we would like to approximate continuous functions from $\Re^n \rightarrow \Re$: the value of an output variable y defined on $V \subset \Re$ is inferred by using a FRB with n input variables defined on $U_i \subset \Re$, such that $U = U_1 \times \ldots \times U_n$. This means that each continuous variable should be properly *fuzzified*. The *fuzzification* operation performs a mapping from $x_i \in U_i$ into a fuzzy set. In this paper we will exploit the *singleton fuzzifier*, that transforms a real number $x_i \in U_i$ into a fuzzy set with membership function defined over U_i, such that it is equal to 1 in x_i and to 0 elsewhere. Once a quantitative measure of the inputs is fuzzified, it is evaluated as an input of all the rules in the FRB.

In order to perform inferences, it is necessary to resort to a machinery that gives a precise interpretation of the terms is, and and then that appear in a fuzzy rule. For our purposes, it is sufficient to say that it is possible to select a *fuzzy inference engine* (FIE), in which the fuzzy logic principles are used to map fuzzy sets in U to fuzzy sets in V. Within the context of function approximation, two different classes of FSs have been widely used, the Takagi-Sugeno Fuzzy System [15] and the Fuzzy System with Defuzzifier [12].

Takagi-Sugeno FS. In the classical (first order) Takagi-Sugeno FS, a rule is expressed in the following form:

$$\text{IF } x_1 \text{ is } F_1 \text{ and ... and } x_n \text{ is } F_n \text{ THEN } y = c_0 + c_1\, x_1 + \ldots c_n\, x_n$$

where $c_{i,i=0,\ldots,n}$ are real-valued parameters. The output of each rule is hence a real number obtained as a linear combination of the input (crisp) values. This approach has been extended also to higher order models of the input–output relation. If the FRB is composed by M rules, the output of the system is calculated as:

$$y(\underline{x}) = \frac{\sum_{j=1}^{M} w_j y_j}{\sum_{j=1}^{M} w_j} \tag{1}$$

with $\underline{x} = \{x_1, \ldots, x_n\}$. Each w_j is calculated as:

$$w_j = \prod_{i=1}^{n} \mu_{F_i^j}(x_i) \tag{2}$$

where $\mu_{F_i^j}$ is the membership function associated with the linguistic variable of x_i that appears in the j-th rule.

The Takagi-Sugeno FS is quite appealing for identification purposes, since it is possible to identify each c_i from the data, as well as the most suitable number of rules [7]. Nevertheless, it is difficult to apply this framework when the available information is not rich enough to explicate the functional relation between the output and input variables. Since the goal of this paper is to provide a framework capable of dealing with incomplete knowledge, we have decided to resort to a more flexible class of FSs, able to preserve the fuzzy nature of the input-output rules.

FS *with Defuzzifier.* In FSs with defuzzifier, given an input in U, we obtain a collection of M fuzzy sets as outputs, where M is the number of rules of the FRB. Then, we transform into a real number the output of the FIE through a *defuzzification* operation. In this paper we will exploit the *Center Average Defuzzifier*, in which the collection of M fuzzy sets is averaged as follows:

$$y(\underline{x}) = \frac{\sum_{j=1}^{M} w_j \hat{y}_j}{\sum_{j=1}^{M} w_j} \tag{3}$$

where $\hat{y}_j$ is the point in V where G_j reaches its maximum value, and w_j is calculated as in equation (2). This functional form can therefore be easily exploited in function approximation without requiring strong assumptions on the input-output relation. If we choose as FIE the product-inference rule [17], the system described by the equation (3) can be rewritten as:

$$y(\underline{x}) = \sum_{j=1}^{M} \hat{y}_j \ \Phi_j(\underline{x}) \tag{4}$$

where

$$\Phi_j(\underline{x}) \quad = \quad \frac{\prod_{i=1}^{n} \mu_{F_i^j}(x_i)}{\sum_{j=1}^{M} [\prod_{i=1}^{n} \mu_{F_i^j}(x_i)]}$$

and $\mu_{F_i^j}$ has the same meaning as in equation (2). The functions $\Phi_j()$s are called Fuzzy Basis Functions (FBF); the FS is hence viewed as a linear combination of such FBF.

In the following, we will exploit a useful class of FS for fuzzy approximation with Gaussian membership functions. Then, FS assumes the mathematical form:

$$y(\underline{x}) = \frac{\sum_{j=1}^{M} \hat{y}_j [\prod_{i=1}^{n} exp(-(\frac{x_i - \hat{x}_i^j}{\sigma_i^j})^2)]}{\sum_{j=1}^{M} [\prod_{i=1}^{n} exp(-(\frac{x_i - \hat{x}_i^j}{\sigma_i^j})^2)]} \tag{5}$$

Such an expression allows us to interpret the non-linear function approximation problem with FS as the process of identifying the vector of parameters $(\hat{y}_j, \hat{x}_i, \sigma_i)$ of a known non–linear function from a set of data. Moreover, the FS defined by equation (5) is known to possess some desirable properties, like the capability of approximating any continuous function with an arbitrary degree of accuracy [17]. Other properties can be found in [9, 17].

3 Description of the method

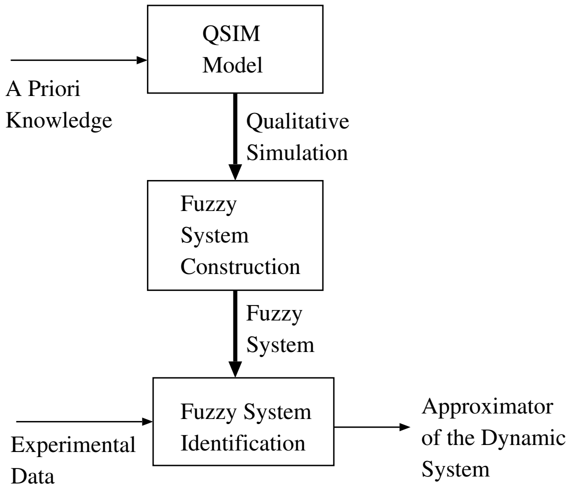


Figure 2: The basic steps of the method

The system identification procedure we propose proceeds in three main phases (Fig. 2):

1. QSIM *model formulation and simulation*. The prior patho-physiological knowledge of the system under study must be organized so that its structural and behavioural model can be defined. More precisely, the variables of interest and the network of interactions between them, along with their mathematical descriptions, must be specified: variables are described by their respective quantity spaces, whereas their interactions by a set of qualitative constraints which include both functional dependencies and equations governing the system dynamics. Then, an initial state of the system, which may describe a perturbation on it, has to be provided to simulate its behaviour. Qualitative simulation produces in one run all possible behaviours that could follow from the given incomplete specification, and shows us the entire range of possible system dynamics at once.

2. *Construction of the* FS. The prior knowledge, not precise but correct, of the dynamics of the system captured by the QBs derived at phase 1 is exploited to generate automatically

a base of FRs whose antecedents and consequents are the input and output variables to be used to quantitatively identify the dynamics of the system. The idea underlying the mapping of a QB into a set of FRs, which is the core of our method, exploits the semantic correspondence between the elements of quantity spaces and linguistic variables whose values can be defined through fuzzy membership functions μ. Then, the definition of the linguistic variables associated with the quantity spaces of the input-output variables, of their corresponding μ, as well as the fuzzification and defuzzification methods, complete the definition of the FS.

3. *Identification of the* FS *from the experimental data.* The generated rules, interpreted in accordance with the FIE selected at the previous phase, initialize an optimization procedure for the identification of the parameters in the FS, which learns from the available experimental data an accurate input-output relation.

The next two subsections detail the methods and algorithms concerning phases 2 and 3. Phase 1 will be exemplified in section 4 through the application of the overall method for the identification of the glucose response to the insulin therapy from insulin-dependent diabetic patients.

3.1 From qualitative behaviours to a fuzzy system

Our method is grounded on the intuition that analogies between QSIM and fuzzy formalisms can be highlighted (Fig. 3).

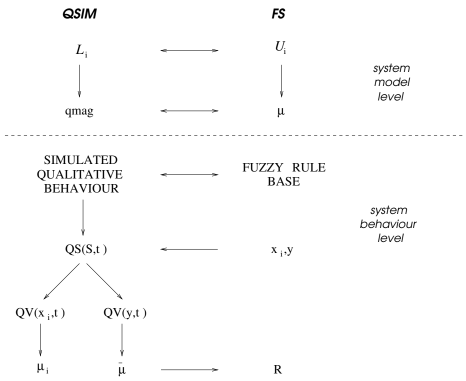


Figure 3: Analogies between the QSIM and FS formalisms. Bi-directional arrows indicate a semantic correspondence, whereas the other ones have the usual meaning

At a first level, namely the modeling one, the quantity space L_i associated with the variable x_i may find its semantic linguistic correspondence with the universe of discourse U_i of x_i. The set $L_i \cup \{(l_j, l_{j+1}),\ l_j \in L_i\}_{j=1,j'-1}$, where j' is the cardinality of L_i, contains all significant distinct qualitative magnitude values ($qmag$) of x_i, whereas the elements of U_i are the linguistic values which x_i can assume, i.e. the linguistic names of the membership functions μ which define the fuzzy sets. For the sake of clearness, let us consider again as example the variable BGL which may assume real positive values. Its universe of discourse may correspond to the quantity space (0 BGL_N BGL_{VH}), where BGL_N and BGL_{VH} are landmarks respectively associated with the terms (or, equivalently with their associated μ) Normal and Very High, and the intervals (0, BGL_N), (BGL_N, BGL_{VH}) with the terms Low and High.

At a second level, more related to the simulated system behaviour, a mapping from simulated qualitative predictions into fuzzy rule-bases can be defined. Each simulated QB is defined by a sequence $QS(S, t_k)$ of qualitative states of the system, where $QS(S, t_k)$ is an m-tuple of the qualitative values of each individual system variable. Given n input variables x_i $(n \leq m)$, and the output variable y, a QB is automatically mapped into a FRB in the following steps of the method:

1. from T, draw out its subset $\overline{T} = \cup_{i=1}^{n} T_{x_i} \cup T_y$, whose elements are the significant time-instants of both x_i and y (T_{x_i} and T_y are the sets of distinguished time-points of x_i and y, respectively);
2. from the elements of $\overline{T}$, built $\mathcal{T} = \{t_0\} \cup \{(t_{j-1}, t_j), t_j\}_{j=1\ldots k}$, where k is the cardinality of $\overline{T}$, and $\forall t_k \in \mathcal{T}$, where t_k may be either a time-point or a time-interval, consider $QS(S, t_k)$;
3. from $QS(S, t_k)$, draw out the qualitative values of input and output variables, namely $QV(x_i, t_k)$ and $QV(y, t_k)$ (necessarily, $QV(y, t_{k+1})$ if $\{x_i\} \cap \{y\} \neq \emptyset$);
4. from $QV(x_i, t_k)$ and $QV(y, t_k)$, draw out its related $qmag$, i.e. $qmag(x_i, t_k)$ and $qmag(y, t_k)$;
5. consider the linguistic values, and therefore the membership functions μ_i and $\overline{\mu}$ which are associated with $qmag(x_i, t_k)$ and $qmag(y, t_k)$, respectively;
6. generate a linguistic rule R where x_i are the antecedents, y the consequent, and then the corresponding fuzzy rule where μ_i and $\overline{\mu}$ are the fuzzy sets.

Fig. 4 details, from an operational point of view, the algorithm described.

Obviously, the number of rules generated in correspondence with each QB cannot be greater than the cardinality of $\mathcal{T}$. Identical rules may happen to be generated as variables may have the same $qmag$ either at different time-points or time-intervals: in such a case we group the equivalent rules and keep only one of them as representative of an input-output relation. The entire range of possible system dynamics is captured by the whole tree of behaviours. Such a tree, as it includes all logically possible outcomes of the given qualitative information, may contain ambiguous results and may be quite large to be efficiently explored. Such ambiguities, as well as the dimension of the behaviour tree, may be significantly reduced by additional knowledge on the system which can be expressed either by further constraints or by semi-quantitative information on the variable values [10]. Moreover, let us remark that many behaviours in the tree may not present any difference as far as the input-output variables are concerned. Then, behaviour aggregation procedures, which aim at taking the significant distinctions out of the tree, have to be performed to cope with the problem of an efficient generation of a complete and meaningful fuzzy rule base. Given the behaviour tree, the algorithm for the generation of the FBR which describes the overall system dynamics is performed as follows:

1. selection of a representative for each class of equivalent behaviours;
2. generation of the FRB which corresponds to each individual representative behaviour;
3. union of all the FRBs generated at step 2, and filtering of the equivalent rules.

As shown in Fig. 4, the FS is completely defined in the form of equation (5) once a FIE is given along with the shape of the membership functions.

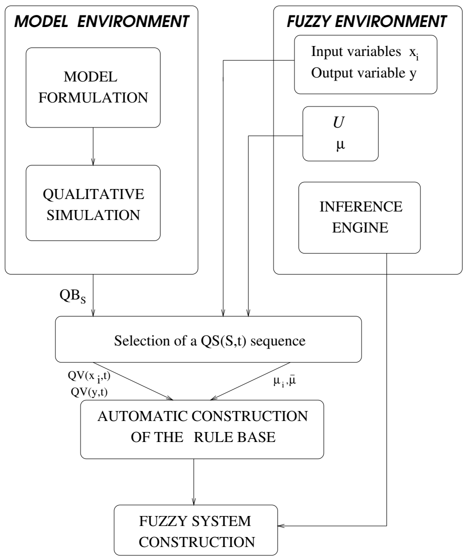


Figure 4: Main phases of the method

3.2 Fuzzy System identification

Once the FS has been derived as described in the previous subsection, a function approximator $y(\underline{x})$ may be automatically obtained.

Such a function approximator is dependent on a parameter vector $\underline{\theta}$, such that $y(\underline{x}) = y(\underline{x}, \underline{\theta})$, where $\underline{\theta} = \{\underline{\hat{y}}, \underline{\hat{x}}, \underline{\sigma}\}$ with $\underline{\hat{y}} = \{\hat{y}_j\}$, $\underline{\hat{x}} = \{\hat{x}_i^j\}$ and $\underline{\sigma} = \{\sigma_i^j\}$, where $i = 1, \ldots, n$, $j = 1, \ldots, M$.

Numeric values, which express the prior knowledge included in the system, and which provide for an initial guess of the system dynamics, are assigned to the parameter vector $\underline{\theta}$ in the construction phase of the FS. Given a set of experimental data, the estimate of $\underline{\theta}$ is then refined through optimization procedures. The identification process can be carried out considering the meaning of the antecedents and consequents of each derived fuzzy rule.

In the herein proposed framework, the description of the system dynamics is performed through rules that give the next value y_{k+1} of the system output as a function of the values of the current inputs ($\underline{u}_k$) and output (y_k). Then, the output behaviour can be described with a Non-linear AutoRegressive eXogenous input model (NARX) of the kind:

$$y_{k+1} = y(\underline{x}_k, \underline{\theta}) + v_k \tag{6}$$

where k is a discrete time index, $\underline{x}_k = \{\underline{u}_k, y_k\}$, v_k is the measurement error and $y(\cdot)$ has the same meaning as equation (5).

Since the model (6) is non-linear in the model parameters, it is necessary to resort to non-linear identification techniques to estimate the vector $\underline{\theta}$. A classical way of coping with this complex task is to identify $\underline{\theta}$ using the back-propagation (BP) technique, by exploiting the Neural Network representation of a FS described in [17]. The BP technique allows us to estimate all the FS parameters through an iterative search in the solution space.

In this paper we will show that our method provides for a significant initialization of the BP algorithm, resulting in a fast convergence to the global minimum. This feature is particularly appealing since it is well known that BP neural nets, as well as all non-linear optimization procedures, are difficult to train because of the presence of local minima in the solution space.

Although in this paper we will mainly concentrate on the BP-algorithm, within the proposed framework other approaches to parameter estimation may be considered. A potentially very interesting strategy to be investigated consists in fixing the parameters $\hat{x}_i^j$ and σ_i^j of the vector $\underline{\theta}$, so that only the parameters $\hat{y}_j$ are estimated from the data. Since equation (5) is *linear* in the parameters $\hat{y}_j$, the identification problem expressed by equation (6) is also linear, and it is hence possible to resort to close-form efficient methods, such as classical linear least squares.

4 An application: identification of BGL dynamics in diabetic patients

The identification and prediction of the BGL dynamics in patients suffering from Insulin Dependent Diabetes Mellitus (IDDM) is a well-known problem in the bioengineering field. The Blood Glucose Levels (BGL) in IDDM patients are not kept within acceptable values because of the insufficient production of endogenous insulin, the main glucoregulatory hormone. Herein, we will concentrate on the problem of forecasting the patient's response to conventional exogenous insulin therapy, i.e. several insulin injections per day; the goal of such a therapy is to provide for the basal insulin need and to compensate for the meal ingestion. This problem is particularly hard to cope with, since BGL metabolism is rather complex to model. However, several classical mathematical models of the system behaviour have been proposed in the literature, the majority of them being grey-box models expressed as systems of differential equations. As shown by [18], the data collected during patient's home monitoring are often insufficient to reconstruct the daily BGL dynamics, as well as to significantly estimate some physiological parameters, such as insulin sensitivity [11]. For these reasons, the parameters in the equations are often non identifiable. Therefore, alternative approaches, ranging from Causal Probabilistic Networks [1] to black-box NARX models [13] have been considered.

The BGL dynamics identification is a good benchmark for our proposed method: the a-priori knowledge of the IDDM patho-physiology is sufficient to formulate a structural model of the BGL dynamics but the observed data are not good enough to completely identify the model. In order to carefully evaluate the actual potentials of our framework, we resorted to simulated data, in which the noise level may be suitably manipulated, as well as the number of missing data conveniently increased. The goals of this evaluation are three-fold:

1. Show that the proposed system performs better than comparable black-box frameworks, such as FS derived from the data only.
2. Show that the one-step ahead predictions calculated by equation (6) are reliable. This will demonstrate the applicability of the proposed framework in continuous monitoring applications.
3. Show that it is also possible to use the derived function approximator for forecasting the patient's behaviour when few data are available, for example when data come from home monitoring.

4.1 The qualitative model

A qualitative model of glucose/insulin interaction in IDDM patients has been derived on the basis of the patho-physiological knowledge, and relying on a number of quantitative and qualitative models described in the literature [2, 4, 5, 11].

The qualitative model exploited in our work is based on the compartmental structure shown in Fig. 5. Insulin controls the BGL, $g(t)$, through two different mechanisms: the regulation of the glucose elimination (g_{out}) and the modulation of the Net Hepatic Glucose Balance ($nhgb$), a variable that accounts for the liver capability of releasing or up-taking glucose.

From a qualitative point of view, it is possible to represent the insulin distribution in the

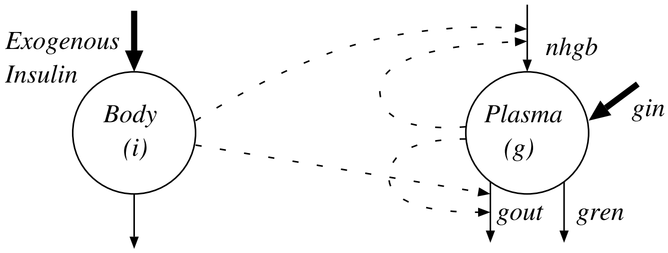


Figure 5: The compartmental structure of the qualitative model of Insulin/Glucose dynamics (see text). Continuous lines represent flows of matter, while dashed lines represent control signals

body, $i(t)$, with a triangular (or trapezoidal) signal shape; as the insulin subsystem is decoupled from the glucose one, we model the insulin dynamics exactly as its input signal shape. Under this assumption, the system dynamics may be described by a single qualitative differential equation:

$$\frac{dg}{dt} = nhgb(i,g) + g_{in}(t) - g_{out}(i,g) - g_{ren}(g) \tag{7}$$

where

1. $g_{in}(t)$ is a triangular shaped input function, representing the exogenous glucose intakes (meals). The quantity space is defined as $(0\ G^*)$, where G^* is the maximum quantity of absorbable carbohydrates.
2. $nhgb(i,g) = M^-(i) + S^-(g)$. $nhgb$ decreases either when g or i increases. Furthermore, the contribution given by the variable g saturates at a certain threshold value, indicated as GS. Finally, for each value of g, $nhgb > 0$ if $i = 0$. Following these constraints, the derived quantity space is *(L* 0 *HBG UP)*, where L is a minimum negative value, $HBG = M^-(0) + S^-(GS)$, and $UP = M^-(0) + S^-(0)$.
3. $g_{ren}(g) = M^+(g - GN)$, where GN describes the renal threshold of glucose. Its quantity space is $(0\ \ \infty)$.
4. $g_{out}(i,g) = M^+(i) + M^+(g)$. g_{out} is a monotonic increasing function of both g and i. The quantity space of these variables is $(0\ \ GOUT)$, where $GOUT$ is the maximum value the variable g_{out} can reach.

The quantity space of the variable g may be hence defined by ordering the previously introduced landmarks as (0 $GS\ \ GN\ \ \infty$).

4.2 Mapping the quantity spaces into fuzzy elements

Once the qualitative model has been assessed, it is necessary to define the input and output variables used to approximate the system dynamics. In our case, the choice of the output variable is natural, being g the target of the insulin control action. As far as the inputs are concerned, we take the sign of the derivative of the input signals (di and dg_{in}), being the direction of change of the input signals more reliably assessed in clinical practice than their magnitude. The quantity space of the two signals is defined as $(-\infty \;\; 0 \;\; \infty)$.

Therefore, the FS is derived with a rule-base in which the antecedents are the variables $g(t),\ di(t), dg_{in}(t)$, and the consequent is $g(t+1)$.

By using the method proposed in the previous section, the linguistic levels of the variables are immediately defined. By exploiting the physiological knowledge available, and in particular by referring to the studies presented by Berger and Lehmann [2, 11], we initialize the parameters in the membership functions of the fuzzy system. Table I describes the correspondence between the quantity space and the fuzzy elements for the glucose variable.

glucose			
Qualitative Values	Linguistic Values	$\hat{x}$ (mg/dl)	σ (mg/dl)
(0,GS)	Very-Hypo	60	14
GS	Hypo	80	11
(GS,GN)	Normal	120	14
GN	Hyper	180	11
(GN,INF)	Very-Hyper	280	30

Table I: Correspondence between Qualitative Values, Linguistic Values and Fuzzy Sets. $\hat{x}$ and σ denotes Mean Values and Standard Deviations, respectively.

Once both quantity spaces have been mapped into fuzzy elements, it is possible to derive from the qualitative simulation the FS needed for the system identification.

4.3 Mapping the system behaviours into fuzzy rules

From a qualitative simulation of the model described above, we have obtained the IDDM patient response to a regular insulin injection, followed by a meal: the meal absorption starts when i reaches its maximum value, and the initial value of g corresponds to a situation of severe hyperglycemia, i.e. to the BGL linguistic value *very-Hyper*.

Given the scenario described above, a reasonable physiological assumption is that the evolution over time of glucose is not oscillating. Under this assumption, we have identified from the behaviour tree only three different classes of behaviours. Fig. 6 shows the representative behaviour of each class which differs in the steady state qualitative value of BGL. Table II presents the correspondent FRB, generated as described in section 3.1.

The derived FS is a NARX model of the glucose/insulin dynamics in IDDM patients, that can be optimized on the individual patient's data, as outlined in section 3.2.

(1) (2) (3)

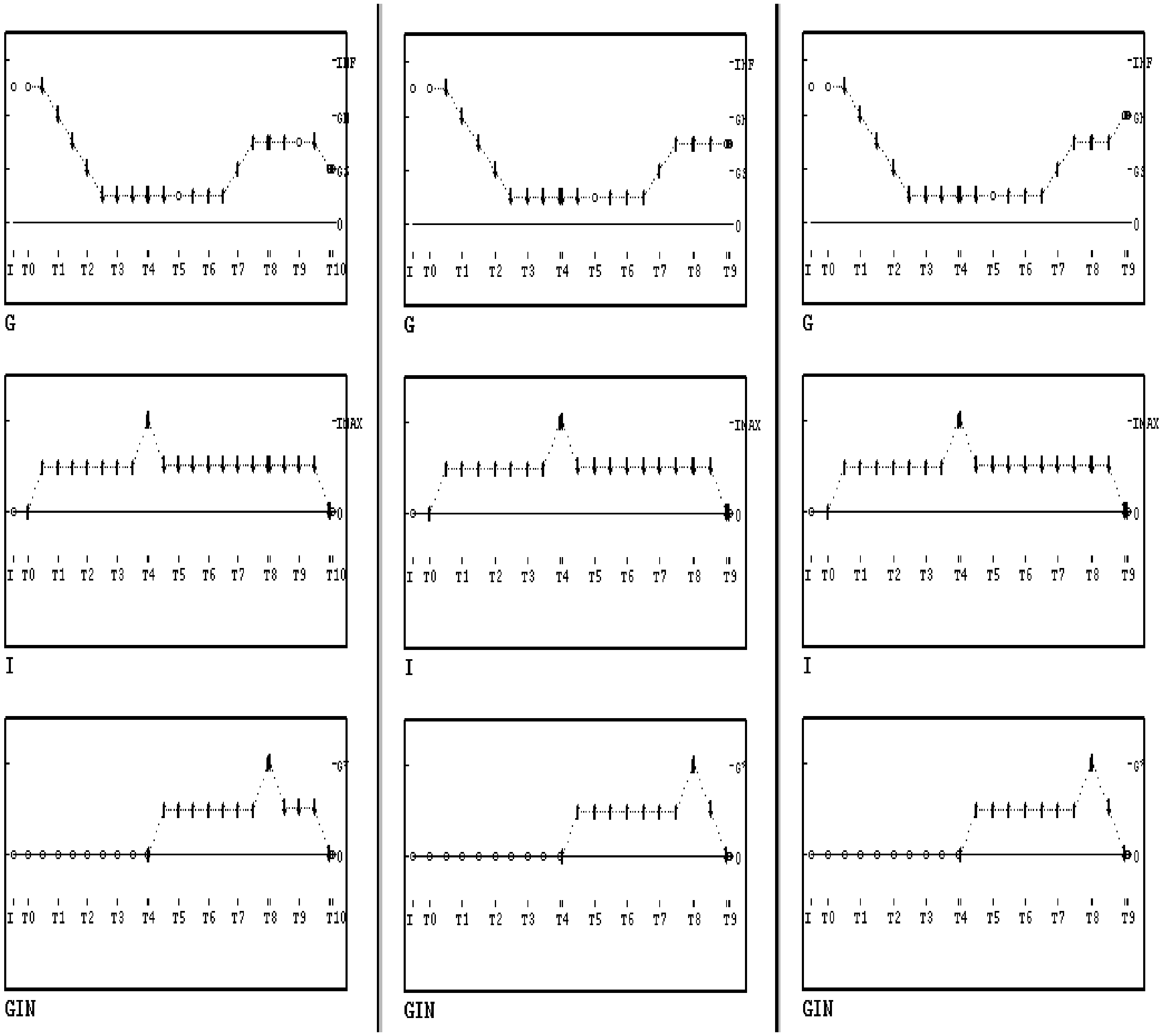


Figure 6: QSIM plots of the variables of interest, $g,\ i,\ g_{in}$. Each column reports the plot of the representative of each class of equivalent behaviours with respect to g. The g steady state value is equal to: (1) Hypo, (2) Normal, (3) Hyper. The symbol ‘I’ on the time-axis corresponds to the initial condition.

1. "If $g(t)$ is very-Hyper and $di(t)$ is Zero and $dg_{in}(t)$ is Zero then $g(t+1)$ is very-Hyper"
2. "If $g(t)$ is very-Hyper and $di(t)$ is Positive and $dg_{in}(t)$ is Zero then $g(t+1)$ is very-Hyper"
3. "If $g(t)$ is very-Hyper and $di(t)$ is Positive and $dg_{in}(t)$ is Zero then $g(t+1)$ is Hyper"
4. "If $g(t)$ is Hyper and $di(t)$ is Positive and $dg_{in}(t)$ is Zero then $g(t+1)$ is Normal"
5. "If $g(t)$ is Normal and $di(t)$ is Positive and $dg_{in}(t)$ is Zero then $g(t+1)$ is Hypo"
6. "If $g(t)$ is Hypo and $di(t)$ is Positive and $dg_{in}(t)$ is Zero then $g(t+1)$ is very-Hypo"
7. "If $g(t)$ is very-Hypo and $di(t)$ is Positive and $dg_{in}(t)$ is Zero then $g(t+1)$ is very-Hypo"
8. "If $g(t)$ is very-Hypo and $di(t)$ is Zero and $dg_{in}(t)$ is Positive then $g(t+1)$ is very-Hypo"
9. "If $g(t)$ is very-Hypo and $di(t)$ is Negative and $dg_{in}(t)$ is Positive then $g(t+1)$ is very-Hypo"
10."If $g(t)$ is very-Hypo and $di(t)$ is Negative and $dg_{in}(t)$ is Positive then $g(t+1)$ is Hypo"
11. "If $g(t)$ is Hypo and $di(t)$ is Negative and $dg_{in}(t)$ is Positive then $g(t+1)$ is Normal"
12. "If $g(t)$ is Normal and $di(t)$ is Negative and $dg_{in}(t)$ is Positive then $g(t+1)$ is Normal"
13. "If $g(t)$ is Normal and $di(t)$ is Negative and $dg_{in}(t)$ is Zero then $g(t+1)$ is Normal"
14. "If $g(t)$ is Normal and $di(t)$ is Negative and $dg_{in}(t)$ is Negative then $g(t+1)$ is Normal"
15. "If $g(t)$ is Normal and $di(t)$ is Negative and $dg_{in}(t)$ is Negative then $g(t+1)$ is Hypo"
16. "If $g(t)$ is Normal and $di(t)$ is Negative and $dg_{in}(t)$ is Negative then $g(t+1)$ is Hyper"

Table II: The linguistic FRB derived from the simulated qualitative behaviours in Fig. 6

4.4 Identification results

The performance of the method has been evaluated on data obtained by exploiting the simulator proposed by Lehmann and Deutsch [11]. The overall procedure has occured in two steps:
1 – *Training phase*: identification of the parameter vector $\underline{\theta}$ of equation (6) on a set of experimental data, and cross-validation of the obtained function approximator $y(\underline{x})$. We have simulated, over a period of 24 hours with different sampling time ranging from 15 minutes to 8 hours, the patient response to an injection of regular insulin followed by a meal. The performance of $y(\underline{x})$, obtained by using the QM (denoted by FS-QM), has then been compared, through Root Mean Square Error (RMSE) calculation, with that of a function approximator identified by using only the data (indicated as FS-Black-Box, FS-BB), as proposed by Wang [17].
2 – *Validation phase*: evaluation of the predictive accuracy of $y(\underline{x})$ when dealing with a new data set. In particular, the new data set has been obtained by simulating the patient response to a typical daily insulin protocol, composed by two injections of NPH insulin and two injections of regular insulin, followed by a meal.

We have tested both steps in different experimental settings; the results obtained may be summarized as follows:

(a) Training and Validation with noise-free data; minimum sampling time.

Table III shows the results obtained by *training* both FS-QM and FS-BB without adding experimental noise on the data, and with a sampling time of 15 minutes.

BP-*Loops*	FS-QM	FS-BB
0	23.576	44.459
2	14.467	25.163
5	10.826	4.158
10	7.837	3.481
20	7.816	3.410
30	6.336	3.379
50	4.177	3.348
100	2.076	3.324
150	1.868	3.314

Table III: Training with noise-free data (RMSE (mg/dl))

BP-*Loops*	FS-QM	FS-BB
0	27.476	104.193
2	13.831	50.432
5	9.637	60.153
10	9.583	61.293
20	15.360	61.812
30	16.296	62.201
50	18.227	62.784
100	19.272	63.478
150	18.999	63.690

Table IV: Validation after training with noise-free data (RMSE (mg/dl))

We notice that the initial guess of the FS-QM has good approximation capabilities. Moreover, when the number of BP iterations (loops) increases, the FS-QM converges to the global minimum (i.e. RMSE$\rightarrow$ 0) while the FS-BB seems to converge to a local one (i.e. RMSE$\rightarrow$ 3).

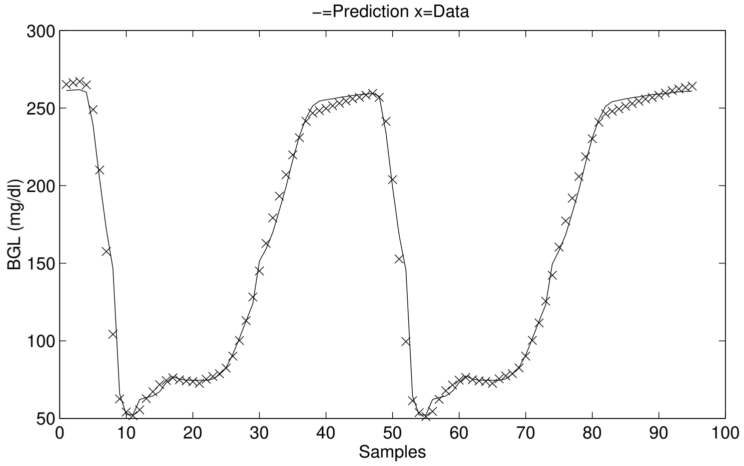
In the *validation phase*, the predictive accuracy of the fuzzy approximators, obtained in the training phase both by the FS-QM and by the FS-BB with a different number of loops, are compared. The FS-QM exhibits better performance than the FS-BB, as shown in Table IV.

Fig. 7 and Fig. 8 clearly depict the results shown by Tables III and IV. In a noise-free setting, the training data (see Fig. 7) are better approximated by the FS-QM than by the FS-BB; moreover, the FS-QM outperforms the FS-BB in the capability of approximating the validation data (see Fig. 8).

(b) Training and Validation with noisy data; minimum sampling time.

Table V shows the results obtained in presence of experimental noise added to the data ($\pm 5\%$ of each datum).

(A)



(B)

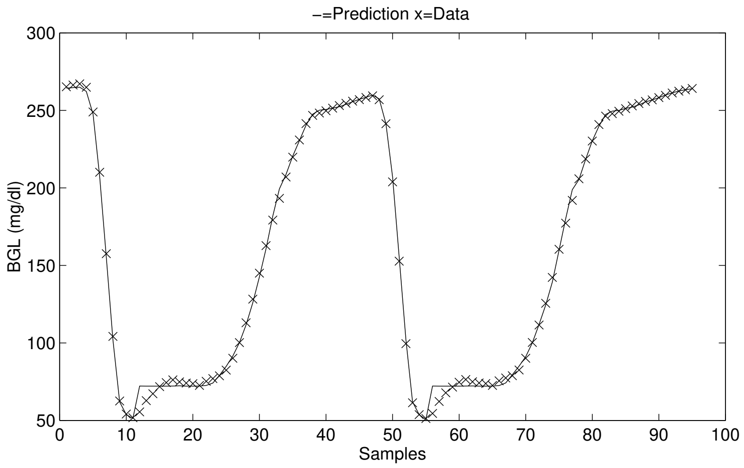
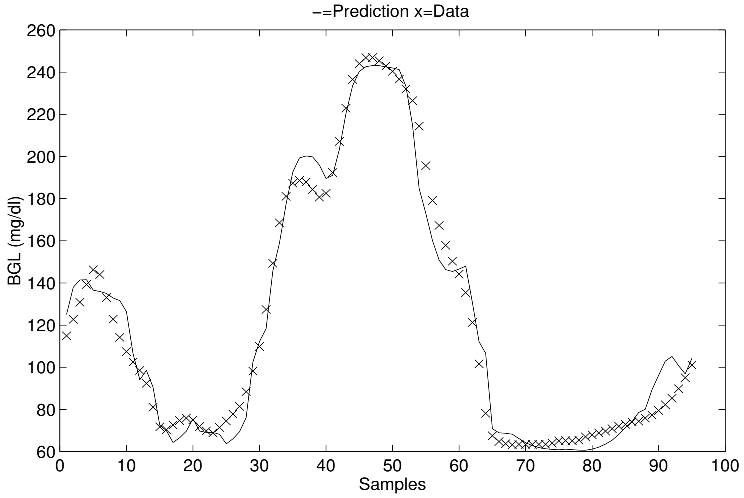


Figure 7: (A)=FS-QM, (B)=FS-BB (10 BP–loops). The plot shows the performance of the two approximation systems on the training set without experimental noise

(A)



(B)

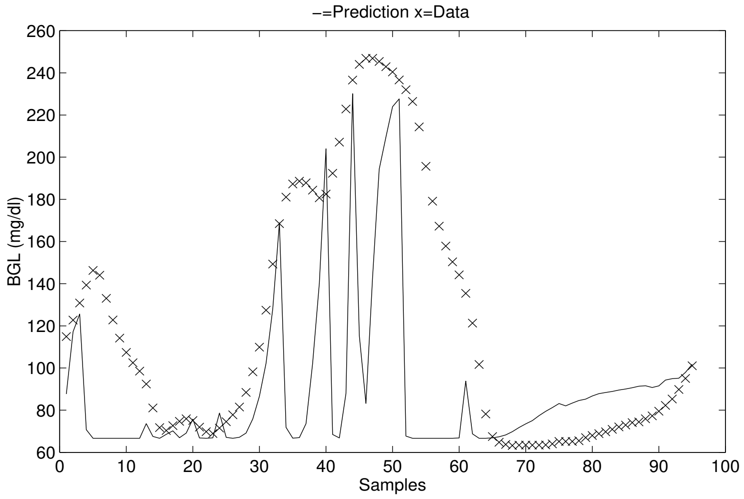


Figure 8: (A)=FS-QM, (B)=FS-BB. The plot shows the performance of the two approximation systems on the validation set

BP-*Loops*	FS-QM	FS-BB
0	40.757	41.882
2	23.950	29.159
5	21.604	25.012
10	21.517	23.029
20	19.497	21.091
30	18.646	21.238
50	18.271	20.821
100	18.051	20.635
150	17.928	20.552

Table V: Training with noise added to the data (RMSE (mg/dl))

The two approaches perform in a nearly-similar manner, although the FS-QM has a lower minimum of RMSE. However, in the *validation phase*, the FS-QM shows better performance than the FS-BB, being less prone to over-training problems. Table VI clearly illustrates this result.

BP-*Loops*	FS-QM	FS-BB
0	32.310	102.980
2	21.332	64.045
5	21.163	70.318
10	22.001	55.674
20	22.513	40.144
30	23.816	35.741
50	26.152	34.985
100	29.504	39.786
150	34.286	41.273

Table VI: Validation after training with noisy data (RMSE (mg/dl))

(c) Training and Validation with maximum sampling time.

Rather surprisingly, the derived FS-QM exhibits quite good approximation properties even if the training and validation phase are performed with only three samples a day. Clearly, it is meaningless to compare the system performance with the FS-BB, since in this case it is not resonable to use a purely FS-black-box identification scheme because of the lack of data. Tables VII and VIII report the RMSE calculated in this situation.

BP-*Loops*	FS-QM
0	32.661
2	31.512
5	22.275
10	12.999
20	4.951
30	1.590
50	0.198
100	0.001
150	6.5729e-6

Table VII: Training with three samples a day (RMSE (mg/dl))

BP-*Loops*	FS-QM
0	25.664
2	27.121
5	20.904
10	15.211
20	12.130
30	12.127
50	12.261
100	12.290
150	12.290

Table VIII: Validation after training with three samples a day (RMSE (mg/dl))

Some comments are needed on these results. Since the model is over-parameterized with respect to the number of data available, it is not surprising that the RMSE will tend to zero as the number of BP-loops increases. However, the performance of the validation phase is really interesting since it is comparable with that obtained by other authors who used all the available experimental data to identify the parameters. For example, in a recent study by Naylor et al. [13], the predictive accuracy of the one-step ahead predictions of their proposed model is very close to the predictive accuracy achieved after 30 BP-loops by our method.

These preliminary results therefore motivate further work in this application domain, towards an evaluation of the method on real patients' data.

5 Discussion

The work proposed in this paper describes a methodological framework that may be applied to a number of different applications. We use as a test benchmark a quite complex application problem, for which our proposed methodology could provide valuable contributions.

Of course, several problems are still open, and they will need further work. Some of these issues are described below:

Linear identification.

As introduced in section 3.2, if the parameters, $\hat{x}_i^j$ and σ_i^j, of the membership functions in equation (5) are fixed to their prior values, the identification of the FS turns from a non-linear problem into a linear one. Besides providing for a clear advantage from a computational point of view, this choice also allows us to preserve the structure of the FS initialized on the basis of the *a-priori* knowledge expressed in the qualitative model. Nevertheless, this choice may hamper the system in obtaining a really 'good' approximation of the unknown function, since the structure of the FS is fixed. A valuable compromise is to improve the initial guess of the parameter vector by applying a BP with a low number of loops on the training set, and then to recursively estimate only the linear parameters $\hat{y}_j$. In this way it is possible to exploit our proposed method in an on-line context as well, like adaptive control. Quite interestingly, an approach based on a two-step identification procedure has been applied to an on-line adaptive control of blood glucose level, based on sub-cutaneous sensor [16]. In that work, a Radial Basis Function (RBF) Neural Network is trained on simulated data, and then adapted to the real patient data by recursively estimating the parameters of the linear combination of the RBF. We believe that the preliminary results herein presented motivate further efforts in using the QM-FS approach as a possible competitor in this area.

Membership functions

The choice of the membership functions is an important step of the design of a FS, and becomes crucial when the FS has to be tuned on a set of experimental data. In an FS of the form expressed in equation (4), the choice of the membership function determines both the structural and approximation properties of $y(\underline{x})$.

In this paper we have chosen Gaussian Membership Functions (G-MFs), so that $y(\underline{x})$ assumes the form of equation (5). G-MFs have a number of desirable properties for estimation purposes: they are functions of only two parameters (mean and variance), that can be estimated using the BP-technique. Moreover, they are known to possess the *Universal Approximation Properties* [17], i.e. they are able to approximate any continuous function with an arbitrary degree of accuracy; if we want to estimate only the linear parameters $\hat{y}_j$, the proposed framework is also able to guarantee the *Best Approximation Property* [14], i.e. that it is possible to find the combination of parameters that better approximates the unknown function within the functional space defined by equation (4). Finally, G-MFs provide for good generalization properties as they ensure completeness ($\forall \underline{x} \in U, \mu(\underline{x}) > 0$), even when the fuzzy rule base spans only a subset of the Cartesian products of the input space.

On the other hand, G-MFs are symmetric and with a maximum value located in a single point: this means that some desirable properties, such as different shapes of the μ_i associated with either a landmark or an interval, cannot be represented. In order to preserve the advantages coming from G-MFs but to improve the capability of expressing prior knowledge, in the future we will investigate the use of *Pseudo-trapezoidal functions* [19].

Semi-quantitative models

The more complete is the a-priori knowledge exploited in the model formulation phase, the more close to the solution is the initial guess generated, resulting in improved efficiency of the method. Actually, the knowledge available, even when incomplete, is often richer than the pure qualitative one: *bounding intervals* or *order of magnitudes* may properly represent quantities partially known, and *bounding regions* may envelop the variability domain of the functional relations.

As in our application context the quantitative information on the input signals and on the landmark values is partially known (for example, the value of GN is around 180 mg/dl), further work will consider a semi-quantitative model formulation of the BGL dynamics. Such a model will be implemented using an extended version of QSIM (Q2 [10]), which is able to perform semi-quantitative reasoning. The introduction of additional knowledge will significantly reduce the size of the behaviour tree by filtering those behaviours inconsistent from a quantitative point of view, and consequently make the behaviour classification procedure more efficient. A further reduction of the behaviour tree will be obtained by introducing in the model additional temporal constraints on the dynamics of the input signals.

6 Conclusions

Medical applications are often characterized by problems of a two-fold nature:

- the physician usually has a deep patho–physiological knowledge of the patient's behaviour.
- it is not possible to measure all the quantities necessary to completely assess the patient's state.

As a consequence, although many mathematical models of physiological systems are available, it is usually not possible to identify such systems, and it is hence necessary to resort to black-box strategies, with a consequent loss of the available prior information on the domain.

This work represents a valuable answer to the above presented problems: it describes a novel approach to the identification of non-linear dynamical systems, based on fuzzy systems and qualitative models. The outcomes obtained from the simulation of a set of qualitative differential equations are used to automatically encode the available knowledge in a fuzzy rule-based system; such a system is then tuned to a set of experimental data. The results obtained show that the presented framework generates fuzzy systems that may be used to reliably and efficiently identify non-linear systems.

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