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Off-line control of the postprandial glycemia in type 1 diabetes patients by a fuzzy logic decision support

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ABSTRACT

The target of this paper is to describe the use of fuzzy techniques in the development of a decision support system that allows the optimization of postprandial glycemia in type 1 diabetes patients taking into account the kind of meal taken by patients, the preprandial glycemia and the insulin resistance (the response of the body to insulin dose injection therapy). The decision support system can, in many cases, provide patients with the correct number of rapid insulin units that must be assumed to assure an optimal glycemic profile, keeping the blood glucose level close to the homeostatic condition, several hours after the meal.

1. Introduction

Diabetes mellitus is actually one of the most diffuse metabolic diseases and represents a growing serious problem around the world. Who is affected by diabetes mellitus has usually got a high blood glucose level as a consequence of either the body not producing enough insulin, or the body cells not properly responding to the insulin produced by pancreas (insulin-resistance). Insulin is a hormone produced in pancreas which enables body cells to absorb glucose, turning it into energy. If body cells do not absorb glucose, this last one accumulates in the blood (hyperglycemia), leading to various potential medical complications (World Health Organization, 2006). There are many types of diabetes (Expert Committee, 2003), but the most common of which are called type 1 diabetes and type 2 diabetes. The cause of the first form of diabetes (type 1 diabetes) is a pancreatic beta-cells failure to produce insulin, obliging patients to inject it subcutaneously, with external insulin doses, necessary for their survival. The second form of diabetes (type-2 diabetes) is due to a condition in which an absolute or relative insulin deficiency is combined with cell failure to use insulin properly. Insulin therapy simulates the activity of pancreas and different kinds of insulin may be used, with different time of action (rapid, ultra-rapid, slow or basal etc.). The patients affected by type 1 diabetes are exposed to frequent post-prandial hyperglycemia defined as an high blood glucose concentration after meal and/or post-prandial hypoglycemia defined as a low blood glucose concentration. Diabetes has therefore to be kept under control necessarily, because these abnormal low or high blood glucose levels may lead respectively to cardiovascular problems or to fainting and also diabetic coma. Unfortunately, there are not, until now, useful tools that provide the correct dose of insulin that patients assume just before the meal (rapid insulin), taking into account the kind of meal and to the clinical state of the patient.

The changes of the insulin therapy made by diabetologists are subsequent to glycemic decompensations (Ahern et al., 1993; Jenkins & Jenkins, 1987; Smith, 1994). It is well known from literature that insulin pump manufacturers have recently engineered a *bolus calculator*. The bolus calculator takes into account the current patient blood glucose level, the target blood glucose, the amount of carbohydrate consumed, and other factors such as the insulin sensitivity, the insulin-to-carbohydrate ratio and the duration of the insulin action helping patients to obtain a good control over the blood glucose level by calculating bolus insulin doses based on data input inserted by the pump wearer. Each pump company calculates insulin doses in a slightly different way but the results are actually not satisfactory in clinical practice (Zisser et al., 2008). Several systems have been already proposed. They differ for the variables used as inputs and outputs, the calculation algorithm and the validation method. Ambrosiadou, Gogou, Maglaveras, and Pappas (1996) proposed a decision support for insulin regime prescription based on neural-network approach as well as Mougiakakou and Nikita (2000) and Gogou, Maglaveras, Ambrosiadou, Goulis, and Pappas (2001). These last investigate the application of a neural network approach for the development of a prototype system for knowledge classification in insulin regimen specification and dose adjustment. Lehmann (2004) examined the hurdles that may rise implementing computerized decision-support tools in diabetes care; Campos Delgado, Hernandez-Ordonez, Femat, and Gordillo-Moscoso (2006) proposed, on the contrary, a system that works like a two loops off line control system: one control loop regulates the rapid insulin to be injected at meals time while the second loop works on a daily basis regulating the slow insulin. Their controller uses as input only

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the preprandial glycemia. The validation of the system has been carried out by simulation using a compartmental model. A bolus calculator that takes into account the energy of carbohydrates, the metabolic efficiency and the dependence on the person of the energy transformed in blood glucose was proposed by Mathews and Pelzer (2009). Shapira, Yodfat, HaCohen, Feigin, and Rubin (2010) took into account the carbohydrate content of the meal as well, but to overcome the uncertainty of its determination they proposed a decision support tool based on the optimization of insulin doses for carbohydrate ranges. Pankowska and Blazik (2010) proposed a bolus calculator taking into account proteins and lipids, in addition to carbohydrates for two out of phase insulin injections that are justified by the different absorption time. Tadic, Popovic, and Djukic (2010) presented a new fuzzy model for evaluation and choice of optimal therapeutic procedure on individual level for patients with type 2 diabetes. More recently Simon et al. (2011) developed a web-based decision support system for evaluation of blood glucose levels and adjustment of the insulin dose (insulin self-titration).

The author developed a decision support system conceived to provide patients with the number of rapid insulin units that may assure optimal glycemic behavior after a meal. The decision support system must be fed with data concerning the meal, the physical and clinical personal conditions, including pre-prandial glycemia. The operation principle is the same of an offline mixed feedback-feedforward controller. It is based on the measurement of the output controlled variable (blood glucose level) and the measurement of the main disturbances (kind and amount of the food taken). Fuzzy and neurofuzzy techniques were chosen for the implementation of the offline decision support system. The choice of fuzzy system (Kahramanli & Allahverdi, 2008; Osuagwu & Okafor, 2010; Ganji & Abadeh, 2011) is justified by the need of both handling food data that are usually not accurate, and inherently fuzzy, and taking into account the features of a very complex biological system as the glucose metabolism in the human body may be, for which until now a reliable and effective mathematical model is not available, despite many research attempts already tried (Bergman, Ider, Bowden, & Cobelli, 1979; Sorensen, 1985). Three main phases characterize the development of the decision support. In the first phase, data concerning the physical and clinical conditions of a group of type 1 diabetes patients involved, the kind and amount of food eaten during their meals together with glycemia levels before and after them, were recorded for a period of time. In the second phase the development of the hierarchical

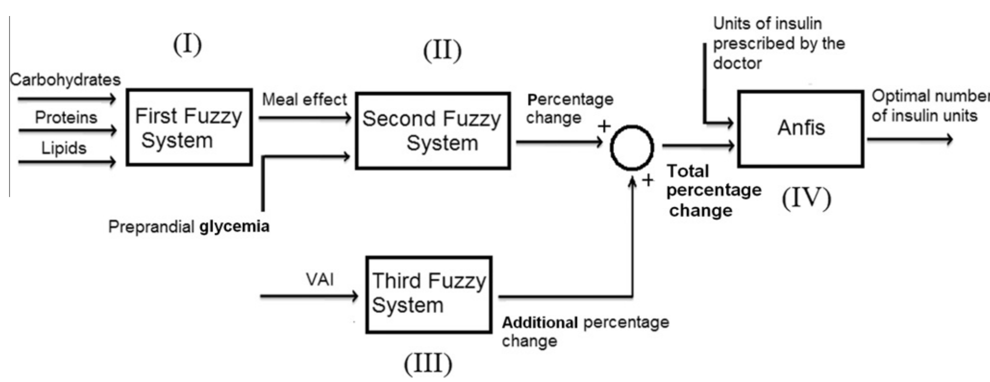

Fig. 1. Block diagram of the fuzzy system.

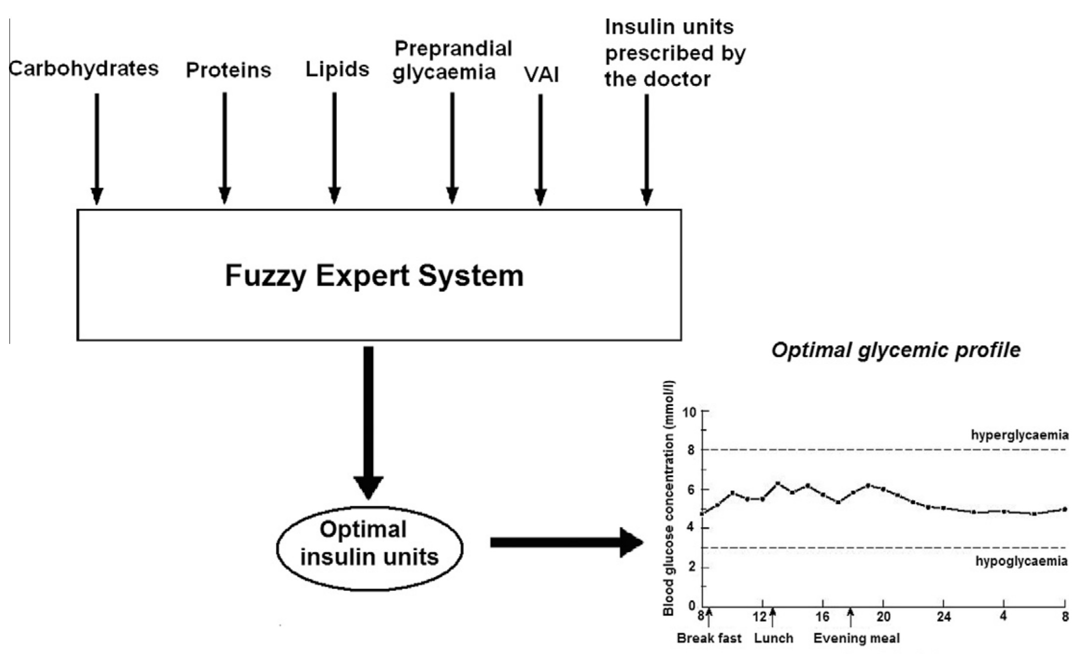

Fig. 2. Input–output of the fuzzy expert system. The output of the fuzzy expert system assures an optimal glycemic profile.

fuzzy system was realized. All the fuzzy system rules and all the fuzzy set parameters (range and membership functions) were chosen on the base of the knowledge and experience of the doctors, while the neurofuzzy subsystem was realized using, for training and validation the experimental data provided by patients. In the third phase the hierarchical fuzzy system was tested with the experimental data collected in the first phase. An improvement for the fuzzy expert system could come from the use of type-2 fuzzy sets instead of traditional fuzzy sets, in particular in the first subsystem considering that food data, for several reasons, are affected by uncertainty (Mendel, 2001; Galluzzo & Cosenza, 2012).

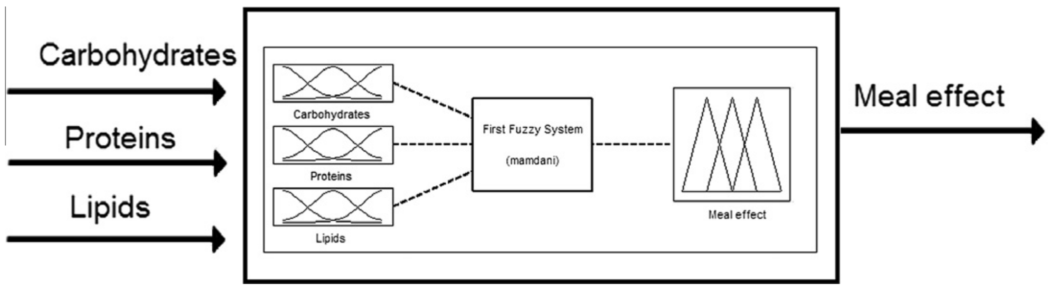

Fig. 3. Block diagram of the first fuzzy system.

Table 1
Fuzzy set parameters.

First fuzzy system			
Carbohydrates (I Input): membership functions		Proteins (II Input): membership functions	
Low (trapezoidal)	[−153.7 −100 30 50.2]	Low (trapezoidal)	[−135 −15 12 15.9]
Medium (triangular)	[27.1 60 100.1]	Medium (triangular)	[12.05 18 27.5]
High (trapezoidal)	[73.76 120 430 430]	High (trapezoidal)	[23 30 165 285]
Lipids (III Input): membership functions		Meal effect (Output): membership functions	
Low (trapezoidal)	[−89.88 −9.884 3 6]	Low (trapezoidal)	[−8.1 −0.9 1.5 3.501]
Medium (triangular)	[4 7 12]	Medium (triangular)	[2 4.5 6.5]
High (trapezoidal)	[9.12 17 110 190]	High (trapezoidal)	[4.989 7.5 9.89 17.1]
Second fuzzy system			
Meal effect (I Input)		Preprandial Glycemia (II Input)	
Low (trapezoidal)	[−8.1 −0.9 1.5 3.501]	Very low (trapezoidal)	[−206 −13.7 25.3 42.5]
Medium (triangular)	[2 4.5 6.5]	Low (triangular)	[30 60 90]
High (trapezoidal)	[4.989 7.5 9.89 17.1]	Medium (triangular)	[80 140 200]
		High (triangular)	[169 250 329]
		Very high (trapezoidal)	[312.5 384.5 498.5 630.5]
Percentage change (Output): membership functions			
Very low (trapezoidal)	[−54.3 −30.3 −25 −16.3]		
Low (triangular)	[−19.7 −12 −4.92]		
Medium (triangular)	[−8.184 0 6]		
High (triangular)	[2.841 12.07 19.77]		
Very high (trapezoidal)	[15.16 25 35.45 59.45]		
Third fuzzy system			
VAI (Input)		Additional percentage change (Output: Crisp number)	
Low (trapezoidal)	[−6.75 −0.75 1.06 1.33]	Low	0
Medium (trapezoidal)	[1.06 1.33 1.45 5.53]	Medium	5
High (trapezoidal)	[1.45 5.53 20 21.3]	High	10

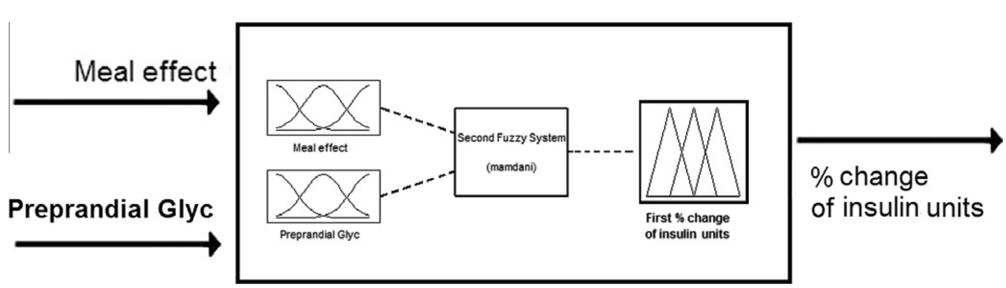

Fig. 4. Block diagram of the second fuzzy system.

2. Fuzzy system

The fuzzy system is constituted by three fuzzy systems (Zadeh, 1965, 1973) and one Anfis system (Jang, 1993) as shown in Fig. 1 and is characterized by a hierarchical structure. The second fuzzy system decision (output) is in fact subordinate to the first fuzzy system decision and the Anfis final output is in turn subordinate to the second and third fuzzy system decision. Only the first and the third fuzzy system are not subordinated to other entity output in this organizational structure. The hierarchical structure let us

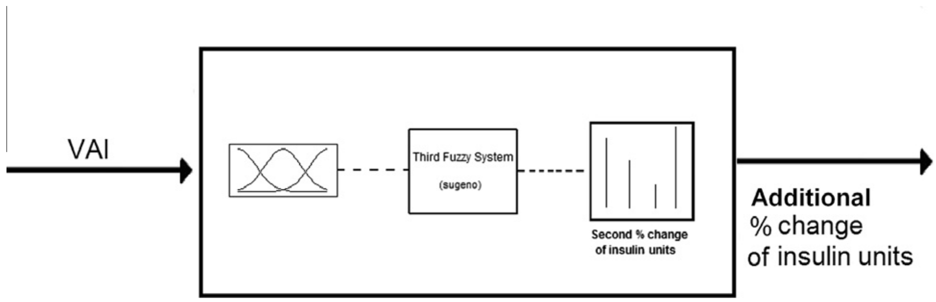

Fig. 5. Block diagram of the second fuzzy system.

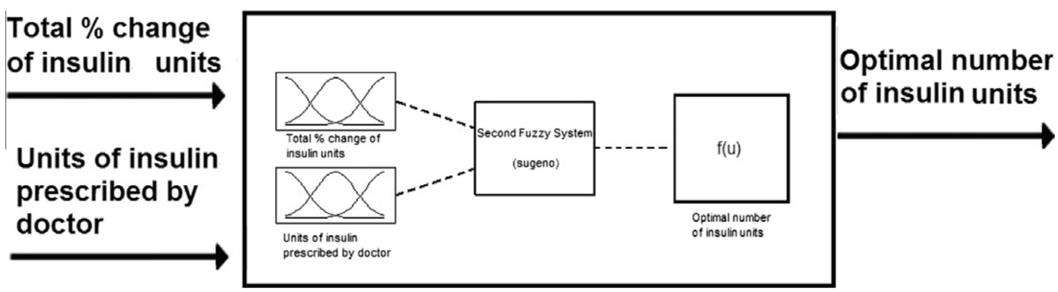

Fig. 6. Block diagram of the second fuzzy system.

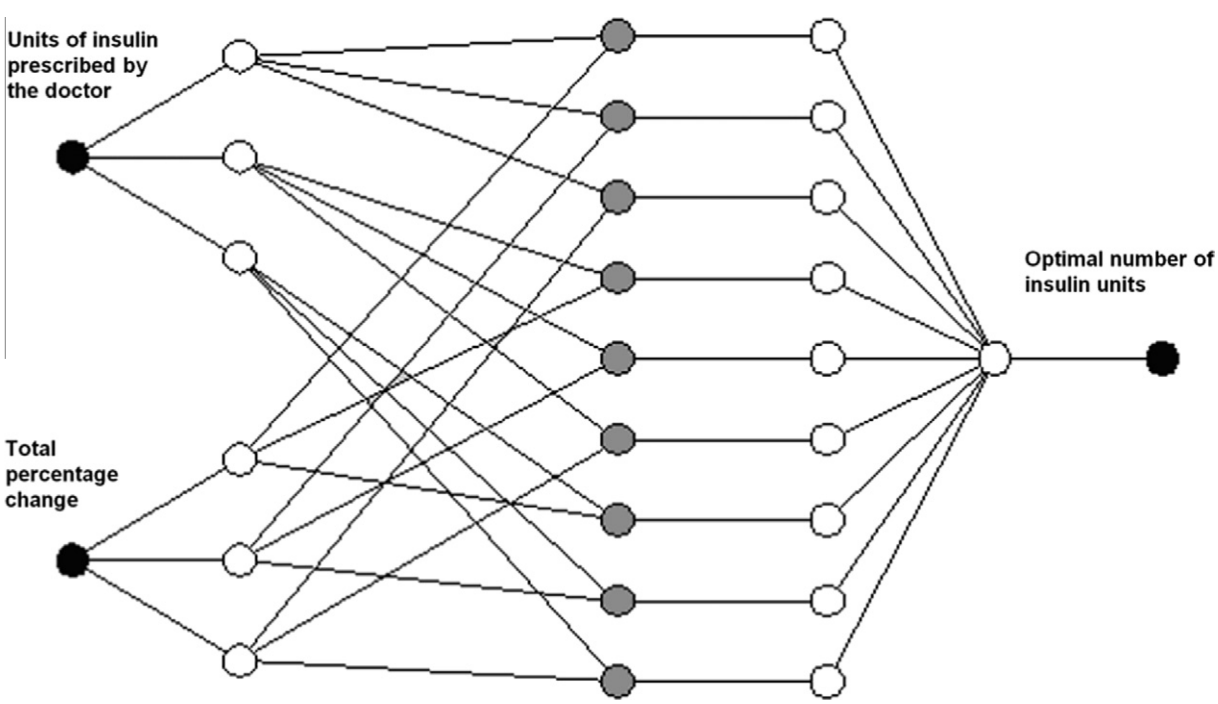

Fig. 7. Anfis system structure.

correct the output of the first fuzzy system, taking into account other physiologic characteristics of the patients by the use of the other fuzzy systems.

From Figs. 1 and 2 it is possible to see that the inputs of the whole fuzzy system are the type and the amount of food eaten during the meal, converted in amounts of carbohydrates, proteins and lipids (first fuzzy system block), the preprandial glycemia (second block), the number of rapid insulin units recommended by the doctor therapy and an index number called VAI (Amato et al., 2010) (third block), gender specific, calculated through the values of triglycerides, high density lipoprotein (HDL) and the body mass index of the patient. This number allows to estimate the patient insulin sensitivity and has a good correlation with the euglycemic hyperinsulinemic Clamp test (DeFronzo, Tobin, & Andres, 1979), considered as the Gold standard for the insulin sensitivity estimation.

2.1. First fuzzy system

The inputs of the first fuzzy system (Fig. 3) are the amounts of carbohydrates, proteins and lipids assumed by the patient during the meal. The fuzzy system inference uses the Mamdani inference method (Mamdani, 1977).

It is possible to evaluate the input values by a calculation module using the informations about the kind and amount of food and the nutrition tables drawn by the Italian National Research Institute for Food and Nutrition (http://www.inran.it). The output of the first fuzzy system is a parameter called ''meal effect'' representing the effect that the meal has on the blood glucose concentration. All the inputs and output of the first fuzzy have got three membership functions; the range of the inputs and the output, the membership function parameters and the rules were established on the basis of several doctors knowledge (Table 1).

2.2. Second fuzzy system

The input of the second fuzzy system are the ''meal effect'' (the output of the first fuzzy system) and the preprandial glycemia, a check up that patients usually use before a meal (Fig. 4).

The membership functions and the parameters for the ''meal effect'' are the same provided for the first system, while there are five membership functions for the preprandial glycemia. The output of the second fuzzy system represents the percentage change of the number of rapid insulin units prescribed by doctors in the traditional therapy that should be applied as a consequence of the two inputs, the meal effect and the preprandial glycemia value (Table 1).

2.3. Third fuzzy system

The third fuzzy system uses the Sugeno inference method (Sugeno & Kang, 1998) and is constituted by one input and one output: the input is the VAI and the output is an additional percentage change of prescribed insulin units depending on the VAI (Fig. 5).

This fuzzy system is in fact the only system that can take into account the insulin-resistance of a patient (Amato et al., 2010; DeFronzo et al., 1979; Borghi, Zambrelli, Fontanesi, Zavaroni, & Strozzi, 2006). Consequently, the third block may determine a further increase of the dose of insulin necessary to achieve a good

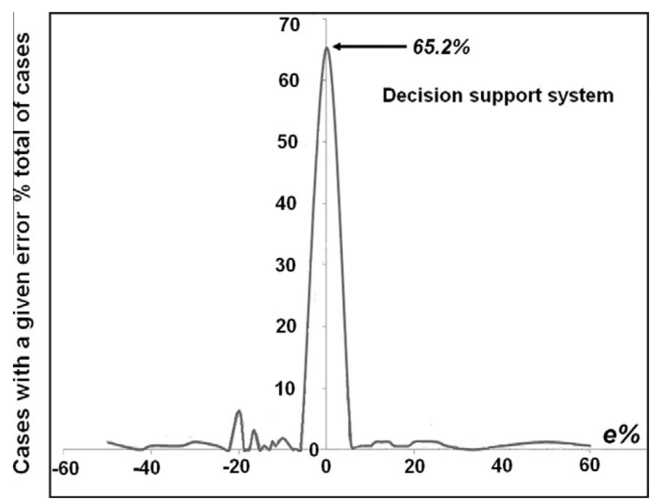

Fig. 9. Percentage of cases with a given error vs % error (percentage of prescribed insulin units) produced by the decision support system.

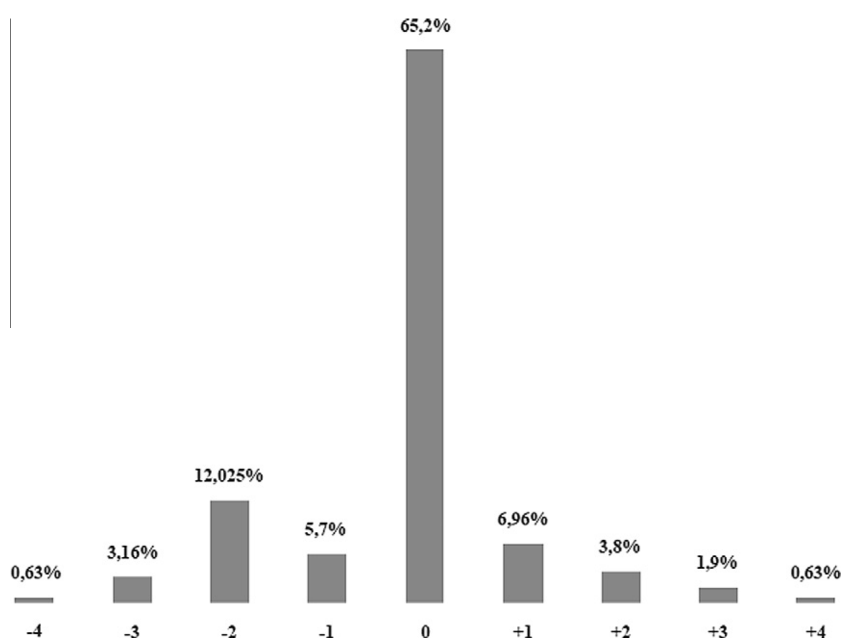

Fig. 8. Histogram for the error of the support system decision in terms of insulin units.

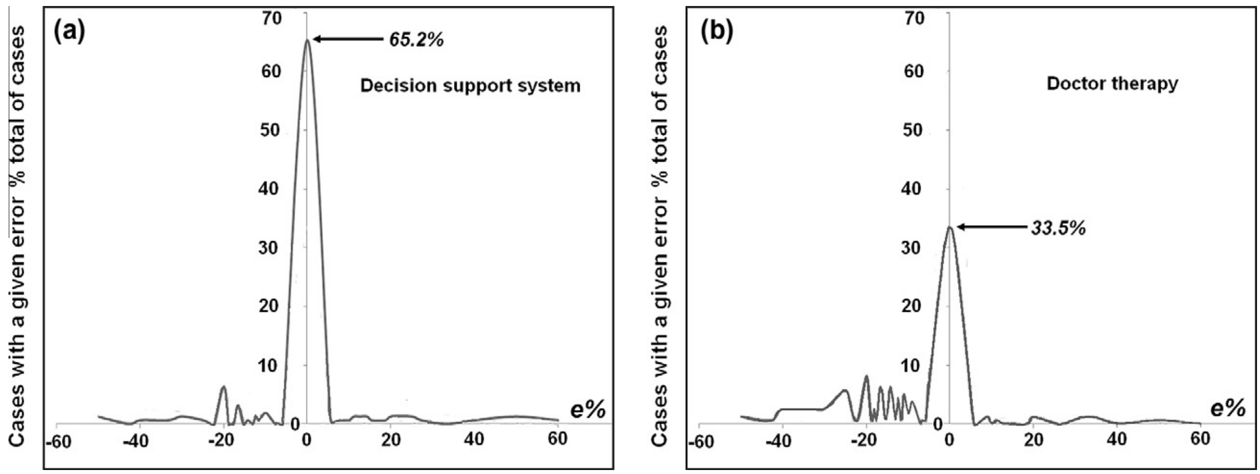

Fig. 10. Comparison between therapy with decision support system and original doctor therapy. (a) Percentage of cases with a given error vs. % error (percentage of prescribed insulin units) produced by the decision support system. (b) Percentage of cases with a given error vs. % error (percentage of prescribed insulin units) when original prescribed insulin units are used in the traditional doctor therapy.

control of blood glucose concentration. Even in this case, like for the first and the second, all fuzzy system parameters (membership functions, range of the inputs and the output) and rules have been established on the basis of several doctors' knowledge (Table 1).

2.4. Neuro fuzzy system

The sum of the two percentage changes, from the second and the third fuzzy system, constitutes one of the two inputs of the fourth block (Fig. 6): an Adaptive Neuro Fuzzy Inference System (ANFIS) (Jang, 1993; Jang & Sun, 1995; Jang & Sun, 1997; Wang & Elhag, 2008).

The second input is the number of rapid insulin units prescribed by the doctors in the traditional therapy. The output is the number of units which can keep the concentration of glucose in the blood close to the homeostatic condition. The presence of this block is necessary to avoid the high sensitiveness of the algorithm to high insulin units and the low sensitiveness to low insulin units. An alternative to the Anfis system can be an algorithm (possibly an other fuzzy system) that multiplies the high numbers of insulin units for some coefficients < 1 and the low numbers of insulin units for some coefficients > 1, but in this last case the performance of the whole fuzzy hierarchical system decreases slightly despite a more simple structure of the fourth block. In this paper only the Anfis structure is considered for the fourth block trained making use of input–output data (Fig. 7).

The input data are the sum of percentage changes calculated by the previous fuzzy systems and the insulin units originally prescribed by doctors; the output, i.e. the target, is instead the number of optimal units suggested by expert doctors on the base of the knowledge of the clinical state (preprandial glycemia, VIA) and the meal characteristics. The proposed system has been tested on a set of 158 cases, 120 used for the training 38 for the validation. The number of patients is 29, aged between 18 and 48, including individuals with a tendency to postprandial hyperglycemia, a tendency to postprandial hypoglycemia and unstable diabetes.

3. Results

The evaluation of the fuzzy expert system is the result of the comparison between the insulin units suggested by the fuzzy expert system (decision support system), and the insulin units indicated by doctors examining the glycemia profile after a meal and correcting the initial prescription. In the histogram of Fig. 8 and in the graph of Fig. 9 the number of cases with a given error (as percentage of total cases) versus the error produced by the decision support system (as percentage of prescribed insulin units in Fig. 9) is shown.

An encouraging result is that the percentage of cases with zero error is about 65.2%. The performance is even better appreciable considering that cases with a prescription of few insulin units need a relatively higher percentage change to produce effective changes in the therapy (for example if 2 insulin units were prescribed a 25% change is at least needed).

To appreciate furtherly the performance of the fuzzy expert system in Fig. 10 the comparison between the therapy with the fuzzy expert system and the original doctor's therapy is shown. Fig. 10b shows in fact the analogue graph if the original doctor's prescriptions was followed. It must be stressed that the percentage of cases with zero error is much lower (about 33.5 %) than the one with a decision support system (Fig. 10a). The reference used for the evaluation of the decision support system is, as above referred, the prescription of expert doctors based on the same input data. It is evident that in almost all cases the fuzzy expert system is able to suggest the same therapy change indicated by the doctors, therefore avoiding glycemic diseases dangerous for patient health. The system is intended to be used as a decision support system by type 1 diabetes patients in the interval between two medical visits.

4. Conclusions

The results obtained with the proposed fuzzy expert system are very encouraging. The decision support system is in fact able to suggest the appropriate change of insulin units to be injected before a meal, taking into account the characteristics and the amount of the food, the preprandial glycemia and the insulin resistance. All the results obtained with the fuzzy expert system are furtherly encouraging if compared with those of original doctor prescription. The performance of the fuzzy expert system might probably improve if the physical activity after the meal is also considered. Another improvement could come from the use of type-2 fuzzy sets, in particular in the first subsystem, considering that food data are affected by uncertainty. Moreover the system could be tuned also for a specific patient through an offline application of the Anfis module.

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