Adaptive Controllers for Intelligent Monitoring

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Introduction

In the Insulin Dependent Diabetes Mellitus (I type diabetes), the insufficient insulin production impairs the closed-loop insulin/glucose regulation system. Diabetic patients need exogenous insulin in order to restore the correct glucose metabolism. The challenging problem of managing diabetic patients is essentially a long term control problem, whose goals are to normalize the Blood Glucose Levels (BGL) and to avoid hyperglycemic peaks and hypoglycemic episodes. Although this task is very complex, involving various factors, as patient's life-style and treatment compliance, we have chosen the diabetes problem as a benchmark for the definition of a novel methodology for intelligent patient monitoring based on adaptive controllers.

Background

Modelling glucose metabolism has been one of the leading problems in bioengineering research. Studies of physiological models are widely reported in the work of Cobelli [1],[2]. Moreover, also the problem of diabetic patients management has been faced since the 60s. Early modeling studies refer particularly to the project of the artificial pancreas [3], whose first commercial prototype was called BIOSTATOR [4]. The BIOSTATOR evolved successively to more modern systems based on *adaptive control* of Blood Glucose Levels (BGL) [5]. *Adaptive controllers* are particular kinds of controllers, able to modify their control strategy by estimating recursively the parameters of the process response model (in our case the model describes the response to the insulin drug delivery). Usually the model is not a physiological one, but a linear, low order model, with time-varying parameters (for example an Auto Regressive Moving Average with eXogenous inputs model, namely ARMAX). The roughness of the model is made up for the adaptation capability of the system. The adaptive systems often need a supervisor [5], able to assess both the order and the structure of the model. Although latest artificial pancreas are portable by patients, the lack of an implantable glucose sensor, able to detect correctly and for a long time the BGL, and the risks connected with a permanent subcutaneous injector hinders the artificial pancreas utilization in the every day treatment of diabetes.

Usually subcutaneous insulin injections are planned on the basis of an open loop strategy, decided by physicians according to their experience. When possible, an effective strategy is to define a partially closed loop control, managed by the patients themselves. To this aim the patient is taught to select the insulin dosage by using decision tables tailored by the physician. During the 80s some techniques have been studied in order to rationalize the definition of the decision tables [6],[7], on the basis of mathematical models of glucose metabolism, and of clinical experience. After these preliminary studies, expert systems have been developed in order to assist the management of Diabetes Mellitus [8],[9]. Recently Andreassen has proposed an approach to insulin adjustment based on Bayesian Networks and Decision Theory [10].

In the system proposed here, we take into account both the experience developed in the artificial pancreas studies and the previously mentioned expert system approaches, in order to propose a two-level adaptive controller for managing diabetic patients.

The monitoring system

Figure 1 shows an overview of our proposed methodology. Note that Fig.1 is *not* a sketch of an artificial pancreas, but a diagram showing the definition of a general intelligent adaptive monitoring system, applied to diabetes care. In Fig. 1 we distinguish two kinds of control actions: a *low level* strategy, and a *high level* strategy.

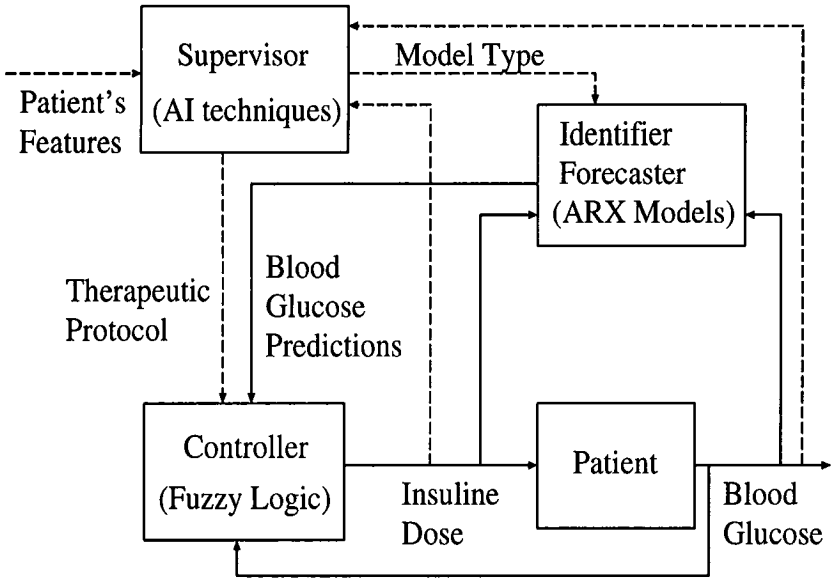

Figure 1: A block diagram of the proposed methodology for intelligent adaptive control: the Fuzzy Set Controller adapts its decisions (low level strategy) to the appropriate insulin dosage by using the actual Blood Glucose Levels (BGL) and the predictions on the future BGL given by the identifier/forecaster block; moreover the overall strategy (high level strategy) of drug delivery is planned by a supervisor, and periodically revised on the basis of the treatment outcomes. The dashed lines represent the information flows *from* and *to* the supervisor, while the continuous lines represent the information flows exploited to assess and to modify the low level strategy.

Low level strategy

The Low Level Strategy (L.L.S.) is based on an adaptive controller, built by using a Fuzzy Set Controller (F.S.C.)[11] and an adaptive ARX (Autoregressive eXogenous input) Model. The goal of the L.L.S. is to suggest to the patient the *next dosage* of insulin to be taken, according to the actual BGL and a given pre-defined insulin delivery protocol. In other words, the L.L.S. acts directly only on the *dosages* of insulin. The F.S.C. assesses opportune dosages by using decision making tables derived by physicians' experience. For example, the maximal and minimal allowed insulin dosages may be defined, as well as different desired BGL, according to the BGL measurement time (pre or post meal), or in the presence of non standard meal or physical exercise. Moreover, the F.S.C. is capable to use as input also the predictions on the future BGL given by an adaptive ARX model. Particularly, we have defined a F.S.C. with a strategy expressed by a set of rules as the following one:

IF actual BGL is LOW and future BGL prediction is VERY LOW THEN Insulin Dose Adjustment is STRONGLY DECREASE

By analyzing a large number of cases (60) from the data-base provided by the Organizing Committee for the 1994 AI in Medicine Spring Symposium, it was possible to define a low order ARX model of patient's response. Particularly, by using a two-hour linear interpolation to obtain a regular grid of measurements, we identified a class of ARX models, that can be used for the one and two step forecasting (two and four hours ahead forecasting), in dependence of the insulin delivery protocol: the model is a second order ARX, with *insulin activity* and *presence of meal ingestion* as exogenous inputs. The *insulin activity* was calculated as proportional to the area under the time profile of the plasma insulin concentration, previously calculated by using a one-pool compartmental model [1]. The *presence of meal ingestion* was taken to be a binary variable with value 1 at the meal time and 0 elsewhere. The order of the exogenous model components is individually selected and periodically (every two weeks) updated by using the Information Theoretic Criterion [12]. Figure 2 shows an example of the model fitting performance (patient n. 30 of the data base). An overall performance evaluation of the model for a one-step prediction has been made on the available data. The mean value of the one-step prediction error is 18.79

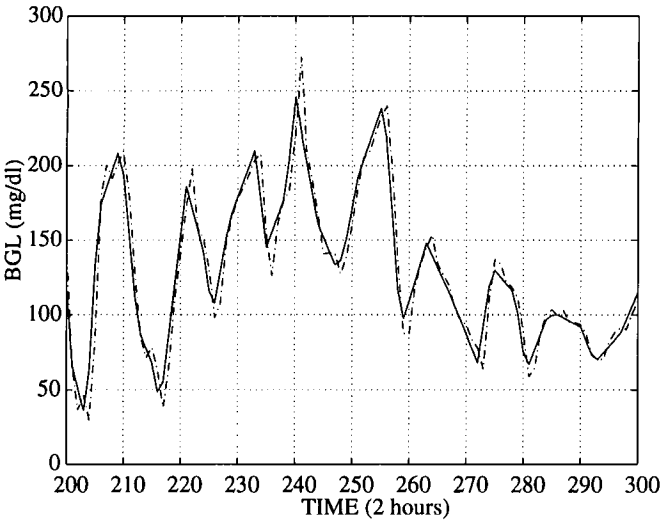

Figure 2: One-step ahead prediction provided by the ARX model defined on patient n. 30 of the data-base. The one-step ahead prediction line (dashed line) fits well the glucose profile obtained by linear interpolation of the data. The ARX model identified for this patient was the following: $G(t) = 1.5931\ G(t-\Delta t) - 0.6151\ G(t-2\Delta t) - 0.4521\ I(t-\Delta t) + 0.7867\ I(t-2\Delta t) + 0.3630\ I(t-3\Delta t) + 1.6470\ Meal(t-\Delta t) + 2.059\ Meal(t-2\Delta t) - 0.3236\ Meal(t-3\Delta t)$, were $G(t)$ stands for Blood Glucose Concentration at time t, $I(t)$ stands for plasma Insulin concentration at time t, $Meal(t)$ stands for presence (1) or absence (0) of Meal ingestion at time t and $\Delta t = 2\ hours$.

mg/dl, while the standard deviation is 7.97 mg/dl. The best performance was obtained for the patient n. 40 of the data-base with a mean prediction error of 2.09 mg/dl, while the worst performance was obtained with patient n. 62 with a mean prediction error of 34.76 mg/dl.

Although the results are satisfactory, it is worth to stress that an ARX model is *not* a physiological model, but a mathematical interpretation of the data, to be used at most for two or three-step ahead predictions.

During the patient monitoring, the model parameters are recursively identified (by using the recursive least squares method [12]), so that the ARX model predicts the BGL at the next measurement, and communicates its results to the F.S.C. Therefore the F.S.C. utilizes the actual BGL and the predicted BGL to adjust the pre-defined insulin protocol increasing or decreasing the drug dosage. Finally, the F.S.C. suggests an immediate meal ingestion when the Blood Glucose Level or the one-step prediction reaches a minimum, typically 60 mg/dl.

Figure 3 shows the F.S.C. performance on a simulated patient. We have supposed that the fictitious patient modifies the meal plan from step 60 to step 100, strongly augmenting the carbohydrate intake. The subsequent BGL increase is then partially compensated by the control action performed by the F.S.C. Moreover, outside this critical period the F.S.C. provides a short term therapy adjustment to the physiological BGL cycling. The simulation was performed adding white noise to a BGL profile, obtained by using a compartmental model of the insulin and glucose metabolism that is a simplified version of that proposed by Cobelli et al. [1].

High level strategy

The management of diabetic patients, as well as the management of a variety of chronic patients, requires a supervising activity, that can be viewed as an adaptive high level control. The High Level Strategy (H.L.S.) has to exploit both medical knowledge and clinical information coming from the physician's experience and the patient's characteristics, in order to assess the patient's management strategy. We have identified the high level controller tasks as follows:

a) The characterization of the patient, on the basis of the actual metabolic control, of the patient's treatment compliance, and of some important measurements, such as ketonuria and glycosylated hemoglobin. This characterization may be obtained by using production rules. Other rules might suggest the insulin protocol, defined in terms of the number of insulin injections, time spacing of drug deliveries and insulin type. Moreover the H.L.S. should suggest the diet plan and the daily physical exercise. Table I shows an example of REGULAR insulin protocol, that is a slight modification of the one proposed by the expert system CADMO [9].
For example a rule might be

IF hypoglycemic events occur during the night THEN choose a protocol with no injections at Bed Time.

The H.L.S. must decide also the goal of the therapeutic action, i.e. the mean and the range of admissible Blood Glucose Levels.

b) Once the goals and the protocol are defined, the H.L.S. chooses the appropriate rule table of the F.S.C. and selects the maximum ARX model order to be used during the identification and the forecast-

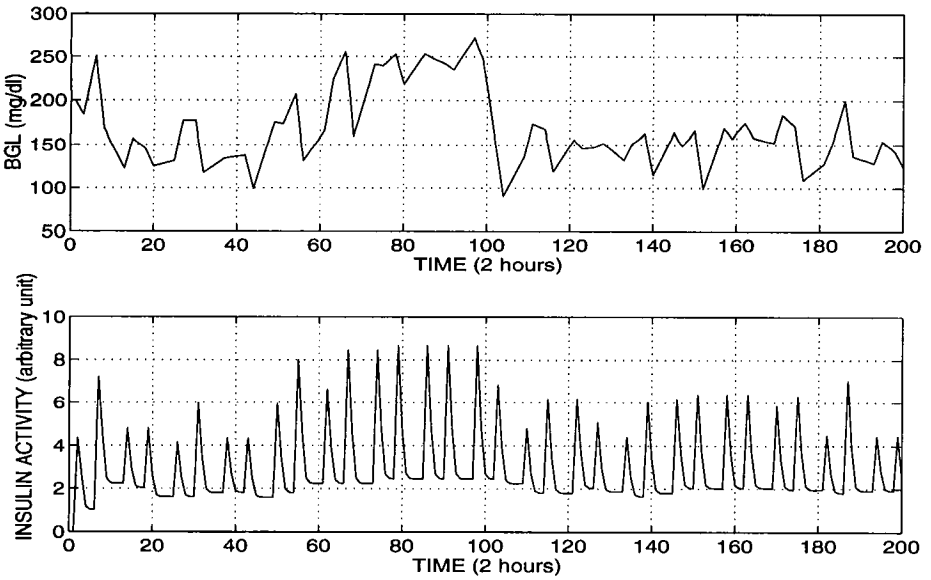

Figure 3: The F.S.C. performance on a simulated patient. Figure 3a shows the BGL profile, meanwhile Figure 3b represents the control action in terms of insulin activity, proportional to the plasma insulin concentration derived from a one-pool compartmental model. The simulation was performed superimposing random gaussian noise on a profile obtained by using a compartmental model of the insulin and glucose metabolism (see text).

ing task of the L.L.S..

c) During the patient monitoring, the H.L.S. weekly evaluates the time series of glucose and insulin, as well as the ARX model order adequacy. Average values and peaks of BGL, the number of hypoglycemic episodes and the well known M index [13] are taken into account in order to formulate a score for the chosen protocol.

Table I

Regular Insulin	Day Time				
	BB	BL	BD	BT	NT
Dose	0.2	0.4	0.5	0	0
Range	0.1	0.2	0.25	0	0
Time	08.00	12.00	18.00	22.00	02.00

where BB stands for Before Breakfast, BL for Before Lunch, BD for Before Dinner, BT for Bed Time and NT for Nigth Time; *Range* denotes the maximum variation around the suggested dose; insulin dose and range are expressed in Units/Kg.

Moreover, the system may require a monthly evaluation of ketonuria and glycosylated hemoglobin, together with other routine clinical findings. The evaluation score is then used to decide if the actual protocol has to be confirmed or not. If the H.L.S. decides for a new protocol, the change is done following the indications coming from the data analysis. For example, by evaluating the BGL time series, it will be possible to derive the mean BGL daily profile, that could evidentiate the day periods of insufficient metabolic control. The H.L.S. should hence be able to exploit this information, suggesting an appropriate change in the treatment protocol and assessing the new strategy.

Discussion

We presented a general methodology for an intelligent patient monitoring based on a strong link among quantitative and qualitative data analysis techniques. Particularly we have defined a strategy that utilizes a combination of two different kinds of adaptive controllers.

One of them, the *low level controller*, is devoted to assess the short term treatment, by using data processing techniques belonging to the field of identification theory and adaptive control, integrated with Fuzzy Set Controllers. F.S.C.s represent an area of growing interest in the context of non-linear, multi-input/multi-output processes, where the classic automatic control theory is not exploitable; the control of Blood Glucose Levels (BGL) in out-patients falls into this class of problems. Difficulties are due to the under-sampling of the every day treatment (three or

four samples a day are not sufficient to capture the dynamics of BGL [14]), as well as to the non linear relationships between BGL, insulin and carbohydrate intakes. Using a F.S.C. seems a convenient approach to this problem for its flexibility and for its capability of representing the every-day physician strategy. Moreover, the actual level of miniaturization and the commercial availability of fuzzy processors may suggest the implementation of the L.L.S. on a portable microcomputer.

The *high level controller* coordinates the overall strategy on the basis of the medical knowledge, and adapts this strategy by using statistical techniques and empirical rules. The high level controller also decides which are the models and the rule tables to be used by the low level one. Both the overall structure of the system and the single components represent the knowledge that the physician should utilize during the management of these patients.

The scheme here presented may be conveniently viewed in a telemedicine context, in which the low level controller is implemented on a portable device, that may communicate to the high level controller, implemented on a remote computer, the glucose time series together with the corresponding insulin deliveries. By this way, periodically, the high level controller may evaluate the actual protocol and consequently change, if needed, the low level control strategy, selecting different settings of the portable device.

Acknowledgments

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