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APPLICATION OF ADAPTIVE CONTROL TECHNIQUE TO DIABETIC MANAGEMENT[1]

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Abstract

The theoretical and practical issues of a model reference adaptive system for simulation and optimization of insulin therapy in patients with insulin-dependent diabetes is described in this paper. The adaptive optimizer, denoted AdASDiM, can operate with sparse (3-5 times/day) blood glucose measurements in contrast to most of the similar adaptive blood glucose controllers which needs a relative high frequency of blood samples (2-30 times/hour) taken from the diabetic patient. In the absence of real data, a reference model behaving as a 'healthy subject' generates 'pseudo' blood glucose values. Also, the proposed scheme makes use of the knowledge of the time and quantity of future meals.

Keywords: biomedical engineering, simulation, adaptive control, advisory system, diabetes mellitus.

Introduction

Despite many years of research (SANO, 1986, SALZSIEDER, 1990, CANDAS, 1991), the application of adaptive techniques for diabetic management has found clinical use only in limited cases. It seems reasonable to assume that the main reason for this is that a human diabetic subject can be considered as 'an information-poor system' from the control engineer's point of view. As apparently no adequate sensors have been available by which the blood glucose level could continuously be monitored in out-patients, very frequent blood samples should be taken on them in order to obtain sufficient data. In practice, however, the feasible and for the patients acceptable

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daily number of blood glucose measurements is in the range 3–7. This amount of data is usually not suitable for conventional adaptive controller on a minute-by-minute basis (GOODWIN, 1984). To overcome this problem a new scheme has been developed (JUHÁSZ, 1992).

System Components

The basic configuration of the proposed scheme is shown in *Fig. 1.* The box 'Physiological System' represents the gluco-metabolic system of the patient (CARSON, 1983). G_x denotes the exogenous (oral) glucose loading by regular meals. This can be considered as a deterministic and *predictable* disturbance in the sense that the timing and the quantity of each meal are known in advance. So it seems to be reasonable to define the preview function of the future oral glucose input, G_x^f, which also can be considered as an estimation of G_x at a future instant of time.

BG denotes the glucose concentration in the plasma determined from blood samples taken from the diabetic patient 3–7 times a day.

The symbolic switch hints at the fact that this quantity is only periodically available for the advisory system.

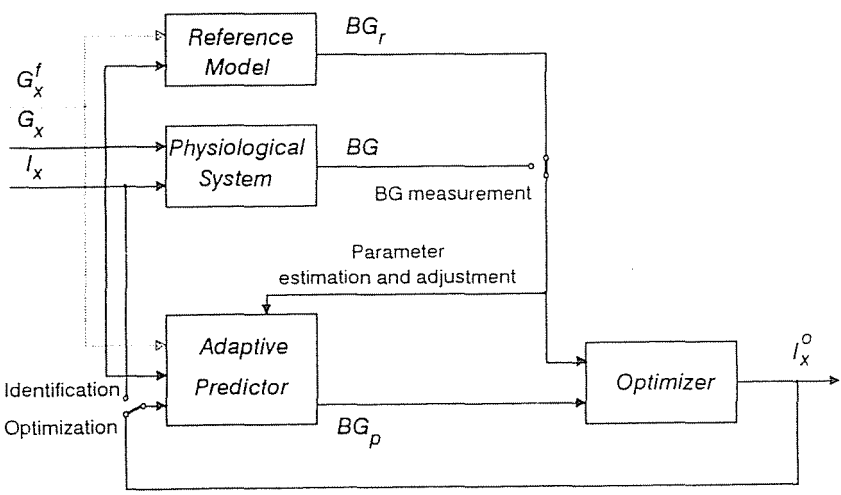

Fig. 1. Basic configuration of the system

I_x is the exogenous insulin infusion given to the patient in form of subcutaneous injections. The system consists of three major parts:

- The *Reference Model*, the parameters of which are set to the average of the non-diabetic population, describes the glycaemic control system of 'a healthy subject' (CARSON, 1983).
- The *Adaptive Predictor* forecasts the future blood glucose levels (BG_p) in the patient, based on the past and present values of BG, G_x and I_x as well as the preview input G_x^f.
- The third part is the *Optimizer* which is to produce an advice for the insulin administration (I_x^0) for the actual instant of time.

Reference Model

This part has a dual role. First it serves as a reference. The most important goal of the optimization is to produce an insulin administration which brings the blood glucose level of the diabetic subject 'close' to this reference. On the other hand, its output (BG_r) can be used as BG values in the absence of real data. By this means, even if only to a certain extent, we can overcome the problem of sparse measurement data.

This solution involves the assumption that the blood glucose response of an insulin treated diabetic patient is close to that of the Reference Model simulating the non-diabetic physiological glucose regulatory system. The mathematical model can be described by an autoregressive moving average (ARMA) model. After examining the blood glucose response of human subjects, the following fourth-order ARMA model seemed to provide the best fitting:

$$a_0 BG_r[k] + a_1 BG_r[k-1] + a_2 BG_r[k-2] + a_3 BG_r[k-3] + a_4 BG_r[k-4] =$$

$$= b_1 G_x[k-1] + b_2 G_x[k-2] + b_3 G_x[k-3] + b_4 G_x[k-4] \,. \qquad (1)$$

The parameters were fitted to clinical data derived by statistical evaluation from oral glucose tolerance tests (OGTT).

Table 1
Reference model parameters

i	0	1	2	3	4
a_i	1	- 3.2621	4.0689	- 2.2973	0.4951
b_i	-	5.311E-3	- 8.795E-3	5.500E-3	0

Adaptive Predictor

The predictor is adaptive in the sense that its parameters are adjusted so that past predictions match closely the observed data BG, or, in its absence, the output of the Reference Model, BG_r. It forecasts the future blood glucose levels, BG_p, in the patient based on the past and present values of BG, G_x and I_x as well as the preview input G_x^f. In the system future prediction is generated only when the parameters have been updated by real measurement. The indirect predictor being used is a fourth order multi-input multi-output (MIMO) ARMA model:

$$\begin{bmatrix} BG_p[t+1] \\ IL_p[t+1] \end{bmatrix} = \Phi^T[t]\hat{\Theta}[t]\,. \tag{2}$$

The elements of $\Phi[t]$ are the values of variables BG_p, IL_p, G_x and I_x at the time $t, ..., t-3$. $\hat{\Theta}[.]$ denotes the estimated parameter vector. The values of the parameter vector are calculated by the adaptive algorithm. We implemented the following Weighted Multivariable Least-Squares Algorithm making it possible for the observed data (BG) and the values generated by the reference model (BG_r) to be taken into account with different weights (GOODWIN, 1984):

$$\hat{\Theta}[t] = \hat{\Theta}[t-1] + \mathbf{P}[t-2]\Phi[t-1]\times \\ \left\{\Phi^T[t-1]\mathbf{P}[t-2]\Phi[t-1] + \mathbf{R}\right\}^{-1}\left\{\begin{bmatrix} BG[t] \\ IL[t] \end{bmatrix} - \Phi^T[t-1] - \hat{\Theta}[t-1]\right\}, \tag{3}$$

for $t \geq 0$

$$\mathbf{P}[t-1] = \mathbf{P}[t-2] - \mathbf{P}[t-2]\Phi[t-1]\times \\ \{\Phi^T[t-1]\mathbf{P}[t-2]\Phi[t-1] + \mathbf{R}\}^{-1}\Phi^T[t-1]\mathbf{P}[t-2]\,,$$

for $t = -1$

$$\mathbf{P}[-1] = \mathbf{P}_0. \tag{4}$$

Optimizer

This part of the system has the task to determine the optimum insulin dose, I_x^0, for the actual instant of time, T_{now}, by using the Adaptive Predictor. The optimizing algorithm is the 'Brutal Force Method' (also in JUHÁSZ,

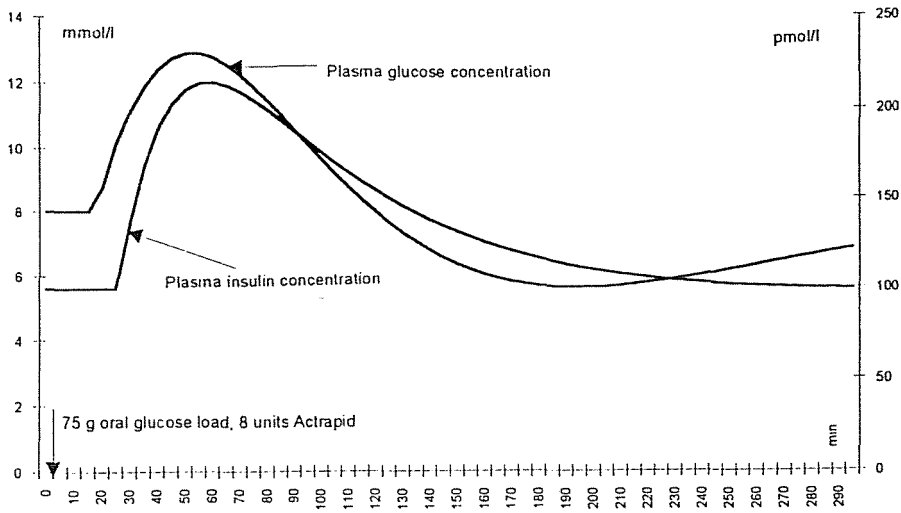

Fig. 2. Predicted behaviour of a diabetic patient's plasma glucose and insulin level

1990) which has appropriate numerical robustness. Up to the next real measurement the following cost function is calculated for all feasible insulin dose to be administered:

$$C(I_x) = \sum_{t=T_{\text{now}}}^{T_{\text{next}}} w[t](BG_p[t] - BG_r[t])^2 + w_I I_x^2, \tag{5}$$

where T_{next} denotes the time of the next planned insulin injection, $w[t]$ and w_I are weighting coefficients.

I_x considered as 'optimum' if the minimum cost belongs to it.

There have been prospective experiences to improve the performance of the Optimizer in the following fields:

- optimizing for time period containing more than one insulin injection,
- opimizing for multicomponent insulin administration (short, medium, long-acting insulin preparations),
- decreasing calculation time by using different kinds of algorithms,
- applying different types of cost function (e.g., M-value (HOVORKA, 1990), the widely accepted logarithmic index of diabetics control which penalizes the deviation of BG towards hypoglycaemia in a higher degree than towards hyperglycaemia).

Software Implementation

On the basis of the mathematical representation of the components of the system, a modular computer program, denoted AdASDiM (*Ad*aptive *A*dvisory *S*ystem for *Di*abetic *M*anagement), has been developed for PC environment. AdASDiM is written in Borland C++ 3.1 for WINDOWS. The program is interactive, menu driven and therefore can be used by healthcare professionals and patients with only a moderate computer experience.

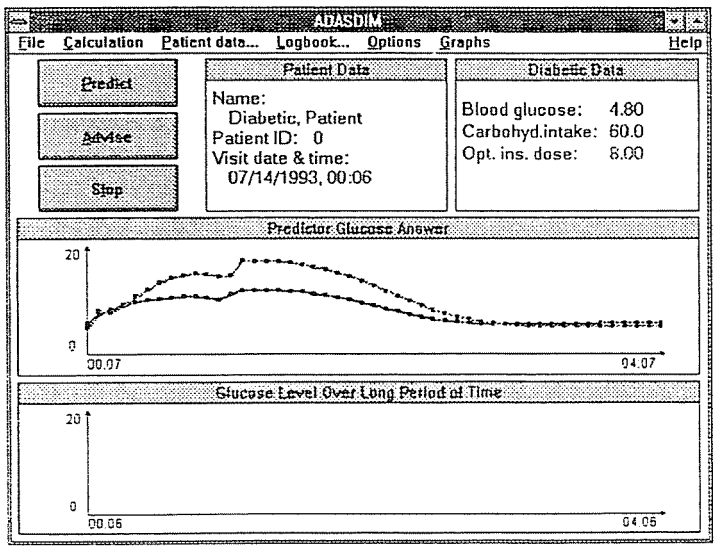

Fig. 3. User-interface of the program system AdASDiM in Windows environment

The menu structure of the decision-aid system AdASDiM is depicted in *Fig. 4.*

The *File* submenu allows an easy way of managing patient folders. A folder contains three kinds of patient-specific files: the identifier block (see Patient *ID*), the diabetic logbook (see Logbook) and the file of the varying estimated parameter vectors $\hat{\Theta}[.]$ used for the evaluation of the adaptive algorithm.

In the *Calculation* option one can change the time scaling of the calculations, select the appropriate type of model, set up the predictor (initial parameters) and the optimizer (legal insulin range) and after then carry out a prediction or require an advice.

During a prediction the program forecasts the patient's blood glucose level for an arbitrary period up to 24 hours based on past, present and future (if available) information on blood tests, insulin doses and meals.

Performing the feature Advice, one can obtain an optimum insulin dose which takes into account the same information as in the previous case with the difference that the present and future insulin doses are not inputs but calculated outputs.

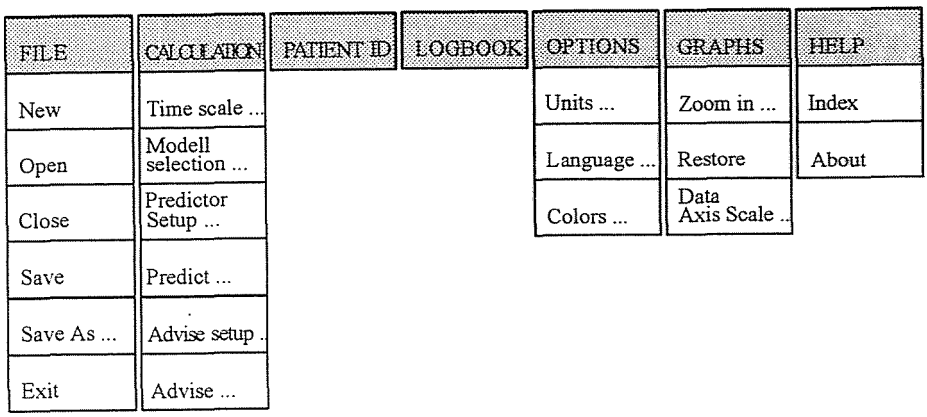

Fig. 4. Menu structure of AdASDiM

The optimization process consists of two loops. The external one corresponds to the legal insulin dose (I_x) selection and in the second one the simulation/prediction is executed and the cost function ($C(I_x)$) is calculated.

During the calculation in both cases a graph shows the predicted glucose level and that generated by the Reference Model in the Short- and (if enabled) Long-term Glucose Level Window.

By selecting the *Patient ID* dialog box, all the personal and medical data of the patient can be displayed and modified, if necessary.

A scrollable listbox in the *Logbook* option allows a quick overview of the patient's diabetic logbook recording the time and quantitative information on blood tests, insulin injections and meals. There is an easy way to modify existing or add new entries into the logbook. Besides manual data entry AdASDiM allows the import of files previously created. The direct interfacing to digital glucometers with memory is under development.

The *Options* submenu is for adjusting the software environment to the individual demands, like selection of units, language, colors, etc.

The feature *Graphs* controls the layouts of the plots in both Short- and Long-term Glucose Level Windows. The graphs can be zoomed in and out or rescaled.

The *Help* provides complete instructions how to use AdASDiM.

Validation

The evaluation considerations have been integrated with system design. Besides control engineers, clinicians have also been initiated to this complex task.

The retrospective validation of the insulin dose advice of the system has already begun and is in progress at the National Korányi Institute of Pulmonology.

Peer review techniques (ROUDSARI, 1992) are recommended in any branch of medicine where the proposed advice cannot be compared with 'gold standard'. These techniques should be applied, therefore, in the assessment of any advice involving patient management. Chronic health management such as diabetes, however, presents additional problems, both practical and theoretical.

Peer review is an extension of the Turing test. A decision-aid is treated as a clinician among fellows and all are required to provide medical advice based on a set of patient data. A second group of peer clinicians assesses then the advice, unaware of the sources.

By varying the number and difficulty of patient cases, and the number and expertise of advisors and assessors, it is possible to balance the workload and to analyze inter-advisor and inter-assessor variation. Furthermore, it is possible to determine statistically whether clinicians can distinguish computer from human performance.

Variation of identification algorithms, formulation and test of different reference models may contribute considerably to examination of system effectiveness.

Conclusions

A model reference adaptive advisory system for diabetic management has been developed which can (1) cope with the problem of sparse measurement data and (2) make use of future information on regular meals.

On the basis of numerical simulations with clinical data, the evaluation of which is in progress, it is expected that the combined adaptive and preview optimization scheme will significantly improve the performance of the insulin administration in diabetes.

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