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Neural Network based Glucose – Insulin Metabolism Models for Children with Type 1 Diabetes

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Abstract—**In this paper two models for the simulation of glucose-insulin metabolism of children with Type 1 diabetes are presented. The models are based on the combined use of Compartmental Models (CMs) and artificial Neural Networks (NNs). Data from children with Type 1 diabetes, stored in a database, have been used as input to the models. The data are taken from four children with Type 1 diabetes and contain information about glucose levels taken from continuous glucose monitoring system, insulin intake and food intake, along with corresponding time. The influences of taken insulin on plasma insulin concentration, as well as the effect of food intake on glucose input into the blood from the gut, are estimated from the CMs. The outputs of CMs, along with previous glucose measurements, are fed to a NN, which provides short-term prediction of glucose values. For comparative reasons two different NN architectures have been tested: a Feed-Forward NN (FFNN) trained with the back-propagation algorithm with adaptive learning rate and momentum, and a Recurrent NN (RNN), trained with the Real Time Recurrent Learning (RTRL) algorithm. The results indicate that the best prediction performance can be achieved by the use of RNN.**

I. Introduction

DIABETES Mellitus (DM) is a chronic metabolic disease resulted from insufficient secretion of hormone insulin. Diabetes patients are mainly classified into Type 1 (or insulin dependent diabetes patients), which are characterized by absent of insulin secretion due to destruction of the β-cells of pancreas, and Type 2 (or insulin independent diabetes patients), which are characterized by reduced action of insulin. This dysfunction of insulin results in many short- (hypoglycaemia, hyperglycaemia) and long-term (like neuropathies, nephropathies, retinopathies, *etc.*) complications. The result of the Diabetes Control and Complications Trial (DCCT) [1] and the U.K. Prospective Diabetes Study (UKPDS) [2] indicate that the intensive glucaemic control reduces many short- and long-term complications of DM. Advances in technology have allowed individuals with Type 1 diabetes to i) measure their glucose levels using either conventional finger-stick glucose meters (three to four times per day), or continuous glucose monitoring systems, and ii) to choose their insulin delivery method between Multiple Daily Injection (MDI) and Continuous Subcutaneous Insulin Infusion (CSII). Furthermore, many computer-based simulation of glucose-insulin metabolism system have been proposed in order to predict short-term blood glucose levels, and avoid hypoglycaemic and hyperglycaemic events. Usually these systems, using among others glucose data from finger-stick glucose meters, are based on Compartmental Models (CMs) [3], and causal probabilistic networks [4]. The acceptance of these systems is limited because they take into account only a confined number of the factors associated with glucose metabolism, and they are not easily individualized to accurately simulate metabolic processes for a specific Type 1 diabetes patient. In order to overcome the aforementioned difficulties, the use of artificial Neural Networks (NNs) for the simulation of glucose-insulin metabolism has been proposed [5].

In this paper, two glucose-insulin metabolism models for children with Type 1 diabetes are presented. The models, which are able to make short-term glucose predictions, are based on the combined use of CMs and NNs. The models are comparative assessed using data about glucose levels, insulin intake (type and dose), and diet during previous time periods, from four (4) children with Type 1 diabetes.

II. Methodology

The outline of the proposed models is shown in Fig. 1. The models consist of a Mathematical Model (MM) module and a NN module. The MM module incorporates five CMs, which are commonly used for modeling complex dynamics systems, such as the physiological systems [6], [7]. The first four estimate plasma insulin concentration due to Quick

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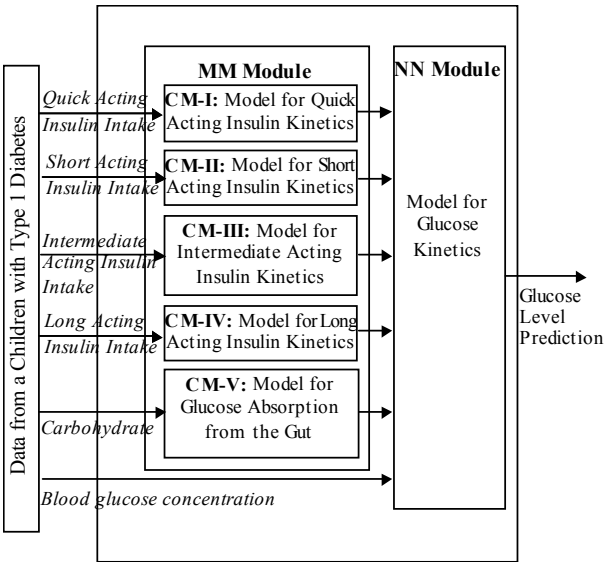

Fig. 1. General diagram of the proposed glucose – insulin metabolism models.

Acting (QA), Short Acting (SA), Intermediate Acting (IA), and Long Acting (LA) insulin intake, while the fifth the glucose absorption from the gut in response to carbohydrate intake. The outputs of the MM module along with the most recent glucose measurement are passed to the NN module, which provides prediction of short-term glucose levels.

A. Data Collection

Data from four (4) children with Type 1 diabetes have been used for the development and testing of the glucose - insulin metabolism models. The characteristics of the patients are summarized in Table I. Glucose data are collected using the Continuous Glucose Monitoring Sensor (CGMS, Medtronic MiniMed), which allow the measurement of interstitial glucose every 5 minutes. The statistic of the glucose data is given in Table II. The patients were monitored for a period between 3 to 5 days. For this period the children recorded the time of insulin injection, the insulin type (QA, SA, IA, and LA) and dose, and the amount of carbohydrate ingested.

B. Mathematical Model Module

As aforementioned, the MM module consists of five CMs.

1) Compartmental Models for Insulin Kinetics (CM-I, …, CM-V): After the injection of $D\,(U)$ units of insulin, the change in plasma insulin concentration $I\,(mU/lt)$, is given

TABLE I
CHARACTERISTICS OF THE CHILDREN WITH TYPE 1 DIABETES

Patient #	Age (years)	Sex	Diabetes Duration (years)	BMI (kg/m^2)	HbA1c
Patient 1	15	F	06	23.3	6.7
Patient 2	15	F	13	29.5	7.5
Patient 3	13	M	11	18.6	8.5
Patient 4	22	M	02	18.6	6.8

TABLE II
STATISTICS OF THE AVAILABLE GLUCOSE DATA

Patient #	# measurements	Glucose levels (mg/dl)		
		Min	Max	Mean (Standard Deviation)
Patient 1	1311	44	400	157.07 (71.88)
Patient 2	1392	40	395	196.01 (94.53)
Patient 3	863	40	400	233.75 (96.61)
Patient 4	1069	57	228	123.03 (39.53)

[8] as

$$\frac{dI}{dt} = \frac{st^s (T_{50})^s D}{V_i[(T_{50})^s + t^s]t} - k_e I \tag{1}$$

$$T_{50} = aD + b \tag{2}$$

where $k_e = 5.4\ lt/h$ is the first-order rate constant of insulin elimination, $V_i = 9.94\ lt$ is the volume of insulin distribution, and T_{50} is the half- time insulin dose absorption. The constant parameters *a*, *b*, and *s* characterize insulin absorption patterns of the different insulin types entered in the model, and are given in [8]. The differential equation (1) is solved using the fourth order Runge - Kutta method with a 5 minute step.

2) Compartmental Model for Glucose Absorption from the Gut (CM-V): After food intake, the glucose amount in the gut G_{gut} can be estimated by the equation

$$\frac{dG_{gut}}{dt} = G_{empt} - k_{gabs} G_{gut} \tag{3}$$

where $k_{gabs} = 1\,h^{-1}$ is the rate constant of glucose absorption from the gut into systemic circulation, and $G_{empt}\ (mg/h)$ is the gastric emptying function given by a trapezoidal or triangular function, according to [9]. Then, the glucose input into the blood from the gut wall is given by

$$G_{in} = k_{gabs} \cdot G_{gut} \tag{4}$$

and it is estimated with a 5 minute step.

C. Neural Network Module

In order to predict the glucose level $G\,(mg/dl)$ at a time instant t, the most recently measured blood glucose concentration along with parameters reflecting the effects of taken insulin and food are applied to the NN module. For comparative reasons two different NN architecture have been developed and tested: a Feed-Forward NN (FFNN), and a Recurrent NN (RNN).

1) Feed Forward Neural Network: The output of the FFNN is the glucose level $G(mg/dl)$ prediction at time t,

given by

$$G(t) = FFNN(\mathbf{G_{meas}}, \mathbf{G_{in}}, \mathbf{I_1}, \mathbf{I_2}, \mathbf{I}_3, \mathbf{I}_4) \quad (5)$$

where $\mathbf{G_{meas}}$ corresponds to the most recent glucose measurements, $\mathbf{G_{in}} = \{\mathbf{G_{in,t-t_1}}, \mathbf{G_{in,t-t_2}}, \mathbf{G_{in,t-t_3}}, \mathbf{G_{in,t-t_4}}\}$ is a vector describing the effect of food intake in the time-windows $t - t_i$ with $i = 1, 2, 3, 4$, $\mathbf{I_1} = \{\mathbf{I_{1,t-t'_1}}, \mathbf{I_{1,t-t'_2}}, \mathbf{I_{1,t-t'_3}}, \mathbf{I_{1,t-t'_4}}\}$, is a vector describing the effect of taken QA insulin in the time-windows $t - t'_i$, $\mathbf{I_2} = \{\mathbf{I_{2,t-t''_1}}, \mathbf{I_{2,t-t''_2}}, \mathbf{I_{2,t-t''_3}}\}$, is a vector describing the effect of taken SA insulin in the time-windows $t - t''_i$ with $i = 1, 2, 3$, $\mathbf{I_3} = \mathbf{I_{3,t-t'''_1}}$ is a vector describing the effect of taken IA insulin in the time-window $t - t'''_1$, and $\mathbf{I_4} = \mathbf{I_{4,t-t''''_1}}$ is a vector describing the effect of taken LA insulin in the time-window $t - t''''_1$. Each element, of the above vectors is estimated as the sum of the prediction in the corresponding time windows. The used time-windows are indicated in Fig. 2, and have been selected according to the expertise of physicians [5]. If in a time-window more than one event of the same type occurs, then the combined effect of the events is taken into account.

In eq. (5) the symbol *FFNN* denotes the non-linear transformation of the data according to the used NN architecture. A fully connected feed-forward NN, trained by the batched back-propagation algorithm with adaptive learning rate and momentum [10], has been used. The NN consists of three layers: input, hidden, and output layer. The input layer is formed by a number of neurons equal to the number of parameters used for the description of previous blood glucose measurements, insulin and food intake.

2) Recurrent Neural Network: The used RNN is a second-order RNN with one state variable. The output of the RNN is the glucose level $G(mg/dl)$ prediction at time t, given by

$$G(t) = G(t-1) + RNN(G(t-1), G(t-2), G_{in}, I_1, I_2, I_3, I_4) \quad (6)$$

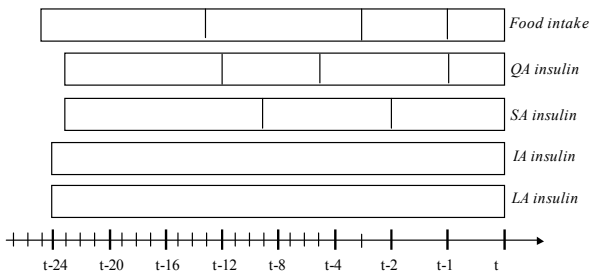

Fig. 2. Time windows (*h*) used for the description of insulin and food intake effects associated with blood glucose measurement at time *t*.

where $G(t-1)$, $G(t-2)$ are the current and previous blood glucose predictions, respectively, G_{in} is the glucose input into the blood from the gut, I_1 is the plasma insulin concentration due to QA insulin intake, and I_2 is the plasma insulin concentration due to SA insulin intake, I_3 is the plasma insulin concentration due to IA insulin intake, and I_4 is the plasma insulin concentration due to LA insulin intake .

The RNN is a fully connected NN trained with the on-line Real Time Recurrent Learning (RTRL) algorithm [10]. The used training algorithm has the ability to update on-line the RNN weights. As long as the RNN is provided with new inputs (external and internal) it adapts the weights accordingly, trying to simulate the dynamic system at real time. For comparative reasons, two strategies have been applied: the Free-Run (FR), and the Teacher-Forcing (TF). In the case of FR (on-line RTRL–FR) the RNN ignores the available glucose measurement, while in the case of TF (on-line RTRL–TF) strategy the RNN replace the actual output, during training, with the corresponding available glucose measurement.

III. Results and Discussion

Aiming at the minimization of overtraining risk, and at the maximization of the models ability to predict glucose levels, the recorded days have been divided into two disjoint datasets: training, and testing sets. For each patient, the data of the first days (minimum 3 days) using CGMS have formed the training set, and the data of the last day using CGMS the testing set.

In order to assess the performance of the developed models, the Root Mean Square Error (RMSE), and the correlation coefficient (cc), have been calculated for both data sets. In Table III, the RMSE, and the cc are given for each model.

From Table III it can be shown that the results obtained from the FFNN and the RNN trained with the on-line RTRL-TF are superior to those obtained by the on-line RTRL-FR trained RNN for all diabetes patients. Furthermore, it can be observed that the performance of FFNN is slightly better as compared to the on-line RTRL-TF trained RNN. Despite this, the on-line RTRL-TF trained RNN is preferable due to its ability to adapt the weights whenever a new input is applied.

Finally, in Fig. 3 the measured and the estimated blood glucose levels versus time are presented for the testing set of all patients, using on-line RTRL-TF trained RNN. From the above results it is obvious that further studies need to be performed including a greater number of Type 1 diabetes patients in order to improve the significance of the results. Future direction includes the estimation of plasma glucose which is needed for the CGMS calibration aiming to reduction of the required invasive measurements. Furthermore, in order to enhance the performance of the

TABLE III
ROOT MEAN SQUARE ERRORS (RMSE), ALONG WITH CORRELATION COEFFICIENTS (CC) BETWEEN MEASURED AND ESTIMATED BY THE MODELS GLUCOSE LEVELS FOR THE TESTING SET.

Patient #	Model	RMSE	cc
Patient 1	FFNN	27.82	0.94
	RNN/FR	39.32	0.80
	RNN/TR	15.13	0.97
Patient 2	FFNN	7.19	0.99
	RNN/FR	38.11	0.91
	RNN/TR	11.58	0.99
Patient 3	FFNN	41.34	0.98
	RNN/FR	71.69	0.79
	RNN/TR	55.38	0.90
Patient 4	FFNN	12.31	0.92
	RNN/FR	33.47	0.62
	RNN/TR	14.25	0.91

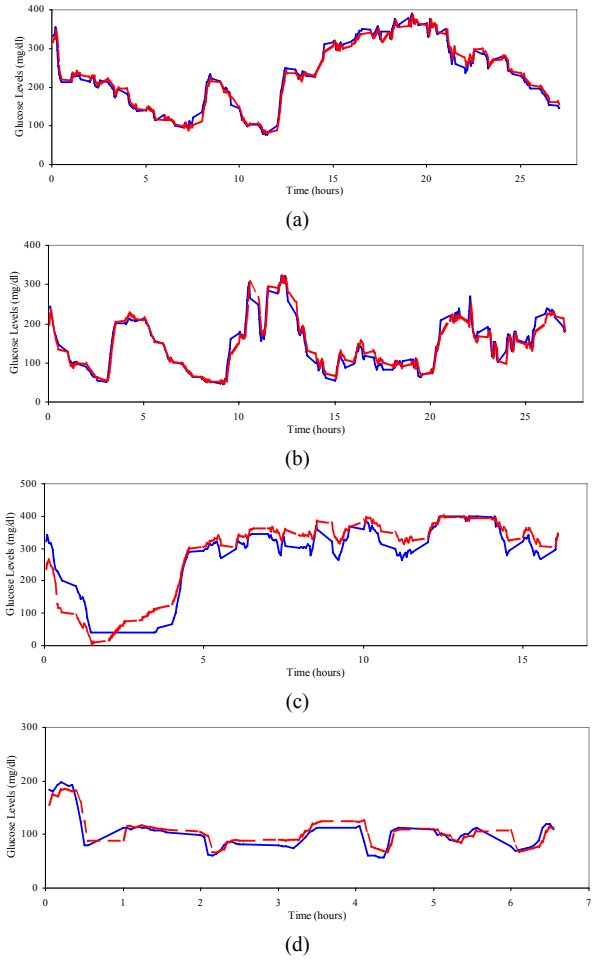

Fig. 3. Comparison between estimated by the model using the on-line RTRL – TF trained RNN (-) and the measured (-) glucose levels for the testing set, in case of (a) patient 1, (b) patient 2, (c) patient 3, and (d) patient 4.

metabolism models information regarding physical activity will be integrated into the models using CMs. Finally the development of an automatic advisor, which can make recommendations about the appropriate time and the doses of insulin (for patient using either MDI or CSII), as part of an integrated system for tele-management and tele-monitoring of Type 1 diabetes patients is in progress.

IV. CONCLUSIONS

Two glucose-insulin metabolism models for children with Type 1 diabetes have been presented. The models, which are based on the combined use of CMs and NNs, uses data about glucose measurements from continuous glucose monitoring systems, insulin and food intake. Outputs of the models are the short-term predictions of glucose levels. For comparative reasons two different NN architectures have been tested. A FFNN trained with the back-propagation algorithm with adaptive learning rate and momentum, and a RNN trained with the RTRL algorithm. The obtained results have shown that the model using the RTRL-TF trained RNN can simulate more accurate the metabolism of children with Type 1 diabetes.

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