Personalized Glucose-Insulin Metabolism Model based on Self-Organizing Maps for Patients with Type 1 Diabetes Mellitus

K. Zarkogianni, E. Litsa, A. Vazeou, K. S. Nikita

***Abstract*—The present paper aims at the design, the development and the evaluation of a personalized glucose-insulin metabolism model for patients with Type 1 Diabetes Mellitus (T1DM). The personalized model is based on the combined use of Compartmental Models (CMs) and a Self Organizing Map (SOM). The model receives information related to previous glucose levels, subcutaneous insulin infusion rates and the time and amount of carbohydrates ingested. Previous glucose measurements along with the outputs of the CMs which simulate the sc insulin kinetics and the glucose absorption from the gut into the blood, respectively, are fed into the SOM which simulates glucose kinetics in order for the latter to provide with future glucose profile. The personalized model is evaluated using data from the medical records of 12 patients with T1DM for the time being on insulin pumps and CGMS. The obtained results demonstrate the ability of the proposed model to capture the metabolic behavior of a patient with T1DM and to handle intra- and inter-patient variability.**

I. Introduction

Type 1 Diabetes Mellitus (T1DM) is a chronic autoimmune disease characterized by deregulation of glucose metabolism. This metabolic disorder is caused by the autoimmune destruction of insulin-producing beta cells of the pancreas resulting in the absence of insulin secretion. The lack of insulin provokes elevated blood glucose levels (hyperglycemia) leading to spillage of glucose into urine. The excess glucose circulating through the body in the blood stream over time, leads to damage of blood vessels (angiopathy), resulting in serious long-term complications, such as kidney failure, blindness, amputations and heart problems. According to the diabetes control and complications trial [1], the aforementioned complications can be reduced by intensive glycemic control, which involves regular glucose measurements and exogenous insulin administration.

Latest advances in technology have led to the development of continuous glucose monitors (CGMs) that provide subcutaneous (sc) glucose measurements at a high frequency [2], and insulin pumps for continuous sc insulin infusion. However, glucose metabolism is strongly affected by several environmental factors such as nutrition, physical activity, patient's psychological status and his overall lifestyle. Endogenous processes such as circadian rhythms are also involved in the regulation of glucose homeostasis. Moreover, taking into account intra- and inter- patient variability in response to therapy, tight glycemic control is difficult to be achieved. Regarding this, computational models able to produce accurate and reliable estimations of future glucose profile in response to various stimuli, are essential within the context of diabetes management.

Several considerable efforts have been reported towards the development of computational models for the simulation of glucose to insulin metabolism. These can be physiological models representing fundamental glucoregulatory processes, which are derived by compartmentalizing the various physiological components involved in the human metabolic process [3], [4]. However, the fact that some of the endocrine processes affecting glucose metabolism are still not fully understood, these models take into account only a confined number of 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 data-driven modeling techniques has been proposed leading to the development of models which disregard the physiological insights but learn the insulin–glucose relationships using pattern recognition techniques. Within this context, several glucose prediction models have been developed based on Voltera series models, Time Series Analysis and Machine Learning Methods. In particular, nonlinear Volterra models of glucose to insulin dynamics have been shown to provide accurate predictions in the absence of noise [5]. A comparison between simulated compartmental and Volterra models of the dynamic effects of insulin on blood glucose concentration has been carried out [6]. Autoregressive exogenous input (ARX) and Box-Jenkins (BJ) models with constant parameters and various model orders (high and low) have been applied to simulate glucose-insulin dynamics [7]. Several types of Artificial Neural Networks (ANN) such as multilayer perceptron (MLP) Neural Networks (NN) [8], Radial Basis Function (RBF) NN (RBF) [9], wavelet NN [10], and Recurrent Neural Networks (RNN) [11]-[13] have been used towards the simulation of glucose dynamics. Furthermore, glucose

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prediction models based on Gaussian processes [14] and SVR [15] have been developed. Additionally, hybrid glucose-insulin metabolism models based on the combined use Compartmental Models and data-driven modeling techniques, such as RNN and SVR, have derived prominent results [11]-[13], [15].

This paper presents the design, the development and the evaluation of a personalized hybrid glucose-insulin metabolism model. To address the intra- and inter- patient variability, the model incorporates a Self Organizing Map (SOM) able to capture the glucose metabolic behavior taking into account patient specific information. The personalized model was evaluated using data from the medical records of 12 patients with T1DM. To the best of the authors' knowledge this is the first work proposing a SOM towards the development of glucose prediction model.

II. Materials and Methods

A. Dataset

The personalized glucose-insulin metabolism model was developed and retrospectively evaluated using data from the medical records of 12 (7 male and 5 female) patients with T1DM for the time being on insulin pumps and CGMS, which were granted from the Diabetes Center, First Department of Pediatrics, P&A Kyriakou Children's Hospital, Athens [12], [13]. Patients were monitored for a ten day period. For this period, all patients recorded information regarding the time and the amount of carbohydrates ingested and the insulin boluses administered for the meals or for correction purposes. The patients' characteristics are shown in Table I.

B. Methodology

The proposed personalized glucose-insulin metabolism model is based on the combined use of a mathematical model (MM) module and NN module (Fig. 1). The MM module consists of two Compartmental Models (CMs), which simulate sc insulin kinetics and glucose absorption into the blood from the gut, respectively, while the NN module incorporates a SOM which models the patient's glucose kinetics. Information regarding recent sc insulin infusion rate and meal intake are fed to the MM module. CMs' outputs along with previous sc glucose measurements are applied to the SOM that provides glucose predictions. Each of the modules are described in the following.

1) *CM for Sc Insulin Kinetics*: Following a sc insulin injection, the rate of appearance of insulin in plasma is described by a linear CM [16], [11].

TABLE I
T1DM Patients' Characteristics

	Mean ± Standard Deviation
Age	19.83 ± 12.28
Diabetes Duration	12.67 ± 7.74
BMI	22.00 ± 4.88
HbA1c	6.78 ± 0.94

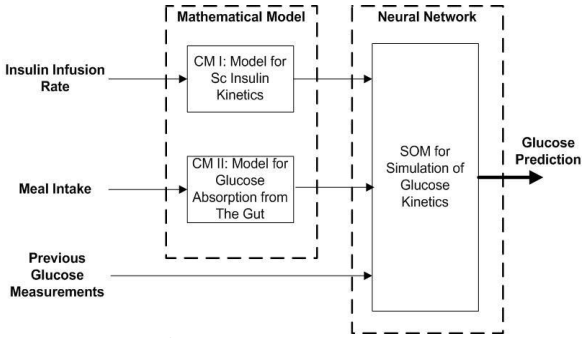

Fig. 1. Outline of the Personalized Glucose-Insulin Metabolism Model

2) CM for Glucose Absorption from the Gut: The physiological model of glucose intestinal absorption is a three-compartment nonlinear model with two compartments representing the stomach (solid and liquid phases) and the third compartment representing the intestine [11], [16], [17]. The model assumes a constant rate of the intestinal absorption but describes gastric emptying rate to be dependent on the total amount of nutrient in the stomach.

3) SOM: In general, SOMs are mainly used for data clustering and visualization of high dimensional data. However, SOMs can also be trained to learn input-output mappings and used for function approximation. The SOM usually, consists of a two dimensional grid of neurons. Every input vector is associated with a neuron in the grid which is called the winner neuron. Every neuron is associated with a weight vector which has the same dimensions as the input vector. During the training stage the weights of the neurons in the neighbor of the winner neuron are updated. The learning rate as well as the scope of the neighbor are decreased as the epochs go by. After the training stage, areas with similar input vectors are created and these vectors are represented by a neuron. In this sense, this method of training could be regarded as a Vector Quantization Method [18].

This technique is implemented in order to produce estimations for future glucose levels. Particularly, a two dimensional grid of *N* neurons is created and every neuron *i* is associated with a weight vector w_{in} and a weight value w_{out}. The input vector (x^{in}) has the form:

$$x^{in}(t) = [G(t-n_y+1),..G(t), I(t+1), Ra(t+1)] \quad (1)$$

where G represents the glucose, I is the rate of appearance of insulin in plasma, Ra is the appearance rate of glucose in plasma, and n_y is the number of steps that determine the time window to be considered for the past glucose measurements. A value $x_{out}(t)$ corresponds to each input vector, which is the next glucose value:

$$x_{out}(t) = G(t+1) \quad (2)$$

The vector w_{in} has the same dimensions as the input vector. During training, the winning neuron is determined by calculating the euclidean distance between the input vector and the weight vectors (w_{in}) of every neuron. The neuron with the lowest euclidean distance is the winner ($i^*(t)$):

$$i^*(t) = \arg\min\{\|x_{in}(t) - w_{in}(t)\|\} \quad (3)$$

At every iteration the weights w_{in} and w_{out} are changed according to the rule:

$$\Delta w_{in}(t) = a(t) \cdot h(i^*, i, t) \cdot [x_{in}(t) - w_{in}(t)] \quad (4)$$

$$\Delta w_{out}(t) = a(t) \cdot h(i^*, i, t) \cdot [x_{out}(t) - w_{out}(t)] \quad (5)$$

where $a(t)$ is the learning rate which decreases exponentially with time starting from value a_o until a_T :

$$a(t) = a_0 \cdot \left(\frac{a_T}{a_0}\right)^{\frac{t}{T}} \quad (6)$$

where T is the number of total epochs. Moreover, $h(i^*, i, t)$ is the neighborhood function with a Gaussian form:

$$h(i^*, i, t) = e^{\left(\frac{-\|r_i(t) - r_{i^*}(t)\|^2}{2 \cdot \sigma(t)^2}\right)} \quad (7)$$

where $r_i(t)$ and $r_{i^*}(t)$ are the locations of neurons i and i* respectively. Parameter $\sigma(t)$ also decreases exponentially with time starting from value σ_0 until σ_T :

$$\sigma(t) = \sigma_0 \cdot \left(\frac{\sigma_T}{\sigma_0}\right)^{\frac{t}{T}} \quad (8)$$

In this way, at the beginning of the training procedure, a wide area of neurons is affected and as the procedure goes by, a smaller area around the winner neuron is affected until only the winner neuron changes its weights.

After the training stage SOM can be used to obtain estimates of future glucose values. For every new input vector the winner neuron (i^*) is found and the corresponding w_{out} value is the glucose prediction $G(t+1)$. However, this technique requires a great number of neurons in order to have a small prediction error [18]. To overcome this problem, a technique towards the creation of multiple local linear models is applied [19]. Particularly, the estimated glucose levels are produced from a linear Autoregressive Model with Exogenous Inputs (9).

$$G(t+1) = \sum_{k=1}^{n_y} ac_k \cdot G(t-k) + b \cdot I(t+1) + c \cdot Ra(t+1) \quad (9)$$

where coefficients ac, b, and c are calculated during training [20], [21] starting from zero values. In every neuron corresponds a vector of these coefficients ($v_i(t)$) which is updated according to the following equation:

$$\Delta v_i(t) = a(t) \cdot h(i^*, i, t) \cdot [x_{out}(t+1) - v_i(t) \cdot x_{in}(t)] \cdot \frac{x_{in}(t)}{\|x_{in}(t)\|^2} \quad (10)$$

This way the neighborhood around every neuron forms a local linear model. After the training stage, when a new input vector arises the winner neuron is computed and the corresponding coefficients are used to produce the future glucose value from (9).

4) SOM's Tuning: The number of past glucose measurements (n_y) was set to 5, which corresponded to a 25 *min* time interval. Parameter *N* and number of epochs were determined through trial and error. A grid of 3×3 (N=9 neurons) was found to be sufficient to capture the dynamic of the system. Moreover, 200 epochs was large enough in order for the coefficients to be stabilized. Regarding the parameters associated with the learning rate, a_0 and a_T were set equal to 0.9 and 0.01, respectively. σ_0 was set to 2 which corresponded to the maximum distance between all neurons while σ_T was set equal to 1. The initial values of the weights were randomly selected within the range [0 1].

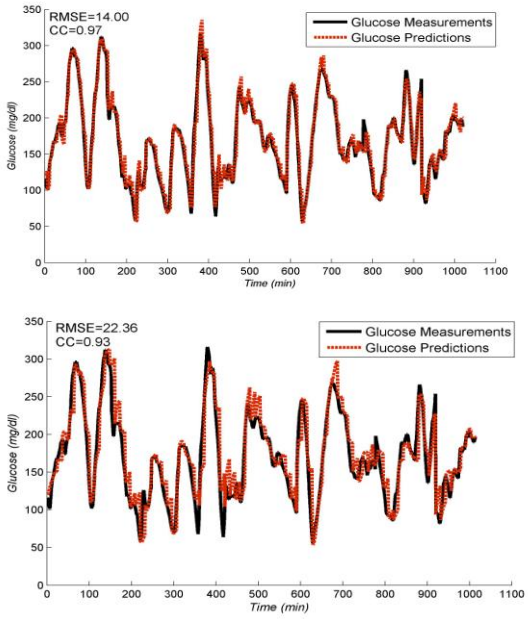

Fig. 2. Representative example of glucose predictions (dashed line) and glucose measurements (solid line). Upper panel: 30 *min*, Lower panel: 60 *min* PH

III. Results And Discussion

For each patient, data corresponding to the 60% of the monitored days were used for training purposes (model development), while the remaining 40% for testing (model evaluation). The predictive performance of the proposed model was evaluated considering a prediction horizon (PH) equal to 30 *min* and 60 *min* with a 5-*min* resolution. In order to provide with a reliable evaluation, 30 *min* and 60 *min* time intervals, where at least one event (i.e carbohydrates

TABLE II
Continuous Glucose Error Grid Analysis

	Hypoglycemia (%)		Normal Glycemia (%)		Hyperglycemia (%)	
	30 *min*	60 *min*	30 *min*	60 *min*	30 *min*	60 *min*
Accurate readings	81.06	63.22	92.18	91.71	88.27	87.19
Benign Errors	3.48	2.83	7.59	7.97	2.96	3.45
Erroneous Readings	15.46	33.95	0.23	0.32	8.77	9.36

ingested, change in basal insulin infusion rate, insulin bolus ingested) occurred, were excluded from the original testing data.

Root-mean-squared error (RMSE) and correlation coefficient (CC) corresponding to the testing dataset were calculated to evaluate the performance of the model in terms of matching the predicted glucose with the original ones. Furthermore, in order to evaluate the clinical accuracy of the glucose predictions and their effects on decisions to avoid hypo- and hyperglycemic events, the Continuous Glucose Error Grid Analysis (CG-EGA) [33] were used.

From both the RMSE (mean ± standard deviation (SD): 14.10 ± 4.57) and CC (mean ± SD: 0.94 ± 0.02), it is obvious that the predicted glucose profile follows the original one for 30 min PH. Even for the case of 60 *min* PH, the RMSE (mean ± SD: 23.19 ± 6.40) and the CC (mean ± SD: 0.84 ± 0.05) indicate that the glucose predictions are close to the original ones. This is also obvious in Fig. 2, which shows a representative example of the glucose predictions along with the glucose measurements as resulted when the model provides predictions every 30 *min* (upper panel) and 60 *min* (lower panel), respectively. Moreover, from the CG-EGA presented in Table II, it is observed that for 30 *min* PH, high percentage of glucose predictions are accurate readings. Regarding the 60 *min* PH, most of the glucose predictions are accurate readings in the ranges of normal glycemia and hyperglycemia while most erroneous errors are observed in the range of hypoglycemia.

Future work concerns the enhancement and extension of the model by introducing more inputs related to physical activity. Furthermore, the model will be integrated into a closed-loop glucose controller in order to provide with future glucose profile to be used by the controller towards the estimation of insulin infusion rates.

IV. Conclussions

A personalized hybrid glucose-insulin metabolism model is presented. The model is based on the combined use of CMs and a SOM. The predictive performance of the model is tested using data from the medical records of 12 patients with T1DM. The algorithm described above is simple and the computation time is low since only a small number of neurons is required. The obtained results demonstrate the model's ability to capture the metabolic behavior of a patient with T1DM and to handle inter- and intra- patient variability

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