Predictive Metabolic Modeling for Type 1 Diabetes Using Free-Living Data on Mobile Devices

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Abstract. This study presents a metabolic modeling scheme for glucose prediction of diabetic patients that is intended for use in mobile devices. We investigate the ability to model the multivariate, nonlinear and dynamic interactions in glucose metabolism using free-living data acquired from wearable sensors or inserted through suitable mobile applications. The physiological processes related to diabetes are simulated by compartmental models, which quantify the absorption of subcutaneously administered insulin, the absorption of glucose from the gut following a meal, as well as the effects of exercise on plasma glucose and insulin dynamics. In addition, Support Vector machines for Regression are employed to provide individualized predictions of the subcutaneous glucose concentrations. The proposed scheme is evaluated in terms of its predictive ability using real data recorded from two type 1 diabetic patients. Also, the incorporation of the predictive model in an integrated diabetes monitoring and management system is discussed.

Keywords: glucose prediction, type 1 diabetes, compartmental models and support vector regression.

1 Introduction

Diabetes care has been significantly improved by the development of advanced sensors, mobile devices and information systems that enable the continuous and multiparametric monitoring and control of the disease. This has also been facilitated by the development of continuous glucose sensing technologies that are available in non- or semi-invasive wearable devices. However, diabetes control further necessitates the monitoring and analysis of all patients' contextual information, such as physical activity and lifestyle. In this direction, data recorded from activity monitoring devices could significantly assist diabetes management systems in the prediction of glucose variations; however, their use remains limited.

An essential component of a diabetes management system concerns the modeling of blood glucose metabolism. Thus, several recent studies have considered advanced data-driven techniques for developing accurate glucose predictive models. The authors in [1], [2] proposed autoregressive models for predicting individual specific glucose concentrations using only the glucose time-series signal. Stahl et al. [3], based

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on blood glucose values, food and insulin intake, made an attempt to predict the glycemic behavior for the next 2 hours through linear and nonlinear time-series models (i.e. ARMAX and NARMAX). Recently, the effect of free-living data on glucose behavior was taken into consideration [4], [5]. A method based on Wiener models that accurately maps input disturbances concerning food, exercise and stress in blood glucose levels is reported in [4]. Finally, Gaussian Processes were used in [5] in order to model the glucose excursions in response to exercise data.

The aim of this study is to develop and evaluate a predictive metabolic model for type 1 diabetic patients using free-living data. This model will be incorporated in mobile devices as part of the decision support subsystem of an integrated diabetes monitoring and management system, called METABO [6].

2 Materials and Methods

2.1 Materials

The Guardian Real-Time Continuous Glucose Monitoring System (CGMS) (Medtronic Minimed) is used to record glucose measurements in order to obtain a sufficient fast sampling rate necessary for glucose modeling. The physical activity measurements are obtained using the SenseWear Body Monitoring System armband (BodyMedia Inc.) which collects data using five sensors: heat flux, skin temperature, near body temperature, galvanic skin response and a two-axis accelerometer. Also, the food ingested the serving sizes and the time of each meal or snack, as well as the type, dose and time of insulin injections are manually notified by the patient. The food composition (i.e. calories, carbohydrates, fat etc.) is post-analyzed by a dietician.

2.2 Methods

The prediction of the dynamic behavior of glucose metabolic process in time as a function of process input parameters can be considered as a regression problem with a time component. In this study a Support Vector machine for Regression (SVR) [7] is employed for the task of subcutaneous (s.c.) glucose time series prediction. The overall modeling of glucose dynamics is achieved by combining SVR with compartmental models that describe the absorption of subcutaneously-administered insulin and the ingestion of carbohydrates, as well as, the effects of mild to moderate exercise events on plasma glucose and insulin dynamics.

2.3 Subcutaneous Insulin Absorption

The absorption process of subcutaneously injected insulin is described by the pharmacokinetic model proposed in [8], which covers all the commercially available insulin classes. The evolution of the exogenous insulin flow, I_{ex} (U/min), is given by:

$$I_{ex}(t) = \int_{V_{sc}} B_d c_d(t,r), \tag{1}$$

where c_d is the dimeric insulin concentration in the subcutaneous tissue, B_d is the absorption rate constant and V_{sc} is the complete subcutaneous volume. The plasma insulin concentration, I_p (uU/ml), after a subcutaneous injection is estimated as:

$$\dot{I}_p = \frac{I_{ex}(t)}{V_d} - k_e I_p(t), \tag{2}$$

where V_d is the plasma insulin distribution volume and k_e is the rate constant of insulin elimination.

2.4 Carbohydrates Absorption

The model by Lehmann and Deutch [9] is used to describe the time course of glucose appearance in plasma due to food intake. The amount of glucose in the gut, q_{gut}, after the ingestion of a meal containing D grams of glucose-equivalent carbohydrates is defined as:

$$\dot{q}_{gut(t)} = -k_{abs} q_{gut}(t) + G_{empt}(t, D), \tag{3}$$

where k_{abs} is the rate constant of intestinal absorption and G_{empt} is the gastric emptying function. Then, the rate of appearance of glucose in plasma, Ra (mg/min), is given as:

$$Ra(t) = k_{abs} q_{gut}(t). \tag{4}$$

2.5 Exercise Effects

The effects of the exercise on plasma glucose and insulin dynamics vary according to the exercise intensity and duration. In particular, the plasma glucose variation, G_{exer} (mg/min), due to exercise events is given by:

$$G_{exer} = \left(G_{prod} - G_{gly}\right) - G_{up}\ , \tag{5}$$

where G_{up} and G_{prod}, represent the rate (mg/min) of glucose uptake and hepatic glucose production (glycogenolysis) induced by exercise, respectively, while G_{gly} denotes the decrease in the rate of glycogenolysis during prolonged exercise due to the depletion of liver glycogen [10].

Furthermore, the insulin dynamics in (2) are modified as:

$$\dot{I}_p = \frac{I_{ex}(t)}{V_d} - k_e I_p(t) - I_e(t), \tag{6}$$

where I_e (uU/(ml.min)) is the insulin removal from the circulatory system due to the exercise-induced physiological changes [10].

2.6 Glucose Predictive Model

The prediction of the s.c glucose concentration, y, at the time $t+l$, assuming that t is the current time, is described by:

$$y(t+l) = SVR\left(x_1,\ldots,x_d\right), \tag{7}$$

where $x_i = x_i\left(t\right),\ldots,x_i\left(t-n_i\Delta t\right)$, with $i=1,\ldots,d$, denotes the inputs in the model, $n_i\Delta t$ is the time lag for the input x_i, Δt is the sampling time and l is the prediction length.

The inputs of the model considered in this study include the plasma insulin concentration, I_p, the rate of glucose appearance in plasma after a meal, Ra, the s.c. glucose measurements, gl, as well as a set of exercise-related variables. In particular, we assume two approaches to investigate the dynamic effect of exercise on glucose variation. In the first approach, the Metabolic Equivalent of Task (*MET*), the heat flux (*hf*) and the skin temperature (*st*) variables, as recorded by the SenseWear armband, are used as inputs in the model. However, in the second approach the output from the exercise compartmental models is used.

2.7 Model Training and Evaluation

The SVR is evaluated using data from two type 1 diabetic patients who were monitored over a period of 5 and 11 days, respectively. The training of the SVR is performed individually for each patient by applying a technique called leave-one-day-out. More specifically, the dataset of each patient is divided into two groups. The first group (i.e. test set) contains the data of i^{th} day, with $i=1,\ldots,k$, where k is the total number of days. The second group (i.e. training set) contains the remaining data. The error is measured by testing the SVR on the data of the i^{th} day. The specific evaluation method is repeated k times and, subsequently, the average of the error is calculated. Considering that the performance of the SVR is affected by the value of parameter C, the evaluation procedure is applied for different values of the specific parameter. The value of the parameter C which produces the lowest average error is selected. Regarding the other parameters of the SVR, a linear kernel is employed and the parameter ε in the insensitive loss function is set equal to 0.001.

Time lags of 30 min are considered for the I_p, R_a and gl. Since it is well-known that the effect of the exercise lasts for several hours, the time lag for the exercise-related inputs (i.e. *MET*, *st*, *hf* and G_{exer}) is assumed to be 3 hours. The sampling time, Δt, was 5 min for all the above cases. Predictions are performed for four different values of prediction length l, i.e. 15, 30, 60 and 120 min.

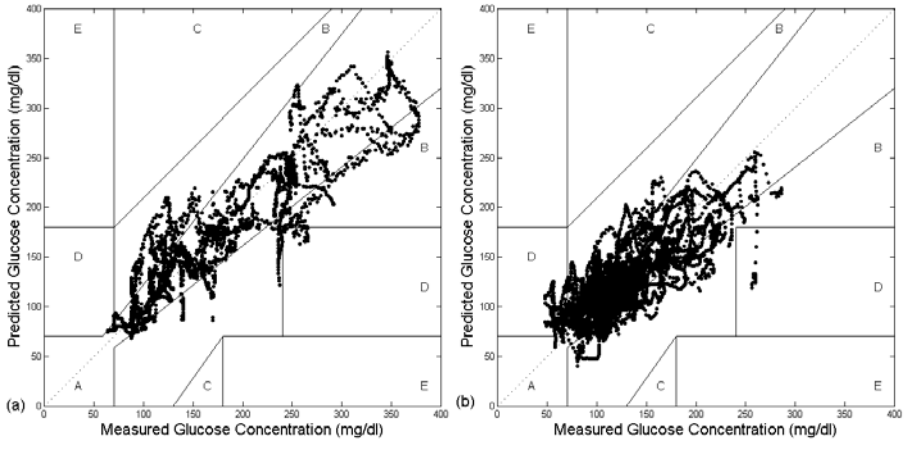
The prediction performance of the proposed method is assessed by calculating the Root Mean Squared Error, *RMSE,* and the correlation coefficient, estimated by *r,* for each patient's dataset. The Clarke's Error Grid Analysis (EGA) [11] is used to assess the clinical significance of the differences between the predicted and the measured s.c. glucose concentrations. The Clarke's EGA method uses a Cartesian diagram, in which the values predicted are displayed on the y-axis, whereas the values from glucose sensor are displayed on the x-axis. This diagram is subdivided into 5 zones: A, B, C, D and E which are defined in [11]. Briefly, the values that fall within zones A and B represent sufficiently accurate or acceptable glucose results, whereas the values included in the areas C-E indicate potentially dangerous overestimation or underestimation of the actual values.

3 Results

In Table 1, it can be seen that the glucose response is predicted with sufficiently low *RMSE* in the short-term (i.e. for 15 and 30 min), whereas *RMSE* increases for medium-term predictions (i.e. for 60 and 120 min). An important observation is that either using directly the real sensor data to indicate exercise intensity or the simulation output from the exercise compartmental models, the differences in the *RMSE* and the *r* are relatively small.

Table 1. The *RMSE* and the *r* values obtained for both patients

Physical Activity Input	Prediction Length (min)	r	RMSE (mg/dl)	r	RMSE (mg/dl)
		Patient1		*Patient2*	
Sensor Data	15	0.96	12.57	0.95	9.69
	30	0.90	21.36	0.87	16.32
	60	0.75	33.06	0.68	24.52
	120	0.28	62.29	0.37	31.10
Exercise Modeling	15	0.96	12.069	0.96	9.58
	30	0.91	19.93	0.88	15.91
	60	0.80	30.99	0.69	24.06
	120	0.46	55.43	0.42	31.24



(a) (b)

Fig. 1. Clarke's-EGA for measured vs predicted s.c. glucose concentrations using sensor data for 60 min prediction length of (a) Patient 1 and (b) Patient 2

The predicted versus measured s.c. glucose concentrations of both patients for one indicative input case are plotted as Clarke's-EGA diagrams in Figs. 1(a) and 1(b), respectively. As shown in Fig. 1, the vast majority of the points for Patient 1 are

within zones A (73.84%) and B (24.66%), which indicate clinically acceptable results, whereas a small amount of points (1.5%) are included in zone D. The percentages for Patient 2 are 70.31% for A, 25.78% for B and 3.91% for D. Note that although the predictions for Patient 2 are systematically more accurate than those for Patient 1, more points lie in non-clinically acceptable zones (i.e. D), which was also indicated by the smaller r values for Patient 2.

4 Discussion

A glucose prediction method based on a multi-parametric set of data (i.e. food, insulin, exercise and glucose measurements) was presented. The method employs compartmental analysis and SVR, and was evaluated using a dataset from two type 1 diabetic patients. Training and testing of the SVR was performed individually for each patient by applying a leave-one-day-out technique. The Clarke's-EGA was used to assess the performance of the proposed prediction method from a clinical point of view. The results obtained demonstrate the ability of the method to predict glucose response with a sufficient numerical accuracy and clinical acceptability.

This study makes an innovative use of exercise compartmental models in the sense that (a) feeds the compartmental models with real sensor data to indicate activity intensity and (b) uses the variations in plasma glucose and insulin concentrations induced by exercise as input to predictive modeling. One advantage of exercise compartmental modeling with respect to practical conditions is that even if the patient does not wear the armband continuously, accurate predictions can still be achieved by means of patient's manual notifications for any past exercise events. Similarly, the ability to analyze and predict the effects of exercise on glucose concentrations can be exploited for providing to the patient what-if advice on future hypothetical exercise scenarios. This type of decision support is important for everyday diabetes management and is foreseen in METABO functionalities.

Considering that the dynamics of insulin absorption and intestinal glucose absorption vary significantly among different individuals, it could be very important to estimate the parameters involved in the corresponding compartmental models, individually. Furthermore, we assume that solely the carbohydrates intake affects the glucose metabolism. However, the influence of the fats, the proteins, glucose index and other food nutrients on the dynamics of the digestive and absorptive processes will be also analyzed in the future. In this observational study, patients used a specially designed diary and a dietician analyzed food data. However, in METABO advanced mobile applications and efficient graphical user interfaces have been developed to allow the patient to manually notify of food intake, insulin injections and other information.

When more data will become available from planned observational studies, the validated models will be used in METABO to provide alerts for clinically critical events in both hypoglycemia and hyperglycemia and decision support to assist the patient in the self-management of the disease in daily life.

5 Conclusions

We proposed an innovative modeling methodology which combines compartmental models and SVR for the prediction of glucose concentrations in type 1 diabetic patients. Our future work includes the estimation of the parameters involved in the different compartmental models, as well as the determination of the kernel function and the parameter ε in the insensitive loss function of the SVR. In addition, we will model more individuals to validate the results obtained in this work. The proposed predictive scheme will be incorporated into mobile devices for diabetes management.

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