Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/bbe

Original Research Article

Accurate prediction of continuous blood glucose based on support vector regression and differential evolution algorithm

Takoua Hamdi [a,b], *Jaouher Ben Ali* [a,*], *Véronique Di Costanzo* [c], *Farhat Fnaiech* [a], *Eric Moreau* [b], *Jean-Marc Ginoux* [b]

[a] *Université de Tunis, ENSIT, LR13ES03 SIME, Montfleury, Tunisia*

[b] *Laboratoire d'Informatique et des Systèmes, UMR, CNRS 7020, Ecole d'Ingénieurs SeaTech, Université de Toulon, France*

[c] *Centre Hospitalier Intercommunal de Toulon La Seyne, 54, rue Henri Sainte Claire Deville, Toulon Cedex, France*

ARTICLE INFO

Article history:
Received 17 August 2017
Received in revised form
28 November 2017
Accepted 15 February 2018
Available online 23 February 2018

Keywords:
Continuous glucose monitoring (CGM)
Differential evolution (DE)
Support vector regression (SVR)
Time series forecasting
Type 1 diabetes (T1D)

ABSTRACT

Type 1 diabetes (T1D) is a chronic disease requiring patients to know their blood glucose values in order to ensure blood glucose levels as close to normal as possible. Hence, the ability to predict blood glucose levels is of a great interest for clinical researchers. In this sense, the literature is rich with several solutions that can predict blood glucose levels. Unfortunately, these methods require the patient to specific their daily activities: meal intake, insulin injection and emotional factors, which can be error prone. To reduce this burden on the patent, this work proposes to use only continuous glucose monitoring (CGM) data to predict blood glucose levels independently of other factors. To support this, support vector regression (SVR) and differential evolution (DE) algorithms were investigated. The proposed method is validated using real CGM data of 12 patients. The obtained average of root mean square error (RMSE) was 9.44, 10.78, 11.82 and 12.95 mg/dL for prediction horizon (PH) respectively equal to 15, 30, 45 and 60 min. The results of the present study and comparison with some previous works show that the proposed method holds promise. The SVR based on DE algorithm achieved high prediction accuracy while being robustness, automatic, and requiring no human intervention.

* *Corresponding author at:* Université de Tunis, ENSIT, LR13ES03 SIME, 1008, Montfleury, Tunisia.
E-mail address: benlijaouher@yahoo.fr (J. Ben Ali).

https://doi.org/10.1016/j.bbe.2018.02.005

1. Introduction

In the human body, the regulation of blood glucose is controlled by the action of two hormones: glucagon and insulin. The loss or destruction of β cells in the pancreas is known to causes Type 1 diabetes (T1D). Consequently, a reduction in insulin production leads to an increase of blood glucose and hyperglycemia [1]. Insulin has a significant role in the ability of cells to metabolize glucose [2]. Fig. 1 describes the cycle of insulin on glucose uptake.

Hyperglycemia is generally associated with complications such as: long-term micro-vascular complications (diabetic neuropathy, retinopathy and nephropathy), in addition to macro-vascular issues (stroke, peripheral arterial disease, and coronary artery disease). In addition, a decrease in blood glucose (hypoglycemia) can rapidly turn into critic situations, such as nervousness, sweating, rapid heartbeat, headaches and even coma. The remediation of these diabetic complications is the use of multiple doses of insulin injections (generally 2–3 injections per day) to supervision and control glycemic levels [3].

The latest technological advances in diabetes provide patients the ability to monitoring their blood glucose levels continuously (every few minutes). Hence, users can assess their response to insulin treatment in a more effective way [4]. Based on these technologies, a clinical goal has appeared: Is it possible to predict accurately blood glucose levels and give the opportunity for T1D patients to stabilize their blood glucose excursions?

To address this question, researchers have developed a number of techniques. In the open literature, two directions have extensively validated their efficiency:

Mathematical modeling: these methods could be used and implemented in electronic devices. However, in practice they have not fallen short in their performance expectations due to limited precision and their dependence on measuring patient activity.

Artificial intelligence and advanced signal processing techniques: although more difficult to implement in a run time system due to their complexity in described by mathematical models, tend to have higher performance.

Bremer and Gough (1999) exploited blood glucose levels [5] by recording data every 10 min. The experimental results obtained from modeling blood glucose data, allowed a prediction horizon (PH) equal to 10 min. This study demonstrated that blood glucose levels could be predicted by exploiting past blood glucose values. Since then, numerous methods have been proposed using continuous glucose monitoring (CGM) data and larger PHs.

The works of Sparacino et al. in [6,7] compared the predictive accuracy of a first-order autoregressive model (ARM) with a first-order polynomial model. For each model, the inputs were past blood glucose levels. These approaches assessed data from T1D patients recorded every 3 min using the GlucoDay CGM system. The results showed that the ARM model was the most consistent for obtaining a significant performance with PHs of 30 min and 45 min.

In [8], Palerm et al. exploited a Kalman filter to forecast blood glucose levels based on reconstructing the derivative of the glucose level. They predicted hypoglycemia using data from a CGM system (Medtronic) with an alarm threshold of 70 mg/dL, and they used a variable PH from 1 to 30 min. Experimental results of predicting hypoglycemia were sensitive to 90% and specific to 79%.

Pappada et al. [9,10] proposed an artificial neural network (ANN) engendered from the ''NeuroSolutions'' package software to predict blood glucose for a PH of 50–180 min. The training data set was acquired from 18 T1D patients based on CGM for a period of 3–9 days. Furthermore, the authors used an electronic diary to record hypo/hyperglycemia symptoms, meal intake, insulin doses, emotional states and activities. Experimental results showed that the predicted blood glucose levels were more accurate in the hyperglycemia and normoglycemic stages than those in the hypoglycemic stage. The authors reported that the cause of the discrepancy was that the training database employed fewer samples of hypoglycemic events. Consequently, one can conclude that ANN prediction results depend heavily on the quality and the number of the training dataset for these networks.

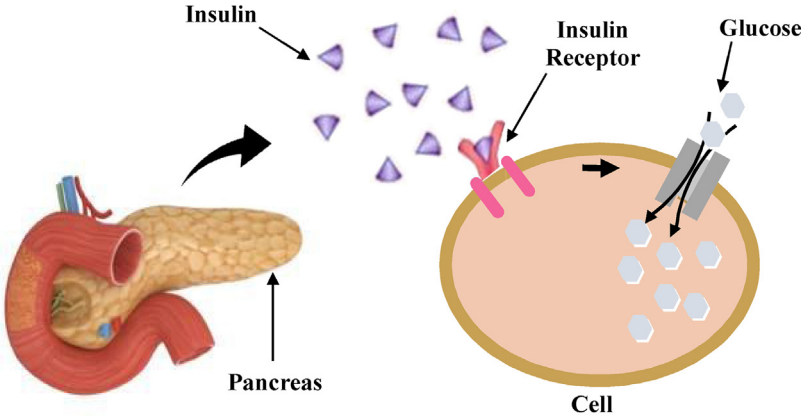

Fig. 1 – Cycle of insulin on glucose uptake.

To overcome this problem, Sandham et al. in [11] presented a big ANN architecture containing 95 neurons in the hidden layer to predict the blood glucose level accurately. The input parameters were: blood glucose level, stress, illness, exercise, insulin, diet, and some other factors.

To improve performance, Mougiakakou et al. developed a hybrid system based on three compartmental models (CMs): The first two models used short acting and the long-acting insulin effects, and the third model used glucose absorption in the gut [12]. A recurrent ANN based on CM estimations was shown to provide an improved predictions. The data were collected from T1D patient for a period of 69 days relating to blood glucose (at breakfast, lunch, dinner), food intake and insulin injections. The estimation results were evaluated by comparing ANN predictions and original data recorded from patients who were not used in the original training set. Despite the complexity of the proposed model, the experimental results were relatively accurate. The authors state that other information relating to age, years of diabetes, other diseases and gender, are considered important to improve accuracy of long-term prediction.

Zarkogianni et al. proposed a combination of ANN with one CM to ensure short-term blood glucose prediction to provide advice on insulin doses [13]. The dataset used by the model sampled the T1D patient every 3 min. Experimental results showed that the proposed method could control blood glucose level on condition of realistic meal intakes.

To develop a more reliable prediction compared to the cited works, a recent approach based on support vector regression (SVR) was proposed in [14]. Georga et al. suggested treating the problem of blood glucose level prediction as a multivariate regression task. Depending on the inputs, several cases were investigated: (i) the CGM data, (ii) the insulin doses, (iii) the appearance of the meal in the systemic circulation, and (vi) the energy spent during activities. These four cases model the influence of blood glucose to facilitate prediction. The SVR method was evaluated using a database of 27 patients that leaded authors to conclude that the average prediction error increases when the PH become more important.

Because of the reliability of SVR for prediction, Georga et al. combed a feature ranking technique with regression models [15]. In this study, multivariate inputs (CGM data, meal intake, energy spending and insulin doses) were ranked using a random forests (RF) algorithm, then the SVR was used as the glucose predictive model. The proposed method was evaluated on a database of 15 T1D patients. The most predictive inputs were the time and the insulin concentration resulting in a PH of 30 min.

This paper suggests the use of SVR algorithm in the prediction of blood glucose. The goal is to accurately predict blood glucose level of T1D patients using only using CGM data as inputs for the learning phase. We are able prove that the prediction can be done accurately using just previous glycemic data. Hence, previous CGM measurements will be used to predict the future blood glucose levels. This assumption facilitates the practical implementation of the proposed method in terms of computational complexity and memory stacking elements.

The rest of the paper is structured as follows: Section 2 introduces the SVR method and its application for the prediction phase. This section presents the proposed combination of SVR method and differential evolution (DE) algorithm. Section 3 presents the experimental setup, the data recording and the prediction results. In addition, it analyses and evaluates the application of the proposed DE-SVR for blood glucose prediction of T1D. Further, it includes a discussion and comparison with previous works to highlight the robustness and the reliability of the proposed method. Finally, our conclusions and future works are provided in Section 4.

2. Support vector regression based on differential evolution algorithm

2.1. *Support vector regression*

Support vector regression (SVR) is a powerful technique for predictive data analytics used in many applications, such as: sunspot frequency prediction, biological contexts, civil engineering, image compression and image tracking, etc. [16]. SVR is based on the theory of the structural risk minimization principle. SVR estimates a function by minimizing an upper bound of the generalization error [17].

Mathematically, SVR reduces the tolerated error by maximizing the hyper-plane margin. For the example, in blood glucose, the predicted value at time $t + PH$, assuming that t is the current time and PH is the prediction horizon, is expressed by the below function:

$$f(x) = f(x_1, \ldots, x_N) \tag{1}$$

The proposal of SVR maps a potentially nonlinear dataset x into a higher-dimensional, linear feature space which allow linear regression of the new feature space. In the SVR methodology [18], the prediction function $f(x)$ given in Eq. (1) is specified by the following linear form:

$$f(x) = w^T \phi(x) + b \tag{2}$$

where $\phi(x)$ is a fixed feature space transformation, w is the weight matrix and b is the bias.

As noted, the SVR algorithm aims to solve a nonlinear regression problem by mapping the training data x_i (where $i = \{1,\ldots, N\}$ and N is the size of the training dataset) into a new feature space called ϕ where the relation between the input x_i and the output y_i becomes linear.

For sparse solutions, a ε-insensitive loss function is defined where the error increases linearly with the distance above the insensitive region. Nevertheless, errors larger than $\pm\varepsilon$ are treated by introducing the variables ξ_i and ξ_i^* for each data point x_i. The optimization problem minimizes $C*\sum_{i=1}^{N}(\xi_i + \xi_i^*) + \frac{1}{2}\|w\|^2$ subjects to:

$$\begin{cases} y_i \leq f(x_i) + \varepsilon + \xi_i \\ y_i \geq f(x_i) - \varepsilon - \xi_i \\ \xi_i, \xi_i^* \geq 0 \end{cases} \tag{3}$$

The constant C defines the compromise between the uniformity of the SVR function $f(x)$ and the deviations superior to ε are tolerated. Several kernel functions have been defined in

the literature. In this work, we have used the radial basis function (RBF) which is defined by:

$$k(x_i, x_j) = \exp\left(\frac{-||x_i - x_j||^2}{2\gamma^2}\right) \quad (4)$$

where γ is the kernel parameter that is always greater than zero.

Because Eq. (3) meeting the Karush–Kuhn–Tucker theory (KKT condition), the regression function can be used to predict a new x as [18]:

$$f(x) = \sum_{i=1}^{N}(a_i - a_i^*)k(x, x^i) + b \quad (5)$$

where (a_i, a_i^*) are the Lagrange multipliers and k is the kernel function used for computing the similarity between the two input vectors (x and x^i) in the transformed space.

Visually, Fig. 2 shows the final solution for the given input variables after mapping to a reproducing Kernel Hilbert space (KHS) and a linear regression. All samples outside a fixed margin, named support vectors, are drawn with blue double circles in this figure.

Generally, SVR is applied to time series prediction [19]. However, in practical application using SVR, performance is depended on proper parameters selection. Therefore, we propose to combine the SVR method with an optimization algorithm to better estimate the hyper-optimized parameters (C, ε and γ). We propose the differential evolution (DE), which improves the forecasting accuracy [20]. The next section describes briefly the DE algorithm.

2.2. Differential evolution algorithm

Differential evolution (DE) algorithm is a evolutionary techniques originally proposed by Storn and Price in 1995 [21]. DE algorithm is a global search strategy based on population differences and is generally used as a robust global optimizer [22]. The DE assumes that the difference evolution sampling techniques (which has mutation, crossover and selection steps) results in a multivariate Gaussian distribution with improved qualities. Optimality is read through repeated generations, until the stopping condition is reached [23,24]. The different steps of the DE algorithm are summarized as follows [25].

2.2.1. Step 1: initialization

Each generation of population can be presented by the following vector parameter:

$$x_{i,G} = (x_{1i,G}, x_{2i,G}, \ldots, x_{Di,G})_{(i=1,2,\ldots,NP)} \quad (6)$$

where $x_{ji,G}$ is the jth component of the ith individual in the Gth generation, NP is the population size which is unchanged in the optimization process, and D is the dimension of the vector parameter.

The selection of the initial population is done randomly within the boundary constraints as:

$$x_{ji,G} = rand_{[0,1]} \times (x_j^{(H)} - x_j^{(L)}) + x_j^{(L)} \quad (7)$$

where $rand_{[0,1]}$ is a random number between 0 and 1, $x_j^{(L)}$ is the lower bound of the jth component $x_j^{(H)}$ is the upper bound of the jth component.

2.2.2. Step 2: mutation

Let one denote the *target vector* as the vector in the current population. For each target vector, the mutant vector $v_{i,G+1}$ is generated as follows:

$$v_{i,G+1} = x_{r_1,G} + F \times (x_{r_2,G} - x_{r_3,G}) \quad (8)$$

where r_1, r_2, and r_3 are random indexes in the range [1,NP] and F is the scaling factor in the range [0,1] which controls the difference between $x_{r2,G}$ and $x_{r3,G}$.

2.2.3. Step 3: crossover

The main objective of this step is to increase the diversity of the population. Consequently, a new vector is created. This vector is well known as the trial vector $U_{ji,G+1}$, is expressed as follow:

$$U_{ji,G+1} = \begin{cases} V_{ji,G+1}, \text{ if } \{(rand(b(j)) \le C_r) \text{ or } (j = randn(j))\} \\ X_{ji,G+1}, \text{ if } \{(rand(b(j)) > C_r) \text{ and } (j \ne randn(j))\} \end{cases} \quad (9)$$

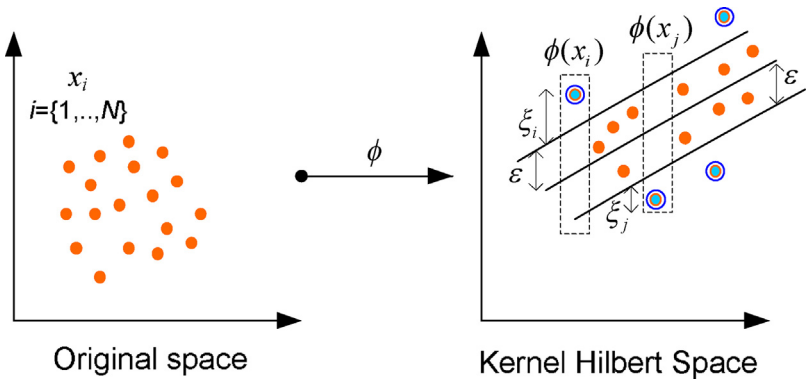

Fig. 2 – Illustrative schema of the SVR model.

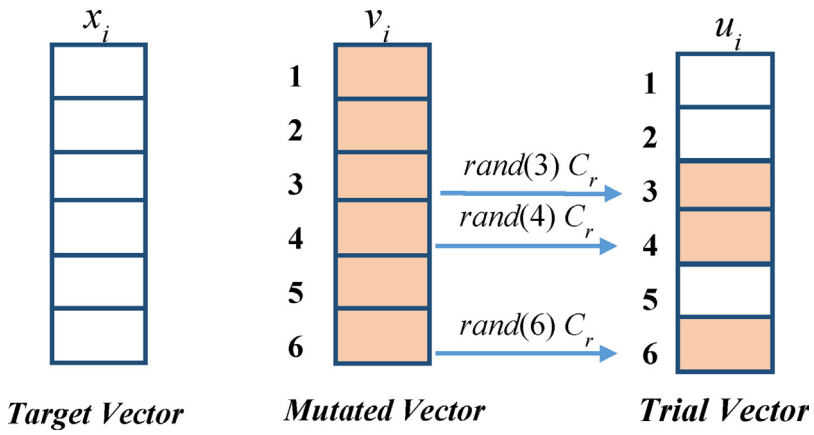

Fig. 3 – An example of the crossover process for six-dimensional variables.

where j is the index of the element for any vector, $rand(b(j))$ is a random number in the range [0,1], $randn(j)$ is a random number in the range [1, D] and C_r is the crossover probability in the range [0,1].

For more convenience, a crossover process example with six-dimensional variables is represented in Fig. 3.

2.2.4. *Step 4: selection*

This step is based on the greedy algorithm to select individuals competing in the next generation. The principle of this operation is the comparison between each individual's fitness function values. Therefore, if the *trial vector* has an inferior objective function value than its parent, the *trial vector* substitutes the position of the target vector. For a given fitness function f, the selection operator $X_{i,G+1}$ is expressed by the following expression:

$$X_{i,G+1} = \begin{cases} U_{i,G}, & \text{if } f(U_{i,G}) \leq f(X_{i,G}) \\ X_{i,G}, & \text{else} \end{cases} \quad (10)$$

2.3. *Combination of SVR and DE algorithm for prediction tasks*

The steps of the SVR model based on DE algorithm are shown as follows.

2.3.1. *Step 1: initialization*

The initialization of DE algorithm parameters depends on the specific problem. In this paper, these parameters were: the population size (NP = 10), the evolution generation (G = 200), the mutation scaling (F = 0.6), and the crossover probability (C_r = 0.9).

2.3.2. *Step 2: optimization based on DE*

The initial of DE algorithm is generated according to Eq. (5). Note that the SVR is sensitive to two parameters: the regularization parameter (C) and the kernel parameter (γ). In addition, the fitness function used in DE algorithm is was:

$$f(C,\gamma,\varepsilon) = \frac{1}{n}\sum_{1}^{n}\left|\frac{R_i(C,\gamma,\varepsilon) - F_i(C,\gamma,\varepsilon)}{R_i(C,\gamma,\varepsilon)}\right| \times 100\% \quad (11)$$

where R_i is the actual value and F_i is the predictive value, and n is the size of training dataset. The optimal parameters C and γ are found after the standard steps of DE algorithm: mutation, crossover, and selection.

2.3.3. *Step 3: forecasting with SVR model*

After reaching the optimal parameters using the DE algorithm, the forecasting values of the SVR model are obtained. To illustrate briefly, the proposed processing is a combination of SVR model and DE algorithm, as shown in the flowchart, Fig. 4.

3. Application of SVR based on DE algorithm for blood glucose level prediction

3.1. *Database description*

Continuous glucose monitoring (CGM) devices started development in 1980 and since 2000 the first commercial systems have been available to the public [26,27]. As such, CGM technologies have opened many new ways to analysis T1D. It is now possible for diabetic to control their blood glucose level simply by apply the sensor, transmitter and a glucose monitor. The CGM device contains a sensor inserted under the skin of the patient to continuously measure the interstitial glucose, which is transmitted to a glucose monitoring device for displaying data and trends.

As shown in Fig. 5, the subcutaneous sensor measures glucose in the interstitial fluid. In reality, there is a lag time between blood glucose and interstitial glucose, which is on the order of 5 min [28]. This is the time needed time for the diffusion to the sensor and the computational time delay caused by filtering operations applied to the CGM measurements [29]. Consequently, there is high correlation between interstitial and blood glucose [30]. Hence, the estimation of interstitial glucose is a good estimation of blood glucose [31]. Hence, this is why the CGM measurement blood glucose values are used throughout this paper.

In this study, blood glucose levels were recorded using the Freestyle Navigator CGM System (Abbott Laboratories). This system yields a blood glucose value every 15 min (96 values

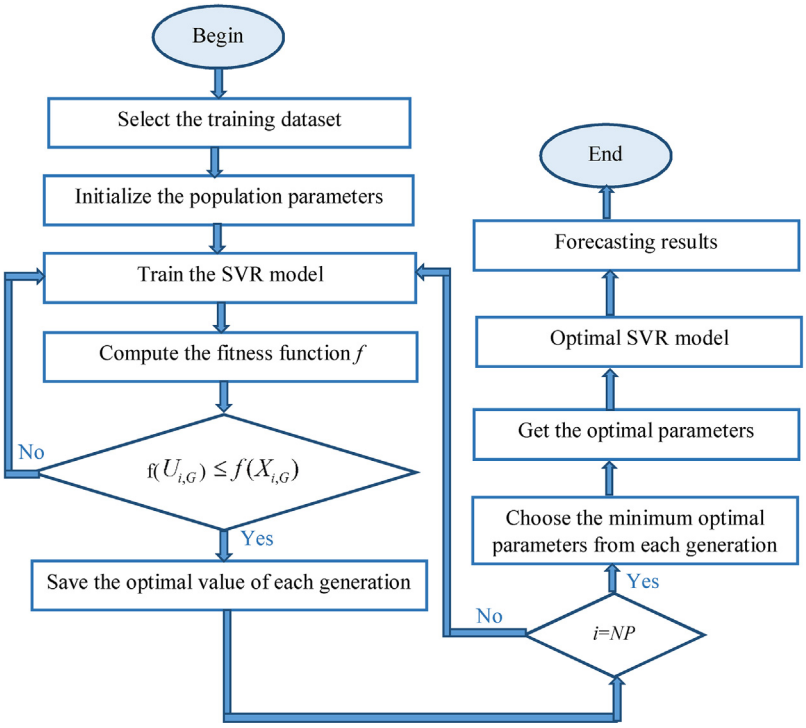

Fig. 4 – Flowchart of SVR model based on DE algorithm.

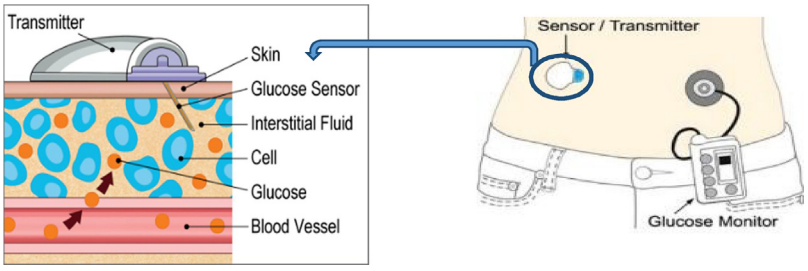

Fig. 5 – Glucose monitoring system.

per day). The entire dataset is composed of 12 T1D and continues his daily life ordinarily. Typically, the patient went to the hospital, received the CGM sensor and he returned to home with the system. After 14 days (the duration of the sensor), he returned to the hospital to change the sensor. The CGM allows the patient to receive monitor as an outpatient.

3.2. *Prediction using the proposed combination of SVR and DE algorithm*

For this study, before the estimation of SVR parameters, it is necessary to find the optimal parameters of the DE algorithm (*NP*, *F* and *Cr*). This is needed for an accurate prediction glucose level prediction. Thus, we propose:

NP = 10 to ensure that the DE algorithm will have enough mutually different vectors,
F = 0.5 to be used for the initialization,

Cr = 0.5 to increase the diversity of the population.

For each patient, we used 70% of his recorded blood glucose data for the training step and used the remaining 30% of glycemic data to test the predictions. The training step allows building of an adequate model by defining the relationship between SVR input and output measures. During this phase, the DE algorithm automatically determines the model parameters of SVR (C, ε and γ). Indeed, the DE algorithm performs three different operations: mutation, crossover, and selection for a precise optimization of the model parameters. Then, the SVR model can be defined by optimizing the parameters conforming to the least fitness function. In the test step, the remaining 30% of data is used to verify the performances of the proposed approach.

The output of the proposed DE-SVR combination is the predicted blood glucose at time $t + PH$, where the prediction horizon (PH) is defined by the user before training the SVR and it could be 15, 30, 45 and 60 min.

In order to assess the prediction performances of the proposed approach, Fig. 6 presents a comparison between the

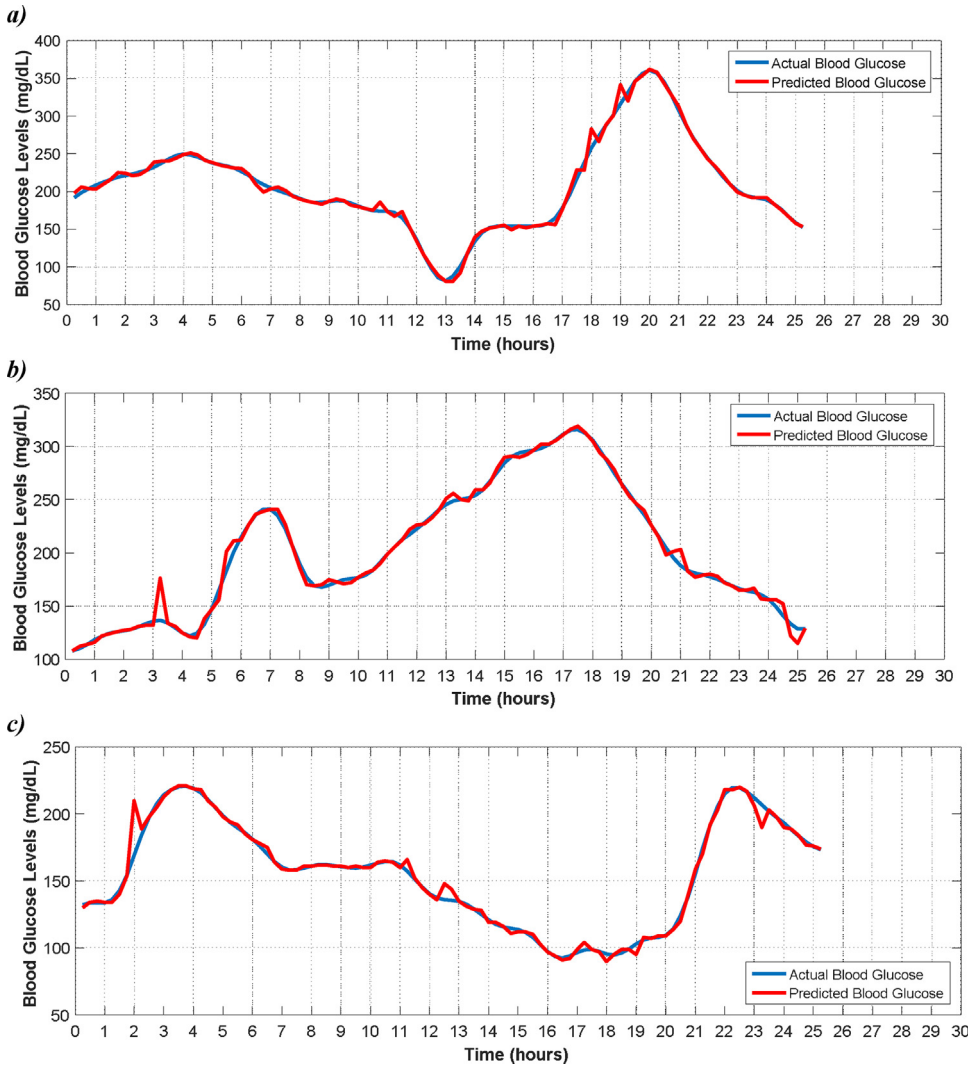

Fig. 6 – SVR results of Blood Glucose for PH = 15 min: (a) patient 1 (C = 557.32, ε = 0.68, γ = 6.07); (b) patient 2 (C = 562.14, ε = 0.65, γ = 6.03); (c) patient 3 (C = 559.57, ε = 0.62, γ = 6.02).

actual blood glucose and SVR prediction results for three different patients and for PH = 15 min. Note that the error between predicted and actual blood glucose increases mostly between peaks and nadirs. This could be explained by the limited quantity of hypoglycemia and hyperglycemia in the training data. Moreover, this may be due to the kind of diabetes that is influenced by other factors such as: physical activity, emotion state, and stress. As seen in Fig. 6 the proposed SVR strategy is remarkably accurate and could be potentially applied for biomedical prediction tasks and time series forecasting.

For more accurate performance assessment, we propose to use the entire clinical database derived from 12 patients. Thus, for each patient, the DE algorithm fixed the optimal parameters and the SVR was trained automatically. To quantify the prediction performance, several measures were used and defined in the literature [14,32,33]. In this work, we have used the root mean square error (RMSE), the mean absolute percentage error (MAPE) and the fitness degree (R^2). These measures are common in the literature for prediction tasks and especially for blood glucose prediction.

The RMSE is good measure of the prediction's accuracy because it allows the error to be as the same units as the quantity being predicted [34]. Consider a series of blood glucose levels (denoted X) and its predicted measures ($\hat{X}$) with a length equal to n. The RMSE is expressed as:

$$RMSE = \sqrt{\frac{1}{n}\sum_{1}^{n}\left(X_i - \hat{X}_i\right)^2} \tag{12}$$

The MAPE is expressed by Eq. (13) and it is usually used to define the size of the error in percentage terms. In addition, it may be over sensitive to outliers and should not be used when working with low-volume data. Moreover, the MAPE is undefined when actual demand is zero because it is in the denominator.

$$MAPE = \frac{100}{n}\sum_{1}^{n}\left|\frac{X_i - \hat{X}_i}{X_i}\right| \tag{13}$$

R^2, the correlation coefficient, or also know as the fitness degree, is expressed in Eq. (14), where X_m is the mean of blood glucose levels for each patient. The best performances are achieved when R^2 values are near to 1. Ideally, if $R^2 = 1$, the original series and the predicted one would be superimposed.

$$R^2 = 1 - \frac{\sum_1^n \left(X_i - \widehat{X}_i\right)^2}{\sum_1^n (X_i - X_m)^2} \quad (14)$$

Based on the statistical criteria presented previously, Table 1 summarizes DE-SVR results for blood glucose prediction of 12 patients. For the entire test dataset and for PH = 15 min, the average of RMSE (mg/dL) was 9.44, the average of MAPE was 3.74% and the average of R^2 coefficient was 0.971. Individually, the evaluation of model performance for each patient shows that the RMSE ranged from 5.17 mg/dL to 18.28 mg/dL, MAPE ranged from 1.50% to 6.66% and R^2 ranged from 0.88 to 0.994.

Table 2 includes RMSE performances for DE-SVR algorithm with 12 patients for 30, 45 and 60 min PHs. The obtained averages of RMSE were 9.44 mg/dL, 10.78 mg/dL, 11.82 mg/dL and 12.95 mg/dL respectively, for PH = 15 min, 30 min, 45 min and 60 min. This finding emphasizes the validity of the proposed DE-SVR combination. As expected, we note that a considerable increase of RMSE is observed with an increase in PH.

Note that the DE-SVR modeling performances were higher for patient 1 and patient 3 and they were low for patient 5 and 7. This is due to the important non-stationary of these two cases, which is explained by the clinician as an uncontrolled consumption of sugary foods. These observations have revealed that the proposed DE-SVR combination presents a powerful methodology for blood glucose prediction.

3.3. Comparison of DE optimization results with other metaheuristic algorithms

Because the SVR prediction performance is dependent on parameters C, ε and γ, care is needed in the selection of these parameters. Hyperparameters play a critical role in the prediction performance of a SVR model. Many approaches have been proposed for tuning hyperparameters, but none of the proposed approaches is efficient and accurate in all applications. In this work, three methods are presented to estimate the optimal SVR parameters. As the SVR prediction is sensitive to these parameters, the SVR was compared to different optimization techniques: genetic algorithm (GA) and the particle swarm optimization (PSO) technique. Fig. 7 illustrates the SVR prediction performances based on PSO, GA and DE techniques for one patient and Table 2 summarizes the RMSE performance for the first five patients.

From Table 3, one observes that the performances of the SVR based on the choice of the optimization technique. Furthermore, this table shows that neither GA-SVR model nor the PSO-SVR model forecasts as accurately as the DE-SVR model. As such, one can conclude that DE-SVR model is more effective than the GA-SVR model or the PSO-SVR model, resulting in higher accuracy and reliability.

3.4. Discussion and comparison with some previous works

In this work, a study of the prediction of blood glucose levels for T1D patients was presented. The innovative element of this study is that the prediction of blood glucose level used only CGM data as inputs. The proposed SVR technique approximates the nonlinear changes of the blood glucose, while avoiding over-fitting. Furthermore, we describe the error function with the absence of local minima. This is contrary to other machine learning techniques.

Despite the rapid development of CGM systems as a hardware device, there has been little evolution in prediction algorithms and strategies for predicting blood glucose level over any meaningful PH. The essential problem facing the industry is: first, to enhance the prediction accuracy and to minimize the errors, and secondly to ensure the prediction of blood glucose accurately. These problems need to be solved used using only CGM data as input. As such, what is the most effective method for blood glucose prediction using only CGM data as input?

To answer this question, numerous research studies have been developed and reported in the literature. Table 4 summarizes a comparison of the proposed method.

A direct comparison of the presented results is not fair because several factors affect the performance of blood glucose prediction such as: the number of inputs, the size of the used database and the length of the prediction horizon.

Table 1 – Evaluation results of DE-SVR performances for all patients (PH = 15 min).

Patient	RMSE	MAPE	R^2
1	5.27	1.52	0.992
2	5.87	1.77	0.990
3	5.17	1.50	0.982
4	8.37	3.5	0.971
5	18.28	3.74	0.88
6	9.12	4.38	0.973
7	12.84	5.65	0.984
8	12.22	6.66	0.955
9	12.19	4.68	0.959
10	9.47	3.84	0.989
11	7.53	3.49	0.994
12	7.05	4.17	0.989

Table 2 – RMSE of DE-SVR for different prediction horizons (PHs).

Patient	RMSE (mg/dL) at PH of		
	30 min	45 min	60 min
1	6.14	7.27	8.15
2	7.03	8.12	9.76
3	5.96	7.46	8.38
4	9.28	9.78	11.02
5	20.11	20.89	21.54
6	11.23	12.48	13.61
7	13.88	14.74	15.36
8	14.01	15.05	16.43
9	13.75	15.03	16.56
10	10.59	11.34	12.63
11	9.08	10.26	11.38
12	8.36	9.43	10.61

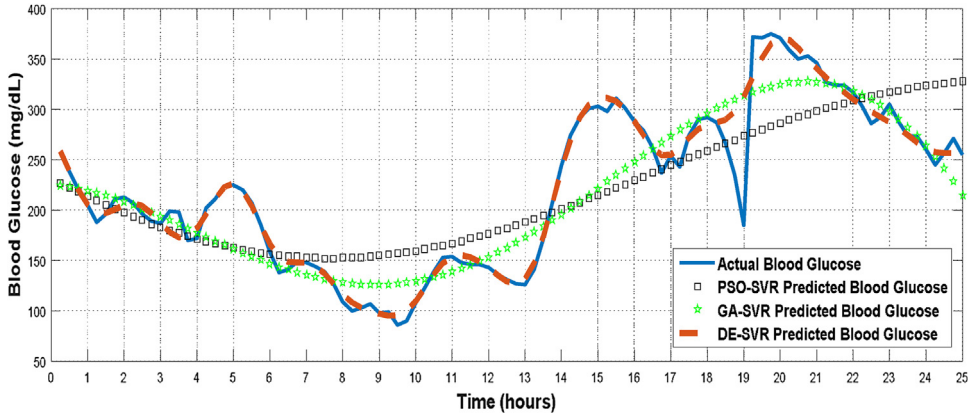

Fig. 7 – Blood glucose SVR prediction performances based on different optimization techniques.

Table 3 – The RMSE obtained from SVR prediction using different optimization techniques.

Patient	PSO-SVR	GA-SVR	DE-SVR (proposed method)
1	27.05	32.29	5.27
2	27.54	27.28	5.87
3	30.86	29.93	5.17
4	49.50	38.91	8.37
5	46.61	35.56	18.28

Nevertheless, based on Table 4, experimental results prove that proposed SVR based on DE algorithm outperforms the other methods excepting Georga et al. [14,15]. However, experimental results of our method were computed based only on CGM data. This is an important advantage, because in a real application, it is really very convenient to design a prediction system taking into account only CGM data. The used of CGM allows an autonomous system and without any human intervention. Experimental results of the proposed DE-SVR combination show high prediction accuracy.

As seen in Fig. 8 highlights the difference between proposed DE-SVR method and other methods existing in the literature. While other methods have considered the physical activities: meal intake, insulin injection and emotional factors, the proposed between proposed DE-SVR uses only CGM data, facilitating automatic system without need of any human intervention.

Certainly, additional modeling information, such as life-style details and psychological status, improve the accuracy

Table 4 – Comparison with some previous works reported in the literature.

Study	Method	Inputs	Database	Prediction horizon (min)	RMSE (mg/dL)
Mougiakakou et al. [35]	Neural networks	CGM data, CHO, insulin	4 type 1 diabetes	5	13.65
Sparacino et al. [7]	AR	CGM data	28 type 1 diabetes	30	18.78
				45	34.64
Pérez-Gandia et al. [36]	Neural networks	CGM data	6 type 1 diabetes	15	9.7
				30	17.5
				45	27.1
Robertson et al. [37]	Recurrent NN	CGM data, meal intake, insulin injections.	2 type 1 diabetes	15	10.09
Pappada et al. [9]	Neural networks	CGM data, time, insulin, nutrition, emotional factors	17 type 1 diabetes	75	43.9
Zecchin et al. [38]	Feed-forward NN and first-order polynomial model	CGM data, glucose rate of appearance after a meal	15 type 1 diabetes	30	14
Turksoy et al. [39]	Recursive ARMAX model	CGM data, insulin on board, energy expenditure, galvanic skin response	14 type 1 diabetes	30	11.7
Georga et al. [14]	SVR	CGM data, insulin, CHO, exercise, time	27 type 1 diabetes	15	5.21
Georga et al. [15]	SVR—random forests (RF)	CGM data, meal intake, insulin concentration, energy expenditure, time	15 type 1 diabetes	30	5.7
Proposed method	SVR based on DE algorithm	CGM data	12 type 1 diabetes	15	9.44
				30	10.78
				45	11.82
				60	12.95

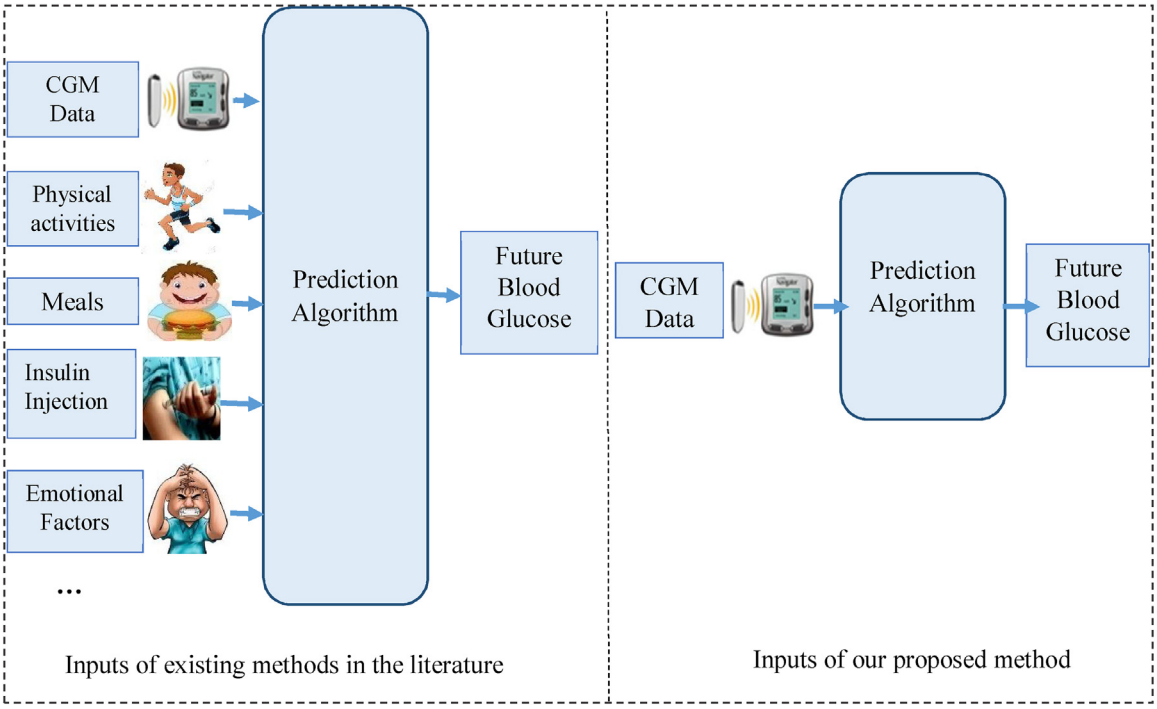

Fig. 8 – Importance of the proposed method as input perspective.

of the prediction algorithm. However, in the real life application, it is not practical for the patient. It is uncomfortable and boring for the patient who will be obliged to introduce his information A more complex model would require the patient enter this lifestyle information 3 or 4 times per day. Consequently, the goal in this work is to use only CGM data as inputs and to obtain accurate performances of prediction. The advantages offered by the proposed blood glucose prediction algorithm are enormously beneficial as a personal diabetes advisory system. In fact, the suggested method could be integrated into CGM devices, which would be able to predict hyper or hypoglycemia and would give an opportunity to patients to avoid them blood glucose fluctuations, improving overall safety, quality of life and health. Ideally, these would include the smart CGM, which is a system able to generate alerts when glucose concentrations exceed the normal range thresholds [40].

4. Conclusions and prospects

In this study, a weighted SVR based on the DE algorithm is proposed to predict blood glucose level of T1D. The DE algorithm is used to optimize the SVR parameters and to estimate effective values for this task. Compared to techniques reported in the literature, the proposed method presents numerous advantages such as accuracy, adaptively, robustness and easiness for practice. Verified by experimental results, the proposed combination of SVR with DE optimization algorithm presents high prediction accuracy because of its effectiveness in modeling nonlinear and complex data series.

As future works, we will focus on increasing the number of patients for a larger validation dataset. Further, an extensive clinical validation of the SVR prediction algorithm will be continued for a potential real-life application. Indeed, while we have used a well-established machine learning technique, further machine learning approaches should be applied and compared specially in terms of accuracy.

REFERENCES

[1] A.D. Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2011;34(January (1)):62–9.
[2] Thakkar CS, Kshirsagar R, Naik V, Ghosh A, Vijayakumar V, Saklani A, et al. (E)-9-oxooctadec-10-en-12-ynoic acid from Ixora brachiata Roxb. increases glucose uptake in L6 myotubes by activating the PI3K pathway. Fitoterapia 2016.
[3] Association AD. Standards of medical care. Diabetes Care 2011;34(January (1)):11–61.
[4] Klonoff DC. Continuous glucose monitoring – roadmap for 21st century diabetes therapy. Diabetes Care 2005;28(May (5)):1231–9.
[5] Bremer T, Gough D. Is blood glucose predictable from previous values? A solicitation for data. Diabetes 1999;44:445–51.
[6] Sparacino G, Zanderigo S, Aran A, Cobelli C. Continuous glucose monitoring and hypo/hyperglycemia. Diabetes Res Clin Pract 2006;74(2):S160–3.
[7] Sparacino G, Zanderigo F, Corazza S, Maran A, Facchinetti A, Cobelli C. Glucose concentration can be predicted ahead in time from continuous glucose monitoring sensor time-series. IEEE Trans Biomed Eng May 2007;54(5):931–7.

[8] Palerm C, Willis J, Desemone J, Bequette B. Hypoglycemia prediction and detection using optimal estimation. Diabetes Technol Ther 2005;7(1):3–14.
[9] Pappada S, Cameron B, Rosman P, Bourey R, Papadimos T, Oloruntu W, et al. Neural network-based real-time prediction of glucose in patients with insulindependent diabetes. Diabetes Technol Ther 2011;13(2):135–41.
[10] Pappada SM, Cameron BD, Rosman PM. Development of a neural network for prediction of glucose. J Diabetes Sci Technol 2008;2(September (5)).
[11] Sandham W, Nikoletou D, Hamilton D, Patterson K, Japp A, Macgregor C. Blood glucose prediction for diabetes therapy using a recurrent artificial neural network. Proceedings of the 9th European Signal Processing Conference (EUSIPCO'98), vol. 11; 1998. p. 673–6.
[12] Mougiakakou SG, Prountzou K, Nikita KS. A real time simulation model of glucose-insulin metabolism. Proceedings of the 27th Annual International Conference of the Engineering in Medicine and Biology Society (IEEE-EMBS'05), vol. 1; September 2005. p. 298–301.
[13] Zarkogianni K, Mougiakakou SG, Prountzou A, Vazeou A. An insulin infusion advisory system for type 1 diabetes patients based on non-linear model predictive control methods. Proceedings of the Annual International Conference of the IEEE Engineering in Medicine and Biology Society; 2007. p. 5972–5.
[14] Georga EI, Vasilios C, Ardigo D, Marina M, Zavaroni I, Polyzos D, et al. Multivariate prediction of subcutaneous glucose concentration in type 1 diabetes patients based on support vector regression. IEEE J Biomed Health Inform 2013;17(January (1)):71–81.
[15] Georga EI, Protopappas V, Polyzos D, Fotiadis D. Evaluation of short-term predictors of glucose concentration in type 1 diabetes combining feature ranking with regression models. Med Biol Eng Comput 2015;53(12):1305–18.
[16] Soman KP, Loganathan R, Ajay V. Machine learning with SVM and other kernel methods. Prentice Hall; 2009.
[17] Nuryani N, Ling SS, Nguyen HT. Electrocardiographic signals and swarm-based support vector machine for hypoglycemia detection. Ann Biomed Eng 2012;40:934–45.
[18] Smola AJ, Scholkopf B. A tutorial on support vector regression. Stat Comput 2004;14(August (3)):199–222.
[19] Weiwei W. Time series prediction based on SVM and GA. Conf Proc Electron Measure Instrum 2007;2-307–10.
[20] Storn R. Differential evolution: a simple and efficient heuristic for global optimization over continuous spaces. J Glob Opt 1997;11(December (4)):341–59.
[21] Storn R, Price K. Differential evolution – a simple and efficient adaptive scheme for global optimization over continuous spaces, vol. 3. Berkeley: ICSI; 1995.
[22] Xuemei L, Jin-hu L, Lixing D, Gang X, Jibin L. Building cooling load forecasting model based on LS-SVM. Asia-Pacific Conf Inf Process 2009;1:55–8.
[23] Tan G, Yan J, Gao C. Prediction of water quality time series data based on least squares support vector machine. Procedia Eng 2012;31:1194–9.
[24] Fei SW, Sun Y. Forecasting dissolved gases content in power transformer oil based on support vector machine with genetic algorithm. Electr Power Syst Res 2008;78:507–14.
[25] Sun W, Liang Y. Research of least squares support vector regression based on differential evolution algorithm in short-term load forecasting model. J Renew Sustain Energy 2014;6(5):053137.
[26] Djakouré-Platonoff C, Radermercker R, Reach G, Slama G, Selam J. Accuracy of the continuous glucose monitoring system in inpatient and outpatient conditions. Diabetes Metab 2003;28:159–62.
[27] Benhamou PY, Catargi B, Delenne B, Guerci B, Hanaire H. Real time continuous glucose monitoring (CGM) integrated into the treatment of type 1 diabetes: consensus of experts from SFD, EVADIAC and SFE. Diabetes Metab 2012;38:67–83.
[28] Basu A, Dube S, Slama M. Time lag of glucose from intravascular to interstitial compartment. Hum Diabetes 2013;62:4083–7.
[29] Schmelzeisen-Redeker G, Staib AA, Strasser M, Muller U, Schoemaker M. Overview of a novel sensor for continuous glucose monitoring. Diabetes Sci Technol 2013;7:808–14.
[30] Sachedina N, Pickup J. Performance assessment of the Medtronic-MiniMed Continuous Glucose Monitoring System and its use for measurement of glycaemic control in Type 1 diabetic subjects. Diabetic Med 2003;20(12):1012–5.
[31] Rossetti P, Bondia J, Vehí J, Fanelli C. Estimating plasma glucose from interstitial glucose: the issue of calibration algorithms in commercial continuous glucose monitoring devices. Sensors 2010;10(12):10936–52.
[32] Koutny T. Glucose predictability,blood capillary permeability,and glucose utilization ratein subcutaneous, skeletal muscle, and visceral fat tissues. Comput Biol Med 2013;(43):1680–6.
[33] Hayashia Y, Setiono R. Combining neural network predictions for medical diagnosis. Comput Biol Med 2002;(32):237–46.
[34] Han J. Accuracy and error measures Concepts and Techniques. Data mining. United States of America: Elsevier; 2006. p. 770.
[35] Mougiakakou SG, Prountzou A, Iliopoulou D, Nikita KS, Vaze A, Bartsocas CS. Neural network based glucose-insulin metabolism models for children with type 1 diabetes. Proc. 28th Annu. Int. Conf. IEEE Eng. Med. Biol. Soc.; August/September 2006. pp. 3545–8.
[36] Pérez-Gandia C, Facchinetti A, Sparacino G, Cobelli C, Gomez EJ, Rigla M, et al. Artificial neural network algorithm for online glucose prediction from continuous glucose monitoring. Diabetes Technol Therapeut 2010;12(1):81–8.
[37] Robertson G, Lehmann ED, Sandham W, Hamilton D. Blood glucose prediction using artificial neural networks trained with the AIDA diabetes simulator: a proof-of-concept pilot study. J Electr Comput Eng 2011;2011:2.
[38] Zecchin C, Facchinetti A, Sparacino G, De Nicolao G, Cobelli C. Neural network incorporating meal information improves accuracy of short-time prediction of glucose concentration. IEEE Trans Bio-Med Eng 2012;59(6):1550–60.
[39] Turksoy K, Bayrak E, Quinn L, Littlejohn E, Rollins D, Cinar A. Hypoglycemia early alarm systems based on multivariable. Ind Eng Chem Res 2013;52:12329–36.
[40] Bode B, Gross K, Rikalo N, Schwartz S, Wahl T, Page C, et al. Alarms based on realtime sensor glucose values alert patients to hypo- and hyperglycemia: the guardian continuous monitoring system. Diabetes Technol Ther 2004;6:105–13.