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Original Article

# A Hybrid Dynamic Wavelet-Based Modeling Method for Blood Glucose Concentration Prediction in Type 1 Diabetes

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## Abstract

**Background:** Diabetes mellitus (DM) is a chronic disease that affects public health. The prediction of blood glucose concentration (BGC) is essential to improve the therapy of type 1 DM (T1DM). **Methods:** Having considered the risk of hyper- and hypo-glycemia, we provide a new hybrid modeling approach for BGC prediction based on a dynamic wavelet neural network (WNN) model, including a heuristic input selection. The proposed models include a hybrid dynamic WNN (HDWNN) and a hybrid dynamic fuzzy WNN (HDFWNN). These wavelet-based networks are designed based on dominant wavelets selected by the genetic algorithm-orthogonal least square method. Furthermore, the HDFWNN model structure is improved using fuzzy rule induction, an important innovation in the fuzzy wavelet modeling. The proposed networks are tested on real data from 12 T1DM patients and also simulated data from 33 virtual patients with an UVa/Padova simulator, an approved simulator by the US Food and Drug Administration. **Results:** A comparison study is performed in terms of new glucose-based assessment metrics, such as gFIT, glucose-weighted form of $ESOD_n$ ($gESOD_n$), and glucose-weighted $R^2$ ($gR^2$). For real patients' data, the values of the mentioned indices are accomplished as gFIT = 0.97 ± 0.01, $gESOD_n$ = 1.18 ± 0.38, and $gR^2$ = 0.88 ± 0.07. HDFWNN, HDWNN and jump NN method showed the prediction error (root mean square error [RMSE]) of 11.23 ± 2.77 mg/dl, 10.79 ± 3.86 mg/dl and 16.45 ± 4.33 mg/dl, respectively. **Conclusion:** Furthermore, the generalized estimating equation and *post hoc* tests show that proposed models perform better compared with other proposed methods.

**Keywords:** *Blood glucose prediction, diabetes mellitus, fuzzy rule induction, fuzzy wavelet neural network, wavelet neural network*

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## Introduction

### Diabetes mellitus

Diabetes mellitus (DM) is a disease known as abnormality in the level of blood glucose. DM is a significant risk factor of cardiovascular diseases, neuropathy, nephropathy, and retinopathy.[1] Worldwide, DM is one of the most fast-growing diseases. As reported by the International Diabetes Federation, the number of people who have diabetes worldwide was over 425 million by 2017and is estimated to exceed 693 million by 2045.[2] DM is usually classified into type 1 DM (T1DM), type 2 DM (T2DM), and gestational diabetes. In the first case, the patient has high blood glucose concentration (BGC) due to an inadequate beta-cell or pancreas insulin production, while, in the second case, the disease results from the body's inefficient use of insulin. Gestational diabetes, however, progresses during pregnancy.[3] T1DM symptoms suddenly occur and are not currently curable or are at least challenging to treat.[4] Nonetheless, subcutaneous insulin injections, insulin infusion, diet, and exercise are the commonly-used treatments applied for T1DM.[5] In advanced treatment, insulin infusion is continuously used via an insulin pump known as "artificial pancreas." In the insulin pump, control strategies such as model predictive control (MPC) is employed to regulate BGC by justifying the amount of infused insulin.[6-8] MPC is an advanced control method suitable for severe multivariate control problems which need to remove constraints.[9,10] MPC has been proven to be effective to be applied in BGC control in DM patients.[11,12] However, BGC

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control methods, particularly MPC, require the prediction of BGC.[13,14] Thus, it is essential to develop a model that can predict BGC.[15]

### Related works

BGC predictive models often used in the MPC controllers are divided into data-driven and hybrid models.[16] Data-driven models are derived from time-series analysis using advanced methods, such as artificial and computational intelligence, soft computing, machine learning, data mining, and intelligent data analysis.[17] In BGC modeling, data-driven models are often combined with mathematical equations derived from physiology to develop a hybrid model as an improved solution.[18] For instance, the glucose absorption submodel described by Dalla Man *et al.*[19] and the insulin absorption submodel proposed by Dalla Man *et al.*[20] were used as a hybrid structure in the study by Zecchin.[21] One of the most common data-driven models, called neural networks (NNs), has been proposed, either in a hybrid mode with linear models or on its own, to predict BGC. For example, the artificial NNs,[22] the MLP NN,[23] the RBF NN,[24] and the jump NN[25] have been used to predict BGC. The jump NN is a feed–forward NN whose inputs are linked not only to the nonlinear neurons in the hidden layer but also to the output layer.[25] Among the efforts recently been made to improve the accuracy of BGC prediction, the study by Zecchin *et al*.[25] has been one of the most thorough and accurate studies in the area of BGC prediction. Nevertheless, it is expected not to choose input derivatives in modeling. Moreover, the NN has some deficiencies, however, in presenting a clear interpretation of the system, providing an analytical procedure of the structure selection, and making assurance of the NN convergence.[26] Wavelet NN (WNN) is introduced,[27] to consider such deficiencies. WNN is a nonlinear input–output mapping, which can approximate any functions to desirable precision.[28] This network was used for BGC prediction in the study by Zainuddin *et al*.[29]

In this study, a collection of wavelets with random parameters was initially formed, and then, the least-squares approach was used to calculate WNN coefficients. However, no practical approach was applied to choose dominant wavelets. WNN has additionally been combined with fuzzy logic to formulate the uncertainty of data in the model, resulting in an improvement of function approximation, especially when there are uncertainties.[26] In the study by Zarkogianni *et al*.,[30] a neuro-fuzzy network with wavelets, as activation functions, was used to predict BGC, while no solutions, no approaches, and no ways were ordered to select the important wavelets, to organize the structure, and to initialize model parameters properly. According to what was mentioned above, in general, there have been deficiencies in the provided models concerning BGC prediction. The specified defects include insufficient attention to the selection of influential inputs, lack of a proper procedure to form the model structure based on BGC data, and lack of attention to the various risks of prediction errors in BGC modeling in normal BGC, low BGC (hypoglycemia), and excessive BGC (hyperglycemia).

### Purpose of this research

In this paper, we propose new wavelet-based models for BGC prediction while trying to eliminate the defects of previous models. Initially, the physiological insulin and meal models are applied. Then, the input selection is considered to select the most effective factors in the foreseeable model for each patient. Next, based on the selected inputs, candidate wavelets with various parameters are created, while only dominant wavelets, proper for BGC prediction, are chosen through a cross-validation genetic algorithm-orthogonal least square (GA-OLS) method. Then, the selected dominant wavelets form a WNN, the first proposed wavelet-based model. Next, to handle uncertainties common in BGC data, chosen wavelets are incorporated with fuzzy inference. Therefore, as a second proposed model, a novel fuzzy WNN (FWNN) is created. In this novel FWNN, to prevent an extreme increase in the parameters, two solutions are considered. First, similar to the first proposed WNN model, only the chosen dominant wavelets are used. Second, fuzzy rule induction is used to prune unnecessary parts. Furthermore, in all steps, various weighting rates, based on expert knowledge of diabetes, are used for estimating the modeling errors of normal, hypoglycemia, and hyperglycemia episodes. While particular attention has been paid to the choice of model inputs, to form the data-based structure of each patient, efforts have been made to simplify the structure to have a lot of capabilities.

### Paper organization

The case study used in the BGC prediction system, together with the proposed wavelet-based models, is introduced in "Subjects and Methods" Section. In "Result" Section, the results of the proposed system, the validation process, and the comparison between the proposed models and the state-of-the-art are presented. Finally, the concluding remark is stated in "Conclusion" Section.

## Subjects and Methods

In this Section, after a brief introduction of the case study used in our BGC prediction problem, the process of input selection, the equations of the proposed models, the validation method, and the proposed modeling algorithm are briefly discussed.

### Data description

In this work, a real dataset from 12 adolescents with type 1 diabetes provided in the study by Elleri *et al.*[31] is considered. Data of each patient include both basal insulin delivery and conventional pump therapy for 36 h.

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Subcutaneous glucose values are taken every 5 min using the Dexcom continuous glucose monitor (CGM). The relative absolute difference of the Dexcom CGM median is obtained to be 14.7% (7.0%–25.3%),[31] the accuracy calibration of which is verified every 12 h. Furthermore, data from meal intake in the carbohydrate unit and the exercise at 0 or 1 level are recorded. More details are provided in the study by Elleri *et al.*[31] All procedures followed in this study, involving human participants, are following the ethical standards of the Southampton and South West Hampshire Research Ethics Committee, also complying with the principles laid down in the Declaration of Helsinki. Participants <16 years of age provide consent for the study procedures, and the parent or caregiver signed the informed consent. Participants >16 years of age sign their consent letters before participation.[31] Moreover, 33 T1DM *in silico* patients are simulated using a UVa/Padova simulator conformed to the US Food and Drug Administration in 2013.[32] Data simulated by this simulator have been used as a benchmark in numerous papers.[18,21,33,34] The UVa/Padova simulator model involves several submodels, describing insulin injection, appearance rates of glucose, and meal intake.[35] Equations of the model are presented in detail.[32]

## Input selection

Input selection, the first step in system identification, enhances model generalization because numerous input terms lead to overfitting or high model complexity.[36] In particular, for BGC modeling, the prediction accuracy of the model is affected by input variables and their different time lags.[29] The main input variables affecting BGC prediction are meal, insulin, physical activities, and stress.[37] In previous works, prior knowledge, correlation analysis,[21] and principal component analysis[29] have been used to select the main effective model inputs concerning BGC prediction, while the effect of severity of each input has somehow varied from person to person.[24,38] Therefore, important regressors should be selected from the input dynamic regressor space. The input dynamic regressor space is a set that includes input variables with varying time lags. This set includes delayed regressors showing meal eaten by a person, different delayed regressors showing physical activities, different delayed regressors showing injected insulin, BGC time-delayed regressors, and any other factors. Orthogonal-based methods are proper options for selecting inputs from a large collection of regressors,[39] which OLS method is a well-known simple one to provide information about the structure in linear-in-the-parameter models. In this method, the reduction ratio of criterion error (err) is introduced to omit insignificant terms in the model.[40] On the other hand, the OLS mostly faces difficulty in terms of nonlinear system input selection.[41] Thus, the OLS is enhanced using a heuristic method, i.e., a GA. The GP-OLS is a hybridization of OLS and genetic programming to introduce input regressors for nonlinear system modeling and is more robust than the OLS.[42] In this work, the GA-OLS[43] is used for choosing the main effective input variables among the candidate regressors. First, through the OLS method, the initial main effective regressors are chosen. After choosing the initial regressors, GA at this initial input selection is then used to search for final main effective regressors from the candidate regressors that result in minimum root mean square error (RMSE) in the validation data. Furthermore, as reporting the data of bolus insulin and meal values is in the discrete format, it is more convenient to consider the subcutaneous insulin model for the bolus insulin data[44] and the glucose absorption model[45] for the meal data. Using these physiological submodels contributes to incorporating the term "hybrid" in the title of the proposed models in this article.

## Proposed wavelet-based models

The structure of the proposed model is nonlinear, auto-regressive with exogenous inputs (NARX). For nonlinear system identification, NARX models have widely been used in the literature, such as in the study by Billings.[36] NARX formulation used in this work is described as:

$$\hat{G}(k+PH)=F\begin{bmatrix}G(k),G(k-1),\ldots,G(k-n_g),u(k)\\,u(k-1),\ldots,u(k-n_u)\end{bmatrix}+e(k) \quad (1)$$

Where the noise $e(k)$ is an independent sequence; $\hat{G}$ is the prediction of BGC; $G$ is the BGC measured by CGM; PH is the prediction horizon; $G(k)$, $G(k-1)$,…, $G(k-n_g)$; $u(k)$, $u(k-1)$,…, $u(k-n_u)$ are the regressors selected as the model input; and $F$ is the term estimated by the proposed wavelet-based models.

### *Hybrid dynamic wavelet neural network model*

The structure of the proposed HDWNN model for BGC prediction is presented in Figure 1a. The main practical input dynamic regressors are first selected using the GA-OLS method. Then, the selected dynamic regressors are entered into the wavelet layer. The wavelet layer includes neurons with activation functions which dominate wavelet functions $\varphi_i$ for $1 \le i \le n$. Dominant wavelets are selected from a lattice of wavelets with scaled and shifted parameters varying in specific intervals.[46] $\varphi_{(a_i,B_i)}$, $i = 1, 2., r$ are scaled and shifted versions of the mother wavelet. In this work, the single-scale multidimensional Mexican hat wavelet is used as the mother wavelet:

$$\varphi(U)=\left(m-\|U\|^2\right)exp\left(-\|U\|^2/2\right) \quad (2)$$

Where $U$ is the input regressor vector and $m$ is the dimension of the input vector. Then, the output of the HDWNN model is calculated from the $n$ dominant wavelets as:

$$\hat{G}_{HDWNN}(k+PH)=w_0+\sum_{i=1}^{n}w_i\ \varphi_{a_i,B_i}(U)\quad i=1,2,\ldots,n \quad (3)$$

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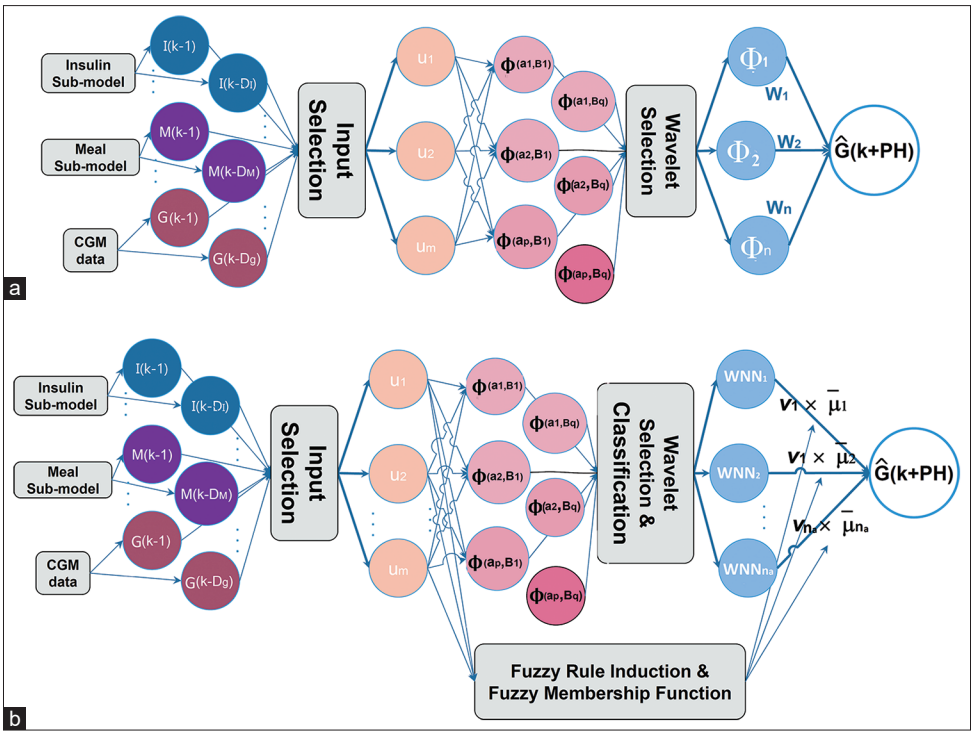



**Figure 1: (a) The proposed hybrid dynamic wavelet neural network modeling structure and (b) the proposed hybrid dynamic fuzzy wavelet neural network modeling structure, in which *I(k−D$_I$)*, *M(k−D$_M$)*, and *G(k−D$_g$)* are the exogenous insulin rate, carbohydrate, and blood glucose concentration delayed regressors, respectively; $u_1$, $u_2$,..., $u_m$ are the useful selected inputs; Φ($a_1$, $b_1$), Φ($a_2$, $b_2$), ..., Φ($a_p$, $b_q$) are all wavelet lattice neurons; $\Phi_1$, $\Phi_2$, ..., $\Phi_n$ are the selected dominant wavelet neurons; $W_1$, $W_2$, ..., Wn are the weights attributed to the dynamic wavelet neural network output layer; $WNN_1$, $WNN_2$, ..., $WNN_{na}$ are the $n_a$ subwavelets made from the n dominant selected wavelets, $v_1$, $v_2$, ..., $v_{na}$ are $n_a$ weights attributed to the dynamic wavelet neural network output layer; $\bar{\mu}_1,\bar{\mu}_2,\ldots,\bar{\mu}_{n_a}$ are membership functions of each rule in the dynamic fuzzy wavelet neural network modeling; and PH is the prediction horizon**

in which $a_i$ are scaled parameters, $B_i$ are the vector for the shifted parameters of the $n$ dominant wavelets, and $\varphi_{a_i,B_i}(U)$ is given below:

$$\varphi_{a_i,B_i}(U) = [2^{-(a_i\, m/2)}\varphi\left(2^{a_i}U - B_i\right)] \tag{4}$$

*Hybrid dynamic fuzzy wavelet neural network model*

The structure of the proposed HDFWNN model for BGC prediction is depicted in Figure 1b, composed of different layers relating inputs to the output. In the input layer, the selected inputs $u_i$, $i$ = 1, 2,…, $m$ are entered into the fuzzification layer using GA-OLS. The fuzzification layer comprises $n_a$ fuzzy rules $R_l$, 1,…, $n_a$ complementing each other to make the final output model.

$$R_l : u_1 \text{ is } A_1^l \text{ AND } u_2 \text{ is } A_2^l \text{ AND } \ldots \text{ AND } u_m \text{ is } A_m^l$$
$$\eta_l = w_0 + \sum_{i=1}^{N_l} w(i,l)\ \varphi_{a_{i,l},B_{i,l}}(U) \tag{5}$$

Where each fuzzy rule corresponds to a single-scale parameter of sub-WNN, $n_a$ is the number of unique scale parameters of the selected dominant wavelets (the number of fuzzy rules), $N_l$ is the number of selected dominant wavelets with same-scale parameter, $a_l$, $a_l$ is the $l$-th unique scale parameter of the selected dominant wavelets corresponding to the $l$-th rule, $B_{il}$ ($i$ = 1,…, $n_a$) are the shift parameter vectors of the dominant wavelets corresponding to the $l$-th rule, and $w_{(i,\,l)}$ are the weight coefficients between hidden and output layers of the $l$-th sub-WNN. The $l$-th sub-WNN has $m$ inputs and $N_l$ nodes in the hidden layer and one output ($\eta_l$). The sub-WNN is constructed of the same-scaled wavelets from the selected dominant wavelets. Furthermore, the AND operator is the multiplication, and $A_j^l$ are Gaussian fuzzy membership functions calculated as follows:

$$A_j^l = \exp\left(-\frac{1}{2}\left(\frac{u_j - mu_{lj}}{su_{lj}}\right)^2\right),\ l = 1, 2,\ldots, n_a\ ,\quad j = 1, 2,\ldots, m \tag{6}$$

Where $mu_{lj}$ and $su_{lj}$ are the mean and standard deviation (SD) values of Gaussian fuzzy membership functions.

In this work, to improve the proposed HDFWNN model, fuzzy rule induction is applied to upgrade the fuzzy rules using the imperialist competition algorithm (ICA). Here, the fuzzy rule induction includes optimizing the antecedent parts of fuzzy rules and allocating a weight to each rule. The antecedent part of fuzzy rule optimization specifies the role of each input in each rule. This role is represented as 0 or 1 in ICA. Thus, the calculation of the contribution degree of each fuzzy rule should be modified to remove the function of one or more input variables. Therefore, there are different numbers of input variables playing a role in various fuzzy rules. Then, in the study by Das *et al.*,[6] to determine the contribution degree of the $l$-th fuzzy rule,



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instead of just multiplying the membership functions of input variables, their geometric mean, participating in each rule antecedent part, is calculated as follows:

$$\mu_l = \sqrt[d_l]{\left(A_1^{c_1^l}\right)\times\left(A_2^{c_m^l}\right)\times\ldots\times\left(A_m^{c_m^l}\right)} \quad (7)$$

Where $d_l = \sum_{i=1}^{m} c_i^l$ and $c_i^l$ ($l$ = 1, 2,…, $n_a$, $j$ = 1, 2,…, $m$) are the antecedent assignments represented as 0 or 1.

To allocate the weights, a continuous weight $v_i$ ($i$ = 1, 2,…, $n_a$) inside within [0, 1] is allocated to each $n_a$ fuzzy rule. This weight specifies the significance of the given rule in the proposed HDFWNN model. The fuzzy rules with weights smaller than the threshold are eliminated from the HDFWNN model. Consequently, fuzzy rules with optimized structures are provided using fuzzy rule induction.

After calculating the output of the dynamic wavelet network, the defuzzification step – as an inference process – is implemented, and the final output is computed as:

$$\hat{G}_{HDFWNN}(k+PH) = \sum_{l=1}^{r} v_l \overline{\mu_l}\eta_l \quad (8)$$

Where

$$\overline{\mu_l} = \frac{\mu_l}{\sum_{j=1}^{r}\mu_j} \quad (9)$$

### *Model parameters learning*

In the final step of BGC prediction, according to the structure of the model constructed for each patient, the unknown parameters of the wavelet-based models should be adjusted to match the model output with the personal BGC physiological behavior of a given patient. For the HDWNN model, the model parameters, including the weight coefficients of the output layer, are learned using the LS method. Further, for the HDFWNN model, the parameters of the HDFWNN model, including the mean and SD values of Gaussian fuzzy membership functions, the translation and dilation parameters of the wavelets, and the weights of the output layer should be adjusted. In the HDFWNN structure, the importance of the output layer is learned by the LS method, while other parameters mentioned above are tuned using ICA.

## Model validation

For the sake of validation, a three-fold cross-validation procedure is applied. For each patient, the dataset is divided into training, validation, and testing sets, each of which includes one-third of the total data. The training set is used to extract the model architecture and optimize its related parameters, while the validation data are used to end the training algorithm through the cross-validation process. The outcomes of the models' performance for both training and validation datasets are expressed in train metrics. For the testing dataset, however, they are shown in test metrics.

### *Performance metrics*

The performance of the proposed models is expressed in terms of goodness-of-fit. Various goodness-of-fit measures have been introduced in the literature. In BGC prediction, RMSE and $R^2$ are used as well-known metrics for comparing different BGC models.[33,47] In addition, due to various risk levels of hypo- and hyper-glycemia in the assessment of prediction errors of BGC,[6] glucose-specific MSE (gMSE), as another metric, is used.[48] The criterion gMSE can be interpreted as a weighted MSE, the weights of which are extracted from the Clark error grid. Based on this view, other metrics, for example, glucose-weighted root mean square error (gRMSE), glucose-weighted ESOD (gESOD), and glucose-weighted $R^2$ ($gR^2$), can be used to make a better judgment about the potential of the models in predicting BGC. Then, gRMSE between the predicted $\hat{}$ and the real output $y$ is computed as:

$$\text{gRMSE} = \sqrt{\frac{1}{n\sum_{k=1}^{n} w(k)}\sum_{k=1}^{n}\left[w(k)\left(y(k)-\hat{y}(k)\right)^2\right]} \quad (10)$$

Where $w(k) = \text{Pen}\left(y(k),\hat{y}(k)\right)$ was described in the study by Del Favero *et al.*[48] In this work, gRMSE is represented as gFIT = 1 − gRMSE for judging the results, similar to other metrics introduced here. $R^2$, another metric for testing the goodness-of-fit, is more sensitive to outliers;[34] the glucose-weighted form of $R^2$ is thus calculated as

$$gR^2 = 1-\left[\sum_{k=1}^{n} w(K)\left(y(k)-\hat{y}(k)\right)^2\right] / \left[\sum_{k=1}^{n} w(k)\left(y(k)-\bar{y}\right)^2\right] \quad (11)$$

Normalized ESOD is the predicted output of ESOD normalized by the real output of ESOD. The glucose-weighted form of $ESOD_n$ is defined as the following ratio:

$$gESOD_n = \left\{\sum_{k=3}^{n}\left[w(k)\left(\hat{y}(k)-2\,\hat{y}(k-1)+\hat{y}(k-2)\right)^2\right]\right\} / \left\{\sum_{k=3}^{n}\left[w(k)\left(y(k)-2\,y(k-1)+y(k-2)\right)^2\right]\right\} \quad (12)$$

The lower amounts of $gESOD_n$ denote a decrease in the prediction error in the case of hypo-and hyper-glycemia. The gFIT, $gESOD_n$, and $gR^2$ between the predicted and the real BGC are analyzed for all patients, reported as mean ± SD.

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### Statistical analysis

Descriptive statistics are reported as mean ± SD. In this work, the generalized estimating equation (GEE) statistical test is used to find significant factors (i.e., methods) affecting the goodness-of-fit of the model. Multiple comparison *post hoc* tests are later used for the sake of pairwise comparison.

It is worth mentioning that the GEE statistical test is more rigorous than RM-ANOVA (one of the primary proposed methods for analyzing correlated responses) due to higher power achievement, while the smaller sample size or the lower number of repeated measurements is accessible in both complete and missing data scenarios.[49] This feature can significantly benefit studies in which data are skewed or the distribution of data is difficult to verify due to a small sample size, while RM-ANOVA requires normally-distributed data.[50] Then, due to the GEE, the level of statistical significance is set to be $P = 0.05$. The statistical analysis is performed using SPSS version 16 (SPSS for Windows, Released 2007, Chicago, SPSS Inc., USA).

### The proposed methods

In the following, we describe the steps taken to develop the proposed wavelet-based modeling algorithm. Also the glossary of terms is mentioned in Table 1.

0. Preprocessing step: Data of meal and insulin infusion are entered into their submodels. Then, all the data are scaled to 0 or 1
1. Input selection: First, different time lags of various available variables that might influence BGC to form a regressor array. Then, among the shaped regressor arrays, regressors with the most significant impact on BGC prediction are selected as the input vector using the GA-OLS
2. Wavelet selection: For the inputs chosen in the previous step, the lattice of wavelets is created with different scaled and shifted forms of the mother wavelet. The dominant wavelets are selected through the GA-OLS
3. Proposed wavelet-based models: First, a linear combination of the selected dominant wavelets form the HDWNN model, the coefficients of which are adjusted by the LS method. Second, in the HDFWNN model, each rule corresponds to the sub-WNN in its consequent part, composed of wavelets that have the same scale parameter among the selected dominant wavelets. Then, the fuzzy rule induction is used to improve the fuzzy rules. It includes rule weight allocation and rule antecedent arrangement. Finally, the HDFWNN model's unknown parameters are learned via a heuristic algorithm, such as ICA and LS methods
4. Validation framework: The validation framework contains a three-fold cross-validation procedure, which includes residual assessment metrics, e.g., gFIT, $gESOD_n$, and $gR^2$.

## Results

The proposed wavelet-based models are derived from clinical and simulated data. Along with the suggested methods, the jump NN model, introduced in the study by Zecchin,[21] is simulated to compare the results with the proposed wavelet-based models. In the study by Zecchin *et al.*,[25] the BGC jump NN had four inputs which include currently measured BGC by the CGM sensor, information on the carbohydrate content of ingested meals, information on doses of the injected bolus of insulin, and the glucose rate of appearance and its derivative.

### Modeling clinical data

In this work, the available data include meal data per carbohydrate unit, infused insulin boluses data per unit, closed-loop insulin infusion rates described in unit/hour, and delayed BGC data in mg/dl. All the data are scaled

**Table 1: Glossary of terms**

| Term | Definition |
|---|---|
| $G$ | Blood glucose concentration (mg/dl) |
| | Blood glucose concentration estimation (mg/dl) |
| $n_g$ | $G$ regressor delay |
| $k$ | Time step |
| PH | Prediction horizon |
| $u$ | Input regressor |
| $n_u$ | u regressor delay |
| e | Noise regressor |
| $U$ | Input regressor vector |
| $m$ | U dimension or number of selected inputs |
| $\varphi$ | Mother wavelet |
| $\varphi_{ai, Bi}$ | Shifted and scaled wavelet |
| Sub-WNN | Sub-WNN |
| $w$ | Sub-WNN wavelet weight |
| $a_i$ | Scale parameter of wavelet |
| $b_i$ | Shift parameter of wavelet |
| $B$ | Vector of shift parameters ($b_1$, $b_2$, …, $b_m$) |
| $n$ | Number of selected dominant wavelets |
| $N_l$ | Number of $l$-th sub-WNN wavelets |
| $R$ | Fuzzy rule |
| $\eta$ | Sub-WNN output |
| $\mu_l$ | Degree of contribution of fuzzy rule |
| $v$ | Fuzzy rule weight |
| $n_a$ | Number of unique scale of selected dominant wavelets or number of fuzzy rules |
| $A$ | Gaussian fuzzy membership function |
| $mu$ | Mean value of Gaussian fuzzy membership function |
| $su$ | Standard deviation of Gaussian fuzzy membership function |
| $c$ | Antecedent assignment value |
| $d$ | Number of fuzzy rule inputs |
| NN | Neural network |
| HDWNN | Hybrid dynamic wavelet NN |
| HDFWNN | Hybrid dynamic fuzzy wavelet NN |
| WNN | Wavelet neural network |
| ICA | Imperialist competition algorithm |

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between 0 and 1. Furthermore, the PH is 30 min and the sample time sets to be 5 min. In terms of assessment metrics, the results are provided in Table 2. The RMSE of BGC prediction without weighing the test data is as follows: RMSE = 10.7939 ± 3.8567 mg/dl for the HDWNN, RMSE = 11.2335 ± 2.7677 mg/dl for the HDFWNN, and RMSE = 16.4466 ± 4.3253 mg/dl for the jump NN. Consequently, RMSE of BGC prediction for HDWNN and HDFWNN is significantly less in comparison with jump NN. CGM data, in comparison with various model predictions for one of the participants, are also plotted in Figure 2.

The GEE analysis reveals that gFIT, $gESOD_n$, and $gR^2$ significantly differ in each method ($P < 0.001$). The *post hoc* tests additionally show that the HDFWNN model performs better compared with other methods, according to the gFIT and $gR^2$ metrics ($P < 0.01$). For the $gESOD_n$ metric, the *post hoc* test shows that the HDFWNN model has a better performance in comparison with the HDWNN ($P < 0.04$).

## Modeling simulated data

After applying the proposed models to the clinical data, a UVa/Padova simulator is used to simulate 33 T1DM virtual participants.[32] For each participant, the simulation scenario consists of about 3 days of monitoring with three meals and one or two snacks per day. Breakfast for 3 days is set at 7:00, 8:00, and 09:00 h and consists of 45, 5, and 75 g of CHO, respectively. Lunch is scheduled at 12:00, 12:00, and 13:00 h and consists of 70, 90, and 30 g of CHO, respectively. The first snack is served at 16:00 h, composed of 20 g of CHO for only the 1st and 2nd day. The second snack is served at 23:00 h, including 20 g of CHO for the 2nd and 3rd day. Finally, the dinner is held at 18:00, 17:00, and 18:00 h, consisting 80, 80, and 100 g of CHO. The diet is assumed to be the same for all patients. A noise sequence embedded in the simulator is added to CGM data, considering to be similar to the real data. The CGM data, the data of insulin infusions, and the data of carbohydrate meals compose the simulated data. The sampling time is chosen to be 5 min. Similar to the procedure followed in the clinical data, the proposed models are applied to the simulated data.

The results are provided in Table 3, confirming the theoretical and practical potential of the wavelet-based models for predicting BGC. In addition, the RMSE of BGC prediction for the test data is as follows:

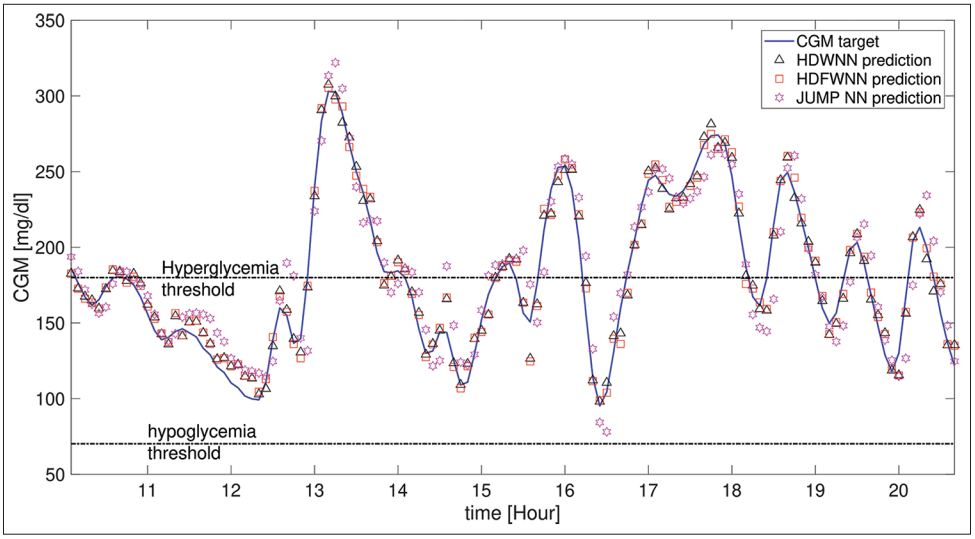



**Figure 2: Continuous glucose monitor signal (blue line), hybrid dynamic wavelet neural network model prediction (black triangle), hybrid dynamic fuzzy wavelet neural network model prediction (red square), and the reference jump neural network (magenta hexagram) for one of the real patient data. Horizontal red lines denote the hypo- and hyper-glycemic thresholds**

**Table 2: The performance of different models concerning blood glucose concentration prediction (two proposed models in comparison with the jump neural network) on the training and test real datasets (mean±standard deviation and *P* values of performance indices)**

| Model* | *n*** | Train *gFIT* | Test *gFIT* | Train $gESOD_n$ | Test $gESOD_n$ | Train $gR^2$ | Test $gR^2$ |
|---|---|---|---|---|---|---|---|
| Jump NN | 49 | 0.94995±0.016387 | 0.94700±0.01601 | 2.7735±0.91820 | 4.0621±1.5402 | 0.89512±0.05262 | 0.88316±0.05410 |
| HDWNN | 15 | 0.96259±0.009308 | 0.96238±0.00971 | 2.9825±0.61039 | 4.3331±1.0674 | 0.93628±0.02691 | 0.93563±0.02693 |
| HDFWNN | 155 | 0.96762±0.007948 | 0.96749±0.00886 | 3.0081±0.64828 | 3.8187±0.7444 | 0.95349±0.01936 | 0.95239±0.02040 |
| *P* | | <0.001 | | <0.001 | | <0.001 | |

*Models are for PH=30 min, **The mean number of model parameters for each patient. NN – Neural network; HDWNN – Hybrid dynamic wavelet NN; HDFWNN – Hybrid dynamic fuzzy wavelet NN

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**Table 3: The performance of different models concerning blood glucose concentration prediction (two proposed models in comparison with jump neural network) on the training and test simulated datasets (mean±standard deviation and *P* values of performance indices)**

| Model* | *n*** | Train *gFIT* | Test *gFIT* | Train $gESOD_n$ | Test $gESOD_n$ | Train $gR^2$ | Test $gR^2$ |
|---|---|---|---|---|---|---|---|
| Jump NN | 83 | 0.92994±0.039143 | 0.92771±0.04093 | 9.6496±4.03960 | 4.1111±1.6835 | 0.58705±0.14323 | 0.56716±0.15841 |
| HDWNN | 14 | 0.97123±0.014297 | 0.96950±0.01535 | 1.4776±0.58959 | 1.163±0.39090 | 0.87164±0.07016 | 0.85936±0.07716 |
| HDFWNN | 150 | 0.97476±0.012394 | 0.97183±0.01440 | 1.4487±0.50693 | 1.176±0.37807 | 0.89693±0.06268 | 0.87829±0.07105 |
| *P* | | <0.001 | | <0.001 | | <0.001 | |

*Models are for PH=30 min, **The mean number of model parameters for each patient. NN – Neural network; HDWNN – Hybrid dynamic wavelet NN; HDFWNN – Hybrid dynamic fuzzy wavelet NN

RMSE = 12.4186 ± 6.1671 mg/dl for the HDWNN, RMSE = 11.1597 ± 5.4751 mg/dl for the HDFWNN, and RMSE = 20.8360 ± 11.4547 mg/dl for the jump NN.

The GEE analysis presents that gFIT, $gESOD_n$, and $gR^2$ vary in the methods ($P < 0.001$). Then, the *post hoc* tests determine that the HDFWNN model has a better performance than other methods, according to $gR^2$ ($P < 0.02$). However, based on gFIT, $gESOD_n$, and $gR^2$, the *post hoc* tests show the HDFWNN model to perform better than the jump NN model ($P < 0.001$).

## Discussion

The proposed wavelet-based models are tested in a three-fold cross-validation procedure on the training, validation, and test data sets. A comparison is performed between the results of the proposed wavelet models applied so far in the literature, and the jump NN model investigated here.[19] To evaluate the predictive accuracy of the proposed model, gFIT, $gESOD_n$, and $gR^2$ metrics are presented. The statistical analyses of such metrics are performed using GEE and *post hoc* methods, showing that the HDFWNN performs the best in predicting BGC, based on both real and simulated data. The results of modeling the actual data are presented in Table 2. Although both wavelet-based models perform better than the jump NN model in all mentioned metrics, the best BGC prediction is obtained from the HDFWNN model in terms of the $gESOD_n$ parameter. This is due to more detailed features of the HDFWNN model compared with the jump NN and HDWNN. According to the *post hoc* tests in terms of $gESOD_n$, the HDFWNN model performs better than the HDWNN model, showing the effect of using fuzzy logic to prevent unwanted fluctuations. It can be seen that the oscillations are successfully predicted by the proposed HDFWNN [Figure 2]. For virtual patients, HDFWNN is the best model based on $gR^2$.

According to the *post hoc* tests concerning gFIT and $gESOD_n$, the HDFWNN model performs better than the jump NN model. The results of the simulated data and the real data are alike – while the HDFWNN model enjoys more parameters. It can be concluded that the predictive accuracy of the HDWNN model is acceptable, although the number of parameters is considerably higher in other models. Looking from a different angle, i.e., based on the complexity of the model and the name of the selected parameters, we can come to the conclusion that the proposed HDWNN model is a better choice. As presented in Tables 2 and 3, the number of model parameters of the HDWNN is lower than that of the jump NN and HDFWNN models. The accuracy of the HDWNN model outperforms that of the jump NN model, and although it is less than the accuracy of the HDFWNN model, it is acceptable. Hence, it can be a more appropriate choice for applications where the simplicity of the model is essential, such as real-time applications. This is due to its acceptable performance compared to the jump NN model and its lower number of parameters in comparison with the HDFWNN model.

Furthermore, in the proposed models, the derivatives of the existing data are not used in the model inputs in comparison with previous study.[42] Using derivatives can significantly decrease the efficiency of the model due to disturbance or noise. It is inferred from the overall results that the wavelet-based models have acceptable predict accuracy, and perform better than the jump NN proposed by Berger and Rodbard[42] in terms of standard BGC metrics. It is worth noting that when applying the proposed models in real-time data, it is recommended to use real-time optimization. Thus, the gradual changes in the patient's body made over time should be considered in predicting the BGC efficiency of the model due to disturbance or noise.

## Conclusions

This work is focused on novel models based on hybrid dynamic wavelet-based NNs to predict BGC in T1DM patients. In this study, two wavelet-based models (namely HDWNN and HDFWNN) are proposed to organize the structure of the model based on the data for each patient. Different approaches are considered in normal, hypoglycemia, and hyperglycemia episodes of BGC behaviors. The obtained results demonstrate the potential of the proposed HDWNN model in applications where the number of the model parameters should be less. However, if further parameters are allowed in the model, and subsequently, more information is available concerning the patients, the proposed HDFWNN model is the best choice in terms of glucose-based metrics. The results of this study can be enhanced using on-line optimization in real-time implementations.

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## Conflicts of interest

There are no conflicts of interest.

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