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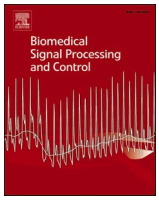

A Self-Attention Deep Neural Network Regressor for real time blood glucose estimation in paediatric population using physiological signals

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A B S T R A C T

With the advent of modern digital technology, the physiological signals (such as electrocardiogram) are being acquired from portable wearable devices which are being used for non-invasive chronic disease management (such as Type 1 Diabetes). The diabetes management requires real-time assessment of blood glucose which is cumbersome for paediatric population due to clinical complexity and invasiveness. Therefore, real-time non-invasive blood glucose estimation is now pivotal for effective diabetes management.

In this paper, we propose a Self-Attention Deep Neural Network Regressor for real-time non-invasive blood glucose estimation for paediatric population based on automatically extracted beat morphology. The first stage performs Morphological Extractor based on Self-Attention based Long Short-Term Memory driven by Convolutional Neural Network for highlighting local features based on temporal context. The second stage is based on Morphological Regressor driven by multilayer perceptron with dropout and batch normalization to avoid overfitting. We performed feature selection via logit model followed by Spearman's correlation among features to avoid feature redundancy. We trained as tested our model on publicly available MIT/BIH-Physionet databases and physiological signals acquired from a T1D paediatric population.

We performed our evaluation via Clarke's Grid error to analyse estimation accuracy on range of blood values under different glycaemic conditions. The results show that our tool outperformed existing regression models with 89% accuracy under clinically acceptable range. The proposed model based on beat morphology significantly outperformed models based on HRV features.

1. Introduction

With the advancement of digital technology and increased number of wearable sensors developed for tracking real-time physiological signals, the real-time non-invasive identification of glycaemic events (e.g. hypoglycaemia as low blood glucose and hyperglycaemia as high blood glucose) and blood glucose estimation have now become of great interest for effective diabetes management. Type 1 diabetes mellitus (T1D) is one of the most common chronic diseases among children and adolescents since the last two decades. Moreover, the paediatric patients suffering from T1D are at greater risk for developing acute rather than chronic complications compared to adult patients [1]; therefore an effective diabetes management during the paediatric age not only reduces the risk of adverse events but is able to delay the onset of long-term complications [2,3].

The T1D management requires daily Self-Monitoring of Blood Glucose (SMBG) as the increase in daily frequency of SMBG is highly correlated with the reduction in HbA1c level which is associated with occurrence of complications [4]. However, the paediatric and adolescent population may struggle with existing finger prick method of self-blood glucose monitoring due to its invasive and cumbersome nature which may affect patient compliance with diabetes management. The Continuous Glucose Monitoring (CGM) can monitor blood glucose on regular intervals by inferring to interstitial fluid measurement however CGM devices require calibration [5–9], can be only worn between 7 and 14 days once [10,11] and they require cannula to be inserted in

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subcutaneous tissue which still make them invasive and intolerable by the skin of the paediatric subjects. Therefore, the non-invasive measurement of blood glucose and automatic blood glucose estimation under real-time has the great potential to allow T1D subjects to effectively manage the diabetes in non-cumbersome manner as well as keeping their diet and physical activity compliant with the clinical guidelines.

With the advent of modern wearable sensors and devices, there are several studies which suggest use of physiological signals (e.g. electrocardiogram (ECG)) acquired non-invasively in order to estimate the glycaemic events non-invasively. The impact of glycaemic events can be reflected through Heart Rate Variability (HRV) features which represent the variation in time between each heartbeat [12–14]. Recent studies utilized the ECG beat morphology to determine the hypoglycaemic events [15,16]. The features of ECG beat morphology include prolongation of QT-interval, flattening of T-wave, shortening of P-R interval, ST-segment depression for hypoglycaemic events, reduction of R-R variability, variability in QT interval and increase of P-R interval for hyperglycaemic events [17,18]. With the relatively recent introduction of Artificial Intelligence (AI) in health diagnosis and monitoring, several machine learning (ML) and deep learning (DL) models have been developed for hypoglycaemia and hyperglycaemia detection, all relying on the analysis of the previously mentioned ECG alterations.

There are certain key questions which need to be addressed in existing state-of-the-art approaches to develop an efficient DL model explaining the role of individual features representing glycaemic altercations. Firstly, to the best of our knowledge, no study has focussed on automated blood glucose estimation for paediatric population as high activity levels in paediatric population may affect the blood glucose level estimation. Secondly, most of the existing state-of-the-art approaches focus on hypoglycaemia event detection rather than blood glucose levels as the threshold value, below which blood glucose value can be detected as hypoglycaemia varies across clinical setup [19]. Thirdly, most of these methods have been developed on limited HRV features which delimits the applicability under real-time settings. Fourthly, most of the ML models have been trained and tested on small datasets and their robustness is questionable.

To address these, we designed and developed a Deep Learning driven Neural Regression model for automatic blood glucose estimation under real-time conditions. Firstly, we developed deep learning based ECG segmentation tool to extract ECG beat morphology parameters (e.g. time intervals, slope among fiducial points etc.). Secondly, we developed the Morphological Regressor (MR) to estimate blood glucose based on ECG beat morphology extracted under real-time. To the best of our knowledge, this is the first technique which is based on estimating blood glucose based on automatically extracted ECG morphology via deep learning-based approaches. Therefore, the main novelties of this study are (i) the design and development of self-attention driven Morphological Extractor (ME) for real-time extraction of beat morphology; (ii) the design and development of real-time Morphological Regressor (MR) for real-time non-invasive blood glucose estimation.

2. Literature

We performed a systematic literature survey based on blood glucose estimation and glycaemic event detection via non-invasive ECG signals and we found only 18 studies across different health and diabetic subjects; most of them related to HRV parameters [20]. However, most of these studies do not provide a comprehensive view on how these HRV features were selected. Nevertheless, they developed their predictors by utilizing common parameters such as R to R intervals, absolute power at low and high frequency bands, heart rate and rate of change of these parameters [21 22 23 24]. One of the studies utilized Area Under the Curve (AUC) analysis for feature ranking and feed forward selection approach [25]. Most of these studies were related to hypoglycaemia detection. One of the studies was developed based on blood glucose concentration prediction [26].They utilized Pearson's correlation coefficient to select relevant features among heartbeat intervals and HRV features. Nevertheless, they only recruited one patient.

In terms of machine learning models, most of these methods were related to hypoglycaemia and hyperglycaemia event detection. Therefore, they developed 'black-box' natured machine learning models which varied from traditional methods (such as rule-based approaches [21 22 23 24], support vector machines (SVM) [27], particle swarm optimization [28 24]) to modern deep learning approaches [29 30 31 32]. Traditional machine learning approaches utilized HRV features to develop the glycaemic prediction model whereas one of the recent studies developed Convolutional Neural Network-Recurrent Neural Network (CNN-RNN) based model for detecting hypoglycaemic based on ECG beats [29 30]. The deep learning based glycaemic detection model developed on ECG beat levels significantly outperformed the model based on HRV parameters. Nevertheless, the model was not only developed on healthy subjects but also its hypoglycaemia detection capabilities were limited to a personalized level. The only study based on estimating blood glucose developed Decision (DT) Trees for predicting blood glucose for only one subject.

Different from existing methods which focused on hypoglycaemia detection, we aimed to develop a deep neural network regression model based on deep learning driven ECG morphological features for estimating blood glucose values under real-time conditions. This contrasts with most of these studies which utilized HRV features under static conditions. We calculated ECG morphological features by utilizing our ECG segmentation tool developed in a previous study [33,34]. We further developed the regression based on Ensemble Learning Regression where the results of multiple regression models were ensembled. To the best of our knowledge, this is the first study for estimating blood glucose for T1D paediatric population under real-time conditions.

We compared our methodology with existing HRV features under different time intervals [35]. The details are presented in the upcoming sections.

3. Datasets

3.1. PhysioNet's QT database

The Morphological Extractor was developed and tested using PhysioNet's QT database, a dataset of 105 2-lead ambulatory ECG recordings with P, QRS and T waves clearly annotated by their peaks, starting point and ending point [36]. The records were chosen from existing ECG databases, including the MIT-BIH Arrhythmia Database, the European Society of Cardiology ST-T Database, and several other ECG databases collected at Boston's Beth Israel Deaconess Medical Center. Further information can be accessed here https://physionet.org/content/qtdb/1.0.0/. Out of 105 subjects, 11 subjects were excluded as there were no annotations for either P, QRS or T wave.

3.2. Type 1 diabetes dataset

Data for this study was collected from an observational study at the Unit of Endocrinology and Diabetes at Bambino Gesù Children's Hospital, Rome, Italy between July 2021 and July 2022 [37]. Twenty-seven paediatrics with T1D who were under the care of the unit and already routinely used a CGM device were enrolled onto the protocol and physiological data was recorded for a period of up to 3 days. The cohort consisted of 18 Male and 9 Female with a mean age of 14.03 $\pm$ 4.24 years. The study was registered with the clinical trials database (ref NCT05278143).

Physiological data was recorded using the Medtronic Zephyr Biopatch, a CE marked device that records ECG across a single lead and operates within an amplitude range between 0.25 and 15 mV, with a sampling frequency of 250 Hz. The device was positioned on the wearer's skin via two electrodes placed in the centre of the chest, at the

4th left and right intercostal spaces. This electrode position provides a view of the heart in the frontal horizontal plane. In addition to ECG, the Zephyr BioPatch also records breathing rate, and a 3-axis accelerometer detects activity level and posture. The participants' regular CGM system were used to record glucose data. The CGM devices eligible for this study were Dexcom G6, Abbott FreeStyle Libre Flash, and Medtronic Guardian. All 3 CGM devices sample glucose in the interstitial fluid and are situated on the back of the upper arm, abdomen, or upper buttocks, depending on the specific device specifications and user preference. The Libre Flash reports glucose measurements at 15-minute intervals, whereas the Dexcom and Medtronic devices report every 5 min.

4. Methods

The block diagram of the methodology has been shown in Fig. 1. As a first step, we developed ECG Morphological Extractor (ME) to represent beat properties estimated by deep learning methods. We then developed multilayer Morphological Regressor (MR) to estimate blood glucose utilizing ECG morphologies. Different from existing methods focussed mainly on HRV parameters, this method estimates the blood glucose based on automatic extraction of ECG beat morphology with applicability under real-time settings. The details are as follows:

4.1. ECG morphology

Our approach of extracting ECG beat morphology is two-fold i.e. i) detecting the fiducial points present in the ECG beat and ii) determination of intervals and slopes among ECG beat fiducial points (collectively known as ECG beat morphology). Our approach of determining the fiducial points is to segment the entire ECG beat into P-wave, QRS complex and T-waves. T waves as well as gaps in between these waves. These require not only local features but also temporal features. Given the sampling size of both PhysioNet's QT database [36] and Type 1 Diabetes signals as 250 Hz and length ECG signals spanning up to 3 days, we decided to divide the signals into intervals of$L = 4$ s for better training efficiency and computational time. Besides, for efficient temporal context from both past and future, we added the signal overlap of$w_p = 1$ s from pre-4 s interval and$w_f = 1$ s from post-4 s interval; making the total length of input interval as $L^t = 6$ s (see Fig. 1).

To extract the fiducial points, we developed deep learning based segmentation tool capability to extract local features while amplifying them based on the temporal context [34]. Particularly we proposed Self-Attention Convolutional Bidirectional Long Short Term Memory Neural Network (SelfAtt-ConvBiLSTM) which is composed of following blocks:

(i) *Convolutional Block:*

Deep Convolutional Neural Networks (CNN) is effective to train multi-level features with multi-layers of convolutional operations in an end-to-end fashion [38]. Essentially, the local high level ECG features were obtained by composing low-level features and their levels were enriched by number of stacked layers. In our case, we deployed 1D CNN which moved across time to calculate low-level feature representations of the ECG beat as a 1-dimensional temporal space. The input signal x_{1d} of length L^t had been convolved with total number of filters$n^f = 32$ with each of them had kernel size $K = 32$. The kernel in the convolutional layer had been initialized by *Glorot Uniform* which initializes the convolutional weights W_{1d} based on uniform distribution within range [-limit, limit] where limit $= \sqrt{\frac{6}{f_{in}+f_{out}}}$ where f_{in} is numbe rof input units and f_{out} is number of output units.

In order too avoid overtraining and overfitting due to cohort heterogeneity, we performed 20 % dropout which nullifies the impact of 20 % of the convolutional weights. This can be expressed as equation with x_{1d} as ECG sequence, W_{1d} as 1-D convolutional weights (eq. (1)):

$$y_{1d} = [\![Dropout(W)]\!]_{1d} \otimes x_{1d} + b) \tag{1}$$

(ii) *BiLSTM Block*: For tasks that involve sequential inputs (such as time series ECG signals), Recurrent Neural Networks (RNN) are highly effective to train sequential context [38]. One of their derivative is Long Short Term Memory (LSTM) which utilizes accumulator architecture to remember longer temporal context. In our case, we trained temporal context from both past and the future for window sizes of 1 s (w_p and w_f). Therefore, we opt. for

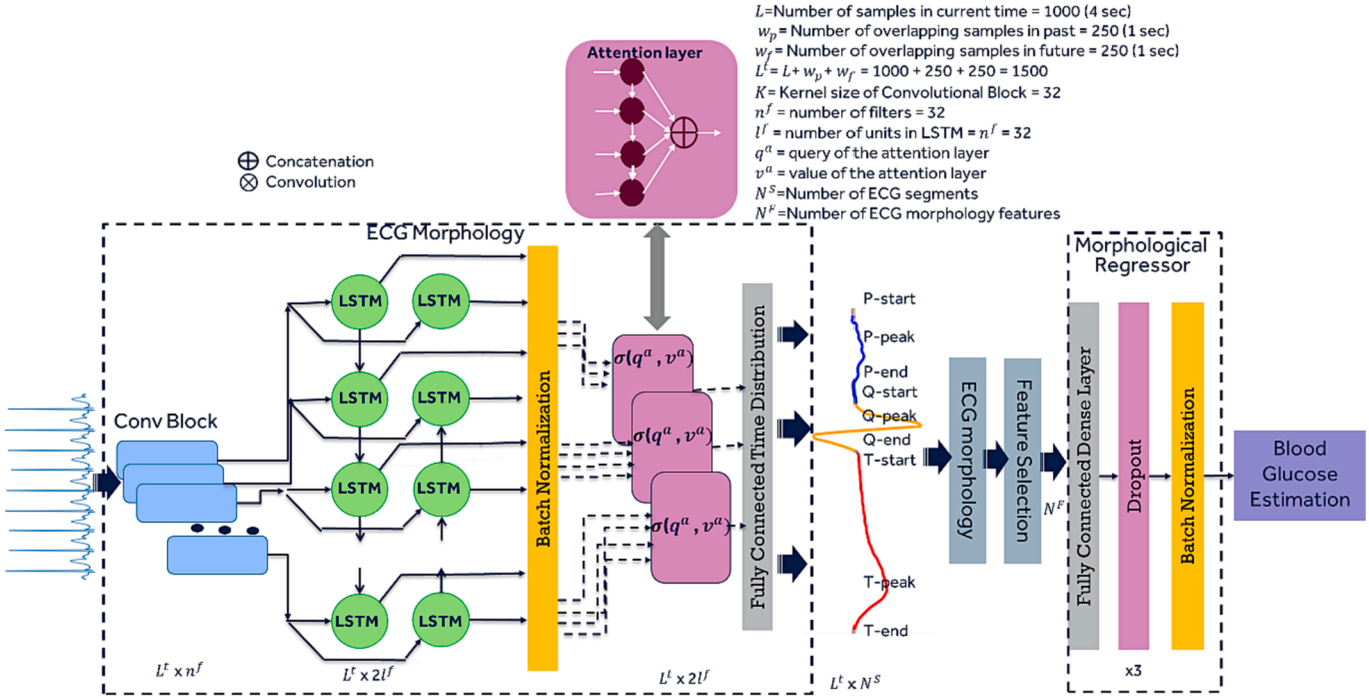

Fig. 1. Block Diagram of ECG Morphology Driven Blood Glucose Estimation System.

Bidirectional architecture which allowed training the temporal contexts in both directions. To extract temporal context associated with ECG segments in both directions, we deployed Bi-directional LSTM (BiLSTM). This can be expressed as (eq. (2)):

$$h_t = BN\left(Dropout\left(\left[LSTM\left(y_{1d_t}, \overrightarrow{h}_{t-1}\right), LSTM\left(y_{1d_t}, \overleftarrow{h}_{t+1}\right)\right]\right)\right) \quad (2)$$

where $\overrightarrow{h}_t$ are $\overleftarrow{h}_t$ are forward and backward LSTM outputs respectively at time t; BN represent bacth normalization. The numbert of units for LSTM in both directions were $\mathbb{f} = 32$; making the output of 1500×64.

(iii) *Self Attention:* The self-attention layer had been deployed to highlight the local features under consideration based on the temporal context. They train the correlation between ECG segment under consideration and the ECG segment occuring temporally in both directions. This can be represented by $\sigma(q^a, v^a)$ which is the softmax function between query (context) of the attention layer q^a and value of attentionm layer v^a.

The attention weights can be calculated as (eq. (3)):

$$\sigma(q^a, v^a)_{t,t'} = \frac{e^{dot\left(q_t^a, v_{t'}^a\right)}}{\sum_{t=0}^{\mathbb{f}} e^{dot\left(q_t^a, v_{t'}^a\right)}} \quad (3)$$

Where $\sigma(q^a, v^a)_{t,t'}$ is the softmax function representing the attention weights between query and value at time t and contextual time t', $dot(q_t^a, v_{t'}^a)$ is attention score which is the dot product of LSTM weights at time t and contextual time t'. Noting that it is self-attention mechanism; therefore the value of both q^a and v^a would be h_t. Besides, equation (3) leads to development of equation as:

$$Attention(Q, V) = \sigma\left(QV^T\right) \quad (4)$$

where Q and V reprpresent query and value matrix respectively (both of them representing matrix H from BiLSTM). The output of attention layer then trained to Time Distributed Dense Layer to return the sequences with segment labels. After the ECG segmentation, the ECG signal is further divided at the beat level for extraction of ECG morphology.

(iv) *ECG Beat Morphology Extractor*: After the segmentation of individualized ECG beats (P, QRS and T), we perform fiducial point detection which is the key step for extraction of ECG morphology. We have five fiducial points namely P, Q, R, S and T and we can have a total of 10 intervals among them. Additionally, the slope among each fiducial points makes the total of 20 ECG-derived parameters. As an example, the time interval between P and Q can be calculated as:

$$interval(P, Q) = \sqrt{(Q_x - P_x)^2 + (Q_y - P_y)^2} \quad (5)$$

where x represent location and y represent the amplitude of P, Q or other fiducial points. The slope can be calculated as:

$$slope(P, Q) = \frac{Q_y - P_y}{Q_x - P_x} \quad (6)$$

4.2. Feature selection

We have N number of samples with each sample is represented by ECG morphological features $X_j = \{x_1, x_2, \cdots, x_d\}$ with $d = [1{:}20]$ and the blood glucose value to be estimated Y_j ($j \in \{1,2,\cdots,N\}$). To determine morphological features relevant to the continuous blood glucose estimation, we first performed logit modelling [39] to identify the features which are statistically significant based on the equation:

$$p(X_i) = \frac{1}{1 + e^{\sum_{i=1}^{d} b_i X_i + b_0}} \quad (7)$$

Where $p(X_i)$ is the logistic function of X_i, b_0 is known as the intercept, and b_i is the inverse scale parameter or rate parameter. We selected the p-value with confidence of more than 95 %. We then performed redundancy analysis which is the process of selecting the morphological features which are less correlated in the feature space and highly correlated with the blood glucose [40]. In this paper, we followed absolute feature redundancy in which two morphological features are redundant with respect to blood glucose estimation if they provide same amount of information. In other words:

$$SU(X_i, Y) = SU\left(X_j, Y\right) \quad (8)$$

where SU represents symmetrical uncertainty[41].

$$SU(X, Y) = 2 \times IG(X|Y)E(X) + E(Y) \quad (9)$$

with,

$$IG(X|Y) = E(X) - E(X|Y)$$

where E(X) and E(Y) are the entropy of features X and Y, and IG(X|Y) is the information gain of X after observing Y. If X_i and X_j are redundant, the morphological feature with less correlation with Y will be deleted.

We performed Spearman Correlation Coefficient considering the nature of our skewed data [42]. In contrast to Pearson's correlation [43], the Spearman correlation assess the monotonic relationship (whether linear or non-linear). It is often defined as Pearson correlation among ranked variables and are represented as:

$$r^s = 1 - \frac{6\sum d_i^{r\,2}}{n(n^2 - 1)} : d_i^r = R(X_i) - R(Y_i) \quad (11)$$

where d_i^r is the difference between rank of morphological features X_i and rank of blood glucose values to be predicted Y_i; n is the total number of observations. For features to be redundant, they have the mutual correlation of 0.8 and above within the feature cluster. In fact, the absolute values of pair-wise correlations were also considered. In particular, if two variables have a high correlation, the algorithm looks at the mean absolute correlation of each variable and removes the variable with the largest mean absolute correlation.

4.3. Neural network regressor

The selected beat morphologies were then fed into multilayer neural network regressors as shown in Fig. 1. Each layer is composed of fully connected perceptron followed by dropout layer and batch normalization layer. This can be represented in equation as:

$$Y_i = BN\left(Dropout\left(\sum_{i=1}^{d} b_i X_i + b_0\right)\right) \quad (12)$$

The output of the morphological regressor is the estimated blood glucose value representing the beat. The performance of the neural network regressor was tested and compared against different types of linear and non-linear regressors along with their ensemble learning regression model. An ensemble learning regression model fits several base regressors on the training set. It then averages the individual estimations to form final a final estimation. In our case, we included following based regressors:

i) Linear Regression: Identifies the linear model between multivariate ECG morphology $X_j = \{x_1, x_2, \cdots, x_d\}$ and blood glucose Y_j of the form $Y_j = \sum_{i=1}^{d} b_i X_i + b_0$

ii) Decision Trees: The regression trees split up in accordance with minimization of loss function i.e. mean square error for estimating blood glucose Y_i. The depth of the decision trees is decided according to total number of ECG morphological features which split up in a sequential fashion starting from most significant feature to less significant feature [44].

iii) Random Forest: Random Forest Regressor is based on ensemble multiple decision trees while limiting their disadvantages of overfitting problem. It creates k subsets of features (ECG morphology) and decision trees are built on each feature. The trees are built until the number of estimators reach maximum value (in our case we empirically set 100). The result is obtained by averaging estimation of individual trees.

iv) Gradient Boosting Regression (GBR): Weak regressors are ensembled with the aim to minimize the loss function by iteratively adding the weak predictors into the model based on training set. This can also be represented as $\bar{f}(X) = \sum_{i=1}^{M}\beta_i f_i(X) = \sum_{i=1}^{M}\beta_i h_i(X;\theta_i)$; where, $\bar{f}$ is the additive model with minimized loss function for the multivariate ECG morphology features X and univariate blood glucose output variable Y, f is the additive model, M is number of model iterations, and f_i is the weak regressor and β_i is the expansion coefficient. The expansion coefficients β_i can be estimated as minimization loss function $\beta_j = argmin_{\beta}\sum_{j=1}^{N}L(Y_j, f_{i-1}(X_j) + \beta h(X_i;\theta_i))$; where L is the loss function and the construction of new regression model with (β_i, θ_i) by using least square fit method can be represented as $\bar{f}_i = \bar{f}_{i-1} + \beta_i h(X,\theta_i)$:

v) Extreme Gradient Boosting: Based on the principle of Gradient Boosting but utilizes the Newton Raphson method instead of gradient boosting for faster optimization. In eq. (3), the term $\beta_i h(X,\theta_i)$ can be replaced by $\underset{\phi\in\Phi}{argmin}\sum_{j=1}^{N}\frac{1}{2}\widehat{h}_i(X_j)\left[-\frac{\widehat{g}_i(X_j)}{\widehat{h}_i(X_j)} - \phi(X_j)\right]^2$ with $\widehat{g}_i(X_j) = \frac{\partial L(Y_j, f_{i-1}(X_j))}{\partial f_{i-1}(X_j)}$ and $\widehat{h}_i(X_j) = \frac{\partial^2 L(Y_j, f_{i-1}(X_j))}{\partial f_{i-1}(X_j)^2}$

4.4. Training, testing and validation

We trained and tested our model using 5-fold cross validation. Considering low number of hypoglycaemic values in our training set (blood glucose < 3.9 mmol/L), we generated the training set at each fold to keep the beat samples of hypoglycaemic, hyperglycaemic (blood glucose > 10 mmol/L) and euglycaemic (3.9>= blood glucose < 10 mmol/L) equal to avoid data imbalance problems. To achieve this, we double trained the hypoglycaemic features while randomly selecting the samples of euglycaemia and hyperglycaemia equal to twice of hypoglycaemic events. At each fold, we trained 80% while testing the regression model on the remaining 20 % data.

For determination of clinical accuracy for trustworthiness of the AI model, we performed *Clarke's Grid Error analysis* [45] to analyse the accuracy for a range of blood glucose values. The Clarke's grid error classifies the scatter plot of predicted blood glucose and reference blood glucose in five different zones i.e. A, B, C, D and E. The estimation in zone A would be considered as ideal whereas estimation in zone B would be considered as clinically acceptable. Therefore, we determine the clinical accuracy by taking the sum of estimation values in zone A and B and determining the percentage of total estimations.

5. Results

5.1. ECG morphology feature selection

We started our feature significance analysis utilizing logit modelling [39] and Spearman's Correlation [42] for redundancy analysis. Considering high impact of activity levels under paediatric population, we selected the ECG beats with activity levels of 0.2, equivalent physical activity to walking, or less This contrasts with previous research where personalized classifiers were developed based only on nocturnal events [16].

As first step, the features were reduced via the logit modelling, and we found that morphological features such as interval lengths from P to Q, R, R to S and slope between S and T were not statistically significant with blood glucose, therefore they were removed.

In the next step, we performed redundancy analysis based on absolute values of Spearman correlation among statistically significant morphological features, selected via the logit modelling in the previous step. The results show that there have been higher correlations among different morphological features (e.g. RT interval and PR, PS, PT slopes) with Spearman correlation above 0.8 and p-value less than 0.05. Therefore, the features which were having higher correlation (threshold of Spearman's correlation values above than 0.8) with blood glucose values and also if they had the largest mean absolute correlation among the cluster of features, were labelled as redundant and removed from final morphological feature list (Fig. 2).

5.2. Morphological regressor

We estimated the blood glucose based on multilayer deep neural network developed on Morphology Extractor. We performed 5-fold cross validation and estimated the clinical accuracy utilizing Clarke's Grid Error [45]. We added the percentage in clinical accuracy if the estimated glucose lay in clinically acceptable zones (zones A and B). The percentages have been expressed by concatenating test results from each fold along with standard deviation of percentages calculated at different folds. We compared the performance of Morphology Extractor with other regression models (e.g. linear regression, neural networks, decision trees etc.) along with their ensemble model. The results in Table 1 shows that deep neural network driven Morphology Extractor outperformed other regression models, with 88.8 % of the tested beats falling in the clinically acceptable zones. Moreover, the method estimated the fewest number (10.4 %) falling into zones D and E. Zone D represents dangerous errors where values within this zone could lead to incorrect treatment decisions and pose a significant risk to the patient and zone E is the area of serious clinical risk. Values within this zone could result in life-threatening situations or severe clinical consequences. Although ensemble learning yielded the highest percentage in Zone A, the model was unable to estimate the blood glucose values between 100 and 250 mg/dL as shown in Fig. 3(a). In contrast, Figure 3 (b)shows neural network driven Morphological Extractor has significantly higher density of estimated values within Zone A and B and was able to estimate blood glucose with less than 50 mg/dL with high accuracy.

5.3. Morphological features vs heart rate variability features

We compared our real-time morphology driven blood glucose estimator with that driven by HRV features at different minute intervals. For this, we aggregated the ECG morphology features at mean level of each minute interval (1, 3, 5 and 10 min) and developed the model separately for each ECG morphology and HRV. The HRV features were selected based on availability at different time intervals [35]. The results in Table 2 show that the morphology driven blood glucose estimator outperformed the regressor model developed on HRV features at every minute interval under non-real-time conditions (considering Zone A + B that represent the clinically acceptable zones). This shows that the changes in blood glucose can be highly associated with changes in beat morphology.

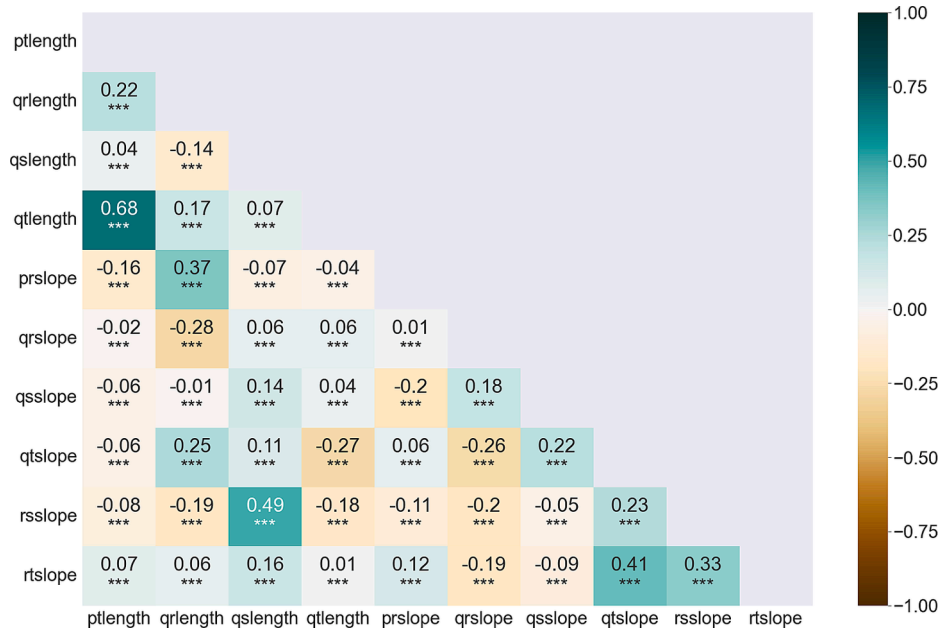

Fig. 2. Feature Selection based on redundancy analysis (*p < 0.01; **p < 0.001, ***p < 0.0001). The features selected by the logit modelling and after removing features that were redundant.

Table 1
Clarke's Grid error zone distribution comparison for different classifiers. The summation of Zone A and B represent the clinical accuracy and effectiveness by concatenating test results from each fold along with standard deviation of percentages calculated at different folds Best results for each zone are shown in bold where a higher value in zones A and B and lower value in zones C, D, and E are considered best.

	Zone A + B (mean ± std)	**Zone A**	**Zone B**	**Zone C**	**Zone D**	**Zone E**
Decision Tree	80.4 ± 2.1 %	27.8 %	52.6 %	8.7 %	**7.2 %**	3.7 %
Linear Regression	86.8 ± 3.1 %	35.7 %	51.2 %	1.7 %	10.1 %	1.4 %
Random Forest	87.7 ± 2.6 %	35.8 %	51.9 %	1.2 %	10.4 %	0.7 %
Gradient Boosting	86.9 ± 3.4 %	35.9 %	51.1 %	**0.3 %**	12.6 %	**0.2 %**
Extreme Gradient Boosting	87.5 ± 3.5 %	34.6 %	52.8 %	1.1 %	10.8 %	0.7 %
Voting Ensemble	87.7 ± 3.6 %	**36.8 %**	51.0 %	0.4 %	11.6 %	0.3 %
Neural Networks	**88.8 ± 3.0 %**	36.0 %	**52.8 %**	0.9 %	8.6 %	1.8 %

6. Discussion

In this study we presented the novel automated tool for estimating blood glucose based on non-invasive biomedical signals for a paediatric population. Our novel automated tool addresses several key questions, and, to the best of our knowledge, this is the first study to develop and evaluate a method for non-invasive blood glucose estimation in a paediatric population. This study estimates the blood glucose regardless of the glycaemic status and has the potential to be helpful in the real-time detection of both hyperglycaemia and hypoglycaemia, Furthermore, this study introduces an innovative automated tool for the extraction of ECG beat morphological features that exhibit a significantly higher correlation with blood glucose values when juxtaposed with the features of HRV. Finally, the technique was tested on a specific dataset of continuous single-lead ECG signals collected in real-world conditions from a paediatric population with type 1 diabetes, characterised by high glycaemic variability [46]. The use of this original dataset highlights the robustness of the method in handling the complexities and challenges inherent in blood glucose monitoring.

The tool was developed under two stages i.e. (i) the ECG segmentation tool driven Morphological Extractor and (ii) neural network driven Morphological Regressor for predicting real-time blood glucose. Initially, we trained the Self-Attention Convolutional Bidirectional Long Short Term Memory Neural Network on public dataset available on physionet [36]. The main purpose of deriving this network is to train local sequential features while highlighting them based on temporal context. We then identified the morphological features which are significant and non-redundant in predicting blood glucose. Finally, we then trained the Morphological Regressor trained on Morphological Extractor driven selected features. We compared the blood glucose estimation model with the model trained on traditional HRV features while aggregating in intervals of (i) 1 min, (ii) 3 min, (iii) 5 min, and (iv) 10 min in terms of clinical accuracy using the Clarke Error Gird, a graphical tool used to evaluate the accuracy and clinical relevance of blood glucose monitoring that assesses the clinical impact of errors in blood glucose measurements.

For feature selection, we performed logit model to determine the statistical significance of morphological features. Then, we performed Spearman's correlation among the ECG morphological features to remove redundant features. The correlation was performed at the beat level i.e. blood glucose value and the corresponding features of ECG beat at 10-minute lag, to account for the delay between glucose in the blood and interstitial fluid [47]. In contrast to our previous studies which focused on nocturnal events, we tested our model on ECG recorded during low activity to minimise the impact of activity related ECG changes Our analysis showed that some features such as interval length between PQ, PR, RS and slopes between PQ and ST were not statistically significant and were removed. Additionally, the length between PS, ST and slopes between PS and PT were highly correlated with other features with comparatively lower correlation with blood glucose values,

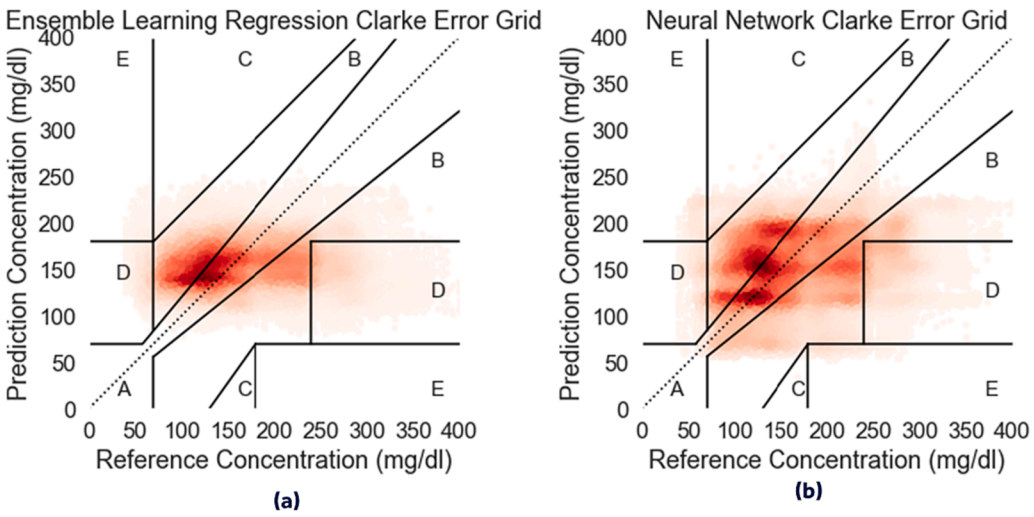

Fig. 3. Visual comparison of Clark's Grid Error between (a) Ensemble Learning Regressor and (b) Neural Network Driven Morphological Extractor.

Table 2
Clarke's Grid Error comparison of ECG beat morphology with HRV aggregated at a) 1 min, b) 3 min, c) 5 min and d) 10 min.

	Zone A + B		Zone A		Zone B		Zone C		Zone D		Zone E	
Min	**HRV**	**Morph**	**HRV**	**Morph**	**HRV**	**Morph**	**HRV**	**Morph**	**HRV**	**Morph**	**HRV**	**Morph**
1	85.6 ± 3.4 %	86.5 ± 3.0 %	34.2 %	32.4 %	51.4 %	54.2 %	0.1 %	0.6 %	14.2 %	12.7 %	0.1 %	0.2 %
3	85.8 ± 3.2 %	86.1 ± 3.3 %	34.4 %	33.4 %	51.6 %	52.7 %	0.2 %	0.1 %	13.8 %	13.8 %	0.0 %	0.0 %
5	85.9 ± 3.3 %	86.1 ± 3.2 %	34.1 %	37.3 %	51.9 %	48.8 %	0.5 %	0.1 %	13.5 %	13.8 %	0.1 %	0.0 %
10	86.8 ± 3.4 %	87.1 ± 3.0 %	38.8 %	35.0 %	48.0 %	51.8 %	0.0 %	0.1 %	13.2 %	13.2 %	0.0 %	0.0 %

therefore, they were removed due to redundancy.

We then developed the Morphological Regressor based on deep neural networks. We added multilayer neural perceptron followed by dropout and batch normalization to avoid overfitting. We performed the 5-fold cross validation and in each fold, we generated the training set by determining equal samples of hypoglycaemia (blood glucose $<$ 3.9 mmol/L), euglycaemia (3.9<=blood glucose $>$ 10) and hyperglycaemia (blood glucose $>$ 10 mmol/L) to address the data imbalance problems. We compared the results of MR model with other regression methods and determined the clinical accuracy in terms of the Clarke Error Grid. The results show that MR model significantly outperformed its other counterparts as $\sim$ 89 % of predicted blood glucose lied in clinically acceptable zones of A and B at beat level. This shows that blood glucose can be estimated with high accuracy at beat level under real-time conditions. There are some limitations in terms of estimating the low blood glucose related to hypoglycaemia as there were little events to be trained from the dataset and up sampling did not have significant improvement.

We then compared our results with the model trained by HRV features. This was performed by determining the HRV features at 1 min, 3 min, 5 min and 10 min intervals. The ECG morphology features were calculated by taking the mean value across these intervals. The results of blood glucose estimation accuracy while training the MR model at ECG morphology were compared to the models trained under HRV features across the intervals. The results show that aggregated ECG morphological features outperformed the HRV features in terms of blood glucose estimation accuracy under Clarke's Grid Error and can be considered as more powerful features under aggregated time conditions.

A qualitative comparison with existing approaches presents a challenge due to the innovative architecture of our proposed two-stage system and originality of our dataset. Early works in this domain by Nguyen et al. proposing a machine learning approach to detect specific glycaemic events demonstrated that several ECG parameters, including heart rate, PR, QT, and RT intervals as well as several features of HRV in both time and frequency domains were discriminative of hypoglycaemia when compared to euglycemia in people with T1D [48]. Subsequent studies aiming develop methods for the detection of hypoglycaemia using ECG data for a type 1 diabetes paediatric population typically relied on a limited feature selection including heart rate and the QT interval, corrected for heart rate, and their associated rates of change [24,49]. More recent studies have incorporated a more comprehensive feature extraction for the ECG morphology. Cordeiro et al. [32] extracted 18 features comprising the distances and slopes between the 5 fiducial points in their deep neural network to detect hyperglycaemia. Meanwhile, Chiu et al. [50] continued the approach and incorporated the relative amplitude amongst the points to detect dysglycaemia. However, both studies featured datasets consisting of adults whose diabetic status was not disclosed, and single-lead ECG data was recorded in controlled settings of a laboratory and intensive care unit, respectively.

Finally, the choice of single-lead ECG allows for continuous ambulatory recording however we must consider some limitations. The relative amplitudes and corresponding slopes amongst the key fiducial points can vary depending on the specific lead used or placement of the sensor as well as individual characteristics and any underlying cardiac conditions. The study primarily focused on a paediatric population with no know cardiovascular disease, therefore, its applicability to adult populations or individuals with cardiac conditions remains an open question and further research and testing is warranted. Considering this, we are also conducting a similar study to obtains data form adults with T1D [51]. We aim to validate the method in the adult population to enhance the robustness of our method.

7. Conclusion

In this paper, we designed and developed a novel Self-Attention Deep Neural Network Driven Regression Model for non-invasive estimation of blood glucose in Type 1 diabetic paediatric study. To the best of our knowledge, this the first study of estimating blood glucose values based

on ECG beat morphological features under real-time conditions. In contrast to previous studies focusing on glycaemic event detection via traditional HRV features, this study focuses on estimating blood glucose based on the changes in parameters of ECG beat morphology that were automatically extracted using our Morphological Extractor. We achieved the clinical accuracy of 89 % in estimating blood glucose while addressing the clinical trustworthiness of our model. Besides, in contrast to HRV features, the model for estimating blood glucose based on ECG morphology features aggregated on different time intervals have improved estimation performance compared to models built upon HRV features for those time intervals. The model has limitations in terms of estimating the low blood glucose values as there were few hypoglycaemic events found in the data. Therefore, as our next step, we aim to develop the synthetic data which can preserve the correlation between ECG morphology and the blood glucose. Planned future works aim to develop a multimodal approach based on features from other physiological parameters (breathing, accelerometer etc.) that could also detect hypoglycaemic and hyperglycaemic events under real-time conditions.

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CRediT authorship contribution statement

Muhammad Salman Haleem: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. **Owain Cisuelo:** Formal analysis, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. **Martina Andellini:** Data curation, Investigation, Resources, Writing – review & editing. **Rossana Castaldo:** Conceptualization, Formal analysis, Writing – review & editing. **Massimiliano Angelini:** Writing – review & editing, Resources. **Matteo Ritrovato:** Writing – review & editing, Resources. **Riccardo Schiaffini:** Resources, Writing – review & editing. **Monica Franzese:** Writing – review & editing. **Leandro Pecchia:** Conceptualization, Project administration, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Leandro Pecchia reports financial support was provided by Warwick-Wellcome Trust Translational Partnership.

Data availability

The data that has been used is confidential.

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