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Non-invasive method for blood glucose monitoring using ECG signal

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Abstract

Introduction: Tight glucose monitoring is crucial for diabetic patients by using a Continuous Glucose Monitor (CGM). The existing CGMs measure the Blood Glucose Concentration (BGC) from the interstitial fluid. These technologies are quite expensive, and most of them are invasive. Previous studies have demonstrated that hypoglycemia and hyperglycemia episodes affect the electrophysiology of the heart. However, they did not determine a cohort relationship between BGC and ECG parameters.

Material and method: In this work, we propose a new method for determining the BGC using surface ECG signals. Recurrent Convolutional Neural Networks (RCNN) were applied to segment the ECG signals. Then, the extracted features were employed to determine the BGC using two mathematical equations. This method has been tested on 04 patients over multiple days from the D1namo dataset, using surface ECG signals instead of intracardiac signal.

Results: We were able to segment the ECG signals with an accuracy of 94% using the RCNN algorithm. According to the results, the proposed method was able to estimate the BGC with a Mean Absolute Error (MAE) of 0.0539, and a Mean Squared Error (MSE) of 0.1604. In addition, the linear relationship between BGC and ECG features has been confirmed in this paper.

Conclusion: In this paper, we propose the potential use of ECG features to determine the BGC. Additionally, we confirmed the linear relationship between BGC and ECG features. That fact will open new perspectives for further research, namely physiological models. Furthermore, the findings point to the possible application of ECG wearable devices for non-invasive continuous blood glucose monitoring via machine learning.

Keywords: blood glucose concentration; electrocardiogram signal; signal processing; physiological signal; non-invasive continuous glucose monitor

Introduction

According to the International Diabetes Federation in 2019, diabetes mellitus has grown into a pandemic pathology problem that threatens global health. The Atlas of IDF mentioned that the prevalence of this chronic disease has increased to 9.3% of the world population, with almost 463 million diabetics in 2019 and estimating approximately 578 million diabetes cases in 2030.[1,2] This pandemic urged the need for medical solutions that facilitate remote care, remote control, support diabetes self-management technologies and adopt a wholesome environment-friendly approach. Furthermore, an elevation in blood glucose levels (hyperglycemia) leads to long-term complications such as cardiovascular disease,[3] diabetic neuropathy, and diabetic retinopathy.[4] Low blood glucose levels (hypoglycemia), on the other hand, may result in a critical fluctuation of health conditions in the short term, including confusion, shakiness, sweating, and even loss of consciousness, coma, or death.[3,4] However, if diabetes is diagnosed at the first stage, it can be curable without reaching the danger zone. If not, it can become a serious issue. Therefore, tight continuous glucose monitoring is crucial for both prediabetes and diabetic patients.[5]

The traditional method to monitor the blood glucose level was by analyzing a drop of blood resulting from a finger prick at least 4-5 times a day. This method is considered as invasive, expensive, cumbersome and one which does not allow continuous monitoring of BGC.[6] Nowadays, the existing devices for blood glucose monitoring are CGMs. They can determine the BGC value in real and continuous time (every 5 min). The CGM method has significantly improved the control of BGL for diabetes.[7-9] However, it still presents some constraints such as the working time limit, which is between 7 and 14 days. Additionally, it is an invasive device because it requires a

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Authors' contribution:
A – Research concept and design, B – Collection and/or assembly of data, C – Data analysis and interpretation, D – Writing the article, E – Critical revision of the article, F – Final approval of the article.

cannula insertion into the subcutaneous tissue to measure the BGC from the interstitial liquid.[10] Moreover, most of CGMs require finger prick calibration, in addition to being a cost-effective technology.[11] These limitations make the daily use of CGMs unattractive for both diabetic and pre-diabetic patients. In this context, several approaches are being proposed as non-invasive methods for blood glucose monitoring (without skin penetration).[12,13] Different techniques are taking advantage of the changes in the chemical and physical properties of the tissues, which are conducted by glucose variations such as optical-polarimetry[14,5], fluorescence technology[15] and Raman spectroscopy[16].

Researchers were able to develop an earlier alarm for hyper and hypoglycemia events. They explored the correlation between BGC and different vital signals such as, Electroencephalogram (EEG)[17-20] accelerometer signal/heart rate[21-23], skin temperature (ST), skin impedance[24-26] galvanic skin response (GSR), and energy expenditure (EE)[24-27]. Other studies investigated autonomic nervous system responses during hypoglycemia and hyperglycemia events using ECG[28,29] signal.

It has been found that sudden death can be caused by QT interval prolongation with subsequent ventricular tachyarrhythmia in response to nocturnal hypoglycemia.[29-32] They demonstrated that a prolongation of QT interval results from hypoglycemia in a patient with type 01 diabetes. In[33], they argued that the increase of QTc (corrected QT) was positively correlated with the increase in adrenaline. Another significant characteristic of hypoglycemia is T-wave flattening which is considered important in the classification of hypoglycemia and euglycemia clamps in[34,35]. However, Mihaela Porumb[36] indicated that the changes in the T wave amplitude are personal. In several studies, Heart rate (HR) during hypoglycemia was significantly increased. In[33], it was found that HR during HYPO-clamp was significantly slower than during the EU-clamp. Nguyen et al.[37] presented another multivariable study analyzing parameters (HR, PR interval, corrected RT interval, corrected TpTe interval (T-peak to T end)) that can be introduced in the classification of hyperglycemia and hypoglycemia episodes. They identified that low blood glucose was associated with prolonged RTc, QTc, and TpTec. Another study explored the correlation between BGC and other ECG features such as Heart Rate Variability (HRV), ST, PRQ, and P-H.[38] Different methods are proposed to predict low glucose levels using different combinations of ECG features, including Principal Component Analysis (PCA)[39], Hybrid Swarm Optimization[40], Neural Networks[41] and Genetic Algorithms[42]. In a recent study, Mihaela Porumb et al[36] proposed a new method based on an extreme learning machine to detect low-glucose levels using the raw ECG waveform automatically. Along with it, in a comparative study[43], the ECG is presented as the most suitable electrophysiological signal that can be integrated into the artificial pancreas. Since ECG devices are non-invasive, less expensive, miniaturized, durable[36] and commercially available[44] they can be found as belts, smartwatches, or wristbands, and people need to exploit them in order to monitor their glucose level.

In this paper, we propose the potential use of a new method for BG estimation based on ECG features. Furthermore, we confirmed the linear relationship between BGC and ECG features (QTc and t-wave amplitude). Our method has two main stages. The first stage consists of a preprocessing method, a segmentation phase utilizing a Recurrent Convolutional Neural Network (RCNN), and a characterization step. In the second stage, we applied mathematical equations to calculate the BGC utilizing the retrieved ECG features. Thus, the paper is organized as follows: In section two, we present the methodology described previously, whereas section three includes the different results and discussions. We finish with the conclusion and perspectives of our work.

Methodology

Database description

In this work, two open-source datasets have been used:

i) The first one is QTdata from Physionet[45]. The data consists of roughly 15 minutes of ECG recording, with a sample rate of 250 Hz, measured from 105 patients. The database provides signal region labels generated by an automated expert system.

ii) The second database is the D1NAMO, which is a multi-modal dataset for research on non-invasive type 1 diabetes management.[46] It contains data from 20 healthy subjects and 9 patients with type-1 diabetes. The data consists of ECG signals, breathing and accelerometer signals, as well as glucose measurements and annotated food pictures. The acquisition of these physiological signals has been made using the Zephyr-Bioharness 3 device for both subsets. Glucose levels of patients with diabetes have been recorded with an iPro2 Professional CGM sensor, allowing for a precision of 5 min between two glucose measurements. The dataset has been acquired in real-life conditions. Therefore, it contains many noisy parts and missing data. The whole dataset has been studied, and just the clearly available ECG signals that refer to diabetic patients have been tokenized. A preprocessing signal step is necessary to eliminate unwanted artifacts before segmenting and extracting the different features.

Proposed method

In patents (2006,2010)[47-48], Mark W. Kroll invented a method for monitoring blood glucose levels utilizing an intracardiac signal received wirelessly from a pacemaker implanted in a type 1 diabetes patient.

The intracardiac signal was processed in order to achieve various features. then, the following mathematical equation was established to calculate:

$$BGC = A - B * (QTc_{delta}) - C * \left(T_{wave\ amplitude\ fraction}\right) \quad \text{Eq. 1}$$

with:

- QTc delta represents the corrected QT interval (QTc).
- The T-Wave amplitude fraction is determined by the subtraction of the baseline value from the T-Wave amplitude.
- The parameters A, B and C are predetermined parameters or coefficients calibrated for a particular patient.

Mark W. Kroll validated this equation using 05 samples from intracardiac signal of one patient, as shown in[48]. In this paper, first, we validate the use of the previous equation using features extracted from the surface ECG signal instead of the intracardiac signal. Additionally, based on the same equation, we suggested another **Equation 2**, to understand better the evolving correlation between HR and BGC changes(hyper-hypo-euglycemia).

$$BGC = A - B * (QTc_{delta}) - C * \frac{(T_{wave\ amplitude\ fraction})}{HR} \quad \text{Eq. 2}$$

Reliable ECG features are extracted and used in the equations following the diagram in **Figure 1**.

a. Signal Filtering

The electrical activity of the heart was measured as a series of amplitudes away from a baseline signal. The D1namo dataset, on the other hand, was obtained in real-world conditions using the Zephyr-BioHarness 3 wearable device. Since every movement made by the subject affects the measurements, ECG includes other types of noise sources, as well as electrode movement and motion artifacts. These noises can have a bad impact on the accuracy of the segmentation step as well as the extracted ECG features and then the estimated BGC. Therefore, extensive signal cleaning and conditioning are necessary to accurately segment the ECG signals from the D1namo dataset, as follows:

- The wander line and the high frequency have been removed using a band-pass filter constructed based on FFT (Fast Fourier Transform). It has been constructed using a passband frequency range of [0.5 Hz, 40 Hz]
- We eliminate those ECG portions that comprise noises from electrode movement or motion artifacts. We used in our work only the clean/usable portions to ensure high accuracy in the segmentation step.

b. Signal segmentation

The next step is automatic waveform segmentation. It is performed to ensure accurate characterization of ECG temporal features. We used a waveform segmentation algorithm based on Recurrent Convolutional neural networks was used. This approach enables automated annotation of various ECG regions.

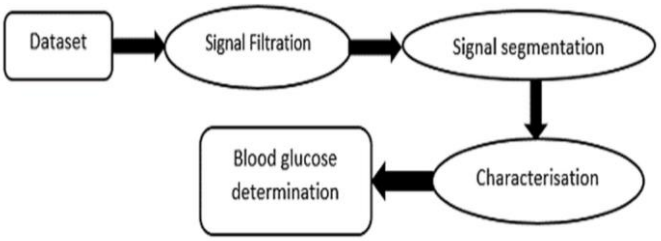


Figure 1. Block diagram for ECG processing.

The Long /Short-Term Memory (LSTM) network was employed to train the deep neural network to classify signal regions. We used a modified version of an algorithm, which is implemented in MATLAB® toolbox 2021. The network architecture used is as follows:

- Set the parameter *sequenceInputLayer* of 40 input features to the number of frequencies.
- Specify an *L&STM* layer with the 'sequence' output mode to provide a classification for each sample in the signal. Use 200 hidden nodes for optimal performance.
- Set the parameter *fullyConnectedLayer* with an output size of 4 corresponding to 4 waveform classes (P-wave, QRS, T-wave, and non-defined wave (transition between waves)).
- Add the parameters *softmaxLayer* and *classificationLayer* to output the estimated labels.

To represent the nonstationary behavior of the ECG signal, time-frequency analysis has been incorporated into the algorithm using a Fourier Synchro-Squeezed Transform (FSST). The above function computes the frequency spectrum of each signal sample and indexes the relevant content from the transform output. We treat the real and imaginary parts of FSST separately and feed both of them into the network.

c. Characterization

The ECG signal for each day and subject was recorded for approximately 1 hour. We use only the clean ECG portions which do not contain any artifacts noises. Thus, heartbeat cycles were segmented and classified once every few minutes during these hours. The characterization stage was carried out automatically, based on the outcomes of the preceding step, as follows:

- QT durations were extracted automatically after segmenting the ECG signal and classifying it. For each cardiac cycle we have, the distance between the Q-wave onset and T-wave offset defined as QT interval. The Bazett formula[51] was then used to correct the QT using heart rate, as shown below.

$$\text{QTc} = \frac{\text{QT}}{\sqrt{\text{HR}}} \quad \text{Eq. 3}$$

- The Heart Rate was computed by inverting the RR interval value from the ECG signal as follows:

$$HR(bpm) = \frac{60}{RR} \quad \text{Eq. 4}$$

Initially, the R peaks were identified using the MATLAB® function find peaks. The RR intervals(ms) were then

calculated by measuring the distance between the R peaks for each 02 successive cardiac cycles.

- T-wave amplitude: Similarly to R peak, we used MATLAB's built-in function for peak detection algorithm find-peaks. For each cardiac cycle used for BG estimation, the T-wave amplitude value has been retrieved.

d. Determination of Blood glucose concentration

In this section, we will confirm the usability of the two equations previously mentioned. To do that, a system of equations should be resolved in order to determine the parameters A, B and C. Then, we applied the calculated coefficients in order to determine the BGC for the rest of the data.

Result

From the D1namo dataset, we were able to treat the ECG signals of 04 diabetic patients for multiple days. We excluded the signals of the other patients because some of them recorded their ECG at a different time than they recorded their BGC. Others did not wear the ECG belt properly.

Using the FSST approach, the convolution neural network utilized for ECG segmentation reaches 94% accuracy, producing more precise and reliable results.

In this work, we validate the use of **Equation 1** using surface ECG signals rather than intracardiac signal. We proposed **Equation 2** in order to better understand the behavior of heart rate and its impact on the BGC changes during different camps (hypoglycemia, euglycemia, hyperglycemia). The two equations have been validated using 04 patients from the d1namo dataset; each patient has multiple days of measurements. In total, there are 1600 samples. The performance metrics employed to evaluate this work are Mean Absolute error (MAE) to calculate the difference between the Real Blood Glucose (RBG) and Calculated Blood Glucose (CBG), and Mean Squared Error (MSE) to visualize the behavior of the system used to estimate BGC.

Root Mean Square Error (RMSE) indicates how close the actual blood glucose values are to the calculated blood glucose. These metrics are determined as follows:

$$MAE = \frac{1}{N}\sum_{i=1}^{N}|y_i - \hat{y}_i| \quad \text{Eq. 5}$$

$$MSE = \frac{1}{N}\sum_{i=1}^{N}(y_i - \hat{y}_i) \quad \text{Eq. 6}$$

$$RMSE = \sqrt{\frac{1}{N}\sum_{i=1}^{N}(y_i - \hat{y}_i)} \quad \text{Eq. 7}$$

where y_i is the real BGC of sample i, $\hat{y}_i$ is the calculated BGC at that sample, and N is the total number of BG samples used.

For each patient, the predetermined parameters A, B, and C are calibrated during our investigation. Whenever the BG range changed, these coefficients were updated. The obtained results for each patient using the two equations are presented in **Table 1**. **Figures 2-4** show the distribution of BGC respectively based on QTc, Heart Rate, and T-wave amplitude.

Table 1. Mean absolute error and mean square error according to different clamps.

	Patient 1		Patient 2		Patient 3		Patient 4	
	Eq. 1	Eq. 2	Eq. 1	Eq. 2	Eq. 1	Eq. 2	Eq. 1	Eq. 2
MAE	0.2522	0.2784	0.3502	0.2608	0.1486	0.1423	0.0788	0.0797
MSE	0.1066	0.1358	0.2409	0.1085	0.0447	0.0397	0.0110	0.0112

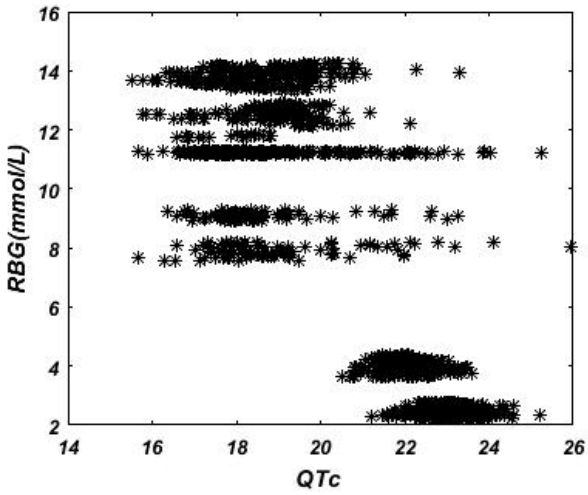


Figure 2. The distribution of BGC according to QTc.

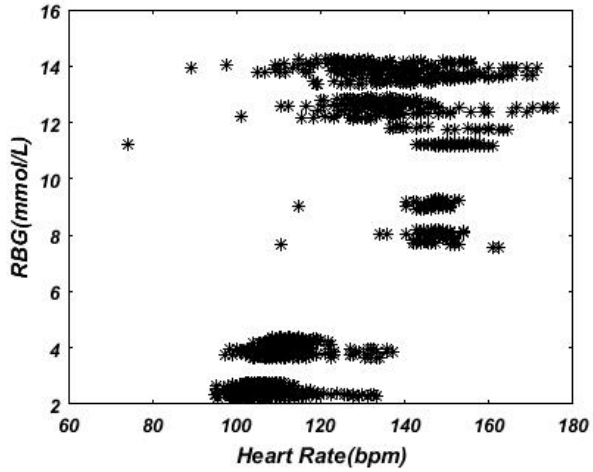


Figure 3. The distribution of BGC according to Heart Rate.

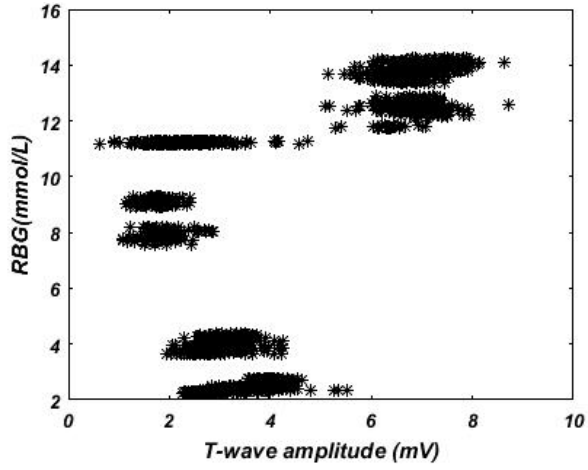


Figure 4. The distribution of BGC according to T wave amplitude.

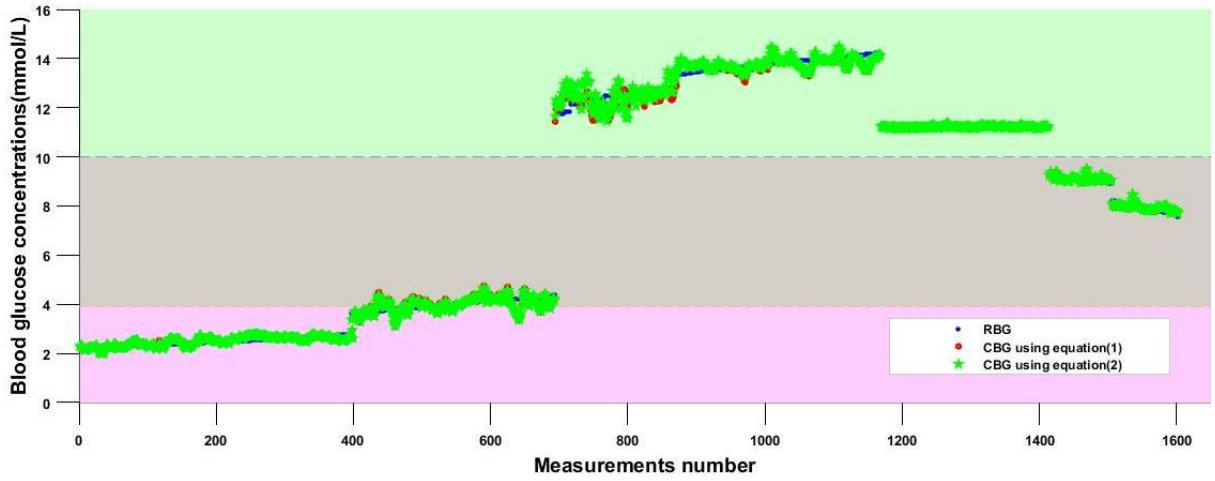


Figure 5. The evolution of Real BGC (RBG) and calculated BGC using the two equations (all patients' BG profiles).

Figure 5 depicts the multiple blood glucose profiles (real blood glucose, and the calculated blood glucose using the two equations). In **Figure 6**, we present the curve fitting between RBG and CBG. The threshold chosen to distinguish between the different blood glucose ranges (hypoglycemia, hyperglycemia and euglycemia) was recommended by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD).[52] It means:

- hypoglycemia, < 3.9 mmol/l (< 70 mg/dl),
- hyperglycemia, > 10 mmol (> 180 mg/dl),
- euglycemia, 3.9-10 mmol/l (70-180 mg/dl).

Discussion

A relationship between the change in BGC and the change in QTc delta, T-wave amplitude and heart rate has been proved in this work. Figure.2 shows that there is an inverse correlation between BGC and QTc. These results have been confirmed in different studies.[32-33]

Figure 3 presents the distribution of the real blood glucose according to T-wave amplitude. As it mentioned previously[35-38] in the state of art, our results shown that there is proportional correlation between BG and T-wave amplitude in the euglycemia and hyperglycemia clamps. However, in hypoglycemia clamp (< 3.9 mmol/L) which represent data from patient 03, we found an inverse relationship between BG and T-wave amplitude. This means that patient 04 has a significantly higher T-wave amplitude average for low glucose heartbeats than for normal glucose heartbeats. These findings are consistent with Mihaela Porumb.[36] We assume that different personal factors can affect the change in T-wave morphology. First, the data was collected in real-world scenarios, and the hypoglycemic event occurred during the day. In comparison to night hypoglycemia, diurnal hypoglycemia can be affected by several hormonal counterregulation components.[53] Other factors that can affect T wave amplitude morphology such as meals[54-55], exercise[55-56] or medications[54]. According to studies, a decrease

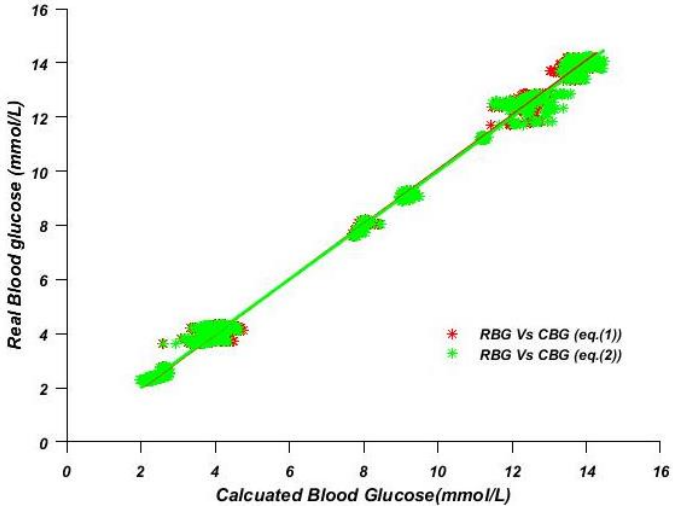


Figure 6. Real Blood Glucose versus Calculated Blood Glucose.

in T wave amplitude occurs commonly within half an hour of eating.[54-55] The same T wave amplitude behavior occurred throughout the exercises.[56] It has been established that low potassium levels can result in T-wave flattening. For that reason, additional investigations could be undertaken to discover whether drops in potassium levels coincide with natural glucose dips[35], taking into account food intake, activities, drugs, and cardiovascular diseases. The heart rate increased significantly with the increase of BGC in the hyperglycemia range, but their increase was slower during the hypoglycemia clamp than during the euglycemia clamp, corroborating previous researchs.[34]

We can see that the obtained MAE differs between patients. These variations can be attributed to the accuracy of ECG features extraction or to inherent patient parameters. The highest MAE derived with **Equation 1** was 0.3502. Using the same equation, the lowest MAE of 0.0788 was achieved in this work. We can see that adding heart rate to the equation has a small effect on the results. In hypoglycemia, it reduces the mean absolute error to 0.0063, which is preferable. However, it has a deleterious impact on the outcomes during hyperglycemia, where the MAE value has been decreased to 0.0262. Patient 04's

glucose profile consists of normoglycemia and hyperglycemia; he presents the best results among the fourth patients, with MAE of 0.0788, 0.0797, and MSE of 0.0110, 0.0112, utilizing **Equations 1** and **2,** respectively. To clearly visualize the results, **Figure 5** illustrates the BG profiles of all patients, compared to calculated BG profiles utilizing the two equations. Using all data, **Equation 1** yields an MAE of 0.0539 and an MSE of 0.1604. The MAE for **Equation 2** was 0.0602, and the MSE was 0.1657.

We use the results of these two equations to demonstrate the linearity between BGC and ECG features. To depict this, we present the distribution of real blood glucose versus calculated blood glucose using the two equations. The curve fitting in **Figure 6** shows that there is a linearity between RBG and CBG. Using **Equations 1** and **2**, the CBG was fitted with the RBG with RMSEs of 0.23 and 0.24, respectively.

As so, based on these results, we reveal that there is a linear relationship between the BGC and ECG features. Furthermore, we proposed the potential use of a new method to estimate BGC based on ECG features rather than intracardiac signal. The intracardiac signal usually consists of the three components of a surface ECG lead: P-wave, QRS, and T-wave. Corresponding to atrial depolarization, ventricular depolarization, and repolarization, respectively. On the other hand, it has a different morphology, with a relatively small amplitude (μV) and a different frequency content.[49,50] Surface ECG lead and intracardiac signal properties are suited for morphological characterization.[49] However, the acquisition of intracardiac signals involves the application of additional bioelectric sources along with invasive catheter-based approaches[50] reducing its availability. On the contrary, as previously mentioned, ECG device is non-invasive, simple to implement, and widely available on the market with a diverse variety of processing methods.[43] This study presented a step toward BGC estimation using surface ECG signal.

To sum up, researchers are working to early predict hypo- or hyper- glycaemia episodes. On the contrary, our major aim in this paper is to highlight the linear relationship between BGC changes and ECG features and propose the possibility of utilizing ECG features to estimate the BGC value. We demonstrate and validate the use of **Equation 1** based on ECG parameters instead of intracardiac signal to calculate BGC (using 04 patients with multiple days). To better understand the correlation between BGC changes and HR, **Equation 2** was developed. Based on our results, we validate that the relationship between BGC and ECG futures can be established using physiological models. Additionally, with advances in AI, we attend to estimate the BGC value-based ECG features using machine learning (Artificial neural network) in future work. The use of an artificial neural network will solve the calibration problem that has been noticed using mathematical equations.

Finally, the proposed method must also be seen with regard to its limitations, which also represent important calls for future research directions. ECG feature morphology is extremely sensitive to ECG abnormalities. Since there is a correlation between the severity of electrolyte imbalance and the morphology of ECG alterations, further research is needed to determine whether other conditions (cardiovascular diseases, drugs, meals… etc.) that induce electrolyte imbalance should be considered in our approach. For that reason, additional studies should be carried out on a larger population, involving healthy people as well as diabetics who may have other clinical problems that affect ECG morphology. Moreover, our strategy necessitates extensive data preprocessing and feature extraction. These stages must be performed with high precision because the BGC value can be affected by a minor error in ECG features. In our case, we use the D1namo dataset, which was assembled under real-world situations, including many factors influencing ECG signal recording, such as electrode contact loosening induced by sweet or sensor displacement. All of this, as well as body motions, might add noise to the ECG recording. These significant elements can influence the quality of ECG parameter extraction, emphasizing the idea that an advanced preprocessing technique is required to assure the high accuracy of ECG segmentation.

Conclusion

In this study, we were able to achieve the BGC value for 04 patients over multiple days of measurements using ECG features with minimal error. However, this method requires **calibration each time the BGC range changes.** The results obtained are very convenient, making the method very promising. The estimation of blood glucose levels from ECG parameters is a new method that will lead to the appearance of a new trend of non-invasive CGMs, which are more durable and less expensive. Furthermore, it will offer the opportunity to predict hyperglycemia and hypoglycemia events in parallel. The proposed method will take the Artificial Pancreas system lead and will open new challenges in this field. In addition, supporting the integration of such technologies into the artificial pancreas is a step towards a cleaner and healthier environment.
In the near future perspectives, we plan to use the artificial neural network to estimate the BGC using different ECG features extracted with high accuracy (QTc, HR, T-wave amplitude, ST segment, P-wave amplitude, and duration… etc.). Currently, we are trying to collect a large number of data, including healthy and diabetics subjects with different scenarios and different health conditions.

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