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Hand tremor-based hypoglycemia detection and prediction in adolescents with type 1 diabetes

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ABSTRACT

Diabetes is a chronic disease where blood glucose (BG) concentrations are consistently high. A dangerous diabetes-associated condition is hypoglycemia, where BG level drops below the normal threshold. Hypoglycemia is often accommodated by tremors, sweating, fatigue, anxiety, lightheadedness, disorientation, irritability, and tachycardia. Very few studies are focused on detecting enhanced tremor as a peripheral physiological response to declining BG concentrations. This study undertakes a machine-learning approach to predict hypoglycemia using hand tremors. Tremors were detected and characterized by frequency and amplitude in non-hypoglycemic and hypoglycemic conditions. Accelerometers and continuous glucose monitoring devices recorded the tremor and BG datasets. A home study of 32 T1D adolescents in a free-living condition was conducted. Simultaneously recorded accelerometer and continuous glucose monitor (CGM) data of 194.6 h were collected from 15 participants. These data were utilized for training and testing the predictive model. Four lengths of the sliding window (1, 2, 5, and 10 s) and four machine learning algorithms (decision tree, support vector machine, k-nearest neighbor, and bagged trees ensemble classifier) were applied to classify tremor as non-hypoglycemic or hypoglycemic. The greatest accuracy (86.65%) was achieved by the ensemble classifier (bagged trees based on the subspace k-NN) for 1 s window length. Multiple prediction windows are merged to generate aggregate sequential predictions. Prediction accuracy of 86.05% was achieved for a 15 s batch (3 s window length). This study demonstrates the feasibility of detecting and predicting the onset of hypoglycemia based on hand tremor data collected by wrist-worn accelerometer sensors.

1. Introduction

Diabetes mellitus is a chronic disease where blood glucose (BG) concentrations are too high. Type 1 diabetes (T1D) may appear at any age but most frequently emerges in children and adolescents due to a dysfunctional pancreas that does not produce enough or any insulin. More than 1.1 million children and teenagers (0–19 years) live with T1D [1]. Diabetes is associated with severe complications such as heart disease, stroke, blindness, neuropathy, and kidney failure. A dangerous condition in diabetic patients is hypoglycemia (HG; where BG concentrations fall below 70 mg/dL) as a reaction to diabetes medication, increased insulin production, hormone deficiency, critical illness, overexercising, stress, excessive alcohol consumption, delayed meals, and fasting. Symptoms of hypoglycemia are tremors, sweating, fatigue, anxiety, lightheadedness, disorientation, irritability, and tachycardia [2,3]. Frequent hypoglycemic episodes affect the patient's quality of life and result in dizziness, visual disturbances, behavioral changes (i.e., confusion), seizures, loss of consciousness, and even death. To minimize hypoglycemia and its effects, it is essential to follow the BG trends and increase BG concentrations to normal before or soon after a hypoglycemic event occurs.

Continuous glucose monitors (CGMs) are the most popular tool for monitoring BG. This technology provides real-time information about glucose levels in patients' interstitial fluid by inserting a glucose oxidative-enzyme-coated catheter under the skin. The enzymes generate electronic signals when reacting with glucose in the interstitial fluid

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[4,5]. Although CGM provides valuable data, there are a few disadvantages. The time lag is highly important since CGM estimates the interstitial fluid glucose under the skin instead of directly measuring the glucose in the blood [5,6]. Furthermore, CGM users often experience bleeding during sensor insertion and accidental dislodging [7]. Likewise, the invasiveness of this method, inherent noises, cost, combined with the sensor's inaccuracy [8] and need for calibration several times per day, are critical drawbacks that reduce its acceptance and use in special populations, such as children.

A significant portion of type 2 diabetic patients currently do not use CGMs and cannot monitor hypoglycemic events. Self-monitored glucose approaches are intermittent and miss hypoglycemic events, especially at night. CGM devices can give continuous real-time alerts for glucose deviations above or below customized thresholds. Recently, Dexcom G6 offered a predictive "Urgent Low Soon" alert to alarm the user for potential hypoglycemic events (55 mg/dL or below) [9,10]. Numerous examinations have investigated CGM and hemoglobin A1c data to foresee hypoglycemia [11,12]. In [13], a prediction model that achieved more than 97% sensitivity and specificity for both 30- and 60-minute prediction horizons was reported. Dave et al. [14] predicted hypoglycemic events with a reported 8%-10% false positives (with accuracy above 90%) for 0–15-minute and 45–60-minute prediction intervals with a sensitivity between 58% and 91% in 45–60-minute window depending on the used algorithm. Sudarshan et al. [15] reported a model for predicting hypoglycemia events in a 24-hour time frame with sensitivity and specificity values of 92% and 70%, respectively. In [16], oral glucose tolerance test, age, ethnicity, and body-mass index were used to develop a predictive support vector machine (SVM) model with an average accuracy of 96.80% and a sensitivity of 80.09%.

New approaches to universal blood glucose monitoring systems should be considered, especially when conventional CGM devices are inaccessible or awkward to wear. The advances in sensor technologies and machine learning (ML) algorithms may enable non-invasive techniques to monitor early signs of low BG. Blood glucose correlates to physiological parameters, physical activities, energy expenditure, sleep quality, and emotional states [17–22]. Biosensors and accelerometers implanted in commercially available wearables and smartphones could be used to monitor such BG correlates, including temperatures, heart rates, blood pressures, electroencephalogram changes, respiration rates, galvanic skin responses, as well as daily activities, fatigue, and energy expenditure [23,24]. Our previous work [23] documented a system that detects voluntary effort and classifies fatigue phases based on the tremor in healthy and T1D adults. We did not establish dependence between the participants' health condition and fatigue phase recognition; BG levels were not considered during the study.

Several studies proposed using hypoglycemia-related physiological parameters to detect and predict low BG events [25–31]. A fitness band that records heart rate, galvanic skin response, skin and air temperatures, meals, sleep, activity reports (via smartphone), and medical devices (insulin pump and CGM) were used to verify the concept that physiological data can be used for hypoglycemia detection [31]. In [25], records of food and drug intake, physical activity, and sleep quality were used to monitor blood glucose concentrations and build a blood glucose model. Cvetković et al. [32] recorded electrocardiogram (ECG) and respiration rate to predict glycemia for T1D and T2D patients with 84 % and 88 % accuracy, respectively. A system that consists of a CGM device with sensors to measure physiological parameters (heart rate, perspiration, skin temperature, and tremors) detected nocturnal hypoglycemic events with a specificity of 85.7% [26]. Another study used a non-linear recursive approach for short-term prediction in T1D patients using physiological data (activity, galvanic, skin response, temperature), daily food, and insulin intake [33]. It was reported, that "an average root mean squared error of 18.66 ± 3.19 mg/dl for a prediction horizon of 30 min with 82.04% of hypoglycemic readings and 93.30% of hyperglycemic ones being classified as clinically accurate or with benign errors". In [29], artificial intelligence and machine learning models were established to detect hypoglycemia based on heart rate variability data. Heart rate and ECG data were used to detect hypoglycemic episodes with a sensitivity and specificity of 76.74% and 50.91%, respectively, [28]. Cichosz et al. [27] proved that heart rate variability patterns and CGM data could be used to detect low BG in real-time. A recurrent Neural Network algorithm was applied to improve the BG levels control using T1D patients' activity data tracked by wearable devices supplied with accelerometers and gyroscopes [34]. However, studies that employ hand tremors as a sole feature to detect hypoglycemia are few and far between.

Our previous work [35] found that while many researchers endeavored to recognize hypoglycemia through other physiological changes, very few studies are focused on detecting enhanced tremor as a peripheral physiological response to declining BG concentrations. The research aims to objectively document non-invasive and non-intrusive methods to detect hypoglycemia onset using hand tremor acceleration data. This paper demonstrates an ML model that detects hypoglycemia based on the tremor in T1D adolescents. We categorically detect and characterize the frequency and amplitude of tremors when BG concentrations are both in the normal and low concentration ranges to predict hypoglycemia onset.

2. Methods

2.1. Consent procedures

Texas A&M University and Sidra Medicine's institutional review boards approved the study protocol, consent, and assent forms. Adolescents and their parents/guardians were informed of the study details and signed written assent and parental permission forms.

2.2. Participants and study design

Study participants consisted of TD1 patients aged between 10 and 17 years who used a CGM device. All subjects were recruited from T1D patients receiving care at the Endocrinology and Diabetic Clinic in Sidra Medicine, Qatar. We recruited 32 patients, 17 boys and 15 girls: mean age of 13.72 ± 2.30 years (mean ± standard deviation (SD)).

To test if hypoglycemia can be detected through tremors, BG concentrations were collected. A commercially available Apple Series 5 smartwatch with an integrated 3-axis accelerometer was used for tremor data collection. An iOS application (TREMOR app) was developed to archive timestamped tremor events with a self-reporting feature. Participants were asked to wear the watch continuously for the study duration. They were instructed to use/charge it and report perceived hypoglycemia. The CGM devices used were FreeStyle Libre by Abbott (25 patients), Dexcom G5 CGM by Dexcom Inc. (4 patients), and Medtronic's Insulin pump (3 patients). The study was conducted in free-living conditions with a mean duration of 15.94 ± 2.65 days.

2.3. Data analysis

Matlab R2020 A (MathWorks, Inc., Natwick, MA, USA) software was used for data processing and analysis. Data analysis steps are presented in Fig. 1. Collected tremor and BG concentration data were cleaned, categorized into two sub-files according to BG values, and spit into equal segments. The algorithm's modeling approach was based on the feature extraction in the time and frequency domain. The normalized data were tested and trained using a 10-fold cross-validation approach to estimate performance metrics.

Data were cleaned during the pre-processing stage. In the case of a few missing accelerometer samples, they were filled by the segment's mean value (the segment has a duration of 1 s and consists of 64 samples). According to the CGM sensor's instructions, the user manually measures the BG level several times per day to calibrate the device. The BG shown as NaN was replaced with a manually measured BG value if

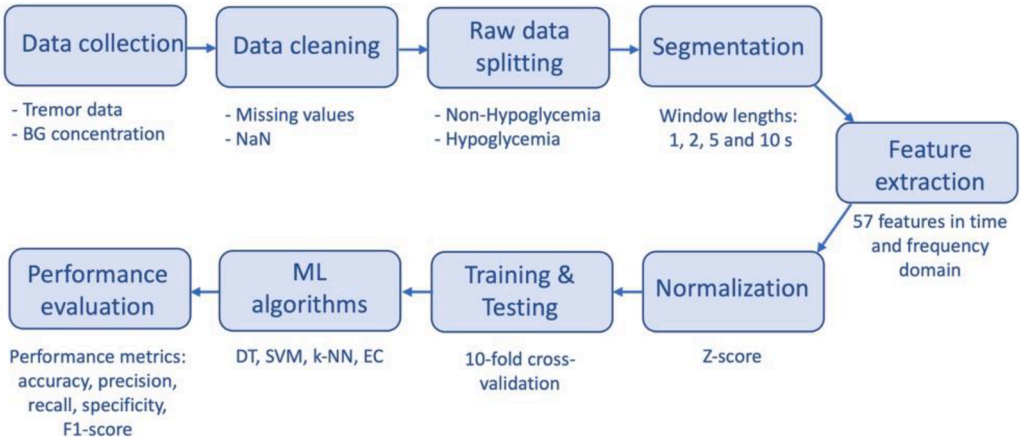

Fig. 1. Overview of the data analysis process.

available for the same timestamp; otherwise, it was removed. A review of the collected files showed that the duration of the accelerometer data was less than the data downloaded from the CGM devices for all the participants suggesting intermittent watch wearing or data loss during the time watches were being charged. Direct matching of accelerometer and CGM log files was complex since the number of accelerometer samples was significantly higher than the number of CGM readings due to different frequency rates. Accelerometer data were collected with 64 samples/s. At the same time, a BG value was recorded every 5 or 15 min depending on the used CGM device. Thus, we categorized the accelerometer data into two sub-files corresponding to normal and low BG values instead of matching both log files. The timestamp of the grouped BG readings served to categorize the accelerometer dataset into two classes: tremor data collected during the non-hypoglycemic and hypoglycemic conditions. Two data groups were extracted from the cleaned CGM data: a non-hypoglycemia (non-HG) group that includes CGM values between 100 and 140 mg/dL and an HG group – with CGM values below 70 mg/dL. We used these ranges to avoid classification mistakes due to the CGM sensor's inaccuracy. Besides, according to [36], the glycemic target of random BG for adolescents above 14 years is 100 – 140 mg/dL. The exact target range is used in "artificial pancreas" or "closed-loop" systems [37,38]. The delay between the BG measurement and the record of the tremor data was compensated by starting each categorized accelerometer file 5 min before the timestamp of the corresponding CGM value. The time that patients were in non-hypoglycemic condition (BG concentration between 100 and 140 mg/dL) was much higher than the time spent in hypoglycemic conditions; therefore, we used an equal number of accelerometer samples corresponding to BG values below 70 mg/dL and randomly chosen accelerometer samples corresponding to normal BG values to balance both classes (non-HG and HG) for each patient.

A sliding window approach [39] with four different window lengths was used for feature extraction. The accelerometer signal was divided into equal segments with window lengths of 1, 2, 5, and 10 s (64, 128, 320, and 640 samples, respectively) without overlapping. A sliding window technique for a window consisting of 10 segments with a length of 1 s is presented in Fig. 2. This resulted in 393198, 196459, 78639, and 39319 segments. A subset of 57 statistical features in the time and frequency domain was extracted from the three axes of acceleration signal and magnitude for each time frame of the categorized data (Table 1). Time domain processing utilizes the temporal dependencies between data points.

On the other hand, in frequency domain techniques, the times series can be presented as a sum of sinusoids characterized by a specific

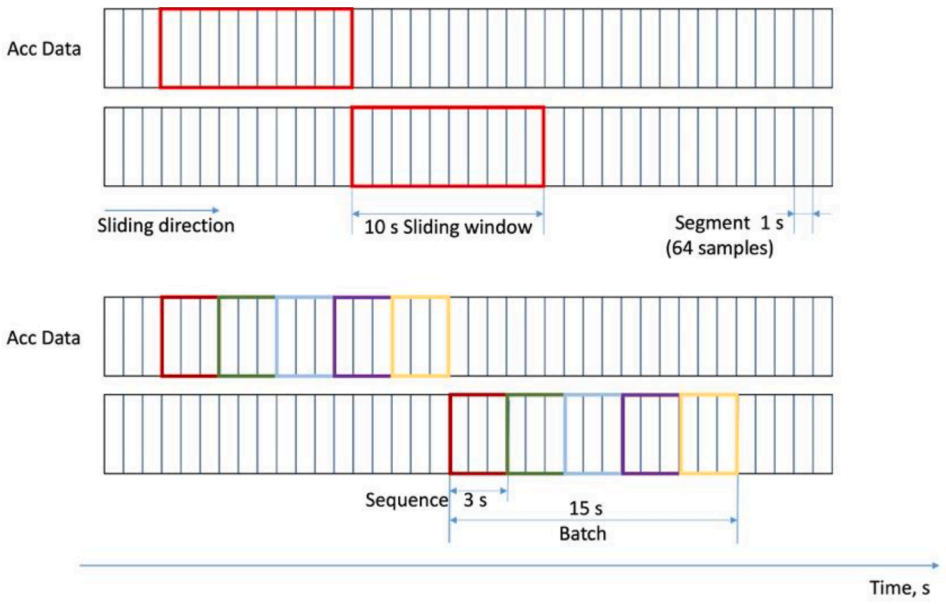

Fig. 2. Time series accelerometer (acc) data classification and prediction using sliding window (10 s window) and sequential (15 s batch) techniques; a sliding window consists of randomly chosen ten 1 s-segments from the dataset, while a batch consists of five 3 s-sequences.

Table 1
Features extraction from the acceleration signal (x-, y-, and z-axis).

Feature category	Features	N° 3-axial features	N° Magnitude features*
Time domain: 41 features	Maximum	3	1
	Minimum	3	1
	Average	3	1
	SD	3	1
	Root mean square error	3	1
	Number of peaks	3	–
	Range	3	1
	Skewness	3	1
	Kurtosis	3	1
	Correlation between axes	6 features	
Frequency domain: 16 features	PSD features in 6 to 14 Hz range		
	Mean	3	1
	Maximum	3	1
	SD	3	1
	Dominant frequency	3	1

* Magnitude (x, y, and z):. $\sqrt{x_i^2 + y_i^2 + z_i^2}$.

oscillation frequency, amplitude, and phase shift [40]. Time domain features as minimum, maximum, and average values of the data points in a specific time interval were determined. Skewness estimates the degree of asymmetry in the dataset distribution [41], while Kurtosis measures "peakedness near the center of the distribution" [42]. Time series were converted into frequency domain applying the Fast Fourie Transformation algorithm. For frequency domain analysis, power spectral density features in the frequency range of 6 to 14 Hz were calculated. We used a z-score normalization method for each particular feature to reduce the feature's variability.

To classify the tremor as non-hypoglycemic or hypoglycemic using supervised ML, we applied Matlab's Classification Learner app. Four binary classification algorithms were performed separately: decision tree (DT), support vector machine (SVM), k-nearest neighbor (k-NN), and bagged tree ensemble classifier (EC). Using a decision tree model, the classification starts from the root node and assigns the sample to one of the classes according to the sample's extracted features [43]. A fine tree classifier type of decision tree algorithm with many leaves (up to 100 splits) was applied to refine classes. SVM is a binary classification model capable of managing multiple continuous and categorical variables and constructs hyperplanes in multidimensional space to split it into two different classes [43,44]. Utilizing SVM, three kernels, named cubic, fine gaussian, and quadratic, were used due to the best performance metrics. Non-parametric classification algorithm k-NN was used due to its implementation simplicity and short calculation time. It groups data based on closest or neighboring training examples in a given region using the Euclidean distance [43,45]. Cosine k-NN classifier (number of neighbors set to 1; the angle between the observation as distance parameter) was used. In ensemble classifiers, multiple classifiers are used to determine a sample's class label generating more precise results than a single classifier's output. The bagging method reduces the prediction's variance using the original dataset to generate a supplementary training dataset [46]. Also, k-NN is sensitive to input perturbations, such as subspace selection or nonlinear projection [47]. From the ensemble classifier, bagged trees based on the subspace k-NN were chosen, given that it has the best accuracy.

We applied classical and sequential supervised classification algorithms to detect and predict hypoglycemic events. In the classical approach, the segments used for the classification were chosen randomly from the dataset. The sequential approach attempts to learn from the past event sequences and predict the category of aggregated sequences [48]. To predict the upcoming condition as non-hypoglycemic or hypoglycemic, three batches' lengths consisting of the 5, 10, or 11 consecutive sequences were considered (Fig. 2); we assembled 26213, 13106, or 11915 batches, respectively. As each sequence had a duration of 3 s with no overlapping, the prediction horizon was 15, 30, or 33 s. The batch was classified as HG if more than 50% of the constituent windows were predicted as HG.

Pre-processed accelerometer data were split into training (80%) and testing (20%) sets. When the model was run for each patient separately, the patient's data were split into training (80 %) and testing (20 %). If the model was run on all patients' combined datasets, data were divided (80% vs. 20%) based on accelerometer samples that were randomly mixed no matter the data from which participant.

Data analysis was implemented on the training dataset while the model was verified using the test dataset. Models' performance was estimated by applying 10-fold cross-validation. Various metrics such as accuracy (ratio of correctly classified and all tested samples), precision (positive assigned samples or exactness), recall (true positive rate or completeness), specificity (true negative rate), and F1-score (balance between the classifier's completeness and exactness or how precise the classifier) were calculated to evaluate the effectiveness of the models, Eqs. (1) – (5) [23].

$$\text{Accuracy} = \frac{TP + TN}{TP + FP + TN + FN} \times 100\,[\%] \tag{1}$$

$$\text{Recall} = \frac{TP}{TP + FN} \times 100\,[\%] \tag{2}$$

$$\text{Specificity} = \frac{TN}{FP + TN} \times 100\,[\%] \tag{3}$$

$$\text{Precision} = \frac{TP}{TP + FP} \times 100\,[\%] \tag{4}$$

$$\text{F1} - \text{score} = \frac{\text{Precision} \times \text{Recall}}{\text{Precision} + \text{Recall}} \times 100\,[\%] \tag{5}$$

where TP, TN, FP, and FN refer to true positive, true negative, false positive, and false-negative rates, respectively; TP: the task is labeled as non-HG and input is predicted as non-HG; TN: the task is labeled as HG and input is predicted as HG; FP: the task is labeled as HG and input is predicted as non-HG; FN: the task is labeled as non-HG and input is predicted as HG.

The correlation of the true classes (non-HG) with the predicted label was determined by computing Matthews correlation coefficient (MCC) [49]:

$$\text{MCC} = \frac{TP.TN - FP.FN}{\sqrt{(TP + FP).(TP + FP).(TN + FP).(TN + FN)}} \tag{6}$$

To compare the model prediction with the manually established labels (non-HG or HG), Cohen's kappa was calculated, Eq. (7) [50]:

$$k = \frac{p_0 - p_e}{1 - p_e} \tag{7}$$

where p_0 is the model's overall accuracy; p_e is the measure of the agreement between the model prediction and the actual class values as if happening by chance. In our case, p_e is a sum of the probability of the predictions agreeing with actual values of class 1 (non-HG) by chance and the probability of the predictions agreeing with the actual values of class 0 (HG) by chance.

3. Results

The recorded 32 participants' tremor and BG data consisted of 5374.56 and 7903.86 h, respectively. Overall, 405 hypoglycemic events with a total duration of 557.24 h were recorded across 32 patients. Plots of the raw accelerometer and BG data are presented in Fig. 3. After reviewing the raw data, data from 17 patients were removed. The

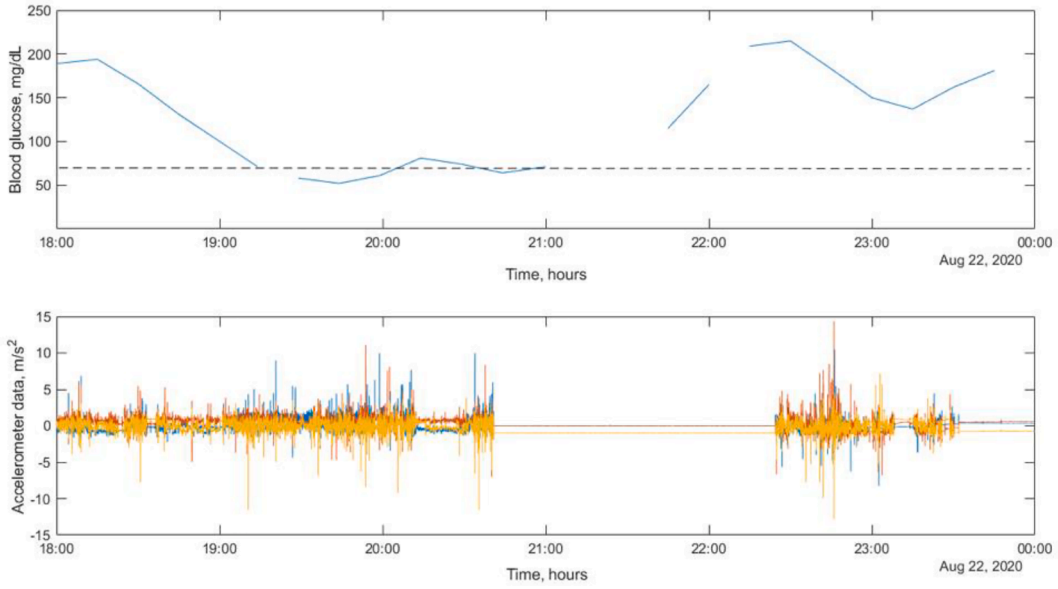

Fig. 3. Example of raw BG (top) and three-axis accelerometer data (bottom) during non-hypoglycemic BG levels and hypoglycemia.

accelerometer data were missing for four participants (perhaps due to poor compliance); CGM data were missing for six participants (they did not wear the CGM sensor, or the data were deleted); for four participants, there was no match between accelerometer and CGM data; and finally, three participants did not have hypoglycemic events during the study sessions. The reduced group of participants whose data were used consisted of 15 T1D patients: six boys and nine girls: mean age 13.87 ± 1.81 years (mean ± standard deviation (SD)); mean body mass index (BMI) 22.23 ± 4.46 kg/m^2; mean duration with diabetes five years. For the contributed 15 patients, 3348.96 h of accelerometer data and 5035.75 h of BG data were recorded. From the CGM data of the reduced group, 20.09% corresponded to BG values between 100 and 140 mg/dL, and 9.3% corresponded to less than 70 mg/dL, respectively; 248 hypoglycemic events with a duration of 425.88 h were documented. Simultaneously recorded accelerometer and hypoglycemic data of 194.6 h were collected from 15 participants.

Four ML algorithms (DT, SVM, k-NN, and EC) were applied to classify the tremor as a non-hypoglycemic or hypoglycemic class. The accuracy performance of the models is presented in Table 2. The best performance (accuracy of 86.65%) was achieved by applying a bagged trees ensemble classifier with a sliding window length of 1 s. For DT and k-NN models, the highest accuracies were 75.08 % and 78.82%, respectively, and were achieved for the window length of 3 s. For the SVM model, the highest accuracy was achieved in the 2 s length of the segment. Regarding the EC model, the accuracy increased from 83.83% to 86.65% when the window length decreased from 10 s to 1 s.

The best performance of the EC method is also confirmed by MCC (MCC = +0.71, 1 s window length). The worst MCC (+0.31) was obtained for the DT model with 1 s window length. As data were balanced, the Cohen's Kappa is high, between 0.25 and 0.70 depending on the model (Table 2); the highest value (0.69) was reached by EC (1 s window length).

Based on the results from the ML algorithm for the models' metrics, we implemented the EC model (1- and 2-second window duration) on each patient's dataset and all patients' combined datasets. The performance metrics are presented in Table 3. The performance metrics for both classes, named non-HG and HG, associated with physiological tremors when BG concentrations ranged between 100 and 140 mg/dL and during hypoglycemia (BG below 70 mg/dL), respectively, were computed. Applying classical classification, the accuracy of recognizing

Table 2
Accuracy performance of the models classifying tremors in non-hypoglycemic and hypoglycemic conditions; HG is a positive class.

ML algorithm	Precision, %	Recall, %	Specificity, %	F1-score, %	Accuracy, %	MCC	Kappa
Window length 1 s							
DT	70.24	95.32	25.72	80.88	70.80	+ 0.31	0.25
SVM	78.37	94.78	51.90	85.80	79.67	+ 0.54	0.51
k-NN	79.36	93.99	55.04	86.06	80.27	+ 0.55	0.53
EC	84.51	97.20	67.25	90.42	86.65	+ 0.71	0.69
Window length 2 s							
DT	72.68	91.98	36.42	81.20	72.41	+ 0.35	0.32
SVM	78.45	95.06	51.71	86.18	80.14	+ 0.55	0.52
k-NN	78.19	92.88	52.35	82.81	84.90	+ 0.51	0.49
EC	83.75	97.11	65.36	89.94	85.93	+ 0.69	0.70
Window length 5 s							
DT	73.79	95.43	37.66	83.22	75.08	+ 0.43	0.38
SVM	77.85	96.13	49.71	86.03	79.78	+ 0.55	0.51
k-NN	78.18	93.36	52.08	85.10	78.82	+ 0.52	0.49
EC	82.72	96.58	62.92	89.12	84.72	+ 0.66	0.64
Window length 10 s							
DT	75.47	90.67	45.77	82.37	74.86	+ 0.42	0.40
SVM	76.99	95.95	47.22	85.43	78.79	+ 0.52	0.48
k-NN	77.43	92.28	50.51	84.21	77.57	+ 0.49	0.47
EC	82.14	95.89	61.64	88.49	83.83	+ 0.64	0.62

Table 3
Performance of the EC model classifying the non-hypoglycemic and hypoglycemia tremor for each patient separately.

Patient ID	Window length	# of samples	Class	Precision, %	Recall, %	F1-score, %	Accuracy, %
1	1 s	81835	non-HG/HG	95/94	50/100	88/92	93.77
	2 s	40782		97/93	44/100	61/96	93.17
2	1 s	37554	non-HG/HG	96/98	97/97	97/98	97.39
	2 s	18776		96/98	97/98	98/97	97.23
3	1 s	10814	non-HG/HG	92/84	78/95	84/89	87.05
	2 s	5407		93/83	75/95	83/88	86.31
4	1 s	28886	non-HG/HG	86/82	71/92	78/86	83.11
	2 s	14443		86/80	68/92	76/86	81.86
5	1 s	55234	non-HG/HG	94/89	84/96	89/97	91.04
	2 s	27616		93/88	82/96	87/92	89.82
6	1 s	8249	non-HG/HG	91/85	76/95	82/90	86.96
	2 s	4124		88/84	73/93	80/88	85.07
7	1 s	5273	non-HG/HG	95/92	62/99	75/95	92.03
	2 s	2636		96/92	64/99	77/95	92.41
8	1 s	1448	non-HG/HG	100/98	99/100	99/99	99.31
	2 s	723		100/100	100/100	100/100	100.00
9	1 s	11674	non-HG/HG	99/92	90/99	94/95	94.86
	2 s	5836		99/92	99/100	95/96	95.20
10	1 s	2521	non-HG/HG	95/93	98/88	97/90	94.86
	2 s	1263		96/90	96/88	96/89	94.05
11	1 s	29783	non-HG/HG	93/97	93/97	93/97	95.30
	2 s	14891		93/96	91/97	92/96	94.80
12	1 s	28802	non-HG/HG	77/84	69/89	73/87	82.07
	2 s	14401		75/83	65/88	70/85	80.14
13	1 s	4258	non-HG/HG	94/90	64/99	76/94	90.72
	2 s	2128		87/91	69/97	77/94	90.59
14	1 s	37598	non-HG/HG	96/88	76/98	85/93	90.38
	2 s	18799		95/86	70/98	81/91	88.16
15	1 s	49269	non-HG/HG	86/82	86/82	86/82	84.43
	2 s	24634		85/82	86/80	85/80	83.09
All patients	**1 s**	**393198**	**non-HG/HG**	**91/84**	**69/96**	**79/90**	**86.85**
	2 s	**196459**		**92/84**	**68/96**	**78/90**	**85.93**

non-hypoglycemic and hypoglycemic tremors changed from patient to patient (range of 82.07–99.31% and 80.14–100% for 1 s and 2 s window lengths, respectively).

In the sequential classification, a 3 s window length was used. The best accuracy performance for the classical approach was achieved with a window length of 1 s, but data transfer and calculation every second would require powerful computational capabilities from an engineering point of view. The sequential classification results in multiple segments based on the 3 s sequence's length are aggregated in Table 4. We tested the model using 5, 10, and 11 sequences; the batches' durations were 15, 30, and 33 s. The accuracy achieved by the sequential classification was about 1% higher than the classical one for all three batch lengths.

4. Discussion

We collected continuous tremor and BG concentration data from T1D adolescents in the home study over multiple days. We established detectable changes in frequency and amplitude of hand tremor data that distinguish between non-hypoglycemic and hypoglycemic tremors.

Table 4
Performance metrics of EC model applying classical and sequential classification (all patients).

Classification	Precision, %	Recall, %	Specificity, %	F1-score, %	Accuracy, %
3 s window, 15 s batch					
Classical	82.91	96.32	63.59	89.11	84.77
Sequential	82.89	98.53	63.91	90.04	86.05
3 s window, 30 s batch					
Classical	83.14	94.54	65.85	88.47	84.23
Sequential	81.65	98.09	60.64	89.12	84.64
3 s window, 33 s batch					
Classical	82.26	94.78	63.99	88.08	83.63
Sequential	82.62	95.86	63.85	88.75	84.40

Similar observable differences in BG and tremor data were reported by George et al. in [51]. They examined physiological responses of blood pressure and pulse, sweating, and finger tremor on days 1, 3, and 8 after a hypoglycemic clamp experiment. Despite a non-sufficiently sensitive accelerometer (according to the authors) being used, a significant increase in tremor amplitude (root mean square) during hypoglycemia (BG of 2.5 mmol/l) was consistently detected compared to periods of average BG values (5 mmol/l (Fig. 6 [51]).

The present study developed four ML models that monitored and classified hand tremors in non-hypoglycemic or hypoglycemic classes. The positive and negative class labels were assigned to the non-HG and HG tremors, respectively. The best performance metrics (accuracy, MCC, Cohen's Kappa) were achieved by applying EC and a window length of 1 s (Table 2). Despite the model's promising accuracy to detect and classify samples related to low BG concentrations, it is also important to aim for a trade-off with high recall and specificity. The recall (sensitivity) is considered as correctly classified/predicted HG events. The recall of all models was decent; it was at 91 % and above. The EC model recognized the HG class with higher accuracy than non-HG. The highest values of specificity (true negative rate) were reached by of EC model (between 61.64 and 67.25% depending on the window length). In contrast, it was approximately 50 % and below for the other models.

In the low BG condition, tremor increased and was correctly recognized. The most likely reason for this was enhanced physiological tremor during the hypoglycemic event. Tremor enhancement could be caused by hypoglycemia, fatigue, stress, medications, diseases, etc. [52]. Also, as data were collected in free-living conditions, motion artifacts such as hand movement, the device's sliding on the wrist if it was not attached properly, and an individual's physiological tremor could enhance tremor. The model detected the enhanced tremor characteristics and classified it as hypoglycemic even if it is a motion artifact, physical or emotional condition that increased the number of false-negative events, reducing the specificity. Due to the factors mentioned above, the model

did not classify positive class (non-HG) correctly for some patients, and true positive rate (recall) is lower (Table 3). The exactness (precision) of detecting HG tremor appearance was the highest for the EC model; the lowest was for a 10 s window (82.14%) and increased to 84.51% for the segment with a length of 1 s (Table 2). As shown in the F1-score results presented in Table 2, all models achieved values between 80.88% and 90.42% (achieved by EC model, 1 s window). The EC model with sliding window lengths of 1 and 2 s was considered for further analyses.

The computed MCC and Cohen's Kappa values showed a good correlation between true and predicted classes as data were balanced. High values of MCC are due to the correctly predicted most of the non-HG and HG classes (Table 2). As we target to predict hypoglycemia, specifically BG level in real-time, the dataset will be unbalanced due to the fact that diabetes patients spend much more time in non-hypoglycemic condition (BG greater than 70 mg/dL), less than 4% of the time [36,53]. In future work, when unbalanced data will be used, the MCC and Cohen's Kappa would be more informative.

When the model was applied to each patient's data, the achieved accuracy varied between 80.14% and 100%, depending on the patient (Table 3). This may be due to the large variability of the amplitude and frequency of hand tremors among patients. Some patients experienced weaker physiological and/or less severe hypoglycemic hand tremors, and consequently, the classifiers would not be able to recognize HG and non-HG classes with high accuracy. The EC model's accuracy values were diverse due to the personal tremor response to the changing glucose levels. The results presented in Table 3 confirm the individual responses to hypoglycemia. In [51], the authors measured peripheral physiological responses of blood pressure, pulse, rates of sweating, and finger tremor. They established that the subjective components of physiological reactions to low BG concentrations were actuated at diverse glucose levels. It cannot be noticed any tendency in the precision, recall, and F1-score among the separate patients' results due to the mentioned individual tremor response to the low BG concentration. A correlation between the duration of the hypoglycemic event and estimated accuracy performance was not found. The event duration was presented as a number of samples (Table 3) because the data were balanced: the number of samples in HG was equal to the number of the samples in the non-HG class. The correlation coefficients for 1- and 2-s windows were −0.118 and −0.102, respectively.

Overall, when all patients' data were combined and classified, the accuracy was 86.65% and 85.93% for 1 s and 2 s sliding windows, respectively (Table 3). The effect of the length of the sliding segment was not significant. Regarding the precision, a higher fraction from the samples was correctly assigned to the non-HG class (91 – 92%) than the BG class (84%) for both windows' sizes - Table 3. According to the recall results, the true-positive rate of detecting hypoglycemia was 96%, while the false-positive rate was 68 – 69 % (for 1 and 2 s, respectively) due to the advanced tremor characteristics. Therefore, the model is more sensitive in detecting the HG class. As the specificity estimates the correctly predicted negative class and complements recall metrics, the specificity of non-HG and HG classes was 96% and 69%, respectively.

The bagged trees ensemble model was trained and tested as a sequential classification predictor. Comparing the performance metrics of classical and sequential classification, higher metrics were observed for the sequential algorithm (Table 4) due to the fusion of the individual results. Furthermore, the best results were reached utilizing the smallest batch, but prediction time should also be considered. Increasing twice the number of segments in the batch (10 instead of 5) assured a doubled predicting time and ~ 1.5% decrease in the accuracy.

To verify how the model continuously detects and predicts the events (non-hypoglycemic vs. hypoglycemic) over the duration of the recording, we run the EC model applying sequential classification over a few patients' long raw accelerometer recordings. Even though the prediction horizon is short (15 s) the obtained results for the performance metrics were good (Table 5). Despite the used data being unbalanced, both classes were predicted well; the model showed a good correlation between true and predicted classes. This simulation confirmed that the model could work under a real-time application scenario.

As mentioned in the introduction, several previous studies have used ML for hypoglycemic event detection/prediction; however, it is difficult to compare the results since none have used only tremor. In addition, there are several differences in the design of these studies, which makes such comparison difficult (e.g., variability in sensors used to collect data, patient cohorts and datasets, features extracted, models applied, ways to evaluate the models as predictive horizons or evaluation metrics, and duration of the monitoring time). Table 6 summarizes descriptive details and results from other studies to detect or predict hypoglycemia based on different physiological parameters.

In the studies listed in Table 6, physiological parameters like BG concentration, blood pressure, pulse, ECG, sweating, temperature, galvanic skin response, physical activities and energy expenditure, the record of food, drug, and insulin intake, and sleep quality were used to detect or predict hypoglycemia. Two of the studies considered and utilized tremors as one of the signs of hypoglycemia along with other indicators [26,51]. A complex non-invasive system that monitors heart rate, respiration, skin temperature, and tremor data combined with a CGM system showed better performance in detecting nocturnal hypoglycemic events (sensitivity and specificity of 100% and 85.7%, respectively) than the presented one. This was reported based on data collected from 10 T1D adolescents [26]. In [51], blood pressure, pulse, sweating rate, and finger tremor data were considered to evaluate the effect of hypoglycemia on the peripheral physiological, endocrine, and symptomatic response in non-diabetic subjects during the clamp experiment and 1, 3, and 8 days later. Another group of studies [25,27,28,31], reported good models' performance metrics in detecting hypoglycemic episodes based on different physiological parameters listed in Table 6. The performance metrics of our model based on the tremor response to hypoglycemia were close to the results reported in these studies that used sets of physiological parameters. Other research aimed to predict BG levels [24,32,33]. The authors interpreted different physiological parameters and utilized ML algorithms for short-term predictions of abnormal BG levels (Table 6). The prediction accuracy we report is good and close to the reported in these papers. The disadvantage of our model is the short prediction horizon (15, 30, or 33 s) compared to the 30- or 60-min prediction horizon of the algorithms in [24,33]. We plan to increase the prediction horizon in subsequent work using other features selection methods and deep learning algorithms (LSTM, CNN, RNN).

The present study is part of a collaborative project with parallel studies in Qatar and the USA. The US team conducted the same home study with adults. Data collected from both studies were processed and analyzed, applying the same techniques. We aimed to evaluate if a similar approach is able to achieve model performances seen here with adults. As a next step, the data related to the frequency and duration of

Table 5
Performance metric of the EC model applying sequential classification run over separate patients' long raw accelerometer recordings.

Patient	Precision, %	Recall, %	Specificity, %	F1-score, %	Accuracy, %	MCC	Kappa
4	74.90	97.85	63.91	84.85	81.69	+ 0.66	0.63
5	87.17	96.10	79.58	91.42	89.34	+ 0.78	0.77
14	86.77	98.26	75.57	92.16	89.63	+ 0.78	0.77
15	84.85	80.66	90.28	82.70	86.40	+ 0.72	0.72

Table 6
Reported models for detection and prediction of hypoglycemia.

Collected data	Cohort	ML model	Performance metrics	Ref.
Detection of hypoglycemia				
- Blood pressure Pulse Sweating rate Finger tremor Blood glucose	8 non-diabetics Subjects, 23–35 years		RMS, AUC	[51]
- Heart rate, Perspiration Skin temperature Tremor Blood glucose	10 T1D patients, 14–18 years		Sensitivity of 100% Specificity of 85.7%	[26]
- Heart rate Galvanic skin response Skin temperature Air temperature Blood glucose	1 middle-aged T1D subject	SVM with a linear kernel	Precision-Recall Curve	[31]
- Food record Drug and insulin intake Physical activities Sleep quality Blood glucose	35 non-diabetic, 38 T1D and 39 T2D patients	Md3RNN	Average accuracy in inferring the BG of 82.14%	[25]
- Heart rate variability Blood glucose	1 T1D patient	Gradient boosting decision tree	Mean accuracy of BG level 82.7%	[29]
- Heart rate ECG Blood glucose	15 children with T1D	Block-based neural networks	Sensitivity of 76.74% Specificity of 50.91%	[28]
- ECG Blood glucose	10 T1D patients	Welch and autoregression	Sensitivity of 79% Specificity of 99%	[27]
Prediction of hypoglycemia				
- ECG Respiration rate Blood glucose	30 T2D and 22 T1D patients	Naïve Bayes, Logistic Regression, SVM, IB3, AdaBoostM1, Bagging, Rip, J48, Random Forest, and Zero	Accuracy in predicting glycemia: 84 % (T1D) and 88 % (T2D) Accuracy in recognition of glycaemia: 78 % (T1D) and 76 % (T2D)	[32]
- Heart rate Sleeping time Exercises Blood glucose	25 T1D adults	LR, Random Forest, SVM, GP	RF - RMSE = 18.54 mg/dL; SVM - RMSE = 20.58 mg/dL; LR - RMSE = 24.93 mg/dL; GP - RMSE = 30.89 mg/dL	[24]
- Physical activity Galvanic skin response Temperature Heat flux Food intake Insulin intake Blood glucose	15 T1D adults	Non-linear recursive approach based on kernel adaptive filtering algorithm	RMSE between 4.59 and 29.95 mg/dL; For 30 min prediction horizon: - RMSE of 18.66 ± 3.19 mg/dl; - Hypoglycemia – 82.04% - Hyperglycemia – 93.30%	[33]

hypoglycemic events in both groups (adolescents and adults) and self-reports will be analyzed and included in another work.

The presented model classifies the tremor in non-hypoglycemic or hypoglycemic class and predicts hypoglycemia onset. It proves the concept that hand tremor could be used to detect/predict hypoglycemia non-invasively.

The following study's limitations that should be avoided in future work could be mentioned. First, the participants' data contributing to the final dataset were limited (194.6 h simultaneously recorded accelerometer and CGM data). Data from more than half of the patients were not useful due to the lack of accelerometer and/or CGM data, no match between accelerometer and CGM data, or absence of hypoglycemic events during the study sessions. As data were collected during daily living, motion artifacts such as hand movement or posture, device sliding, and physiological and emotional conditions influenced the analysis. They should be accounted for in future works.

The low participants' number affects the diversity of the individual tremor characteristics used to train the model. For the EC model with a window length of 1 s, when 20 % of all combined data were used to test the model, the accuracy was 86.65 % versus 58.72 % when the model was tested with four patients' data unseen by the model. As the physiological tremor and response to the changing glucose levels are different for each patient, we assume that the combined data cover the individual tremor characteristics of all available patients. When unseen data from four patients were used for testing, the number of samples of their data was 20 % of all collected data, but these four patients were almost one-fourth of all patients. This is confirmed by the fact that when the model was applied for each patient data, the achieved accuracy varied between 80 % and 100 %, depending on the patient (Table 4).

Furthermore, the performance metrics of the model could be improved by optimizing the number of calculated features using other feature selection methods. Different classification and prediction deep learning techniques such as neural networks, CNN, and LSTM could also enhance prediction performance. It would be helpful if the model could distinguish classes that correspond to the blood glucose levels low (hypoglycemia), normal, prediabetes, and diabetes (hyperglycemia). As the project aims to alert the user of impending low BG concentration, a personalized model that assures real-time computation and a longer prediction horizon might benefit. Another limitation is the usage of watch-based sensors because of the short battery life (around 10–12 h in the tremor recording mode). During the watch charging, hypoglycemia onset signs would be missed. The CGM error rate should also be considered due to the different devices used to measure BG and inaccuracy.

5. Conclusions

In this study, an ML-based model detects hypoglycemia and predicts the samples' category using tremor and BG data. The tremor was detected and characterized by frequency and amplitude in normal and low BG concentration conditions. Thirty-two T1D adolescents aged 10 to 18 years participated in the study. During the study, rich and complete trembling and BG datasets in a free-living condition were recorded. One hundred ninety-four hours of simultaneously recorded accelerometer and CGM data downloaded from 15 participants were utilized for training and testing the predictive model. Four lengths of the sliding window (1, 2, 5, and 10 s) and four ML algorithms (DT, SVM, k-NN, and EC) were applied to classify tremor as non-hypoglycemic or hypoglycemic. The highest accuracy (86.65 %) and best performance metrics in the classification of tremors as hypoglycemic and non-hypoglycemic were achieved by the bagged trees ensemble classifier and 1 s window lengths. The sequential classification was used to predict the category for the sequential based on the preceding samples. The prediction model achieved an accuracy of 86.05% for the prediction horizon of 15 s. The results in detecting and predicting hypoglycemia onset based on hand tremors were encouraging. The proposed method could be used as a real-

time proactive non-invasive tool for hypoglycemia forecast.

CRediT authorship contribution statement

Lilia Aljihmani: Data curation, Formal analysis, Investigation, Visualization, Writing – original draft, Writing – review & editing. **Oussama Kerdjidj:** Data curation, Software, Formal analysis, Investigation, Visualization. **Goran Petrovski:** Conceptualization, Investigation, Methodology, Supervision. **Madhav Erraguntla:** Conceptualization, Software, Formal analysis, Methodology, Writing – review & editing. **Farzan Sasangohar:** Conceptualization, Formal analysis, Investigation, Methodology, Writing – review & editing. **Ranjana K. Mehta:** Conceptualization, Data curation, Methodology, Supervision, Resources, Writing – original draft, Writing – review & editing. **Khalid Qaraqe:** Formal analysis, Funding acquisition, Project administration, Resources, Supervision, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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