Non-invasive Wearable System for Hypoglycemia Detection: A Proof of Concept User-Centered Design Process

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About 425 million adults around the world were living with diabetes in 2017. A relevant condition called Hypoglycemia is characterized by a dangerous low level of blood sugar that could be fatal to diabetic patients. Continuous glucose monitoring systems (CGMS) are the most popular commercially available technology for detecting diabetic hypoglycemia. However, CGMSs are invasive, costly, and not user-centric thereby not sustainable for diabetes management. This paper documents our initial efforts in designing an inexpensive, non-invasive, wearable physiological tremor sensory system to detect the onset of hypoglycemic events of diabetic patients. The design cycle briefly presented here includes: 1) determination of system (technology and user) requirements, 2) development of the tremor detection prototype, and 3) testing and validation of the system in non-clinical and clinical settings using human factors, data analytics, and biomedical sciences techniques and approaches.

INTRODUCTION

According to the International Diabetes Federation, approximately 425 million adults were living with diabetes in 2017 with this number set to increase to 629 million in less than three decades (IDF Diabetes Atlas 8th Edition, 2017). In addition, 212 million diabetic patients still remain undiagnosed, while 352 million others are at risk for getting type 2 diabetes (IDF Diabetes Atlas 8th Edition, 2017). In 2012, the total costs of diagnosed diabetes in the US reached 245 billion dollars including 176 billion in direct medical cost and 68 billion in reduced productivity (American Diabetes Association, 2013). Diabetes is associated with heart disease, stroke, blindness and many other serious complications. According to the American Diabetes Association, diabetes was the 7th leading cause of death in the US in 2015. One of the most life-threatening conditions for diabetic patients is hypoglycemia, a condition resulting from low blood glucose. Not eating enough carbohydrates, skipping a meal, drinking too much alcohol without food can all result in hypoglycemia among diabetic patients. Hypoglycemia symptoms include fatigue, sweating, anxiety heart palpitations and tremor (American Diabetes Association Hypoglycemia, n.d.). Hypoglycemia can further result in seizures, loss of consciousness and death.

Continuous glucose monitoring systems (CGMSs) are currently the most popular approach for detecting diabetic hypoglycemia in the market. CGMSs provide real-time glucose level in patients' interstitial fluid by inserting a glucose oxidative enzyme coated catheter under the skin. The enzyme generates electronic signals when reacting with glucose in interstitial fluid (Minnock, 2011). However, a recent study on continuous glucose error analysis of CGMS products in the market showed the clinical accuracy of detecting hypoglycemia is merely 56% (Bay, 2013). Other limitations of CGMSs include frequent false alarms, invasive catheter placement, and expensive equipment costs. Cost of some available CGMSs is listed in Table 1. The devices costs more than $999 and the sensor which is coated with enzymes are only active for 3~7 days. The transmitter battery module would cost an additional $500 and needs annual replacement (Minnock, 2011). In addition, CGMS users often experience bleeding during sensor insertion as well as improper inserting and accidental dislodging (Minnock, 2011).

Table 1. Available CGMSs (Minnock, 2011).

CGMS	FreeStyle Navigator (Abbott)	Dexcom Seven Plus (Dexcom)	Real-Time Guardian (Medtronic MiniMed)	Real-Time Revel System (Medtronic MiniMed)
Cost	Device: $1450 Sensor: $75	Device: $999 Sensor: $79	Device: $1199 Sensor: $36.25	Device: $999 Sensor: $35

Electroencephalogram (EEG) and electrocardiogram (ECG) devices have been used in several research studies targeting hypoglycemia detection. It has been found that EEG signals show lower frequency and higher amplitude about 30 minutes before the onset of hypoglycemic events (Juhl, 2010; Snogdal, 2012). However, the EEG devices needs to be inserted subcutaneously behind the ear which makes it very invasive and suffer from poor wearability. Besides EEG, ECG studies have shown abnormally QTc interval caused by hypoglycemia. Nevertheless, the ECG electrodes are not suitable for daily use (Nuryani, 2012; Murphy, 2004).

Tremor is one of the main symptoms of hypoglycemia. Tremor detection is well documented for clinical disorders, such as Essential Tremor (ET) and Parkinsons Disease (PD). However, usage of tremor detection for hypoglycemia event diagnosis remains a research gap. In several studies, piezoelectric accelerometers were attached by a "Perspex" ring to the terminal phalanx of the middle finger to measure postural tremor during arm and hand outstretching tasks (Wharrad, 2000; George, 1995). While this approach is promising for hypoglycemia detection applications, the piezoelectric accelerometer is not comfortable for recording activities of daily life (George, 1995).

The objective of this research is to demonstrate a proof of concept design of an inexpensive, non-invasive, wearable physiological tremor sensory system to detect the onset of hypoglycemic events of diabetic patients. While the overall design of the proof-of-concept includes: 1) determination of system (technology and user) requirements, 2) development of the tremor detection prototype, and 3) testing and validation of the system in non-clinical and clinical settings using human factors, data analytics, and biomedical sciences techniques and approaches, the focus of this paper will be on reporting research efforts on the second phase, namely, development of the tremor detection prototype while briefly discussing the user-centered evaluation plan.

METHODOLOGY

Unique Hypoglycemia Tremor Signature

Hypoglycemic tremor can be classified as the enhanced physiological tremor not caused by a neurological disease (Heller, 1987; Kelly, 2008). Compare to ET (7~10 Hz) and PD (3~6 Hz), hypoglycemic tremor has a higher frequency range of 10~14 Hz. Besides that, hypoglycemic tremor is bilateral and symmetrical compared to ET (bilateral and asymmetrical) and PD (unilateral or bilateral, and asymmetrical) (Rana, 2015). As a result, hypoglycemic tremor detection requires a multidimensional and novel analysis method.

Overall Systems Design

The hypoglycemia detection system will be designed such that both finger and wrist tremors are measured with compact high-precision accelerometers. The low-frequency physiological tremor signals will be transmitted wirelessly to a smartphone or a server where the signal processing algorithm will identify the corresponding glycemic level. Vibratory and auditory alerts will be triggered once the onset of the hypoglycemic event is detected (Figure 1). This system aims to use a novel, noninvasive approach to monitor blood glucose levels through tremor detection and provide feedback alerts about impending hypoglycemic events. It is expected that upon verification and validation of high detection diagnositicity and sensitivity, this system will drastically reduce the cost of healthcare and lost productivity and will significantly improve quality of life for millions suffering from diabetes.

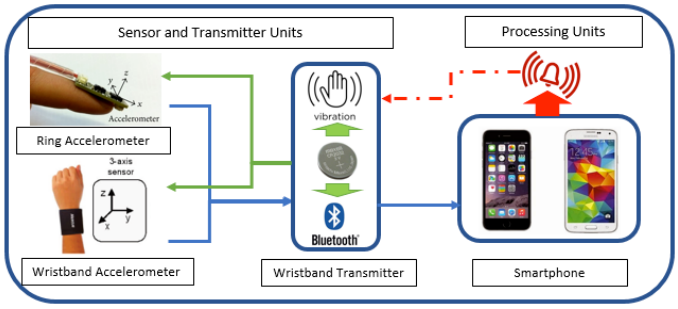

Figure 1. Simple block diagram of the overall instrumentation

Initial development of the prototype included a wired tremor detection system built for the proof of concept and sensor calibration. The type of accelerometer was determined by literature review. Based on subject matter expert feedback, the system was improved to be wireless, lightweight and wearable. The improved sensor described below provides a suitable testbed for tremor frequency validation and data collections.

RESULTS

Initial System Prototype

The hypoglycemia tremor sensor's initial prototype design utilizes a wired device which includes an Arduino UNO board and two ADXL-335 accelerometers (Figure 2). A computer powers and sends the code to the Arduino UNO board while the board controls the two accelerometers and transmits the signal back to the computer. The jumper wires that connect accelerometers to the Arduino UNO board were replaced by lightweight flexible 28 AWG cable ribbon to reduce weight and enhance flexibility. This prototype design was used to validate the concept and calibrate the accelerometers.

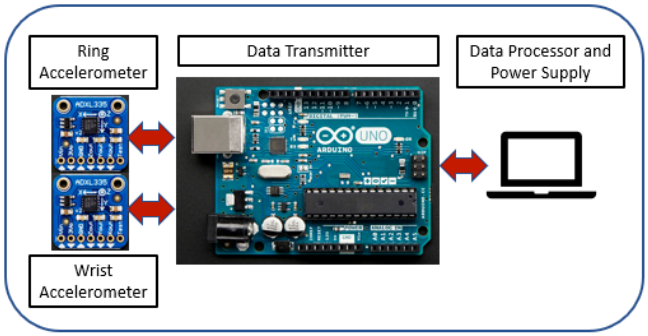

Figure 2. Simple block diagram of the prototype sensor design

The initial prototype design was found to be too bulky for daily use. Thus, the design was improved by using wireless modules and lightweight boards (Figure 3). The improved sensor design consisted of a wristband transmitter and a signal receiver. The wristband transmitter was a wearable physiological tremor detection device which included two accelerometers, a poly-Lithium battery, an Adafruit Feather board and a signal transceiver. On the other side, the signal receiver included an Arduino UNO board and another signal transceiver. Powered by a lightweight 3V poly-Lithium battery, the wearable physiological tremor detection device was able to obtain 3-

axis accelerometer signals and transmit to the receiver wirelessly with an 80-meter communication range (in ideal conditions).

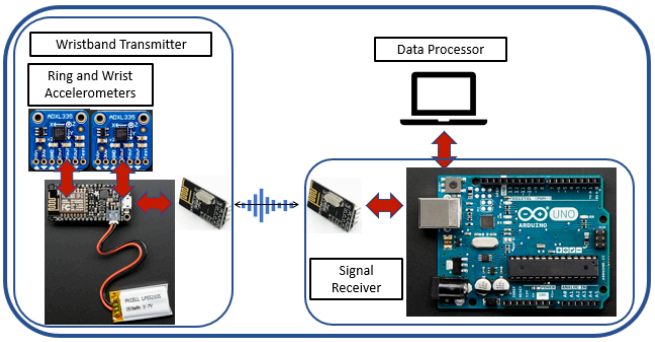

Figure 3. Simple block diagram of the improved sensor design

Accelerometer Calibration

ADXL 335 is a small, thin and low-power 3-axial micro electro mechanical system (MEMS) accelerometer, with a minimum full-scale range of ±3 g. It outputs 3 voltage signals whose amplitudes are proportional to acceleration. Arduino IDE install was used to collect the 3 axial accelerometer voltage outputs. The initial prototype design had a sampling frequency of 500 Hz while the improved sensor design had a sampling frequency of 100 Hz. The computer received the signals in packages (Table 2) that included the package number (column 1 in Table 2) and 6 channels voltage outputs (column 2-7 in Table 2) from two accelerometers. The package number served as the timestamp and showed any loss of packages due to signal disturbance.

Table 2. Sampel raw voltage outputs from two accelerometers

Package number	hand x-axis (mV)	hand y-axis (mV)	hand z-axis (mV)	wrist x-axis (mV)	wrist y-axis (mV)	wrist z-axis (mV)
1	457	511	580	411	496	460
2	457	551	581	412	496	461
3	472	538	603	415	493	464
4	464	547	582	406	501	469
5	457	558	582	413	495	465

Both hand and wrist accelerometers were calibrated by corresponding the accelerometer voltage outputs with different static inclination conditions. The calibration curve was formulated as the linear regression of raw signals at +g, -g and 0g. The hand accelerometer calibration curves with the equations for each axis are shown in Figure 4.

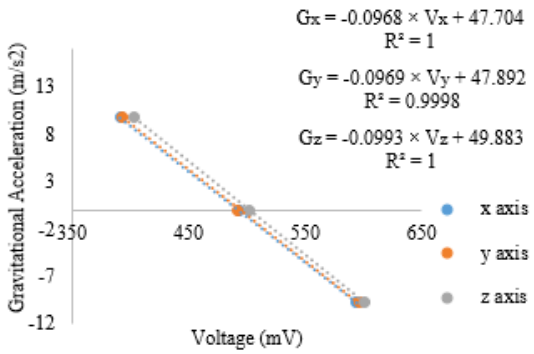

Figure 4. Hand accelerometer calibration curves

Pilot Data

A pilot study of physiological tremor detection was conducted to visualize the raw voltage outputs from the improved sensor design. One pilot participant was recruited and was instructed to extend his shoulder with elbow and wrist straight until the arm was perpendicular to the upper body in the sagittal plane. Two accelerometers were worn on the wrist and the terminal phalanx of the index finger. During the task, the physiological tremor amplitude of both hand (3 channels) and wrist (3 channels) increased (Figure 5 right) compared to the resting condition (Figure 5 left).

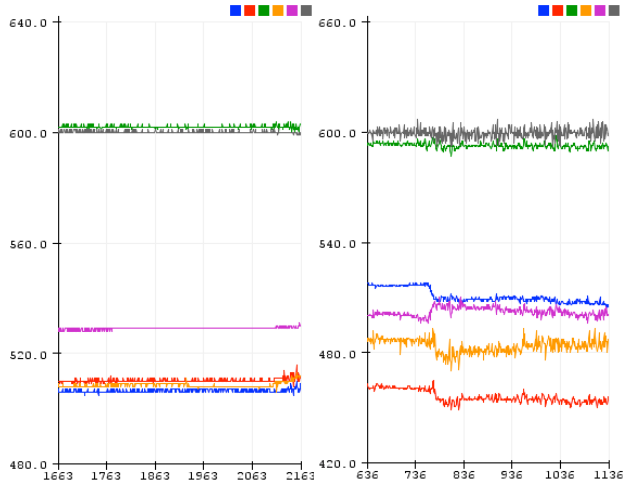

Figure 5. Accelerometers voltage outputs at resting (left) condition and shoulder extension condition (right)

PLANNED VALIDATION PROCESS

Sensor Validation

The improved sensor design must be validated in the physiological tremor frequency domain, which is from 10 to 16 Hz. To do this, a bipolar stepper motor (NEMA 17), will be used to generate desired frequencies. To transform the oscillating motion to linear vibration, the stepper motor will be mounted with a T8-350 mm lead screw, 2 pillow bearing blocks, a coupling nut, and a coupling shaft.

The vibration frequency of stepper motor will be set to 10, 12, 14 and 16 Hz using an Arduino UNO board. Accel-

erometers of the sensor will be attached to the coupling nut and the voltage outputs will be collected (Figure 6). On the other hand, a validated tri-axial piezoelectric accelerometer sensor, will be attached to the coupling nut (Figure 6). To validate the sensor in the physiological tremor frequencies, the signals from the piezoelectric will be compared with the sensor outputs using power spectral density function. The calculated coherence factor will be used to evaluate whether the ADXL 335 is suitable for measuring physiological tremor. (Bhattacharya, 2012)

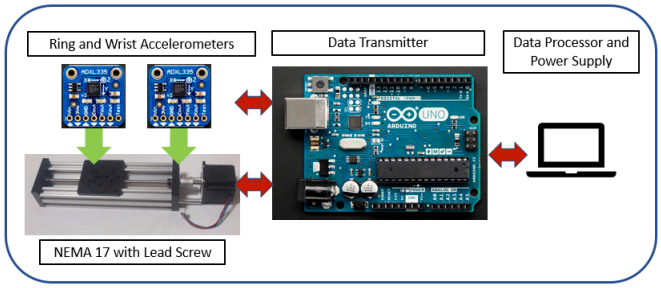

Figure 6. Simple block diagram of the sensor validation system using NEMA 17 stepper motor

Future validation efforts include testing the prototype with physiological tremors in the non-clinical (user-centered testing) and clinical settings (hypoglycemic clamp) to refine the data processing algorithm.

Work-in-Progress: User-Centered Testing

Participants. 60 participants of varying age groups and health conditions (Table 3) will be recruited to participate in a lab study. The participants need to be cognitively intact and able to follow directions and demonstrate learning capability. Participants with cardiovascular diseases, metabolic conditions, or muscular pain or injuries that interfere with hand outstretching tests will be excluded.

Table 3. Participants age groups and health conditions

Age Groups	Healthy	Type-1 Diabetic
18-30 yrs	10	10
45-60 yrs	10	10
70+ yrs	10	10

Data Collection and Analysis. Participants will start by completing the informed consent form, demographic information survey, and will provide their health history. Anthropometric measurements will also be taken.

Before exposure to the prototype, participants will complete a short interview to understand their unbiased preferences and acceptability of a wearable technology to help them with their hypoglycemia conditions. Participants will then be asked to wear the sensor on their dominant hand using nylon hook and loop strap throughout the study. Participants are then asked to participate in series of structured (perform everyday tasks such as eating, writing, typing, driving using a simulator, etc.) and unstructured (free-from exploring) tasks in order to inform a taxonomy of user requirements for such a device. A post-test interview will be conducted to extract important considerations for sensor interface, wearability, and interference with daily habits. The usability test will take around 30 minutes to complete.

After a short break, participants will be asked to participate in a second lab experiment for prototype validation. First, a hand outstretching test will be performed in the following conditions (Figure 7). In the resting condition, participant's forearm will be fully supported to the wrist with the hand and fingers relaxed such that there is no voluntary muscle activity in the forearm and hand (rest tremor) condition; for posture condition, the participant's hand will be stretched forwards from the wrist. In the loaded posture condition, posture tremor will be measured when subjects are either holding some weights in their hand or writing.

At the start of the experiment, participants will be seated in a specific posture and will be asked to perform the hand outstretching tasks in three conditions. Measurements in each posture will be made for one minute on each hand. Adequate resting time will be provided so that the results won't be affected by muscle fatigue. The presentation of these conditions will be randomized. Each participant need to complete five tasks.

Shortly after the Hand Outstretching Task, each participant will be asked to perform three trials of handgrip task with their maximum voluntary contraction (MVC) using grip dynamometers. Upon adequate rest, participants will be encouraged by the experimenter to maintain 30% MVC through repetitions of exertion (15 seconds) and rest (5 seconds) trial towards hand muscle fatigue. Once the hand muscle of the participant is exhausted (fatigue), he will be asked to perform 1 trial of MVC (post-MVC).

Shortly after the post-MVC, the Hand Outstretching Task in rest, posture, and loaded posture conditions will be conducted again. The collected physiological tremor signal will be filtered to remove noises and analyzed to correctly identify to the vibration frequency of physiological tremor.

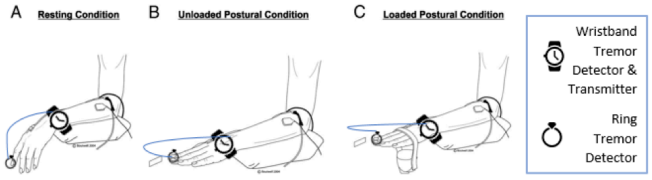

Figure 7. Resting condition (left), unloaded (middle) and loaded Posture condition (right)

Future Work: Clinical Testing and Hypoglycemia Detection Algorithm

A clinical testing, through a hypoglycemic clamp experiment, of the improved sensor design will take place in Hamad General Hospital in Qatar. 20 healthy, 20 type 1 and 20 type 2 diabetic participants will be recruited for the study. The hypoglycemic tremor signals will be collected by the sensors worn on both hands of each participant. The collected signal will be used to develop the hypoglycemia detection algorithm.

CONCLUSION

Our research aims at investigating the efficacy of a CGM-alternative technology to detect hypoglycemic events using high-precision hand tremor detection. This paper provided a brief overview of the initial phases of the design and development of a proof-of-concept. The prototype hypoglycemia detection sensor design has been improved to be wireless, lightweight and wearable. Work is in progress to improve the sensor using a user-centered approach and both machine simulated tremor and human-subject physiological tremor validation. Future work involves collection of hypoglycemic tremor data from the clinical test to inform the design of hypoglycemia detection algorithms.

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