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Device for Noninvasive Optical Measurement of Blood Glucose Level Based on Discrete Fourier Transform and Fast Artificial Neural Network

A prototype noninvasive blood glucose level measurement optical device (NI-BGL-MOD) has been developed. The NI-BGL-MOD uses a discrete Fourier transform (DFT) method and a fast artificial neural network (FANN) algorithm to optimize device performance. The appropriate light-emitting diode (LED) for the sensory module was selected based on near-infrared spectrophotometry of a blood glucose model and human blood. DFT is implemented in an analog-to-digital converter (ADC) module. An in vitro trial using the blood glucose model along with a clinical trial involving 110 participants were conducted to evaluate the performance of the prototype. The root-mean-square error (RMSE) of the prototype was 10.8 mg/dl in the in vitro trial and 3.64 mg/dl in the clinical trial, which is lower than the ISO-15197:2016 mandated value of 10 mg/dl. In each trial, consensus error grid analysis (EGA) indicated that the measurement error was within the safe range. The sensitivity and specificity of the prototype were 0.83 (0.36, 1.00) and 0.90 (0.55, 1.00) in the in vitro trial and 0.81 (0.75, 0.85) and 0.83 (0.78, 0.87) in the clinical trial, respectively. In general, the proposed NI-BGL-MOD demonstrated adequate performance compared to gold-standard measurement. [DOI: 10.1115/1.4044336]

Keywords: noninvasive blood glucose measurement, optical device, discrete Fourier transform, multiformulatric regression, fast artificial neural network

Introduction

Blood glucose measurements are critical for monitoring glycemic status as a part of health management, patient management, and the diagnosis of metabolic disorders such as diabetes [1]. Blood glucose measurements are important for individuals who have already been diagnosed with glucose-related metabolic disorders or are at risk from similar disorders [2].

The number of people with diabetes grew from 108×10^6 adults in 1980 to 422×10^6 adults in 2014 and continues to increase [3]. Half of these people do not know that they had diabetes [4], and complications arising from diabetes caused 1.5×10^6 deaths in 2012. As a precursor to diabetes, higher-than-optimal blood glucose has caused additional 2.2×10^6 deaths in 2012 [3]. Worldwide, the health burdens related to diabetes include loss of vision, end-stage renal disease, cardiovascular events, and risk of lower extremity amputations. In 2014, the estimated average

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health expenditure per person with diabetes was between 1583 USD and 2842 USD worldwide, and the estimated annual global health expenditure attributable to diabetes is between 612×10^9 USD and 1099×10^9 USD [5].

Several conventional measurement methods are available for the determination of blood glucose. These methods typically involve some form of blood drawing or phlebotomy using finger prick [6] or venipuncture methods [7]. Conventional methods for measuring blood glucose include methods based on glucose oxidase [8], hexokinase [9], immobilized enzyme reaction, photoenzymes, and electrochemical biosensors. Conventional devices for blood glucose measurement include glucose meters [10], automated chemical analyzers, blood gas analyzers, and continuous glucose monitoring systems.

Procedures for blood drawing are accompanied by unacceptable levels of risk. Blood drawing can result in physical and psychological trauma to the patient. Human blood itself is a potent vector for various viruses, bacteria, and diseases, including human immunodeficiency virus, hepatitis B and C viruses, human T-lymphotropic virus, parvovirus B19, herpes simplex virus, bacterial agents, *Mycobacterium tuberculosis*, H5N1, rabies, severe acute respiratory syndrome, and *Escherichia coli*. Furthermore, the blood drawing procedure can be relatively complicated [11]. For patients with glycemic disorders, the cost of blood glucose measurements may amount to a fourth of their total healthcare expenditures. The greatest expenditure of most patients is on glucose strips [12], which account for 85% of the biosensor market worldwide [13].

For the aforementioned reasons, researchers are interested in developing noninvasive methods for blood glucose measurement. The most common noninvasive methods involve optical or spectrophotometric measurement [14], in which the conventional needle is replaced with light to penetrate the skin without damaging the body. Spectrophotometric methods virtually eliminate any need for drawing blood. Several types of spectrophotometry exist, including absorbance, Raman, midinfrared, ocular, optical coherence tomography [15], amplitude-modulated ultrasound [16], dielectric, impedance, laser reflectance spectral pattern, near-infrared [17], and occlusion [18] spectroscopy. Presently, four groups of wavelengths have been applied for the spectrophotometric determination of blood glucose level (BGL): visual (350–1200 nm) [19], near-infrared (800–2500 nm) [20], midinfrared (5714–10,000 nm) [21], and Raman (532–1200 nm) [22]. Several trademarks have been filed based on these methods, including Pendra (Pendragon Medical Ltd., Zurich, Switzerland), GlucoTrack (Integrity Applications Ltd., Israel), OrSense (OrSense Ltd., Israel), GlucoWatch (Cygnus Inc.), Symphony (Sontra Medical Corporation), and Diasensor (Biocontrol Technology, Inc.) [15], and measurement performance in clinical trials has been reported for a few.

Discrete Fourier transform (DFT), which is widely used in signal processing [23], could be used to improve the performances of spectrophotometric methods. Fast Fourier transform in the west (FFTW; FFTW.org) is a prominent provider of DFT services.

The goal of this study was to develop a DFT-based noninvasive BGL measurement optical device (NI-BGL-MOD). A multiformulatric regression (MFR) or fast artificial neural network (FANN) algorithm was used to interpret the DFT output, allowing accurate BGL measurement using the prototype NI-BGL-NOD. The prototype performance in fasting and preconditioned participants was compared with that of an invasive method based on venipuncture spectrophotometry.

Materials and Methods

This study was conducted in four phases. First, a BGL model was assessed spectrophotometrically to select an appropriate light-emitting diode (LED) for the NI-BGL-MOD. in vitro and clinical trials of the prototype have been summarized as follows.

Spectrophotometric Assessment of Blood Glucose Level Model. Dextrose anhydrous/pure glucose (HiMedia Laboratories, India), doubly distilled water, solutions of glucose in water with five different concentrations, and a human blood sample from one healthy adult male were analyzed using a Büchi spectrophotometer (BÜCHI Labortechnik AG, Switzerland). The human blood sample was taken at fasting and 30-min-postprandial conditions after the patient consumed 75 g of glucose solution in 200 ml water. The resultant spectral data were compared to obtain windows for detecting BGL. All measurements were done in triplicate. R (the R Foundation), RKward (KDE e.V., Germany), and Rstudio (RStudio, Inc., Boston, MA) were used for data analysis. The results were compared with data in the Thorlabs LED and photo-diode database (Thorlabs, Inc., Newton, NJ).

Noninvasive Blood Glucose Level Measurement Optical Device Development, Design, and Consideration. The noninvasive BGL optical measurement device was developed according to both the Scrum [24] and simplified Pressman standards [25]. The design considerations and limitations are reported alongside the proposed design.

Several aspects of human BGL metabolism were considered when designing the NI-BGL-MOD. Chronic and long-term higher-than-normal BGL is known to put people at risk of cardiovascular disease [26]. Blood glucose and other compounds in blood have different and specific wavelength responses; thus, the prototype device for detecting BGL was designed with a modular architecture.

The simplified von Neumann architecture was used as the basis for the device design [27]. The prototype consists of five modules (Fig. 1), sensor/probe module, central processing unit (CPU) module, analog-to-digital converter (ADC) module, repository module, and transmission module. The first one is a sensor/probe module that holds the LEDs and photo-diodes (Thorlabs, Inc., Newton, NJ) in a 3D printed case and is connected to a CPU (Raspberry Pi 3; Raspberry Pi Foundation, UK) module via jumper wires. An (ADC; MCP 3424, Microchip Technology Inc.) module is also present housing the components necessary for probe control and data communication. The repository module was built using SQLite (Hwaci, Charlotte, NC), and the software was developed using the Qt software development kit (the Qt Company, Finland).

The probe (Fig. 2(*a*)) houses LED and photo-diode pairs, which serve as the primary interface with each finger. The probe was

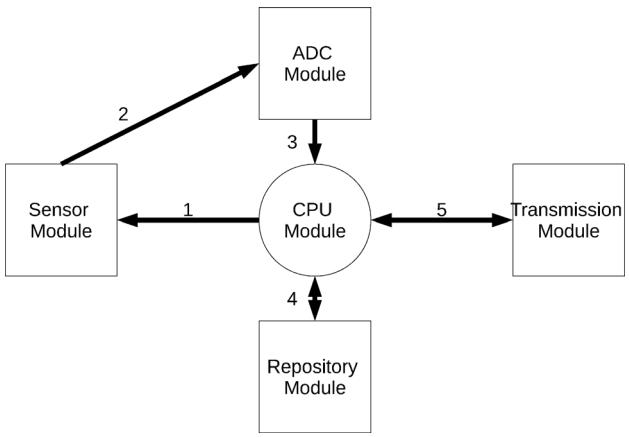

Fig. 1 Schematic showing how the noninvasive blood glucose level measurement device works: (1) The CPU module sends the read instruction to the sensor module, (2) The sensor module sends the sensor response to the ADC module as voltage differential, (3) The ADC module converts the voltage differential to integer values and sends them to the CPU module, (4) The CPU module stores the integer list in the repository module, and (5) The CPU module sends the integer list to the transmission module (in this case, a monitor)

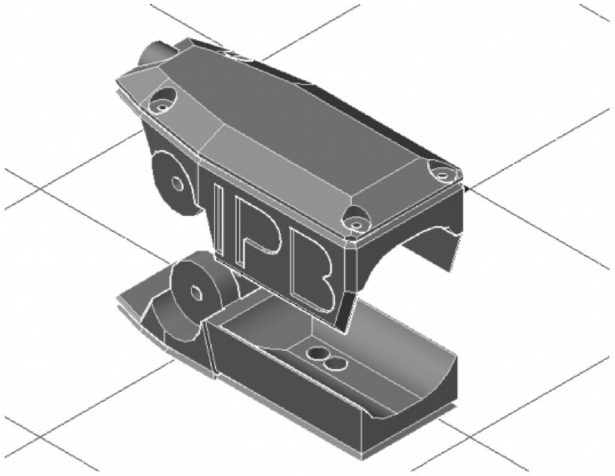

Fig. 2 Images showing the (*a*) probe design and (*b*) testing interface used in the optical noninvasive blood glucose level (BGL) measurement device. The upper and lower parts of (*b*) show the DFT real values and the actual sensor responses, respectively. The lines are a juxtaposition of four LED conditions: all LEDs OFF, 1550-nm LED ON, 1600-nm LED ON, and both LEDs ON, wherein each consists of ten quantized intensity periods.

designed for the distal part (outermost point) of the left hand, digitus secundus manus (pointing finger), digitus medius (middle finger), and digitus annularis (ring finger). The probe has a clamshell shape to prevent the leakage of light from the outside or inside of the measurement site. The LEDs and photo-diodes are arranged in the shape of the letter *Y*.

The LEDs are controlled with using three general-purpose input/output pins of the Raspberry Pi (Wiring Pi). GPIO1 is the source of pulse-width modulation [28], and GPIO28 and GPIO29 serve as the LED grounds. The LEDs generates light that passes through the user's distal phalanx. The phalanx absorbs part of the light, and the photo-diode detects the remainder of the light and converts the light intensity into a voltage differential. The residual light was approximately 10% of the incoming LED intensity; thus, the residual light needs to be amplified using an operational amplifier. The voltage differential values are converted to 13-bit values by the ADC.

Binary-like methods for LED modulation are used to identify sensor delay and different responses for increased or decreased intensity. Both zero and nonzero blocks are used to guarantee the lack of interference between them. The intensity in the interval is modulated with a gradual increase in peak intensity, and each section is named as a period (Fig. 3).

Fast Fourier transform in the west is implemented to widen the spectral intensity data using the non-normalized one rank form of DFT [29]. This procedure yields real, absolute, imaginary, and

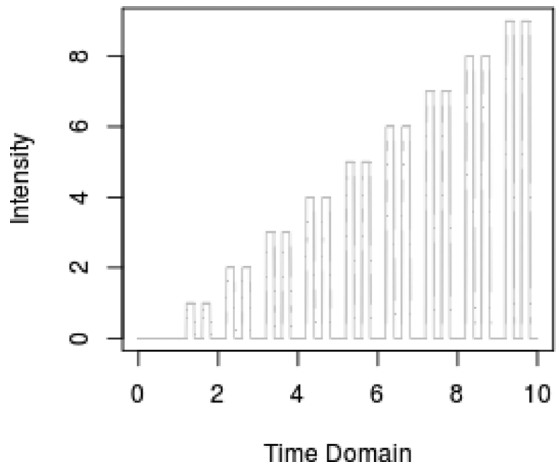

Fig. 3 Binary-like model showing how the LEDs are controlled (solid line). The sensor always responds slightly later than the LED, and there may be some delay in the reported voltage (dotted line). Ladder illustrating how periods are separated and how the maximum LED intensity is gradually increased.

argumentative components of a complex value, standard, or integrated form. Mean, maximum, minimum, interval, and standard of deviation in real or cleaned (<4 standard deviations) form are used as the characteristics for each period from one base data. Pearson correlation was conducted using ALGLIB (ALGLIB Project, Russian Federation) to determine optimal parameter combinations. The inference engine was built based on FANN.

Fast artificial neural network works by learning the pattern between the input parameters provided by the FFTW output and the real BGL values provided by gold-standard measurements. This entire process is formally termed pattern recognition.

Sensor modules house LEDs' pulse-width modulation [28] controller, photo-diode, and MCP 3424 controller to control the LED intensity and duration. The ADC module was handling all procedures related to DFT calculation. The CPU module houses the interfaces and calls between each module. The repository module houses classes related to SQLite database manipulation. The transmission or transducer module (Fig. 2(*b*)) consists of control classes for displaying spectral data. The spectral diagrams were rendered using QCustomPlot (QCustomPlot, Germany).

The database model has designed in fourth-normal form. A testing interface was created using QtWidgets. This interface is only for testing use and will be replaced by BGL measurement numbers during production.

In Vitro Preclinical Trial. An experimental study was conducted to evaluate the performance of the NI-BGL-MOD prototype. The relation between the absorbance of solutions of pure glucose/anhydrous dextrose in doubly distilled water and the response of the photo-diodes to residual light through the solutions was analyzed. Seven glucose solutions were made with glucose concentrations ranging from 70 to 190 mg/dl in increments of 20 mg/dl. The LED and photo-diode pairs were chosen based on the results of the spectrophotometric assessment. HiMedia (HiMedia Laboratories, Mumbai, India) provided the pure glucose for this experiment.

A solution of 2 ml glucose in water was placed in a cuvette using a pipettor (Dragon Laboratory Instruments, China). The residual light intensity was measured in triplicate using each LED/photo-diode pair with a different sample batch for each replicate measurement. MFR (Zunzunsite), consensus error grid analysis (EGA) [30,31], and sensitivity and specificity analysis [32] were conducted to evaluate the performance of the prototype. We have used the glucose concentration median as the sensitivity and specificity threshold in this study. ALGLIB, Zunzunsite, R (the R

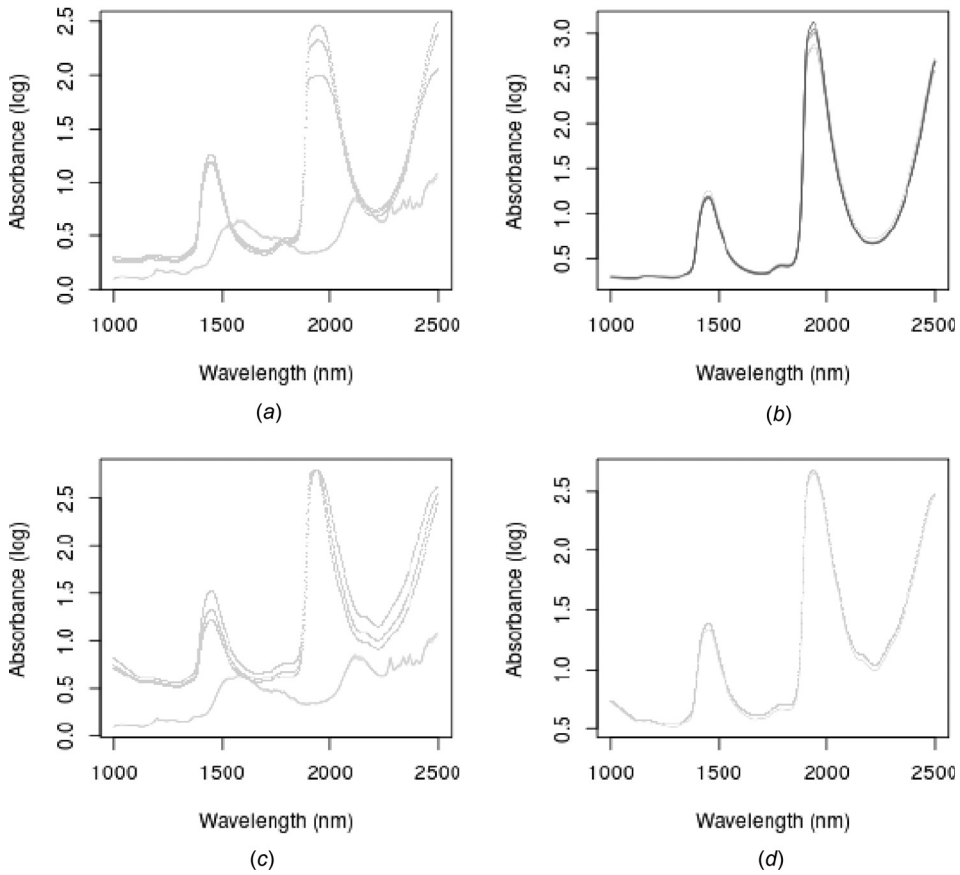

Fig. 4 Absorbance spectra of (*a*) pure water (dotted line) and pure glucose (solid line) and (*b*) pure water (blue) and different concentrations of glucose in water: 51.3 mg/dl (lightest line), 102 mg/dl (lightest dotted line), 205 mg/dl (medium gray line), 499.5 mg/dl (medium gray dotted line), and 1002.9 mg/dl (darkest line). The lines are aggregates of three replicates. Absorbance spectra of (*c*) human blood (dotted line) and pure glucose (line) and (*d*) human fasting blood (dotted line) and 30-min postprandial blood (line).

Foundation), RKward (KDE e.V., Germany), Rstudio (RStudio, Inc.), EGA [30,31], and epiR (epiR, Australia) were utilized for statistical analyses.

In Vivo Clinical Trial. A clinical trial protocol was designed and registered in the database of *Komisi Etik Penelitian Kesehatan*, *Badan Litbang Kesehatan*, *Kementerian Kesehatan Negara Kesatuan Republik Indonesia* (Health Research Ethical Committee, National Institute of Health Research and Development, Indonesian Ministry of Health; no LB.02.01/5.2/KE.493/2016). Ethical clearance approval was obtained. *Komisi Etik Penelitian Kesehatan* retains full access to the details of the trial protocol.

Using the equation of Juneja and Sharma [33], we determined the minimum sample size to be 120 participants. The participants were purposely selected to participate in this trial, and the inclusion criteria were as follows: $\geq$17 years of age, good health, no recent smoke or alcohol intake within three months, and no pregnancy. A queue guide was assigned to supervise the participant queue, which was handled in a first-in/first-out fashion. One enumerator supervised each measurement device and the front door, and two representatives from Prodia (PT Prodia Utama, Indonesia) handled the entire venipuncture process. Each participant was informed of only his or her results. The venipuncture results were delivered to each participant the day after the measurement was completed. Participant profiles and measurement results were stored in a secure database available only for this research. Due to the very different natures of the prototype and venipuncture measurements, participants, enumerators, and health practitioners were informed about the clinical trial details before the trial.

We have stored the resultant data as data pairs between the device's raw outputs and venipuncture measurement results, and split the data pairs equally and purposively into training and testing data. FANN testing and evaluation was concurrently performed per epoch as opposed to subsequentially, and this training method acted as an overtraining caution system. The measurement performance was evaluated based on root-mean-square error (RMSE), which was compared to the ISO 15197:2016 standard. EGA was conducted using the Schmolze method [34]. Sensitivity and specificity were calculated using the Stevenson method (epiR, Australia). We have used the venipuncture concentration median as the sensitivity and specificity threshold here. R (the R Foundation) with both RKward (KDE e.V., Germany) and Rstudio (RStudio, Inc.) were used for statistical analyses. This clinical trial report was written according to the Consort Standard [35].

Results

Spectrophotometric Assessment of Blood Glucose Level Model. The wavelength in the range of 1550–1700 nm has the potential to be used for spectrophotometric BGL measurement, indicated by high water absorbance. Water absorbance occurs at 1400–1550 nm, 1800–2100 nm, and above 2300 nm (Fig. 4).

In Vitro Preclinical Trial Results. The EGA scores of the prototype were 93.75% A and 6.25% B for Clarke grid analysis and 100% A for Parkes grid analysis. The prototype achieved high sensitivity and specificity (Table 1 and Fig. 5(*a*)).

Table 1 Comparison of prototype performances during in vitro and clinical trial evaluations

Characteristic	In vitro values	Clinical trial values	Peers
Apparent prevalence	0.38 (0.15, 0.65)	0.47 (0.43, 0.52)	
True prevalence	0.38 (0.15, 0.65)	0.47 (0.43, 0.52)	
Accuracy	10.8 mg/dl	3.64 mg/dl	
			12.0 mg/dl [36], 11.0 mg/dl [37], 6.4 mg/dl [38], 1.0 mg/dl [37]
Sensitivity	0.83 (0.36, 1.00)	0.81 (0.75, 0.85)	
			0.52 mg/dl [39], 0.56 mg/dl [40], 0.77 mg/dl [41], 0.78 mg/dl [42], 0.82 mg/dl [43], 0.95 mg/dl [44], 0.98 mg/dl [45]
Specificity	0.90 (0.55, 1.00)	0.83 (0.78, 0.87)	
			0.85 mg/dl [39], 0.88 mg/dl [43], 0.90 mg/dl [45], 0.93 mg/dl [42] 0.96 mg/dl [40], 0.96 mg/dl [41], 0.96 mg/dl [44]
Diagnostic accuracy	0.88 (0.62, 0.98)	0.82 (0.78, 0.85)	
Number needed to diagnose	1.36 (0.00, 1.00)	1.57 (1.38, 1.87)	

In Vivo Clinical Trial Results. A gold-standard controlled trial was conducted. Although 120 participants were enrolled, two deviations in protocol resulted in the analysis of data from 110 participants. First, two participants did not disclose their email addresses, preventing indexing with the survey system. Second, the data of eight participants were omitted as outliers (BGL outside the range of three times the standard deviation). The average body mass index of the participants was $21.6 \pm 3.28\,kg/m^2$, and the average BGL based on the venipuncture method was 79.1 ± 6.40 mg/dl.

The RMSE of the prototype was 3.64 mg/dl. Both the Clarke and Parker EGA scores of the prototype were 100% class A. The sensitivity and specificity of the prototype were 0.81 (0.75, 0.85) and 0.83 (0.78, 0.87), respectively (Table 1 and Fig. 5(*b*)). No severe adverse effects were observed in the participants. However, one participant was afraid and showed signs of short-term stress resulting from the measurements.

Discussion

Spectrophotometric Assessment of Blood Glucose Level Model. The wavelength range determined for measuring BGL agrees with the reports of Lawand et al. [20], Goodarzi et al. [46], and Ryckeboer et al. [47]. The glucose model does not account for other materials in blood such as fat, proteins, cells, skin, and skeleton components, which may interfere with the measurement results because they do not change at a rapid rate; therefore, their value remains constant. Trans-reflectance was measured rather than absorbance; thus, the values in Fig. 4 are calculated values. We plan to verify the results using standardized blood-glucose calibration-control-sample, such as Lypocheck (Bio-Rad Laboratories, Inc.).

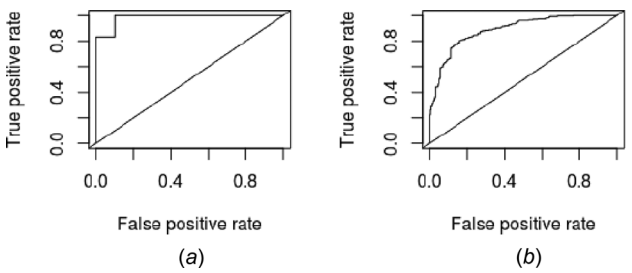

Fig. 5 Curves showing the operating characteristics of the receiver in the noninvasive BGL measurement device during the (*a*) in vitro evaluation and (*b*) clinical trial

However, the reason for the absorbance of human adult male postprandial blood decreasing rather than increasing in comparison with the result from glucose in water concentration is still unknown. We assume this may be related to hematocrit and hydration status, which have not been measured. The human subjects were in a dehydrated state (because of fasting), and the difference in pre- and postprandial blood water levels might have a minimal effect on the spectrophotometer reading. Future studies should consider the hematocrit and hydration status.

Design Limitations of the Noninvasive Blood Glucose Level Measurement Optical Device. The prototype design has several technical limitations. The blood glucose metabolism mathematical model was borrowed from the works of Lopes and de Toledo Fleury [48]. The same finger position used by finger prick and glucose meter methods was used in the prototype [10]. The modulation methods of Chowdhury et al. inspired the prototype [14]. Intensity-based modulation and DFT widening were used to improve the accuracy of the prototype, as described in our previous publication [49].

At the time of development, sufficient information regarding the proper light intensity and light modulation for BGL measurement was not available. Thus, a binary-like ladder model was used. By design, the prototype measured blood glucose as well as all other glucose accumulation inside the finger.

The prototype needed to cover all possible discrete values between 0 and 500.0 mg/dl. The ADC converted the sensor values to 13 bit (8192 discrete numbers). The ADC was limited to 60 samplings per second, which is the main limitation of the prototype design.

In Vitro Preclinical Trial. Based on the test results, usage of more than two nodes of input was not redundant. Pairing the outputs of a 1600-nm LED and a 1050-nm LED yields the best results, although the difference of Pearson correlation with 1550-nm LED instead of the 1050-nm LED is not significant.

The RMSE of the prototype (10.8 mg/dl) was slightly higher than the ISO 15197:2016 standard (10.0 mg/dl) [50], indicating that a noninvasive blood glucose measurement system is feasible. All prototype results were within zones A and B of both Clarke and Parkes EGA, indicating no expected adverse clinical consequences [30,31]. The device sensitivity (0.83) and specificity (0.90) were well above the expected values based on McLaughlin et al. [39] and dan Bennett et al. [40] (0.52 and 0.85, respectively).

This study focused on the typical BGL range of 50–200 mg/dl. Testing in the range of 200–500 mg/dl still needs to be completed. Additionally, this study did not consider the prototype's responses to other components of the human body, including proteins, skeletal components, skin, and cells. These factors will be considered in future research using calibration control samples (Bio-Rad Laboratories, Inc.).

In Vivo Clinical Trial. The results of the clinical trial raised some interesting points of discussion. No severe adverse effects of the prototype on the users were found. Only a small range of BGLs (50–100 mg/dl) were measured in the clinical trial. Thus, the prototype still needs to be tested in the BGL range of 100–500 mg/dl. Stress testing in the postprandial BGL range of 100–200 mg/dl is also needed.

Furthermore, in this trial, the venipuncture BGL was not cross-checked with a portable glucose meter, preventing us from confirming the accuracy of the venipuncture results. The prototype system relies on pattern recognition; thus, the multiplicity of analysis or interpretation of data was inevitable. This raw data set is due for revisitation during further analysis. The results indicated that the prototype method can be implemented in the BGL range of 50–100 mg/dl for both sexes of all ages.

The RMSE of the prototype in the clinical trial was 3.64 mg/dl, lower than ISO 15197:2016 mandated value (10 mg/dl). The obtained RMSE is comparable to those reported for several invasive glucose meters, including AccuChek Inform (11 mg/dl) [37], AccuChek Inform II (12 mg/dl) [36], Platinum (6.4 mg/dl) [38], and Nova StatStrip (1 mg/dl) [37]. The accuracy of the prototype indicates that it can be used for noninvasive BGL measurement. In both Clarke and Parker EGA, 100% of the prototype results were classified as zone A [30,31], indicating no expected adverse clinical consequences. These EGA results are superior to those reported by Bailey et al. [38], Sobel et al. [51], Laffel [52], and Thabit et al. [53]. The prototype sensitivity of 0.81 (0.75, 0.85) was better than those reported by McLaughlin et al. [39], Bennett et al. [40], Bhavadharini et al. [42], and Wang et al. [41]. The prototype specificity of 0.83 (0.78, 0.87) was worse than those reported by Prabhudesai et al. [45], DuBois et al. [44], and Uemura et al. [43].

The RMSE of the prototype in the clinical trial (3.64 mg/dl) was much lower than the RMSE obtained in the in vitro trial (10.8 mg/dl). This difference is primarily attributed to the much larger training data size and the usage of FANN as opposed to MFR.

Currently, only 13 clinical trials of noninvasive methods for measuring BGL are available in the Clinical Trial Database (National Library of Medicine Bethesda, MD). Lamberg (NCT01508065) and Nimri (NCT01247649) conducted the most representative clinical trials but did not publish desirable results. To the best of our knowledge, this is the first report of the implementation of DFT in an optical and noninvasive BGL measurement device.

Conclusion

We developed a prototype NI-BGL-MOD based on DFT and FANN. The prototype NI-BGL-MOD showed adequate performance in both an in vitro experiment and a clinical trial for predetermined ranges of BGL. In future works, the prototype will be reevaluated in larger scale clinical trials than the one conducted herein with a wider range of BGL. We have also confirmed several wavelengths for BGL measurement based on blood sample FTIR characterization. The wavelengths are to be reevaluated when the blood control sample characterization result is available. Several technical limitations with the prototype NI-BGL-MOD are to be addressed in further design iterations.

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Nomenclature

ADC = analog-to-digital converter
BGL = blood glucose level
DFT = discrete Fourier transform (a variant of Fast Fourier transform)
EGA = error grid analysis
FANN = fast artificial neural network
FFTW = fast Fourier transform in the west
LED = light-emitting diode
NI-BGL-MOD = noninvasive optical blood glucose level measurement device
Prototype = prototype NI-BGL-MOD
RMSE = root-mean-square error

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