An Infrared Non-Invasive System for Measuring Blood Glucose: A Primary Study using Serum Samples

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ABSTRACT

Background: Diabetes is a global concern, with an estimated 2 million individuals expected to be affected by the condition by 2024. Non-invasive glucose monitoring devices can greatly enhance patient care and management.

Objective: This study aimed to develop an instrument capable of non-invasively measuring blood glucose levels using an infrared transmitter and receiver, with data processing performed by a dedicated processor.

Material and Methods: This analytical study develops a glucometer that incorporates a power supply, a light source, a light detector, a sampler, and signal processing components to enable non-invasive glucose measurements. The instrument was calibrated using sugar solution samples with known glucose concentrations. It was then tested using serum samples from diabetic patients with accuracy, which was evaluated using Clarke's grid analysis.

Results: Testing of the designed glucometer revealed that 83% of the serum samples fell within zone A of Clarke's grid analysis, indicating high accuracy. The remaining 17% of samples were classified in zone B, with no samples falling in zones C, D, or E.

Conclusion: The developed glucometer demonstrated higher accuracy in measuring glucose concentrations above 200 mg/dl. Despite the use of serum samples in this experiment, 83% of the results were located in zone A leads to the capability of non-invasively measuring blood glucose levels. Further studies are required to validate the device's accuracy in a larger population and assess its utility in clinical practice.

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Keyword

Blood Glucose; Blood Glucose Self-Monitoring; Continuous Glucose Monitoring; Diabetes; Glucometer; Non-Invasive Blood Glucose Measurement

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Introduction

Diabetes, a disorder of the endocrine system characterized by abnormally high blood sugar levels, is considered a prevalent and rapidly growing global disease. It is projected that by 2045, approximately 693 million individuals will be affected [1]. In the

United States, diabetes accounted for 24% of all healthcare expenditures, with a total economic cost of $327 billion in 2017 [2]. However, type 1 diabetes was believed to be a singular autoimmune disorder caused by a T-cell mediated attack on insulin-producing cells, it is known as a multifactorial disease influenced by various factors, such as the environment, microbiome, genome, metabolism, and immune systems, which are different between individual cases. Despite advancements in technology, optimal glycemic control remains a challenge for many individuals with type 1 diabetes. Additionally, access to modern therapies is limited for several patients due to the high costs associated with even basic care [3].

Type 2 diabetes occurs as a result of a relative insulin shortage caused by dysfunction in β cells and cellular insulin resistance [4]. The global increase in obesity, sedentary lifestyles, and an aging population have been identified as contributing factors to the rising prevalence of type 2 diabetes between 1980 and 2004 [5].

Intensive glucose management has benefits in reducing the risk of various microvascular complications, including retinopathy, nephropathy, and neuropathy [6-8]; however, these benefits necessitate careful control of blood glucose levels, which is done through the measurement of plasma glucose using venous samples or commercially available glucometers. Additionally, continuous glucose monitoring using needles can be unpleasant and inconvenient, particularly for young patients with type 1 diabetes. To address this issue, non-invasive glucometers have emerged as a potential solution to monitor blood glucose levels without the need for invasive procedures.

Non-invasive glucose monitoring systems have gained significant attention as alternatives to continuous glucometers to overcome invasive method limitations. Various non-invasive glucose monitoring techniques have been developed, including Optical Coherence Tomography (OCT) [9], Raman scattering [10], Mid-Infrared (MIR) [11], Near-Infrared (NIR) [11], and Impedance Spectroscopy methods. The MIR method utilizes light with a wavelength range of 2.5-50 micrometers to irradiate the material. The intensity of the light is measured after interacting with the material [11]. This method has been primarily used for measuring sugar levels in solutions outside the body (in vitro). However, it is limited to penetrating deep into the tissue, thus only measuring surface concentrations.

On the other hand, the NIR method employs a wavelength range of 0.7-1.4 micrometers to pass through the skin layers, including the stratum corneum, epidermis, and subcutaneous tissue. One challenge with this method is its sensitivity to tissue pressure and the requirement of fat tissue to travel a 5 mm path. Despite these challenges, 99.3% of the results have been successful in the clinically accepted Clark's A and B regions.

The dielectric capacity of the tissue is measured in the impedance spectroscopy method. A small alternating current is applied to the tissue, and the impedance of particles is measured [11]. Glucose is indirectly measured based on its interaction with red blood cells. This method provides valuable information about glucose levels in the vascular compartment. However, factors, such as temperature, perspiration, and movement can introduce errors in this method.

Yadav developed a wearable glucose monitoring system that analyzes gases in exhaled breath to measure glucose levels. Metal oxide gas sensors have shown promise in measuring glucose concentration, but challenges, such as poor selectivity, high operational temperature, and poor reliability have limited their use outside of laboratory settings [12,13]. Considering the available methods, a non-invasive method to measure blood glucose would be highly beneficial in diabetic patients, resulting in eliminating the need for frequent invasive procedures and providing a more convenient and comfortable monitoring solution.

Material and Methods

In this analytical study, the hardware of the developed glucometer comprises a power supply, a light source, a light detector, a sampler, and signal processing.

Power supply: The power supply of the circuit includes ±5 V analog and 3.3 V digital voltages. Linear and low-dropout (LDO) regulators and low-noise regulators were used to improve the stability of the power supply line and reduce noise. Additionally, the ground of digital and analog parts was separated by an inductor to reduce individually high-frequency noise. The negative generator can cause this circuit to generate all the required voltages with the +5 V voltage of the USB port. The schematic of the power supply is presented in Figure 1.

Light source: The light source in the system generates the specific wavelength of light to pass through the blood sample. The block diagram depicting the light source is illustrated in Figure 2. To achieve this, the microcontroller's Digital-to-Analog Converter (DAC) unit generates a pulse or sine wave with a frequency, adjusted as desired. The signal then goes through the regulator and offset unit before the transmit to an Infrared light-emitting diode (IR LED) with a wavelength of 950 nm. Prior to reaching the IR LED, the signal is filtered using a fourth-order low-pass filter with a cutoff frequency of 3 KHz.

Light detector: The light detector circuit measures the amount of light that passes through the sample, and several photodiodes with a 950-nanometer peak sensitivity wavelength were used to detect the light. After amplification and offset adjustment, the signal enters a fourth-order band pass filter layer. This signal is sent to the computer by a 16-bit analog-to-digital converter (ADC) with a sampling rate of 12 Mbps (Figure 3).

Signal Processing: The signal processing step involves the processing and analysis of

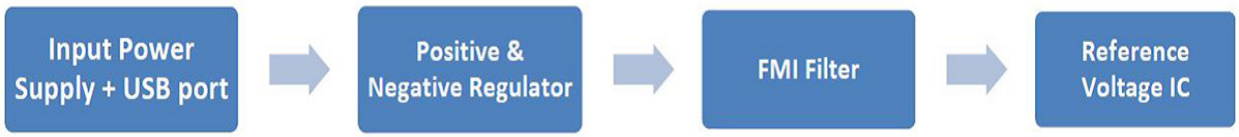

Figure 1: Block diagram of the power supply circuit of the designed non-invasive blood glucometer.

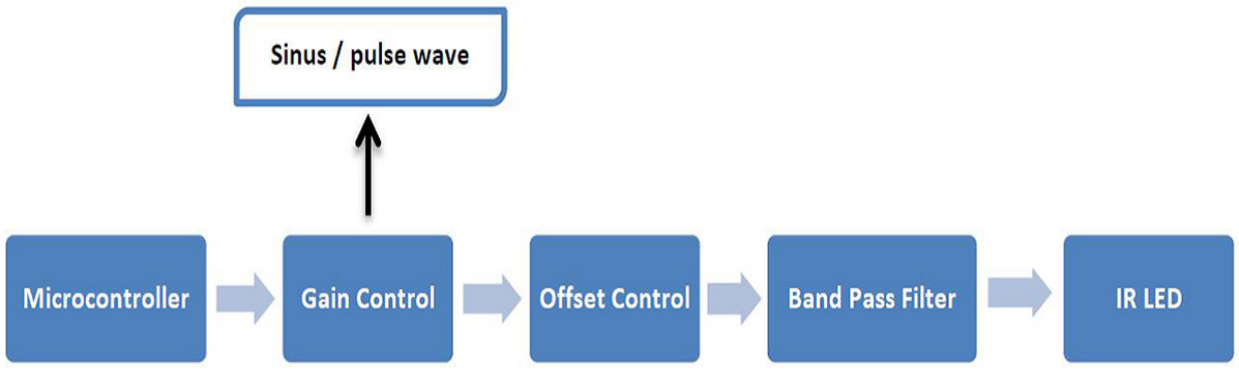

Figure 2: Diagram for the light source of the designed non-invasive blood glucometer to produce light with the wavelength of 950 nm. (IR LED: Infrared Light-Emitting Diode)

the signal from light passing through the sample. Figure 4 illustrates the three key components of this step, bandpass filtering, peak detection, and median filtering. The signal is first passed through a bandpass filter to improve the signal-to-noise ratio. Next, the peaks in the filtered signal are detected. Finally, the median of the detected peaks is calculated and used as the output of this step.

Calibration

The step aimed to determine a function that relates the glucose concentration to the output of the signal- processing step. Accordingly, 25 sugar solution samples with concentrations ranging from 60 mg/dl to 380 mg/dl were evaluated using a device with multiple repetitions. After the preparation of the solutions, they were transferred into cuvettes and inserted into a specially designed three-dimensional chamber in order to ensure that no external light passes through and interferes with the accuracy of the test results. Cuvettes are commonly used as chambers for spectrometric purposes.

The device provided a numerical value, which was recorded for further analysis. The relationship between the output of the signal processing step and glucose concentration is described by the model presented in Equation 1, as follows:

$$y = -4.137x^3 + 1408x^2 - 1.6 \times 10^5 x + 60.3 \times 10^5 \quad (1)$$

where y is glucose concentration in a sample, and x is the values provided by the signal processing step.

Results

Figure 5 shows the printed circuit board designed glucometer evaluate the performance of the instrument, in including testing actual serum samples from six patients, in which the glucose concentrations were known. The experimenters were unaware of the blood glucose concentrations, and only the laboratory manager had access to this information. The results obtained from the evaluation are presented in Table 1.

A Clarke Error Grid Analysis was conducted to assess the accuracy and compare different approaches. The original Clarke Error Grid Analysis (EGA) was developed in the 1970 s

Figure 3: The light detector circuit includes steps of detecting, amplifying, removing noise, and finally converting the optical signal into a digital signal. (ADC: Analog-to-Digital Converter, IR: Infrared)

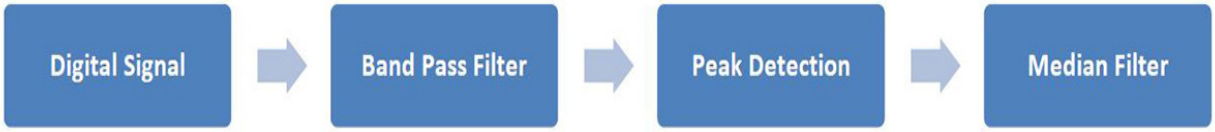

Figure 4: The steps of signal processing algorithm that comprises two critical steps: removing malicious signals and detecting signal peaks. After detecting the signal peaks, the Median filter is applied to calculate their median value.

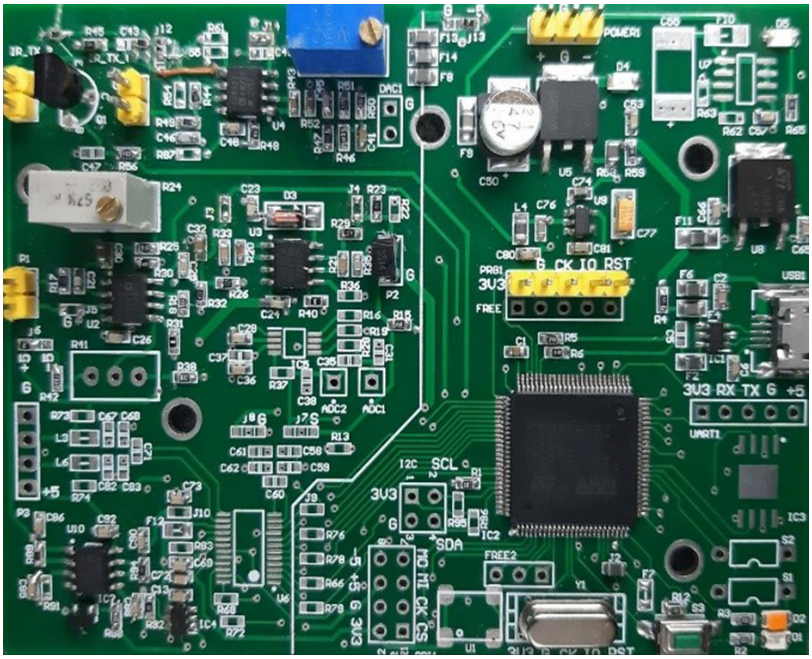

Figure 5: The circuit of the designed non-invasive blood glucometer

Table 1: Comparison of reference blood glucose (BG) levels with BG levels measured using the designed device and percentage of system error.

Sample#	True BG level (mg/dl)	Measured BG level (mg/dl)	Error (%)
1	98	90	-8.1
2	114	103	-9.6
3	112	124	+10.0
4	120	110	-8.3
5	80	90	+12.5
6	204	250	+22.5

BG: Blood Glucose

to quantitatively evaluate the clinical accuracy of patients' estimates of their current blood glucose compared to those obtained from their glucometer [14]. Out of the six serum samples tested, five (83%) were placed in zone A, indicating clinically accurate glucose measurements (Figure 6). One sample (17%) fell into zone B, showing that the glucose measurement was still acceptable but may have led to over- or under-treatment.

Discussion

The development of non-invasive methods for monitoring blood glucose levels has garnered significant interest, especially among diabetic patients who may have reservations about traditional blood glucose monitoring techniques. This study focused on designing and evaluating a non-invasive glucose monitoring system.

The hardware components of the developed

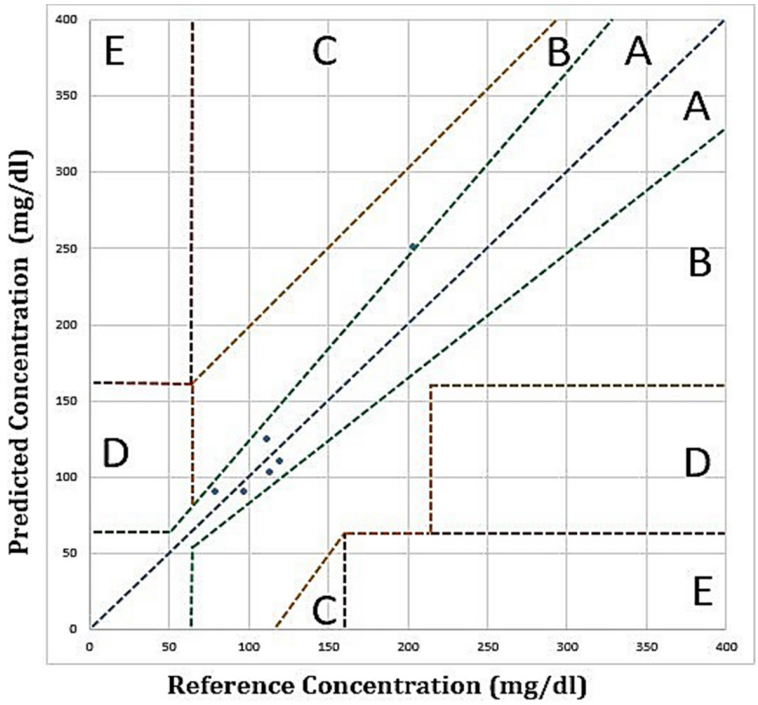

Figure 6: Clarke's Error Grid Analysis, 83% of the serum samples were placed in Zone A, 17% were located in Zone B, and none in Zone C, D, and E.

glucometer encompassed a power supply, a light transmitter, a light receiver, a sampler, and signal processing capabilities. Sugar solution samples were used with known concentrations of glucose to establish calibration. Additionally, the accuracy of the proposed system was compared with that of the reference blood glucose measurements, using Clarke's Error Grid Analysis as the evaluation metric.

The results obtained from the present study demonstrate the potential of the developed non-invasive glucose monitoring system as a viable alternative to conventional methods. Clarke's Error Grid Analysis revealed that 83% of the serum samples tested fell within zone A, indicating clinically accurate glucose measurements. Furthermore, one sample (17%) was placed in zone B, signifying acceptable measurements but with a possibility of over or under-treatment. Therefore, the non-invasive glucose monitoring system had accurate and reliable glucose measurements for diabetic patients, resulting in improving the monitoring experience and overall well-being of individuals, managing their glucose levels.

One important limitation of the current study is the small sample size for evaluating the non-invasive glucose monitoring system. Further studies with larger sample sizes are necessary to establish the accuracy and clinical utility of the system. Moreover, these studies should involve diverse patient populations to ensure the generalizability of the findings.

Additionally, the developed non-invasive glucose monitoring system must be evaluated in various clinical settings to assess its practicality and feasibility of use. Different environments and patient populations may present unique challenges and variables that could impact the system's performance.

Conclusion

The utilization of non-invasive glucose monitoring systems can enhance the quality of life

for diabetic patients and alleviate the burden on healthcare systems. This study focused on exploring the feasibility of designing a low-cost non-invasive glucometer and investigated the developed glucose monitoring system using serum samples. The results revealed that a majority (83%) of the serum samples fell within zone A of Clarke's grid analysis, showing accurate glucose measurements. Accordingly, the developed glucose monitoring system can revolutionize the monitoring of blood glucose levels in diabetic patients.

However, further research is necessary to optimize the hardware of the developed glucometer to improve its accuracy and reliability. Additionally, larger-scale studies involving a more extensive range of patient populations are required to validate the accuracy and clinical utility of the non-invasive glucose monitoring system.

Authors' Contribution

H. Parsaei contributed to the conceptualization, methodology, supervision, formal analysis, resource management, and writing and editing of the manuscript. Gh. Abdollahifard contributed to the supervision, conceptualization, validation, formal analysis, resource management, and reviewing and editing of the manuscript. Z. Mahyari was responsible for designing hardware, developing software, and editing the manuscript. MJ. Moulodi contributed to the hardware design and editing of the manuscript. SM. Fatemi Ghiri handled digital signal processing and contributed to reviewing and editing the manuscript. H. Tajalizadeh developed the algorithm and contributed to editing the paper. A. Loloee Jahromi was a member of the hardware and device assembly unit, and A. Nakhostin managed and researched the device manufacturing project, both contributed to writing and editing the manuscript. R. Jokari was responsible for methodology, validation, investigation, resource management, and data curation, and had full access to all study data with ultimate responsibility for data integrity and accuracy of analysis. R. Jokari also contributed to writing the original draft and reviewing and editing the manuscript. All authors contributed to the revision and finalization of the manuscript.

Ethical Approval

The authors did not conduct any studies involving human or animal subjects for this article.

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Conflict of Interest

None

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