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Determination of Light Source Modules on Blood Glucose Biomimetics Using the Reflectance Method

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Abstract. Developing blood glucoselevels measurement based on the prevalence of people with impaired glucose metabolism, which is increasing every year. Estimates of the International Diabetes Federation and the American Diabetes Association in 2030 sufferers of glucose metabolism disorders have twofold from 2018. Prevention can be done with monitoring measurement methods that have been available commercially. This research develops a non-invasive biomarker device method that aims at continuous measurement efficiency with minimal risk and reduces production costs. The measurement used standard samples Lyphocheck Assayed Chemistry Control from Bio-Rad Laboratory. The light source modules were tested in the wavelength range of 1050 nm to 1550 nm and FDG03-Ge Photodiode as a photodetector. Then the reflections of the LEDs is a voltage that is converted to analog with Analogue to Digital Converter devices to be processed at the SQ Lite and LibreOffice Calc. Based on the test analysis parameters obtained the two best candidate light source modules are 1050 nm and 1085 nm with a 0.99 pearson correlation, 86% accuracy and zone factor A or 100% value of error grid analysis. Both of these LEDs can be applied as modules in the measurement of blood glucose biomimetic with reflectance method.

INTRODUCTION

The measurement of blood glucose levels has developed in recent decades. These developments happen due to the high rates of sufferers of glucose metabolism disorders. Estimates of patients each year continue to increase dramatically. In 2018 it was 285 million people, and in 2025 it is estimated that there will be 380 million people, and in 2030 there will be 439 million people from the world's population [1,2]. Various factors could influence glucose

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metabolism, such as biological and nonbiological [3-6]. People can do early prevention by controlling and glucose tests routinely [1,2].

Developers or researchers offer several types of methods to measure the blood glucose. Available methods include measuring portable glucose levels [7], Cu reagents [8], chemical auto-analysis [9], blood gas analysis [10], continuous monitoring [11], venipuncture [12], glucose oxidation [13], hexokinase [14] and enzyme reactions [15]. The researches still evaluate these methods levels of optimization and precision. The purpose of using the near-infrared method for measuring blood glucose biomimetics is to reduce production costs. Furthermore, this method can reduce excessive body reaction after invasive measurements, such as oedema and discomfort [16]. In contrast, this study aims to find the ideal light-emitting diode (LED) candidate for blood glucose biomimetics measurement using the reflectance method. Device updates on Analogue to Digital Converter (ADC) hardware and statistical learning software is the best option to improve and find out biomarker non-invasive device performance [17].

METHOD

The researcher carried out this validity measurement experimental at the Laboratory of Electronics and Material Physics, IPB University, from March 2019 to January 2020. This research consists of four processes. The first process, a library study to design a blood glucose biomarker design. Development of design and method renewal based on references from near-infrared spectrophotometry research [16], precision, and accuracy of measurements with the principle of signal machine learning [18], multi formula regression equations [19], standard pressman and scrum methodology [20,21].

The second process is the design-build and installation of blood glucose biomarkers. The researcher is using Qt Software Development Kit [22], ALGLIB [23], WiringPi, SQ Lite [24], Repetier, SolidWork, EasyEDA Printed Circuit Board (PCB) design software, Raspberry Pi [25], 3D printer and the other supporting electronic devices.

The third process, measuring blood glucose using UV-cuvettes ultra-micro (8.5 mm windows hight), an ultra-micro bag of 100 blue cuvette caps as a sample. The sample used biomimetic Lyphocheck Assayed Chemistry Control-Hexokinase level-1 87.30 mg/dL, level-2 278.00 mg/dL and level-3 182.65 mg/dL (combination of level 1 and 2) [26]. 70 microliter samples added to the cuvette using a pipette. We have placed the cuvette that has filled with the sample in a probe. Then the measurement process is carried out with adjusting the LEDs as an incident light and connecting it to the biomarker circuit. The module of the light source used includes LED wavelengths of 1050 nm, 1070 nm, 1085 nm, 1450 nm, 1550 nm, and FDG03-Ge photodetector from Thorlab Inc.

The final process is calculating and analyzing data of Pearson correlation using ALGLIB [23]. We find the best value of standard deviation from the collective data period (P11-P30) using the LibreOffice Calc [27]. The researcher has done both the multi formula regression equations, and the value of listing errors and data predicted using the ZunZun [19]. The plotting the Clarkes Error Grid (CEG), Parkes Error Grid (PEG) [28,29], and analyzing sensitivity and specificity [30]. That analysis process uses RStudio statistical software [31]. The researcher then compares the results of the processing and analysis with the data of gold standard from Bio-Rad Laboratory [26].

RESULTS AND DISCUSSION

Result

Integration of Biomarker Non-Invasive Devices

The process of software integration is installing the Raspberry Pi operating system to the microcontroller and adjusting the operating system with the Qt Software Development Kit [22,25]. Hardware device integration uses a breadboard to minimize the complexity of reintegration when an error occurs in the circuit. The breadboard can use a jumper cable without soldering. The developer implements The scheme with the best results of temporary integration on a PCB design. The development does the printing process of PCB design by etching method after the stability of the biomarker series is obtained [17,32].

The researcher tested the stability evaluation of the detector reading using precise mathematical equations (1). The p symbol is a representation of precision, the symbol x1 is a representation of number precision, and the symbol x' is a representation of average precision. The researcher has used The 1050 nm light source as a testing medium with a repeat of 3 times, and the measurement results obtained reached 99.40% precision [32]. This value represents that the developer can use the integrated circuit as a test on biomimetic blood glucose levels.

$$p = 1 - \left(\frac{x_1 - x'}{x'} \right) 100 \tag{1}$$

Biomarker Non-Invasive Measurement

Biomimetic measurement of glucose using a white probe colour printed by an adjusted 3D printer to the size of the cuvette, light-emitting diode and photodiode. The probe design uses of TinkerCAD's 3D create an online design (Figure 1). The setting of light sources and detectors sequentially are LED1-Photodiode-LED2. The two LED components used have the same wavelength with intermittent light settings. This arrangement is due to the use of a binary method for the modulation system, detection of sensor delays, and to prevent the effects of hysteresis responses that vary with each decrease or increase in intensity [33]. The researcher intends that this effect could prevent changes in the spontaneity of the electric displacement field. These additions are important to the reminder engine circuit or change current with changes in the value of resistor or memristors. The binary method can be used as a marker, whether there is noise when in the measurement process [17,33].

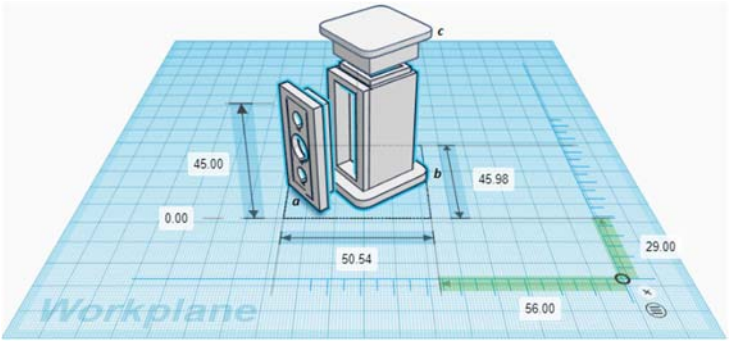

FIGURE 1. The layout of 3-dimension probe design, a) cover of incident light source-photodetector, b) cover of sample and c) headcover of the probe

The measurement process is affected by the optimization of the use of analogue to digital converters. This biomarker used Analogue to Digital Converter (ADC) 1115 and implemented on MCP3424 so that it can convert up to 18 bits 840 SPS [35]. The display biomarker interface is arranged in advance using SQLite software as a naming or initials experiment and file storage. The profile file data automatically saves the measured value. The data is opened with DB Browser software from SQLite and transferred to LibreOffice Calc [24,27].

Multi-Formula Regression Analysis

Based on the dataset from LibreOffice Calc, researchers sought the Pearson correlation value and the best standard deviation in the period of each LED [23]. Correlation values selected consecutively from periods 29 and 28 on LED 1050 nm, periods 16 and 17 on LED1550 nm, periods 27 and 24 on LED 1085, nm periods 27 and 28 on LED 1070 nm, and periods 25 and 15 on LED 1450 nm. Periods are the number of periods the LED blinks. The period of this measurement is 40 times or periods.

This period act as a parameter for the process of finding the best equation and error listing using the function finder on ZunZun [19]. The output results from the data processing act as a comparison parameter between the average values of the standard glucose real and the predicted value of glucose from the biomarker (Table 1). The real standard average values consist of level-1 87.30 mg/dL, level-2 278.00 mg/dL and level-3 182.65 mg/dL [26]. The equation from ZunZun shows that there are three best modules, as follows 1050 nm, 1070 nm, and 1085 nm [19].

TABLE 1. The mathematical equation of each wavelength using multi-formula regression (MFR).

LEDs (nm)	Periods	Mathematical Equations	RMSE
1050	P29, P28	$z = a * \exp(-0.5 * (((\ln(x)-b)/c))) + d * \exp(-0.5 * (((\ln(y)-f)/g))) + Offset$	2.70
1070	P27, P28	$z = a * \exp(-0.5 * (((\ln(x)-b)/c)^2)) + d * \exp(-0.5 * (((\ln(y)-f)/g)^2)) + Offset$ $s^2 = (ax+b)^2 + (cy+d)^2$	2.05
1085	P27, P24	$z = (s^2/r) / (1+(1-(k+1)(s/r)^2)1/2) + A4*s4 + A6*s6 + A8*s8$ $z = xy / (z + Offset$	2.60
1450	P25, P15	$z = (a + bx + cy + dxy)/(1 + f*\ln(x) + g*\ln(y) + h*\ln(x)*\ln(y))$	42.1
1550	P16, P17	$z = a * \exp(-\exp(-(x-b)/c)-(x-b)/c+1) + d * \exp(-\exp(-(y-f)/g)-(y-f)/g+1)$ $z = z / (h * xy) + Offset$	34.7

Error Grid Analysis

The researcher has plotted the process of analyzing the measurement error rate in the biomarker series using the CEG and PEG methods [28,29]. Based on the analysis of 3 samples x 5 repetitions/samples, the percentage of CEG LED with a wavelength of 1050 nm at zone factor A 100% (Fig. 2a), 1070 nm at zone factor A 100% (Fig. 2b), 1085 nm at zone factor A 100% (Fig. 2c), 1445 nm at zone factor A 73.33%, B 26.66% (Fig. 2d), and 1550 nm at zone factor A 73.33%, B 26.66% (Fig. 2e).

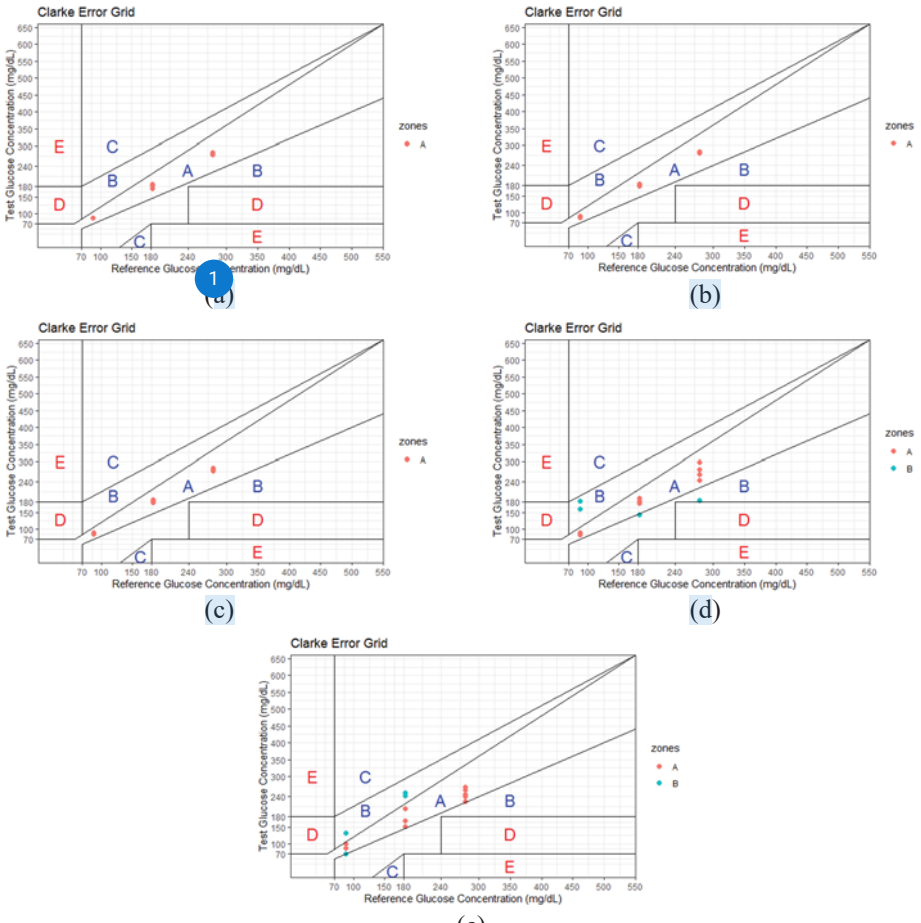

FIGURE 2. The results of CEG analysis using RStudio between biomarker test glucose concentration (mg/dL) and reference glucose concentration (mg/dL) with a wavelength LED light source, a) 1050 nm, b) 1070 nm, c) 1085 nm, d) 1445 nm and e) 1550 nm.

Percentage of PEG LED with a wavelength of 1050 nm at zone factor A 100% (Fig. 3a), 1070 nm at zone factor A 100% (Fig. 3b), 1085 nm at zone factor A 100% (Fig. 3c), 1445 nm at zone factor A 73.33%, B 13.33%, C 13.33% (Fig. 3d), and 1550 nm at zone factor A 73.33%, B 26.66% (Fig. 3e).

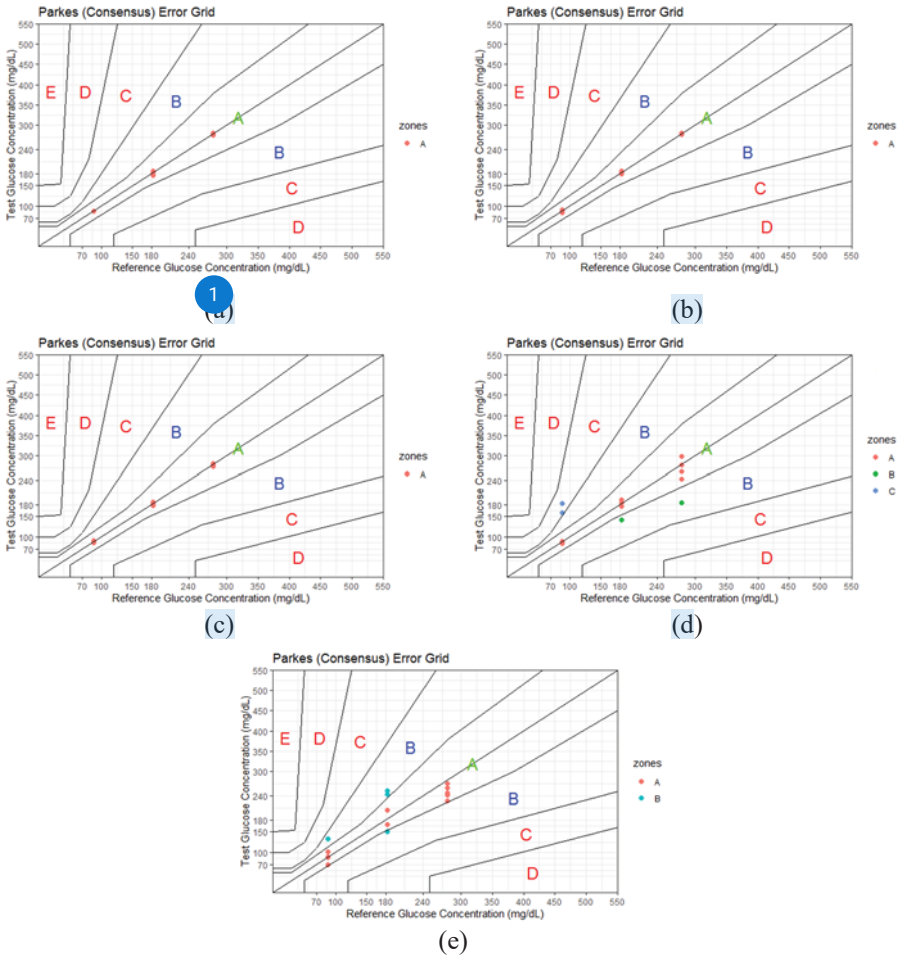

FIGURE 3. The results of the analysis of PEG using RStudio between biomarker test glucose concentration (mg/dL) and reference glucose concentration (mg/dL) with the wavelength LED light source, a) 1050 nm, b) 1070 nm, c) 1085 nm, d)1445 nm, dan e) 1550 nm.

Selection of Wavelength Light Source Modules

The built biomarker can make optimal measurements based on an assessment of sensitivity and specificity [30,31]. The analysis was referring to the valuation of values with the real value of the standards [26]. Estimator and real values put into two groups with median value parameters. Output value as a parameter whether this wavelength can measure biomimetics optimally [28,29]. These results indicate that developers can use LEDs with wavelengths of 1050 nm, 1070 nm, and 1085 nm as optimal light source modules in this research (Table 2).

TABLE 2. Analysis of epidemiological data from biomarker non-invasive with reflectance method

LEDs (nm)	Parameters				
	Sensitivity	Specificity	Diagnostic Accuracy	Diagnostic Repetition	Pearson
1050	1.00 (0.48, 1.00)	0.80 (0.44, 0.97)	**0.86**	**1.25**	**0.99**
1070	1.00 (0.48, 1.00)	0.70 (0.35, 0.93)	0.80	1.42	0.99
1085	1.00 (0.48, 1.00)	0.80 (0.44, 0.97)	**0.86**	**1.25**	**0.99**
1450	1.00 (0.48, 1.00)	0.60 (0.26, 0.88)	0.73	1.66	0.84
1550	1.00 (0.48, 1.00)	0.70 (0.35, 0.93)	0.80	1.42	0.89

Discussion

The development of an electronic device for measuring glucose levels using a combination of various methods from previous research can improve the measurement ability of the biomarker. Component renewal in the series supports the performance of biomarkers with a precision level reaching 99.40% [32,33]. The researcher has compared the device output to the real value of a standardized sample. Measurement values are the main data source in the mathematical and statistical analysis process [19,23,31]. There are three the best LEDs on the measurements biomimetic glucose, 1050 nm, 1070 nm, and 1085 nm.

Detection and light source setting is to determine the success of reading the emission reflectance value in the biomarker. In this research, we try to model the setting with the first formation of LED1-Photodiode-LED2 and the second LED1-LED2-Photodiode. In the second formation experiment, the results of detection the reflectance of emissions are not optimal, and there is noise, in contrast to the first form, which is the optimal results. However, this research does not discuss the differences between LED and Photodiode formations. Biomimetic cuvette during the measurement process has created noise in measurement [33]. This research uses transparent quartz UV-cuvette, which can help with biological sources or light sources with relatively lower energy. The resistance of light reflection in the ultra-micro cuvette increases because it has a dimension of 2 mm x 3.5 mm and a 10 mm light path [34]. Users can use a Non-invasive biomarker prototype as a measurement tool and metabolism indicator of normality or abnormality of blood glucose level. The prototype has an accuracy value of 8.60 mg/dL. A similar prototype has measure glucose in the transmittance method with an accuracy value of 5.16 mg/dL and 10.8 mg/dL [36,37]. The gold standard from the ISO standard for blood glucose levels is 10.00 mg/dL [13]. In the future development, the researcher can expand the data using Fast Fourier Transform (FFT) to improve the accuracy of the measurement. The FFT is proven in the measurement accuracy when compared to without using FFT [33,36].

Based on previous research, there are wavelengths of 1050 nm, 1070 nm, 1085 nm, 1200 nm, 1300 nm, 1600 nm, 1650 nm, and 1850 nm, which have the potential as light source modules in the reflectance method [38]. This study did not test all light sources in the 1000 nm range directly due to limited module availability. CEG and PEG show that the LED wavelengths of 1050 nm, 1070 nm, and 1085 nm do not indicate the occurrence of measurement errors. All predicted, and real sample data values on the three LEDs are in zone factor A. The 1450 nm LEDs yields 11 zone factors A, four at zone factors B on CEG and 11 zone factors A, two-zone factors B, two-zone factors C on PEG and LEDs 1550 nm 11 zone factors A, four-zone factors B on CEG and PEG plot. However, for both LEDs, it has the potential as a light source module because it is still in the B or C zone factor or fault tolerance [28,29,30].

Analysis of epidemiological data (Table 2) LEDs 1050 nm, and 1070 nm is the best module on 0.99 correlation value, sensitivity 1.00 (0.48, 1.00), specificity 0.80 (0.44, 0.97) and with 1.25 number needed to diagnose. These results are better than compared to the measurement of the transmittance method with a sensitivity of 0.83 (0.36, 1.00), a specificity of 0.90 (0.55, 1.00), and 1.36 number needed to diagnose [37]. Without the use of FFT in the reflectance, the method is much better. The addition of FFT to the transmittance method resulted in a sensitivity value of 0.65 (0.59, 0.71), a specificity of 0.76 (0.70, 0.80) and a number of the diagnosis of 2.44 [36,37].

The validity level of biofluid measurements using the biophotonic interaction method can be measured. The measurement came from the amount of light absorbance value of each light source on the material. Based on existing references that the absorbance values of wavelengths are 1050 nm 0.1142, 1070 nm 0.1094, 1450 nm 0.3111, and 1550 nm 0.0657 [17,38,39]. However, researchers have not yet investigated whether the absorbance or reflectance values fully carry glucose information and whether glucose is self able to absorb or reflect the light source.

CONCLUSIONS

The conclusion of this research refers to the parameter tests of Pearson correlation, ZunZun, analysis of epidemiological, and error grid analysis. Parameter test value shows that the Pearson correlation is 0.99, accuracy is 8.60 mg/dL, and error grid analysis is in zone factor A on LEDs 1050 nm and 1085 nm. Positive correlation >0.5 represents an almost perfect relationship between the research variables, and zone factor A represents a value of 100% error grid, or almost no error occurs in the measurement process. The future research is to test the entire LED module in the wavelength range of 1000 nm to 2500 nm for the standard blood-glucose-level measurement using the reflectance method. The next challenge that researchers need to do is answer how the measurement performance of non-invasive glucose level biomarkers on biomimetics compared to human biofluids directly.

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We declare no competing interest.

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