Non-invasive Hemoglobin Measurement for Anemia Diagnosis

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***Abstract*-Hemoglobin is important part of red blood cell to transport oxygen and carbon dioxide. Hemoglobin concentration in the blood can be used as physical condition parameter. A low hemoglobin level is called anemia and high hemoglobin level is called polycythemia. WHO has determined the anemia cut off level of hemoglobin concentration based on age, sex, and condition (pregnant or not). Currently, accurate and reliable hemoglobin concentration measurement uses invasive methods such as cyanmethemoglobin and automated hematology analyzer. But these methods are expensive, not real time, high infection risk, and need special techniques. Non-invasive methods offer a better alternative because it has low infection risk, instant result, and portable in size. This work developed a non-invasive hemoglobin measurement for anemia diagnosis based on optical spectroscopy. The system utilized LED and photodiode as optical sensor placed on the fingertip. Photodiode just could obtain DC component, so the signal conditioning circuit which consisted of HPF, LPF and amplifier was used to obtain the AC component of the signal. This system used microcontroller to control the operation of the hardware and to calculate the hemoglobin concentration.**

Keyword—Hemoglobin; optic; spectroscopy; non-invasive; anemia.

I. INTRODUCTION

Hemoglobin is the main component of red blood cell [1] which is used to transport oxygen from the lungs to the other tissues in body, exchange oxygen with carbon dioxide, and then transporting carbon dioxide back to the lungs to exchange it for oxygen [2]. Hemoglobin contains four protein molecules called globulin chains. In every globulin chain, there is important central structure called the heme molecule. Heme molecule contains iron that is responsible to transporting oxygen and carbon dioxide and make red color in blood [2]. Hb concentration in blood is used to evaluate the individual physiological condition [3]. The need for hemoglobin for every person is vary depends on a person's gender, age, smoking behaviour, different stages of pregnancy and residential elevation above sea level (altitude)[4]. A condition when the amount of hemoglobin drops below normal is called anemia, and when it exceed normal is called polycythemia [2]. WHO has determined the anemia cut off level of hemoglobin concentration. Children 6-59 months old is 11 g/dL, children 5-11 years old is 11.5 g/dL, children 12-14 years old and non-pregnant women are 12 g/dL, pregnant women is 11 g/dL, and men (15 years old and above) is 13 g/dL [5].

The major cause of anemia is iron deficiency. Other minor causes include acute and chronic inflammation, parasite infections, red blood cell production or survival, and nutritional deficiencies (folate, vitamin A and vitamin B_{12})[5]. Anemia indicated by fill of weakness, fatigue, drowsiness and dizziness and can cause dead [6].

In developing country, anemia is one of the major causes of mortality and morbidity among pregnant women with the prevalence is 41.8% compared with non-pregnant women of just 30.2% [7,8]. It occur because pregnant women require more hematopoietic to achieve augmented erythropoiesis during pregnancy and for storage by the fetus [9].

Reliable indicators for anemia is the concentration of hemoglobin in blood [10]. Hemoglobin is usually measured by using invasive methods such as cyanmethemoglobin or automated hematology analyzer. These methods gave very accurate and reliable result, but have some disadvantages which are expensive, high infection risk, and when blood sample is far away from the laboratory it will need more time to transport the sample and can causes delay on the measurement result [11,12].

The non-invasive methods became popular alternative for hemoglobin measurement because it require no blood sample, no scars, minimum infection risk, patient can be monitored in real time, and portable in size [12,13,14]. One of the non-invasive method to measure hemoglobin concentration that is widely used is optical technique, using the principle of transmission spectroscopy and Beer-Lambert Law to analyze the concentration of hemoglobin in blood [15,16].

In a cardiac cycle, blood volume in arteries is higher during systolic phase compared to diastolic phase, but not in veins. Higher systolic pressure causes arteries diameter to increase [13]. This phenomenon can be observed by measuring the transmission of light through fingertip which is called photoplestimograph (PPG). LED array are placed in the fingertip area to trans-illuminated lights through the finger and then the transmitted light is detected by

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photodiode. The intensity of transmitted light in diastolic phase and systolic phase is different depending on the blood volume in arteries.

This paper proposed a method for anemia diagnosis to determine the anemia status of pregnant women by non-invasive method based on spectroscopy, Beer-Lambert Law and PPG were used to measure hemoglobin concentration. Two LEDs with wavelength of 670 nm and 940 nm were used as the light source to detected the presence of deoxyhemoglobin and oxyhemoglobin [17]. The anemia status of pregnant women determined by cut off level of hemoglobin concentration in blood of 11 g/dL.

II. Measurement Principles

The method to measure Hb concentration is based on multi-spectral spectrophotometry. Blood consists primarily by water and hemoglobin that have different absorption coefficient across different wavelength [13]. Absorption coefficient of transmitted light through the finger tissue is different in every wavelength and is relatively low in range 600-1300 nm [18]. The presence of deoxyhemoglobin and oxyhemoglobin in blood are detected by light emitting diode (LED) - red (670 nm) and infrared (940 nm), respectively [18]. Hemoglobin also contain other component such as Meth-hemoglobin and carboxy-hemoglobin, but have minor constituents so it can be ignored [19].

LEDs are placed on the one fingertip side and photodiodes as detector that have sensitivity range 400-1000 nm are placed on the other side. The intensity of transmitted light through the fingertip depends on the amount of blood volume in the fingertip arteries. In systolic phase, heart pumps blood to the arteries and increase quantity of blood volume in arteries. Higher blood volume carries more hemoglobin in the arteries causing higher light absorber in optical path length. Blood volume then decreases at diastolic phase. Hence, light absorption in diastolic phase is less than systolic phase. The intensity of transmitted light is detected by a sensor that is depended on absorber quantity in the optical path length. The changes of transmitted light intensities are called PPG-waves [20]. PPG waves contain AC component that time varying is caused by cardiac cycle. While, DC component that non-time varying is caused of venous blood and other tissues. AC component represents the changes of blood volume in arteries due to the cardiac cycle. DC component represents light absorption by venous blood, tissues and bone.

The fundamental law that leads quantitative analysis by absorption spectroscopy is based on The Beer-Lambert Law (equation 1). The Beer Lambert Law describes the relation between extinction coefficient, thickness, and concentration of the absorbing medium. When the light goes through the medium, only part of the light is transmitted and the remaining is absorbed or reflected. It depends on the wavelength which is measured and concentration of the medium. The light may also be scattered if particles are present in the medium [21].

$$OD = \varepsilon(\lambda)cl = \log(\frac{I_0}{I_T}) \quad (1)$$

With OD is non-dimensional parameter that represents the optical density of the absorption. $\varepsilon(\lambda)$ is the molar extinction coefficient at a specific wavelength, c is the concentration, and l is the optical path length along the medium. I_0 and I_T are the intensities of the incident and transmitted light, respectively [21]. For more than one absorbing substance, the Beer Lambert's Law is still valid and defined that each absorber affect to the total absorbance or optical density (equation 2). The total optical density of a medium with n absorbing substances is given by equation 2.

$$OD = \log(\frac{I_0}{I_T}) = \sum_{i=1}^{n} \varepsilon_i(\lambda)c_i l_i \quad (2)$$

From the equation (1) and (2), the concentration of substances in a medium can be determined if the extinction coefficient of the substances, optical path length and optical density are determined [19]. In this paper, extinction coefficient is assumed to be the same for each person. Optical density can be determined by measuring the intensities of incident and transmitted light from sensor. Light intensities from each LED will be different because the variations of manufacturing process, drive current, and efficiency values. Thus, normalization is needed to compare one wavelength with the other [13].

For the Hb measurement, PPG signal from each wavelength is analysed by AC/DC ratio for each component. Calibrations of the system using some volunteers which are measured by invasive methods with Sysmex-KN21. Linear regression is used to obtain the correlation formula between AC/DC ratio and Hb concentration value. The system detects anemia if Hb concentration is lower than 11 gr/dL.

III. Methods

The hardware system consists of two LEDs, sensor (photodiode) signal with conditioning circuit, and microcontroller. LED is used to illuminate light with specific wavelength which is transmitted through optical path length (finger tissues, bone and vein). The transmitted light that brings information about concentration of hemoglobin in the blood is detected by sensor. Sensor changes transmitted light intensities to voltage output.

PPG signal from sensor output can be divided in to AC and DC component. AC component has very small magnitudes compared to DC offset, so signal conditioning circuit is needed to extract the AC component. Diagram block of the system hardware is given in Fig. 1.

Microcontroller is used to control the LEDs, display and process the signal. The LED driver connect microcontroller I/O pin to LED. With this driver, the LED's current is not taken from microcontroller pin but directly from the power supply.

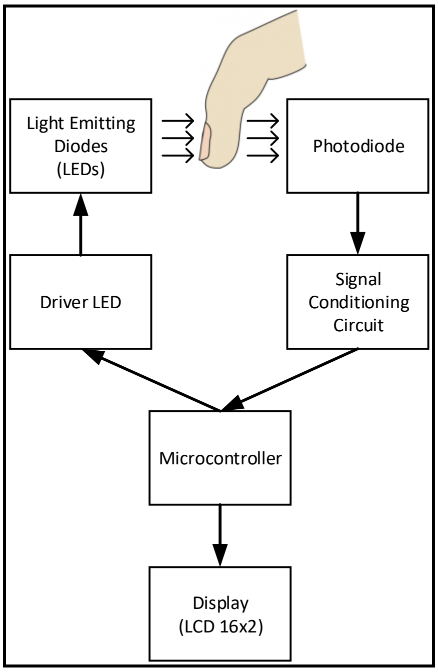

Fig 1. Block diagram of the system hardware

Signal conditioning circuit consisted of filter and amplifier circuit. Filter circuit can be divided in to Low Pass Filter and High Pass Filter. The filter cut off frequencies depends on heart rate which is between 30 bpm to 150 bpm (0.5 to 2.5 Hz). To get the AC component, the DC component must be removed from the signal with high pass filter. According to heart rate frequency, the high pass filter cut off must be lower than 0.5 Hz. This system was designed with high pass filter having a cut off frequency approximately 0.1 Hz. Low Pass filter in this system was used to block the noise signal from local power line that run at 50 Hz and other possible noises. This system was designed with low pass filter having a cut off frequency approximately 3 Hz. The result from the filter is an AC component with very small magnitude, so the amplifier circuit was needed. The order of magnitude from this amplifier circuit was in thousands. Because of the order of the big magnitude, the conditioning circuit was designed with two stage with every stage have High Pass Filter (HPF), Low Pass Filter(LPF) and Amplifier. The Design of Signal Conditioning circuit is given in fig. 2.

The output of signal conditioning circuit was in voltage. To process it in microcontroller this output must be changed to the digital data with Analog to Digital Converter (ADC). ADC was one of the feature from the microcontroller which was used by the system. Microcontroller processes PPG signal to calculate the hemoglobin concentration and anemia status.

Microcontroller works based on the program which was downloaded to the microcontroller. The flowchart for programming the microcontroller is given in fig. 3. The peak and valley detection algorithm was used to calculate the AC component of the signal. The Hb concentration was calculated based on ratio of AC to DC component of the red and infrared signals as described in formula (1).

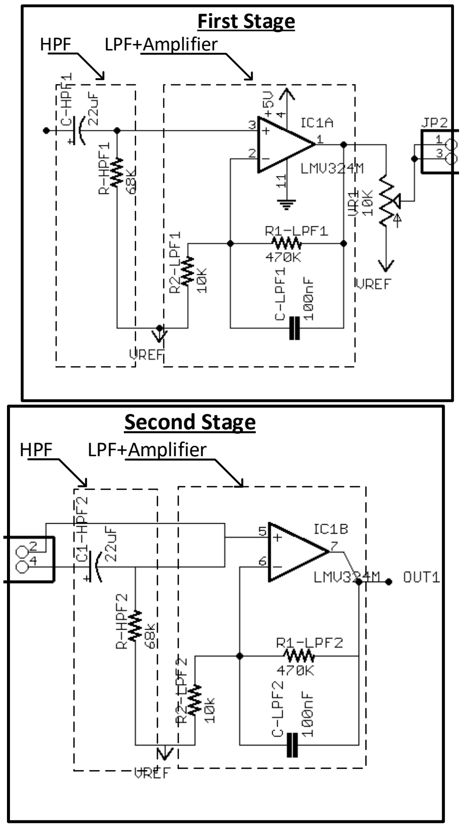

Fig. 2 Design of Signal Conditioning Circuit

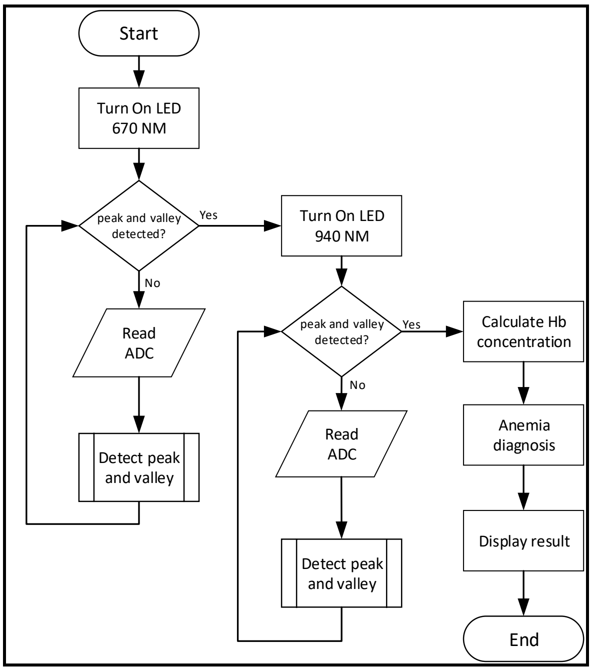

Fig 3. Flowchart of the microcontroller software

IV. RESULT

This system measure PPG signal with red and infrared light source. The signal result from this system with red and IR LED is given in fig. 4.

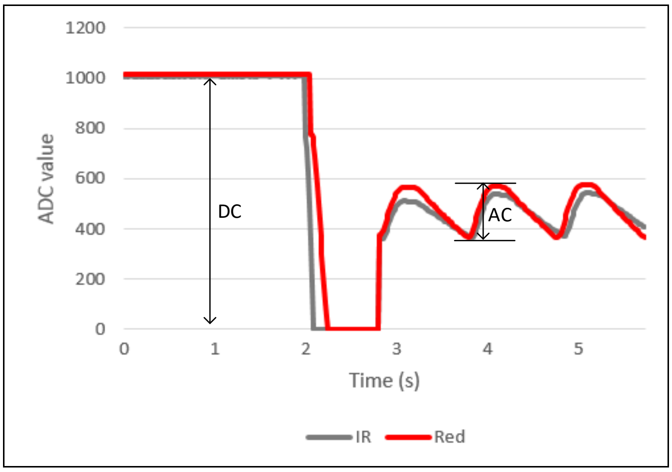

Fig. 4. PPG wavelength from RED and IR LED

There were 78 subjects of pregnant women with good health condition. Data from 21 subjects were used for training while the remaining 57 subjects were used for testing. Sysmex KN-21, one of the most popular automated hematology analyzer to measure Hb, was use for invasive methods (gold standard). Blood sample was extracted from the subject veins. The Hb concentration compared to the normal level to determine the status of anemia of subjects.

Linear regression was used to obtain the conversion formula from training data to Hb concentration value (see Fig. 5).

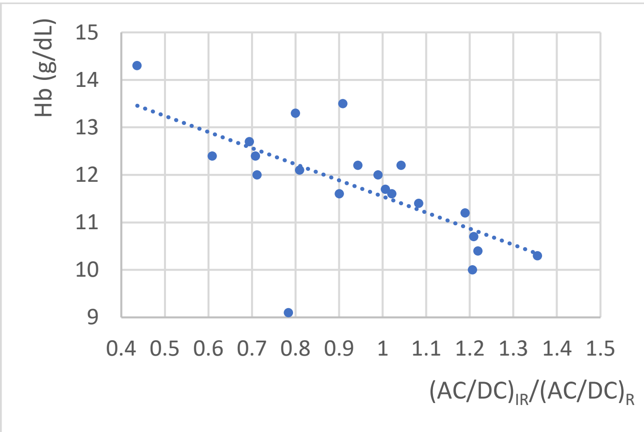

Fig 5. Linear regression

The Hb concentration is given by formula (1) below:

$$Hb = -3.3912x + 14.937 \quad (1)$$

where x represented the ratio of $(AC/DC)_{IR}/(AC/DC)_R$.

Paired *t*-test from Hb concentration measured by developed non-invasive device and standard method is given in Table I. Table I showed that both methods gave similar quantitative results although the non-invasive method gave slightly less accurate results.

TABLE I. PAIRED T-TEST FROM INVASIVE AND NON-INVASIVE METHODS

	Mean	P
Non-invasive	12,2 ± 1,7	0,001
Invasive	11,6 ± 1,2	

The effectiveness of non-invasive device can be determined from sensitivity, specificity, positive predictive value, negative predictive value, and accuracy values. Diagnostic test result from all subjects are given in table II.

TABLE II. DIAGNOSTIC RESULT

		Invasive		Total
		Anemia	Normal	
Non-invasive	Anemia	4 (5.1%)	19 (24.4%)	23 (29.5%)
	Normal	5 (6.4%)	50 (64.1%)	55 (70.5%)
Total		9 (11.5%)	69 (88.5%)	78 (100%)

The values of sensitivity, specificity, positive predictive value, and negative predictive value are 44.4%, 72.5%, 17.4%, and 91%, respectively. The positive likelihood ratio was 1.61 (fair). The negative likelihood ratio was 0.77 (useless). The accuracy of the new non-invasive device was 69.2%.

The accuracy of the non-invasive device was low. The low accuracy was probably caused by many factors such as the movement of subject when measurement was taken, unfit fingertip position, influence from other substances, and false in peak and valley detection because of signal noises. To improve the accuracy of the system, more LEDs can be used. Proper grounding can also be used to reduce the noise.

V. CONCLUSION

The non-invasive hemoglobin measurement device for anemia diagnosis has been developed with spectroscopy methods using two LEDs at wavelength of 670 nm and 940 nm. Photodiode was used as sensor to detect the transmitted light through the finger. Signal conditioning circuit was used to get the AC component of the signal. This system was based on microprocessor to control the operation of LEDs, process data from sensor, calculate hemoglobin concentration, and determine anemia status. The ADC in microcontroller was used to convert analog sensor data in voltage to digital data so it can be further process by microcontroller. Anemia status can be determined after hemoglobin concentration is calculated. This developed system still has relatively low accuracy.

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