Development of Altera NIOS II Soft-core system to predict total Hemoglobin using Multivariate Analysis

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Abstract: In Today’s world, Hemoglobin is measured using an invasive method. This method leads to delayed diagnosis, painful experiences for patients, and a lot of biomedical waste. To overcome these problems, an Altera NIOS II soft-core based system was built to monitor hemoglobin non-invasively. The heart of the system is NIOS II soft-core processor which was configured on the DE0 Nano FPGA board having Cyclone IV EP4CE22F17C6N. This system also has a finger probe which consists of five LED sources (670 nm, 770 nm, 810nm, 850nm and 950nm) and a photodetector (OPT101) to acquire the signal using photoplethysmography (PPG). The incoming real-time PPG signal is recorded at five different wavelengths for fifteen individual subjects. Before applying Multivariate Partial Least Square Regression (PLSR), mathematical empirical formulas was used to predict hemoglobin which gave Root Mean Square Error (RMSE) of 0.442 g/dL and the prediction accuracy of 97.05%. To further improve the system accuracy, the PLSR model was implemented on the NIOS II soft-core system. With this, the hemoglobin was predicted with an accuracy of 98.98% and a RMSE of 0.179 g/dL. The designed system was validated with Bland-Altman analysis which shows good agreement between predicted and reference hemoglobin.

Keywords: Anemia, Embedded system, FPGA, Hemoglobin, PLSR, Multivariate, NIOS II.

1. INTRODUCTION

Anemia is a serious global public health problem that affects pregnant women and young children [1]. World Health Organization (WHO) estimates that 42% of children below 5 years of age and 40% of pregnant women worldwide are anemic. Anemia is a condition wherein the blood does not have sufficient number of red blood cells. Hemoglobin is needed to carry oxygen to the body’s tissue and if it has fewer red blood cells, it will lead to symptoms such as weakness, fatigue, dizziness, and shortness of breath. The normal hemoglobin concentration varies by gender, age, and altitude. The main causes of anemia are due to nutritional deficiencies like iron deficiency and also due to other deficiencies in folate, vitamins B12, and vitamin A [2]. Anemic pregnant women have an increased rise in low birth weight and increased prenatal and maternal mortality. Anemia also results in blood loss due to traumatic hemorrhages or due to cardiac surgery [3]. In the current diagnostic method for hemoglobin measurement in a clinical laboratory, the blood is drawn from the vein which involves the insertion of a needle where the subjects will have slight discomfort and pain. Also, the subjects have to travel to the medical facility which is very time-consuming and involves some expenses too [4]. A non-invasive method allows on the spot or continuous monitoring of hemoglobin and provides safe management of subjects. In this method, the results are available within one minute which permits immediate clinical assessment [5].
There are some commercial non-invasive point-of-care (POC) tools for hemoglobin estimation. Masimo Corporation has developed Radical 7, a non-invasive Pulse CO oximeter that measures hemoglobin concentration on the absorption of light in the blood by using multiple wavelengths of light [6]. The NBM 200 is a non-invasive hemoglobin monitor based on an occlusion spectroscopy technology. It uses a ring-shaped sensor probe that fits on the subject’s finger to measure the intensity of multiwavelength light passing through the finger when the blood flow is temporarily ceased [7]. The ASTRIM FIT estimates the hemoglobin levels in approximately 40 seconds when the finger is placed [8]. Smart-Hb is used for measuring hemoglobin concentration in the blood using a non-invasive method. It showed high accuracy of 90% in trials conducted in multiple countries and their sensitivity and specificity were over 80% [9]. Most of these devices had one or more drawbacks like complex data analysis and feature extraction processes, portability and costly external modules [10]. Apart from commercially available non-invasive devices several researchers are working to improve the prediction accuracy level. Edwards et al. [11], developed a non-invasive method of measuring hemoglobin flow using NIRS. They used six laser diodes at wavelengths 797.5, 802.5, 831.2, 848.7, 866.5, and 907.8 nm to capture the spectral response and estimated hemoglobin using least-squares linear regression. Xiaoqing et al. [12], utilized spectroscopy methods for non-invasive hemoglobin measurement using eight laser diodes (wavelength range from 600 nm to 1100nm) to record PPG signals in 220 subjects. However, their instrument set up was not portable for the noninvasive measurement of hemoglobin. Suzaki et al. [13], designed a non-invasive hemoglobin spectrophotometer with seven wavelengths to measure hemoglobin. Timm et al. [14], developed an optical-based sensor system with three LEDs to estimate the hemoglobin concentration using the PPG method and later improved theirs by using an additional wavelength at 1300 nm to calculate absorption of water [15]. A. Deep et al. [16], acquired two PPG signals at 810nm and 1300nm along with a photodiode to calculate hemoglobin concentration using LABVIEW. C. Pinto et al. [17], designed non-invasive hemoglobin meter which consisted of a finger probe with five LED’s and a photodetector to acquire the PPG signal. The system was validated with the pathology laboratory measurement and the result showed that five wavelength PPG system improved the accuracy of estimating hemoglobin.

Field Programmable Gate Array (FPGA) devices are used for the implementation of parallel algorithms while microprocessors are used for sequential algorithms. The biggest challenge for hardware architects is to have high-performance, good power efficiency, flexibility and reduction in time to design the product [18]. A soft-core processor allows a designer to modify the peripherals from the System on a Programmable chip (SOPC). It also offers the flexibility of reconfiguring the soft-core [19]. PLS is a regression technique used to analyze spectroscopy data. It has been used for the chemometric analysis of multivariate data to model spectra in the visible and near-infrared (NIR) for predictions of biological, chemical, soil and physical properties [20]. PLS performs multiple linear regression to build a linear model by maximizing the covariance between response variables and predictor variables [21, 22].

In our present study, the authors have developed a soft-core system to predict hemoglobin concentration non-invasively with a multivariate PLSR model. The main objectives of this research paper are to design a finger probe that consists of five LED sources and a photodetector to acquire the PPG signal. To develop a PLSR Model and implement it on NIOS II soft-core system in DE0 Nano FPGA Board. And to improve the system accuracy by predicting total hemoglobin concentration with an error of less than 0.5 g/dL.

2. METHODS

2.1. System design for Hemoglobin prediction

The main objective is predicting the total hemoglobin with the PLSR model designed using a soft-core system with five wavelengths PPG. The block diagram of the Hemoglobin Meter in the FPGA Platform is shown in Figure 1.
The finger probe consists of a light source (Multichip LED) on one side and a photodetector (OPT101) on the other side. It uses the principle of Transmission Photoplethysmography. The LEDs with wavelengths 670nm, 770nm, 810nm, 850nm, and 950 nm are chosen since the blood absorption is highly dominated by hemoglobin at these wavelengths. The LED sources were controlled using the DE0 Nano FPGA Board. The light emitted from one side travels through the finger tip and reaches to the detector. Most of the light is absorbed by the tissues and the venous blood. The flow of blood is heartbeat induced, or pulsatile so the transmitted light changes with time. The incoming real-time PPG signal is converted into digital using an in-built A/D converter NS ADC128S022 (8 channels, 12 bit). The PPG signal is then pre-processed to remove the noise and baseline wandering using the moving average algorithm. The Quality Assessment of the PPG signal is also done to extract good quality PPG signal. The optical densities are then calculated from the extracted PPG signal of the subjects. These are then given as inputs to the PLSR model along with the reference hemoglobin to calibrate the PLSR model. The PLSR model is then validated with another set of PPG signals and the hemoglobin was predicted and displayed on LCD.

Fig 1. Block diagram of Non-Invasive Hemoglobin Meter in FPGA Platform.

2.1.1. Creation of a Soft-core system
In our design, with the help of platform designer (SOPC builder) in Quartus 18.1, a system was created based on the 32 bit NIOS II processor core with all the required components like On-chip memory, SDRAM, RS232 UART, Interval Timer, Parallel Ports, ADC, and LCD. After selecting the SOPC components, the SOPC builder generates the hardware descriptive language (HDL) files that define all the components of the system. The NIOS II processor is interfaced to the SDRAM memory to store the C++ code and the digitized PPG signal using 12-bit ADC present in the DE0 Nano FPGA board. The generated system is then brought to the Quartus Block diagram file window, and later, the pin mapping is done as shown in Figure 2.

Once the design is compiled, the FPGA is configured and downloaded with SRAM Object File (.sof) which contains the NIOS II hardware system. When the configuration is completed, the application software is written and compiled using the NIOS II SBT for Eclipse and loaded into the SDRAM of the DE0 Nano FPGA board.
Once the hardware setup is ready, the next step is to program the system to predict total hemoglobin. The flowchart depicting the steps is shown in Figure 3.

![Flowchart for the Entire System](image)

Fig 3. Flowchart for the Entire System

First the ADC and LCD is configured. Then the PPG signal is acquired for five different wavelengths of LEDs in sequential order (670nm, 770nm, 810nm, 850nm, and 950nm) for duration of five seconds each. The PPG signal is preprocessed using a moving average filter and the Quality Assessment for PPG signal for each PPG signal is done. Also, the optical density for each PPG signal is calculated for each subject. Next the PLSR model is calibrated with the optical densities at five different wavelengths along with the reference hemoglobin. Then the PLSR model is validated with the unknown data i.e. optical densities of the PPG signal. Finally, the Hemoglobin concentration is predicted using PLSR model and displayed on the LCD. The entire system designed for hemoglobin estimation is shown in Figure 4.
Fig 4. The designed Hemoglobin measurement system.

3. RESULTS AND DISCUSSION

The study was conducted on fifteen subjects. The formal consent was taken by explaining the procedure to the subjects before PPG signal recording. The subjects were aged between 18 and 60 years. The sensor was placed on the forefinger of the right arm of the subject. The PPG signal from the subjects was acquired for 30 seconds, followed by venous blood sample collection by a trained professional in the laboratory.

Figure 5 (a) shows the acquired PPG signal for five different wavelengths for a subject. Figure 5 (b) shows the enlarged PPG signal at 810 nm which shows DC and AC components. The DC component of the PPG signal corresponds to the amount of transmitted light absorbed by the tissues and the venous blood. The AC component of the PPG signal corresponds to the changes in volume of blood during the cardiac cycle [23].

\[
\triangle OD^\lambda = -\log \left[ \frac{\text{AC Comp. of PPG}}{\text{DC Comp. of PPG}} \right] - \left\{ \varepsilon \Pi Hb \triangle \Pi Hb + \varepsilon \Pi HbO_2 \triangle \Pi HbO_2 \right\} L
\]

(1)

where the AC Component of the PPG signal is the difference between the Maximum and Minimum of the PPG signal and the DC component of the PPG signal is the Minimum of the PPG signal as shown in figure 5.

\( \triangle OD^\lambda \) represents a change in optical density for a PPG signal at a specific wavelength.

\( \varepsilon Hb^\lambda \) & \( \varepsilon HbO_2^\lambda \) \( \rightarrow \) Molar extinction coefficient for deoxyhemoglobin and oxyhemoglobin at a specific wavelength.

\( \triangle Hb \) & \( \triangle HbO_2 \) \( \rightarrow \) Change in concentration of deoxyhemoglobin and oxyhemoglobin.

L \( \rightarrow \) is the length of the light path through the finger.
Fig 5. Acquired PPG signal.

The optical density is calculated at five different wavelengths of the PPG signal for fifteen subjects using Equation (1) and the individual optical densities for each subject at five LED wavelengths are depicted in Figure 6.

**Fig 6. Optical densities at five different wavelengths with reference hemoglobin for 15 subjects**

### 3.1. Predicting hemoglobin using Mathematical Empirical formula and PLSR model

Before applying Multivariate PLSR, we have used mathematical empirical formulas to predict hemoglobin. The concentration of oxyhemoglobin and deoxyhemoglobin were calculated using the five optical densities along with the well-known molar extinction coefficients of oxyhemoglobin and deoxyhemoglobin using Equation (2).

\[
\begin{bmatrix}
\Delta Hb \\
\Delta HbO_2
\end{bmatrix} =
\begin{bmatrix}
\Delta OD_{670} \\
\Delta OD_{770} \\
\Delta OD_{850} \\
\Delta OD_{950}
\end{bmatrix}
\times
\begin{bmatrix}
\varepsilon_{Hb}^{670} & \varepsilon_{HbO_2}^{670} \\
\varepsilon_{Hb}^{770} & \varepsilon_{HbO_2}^{770} \\
\varepsilon_{Hb}^{850} & \varepsilon_{HbO_2}^{850} \\
\varepsilon_{Hb}^{950} & \varepsilon_{HbO_2}^{950}
\end{bmatrix}^{-1}
\times [\text{L}]^{-1}
\]

(2)

From Equation (2), total hemoglobin is calculated by adding the concentration of oxyhemoglobin and deoxyhemoglobin.
Equation (3) indicates the concentration of total hemoglobin in g/dL where 64500 is the molecular mass of hemoglobin.

For PLSR model, 12 Subjects’ PPG signals are used for calibrating the model, and 3 Subjects’ PPG signals for validating the model. In the PLSR method, the optical densities at five different wavelengths are used as predictor variables and the reference hemoglobin concentration is used as response variables. The PLSR algorithm was developed using C++ and ported on NIOS II Soft-core system on DE0 Nano FPGA Board to predict the hemoglobin concentration.

The Root Mean Square Error (RMSE) is the square root of the mean of the square of all errors.

\[
RMSE = \sqrt{\frac{\sum_{i=1}^{N} (y - \hat{y})^2}{N}}
\]  

where \(y\) = Reference hemoglobin, \(\hat{y}\) = Predicted Hemoglobin, \(N\) is the number of subjects.

The accuracy of the system is shown in Equation (5).

\[
\text{Accuracy} = 1 - \left( \frac{\sum_{i=1}^{N} (y - \hat{y})/y}{N} \right) \times 100
\]

In our PLSR model, we have only one response variable and five predictor variables. Since we have only one variant, the number of principal components is only two [24]. But, we also have carried out the analysis with three, four and five components as shown in Table 1. The RMSE for hemoglobin with one principal component is more as it does not explain the total variance. It is also observed that the RMSE does not improve significantly beyond two principal components. Table 2 shows the predicted results with the mathematical calculations and PLSR model. The predicted hemoglobin with empirical formula was obtained using equation (3) and the predicted hemoglobin using PLSR model was obtained using the PLSR algorithm running on designed NIOS II soft-core system. The RMSE and accuracy for both the predictions were calculated using Equation (4) and Equation (5). The RMSE and Accuracy between predicted hemoglobin with empirical formula and laboratory measurement was 0.442 g/dL and 97.05% respectively and the RMSE, and accuracy between estimated hemoglobin with PLSR model and laboratory measurement was 0.179 g/dL and 98.98 % respectively.
3.2. Validation
The Bland–Altman analysis graphically compares the predicted and reference values of measurement. It is a scatter plot of the difference between the reference and the predicted reading on the Y-axis and the corresponding mean of the reference and predicted measurements on the X-axis [25]. The bias is the mean of differences between reference and predicted values between the two measurements of the same variable. The limits of agreements which are defined ± 1.96 times the Standard Deviation (SD) from the mean of difference are represented by the outer dotted lines, and bias (mean difference) is represented by the middle black line. Figure 7 shows the Bland-Altman plots for Total hemoglobin.

![Fig 7. Bland-Altman Plot.](image)

From Figure 7, it is observed that the Bias is -0.23 g/dL, SD of 0.45 g/dL, and limits of agreement from -1.1 to -0.68 g/dL for predicted hemoglobin with empirical formula. The Bias, SD, and limits of agreement are -0.15 g/dL, 0.13 g/dL, and -0.39 to 0.1 g/dL respectively for predicted hemoglobin with the PLSR model. The readings show a reduced spread for predicted hemoglobin with the PLSR model.

4. CONCLUSION
A low-cost, portable, non-invasive hemoglobin meter has been designed using fixed LED sources (Multichip LEDs) with a wavelength ranging from 670 to 950 nm along with Silicon detector OPT101 for PPG signal acquisition. The soft-core system was designed for predicting Hemoglobin using the PLSR model in Altera Nano DE0 Board. The PLSR algorithm was written in C++ language and was loaded into the FPGA for predicting hemoglobin in blood. The result of this study showed a good significant correlation between hemoglobin concentration and characteristics of the PPG signal. Initially, we have used mathematical empirical formulas to predict hemoglobin which gave a RMSE of 0.442 g/dL and a prediction accuracy of 97.05%. To improve system accuracy, we have implemented the PLSR model in the FPGA board. We had calibrated the model with 12 subjects’ optical densities for five different wavelengths along with the reference hemoglobin and validated the same model with 3 subjects’ data. With the PLSR, the hemoglobin was estimated with an accuracy of 98.98% and a RMSE of 0.179 g/dL for estimating hemoglobin. The designed system with the PLSR model can be used to quickly predict hemoglobin concentrations with high accuracy.

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