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Shifat Hossain

Kookmin University

Shantanu Sen Gupta

Kookmin University

Tae-Ho Kwon

Kookmin University

Ki-Doo Kim (✉ kdk@kookmin.ac.kr)

Kookmin University

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Derivation and Validation of Gray-Box Models to Estimate Non-Invasive In-vivo Percentage Glycated Hemoglobin using Digital Volume Pulse Waveform

Shifat Hossain¹, Shantanu Sen Gupta¹, Tae-Ho Kwon¹, Ki-Doo Kim^{1*}

Abstract

Glycated hemoglobin and blood oxygenation are the two most important factors for monitoring a patient's oxygen levels in the blood and the amount of average blood glucose levels. Digital Volume Pulse acquisition is a convenient method, even for a person with no previous training or experience, can be utilized to estimate the two abovementioned physiological parameters. The physiological basis assumptions are utilized to develop two-finger models for estimating the percent glycated hemoglobin and blood oxygenation levels. The first model consists of a blood vessel only hypothesis, while the second model is based on a whole-finger model system. We validated our two gray-box systems on diabetic and non-diabetic patients and obtained the mean absolute errors for the percent glycated hemoglobin (%HbA1c) and percent oxygen saturation (%SpO₂) of 0.375 and 1.676, respectively, for the blood vessel model and 0.271 and 1.395, respectively, for the whole-finger model. The precision analysis indicated that these models resulted in 2.08% and 1.74% mean %CV for %HbA1c and 0.54% and 0.49% mean %CV for %SpO₂ in the respective models. Herein, both models exhibit close performances to each other (HbA1c estimation Pearson R values are 0.92 and 0.96, respectively), even though the model assumptions greatly differed between them. Both of the models have a very high potential to be used in real-world scenarios. The whole-finger model performs better in terms of higher precision and accuracy compared to the blood vessel model.

¹ Department of Electronics Engineering, Kookmin University, Seoul, Korea. Correspondence and requests of materials should be addressed to Ki-Doo Kim (kdk@kookmin.ac.kr)

Digital Volume Pulse (DVP) acquisition system is an optical method for detecting the blood volume variation in tissue. For blood volume detection, the tissue is lit with specific light sources having a plane similar or perpendicular to the photodetector. The photodetector then registers the DVP signal.

DVP signals are generally used to detect time domain properties (e.g., heart rate ¹, respiration rate ², etc.) and quantitative parameters (e.g., blood oxygenation ^{3,4}, hypo- and hypervolemia ⁵, blood glucose level ⁶, etc.) from the human body. Time-domain properties can be estimated with only one wavelength of light, but quantitative properties will require multiple wavelengths of light with some model assumptions. Also, in a previous work, we proposed a new electronic circuit based on an analog filter, that can separate red and green PPG signals, acquire clean PPG signal, and estimate pulse rate (PR) and peripheral capillary oxygen saturation (SpO₂) ⁷.

Diabetes mellitus is a serious metabolic disease that severely affects over 422 million people around the world ⁸. Patients with diabetes are very likely to be affected by other serious diseases like heart disease, kidney failure, stroke, eye cataracts, and/or sudden mortality. Therefore, diagnosing diabetes is very important in the pre-diabetic stages to prevent the permanent failure of the bodily sugar control system that results in diabetes. Two methods can be used for diabetes diagnosis: glucose test (random, fasting, or oral) and glycated hemoglobin test. Glycated hemoglobin tests perform as well as or better than plasma glucose tests in diabetes diagnosis ⁹. Moreover, in a glycated hemoglobin test, one can avoid the variability of the plasma glucose in a full day depending on the lifestyle of the examined person.

Many methods are employed to estimate blood glucose and glycated hemoglobin levels. Over the past few decades, many enzymatic and non-enzymatic electrochemical glucose sensors have also been developed ^{10–15}, though these methods are invasive. On the contrary, non-invasive glucose estimation is a comparatively new topic, although some of its implementations using external bodily tissues (skin tissues) and fluids (e.g., saliva and tears) have been reported ^{16,17}. Implementations of PPG signals for the blood glucose level estimation have also been presented ⁶.

The four most common methodologies used for glycated hemoglobin estimation are immunoassay, ion-exchange high-performance liquid chromatography (HPLC), boronate affinity chromatography, and enzymatic assays ¹⁸. These methodologies require a whole blood sample and are performed by different chemical and/or electrochemical means. However, no non-invasive in-vivo research methodologies have yet been performed on the %glycated hemoglobin estimation as regression analysis until now. A non-invasive classification-based solution (classification among diabetic, obese, and normal control groups) has been applied to mice models by measuring hyperglycemia-associated conditions ¹⁹. One research discussed the estimation of in-vitro HbA1c ²⁰, but only focused on the PPG sensor design and did not cover non-invasive in-vivo estimation methods. And there are other conference papers, which also focuses on the classification of a person's diabetic status, but not estimation of glycated hemoglobin ^{21,22}. And another paper focuses on breath acetone-based HbA1c estimation ²³, but the error rate is very high.

In the present study, glycated hemoglobin (HbA1c) is estimated through an optical plethysmographic system. A single white light is transmitted through the fingertip, and the transmitted light waves of different wavelengths are received with three different optical filters on the optical sensor side. This received light wave is called the DVP signal.

The %HbA1c in blood is estimated along with the %SpO₂ value using this received DVP signal of multiple wavelengths of light. The DVP signals of three wavelengths are taken to perform this research and estimate the two abovementioned parameters.

I. Gray-box model

In mathematics and computational models, the gray-box models have a special role. This model can explain how the whole system is operating (like a white-box model), and on the other hand, it also corresponds with the practical reference data matched statistically. So, a gray-box model is a combination of theoretical parts, as well as the data-based black-box model. Here, in this study, we develop theoretically-based models based on the physiology of blood transportation and glycation of hemoglobin and combine this model with black-box calibration models.

II. Finger models and coefficients

Glycated hemoglobin or HbA1c was estimated herein through an optical sensor and transmitter system. Multiple light waves were transmitted through the fingertip, and the transmitted light waves (for a transmissive system) were recorded with an optical sensor. These recorded signals are called the DVP signals.

Using the DVP signal received from multiple light sources, we calculated the percent glycated hemoglobin (%HbA1c) in the blood along with the percent oxygen saturation (%SpO₂). These two parameters were estimated at the same time; hence, three light sources were required (i.e., 525, 465, and 615 nm denoted by λ_1 , λ_2 , and λ_3 , respectively). According to this physiological basis gray-box model-based approach, any three different wavelengths of light can be chosen. But these wavelengths were chosen to easily implement these models with a simple color sensor. And it is also possible to utilize a mobile camera sensor to record DVP signals.

The location of the DVP signal acquisition (e.g., fingertip, upper and lower wrists, earlobe, etc.) was modeled as a simple mathematical model of only the blood components for the first model and the homogenous mixture of tissues, arterial and venous blood, and water for the second model, which is the whole-finger model. The bones were ignored because we assumed that the bone tissues will not transmit enough light to be detectable by the optical sensor. The assumption states the bone as a fixed perfect absorber of light contributing to the DC parts of the signal only. In the abovementioned models, we stated the blood as a homogenous mixture of glycated hemoglobin (HbA1c), oxygenated hemoglobin (HbO), and reduced deoxygenated hemoglobin (HHb).

%HbA1c and %SpO₂ are described as follows:

$$\%HbA1c = \frac{c_{HbA1c}}{c_{HHb} + c_{HbO} + c_{HbA1c}} \times 100\% \quad (1)$$

$$\%SpO_2 = \frac{c_{HbO}}{c_{HHb} + c_{HbO}} \times 100\% \quad (2)$$

where, c_{HbA1c} , c_{HbO} , and c_{HHb} are the molar concentrations of HbA1c, HbO, and HHb, respectively. The denominator of %SpO₂ does not include c_{HbA1c} or any other components because the base for %SpO₂ contains only oxygen-bonded hemoglobin cells and hemoglobin cells available for binding with oxygen²⁴.

The %Glycated hemoglobin and %Oxygen saturation were estimated using two forms of the finger model. The two models were based on two different hypotheses and described in the following sections.

a. Blood vessel model

The first model was built based on the hypothesis that when blood comes into the blood vessel, the diameter of the vessel slightly expands for the incoming blood volume and reduces the diameter when the blood leaves. Figure 1 depicts the blood vessel model hypothesis.

Figure 1: Blood vessel model illustration with hypothetical blood pulses: (a) DVP signal; (b) light intensity in the systolic phase; and (c) light intensity in the diastolic phase.

The first model only considers blood in the blood vessels; thus, the absorption coefficient of the homogenous mixture of the HbA1c, HbO, and HHb blood components can be calculated as

$$C_a = \epsilon_a^{HbA1c}(\lambda) \times c_{HbA1c} + \epsilon_a^{HbO}(\lambda) \times c_{HbO} + \epsilon_a^{HHb}(\lambda) \times c_{HHb} \quad (3)$$

$$\text{Therefore, } C_a = \mu_a^{HbA1c}(\lambda) + \mu_a^{HbO}(\lambda) + \mu_a^{HHb}(\lambda) \quad (4)$$

In Eq. (3), C_a is the total absorption coefficient of the model solution; ϵ is the molar absorption coefficient [$L \text{ mol}^{-1} \text{ cm}^{-1}$]; c is the molar concentration of the attenuator [mol L^{-1}]. In Eq. (4), μ_a^{HbA1c} , μ_a^{HbO} , and μ_a^{HHb} are the absorption coefficients, while $\epsilon_a^{HbA1c}(\lambda)$, $\epsilon_a^{HbO}(\lambda)$, and $\epsilon_a^{HHb}(\lambda)$ are the molar absorption coefficients of HbA1c, HbO, and HHb, respectively.

b. Whole-finger model

The whole-finger model was constructed based on the homogenous mixture of the lumped finger elements (e.g., dermal tissue, water, and arterial and venous blood). Similar to the previous model, blood is also considered as a homogenous mixture of HbA1c, HbO, and HHb hemoglobin cells. Figure 2 illustrates the fractional volume composition of the whole-finger model.

Figure 2: Fractional volume composition of the whole-finger model.

The absorption coefficient of the finger elements can be calculated as

$$C_a = V_a \mu_a^{art}(\lambda) + V_v \mu_a^{vein}(\lambda) + V_w \mu_a^{water}(\lambda) + [1 - (V_a + V_v + V_w)] \mu_a^{baseline} \quad (5)$$

$$\text{where, } \mu_a^{art} = \mu_a^{HHb} + P_{HbO}^{art}(\mu_a^{HbO} - \mu_a^{HHb}) + P_{HbA1c}^{art}(\mu_a^{HbA1c} - \mu_a^{HHb}) \quad (6)$$

$$\mu_a^{vein} = \mu_a^{HHb} + P_{HbO}^{vein}(\mu_a^{HbO} - \mu_a^{HHb}) + P_{HbA1c}^{vein}(\mu_a^{HbA1c} - \mu_a^{HHb}) \quad (7)$$

In Eq. (5), V_a , V_v , and V_w are the partial volume fractions of the artery, vein, and water, respectively; and μ_a^{art} , μ_a^{vein} , μ_a^{water} , and $\mu_a^{baseline}$ are the absorption coefficients of the arterial composition, venous composition, water, and lumped dermal skin layer, respectively. In Eqs. (6) and (7), the μ_a^{HHb} , μ_a^{HbO} , and μ_a^{HbA1c} are not the true absorption coefficients of deoxy-, oxy-, and glycated-hemoglobin. These are the result of multiplication of the molar absorption coefficient of respective hemoglobin types with whole blood concentration. The P_{HbO}^{art} , P_{HbA1c}^{art} , P_{HbO}^{vein} , and P_{HbA1c}^{vein} are the partial molar concentrations of HbO and HbA1c in the artery and vein, respectively. They can be mathematically stated as

$$P_{HbO} = \frac{c_{HbO}}{c_{HHb} + c_{HbO} + c_{HbA1c}} \quad (8)$$

$$P_{HbA1c} = \frac{c_{HbA1c}}{c_{HHb} + c_{HbO} + c_{HbA1c}} \quad (9)$$

$$P_{HHb} = 1 - (P_{HbO} + P_{HbA1c}) \quad (10)$$

where P_{HHb} represents the partial molar concentration of HHb(deoxy-hemoglobin). Eqs. (6) and (7) can be easily derived from the following form:

$$\mu_a = \epsilon_a^{HbA1c}(\lambda) \times c_{HbA1c} + \epsilon_a^{HbO}(\lambda) \times c_{HbO} + \epsilon_a^{HHb}(\lambda) \times c_{HHb}$$

$$\mu_a = (c_{Tot}) \times \left(\epsilon_a^{HHb} + P_{HbO}(\epsilon_a^{HbO} - \epsilon_a^{HHb}) + P_{HbA1c}(\epsilon_a^{HbA1c} - \epsilon_a^{HHb}) \right) \quad [\text{From (8), (9), and (10)}]$$

$$\text{where, } c_{Tot} = c_{HbA1c} + c_{HbO} + c_{HHb} = \frac{150}{64500} \text{ mol dm}^{-3}.$$

Eqs. (8)–(10) have the same structure for both artery and vein locations. The molar concentration values in the abovementioned equations were changed according to the location (i.e., artery or vein). Using the partial molar concentration terminologies (i.e., P_{HbA1c} , P_{HbO} , and P_{HHb}) as described above, the %HbA1c and %SpO₂ formulas in Eqs. (1) and (2) can be redefined as follows:

$$\%SpO_2 = \frac{P_{HbO}}{P_{HHb} + P_{HbO}} \times 100\% \quad (11)$$

$$\%HbA1c = P_{HbA1c} \times 100\% \quad (12)$$

III. Beer-Lambert law

When blood enters a blood vessel in a certain region, the incident light is absorbed differently compared to the region with no blood in it because different blood components also absorb light differently. The total absorbance of a homogeneous solution can be mathematically described by the Beer-Lambert Law as follows:

$$A = \sum_{i=1}^N A_i = \sum_{i=1}^N \epsilon_i \times c_i \times d = -\log \left(\frac{I}{I_0} \right) \quad (13)$$

where A is the total absorbance of the solution; N is the number of attenuating species; ϵ is the molar absorption coefficient [$L \text{ mol}^{-1} \text{ cm}^{-1}$]; c is the molar concentration of the attenuating species [mol cm^{-1}]; and d is the distance traversed by the light beam inside the specimen.

The absorbance of the solution obtained by the Beer-Lambert Law can be directly measured by applying the incident light (I_0) and measuring the intensity of the light transmitted by the solution (I). Therefore, if any homogeneous solution can be represented in the form of (13), it can be solved for an unknown parameter.

The Beer-Lambert Law can be applied to the previously described finger models to obtain the total absorbance of the model solution. The decadic absorption coefficient described in the finger model Eqs. (3)–(5) can be described in terms of absorbance (A) in the following form because the solution is considered homogeneous and will have a uniform absorption along the light traversal path. Figure 3 depicts the parameter estimation utilizing the Beer-Lambert law.

$$A = C_a d \quad (14)$$

Figure 3: Parameter estimation with the Beer-Lambert law.

a. Blood vessel model

We obtain the following when solving the blood vessel model from Eqs. (3) and (14):

$$A = (\epsilon_a^{HbA1c}(\lambda) \times c_{HbA1c} + \epsilon_a^{HbO}(\lambda) \times c_{HbO} + \epsilon_a^{HHb}(\lambda) \times c_{HHb}) \times d \quad (15)$$

According to this current hypothesis, the molar concentration of the individual components of the model solution will be the same, even when blood comes into the vessels, increasing the volume of the vessel tracts. Therefore, in this assumption, the distance traversed by the light beam inside the finger model will be increased when blood comes in and will be reduced when blood leaves the vessel.

In other words, if absorbance is measured in the two states (i.e. when blood comes in $[A_1]$ and flows out $[A_2]$), the difference between the two states is obtained as

$$\delta A = (\epsilon_a^{HbA1c}(\lambda) \times c_{HbA1c} + \epsilon_a^{HbO}(\lambda) \times c_{HbO} + \epsilon_a^{HHb}(\lambda) \times c_{HHb}) \times \delta d \quad (16)$$

where

$$\delta d = d_1 - d_2, \quad \delta A = A_1 - A_2.$$

For the three light wavelengths (i.e., λ_1 , λ_2 , and λ_3), Eq. (16) can be written as

$$\delta A_{\lambda_1} = (\epsilon_a^{HbA1c}(\lambda_1) \times c_{HbA1c} + \epsilon_a^{HbO}(\lambda_1) \times c_{HbO} + \epsilon_a^{HHb}(\lambda_1) \times c_{HHb}) \times \delta d \quad (17)$$

$$\delta A_{\lambda_2} = (\epsilon_a^{HbA1c}(\lambda_2) \times c_{HbA1c} + \epsilon_a^{HbO}(\lambda_2) \times c_{HbO} + \epsilon_a^{HHb}(\lambda_2) \times c_{HHb}) \times \delta d \quad (18)$$

$$\delta A_{\lambda_3} = (\epsilon_a^{HbA1c}(\lambda_3) \times c_{HbA1c} + \epsilon_a^{HbO}(\lambda_3) \times c_{HbO} + \epsilon_a^{HHb}(\lambda_3) \times c_{HHb}) \times \delta d \quad (19)$$

From Eqs. (17)–(19), three ratio equations can be obtained, and any two ratio equations can be used to estimate the two unknowns, %HbA1c and %SpO₂. For convenience, we now define two ratio equations as follows:

$$R_1 = \frac{\delta A_{\lambda_1}}{\delta A_{\lambda_3}} = \frac{\epsilon_a^{HbA1c}(\lambda_1) \times c_{HbA1c} + \epsilon_a^{HbO}(\lambda_1) \times c_{HbO} + \epsilon_a^{HHb}(\lambda_1) \times c_{HHb}}{\epsilon_a^{HbA1c}(\lambda_3) \times c_{HbA1c} + \epsilon_a^{HbO}(\lambda_3) \times c_{HbO} + \epsilon_a^{HHb}(\lambda_3) \times c_{HHb}} \quad (20)$$

$$R_2 = \frac{\delta A_{\lambda 2}}{\delta A_{\lambda 3}} = \frac{\epsilon_a^{HbA1c}(\lambda_2) \times c_{HbA1c} + \epsilon_a^{HbO}(\lambda_2) \times c_{HbO} + \epsilon_a^{HHb}(\lambda_2) \times c_{HHb}}{\epsilon_a^{HbA1c}(\lambda_3) \times c_{HbA1c} + \epsilon_a^{HbO}(\lambda_3) \times c_{HbO} + \epsilon_a^{HHb}(\lambda_3) \times c_{HHb}} \quad (21)$$

To represent Eqs. (20) and (21) with the %SpO₂ and %HbA1c terms, the equations can be simplified with P_{HbA1c} , P_{HbO} , and P_{HHb} terms from Eqs. (8)–(10). The solved P_{HbO} and P_{HbA1c} terms can then be easily converted to the %SpO₂ and %HbA1c terms, respectively, using Eqs. (11) and (12).

Thus, applying Eqs. (8)–(10) to Eqs. (20) and (21), we obtain

$$R_1 = \frac{P_{HbA1c}(\epsilon^{HbA1c}(\lambda_1) - \epsilon^{HHb}(\lambda_1)) + P_{HbO}(\epsilon^{HbO}(\lambda_1) - \epsilon^{HHb}(\lambda_1)) + \epsilon^{HHb}(\lambda_1)}{P_{HbA1c}(\epsilon^{HbA1c}(\lambda_3) - \epsilon^{HHb}(\lambda_3)) + P_{HbO}(\epsilon^{HbO}(\lambda_3) - \epsilon^{HHb}(\lambda_3)) + \epsilon^{HHb}(\lambda_3)} \quad (22)$$

$$R_2 = \frac{P_{HbA1c}(\epsilon^{HbA1c}(\lambda_2) - \epsilon^{HHb}(\lambda_2)) + P_{HbO}(\epsilon^{HbO}(\lambda_2) - \epsilon^{HHb}(\lambda_2)) + \epsilon^{HHb}(\lambda_2)}{P_{HbA1c}(\epsilon^{HbA1c}(\lambda_3) - \epsilon^{HHb}(\lambda_3)) + P_{HbO}(\epsilon^{HbO}(\lambda_3) - \epsilon^{HHb}(\lambda_3)) + \epsilon^{HHb}(\lambda_3)} \quad (23)$$

We can combine the right side of Eq. (13) with Eqs. (22) and (23) to calculate the ratio equations directly from the received light from the fingertip and obtain

$$R_1 = \frac{\delta A_{\lambda 1}}{\delta A_{\lambda 3}} = \frac{\delta \left[-\log \frac{I}{I_0} \right]_{\lambda 1}}{\delta \left[-\log \frac{I}{I_0} \right]_{\lambda 3}} = \frac{\left[\log \frac{I_0(d_1)}{I(d_1)} - \log \frac{I_0(d_2)}{I(d_2)} \right]_{\lambda 1}}{\left[\log \frac{I_0(d_1)}{I(d_1)} - \log \frac{I_0(d_2)}{I(d_2)} \right]_{\lambda 3}} = \frac{\left[\log \frac{I(d_2)}{I(d_1)} \right]_{\lambda 1}}{\left[\log \frac{I(d_2)}{I(d_1)} \right]_{\lambda 3}} \quad (24)$$

$$\text{Similarly, } R_2 = \frac{\delta A_{\lambda 2}}{\delta A_{\lambda 3}} = \frac{\left[\log \frac{I(d_2)}{I(d_1)} \right]_{\lambda 2}}{\left[\log \frac{I(d_2)}{I(d_1)} \right]_{\lambda 3}} \quad (25)$$

Solving Eqs. (22) and (23) for P_{HbA1c} and P_{HbO} yields:

$$P_{HbA1c} = \frac{C_1 R_1 + C_2 R_2 + C_3}{C_4 R_1 + C_5 R_2 + C_6} \quad (26)$$

$$P_{HbO} = \frac{C_7 R_1 + C_8 R_2 + C_9}{C_{10} R_1 + C_{11} R_2 + C_{12}} \quad (27)$$

The coefficients C_1 to C_{12} are the values we get after solving Eqs. (22) and (23). The values of these coefficients are given in the results section (Section III-c) of this manuscript.

b. Whole-finger model

As stated earlier, the whole-finger model considers a homogenous mixture of lumped fingertip constitutes. The blood coming inside this model will increase the partial volume fraction of the arterial blood. At the same time, the partial volume fractions of the venous blood and water will decrease along with the baseline skin volume fraction. However, note that these transient changes of the venous, water, and skin components were neglected herein for simplicity. The increase in the partial volume fraction of the arterial blood is denoted by ΔV_a . Therefore, only considering the arterial fraction increment, the absorption coefficient equation becomes

$$C_a + \Delta C_a = (V_a + \Delta V_a) \mu_a^{art}(\lambda) + V_v \mu_a^{vein}(\lambda) + V_w \mu_a^{water}(\lambda) + [1 - (V_a + \Delta V_a + V_v + V_w)] \mu_a^{baseline} \quad (28)$$

The change in the absorption coefficient for the change in the arterial blood volume is denoted by ΔC_a .

Now, subtracting Eq. (5) from Eq. (28), we obtain

$$\Delta C_a = \Delta V_a \left(\mu_a^{art}(\lambda) - \mu_a^{baseline}(\lambda) \right) \quad (29)$$

We also know from Eqs. (13) and (14) that

$$I = I_0 10^{-C_a d} \quad (30)$$

We need to differentiate Eq. (30) in terms of C_a to determine the relation of the physical light intensity with Eq. (29):

$$\frac{dI}{dC_a} = -\ln(10) I_0 d 10^{-C_a d} \quad (31)$$

We also know that

$$\frac{dI}{dC_a} \approx \frac{\Delta I}{\Delta C_a} \quad (32)$$

Eqs. (31) and (32) yield:

$$\Delta I \approx -\ln(10) I_0 \Delta C_a d 10^{-C_a d} \quad (33)$$

We now generate the AC–DC intensity ratio by the assumption $\frac{I_{AC}}{I_{DC}} = \frac{\Delta I}{I}$. The AC part of the signal denotes the pulsatile part of the signal, and vice-versa. Let us then divide Eq. (33) with Eq. (30) and replace ΔC_a from Eq. (29):

$$\frac{\Delta I}{I} = -\ln(10) \Delta V_a \left(\mu_a^{art}(\lambda) - \mu_a^{baseline}(\lambda) \right) d \quad (34)$$

Similar to the previous model, this equation can be used to make the ratio equations of any two of the three wavelengths. The ratio equations become

$$R_1 = \frac{\left[\frac{\Delta I}{I} \right]_{\lambda_1}}{\left[\frac{\Delta I}{I} \right]_{\lambda_3}} = \frac{\mu_a^{art}(\lambda_1) - \mu_a^{baseline}(\lambda_1)}{\mu_a^{art}(\lambda_3) - \mu_a^{baseline}(\lambda_3)} \quad (35)$$

$$R_2 = \frac{\left[\frac{\Delta I}{I} \right]_{\lambda_2}}{\left[\frac{\Delta I}{I} \right]_{\lambda_3}} = \frac{\mu_a^{art}(\lambda_2) - \mu_a^{baseline}(\lambda_2)}{\mu_a^{art}(\lambda_3) - \mu_a^{baseline}(\lambda_3)} \quad (36)$$

Finally, solving Eqs. (35) and (36) gives two equations with the following forms:

$$P_{HbA1c}^{art} = \frac{C_1 R_1 + C_2 R_2 + C_3}{C_4 R_1 + C_5 R_2 + C_6} \quad (37)$$

$$P_{HbO}^{art} = \frac{C_7 R_1 + C_8 R_2 + C_9}{C_{10} R_1 + C_{11} R_2 + C_{12}} \quad (38)$$

The coefficients C_1 to C_{12} are the values we get after solving Eqs. (35) and (36). The values of these coefficients are given in the results section (Section III-c) of this manuscript.

IV. Result and comparison between models

a. Coefficient values on different wavelengths

Our data acquisition device used three dominant wavelengths of 465, 525, and 615 nm; thus, we must evaluate the values of the wavelength-dependent parameters for the respective light wavelengths to solve the model equations. These parameters include the molar absorption coefficient of HHb, HbO, and HbA1c given in Table 1 and the absorption coefficient of HHb, HbO, HbA1c, skin baseline, and water given in Table 2. The molar absorption coefficient data of the HbA1c, HbO, and HHb were taken from ²⁵ and ²⁶, respectively. The absorption coefficient data of HbA1c, HbO, and HHb were calculated from the molar absorption coefficient multiplied by 150/64500 mol/L for the whole blood hemoglobin. The absorption coefficient data of the skin baseline and water were taken from ²⁷ and ²⁸, respectively.

Table 1: Molar absorption coefficient of HbA1c, HbO, and HHb for the respective wavelengths.

Wavelength (nm)	Molar absorption coefficient ($M^{-1}cm^{-1}$)		
	HbA1c	HbO	HHb
465	549,024.7353	38,440.2	18,701.6
525	455,139.5677	30,882.8	35,170.8
615	170,555.4218	1166.4	7553.4

Table 2: Absorption coefficients of HbA1c, HbO, HHb, skin baseline, and water for the respective light wavelengths.

Wavelength (nm)	Absorption coefficient (cm^{-1})				
	HbA1c	HbO	HHb	Skin baseline	Water
465	1276.8017	89.3958	43.4921	1.6279	0.00020277
525	1058.4641	71.8205	81.7926	1.0966	0.0003927
615	396.6405	2.7126	17.566	0.6552	0.0027167

The absorption coefficient values of HbA1c, HbO, and HHb described in Table 2 are not true absorption coefficients of those parameters. Rather, they are the multiplication of molar absorption coefficients of respective elements with the whole-blood molar concentration.

b. Ratio equations with coefficient values

For the blood vessel model, we obtain the following equations by taking the wavelength (λ) values as $\lambda_1 = 525$ nm, $\lambda_2 = 465$ nm, and $\lambda_3 = 615$ nm and placing the parameter values from Table 1 into Eqs. (22) and (23):

$$R_1 = \frac{419968.1653 \times P_{HbA1c} - 4288.0 \times P_{HbO} + 35170.8}{163002.0218 \times P_{HbA1c} - 6387.0 \times P_{HbO} + 7553.4} \quad (39)$$

$$R_2 = \frac{530323.1353 \times P_{HbA1c} + 19738.6 \times P_{HbO} + 18701.6}{163002.0218 \times P_{HbA1c} - 6387.0 \times P_{HbO} + 7553.4} \quad (40)$$

We acquire the following equations by defining similar wavelength (λ) values for the whole-finger model and placing the values from Table 2 into Eqs. (35) and (36):

$$R_1 = \frac{976.6715 \times P_{HbA1c} - 9.9721 \times P_{HbO} + 80.696}{379.0745 \times P_{HbA1c} - 14.8534 \times P_{HbO} + 16.9108} \quad (41)$$

$$R_2 = \frac{1233.3096 \times P_{HbA1c} + 45.9037 \times P_{HbO} + 41.8642}{379.0745 \times P_{HbA1c} - 14.8534 \times P_{HbO} + 16.9108} \quad (42)$$

c. P_{HbA1c} and P_{HbO} equations with coefficient values

At this stage, Eqs. (39)–(42) were solved for P_{HbA1c} and P_{HbO} . For the blood vessel model, Eqs. (39) and (40) were solved, and we obtained equations in the form of Eqs. (26) and (27) with the coefficient values (rounded with 10^{12}) given in Table 3.

Table 3: Coefficient values for the P_{HbA1c} and P_{HbO} equations of the blood vessel model.

c_1	c_2	c_3	c_4	c_5	c_6
13.427	-9.612	-38.721	-330.230	99.169	528.181
c_7	c_8	c_9	c_{10}	c_{11}	c_{12}
-47.867	-128.036	539.890	-330.230	99.169	528.181

Similarly, for the whole-finger model, Eqs. (41) and (42) were solved in the form of Eqs. (37) and (38), with the coefficients (rounded with 10^{11}) given in Table 4.

Table 4: Coefficient values for the P_{HbA1c} and P_{HbO} equations of the whole-finger model.

c_1	c_2	c_3	c_4	c_5	c_6
1.398	-1.030	-4.122	-35.720	10.727	57.132
c_7	c_8	c_9	c_{10}	c_{11}	c_{12}
-4.987	-14.073	58.636	-35.720	10.727	57.132

d. Clinical dataset information

We conducted a small “proof of method” test with 20 participants to test our hypothesis and model performance. Four of the volunteers were normal; 13 were in the pre-diabetic range; three had diabetes (Fig. 4). The age range of the subjects was from 24 to 64 years (31.6 ± 10). Among the subjects, 5 of them were females and 15 of them were males.

Figure 4: Dataset diabetes class plot.

For each volunteer, we recorded 4 min of DVP and measured SpO₂ data and a National Glycohemoglobin Standardization Program (NGSP) %HbA1c value using an invasive device. The SpO₂ data were acquired using the Schiller Argus OXM Plus clinical blood oxygenation patient-monitoring device, while the invasive %NGSP HbA1c was measured using the BioHermes A1C EZ 2.0 device.

The volunteers were first checked for any known previous complications that might cause problems either to them or to the experiment. They were then asked to seat idly for approximately 1–2 min to stabilize their heart rate. Subsequently, the DVP waveform was recorded with the corresponding devices. The SpO₂ parameter of a volunteer was recorded in video format from the Argus device display. The volunteers were steady at the time of data acquisition; thus, the variability of the blood oxygen saturation was very low. Due to the SpO₂ invariability, the average of the blood oxygen saturation values was taken for each individual to evaluate the model. Figure 5 depicts the distribution of the %NGSP HbA1c and %SpO₂ values for our dataset. Table 5 presents the statistics of the %NGSP HbA1c and %SpO₂ values.

Figure 5: Histogram plot of the measured dataset (a) %NGSP HbA1c value and (b) %SpO₂ value.

Table 5: Statistics of the measured %HbA1c and %SpO₂ data.

	Min	Max	Mean	Median	STD	Variance	25th Percentile	75th Percentile
%HbA1c	4.9	9.1	6.22	5.9	1.103	1.216	5.7	6.125
%SpO ₂	93	99.0	96.55	97.0	1.322	1.747	96.0	97.0

e. Calibration

After the dataset creation, we now calibrate the model with experimental data. These models were based on simple assumptions and processes. Consequently, the models will eventually generate erroneous values without calibration due to model inaccuracy.

To calibrate these models, we assumed that the measured %NGSP HbA1c and %SPO₂ values were correct. Based on this assumption, we first adjusted the recorded DVP signal values by calibrating the two ratio values (R_1^{sig} and R_2^{sig}) obtained from the signal amplitudes with the calculated ratio values from Eqs. (39) and (40) for the blood vessel model and Eqs. (41) and (42) for the whole-finger model given the normalized values of the measured %HbA1c and %SpO₂. This step of calibrating the ratio

values is crucial because different individuals have different finger width and different skin and fat layer properties. To reduce the effects of skin, fat layer, and finger width effects on DVP signal amplitudes, this calibration process is applied. In this calibration step, the ratio values from the signal are calibrated to calculated ratio values (R_1' and R_2') from the Eqs. (39)-(42) with two more features, that can compensate for the ratio variability among individuals. These two features are – finger width and body mass index (BMI). So, there are four input features, R_1^{sig} , R_2^{sig} , finger width, and BMI. And the targets are R_1' and R_2' for two independent ratio calibrators respectively.

Then after calibrating the ratio values, the finger model equations are used to estimate the normalized HbA1c and SpO₂ values. Though these values are close to the reference measurements, these require further calibration to mitigate the model errors (i.e. model inadequacy and propagation errors). This second-level calibration is done on the calculated HbA1c and SpO₂ values given the reference HbA1c and SpO₂ as targets, respectively.

The ratio calibration system, and the HbA1c and SpO₂ value calibration systems are implemented by the XGBoost Regression algorithm with default parameters. And to evaluate the calibrated results, Leave One Out Cross Validation (LOOCV) was used. The whole calibration process block diagram is depicted in Figure 6.

Figure 6: Calibration description block diagram. (h = normalized HbA1c, s = normalized SpO₂)

In Fig.6, the orange blocks represent reference and input data sources, the green blocks represent calibration steps, and the blue blocks represent finger models. The calibrated ratio values using XGBoost regressor with LOOCV test results are passed to the finger model to estimate the normalized HbA1c and SpO₂ values. Then these estimated normalized HbA1c and SpO₂ values are again calibrated and LOOCV test results are considered as final estimated %HbA1c and %SpO₂ values.

f. Result deduction

The following results were obtained with the two models after the %HbA1c value calibration: the plot of Clarke's error grid analysis ^{29,30} is given with the Bland–Altman analysis in Figure 7 for the blood vessel model and Figure 8 for the whole-finger model.

Figure 7: HbA1c Clarke's Error Grid Analysis (EGA) and Bland–Altman analysis for the blood vessel model.

Figure 8: HbA1c Clarke's Error Grid Analysis (EGA) and Bland–Altman analysis for the whole-finger model.

Figure 7 illustrates that the error grid analysis, with Zone A (clinically accurate data) containing 14 samples (73.68%), Zone B with 5 (26.31%) (data outside of 20% of the reference, but would not lead to inappropriate treatment), and Zone C with 0 (0%) (data that would lead to uncertain treatment).

Figure 8 shows the rigid artery vein model consisting of 18 (90.0%), 2 (10.0%), and 0 (0%) samples in zones A, B, and C, respectively.

The Bland–Altman analysis indicated that the blood vessel model provided a bias of -0.03 ± 0.898 , and the limits of agreement (95%; 1.96 STD) ranged from -0.93 to 0.87 . For the whole-finger model, the bias was -0.06 ± 0.638 , and the level of agreement (-0.70 to 0.57) was smaller than that of the blood vessel model.

We also tested the prediction variability for each patient's data. We took 4 min of the DVP data; thus, the %Coefficient of Variation (%CV) for the predicted %NGSP HbA1c for each data frame (single DVP wave) for each patient is indicated as a measure of the precision in the full range of 4 min data. Figure 9 depicts the %CV vs reference %HbA1c data.

Figure 9: Percent coefficient of variation for the reference and estimated %HbA1c values for both models.

The %CV plot of all frames of the data illustrates that the mean %CV was 2.08% for the blood vessel model and 1.74% for the whole-finger model. These results are very accurate for the repeatability analysis.

The statistical analysis of the estimated and reference %HbA1c data from the blood vessel model yielded the mean square error (MSE) of 0.211, mean error (ME) of -0.031 , mean absolute deviation (MAD) of 0.375, and root mean square error (RMSE) of 0.459. The Pearson R coefficient metric resulted in 0.916.

Similarly, the statistical analysis of the whole-finger model provided 0.110, -0.065 , 0.271, and 0.332 for the MSE, ME, MAD, and RMSE, respectively. And the Person R coefficient metric resulted in 0.959.

The estimated %SpO₂ values were also calibrated and analyzed. Figures 10 and 11 depict the scatter plot and the Bland–Altman analysis of the estimated vs reference %SpO₂ values for the blood vessel and whole-finger models, respectively. The Bland–Altman analysis of the %SpO₂ values showed a bias of 0.178 ± 3.923 and -0.246 ± 3.312 for the blood vessel and whole-finger models, respectively. The limit of agreement ranged from -3.74 to 4.10 and -3.56 to 3.07 for the models, respectively.

(a) Scatter plot

(b) Bland–Altman analysis

Figure 10: Scatter plot and Bland–Altman analysis of the estimated vs reference (measured) %SpO₂ values for the blood vessel model.

(a) Scatter plot

(b) Bland–Altman analysis

Figure 11: Scatter plot and Bland–Altman analysis of the estimated vs reference (measured) %SpO₂ values for the whole-finger model.

For the precision analysis of the estimated %SpO₂ values, the %CV was calculated similarly to the case of %HbA1c values. The maximum %CV was 1.58 and 1.77 for the blood vessel and whole-finger models, respectively, while the mean of %CV was 0.54 and 0.49, respectively (Fig. 12).

Figure 12: Percent coefficient of variation for the reference and estimated %SpO₂ values for both models.

The statistical analysis for the estimated %SpO₂ values gave 4.038, 0.178, 1.676, and 2.010 for the MSE, ME, MAD, and RMSE, respectively, for the blood vessel model and 2.924, -0.246, 1.395, and 1.710, respectively, for the whole-finger model. The Reference Closeness Factor (RCF) was found to be 0.983 and 0.986, respectively for the two models.

V. Data acquisition methodology

We designed a system to acquire the DVP signals from the volunteers and perform experiments on these mathematical models. As the theory for the Beer-Lambert Law states, the nature of the DVP system should be transmissive. Thus, for the fingertip DVP acquisition, the light sources should be on one side of the fingertip, and the sensor should be on the other side. The light rays should pass the fingertip and be received by the sensor. For this reason, a high-intensity light source was required to detect a good-quality signal.

Our model depended on three different wavelengths for the same signal; hence, we utilized an RGB color sensor and a white light for the light source. The color sensor had three different filters on top of the sensor die: blue (465 nm), green (525 nm), and red (615 nm). Clear (i.e., no filter) regions were also present on the sensor. Hence, the space constraint problem in the transmissive DVP system for the light source was solved. Instead of using three high-intensity light sources of different wavelengths, only one white light source and three-wavelength light filters were used on the sensor side (Fig. 13). Figure 14 depicts a basic diagram of the signal acquisition device. In addition to the DVP data, the HbA1c and SpO₂ reference data were also taken to calibrate and validate these models.

Figure 13: Multiple light sources vs multiple sensor filter systems.

Figure 14: DVP signal acquisition device block diagram.

VI. Discussion

The analysis of the volunteers' data and results evidently showed that both the physiological basis gray-box models performed mostly similar in the cases described above. The error metrics between the models were similar for the individual volunteer's data. The analysis done in these error metrics was based on the mean of a full 2 min of recorded data. However, if we look at the model precision or repeatability, we can see that the blood-vessel model has a higher mean %Coefficient of Variation (%CV) compared to the whole-finger model in both cases of %HbA1c and %SpO₂ estimations. This can happen due to the model inaccuracy in the blood-vessel model compared to the whole-finger model.

It is very important to stress that both models are very simple compared to the physical structure of the fingertip. A physical fingertip differs from person to person in terms of the epidermal, dermal, fat, and muscle layer thickness and volume. The blood volume also differs due to any physical effect or abnormality. Also, pressure on the measurement site changes the DVP waveform. These parameters highly affect the calculated ratios because these models cannot consider these uncertainties and might result in high errors. Though we tried to compensate for the effects of fat tissues, skin types, and finger width of the individuals' finger, some unknown parameters can always arise to cause regression errors. However, if these models are calibrated for individuals, they should give a much higher accuracy in the regression analysis as the uncertain parameters are included in the individualistic calibration process.

We should also take note of the variance in the measured reference data. The advertised accuracy for the Schiller Argus OXM Plus device (SpO₂ monitor) was $\pm 2\%$ for the 70–100% range. On the other hand, the BioHermes A1C EZ 2.0 device (reference HbA1c device) had an advertised precision of %CV < 3% in the 4.0–6.5 %HbA1c range. The device manufacturer, however, did not guarantee the precision above and below the specified range. Our tests showed that the measured %HbA1c value in the range conformed with the advertised precision value, but above 6.5%, the %CV went close to 4.9%. These inaccuracies in the reference data led to the error propagation in the model parameters and calibration steps. Taking more patient samples can improve the estimation accuracy greatly for both of the models.

VII. Conclusion

In this research, we deduced two gray-box models with physiological basis assumptions to estimate the %HbA1c levels in human blood. The first model only comprised a blood vessel, whereas the second model considered a full-finger system for absorption effects only. Although these models are simple compared to the realistic fingertip structure, upon validation, we were able to estimate the %NGSP HbA1c and %SpO₂ in clinically accurate regions (region A in EGA plots) in most of the cases, and the estimation was clinically plausible (region B in EGA plots) in the other cases for multiple volunteers' data. No in-vivo non-invasive studies were previously performed as regards the estimation of the %glycated hemoglobin with digital volume pulse waveform performing regression analysis. Therefore, this study is a strong proof of method in this scope.

Some more factors can be considered in future studies. For example, light scattering in biological media, finger structure variability, light sources, and detector properties should be examined to obtain better results. A more controlled calibration can also be performed to reduce the error in the reference data by increasing the data sample size and purification.

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Author Contributions

S.H. and K.-D.K. conceptualized the work. S.H. conducted the theoretical derivations, data acquisition device designing, and hardware programming. S.H and S.S.G. analyzed and purified the reference and input data. S.H. and S.S.G conducted the calibration process. The formal analysis was done by T.H.K and K.-D.K. This whole work is also supervised by K.-D.K. All authors discussed the results and commented on the manuscript.

Additional Information

Conflict of interest: The authors hereby declare that they have no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or the publication of the results.

Human participant ethical compliance: We have compiled ethical regulations for our research methodology from the Institutional Review Board (IRB), Kookmin University, Seoul, Korea. This research was conducted in accordance with the guidelines provided by the IRB, Kookmin University, Seoul, Korea. And we also have obtained informed consent from all the participants for utilizing the data obtained from them, for academic research purposes.

Data availability: The dataset used in this research is available upon a valid request to any of the authors of this research paper.

Code availability: The codes used in this study are available in Github (https://github.com/ShifatHossain/hba1c_BLM).

Supplementary document: This manuscript contains supplementary documents to support the research dataset and the calibration analyses.

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Figures

Figure 1

Blood vessel model illustration with hypothetical blood pulses: (a) DVP signal; (b) light intensity in the systolic phase; and (c) light intensity in the diastolic phase.

Fractional volume composition of model

Figure 2

Fractional volume composition of the whole-finger model.

Figure 3

Parameter estimation with the Beer-Lambert law.

Figure 4

Dataset diabetes class plot.

Figure 5

Histogram plot of the measured dataset (a) %NGSP HbA1c value and (b) %SpO2 value.

Figure 6

Calibration description block diagram. (h = normalized HbA1c, s = normalized SpO2)

Figure 7

HbA1c Clarke's Error Grid Analysis (EGA) and Bland-Altman analysis for the blood vessel model.

(a) Error Grid Analysis (EGA)

(b) Bland–Altman analysis

Figure 8

HbA1c Clarke's Error Grid Analysis (EGA) and Bland–Altman analysis for the whole-finger model.

(a) Blood vessel model

(b) Whole-finger model

Figure 9

Percent coefficient of variation for the reference and estimated %HbA1c values for both models.

(a) Scatter plot

(b) Bland–Altman analysis

Figure 10

Scatter plot and Bland–Altman analysis of the estimated vs reference (measured) %SpO2 values for the blood vessel model.

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(b) Bland–Altman analysis

Figure 11

Scatter plot and Bland–Altman analysis of the estimated vs reference (measured) %SpO2 values for the whole-finger model.

Figure 12

Percent coefficient of variation for the reference and estimated %SpO2 values for both models.

Figure 13

Multiple light sources vs multiple sensor filter systems.

Figure 14

DVP signal acquisition device block diagram.

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