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NON-INVASIVE ESTIMATION OF BLOOD OXYHEMOGLOBIN AND CARBOXYHEMOGLOBIN SATURATIONS USING CUMULANT BASED FORWARD MODEL

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ABSTRACT

This paper aims to study the feasibility of using optical reflectance spectroscopy and Cumulant based forward model (CM) for non-invasive investigation of differences in mean blood oxyhemoglobin (S_mO_2) and carboxyhemoglobin saturations (S_mCO) amongst the participated smoking and nonsmoking recruits, and the effects of different smoking characteristics of smokers on the predicted S_mCO level. The value of S_mO_2 and S_mCO is given by those that produce the best agreement between the employed CM and measurement data optimized using the developed fitting routine. The fitting algorithm required the use of extinction coefficients of hemoglobin components as the background information. This work conducted reflectance point spectroscopy measurement on right index finger of seventeen smoking and eleven nonsmoking Asian volunteers at resting condition. The quantitative analysis of the collected data using the employed CM and fitting strategy revealed S_mO_2 and S_mCO with mean value of $88 \pm 2.2\%$ and $4.6 \pm 3.6\%$, respectively, for the nonsmoking population. Meanwhile mean S_mO_2 of $78 \pm 10\%$ and mean S_mCO of $7.6 \pm 5.6\%$ are estimated for the smoking volunteers. These blood saturation values agreed acceptably well with the value reported in literature. This preliminary study found a high correlation between one's CO poisoning level and their number of years smoked but no relationship is observed between the poisoning level and one's average daily cigarette consumption.

Key words: Cumulant based forward model, Mean blood oxygen saturation, Mean blood carboxyhemoglobin saturation, Skin oximetry, Spectroscopy.

INTRODUCTION

Carbon monoxide (CO) poisoning is one of the leading causes of death worldwide and is a serious health problem (Atescelik *et al*., 2012). Moderate and heavy smokers are amongst the populations commonly diagnosed with high concentration of CO in blood or commonly known as blood carboxyhemoglobin saturation (SCO). The inhalation of CO, one of the major contents of cigarette smoke, into one's respiratory system decreases the concentration of oxygen in blood to be delivered to tissue. This is due to the higher affinity of CO to bind with hemoglobin, thereby displacing the oxygen (Pavelchak *et al.*, 2009). Other factors that may contribute to CO poisoning including exposure of CO in residential and industrial settings due to incomplete burning of subject that contains carbon such as gasoline and coal (Samerjai *et al*., 2012). Gas plant workers, for example, are expected to have a high level of SCO due to consistent and long period exposure to CO. The symptoms of CO poisoning include headache, dizziness, weakness and nausea. These symptoms are often misdiagnosed as flu, and hence may go undetected (Yarar *et al.*, 2008). Prolonged exposure to CO may lead to loss of consciousness and even death if immediate medical action is not being taken.

Techniques able to provide continuous, non-invasive and accurate measurement of SCO are, therefore, highly sought after. Accurate measurement of both arterial and venous blood carboxyhemoglobin concentration can be provided by Food Drug Administration (FDA) approved blood gas analyser. This technique is, however, required drawing of blood sample. Meanwhile the clinically available pulse oximeter is only able to provide estimation of arterial blood oxyhemoglobin saturation, S_aO_2. The RAD-57 CO-oximeter has recently emerged as a new method for continuous and non-invasive measurement of arterial blood carboxyhemoglobin; its accuracy is, however, a subject of dispute in previous studies (Maisel & Lewis, 2010). Both pulse oximeter and CO oximeter required the use of a look-up table in the prediction of blood saturation values.

Non-invasive methods that do not required calibrated data include the use of either time domain, or frequency domain, or continuous wave experimental technique for measurement of signals reflected (or transmitted) from skin. These signals are then processed and analyzed using either a nonlinear fitting method or simultaneous solution of Modified Lambert Beer model (Huong *et al.*, 2009; Pittman & Duling, 1975) to give an estimation of the required blood saturation values. The nonlinear fitting technique includes fitting of the experimental data using either a library of data simulated using Monte Carlo model or diffusion equation, or a forward model. The forward models employed for this fitting process are commonly known to have increased complexity to better represent the propagation of light in skin, and hence provide a more accurate estimation of blood saturation values. Amongst these fitting models are Extended Modified Lambert Beer model (EMLB) (Huong A. & Ngu X., 2013), cumulant based forward model (CM) (Huong, 2012), cubic model (Vogel *et al*., 2007), and derivations from Kubelka Munk and diffusion model (Caspary *et al.*, 1995; Kobayashi *et al*., 2001). Most of

these models are determined by their ability to solve an inverse problem using data simulated by light propagation model such as Monte Carlo method and diffusion model, wherein the optical properties of skin are determined prior to simulation.

The objective of this work is to experimentally explore the feasibility of using CM model as an alternative to extensively employed Modified Lambert Beer Law and its derivatives for the estimation of percent mean blood oxyhemoglobin, S_mO_2, and carboxyhemoglobin saturations, S_mCO, amongst smoking and non-smoking populations. This is following the demonstration of the good performance of this model in the estimation of blood saturation values using simulation method (Huong, 2012). This work also aims to conduct a preliminary investigation of the possible correlation between cigarette consumption of smokers and their S_mCO level, and between their numbers of years smoked and the estimated S_mCO using SPSS software. This paper is arranged as followed: The reflectance spectroscopy system designed for this purpose and the employed analytical method are described in Material and Method section. Results section reports the mean S_mO_2 and S_mCO estimated for the smoking and nonsmoking populations using CM model, and the values reported in literature. Statistical analysis of the relationship between smoking characteristics of participants and their estimated S_mCO is also included in this section. This is followed by a discussion of the results and conclusion of this study.

MATERIAL AND METHOD

Optical Reflectance System and Experimental Procedure

Figure 1 shows the reflectance spectroscopy system employed in this work. This work used 9W white light emitting diode (from Lumiled Inc.) to illuminate right index finger of the recruited volunteers. The reflected light is collected into the detection system by an optical fiber bundle, and diffracted by a dispersive element before the detection of light intensity at wavelength in the range of 200–900nm by a charge coupled array detector (CCD). Both diffraction grating, which is used to disperse light at different wavelength, and CCD are mounted inside a commercially available spectrometer (Ocean Optics USB4000). A comprehensive diagram of the arrangement of diffraction grating and CCD in the USB4000 can be found in Ocean Optics' website (http://www.oceanoptics.com). The detected signals are sent to a computer for further offline processing and analysis. In this system, the light source is placed at a distance of 80mm from measurement sample and an angle of 10° from normal. Meanwhile light detection is at opposite side of the illumination system, it is at an angle of approximately 30° from normal to reduce glare. This detection system is at a distance of 30mm from the sample to produce high spatial resolution data and increase signal to noise ratio.

This study recruited a total number of 28 Asian volunteers (17 smokers and 11 nonsmokers). First, the participants gave their informed consent and declared no serious underlying medical illness such as pulmonary disease, heart cancer, lung disease and anemic before the measurement. The particulars of the smoking volunteers, i.e. age, number of years smoking and smoking habits are collected and tabulated in Table 1. The nonsmokers are aged between 20 and 25. Next, these volunteers are instructed to relax in sitting position, remained still and rest their right hand against a black matte paper during the experiment. Finally, three spectroscopy measurements are consecutively performed on the right index finger of each individual; these data are averaged prior to signal processing to reduce the effects of noise on signals.

This work used the measured light attenuation to find the required percent blood saturation values. The white and dark reference data used in the calculation of light attenuation are given from reflectance of Spectralon (from Labsphere, Inc.) with 99% reflectance and with the optical fiber tip blocked by a shutter, respectively. The wavelength dependent light attenuation is expressed as (Phillips & Ho, 2008):

$$A(\lambda) = \log \frac{I_{\text{white}}(\lambda) - I_{\text{dark}}(\lambda)}{I_{\text{sample}}(\lambda) - I_{\text{dark}}(\lambda)} \quad (1)$$

where I_{sample}, I_{white} and I_{dark} represent reflectance data of human subject, white and dark reference, respectively.

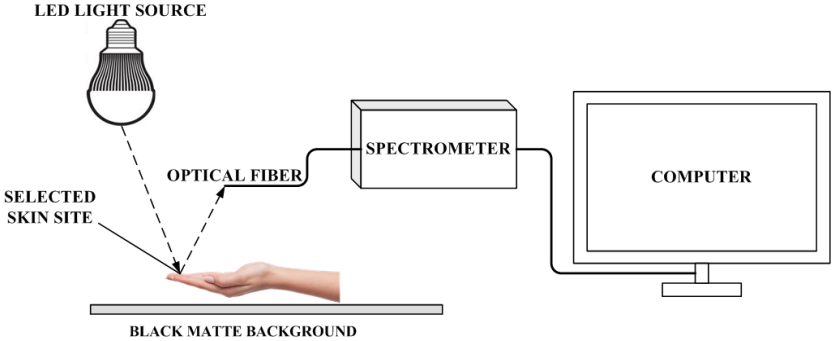

Figure 1: Non-contact spectroscopy system

Table 1: The information on age, quantity of daily cigarette consumption and number of years smoking for each smoking individual (referred to as volunteer no. $1-17$) recruited in this study.

No.	Age	Average daily cigarette consumption (sticks)	Number of years smoking
1	22	9	5
2	28	8	10
3	20	5	2
4	21	5	3
5	52	12	37
6	38	10	20
7	20	14	8
8	43	12	20
9	25	2	2
10	20	7	7
11	23	10	5
12	48	20	20
13	43	20	25
14	58	20	15
15	62	36	50
16	51	4	20
17	24	20	10

The sample reflectance data, I_{sample}, obtained from this system is taken to be an integration of light encompassed capillaries, arteries and veins in skin, so blood oxygen saturation estimated using the analytic model described in the subsequent section is assumed to be the mean of blood oxyhemoglobin, S_mO_2, and blood carboxyhemoglobin saturation, S_mCO, across these vessels. This work assumed oxyhemoglobin (HbO_2), deoxyhemoglobin (Hb) and carboxyhemoglobin (COHb), which wavelength dependent extinction coefficients from the report of Zijlstra (Zijlstra *et al.*, 2000) shown in Figure 2, are the only absorbing species in blood. This work uses only their extinction coefficients in the wavelength range of 520–600nm in the fitting process owing to the distinctive difference in their absorption characteristics.

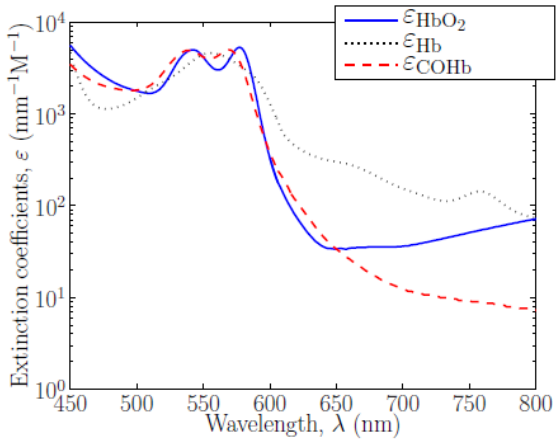

Figure 2: Extinction coefficients of oxyhemoglobin (ε_{HbO_2}), deoxyhemoglobin (ε_{Hb}) and carboxyhemoglobin (ε_{COHb}) from the report of Zijlstra (Zijlstra *et al.*, 2000).

Cumulant Based Forward Model and Nonlinear Fitting Routine

The cumulant based forward model (CM) shown in equation (2) is previously proposed in the work of Huong (Huong, 2012) for accurate estimation of percent blood oxygen saturation. The performance of this model was evaluated using Monte Carlo simulation as the true blood oxygen saturation value in the medium is known.

$$A(\lambda)=a_0+b_0\lambda-f\exp\left(-\mu_a(\lambda)g\right)-h\lambda\exp\left(-\mu_a(\lambda)k\right)+\mu_a(\lambda)m \quad (2)$$

The parameter a_0, b_0, f, g, h, k and m in equation (2) are constants. The development and derivation of the CM model have been extensively discussed in the previous work [6] but they are briefly described here again. In the corresponding work, a linear relationship is observed between TPSF cumulants and wavelengths using Monte Carlo simulation of light propagating in a non-absorbing infinite slab. The wavelength dependent scattering coefficients of the medium used in the corresponding work are from the report of Van Staveren (Van Staveren *et al.*, 1991). This linear wavelength dependent cumulant relationship is substituted into the moments dependent intensity model proposed in previous work (Sassaroli *et al.*, 2006) to give an expression of light attenuation as a summation function of TPSF cumulants. The latter can then be represented by equation (2) (Huong, 2012).

The symbol μ_a in equation (2) denotes light absorption. In the case of blood medium with HbO_2, Hb and COHb as its absorbing components, μ_a is given by:

$$\mu_a(\lambda)=\varepsilon_{HbO_2}(\lambda)C_{HbO_2}+\varepsilon_{Hb}(\lambda)C_{Hb}+\varepsilon_{COHb}(\lambda)C_{COHb} \quad (3)$$

where the symbol C and ε, respectively, represent concentration and extinction coefficient of the associated absorber indicated in subscript. The light absorption can also be expressed as a function of S_mO_2 and S_mCO in Eq. (4) as demonstrated in the previous work (Huong A. & Ngu X., 2013), where T is total absorber concentration given by: $T=C_{HbO_2}+C_{Hb}+C_{COHb}$.

$$\mu_a(\lambda)=\left(\left(\varepsilon_{HbO_2}(\lambda)-\varepsilon_{Hb}(\lambda)\right)S_mO_2+\left(\varepsilon_{COHb}(\lambda)-\varepsilon_{Hb}(\lambda)\right)S_mCO+\varepsilon_{Hb}(\lambda)\right)T \quad (4)$$

The S_mO_2 and S_mCO in Eq. (4) are expressed as:

$$S_mO_2=\frac{C_{HbO_2}}{T} \quad (5)$$

$$S_mCO=\frac{C_{COHb}}{T} \quad (6)$$

The iterative fitting routine developed in this work used *fminsearch* function in MATLAB to give the best guess of S_mO_2 and S_mCO value. The extinction coefficients of absorbing components in the wavelength

range of 520 – 600nm are shown in Figure 2. The unknown fitting parameters in equation (2) (i.e. S_mO_2, S_mCO, a_0, b_0, f, g, h, k and m) are assigned with an initial value of '1' at the beginning of this process. The value of these parameters is substituted into the CM model shown in equation (2) before the wavelength dependent light attenuations are calculated and compared to that experimentally measured in equation (1). A new value of these fitting parameters is iteratively searched according to the absolute difference between the measured attenuation value and that given from the CM model, ΔE . This fitting algorithm does not assign boundary to the values of these fitting parameters. The fitting process is terminated when either the number of iteration has exceeded 1000 or mean ΔE is less than 1×10^{-20}, where the optimum value of these parameters is assumed to have found.

RESULTS

The percent mean blood oxyhemoglobin and carboxyhemoglobin saturations estimated for smoking and nonsmoking individuals using the CM model and the iterative fitting procedure described above are plotted in box plot (median, $25-75\%$) in Figure 3 and Figure 4, respectively. Since the clinical available pulse oximeter, RAD-57 CO-oximeter and blood gas analyzer are not able to provide the measurement of percent mean blood oxyhemoglobin and carboxyhemoglobin, the S_mO_2 and S_mCO obtained in this work are compared to that reported in the literature in Table 2. These researchers employed either optical reflectance spectroscopy or near infrared spectroscopy technique in their works owing to their non-invasive nature. Also shown in Table 2 is the mean and standard deviation of S_mO_2 and S_mCO value predicted for the recruited volunteers in this work.

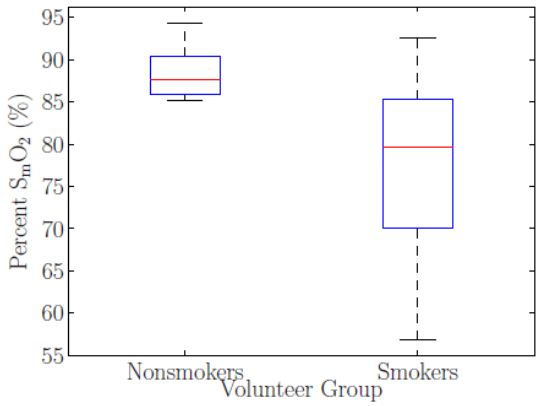

Figure 3: Percent mean blood oxyhemoglobin saturation, S_mO_2, estimated for smoking and nonsmoking populations.

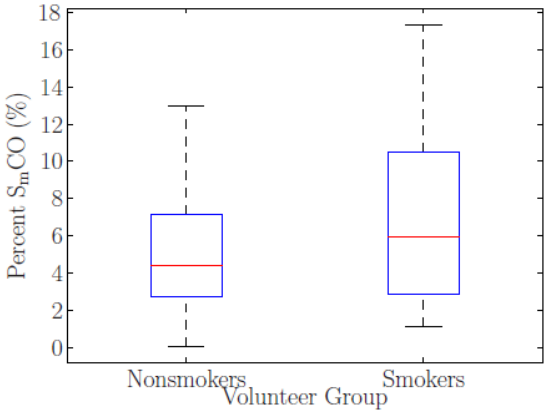

Figure 4: Percent mean blood carboxyhemoglobin saturation, S_mCO, estimated for smoking and nonsmoking populations.

The relationship between the number of years of smoking for each individual listed in Table 1 and the estimated S_mCO is plotted in Figure 5. The correlation between these parameters is statistically determined using Spearman rank-order correlation test in SPSS software (SPSS 22, Inc., Chicago, Illinois). Also shown in Figure 5 is the S_mCO estimated for smoking volunteers with different average daily cigarette consumption. The same statistical test is also performed to determine their relationship. The statistical analysis revealed significance value (ρ value) of 0.074 for the number of years smoking and S_mCO correlation test, while $\rho = 0.000$ is obtained for the association test between daily cigarette consumption and the S_mCO.

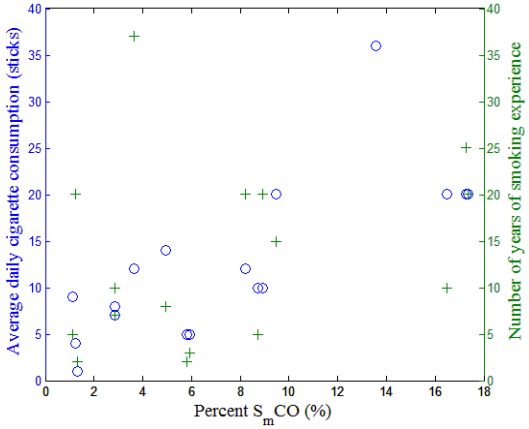

Figure 5: The scatter plot on the relationship between average daily cigarette consumption and the estimated S_mCO ('∘'), and between number of years smoking and the S_mCO value ('+').

Table 2: Comparison of percent blood oxyhemoglobin, S_mO_2, and carboxyhemoglobin saturation, S_mCO, estimated for smokers and nonsmokers in this work and in the literature.

No.	Investigator	Volunteer group	Reported mean blood oxygen saturation
1	Caspary *et al*., 1995	nonsmokers	$S_mO_2 = 92 \pm 2.6\%$
2	Zhang *et al*., 2005	nonsmokers	$S_mO_2 = 92 \pm 2.6\%$
3	Ilano & Raffin, 1990	nonsmokers	$S_mO_2 = 1\%$
4		smokers	$S_mCO = 10 - 15\%$
5	Huong A.& Ngu X.,	nonsmokers	$S_mO_2 = 86.5 \pm 1.6\%$
6	2014	nonsmokers	$S_mCO = 11.7 \pm 1.6\%$
7		smokers	$S_mO_2 = 81.9 \pm 8.8\%$
8		smokers	$S_mCO = 16.2 \pm 4.8\%$
9	This work	nonsmokers	$S_mO_2 = 88 \pm 2.2\%$
10		nonsmokers	$S_mCO = 4.6 \pm 3.6\%$
11		smokers	$S_mO_2 = 78 \pm 10\%$
12		smokers	$S_mCO = 7.6 \pm 5.6\%$

DISCUSSION

The percent blood saturations shown in Figure 3 and Figure 4 estimated using the CM model in equation (2) revealed an averagely higher S_mO_2 and lower S_mCO amongst nonsmoking individuals as compared to that of the smokers. The median of the S_mO_2 value for nonsmokers and smokers in Figure 3 are given by 87.6% and 79.6%, respectively. A smaller variation in this value with standard deviation given by 2.2% shown in Table 2 for nonsmokers is also noticeable in Figure 3 as compared to 10% for the recruited smokers. This work measured the mean S_mO_2 value of 88% for right index finger of nonsmokers. This value is similar to that reported by Caspary *et al*. (Caspary *et al.*, 1995) and Zhang *et al*. (Zhang *et al.*, 2005) in Table 2, whose work used Kubelka Munk derived reflectance model and genetic algorithms, respectively. The mean S_mCO predicted in this work is close to that presented in our counterpart paper that used EMLB model (Huong, A. K. & Ngu, X. T., 2014), wherein the corresponding work used a different group of human subjects. This, therefore, verified the validity of the estimated value and implied the feasibility of using the CM model and the proposed fitting algorithm for non-invasive estimation of S_mO_2. A lower mean S_mO_2 of 78% predicted for smoking population in this work suggests a possible decrease in binding of oxygen to hemoglobin, and hence a reduce in the concentration of oxygen measured on the right index finger of these volunteers.

Meanwhile Figure 4 revealed a higher S_mCO with mean and standard deviation value of $7.6 \pm 5.6\%$ for smokers as compared to $4.6 \pm 3.6\%$ for the nonsmokers. This is in accordance to the hypothesis that inhalation of CO from cigarette smoke yields an increase in S_mCO. The difference in this value is, however, insignificant amongst the smoking and nonsmoking groups. In addition, the range of S_mCO estimated in this work for these two groups is different from that in the report of Ilano and Raffin (Ilano & Raffin, 1990). This could be due to differences in the extinction coefficients of carboxyhemoglobin used. These differences would contribute to the variation in the calculated attenuation values in equation (2) used in the developed iterative fitting routine, and hence modify the estimated blood saturation values. Other factors that may contribute to the differences in the estimated blood saturation values include differences in one's skin thickness, skin color, human populations, country of origin and physical condition. It must also be mentioned that blood saturation values could also varied with time as observed in the work of Caspary (Caspary *et al*., 1995). In addition the large variation in the estimated S_mO_2 and S_mCO amongst the recruited smokers is possibly due to the variation in the type of cigarette smoked.

The statistical analysis of the relationship between the estimated S_mCO and different characteristics of the recruited smokers in Figure 5 revealed a positive correlation between number of years smoking and one's S_mCO, which is statistically significant at $\rho = 0.074$. No correlation is, however, observed between one's quantity of daily cigarette consumption and the calculated S_mCO ($\rho = 0.000$). While these observations may be debatable given the small sample size involved, the current finding suggests the possibility that the concentration of CO in blood is dependent on one's cumulative exposure to CO, and is irrelevant to the smoking habits.

CONCLUSION

This work observed a reduce in mean S_mO_2 accompanied with an increase in mean S_mCO amongst smoking population as compared to that of nonsmoking individuals. The S_mO_2 value estimated for the nonsmoking population is similar to that reported in the previous works suggesting the feasibility of using cumulant based forward model and the proposed approach to estimate one's S_mO_2. The large variation in the S_mCO and S_mO_2 value estimated for the smoking recruits could be due to physical condition of the recruited volunteers and the type of cigarette they smoked. This preliminary study shows a high correlation between one's number of years smoking and the S_mCO value but no relationship is observed between quantity of cigarette consumed daily and the S_mCO value. The present study concluded that the concentration of CO in blood

could be highly influenced by an individual's number of years smoking, and has no strong association with the quantity of cigarette consumed daily.

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