General equation for the differential pathlength factor of the frontal human head depending on wavelength and age

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Abstract. Continuous-wave near-infrared spectroscopy and near-infrared imaging enable the measurement of relative concentration changes in oxy- and deoxyhemoglobin and thus hemodynamics and oxygenation. The accuracy of determined changes depends mainly on the modeling of the light transport through the probed tissue. Due to the highly scattering nature of tissue, the light path is longer than the source–detector separation ($d$). This is incorporated in modeling by multiplying $d$ by a differential pathlength factor (DPF) which depends on several factors such as wavelength, age of the subject, and type of tissue. In the present work, we derive a general DPF equation for the frontal human head, incorporating dependency on wavelength and age, based on published data. We validated the equation using different data sets of experimentally determined DPFs from six independent studies.

Keywords: continuous-wave near-infrared spectroscopy; differential pathlength factor.

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1 Introduction

By shining near-infrared (~650 to 950 nm) light into tissue and measuring the diffuse reflected light at different wavelengths ($\lambda$), continuous-wave (CW) near-infrared spectroscopy (NIRS) and imaging (NIRI) enable the determination of concentration changes in oxy- and deoxyhemoglobin ($[O_2Hb]$, $[HHb]$), which are related to changes in hemodynamics and oxygenation. NIRS refers to a measurement at a single position (i.e., one light-path), whereas NIRI measures simultaneously at different positions.

Light transportation through tissue is a complex process. In a first approximation, it can be modeled using the modified Lambert–Beer law given as

$$ I(\lambda) = I_0(\lambda) e^{-\mu_a(\lambda) d + G(\lambda)}, $$

where $I(\lambda)$ is the measured wavelength-dependent diffuse reflected light intensity, $I_0(\lambda)$ is the incident light intensity, $\mu_a(\lambda)$ is the absorption coefficient of the probed tissue, $d$ is the distance between the positions of incident and measured light, i.e., the source–detector separation, $DPF(\lambda)$ the differential pathlength factor (DPF), and $G(\lambda)$ is a wavelength-, medium-, and geometry-dependent constant. The term $d DPF(\lambda)$ corresponds to the mean light propagation distance in the medium, i.e., the parameter $DPF(\lambda)$ is a scaling factor that indicates how many times farther than $d$ the detected light has traveled.

Based on the diffusion equation for modeling light transport through a homogeneous semi-infinite medium, it can be shown that the DPF depends on $\mu_a(\lambda)$, the reduced scattering coefficient $\mu_s(\lambda)$, and $d$:3,4

$$ DPF(\lambda) = \frac{1}{2} \left( \frac{3\mu_s'(\lambda)}{\mu_a(\lambda)} \right)^{1/2} \left[ 1 - \frac{1}{(1 + d(3\mu_a(\lambda)\mu_s'(\lambda))^{1/2})} \right] $$

$$ \approx \frac{7}{2} \left( \frac{3\mu_s'(\lambda)}{\mu_a(\lambda)} \right)^{1/2}. $$

Consequently, DPF($\lambda$) increases with $\mu_s'$ and decreases with $\mu_a$. The dependence of DPF on the source-detector separation ($d$) is crucial to be considered for small $d$ values, but for $d \geq 2.5$ cm, the DPF is virtually independent of $d$. From the mathematical point of view, the dependence of DPF on $d$ is negligible when the inequality $d\sqrt{3\mu_a\mu_s'} \gg 1$ holds. Since Eq. (2) is only valid for a homogeneous semi-infinite medium and since the brain is inhomogeneous, the equation only gives an approximation of the real situation in human brain tissue. However, the conclusion about the dependence of the DPF on $\mu_s'$ and $\mu_a$ remains true. For biological tissue, DPF($\lambda$) is generally in the range of 3 to 6. The DPF value affects the magnitude of the calculated concentration changes of chromophores in the tissue (i.e., $[O_2Hb]$, $[HHb]$). For CW-NIRS/NIRI, the concentration changes are often determined based on consecutive measurements of $I(\lambda)$ and applying Eq. (1), whereas $\mu_s(\lambda)$ is given as the sum of the specific absorption coefficients $\alpha(\lambda)$, of $O_2Hb$ and $HHb$, times the concentration $c$: $\mu_s(\lambda) = c(\alpha(\lambda))O_2Hb + c(HHb)\alpha(\lambda)$. Using a wrong wavelength dependence of DPF leads to crosstalk similar to using a wrong $\alpha(\lambda)$ value. CW-NIRS cannot measure the actual value of DPF($\lambda$) which must be estimated according to tabulated values. Frequency-domain (FD) or time-domain NIRS/NIRI does not need the DPF to calculate the concentration changes, and these techniques are able to measure the $\mu_a$ directly.13,14

Another solution is to measure the DPF by employing an optical pathlength meter as developed by Tullis and Delpy or to determine continuously the DPF with CW-NIRS by extended Kalman filtering and dynamic system modeling.

In 1996, Duncan et al. showed in a seminal paper that the DPF depends on the age of the subjects. The older the
subject, the larger the DPF. Physiological reasons for the age
dependence of the DPF can be attributed to different develop-
mental or aging processes in the human brain, such as the
change in intracranial volume (increase from birth to adoles-
cence; decrease after ∼50 years of age),16,17 myelination (expo-
nential increase over the first 3 years of life; myelin: strong
scatterer),18 gray matter (GM) and white matter (WM) properties
(after adulthood onwards: reduction in GM volume and deterio-
ration in WM microstructure),19 cerebrospinal fluid layer thickness (increase with advanced age),20 or cortical
thickness, bone mineral content, and cortical bone density
(decrease starting from adulthood on).21

Duncan et al.15 measured the DPF of 283 subjects (137 male,
146 female, age: 1 day to 50 years) for four different wave-
lengths (690, 744, 807, and 832 nm) by a FD-NIRS system
with a d of 4.3 cm. The optode was placed on the left frontal
region (adults) and on the left or right frontotemporal region (on
neonates). By using a least squares fitting method, they derived
four equations that relate the DPF with age (A):

$$DPF(\lambda = 690 \text{ nm}, A) = 5.38 + 0.049 A^{0.877}, \quad (3)$$

$$DPF(\lambda = 744 \text{ nm}, A) = 5.11 + 0.106 A^{0.723}, \quad (4)$$

$$DPF(\lambda = 807 \text{ nm}, A) = 4.99 + 0.067 A^{0.814}, \quad (5)$$

$$DPF(\lambda = 832 \text{ nm}, A) = 4.67 + 0.062 A^{0.819}. \quad (6)$$

Since the CW-NIRS/NIRI devices also apply wavelengths
other than those employed by Duncan et al.,15 a general equation
modeling the DPF as a variable depending simultaneously on
age and wavelength would be desirable. Surprisingly, no
such equation has been published to date to the best of our
knowledge. The aim of the present work was (1) to derive
such an equation and (2) to compare its predictions to various
published values of measured DPF.

2 Derivation and Validation of the General
Equation

2.1 Derivation: Nonlinear Least Squares Surface
Fitting

The general equation relating the DPF with age and wavelength
is based on Eqs. (3)–(6).

All data processing was performed using MATLAB (version
2008b, The MathWorks, Natick, Massachusetts). To derive the
formula, the general mathematical type of surface equation was
first determined. Therefore, the DPF (A) dependence was mod-
elled as power law, $DPF(A) = \alpha + \beta A^\gamma$, according to Eqs. (3)–(6). The
DPF(\lambda) equation was modeled as a cubic function,
$DPF(\lambda) = \delta \lambda^3 + \epsilon \lambda^2 + \zeta \lambda + \eta$, since this ensures that the function
fits to all four wavelengths [see Fig. 1(a)]. A higher poly-
nomial degree than three would cause overfitting since only four
data points are available.

Thus, the surface to be fitted to the data was defined as

$$DPF(\lambda, A) = \alpha + \beta A^\gamma + \delta \lambda^3 + \epsilon \lambda^2 + \zeta \lambda. \quad (7)$$

All values obtained by evaluating Eqs. (3)–(6) for $A = 0, 1, \ldots, 50$ were fitted by a robust nonlinear least squares
fitting with the least absolute residuals (LAR) method23 and the
Levenberg–Marquardt algorithm (LMA).24,25 The LAR method
is a version of the least sum of squares residuals fitting method
based on minimizing the (constrained) sum of the absolute resid-
uals, in comparison to ordinary least squares (OLS) that mini-
mize the sum of squared residuals. LAR has the advantage over
OLS of being robust against deviations from the normality
assumption of the data. LMA is a cross between the Gauss–
Newton algorithm and the steepest descent method; it has the
advantage of being robust and iteratively more efficient.

The following parameter values were obtained: $\alpha = 223.3,$
$\beta = 0.05624,$ $\gamma = 0.8493,$ $\delta = -5.723 \times 10^{-2},$ $\epsilon = 0.001245,$
and $\zeta = -0.9025.$ The goodness-of-fit statistics obtained
were: summed squared of residuals: 0.09668, R-square: 0.9983,
adjusted R-square: 0.9983, and root mean squared error
(RMSE): 0.0221. These values indicate an excellent fit of the
surface to the empirical data. An illustration of the determined
DPF(\lambda, A) function can be seen in Fig. 2.

2.2 Validation of the General Equation

In order to validate the derived general $DPF(\lambda, A)$ Eq. (7),
it was compared to (1) the results of Eqs. (3)–(6) and
(2) five data sets of DPFs measured in independent stud-
ies.6,26–29 Due to the fact that the DPF depends on tissue
type, only DPF measurements of the forehead (frontal or
frontotemporal) were used for the validation to ensure a homo-
genous sample. In addition, only DPF values where $d > 2.5 \text{ cm}$ holds were included since this ensures a value
independent of $d$. Table 1 lists the details of the six studies employed in our validation.

The comparison of the values obtained by the general DPF($\lambda, A$) equation with the values obtained by Eqs. (3)–(6) revealed a good agreement: DPF($\lambda, A$) versus Eq. (3), RMSE: 0.0320; versus Eq. (4), RMSE: 0.0545; versus Eq. (5), RMSE: 0.0311; versus Eq. (6), RMSE: 0.0348.

As expected, the comparison with the different data sets of measured DPF values also revealed a good agreement in general (see Fig. 3). If the predicted value was inside the standard deviation (SD) or quartiles (first to third) of the value measured, we defined this as a correct prediction. The predicted DPF values agree with the measured ones for the data set of Duncan et al.\textsuperscript{26} and Cooper et al.\textsuperscript{27} For the van der Zee et al.\textsuperscript{6} data set, the

<table>
<thead>
<tr>
<th>References</th>
<th>Subjects</th>
<th>DPF</th>
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<tbody>
<tr>
<td>Zee et al.\textsuperscript{6}</td>
<td>OP: frontal (adults), frontotemporal (neonates); SDS: $&gt;2.5$ cm. (i) Adults; $n=10$; age (years): 26 (22 to 54); (ii) Preterm (postmortem) neonates; $n=10$; GA (weeks): 30.6 $\pm$ 5.4</td>
<td>[i] Adults: $5.93 \pm 0.42$ (761 nm) [ii] Neonates: $3.85 \pm 0.57$ (783 nm)</td>
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<tr>
<td>Essenpreis et al.\textsuperscript{30}</td>
<td>OP: frontal (adults and neonate); SDS: 4 cm. (i) Adults; $n=7$; age (years): 23 to 55; (ii) Neonate (postmortem); $n=1$; GA (weeks): 41</td>
<td>[i] Adults: $6.59$ (740 nm) [ii] Neonates: $4.17$ (735 nm)</td>
</tr>
<tr>
<td>Duncan et al.\textsuperscript{26}</td>
<td>OP: frontal (adults), frontotemporal (neonates); SDS: 4.3 cm. (i) Adults; $n=100$; age (years): 33 (21 to 59); (ii) Neonates; $n=35$; GA (weeks): 40 (35 to 42); age (days): 2 (0 to 16)</td>
<td>[i] Adults: $6.51 \pm 1.13$ (690 nm) [ii] Neonates: $5.38 \pm 0.49$ (690 nm)</td>
</tr>
<tr>
<td>Cooper et al.\textsuperscript{27}</td>
<td>OP: frontotemporal SDS: 4.9 cm. Neonates; $n=19$; GA (weeks): 34 (23 to 38); age (days): 21 (1.4 to 23)</td>
<td>$4.66 \pm 1.06$ (730 nm)</td>
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<tr>
<td>Zhao et al.\textsuperscript{28}</td>
<td>OP: (i) frontal, (ii) frontotemporal; SDS: 3.0 cm. Adults, $n=11$; age (years): 33 (22 to 53)</td>
<td>(i) Frontal: $7.5$ (759 nm) (ii) Frontotemporal: $7.25$ (799 nm)</td>
</tr>
<tr>
<td>Bonnéry et al.\textsuperscript{29}</td>
<td>OP: frontal; SDS: 3.0. (i) Adults; $n=19$; age (years): 24.4 $\pm$ 2.5. (ii) Adults; $n=23$; age (years): 67.6 $\pm$ 2.9</td>
<td>(i) Adults (young): $6.2$ (5.6–6.9) (690 nm) (ii) Adults (old): $5.8$ (5.2–6.1) (830 nm)</td>
</tr>
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</table>

\textsuperscript{a}GA: gestational age, OP: optode placement, SDS: source-detector separation. Data were reported as either mean \pm standard deviation (SD) or median (first quantile, third quantile), or median (span).

\textsuperscript{b}Only the data for the neonate with a gestational age of 47 weeks was used since the other reported neonate (gestational age: 27 weeks) was a preterm one with a bilateral hemorrhagic parenchymal infection.

\textsuperscript{c}From the authors recommended general values to use.
predicted DPF for the adults agrees with the measured value. For
the neonates, the predicted value was outside the SD range of the
measured one. Since experimental data were not reported with
SD values for the data set of Zhao et al., the agreement was
only determined qualitatively. Two out of six values agreed. The
agreement was greatest for the values from the frontotemporal
region. Concerning the data set of Bonnéry et al., all four val-
ues agreed with the predicted ones.

For the Essenpreis et al. data set of adults, the predicted
DPF values agree with the measured ones. For the data set of
a neonate also reported by Essenpreis et al., the predicted values
differed from the measured ones. However, it must be noted that
these data set originates only from one subject, making the deci-
sion of agreement difficult, especially in the region of approx-
imately 800 to 840 nm where the measured and predicted values
are close together and might coincide when more than one neo-
nate had been measured and thus SD values were available.

In summary, excluding the data sets of Zhao et al. and the
neonate data set of Essenpreis et al., 34 out of 36 values were
predicted with satisfactory accuracy by the new equation, excluding
the data sets of Zhao et al. and the neonate data set of
Essenpreis et al. where the validation was difficult since no
SD values were given and only one subject was measured,
respectively.

The discrepancy between the predicted and measured DPF
values for the neonatal data sets of Van der Zee et al. and
Essenpreis et al. are likely due to the fact that the neonates
were measured post mortem. In addition, the neonate measured
by Essenpreis et al. was kept at 4°C prior to the measurement.
Both death and low temperature influence the optical properties
of the tissue. Our derived DPF equation is valid only for living
humans. It is known that the optical properties of tissue are dif-
ferent for the in vivo and post mortem case although a study in
rats found only a small change in the DPF upon death. Besides
death, the cooling of the body is likely to influence the PDF
measurement since a change in temperature has an effect on
the optical properties of tissue.

As previous studies have shown, the DPF does not depend on
skin color. But as already shown by Zhao et al., the DPF depends clearly on
the head region investigated. Therefore, to go one step further in
the modeling of DPF values, it would be necessary to incorpo-
rate the dependency on the head region, i.e., composition of dif-
ferent tissue types, as a third variable, besides wavelength and
age. It is known that variations in tissue type and the presence of
the cerebral spinal fluid (CSF) have a significant effect on the
light-propagation characteristics and thus the DPF. For example,
Okada et al. concluded that for a source–detector distance of 5 cm, the mean light propagation distance in the
medium, i.e., d DPF, is composed of 65% contribution from
the scalp and skull, 35% from the CSF, and 5% from the

3 Discussion, Conclusion, and Outlook
We derived a general formula for the DPF depending on the
wavelength and age based on the data of Duncan et al. For
validation purposes, the derived formula was compared with
(1) the values calculated by Eqs. (3)–(6) derived by Duncan
et al. and (2) six independent data sets of measured DPF
values from adults and neonates. The comparisons revealed that
34 out of 36 of the experimentally obtained values were
predicted with satisfactory accuracy by the new equation, excluding

Fig. 3 (a–g) The five different data sets with measured DPF values (blue dots and error bars) and predicted DPF values (red dots). The error
bars correspond to the standard deviation (SD) (a–c, f) or the quartiles (e).
GM. However, later works demonstrated that the light-piping effect of the CSF is reduced due to the presence of scattering structures, i.e., arachnoid trabeculae, within the CSF, reducing the influence of the CSF. To account for the mean path length in each tissue layer, the concept of the “partial differential pathlength” (also termed “partial optical path length”), i.e., the mean pathlength of the light in a specific layer, the “partial differential pathlength factor,” and the “partial pathlength factor,” were introduced.

Since the basis of the equation derived in this work comprises DPF values measured on the frontal and frontotemporal region, this equation is only valid for this head region. Another source of variation of the DPF is the intersubject variability indicating that the DPF varies by individual subject due to anatomical differences. These factors might explain not only the discrepancy of the DPF prediction and the actual values as obtained DPF values for the same age group, i.e., Van der Zee et al.6 versus Cooper et al.27 but also the discrepancy of reported experimentally obtained DPF values for the same age group, i.e., Van der Zee et al.6 versus Cooper et al.27

Concerning the validity of the newly derived equation, we recommend its usage for the age range of 0 to 70 years and the wavelength range of 690 to 832 nm since it is derived from and validated using values in these ranges. For <690 nm, the equation is probably not correct due to a decrease of the DPF in this range. It is safe for application to values ranging from 832 nm to 950 nm because the wavelength dependence in this region should continue according to the model.

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References