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Citation

Published Version
doi:10.1364/BOE.2.000552

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Accessibility
Assessment of the frequency-domain multi-distance method to evaluate the brain optical properties: Monte Carlo simulations from neonate to adult

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Abstract: The near infrared spectroscopy (NIRS) frequency-domain multi-distance (FD-MD) method allows for the estimation of optical properties in biological tissue using the phase and intensity of radiofrequency modulated light at different source-detector separations. In this study, we evaluated the accuracy of this method to retrieve the absorption coefficient of the brain at different ages. Synthetic measurements were generated with Monte Carlo simulations in magnetic resonance imaging (MRI)-based heterogeneous head models for four ages: newborn, 6 and 12 month old infants, and adult. For each age, we determined the optimal set of source-detector separations and estimated the corresponding errors. Errors arise from different origins: methodological (FD-MD) and anatomical (curvature, head size and contamination by extra-cerebral tissues). We found that the brain optical absorption could be retrieved with an error between 8–24% in neonates and infants, while the error increased to 19–44% in adults over all source-detector distances. The dominant contribution to the error was found to be the head curvature in neonates and infants, and the extra-cerebral tissues in adults.

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OCIS codes: (170.3660) Light propagation in tissues; (110.3080) Infrared imaging; (170.5280) Photon migration.

References and links


1. Introduction

Near-infrared spectroscopy (NIRS) measures the attenuation of diffuse near-infrared light (650–950 nm) propagating through biological tissues at two or more wavelengths, allowing for the characterization of the two main chromophores in this spectral window: oxygenated hemoglobin (HbO) and reduced hemoglobin (HbR). Therefore, NIRS is highly sensitive to tissue vascularization and oxygenation, making it an ideal tool for cerebral monitoring and imaging. Applications to functional brain imaging have spanned a diverse range of studies, including visual [1–3], sensori-motor [4], auditory [5, 6], and cognitive [7, 8] tasks. While in this context of functional imaging NIRS measures the hemodynamic changes associated with brain activation, the determination of the absolute optical absorption of the brain, directly related to baseline hemoglobin concentrations, is a more challenging application [9, 10]. Such quantitative absolute measurements are of considerable interest for longitudinal and cross-sectional studies, allowing comparison of cerebral oxygenation and blood volume between subjects, as well as monitoring within a subject over time, opening the door to a number of diagnostic and treatment monitoring applications [11, 12].

The most commonly used modality for functional NIRS, the continuous-wave (CW) ap-
approach, is not suited for absolute characterization of tissue optical properties, because it cannot
distinguish between the absorption $\mu_a$ and scattering $\mu'_s$ of a medium [13]. Some publications
have nonetheless presented CW estimates of baseline optical properties of tissues [14–16].
However they either report a tissue oxygenation index (TOI) [14, 16], which is the product
$\mu'_s \times \mu_a$, or they require that oxygen saturation be varied within a physiological range through
such manipulations as hypoxic events [15] which ethically cannot be performed in infants.

Unlike CW measurements, NIRS in the time-domain (TD) and frequency-domain (FD) al-

lows for the characterization of the baseline $\mu_a$ and $\mu'_s$ of a biological tissue [17–20] without in-
ducing changes in saturation, or making assumptions about $\mu'_s$. Pulsed (TD method) or radiofre-
quency modulated (FD method) light is injected into the medium and its detection provides
information about mean time of flights of photons (TD method) or phase shift (FD method),
both related to $\mu'_s$. The commonly used FD multi-distance (FD-MD) method takes advantage
of the phase shift and attenuation of modulated light at several distances to retrieve the baseline
optical properties of the medium assumed homogeneous [18]. These TD and FD methods have
been validated with simulations, phantom experiments and animal studies [21–28]. In vivo ap-
plications of baseline measurements of the optical properties of the human brain include studies
in premature and term neonates and infants [10–12, 29, 30], as well as adults [28, 31–33]. For
example, our group has applied the FD-MD method on a large scale to the study of healthy
brain development in term and pre-term infants during the first year of life [10, 11], as well as
to the assessment of brain injury in a neonatal population [12].

With the exception of a few studies, most approaches rely on a homogeneous semi-infinite
model of the head because of its simplicity. However this lack of realism introduces error in
the recovered optical properties. Two- [22, 24, 28, 34] or three-layer [35] geometries have been
suggested instead, as well as more realistic brain structure obtained from magnetic resonance
imaging (MRI) segmentation [36], but practical applications remain challenging. In newborns
the measurement can be influenced by the presence of a thick low-scattering CSF layer, as
well as the small head size and the stronger curvature of the head’s surface. In adults, the main
challenge is the thickness of the extra-cerebral layers, which can reach more than 1 cm. No
systematic study of these effects has been published to our knowledge. Validation studies are
difficult to perform because there is no access to actual cerebral absorption values in humans.

In the present study, our aim was to use Monte Carlo simulations to systematically investigate
the accuracy of the FD-MD method for retrieving brain absorption coefficients using a semi-
infinite homogeneous model with a range of age groups, from the newborn to the adult.

2. Methods

2.1. Simulated measurements: Monte Carlo approach

Realistic data were generated using a 3D Monte Carlo (MC) code [37], modeling the photon
propagation in head segmentations obtained from MRI scans.

2.1.1. Head models

We simulated data sets for four different ages: a term newborn of 38 weeks gestational age, 6
and 12 month (mo.) old infants, and an adult. A realistic 3D head model was obtained from
each data set by segmentation of an MR T1 scan into four tissue types (see Fig. 1): white matter
(WM), gray matter (GM), cerebrospinal fluid (CSF) and a superficial layer (superf) comprising
scalp and skull. The voxel size was 1.0 mm in all directions for all head models. Figure 1 shows
3D views and axial slices of the segmented heads at each age. Gray and white matter were
subsequently combined into a single “brain” tissue type with identical optical properties [38].

The effect of extra-cerebral inhomogeneities was investigated by simulating a blood vessel
in the scalp of the adult. Located parallel to the optical probe at a depth of 4 to 6 mm from the
surface of the skin, the vessel was 30 mm long and had a diameter of 2 mm.

<table>
<thead>
<tr>
<th>Tissue</th>
<th>$n$</th>
<th>$g$</th>
<th>$\mu'_s$ [cm$^{-1}$]</th>
<th>$\mu_a$ [cm$^{-1}$]</th>
</tr>
</thead>
<tbody>
<tr>
<td>superf</td>
<td>1.3</td>
<td>0.01</td>
<td>5</td>
<td>[0.1, 0.2]</td>
</tr>
<tr>
<td></td>
<td>1.3</td>
<td>0.01</td>
<td>10</td>
<td>[0.1, 0.2]</td>
</tr>
<tr>
<td>brain</td>
<td>1.3</td>
<td>0.01</td>
<td>10</td>
<td>[0.05, 0.06, ..., 0.29, 0.3]</td>
</tr>
<tr>
<td>CSF</td>
<td>1.3</td>
<td>0.01</td>
<td>0.1</td>
<td>0.04</td>
</tr>
</tbody>
</table>

2.1.2. Optical properties

The optical properties of the scalp, skull and brain vary widely in the literature depending on the method of measurement [28–33]. Ex-vivo and post-mortem values are bound to differ significantly from in-vivo data due to changes in blood content. To simulate realistic absorption values, we considered a wide range of hemoglobin concentrations spanning those found in the literature (between 40 and 120 μM total hemoglobin) and converted them into absorption coefficients using tabulated values for the extinction coefficients of HbO and HbR [39]. This hemoglobin range yielded brain absorption coefficient between 0.05 and 0.3 cm$^{-1}$, while superficial absorption was set to 0.1 and 0.2 cm$^{-1}$. The absorption coefficient of the scalp blood vessel described in section 2.1.1 was set to 5 cm$^{-1}$, a typical value for whole blood absorption in the NIR spectrum [40]. Some studies report higher scattering in the brain than in the superficial tissues [31–33], while others present the opposite result [28], accompanied with inter-individual variability [30,32]. For simplicity, the reduced scattering coefficient $\mu'_s$ was fixed at 10 cm$^{-1}$ in the brain. The value of $\mu'_s$ in the superficial layer was set successively to 10 cm$^{-1}$ and 5 cm$^{-1}$, to evaluate the effect of a spatial variation between tissues. The CSF was either considered part of the brain, with the same absorption and scattering coefficients, or, more realistically, as a
relatively clear medium with low absorption and scattering coefficients \( \mu_a = 0.04 \text{cm}^{-1} \) and \( \mu'_s = 0.1 \text{cm}^{-1} \). The refractive index \( n \) was set to 1.3, and the anisotropy coefficient \( g \) to 0.01 in all tissue types (the MC code does not accept a null value for \( g \); see Table 1).

2.1.3. Probe geometry

Measurements were modeled from one source seen by four detectors positioned in a straight line, with 5 mm between successive detectors, as in a common FD-MD configuration. To test the effect of different groups of source-detector separations (SDs), a total of 10 detectors located every 5 mm were used and subsequently analyzed in subsets of four detectors, yielding 7 different probe configurations. The probe was positioned over the right parietal area (right and left parietal for the newborn) where the head surface is relatively flat (Fig. 1). The 1 mm voxelization of the heads creates a degree of “stair” effect in the curved regions, leading to artefacts in the simulated data, especially at short distances. To reduce this effect, 5 different probe locations within a small neighborhood (2 mm radius) were simulated and averaged together.

2.1.4. Monte Carlo simulations

The MC code has been described in details by Boas et al. [37]. FD measurements were simulated at a modulation frequency of 110 MHz, and the phase and modulated intensity were computed at each detector. 500 million photon packets were launched for each simulation, which took between 8 and 16 hours depending on the number of voxels included in the head.

2.2. Noise modeling

The large number of photons propagated in the MC simulations yields measurements with a very high signal to noise ratio, unrepresentative of actual experimental data. Therefore, measurements generated from MC simulations were modified by the addition of a Gaussian random noise. From each MC simulation data set of phase and intensity, we created 150 noisy measurements by adding 150 different values of phase and intensity noises. The variance of the phase and intensity noises were based on realistic values obtained experimentally with a FD instrument (Imagent, ISS Inc.) in neonates [10, 11] (noise data not published). The noise to signal ratio increases as the source-detector separation increases, for both intensity (1.6% to 4.6%) and phase (0.02% to 3.7%) from 0.5 to 5 cm, respectively. The standard deviation of the retrieved absorption coefficients over the 150 values of noise gives a realistic estimate of uncertainty due to both instrumental and physiological noises.

2.3. Optical properties recovery

The estimation of brain optical properties from simulated data was conducted using the homogeneous FD-MD method described previously [9, 18]. Briefly, in a semi-infinite homogeneous medium, the phase \( \phi \) and natural logarithm of the modulated intensity of light \( I_{AC} \) vary linearly with source-detector separation \( d \) such that

\[
\ln(d^2 I_{AC}) = d S_{AC} + C_{AC} \quad \text{and} \quad \phi = d S_{\phi} + C_{\phi}
\]

where \( S_{AC} \) and \( S_{\phi} \) are the slopes and \( C_{AC} \) and \( C_{\phi} \) are the y-intercepts of the linear regressions. Absorption and reduced scattering coefficients of the homogeneous model can then be estimated by

\[
\mu_a = \frac{\omega}{2v} \left( \frac{S_{\phi}}{S_{AC}} - \frac{S_{AC}}{S_{\phi}} \right) \quad \text{and} \quad \mu'_s = \frac{S_{AC}^2 - S_{\phi}^2}{3 \mu_a} - \mu_a
\]

where \( \omega \) is the angular modulation frequency of the source intensity and \( v \) is the speed of light in the tissue.
2.4. Calibration method

The intensity and phase signals were calibrated prior to recovery. The calibration method implemented [18] is the same as that used in experimental data acquisition [10, 11]. It calculates corrective factors for the DC, AC, and phase of the light source [41], based on measurements in a phantom block of known optical properties. In this study, we modeled the measurements of the calibrated block with MC simulations in a large homogeneous slab imitating a semi-infinite medium. The dimensions of the slab were $18 \times 18 \times 10$ cm$^3$ and its optical properties set to $\mu_a = 0.1$ cm$^{-1}$, $\mu_s' = 10$ cm$^{-1}$, $g = 0.01$, and $n = 1.3$. The corrective calibration factors $(I^\text{calib}_\text{AC}, \phi^\text{calib})$ were calculated so that the slopes of intensity and phase simulated from the slab $(I^\text{slab}_\text{AC}, \phi^\text{slab})$ matched the theoretical ones:

\[
I^\text{calib}_\text{AC} = I^\text{theo}_\text{AC} / I^\text{slab}_\text{AC} \quad \text{with} \quad I^\text{theo}_\text{AC} = \exp \left( d S^\text{theo}_\text{AC} / d^2 \right) \tag{3}
\]

and

\[
\phi^\text{calib} = \phi^\text{theo} - \phi^\text{slab} \quad \text{with} \quad \phi^\text{theo} = d S^\text{theo}_\phi \tag{4}
\]

where the expressions $S^\text{theo}_\text{AC}$ and $S^\text{theo}_\phi$ are detailed in [42]. These calibration factors were then applied to noisy intensity and phase signals from the simulated head data. Finally, Eq. (2) were used to recover the values of optical properties.

We show in Fig. 2 the effect of the calibration procedure in the homogeneous slab itself. In particular, the calibration helps reducing large errors due to the FD-MD approximations at short SDs. However the effect of the absorption coefficient of the calibration block appears clearly. When the absorption coefficient of the measured sample is close to that of the calibration block (0.1 cm$^{-1}$, green set), the calibration process improves the results. When the absorption of
the medium is much higher than that of the calibration block (e.g. 0.3 cm$^{-1}$, yellow set) the
calibration process results in an underestimation of the absorption in the medium.

$$\mu_{a,\text{brain}} [\text{cm}^{-1}]$$

Infant − 12 mo. Adult

0.1 0.2 0.3

Fig. 3. Estimated $\mu_{a,\text{brain}}$ when the head is treated as a homogeneous medium, i.e. when
$\mu_{a,\text{superf}} = \mu_{a,\text{brain}} = [0.05, 0.06, \ldots, 0.29, 0.3] \text{ cm}^{-1}$. For each sub-figure, solid lines repre-
sent the 7 groups of SDs used in the estimation (legend is shown in top left sub-figure) and
dotted lines represent the 1-ratio between estimated and true brain absorption values.

3. Results

3.1. Homogeneous head model

To separate the errors due to the diffusion approximation, finite geometry, and curvature from the
effects due to the layered structure of the head, we first treated the head as a homoge-
nous medium by setting equal the superficial and brain absorptions, i.e.
$\mu_{a,\text{superf}} = \mu_{a,\text{brain}} = [0.05, 0.06, \ldots, 0.29, 0.3] \text{ cm}^{-1}$. In Fig. 3, each graph presents the retrieved brain absorption for
the 7 sets of SDs. The adult model shows better estimate than the young models. This is due
to the stronger head curvature for the newborn and infants. In addition, all estimations at 5−20
mm are less accurate because of the diffusion approximation utilized in the FD-MD formula-
lation [41].

In Fig. 4, retrieved absorption coefficients and standard deviation due to experimental noise
are shown for three specific cases when $\mu_{a,\text{superf}} = \mu_{a,\text{brain}} = [0.05, 0.15, 0.3] \text{ cm}^{-1}$. While the retrieved values improve with longer SDs, the uncertainty increases due to decreasing signal
to noise ratio. In addition, the underestimation of retrieved absorption coefficient for $\mu_{a} = [0.15, 0.3] \text{ cm}^{-1}$ is due to the unmatched calibration medium (calibration $\mu_{a} = 0.1 \text{ cm}^{-1}$).

Figure 5 presents averages and standard deviations of the retrieved $\mu_{a,\text{brain}}$ over 26 combina-
tions of $\mu_{a,\text{superf}} = \mu_{a,\text{brain}} = [0.05, 0.06, \ldots, 0.29, 0.3] \text{ cm}^{-1}$. In newborn and infants, the errors
vary between 14–21% and 7–20%, respectively, and decreases to 3–14% for the adult head
model. At very short distances (5–20 mm), the error is large for all ages (15–20%) due to the
non-validity of the diffusion approximation. At long distances, the error decreases down to less
than 5% for the adult head, while the stronger curvature of the head is responsible for additional
errors in the case of newborn and infants.
Fig. 4. Uncertainty and retrieved absorption for three particular cases of the homogeneous head: $\mu_{a,\text{superf}} = \mu_{a,\text{brain}} = [0.05, 0.15, 0.3]\,\text{cm}^{-1}$ for the 7 sets of SDs.

Fig. 5. Averages and standard deviations of the relative error on retrieved $\mu_{a,\text{brain}}$ over 26 combinations of head absorption $[0.05, 0.06, \ldots, 0.29, 0.3]\,\text{cm}^{-1}$, for the 7 sets of SDs.
3.2. Two-tissue head model

Figure 6 depicts the evolution of the recovered brain absorption values as a function of true absorption for the 7 groups of SDs in all head models (row-wise) treated as a two-tissue structure. The superficial absorption coefficient $\mu_{a,\text{superf}}$ was set successively to 0.1 and 0.2 cm$^{-1}$ (column-wise). In each sub-figure, the dotted line corresponds to the true brain absorption, while the dash-dotted line identifies the superficial absorption. Solid curves represent the 7 groups of SDs.

Fig. 6. Brain absorption coefficients $\mu_{a,\text{brain}}$ estimated across subject age (row-wise) and for two values of superficial absorption $\mu_{a,\text{superf}} = [0.1, 0.2]$ cm$^{-1}$ (column-wise). For each sub-figure, solid lines represent the 7 groups of SDs used in the estimation (legend is shown in bottom left sub-figure), dotted lines represent the 1-ratio between estimated and true brain absorption values and dash-dotted lines represent the superficial absorption.
The effect of the superficial layer is to pull the recovered absorption value of the brain towards the superficial absorption value, especially at short SDs and for the adult case. Because of the specific sets of optical properties we chose, this selection leads to a generally weaker than true value $\mu_{a,\text{brain}}$, especially for high brain absorption coefficients. The three young head models present similar brain absorption estimations, mostly underestimated, probably due to the head’s curvature. The adult head presents a less precise estimation including over- and underestimations, due to the large thickness of the superficial layer which contaminates the signal especially at short SDs.

Figure 7 shows the average error at each age for all SDs groups, over 52 absorption combinations covering the whole range of coefficients for the brain ($\mu_{a,\text{brain}}$ between 0.05 and 0.3 cm$^{-1}$ in steps of 0.01 cm$^{-1}$) and the superficial layer ($\mu_{a,\text{superf}}$ = 0.1 or 0.2 cm$^{-1}$).

For the newborn, the optimal SDs group is 10–25 mm and shows a relative error of 12 ± 6%. The 6 and 12 month old infants present a similar trend: the relative error is about 10 ± 5% for all SDs groups, except for the two shortest (5–20 and 10–25 mm). For both infants, the optimal SDs group can be selected from the five longest SDs (from 15–30 to 35–50 mm), since the error is minimized and shows similar values. The adult head shows the highest relative error for almost all SDs groups (with certain combinations of optical properties yielding errors of more than 80%). The optimal SDs group is reached at 35–50 mm with a corresponding error of 19 ± 13%.

The effect of the scattering coefficient was investigated by modifying the value in the superficial layer to $\mu'_{s,\text{superf}} = 5$ cm$^{-1}$. The relative error decreases in the newborn (ranging from 6 to 19%) and infant models (2–10%) for all SDs except the shortest group (5–20 mm), and slightly increases in the adult head (from 26 to 45%) for almost all groups (except for 10–25 and 15-30 mm). Again, this is probably due to the thicker superficial layer in the adult model that causes a stronger error in $\mu'_{s}$ translating through cross-talk in higher error in $\mu_{a}$.

The same analysis was performed with the adult model in which a large vessel was introduced. Relative errors and standard deviations [%] for the 7 SDs (from 5–20 to 35–50 mm) are...
Fig. 8. Brain absorption coefficients $\mu_a,\text{brain}$ estimated across subject age (row-wise) and for two values of superficial absorption of $\mu_d = [0.1, 0.2] \text{ cm}^{-1}$ (column-wise) when the CSF tissue is taken into account. For each sub-figure, solid lines represent the 7 groups of SDs used in the estimation (legend is shown in bottom left sub-figure), dotted lines represent the 1-ratio between estimated and true brain absorption values and dash-dotted lines represent the superficial absorption. Note the presence of the axial slice of the newborn (NB) left and right hemispheres superimposed with the optical probe.
the following: 51.6 ± 58.2; 48.3 ± 53.9; 35.4 ± 33.4; 26.3 ± 18.1; 23.7 ± 14.7; 22.0 ± 14.5; 19.2 ± 13.2. The error is higher than the case without inhomogeneity in the first 3 groups and then similar for the next 4 groups. The contamination of the shortest estimations is related to the length of the vessel (3 cm) which was located around the beginning of the probe where the light source is positioned. This type of inhomogeneity can be detected experimentally, and data automatically discarded, because of the corresponding low correlation factor $r^2$ of the linear fitting process from Eq. (1).

3.3. Three-tissue head model

We investigated the influence of the CSF structure by setting its optical properties to low absorption and scattering values: $\mu_a = 0.04 \text{ cm}^{-1}$ and $\mu'_s = 0.1 \text{ cm}^{-1}$. The two hemispheres (left and right parietal) of the newborn were studied, because the right hemisphere possessed a thick “pocket” of CSF located underneath the optical probe (white arrow on the axial slice of the second row in Fig. 8), while the left hemisphere possessed a “normal” amount of fluid.

Figure 8 shows retrieved $\mu_a,\text{brain}$ with respect to true values for the 7 groups of SDs. The first two columns correspond to $\mu_{a,\text{superf}}$ set to 0.1 and 0.2 cm$^{-1}$, respectively. The third column shows an axial slice of the left and right newborn (NB) hemispheres. Each graph was created in the same way as in Fig. 6. Distortion of the value of $\mu_a,\text{brain}$ by the superficial layer is similar to the effect observed when ignoring CSF, with the difference that the low absorption of CSF pulls the retrieved $\mu_a,\text{brain}$ to lower values than in the previous case.

![Graph showing error and standard deviation in $\mu_a,\text{brain}$.](image)

Fig. 9. Three-tissue head model: averages and standard deviations of the relative error on retrieved $\mu_a,\text{brain}$ over 52 combinations of $\mu_{a,\text{superf}} = [0.1, 0.2] \text{ cm}^{-1}$ and $\mu_a,\text{brain} = [0.05, 0.06, \ldots, 0.29, 0.3] \text{ cm}^{-1}$ for the 7 sets of SDs.

For the newborn, the estimations computed at shorter SDs in the left hemisphere are less distorted than those estimated in the right hemisphere. This is due to the large volume of CSF in the vicinity of the optical probe. The clear pocket of CSF contributes to modification of the signal through the combined effects of very low absorption and scattering. In general, short SDs groups, from 5–20 to 15–30 mm, are poorly estimated for all head models.
Figure 9 shows the averages of the relative errors and standard deviations in percentage [%] of $\mu_{a_{brain}}$ for all 52 combinations of optical properties of brain and superficial tissues. The error rises to a maximum of 51% for the newborn right hemisphere, mostly due to the effect of the CSF pocket. For the newborn left hemisphere, the optimal set of SDs is 20–35 mm and the error is 19±5%. Decreasing error with increasing SDs is still true for the adult model to a slightly higher extent. The distinction between 6 and 12 month old infants is more visible than in the case without CSF. The 12 month old infant shows less accurate estimations for almost all SDs because of the thicker superficial layer. In both cases, optimal SDs are between 20–35 and 30–45 mm, where the errors is less than 16±10%. For the adult, the longest SDs group (35–50 mm) is needed to minimize the error to a value of 23±15%.

The influence of the CSF was also studied for a superficial scattering coefficient of 5 cm$^{-1}$. For all head models, the error at 5–20 mm increases. For the newborn, both hemispheres show lower errors (ranging from 7 to 45%) with the lower scattering coefficient (except for 25–40 mm in the right hemisphere: error increased to 13%). In the case of the 12 mo. old infant, the error increases from 15 to 61% (except for 10–25 and 15–30 mm: down to 30 and 16%, respectively) while decreases to a minimum of 6 and 25% in the 6 mo. old infant and adult, respectively (data not shown).

4. Discussion

4.1. Effect of the curvature

Generally, the estimations computed at longer distances are strongly affected by head curvature in young subjects. The fitted slopes from Eq. (1) deviate from the theoretical slopes computed with the flat calibration slab. In practice, measurements on a curved region of the head lead to a non-linear variation of the phase and intensity with source-detector separation. This error is easily visible in the raw data and such data can be objectively discarded, as performed in [10–12].

4.2. Effect of the superficial layer

When modeling the head with two layers, the adult model shows larger errors for almost all SDs groups. This is due to the thicker layer of extra-cerebral tissue in adults. Even at the optimal SD separations, the brain absorption is still estimated with 19% error, compromising the validity of longitudinal or cross-sectional studies. Implementing more complex models of the head that incorporate the layered structure more realistically can help solve this issue.

4.3. Effect of the CSF layer

In newborn, we studied one location where a thick region of CSF was located directly underneath the optical probe, hindering the recovery of brain optical properties at short distances (from 5–20 to 15–30 mm). This lateral "CSF pocket” could have been produced by the positioning of the head during the MR scan. At this age, the skull is very flexible and the CSF can be distributed according to the pressure applied on the surface of the head. Even though the skull layer is very thin in neonates, facilitating the measurement of brain absorption coefficients, the relatively thick CSF layer can affect the performance of the method. For the adult head model, results with and without CSF were very similar. The 6 and 12 month old infants often yield more accurate estimates than the newborn, with and without the optical properties of the CSF. This is probably due to the description of the CSF, the size of the superficial layer (scalp and skull) and the head size of the infant models. This suggests that the dominant error is not related to the CSF compartment.
4.4. Effect of the scattering coefficient
Surprisingly, decreasing the scattering coefficient of the extra-cerebral tissue from 10 to 5 cm\(^{-1}\) produced better results for the newborn and infants, which can probably be explained by compensatory errors. On the contrary, it deteriorated the estimation for the adult at almost all SDs groups. A more extended study of this effect should yield more robust conclusions.

4.5. Large vessel, hair obstruction and extra-cerebral inhomogeneities
The presence of extra-cerebral inhomogeneities such as vessel or hair is generally uncontrolled and their locations are unknown except if angiography data are accessible. We showed how such strongly absorbing local structure can affect the retrieved absorption, but also how it deteriorates the linear fit of the slope. In practice, such data are easily rejected based on objective criteria employed in experimental studies [10–12], and the probe is slightly moved to avoid the inhomogeneities.

4.6. Derived physiological variables
Computation of baseline hemoglobin concentrations from the retrieved absorption coefficients allows clinical investigations [10–12] and derivation of physiological variables such as cerebral blood volume (CBV) and oxygen saturation (StO\(_2\)). For the typical wavelengths of 690 and 830 nm, the propagation of the error from retrieved absorption to hemoglobin concentration was computed [43] for the newborn and the adult using specific extinction coefficients [39]. For the newborn, the typical error of 12% in absorption propagates into an error of 17, 20 and 11% for HbO, HbR and HbT, respectively. For the adult, the minimal error of 19% corresponds to 27, 31 and 17% for HbO, HbR and HbT, respectively. The propagation of the error for CBV has the same rate than HbT while the error for StO\(_2\) propagates to 8% and 13% for the newborn and adult, respectively.

4.7. Error arising from the diffusion approximation
The FD-MD method is based on the diffusion approximation and its formulation relies on additional approximations [41]. These approximations lead to errors in the recovered optical properties, even for a large homogeneous slab and especially at short SDs (Fig. 2). Typically, the recovered \(\mu_a\) for a homogeneous slab is overestimated by 20% at short SDs (5–20 mm), but only 5% at large SDs (from 25–40 to 35–50 mm) when no calibration is applied: this method favors long distance estimations because it neglects terms of order greater or equal to 1 in the Taylor development [41]. Adequate calibration of the data reduces this error.

4.8. Error arising from the finite geometry
The FD-MD method also considers that the light is propagating in a semi-infinite medium. This assumption is less true for the newborn model since the head size is markedly smaller than the adult (Fig. 1). The error related to the finite geometry is higher in the newborn estimations compared to the three other head models.

4.9. Limitations
All head models originated from anatomical MRI data sets and were created with a semi-automatic tissue segmentation procedure. This method enabled us to simulate light propagation with Monte Carlo methods in a voxel-wise approach. However, since each voxel has a discrete 3D resolution of 1 mm\(^3\) for each head model, the boundaries of all segmented tissues are represented non-uniformly, especially curved layers. The number of photons detected on the skin
depends strongly on local geometry, i.e. on the position of the detector with respect to the voxelization defining the local curvature. This local geometry can be slightly irregular across head models, which can then lead to under- or overestimated fluences.

Also, a consequence of voxelization and voxel size is imprecision of the SD separations. The distances $d$ used in the fit procedure are the theoretical distances used with the calibration slab phantom, which correspond to the set $[5, 10, \ldots, 50]$ mm. However, the “real”, or simulated, distances for all head models are those determined by the voxel difference between the source and detector positions that belong to the skin. These distances can differ by 0.1 to 0.5 mm from those used in the flat slab, where the curvature is null. These artefacts are higher for the newborn than the adult because the neonate head presents more curvature poorly sampled by the 1 mm$^3$ voxels. However, these artefacts are due solely to the simulation process, and are not representative of any errors observable in experimental studies. We reduced these errors by averaging multiple probe locations. These errors in our method set the minimum on the accuracy with which absorption coefficients can be recovered.

4.10. Future work

In the present study, the effect of the heterogeneous anisotropy across the head [44] was not investigated. Future simulations could incorporate realistic tissue-dependent anisotropy factors.

Future simulations at intermediate ages are necessary to determine the age limit at which the FD-MD method becomes less accurate than 10 or 15%. Also, more accurate segmentation algorithms can provide improved head models and thus better estimates for the young population [45]. In addition, the study of the FD-MD method performance in premature neonates will also be crucial in order to characterize the effects of the thick CSF layer in this population.

5. Conclusion

In this study, we investigated the performance of the FD-MD method when measuring the brain optical absorption at different ages from newborn to adult. In the neonate and infants, the error is dominated by the head curvature and can be minimized around 10–15%. At these ages, the effect of the extra-cerebral layer is small and visible only at short SDs. On the contrary, it becomes dominant in the adult case because of the larger thickness of the scalp and skull. In adults, the strong contamination by the superficial layers leads to both under- and overestimations of the brain absorption coefficient, depending on the relative absorption values assigned to the intra- and extra-cerebral tissues. Not only is the mean error much larger (above 20%) than in the younger head models, but there is a large variability of this error across sets of optical properties. This argument strongly suggests the use of a two- [34] or three-layer [35] model to minimize the deterioration produced by the extra-cerebral layers. In all cases, measurements at 5 mm should be avoided because of the diffusion approximation.

Acknowledgments

The authors thank Myong-Sun Choe (CHB) and Lilla Zollei (MGH). This work was supported by the NIH/NICHD grants # R01-HD042908 and R21-HD058725, the NIH/NCRR grant # P41-RR14075 and the Fonds Québécois de la Recherche sur la Nature et les Technologies (FQRNT-B3, Canada).