Robust estimation of cerebral hemodynamics in neonates using multilayered diffusion model for normal and oblique incidences

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Abstract. The diffusion approximation is useful for many optical diagnostics modalities, such as near-infrared spectroscopy. However, the simple normal incidence, semi-infinite layer model may prove lacking in estimation of deep-tissue optical properties such as required for monitoring cerebral hemodynamics, especially in neonates. To answer this need, we present an analytical multilayered, oblique incidence diffusion model. Initially, the model equations are derived in vector-matrix form to facilitate fast and simple computation. Then, the spatial-temporal reflectance predicted by the model for a complex neonate head is compared with time-resolved Monte Carlo (TRMC) simulations under a wide range of physiologically feasible parameters. The high accuracy of the multilayer model is demonstrated in that the deviation from TRMC simulations is only a few percent even under the toughest conditions. We then turn to solve the inverse problem and estimate the oxygen saturation of deep brain tissues based on the temporal and spatial behaviors of the reflectance. Results indicate that temporal features of the reflectance are more sensitive to deep-layer optical parameters. The accuracy of estimation is shown to be more accurate and robust than the commonly used single-layer diffusion model. Finally, the limitations of such approaches are discussed thoroughly.

1 Introduction

Near-infrared spectroscopy (NIRS) measures tissue optical properties in the near-infrared wavelengths. Specifically, in the 650- to 1300-nm range known as the “tissue optical window,” the main chromophores are the oxygenated (HbO$_2$) and nonoxygenated (Hb) hemoglobin.$^1$ Thus, NIRS is suitable for monitoring cerebral hemodynamics such as tissue oxygen saturation, especially in premature neonatal patients. These patients are at risk of suffering from hemodynamics instability, which has a profound effect on adverse neurodevelopment.$^2$,3

However, optical measurements of neonate and adult brains present great challenges. This is due to deliberate and nondeliberate changes in deep-tissue cerebral hemodynamic variables, which are masked by several superficial layers of highly turbid tissue such as the scalp and the skull. In addition, the complex multilayered geometry and diverse optical properties of the different tissues prohibit simple quantification techniques and necessitate multiple-wavelengths measurements.

Different types of methods are used for forward and inverse modeling in order to extract anatomical information and tissue optical parameters from the measurements performed in the clinic. The most simple and common technique is the Beer–Lambert law.$^4$ In a typical time-resolved NIRS setup, the source and detector are placed with sufficient separation so the average photon path will sample the deep cerebral layers.

The reflectance is measured as a function of time in response to a very short laser pulse.$^5$ This method is subjected to some major constraints which greatly restrict its performance and applicability. In order to sample mainly the scarce photons which are backscattered from deep layers, large source-detector separations and large delays must be used. Thus, only a very small fraction (less than $10^{-6}$) of the photons that are launched into the tissue are measured, causing significant degradation of the signal-to-noise ratio (SNR). Moreover, the forward model that is used provides only a crude estimation of the true absorption in deep layers. Although emphasizing the effect of deep layers over superficial ones, such a model is unable to truly separate the properties of different layers.

Stochastic Monte Carlo (MC) simulations for both time-resolved or steady state are considered to be the most accurate forward models available for macroscopic photon propagation in turbid media. Thus, they serve as a gold standard for comparison and validation of other techniques to be used as forward and inverse models in NIRS.$^5$–$^11$ The MC method may be used to solve the inverse problems but due to its stochastic nature, it is computationally intensive and requires time-consuming algorithms.$^{12}$ This is especially true when complex tissue geometries, large source-detector separations, and/or oblique incidence are present and require many millions of iterations to reduce the variance to an expectable limit. Scaling methods,$^{13,14}$ perturbation methods,$^{15,17}$ and hybrid diffusion-MC$^{18,19}$ methods are used in order to achieve some degree of acceleration.
of the simulations with minor losses in accuracy. Parallel com-
putation and implementation of the MC on graphics processing
units may reduce computation time significantly20,21 but are still
uncommon in practice.

On the other hand, the diffusion approximation of the radi-
ative transfer equation is considered to be quite accurate and
a useful and simple approximation in regions where scattering
dominates over absorption. This is the case in most biological
tissues for wavelengths in the tissue optical window. This
approximation tends to be more accurate when describing
the propagation of photons far enough from the boundaries
and the sources. Several analytical solutions for the diffusion
equation, in both time-dependent and steady state,22,23 may
be used for a single semi-infinite homogeneous medium.
These are based on Green’s function solution in response to
an isotropic point source in an infinite homogenous medium.23
A common, single homogenous layer solution for the reflec-
tance caused by a pencil beam source introduced by Patterson
et al.,24 is commonly used in time-domain or frequency-domain
NIRS.25

For complex biological tissues such as the head, skin,
muscles, and different internal organs, a single semi-infinite
geometry is insufficient and a multilayer model is necessary.
This is especially true for monitoring cerebral hemodynamics
in neonates. A single-layer approximation, which is used in
the literature for this application,25,26 often causes significant
deviations from the actual values due to the strong effect of
the superficial layers such as scalp and skull.

To compensate the effect of multiple layers and to separate
the effects of the layers of interest from the superficial ones, sev-
eral approaches are taken. Numerical approaches which enable
reconstruction of complex tissue geometry are usually based on
the diffusion approximation to the radiative transport equation.
These include finite element method, finite volume method,
finite difference method, and boundary element method,27
which all require significant computation time. Moreover, these
require complex, accurate a priori anatomical information.
Such data can only be acquired by computerized tomography
or MRI scans which have obvious disadvantages that NIRS
aims to avoid. Derivation of analytical solutions for a two-
layered turbid medium using the diffusion equation has been
introduced by several researchers both in time-domain and in
steady state.28–31 Kienle et al.10 suggested an analytical solution
which enables calculation of the reflectance from a two-layered
turbid media having an infinitely thick second layer in the
steady state at frequency and time domains. These analytical
solutions have been used, and their accuracy was further
tested against MC simulations10,30,31 and experimentally.10,34,35
Martelli et al.36–38 introduced time-domain solutions for two and three layers. Das et al.39 presented a solution incorpo-
rating a tilted interface and refractive index difference between
two layers.

For multilayered media, Tualle et al.40 investigated the
asymptotic behavior of reflectance in scattering multilayered
semi-infinite media in order to derive the optical properties
of the deepest layer. Wang and Wang41 have also extended
the solution of Kienle et al.10 for an N-layered mismatched
semi-infinite medium in the steady state and time domain and
compared it with MC simulations. Recently, Liemert and Kienle
have used a similar approach and developed a solution for an
N-layered turbid medium in both semi-infinite and finite.
Their solutions are presented in steady state,42 time domain,42 and
frequency domain43 and were compared with MC simulations.
However, to the best of our knowledge, no general multilayered
model was applied yet to the study of light propagation in neo-

nate heads or for the estimation of the cerebral hemodynamics
with NIRS.

Oblique incidence diffuse reflectance measurements have
many advantages over normal incidence measurements. An
oblique incidence setup can reduce detector saturation due to
specular-reflected photons while ensuring collection of the dif-

fusely reflected photons. These diffuse photons carry informa-
tion from structures deep within the tissue, thus increasing
their collection and the SNR. Oblique incidence is also advanta-
geous in fluorescence measurements, since it enables selection of
the depth of fluorescence origin by varying the angle of inci-
dence.30,44,45 Endoscopic probes, which are used in clinical
applications, often use oblique incidence, and different configu-

rations were designed for such purposes.46 Measuring the
reflectance in curvature geometry, such as neonate heads, may
cause some artifacts47 which could be reduced using oblique
incidence.

Wang and Jacques48 developed an oblique incidence
reflectance method which measures the reduced scattering
coefficient. This method was extended for determining both
reduced scattering and absorption coefficients,49 and the effect
of tissue structures on the estimated coefficients was further
investigated.50,51 Spatially resolved oblique incidence diffuse
reflectance spectroscopy was used in vivo to discriminate melanoma and carcinoma skin cancers from benign and pre-
malignant skin lesions.51 In these methods, only a single set
of absorption and reduced scattering coefficients is estimated
per wavelength, thus assuming a semi-infinite homogeneous
turbid media. Currently, to the best of our knowledge, a method
that combines oblique incidence with a multilayered model has
not been presented.

Here, we introduce an analytical model for calculating the
reflectance from a multilayered turbid media using normal or
oblique incidence. Such a model differs from previous works
as it is written in vector–matrix form to facilitate fast and simple
computation in MATLAB® environment. In addition, it allows
the simple integration of oblique incidence, complex beam
shapes, or arbitrary temporal modulation. Both time-resolved
and spatially resolved reflectance solutions are presented and
compared with MC simulations. We then assessed the appli-
cability of this model for monitoring cerebral hemodynamics
in neonatal intensive care using NIRS. The accuracy is evaluated
in different sets of absorption and scattering coefficients in
multilayered media for synthetic tissue models and real-life neo-
nate head models. The effects of changes in the optical coeffi-
cients in superficial and deep layers are tested and evaluated as
well as the effects of normal or oblique incidence. Finally, we
demonstrate the estimation of the deep-tissue oxygen saturation
with spatiotemporal NIRS using the multilayered model and
compare the estimated values to those estimated using the semi-infinite homogeneous model.8

2 Methods

2.1 Theoretical Model

Presented here is a concise and rigorous mathematical development
for the multilayered diffusion model. To this end, let us

first consider the case of an incident pencil beam. Let the origin
of a Cartesian coordinate system coincide with the beam incidence described in Fig. 1.

Under the diffusion approximation in a $N$-layered turbid medium, and for an incident pencil beam with azimuthal angle $\gamma_{\text{inc}}$ and polar angle $\theta_{\text{inc}}$, the photon fluence rate obeys a set of diffusion partial differential equations:

$$
\left[ \nabla^2 - \frac{n_0^2}{cD_i} \frac{\partial}{\partial t} - \frac{\mu_t}{D_i} \right] \phi_i(t, \mathbf{r}) = - \frac{a'_i}{D_i} \delta(i-1) \delta(\mathbf{r} - \mathbf{r}_s), 
$$

$$
i = 1, 2, \ldots, N,
$$

where $\mathbf{r}_s = (3D_i n_0/n_i) \left[ \sin(\theta_{\text{inc}}) \cos(\gamma_{\text{inc}}) \sin(\theta_{\text{inc}}) \cos(\gamma_{\text{inc}}) \right] \sqrt{n_i^2/n_0^2 - \sin^2(\theta_{\text{inc}})} T$,  

$$
\phi_N|_{z = z_N + \delta z} = 0
$$

$\phi_i = 0$, Fluence vanishes at infinite radius

$$
n^2_{i+1} \phi_i |_{z = z_i} = n^2_i \phi_i |_{z = z_{i+1}}
$$

$D_j \frac{\partial}{\partial z} \phi_j |_{z = z_i} = D_{j+1} \frac{\partial}{\partial z} \phi_{j+1} |_{z = z_i}$, Fresnel B.C.

$$
\phi_j |_{z = -\delta z} = 0
$$

$\phi_j |_{z = z_j + \delta z}$, Extrapolated B.C. at upper interface

$$
\phi_j |_{z = z_j + \delta z} = 0
$$

Extrapolated B.C. at lower interface

where $z_i = \sum_{j=1}^{i} d_j$ is the cumulative depth of the $i$th layer, and $z_{\text{ba}}$ and $z_{\text{al}}$ are the extrapolated boundary locations above and below the tissue, respectively. These can be computed by numerical integration of the Fresnel integrals presented by Haskell et al.22

One should note that under these B.C.s, the fluence rate is time invariant and transversally shift invariant $(x, y)$ coordinates) but not invariant to shifts at the longitudinal coordinate $(z$-coordinate). Consider the transverse spatiotemporal Fourier transform (TFT) defined with its inverse counterpart by

$$
\Phi(\omega; \mathbf{k}, z) = \int_{\mathbb{R}^2} \int_{\mathbb{R}^2} \phi(t; \mathbf{r}, z) e^{-j(\omega t - \mathbf{k} \cdot \mathbf{r})} d\mathbf{r} d\omega ,
$$

$$
\phi(t; \mathbf{r}, z) = \frac{1}{(2\pi)^2} \int_{\mathbb{R}^2} \int_{\mathbb{R}^2} \Phi(\omega; \mathbf{k}, z) e^{j(\omega t - \mathbf{k} \cdot \mathbf{r})} d\mathbf{k} d\omega ,
$$

where $j = \sqrt{-1}$ is the unit imaginary. Such transform will transform the set of diffusion equations into a set of a second-order, nonhomogeneous, ordinary differential equations

$$
\frac{\partial^2}{\partial z^2} \Phi_i(\omega; \mathbf{k}, z) - \frac{\mu_t}{D_i} \frac{\partial}{\partial z} \Phi_i(\omega; \mathbf{k}, z) = - \frac{a'_i}{D_i} \delta(i-1) \Phi_i(\omega; \mathbf{k}, z) e^{-\mathbf{r}_s \cdot \mathbf{k}_i},
$$

where $\mathbf{r}_s$ is the transverse component of the isotropic source position vector. A note should be taken that the B.C.s are almost unaffected by this transform, as the longitudinal coordinate is unaltered. The frequency domain equations have a known solution

$$
\Phi_i^H(\omega; \mathbf{k}, z) = A_i(\omega; \mathbf{k}) e^{j\mathbf{r}_s \cdot \mathbf{k}_i} + B_i(\omega; \mathbf{k}) e^{-\mathbf{r}_s \cdot \mathbf{k}_i},
$$

$$
\Phi_i^P(\omega; \mathbf{k}, z) = - \frac{a'_i}{D_i} H(\mathbf{r}_s \cdot z) e^{-j(\omega t - \mathbf{k} \cdot \mathbf{r}_s)} ,
$$

where $\mathbf{k}_i^2 \equiv |\mathbf{k}_i|^2 + (\mu_t/D_i) - j(\omega n_i/c D_i)$ is the square of the complex wavenumber, and $H(\cdot)$ denotes the Heaviside step function. The superscripts $H$ and $P$ denote the homogeneous and particular solutions, respectively, such that $\Phi_i(\omega; \mathbf{k}, z) = \Phi_i^H(\omega; \mathbf{k}, z) + \delta(\mathbf{r}_s \cdot \mathbf{k}_i) \Phi_i^P(\omega; \mathbf{k}, z)$. Such private solution is similar in form to the one presented by Kinnie et al.18 The transverse functions $A_i$ and $B_i$ are to be defined by the various B.C.s. Considering the Fresnel and photon current density conditions and applying them on the solution given in Eq. (6), one can write the following matrix relation

![Fig. 1 Description of multilayer diffusion model’s geometry and notation.](image-url)
\[
\begin{bmatrix}
A_{i+1} \\
B_{i+1}
\end{bmatrix} = \frac{1}{2} \begin{bmatrix}
\left( \frac{D_{i}}{D_{i+1}k_{i+1}} + \frac{n_{i+1}'}{n_{i+1}} \right) e^{-(k_{i+1}+\kappa_{i})z_{i+1}} - \left( \frac{D_{i}}{D_{i+1}k_{i+1}} - \frac{n_{i+1}'}{n_{i+1}} \right) e^{-(k_{i+1}+\kappa_{i})z_{i+1}} \\
\left( \frac{D_{i}}{D_{i+1}k_{i+1}} + \frac{n_{i+1}'}{n_{i+1}} \right) e^{(k_{i+1}+\kappa_{i})z_{i+1}} - \left( \frac{D_{i}}{D_{i+1}k_{i+1}} - \frac{n_{i+1}'}{n_{i+1}} \right) e^{(k_{i+1}+\kappa_{i})z_{i+1}}
\end{bmatrix} \begin{bmatrix}
A_{i} \\
B_{i}
\end{bmatrix}.
\]  

(7)

Denoting the matrix described in Eq. (7) by \( \mathbf{M}^{(i)} \), one can repeat this process to get the matrix relation (denoted by \( \mathbf{M}^{\text{tot}} \)) between the first and last sets of transverse functions

\[
\begin{bmatrix}
A_{N} \\
B_{N}
\end{bmatrix} = \frac{\mathbf{M}^{(N-1)} \cdots \mathbf{M}^{(3)} \mathbf{M}^{(2)} \mathbf{M}^{(1)}}{\mathbf{M}^{\text{tot}}} \begin{bmatrix}
A_{1} \\
B_{1}
\end{bmatrix}.
\]

(8)

Applying the extrapolated B.C.s for the first and last layers yields a matrix equation with the following solution:

\[
\begin{bmatrix}
A_{1} \\
B_{1}
\end{bmatrix} = \frac{a'_{i}}{2D_{i}k_{i}} \begin{bmatrix}
e^{-2k_{i}z_{b}} - e^{-2k_{i}z_{b}} \\
e^{-2k_{i}z_{b}} - e^{-2k_{i}z_{b}}
\end{bmatrix} \begin{bmatrix}
M_{12}^{\text{tot}} + M_{22}^{\text{tot}} e^{-2k_{i}z_{b}} \\
-M_{11}^{\text{tot}} + M_{21}^{\text{tot}} e^{-2k_{i}z_{b}}
\end{bmatrix} \begin{bmatrix}
M_{12}^{(i)} + M_{22}^{(i)} e^{-2k_{i}z_{b}} \\
-M_{11}^{(i)} + M_{21}^{(i)} e^{-2k_{i}z_{b}}
\end{bmatrix} \begin{bmatrix}
\mathbf{M}^{(N-1)} \cdots \mathbf{M}^{(3)} \mathbf{M}^{(2)} \mathbf{M}^{(1)} \\
\mathbf{M}^{\text{tot}}
\end{bmatrix} \begin{bmatrix}
A_{1} \\
B_{1}
\end{bmatrix}.
\]

(9)

Thus, the frequency-domain fluence rate may be calculated for all other layers by repeated application of Eq. (6). However, for the sole calculation of the reflectance, this is not required as it depends only on the fluence in the top layer.

To account for an arbitrary spatiotemporal beam shape, \( I(t; r, z) \), one can compute the spatiotemporal reflectance rate by

\[
\phi(t; r, z) = \mathcal{F}^{-1} \{ \Phi(\omega; k_{b}, z) \mathcal{F}[I(t; r, z)] \},
\]

(10)

where \( \mathcal{F} \{ \cdot \} \) and \( \mathcal{F}^{-1} \{ \cdot \} \) denote the forward and inverse TFTs defined by Eq. (4). These can be easily and efficiently computed numerically by the FFT algorithm implemented in MATLAB and other environments.

Finally, the physical parameter commonly measured in practice is the spatiotemporal reflectance \( R(t; r_{i}) \), which is related to the upper layer fluence for a refractive index of 1.4 by

\[
R(t; r_{i}) = \left\{ 0.118 \phi_{1}(t; r_{i}, z) + 0.306 D_{1} \frac{\partial}{\partial z} \phi_{1}(t; r_{i}, z) \right\} \bigg|_{z=0}.
\]

(11)

For other refractive indices, the reflectance may be calculated according to the general expression

\[
R(t; r_{i}) = R_{\text{eff}} \left\{ \frac{\phi_{1}(t; r_{i}, z) + D_{1} \frac{\partial}{\partial z} \phi_{1}(t; r_{i}, z)}{4} \right\} \bigg|_{z=0},
\]

(12)

where \( R_{\text{eff}} \) is the effective reflectance coefficient, which may be calculated according to Haskell et al.\(^{22}\) of four layers—scalp, skull, gray matter, and white matter. The accuracy of the predicted reflectance was tested for a wide range of optical properties, such as the absorption and scattering of the gray and white matters, and for a different refractive index of the scalp and skull. The variation of these properties simulates variation in human anatomy and different oxygenation levels of the brain. The anatomical and optical properties which were chosen for each layer are based on previous reports for NIR light\(^{47,53,54}\) and are summarized in Table 1. For each test, only one of the optical properties was varied, keeping the rest with their default values indicated in Table 1 by bold characters.

In order to evaluate the error between the diffusion model and the MC simulations, the root mean square of the normalized deviation (RMSND) was calculated using the following relation:

\[
\text{RMSND}(r) = \sqrt{\left\langle \frac{R_{\text{MC}}(t; r_{i}) - R_{\text{Model}}(t; r_{i})}{R_{\text{MC}}(t; r_{i}) + R_{\text{Model}}(t; r_{i})} \right\rangle^{2}},
\]

(13)

where \( R_{\text{MC}} \) and \( R_{\text{Model}} \) are the MC and diffusion [calculated using Eqs. (11) or (12)] spatiotemporal reflectances at a given point on the tissue surface, and \( \langle \cdot \rangle \) denotes the time averaging.

Table 1 Optical parameters of the different tissues used in the model.

<table>
<thead>
<tr>
<th>Tissue type</th>
<th>Absorption coefficient, ( \mu_{a} ) (cm(^{-1}))</th>
<th>Reduced scattering coefficient, ( \mu_{s} ) (cm(^{-1}))</th>
<th>Refractive index, ( n_{i} ) (#)</th>
<th>Layer thickness, ( d_{i} ) (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scalp</td>
<td>0.18</td>
<td>19.0</td>
<td>1.4 (matched)</td>
<td>0.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.55 (mismatched)</td>
<td></td>
</tr>
<tr>
<td>Skull</td>
<td>0.16</td>
<td>16.0</td>
<td>1.4 (matched)</td>
<td>0.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.55 (mismatched)</td>
<td></td>
</tr>
<tr>
<td>Gray matter</td>
<td>0.24 (Medium)</td>
<td>5.0 (Low)</td>
<td>1.4</td>
<td>0.4</td>
</tr>
<tr>
<td></td>
<td>0.12 (Low)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White matter</td>
<td>0.37 (High)</td>
<td>10.0</td>
<td>1.4</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td>0.19 (Medium)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.09 (Low)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
2.3 Estimation of Oxygenation Level

The most valuable clinical parameter monitored using NIRS is the tissue oxygen saturation \( \text{StO}_2 \). It is dependent on the concentrations of the nonoxygenated hemoglobin and oxygenated hemoglobin according to the following relation:

\[
\text{StO}_2(\%) = \frac{[\text{HbO}_2]}{[\text{Hb}] + [\text{HbO}_2]} \times 100, \tag{14}
\]

where \([\cdot]\) denotes the concentration of each analyte.

The absorption coefficients of the brain tissues in the NIRS are dependent on several chromophores concentrations including mainly: water, \( \text{HbO}_2 \), \( \text{Hb} \), and the cytochrome \( \text{aa}_3 \) in its oxidized \( (\text{aa}_3,\text{oxi}) \) and reduced \( (\text{aa}_3,\text{reduce}) \) forms, whose oxidation state is affected by the \( \text{StO}_2 \) value. The water absorption can be ignored for wavelengths up to 950 nm, since it is negligible compared with other chromophores.

Assuming that only these chromophores contribute to the brain tissue absorption, the absorption coefficient of the brain may be calculated according to the following equation:

\[
\mu^\lambda_{\text{brain}} = \varepsilon^\lambda_{\text{Hb}}[\text{Hb}] + \varepsilon^\lambda_{\text{HbO}_2}[\text{HbO}_2] + \varepsilon^\lambda_{\text{aa}_3,\text{oxi}}[\text{aa}_3,\text{oxi}] + \varepsilon^\lambda_{\text{aa}_3,\text{reduce}}[\text{aa}_3,\text{reduce}], \tag{15}
\]

where \( \mu^\lambda_{\text{brain}} \) is the brain tissue absorption coefficient, \( \varepsilon^\lambda_{\text{chromoph}} \) is the extinction coefficient, and the superscript \( \lambda \) denotes the wavelength.

The brain absorption coefficient was calculated for different oxygen saturation levels between 4\% and 99\%. The total concentration of cytochrome \( \text{aa}_3 \) was chosen to be 22 \( \mu \)mol, and the total hemoglobin concentration was chosen to be 65 \( \mu \)mol based on the literature.\(^{1,26,47,55}\) The chosen wavelength was \( \lambda = 700 \) nm, and the extinction coefficients of each chromophore were taken for this wavelength from literature.\(^{1,56}\)

A set of time-resolved MC simulations was used to estimate the performance of the multilayered diffusion model versus the semi-infinite homogeneous diffusion model of Kienle and Patterson.\(^8\) The simulation parameters were the same as presented in Table 1, apart from the absorption coefficient of the gray and white matters, which was calculated according to Eq. (15) for various levels of oxygen saturation from 4\% to 99\%. Normalized time-resolved reflectance curves were deduced from the simulations for a source-detector separation of 1.9 cm. A nonlinear least square curve-fitting algorithm\(^{57,58}\) was used for fitting the time-resolved reflectance predicted by the single-layer and multilayer models. For the single-layer model, both the absorption and reduced scattering coefficients were estimated. For the multilayer model, the optical parameters of the superficial layers were assumed to be known. The estimated parameters were the gray and white matters’ absorption coefficients and the white matter scattering coefficient. In both cases, the brain tissue oxygen saturation levels were calculated based on the estimated absorption coefficients according to Eq. (15) and were compared with true values. The upper and lower limits used in the curve fitting represent oxygen saturation levels between 1\% and 99\%. The curve fitting was tested for different combinations of reduced scattering coefficient limits, initial guesses, and time ranges.

3 Results

3.1 Comparison with Semi-Infinite Homogeneous Solution

In order to validate the accuracy of the multilayer model, it was first compared with the semi-infinite homogeneous solution of Kienle and Patterson.\(^8\) For this comparison, four identical layers were used for the multilayer model with the default optical parameters of the skull detailed in Table 1. The time-dependent reflectance was calculated using the multilayer diffusion analytical model according to Eq. (11). For the semi-infinite homogeneous model, the same parameters of the skull were chosen and the time-resolved reflectance was calculated according to the extrapolated B.C. solution presented by Kienle and Patterson.\(^8\) The time-resolved reflectance of both models was calculated in a radius of 1.9 cm, and the high correlation between both solutions is presented in Fig. 2. The RMSND between the two curves presented in Fig. 2 is 5.5\%.

3.2 Model Validation against MC Simulations

The diffusion approximation is known to be accurate in regions far from sources, since the ballistic photons are neglected and only the diffuse photons are taken into account.

In close proximity to the source, the portion of the ballistic photons is large compared with the diffused ones. Thus, the accuracy of the diffusion approximation increases with an increase of source-detector separation. This limitation is demonstrated in Fig. 3 where the time-resolved reflectance is presented for several distances from the incident light source, in the range of 1 to 2 cm, which is suitable for efficient sampling of photons propagating through brain tissue. The optical parameters for all three cases are identical and taken as the default values in Table 1. The time-dependent reflectance was calculated for each case using the diffusion analytical model according to Eq. (11). The intensity of reflectance is always displayed in logarithmic scale on all graphs to emphasize differences in both

![Fig. 2 Comparison between the time-resolved reflectance curves calculated using the multilayer diffusion model for four identical layers (solid line) and the semi-infinite homogeneous model (dashed line).](image-url)
It is clear that the correlation between the diffusion model and the MC simulations increases with the increase in the distance from the source. In addition, even for the largest distance case, the model fails to accurately predict the MC reflectance at short times after the incident light pulse. This inaccuracy is again due to the larger portion of ballistic photons at short times compared with long times after incident pulse. The RMSND was calculated for the decaying part of the time-resolved reflectance of each case presented in Fig. 3 and was found to be 6.8%, 14.7%, and 22.7% for a distance of 1.8, 1.4, and 1 cm, respectively.

### 3.3 Assessment of Model’s Accuracy for Different Optical Properties

The absorption coefficients of the gray and white matter are affected by the cerebral oxygenation and hemodynamics. In order to simulate these changes, several representative absorption coefficients were used for the gray and white matter in the head model. Three cases were tested—low, medium, and high brain absorption, as indicated in Table 1. Figure 4 demonstrates the effect of the brain absorption on the accuracy of the diffusion model compared with MC simulations at a distance of 1.9 cm from the incident light source. Only the decaying part of the time-resolved reflectance is presented due to the inaccuracy of the diffusion approximation in short times after the incidence, which is caused by the contribution of the ballistic photons to the reflectance.

As evident from Fig. 4, the decay of the fluence rate is highly sensitive to absorption of the deep layer. For the case where low- and medium-absorption coefficients were used for the brain tissue, the model and the MC are highly correlated. However, for the high brain absorption case, the diffusion model is less accurate in predicting the reflectance although the time derivatives of the reflectance are very similar. This case presents some extremity where the absorption approaches its upper limit. The RMSND was calculated for the cases presented in Fig. 4. The RMSND for the decaying reflectance was 10.7%, 7.2%, and 35% for the low, medium, and high brain absorption cases, respectively. These results suggest that the correlation between the MC simulations and the diffusion model is rather high for a broad range of absorption coefficients. In many cases, these errors are comparable with measurement errors often encountered in clinical practice.

The influence of changes in the scattering coefficient was investigated as well. Previously reported reduced scattering coefficients for neonates in the NIR region\(^ {47,53,54}\) are in the range of 4 to 10 cm\(^{-1}\). The high scattering is often correlated with higher absorption (as both are dependent on the density). Thus, the combination of high or low scattering with high absorption was studied. Figure 5 displays the MC and the model’s time-dependent reflectance for low- and high-reduced scattering coefficients in the gray matter at a distance of 1.9 mm from incident light source.

The correlation between the decaying reflectance of the model and the MC is shown to be stronger in the high gray matter scattering case than in the low scattering case. The RMSND for the decaying reflectance decreased from 35% in the low scattering case to 12% in the high scattering case.

Finally, the multilayered diffusion model takes into account the refractive index mismatch between layers. In order to test the influence of such an internal mismatch on the model’s accuracy, two cases were compared. In the first case, a refractive index of 1.4 was used for all four tissue layers and in the second case, a refractive index of 1.55 was used for the superficial layers (scalp and skull), while a refractive index of 1.4 was used for the brain tissue layers (gray and white matter).
Figure 6 demonstrates the high correlation between the decaying time-resolved reflectance of the model and the MC simulation, in both cases, at a distance of 1.8 cm from incident light source. The RMSND for the decaying reflectance presented in Fig. 6 is 7.9% for the refractive index matched case and 7.2% for the refractive index mismatched case.

Figure 7 demonstrates the high correlation between the ratios of the spatially resolved reflectance in several vertical locations for two cases: Case A, medium brain absorption and low scattering, and case B, high brain absorption and high scattering. The ratios presented are \( R(x_2 = 1.2 \text{ cm}, y) / R(x_1 = 0.7 \text{ cm}, y) \) and \( R(x_3 = 1.6 \text{ cm}, y) / R(x_1 = 0.7 \text{ cm}, y) \). The ratios were calculated using both MC simulations (presented using the symbols) and the diffusion model (presented using the lines).

### 3.4 Spatially Resolved Reflectance

The multilayered diffusion model provides a simple calculation of the spatially resolved reflectance for steady state or modulated illumination. The steady-state, spatially resolved reflectance from the MC simulations was compared with the diffusion model for two cases where both the scattering and absorption were changed: case A, medium brain absorption and low scattering, and case B, high brain absorption and high scattering.

The correlation between the reflectance simulated by MC and that calculated using the diffusion model was very high. However, there was a significant overlap between reflectance in the two cases and distinguishing between the cases was quite difficult. In order to enable distinguishing between the two cases, additional analysis was performed. Since our model provides us the spatially resolved reflectance as a function of both horizontal and vertical distances from incident light source, the reflectance along the horizontal coordinate was calculated for three fixed vertical positions: \( x_1 = 0.7 \text{ cm}, \) \( x_2 = 1.2 \text{ cm}, \) and \( x_3 = 1.6 \text{ cm}, \) at a distance of 1.8 cm from incident source. The correlations between the two cases, the following ratios were calculated:

\[
R(x_2, y) / R(x_1, y) \quad \text{and} \quad R(x_3, y) / R(x_1, y).
\]

Figure 7 demonstrates these ratios for both the MC simulations and the analytical model.

One can see that the MC simulation and analytical model predictions are highly correlated. For both reflectance ratios \( R(x_2, y) / R(x_1, y) \) and \( R(x_3, y) / R(x_1, y) \), the difference between cases A and B is easily noticeable. However, these differences are accentuated in the time-resolved reflectance, and thus it is preferable to work with time-resolved or modulated (frequency-resolved) measurements. For comparison, Fig. 8 presents the time-resolved reflectance for both cases at a distance of 1.8 cm from the source. One can easily notice the profound effect that the two cases have on the decay rates of the fluence.
3.5 Oblique Incidence

The spatially resolved reflectance is highly dependent on the angle of incidence. In most multilayered models, normal incidence is assumed. However, in the presented multilayered diffusion model, cases of oblique incidence were taken into account. The effect of oblique incidence on the fluence in the case of medium brain absorption is demonstrated for an incident angle of $\theta_{\text{inc}} = 60$ deg and $\gamma_{\text{inc}} = 0$ deg. Figure 9 presents the fluence as a function of depth ($z$-axis) and $x$-axis for different times after light incidence, for the oblique case (upper images) and normal incidence case (lower images). The offset of the isotropic source location from the $x$-axis in the oblique incidence case is demonstrated. Notice that the depth of the isotropic source is also shifted compared with the normal incidence case due to the oblique incidence.

In order to emphasize the difference between the reflectance of oblique and normal incidences, the superficial layers of the head model were neglected and a simplified two-layered case of gray and white matter in an ambient cerebrospinal fluid was tested. The optical parameters of the layers are detailed in Table 2. The angle of incidence for the oblique case was chosen to be $\theta_{\text{inc}} = 60$ deg and $\gamma_{\text{inc}} = 0$ deg. The refractive index of the ambient medium was similar to a watery medium, such as the cerebrospinal fluid, and was chosen to be $n_0 = 1.33$.

Figure 10 compares the normal and oblique incidence spatially resolved reflectances as a function of the $y$ coordinate for $x = 1.2$ cm. The correlation between the model and the MC is high for both cases, which are clearly distinguishable.

The spatial shift of the maximal intensity presented in Fig. 10, calculated by both the MC simulation and the diffusion

### Table 2 Optical parameters of the layers used for normal and oblique incidences comparison.

<table>
<thead>
<tr>
<th>Tissue type</th>
<th>Absorption coefficient $\mu_{\text{ai}}$ (cm$^{-1}$)</th>
<th>Reduced scattering coefficient $\mu_{\text{si}}$ (cm$^{-1}$)</th>
<th>Refractive index, $n_i$ [#]</th>
<th>Thickness, $d_i$ (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gray matter</td>
<td>0.12</td>
<td>4.0</td>
<td>1.4</td>
<td>0.4</td>
</tr>
<tr>
<td>White matter</td>
<td>0.09</td>
<td>10.0</td>
<td>1.4</td>
<td>2.0</td>
</tr>
</tbody>
</table>
model, is about 2 mm. Wang and Jacques presented a formula for the spatial shift of the maximal intensity in case of oblique incidence. The reflectance was calculated for a two-layer model, detailed in Table 2, at a location of x = 1.2 cm. The MC simulations are presented using the triangle and circle symbols for the normal and oblique incidence cases, respectively. The diffusion model reflectance is presented in the solid and dashed lines for the normal and oblique cases, respectively.

\[ \Delta x = 3D_1 \sin(\theta_{inc}) n_0/n_1. \]  

(16)

Calculation of the predicted shift using the above equation yields 1.95 mm, which is just shy of the accurate value.

3.6 Estimation of the Oxygenation Saturation Level

Finally, the use of a semi-infinite homogeneous diffusion model was tested against the multilayer model in order to compare their accuracy in estimating the oxygenation saturation level in neonates. In clinical systems and applications, many parameters such as energy loss in the optical path and coupling efficiency may affect the measurement, therefore only uncalibrated curves are measureable. Thus, in order to make the comparison more realistic, the MC simulations, which provide reflectance in absolute units, were normalized at their maximal value. The curve fitting was then performed on the normalized MC curves and diffusion curves in order to avoid over-estimation of the algorithm performance compared with a true optical setup.

Using a nonlinear least square curve fitting, normalized MC time-resolved reflectance curves were fitted to normalized four-layer diffusion reflectance curves, assuming known optical properties of the superficial layers \((\mu_a, \mu_s, g, n)\) and the length of each layer. The curve fitting was tested in different combinations of reduced scattering coefficient limits, initial guesses, and time ranges. Variation in the initial guesses rarely changed the results of the curve fit in both models. However, the reduced scattering coefficient limits and mainly the variations of the time range of the curve did affect the fit results. For the case of the homogeneous model, the chosen time ranges adversely affected the accuracy of the estimated parameters, causing significant errors. On the other hand, the four-layer model was robust to changes in the data range, and the accuracy remained high.

The estimated oxygen saturation levels using the four-layer model and the homogeneous diffusion model were compared with the true oxygenation levels used in the MC simulations. Figure 11 presents the mean estimated saturation levels with 90% confidence intervals for the homogeneous model and the four-layer model (shown in Figs. 11(a) and 11(b), respectively). The average error of all oxygen saturation levels estimated by the four-layered model was 3.8% with a maximum error of 12.4%. For the semi-infinite homogeneous model, the average error of all estimated saturation levels was 14.2% with a maximal error of 35%.

4 Discussion

This work describes the development and application of a multilayer model for light propagation in tissue based on the diffusion approximation. It was used for prediction of the spatiotemporal reflectance in response to normal or oblique excitation. The validity of this model was tested against MC simulations under various conditions. Finally, the proposed model was applied for NIRS, which monitors cerebral hemodynamics in neonates. The more realistic multilayer model was proven to be more accurate and robust to the choice of numerical scheme. This is in contrast to the simplistic semi-infinite homogeneous model used today.

The effects of changes in the various optical parameters of deep brain tissue on superficial reflectance were thoroughly studied and compared with gold-standard MC simulations. The model was found to be quite accurate as long as the assumptions of the diffusion approximation were respected. Typical RMSND values indicate less than 12% error in prediction of the spatio-temporal reflectance decay. This is true even for complex multilayered tissue with varying optical parameters and external and internal index mismatches. Even under the most difficult physiologically feasible scenario, in which the absorption is highest compared with the scattering, the typical error is 35%. Thus, this model is suitable to serve as a flexible, computationally light, forward solution for the estimation of optical parameters. It has advantages over the computationally heavy stochastic models such as time-resolved MC. Thus, this method can be easily implemented for the estimation of hemodynamic variables of clinical importance using spatiotemporal NIRS for neonates.
The estimation of the optical properties from the spatial distribution was also investigated. The effect of major changes in deep brain tissue on the spatial distribution of the diffusely reflected photons is almost nonexistent. Under such conditions, estimation of deep-tissue optical parameters is impossible unless some processing is performed to stress the effect of deeper layers. We demonstrated such a process by normalizing the spatial distribution along one dimension with respect to a parallel distribution closer to the equivalent isotropic source, as shown in Fig. 7. This process has successfully emphasized the spatial changes due to different optical properties of the deep layers. However, it seems less accurate than time-resolved measurements, as demonstrated in Fig. 8.

Reduction in the number of unknown optical parameters is possible by the use of oblique incidence, as demonstrated in Fig. 10. The work of Wang and Jacques showed that for a single-infinite layer, if the refractive index of the superficial layer is known, then the optical diffusion coefficient can be simply deduced from the shift in the location of maximal reflectance. The model presented here, to the best of our knowledge, is the first to take into account oblique incidence in a multilayered diffusion model. Although a rigorous multilayer model is presented here, it is evident from Fig. 10 that this relation still holds provided that the depth of the superficial layer is sufficiently large compared with \( l_s \). In the example shown in Fig. 10, the depth of the superficial layer is 1.6 times \( l_s \) and it is clearly evident that the estimation presented in Eq. (16) approximates well the results of both the MC and diffusion model. Another advantage of oblique incidence is evident when the detectors used for measuring the reflectance are not in contact with the tissue (such as in the case of cameras). The use of oblique incidence allows deflecting the intense specular Fresnel reflection away from the detector and avoiding saturation.

Finally, an inverse algorithm was applied in order to extract the brain oxygen saturation level using both the multilayered model and the commonly used semi-infinite homogeneous model. The estimated values using the homogeneous model were highly sensitive to the chosen curve-fitting conditions such as the reflectance time range on which the fit was performed. This caused high errors in the estimated oxygen saturation level, in some cases reaching 35%. However, the inverse algorithm applied on the multilayer model was robust to changes in the curve-fitting conditions and in all cases, the estimated saturation level was accurate with less than 12% error.

Although useful, the diffusion approach suffers from some apparent drawbacks which reflect from the results shown earlier. One of the major drawbacks of such a model is its inherent inaccuracy near the incident beam or the equivalent isotropic source. It is commonly accepted that at distances of 10 mean free paths (MFP \( \equiv 1/\mu_a \)) from the isotropic source, the diffusion approximation becomes accurate. Since the superficial layers of the body such as skin, or the combined skin and scalp tissues for the head model presented here, are highly scattering, this restriction is not severe in most cases. For example, Fig. 3 demonstrates that at distances above 20 MFP (\( \sim 1 \) cm), the RMSND is less than 20% and at distances above 30 MFP (\( \sim 1.6 \) cm), the RMSND decreases below 10%. For neonates with thin scalp and skull tissues of 4 mm and more in thickness, a source-detector separation of 0.8 to 1.6 cm is required for covering the gray matter, and even larger separations are required in order to efficiently sample the white matter. These are large distances since the separation must be at least twice the depth of the tissue to be probed, thus the loss of accuracy in lower distances does not pose serious difficulties.

Another assumption which needs to be respected is that scattering should dominate absorption. The reduced albedo defined as \( a'' = \mu_a/\mu_a + \mu_s' \) should not fall below a certain value in order for the model results to be sufficiently accurate. This is well evident in Figs. 4 and 5. For high brain absorption, the reduced albedo is \( \sim 0.9 \), which leads to some small discrepancies between the MC simulations and the diffusion approximation. For low and medium absorptions, the reduced albedos are \( \sim 0.95 \) and \( \sim 0.97 \), respectively. In these cases, the matching between the MC simulation and analytical model is almost perfect. It is expected that for reduced albedos of 0.8 and below, the diffusion model will not be accurate enough. However, determination of the exact deterioration of performance as a function of the deterioration in the albedo is beyond the scope of this article and requires further investigation.

Additionally, the head model, which was used for this analysis, consists of the scalp, skull, gray matter, and white matter. A more realistic model should take into account also the cerebrospinal fluid layer, which is between the skull and the gray matter. The cerebrospinal fluid is known to be a clear medium with low scattering compared with absorption, and therefore the accuracy of the diffusion model in the presence of this layer may be decreased. However, since the thickness of this layer is very small compared with the gray and white matter, it may be combined with these layers without significant loss of accuracy of the diffusion approximation.

To conclude, this work outlines the derivation and validation of a multilayer diffusion model for NIR monitoring of cerebral hemodynamics in neonates. It was demonstrated that even for complex media such as neonate heads, our approximated model is highly accurate and its predictions are very similar to those of the gold standard MC simulations. This model is robust and accurately coincides with any type of MC simulations—whether spatially resolved or temporally resolved, normal or oblique incidence, single or multiple layers. Since this model predicts the fluence accurately and much more rapidly compared with MC simulations, it may be used to solve inverse problems where the optical coefficients are to be estimated by iterating the forward solution proposed by this model. Finally, it was demonstrated on pure theoretical grounds that deep-tissue optical properties and consequently hemodynamics status can be estimated easily and accurately from the spatiotemporal reflectance curve using a quick and simple curve-fitting algorithm. This is even in the presence of unknown optical parameters of the superficial layers.

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References


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