Modeling of PpIX Fluorescence of a Two Layered Medium: A Monte-Carlo Study

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Abstract. An advancement of an exponential model of protoporphyrin IX (PpIX) fluorescence of two-layered media has been accomplished to mimic healthy and tumor brain tissues. The optical properties of these layers were selected to mimic meningioma as a tumor tissue and white matter as a healthy tissue at 405 nm excitation and 635 nm emission wavelengths. The media were considered to be homogeneous and the mismatched boundary was not taken into account. Then, the refractive index of these two layers was the same and equal to 1.4. The thickness of the tumor layer turned out to be varied between 0.1 μm and 0.6 cm, and 10 cm thick of the lower normal layer (infinity). Fluorescence was estimated theoretically based on the Monte-Carlo algorithm and fitted to the developed model. Finally, the relative error of the presented model was less than 5%. The simplicity and robustness of the presented model make it a good choice to estimate fluorescence and reproduce the thickness of the upper layer in real-time.

Keywords: Fluorescence; meningioma; Monte Carlo method; PpIX.

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1 Introduction

Meningioma is a central nervous system tumor that means it begins in the brain and spinal cord, which is classified into three grades (grade I, II & III). The most common type of meningioma is low-grade meningioma, which is characterized by slow growth and can be totally resected without recurrence. Predominantly, meningioma is a benign tumor that accounts for approximately 20% overall of the intracranial tumors of humans [1−3]. The widely spread approach used to cure meningioma, regardless the grade, is surgery during which a biopsy can be taken to determine which grade of the tumor is [1−3]. It is worth noting that the recovery rate depends mainly on the complete resection of the tumor, which requires a deep knowledge of the tumor structure. That could be achieved by using an assistant tool to determine the tumor's structural characteristics in real time during surgery [2−6].

On the other hand, laser-induced fluorescence is one of the promising modalities used to discriminate tumor margins in real-time, which depends on accumulation of endogenous and exogenous fluorophores in tumor tissue [2−4]. Protoporphyrin IX (PpIX) fluorescence spectroscopy, as an example, is currently utilized as a pointer for surgeons during surgery to distinguish brain tumor margins. However, fluorescence spectra carry potential information of tumor characteristics if it is well interpreted due to the relationship between the spectrum and the optical and morphological tissue properties [2−4]. In that context, Richards-Kortum and co-authors developed an exponential model of fluorescence of semi-infinite medium and evaluated the robustness of the presented model for determining atherosclerosis, which exceeded 88% in distinguishing normal aorta [7]. Furthermore, a spatially resolved fluorescence model was developed for multi-layered media based on diffusion approximation [8]. Although the time of calculation could not be neglected, the validity of that model was examined, and the differences were found in a small radial distance, which approximated 2% [8]. An analytical model of fluorescence spectra of a two layered medium mimicked epithelial tissue was developed based on diffusion theory and Beer-Lambert law. The model used to detect the fluorescence spectra of the tumor with mean square error equaling 15% [9]. On the other hand, Yudovsky et al. developed a semi-empirical model based on the two-flux approximation of layered media with different fluorescent slab thicknesses. The optical properties of slabs were identical and matched human tissue optical properties (dermis, muscle) [10]. However, the

fluorescence calculated for transport albedo varied between 0.7 and 0.9 and the relative error enhanced 25% for small transport albedo [10]. An analytical model of fluorescence from a layered medium was developed that was based on diffusion theory to estimate fluorescent layer thickness. In spite of its simplicity and reproducibility to estimate optical properties, the relative error enhanced 30% in some cases of thickness varying between 0.1 and 2 mm [11]. To the best of our knowledge, there is no fluorescence model for two layered medium with distinct optical properties, the peripheral layer mimics meningioma.

The aim of the current work is to develop a simple exponential model of fluorescence for two-layered media mimicking the optical properties of tumor and normal brain tissue, respectively. For these purposes, a Monte Carlo simulation has been implemented to predict the fluorescence of this medium, and the dataset has been fitted to the developed exponential model.

2 Materials and Methods

2.1 Exponential Model

As known, the radiative transport equation (RTE) describes precisely light-tissue interaction in spite of its complexity. Thus, an analytical solution of RTE has been developed to simplify its solution, such as diffusion and two-flux approximations. Exponential approximation was widely used to simulate light propagation through biological tissues, and the validity was evaluated. In this work, there are some presumptions regards the studied case: 1) the optical properties of these two layers are distinct for excitation and emission wavelengths, 2) both layers are optically homogenous with matched refractive index, and 3) the light source is a pencil homogenous beam that incident perpendicularly to the surface. Then, the photon density of fluorescence can be regarded as the sum of two terms as follows [10]:

$$d\emptyset = d\emptyset_1 + d\emptyset_2 \,. \tag{1}$$

Then, the first term determines the attenuation of the excitation and emission light through the first layer, which is attenuated exponentially upon passing a dz thickness. Furthermore, the emitted photon density is linearly proportional to absorbed intensity and quantum yield; then, it can be expressed as follows [7, 11]:

$$d\emptyset_1 = I_{absorbed} \cdot \varphi \cdot e^{-2\left(\mu'_{t(ex_1)} + \mu'_{t(em_1)}\right)\cdot z}\,, \tag{2}$$

where $I_{absorbed}$ is the absorbed excitation intensity, φ is the fluorescence quantum yield, $\mu'_{t(ex_1)}$ is the reduced extinction coefficient of the first layer at excitation wavelength and $\mu'_{t(em_1)}$ is the reduced extinction coefficient of the first layer at emission wavelength. In the second layer, the excitation and emission light is attenuated exponentially by absorption and scattering events; then, the second term can be expressed as follows:

$$d\emptyset_2 = k \cdot e^{-2\left(\mu'_{t(ex_2)} + \mu'_{t(em_2)}\right)\cdot z}, \tag{3}$$

where $\mu'_{t(ex_2)}$ is the reduced extinction coefficient of the second layer at excitation wavelength, $\mu'_{t(em_2)}$ is the reduced extinction coefficient of the second layer at emission wavelength and k is a constant that represents the amount of light passing through the boundary between the two layers and propagating through the second layer. In order to calculate total photon density, an integration must be applied as follows [5, 6]:

$$\emptyset = \int_0^L I_{absorbed} \cdot \varphi \cdot e^{-2\left(\mu'_{t(ex_1)} + \mu'_{t(em_1)}\right)\cdot z} dz + \\ + \int_L^\infty k \cdot e^{-2\left(\mu'_{t(ex_2)} + \mu'_{t(em_2)}\right)\cdot z}\,. \tag{4}$$

Then:

$$\emptyset = \frac{I_{absorbed}\cdot\varphi}{2\left(\mu'_{t(ex_1)} + \mu'_{t(em_1)}\right)} \cdot \left(1 - e^{-2\left(\mu'_{t(ex_1)} + \mu'_{t(em_1)}\right)\cdot L}\right) \\ + \frac{k}{2\left(\mu'_{t(ex_1)} + \mu'_{t(em_2)}\right)} e^{-2\left(\mu'_{t(ex_2)} + \mu'_{t(em_2)}\right)\cdot L}. \tag{5}$$

Although Eq. (5) is simple to use and able to reproduce to predict any variables involved, the difference between its results and the real measurements cannot be neglected; then, semi-empirical parameters can be proposed to reduce the relative error of this equation. Thus, the equation can be rewritten as Ref. [5, 6]:

$$\emptyset = \frac{k_1 \cdot I_{absorbed}\cdot\varphi}{2\left(\mu'_{t(ex_1)} + \mu'_{t(em_1)}\right)} \cdot \\ \cdot \left(1 - e^{-k_2\left(\mu'_{t(ex_1)} + \mu'_{t(em_1)}\right)\cdot L}\right) + \\ + \frac{k_3}{2\left(\mu'_{t(ex_1)} + \mu'_{t(em_2)}\right)} e^{-k_4\left(\mu'_{t(ex_2)} + \mu'_{t(em_2)}\right)\cdot L}, \tag{6}$$

where k_i (i = 1, 2, 3, and 4) are the fitting parameters of the presented model which can be determined by fitting the equation to the standard results.

2.2 Monte Carlo Simulation

In the present work, the Monte-Carlo algorithm was used to solve the radiative transport equation (RTE), which can be considered as a gold standard [12]. A custom Monte-Carlo code (FLMC) was used to predict the emission photon density (fluorescence) of a two-layered medium [13]. The simulated fluorophore is PpIX that has an absorption peak at 405 nm and two emission peaks, the highest corresponds 635 nm. This type of fluorophore was widely used in vivo to point out tumor margins with high sensitivity and specificity [2–4]. Fluorescence quantum yield was 0.011 that corresponding to the

concentration 3.26 mg/L [14]. The peripheral layer mimics the optical properties of meningioma at 405 nm (excitation wavelength) and 635 nm (emission wavelength) of PpIX [2−4]. The lower layer was chosen to mimic the optical properties of normal brain tissue (white matter) at these wavelengths with a thickness enhanced to 10 cm (infinity), Table 1 [15]. The thickness of the upper layer turned out to be varied between 0.1 μm and 6 mm. In the literature, the refractive index of both layers is not determined at excitation and emission wavelengths; then, the refractive indexes of both layers were supposed to be 1.4 [5, 6].

An infinitely thin pencil beam was implemented with 0.5 million photons that incident perpendicularly on the surface of the presented medium [12, 13]. FLMC code simulates the excitation light firstly to map the absorption of the excitation wavelength that is called the absorbed intensity matrix in which the absorbed intensity is depicted as a function of radial distance and depth (r, z) [13]. Then, the Monte-Carlo simulation is performed in second time to map light propagation of the fluorescence wavelength that depicted as a function of radial distance and depth, which is called the emission matrix. Finally, a custom FLMC code is supplied by a MATLAB interface to begin simulation and show the matrices of fluorescence and absorbed intensity [13, 14].

Table 1 Depicts the optical properties of both two layers at excitation and emission wavelengths [15].

Optical Properties	**Meningioma**		**Normal Tissue**	
	405 nm	635 nm	405 nm	635 nm
Absorption Coefficient (cm^{-1})	4.5	0.3	3	0.8
Scattering Coefficient (cm^{-1})	200	170	400	400
Anisotropy Factor (….)	0.86	0.95	0.75	0.85

3 Results

Depending on the FLMC code, the fluence of the absorbed and emitted light was predicted as a function of the peripheral layer thickness that mimics meningioma at both wavelengths 405 nm and 635 nm. Figure 1 (a) depicts the correlation of absorbed light as a function of the thickness of the upper layer. The total absorbed light increased dramatically as the thickness increased until the thickness approximated 0.05 and; then, the absorbed light increased slightly as the thickness increased until reaching the end of the studied thickness region. That is resulted from increasing of the number of fluorophores that absorb light until thickness exceeds the optical penetration depth at excitation wavelength that approximated 0.05 cm for meningioma. After reaching this distance, a saturation occurred and absorbed light increased slightly. On the other hand, the fluorescence of the surface decreased exponentially as the thickness of the peripheral layer increased. That could be explained by a distribution of fluorescence light inside tissue and decreases at the surface, Fig. 1(b). Fluorescence light emitted from an embedded fluorophore could be absorbed or scattered inside tissue after reaching the surface. Furthermore, it is worth noting that the detected fluorescence at the surface is higher due to a contribution of the lower layer that has high scattering property. That can increase the detected fluorescence at the surface compared to a large thickness.

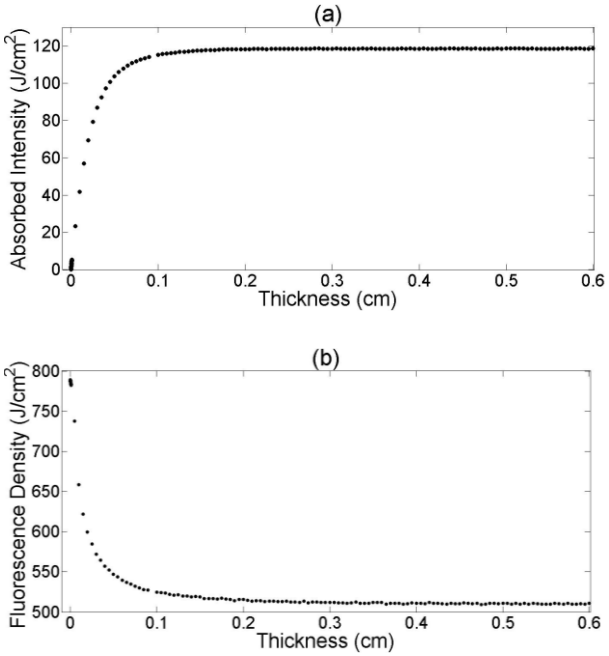

Fig. 1 (a) Depicts the correlation of absorbed light estimated by Monte-Carlo simulation as a function of thickness at 405 nm, (b) depicts the relationship of fluence of fluorescence light at surface to thickness of peripheral layer at 635 nm.

Using the fitting function procedure in MATLAB (Matlab 2015, Mathworks Inc, USA), the Monte-Carlo results were fitted to the exponential equation developed for two-layered homogenous media (Eq. (6)). The fitting parameters were predicted and depicted in the following Table 2.

Table 2 Depicts the fitting parameters of Eq. (6).

Fitting Coefficient	$k_1(\dots)$	$k_2(\dots)$	$k_3(J/cm^2)$	$k_4(\dots)$
	−17214.5	12.87802	21.42996	$3.91\cdot10^{-5}$

Then, the fluence of fluorescence light was estimated by the developed model (Eq. (6)) and the relative error predicted by the following Eq. (7):

$$relative\ error = \left(\frac{(F_{MC}-F_{predicted})}{F_{MC}}\right)\cdot 100\%. \qquad (7)$$

Figure 2 (a) represents fluorescence fluence predicted by Eq. (6) as a function of upper layer thickness in comparison with the Monte-Carlo results. The convergence was obvious, and the relative error for our developed model was less than 5% for all situations. Large differences were observed for five thicknesses, and the relative error was less than 1% in general.

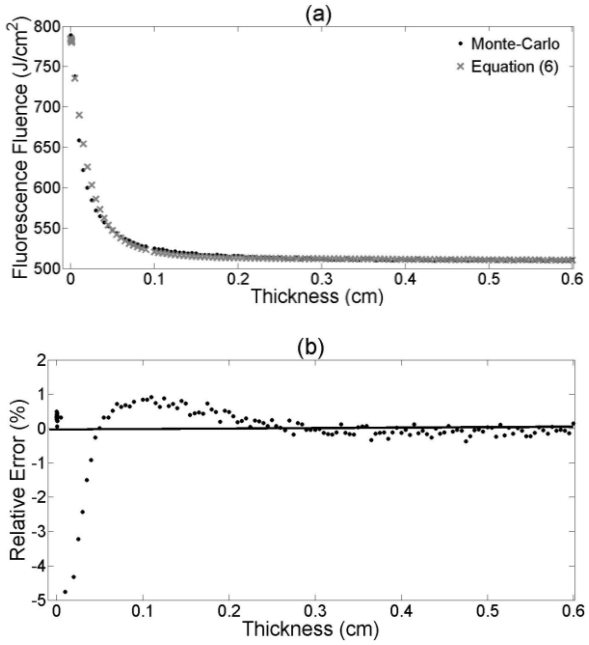

Fig. 2 (a) Comparing of fluence estimated by Monte-Carlo simulation (black) and Eq. (6) (grey) as a function of meningioma thickness, (b) relative error relationship to thickness.

4 Discussion

Fluorescence of two-layered media, which mimicked the optical properties of meningioma and healthy brain tissue, respectively, were estimated using Fluorescence-Layered Monte-Carlo simulation (FLMC) of PpIX as an endogenous fluorophore. That has an absorption peak corresponding to 405 nm and an emission peak at 635 nm [2−4]. Absorbed light was estimated and depicted as a function of thickness. It is noted that the absorbed light increased as the fluorescent layer thickness increased because of the increase in the number of fluorophores. After a specific thickness that is comparable to 0.05 cm, the absorbed light increased slightly due to exceeding the optical penetration depth of the first layer at the excitation wavelength, Fig. 1(a). The fluorescence of the presented medium decreased exponentially as the thickness increased, Fig. 1(b). It is supposed that the increase of thickness may increase the number of fluorophore, and, then, the fluence of fluorescence intensified. However, fluorescence distribution increases inside tissue as thickness increases, but the peripheral fluence that can be measured, decreases exponentially. Furthermore, we could not neglect the contribution of the lower layer that has a highly scattering property, which intensifies the fluorescence at the surface of thin peripheral layer thickness. In that context, all these points explain why the total photon density of fluorescence at the surface decreased as the thickness increases. After a specific thickness, that is comparable to 0.3 cm, the fluence remains the same that could be explained by the optical penetration depth of meningioma at 635 nm that is equal to 0.3 cm.

Then, the developed model based on exponential decay was fitted to the Monte-Carlo results to estimate fitting coefficients that were proposed for scale invariance to reduce the divergence between both methods, Table 2. This model was sensitive to thickness variation, and the relative error, in comparison to Monte-Carlo, did not exceed 5%. However, the developed model's error was less than or equal to the error of other models developed by other research groups in spite of its simplicity [9, 10]. In that context, the relative error of the fluorescence model for a two-layered medium developed using diffusion theory was 15% [9]. Another semi-empirical model developed by the two-flux approximation has a relative error comparable to 30% [10]. Furthermore, the robustness of the presented model was comparable to an analytical model developed by solving the radiative transport equation using the Fourier transform and modified spherical harmonics for semi-infinite and multi-layered media with distinct optical properties [16]. Then, the small relative error of the presented model makes it more likely to predict the photon density that emitted from meningioma, which is supplied by PpIX and excited by a violet laser with an operating wavelength being 405nm. A reproduction of the thickness of meningioma can be made after measuring the emitted fluence of meningioma in real-time using the abovementioned equation (Eq. (6)).

5 Conclusion

In the present work, an exponential model of fluence emitted by a two-layered medium with a peripheral fluorescent layer was developed to mimic PpIX fluorescence of a two-layered medium with optical properties corresponding to meningioma, and normal tissue, respectively. Monte-Carlo simulation was used to generate a data set of our work, and the developed model was fitted to these results. Then, fitting parameters were predicted and used to generate fluorescence of the same medium with thickness varied between 0.1 μm and 0.6 cm. Since the relative error of the presented model did not exceed 5%, the model could be utilized to estimate PpIX fluorescence for known thickness and vice versa. Finally, the thickness of the peripheral layer (meningioma) can be reproduced upon measuring the fluence of the fluorescence signal. Furthermore, the simplicity of our model makes it more likely to help surgeons to determine the structural properties of the tumor in real-time.

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Disclosures

The authors declare no conflicts of interest in this paper.

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