Comparison of Simplified Monte Carlo Simulation and Diffusion Approximation for Fluorescent Signal from Phantoms with Typical Mouse Optical Properties

Guobin Ma, Jean-François Delorme, and Pascal Gallant

ART Advanced Research Technologies Inc., 2300 Alfred-Nobel Blvd., Saint-Laurent, Quebec, Canada H4S 2A4

gma@art.ca

David A. Boas

Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Harvard Medical School, Charlestown, MA 02129

Abstract

Fluorescent signals from mouse-tissue-like phantom are computed using both a Monte Carlo simulation and the diffusion approximation. The relative difference is less than 30% for a fluorophore placed in the middle of a 3mm separated source-detector pair.

OCIS code: (170.3660) Light propagation in tissues; (290.1990) Diffusion; (170.6280) Spectroscopy, fluorescence and luminescence

Introduction

Light propagations in strongly scattering tissue have been extensively studied in the past few decades in response to expanding interest in applications of light for biomedical diagnostic and therapeutic use. Fluorescence techniques represent an important class of optical methods being applied to *in vitro* and *in vivo* biomedical diagnostics, including noninvasive molecular sensing and imaging [1]-[8]. Measured tissue fluorescence signals reflect both intrinsic tissue pathology (local morphological, biochemical, and optical properties), as well as experimental design features (including excitation and emission wavelengths, fiber-optic probe design, and contrast agent concentration). Model based computations are often employed to quantitatively simulate photon migration characteristics in tissues, thereby enabling accurate analysis and interpretation of measured tissue fluorescence signals.

Photon propagation in biological tissue is governed by the radiative transfer equation (RTE) by considering light to be composed of neutral particles [9]. However, the RTE is computationally expensive in practical biomedical imaging. Alternative stochastic approaches can be used to model photon transport in turbid media. Monte Carlo (MC) modeling was first applied to study light dosimetry in tissues in 1983 [10] and has been shown to provide the most accurate results in comparison with the experiment [11],[12]. Recently, MC simulations of heterogeneous tissue model based on MRI [13] or CT [14] results have been explored, although the computation is heavier. Some researchers even examined the temporal and spectral effect on fluorescence in tissue with the MC method [15]. Given the dominance of scattering over absorption in biological tissue, a common simplification to these approaches is the diffusion approximation (DA), which yields analytical solutions for the light energy distribution when applied to simple geometries [16]. It is well established that the DA provides an accurate description of near-infrared (NIR) light propagations in tissue both for optical tomography and fluorescence imaging if applied to bulk tissue in which photons travel longer than several mean free path lengths.

ART developed a time domain *in vivo* small animal fluorescence imager, eXplore Optix [18]. Using the measured time-resolved fluorescence signal, fluorophore location and concentration can be quickly estimated [19] thanks to the analytical solution of the DA. Concerns exist about the validity of the DA when applied in small tissue volume. In this paper, we compare the fluorescence signals from tissue-like phantoms predicted by the DA and simplified fluorescent MC simulations in order to estimate the error range of the DA model specifically for the hardware configuration of eXplore Optix and typical optical properties of small animal. Further, the simplified approaches can be used elsewhere to run fluorescent MC results more efficiently even in a typical personal computer.

Model description

Monte Carlo simulation

Detailed description of the Monte Carlo simulation of photon migration in tissue can be found elsewhere [11]-[15]. Basically, it generates a statistical distribution of photons absorbed in each voxel in tissue by following the trajectory of a large number of photons. Many measurable quantities can be deduced from this distribution. In our simulation, the well validated MCML code [11] is used.

The scenario of photon propagation in non-fluorescent tissue is like that photons are launched at the source location; some are absorbed; some are scattered; and only a portion of them will reach the detector. The fluorescence tissue can be treated as a two-step process. The fluorophore acts like a detector to receive excitation photons in the first step and a source to emit fluorescent photons in the second step. Thanks to the reverse property of light propagation in the medium, the fluorescent photons flux can be obtained from the distribution of excitation photons by only shifting the coordinates, if the difference of optical properties due to excitation and emission wavelength is neglected. In this way, the measurable fluorescent signal can be calculated from a single MC simulation of excitation light.

Diffusion approximation

The DA model developed by Contini et al [16] is used in our comparison. Similar to the MC approach, first the light propagation from the source to the fluorophore is calculated. Second, the propagation of fluorescent emission is computed by an equivalent source at the fluorophore location to the detector. And then the measurable fluorescent signal is obtained by convolving the two propagations.

Phantom properties

Results presented below are obtained with a homogenous tissue-like slab phantom with a thickness of 18 mm. Its optical properties are μ_a=0.3 cm^{-1}, μ_s=100 cm^{-1}, *g* =0.9, n=1.4, typical values of mouse tissue. Excitation laser photons are injected perpendicularly to the phantom surface, and fluorescent emission is detected at a position 3 mm away from the source.

Results and discussion

Shown in **Fig. 1** is a comparison in contour plot of the MC and the DA results. Calculated is the fluorescence intensity of a point fluorophore placed in a single pixel at position (*r,z*) inside the medium. When the fluorophore is away from the source and detector, the DA result is close to the MC simulation, as expected. However, if the fluorophore is close to the source and/or the detector, significant differences exist between the DA and the MC. To quantify the difference, **Fig. 2** shows the fluorescence intensity calculated using the MC and the DA of a fluorophore placed in the middle of the source and detector (r=1.5 mm) at various depths. The relative difference of the MC and the DA is plotted over *z* in the lower panel. One can easily see that as long as the fluorophore depth is larger than 2.5 mm, the relative difference is less than 4%. Even at depths smaller than 2.5 mm, the largest difference is only about 30%. We may conclude that the DA is quite good for a fast estimation. Given its advantage of being an analytical solution and fast to compute, the DA is the first choice.

For *in vivo* experiment, there are other error sources in addition to the application of the DA. One is the validity of the homogeneity assumption; the other is the slab geometry. Obviously, the mouse is neither a homogeneous medium nor a flat slab. Future study will estimate the difference caused by these factors using models similar to [13] and [14] by the help of other modalities.

Figure 1: A comparison of the fluorescent intensity of a point fluorophore placed in a single pixel calculated by the MC and the DA for a source-detector separation of 3 mm.

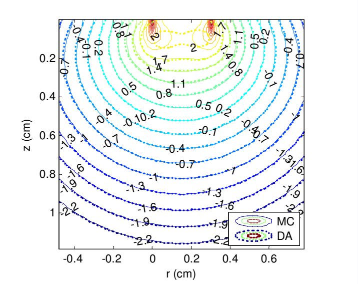
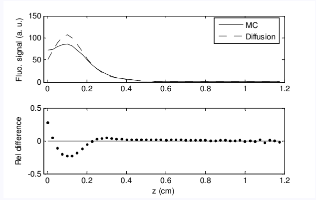


Figure 2: Fluorescence intensity calculated by the MC and the DA (upper panel) and the relative difference of the MC and the DA (lower panel) for a point fluorophore positioned in the middle of the source-detector pair at various depths inside the medium. The source detector separation is 3 mm.



References

[1] M. A. O'Leary, D. A. Boas, X. D. Li, B. Chance, and A. G. Yodh, "Fluorescence lifetime imaging in turbid media", *Opt. Lett.* **21**, 158-160 (1996).

[2] B. B. Das, F. Liu, and R. R. Alfano, "Time-resolved fluorescence and photon migration studies in biomedical and model random media," *Rep. Prog. Phys.* 60, 227–292 (1997).

[3] J. Chang, H. L. Graber, and R. L. Barbour, "Imaging of fluorescence in highly scattering media," *IEEE Trans. Biomed. Eng.* 44, 810–822 (1997).

[4] H. B. Jiang, "Frequency-domain fluorescent diffusion tomography: a finite-element-based algorithm and simulations," *Appl. Opt.* 37, 5337–5343 (1998).

[5] M. J. Eppstein, D. E. Dougherty, T. L. Troy, and E. M. Sevick-Muraca, "Biomedical optical tomography using dynamic parameterization and Bayesian conditioning on photon migration measurements," *Appl. Opt.* 38, 2138–2150 (1999).

[6] V. Ntziachristos and R. Weissleder, "Experimental threedimensional fluorescence reconstruction of diffuse media using a normalized Born approximation," *Opt. Lett.* 26, 893–895 (2001).

[7] V. Ntziachristos, C. Tung, C. Bremer, and R. Weissleder, "Fluorescence-mediated tomography resolves protease activity *in vivo*," *Nat. Med.* 8, 757–760 (2002).

[8] A. B. Milstein, S. Oh, K. J. Webb, C. A. Bouman, Q. Zhang, D. A. Boas, and R. P. Millane, "Fluorescence optical tomography", *Appl. Opt.* **42**, 3081-3094 (2003).

[9] A.D. Klose, V. Ntziachristos, and A.H. Hielscher, "The inverse source problem based on the radiative transfer equation in optical molecular imaging," J. Comput. Phys. **202**, 323-345 (2005).

[10] B. C. Wilson and G. Adam, 'A Monte-Carlo model for the absorption and flux distribution of light in tissue', *Med. Phys.* 10 824–30 (1983).

[11] L.-H. Wang, S. L. Jacques, and L.-Q. Zheng, "MCML - Monte Carlo modeling of photon transport in multi-layered tissues," *Comp. Methods Prog. Biomed.* **47**, 131-146 (1995).

[12] K. Vishwanath, B.W. Pogue, and M.-A. Mycek, "Quantitative fluorescence lifetime spectroscopy in turbid media: Comparison of theoretical, experimental and computational methods," *Phys. Med. Biol.* **47**, 3387-3405 (2002).

[13] D. A. Boas, J. P. Culver, J. J. Stott, and A. K. Dunn, "Three dimensional Monte Carlo code for photon migration through complex heterogeneous media including the adult human head," *Opt. Express* **10**, 159-170 (2002), http://www.opticsexpress.org/abstract.cfm?URI=OPEX-10-3-159

[14] H. Li, J. Tian, F. P. Zhu, W. X. Cong, L. V. Wang, E. A. Hoffman, and G. Wang, "A mouse optical simulation environment (MOSE) to investigate bioluminescent phenomena with the Monte Carlo method", *Academic Radiology* **11**, 1029-1038 (2004).

[15] K. Vishwanath and M. Mycek, "Time-resolved photon migration in bi-layered tissue models," *Opt. Express* **13**, 7466-7482 (2005), http://www.opticsexpress.org/abstract.cfm?URI=OPEX-13-19-7466

[16] D. Contini, F. Martelli, and G. Zaccanti, "Photon migration through a turbid slab described by a model based on diffusion approximation. I. Theory", *Appl. Opt.* **36**, 4587-4599 (1997).

[17] G. A. Johnson, G. P. Cofer, S. L. Gewalt, and L. W. Hedlund, "Morphologic phenotyping with magnetic resonance microscopy: the visible mouse", *Radiology* **222**, 789-793 (2002).

[18] P. Gallant, A. Belenkov, G. MA, F. Lesage, Y. Wang, D. Hall, L. McIntosh, 'A quantitative time-domain optical imager for small animals in vivo fluorescence studies', OSA 2004 Biomed. Opt. Topical Meetings (Miami Beach, Florida), April 14-17, 2004.

David Hall, Guobin Ma, Frédéric Lesage, and Yong Wang, "Simple time-domain optical method for estimating the depth and concentration of a fluorescent inclusion in a turbid medium", *Opt. Lett.* **29**, 2258-2260 (2004).