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Fluorescence photon-density waves in optically diffusive media

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Sergio Fantini dedicates this article to the memory of his friend Paolo Tarini

Abstract

Intensity-modulated light launches traveling photon-density waves into optically diffusive media. In the presence of a fluorophore, excitation photon-density waves generate fluorescence photon-density waves that can be quantitatively described using diffusion theory. We examine a number of limiting cases of the fluorescence photon-density wave to clarify its physical meaning and its implications in quantitative fluorescence spectroscopy of diffusive media. Our discussion may guide the development of experimental protocols for quantitative fluorescence spectroscopy in optically diffusive media. © 2000 Elsevier Science B.V. All rights reserved.

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Keywords: Fluorescence; Luminescence; Diffusion; Photon migration; Photon-density waves

1. Introduction

There are two reasons that account for the relevance of fluorescence spectroscopy of diffusive media. First, in the optical diffusive regime, the excitation and the emission radiances are both essentially isotropic. This symmetrization of the excitation and emission angular distributions allows for the measurement of the absolute quantum yield of a fluorophore without the need of a reference sample [1]. Second, there are applications where one has to deal

with optically turbid samples. Some examples include fluorescence studies of turbid gels, bacteric growth in turbid media, in situ cell count in milk [2], and optical tomography with fluorescent contrast agents [3,4]. A quantitative physical model for the fluorescence signal in diffusive media is required to successfully apply this method and to exploit its potentials. Such a physical model is provided by diffusion theory [1,5,6], which has been used to describe both the stationary and the time-dependent components of the fluorescence signal. Here we examine the frequency-domain approach, where the intensity of the light source is modulated at angular frequency ω , the steady state case being the limit $\omega = 0$. In particular, we analyze the physical meaning and some of the implications of the solution to

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the diffusion equation for fluorescence in diffusive media.

2. Photon diffusion and photon-density waves

The Boltzmann transport equation (BTE) describes light propagation within media where absorption and elastic scattering events occur [7]. These optical phenomena are described by the linear absorption coefficient μ_a , the linear scattering coefficient μ_s , and the anisotropy factor $g = \langle \cos \theta \rangle$, where θ is the scattering angle. The reduced scattering coefficient μ'_s is defined as $(1 - g)\mu_s$, and it may be interpreted as the inverse of the mean distance over which the photon direction of propagation is randomized. In diffusive media, where $\mu'_s \gg \mu_a$, the BTE reduces to the standard diffusion equation, which describes the spatial distribution of the energy-density at distances $\gg 1/\mu'_s$ from photon sources, and providing that the time scale of the energy-density variations is much longer than the isotropic scattering rate $\nu\mu'_s$ (ν is the speed of light in the medium) [8]. In the frequency-domain, the harmonic modulation at angular frequency ω of the optical power emitted by the light source results in the generation of photon-density waves into the diffusive medium [9,10]. For a unit-power (in amplitude) point source located at the origin, the resulting oscillating component of the photon-density (Green's function G) is described in terms of a spherical damped traveling wave [9]:

$$G(r, t) = \frac{1}{4\pi D} \frac{e^{i(kr - \omega t)}}{r}, \quad (1)$$

where the complex propagation constant $k = \sqrt{i(\omega - \nu\mu_a)/D}$, $D = \nu/(3\mu'_s)$ is the photon diffusion coefficient, and r is the radial coordinate. The steady state component of the photon density is given by Eq. (1) with ω set to 0. It is customary to separate the time-dependent factor $\exp(-i\omega t)$ by introducing the term $G^*(r, \omega)$ defined by $G(r, t) = G^*(r, \omega) \exp(-i\omega t)$. The amplitude and the phase of the photon-density wave at angular frequency ω are then written as $|G^*(r, \omega)|$ (which is equivalent to $|G(r, \omega)|$) and $\text{Arg}[G^*(r, \omega)]$, respectively. Furthermore, the modulation m is defined as $|G^*(r, \omega)|/|G^*(r, 0)|$. Two characteristic lengths as-

Fig. 1. The ratio between the wavelength of the photon-density wave ($\lambda^{(\text{PDW})}$) and the diffusion length (L) as a function of the parameter $x \equiv \omega/(\nu\mu_a)$.

sociated with the photon-density wave are the diffusion length $L = 1/|\text{Im}(k)|$ and the wavelength $\lambda^{(\text{PDW})} = 2\pi/|\text{Re}(k)|$. These two characteristic lengths are not independent on each other, since $\lambda^{(\text{PDW})} = 4\pi D/(\omega L)$. It is noteworthy that the ratio $\lambda^{(\text{PDW})}/L$ only depends on the parameter $x \equiv \omega/(\nu\mu_a)$, and that in general $\lambda^{(\text{PDW})}/L > 2\pi$. Consequently, photon-density waves are typically measured in the near-field. The dependence of $\lambda^{(\text{PDW})}/L$ on x is shown in Fig. 1. We observe that both $\lambda^{(\text{PDW})}$ and L decrease with ω , but $\lambda^{(\text{PDW})}$ decreases more rapidly. Processes of refraction [11] and diffraction [12] of diffuse photon-density waves have been investigated.

3. Fluorescence in diffusive media as interference of photon-density waves

The oscillatory density of fluorescence photons emitted at wavelength λ_m as a result of excitation from a unit-power, point-source at λ_x is described by the fluorescence Green's function [1,5,6]:

$$G_f(r, t) = \nu\mu_{\text{afx}} \Lambda \bar{\varphi}_m \frac{(1 + i\omega\tau)}{(1 + \omega^2\tau^2)} \frac{1}{4\pi D_x D_m (k_x^2 - k_m^2)} \times \left[\frac{e^{i(k_x r - \omega t)}}{r} - \frac{e^{i(k_m r - \omega t)}}{r} \right], \quad (2)$$

where the subscripts x and m indicate that the corresponding parameters are evaluated at the excitation (λ_x) or emission (λ_m) wavelengths, respectively. In Eq. (2), μ_{afx} is the absorption coefficient of the

Fig. 2. Amplitude (a) and phase (b) of $G_x^*(r, \omega)$, $G_m^*(r, \omega)$, and $G_f^*(r, \omega)$ versus radial coordinate and amplitude (c) and phase (d) of $G_x^*(r, \omega)$, $G_m^*(r, \omega)$, and $G_f^*(r, \omega)$ versus modulation frequency. In panels (a) and (b), the modulation frequency is set to 100 MHz, while in panels (c) and (d), the radial coordinate is set to 3 cm. The values of the other physical parameters are listed in Table 1.

fluorophore at the excitation wavelength, Λ is the quantum yield and τ the lifetime of the fluorophore, while $\bar{\varphi}_m$ is the emission-spectral-efficiency factor that accounts for the emission bandwidth of interest $\Delta\lambda_m$ about λ_m . Eq. (2) results from the spatial convolution of the source term of fluorescence photons with the Green's function of the diffusion equation at the emission wavelength λ_m . The assumptions made in deriving Eq. (2) are the following: (a) negligible secondary fluorescence (which is the fluorescence generated by the reabsorption of an emitted photon); (b) single exponential decay; and (c) negligible photobleaching. The generalization to multiple fluorescence lifetimes has been presented [2]. The fluorescence Green's function (Eq. (2)) can be interpreted as the interference (or superposition) of two photon-density waves generated at the origin, having propagation constants k_x and k_m , respectively. The quantitative validity of Eq. (2) has been experimentally verified [1]. The factor $G_f^*(r, \omega)$ can be defined from $G_f(r, \omega) = G_f^*(r, \omega) \exp(-i\omega t)$ so that the amplitude and the phase of the fluorescence photon-density wave are defined as $|G_f^*(r, \omega)|$ and

$\text{Arg}[G_f^*(r, \omega)]$, respectively. The modulation m_f is defined as $|G_f^*(r, \omega)|/|G_f^*(r, 0)|$. Fig. 2 shows the radial-coordinate and the modulation-frequency dependencies of the amplitude and phase of $G_x^*(r, \omega)$, $G_m^*(r, \omega)$, and $G_f^*(r, \omega)$. The physical parameters used to generate Fig. 2 are given in Table 1 condition. The values of the background optical coefficients (μ_a and μ_s') are based on typical optical properties of biological tissues in the near-infrared. The value of the fluorophore absorption coefficient (μ_{afx}) is consistent with a molar extinction coefficient

Table 1
Physical parameters used to generate Fig. 2

Parameter	λ_x	λ_m
μ_a (cm ⁻¹)	0.05	0.02
μ_{af} (cm ⁻¹)	0.05	0
μ_s' (cm ⁻¹)	10	9
v (cm/s)	2.26×10^{10}	2.26×10^{10}
L (cm)	0.572	1.17
$\lambda^{(PDW)}$ (cm)	26.3	14.3
$\Lambda \bar{\varphi}_m$		0.01
τ (ns)		1.0

cient of $10^5 \text{ cm}^{-1} \text{ M}^{-1}$ and a concentration of 500 nM. In this article, we analyze some of the features of Eq. (2) to describe its physical meaning in conjunction with practical measurements of fluorescence spectroscopy in diffusive media.

4. Limiting cases of the fluorescence photon-density wave

4.1. $\mu_{\text{afx}} \rightarrow \infty$

This limiting case implies that all of the excitation photons are absorbed by the fluorophore at the origin. The result of this limit is:

$$\lim_{\mu_{\text{afx}} \rightarrow \infty} G_{\text{f}}(r, t) = \Lambda \bar{\varphi}_{\text{m}} \frac{(1 + i\omega\tau)}{(1 + \omega^2\tau^2)} G_{\text{m}}(r, t), \quad (3)$$

where $G_{\text{m}}(r, t)$ is the Green's function for the diffusion equation at λ_{m} (i.e. Eq. (1) with $k = k_{\text{m}}$ and $D = D_{\text{m}}$). As expected, the fluorescence source is located at the origin, has a weight $\Lambda \bar{\varphi}_{\text{m}}$, and contains the lifetime factor $(1 + i\omega\tau)/(1 + \omega^2\tau^2)$.

4.2. $\mu_{\text{afx}} \rightarrow 0$

In this case, one simply gets $\lim_{\mu_{\text{afx}} \rightarrow 0} G_{\text{f}}(r, t) = 0$ since there is no absorption and re-emission by the fluorophore.

4.3. $r \ll \min(L_{\text{x}}, L_{\text{m}})$

The condition $r \ll L$ also implies $r < \lambda^{(\text{PDW})}$, and therefore $r|\text{Re}(k)|$ and $r|\text{Im}(k)|$ are both $\ll 1$. While this limit is beyond the range of quantitative validity of Eq. (2), because the diffusion regime is not yet established at distances from the source $\ll L$, it is nevertheless useful to calculate this limit. This limit is:

$$\begin{aligned} \lim_{r \ll \min(L_{\text{x}}, L_{\text{m}})} G_{\text{f}}(r, t) \\ = \frac{\nu\mu_{\text{afx}} \Lambda \bar{\varphi}_{\text{m}}}{4\pi D_{\text{x}} D_{\text{m}}} \frac{(1 + i\omega\tau)}{(1 + \omega^2\tau^2)} i \frac{\exp\left\{i\left(\frac{k_{\text{x}} + k_{\text{m}}}{2} r - \omega t\right)\right\}}{(k_{\text{x}} + k_{\text{m}})}. \end{aligned} \quad (4)$$

We observe that in this limit the $1/r$ dependence has disappeared, and the propagation constant is the

average of the excitation and emission propagation constants. From Eq. (4), one can readily evaluate the limit $r \rightarrow 0$.

4.4. $r \gg L_{\text{x}} L_{\text{m}} / |L_{\text{x}} - L_{\text{m}}|$

In this limit, only one exponential is retained:

$$\begin{aligned} \lim_{r \gg L_{\text{x}} L_{\text{m}} / |L_{\text{x}} - L_{\text{m}}|} G_{\text{f}}(r, t) \\ = \frac{\nu\mu_{\text{afx}} \Lambda \bar{\varphi}_{\text{m}}}{4\pi D_{\text{x}} D_{\text{m}}} \frac{(1 + i\omega\tau)}{(1 + \omega^2\tau^2)} \frac{1}{(k_{\text{x}}^2 - k_{\text{m}}^2)} \frac{e^{i(k_{<} r - \omega t)}}{r}, \end{aligned} \quad (5)$$

where $k_{<}$ is k_{x} if $\text{Im}(k_{\text{x}}) < \text{Im}(k_{\text{m}})$ or k_{m} if $\text{Im}(k_{\text{m}}) < \text{Im}(k_{\text{x}})$. This limit yields the propagation constant of the fluorescence photon-density wave in the large- r case. This case is of practical relevance when L_{x} and L_{m} are significantly different (say $|L_{\text{x}} - L_{\text{m}}| \geq L_{<}$, with $L_{<} = \min(L_{\text{x}}, L_{\text{m}})$). In this case, the limit is applicable at radial coordinates of the order of a few diffusive lengths, where measurements can still be practically performed. For instance, Fig. 2 shows that at values of r larger than about 4 cm (i.e. $\sim 7L_{\text{x}}$ and $\sim 3.4L_{\text{m}}$), the r -dependencies of the phase and amplitude of the fluorescence photon-density wave closely match those of the photon-density wave at the emission wavelength (because $k_{<} = k_{\text{m}}$ in the case of Fig. 2).

4.5. $k_{\text{m}} = k_{\text{x}} \equiv k$

The case of same optical properties at λ_{m} and λ_{x} is of significant interest because it is often approximately fulfilled. In fact, the reduced scattering coefficient typically shows a weak wavelength dependence, and the absorption coefficient may be approximately the same at λ_{m} and λ_{x} . The result for the fluorescence photon-density in this limit is:

$$\begin{aligned} \lim_{|k_{\text{m}} - k_{\text{x}}| \rightarrow 0} G_{\text{f}}(r, t) \\ = \frac{\nu\mu_{\text{afx}} \Lambda \bar{\varphi}_{\text{m}}}{4\pi D^2} \frac{(1 + i\omega\tau)}{(1 + \omega^2\tau^2)} i \frac{e^{i(kr - \omega t)}}{2k}. \end{aligned} \quad (6)$$

where k (D) is the limiting common value of k_{x} (D_{x}) and k_{m} (D_{m}). We note the spatial dependence

on $\exp(-kr)$ (the factor $1/r$ has disappeared) and the fact that the phase and modulation of $G_f^*(r, \omega)$ are given by:

$$\phi_f(r, \omega) = \phi_x(r, \omega) + \arctan(\omega\tau) + \frac{1}{2}\arctan\left(\frac{\omega}{\nu\mu_a}\right), \quad (7)$$

$$m_f(r, \omega) = m_x(r, \omega) \frac{1}{\sqrt{1 + \omega^2\tau^2}} \left(1 + \frac{\omega^2}{\nu^2\mu_a^2}\right)^{-1/4}, \quad (8)$$

where ϕ_x and m_x are the phase and modulation, respectively, at λ_x . Eqs. (7) and (8) show that the fluorescent phase and modulation are made of three terms. The first one is the value one would measure at λ_x , the second one is the lifetime term one would measure in a non-scattering sample [13], and the third one is a term dependent on the parameter x . The third term accounts for the extra path length, with respect to the path length of detected photons at λ_x , of the combined trajectories of the excitation photons (before conversion to λ_m) and the emission photons generated by fluorescence. This extra path length is minimized in the high absorption limit, in which case the third terms in Eqs. (7) and (8) cancel.

4.6. $\omega\tau \gg 1$

In this case, the lifetime factor $(1 + i\omega\tau)/(1 + \omega^2\tau^2)$ strongly attenuates the fluorescence signal. For this reason, one wants to avoid large values of $\omega\tau$, since they result in measurements of fluorescence light with a low signal-to-noise ratio.

4.7. $\omega\tau \ll 1$

In this case, the fluorescence signal bears no lifetime information since the terms containing τ in Eq. (2) cancel out. The further limit $\omega = 0$, where $k = i\sqrt{\nu\mu_a/D}$, is the steady state case. With regards to limits 4.6 and 4.7, we observe that the spatial dependent factor in $G_f(r, t)$ (the term in square brackets in Eq. (2)) is separated from the lifetime factor. Therefore, the distribution of the photon paths in the medium, as well as the spatial distribution of

the origin of the fluorescence signal, does not depend on the lifetime.

4.8. $\omega\tau \sim 1$

The results of limits 4.6 and 4.7 impose the condition $\omega\tau \sim 1$ to obtain fluorescence lifetime information from a measurement of $G_f(r, t)$. This condition is also required in fluorescence spectroscopy of non-diffusive media. Let us now consider the particular cases of lifetimes much larger or much smaller than the average photon migration time $\bar{t}$. In the diffusion approximation, the average photon migration time-of-flight $\bar{t}$ at a radial coordinate r is given by $r/(2\sqrt{\nu\mu_a D})$ [14]. Let us consider a radial coordinate r in the order of twice the diffusion length, where the diffusion approximation holds, and where the photon-density wave is still practically measurable.

4.8.1. $\tau \gg \bar{t}$

In this limit, the condition $\omega\tau \sim 1$ requires that $\omega \ll 1/\bar{t}$. At $r \sim 2L$, this condition reads $(\omega/\nu\mu_a) \ll 1$. The propagation constant of the photon-density wave thus reduces to:

$$\lim_{\substack{\tau \gg \bar{t} \\ \omega\tau \sim 1}} k = i\sqrt{\frac{\nu\mu_a}{D}}, \quad (9)$$

which is the steady state limit for k . However, the lifetime information in $G_f^*(r, \omega)$ is retained since its phase is solely determined by the fluorescence lifetime.

4.8.2. $\tau \ll \bar{t}$

In this limit, the condition $\omega\tau \sim 1$ requires that $\omega \gg 1/\bar{t}$. At $r \sim 2L$, this condition reads $(\omega/\nu\mu_a)^{1/2} \gg 1$. The propagation constant of the photon density wave thus reduces to:

$$\lim_{\substack{\tau \ll \bar{t} \\ \omega\tau \sim 1}} k = \sqrt{\frac{\omega}{2D}} (1 + i). \quad (10)$$

We observe that the diffusion length in this high frequency limit is much smaller than the steady state diffusion length $\sqrt{D/\nu\mu_a}$. Furthermore, the condition $(\omega/\nu\mu_a)^{1/2} \gg 1$ requires that $\mu'_s \gg \mu_a$ for the diffusion approximation to be valid (because ω must be $\ll \nu\mu'_s$) [8].

5. Discussion

The interpretation of limits 4.1 and 4.2 is straightforward. The disappearance of the factor $1/r$ in the expressions of $G_f(r, t)$ in limits 4.3 and 4.5 (Eqs. (4) and (6)) indicates that the amplitude of the oscillatory photon flux integrated over a sphere of radius R is proportional to $[(1 + i\omega\tau)/(1 + \omega^2\tau^2)]R^2 \exp[-\text{Im}(k)R]$ (where $k = (k_x + k_m)/2$ in the case of limit 4.3). This means that there is an optimum value of R , $R^* = 2/\text{Im}(k) = 2L$, that maximizes the integrated fluorescence photon flux (see Fig. 3). We observe that this optimum value R^* only depends on the optical properties of the diffusive medium (μ_a and μ'_s) and on the angular modulation frequency (ω), while it is independent of the fluorescence properties of the fluorophore. By contrast, the oscillatory excitation photon flux integrated over a sphere of radius R monotonically decreases in amplitude as $(1 + \text{Im}(k_x)R)\exp[-\text{Im}(k_x)R]$. Fig. 3 shows the steady state ($\omega = 0$) excitation and fluorescence photon fluxes integrated over a sphere centered at the origin, as a function of the radius of the sphere. Limit 4.3 further indicates that at small r , the fluorescent photon-density wave has a diffusion length L_f given by:

$$\lim_{r \ll \min(L_x, L_m)} L_f = \frac{2L_x L_m}{L_x + L_m}. \quad (11)$$

Consequently, the projected radial distance for maximal integrated amplitude of the photon flux is $2L_f = 4L_x L_m / (L_x + L_m)$. Furthermore, in this small r limit, the wavelength of the fluorescent photon-density wave is:

$$\lim_{r \ll \min(L_x, L_x)} \lambda_f^{(\text{PDW})} = \frac{2\lambda_x^{(\text{PDW})}\lambda_m^{(\text{PDW})}}{\lambda_x^{(\text{PDW})} + \lambda_m^{(\text{PDW})}}. \quad (12)$$

Limit 4.4 indicates that at large r , the fluorescent diffusion length is:

$$\lim_{r \gg L_x L_m / |L_x - L_m|} L_f = \frac{1}{|\text{Im}(k_<)|} = L_<, \quad (13)$$

while the wavelength of the fluorescent photon-density wave is:

$$\lim_{r \gg L_x L_m / |L_x - L_m|} \lambda_f^{(\text{PDW})} = \frac{2\pi}{|\text{Re}(k_<)|}. \quad (14)$$

Fig. 3. Steady state ($\omega = 0$) excitation and fluorescence photon fluxes integrated over a sphere of radius R (centered at the origin) as a function of R . The optical parameters used to generate this figure are $\mu_{ax} = \mu_{am} = 0.1 \text{ cm}^{-1}$ and $\mu'_{sx} = \mu'_{sm} = 10 \text{ cm}^{-1}$. Note the optimum value $R^* = 2L$, where $L = 2/|\text{Im}(k_x + k_m)|$ in the case of limit 4.3, and $L = 1/|\text{Im}(k_x)| = 1/|\text{Im}(k_m)|$ in the case of limit 4.5.

Eqs. (11) and (13) show that the fluorescence diffusion length at large r is $\leq$ than at small r , the equal sign holding if $L_x = L_m$.

The interpretation of limit 4.7 is straightforward. Limit 4.8.1 shows that long (compared to $\bar{t}$) lifetimes can be measured without knowledge of the optical properties of the diffusive medium. In fact, the phase of the fluorescent photon-density wave is dominated by the lifetime delay, and it contains only a negligible contribution from the photon time-of-flight in the diffusive medium. Limit 4.8.2 indicates that short (compared to $\bar{t}$) lifetimes should be measured at high modulation frequencies and small radial coordinates, so that the lifetime-induced phase shift $\omega\tau$ is comparable to the phase shift induced by the photon time-of-flight.

6. Conclusion

In this article, we have considered various limiting cases of fluorescence photon-density waves in uniform diffusive media. The starting point of our analysis is Eq. (2), which is based on diffusion theory, and which has been experimentally validated [1]. The predictions of Eq. (2) in the limiting cases considered here can help the design of experimental protocols for quantitative fluorescence spectroscopy in diffusive media.

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