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Estimates of minimum pulse width and maximum modulation frequency for diffusion optical tomography

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Abstract

The validity of the time-dependent diffusion equation (DE) requires a condition to be imposed on the time derivative of the radiant current density vector. In the published literature this condition has been studied in connection with forward problems. Using a self-consistency criterion we derive a new condition on the time derivative of the radiant current density for inverse problems. From this condition, and using simple models of the time dependence of the radiant current density vector, we obtain estimates of a minimum pulse width and a maximum modulation frequency for time- and frequency-domain optical tomography of diffuse media. For imaging of biological tissues in the near infrared, with optical parameters $\mu_a(\mathbf{r}) \approx 0.01 \text{ mm}^{-1}$, $\mu'_s(\mathbf{r}) \approx 1 \text{ mm}^{-1}$, and $n \approx 1.4$, the estimated minimum pulse width and maximum modulation frequency are 930 ps and 340 MHz, respectively. The relevance of these results to the practical application of diffusion theory to optical tomography is discussed.

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1. Introduction

Optical tomography (OT) involves solving an inverse problem and recovering spatial maps of the internal physical parameters of a medium (e.g. the coefficients of absorption and scatter) from a set of optical measurements acquired at its surface [1–3]. In scattering media such as biological tissues at near-infrared wavelengths, photon migration is often described by the diffusion equation (DE), which has been subject to intensive study [4–20]. The DE is widely used in OT for medical applications [1–3].

One of the fundamental assumptions involved in the derivation of the time-dependent DE from the radiative transfer equation (RTE) is that a term containing the time derivative of the radiant current density $\partial\mathbf{J}(\mathbf{r}, t)/\partial t$ can be neglected [1–3]. For forward modelling involving the RTE and/or DE, various mathematical conditions have been obtained for the time derivative of the radiant current density $\partial\mathbf{J}(\mathbf{r}, t)/\partial t$ [16] and for the modulation frequency of the light [8]. However, the application of these same conditions to inverse problems could be misleading because of the inherent differences in the approaches towards solving forward and inverse problems. Obviously, conditions imposed on the pulse width and modulation frequency employed by DE-based optical tomography systems are of practical interest for the design of such systems.

In the analysis below, we first explore the conditions imposed on the time derivative of the radiant current density when approximating the P_1 equations of the time-dependent RTE by the DE for OT problems. Using a self-consistency criterion we derive conditions that confirm the negligibility of the time derivative of the radiant current density for time- and frequency-domain systems used for inverse problems. These conditions link the radiant current density, its time derivative, and the optical properties of the medium. Thereafter, using simple analytical models of the radiant current density we derive mathematical expressions linking the optical properties of the medium (refractive index, absorption coefficient, and reduced scattering coefficient) with the pulse width and the modulation frequency of the light source. The results are then used to estimate the minimum allowable pulse width and the maximum allowable frequency for media with tissue-like optical properties. Finally we discuss whether the existence of such limits may have significant implications for the design of experimental systems used for optical tomography, and for image reconstruction schemes based on the time-dependent DE.

2. The physical model

Fig. 1 illustrates the three-stage development of the DE from the RTE, stating the assumptions involved at each stage. It also indicates the application of the DE to both forward and inverse problems. In forward-modelling problems we need to determine the optical fields (typically, the irradiance and the radiant current density vector) from a knowledge of the source characteristics, the boundary conditions, and

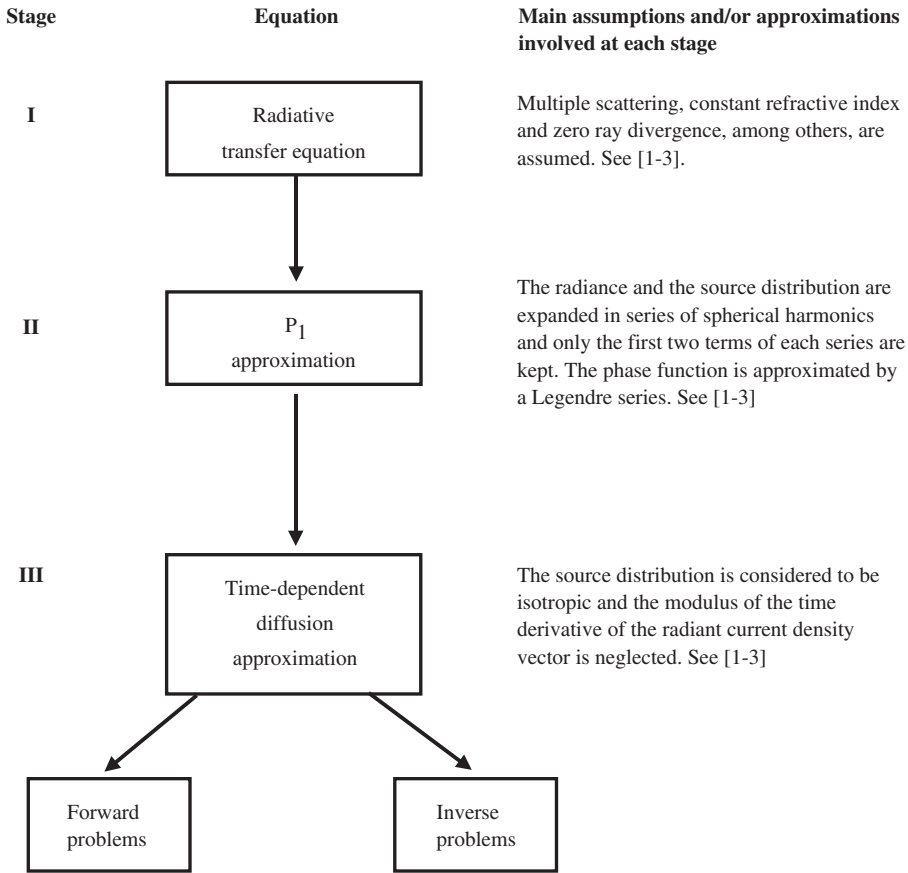


Fig. 1. Flow chart of the physical model and its connection with forward and inverse problems. In the forward problem the absorption coefficient and the reduced scattering coefficients are known, while in the inverse problem we want to retrieve them. We do not include the boundary conditions in the physical model because this is beyond the scope of our paper, although in a complete description they must be included.

the properties of the medium, while in inverse problems the challenge is to derive the unknown optical properties of the medium (e.g. the absorption and the reduced scattering coefficients) from a knowledge of optical fields at boundaries and the source characteristics. Although forward problems and inverse problems cannot be considered as independent of each other, the conditions and approximations that are valid for solving a forward problem are not the same and, in general, do not suffice for solving the corresponding inverse problem.

An assumption at stage III of the flow chart in Fig. 1 is that the time derivative of the radiant current density is negligible. In the following sections we examine the conditions under which this assumption is valid, for both forward and inverse problems.

3. Conditions for neglecting the time derivative of radiant current density vector

The time-dependent DE can be derived from the P_1 approximation of the RTE expressed as follows [1–3]:

$$\frac{n}{c} \frac{\partial}{\partial t} I(\mathbf{r}, t) + \nabla_{\mathbf{r}} \cdot \mathbf{J}(\mathbf{r}, t) + \mu_a(\mathbf{r})I(\mathbf{r}, t) = \varepsilon_0(\mathbf{r}, t), \tag{1}$$

$$\frac{n}{c} \frac{\partial}{\partial t} \mathbf{J}(\mathbf{r}, t) + \frac{1}{3} \nabla_{\mathbf{r}} I(\mathbf{r}, t) + [\mu_a(\mathbf{r}) + \mu'_s(\mathbf{r})]\mathbf{J}(\mathbf{r}, t) = \boldsymbol{\varepsilon}_1(\mathbf{r}, t), \tag{2}$$

where $I(\mathbf{r}, t)$ and $\mathbf{J}(\mathbf{r}, t)$ are the irradiance and the radiant current density vector at a point \mathbf{r} and at time t , respectively, n is the refractive index of the medium (assumed to be constant), c is the speed of light in vacuum, $\mu_a(\mathbf{r})$ and $\mu'_s(\mathbf{r})$ are the absorption and reduced scattering coefficients, $\varepsilon_0(\mathbf{r}, t)$ and $\boldsymbol{\varepsilon}_1(\mathbf{r}, t)$ are the first two components of the expansion of the source distribution in spherical harmonics of the direction of propagation $\boldsymbol{\Omega}$, and $\nabla_{\mathbf{r}}$ denotes the gradient operator with respect to \mathbf{r} .

Eqs. (1) and (2) are valid under the following conditions: (a) the RTE is valid, (b) the radiance $L(\mathbf{r}, \boldsymbol{\Omega}, t)$ can be expanded in a series of spherical harmonics of the direction of propagation $\boldsymbol{\Omega}$, (c) we can retain only the first two terms of that series, so that $L(\mathbf{r}, \boldsymbol{\Omega}, t) \approx I(\mathbf{r}, t)/(4\pi) + 3\mathbf{J}(\mathbf{r}, t) \cdot \boldsymbol{\Omega}/(4\pi)$, and (d) the normalized phase function $\theta(\mathbf{r}, \boldsymbol{\Omega}, \boldsymbol{\Omega}')$ (here $\boldsymbol{\Omega}$ and $\boldsymbol{\Omega}'$ are the directions of incidence and scattering, respectively) is independent of the direction of incident photons, so that $\theta(\mathbf{r}, \boldsymbol{\Omega}, \boldsymbol{\Omega}') \equiv \theta(\mathbf{r}, \boldsymbol{\Omega} \cdot \boldsymbol{\Omega}')$ [1–4,16]. If

$$\boldsymbol{\varepsilon}_1(\mathbf{r}, t) = \mathbf{0}, \tag{3}$$

$$\frac{\partial}{\partial t} \mathbf{J}(\mathbf{r}, t) = \mathbf{0}, \tag{4}$$

then the DE is obtained as follows [1–3]:

$$\frac{n}{c} \frac{\partial}{\partial t} I(\mathbf{r}, t) - D(\mathbf{r})\nabla_{\mathbf{r}}^2 I(\mathbf{r}, t) - \nabla_{\mathbf{r}} I(\mathbf{r}, t) \cdot \nabla_{\mathbf{r}} D(\mathbf{r}) + \mu_a(\mathbf{r})I(\mathbf{r}, t) = \varepsilon_0(\mathbf{r}, t), \tag{5}$$

where $D(\mathbf{r})$ is the diffusion coefficient, given by the expression

$$D(\mathbf{r}) = \frac{1}{3[\mu_a(\mathbf{r}) + \mu'_s(\mathbf{r})]}. \tag{6}$$

However, condition (4) can only be met exactly in time-independent problems. In time-dependent problems the term $(n/c)\partial\mathbf{J}(\mathbf{r}, t)/\partial t$ must be compared with other terms in Eq. (2) to determine whether it can be neglected or not.

For forward problems (where $\mu_a(\mathbf{r})$ and $\mu'_s(\mathbf{r})$ are known) Martelli et al. [16] introduced the inequality

$$\frac{n}{c} \left| \frac{\partial}{\partial t} \mathbf{J}(\mathbf{r}, t) \right| \ll \mu'_s(\mathbf{r})|\mathbf{J}(\mathbf{r}, t)|, \tag{7}$$

where $|\mathbf{J}(\mathbf{r}, t)| \neq 0$, as a condition for neglecting the term containing the time derivative of the radiant current density. If this condition is also sufficient to ensure

the negligibility of the time derivative of the radiant current density for inverse problems (where $\mu_a(\mathbf{r})$ and $\mu'_s(\mathbf{r})$ are unknown), we would expect that its fulfilment will avoid any inconsistencies or contradictions in the physical model. To determine whether this is the case, we first assume that we deal with a time-dependent problem and impose just condition (3) to Eq. (2). Then we obtain

$$\frac{n}{c} \frac{\partial}{\partial t} \mathbf{J}(\mathbf{r}, t) + [\mu_a(\mathbf{r}) + \mu'_s(\mathbf{r})] \mathbf{J}(\mathbf{r}, t) = -\frac{1}{3} \nabla_r I(\mathbf{r}, t). \quad (8)$$

If condition (7) is fulfilled, we can eliminate the term $(n/c)\partial\mathbf{J}(\mathbf{r}, t)/\partial t$ from Eq. (8), which yields Fick's law. However, the contribution of the eliminated term $(n/c)\partial\mathbf{J}(\mathbf{r}, t)/\partial t$ remains in Eq. (8) in the form of a numerical error due to the fact that it is not strictly zero. This error is not associated with either data error or algorithm inaccuracy, but instead with an approximation contained in the physical model. After retrieving the coefficients $\mu_a(\mathbf{r})$ and $\mu'_s(\mathbf{r})$ it could occur that $\mu_a(\mathbf{r})|\mathbf{J}(\mathbf{r}, t)| < (n/c)|\partial\mathbf{J}(\mathbf{r}, t)/\partial t|$ because this is not prevented by condition (7). Therefore condition (7) leads to a contradictory situation in Eq. (8): the term $(n/c)\partial\mathbf{J}(\mathbf{r}, t)/\partial t$ is eliminated while the term $\mu_a(\mathbf{r})\mathbf{J}(\mathbf{r}, t)$, which could be less than the numerical error due to the eliminated term, is retained. Thus we can legitimately question the values $\mu_a(\mathbf{r})$ obtained in the regions of the medium where $\mu_a(\mathbf{r})|\mathbf{J}(\mathbf{r}, t)| < (n/c)|\partial\mathbf{J}(\mathbf{r}, t)/\partial t|$. This inconsistency is a consequence of the use of inequality (7) as a condition for neglecting the time derivative of the radiant current density vector.

We can remove this inconsistency if we impose the condition that the modulus of the term $(n/c)\partial\mathbf{J}(\mathbf{r}, t)/\partial t$ is much less than the modulus of any of the contributions $\mu_a(\mathbf{r})\mathbf{J}(\mathbf{r}, t)$ or $\mu'_s(\mathbf{r})\mathbf{J}(\mathbf{r}, t)$ on the left-hand side of Eq. (8), i.e.

$$\frac{n}{c} \left| \frac{\partial}{\partial t} \mathbf{J}(\mathbf{r}, t) \right| \ll \min[\mu_a(\mathbf{r}), \mu'_s(\mathbf{r})] |\mathbf{J}(\mathbf{r}, t)|. \quad (9)$$

We summarize the above analysis in Table 1. In the following sections we derive estimates of the maximum modulation frequency (for frequency-domain systems) and the minimum pulse width (for time-domain systems) that arise from conditions (7) and (9).

3.1. Minimum pulse width

Consider a pulse of light propagating through a scattering medium. We assume that the radiant current density at an arbitrary point \mathbf{r} during a time interval Δt centred at $t = t_0$, is Gaussian

$$\mathbf{J}(\mathbf{r}, t) = \mathbf{J}(\mathbf{r}) \exp\{-[t - t_0(\mathbf{r})]^2/w_0^2(\mathbf{r})\}, \quad (10)$$

where $w_0(\mathbf{r})$ is the time at which the radiant current density falls to e^{-1} of its maximum value. Although a Gaussian radiant current density is not exactly representative of real optical pulses, this approximation enables a straightforward mathematical expression for pulse width to be derived which is not substantially different from those obtained using non-Gaussian distributions. Now we require

Table 1

Comparison of the conditions on the time derivative of the radiant current density vector for forward problems and inverse problems

	Forward problem: We wish to obtain $I(\mathbf{r}, t)$ and $\mathbf{J}(\mathbf{r}, t)$	Inverse problem: We wish to retrieve $\mu_a(\mathbf{r}) \neq 0$ and $\mu'_s(\mathbf{r}) \neq 0$
Condition	$\left \frac{n}{c} \frac{\partial}{\partial t} \mathbf{J}(\mathbf{r}, t) \right \ll \mu'_s(\mathbf{r}) \mathbf{J}(\mathbf{r}, t) $	$\left \frac{n}{c} \frac{\partial}{\partial t} \mathbf{J}(\mathbf{r}, t) \right \ll \min[\mu_a(\mathbf{r}), \mu'_s(\mathbf{r})] \mathbf{J}(\mathbf{r}, t) $
Rationale for the condition	If the modulus of the term $\frac{n}{c} \frac{\partial}{\partial t} \mathbf{J}(\mathbf{r}, t)$ is small enough, this term can be neglected	The modulus of the term $\frac{n}{c} \frac{\partial}{\partial t} \mathbf{J}(\mathbf{r}, t)$ must be much less than the modulus of any of contributions $\mu_a(\mathbf{r}) \mathbf{J}(\mathbf{r}, t)$ and $\mu'_s(\mathbf{r}) \mathbf{J}(\mathbf{r}, t)$, otherwise the contribution of the term to be neglected could be greater than the contribution of a term containing a parameter to be recovered, leading to an inconsistency of the model
Application to biological tissues	For most biological tissues at NIR wavelengths $\mu_a(\mathbf{r}) < \mu'_s(\mathbf{r})$ The condition does not change	Condition $\left \frac{n}{c} \frac{\partial}{\partial t} \mathbf{J}(\mathbf{r}, t) \right \ll \mu_a(\mathbf{r}) \mathbf{J}(\mathbf{r}, t) $ suffices

that $\mathbf{J}(\mathbf{r}, t)$ meets condition (7) for forward problems, and meets condition (9) for inverse problems at $t = t_0(\mathbf{r}) \pm w_0/2$, where the modulus of its temporal derivative reaches its maximum magnitude. Using the Gaussian model for the radiant current density, it can be shown that conditions (7) and (9) can be re-expressed as follows:

$$2w_0(\mathbf{r}) \gg w_{\min 1} = \frac{2n}{c\mu'_s(\mathbf{r})}, \tag{11}$$

$$2w_0(\mathbf{r}) \gg w_{\min 2} = \frac{2n}{c \min[\mu_a(\mathbf{r}), \mu'_s(\mathbf{r})]}, \tag{12}$$

where $w_{\min 1}$ and $w_{\min 2}$ are estimates of the minimum allowable full-width of the pulse, according to condition (7) for forward problems and condition (9) for inverse problems, respectively.

These results provide us with an elegant way of expressing the spatial and temporal conditions under which the DE is valid when pulsed sources of light are employed. Experimental measurements have shown that the width of a pulse propagating through a scattering medium increases from its initial value at the source, an observation that is supported by various mathematical models. Therefore, even if the radiant current density does not meet (for example) condition (11) at the precise location of the source, the condition may eventually be met at some distance from the source. In such a case expression (11) defines a region in the vicinity of the

source where the pulse width is less than the minimum allowable width and, consequently, where the time-dependent DE does not hold. The same reasoning can be applied to condition (12).

The above conditions (11) and (12) apply to a single pulse. If this single pulse belongs to a train of pulses with a repetition rate f and period $T = 1/f$, then those conditions limit the maximum repetition rate since the period of the pulses must meet the inequality $T > w_{\min 1}$ for condition (11) or $T > w_{\min 2}$ for condition (12). Using this property of the trains of periodic pulses it can be shown that the maximum repetition rates are

$$f_{\max 1} < w_{\min 1}^{-1} = \frac{c\mu'_s(\mathbf{r})}{2n}, \quad (13)$$

$$f_{\max 2} < w_{\min 2}^{-1} = \frac{c \min[\mu_a(\mathbf{r}), \mu'_s(\mathbf{r})]}{2n}, \quad (14)$$

where $f_{\max 1}$ and $f_{\max 2}$ are the maximum repetition rates (modulation frequencies) allowed by conditions (7) and (9), respectively.

3.2. Maximum modulation frequency

Although expressions (13) and (14) can be used to estimate the maximum frequency of the optical source for frequency-domain systems, it is possible to derive more precise expressions. To do that we consider an isotropic source density of the form

$$\varepsilon_0(\mathbf{r}, t) = \varepsilon_0(\mathbf{r})[1 + \alpha \cos(2\pi ft)], \quad (15)$$

where $0 < \alpha \leq 1$ is the modulation depth. Suppose we express the irradiance $I(\mathbf{r}, t)$ and the radiant current density $\mathbf{J}(\mathbf{r}, t)$ in terms of time-independent and time-dependent components:

$$I(\mathbf{r}, t) = I_i(\mathbf{r}) + I_d(\mathbf{r}, t), \quad (16)$$

$$\mathbf{J}(\mathbf{r}, t) = \mathbf{J}_i(\mathbf{r}) + \mathbf{J}_d(\mathbf{r}, t), \quad (17)$$

where $I_i(\mathbf{r})$ and $\mathbf{J}_i(\mathbf{r})$ are solutions to the time-independent equations:

$$\nabla_{\mathbf{r}} \cdot \mathbf{J}_i(\mathbf{r}) + \mu_a(\mathbf{r})I_i(\mathbf{r}) = \varepsilon_0(\mathbf{r}), \quad (18)$$

$$\frac{1}{3} \nabla_{\mathbf{r}} I_i(\mathbf{r}) + [\mu_a(\mathbf{r}) + \mu'_s(\mathbf{r})]\mathbf{J}_i(\mathbf{r}) = \mathbf{0}, \quad (19)$$

and $I_d(\mathbf{r}, t)$ and $\mathbf{J}_d(\mathbf{r}, t)$ are solutions to the time-dependent equations:

$$\frac{n}{c} \frac{\partial}{\partial t} I_d(\mathbf{r}, t) + \nabla_{\mathbf{r}} \cdot \mathbf{J}_d(\mathbf{r}, t) + \mu_a(\mathbf{r})I_d(\mathbf{r}, t) = \alpha \varepsilon_0(\mathbf{r}) \cos(2\pi ft), \quad (20)$$

$$\frac{n}{c} \frac{\partial}{\partial t} \mathbf{J}_d(\mathbf{r}, t) + \frac{1}{3} \nabla_{\mathbf{r}} I_d(\mathbf{r}, t) + [\mu_a(\mathbf{r}) + \mu'_s(\mathbf{r})]\mathbf{J}_d(\mathbf{r}, t) = \mathbf{0}. \quad (21)$$

It is straightforward to show that both $I_d(\mathbf{r}, t)$ and $\mathbf{J}_d(\mathbf{r}, t)$ are periodic functions with a period $T = 1/f$, and that

$$\overline{I(\mathbf{r}, t)} = I_i(\mathbf{r}), \quad \overline{I_d(\mathbf{r}, t)} = 0, \tag{22}$$

$$\overline{\mathbf{J}(\mathbf{r}, t)} = \mathbf{J}_i(\mathbf{r}), \quad \overline{\mathbf{J}_d(\mathbf{r}, t)} = \mathbf{0}, \tag{23}$$

where the over-bar denotes an average over a period T .

From Eqs. (18)–(21) it follows that $I(\mathbf{r}, t)$ and $\mathbf{J}(\mathbf{r}, t)$ are solutions to Eqs. (1) and (8). It may appear that the terms to substitute into conditions (7) and (9) are $(n/c)\partial\mathbf{J}(\mathbf{r}, t)/\partial t = (n/c)\partial\mathbf{J}_d(\mathbf{r}, t)/\partial t$ and $[\mu_a(\mathbf{r}) + \mu'_s(\mathbf{r})]\mathbf{J}(\mathbf{r}, t) = [\mu_a(\mathbf{r}) + \mu'_s(\mathbf{r})][\mathbf{J}_i(\mathbf{r}) + \mathbf{J}_d(\mathbf{r}, t)]$. However, the time-independent terms of Eqs. (1) and (8) cancel out, as seen from Eqs. (18) and (19). Therefore, the terms to be employed are $(n/c)\partial\mathbf{J}_d(\mathbf{r}, t)/\partial t$ and $[\mu_a(\mathbf{r}) + \mu'_s(\mathbf{r})]\mathbf{J}_d(\mathbf{r}, t)$ from Eq. (21). Functions $\mathbf{J}_d(\mathbf{r}, t)$ and $\partial\mathbf{J}_d(\mathbf{r}, t)/\partial t$ are both periodic with a period T , and are out of phase so that when $\mathbf{J}_d(\mathbf{r}, t) = \mathbf{0}$, then $\partial\mathbf{J}_d(\mathbf{r}, t)/\partial t \neq \mathbf{0}$. Consequently, in the frequency-domain case conditions (7) and (9) cannot be met over the entire period of the signal. This inconvenience can be overcome by re-considering the form of conditions (7) and (9). We can assume that the term $(n/c)\partial\mathbf{J}_d(\mathbf{r}, t)/\partial t$ gives a negligible contribution to Eq. (8) if

$$\frac{n^2}{c^2} \left| \frac{\partial \mathbf{J}_d(\mathbf{r}, t)}{\partial t} \right|^2 \ll [\mu'_s(\mathbf{r})]^2 \overline{|\mathbf{J}_d(\mathbf{r}, t)|^2}, \tag{24}$$

for condition (7), and

$$\frac{n^2}{c^2} \left| \frac{\partial \mathbf{J}_d(\mathbf{r}, t)}{\partial t} \right|^2 \ll \{\min[\mu_a(\mathbf{r}), \mu'_s(\mathbf{r})]\}^2 \overline{|\mathbf{J}_d(\mathbf{r}, t)|^2}, \tag{25}$$

for condition (9). From these new conditions (24) and (25) it follows that the maximum modulation frequency depends on $\mathbf{J}_d(\mathbf{r}, t)$ and on its time derivative. To estimate its value we approximate the function $\mathbf{J}_d(\mathbf{r}, t)$ by a cosine as follows

$$\mathbf{J}_d(\mathbf{r}, t) = \mathbf{J}_{d0}(\mathbf{r}) \cos[2\pi ft + \varphi_J(\mathbf{r})], \quad \frac{\partial}{\partial t} \mathbf{J}_d(\mathbf{r}, t) = -2\pi f \mathbf{J}_{d0}(\mathbf{r}) \sin[2\pi ft + \varphi_J(\mathbf{r})], \tag{26}$$

where $0 \leq \varphi_J(\mathbf{r}) < 2\pi$ is a phase term and $\mathbf{J}_{d0}(\mathbf{r})$ is the amplitude of the radiant current density. Substituting the above expressions into conditions (24) and (25) we obtain the following estimates $f_{\max 1}$ and $f_{\max 2}$ of the maximum modulation frequency for a sinusoidal source:

$$f \ll f_{\max 1} = \frac{c\mu'_s(\mathbf{r})}{2\pi n}. \tag{27}$$

$$f \ll f_{\max 2} = \frac{c}{2\pi n} \min[\mu_a(\mathbf{r}), \mu'_s(\mathbf{r})]. \tag{28}$$

Note that expressions (13) and (14) are consistent with expressions (27) and (28), although the latter were derived via a completely different route.

Table 2

Conditions for neglecting the time derivative of radiant current density vector

	Forward problem: We wish to obtain $I(\mathbf{r}, t)$ and $\mathbf{J}(\mathbf{r}, t)$	Inverse problem: We wish to retrieve $\mu_a(\mathbf{r}) \neq 0$ and $\mu'_s(\mathbf{r}) \neq 0$
Condition	$\left \frac{n}{c} \frac{\partial}{\partial t} \mathbf{J}(\mathbf{r}, t) \right \ll \mu'_s(\mathbf{r}) \mathbf{J}(\mathbf{r}, t) $	$\left \frac{n}{c} \frac{\partial}{\partial t} \mathbf{J}(\mathbf{r}, t) \right \ll \min[\mu_a(\mathbf{r}), \mu'_s(\mathbf{r})] \mathbf{J}(\mathbf{r}, t) $
Estimated minimum pulse width	$w_{\min 1} = \frac{2n}{c\mu'_s(\mathbf{r})}$	$w_{\min 2} = \frac{2n}{c \min[\mu_a(\mathbf{r}), \mu'_s(\mathbf{r})]}$
Condition	$\frac{n^2}{c^2} \left \frac{\partial}{\partial t} \mathbf{J}_d(\mathbf{r}, t) \right ^2 \ll [\mu'_s(\mathbf{r})]^2 \mathbf{J}_d(\mathbf{r}, t) ^2$	$\frac{n^2}{c^2} \left \frac{\partial}{\partial t} \mathbf{J}_d(\mathbf{r}, t) \right ^2 \ll \{\min[\mu_a(\mathbf{r}), \mu'_s(\mathbf{r})]\}^2 \mathbf{J}_d(\mathbf{r}, t) ^2$
Estimated maximum modulation frequency	$f_{\max 1} = \frac{c\mu'_s(\mathbf{r})}{2\pi n}$	$f_{\max 2} = \frac{c}{2\pi n} \min[\mu_a(\mathbf{r}), \mu'_s(\mathbf{r})]$

Until now we have not required that the optical signals are Fourier transformable. If we assume that all optical signals are Fourier transformable, we can use the uncertainty relationship:

$$\Delta f \Delta w \sim 1, \quad (29)$$

where Δf is the frequency bandwidth and Δw is the time width of the pulse. Taking $\Delta f \approx f_{\max}$ and $\Delta w = w_{\min}$ we can derive expressions (27) and (28) from expressions (11) and (12), respectively, except for a missing multiplicative factor π^{-1} , due to the definitions of f_{\max} and w_{\min} . We summarize all the above results in Table 2.

4. Estimates of minimum pulse width and maximum modulation frequency

As support for our results, we note that Fishkin et al. [8] report difficulty measuring the optical properties of a medium with an absorption coefficient $\mu_a \sim 0.001 \text{ mm}^{-1}$ using the diffusion approximation and modulation frequencies in the range from 381 MHz to 10 GHz. Using the optical properties of their medium, a skim milk/water solution ($n \approx 1.34$ [21], $\mu_a \sim 0.001 \text{ mm}^{-1}$ and $\mu'_s \sim 0.4 \text{ mm}^{-1}$), we can now estimate the maximum allowed modulation frequency using expressions (27) and (28):

$$f_{\max 1} \approx 15 \text{ GHz} \quad \text{for forward problems,} \quad (30)$$

$$f_{\max 2} \approx 36 \text{ MHz} \quad \text{for inverse problems.} \quad (31)$$

Therefore the employed modulation frequencies do not fulfil condition (28) and, consequently, accurate values of the absorption coefficient cannot be expected. Note that in this case the maximum allowable modulation frequency for a forward problem (27) is far above the maximum frequency used by the researchers.

The simplified conditions (11), (12), (27) and (28) derived above can be used for estimating the minimum allowable pulse width and the maximum allowable modulation frequency in DE-based systems for media with tissue-like optical properties. The reduced scattering and absorption coefficients of biological tissues

have been widely reported, as reviewed by Cheong et al. [22], and values of the typical refractive index have also been measured [23]. Roggan et al. [24] pointed out that even for the same type of tissue, the absorption and reduced scattering coefficients reported in the literature vary over a wide range, due to different tissue preparation techniques, experimental systems, and calculation methods. However, for most tissues at near-infrared wavelengths it is reasonable to assume typical values of $\min[\mu_a(\mathbf{r}), \mu'_s(\mathbf{r})] = \mu_a(\mathbf{r}) \approx 0.01 \text{ mm}^{-1}$, $\mu'_s(\mathbf{r}) \approx 1 \text{ mm}^{-1}$ [1–3], and $n \approx 1.4$ [23]. Substituting these values and $c = 3 \times 10^{11} \text{ mm/s}$ into expressions (11) and (12), we obtain

$$w_{\min 1} \approx 9.3 \text{ ps} \quad \text{for forward problems} \quad (32)$$

and

$$w_{\min 2} \approx 930 \text{ ps} \quad \text{for inverse problems.} \quad (33)$$

Estimates (32) and (33) of the minimum pulse width for human tissues are generally larger than the pulse widths typically employed by experimental time-of-flight tomographic systems. For example, Eda et al. [25], Benaron et al. [26] and Schmidt et al. [27] use pulse widths of ~ 100 , 60, and < 10 ps, respectively. Therefore condition (32) is met by two of those systems, while none meets condition (33). This suggests that for time-domain OT systems with such short-pulse widths, the DE is not an accurate approximation and a DE-based algorithm could lead to large errors in the values of recovered absorption coefficients.

Substituting the above set of tissue parameters in conditions (27) and (28) for the maximum allowed modulation frequency we obtain

$$f_{\max 1} \approx 34 \text{ GHz} \quad (34)$$

and

$$f_{\max 2} \approx 340 \text{ MHz.} \quad (35)$$

Most reported frequency-domain systems employ a modulation frequency less than $f_{\max 2} \approx 340 \text{ MHz}$ (see, e.g. [28–31]). Therefore for above chosen parameters and those frequency-domain systems, the DE is an accurate approximation to the RTE for both forward and inverse problems. Some reported frequency domain systems have a modulation frequency of $f \approx 1 \text{ GHz}$ [32]. In the latter case the DE is accurate for forward problems, but inaccurate for inverse problems. This suggests that in such a case the P_1 approximation should be employed.

5. Conclusions

The main results of our analysis can be summarized as follows.

1. The generally accepted condition for neglecting the time derivative of the radiant current density vector in the time-dependent DE, $(n/c)|\partial\mathbf{J}(\mathbf{r}, t)/\partial t| \ll \mu'_s(\mathbf{r})|\mathbf{J}(\mathbf{r}, t)|$, (see [8]) leads to a serious inconsistency when applied to inverse problems. To remove that inconsistency a new condition for inverse problems $(n/c)|\partial\mathbf{J}(\mathbf{r}, t)/\partial t| \ll \min[\mu_a(\mathbf{r}), \mu'_s(\mathbf{r})]|\mathbf{J}(\mathbf{r}, t)|$ has been proposed. The latter condition

was derived from a self-consistency principle: the error due to a negligible (but non-zero) time derivative of the radiant current density should be much less than the contribution of any other term on the left-hand side of Eq. (8), otherwise the associated numerical error could be comparable with the contribution of a parameter to be recovered.

2. Using Gaussian and sinusoidal models of the radiant current density we obtained expressions for estimating the minimum allowed pulse width and maximum allowed modulation frequency for forward problems and for inverse problems (summarized in Table 2).

3. For biological tissues at near-infrared wavelengths with optical properties $\min[\mu_a(\mathbf{r}), \mu'_s(\mathbf{r})] = \mu_a(\mathbf{r}) \approx 0.01 \text{ mm}^{-1}$, $\mu'_s(\mathbf{r}) \approx 1 \text{ mm}^{-1}$ [1–3], $n \approx 1.4$ [23], the estimates of the minimum allowed pulse widths yield $w_{\min 1} \approx 9.3 \text{ ps}$ (for forward problems) and $w_{\min 2} \approx 930 \text{ ps}$ (for inverse problems). The latter estimate suggests that experimental OT systems that employ sources with shorter pulses should utilize algorithms based on the RTE or its P_1 approximation.

4. For the above tissue parameters the estimates of the maximum allowed modulation frequencies yield $f_{\max 1} \approx 34 \text{ GHz}$ (for forward problems) and $f_{\max 2} \approx 340 \text{ MHz}$ (for inverse problems). The latter estimate suggests that frequency-domain systems with modulation frequencies around $f \approx 200 \text{ MHz}$ can justifiably use the DE.

Finally, we make three observations. First, in regions of low scattering, the so-called void regions [33], the DE does not hold and new conditions must be derived accordingly. Second, the expressions for minimum allowed pulse width and maximum allowed modulation frequency do not take into account the frequency response of the source–detector system, the unavoidable electronic noise, and other sources of error. They provide only practical criteria for defining when the time-dependent DE is an accurate approximation to the RTE. Third, minimum allowed pulse width and maximum allowed modulation frequency depend on the refractive index. Since in biological tissues in the near infrared range it varies from $n = 1.33$ (pure water) to $n \approx 1.5$ (adipose tissue, [23]) we can choose $n \approx 1.4$ for estimating those parameters with a relative uncertainty of about 10%.

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