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Perturbation theory for the diffusion equation by use of the moments of the generalized temporal point-spread function. III. Frequency-domain and time-domain results

Angelo Sassaroli^{1,*}, Fabrizio Martelli², and Sergio Fantini¹

¹Department of Biomedical Engineering, Tufts University, 4 Colby Street, Medford, Massachusetts 02155, USA

²Dipartimento di Fisica, Università degli Studi di Firenze, Via G. Sansone 1, Sesto Fiorentino, Firenze 1-50019, Italy

Abstract

We study the performance of a previously proposed perturbation theory for the diffusion equation in frequency and time domains as they are known in the field of near infrared spectroscopy and diffuse optical tomography. We have derived approximate formulas for calculating higher order self- and mixed path length moments, up to the fourth order, which can be used in general diffusive media regardless of geometry and initial distribution of the optical properties, for studying the effect of absorbing defects. The method of Padé approximants is used to extend the validity of the theory to a wider range of absorption contrasts between defects and background. By using Monte Carlo simulations, we have tested these formulas in the semi-infinite and slab geometries for the cases of single and multiple absorbing defects having sizes of interest ($d=4-10$ mm, where d is the diameter of the defect). In frequency domain, the discrepancy between the two methods of calculation (Padé approximants and Monte Carlo simulations) was within 10% for absorption contrasts $\Delta\mu_a = 0.2 \text{ mm}^{-1}$ for alternating current data, and usually to within 1° for $\Delta\mu_a = 0.1 \text{ mm}^{-1}$ for phase data. In time domain, the average discrepancy in the temporal range of interest (a few nanoseconds) was 2%–3% for $\Delta\mu_a = 0.06 \text{ mm}^{-1}$. The proposed method is an effective fast forward problem solver: all the time-domain results presented in this work were obtained with a computational time of less than about 15 s with a Pentium IV 1.66 GHz personal computer.

1. INTRODUCTION

In near infrared spectroscopy and diffuse optical tomography light in the wavelength range 600–900 nm is used to probe macroscopic regions of tissues. Two of the main applications are focused on the detection and physiological characterization of breast cancer [1–4] and functional imaging of the brain [5–10]. One of the main challenges that these fields are facing is the modeling of photon migration in tissues. The diffusion equation (DE) [11] has been widely used to quantify the features of light collected a few centimeters away from the input source. On the contrary for shorter source-detector separations also the more complex radiative transfer equation (RTE) [12], P_3 [13], and P_N [14] approximations have been used. The general philosophy for solving complex problems of optical properties estimation is either to use simplifying assumptions about the geometry of the medium, location, and shape of defects, and/or *a priori* information on the distribution of the background optical

properties, or to solve the full inverse problem by using sophisticated numerical methods. The former include computational methods that are faster but sometimes lack of quantification power (especially when the assumptions are oversimplifying), while the latter include slower computational methods that are more quantitative. Examples of the first and second categories are analytical models [15–18] and finite difference [19,20] or finite element [21–23] method based calculations, respectively. Other methods for forward problem calculations are based on Monte Carlo simulations [24] and random walk analysis [25]. Among the analytical methods used to solve the DE in the presence of one or multiple defects, perturbation theory has also been used in several geometries of interests [26–28]. In our previous work [29] we developed a perturbative approach to the DE for absorbing defects, based on the knowledge of the path length moments of the collected photons. This method is general in nature, i.e., it does not rely on any particular geometry and distribution of the optical properties. We already showed the potential of this method for continuous wave (CW) calculations carried out in the semi-infinite [30], slab and cylindrical [31], and layered geometries [32]. In this work we show that the method of the moments is also quite effective in the frequency and time domains. While the proposed method is not meant to substitute sophisticated numerical algorithms that are developed for solving partial differential equations in very general conditions, we can argue that it is a useful complement to those algorithms for at least two reasons. First, the method of the moments provides a better insight into the physical process of photon migration in highly turbid media. Second, the proposed method represents a practical fast forward problem solver for those situations beyond Born approximation whenever the Green's function of the medium is available. In the discussion section we will also consider the possible implementations of this method in inversion procedures used to solve general problems. In the theory section we briefly review a few points of the theory that are useful for understanding the results of this work. In particular we show that (a) the time-domain moments are the “building blocks” to derive the frequency-domain (and therefore also CW-domain) moments; (b) we develop heuristic formulas in frequency and time domains for the calculation of self- and mixed moments up to the fourth order that are used for studying absorbing defects; (c) we show how the method of Padé approximants is used to extend the limitations of the fourth order theory for wider absorption contrasts.

All throughout this work we stress the importance of the time-domain mean path lengths for solving not only first order but also higher order problems whenever single or multiple defects are considered. In a very succinct way we can say that the time-domain mean path lengths in the regions of interest constitute the most relevant piece of information for studying perturbation theory in the three domains of investigation.

2. THEORY

A. General Perturbative Approach to Photon Migration in Time and Frequency Domains

We consider a diffusive medium having arbitrary geometry that is divided into N regions where the scattering (μ_s) and the absorption (μ_a) coefficients are considered constant in each region, but for which $\mu_{si} \neq \mu_{sj}$ and $\mu_{ai} \neq \mu_{aj}$ for $i \neq j$ ($i, j=1, \dots, N$). We also consider a Dirac $\delta(t)$, a source point located at $\mathbf{r}_s$ inside the medium, and a point of collection $\mathbf{r}_b$ located at the boundary of the medium. We define the generalized temporal point-spread function (TPSF) as the probability density function per unit time and surface area, $f_{in}(t_1, \dots, t_N)$, of the local transit time of detected photons ($[f_{in}] = L^{-2} t^{-N}$, where L is the length and t is the time). The function f_{in} indicates the probability density that a photon emitted from $\mathbf{r}_s$ at time

$t=0$ is detected at time $t = \sum_{i=1}^N t_i$ after spending time t_i in the region “ i ” ($i=1, 2, \dots, N$). The integration of f_{in} over the N -dimensional Euclidian space R^N yields the CW attenuation per

unit surface area, while its integration over the hyper-plane σ^N defined by $\sum_{i=1}^N t_i = t$ yields the Green's function in time domain, also known as TPSF (defined here as R ; $[R] = L^{-2}t^{-1}$),

$$\int_{\sigma^N} f_{in}(t_1, \dots, t_N) d\sigma = R_{in}(\mathbf{r}_b, t, \mu_a). \quad (1)$$

In Eq. (1) μ_a is the array of the absorption coefficients μ_{ai} ($i=1, \dots, N$) in the initial state of the medium (subscript “in”). By contrast, the final state of the medium (subscript “f” in the following formulas) differs from the initial state only for the distribution of the absorption coefficients: $\mu_a + \Delta\mu_a$, where $\Delta\mu_a$ is the array of the absorption changes $\Delta\mu_{ai}$ ($i=1, \dots, N$). The TPSFs in the initial and final states of the medium are related by the formula [29]

$$R_{fi}(\mathbf{r}_b, t, \mu_a + \Delta\mu_a) = R_{in}(\mathbf{r}_b, t, \mu_a) \times \sum_{k_1, k_2, \dots, k_N=0}^{\infty} (-1)^{k_1+k_2+\dots+k_N} \frac{(\Delta\mu_{a1})^{k_1} \dots (\Delta\mu_{aN})^{k_N}}{k_1! \dots k_N!} \times \langle l_1^{k_1} \dots l_N^{k_N} \rangle(\mathbf{r}_b, t, \mu_a),$$

where $\langle l_1^{k_1} \dots l_N^{k_N} \rangle(\mathbf{r}_b, t, \mu_a)$ is the time-domain mixed path length moment of order $(k_1, k_2, \dots, k_N)$ calculated in the initial state of the medium at the time t and is defined by

$$\langle l_1^{k_1} \dots l_N^{k_N} \rangle(\mathbf{r}_b, t, \mu_a) = \frac{\int_{\sigma^N} (vt_1)^{k_1} \dots (vt_N)^{k_N} f_{in}(t_1, \dots, t_N) d\sigma}{\int_{\sigma^N} f_{in}(t_1, \dots, t_N) d\sigma}. \quad (3)$$

In Eq. (3) v is the speed of light in the medium and $l_i = vt_i$ is a random variable associated with the path length traveled by detected photons in the region i . Note that the time-domain moments are real functions of the time variable. For example, the time-domain mean path length $\langle l_i \rangle(t)$ is defined as the average path length traveled by a photon detected at time t inside the region i as t is varied in the range of interest.

In frequency domain, the source term located at $\mathbf{r}_s$ is described by the temporal function $\exp(i\omega t)$, where $\omega = 2\pi f$ is the pulsation and f is the frequency of modulation. The Green's function in the frequency domain is obtained by carrying out the Fourier transform of Eq. (2),

$$\tilde{R}_{fi}(\mathbf{r}_b, \omega, \mu_a + \Delta\mu_a) = \tilde{R}_{in}(\mathbf{r}_b, \omega, \mu_a) \times \sum_{k_1, k_2, \dots, k_N=0}^{\infty} (-1)^{k_1+k_2+\dots+k_N} \frac{(\Delta\mu_{a1})^{k_1} \dots (\Delta\mu_{aN})^{k_N}}{k_1! \dots k_N!} \times \langle l_1^{k_1} l_2^{k_2} \dots l_N^{k_N} \rangle(\mathbf{r}_b, \omega, \mu_a),$$

where $\tilde{R}_{in}(\mathbf{r}_b, \omega, \mu_a)$ and $\langle l_1^{k_1} l_2^{k_2} \dots l_N^{k_N} \rangle(\mathbf{r}_b, \omega, \mu_a)$ are defined as

$$\tilde{R}_{in}(\mathbf{r}_b, \omega, \mu_a) = FT[R_{in}(\mathbf{r}_b, t, \mu_a)](\omega), \quad (5)$$

$$\langle l_1^{k_1} l_2^{k_2} \dots l_N^{k_N} \rangle(\mathbf{r}_b, \omega, \mu_a) = \frac{FT[R_{in}(\mathbf{r}_b, t, \mu_a) \langle l_1^{k_1} l_2^{k_2} \dots l_N^{k_N} \rangle(\mathbf{r}_b, t, \mu_a)](\omega)}{\tilde{R}_{in}(\mathbf{r}_b, \omega, \mu_a)}. \quad (6)$$

Equation (6) can also be written as

$$\langle l_1^{k_1} l_2^{k_2} \dots l_N^{k_N} \rangle(\mathbf{r}_b, \omega, \mu_a) = \frac{[\tilde{R}_{in}(\mathbf{r}_b, \omega', \mu_a)] \otimes FT[\langle l_1^{k_1} l_2^{k_2} \dots l_N^{k_N} \rangle(\mathbf{r}_b, t, \mu_a)](\omega')(\omega)}{\tilde{R}_{in}(\mathbf{r}_b, \omega, \mu_a)}. \quad (7)$$

In Eqs. (5)–(7) “ FT ” and “ $\otimes$ ” denote the Fourier transform and the convolution, respectively. In frequency domain we are interested in the modulus and phase of the Green’s function which are usually defined as $AC_{in} = |\tilde{R}_{in}(\mathbf{r}_b, \omega, \mu_a)|$ and $\alpha_{in} = \arg[\tilde{R}_{in}(\mathbf{r}_b, \omega, \mu_a)]$, respectively. (AC refers to alternating current.) Note that the frequency-domain moments are complex numbers that depend on the pulsation ω [Eq. (6)]. Only the CW moments that are a particular case of the frequency-domain moments (for $\omega=0$) reduce to real positive numbers. For example, according to Eq. (6), the CW mean path length $\langle l_j \rangle$ ($k_j=1, k_j=0, j=i$) is obtained as the integral of the time-domain mean path length, $\langle l_j \rangle(t)$ weighted by the time-domain Green’s function. The integral is normalized to the CW attenuation per unit surface area (i.e., the integral of the time-domain Green’s function).

B. Derivation of the Moments in Time Domain

Up to this point the formulas derived are very general since they rely only on the microscopic Beer–Lambert law; therefore they do not provide any further insight on how to calculate the moments in a particular geometry. We proposed such a method in our previous work [29] by using a formal similarity between Eq. (2) [or Eq. (4)] and the solution of the perturbative DE expressed by the Neumann series. We derived general formulas for the moments based on the knowledge of the DE Green’s function in the initial state of the medium. Even though we focused mainly on the CW domain we provided a brief introduction to the formulas written in the previous section. We also provided formulas for the first and second order moments in both time and frequency domains. We start from this point and we describe the new developments of the method. In the following formulas the Green’s functions in the initial state of the medium are indicated with the subscript “0.”

1. First Order Moments—We start the description of our method applied to time domain by writing the time-domain mean path length in the region i as [29]

$$\begin{aligned} \langle l_i \rangle(\mathbf{r}_b, t) &= \frac{\int_{V_i} d\mathbf{r}_1 \int_0^\infty R_0(\mathbf{r}_b, \mathbf{r}_1, t-t_1) \varphi_0(\mathbf{r}_1, t_1) dt_1}{R_0(\mathbf{r}_b, t)} \\ &= \frac{\int_{V_i} [R_0(\mathbf{r}_b, \mathbf{r}_1, \tau) \otimes \varphi_0(\mathbf{r}_1, \tau)](t) d\mathbf{r}_1}{R_0(\mathbf{r}_b, t)}, \end{aligned} \quad (8)$$

where $\varphi_0(\mathbf{r}_1, t_1)$ is the Green’s function of the DE calculated in the point $\mathbf{r}_1$ at time t_1 when photons are emitted at $t=0$ from the point $\mathbf{r}_s$, $R_0(\mathbf{r}_b, \mathbf{r}_1, t-t_1)$ is the output flux calculated in the boundary point $\mathbf{r}_b$ at time t when photons are emitted from the point $\mathbf{r}_1$ at time t_1 , $R_0(\mathbf{r}_b, t)$ is the output flux calculated in the point $\mathbf{r}_b$ at time t when photons are emitted from the point $\mathbf{r}_s$ at $t=0$, and V_i is the volume of the region i . Note that the units of both φ_0 and R_0 are $L^{-2}t^{-1}$, which is expressed in this work in $\text{mm}^{-2} \text{ps}^{-1}$. In Eq. (8) and in the following expressions the dependence of the moments and the Green’s functions from the initial distribution of the absorption coefficient (μ_a) is implicit. If we assume that the size of the defect is much smaller than the distance between the point source and the defect and between the defect and the collection point, we have that $R_0(\mathbf{r}_b, \mathbf{r}_1, t-t_1) \approx R_0(\mathbf{r}_b, \mathbf{r}_f, t-t_1)$ and $\varphi_0(\mathbf{r}_1, t_1) \approx \varphi_0(\mathbf{r}_f, t_1)$, where $\mathbf{r}_f$ is an arbitrary fixed point inside the defect. Therefore from Eq. (8) we can derive the approximate formula

$$\langle l_i \rangle(\mathbf{r}_b, t) \approx \frac{V_i}{R_0(\mathbf{r}_b, t)} [R_0(\mathbf{r}_b, \mathbf{r}_i, \tau) \otimes \varphi_0(\mathbf{r}_i, \tau)](t). \quad (9)$$

2. Second Order Moments—There are two kinds of second order moments: the mixed moments which measure the interaction between two points at two distinct regions, and the self-moments which measure the interaction between two points within the same region. In other words we can say that the second order moments are proportional to the cumulative probability for a detected photon to visit two points belonging either to the same region or to different regions. For the mixed moment of regions i and j we have [29]

$$\langle l_i l_j \rangle(\mathbf{r}_b, t) = \frac{1}{R_0(\mathbf{r}_b, t)} \sum_{P(i,j)} \int_{V_i} d\mathbf{r}_1 \int_0^\infty R_0(\mathbf{r}_b, \mathbf{r}_1, t-t_1) dt_1 \times \int_{V_j} d\mathbf{r}_2 \int_0^\infty \varphi_0(\mathbf{r}_1, \mathbf{r}_2, t_1-t_2) \varphi_0(\mathbf{r}_2, t_2) dt_2$$

The number of terms in the series is the permutations of two indices $P(i,j)$ (two terms). If we make the same assumptions used for the derivation of Eq. (9) and we assume also that $\varphi_0(\mathbf{r}_1, \mathbf{r}_2, \tau) \approx \varphi_0(\mathbf{r}_i, \mathbf{r}_j, \tau)$, where $\mathbf{r}_i, \mathbf{r}_j$ are two arbitrary fixed points inside the regions i and j , respectively, we can rewrite Eq. (10) in the form

$$\langle l_i l_j \rangle(\mathbf{r}_b, t) \approx \frac{\sum_{P(i,j)} V_i V_j [R_0(\mathbf{r}_b, \mathbf{r}_i, \tau) \otimes \varphi_0(\mathbf{r}_i, \mathbf{r}_j, \tau) \otimes \varphi_0(\mathbf{r}_j, \tau)](t)}{R_0(\mathbf{r}_b, t)}, \quad i \neq j. \quad (11)$$

The self-moments are written as

$$\langle l_i^2 \rangle(\mathbf{r}_b, t) \approx \frac{2 \int_0^\infty R_0(\mathbf{r}_b, \mathbf{r}_i, t-t_1) dt_1 \int_{V_i} d\mathbf{r}_1 \int_{V_i} d\mathbf{r}_2 \int_0^\infty \varphi_0(\mathbf{r}_1, \mathbf{r}_2, t_1-t_2) \varphi_0(\mathbf{r}_i, t_2) dt_2}{R_0(\mathbf{r}_b, t)}, \quad (12)$$

where we have used the same assumption, as before, that $\mathbf{r}_i$ is an arbitrary fixed point within the region i . If we define $E_{0_int}(t)$ as

$$E_{0_int}(t) = \int_{V_i} d\mathbf{r}_1 \int_{V_i} d\mathbf{r}_2 \varphi_0(\mathbf{r}_1, \mathbf{r}_2, t), \quad (13)$$

we can rewrite Eq. (12) as

$$\begin{aligned} \langle l_i^2 \rangle(\mathbf{r}_b, t) &\approx \frac{2[R_0(\mathbf{r}_b, \mathbf{r}_i, \tau) \otimes [\varphi_0(\mathbf{r}_i, \tau) \otimes E_{0_int}(\tau)]](t)}{R_0(\mathbf{r}_b, t)} \\ &= \frac{2[R_0(\mathbf{r}_b, \tau) \langle l_i \rangle(\mathbf{r}_b, \tau) \otimes E_{0_int}(\tau)](t)}{V_i R_0(\mathbf{r}_b, t)}. \end{aligned} \quad (14)$$

In Eq. (14) we have used the commutative property of the convolution and the approximate formula found for the time-domain mean path length [Eq. (9)]. We note that Eq. (13) defines the energy in the volume V_i at time t due to photons emitted at time $t=0$ within the same volume. The key point of our method is to substitute the double integral in Eq. (13) with a heuristic formula of the kind

$$E_{0_int}(t) \approx \frac{k_1}{2} V_i \int_{V_i} \varphi_0(\mathbf{r}_i, \mathbf{r}, t) d\mathbf{r}, \quad (15)$$

where the parameter k_1 (to be determined) depends on the choice of the fixed point $\mathbf{r}_i$ within the volume V_i . Therefore Eq. (14) can be rewritten as

$$\langle l_i^2 \rangle(\mathbf{r}_b, t) \approx \frac{k_1 \left\{ [R_0(\mathbf{r}_b, \tau) \langle l_i \rangle(\mathbf{r}_b, \tau)] \otimes \int_{V_i} \varphi_0(\mathbf{r}_i, \mathbf{r}, \tau) d\mathbf{r} \right\} (t)}{R_0(\mathbf{r}_b, t)}. \quad (16)$$

By using an approximation similar to Eq. (15) in the CW domain [29,30] we found a parameter c_1 in the expression of $\langle l_i^2 \rangle$ that was quasi-constant regardless of the conditions of the problem; however this was possible only if we used the Green's function of an improved DE in the integral defining the second order moment [29]. The CW solution of the improved DE proposed in [33] has shown excellent comparison up to an albedo $a=0.5$ with the solution of the RTE for isotropic scattering. In this work we have used as the integrand of Eqs. (15) and (16) the time-domain solution of the RTE for the infinite medium geometry and isotropic scattering proposed by Paasschens [34],

$$\varphi_0(r, t) = v \frac{\exp[-vt(\mu_s + \mu_a)]}{4\pi r^2} \delta(r - vt) + v \frac{(1 - r^2/v^2 t^2)^{1/8} \exp[-vt(\mu_s + \mu_a)]}{(4\pi vt/3\mu_s)^{3/2}} \times G[vt\mu_s(1 - r^2/v^2 t^2)^{3/4}] \Theta(vt - r) \quad (17)$$

$$G(x) \approx \exp(x) \sqrt{1 + 2.026/x},$$

where $\Theta(vt - r)$ is the step function. Equation (17) was used as the integrand in Eqs. (15) and (16) with $r = |\mathbf{r} - \mathbf{r}_i|$, and since we have considered spherical regions we have chosen $\mathbf{r}_i$ at their centers. We note that for the correct calculation of the integral in Eqs. (15) and (16) we must consider also the contribution of the ballistic term in Eq. (17). The reason why it is better to use some available solutions of the RTE instead of the DE for the calculation of self-moments is because the DE breaks down at short distances ($1-3$ mm) between the source and field point.

3. Third and Higher Order Moments—There are three different kinds of third order moments that measure the interaction between triplets of points: (a) each point belongs to a different region, (b) two points belong to the same region and the third point to a different region, and (c) three points belong to the same region. In case (a), by making the same assumptions used for the derivation of Eq. (11) we can find the formula

$$\langle l_i l_j l_k \rangle(\mathbf{r}_b, t) = \frac{1}{R_0(\mathbf{r}_b, t)} \sum_{P(i,j,k)} V_i V_j V_k [R_0(\mathbf{r}_b, \mathbf{r}_i, \tau) \otimes \varphi_0(\mathbf{r}_i, \mathbf{r}_j, \tau) \otimes \varphi_0(\mathbf{r}_j, \mathbf{r}_k, \tau) \otimes \varphi_0(\mathbf{r}_k, \tau)](t), \quad i \neq j \neq k,$$

where $\mathbf{r}_i, \mathbf{r}_j, \mathbf{r}_k$ are three fixed points within the three regions i, j, k . The number of terms in the series is the permutations of three indices (six terms). In case (b), the derivation of the formula (which is omitted) follows arguments similar to those used for the derivation of the analogous formula in the CW domain [29]. Both formulas are reported in Appendix A of this work. In case (c) after carrying forward the calculations we get the formula

$$\langle l_i^3 \rangle(\mathbf{r}_b, t) \approx \frac{3!}{V_i R_0(\mathbf{r}_b, t)} [\langle l_i \rangle(\mathbf{r}_b, \tau) R_0(\mathbf{r}_b, \tau)] \otimes \left\{ \int_{V_i} d\mathbf{r}_2 \left[\int_{V_i} \varphi_0(\mathbf{r}_1, \mathbf{r}_2, \tau) d\mathbf{r}_1 \right] \otimes \left[\int_{V_i} \varphi_0(\mathbf{r}_2, \mathbf{r}_3, \tau) d\mathbf{r}_3 \right] \right\} (t),$$

where we have used the same assumptions that led us to Eq. (9). In this case, the approximation we are looking for is

$$\left\{ \int_{V_i} d\mathbf{r}_2 \left[\int_{V_i} \varphi_0(\mathbf{r}_1, \mathbf{r}_2, \tau) d\mathbf{r}_1 \right] \otimes \left[\int_{V_i} \varphi_0(\mathbf{r}_2, \mathbf{r}_3, \tau) d\mathbf{r}_3 \right] \right\} (t) \approx \frac{k_2 V_i}{3!} \left[\int_{V_i} \varphi_0(\mathbf{r}_i, \mathbf{r}_1, \tau) d\mathbf{r}_1 \right] \otimes \left[\int_{V_i} \varphi_0(\mathbf{r}_i, \mathbf{r}_2, \tau) d\mathbf{r}_2 \right] (t),$$

where k_2 is a parameter to be determined that depends on the choice of the fixed point $\mathbf{r}_i$ inside the volume V_i . We note also that in the right hand side of Eq. (20) we changed the order of the variable arguments of φ_0 . Therefore we can rewrite Eq. (19) as

$$\langle l_i^3 \rangle(\mathbf{r}_b, t) \approx \frac{k_2 \left\{ [R_0(\mathbf{r}_b, \tau) \langle l_i \rangle(\mathbf{r}_b, \tau)] \otimes \left[\int_{V_i} \varphi_0(\mathbf{r}_i, \mathbf{r}_1, \tau) d\mathbf{r}_1 \otimes \int_{V_i} \varphi_0(\mathbf{r}_i, \mathbf{r}_2, \tau) d\mathbf{r}_2 \right] \right\} (t)}{R_0(\mathbf{r}_b, t)}. \quad (21)$$

The fourth order moments are characterized by five different kinds of moments according to the location of the interacting points in a quadruplet. The derivation of these moments is rather lengthy and is omitted, but the expression of the moments is reported in Appendix A. Last, we want to spend a few words about the higher order self-moments since the major properties of photon migration in turbid media can be described in terms of such self-moments. Based on Eqs. (16) and (21) we propose the following formula:

$$\langle l_i^n \rangle(\mathbf{r}_b, t) \approx \frac{k_{n-1}}{R_0(\mathbf{r}_b, t)} \left\{ [R_0(\mathbf{r}_b, \tau) \langle l_i \rangle(\mathbf{r}_b, \tau)] \otimes_{j=1}^{n-1} \int_{V_i} \varphi_0(\mathbf{r}_i, \mathbf{r}, \tau) d\mathbf{r} \right\} (t), \quad 2 \leq n, \quad (22)$$

where the parameters k_{n-1} have to be determined. The physical insight that Eq. (22) suggests is that the higher order moments are broken into the convolution of two functions: the first one, $R_0(\mathbf{r}_b, \tau) \langle l_i \rangle(\mathbf{r}_b, \tau)$, depends on the global properties of the medium probed by detected photons; the second function, given by the convolution of the same integral $n-2$ times with itself, depends more on the local optical properties at the site of the region i . Therefore, in many situations we can guess that a proper solution in the infinite medium geometry having the local optical properties at the site of the region i could be used for the calculation of the integral in Eq. (22). This observation has been fruitful in the CW domain where we have shown the potential of this method also when the initial medium is not homogeneous [32].

C. Derivation of the Moments in Frequency Domain

Once the time-domain moments are calculated, we can use Eq. (6) for the calculations of the moments in the frequency domain. The frequency-domain mean path length and the higher order mixed moments where each point belongs to a different region are easily derived. For example, if we apply the definition of frequency-domain moments [Eq. (6)] to the expression of the time-domain mean path length [Eq. (9)], we obtain

$$\langle l_i \rangle(\mathbf{r}_b, \omega) = \frac{\tilde{R}_0(\mathbf{r}_b, \mathbf{r}_i, \omega) \tilde{\varphi}_0(\mathbf{r}_i, \omega) V_i}{\tilde{R}_0(\mathbf{r}_b, \omega)}, \quad (23)$$

where the functions on the right hand side are the Fourier transforms of the functions on the right hand side of Eq. (9). The expressions of the second and third order mixed moments are derived by applying Eq. (6) to Eqs. (11) and (18), respectively. For example, the third order mixed moment is given by the expression

$$\langle l_i l_j l_k \rangle(\mathbf{r}_b, \omega) = \frac{\sum_{P(i,j,k)} \tilde{R}_0(\mathbf{r}_b, \mathbf{r}_i, \omega) \tilde{\varphi}_0(\mathbf{r}_i, \mathbf{r}_j, \omega) \tilde{\varphi}_0(\mathbf{r}_j, \mathbf{r}_k, \omega) \tilde{\varphi}_0(\mathbf{r}_k, \omega) V_i V_j V_k}{\tilde{R}_0(\mathbf{r}_b, \omega)}, \quad i \neq j \neq k, \quad (24)$$

where the functions on the right hand side are the Fourier transforms of the function on the right hand side of Eq. (18). The derivations of higher order mixed moments relative to the interaction of two or more points belonging to the same region and at least one point belonging to a different region are more cumbersome and are omitted; however these moments are reported in Appendix A. Here we want instead to provide and discuss the expression of the self-moments, obtained by applying Eq. (6) to Eq. (22),

$$\langle l_i^n \rangle(\mathbf{r}_b, \omega) = k_{n-1} \langle l_i \rangle(\mathbf{r}_b, \omega) \left(\int_{V_i} \tilde{\varphi}_0(\mathbf{r}_i, \mathbf{r}, \omega) d\mathbf{r} \right)^{n-1}, \quad 2 \leq n. \quad (25)$$

This formula is obtained by using the convolution theorem of the Fourier transform. Since the CW domain is a particular case of frequency domain ($\omega=0$), and Eq. (25) resembles the expression of the CW higher order self-moments [29], we postulate that the parameters k_{n-1} are the same parameters c_{n-1} found in the CW case. This is really the case, as it will be shown in the results section, but only if we use the Fourier transform of Eq. (17) as the integrand in Eq. (25).

D. Method of Padé Approximants

The method of Padé approximants [35] is rather straightforward: given a function of one variable, $\Delta\mu_a$, let us consider its Taylor expansion up to a certain order, say n ; the polynomial function of order n represents a good approximation of the original function up to a certain threshold value $\Delta\mu_{a,\max}$, at which the discrepancy with the original function is smaller than a fixed amount. Is it possible to find a rational function of $\Delta\mu_a$ which uses the same information contained in the Taylor coefficients and that agrees with the original function for values $\Delta\mu_a > \Delta\mu_{a,\max}$ up to a new larger threshold value? This function exists and the purpose of the Padé approximants is to calculate its coefficients [35]. We have already applied this method in the CW domain [32] with excellent results. Here we state the problem in the time domain for the cases of a single defect and two defects. For a single defect we can rewrite Eq. (2) as

$$\frac{\Delta R(t, \Delta\mu_a)}{R_0(t)} \approx -\langle l_i \rangle(t) \Delta\mu_a + \frac{1}{2!} \langle l_i^2 \rangle(t) \Delta\mu_a^2 - \frac{1}{3!} \langle l_i^3 \rangle(t) \Delta\mu_a^3 + \frac{1}{4!} \langle l_i^4 \rangle(t) \Delta\mu_a^4, \quad (26)$$

where the time-domain moments are the coefficients of Taylor expansion and $\Delta\mu_a$ is the variable of the series expansion. The left hand side of Eq. (26) is the relative change in the time-domain Green's function [see Eq. (2)],

$$\frac{\Delta R(t, \Delta\mu_a)}{R_0(t)} = \frac{R_{fi}(\mathbf{r}_b, t, \mu_a + \Delta\mu_a) - R_{in}(\mathbf{r}_b, t, \mu_a)}{R_{in}(\mathbf{r}_b, t, \mu_a)}. \quad (27)$$

On the left hand side of Eq. (27), we have considered the point of collection ($\mathbf{r}_b$) and the initial distribution of the absorption coefficient as implicit parameters. The rational function which approximates the left hand side of Eq. (26) is defined as

$$\frac{\Delta R(t, \Delta \mu_a)}{R_0(t)} \approx P_{M'/N'}(t, \Delta \mu_a) = \frac{\sum_{k=0}^{M'} a_k(t) \Delta \mu_a^k}{1 + \sum_{j=1}^{N'} b_j(t) \Delta \mu_a^j}. \quad (28)$$

For our results we used $M' = N' = 2$, because only five co-efficients can be derived from Eq. (26) (the first being zero). The coefficients $a_k(t)$ and $b_j(t)$ are calculated by imposing that the values of $P_{M'/N'}(t, \Delta \mu_a)$ and its first $M' + N'$ derivatives calculated at $\Delta \mu_a = 0$ coincide with those of Eq. (26) at each time t . For the case of two defects characterized by the same absorption contrast $\Delta \mu_a$, we have to rewrite Eq. (26) into

$$\begin{aligned} \frac{\Delta R(t, \Delta \mu_a)}{R_0(t)} \approx & -[\langle l_1 \rangle + \langle l_2 \rangle](t) \Delta \mu_a + \frac{1}{2!} [\langle l_1^2 \rangle + \langle l_2^2 \rangle + 2\langle l_1 l_2 \rangle] \\ & \times (t) \Delta \mu_a^2 - \frac{1}{3!} [\langle l_1^3 \rangle + \langle l_2^3 \rangle + 3\langle l_1^2 l_2 \rangle + 3\langle l_2^2 l_1 \rangle] \\ & \times (t) \Delta \mu_a^3 + \frac{1}{4!} [\langle l_1^4 \rangle + \langle l_2^4 \rangle + 4\langle l_1^3 l_2 \rangle + 4\langle l_2^3 l_1 \rangle \\ & + 6\langle l_1^2 l_2^2 \rangle](t) \Delta \mu_a^4, \end{aligned} \quad (29)$$

where the subscripts “1” and “2” define the regions where the absorption contrast is considered. In general, the method of Padé approximants can be applied when the medium contains an arbitrary number of defects, as long as the absorption contrasts between the defects and the background medium are equal. Note that the fourth order perturbation theory does not have this restriction and independent absorption contrasts can be considered. In the frequency domain, we can also apply Eqs. (26)–(29) with the only substitution of the Green’s functions on the left hand side and the appropriate moments $\langle l_i^k \rangle(\omega)$ on the right hand side of the equations. The relative change in AC and the absolute change in phase with respect to the values calculated in the initial state of the medium are obtained by the formulas

$$\begin{aligned} \frac{\Delta AC(\omega)}{AC_0(\omega)} &= \frac{|\tilde{R}_{fi}(\mathbf{r}_b, \omega, \mu_a + \Delta \mu_a)| - |\tilde{R}_{in}(\mathbf{r}_b, \omega, \mu_a)|}{|\tilde{R}_{in}(\mathbf{r}_b, \omega, \mu_a)|}, \\ \Delta \alpha &= \arg[\tilde{R}_{fi}(\mathbf{r}_b, \omega, \mu_a + \Delta \mu_a)] - \arg[\tilde{R}_{in}(\mathbf{r}_b, \omega, \mu_a)]. \end{aligned} \quad (30)$$

In the time domain, we used the method of Padé approximants to study the change in the reflectance of the medium as a function of time, for a fixed absorption contrast, while in the frequency domain we studied the changes in AC and phase as functions of the absorption contrast.

E. Monte Carlo Method

The Monte Carlo method is explained in our previous work [30]. For the results presented in this work we consider only spherical inclusions of different sizes and placed at different positions inside the medium. We calculated the time-domain reflectance and the moments from a statistics of about 30,000–100,000 detected photons. The time range of interest of the Green’s function (3–5 ns) was divided into 300 temporal ranges centered at t_k ($k=1, \dots, 300$) and having a width of $\Delta t \approx 10$ –20 ps. The photons were collected 2–4 cm away from the source point by considering square elements with sides in the range 3–5 mm and placed at the boundary of the medium. The time-domain reflectance (TPSF) for an arbitrary distribution of the absorption coefficients in the N regions which divide the medium was calculated by the formula

$$R_{fi}(t_k) = \frac{\sum_{j=1}^{m_k} \exp(-\mu_{a1}l_{1j} - \mu_{a2}l_{2j} - \dots - \mu_{aN}l_{Nj})}{N_{ph}\Delta t\Delta S}, \quad (31)$$

where m_k is the number of detected photons in the temporal window centered at $t=t_k$, and $l_{ij} = vt_{ij}$ ($i=1,2, \dots, N; j=1,2, \dots, m_k$) is the path length spent by the j th detected photon in the region i ; the constraint on the partial times of flight is $\sum_{i=1}^N t_{ij}=t_k$. The denominator of Eq. (31) is used for the correct normalization of the reflectance, where N_{ph} is the total number of injected photons, while Δt and ΔS are the width of a temporal window and the area of the detector, respectively. The mixed moments of order $(k_1, k_2, \dots, k_N)$ are calculated by the formula

$$\langle l_1^{k_1} l_2^{k_2} \dots l_N^{k_N} \rangle(t_k) = \frac{\sum_{j=1}^{m_k} l_{1j}^{k_1} l_{2j}^{k_2} \dots l_{Nj}^{k_N} \exp(-\mu_{a1}l_{1j} - \mu_{a2}l_{2j} - \dots - \mu_{aN}l_{Nj})}{\sum_{j=1}^{m_k} \exp(-\mu_{a1}l_{1j} - \mu_{a2}l_{2j} - \dots - \mu_{aN}l_{Nj})}. \quad (32)$$

Finally the frequency-domain reflectance was calculated by the formula

$$\tilde{R}_{fi}(\omega) = \frac{\sum_{k=1}^{300} \left[\sum_{j=1}^{m_k} \exp(-\mu_{a1}l_{1j} - \mu_{a2}l_{2j} - \dots - \mu_{aN}l_{Nj}) \right] \exp(-i\omega t_k)}{N_{ph}\Delta S}, \quad (33)$$

where the symbols have the same meaning as those of Eq. (31) with the function in the right hand side being the Fourier transform of the time-domain reflectance. All the Monte Carlo simulations were run for the isotropic scattering case; we remind that when diffusion conditions are fulfilled the details of the single scattering event are not important, and similar results are obtained by choosing different phase functions.

3. RESULTS

In this section we show the results of the proposed theory in the slab and semi-infinite geometries. Besides Eq. (17) and its Fourier transform that were used for the calculation of the self-moments, the Green's functions of the DE for semi-infinite [30] and slab [36] geometries with extrapolated boundary conditions were used for the calculation of the mixed moments. The output flux was calculated by Fick's law [36]. We considered two values of the reduced scattering coefficient (μ'_s) of the background medium, respectively, in the low and high ranges commonly found in near infrared spectroscopy and diffuse optical tomography.

A. Time-Domain Results

In the following two subsections, we show one case study for the parameters k_n and for the mixed moments, respectively. Afterward, in the next four sections we show the results concerning perturbations due to single or multiple spherical defects embedded in the media.

1. Study on the Parameters k_{n-1} —The purpose of this subsection is to provide some evidence that the parameters k_{n-1} ($n=2,3,4$) of Eq. (22) are quasi-constant and that they correspond to the same parameters c_{n-1} found in the CW case. Since this result is built upon theoretical arguments (as discussed in the theory section) we will provide only one example in the semi-infinite and slab geometries. Equation (22) was used to derive the expression of k_{n-1} as

$$\frac{\langle l_i^n \rangle_{\text{MC}}(\mathbf{r}_b, t)}{\frac{1}{R_0(\mathbf{r}_b, t)} \left\{ [R_0(\mathbf{r}_b, \tau) \langle l_i \rangle_{\text{MC}}(\mathbf{r}_b, \tau)]^{\otimes n-1} \int_{V_i} \varphi_0(\mathbf{r}_i, \mathbf{r}, \tau) d\mathbf{r} \right\}(t)} \approx k_{n-1}, \quad 2 \leq n. \quad (34)$$

The higher order self-moments and mean path lengths were calculated with the Monte Carlo method [therefore they are identified by the subscript “MC” in Eq. (34)]. We observe that $\langle l_i \rangle(\mathbf{r}_b, t)$ can be calculated also with the Green’s function of the medium investigated. If the parameters k_{n-1} are quasi-constant they should be independent of time, of the region location, of its volume, and of the optical properties of the background medium. In Fig. 1 we show the calculation of the parameters k_{n-1} for the semi-infinite and slab geometries. We considered two spherical regions in each medium in the positions shown in the schematic on top of the figure. We used moving average filters of 50 and 100 ps in the semi-infinite and slab geometries, respectively, for smoothing out the curves k_{n-1} . Figure 1 shows that the parameters are rather stable and their fluctuations reflect only the statistical fluctuations of detected photons in each temporal window. The presence of the spikes is due to a few outlier photons that traveled unusual long paths inside the regions in some temporal windows. As we already observed [32], these photons will affect increasingly the higher order moments. Therefore the graphs of k_2 and k_3 show the same spikes, although amplified, found in the graph of k_1 . The particular case histories of these outlier photons determine also the relationships between the spikes at different times. For example, in the semi-infinite geometry (case $r=2$ mm) there are two spikes in the range (2300, 2800) ps that are barely visible in the graph of k_1 [Fig. 1(a)], but they become increasingly higher in the graphs of k_2 [Fig. 1(c)] and k_3 [Fig. 1(e)]. We observe also that while the earlier spike is higher in k_1 , the opposite is true for k_3 . The reason of this behavior can be explained if we assume that in the late window fewer photons were detected than in the earlier window but traveling longer paths in the sphere. The three large spikes found in the slab geometry in the range (3000, 4000) ps [case $r=2$ mm; Figs. 1(b), 1(d), and 1(f)] are due to a few outlier photons that traveled unusual long paths through the region. The scarcity of photons detected in this temporal range determined a wide variance of the path lengths, which affected increasingly the higher order moments. We also note that, for this case, the probability to detect a photon in this late temporal range is larger in the slab geometry than in the semi-infinite geometry; however the time-domain mean path lengths in the spherical regions are larger in the semi-infinite than in the slab geometry (results not shown). As predicted by theoretical arguments the average value of the parameters k_{n-1} falls within the range of the values found in CW [30]. Therefore, in the following results, we will use the knowledge of these parameters and we will apply Eq. (22) and the equations in Appendix A to derive the higher order moments. In particular we have used the values of $k_1=1.54$, $k_2=3.4$, $k_3=10$.

2. One Case Study on the Time-Domain Mixed Moments—In this section we show some comparisons between Monte Carlo and theoretical results for the calculation of higher order mixed moments reported in Appendix A. In the slab geometry with background properties $\mu_a=0.005 \text{ mm}^{-1}$, $\mu'_s=0.5 \text{ mm}^{-1}$, we considered the interaction of two spherical regions (with radius of $r=5$ mm) embedded in the medium. A schematic of the medium and the spherical regions is shown on top of Fig. 2. The comparison of the moments $\langle l_1 l_2 \rangle(t)$

[Fig. 2(a)], $\langle l_1^2 l_2 \rangle(t)$ [Fig. 2(b)], $\langle l_1^2 l_2^2 \rangle(t)$ [Fig. 2(c)], and $\langle l_1^3 l_2 \rangle(t)$ [Fig. 2(d)] is excellent in all the time range. These results show directly that the mixed moments are computed correctly by our theory.

3. Slab Geometry—In Fig. 3, we show the changes in reflectance $\Delta R/R_0$ for the geometry of the medium and positions of the defects shown in Fig. 2. Figures 3(a)–3(c) refer to the perturbation due to only sphere 2, only sphere 1, and both spheres, respectively. The absorption contrast in these cases is $\Delta\mu_a=0.055 \text{ mm}^{-1}$. In Fig. 3(d) both spherical defects are present in the medium but the absorption contrast is $\Delta\mu_a=0.025 \text{ mm}^{-1}$. We can see a qualitatively different effect due to regions 1 and 2: the effect of the former is an almost linear decrease in intensity starting from the ballistic time [Fig. 3(b)]. On the contrary, whenever region 2 is present the plots show a sharp decrease in intensity in the first 200 ps with a recovery at a later time [see especially Fig. 3(a)]. The results also show, as expected, that increasing orders of perturbation theory yield a better match with Monte Carlo results, but eventually divert from them. For lower values of the absorption contrast [Fig. 3(d)] also fourth order theory yields good agreement with Monte Carlo results in the whole temporal range. However, only the method of Padé approximants shows an excellent match with Monte Carlo results all throughout the temporal range of interest in all the cases considered.

In Fig. 4, we show the results in the same geometry of Fig. 2, but for a background medium having $\mu'_s=1.5 \text{ mm}^{-1}$ and $\mu_a=0.01 \text{ mm}^{-1}$. Plotted in Figs. 4(a) and 4(b) are the curves due to the perturbation of the sole spherical defect 1 having absorption contrasts of $\Delta\mu_a=0.02 \text{ mm}^{-1}$ and $\Delta\mu_a=0.06 \text{ mm}^{-1}$, respectively. For these two cases we calculated the time-domain mean path lengths by using the Green's function of the slab geometry. Plotted in Figs. 4(c) and 4(d) are the curves due to the effect of the sole defect 2 and both defects, respectively, for an absorption contrast of $\Delta\mu_a=0.06 \text{ mm}^{-1}$. For this case we calculated the higher order self-moments using Eq. (22) and the time-domain mean path lengths calculated by Monte Carlo. In the last three cases, fourth order theory performs poorly at times longer than around 1000 ps. Also, the wide noise seen in the plots of Figs. 4(c) and 4(d) in the time range (700, 1000) ps and at earlier times (not shown) is due to the scarcity of detected photons. However, it is remarkable that fourth order theory provided the correct coefficients for the method of Padé approximants, which shows an excellent comparison with Monte Carlo results.

4. Semi-infinite Geometry—In Fig. 5 we show the changes in the time-domain reflectance $\Delta R/R_0$ for the geometry of the medium and positions of the defects indicated in the schematic on top of the figure. Figures 5(a)–5(c) refer to the perturbation due to the sole sphere 1, the sole sphere 2, and the sole sphere 3, respectively. Considered in Fig. 5(d) is the effect of both spheres 2 and 3. The absorption contrasts are $\Delta\mu_a=0.11 \text{ mm}^{-1}$ for Fig. 5(a) and $\Delta\mu_a=0.06 \text{ mm}^{-1}$ for Figs. 5(b)–5(d). In Fig. 6, we show the changes in time-domain reflectance $\Delta R/R_0$ for the same geometry of Fig. 5 but for different background optical properties $\mu'_s=1.5 \text{ mm}^{-1}$, $\mu_a=0.01 \text{ mm}^{-1}$. Plotted in Figs. 6(a)–6(c) are the curves due to the sole sphere 2, the sole sphere 3, and both spheres 2 and 3, respectively, with $\Delta\mu_a=0.05 \text{ mm}^{-1}$. Even for this geometry we can draw the same conclusions as those relative to the slab geometry: increasing perturbation orders show progressively better agreement with Monte Carlo results for wider temporal ranges. However due to the intrinsic limitation of fourth order theory, eventually the perturbation curves depart from the Monte Carlo curves. Only the Padé approximants method show excellent agreement with Monte Carlo results all throughout the temporal range. We notice in Fig. 6(b) one spike followed by one throat in the Padé approximant curve. This happens in correspondence with one pole of Eq. (28), as discussed in our previous work [32]. The occurrence of poles in the rational function does not compromise the overall excellent agreement with the Monte Carlo curves.

5. Are the Mixed Moments Important?—One important aspect of the theory of the moments that is worth understanding is the relevance of the mixed moments' contribution to the total perturbation due to n defects. When we divide a medium into n regions where absorbing perturbations are located, the numbers of second, third, and fourth order mixed moments are on the order of n^2 , n^3 , and n^4 , respectively, while the number of higher order self-moments is on the order of n . Therefore the computational effort of our proposed forward problem solver would be much lighter if we could avoid the calculation of the mixed moments. With the results presented in this subsection, we support the idea that this can really be the case. We remind that a similar result was found also in the CW domain [30]. In Figs. 7(a) and 7(b) we compared the plots of fourth order theory [Eq. (29)] shown in Figs. 3(d) and 5(d), respectively, both calculated for $\Delta\mu_a=0.025 \text{ mm}^{-1}$, with the plots obtained by using the self-moments alone, according to the formula

$$\frac{\Delta R(t, \Delta\mu_a)}{R_0(t)} \approx -[\langle l_1 \rangle + \langle l_2 \rangle](t)\Delta\mu_a + \frac{1}{2!}[\langle l_1^2 \rangle + \langle l_2^2 \rangle](t)\Delta\mu_a^2 - \frac{1}{3!}[\langle l_1^3 \rangle + \langle l_2^3 \rangle](t)\Delta\mu_a^3 + \frac{1}{4!}[\langle l_1^4 \rangle + \langle l_2^4 \rangle](t)\Delta\mu_a^4.$$

As we can see from Figs. 7(a) and 7(b) the exact calculations show just a small improvement with respect to the plots derived by the self-moments alone. Since the defects are rather close to each other we can reasonably argue that the mixed moments of more distant defects would be negligible. These results give some indications that at least for a certain range of absorption contrasts we can use a simplified theory where only the self-moments are computed for describing the effects of multiple defects beyond first order theory.

6. Results for an Initial Heterogeneous Medium—In this subsection we show the potential of the developed theory for the case when the initial state of the medium (as defined in Subsection 2.A) is not homogeneous. We already found interesting results in the CW domain [31,32] and here we want to support the idea that also in the time domain (therefore also in the frequency domain) we can use some simplifications in order to describe more complex situations. The schematic shown in Fig. 8 represents the initial distribution of the optical properties in the slab geometry, comprising three spherical regions with different optical properties. The spherical region 2 (having radius of $r=7.5 \text{ mm}$, $\mu_a=0.01 \text{ mm}^{-1}$, and $\mu'_s=1 \text{ mm}^{-1}$) includes region 3 (having $r=5 \text{ mm}$ and the same optical properties of sphere 2) where an absorbing perturbation is considered. The spherical region 2 is considered as the “local” background of region 3, in contrast with the general background, having optical properties $\mu_{ab}=0.005 \text{ mm}^{-1}$, $\mu'_{sb}=0.5 \text{ mm}^{-1}$. The medium includes also a spherical region 1 with $\mu'_s=0.5 \text{ mm}^{-1}$ and $\mu_a=0.1 \text{ mm}^{-1}$. We applied Eq. (22) for the calculation of the higher order self-moments by using $\langle l_i \rangle(t)$ calculated with the Monte Carlo method and the Green's function given in Eq. (17) for the calculation of the integral. We carried out the calculation of the integral for two different sets of optical properties: those of the local background and those of the general background. We note that the correct function to be used as the integrand of Eq. (22) is the Green's function of the slab geometry relative to the initial distribution of the optical properties and for a source point located at the center of region 3. The physical insight our theory suggests is that the most relevant contribution to the calculation of the integral derives from the local background. This does not mean that region 1, the general background, and the boundary of the medium do not have an effect in the calculation of the perturbation, but this effect is mostly contained in $\langle l_i \rangle(t)$ and $R_0(\mathbf{r}_b, t)$ but not in the integral. Figures 8(a) and 8(b) show five plots that are compared with Monte Carlo curves: those relative to the four orders of perturbation theory [calculated with Eq. (26) truncated accordingly or not] and those relative to the Padé method. In Figs. 8(a) and 8(b) the calculations were carried out by using the optical properties of the local and general backgrounds, respectively. The effect of the perturbation

is calculated when the absorption coefficient of region 3 is $\mu_a = 0.07 \text{ mm}^{-1}$; therefore the absorption contrasts to be considered are $\Delta\mu_a = 0.06 \text{ mm}^{-1}$ for the local background and $\Delta\mu_a = 0.065 \text{ mm}^{-1}$ for the general background. We note that the four orders of approximations seem to agree better with Monte Carlo plots in Fig. 8(b) than in Fig. 8(a). However a closer look to these plots reveals that there is an initial time range where this is not the case and the four orders of approximations in Fig. 8(a) show a better match than those of Fig. 8(b) with Monte Carlo plots. This result is in the logic of the Taylor expansion of a function. A clear indication that the coefficients of the Taylor expansion are better calculated by using the optical properties of the local background is shown by the trend of Padé approximants, which agrees better with Monte Carlo plot when the moments are calculated with the optical properties of the local background [Fig. 8(c)]. The little difference between the two sets of results is explained by the slight difference in the calculation of the integral in Eq. (22) as shown in Fig. 8(d).

B. Frequency-Domain Results

In the following subsections we show the frequency-domain results in the media already studied in the time domain. The modulation frequency of the pointlike source was fixed at $f = 100 \text{ MHz}$ for all the cases considered. We used Eq. (6) for the calculation of the frequency-domain mixed moments and Eq. (25) for the calculation of the self-moments. In the figures the changes in AC and phase values are plotted against the absorption contrast between defect(s) and the background medium, in a range of values typically found in near infrared spectroscopy.

1. Slab Geometry—In Fig. 9, we show the results relative to the medium in the schematic of Fig. 2. Plotted in the left (right) panels are the changes in the AC intensity $\Delta AC/AC_0$ (changes in phase $\Delta\alpha$) for the cases when region 1 alone, region 2 alone, and both regions are present in the medium as shown in Figs. 9(a), 9(c), and 9(e) [Figs. 9(b), 9(d), and 9(f)], respectively, against the absorption contrast. Increasing perturbation orders show better agreement with Monte Carlo results for larger absorption contrasts, as it is expected. However only the Padé method shows excellent comparison with Monte Carlo: for a contrast of $\Delta\mu_a = 0.2 \text{ mm}^{-1}$, the discrepancy of $\Delta AC/AC_0$ is less than 3%, while the discrepancy of phase $\Delta\alpha$ is less than 0.6° . In Fig. 10 the same medium of Fig. 2 is studied when the optical properties of the background medium are $\mu_a = 0.01 \text{ mm}^{-1}$, $\mu'_s = 1.5 \text{ mm}^{-1}$. Similar results are found also for this case: the discrepancy between the Padé and Monte Carlo methods for $\Delta AC/AC_0$ is less than 8.5% for $\Delta\mu_a = 0.2 \text{ mm}^{-1}$. The discrepancy of $\Delta\alpha$ is to within 0.7° , for $\Delta\mu_a = 0.2 \text{ mm}^{-1}$ when region 1 alone is present in the medium, but it becomes larger whenever region 2 is present in the medium. In particular the discrepancies are less than 2° and 4° , for $\Delta\mu_a = 0.1 \text{ mm}^{-1}$ when region 2 alone and both regions are present in the medium, respectively [Figs. 10(d) and 10(f)]. We remind that phase data are proportional to the CW mean time of flight; therefore the discrepancy between phase data reflects different temporal shifts of the time-domain reflectance. Even if the phase discrepancies in Figs. 10(d) and 10(f) are larger than the noise level ($\Delta\alpha = 0.2^\circ$), these results show once again the advantage of using the Padé method over fourth order perturbation theory.

2. Semi-infinite Geometry—Plotted in Fig. 11 are the changes in AC and phase relative to the medium in the schematic of Fig. 5, when in the medium region 1 is present alone [Figs. 11(a) and 11(b)], region 2 alone [Figs. 11(c) and 11(d)], region 3 alone [Figs. 11(e) and 11(f)], and both regions 2 and 3 [Figs. 11(g) and 11(h)]. The parameters $\Delta AC/AC$ and $\Delta\alpha$ are presented on the left and right panels, respectively. The different orders of perturbation theory show the typical behavior already found in our previous results. The method of Padé approximants shows excellent comparisons with Monte Carlo results for all

the cases considered: the discrepancy between the two methods of calculations is less than 4% for $\Delta AC/AC$ and less than 0.2° for $\Delta\alpha$ up to an absorption contrast of $\Delta\mu_a=0.2\text{ mm}^{-1}$. In Fig. 12, we show the results relative to the same medium of Fig. 5 but with different optical properties of the background medium, namely, $\mu_a=0.01\text{ mm}^{-1}$, $\mu'_s=1.5\text{ mm}^{-1}$. Plotted in the left and right panels are the curves of $\Delta AC/AC$ and $\Delta\alpha$, respectively, including the four orders of approximation of perturbation theory, the Monte Carlo, and the Padé approximants' results. Even for this case the results of perturbation theory and Padé approximants show the same trends of previous results. The discrepancies between Padé calculations and Monte Carlo results are less than 13% for $\Delta AC/AC$ and less than 0.6° for $\Delta\alpha$ for $\Delta\mu_a\ 0.2\text{ mm}^{-1}$.

4. DISCUSSION AND CONCLUSION

The results obtained in this work confirm that our proposed theory can be effectively used as a fast forward problem solver for inhomogeneous media in all those situations whenever the Green's function of the background medium is available. We note that despite the existence of sophisticated computational methods, simple models are still used for studying light propagation in tissue. For example, in the detection and characterization of breast cancer, the tumor has been modeled as a spherical defect embedded in a homogeneous slab [28,37]. In this case it might be possible to include our proposed algorithm in a reconstruction procedure where the optical properties of the background medium are measured or known, while the absorption contrast, the position, and the size of the defect are reconstructed for. If also the position and/or size of the defect are known, the algorithm provides a fast and accurate method to carry out forward calculation beyond first order theory (Born approximation).

The results presented in this work in the slab and the semi-infinite geometries strongly suggest that our method can be used in arbitrary geometries, thus confirming the results of our previous publications, where we have also shown the flexibility of this method for different shapes of the embedded defects [31,32].

The fourth order perturbation theory proposed has shown excellent results in the three domains of investigations, namely, CW [30] frequency, and time domains. The coefficients of Taylor expansion provided by perturbation theory, namely, the path length moments of the distribution of collected photons, have been used in the three domains for applying the method of Padé approximants. This method is able to extend the validity of the calculations for larger absorption contrasts between defect(s) and the background. In many situations encountered in near infrared spectroscopy and diffuse optical tomography, it might be even the case that the results of second, third, or fourth order theory can be used to describe the effect of localized perturbations (e.g., a breast lesion, either more absorbing than the healthy breast, or clear regions like a cyst). However, if we want to simulate the effect of stronger absorbers (e.g., blood vessels) we need to apply the method of Padé approximants.

The main drawback of the proposed method is that it deals solely with absorption perturbations; therefore it cannot be used as a forward problem solver in those situations where information on the reduced scattering coefficient is lacking and it is reconstructed for in the inversion procedure. Nevertheless, we can say that our method reduces a higher order perturbation problem to a first order problem. In other words, if we have a way to compute the mean path lengths in the regions of interest and the output flux, we can also compute higher order moments by using Eqs. (22) and (25), and the forward problem can be solved in general conditions (at least whenever the contribution of the mixed moments is negligible; see discussion later). Under this perspective we can view a general forward problem solver embedded in an iterative reconstruction procedure as a method to recalculate the mean path

lengths in the elementary regions (i.e., voxels) as the reduced scattering coefficients are updated during the procedure; however the original distribution (for example, uniform) of the absorption coefficient does not need to be updated since at every step of the reconstruction the new distribution of the absorption coefficient can be treated as a perturbation of the initial one. Therefore we speculate that in some situations it might be useful to combine our method with a numerical method that solves the DE in arbitrary conditions. For example when the Green's function of the medium is not available but we have some *a priori* knowledge of the distribution of the reduced scattering coefficient, we could use the numerical method for the calculation of the mean path lengths in the regions of interest by using, for example, its differential definition [see [29], Eq. (8)]: $\langle l_i \rangle = - \int \mu_a(R) / R_0$, where the symbols are valid in any domain of investigation. In practice the numerical method should calculate the output flux at a detector location for the initial distribution of the reduced scattering and absorption coefficients (R_0); then the same calculation is carried out when the absorption in the region i is changed by a "small" known amount (R). The second calculation should be repeated for all the regions of interest. Once the mean path lengths are calculated our method can be used for the calculation of the absorption perturbation along the steps of the inversion procedure.

Another important point that has emerged from our study is that accurate calculations can be carried out, at least for certain ranges of the absorption contrast, without considering the mixed moments, i.e., by neglecting the interaction between different regions (Fig. 7). This means that we can consistently reduce the computational burden of the method. Given n regions of interest the number of self-moments is n , while the numbers of higher order moments are on the order of n^2 , n^3 , and n^4 for the second, third, and fourth order perturbation theories, respectively. As a better approximation we can propose to carry out the calculations by considering the interaction of adjacent regions (or voxels). We note that also in this case the order of the calculations is still n .

Finally, all throughout this work (as in the previous one [31,32]) we have provided large evidence that the method of Padé approximants can be effectively used to extend the limitation of fourth order perturbation theory. However, as noted in the theory section, the method can be used only for functions of one variable; therefore we cannot study perturbations where the absorption contrasts of different regions are varied independently. Is there any analog of Padé approximants for functions of many variables? This method exists and is called Canterbury approximants [38]. In the future it may be possible to use these approximants to implement a general fast forward problem solver for absorbing perturbations that overcomes the limitations of fourth order perturbation theory.

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APPENDIX A: FORMULAS FOR THE SELF-AND MIXED MOMENTS IN FREQUENCY AND TIME DOMAINS

We report in this appendix the formulas used for calculating the moments. We note that the CW domain is a particular case of the frequency domain ($\omega=0$); therefore only one set of formulas is given. The frequency and time domains are abbreviated as “FD” and “TD,” respectively. Also, in the left sides of the expressions we will omit the symbol denoting the detector’s location “ $\mathbf{r}_b$.”

I ORDER

FD-CW:

$$\langle I_i \rangle(\omega) \approx \frac{\tilde{R}_0(\mathbf{r}_b, \mathbf{r}_i, \omega) \tilde{\varphi}_0(\mathbf{r}_i, \omega) V_i}{\tilde{R}_0(\mathbf{r}_b, \omega)}.$$

TD:

$$\langle l_i \rangle(t) \approx \frac{V_i [R_0(\mathbf{r}_b, \mathbf{r}_i, \tau) \otimes \varphi_0(\mathbf{r}_i, \tau)](t)}{R_0(\mathbf{r}_b, t)}.$$

II ORDER

FD-CW:

$$\begin{aligned} \langle l_i l_j \rangle(\omega) &\approx \frac{\sum_{P(i,j)} \tilde{R}_0(\mathbf{r}_b, \mathbf{r}_i, \omega) \tilde{\varphi}_0(\mathbf{r}_i, \mathbf{r}_j, \omega) \tilde{\varphi}_0(\mathbf{r}_j, \omega) V_i V_j}{\tilde{R}_0(\mathbf{r}_b, \omega)}, \quad i \neq j, \\ \langle l_i^2 \rangle(\omega) &\approx c_1 \langle l_i \rangle(\omega) \int_{V_i} \tilde{\varphi}_0(\mathbf{r}_i, \mathbf{r}, \omega) d\mathbf{r}. \end{aligned}$$

TD:

$$\begin{aligned} \langle l_i l_j \rangle(t) &\approx \frac{\sum_{P(i,j)} V_i V_j [R_0(\mathbf{r}_b, \mathbf{r}_i, \tau) \otimes \varphi_0(\mathbf{r}_i, \mathbf{r}_j, \tau) \otimes \varphi_0(\mathbf{r}_j, \tau)](t)}{R_0(\mathbf{r}_b, t)}, \quad i \neq j, \\ \langle l_i^2 \rangle(t) &\approx \frac{c_1 \left\{ [\langle l_i \rangle(\tau) R_0(\mathbf{r}_b, \tau)] \otimes \int_{V_i} \varphi_0(\mathbf{r}_i, \mathbf{r}, \tau) d\mathbf{r} \right\}(t)}{R_0(\mathbf{r}_b, t)}. \end{aligned}$$

III ORDER

FD-CW:

$$\begin{aligned} \langle l_i l_j l_k \rangle(\omega) &\approx \frac{\sum_{P(i,j,k)} \tilde{R}_0(\mathbf{r}_b, \mathbf{r}_i, \omega) \tilde{\varphi}_0(\mathbf{r}_i, \mathbf{r}_j, \omega) \tilde{\varphi}_0(\mathbf{r}_j, \mathbf{r}_k, \omega) \tilde{\varphi}_0(\mathbf{r}_k, \omega) V_i V_j V_k}{\tilde{R}_0(\mathbf{r}_b, \omega)}, \quad i \neq j \neq k, \\ \langle l_i^2 l_k \rangle(\omega) &\approx c_1 \langle l_i l_k \rangle(\omega) \int_{V_i} \tilde{\varphi}_0(\mathbf{r}, \mathbf{r}_i, \omega) d\mathbf{r} + 2 \langle l_i \rangle(\omega) \tilde{\varphi}_0(\mathbf{r}_i, \mathbf{r}_k, \omega) \tilde{\varphi}_0(\mathbf{r}_k, \mathbf{r}_i, \omega) V_i V_k, \\ \langle l_i^3 \rangle(\omega) &\approx c_2 \langle l_i \rangle(\omega) \left(\int_{V_i} \tilde{\varphi}_0(\mathbf{r}, \mathbf{r}_i, \omega) d\mathbf{r} \right)^2. \end{aligned}$$

TD:

$$\begin{aligned} \langle l_i l_j l_k \rangle(t) &\approx \frac{\sum_{P(i,j,k)} V_i V_j V_k [R_0(\mathbf{r}_b, \mathbf{r}_i, \tau) \otimes \varphi_0(\mathbf{r}_i, \mathbf{r}_j, \tau) \otimes \varphi_0(\mathbf{r}_j, \mathbf{r}_k, \tau) \otimes \varphi_0(\mathbf{r}_k, \tau)](t)}{R_0(\mathbf{r}_b, t)}, \quad i \neq j \neq k, \\ \langle l_i^2 l_k \rangle(t) &\approx \frac{c_1}{R_0(\mathbf{r}_b, t)} \left\{ [R_0(\mathbf{r}_b, \tau) \langle l_i l_k \rangle(\tau)] \otimes \int_{V_i} \varphi_0(\mathbf{r}, \mathbf{r}_i, \tau) d\mathbf{r} \right\}(t) + \frac{2V_i V_k}{R_0(\mathbf{r}_b, t)} \{ [R_0(\mathbf{r}_b, \tau) \langle l_i \rangle(\tau)] \otimes \varphi_0(\mathbf{r}_i, \mathbf{r}_k, \tau) \otimes \varphi_0(\mathbf{r}_k, \mathbf{r}_i, \tau) \}(t), \\ \langle l_i^3 \rangle(t) &\approx \frac{c_2 \left\{ [\langle l_i \rangle(\tau) R_0(\mathbf{r}_b, \tau)] \otimes \int_{V_i} \varphi_0(\mathbf{r}_i, \mathbf{r}, \tau) d\mathbf{r} \otimes \int_{V_i} \varphi_0(\mathbf{r}_i, \mathbf{r}, \tau) d\mathbf{r} \right\}(t)}{R_0(\mathbf{r}_b, t)}. \end{aligned}$$

IV ORDER

FD-CW:

$$\begin{aligned}
\langle l_i l_j l_k l_m \rangle(\omega) &\approx \frac{\sum_{P(i,j,k,m)} \tilde{R}_0(\mathbf{r}_b, \mathbf{r}_i, \omega) \tilde{\varphi}_0(\mathbf{r}_i, \mathbf{r}_j, \omega) \tilde{\varphi}_0(\mathbf{r}_j, \mathbf{r}_k, \omega) \tilde{\varphi}_0(\mathbf{r}_k, \mathbf{r}_m, \omega) \tilde{\varphi}_0(\mathbf{r}_m, \omega) V_i V_j V_k V_m}{P(i,j,k,m)}, \quad i \neq j \neq k \neq m, \\
\langle l_i^2 l_k^2 \rangle(\omega) &\approx c_1^2 \langle l_i l_k \rangle(\omega) \int_{V_i} \tilde{\varphi}_0(\mathbf{r}_i, \mathbf{r}, \omega) d\mathbf{r} \int_{V_k} \tilde{\varphi}_0(\mathbf{r}_k, \mathbf{r}, \omega) d\mathbf{r} + V_i V_k [\tilde{\varphi}_0(\mathbf{r}_i, \mathbf{r}_k, \omega) \tilde{\varphi}_0(\mathbf{r}_k, \mathbf{r}_i, \omega)] \{4 \langle l_i l_k \rangle(\omega) + 2c_1 \\
&\times [\langle l_k \rangle(\omega) \int_{V_i} \tilde{\varphi}_0(\mathbf{r}_i, \mathbf{r}, \omega) d\mathbf{r} + \langle l_i \rangle(\omega) \int_{V_k} \tilde{\varphi}_0(\mathbf{r}_k, \mathbf{r}, \omega) d\mathbf{r}] \}, \\
\langle l_i^2 l_j l_k \rangle(\omega) &\approx c_1 \langle l_i l_j l_k \rangle(\omega) \int_{V_i} \tilde{\varphi}_0(\mathbf{r}_i, \mathbf{r}, \omega) d\mathbf{r} + 2 \langle l_i l_k \rangle(\omega) [\tilde{\varphi}_0(\mathbf{r}_i, \mathbf{r}_j, \omega) \tilde{\varphi}_0(\mathbf{r}_j, \mathbf{r}_i, \omega)] V_i V_j + 2 \langle l_i l_j \rangle(\omega) [\tilde{\varphi}_0(\mathbf{r}_i, \mathbf{r}_k, \omega) \tilde{\varphi}_0(\mathbf{r}_k, \mathbf{r}_i, \omega)] V_i V_k \\
&+ 2 \langle l_i \rangle(\omega) [\tilde{\varphi}_0(\mathbf{r}_i, \mathbf{r}_j, \omega) \tilde{\varphi}_0(\mathbf{r}_j, \mathbf{r}_k, \omega) \tilde{\varphi}_0(\mathbf{r}_k, \mathbf{r}_i, \omega)] V_i V_j V_k, \\
\langle l_i^3 l_j \rangle(\omega) &\approx c_2 \langle l_i l_j \rangle(\omega) \left(\int_{V_i} \tilde{\varphi}_0(\mathbf{r}_i, \mathbf{r}, \omega) d\mathbf{r} \right)^2 + 6c_1 [\tilde{\varphi}_0(\mathbf{r}_i, \mathbf{r}_j, \omega) \tilde{\varphi}_0(\mathbf{r}_j, \mathbf{r}_i, \omega)] \int_{V_i} \tilde{\varphi}_0(\mathbf{r}_i, \mathbf{r}, \omega) d\mathbf{r} \langle l_i \rangle(\omega) V_i V_j, \\
\langle l_i^4 \rangle(\omega) &= c_3 \langle l_i \rangle(\omega) \left(\int_{V_i} \tilde{\varphi}_0(\mathbf{r}_i, \mathbf{r}, \omega) d\mathbf{r} \right)^3.
\end{aligned}$$

TD:

$$\begin{aligned}
\langle l_i l_j l_k l_m \rangle(t) &\approx \frac{1}{R_0(\mathbf{r}_b, t)} \left\{ \sum_{P(i,j,k,m)} [R_0(\mathbf{r}_b, \mathbf{r}_i, \tau) \otimes \varphi_0(\mathbf{r}_i, \mathbf{r}_j, \tau) \otimes \varphi_0(\mathbf{r}_j, \mathbf{r}_k, \tau) \otimes \varphi_0(\mathbf{r}_k, \mathbf{r}_m, \tau) \otimes \varphi_0(\mathbf{r}_m, \tau)](t) V_i V_j V_k V_m \right\}, \quad i \neq j \neq k \neq m, \\
\langle l_i^2 l_k^2 \rangle(t) &\approx \frac{c_1^2}{R_0(\mathbf{r}_b, t)} \left\{ [R_0(\mathbf{r}_b, \tau) \langle l_i l_k \rangle(\tau)] \otimes \int_{V_i} \varphi_0(\mathbf{r}_i, \mathbf{r}, \tau) d\mathbf{r} \otimes \int_{V_k} \varphi_0(\mathbf{r}_k, \mathbf{r}, \tau) d\mathbf{r} \right\}(t) + \frac{2V_i V_k}{R_0(\mathbf{r}_b, t)} [\varphi_0(\mathbf{r}_i, \mathbf{r}_k, \tau) \otimes \varphi_0(\mathbf{r}_k, \mathbf{r}_i, \tau)] \\
&\otimes \left\{ 2[\langle l_i l_k \rangle(\tau) R_0(\mathbf{r}_b, \tau)] + c_1 [R_0(\mathbf{r}_b, \tau) \langle l_k \rangle(\tau)] \otimes \int_{V_i} \varphi_0(\mathbf{r}_i, \mathbf{r}, \tau) d\mathbf{r} + c_1 [R_0(\mathbf{r}_b, \tau) \langle l_i \rangle(\tau)] \otimes \int_{V_k} \varphi_0(\mathbf{r}_k, \mathbf{r}, \tau) d\mathbf{r} \right\}(t), \\
\langle l_i^2 l_j l_k \rangle(t) &\approx \frac{c_1}{R_0(\mathbf{r}_b, t)} \left\{ [R_0(\mathbf{r}_b, \tau) \langle l_i l_j l_k \rangle(\tau)] \otimes \int_{V_i} \varphi_0(\mathbf{r}_i, \mathbf{r}, \tau) d\mathbf{r} \right\}(t) + \frac{2V_i V_j}{R_0(\mathbf{r}_b, t)} \{ [R_0(\mathbf{r}_b, \tau) \langle l_i l_k \rangle(\tau)] \otimes \varphi_0(\mathbf{r}_i, \mathbf{r}_j, \tau) \otimes \varphi_0(\mathbf{r}_j, \mathbf{r}_i, \tau) \}(t) \\
&+ \frac{2V_i V_k}{R_0(\mathbf{r}_b, t)} \{ [R_0(\mathbf{r}_b, \tau) \langle l_i l_j \rangle(\tau)] \otimes \varphi_0(\mathbf{r}_i, \mathbf{r}_k, \tau) \otimes \varphi_0(\mathbf{r}_k, \mathbf{r}_i, \tau) \}(t) + \frac{2V_i V_j V_k}{R_0(\mathbf{r}_b, t)} \{ [R_0(\mathbf{r}_b, \tau) \langle l_i \rangle(\tau)] \otimes \varphi_0(\mathbf{r}_i, \mathbf{r}_j, \tau) \otimes \varphi_0(\mathbf{r}_j, \mathbf{r}_k, \tau) \\
&\otimes \varphi_0(\mathbf{r}_k, \mathbf{r}_i, \tau) \}(t), \\
\langle l_i^3 l_j \rangle(t) &\approx \frac{c_2}{R_0(\mathbf{r}_b, t)} \left\{ [R_0(\mathbf{r}_b, \tau) \langle l_i l_j \rangle(\tau)] \otimes \int_{V_i} \varphi_0(\mathbf{r}_i, \mathbf{r}, \tau) d\mathbf{r} \otimes \int_{V_i} \varphi_0(\mathbf{r}_i, \mathbf{r}, \tau) d\mathbf{r} \right\}(t) + \frac{6c_1 V_i V_j}{R_0(\mathbf{r}_b, t)} \{ [R_0(\mathbf{r}_b, \tau) \langle l_i \rangle(\tau)] \otimes \varphi_0(\mathbf{r}_i, \mathbf{r}_j, \tau) \\
&\otimes \varphi_0(\mathbf{r}_j, \mathbf{r}_i, \tau) \otimes \int_{V_i} \varphi_0(\mathbf{r}_i, \mathbf{r}, \tau) d\mathbf{r} \}(t), \\
\langle l_i^4 \rangle(t) &\approx \frac{c_3 \{ [\langle l_i \rangle(\tau) R_0(\mathbf{r}_b, \tau)] \otimes \int_{V_i} \varphi_0(\mathbf{r}_i, \mathbf{r}, \tau) d\mathbf{r} \otimes \int_{V_i} \varphi_0(\mathbf{r}_i, \mathbf{r}, \tau) d\mathbf{r} \otimes \int_{V_i} \varphi_0(\mathbf{r}_i, \mathbf{r}, \tau) d\mathbf{r} \}(t)}{R_0(\mathbf{r}_b, t)}.
\end{aligned}$$

We note that all these formulas verify the general relationship between FD and TD moments given by Eq. (6).

Fig. 1.

(Color online) Computation of the parameters (a),(b) k_1 ; (c),(d) k_2 ; and (e),(f) k_3 , for the semi-infinite (left side) and slab (right side) geometries. In each medium we considered two spherical regions as indicated in the schematic. Geometrical units are in millimeters.

Fig. 2.

(Color online) Comparison between Monte Carlo (thin noisy lines) and theoretical (thick smooth lines) results on the calculation of time-domain mixed moments for the two spherical regions shown in the diagram. In particular we have (a) $\langle I_1 I_2 \rangle(t)$, (b) $\langle I_1^2 I_2 \rangle(t)$, (c) $\langle I_1^2 I_2^2 \rangle(t)$, (d) $\langle I_1^3 I_2 \rangle(t)$. The geometrical units in the diagram are in millimeters.

Fig. 3.

Relative change in the time-domain reflectance with respect to homogeneous medium for the case of Fig. 2. In each figure six curves are reported: the results of each perturbation order (up to the fourth order), the result of Padé approximants method, and the Monte Carlo results. (a),(b),(c),(d) are relative to the perturbation due to sphere 2 alone, sphere 1 alone, both spheres, and both spheres with different $\Delta\mu_a$'s, respectively. For (a),(b),(c) the absorption contrast was $\Delta\mu_a=0.055 \text{ mm}^{-1}$, while for (d) it was $\Delta\mu_a=0.025 \text{ mm}^{-1}$.

Fig. 4.

Same as Fig. 3, but the optical properties of the background medium are $\mu'_s = 1.5 \text{ mm}^{-1}$, $\mu_a = 0.01 \text{ mm}^{-1}$. (a),(b) refer to the perturbation due to sphere 1 with absorption contrasts $\Delta\mu_a = 0.02 \text{ mm}^{-1}$ and $\Delta\mu_a = 0.06 \text{ mm}^{-1}$, respectively. For these cases the time-domain mean path lengths were calculated analytically with the Green's function of the slab geometry. (c),(d) refer to the perturbation due to sphere 2 alone and both spheres, respectively, with $\Delta\mu_a = 0.06 \text{ mm}^{-1}$.

Fig. 5.

(Color online) Relative change in the time-domain reflectance with respect to homogeneous medium for the case represented in the schematic on top (with geometrical units in millimeters). In each figure there are six curves: the four different orders of perturbation theory, the result of Padé approximants, and the Monte Carlo results. (a),(b),(c),(d) are relative to a perturbation due to sphere 1 alone, sphere 2 alone, sphere 3 alone, and spheres 2 and 3 together, respectively. The absorption contrasts are $\Delta\mu_a = 0.11 \text{ mm}^{-1}$ for (a) and $\Delta\mu_a = 0.06 \text{ mm}^{-1}$ for (b)–(d).

Fig. 6.

Same as Fig. 5, but the optical properties of the background medium are $\mu'_s = 1.5 \text{ mm}^{-1}$, $\mu_a = 0.01 \text{ mm}^{-1}$. (a),(b),(c) refer to the perturbation of sphere 2 alone, sphere 3 alone, and both spheres 2 and 3. In all the cases the absorption contrast is $\Delta\mu_a = 0.05 \text{ mm}^{-1}$.

Fig. 7.

Relative change in the time-domain reflectance with respect to homogeneous medium calculated either by using fourth order theory with the self-moments alone [symbol 4s in the graphs; the curves are calculated with Eq. (35)] or fourth order theory obtained by using the exact expression [symbol 4 in the graphs; the curves are calculated with Eq. (29)]. The Monte Carlo plot (thick line) is almost coincident with the plot of the fourth order calculations (symbol 4), but little difference is found also with the simplified fourth order theory (symbol 4s). (a) refers to Fig. 3(d), while (b) refers to Fig. 5(d). In both cases we considered an absorption contrast of $\Delta\mu_a = 0.025 \text{ mm}^{-1}$.

Fig. 8.

(Color online) Relative change in the time-domain reflectance with respect to the initial medium shown on the top panel when the (a) local ($\mu_a=0.01 \text{ mm}^{-1}$, $\mu'_s=1 \text{ mm}^{-1}$) or (b) general ($\mu_{ab}=0.005 \text{ mm}^{-1}$, $\mu'_{sb}=0.5 \text{ mm}^{-1}$) background optical properties are used for the calculation of the integral in Eq. (22). The absorption coefficient of region 3 was considered in the final state as $\mu_a=0.07 \text{ mm}^{-1}$. In (c) we show a comparison of Padé approximant curves obtained with the optical properties of the local (symbol “Padé-loc”) and the general (symbol “Padé”) background properties and the Monte Carlo plot. In (d) we show the plots of the integral in Eq. (22) calculated with the two sets of properties.

Fig. 9.
(Color online) Change in AC intensity (left panels) and phase (right panels) calculated for the medium in the schematic of Fig. 2, against the absorption contrast. (a),(b); (c),(d); and (e),(f) are calculated when in the medium there is defect 1 alone, defect 2 alone, and both defects, respectively.

Fig. 10.

Change in AC (left panels) and phase (right panels) calculated for the medium in the schematic of Fig. 2, against the absorption contrast. For this case the optical properties of the background medium were $\mu_a = 0.01 \text{ mm}^{-1}$, $\mu'_s = 1.5 \text{ mm}^{-1}$. (a),(b); (c),(d); and (e),(f) are calculated when in the medium there is defect 1 alone, defect 2 alone, and both defects, respectively.

Fig. 11.

Change in AC (left panels) and phase (right panels) calculated for the medium in the schematic of Fig. 5, against the absorption contrast. (a),(b); (c),(d); (e),(f); and (g),(h) are calculated when in the medium there is defect 1 alone, defect 2 alone, defect 3 alone, and both defects 2 and 3, respectively.

Fig. 12.

Change in AC (left panels) and phase (right panels) calculated for the medium in the schematic of Fig. 5, against the absorption contrast. The optical properties of the background medium were $\mu_a = 0.01 \text{ mm}^{-1}$, $\mu'_s = 1.5 \text{ mm}^{-1}$. (a),(b); (c),(d); and (e),(f) are calculated when in the medium there is defect 2 alone, defect 3 alone, and both defects 2 and 3, respectively.