Perturbation theory for the diffusion equation by use of the moments of the generalized temporal point-spread function. I. Theory

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We approach the perturbative solution to the diffusion equation for the case of absorbing inclusions embedded in a heterogeneous scattering medium by using general properties of the radiative transfer equation and the solution of the Fredholm equation of the second kind given by the Neumann series. The terms of the Neumann series are used to obtain the expression of the moments of the generalized temporal point-spread function derived in transport theory. The moments are calculated independently by using Monte Carlo simulations for validation of the theory. While the mixed moments are correctly derived from the theory by using the solution of the diffusion equation in the geometry of interest, in order to obtain the self moments we should reframe the problem in transport theory and use a suitable solution of the radiative transfer equation for the calculation of the multiple integrals of the corresponding Neumann series. Since the rigorous theory leads to impractical formulas, in order to simplify and speed up the calculation of the self moments, we propose a heuristic method based on the calculation of only a single integral and some scaling parameters. We also propose simple quadrature rules for the calculation of the mixed moments for speeding up the computation of perturbations due to multiple defects. The theory can be developed in the continuous-wave domain, the time domain, and the frequency domain. In a companion paper [J. Opt. Soc. Am. A 23, 2119 (2006)] we discuss the conditions of applicability of the theory in practical cases found in diffuse optical imaging of biological tissues. © 2006 Optical Society of America

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1. INTRODUCTION

Current methods for solving the forward problem in the study of light propagation in biological tissues rely either on diffusion theory or on transport theory. While analytical solutions of the diffusion equation (DE) are found in the literature at least for regular boundaries and homogeneous media,1–3 numerical solutions are required whenever the boundaries of the medium are complex and the medium is not homogeneous. Analytical solutions of the DE for heterogeneous media with a single spherical defect are also possible whenever the boundary is absent4 (infinite medium geometry) or is not complex, such as, for example, slab5,6 and spherical6 geometry. Analytical solutions of the radiative transfer equation (RTE), either rigorous or approximate, are known for infinite, homogeneous, isotropic,7–9 or particular anisotropic media,10–12 but they are usually rather elaborate and require complex calculations. The usual methods of solving the DE or RTE for complex boundaries and heterogeneous media are based either on the finite-element method (FEM) or on the finite-difference method (FDM). For the case of a complex geometry the DE is more commonly implemented for the solution of the forward problem according to the FDM13,14 or the FEM15–19, however, recently the solution of the RTE has also been applied according to the discrete-ordinate and finite-volume methods,20 or also the FEM.21 The Monte Carlo method (MC) offers a way to simulate the physical propagation of photons in scattering media; the relevant parameters like the photon energy density within the medium or the energy flux re-emitted from the medium are calculated after running a wide number of photon trajectories. MC can be effectively considered as a numerical method of solving the RTE even though the equation itself is not implemented in the code as is usually done in other numerical methods. MC is quite accurate and much simpler than other methods, but...
it is rather time-consuming; therefore in the literature it has been used mainly for assessing the validity of other methods.\textsuperscript{22–25}

In the mathematical procedures used for optical properties reconstruction, including the solution of both the forward and the inverse problem, perturbation theory of the DE has an important role. In particular, a first-order perturbation theory (Born approximation) of the DE has been extensively used for the calculation of the weight matrix in both iterative\textsuperscript{14,26} (using either FEM or FDM to solve the nonlinear forward problem) and single-step\textsuperscript{27,28} reconstruction procedures. Some studies have also discussed the possibility of using \( n \)-th-order perturbation theory\textsuperscript{29,30} as a nonlinear forward problem solver, and numerical results have been reported for the infinite medium geometry and single spherical inclusion. In the work of Ostermeyer and Jacques\textsuperscript{30} the authors suggested that the Neumann series can be implemented in an iterative manner to calculate the distribution of photon energy density at different orders of approximation. The different orders are defined by increasingly smaller corrections to the distribution of energy density of the unperturbed medium due to the effect of the inclusions. The authors also discussed the singularities inherent in the method whenever the effect of an inclusion on itself is calculated (self-interacting term) and showed a way to handle the calculation. Results were shown in the frequency domain for a spherical inclusion in the infinite medium geometry, but which order of approximation was considered for the calculations was not discussed. Boas\textsuperscript{29} used the \( N \)-th-order perturbation for \( 1 \leq N \leq 10 \) and presented some results in the frequency domain for a single spherical absorbing defect in the infinite medium geometry. The author showed that calculations performed for \( N > 5 \) do not offer the clear improvement expected and gave a possible explanation of this result in that the self-interacting terms were neglected. One of the conclusions of the study was that an algorithm based on fifth-order approximation can be useful for determining the perturbation of defects of radius less than \( 4 \) mm and absorption contrast less than \( 0.04 \) mm\(^{-1}\).

In this work we reframe the perturbation theory for the DE in terms of the estimation of the moments of the generalized temporal point-spread function (GTPSF) derived in transport theory. The path length moments offer a more intuitive way of understanding the meaning of higher-order terms of the Neumann series. In fact higher-order corrections to the distribution of the energy density within the medium and to the energy re-emitted from the medium correspond to higher-order interactions among inclusions, which corresponds in the proposed method to the estimation of higher-order self and mixed path length moments of the GTPSF.

In this work we derive expressions for the moments of the GTPSF by using the terms of the Neumann series solution of the perturbative DE. While the calculation of the mixed moments can be carried out by using the expressions derived from the theory and the solution of the DE for the geometry considered, the self moments can be correctly calculated only within transport theory. In fact the estimation of mixed moments implies the calculation of the effect of source points located in one region on field points located in a separate region; in contrast, higher-order self moments are obtained by calculating the fluence rate at field points that are indefinitely close to the source points. We recall that in diffuse optical imaging of biological tissues it is well known that the classical DE fails to describe the distribution of energy in the range of distances shorter than approximately \( 1–2 \) mm from the source. Therefore the correct theory for the self moments of the GTPSF should be developed from the perturbative RTE and the corresponding Neumann series. The only reason to use perturbation theory of the DE for the calculation of the moments of the GTPSF is that we obtain more practical expressions. In Appendix D we derive the correct expressions of the mixed and self moments from transport theory, and we discuss the conditions under which they reduce to those found from the perturbative DE.

Since the rigorous method for calculating higher-order self moments is not practical, we propose a heuristic approximate method for the calculation of higher-order self moments that is based on the computation of only one single integral and some scaling parameters that are rather insensitive to the optical properties of the medium and to a certain extent also to the position and size of the defect. The method is valid for arbitrary geometries and values of the optical properties typically found in diffuse optical imaging of biological tissues. By use of the proposed method we can improve the results obtainable within first-order perturbation theory for a single inclusion in a quite straightforward manner. Although these relationships are more accurate for smaller inclusions, we investigated the possibility of using them also for larger defects. By the term “small” inclusion we mean inclusions having linear size smaller than their distances to the source and detector and within which sizes the photon energy density can be considered approximately constant. We also propose some quadrature rules for speeding up the computation of mixed moments, and we combine them with the formulas for the self moments in order to calculate mixed moments for the case when one or more regions are counted more than once. We derive some practical rules for the calculation of the moments up to the fourth order, in which the higher-order mixed moments are derived from the lower-order moments. These formulas will be widely used in the companion paper (Part II) in this issue,\textsuperscript{31} where we present some comparisons among the theory and MC results for the case of single and multiple inclusions embedded in a semi-infinite scattering and absorbing medium.

2. THEORY

The theory is developed from general properties of the RTE for the calculation of the inclusions effect, which is eventually expressed in a multiple series expansion over all possible moments of the GTPSF. The integrals in the Neumann series solution of the perturbative DE are broken down into a series that is compared with the multiple series derived from the RTE. The common point of the two series is that each term includes a power of the absorption contrasts between defects and background medium. Since the method is substantially equivalent in the
continuous-wave (CW), frequency, and time domains, we first provide details for the CW domain; we give formulas for the other two domains in separate appendixes.

A. Definition of GTPSF and Its Moments

The purpose of these initial notes is to revise the steps for defining the GTPSF.\(^{32-35}\) We start our argument from the Beer–Lambert law for nonscattering medium, which yields one of the possible solutions of the time-independent RTE.\(^{36-38}\)

Let us now consider a scattering medium having an arbitrary geometry that can be divided into \(N\) elementary regions (or voxels), and where the scattering coefficient \(\mu_s\) can be considered constant in each region but for which in general \(\mu_a \neq \mu_s\), when \(i \neq j\) (see Fig. 1). As a consequence of the Beer–Lambert law, the probability of a photons being detected when the absorption in every voxel is \(\mu_a\) (\(i = 1, 2, \ldots, N\)) is given by the product of the probability of being detected when the medium is nonabsorbing and the expression \(\exp(-\sum_{i=1}^{N} \mu_a(s)/l_i)\), where \(l_i\) is the path length spent by the photon in the region \(i\). For a given CW pencil beam source located at \(r = r_b\) and pointlike detector located at \(r = r_s\) (Fig. 1) we define the GTPSF when \(\mu_a = 0\) (i.e., \(\mu_a = 0, \quad i = 1, 2, \ldots, N\)), as \(f_0(t_1, \ldots, t_N)\) with the normalization

\[
\int_{R^N} f_0(t_1, \ldots, t_N)dt_1 \ldots dt_N = A_0 (r_b, \mu_a = 0),
\]

where \(A_0\) is the attenuation per unit surface, or the probability per unit surface that an injected photon is detected in the absence of absorption. The integration in Eq. (2) is carried out for the positive values of the coordinates in the \(N\)-dimensional Euclidian space \(R^N\). The function \(f_0\) indicates the probability density that a photon injected into the medium is detected after spending the time \(t_i\) (or the path length \(l_i = vt_i\), where \(v\) is the speed of the light in the medium) in the region \(i (i = 1, 2, \ldots, N)\). Based on the previous argument, if the absorption in each region is \(\mu_a\), the GTPSF, \(f_{in}\), is defined as a function of \(f_0\) according to the scaling relationship defined above:

\[
f_{in}(t_1, \ldots, t_N) = f_0(t_1, \ldots, t_N)\exp\left(-\sum_{i=1}^{N} \mu_a(t_i)\right).
\]

We define this state of the medium the initial state (abbreviated as \(in\) in the subscripts), from which we consider an arbitrary absorption perturbation \(\Delta \mu_a\) (i.e., \(\Delta \mu_{a1}, \Delta \mu_{a2}, \ldots, \Delta \mu_{aN}\)). In the same way as Eq. (2) we define the initial attenuation as

\[
\int_{R^N} f_{in}(t_1, \ldots, t_N)dt_1 \ldots dt_N = A_{in}(r_b, \mu_a). \tag{4}
\]

After a change \(\Delta \mu_a\) has occurred, the system is in its final state (abbreviated as \(fin\) in the subscripts), and the corresponding attenuation \(A_{fin}\) will be

\[
\int_{R^N} f_{in}(t_1, \ldots, t_N)\exp\left(-\sum_{i=1}^{N} v t_i \Delta \mu_a\right) dt_1 \ldots dt_N = A_{fin}(r_b, \mu_a + \Delta \mu_a). \tag{5}
\]

By using the Taylor expansion of each exponential and swapping the operation of series and integration we obtain

\[
A_{fin}(r_b, \mu_a + \Delta \mu_a) = A_{in}(r_b, \mu_a) \sum_{k_1, k_2, \ldots, k_N = 0}^{\infty} \frac{(-1)^{k_1 + \cdots + k_N}}{k_1! \cdots k_N!} (\Delta \mu_{a1})^{k_1} \cdots (\Delta \mu_{aN})^{k_N},
\]

where \((l_1^{k_1} \cdots l_N^{k_N})\) is the mixed path length moment of order \((k_1, k_2, \ldots, k_N)\) calculated in the initial state of the medium and defined as

\[
(l_1^{k_1} \cdots l_N^{k_N}) = \frac{\int_{R^N} (v t_1)^{k_1} \cdots (v t_N)^{k_N} f_{in}(t_1, \ldots, t_N)dt_1 \cdots dt_N}{\int_{R^N} f_{in}(t_1, \ldots, t_N)dt_1 \cdots dt_N}, \tag{7}
\]

or otherwise defined as

![Figure 1](image_url)  
 Fig. 1. Absorbing and scattering medium having arbitrary boundary. A pencil beam is impinging in \(r = r_i\) and a pointlike detector is placed at \(r = r_s\). The position of the pointlike source equivalent to the pencil beam is at \(s_i = 1/\mu_a^{in}\) (where \(\mu_a^{in}\) is the reduced scattering coefficient of the voxel struck by the pencil beam). The medium is divided into \(N\) elementary regions or voxels characterized by different values of the optical properties and volumes \(V_i, i = 1, 2, \ldots, N\).
\( i_{1}^{(b_{1}\cdots b_{N})} = \frac{1}{A_{in}(r_{b}, \mu_{a})} \frac{\partial^{b_{1}+b_{2}+\cdots+b_{N}} A_{in}(r_{b}, \mu_{a})}{\partial \mu_{a 1}^{b_{1}} \partial \mu_{a 2}^{b_{2}} \cdots \partial \mu_{a N}^{b_{N}}}, \)

\[ k_{1} + k_{2} + \cdots + k_{N} > 0. \]

(8)

We remind the reader that in Eqs. (6)–(8) \( l_{i} \) is a random variable indicating the path length spent by a detected photon in the region \( i \). In the literature authors have used the concept of GTPSF. In particular in a previous work the authors derived the modified Beer–Lambert law for heterogeneous media and showed the meaning of the first and second derivative of the optical density (OD) \( OD = \ln[A(r_{b}, \mu_{a})/A_{0}(r_{b}, \mu_{a}) = 0] \) with respect to the absorption of an elementary region of the medium. In another study the author defined different statistics of the GTPSF by calculating the changes of OD and its derivatives. However, the interaction among voxels was neglected in the final expressions. To the best of our knowledge a similar closed form of Eq. (6) was reported only by Carraresi et al. for a single perturbation in the time domain.

Here we want to stress that the above formulas (2)–(8) are valid for arbitrary boundaries, optical properties, refractive indices of the medium, and arbitrary changes in the absorption coefficients. The only requirement is that the scattering coefficient of each voxel be constant.

B. Perturbative Diffusion Equation

Let us now consider the same medium of Fig. 1 and assume that we can apply the DE. We will also assume that the medium does not present abrupt changes in the values of the scattering coefficient, so that it can be considered a continuous function of position. We recall that for the validity of the DE, the reduced scattering coefficient \( \mu_{s}' \) \( \mu_{s}' = \mu_{s}(1-g) \) —where \( g \) is the asymmetry parameter and \( \mu_{s} \) the scattering coefficient—should be much higher than the absorption coefficient \( \mu_{a} \). This restriction was not necessary for the validity of the previous Eqs. (2)–(8).

Let us consider the CW diffusion equation for a point-like source when the medium is in its initial state:

\[-\nabla \cdot [D(r) \nabla \phi_{0}(r)] + \mu_{a}(r) \phi_{0}(r) = \delta(r - r_{b}), \]

(9)

where \( r_{b} \) is the location of the point source, which can be placed at a distance of \( 1/\mu_{s}' \) from \( r_{b} \) in the direction of the pencil beam (Fig. 1). In Eq. (9) \( \phi_{0} \) is the Green's function of the fluence rate, and \( D = 1/(3\mu_{s}') \) is the diffusion factor. In the final state, that is, after a change \( \Delta \mu_{a}(r) \) in the absorption coefficient has occurred, the fluence rate will be \( \phi_{1} \) and the change in the fluence rate \( \Delta \phi(r) = \phi_{1}(r) - \phi_{0}(r) \) will satisfy the equation

\[-\nabla \cdot [D(r) \nabla [\Delta \phi(r)]] + \mu_{a}(r) \Delta \phi(r) = -\Delta \mu_{a}(r) \phi_{1}(r),\]

(10)

which is formally equivalent to Eq. (9) except for the source term.

By the convolution theorem we can write the solution of Eq. (10) in the form of the integral equation

\[ \phi_{b}(r) = \phi_{0}(r) - \int_{V} \Delta \mu_{a}(r_{1}) \phi_{a}(r_{1}, r_{1}) \phi_{b}(r_{1}) dV, \]

(11)

where \( V \) is the volume occupied by the medium. Eq. (11) is a Fredholm equation of the second kind, and its solution is provided by the Neumann series \( \phi_{n}(r) = \sum_{k=0}^{n} (-1)^{k} \phi_{k}(r) \),

(12)

and \( K(r, r_{1}) \) is the kernel of the integral Eq. (11):

\[ K(r, r_{1}) = \Delta \mu_{a}(r_{1}) \phi_{b}(r_{1}). \]

(14)

More details about the Fredholm equation and the derivation of the Neumann series can be found in the book of Duderstadt and Martin (p. 71). The attenuation of power at a point of the boundary \( r_{b} \) (Fig. 1) is defined by using Fick’s law:

\[ A(r_{b}) = -D(r_{b}) \nabla \phi(r_{b}) \cdot n, \]

(15)

where \( n \) is the unit vector normal to the boundary at \( r = r_{b} \) outwardly directed. The attenuation \( A \) is the reflection of the power per unit surface area divided by the source strength and has units \( [A] = L^{-2} \). We realize that the attenuation \( A_{b} \) can also be expanded in a Neumann series,

\[ A_{b}(r_{b}) = \lim_{n \to \infty} A_{n}(r_{b}), \]

(16)

where

\[ A_{0}(r_{b}) = A_{in}(r_{b}), \quad A_{n}(r_{b}) = \sum_{k=0}^{n} (-1)^{k} \bar{u}_{k}(r_{b}), \]

(17)

All the kernels in Eq. (16) are the same as in Eq. (13) with the exception of the first one:

\[ \bar{K}(r_{b}, r_{1}) = \Delta \mu_{a}(r_{1}) A_{b}(r_{b}, r_{1}) = -\Delta \mu_{a}(r_{1}) D(r_{b}) \nabla \phi_{0}(r_{b}, r_{1}) \cdot n, \]

(18)

For example the expression of \( A_{n}(r_{b}) \) is given by
A_n(r_b) = A_{n-1}(r_b) + (-1)^n \int_V \Delta \mu_\alpha(r_1)A_0(r_b, r_1) \\
\times \int_V \Delta \mu_\alpha(r_2)\phi_0(r_1, r_2) \ldots \\
\times \int_V \Delta \mu_\alpha(r_{n-1})\phi_0(r_{n-2}, r_{n-1}) \\
\times \int_V \Delta \mu_\alpha(r_n)\phi_0(r_{n-1}, r_n)\phi_0(r_0)dr_n \ldots dr_1.
\tag{19}

We note that after dividing the whole volume \(V\) into \(N\) smaller voxels (Fig. 1) and comparing the multiple integral of Eq. (19) with the terms of Eq. (6) for which \(k_1 + k_2 + \cdots + k_N = n\) we can derive the expressions of the mixed and self moments of order \(n\). For better understanding how the moments are derived from the Neumann series, let us take a closer look at the meaning of the different order of approximations in the attenuation \(A_n(r_b)\).

C. Zeroth-Order Approximation

The zeroth-order attenuation is \(A_0(r_b) = -D(r_b) \times \nabla \phi_0(r)\big|_{r=r_b} \cdot \mathbf{n}\). This is the reflectance of the unperturbed system; that is, when the system is in its initial state and the point source is at \(r_p\). This order corresponds to the term of Eq. (6) for which \(k_1 + k_2 + \cdots + k_N = 0\).

D. First-Order Approximation

The first order (Born approximation) corresponds to the terms of Eq. (6) for which \(k_1 + k_2 + \cdots + k_N = 1\). In this case Eq. (19) becomes

\[
A_1(r_b) = A_0(r_b) - \sum_{i=1}^N \int_{V_i} \Delta \mu_\alpha(r_1)A_0(r_b, r_1)\phi_0(r_1)dr_1.
\tag{20}
\]

Since we assumed that the optical properties are constant within each voxel \(i\), by comparison of Eq. (20) with Eq. (6) we obtain

\[
\frac{A_1(r_b) - A_0(r_b)}{A_0(r_b)} = -\sum_{i=1}^N \int_{V_i} \Delta \mu_\alpha(r_1)A_0(r_b, r_1)\phi_0(r_1)dr_1
\]

\[
\times [\Delta \mu_\alpha(r_1)]^{k_1} \ldots [\Delta \mu_\alpha(r_N)]^{k_N}.
\tag{21}
\]

where \(r_i\) is chosen arbitrarily within the voxel \(i\), and the factors \(k_i\) are the counters of the different voxels. Because the number of terms in both series of Eq. (21) is equal to \(N\), the expression of the mean path length \(\langle l_i \rangle\) for a voxel \(i\) is

\[
\langle l_i \rangle = \frac{\int_V A_0(r_b, r_1)\phi_0(r_1)dr_1}{A_0(r_b)}.
\tag{22}
\]

If we can assume that the integrand of Eq. (22) is approximately constant within voxel \(i\), the simple quadrature rule for \(\langle l_i \rangle\) yields

\[
\langle l_i \rangle = \frac{A_0(r_b, r_i)\phi_0(r_i)\mathcal{V}_i}{A_0(r_b)}.
\tag{23}
\]

We recall that \(\phi_0(r_i)\) is the fluence rate calculated at \(r_i\), when the point source is at \(r_0\), while \(A_0(r_b, r_i)\) is the reflectance calculated at \(r_b\) when the point source is at \(r_i\). Therefore the validity of the quadrature rule depends not only on the size of the voxel \(i\) but also on its location with respect to the source and the detector. It is not surprising that the mean path lengths are proportional to the volumes of the perturbed regions (at least for "small" volumes) and experimental evidence of this property can be found in the literature. We note that the Born approximation does not take into account the interactions among different voxels because the effect of each one is added independently. We note also that we can consider \(\langle l_i \rangle\) as proportional to the probability of a detected photon’s visiting the voxel \(i\).

E. Second-Order Approximation

The second order corresponds to the terms of Eq. (6) for which \(k_1 + k_2 + \cdots + k_N = 2\). In this case Eq. (19) becomes

\[
A_2(r_b) = A_1(r_b) + \sum_{i=1}^N \Delta \mu_\alpha(r_i)\int_{V_i} A_0(r_b, r_1)\sum_{j=1}^N \Delta \mu_\alpha(r_j)
\]

\[
\times \int_{V_j} \phi_0(r_1, r_2)\phi_0(r_2)dr_2.
\tag{24}
\]

We can also rewrite the terms of Eq. (6) for which \(k_1 + k_2 + \cdots + k_N = 2\) as

\[
\frac{A_2(r_b) - A_0(r_b)}{A_0(r_b)} = -\sum_{i=1}^N \sum_{k_1 + k_2 = 2} [\Delta \mu_\alpha(r_1)]^{k_1} \ldots [\Delta \mu_\alpha(r_N)]^{k_N}
\]

\[
\times \langle l_i \rangle^{k_1} \ldots (\langle l_i \rangle)^{k_N},
\tag{25}
\]

where we have rewritten the first-order perturbation with a simpler notation. The number of terms of the double series in Eq. (24) is \(N^2\), while in Eq. (25) the last series has \(N(N+1)/2\) terms. Therefore some terms in Eq. (24) should be grouped to yield the mixed moments. By comparison of Eq. (24) and Eq. (25) we obtain the general expression of the second-order moment \(\langle l_i \rangle^{k_1} \langle l_j \rangle^{k_2}\) (where \(k_i + k_j = 2\) as
In Eq. (26) $P(i,j)$ represents the permutation of two integers; therefore, the series has two terms if $i \neq j$ (mixed moment) or one term if $i = j$ (self moment). Here we note that $(i,i) \ (k_l = k_j = 1)$ is invariant if we swap the volumes of integration $V_i$ and $V_j$ in Eq. (26); this property is expected since $(i,i) = (j,j)$ is a general property of mixed moments. If we can further assume that the integrands in Eq. (26) are constant, we can write a simple quadrature rule for the mixed moments as

$$
\langle l_j \rangle = \frac{\sum_{P(i,j)} A_0(r_b,r_i)\phi_0(r_i)\phi_0(r_j)V_i/V_j}{A_0(r_b)},
$$

where $r_i$ and $r_j$ in Eq. (27) can be chosen arbitrarily within the voxels $i$ and $j$, respectively. The validity of the quadrature rule for this case depends not only on the size of both voxels and on their location with respect to the source and detector but also on their relative location in the medium. We note that the symmetry of Eq. (27) with respect to the exchange of the variables $r_i$ and $r_j$ does not rely on the reciprocity theorem. The second-order moments are calculated considering all the possible ways a photon can visit the regions $i$ and $j$ before being detected. Therefore, $\langle l_j \rangle$ can be interpreted as proportional to the probability of a detected photon’s visiting the regions $i$ and $j$. The interaction among voxels $i$ and $j$ is large or negligible according to their relative location with respect to the source and the detector. For example, their interaction will be large if they are located in regions of high sensitivity of the so-called “banana shape” of photons migrating from source to detector. On the other hand, their interaction will be negligible if they are located in regions of different or poor sensitivity in the banana shape.

Equation (26) also yields the second-order self moment (e.g., $k_1 = 2, k_2 = 0$), which is given by the formula

$$
\langle l_i^2 \rangle = \frac{2 \int_{V_i} A_0(r_b,r_1)\phi_0(r_1)\phi_0(r_2)dr_2}{A_0(r_b)},
$$

If we assume that $A_0(r_b,r_1)$ and $\phi_0(r_2)$ are rather constant within the voxel $i$ (which is a reasonable assumption if the voxel $i$ is far from source and detector) we can rewrite Eq. (28) as

$$
\langle l_i^2 \rangle = \frac{2\langle l_i \rangle}{V_i} \int_{V_i} \phi_0(r_1)dr_1
$$

with $\langle l_i \rangle$ calculated as in Eq. (23). By comparison of the mixed and self moments we note that while the running variables $r_1$ and $r_2$ in Eq. (26) (for the case $k_1 = k_2 = 1$) belong to separate voxels, in Eq. (29) they belong to the same voxel $i$. Therefore in this case we should expect that the solution of DE in the geometry of interest is no longer suitable for the calculation of the second-order self moment. We will discuss more on this point later.

F. Third-Order Approximation

The third-order corresponds to the terms of Eq. (6) for which $k_1 + k_2 + \cdots + k_N \leq 3$. We can repeat the same arguments used before in order to derive the general expression of the third-order moment $\langle l_i^1 l_j^1 l_m^1 \rangle$, which is given by the formula

$$
\langle l_i^1 l_j^1 l_m^1 \rangle = \frac{k_1! k_2! k_3! \sum_{P(i,j,m)} A_0(r_b,r_1)\phi_0(r_1)\phi_0(r_2)\phi_0(r_3)V_i/V_j/V_m}{A_0(r_b)}.
$$

Eq. (30) is the general expression of the third-order path length moments, and $P(i,j,m)$ indicates the permutation of three integers; therefore, the series of Eq. (30) has six elements if $i \neq j \neq m$, three elements if two of the indices are equal, or one element if $i = j = m$. Again $k_i$, $k_j$, and $k_m$ are the counters of the voxels $i, j, m$, respectively, and are constrained by the relationship $k_i + k_j + k_m = 3$. We note that for the case $k_i = k_j = k_m = 1$ the mixed moment $\langle l_i^1 l_j^1 l_m^1 \rangle$ is invariant if we swap the volumes of integration $V_i$, $V_j$, and $V_m$, and this property should be verified by this kind of mixed path length moment. However this property is not valid when two indices are equal; in fact, for example, $\langle l_i^1 l_j^1 l_m^1 \rangle \neq \langle l_i^2 l_j^1 l_m^1 \rangle$ as a general property. In Appendix C we show how the mixed moment $\langle l_i^1 l_j^1 l_m^1 \rangle$ is connected to lower-order moments through some approximate relationships that are used in Part II. If the integrands of Eq. (30) can be assumed rather constant (in this case the three voxels must be distinct) we can write the formula of the mixed moment as

$$
\langle l_i^1 l_j^1 l_m^1 \rangle = \frac{\sum_{P(i,j,m)} A_0(r_b,r_i)\phi_0(r_i)\phi_0(r_j)\phi_0(r_m)\phi_0(r_m)V_i/V_j/V_m}{A_0(r_b)},
$$

where $r_i$, $r_j$, and $r_m$ in Eq. (31) can be chosen arbitrarily within the voxels $i, j, m$, respectively.
For the case \( k_1=3, k_1=k_m=0 \) we can derive one of the third-order self moments as

\[
\langle l^3 \rangle = \frac{3!}{V_i} \int_{V_i} \phi_0(r_1, r_2) \, dr_1 \int_{V_i} \phi_0(r_2, r_3) \, dr_2 \int_{V_i} \phi_0(r_3) \, dr_3,
\]

(32)

where we have assumed that \( A_3(r_3, r_1) \) and \( \phi_0(r_3) \) are rather constant within the voxel \( i \). In general we can derive the expression of the \( n \)th-order self moment as

\[
\langle l^n \rangle = \frac{n!}{V_i} \int_{V_i} \phi_0(r_1, r_2) \, dr_1 \int_{V_i} \phi_0(r_2, r_3) \, dr_2 \ldots \int_{V_i} \phi_0(r_{n-1}, r_n) \, dr_n.
\]

(33)

As we briefly commented previously the estimate of the self moments by relations (29), (32), and (33) requires that we “step aside” from diffusion theory and use a suitable solution of the RTE for the calculation of the multiple integrals. After reframing the perturbative approach within transport theory, we found that the general expressions of the moments derived from the Neumann series of perturbative RTE are not always formally equivalent to those derived from the Neumann series of the perturbative DE. Therefore we should question if relation (33) can always be considered a good approximation of the self moments, even when a suitable solution of the RTE for the fluence rate is used in the integrands. In Appendix D it is shown that the second-order self moment derived from the RTE can be reduced to Eq. (28), but this is not so for higher-order self moments. These arguments are supported by numerical calculation of multiple integrals. We have verified by direct calculation of double integrals that relation (29) yields the correct values of the second-order moments with a discrepancy of up to a few percent of those calculated by MC, under the condition that an approximate solution of the RTE be used for the fluence rate [see Eq. (37) below]. However, we found systematic a underestimate of \(-10–20\%\) of the third-order self moments calculated by MC when relation (32) was used. After studying the statistical error of \( \langle l^3 \rangle \) from independent MC simulations and the convergence of the numerical method used for the evaluation of triple integrals, it is reasonable to conclude that the mismatch lies in the approximation inherent to relation (32).

G. Heuristic Method

For the reasons given above, in this work we did not use relation (33) for the calculation of higher-order self moments. Instead we propose a heuristic method that is based on the calculation of \( \langle l_i \rangle \), a single integral, and some scaling parameters. The method is an extension of the one proposed by Ostermeyer and Jacques\(^{30}\) for the calculation of the self-interacting terms. Our purpose is to show that we can approximate the higher-order self moments calculated by MC simulations by using the expression

\[
\langle l^n \rangle = c_{n-1} \langle l_i \rangle \left( \int_{V_i} \phi_0(r-r_i) \, dr \right)^{n-1},
\]

(34)

where \( r_i \) is chosen for convenience at the center of the voxel \( i \). Relation (34) corresponds to a straightforward “substitution rule” of the multiple integral in relation (33) that can be derived by comparison of the two equations

\[
\int_{V_i} \phi_0(r_1, r_2) \, dr_1 \int_{V_i} \phi_0(r_2, r_3) \, dr_2 \ldots \int_{V_i} \phi_0(r_{n-1}, r_n) \, dr_n
\]

\[
= c_{n-1} \langle l_i \rangle \left( \int_{V_i} \phi_0(r-r_i) \, dr \right)^{n-1}.
\]

(35)

This “substitution rule” can be stated as follows: Every time the calculation of a higher-order moment implies the calculation of a multiple integral where the volumes of integration are coincident we substitute the multiple integral in Eq. (35) with its right-hand term. We will apply this substitution rule not only for the calculation of the self moments, but also for the calculation of higher-order mixed moments whenever the same voxel is counted more than one time (see Appendix C). It will be one of the purposes of Part II\(^{31}\) to show that we can find some parameters \( c_{n-1} \) that are rather insensitive (a) to the shape—and, to a certain extent, to the size and position of the voxel; (b) to the values of the optical properties of the background medium (at least if we consider values of interest in diffuse optical imaging of biological tissues) and (c) to the geometry of the medium. There is another factor that makes the use of relation (34) appealing. Since the integrands in relation (34) represent the fluence rate when both the source and the field point are within the voxel \( i \), we realize that in many situations the computation of the integral can be appropriately and easily carried out by using available solutions of the RTE (either exact or approximate) in the homogeneous infinite medium geometry. For example, if the voxel \( i \) is a few millimeters or farther from the border of a homogeneous, semi-infinite, plane-bounded medium, the effect of the negative image point source used for deriving the correct expression of the Green’s function in this geometry will be totally negligible. If the solution of the RTE in the infinite medium geometry is used in relation (34) the computation of the integral in the right-hand term becomes even more trivial if we choose \( r_i \) at the center of the voxel, which usually has a regular and symmetric shape.

If we can apply the approximations discussed, the \( n \)th order self moment is related to the first moment by a simple formula,

\[
\langle l^n \rangle = c_{n-1} \langle l_i \rangle \left( \int_{V_i} \phi_0(r-r_i) \, dr \right)^{n-1},
\]

(36)

where it is explicitly shown that we are using the solution of the RTE in the infinite medium geometry for the calculation of the integral. To find the parameters \( c_{n-1} \), we ran MC simulations for calculating the self moments of relation (36) (including \( \langle l_i \rangle \)). For the calculation of the integral in relation (36) we used both the solution of the DE in the homogeneous infinite medium geometry,
\[ \phi_0(\mathbf{r} - \mathbf{r}_i) = \frac{\exp(-\mu_0 ||\mathbf{r} - \mathbf{r}_i||)}{4\pi D ||\mathbf{r} - \mathbf{r}_i||}, \tag{37} \]

where \( \mu_{\text{eff}} = [3\mu_2 + \mu_4]^{1/2} \) and \( D = 1/(3\mu_4) \), and an approximate solution of the RTE in the infinite medium geometry with isotropic scattering [Ref. 8, Eq. (14)]:

\[ \phi_0(\mathbf{r} - \mathbf{r}_i) = \frac{1}{4\pi} \left[ \frac{\alpha \exp(-\mu_0 ||\mathbf{r} - \mathbf{r}_i||)}{D_{\text{app}} ||\mathbf{r} - \mathbf{r}_i||} + \frac{\exp(-\mu_i ||\mathbf{r} - \mathbf{r}_i||)}{||\mathbf{r} - \mathbf{r}_i||^2} \right]. \tag{38} \]

In Eq. (38) \( \alpha \) is the albedo of the medium (\( \alpha = \mu_a/\mu_t \), \( \mu_t = \mu_a + \mu_s \)), \( k_0 \) is defined by the transcendental equation

\[ \arctanh(k_0/\mu_t) = 1, \tag{39} \]

and \( D_{\text{app}} = \mu_a/k_0^2 \).

For all the cases that were studied in Part II we found that the difference between \( k_0 \) and \( \mu_{\text{eff}} \) was \( \approx 0.1\% - 0.6\% \), and for this reason the usual expressions of \( \mu_{\text{eff}} \) and \( D \) were used instead of \( k_0 \) and \( D_{\text{app}} \), respectively. The parameters \( c_{n-1} \) were determined by simply studying the ratio that defines them from Eq. (36) for a wide variety of sizes and locations of the defects and the optical properties of the medium. More details about the way of calculating the parameters \( c_{n-1} \) are given in Part II.

From a few trials we found that by using Eq. (37) for the calculation of the integral in relation (36) we obtained parameters \( c_{n-1} \) that were rather insensitive to the optical properties, geometry of the medium, and location of the defects; however, these parameters turned out to be rather sensitive to the size of the defect. On the other hand, when we used Eq. (38) the parameters \( c_{n-1} \) were more insensitive to the size of the defect. Therefore eventually we decided to use Eq. (38) for the study of the parameters \( c_{n-1} \) presented in Part II.

**H. General Expression of nth-Order Moments**

Finally we want to note that, based on the arguments discussed above for \( n = 1, 2, 3 \), the general expression of the \( n \)th order moment is given by the formula

\[
\langle I_1^{i_1} \cdots I_n^{i_n} \rangle = \frac{k_1! \cdots k_n!}{n!} \sum_{\mathbf{p}=(i_1 \ldots i_n)} \int_{V_1} A_0(\mathbf{r}_i, \mathbf{r}_j) d\mathbf{r}_i \int_{V_2} A_0(\mathbf{r}_j, \mathbf{r}_k) d\mathbf{r}_j \cdots \int_{V_n} A_0(\mathbf{r}_j, \mathbf{r}_m) d\mathbf{r}_m \phi_0(\mathbf{r}_1, \mathbf{r}_2) \phi_0(\mathbf{r}_3, \mathbf{r}_4) \cdots \phi_0(\mathbf{r}_{n-1}, \mathbf{r}_n) \phi_0(\mathbf{r}_n) d\mathbf{r}_n \tag{40} \]

The number of terms in the series of Eq. (40) depends on the counters \( k_1, k_2, \ldots, k_n(k_1+k_2+\cdots+k_n=n) \) of the voxels \( i_1, \ldots, i_n \). Therefore the number of terms in the series is given by \( n!/(k_1! k_2! \ldots k_n!) \). In Part II we will provide approximate formulas for the calculations of the mixed moments up to the fourth order following the method described in Appendix C.

**3. DISCUSSION AND CONCLUSIONS**

In this paper we have proposed a different way to look at the solution of the perturbative DE for highly scattering media. The theory developed consists of using the terms of the Neumann series solution of the perturbative DE to provide the expression of the moments of the GTPSF derived in transport theory. In this way the meaning of the different orders of Neumann series is more direct, since they represent higher-order interaction among different regions of the medium. We have discussed that the rigorous theory of the moments of the GTPSF should be developed from transport theory and that we should always understand the conditions on whether the correct expressions of the moments can be reduced to those obtained from diffusion theory. The main reason to use the perturbative DE for deriving the expression of the moments is that we obtain more practical expressions. We have found that the estimation of the mixed moments of separate voxels can be carried out by using the expressions proposed in this work and the solution of the DE in the geometry of interest for the calculation of the multiple integrals in the Neumann series. In contrast, the calculation of the self moments poses more difficulties since the self moments are based on the estimation of the effect of source points on field points indefinitely close to one another. In Appendix D we have derived the expressions of the second- and third-order self moments from the RTE. We have discussed that, under the assumption that a voxel is a few millimeters away from source and detector, the second-order self moment found in transport theory [Eq. (D4)] reduces to Eq. (28) derived from the Neumann series of perturbative DE. However a suitable solution of the RTE for the fluence rate must be used for the calculation of the moments. As for the third-order self moments, we could not reduce Eq. (D8) to Eq. (30), which provide the moments derived from the RTE and the DE, respectively. The same conclusion applies to higher-order self moments. These results were supported by numerical calculation of the double and triple integrals of relations (29) and (32), respectively. For example, in most cases discussed in Part II,\(^1\) it was not uncommon that the second-order self moments calculated by MC were underestimated by \( \approx 15\% - 30\% \) whenever the classical solution of the DE [Eq. (37)] was used for the calculation of the double integral in relation (29). However, by using an approximate solution of the RTE [Eq. (38)] we always found good agreement with the moments calculated by MC simulations (discrepancy of a few percent, which is within the statistical error of MC).

The approximate solution of the RTE used in this work has been demonstrated\(^8\) to yield very good comparison with the exact solution of the RTE (discrepancy less than a few percent) in the range of albedo \( \alpha \) of \((0.5, 1)\); therefore in principle it could be used also for the calculation of higher-order self moments as shown by relation (33).
However, the third-order self moments calculated from Eq. (38) have yielded systematic underestimation (≈10% – 20%) of those calculated by MC simulations. After studying the convergence of triple integrals by increasing the partition of a defect into smaller voxels and considering the statistical error of MC simulations, we concluded that the discrepancy is most likely due to an incorrect model for evaluating the higher-order moments [relation (33)].

Since the exact evaluation of the moments can be rather challenging with respect to both the complexity of the expressions and the numerical evaluation of the multiple integrals, in this paper we have proposed a heuristic method to calculate higher-order self and mixed moments. The method can be applied for a general geometry of the medium and also for a range of values of the optical properties and sizes of the inclusions usually found in diffuse optical imaging of biological tissues. The expression of the self moments given by relation (33) is replaced by relation (36), which involves the calculation of only one single integral and the use of some parameters \(c_{n-1}\) that were found by use of MC simulations in the Part II. As for the mixed moments of distinct voxels, we have also proposed some simple quadrature rules [relations (27) and (31)] for decreasing the computational effort. The substitution rule for the calculation of the self moments [Eq. (35)] is combined with the quadrature rules for the calculation of higher-order mixed moments whenever a voxel is counted more than one time (see Appendix C). The complete set of formulas that were derived for a fourth-order perturbation theory will be given in Part II.

The approximate scaling relationships [relation (36)] between higher-order and first-order self moments can be used for the direct calculation of perturbation of single defects in the region beyond the limits of Born theory in a quite straightforward way. As for single larger defects that require a partition of the volume into smaller voxels, the proposed quadrature rules discussed above have also yielded good agreement—to within ≈10% – 20% with MC—even when adjacent voxels were considered.

A theory based on the calculation of perturbations by use of the moments should also address an important question: Can we avoid partitioning a relatively large defect of fixed absorption contrast into smaller voxels? In Part II we address this question by using the heuristic method proposed. In particular we were interested to check if relation (36) could be applied to the calculation of the perturbation of a relatively large inclusion (having linear size of ≈10 mm) embedded in a semi-infinite scattering medium and avoiding its partition into smaller voxels. In another section of Part II we also compare the results of the theory and those obtained with MC simulations for the case of multiple defects embedded in a homogeneous, semi-infinite medium. The results that were obtained confirm the potential of the method for the calculation of perturbations due to both single and multiple defects.

APPENDIX A: PERTURBATION THEORY FOR THE TIME DOMAIN

In the time domain the pencil beam has a temporal evolution that can be described by a Dirac \(\delta\) function \(\delta(t)\), and the detector can measure the total time of flight of detected photons. The temporal spread of detected photons is usually referred to as the temporal point-spread function (TPSF) and represents the probability per unit area and time to detect a photon at time \(t\). The relationship between the TPSF [here defined as \(R_0(t)\)] and the GTPSF \(f_0(t_1, \ldots, t_N)\) when the medium is nonabsorbing is

\[
\int_{\sigma^N} f_0(t_1, \ldots, t_N) \, d\sigma = R_0(r_b, t, \mu_a) = 0, \tag{A1}
\]

where \(\sigma^N\) is the hyperplane in \(R^N\) defined by \(\Sigma_{i=1}^N t_i = t\). By using the same procedures applied previously for the CW domain, we can derive an expression formally identical to Eq. (6):

\[
R_{fi}(r_b, t, \mu_a + \Delta \mu_a) = R_{in}(r_b, t, \mu_a) \sum_{k_1, k_2, \ldots, k_N=0}^{\infty} (-1)^{k_1+k_2+\cdots+k_N} \times \frac{\Delta \mu_a^{k_1} \ldots \Delta \mu_{an}^{k_N} b_N}{k_1! \ldots k_N!} \langle \ell_{k_1}^1 \ldots \ell_{k_N}^N(t) \rangle, \tag{A2}
\]

where \(\langle \ell_{k_1}^1 \ldots \ell_{k_N}^N(t) \rangle\) is the time-resolved mixed path length moment of order \((k_1, k_2, \ldots, k_N)\) calculated in the initial state of the medium at time \(t\) and defined by

\[
\langle \ell_{k_1}^1 \ldots \ell_{k_N}^N(t) \rangle = \frac{\int_{\sigma^N} (vt_1)^{k_1} \ldots (vt_N)^{k_N} f_{in}(t_1, \ldots, t_N) \, d\sigma}{\int_{\sigma^N} f_{in}(t_1, \ldots, t_N) \, d\sigma}. \tag{A3}
\]

The time-dependent DE is

\[
\frac{1}{v} \frac{\partial \phi_{in}(r, t)}{\partial t} - \nabla \cdot [D(r) \nabla \phi_{in}(r, t)] + \mu_a(r) \phi_{in}(r, t) = \delta(r - r_b) \delta(t), \tag{A4}
\]

where \(\phi_{in}\) is the Green’s function of the fluence rate in the initial state of the medium. In the final state, that is, after a change \(\Delta \mu_a(r)\) in the absorption coefficient has occurred, the fluence rate will be \(\phi_f\) and the change in the fluence rate \(\Delta \phi(r, t)\) will satisfy the equation formally equal to (A4), which also has the Neumann series as its solution.

By using the same method described for the CW domain we find similar expressions of the moments. For example, the first- and second-order moments are given by the formulas

\[
\langle l_i^1(t) \rangle = \int dR_0(r_b, t - t_1) \frac{\int dR_0(r_b, t_1) \phi_0(r_b, t_1) \, dt_1}{R_0(r_b, t)}, \tag{A5}
\]
\( \langle l_i^k l_j^k(t) \rangle = \frac{1}{R_0(r_0,t)} k_i! k_j! \sum_{P_{i,j}} \int_{V_i} \int_0^\infty R_0(r_0, r_1, t - t_1) dt_1 \times \int_{V_j} \int_0^\infty \phi_0(r_1, r_2, t_1 - t_2) \phi_0(r_2, t_2) dt_2 \). \quad (A6)

We recall that the counters of the voxels \( i \) and \( j, k_i, \) and \( k_j \) (respectively) verify the condition \( k_i + k_j = 2 \). In Eqs. (A5) and (A6) \( R_0 = \phi_0 = 0 \) when \( t - t_1 < 0 \) or \( t_1 - t_2 < 0 \), because the solution of Eq. (A4) is defined by use of a step function.\(^{45}\) We note again that for the calculation of a mixed moment \((k_1 = k_2 = 1)\) the solution of the DE in the geometry of interest can be used for the calculation of the integral in Eq. (A6). However, we have to resort to a suitable solution of the RTE\(^9\) for the calculation of the self moments (e.g., \( k_i = 2, k_j = 0 \)).

**APPENDIX B: PERTURBATION THEORY FOR THE FREQUENCY DOMAIN**

The frequency domain case can be treated in the same way as the CW case. In fact if we consider the Fourier transform of Eq. (A4) we obtain

\[
- \nabla \cdot (D(r) [\nabla \phi(r, \omega)] + \mu_a(r) + i \frac{\omega}{v} \phi(r, \omega) = \delta(r - r_0),
\]

(B1)

where \( \tilde{\phi}(r, \omega) \) is the Fourier transform of the time-resolved fluence rate [solution of Eq. (A4)]. Equation (B1) is formally identical to the CW equation for the fluence rate [Eq. (10)]; therefore the perturbative equation can be solved by the same Neumann series. If we also consider the Fourier transform of Eq. (A2) we obtain

\[
\tilde{R}_\alpha(r_0, \omega, \mu_a, \Delta \mu_a) = \tilde{R}_\alpha(r_0, \omega, \mu_0) \times \left\{ \sum_{k_1, \ldots, k_N = 0}^{\infty} (-1)^{k_1 + k_2 + \cdots + k_N} \alpha_{k_1, \ldots, k_N} \times \langle l_{k_1}^1 l_{k_2}^1 \ldots l_{k_N}^1 \rangle(\omega) \right\},
\]

(B2)

where \( \langle l_{k_1}^1 l_{k_2}^1 \ldots l_{k_N}^1 \rangle(\omega) \) is defined as

\[
\langle l_{k_1}^1 l_{k_2}^1 \ldots l_{k_N}^1 \rangle(\omega) = \frac{\tilde{G}(k_1, k_2, \ldots, k_N, \omega)}{\tilde{R}_\alpha(r_0, \omega, \mu_0)}.
\]

(B3)

\( \tilde{G}(k_1, k_2, \ldots, k_N, \omega) \) is the Fourier transform of the term \( \tilde{R}_\alpha(r_0, \omega, \mu_a, \Delta \mu_a)(l_{k_1}^1 l_{k_2}^1 \ldots l_{k_N}^1(t)) \) in Eq. (A2). The moments are found again after comparison of the Neumann series with Eq. (B2). For example the first- and second-order moments are given by the formulas

\[
\langle l_i(\omega) \rangle = \frac{\int_{V_i} \tilde{R}_\alpha(r_0, r_1, \omega) \tilde{\phi}_0(r_1, \omega) dr_1 \tilde{R}_\alpha(r_0, \omega)}{\tilde{R}_\alpha(r_0, \omega)},
\]

(B4)

In Eqs. (B5) and (B6) \( \tilde{\phi}_0(r, \omega) \) and \( \tilde{R}_\alpha(r_0, \omega) \) are the solution of the frequency domain DE [Eq. (B1)] and the complex reflectance defined by Fick’s law, respectively.

**APPENDIX C: QUADRATURE RULE FOR A HIGHER-ORDER MIXED MOMENT**

How can we approximate the expression of a mixed moment such as \( \langle l_i^j l_k^l \rangle \)? Here we propose the following method. We start from its correct expression

\[
\langle l_i^j l_k^l \rangle = \frac{2}{A_0(r_0)} \left[ \int_{V_i} A_0(r_0, r_1) dr_1 \int_{V_j} \phi_0(r_1, r_2) dr_2 \int_{V_k} \phi_0(r_2, r_3) \phi_0(r_3) dr_3 \right. \times \left. \int_{V_i} A_0(r_0, r_1) dr_1 \int_{V_j} \phi_0(r_1, r_2) dr_2 \int_{V_k} \phi_0(r_2, r_3) \phi_0(r_3) dr_3 + \int_{V_i} A_0(r_0, r_1) dr_1 \int_{V_j} \phi_0(r_1, r_2) dr_2 \int_{V_k} \phi_0(r_2, r_3) \phi_0(r_3) dr_3 \right] .
\]

(C1)

We note that in the first multiple integral the variables \( r_2 \) and \( r_3 \) belong to different voxels. In the same integral we assume that \( A_0(r_0, r_1) \) and \( \phi_0(r_3) \) are rather constant within the voxels \( i \) and \( k \), respectively. In the second multiple integral all the variables belong to different voxels; therefore, we assume the integrands constant within the voxels. In the third multiple integral the variables \( r_1 \) and \( r_2 \) again belong to different voxels; we also assume that \( A_0(r_0, r_1) \) and \( \phi_0(r_3) \) are rather constant within the voxels \( k \) and \( i \), respectively. Therefore we can simplify Eq. (C1) as
where $\mathbf{r}_i$ and $\mathbf{r}_k$ can be chosen arbitrarily within the voxels $i$ and $k$, respectively. If we assume the validity of the reciprocity theorem and we recall Eqs. (27) and (35) (the former defines $\langle I_i^2 \rangle$, the latter is the substitution rule) we can rewrite Eq. (C2) as

$$
\langle I_i^2 \rangle = c_1 \langle I_i \rangle \int_{V_i} \phi_0(|\mathbf{r} - \mathbf{r}_i|)d\mathbf{r} + 2\langle I_i \rangle \langle \phi_0(\mathbf{r}_i, \mathbf{r}_k) \rangle^2 V_k, 
$$

(C3)

where we have used also Eq. (23) for the definition of $\langle I_i \rangle$.

In relation (C3) we have assumed that the calculation of the integral is carried out by using Eq. (38) where $\mathbf{r}_i$ is at the center of the voxel. In Part II we provide other approximate formulas for the calculations of the mixed moments up to the fourth order by following the same method.

**APPENDIX D: DERIVATION OF HIGHER-ORDER MOMENTS FROM THE RADIATIVE TRANSFER EQUATION**

The purpose of this appendix is to derive the expression of the second- and third-order moments from the RTE. The RTE is written as

$$
\mathbf{s} \cdot \nabla I(\mathbf{r}, \mathbf{s}) + \left[ \mu_\sigma(\mathbf{r}) + \mu_\alpha(\mathbf{r}) \right] I(\mathbf{r}, \mathbf{s}) = \mu_\sigma(\mathbf{r}) \int_{4\pi} p(\mathbf{s}, \mathbf{s}') I(\mathbf{r}, \mathbf{s}')d\omega' + S(\mathbf{r}, \mathbf{s}). 
$$

(D1)

Here $I$ is the specific intensity where $\mathbf{r}$ and $\mathbf{s}$ are spatial and angular variables, respectively; $p(\mathbf{s}, \mathbf{s}')$ is the phase function; $S$ is a source term; and $d\omega'$ is the infinitesimal solid angle around the direction $\mathbf{s}'$. $\mu_\sigma$ and $\mu_\alpha$ are the scattering and the absorption coefficients, respectively. The Green’s function of Eq. (D1) is obtained when the source term is defined as $S(\mathbf{r}, \mathbf{s}) = \delta(\mathbf{r} - \mathbf{r}_b)\delta(\mathbf{s} - \mathbf{s}_b)$. If we apply an arbitrary change to the absorption coefficient $\Delta \mu_\alpha(\mathbf{r})$ and we define $I_0$ and $I_\Delta$ as the Green’s functions of the medium in the initial and final states of the medium, respectively, we obtain the Fredholm equation of the second kind:

$$
I_\Delta(\mathbf{r}, \mathbf{s}) = I_0(\mathbf{r}, \mathbf{s})
- \int_V d\mathbf{r}_1 \int_{4\pi} I_0(\mathbf{r}, \mathbf{s}, \mathbf{r}_1, \mathbf{s}_1) \Delta \mu_\alpha(\mathbf{r}_1) I_\Delta(\mathbf{r}_1, \mathbf{s}_1)d\omega_1.
$$

(D2)

The $n$th-order approximation to the Neumann series solving Eq. (D2) is given by a formula that is formally identical to Eq. (19). We note that the reflectance can also be developed in a Neumann series, but instead of using Fick’s law we have to apply the rigorous definition. For example the $n$th-order approximation of the reflectance is given by

$$
A_n(\mathbf{r}_b) = \int_{2\pi} I_0(\mathbf{r}_b, \mathbf{s}) \mathbf{s} \cdot n d\omega.
$$

(D3)

Here $\mathbf{n}$ is the unit vector perpendicular to the medium at the detector’s position in $\mathbf{r}_b$, and the integral is carried out in the half-solid angle defined by $\mathbf{s} \cdot \mathbf{n} > 0$. By following the same method described in this work, that is, by comparing the different order of the Neumann series with Eq. (6), we obtain the moments of the GTPSF derived within the RTE. For example the second-order moment is given by the formula

$$
\langle I_i^2 \rangle = \frac{k_i \rho_i}{A_0(\mathbf{r}_b, \mathbf{r}_{b, i})} \sum_{\beta=1}^{\infty} \int_{V_i} \int_{V_j} \int_{2\pi} \mathbf{s} \cdot n d\omega \int_{4\pi} I_0(\mathbf{r}_b, \mathbf{s}, \mathbf{r}_1, \mathbf{s}_1) d\omega_1 \int_{4\pi} I_0(\mathbf{r}_1, \mathbf{s}_1, \mathbf{r}_2, \mathbf{s}_2) d\omega_2.
$$

(D4)

Here $A_0(\mathbf{r}_b)$ is defined by Eq. (D3) for the unperturbed system. Equation (D4) reduces to Eq. (26) (in the general case of separate or coincident voxels) if the voxels $i$ and $j$ are far enough from source and detector (a few millimeters for typical cases of interest). In fact in this situation we can say that photons emitted from the source located at $\mathbf{r}_b$ are diffused when they reach the defects. This condition implies that $I_0(\mathbf{r}_2, \mathbf{s}_2) = \phi_0(\mathbf{r}_2)/4\pi$.

We can also assume that the photons emitted by source points located within the defects are diffused when they reach the detector. This corresponds to the condition $I_0(\mathbf{r}_b, \mathbf{s}, \mathbf{r}_1, \mathbf{s}_1) = I_0(\mathbf{r}_b, \mathbf{s}, \mathbf{r}_1)$. For the derivation of Eq. (26) we note also that $A_0(\mathbf{r}_b, \mathbf{r}_1)$ and $\phi_0(\mathbf{r}_1, \mathbf{r}_2)$ are defined as

$$
A_0(\mathbf{r}_b, \mathbf{r}_1) = \int_{2\pi} I_0(\mathbf{r}_b, \mathbf{s}, \mathbf{r}_1) \mathbf{s} \cdot n d\omega, 
$$

(D5)

$$
\phi_0(\mathbf{r}_1, \mathbf{r}_2) = \int_{4\pi} d\omega_1 \int_{4\pi} \frac{I_0(\mathbf{r}_1, \mathbf{s}_1, \mathbf{r}_2, \mathbf{s}_2)}{4\pi} d\omega_2.
$$

(D6)

The final assumption in deriving Eq. (26) from Eq. (D4) is that Fick’s law is equivalent to Eq. (D3) for the calculation of the reflectance. The third-order moments are obtained in the same way and are expressed by
\[
\langle I^b_j l^b_m \rangle = \frac{k_i! k_j! k_m!}{A_0(r_b)} \sum_{\{i,j,m\}} \int_{V_i} dr_1 \int_{V_j} dr_2 \int_{V_m} dr_3 \\
\times \int_{2\pi} s \cdot nd\omega \int_{4\pi} I_0(r_b, s, r_1, s_1)d\omega_1 \\
\times \int_{4\pi} I_0(r_1, s_1, r_2, s_2)d\omega_2 \\
\times \int_{4\pi} I_0(r_2, s_2, r_3, s_3)I_0(r_3, s_3)d\omega_3. \tag{D7}
\]

By using the same assumptions as before we are led to the following expression:

\[
\langle I^b_j l^b_m \rangle = \frac{k_i! k_j! k_m!}{A_0(r_b)} \sum_{\{i,j,m\}} \int_{V_i} A_0(r_b, r_1)dr_1 \int_{V_j} dr_2 \\
\times \int_{4\pi} \phi_0(r_3)dr_3 \int_{4\pi} I_0(r_1, s_1, r_2, s_2)d\omega_2 \\
\times \int_{4\pi} \frac{1}{4\pi} I_0(r_2, s_2, r_3, s_3)d\omega_3. \tag{D8}
\]

If we are considering a mixed moment of separate voxels \((k_i=k_j=k_m=1)\) we can also assume \(I_0(r_1, s_1, r_2, s_2) = \phi_0(r_1, r_2)/4\pi\) and \(I_0(r_2, s_2, r_3, s_3) = \phi_0(r_2, r_3)/4\pi\) that are obtained by Eq. (D6) when the integrand is rather constant. However, we note that the accuracy of these further approximations depends on the relative location of the voxels in the medium. In this way Eq. (D8) reduces to Eq. (30) for the case of separate voxels. For the case of the third-order self moment \((k_i=3, k_j=k_m=0)\) the assumptions that the specific intensity is almost isotropic is no longer valid, and we are left with Eq. (D8), which cannot be reduced to Eq. (30). After inspection of the last three angular integrals of Eq. (D8) we can say that the discrepancy between Eq. (D8) and Eq. (30) for the calculation of the third-order self moments depends on the relationship among \(I_0(r_2, s_2, r_2)\phi_0(r_1, r_2, s_2)\) and \(I_0(r_2, s_2, r_3)\times \phi_0(r_1, r_2, s_2)\), according to Eq. (D8) and Eq. (30), respectively, where the average values are calculated with respect to the angular variable \(s_2\). We recall that \(I_0(r_2, s_2, r_3)\) is the specific intensity at \(r_2\) in the direction \(s_2\) due to an isotropic source at \(r_3\), while \(\phi_0(r_1, r_2, s_2)\) is the fluence rate at \(r_1\) due to the source \(\delta(r-r_2)\delta(s-s_2)\).

**APPENDIX E: COMPARISON BETWEEN BORN AND RYTOV METHODS AND THE THEORY DEVELOPED**

By reframing the perturbation theory using the moments, we have a different perspective of the relationship between the most commonly used methods for solving the perturbative DE, namely, the Born and Rytov approximations, and the theory developed here. Let us consider a single inclusion, not necessarily “small” but having a fixed absorption contrast \(\Delta \mu_a\). The correct expansion of the fluence rate for the Green’s function of Eq. (9) is

\[
\phi(r) = \phi_0(r) \sum_{k=0}^{\infty} (-1)^k \langle l^b \rangle_k (\Delta \mu_a)^k, \tag{E1}
\]

where \(\phi_0(r)\) is the fluence rate of the unperturbed system and \(\langle l^b \rangle_k\) is the self moment of order \(k\) for the fluence rate. We note that in principle \(\langle l^b \rangle_k\) is different from the self moments of the reflectance (here defined as \(\langle l^b \rangle_k\)) even when the field point \(r\) coincides with the detector’s location at \(r_b\) (this is the case, for example, when a refractive index mismatch is present between medium and surroundings). The Born approximation has already been discussed and consists of retaining only the terms of Eq. (E1) up to the first-order expansion.

In the Rytov approximation we look for a solution of the perturbative DE of the kind

\[
\phi(r) = \phi_0(r) \exp(-\alpha(r)), \tag{E2}
\]

where \(\phi_0(r)\) is the solution of the unperturbed medium. The expression of \(\alpha(r)\) derived after some calculations is

\[
\alpha(r) = \Delta \mu_a \int_V \frac{\phi_0(r, r_1) \phi_0(r_1) dr_1}{\phi_0(r)} = \langle l \rangle_B \Delta \mu_a. \tag{E3}
\]

By comparison of Eqs. (E3) and (E1) we realize that the Rytov approximation consists of the assumption that \(\langle l^b \rangle_k = (\langle l \rangle_B)^k\). This approximation in most cases of interests is a poor one, as can be verified by MC simulations. Therefore we can conclude that even though the Rytov approximation performs better than the Born theory because it takes into account, at least partially, some nonlinear effects, it does not represent the correct way to approach the problem, as instead the theory proposed is meant to.

Finally, we note that the reflectance at \(r_b\) by using the Rytov approximation is given by use of Fick’s law and yields

\[
A(r_b) = [A_0(r_b)\exp(-\langle l \rangle_B \Delta \mu_a) - 1 - \langle l \rangle_B (\Delta \mu_a)^2 \langle l \rangle_B - \langle l \rangle_B^2]]. \tag{E4}
\]

In Eq. (E4), \(\langle l \rangle_B\) is calculated according to Eq. (E3) at \(r = r_b\), and \(\langle l \rangle_B\) is defined by Eq. (22). Therefore the Rytov approximation for the reflectance corresponds to the same approximation for the higher-order self moments only when \(\langle l \rangle_B = \langle l \rangle_B\).

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