Scattering-phase theorem

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We derive two mathematical relations between quantitative phase images of thin slices of inhomogeneous media and the scattering parameters of the bulk, i.e., scattering mean free path, l_s, and anisotropy factor, g. The l_s turns out to be inversely proportional to the spatial variance of the phase shift, and g is related to the variance of the phase gradient. These formulas, referred collectively to as the scattering-phase theorem, allow for extracting l_s and g in a spatially resolved manner and across an entire tissue section, that is, mapping large cross sections of tissues in terms of l_s and g.

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Light–tissue interaction can be modeled by a radiative transport equation, in analogy to the problem of neutron transport in nuclear reactors [1]. With further simplifying assumptions, a diffusion model can be applied to describe the steady-state [2] and time-resolved [3] light transport in tissues. The refractive index of biological structures has been modeled in the past both as discrete particle distribution [4] and continuous or fractal [5].

Light propagation in bulk tissue is described by two statistical parameters: the scattering mean free path, l_s, which provides the characteristic length scale of the scattering process, and the anisotropy factor, g, which scales l_s to higher values, $l_t = l_s/(1-g)$, to account for forward scattering. This new quantity, l_t, is called the transport mean free path and approaches l_s as the individual scattering becomes isotropic ($g \to 0$). The physical meaning of l_t (and its asymptotic limit, l_s) is the distance after which the direction of propagation is randomized. The direct measurement of these scattering parameters is extremely challenging, and, therefore, often simulations, e.g., Monte Carlo [6] or finite difference time domain [7], are used iteratively instead.

Fourier transform light scattering (FTLS) has been developed as the spatial analog of Fourier transform spectroscopy to provide angular scattering information from phase-sensitive measurements [8]. Thus, FTLS was used to measure l_s from angular scattering of tissue slices, and the anisotropy parameter g was determined by fitting the scattering pattern with Gegenbauer Kernel phase function [9].

In this Letter, we show that quantitative phase imaging of thin slices can be used to spatially map the tissue in terms of its scattering properties. Specifically, we establish mathematical relations between the phase map $\phi(x,y)$ associated with a tissue slice of thickness $L \ll l_s$ (see Fig. 1) and scattering parameters of the bulk, i.e., l_s and g. First, we show that the scattering mean free path l_s averaged over a certain area across a tissue slice is directly related to the mean-squared phase (variance of the phase) within that region. Second, we prove that the anisotropy factor g relates to the phase gradient distribution. These relations, which we refer collectively to as the scattering-phase theorem, are expressed as

$$l_s = \frac{L}{\langle \Delta\phi^2(\mathbf{r})\rangle_{\mathbf{r}}}, \tag{1a}$$

$$g = 1 - \left(\frac{l_s}{L}\right)^2 \frac{\langle |\nabla[\phi(\mathbf{r})]|^2\rangle_{\mathbf{r}}}{2{k_0}^2}. \tag{1b}$$

In Eqs. (1a) and (1b), L is the tissue slice thickness, $\langle \Delta\phi^2(\mathbf{r})\rangle_{\mathbf{r}} = \langle [\phi(\mathbf{r}) - \langle\phi(\mathbf{r})\rangle_{\mathbf{r}}]^2\rangle_{\mathbf{r}}$ is the spatial variance of ϕ, with $\langle\rangle_{\mathbf{r}}$ denoting spatial average, $\mathbf{r} = (x,y)$, $k_0 = 2\pi n_0/\lambda$, with λ the (average) wavelength of light in the medium, n_0 is the average refractive index of the tissue, and $|\nabla[\phi(\mathbf{r})]|^2 = (\partial\phi/\partial x)^2 + (\partial\phi/\partial y)^2$.

The starting point in proving the l_s–ϕ relationship [Eq. (1a)] is the definition of l_s as the characteristic length in the medium over which the irradiance ${I_0}'$ of the unscattered (or ballistic) light drops to $1/e$ of the original value I_0, i.e., the Lambert–Beer's law,

$${I_0}' = I_0 e^{-L/l_s}. \tag{2}$$

In Eq. (2), $I_0 = |U_0|^2$ and ${I_0}' = |{U_0}'|^2$, where U_0 and ${U_0}'$ represent, respectively, the incident plane wave and the unscattered field that passed through the slice, as illustrated in Fig. 1. Throughout the derivations, we ignore the effects of absorption. The field after the tissue slice, U'', carries information about the spatial phase distribution, $\phi(\mathbf{r})$, which is available for measurement via quantitative phase imaging, $U'(\mathbf{r}) = U_0 \cdot e^{i\phi(\mathbf{r})}$. Note that, here, we focus on phase objects (i.e., U_0 constant) relevant for unstained tissue measurements. The transmitted field can be expressed as the superposition between the scattered and unscattered components,

$$U'(\mathbf{r}) = {U_0}' + {U_1}'(\mathbf{r}). \tag{3}$$

Note that ${U_0}'$ is the zero-frequency (unscattered, ballistic) component of U' and ${U_1}'$ is the sum of all high-frequency field components. Therefore, ${U_0}'$ can be expressed as the spatial average of U',

$${U_0}' = \langle U_0 \cdot e^{i\phi(\mathbf{r})}\rangle_{\mathbf{r}}. \tag{4}$$

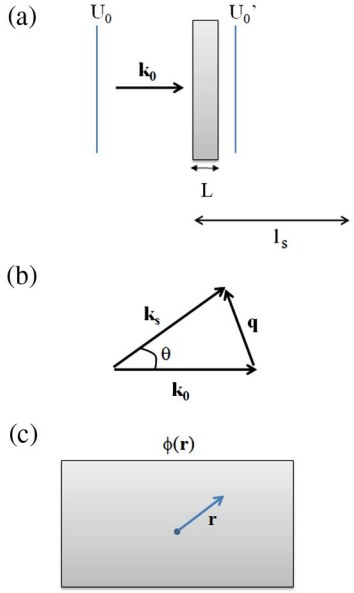

Fig. 1. (Color online) Light scattering by a thin tissue slice. (a) U_0, incident field; U_0', unscattered component of the transmitted field; L, thickness of the tissue slice; l_s, scattering mean free path; $\mathbf{k_0}$, incident wave vector. (b) $\mathbf{k_s}$, scattering wave vector; $\mathbf{q}$, momentum transfer; θ, scattering angle. (c) Position vector in the phase image.

For a normal distribution of phase shifts, where the probability density is a Gaussian function of the form $\exp[-\phi^2/2\langle\Delta\phi^2\rangle_\mathbf{r}]/\sqrt{2\pi\langle\Delta\phi^2\rangle_\mathbf{r}}$, the average in Eq. (4) is readily performed as

$$U_0{}' = \frac{U_0}{\sqrt{2\pi(\Delta\phi)^2}}\int_{-\infty}^{\infty} e^{i\phi}e^{-\frac{\phi^2}{2\langle\Delta\phi^2\rangle_\mathbf{r}}}\mathrm{d}\phi = U_0 e^{-\frac{\langle\Delta\phi^2\rangle_\mathbf{r}}{2}}. \tag{5}$$

In Eq. (5), $\langle\Delta\phi^2\rangle_\mathbf{r}$ is the variance associated with the phase shift distribution. Since $|U_0'/U_0|^2 = I_0'/I_0$, combining Eqs. (2) and (5) yields the expression of the scattering mean free path,

$$l_s = \frac{L}{\langle\Delta\phi^2(\mathbf{r})\rangle_\mathbf{r}}. \tag{6}$$

The assumption of Gaussian statistics provides the analytic formula in Eq. (6), which is simple and insightful at the same time. However, we note that the average in Eq. (4) can be calculated numerically for any non-Gaussian distribution of phase shifts, as long as the quantitative phase image is known. Further, it can be shown that the same result is obtained via the Tailor expansion of Eq. (4) to the second order, $U_0'/U_0 \simeq e^{i\langle\phi(\mathbf{r})\rangle_\mathbf{r}}(1-\langle[\Delta\phi(\mathbf{r})]^2\rangle_\mathbf{r}/2)$. For the zero-average signal, we obtain $|U_0'/U_0|^2 \simeq e^{-\langle[\Delta\phi(\mathbf{r})]^2\rangle_\mathbf{r}}$, which equals the Lambert–Beer's law in Eq. (2) and, thus, yields Eq. (6). Note that the small phase shift approximation is a stronger assumption than the Gaussian distribution. By performing the Taylor expansion to the second order, we approximate an arbitrary distribution, including a Gaussian, with a parabola. Around the origin, all distributions look like a Gaussian, which is the underlying origin of the central ordinate theorem. Therefore, the assumption of normally distributed phase values is more inclusive, as it covers the small values, where all distributions work, as a particular case.

To prove the g–ϕ relationship, by definition, g represents the average cosine of the scattering angle for a single scattering event. Recently, we have extended this concept to continuous distributions of scattering media, such as tissues [9]. We showed that, since l_s also means the distance over which, on average, light scatters once, g can be defined by the average cosine of the field transmitted through a slice of thickness l_s,

$$g = \langle\cos\theta\rangle_\theta. \tag{7}$$

As illustrated in Fig. 1(b), the scattering angle connects the incident wave vector $\mathbf{k_0}$, the scattered wave vector $\mathbf{k_s}$, and the momentum transfer, $\mathbf{q} = \mathbf{k_s} - \mathbf{k_0}$, $q = \sqrt{{q_x}^2 + {q_y}^2}$, as

$$\cos\theta = 1 - \frac{q^2}{2{k_0}^2}, \qquad q = 2k_0\sin\frac{\theta}{2}. \tag{8}$$

Combining Eqs. (7) and (8), we can express the average cosine as

$$g = 1 - \frac{1}{2{k_0}^2}\iint({q_x}^2 + {q_y}^2)P(q_x, q_y)\mathrm{d}q_x\mathrm{d}q_y. \tag{9}$$

In Eq. (9), $P(q_x, q_y)$ is the angular scattering probability distribution, which has the form

$$P(q_x, q_y) = \frac{|\tilde{U}'(q_x, q_y)|^2}{\int|\tilde{U}'(q_x, q_y)|^2\mathrm{d}q_x\mathrm{d}q_y}. \tag{10}$$

Inserting Eq. (10) into Eq. (9), we have

$$g = 1 - \frac{1}{2{k_0}^2}\frac{\int[|iq_xU'(q_x, q_y)|^2 + |iq_yU'(q_x, q_y)|^2]\mathrm{d}q_x\mathrm{d}q_y}{\int|\tilde{U}'(q_x, q_y)|^2\mathrm{d}q_x\mathrm{d}q_y}. \tag{11}$$

Using Parseval's theorem followed by the differentiation theorem [10], we obtain

$$\iint|iq_\alpha U'(q_x, q_y)|^2\mathrm{d}q_x\mathrm{d}q_y = \iint|\partial U'(x, y)/\partial\alpha|^2\mathrm{d}x\mathrm{d}y, \tag{12}$$

where $\alpha = x, y$. Combining Eqs. (12) and (11), we can write

$$g = 1 - \frac{\langle|\nabla[\phi_{ls}(\mathbf{r})]|^2\rangle_\mathbf{r}}{2{k_0}^2}, \tag{13}$$

where $\langle|\nabla[\phi_{ls}(\mathbf{r})]|^2\rangle_\mathbf{r} \equiv \int|\nabla\phi(\mathbf{r})|^2\mathrm{d}^2\mathbf{r}/\int\mathrm{d}^2\mathbf{r}$ is the averaged gradient intensity over the area, i.e., the variance of the gradient. Equation (13) expresses the relationship between g and the gradient of the phase shift distribution through a slice of thickness l_s. If the phase image, $\phi(r)$, is obtained over a thickness L, with $L \ll l_s$, then $\phi_{ls} = \phi\, l_s/L$. Thus, the anisotropy factor depends on the measurable phase image as

$$g = 1 - \left(\frac{l_s}{L}\right)^2 \frac{\langle |\nabla[\phi(\mathbf{r})]|^2 \rangle_{\mathbf{r}}}{2{k_0}^2}. \tag{14}$$

The l_s/L factor is related to the phase variance via Eq. (1a) such that Eq. (14) can also be expressed as

$$g = 1 - \frac{1}{2{k_0}^2} \frac{\langle |\nabla[\phi(\mathbf{r})]|^2 \rangle_{\mathbf{r}}}{\langle \Delta\phi^2(\mathbf{r}) \rangle_{\mathbf{r}}^2}. \tag{15}$$

In summary, the scattering-phase theorem connects the phase image of a thin tissue slice to the scattering properties of the tissue. Note that the tissue can be mapped in terms of l_s and g values that are averaged over patches of area S. While this remarkable result may seem counterintuitive, its physical interpretation is straightforward, as follows. The l_s–ϕ relationship simply establishes that the attenuation due to scattering is stronger (l_s shorter) as the tissue roughness (variance) is larger, i.e., the more inhomogeneous the tissue, the stronger the scattering. For homogeneous tissue, i.e., zero variance, l_s becomes infinite, which indicates the absence of scattering. On the other hand, the g–ϕ formula contains the gradient of the phase. Generally, a phase gradient relates to a tilt in the direction of propagation. The presence of the modulus squared of the gradient (or gradient intensity) indicates that the angular average is intensity based rather than field based. Thus, the higher the gradient variance, the higher the probability for large scattering angles, i.e., the smaller the g value [Eq. (14)]. In essence, a thin tissue slice can be assimilated with a (complicated) phase grating, which is characterized by a certain diffraction efficiency (controlled by l_s) and average diffraction angle (controlled by g).

We propose quantitative phase imaging as a direct method for extracting l_s and g, which is likely to have a significant impact in optical diagnosis. The l_s values are typically in the tens of micrometers and the biopsy slices in the 3–5 μm range, i.e., $L \ll l_s$, which is clearly within the applicability range of our theorem. Note that the amplitude (bright field) image can inform about the absorption in tissue, which may be useful in studying stained biopsies. In the experimental report that accompanies this Letter, we demonstrate this idea by mapping the scattering properties of tissues over broad spatial scales and also discuss the effects of the limited numerical aperture of the imaging optics [11]. Virtually all scattering methods of diagnosis operate on the principle that diseases, especially cancer, affect the architecture and, as a result, the scattering properties of tissues. We envision that our approach will facilitate building a large database, where various tissue types, healthy and diseased, are fully characterized in terms of their scattering parameters. These measurements will provide direct evidence as to whether a certain disease produces measurable effects in terms of light scattering, and, perhaps, will help determine which method is best suited for diagnosis.

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