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Min Xu

Fairfield University, mxu@fairfield.edu

R. R. Alfano

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Fractal mechanisms of light scattering in biological tissue and cells

M. Xu and R. R. Alfano

Institute for Ultrafast Spectroscopy and Lasers, and Department of Physics, The City College and Graduate Center of City University of New York, New York, New York 10031

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We use fractal continuous random media to model visible and near-infrared light scattering by biological tissue and cell suspensions. The power law of the reduced scattering coefficient, the anisotropy factor of scattering, and the phase function are derived with good agreement with experimental results. Implications for spectroscopic tissue diagnosis are discussed. © 2005 Optical Society of America

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The interaction of light with tissue and cells is the underlying mechanism for optical biomedical technology used in optical imaging and spectroscopy for detection of pathology changes. The optical properties of tissue are determined by chromophores, microstructures, and local refractive index variations. Microstructures in biological tissue range from organelles 0.2–0.5 μm or smaller, to mitochondria 1–4 μm in length and 0.3–0.7 μm in diameter, to nuclei 3–10 μm in diameter, to mammalian cells 10–30 μm in diameter. The refractive index variation is about 0.04–0.10 for biological tissue with a background refractive index of $n_0=1.35$.¹ Recently, the nature of light scattering in biological tissue has been actively studied.^{1–5} The fractal dimension of a monolayer of cells was investigated.^{6,7} As many biological tissues have fractallike organization and are statistically self-similar,^{2,8} a discrete particle model of scattering centers in tissue^{1,4} was proposed to model light scattering by tissue. The discrete particle model assumes that the refractive index variations caused by underlying microscopic structures can be treated as spherical particles with sizes distributed according to a power law:

$$\eta(a) = \eta_0 a^{3-D_f}, \quad (1)$$

where $\eta(a)$ is the volume fraction of spherical particles of radius $0 \leq a \leq a_{\max}$ with a maximum radius a_{\max} , η_0 is a constant, and D_f is the fractal dimension. On a microscopic scale the constituents of tissue have no clear boundaries and merge into a quasi-continuum structure. Discrete particles may not be appropriate to describe tissue inhomogeneities. As the refractive index variation in biological tissue is weak, tissue is better modeled as a continuous random medium where light scattering is not due to the discontinuities in refractive index but rather to weak random fluctuations of the dielectric permittivity.⁵

In this Letter, we propose to use fractal continuous random media to model light scattering by biological tissue and cells. The correlation function $R(r)$ of the random fluctuations of the dielectric permittivity depends on the fractal dimension D_f and the cutoff correlation length l_{\max} . Analytical expressions are derived for the power law of the reduced scattering coefficient, the anisotropy factor of scattering, and

the phase function. By examination of the existing experimental results, the fractal fluctuation of the dielectric permittivity is shown to determine visible and near-infrared light scattering by biological tissue and cell suspensions.

Assuming that tissue is statistically space homogeneous and isotropic, the correlation function of the dielectric permittivity can be written as $R(r) = \langle \delta\epsilon(\mathbf{r}') \delta\epsilon(\mathbf{r}'+\mathbf{r}) \rangle$, where $\delta\epsilon$ is the fluctuation of the dielectric permittivity from the background value. $R(\mathbf{r})$ is proportional to the correlation function of the fluctuation of the refractive index $R_n(\mathbf{r})$ and $\delta\epsilon(\mathbf{r}) = 2n_0^2(m-1)$, where m is the relative refractive index at position \mathbf{r} when the fluctuation of the refractive index is weak. Light scattering by the continuous random medium is determined by the power spectrum \hat{R} of the random fluctuations of the dielectric permittivity. The amplitude scattering matrix of the weakly fluctuating continuous random medium at the scattering angle θ is given by

$$S(\theta) \begin{bmatrix} \cos \theta & 0 \\ 0 & 1 \end{bmatrix} = k^3 \sqrt{\frac{\pi}{2} \hat{R} \left(2k \sin \frac{\theta}{2} \right)} \begin{bmatrix} \cos \theta & 0 \\ 0 & 1 \end{bmatrix}, \quad (2)$$

where $k \equiv 2\pi n_0/\lambda$ is the wavenumber and λ is the wavelength of light in vacuum. A simple exponential correlation function was considered by Moscoso *et al.*⁵ for modeling tissue light scattering.

The correlation function of the random fluctuations of the dielectric permittivity, in the fractal continuous medium model, is assumed to be an average of exponential functions weighted by power law distribution (1) for correlation length l :

$$R(r) = \varepsilon^2 \int_0^{l_{\max}} \exp\left(-\frac{r}{l}\right) \eta(l) dl = \varepsilon^2 \eta_0 l_{\max}^{4-D_f} E_{5-D_f} \left(\frac{r}{l_{\max}} \right), \quad (3)$$

where $\varepsilon^2 = 4n_0^4(m-1)^2$, l_{\max} is the cutoff correlation length, and $E_n(z) \equiv \int_0^1 \exp(-z/t) t^{n-2} dt$. Correlation function (3) is adopted based on the observed similarity of the refractive index fluctuation of biological tissue and inspired by the discrete particle model.^{1,4}

The correlation function at the origin is $R(0) = \varepsilon^2 T_v$, where T_v is the total volume fraction of scattering centers ($T_v \approx 0.3$ in soft tissue). The correlation function decays exponentially as $R(r) = \varepsilon^2 \eta_0 l_{\max}^{4-D_f} (r/l_{\max})^{-1} \exp(-r/l_{\max})$ at a large separation $r \gg l_{\max}$. The power spectrum is given by

$$\hat{R}(k) = \int_0^{l_{\max}} \frac{\varepsilon^2 l^3}{\pi^2 (1 + k^2 l^2)^2} \eta(l) dl. \quad (4)$$

The amplitude scattering function $S(\theta)$ in Eq. (2) can now be written as

$$|S(\theta)|^2 = \int_0^{kl_{\max}} \frac{\varepsilon^2 \eta_0 k^{D_f-1} x^{6-D_f}}{2\pi [1 + 2(1-\mu)x^2]^2} dx, \quad (5)$$

where $\mu \equiv \cos \theta$. The anisotropy factor (mean cosine of the scattering angle) can be found:

$$g = \int d\Omega \frac{(1 + \mu^2) \mu |S(\theta)|^2}{2k^2} \bigg/ \int d\Omega \frac{(1 + \mu^2) |S(\theta)|^2}{2k^2}. \quad (6)$$

The unnormalized phase function is given by

$$p(\theta) = \frac{(1 + \mu^2) |S(\theta)|^2}{2k^2} \\ = \frac{\frac{5 - D_f}{2} \pi}{\sin\left(\frac{5 - D_f}{2} \pi\right)} \frac{1 + \mu^2}{2} [2(1 - \mu)]^{-(7-D_f)/2} \\ \propto (1 + \mu^2) (1 - \mu)^{-(7-D_f)/2}. \quad (7)$$

The reduced scattering coefficient, defined as $\mu_s(1 - g)$, is given by

$$\mu'_s = \int d\Omega \frac{(1 + \mu^2) (1 - \mu) |S(\theta)|^2}{2k^2} \approx \varepsilon^2 \eta_0 \alpha \lambda^{3-D_f}, \quad (8)$$

where

$$\alpha \equiv (2\pi n_0)^{D_f-3} \frac{(11 - 4D_f + D_f^2)}{(D_f + 1)(D_f - 1)(D_f - 3)} \\ \times \frac{\frac{5 - D_f}{2} \pi}{2^{5-D_f} \sin\left(\frac{5 - D_f}{2} \pi\right)} \quad (9)$$

is a constant dependent only on D_f . We have assumed that $kl_{\max} \gg 1$ in our derivations of Eqs. (7) and (8).

The values of g in the fractal continuous medium model versus the cutoff size parameter kl_{\max} for various D_f are displayed in Fig. 1(a). g is larger with the increase of l_{\max} and the decrease of D_f . Light scattering equation (5) can be regarded as a weighted sum from components of different correlation lengths where the peak contribution occurs at $kl^* = kl_{\max}$

when $D_f < 4$ and kl^* may be different from kl_{\max} when $D_f > 4$. The value of kl^* when $D_f > 4$ is displayed in Fig. 1(b). The power law of μ'_s , Eq. (8), is obtained due to the cutoff at large correlation lengths as g approaches unity for components of increasing correlation lengths. By fitting the experimental wavelength dependence of μ'_s to Eq. (8), one can determine both the fractal dimension D_f and the parameter $\varepsilon^2 \eta_0$.

We first fit the theoretical power spectrum, Eq. (4), to the power spectrum of index variations in mouse liver tissue reported by Schmitt *et al.*² [see Fig. 2(a)]. The fit is excellent and yields $l_{\max} = 2.3 \mu\text{m}$ and $D_f = 4.0$ for mouse liver tissue. A single exponential correlation function⁵ will not fit. We do not know any results on the wavelength dependence of the reduced scattering coefficient for mouse liver tissue. The wavelength dependence of the reduced scattering coefficient of rat liver tissue was reported by Parsa *et al.*⁹ The reduced scattering coefficients within the range 600 to 1400 nm are displayed in Fig. 2(b) and fitted well to a power law $\lambda^{-0.94}$. The fractal dimension of rat liver tissue is hence $D_f = 3.94$. The cutoff correlation length is found to be $l_{\max} = 1.5 \mu\text{m}$ from $g = 0.94$ of the rat liver tissue at 800 nm. Evidently, both the fractal dimension and the cutoff correlation length extracted from the power spectrum of the refractive index variations of mouse liver tissue agree

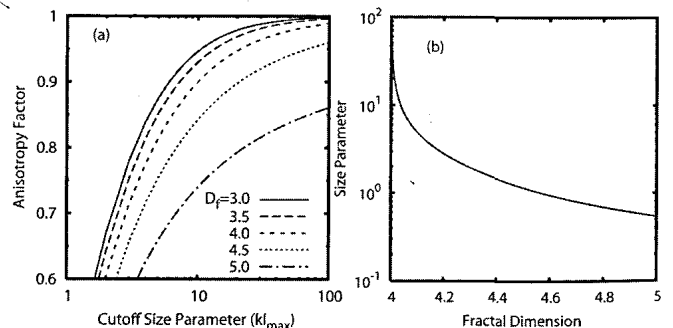


Fig. 1. (a) Anisotropy factor of the fractal continuous random medium versus cutoff size parameter kl_{\max} . (b) Size parameter kl^* of the component contributing most to light scattering when $D_f > 4$.

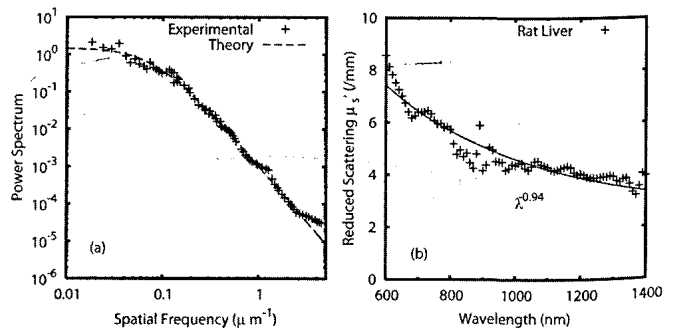


Fig. 2. (a) Power spectrum of refractive index variations in mouse liver tissue fitted to the theoretical power spectrum, Eq. (4). The symbols represent data reported in Ref. 2, and the dashed curve is the theoretical fit. Fitting yields $D_f = 4.0$ and $l_{\max} = 2.3 \mu\text{m}$. (b) Wavelength dependence of the reduced scattering coefficient of rat liver tissue fitted to the power law λ^{3-D_f} . The symbols represent data reported in Ref. 9, and the solid curve shows the fitted curve. Fitting yields $D_f = 3.94$ and $l_{\max} = 1.5 \mu\text{m}$.

reasonably well with those extracted from the light-scattering data for rat liver tissue.

Figure 3 displays the phase functions for suspensions of rat embryo fibroblast cells (M1) and mitochondria reported by Mourant *et al.*³ and the fit to the theoretical phase function (7). The fractal dimension is found to be $D_f=3.86$ and 4.58 for M1 cells and mitochondria, respectively. The value of the fractal dimension for M1 cells was 4 ± 0.07 with the reported wavelength dependence $\mu'_s \propto \lambda^{-1.0 \pm 0.07}$ over the wavelength range 500–800 nm. The agreement between the two values of D_f for M1 cells from fitting either the phase function or the power law of μ'_s is good. The g factor for M1 cells was reported to be 0.98, and the maximum correlation length can be estimated to be $l_{\max} \sim 3.2 \mu\text{m}$. The g factor for mitochondria can be computed from the phase function to be 0.81, and the maximum correlation length is then estimated to be $l_{\max} \sim 0.6 \mu\text{m}$. The component contributing the most to light scattering has size parameter $kl^* = kl_{\max} \approx 40$ and $kl^* \approx 1$ in M1 cells and mitochondria, respectively. M1 cells have much larger scattering centers and a much smaller fractal dimension than mitochondria. The larger scattering centers in M1 cells are due to the nucleus.

The power in the power law of $\mu'_s \propto \lambda^{-b}$ is usually called the scattering power. The scattering power in the fractal continuous medium model relates to the fractal dimension of the underlying fluctuation of the refractive index ($b=D_f-3$) and should be distinguished from that due to Mie particles of narrow size distribution.³ The scattering power has been recognized to be an important parameter in discriminating normal and cancerous tissue.^{10–12} Both the fractal di-

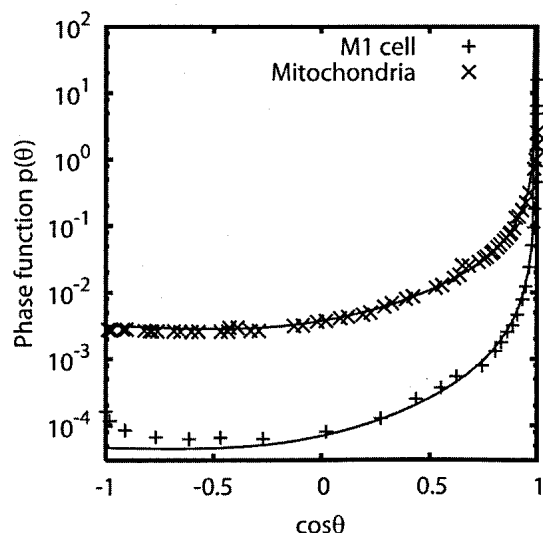


Fig. 3. Phase function of suspensions of rat embryo fibroblast cells (M1) and mitochondria fitted to theoretical phase function (7). The symbols are data reported in Ref. 3, and the solid curves are theoretical curves. Fitting yields $D_f=3.86$ and 4.58 for M1 cells and mitochondria, respectively.

mension D_f and the parameter $\varepsilon^2 \eta_0$ can be estimated from fitting the wavelength dependence of μ'_s to Eq. (8) in the fractal continuous medium model. The value of D_f reveals the relative weight of small scattering centers versus large scattering centers. The value of $\varepsilon^2 \eta_0$ represents the overall density of scattering centers, which is proportional to the radiographic density of tissue of predictive value for cancer risk.¹³ The maximum correlation length l_{\max} can be estimated from the anisotropy factor. The access to all these parameters will yield much more valuable information about the structure and the physiological state of tissue than using the scattering power alone.

In conclusion, we have shown that light-scattering properties of biological tissue and cell suspensions can be well represented by a fractal continuous random medium model where light scattering is due to weak random fluctuations of the dielectric permittivity. The fractal dimension D_f and the cutoff correlation length l_{\max} characterizes the essential features of light scattering by such media. The fractal continuous random medium model should facilitate the analysis of light-scattering spectroscopy for tissue diagnosis.

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