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Path method for reconstructing images in fluorescence optical tomography

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***Abstract*. A reconstruction method elaborated for the optical diffusion tomography of the internal structure of objects containing absorbing and scattering inhomogeneities is considered. The method is developed for studying objects with fluorescing inhomogeneities and can be used for imaging of distributions of artificial fluorophores whose aggregations indicate the presence of various diseases or pathological deviations.**

Keywords: *optical diffusion tomography, fluorescing inhomogeneities, path reconstruction method.*

1. Introduction

Diffusion optical tomography is a method for three-dimensional imaging of the internal structure of opaque objects (in particular, biological ones) based on the measurement and processing of shadows produced due to the different transmission of light by various macroscopic inhomogeneities contained in the object. The imaging of the internal structure of the object by this method is performed in the near-IR region, within the so-called therapeutic window (0.75 – 0.9 μm). In this spectral range, haemoglobin in the oxygenated and deoxygenated states has substantially different absorption spectra, which makes it possible to distinguish a healthy tissue from a tissue with morphological and functional variations.

For the last five years, a new diagnostic method of fluorescence diffusion optical tomography has been developed at several laboratories [1 – 5]. This method uses artificial fluorophores with various pharmacokinetic properties, which are specific to certain diseases. A fluorophore is introduced into a living organism and upon excitation by an external radiation source, emits light at wavelengths lying in the spectral range between 0.5 and 0.9 μm. The fluorescence intensity distribution on the object surface can be used for calculating the spatial distribution of the fluorophore concentration in the object, which depends on various biochemical processes proceeding in a living organism. For example, some fluorophores are retained in the region of a tissue with specific cell receptors, while others begin to fluoresce only when a specific protein is attached. In both cases, a fluorescence signal is proportional to the concentration of the accumulated or activated fluorophore [6, 7].

One of the most promising applications of diffusion fluorescence tomography is the *in vivo* study of small laboratory animals such as mice. This biological model is convenient, on the one hand, for studying tumour growth processes and the efficiency of therapeutic methods and drugs, and on the other hand, it expands the choice of fluorophores because the excitation wavelength can be decreased to perform excitation outside the therapeutic window. This is related to the smallness of objects through which light can be transmitted even in the spectral region of strong absorption in blood [3, 8].

The use of CCD cameras for detecting optical signals considerably shortened the data acquisition time in recent measurements of fluorescence intensity distributions over the entire surface of objects [3, 8]. However, the reconstruction of the fluorophore distribution itself remains a cumbersome and time-consuming process even when modern computers are used for calculations. The main difficulty of the reconstruction is related to strong scattering of photons during their propagation in biological objects. The mean free path of photons in biomedical objects is 10^{-1} cm [9]. This makes invalid the reconstruction algorithms developed in X-ray tomography and requires the solution of the inverse problem for the transport or diffusion equations.

In this paper, we analysed the possibility of the solution of this problem by the mean photon path (MPP) method, which has been successfully used to reconstruct the distribution of absorbing and scattering inhomogeneities and requires less computing time due to some features inherent in it [10].

These features are as follows. The relative shadow from a macroscopic inhomogeneity is used for which the equation is obtained in the form of an integral over the mean path of photons from a radiation source to a detector. The replacement of volume integrals by contour integrals leads to a sparse system of equations, which considerably accelerates calculations. Because the integrand contains the characteristic of a macroscopic inhomogeneity averaged over the distribution of photon paths around the mean path, the averaged characteristic is also reconstructed. However, this does not restrict the resolution limit achieved because

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image-reconstruction methods developed in optics [11, 12] allow the resolution limit to be decreased by several times compared to the width of the photon path distribution around the mean path, the improvement of the image quality being limited by the signal-to-noise ratio for the relative shadow.

Thus, by using the MPP method, it is possible, based on the data on the signal-to-noise ratio and the photon path distribution around the mean path, to select reasonably a finite element in the object cross section according to the Nyquist corollary of the Kotel'nikov–Shannon theorem [13]. The MPP method provides especially great advantage in the calculating speed in the case of three-dimensional objects of a complex shape because it allows one to arrange a three-dimensional reconstruction from two-dimensional layers formed by MPPs [10].

2. General analysis of possibilities for reconstructing the distribution of fluorophores in an object

Upon excitation of a fluorophore by sinusoid-modulated laser radiation illuminating a point site on the surface of an object under study, the reconstruction of the fluorophore distribution over the surface is the inverse problem for the system of equations [14]

$$\Delta\varphi_e(r) + k_e^2\varphi_e(r) = -\frac{S(r)}{D_e}\delta(r), \tag{1}$$

$$\Delta\varphi_f(r) + k_f^2\varphi_f(r) = -\frac{\gamma(\lambda,\Delta\lambda)\delta\mu_{ae}}{D_f(1-i\omega\tau)}\varphi_e(r), \tag{2}$$

where $\varphi_e(r)$ is the density of exciting laser radiation inside the object; $\varphi_f(r)$ is the fluorescence emission density inside the object; $k_e^2 = i\omega n_e/(cD_e) - \mu_{ae}/D_e$; $k_f^2 = i\omega n_f/(cD_f) - \mu_{af}/D_f$; ω is the angular modulation frequency; n_e is the refraction coefficient at the laser wavelength; c is the speed of light; D_e and μ_{ae} are the diffusion and absorption coefficients at the laser wavelength, respectively; $\gamma(\lambda,\Delta\lambda)$ is the fluorescence quantum yield at the detection wavelength; $\delta\mu_{ae}$ is the correction to the absorption coefficient caused by the local concentration of the fluorophore within the detection band; $\delta\mu_{ae} \propto C_f$; C_f is the fluorophore concentration; λ is the detected fluorescence wavelength; $\Delta\lambda$ is the detected wavelength range; and τ is the excited-state lifetime of the fluorophore; the subscript f denotes the corresponding fluorescence parameters.

The direct solution of Eqn (2) has the form

$$\varphi_f(r) = \frac{1}{4\pi}\int_V \frac{\gamma(\lambda,\Delta\lambda)\delta\mu_{af}}{D_f(1-i\omega\tau)}\varphi_e(r)g_f(r-r_1)d^3r_1, \tag{3}$$

or, after passing to the fluorescence flux density per unit surface,

$$\frac{cD_f}{n}\frac{\partial\varphi_f(r)}{\partial\eta} = \frac{c}{4\pi n}\int_V \frac{\gamma(\lambda,\Delta\lambda)\delta\mu_{af}}{1-i\omega\tau}\varphi_e(r) \times \frac{\partial}{\partial\eta}g_f(r-r_1)d^3r_1, \tag{4}$$

where integrals in (3) and (4) are taken over the volume, and the distribution $\delta\mu_{ae}$ is reconstructed from the value of $(cD_f/n)[\partial\varphi_f(r)/\partial\eta]$ measured on the object surface; and $g(r-r_1)$ is the Green function of Eqns (1) and (2). For the infinite space, $g(r) = (1/|r|)\exp ik|r|$. For the important case of rectangular objects, $g(r)$ is represented by the reflection method as a series in Green functions in the infinite space [14]. The series is considerably simplified when a rectangular cell elongated in the longitudinal direction is used [3, 8]. For the values of D and μ_a typical for biological objects, it is sufficient to use two–four terms of the series.

Taking into account that

$$\varphi(r) = \frac{k}{2\pi i}\int \varphi(r_1)g(r-r_1)d^2r_1, \tag{5}$$

in the Huygens–Fresnel approximation, we obtain the relation

$$\left[\frac{\partial}{\partial\eta}\varphi_f(r,\lambda)\right] \Big/ \left[\frac{\partial}{\partial\eta}\varphi_e(r)\right] = \frac{i}{2}\int_L \frac{\gamma(\lambda,\Delta\lambda)}{D_f(1-i\omega\tau)k_e} \times \langle\delta\mu_{af}\rangle \left[\frac{\partial}{\partial\eta}g_f(r-r_1,\lambda)\right] \Big/ \left[\frac{\partial}{\partial\eta}g_e(r-r_1)\right] dl \tag{6}$$

for the solution of the system of equations (1) and (2), where

$$\left[\frac{\partial}{\partial\eta}g_f(r-r_1,\lambda)\right] \Big/ \left[\frac{\partial}{\partial\eta}g_e(r-r_1)\right] \simeq \exp i\delta k|r-r_1|;$$

$\partial/\partial\eta$ is the derivative along the normal to the surface; $\delta k = k_f(\lambda) - k_e$; and

$$\langle\delta\mu_{af}\rangle = \frac{\int_S \delta\mu_{af}\varphi_e(r)(\partial/\partial\eta)g_e(r-r_1)}{\int_S \varphi_e(r)(\partial/\partial\eta)g_e(r-r_1)d^2r_1}d^2r_1.$$

Expression (6) allows us to use the MPP method for reconstructing the fluorophore distribution. Exciting radiation propagating from an external source to a detector along the MPP is partially absorbed by fluorescent inhomogeneities and is measured on the object surface. The fluorescent inhomogeneities serve, in turn, as secondary sources whose fluorescence is also measured on the object surface. Therefore, the reconstruction algorithm should take into account that exciting radiation and fluorescence are attenuated differently, which requires a preliminary estimate of the distribution of inhomogeneities in the object.

In the case of phantom experiments, it is possible to select the conditions under which the absorption coefficient will be almost constant over the entire excitation and fluorescence spectral ranges, i.e. $k_e \simeq k_f$. Then, the condition $\delta kL \ll 1$ will be fulfilled, and the reconstruction algorithm based on Eqn (6) can be realised by using the same methods that have been successfully applied in the case of absorbing inhomogeneities, by employing as a shadow the ratio $[(\partial/\partial\eta)\varphi_f(r)]/[(\partial/\partial\eta)\varphi_e(r)]$ of the flux densities of fluorescence and exciting radiation measured on the object surface [14, 15].

In real objects, it is rather difficult to select regions in the absorption spectra of blood satisfying this condition, especially as a limited region satisfying the condition $\delta kL \ll 1$ should be cut out from the fluorescence spectrum.

For a single inhomogeneity with the known position of its centre $\bar{r}_1^*$ and the path passing through the point $\bar{r}_1^*$,

expression (6) can be simplified by taking the factor $[(\partial/\partial\eta)\, g_f(r - r_1^*, \lambda)]/[(\partial/\partial\eta)\, g_e(r - r_1^*)]$ out the integral sign; then, we obtain

$$F(i,k) = \frac{[\partial g_e(r - r_1^*)/\partial\eta][\partial\varphi_f(r,\lambda)/\partial\eta]}{[\partial g_f(r - r_1^*,\lambda)/\partial\eta][\partial\varphi_e(r,\lambda)/\partial\eta]}$$

$$= \frac{i}{2}\int_{l_i}^{l_k} \frac{\gamma(\lambda,\Delta\lambda)\langle\delta\mu_a\rangle}{D_f(1 - i\omega\tau)k_e} \frac{[\partial g_f(r - r_1,\lambda)/\partial\eta]}{[\partial g_f(r - r_1^*,\lambda)/\partial\eta]}$$

$$\times \frac{[\partial g_e(r - r_1^*)/\partial\eta]}{[\partial g_e(r - r_1)/\partial\eta]}\,dl \simeq \frac{i}{2}\int_L \frac{\gamma(\lambda,\Delta\lambda)\langle\delta\mu_a\rangle}{D_f(1 - i\omega\tau)k_e}$$

$$\times \exp[i\delta k(r_1 - r_1^*)]\,dl. \tag{7}$$

For paths parallel to the path passing through the inhomogeneity centre, $\bar{r}_1^*$ is defined as the intersection point of this path with the perpendicular plane passing through the inhomogeneity centre. The quantity $F(i,k)$ introduced in this way can be called the corrected relative shadow. When the condition $\frac{1}{2}\delta k\delta l \ll 1$ is fulfilled, where δl is the inhomogeneity size, $F(i,k)$ achieves its maximum for paths passing through the inhomogeneity, which provides a fast solution of the system of algebraic equations obtained from Eqn (7). The restriction imposed on the value of δk is even milder for the corrected relative shadow $\langle F(i,k)\rangle$ averaged over opposite directions, for which Eqn (7) takes the form

$$\langle F(i,k)\rangle = \frac{1}{2}[F(i,k) + F(k,i)] \approx i\int_{l_i}^{l_k} \frac{\gamma(\lambda,\Delta\lambda)}{D_f}$$

$$\times \frac{\langle\delta\mu_a\rangle}{(1 - i\omega\tau)k_e}\cosh[i\delta k(r_1 - r_1^*)]\,dl, \tag{7a}$$

and the value of δk is restricted by the relation $\frac{1}{24}(\delta k\delta l)^2 \ll 1$.

This condition determines the admissible difference between the wavelengths of exciting radiation and detected fluorophore fluorescence, which allows the use of the corrected relative shadow for the MPP reconstruction of the distribution $\delta\mu_{af}$ in a single tumour.

In the case of large δk, the distribution $\langle\delta\mu_a\rangle\cosh[i \times \delta k(r_1 - r_1^*)]$ will be reconstructed and this will require the elimination of contribution of hyperbolic cosine from it.

3. Determination of the position of a fluorescing inhomogeneity in a plane layer

It was shown above that to reconstruct the distribution of a fluorescing inhomogeneity, the position of the inhomogeneity itself should be known preliminary. The method for determining the inhomogeneity position can be based on the effect of image transfer through strongly scattering and absorbing layers revealed in [16]. It was shown in [16] that a blurred spot exists opposite to each fluorescing point on the output surface of an object. The intensity distribution in the spot is described by the function $\partial/g(\bar{r}_1 - \bar{r})/\partial\eta$, where $\bar{r}$ is the point coordinate on the surface and r_1 is the coordinate of the fluorescing point.

3.1 Determination of the position of a fluorescing tumour from measurements of the fluorescence intensity upon the displacement of an illuminated site

To calculate the photon density $\varphi_e(r)$ of exciting radiation, it is necessary to find the Green function for the diffusion equation satisfying the boundary conditions $a\,\partial g(r)/\partial\eta + g(r) = 0$ on the surface of a body under study in the form of a layer of a scattering medium. This can be done most simply by the reflection method [17] by using the boundary condition $g(r) = 0$ on a plane separated from the object surface by a distance of the extrapolated length. The extrapolated length is selected depending on the refractive index and absorption coefficient of the medium from the solution of the transport equation for a semi-infinite medium [18].

A light beam incident on the surface is replaced by a point isotropic source located at a distance of the photon transport mean free path from the object surface. The solution of the diffusion equation for a continuous source is constructed in the form

$$\varphi_e(r) = \frac{A\exp(-\sqrt{3\mu_s'\mu_a}\,|\boldsymbol{r} - \boldsymbol{r}_1|)}{|\boldsymbol{r} - \boldsymbol{r}_1|}$$

$$- \frac{A\exp(-\sqrt{3\mu_s'\mu_a}\,|\boldsymbol{r} + \boldsymbol{r}_1|)}{|\boldsymbol{r} + \boldsymbol{r}_1|}, \tag{8}$$

where $\boldsymbol{r}_1$ is the vector with components x_1 and y_1 coinciding with the coordinates of the illuminated point and the component z_1 equal to the sum of the extrapolated length and mean free path.

It is easy to see from (8) that $\varphi_e(r) = 0$ in a plane separated from the object surface by the extrapolated length. The total calculation of $\varphi_e(r)$ requires the construction of a series obtained upon successive reflections from planes separated by a distance of $d + 2z_1$; however, in practice for $d\sqrt{3\mu_s'\mu_a} \ll 1$, it is sufficient to use only two terms of the series, and only in the calculation of the flux density through a layer, when radiation sources and detectors are located on the opposite sides of the layer, it is necessary to add two more terms of the series:

$$\varphi_e(r) = \frac{A\exp(-\sqrt{3\mu_s'\mu_a}\,|\boldsymbol{r} - \boldsymbol{r}_1|)}{|\boldsymbol{r} - \boldsymbol{r}_1|}$$

$$- \frac{A\exp(-\sqrt{3\mu_s'\mu_a}\,|\boldsymbol{r} + \boldsymbol{r}_1|)}{|\boldsymbol{r} + \boldsymbol{r}_1|} - \frac{A\exp(\sqrt{3\mu_s'\mu_a}|\boldsymbol{r}_2 - \boldsymbol{r}_1|)}{|\boldsymbol{r} - \boldsymbol{r}_2 - \boldsymbol{r}_1|}$$

$$+ \frac{A\exp(-\sqrt{3\mu_s'\mu_a}|\boldsymbol{r}_2 + \boldsymbol{r}_1|}{|\boldsymbol{r} - \boldsymbol{r}_2 + \boldsymbol{r}_1|}, \tag{9}$$

where $\boldsymbol{r}_2$ is the vector with components x_2 and y_2 coinciding with the coordinates of the illuminated point and the component $z_2 = 2d + 4z_0$ is equal to the sum of the extrapolated length and mean free path.

The value of A is determined from the condition that for $|\boldsymbol{r} - \boldsymbol{r}_1| \to 0$, the flux incident on the surface is

$$P_e = h\nu\frac{cD}{n}4\pi|\boldsymbol{r} - \boldsymbol{r}_1|^2\frac{\partial}{\partial(\boldsymbol{r} - \boldsymbol{r}_1)}\frac{A\exp(-\sqrt{3\mu_s'\mu_a}\,|\boldsymbol{r} - \boldsymbol{r}_1|)}{|\boldsymbol{r} - \boldsymbol{r}_1|}.$$

This gives

$$A = \frac{P_e n}{4\pi cDh\nu_e'}, \tag{10}$$

where $D = 1/3\mu_s'$.

The volume density n_f of fluorescing molecules is proportional to the exciting radiation density

$$n_{\mathrm{f}} = 4\delta\mu_{\mathrm{af}}\frac{c}{n}\frac{\varphi_{\mathrm{e}}}{h\nu_{\mathrm{e}}}, \tag{11}$$

and the radiation flux emitted by a unit volume is

$$P_{\mathrm{f}}\,\mathrm{d}V = \gamma\delta\mu_{\mathrm{af}}\frac{c}{n}\varphi_{\mathrm{e}}\frac{\nu_{\mathrm{f}}}{\nu_{\mathrm{e}}}\mathrm{d}V, \tag{12}$$

where ν_{f} and ν_{e} are fluorescence and excitation frequencies.

Let the coordinate system be selected as follows: the plane $z = 0$ corresponds to the layer surface on which radiation sources are located, and the plane $x = 0$ passes through the centre of one inhomogeneity. If the unity volume of the fluorescing inhomogeneity is located at the depth z and the excitation source is displaces by the distance x, the calculation of the ratio $P_{\mathrm{f}}(z,x)/P_{\mathrm{f}}(z,0)$, taking into account (8) and (12), gives the expression

$$\frac{P_{\mathrm{f}}(z,x)}{P_{\mathrm{f}}(z,0)} \simeq \frac{z^2\exp[\sqrt{3\mu_{\mathrm{s}}\mu_{\mathrm{ae}}}(\sqrt{x^2+z^2}-z)}{x^2+z^2}$$

$$= \cos^2\varphi\exp[-z\sqrt{3\mu_{\mathrm{s}}\mu_{\mathrm{a}}}(1/\cos\varphi - 1)], \tag{13}$$

where $\cos\varphi = z/\sqrt{z^2+x^2}$.

This expression can be used to calculate the location depth of the fluorescing inhomogeneity from a decrease in the fluorescence intensity upon the displacement of the excitation source. Because upon such measurements the distance from any volume element to the object surface on which photodetectors are located is constant, the fluorescence spectrum is not distorted due to different absorptions at different wavelengths, i.e. these measurements do not require the separation of a limited spectral region.

Note that, if the absorption of exciting radiation inside the inhomogeneity is strongly nonuniform $[(3\mu_{\mathrm{ae}}\mu_{\mathrm{s}})^{1/2} \times \delta l \geqslant 1]$, the positions of the inhomogeneity determined by interchanging the sides of illumination and detection of fluorescence will be different; however, this will not prevent the estimate of its longitudinal size.

The location depth of a fluorescing inhomogeneity can be also determined from the deformation of the fluorescence spectrum at the object output caused by the dependence of absorption on the wavelength.

3.2 Determination of lateral dimensions of a fluorescing inhomogeneity

It was shown in [16] applied to ultrashort-pulse tomography that the estimates of the resolving power from the widths of the banana-like zone and point image on the output surface are rather close. Consider the use of the image transfer for determining lateral dimensions.

The Green function for a point source immersed into a half-space at a depth of z_{s} has the form

$$\varphi(r,\lambda) \simeq \frac{A\exp\left[-\sqrt{3\mu_{\mathrm{s}}\mu_{\mathrm{af}}(\lambda)}\sqrt{(z-z_{\mathrm{s}})^2+x^2+y^2}\right]}{(z-z_{\mathrm{s}})^2+x^2+y^2}$$

$$-\frac{A\exp\left[-\sqrt{3\mu_{\mathrm{s}}\mu_{\mathrm{af}}(\lambda)}\sqrt{(z+z_{\mathrm{s}})^2+x^2+y^2}\right]}{(z-z_{\mathrm{s}})^2+x^2+y^2}. \tag{14}$$

Then, the flux density through the surface of the extrapolated boundary is

$$I(z,y,0) = \frac{cD}{n}\frac{\partial\varphi}{\partial z}, \tag{15}$$

and after calculation for $z_2 \gg x, y$, we obtain

$$I = \frac{c}{n}DA\sqrt{3\mu_{\mathrm{s}}\mu_{\mathrm{af}}(\lambda)}$$

$$\times\frac{2\exp\{-\sqrt{3\mu_{\mathrm{s}}\mu_{\mathrm{af}}(\lambda)}\,[z_{\mathrm{s}}+(x^2+y^2)/2z_{\mathrm{s}}]\}}{\sqrt{z_{\mathrm{s}}^2+x^2+y^2}}. \tag{16}$$

One can see from (16) that each point of the inhomogeneity produces a blurred spot on the output surface of a layer, which is described by a Gaussian distribution with FWHM

$$\Delta = 2\sqrt{2\ln 2}\sqrt{\frac{z_{\mathrm{s}}}{3\mu_{\mathrm{s}}\mu_{\mathrm{af}}(\lambda)}}. \tag{17}$$

The transferred inhomogeneity image $F(x_1, y_1)$ has the form

$$F(x,y) = \int f(x_1,y_1)k(x-x_1,y-y_1)\mathrm{d}x_1\mathrm{d}y_1, \tag{18}$$

where $f(x,y)$ is the true image of the inhomogeneity; $k(\Delta x, \Delta y)$ is the transfer function determined by expression (16); and $F(x,y)$ is the image obtained on the output surface of the layer.

One can see from (16) and (18) that, to increase the resolving power, it is expedient to select the region of the fluorescence spectrum with the maximum absorption. The resolving power can be further increased by using the methods for image reconstruction [11]. Because the distribution $k(\Delta x, \Delta y)$ is described by a Gaussian, it cannot be expected that the resolution can be improved by more than 2–3 times due to the presence of noise artefacts in the reconstructed image [12]. In the absence of selection of the fluorescence spectrum, it is convenient to determine the value of μ_{af} from the maximum of the fluorescence signal measured on the object surface.

4. Reconstruction of the distribution of $\delta\mu_{\mathrm{a}}$

Because

$$f(x,y) \sim \int_{-\delta l/2}^{\delta l/2}\delta\mu_{\mathrm{a}}(r-r_1^*)\,\mathrm{d}z_1, \tag{19}$$

in the cases when the distribution of $\delta\mu_{\mathrm{a}}$ with respect to the inhomogeneity centre r_1^* can be considered symmetric, expression (19) can be used to estimate $\delta\mu_{\mathrm{a}}(r-r_1^*)$ by using conventional tomography reconstruction methods (see, for example, [19]).

In the case of asymmetric inhomogeneities, expressions (7) and (7a) should be used. As follows from studies of plane layers, to obtain a stable reconstruction, it is sufficient to use a set of shadows at aspect angles varying within $\pm 45^\circ$.

5. Conclusions

The MPP method verified by reconstructing scattering and absorbing macroscopic inhomogeneities in a strongly scattering medium can be used to reconstruct the distribution of a fluorophores in an individual fluorescing microscopic inhomogeneity contained in a strongly scatter-

ing object. The obtained theoretical results are used for the development of the algorithm for reconstructing the fluorophore distribution and its program realisation.

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