Russian Federal Nuclear Center –
Zababakhin Institute of Applied Physics

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“ROSATOM” STATE CORPORATION

# Fluorescence molecular tomography using early arriving photons: fundamental equations, numerical experiment, and resolution analysis

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# Contents

# Ways to improve the spatial resolution

- The development of models and methods for time-domain FMT with use of early arriving diffuse photons
- Application of compressed sensing algorithms to the reconstruction of fluorescence tomograms
- The development of methods for mesoscopic FMT and laminar optical tomography

# The novelties of our research

- We propose an original approach to macroscopic early-photon FMT based on a number of simplifications to derive the analytic sensitivity functions for reflectance geometry

V.V. Lyubimov, Opt. Spectrosc. 88: 282 (2000)

- To solve the FMT inverse problem we use an original hybrid algorithm that combines the algebraic reconstruction technique with total variation regularization and adaptive segmentation

V.V. Vlasov et al., J. Electron. Imaging 27: 043006 (2018)

# Light propagation in scattering medium

$$\frac{1}{c^{e,f}}\frac{\partial\varphi^{e,f}(\mathbf{r},t)}{\partial t}-\nabla\cdot\left[D^{e,f}(\mathbf{r})\nabla\varphi^{e,f}(\mathbf{r},t)\right]+\left[\mu_a^{e,f}(\mathbf{r})+\mu_{af}(\mathbf{r})\right]\varphi^{e,f}(\mathbf{r},t)$$

$$=S^{e,f}(\mathbf{r},t)$$

$$S^e(\mathbf{r},t)=I_0\delta(\mathbf{r}-\mathbf{r}_s)\delta(t-t_s)$$

$$S^f(\mathbf{r},t)=\frac{\gamma(\mathbf{r})\mu_{af}(\mathbf{r})}{\tau(\mathbf{r})}\int_{t_s}^{t}\varphi^e(\mathbf{r},t')\exp\frac{t'-t}{\tau(\mathbf{r})}dt'$$

$$\varphi^{e,f}(\mathbf{r}_d,t)+2AD^{e,f}(\mathbf{r}_d)\frac{\partial\varphi^{e,f}(\mathbf{r}_d,t)}{\partial q}=0$$

C. Darne et al., Phys. Med. Biol. 88: R1 (2014)

# Our simplifying assumptions

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- We use the asymptotic approximation for the fluorescence source function
- The contribution of fluorophore absorption is negligible
- Fluorescence quantum yield and lifetime are constant

$$\frac{1}{c^{e,f}}\frac{\partial \varphi^{e,f}(\mathbf{r},t)}{\partial t} - D^{e,f}\Delta\varphi^{e,f}(\mathbf{r},t) + \mu_a^{e,f}\varphi^{e,f}(\mathbf{r},t) = S^{e,f}(\mathbf{r},t)$$

$$S^{e}(\mathbf{r},t) = I_0\delta(\mathbf{r}-\mathbf{r}_s)\delta(t-t_s)$$

$$S^{f}(\mathbf{r},t) = \frac{\gamma\mu_{af}(\mathbf{r})\cdot 4D^e c^e t^2}{\tau|\mathbf{r}|^2 + 4D^e c^e t^2}\varphi^{e}(\mathbf{r},t)$$

V.V. Lyubimov, Opt. Spectrosc. 88: 282 (2000)

# The constraint equation

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$$\varphi^f(\mathbf{r},t) = \int_{t_s}^{t}\int_V c^f S^f(\mathbf{r}',t')G^f(\mathbf{r}-\mathbf{r}',t-t')d^3r'dt'$$

$$\Downarrow \quad S^f(\mathbf{r},t)$$

$$\varphi^f(\mathbf{r},t) = c^f\gamma\int_{t_s}^{t}dt'\int_V \frac{\mu_{af}(\mathbf{r}')\cdot 4D^e c^e t'^2}{\tau|\mathbf{r}'|^2 + 4D^e c^e t'^2}$$

$$\times\varphi^e(\mathbf{r}',t')G^f(\mathbf{r}-\mathbf{r}',t-t')d^3r'$$

# Time-resolved normalized data

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$$g(\mathbf{r}_s, t_s, \mathbf{r}_d, t_d) = \frac{\Gamma^f(\mathbf{r}_s, t_s, \mathbf{r}_d, t)\big|_{t=t_d}}{\Gamma^e(\mathbf{r}_s, t_s, \mathbf{r}_d, t)\big|_{t=t_d}}$$

$$\Gamma^{e,f}(\mathbf{r}_d, t) = -c^{e,f} D^{e,f}(\mathbf{r}_d) \frac{\partial \varphi^{e,f}(\mathbf{r}_d, t)}{\partial q}$$

$$g(\mathbf{r}_s, t_s, \mathbf{r}_d, t_d) = c^f \gamma \int_{t_s}^{t_d} dt \int_V \frac{\mu_{af}(\mathbf{r}) \cdot 4D^e c^e t^2}{\tau |\mathbf{r}|^2 + 4D^e c^e t^2}$$

$$\times \frac{\frac{\partial}{\partial q} G^f(\mathbf{r}_d - \mathbf{r}, t_d - t)}{\frac{\partial}{\partial q} G^e(\mathbf{r}_d - \mathbf{r}, t_d - t)} \times \frac{G^e(\mathbf{r} - \mathbf{r}_s, t - t_s) \frac{\partial}{\partial q} G^e(\mathbf{r}_d - \mathbf{r}, t_d - t)}{\frac{\partial}{\partial q} G^e(\mathbf{r}_d - \mathbf{r}_s, t_d - t_s)} d^3 r$$

# The additional assumption

- The scattering medium and the fluorescent inclusions have identical optical properties

$$c^e \cong c^f \cong c \qquad \mu_a^e \cong \mu_a^f \cong \mu_a \qquad D^e \cong D^f \cong D$$

- The Green function derivatives for the diffusion equations of exciting radiation and fluorescence are equal to each other

$$\frac{\partial G^f(\mathbf{r}_d - \mathbf{r}, t_d - t) / \partial q}{\partial G^e(\mathbf{r}_d - \mathbf{r}, t_d - t) / \partial q} \to 1$$

V.V. Lyubimov, Opt. Spectrosc. 88: 282 (2000)

# Fundamental equation and sensitivity function

$$g(\mathbf{r}_s, t_s, \mathbf{r}_d, t_d)$$

$$= \int_V \left[ c\gamma \int_{t_s}^{t_d} \frac{4Dct^2}{\tau |\mathbf{r}|^2 + 4Dct^2} \frac{G^e(\mathbf{r}-\mathbf{r}_s, t-t_s) \frac{\partial}{\partial q} G^e(\mathbf{r}_d - \mathbf{r}, t_d - t)}{\frac{\partial}{\partial q} G^e(\mathbf{r}_d - \mathbf{r}_s, t_d - t_s)} dt \right] \mu_{af}(\mathbf{r}) d^3 r$$

$$W_{\mu_{af}}(\mathbf{r}_s, t_s, \mathbf{r}_d, t_d, \mathbf{r})$$

$$= c\gamma \int_{t_s}^{t_d} \frac{4Dct^2}{\tau |\mathbf{r}|^2 + 4Dct^2} \frac{G^e(\mathbf{r}-\mathbf{r}_s, t-t_s) \frac{\partial}{\partial q} G^e(\mathbf{r}_d - \mathbf{r}, t_d - t)}{\frac{\partial}{\partial q} G^e(\mathbf{r}_d - \mathbf{r}_s, t_d - t_s)} dt$$

# Further simplification

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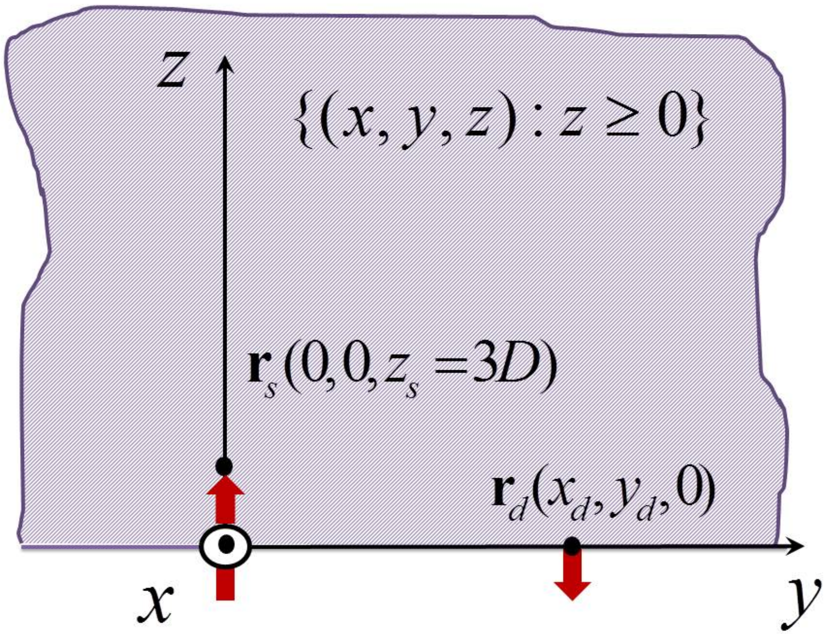
$$W_{\mu_{af}}(\mathbf{r}_s,t_s,\mathbf{r}_d,t_d,\mathbf{r}) = c\gamma\int_{t_s}^{t_d}\frac{1}{\frac{\tau}{4Dc}\frac{|\mathbf{r}|^2}{t^2}+1}\frac{G^e(\mathbf{r}-\mathbf{r}_s,t-t_s)\frac{\partial}{\partial q}G^e(\mathbf{r}_d-\mathbf{r},t_d-t)}{\frac{\partial}{\partial q}G^e(\mathbf{r}_d-\mathbf{r}_s,t_d-t_s)}dt$$

$\frac{|\mathbf{r}|^2}{t^2}$ **can be changed by** $\frac{|\mathbf{r}_d|^2}{t_d^2}$

$$W_{\mu_{af}}(\mathbf{r}_s,t_s,\mathbf{r}_d,t_d,\mathbf{r}) = \frac{4\gamma Dc^2t_d^2}{\tau|\mathbf{r}_d|^2+4Dct_d^2}\int_{t_s}^{t_d}\frac{G^e(\mathbf{r}-\mathbf{r}_s,t-t_s)\frac{\partial}{\partial q}G^e(\mathbf{r}_d-\mathbf{r},t_d-t)}{\frac{\partial}{\partial q}G^e(\mathbf{r}_d-\mathbf{r}_s,t_d-t_s)}dt$$

V.V. Lyubimov et al., Phys. Med. Biol. 47: 2109 (2002)

# 3D reflectance geometry




$$t_s = 0$$

$$\varphi^{e,f}(\mathbf{r}_d, t) = 0$$

$$G(\mathbf{r}-\mathbf{r}', t-t') = \left[4\pi Dc(t-t')\right]^{-3/2} \exp\left[-\mu_a c(t-t')\right]$$
$$\times\left\{\exp\left[-\frac{(x-x')^2+(y-y')^2+(z-z')^2}{4Dc(t-t')}\right]-\exp\left[-\frac{(x-x')^2+(y-y')^2+(z+z')^2}{4Dc(t-t')}\right]\right\}$$

A.B. Konovalov et al., Optik 124: 6000 (2013)

# Integral I

$$I = \int_0^{t_d} \frac{G(\mathbf{r}-\mathbf{r}_s, t-t_s)\dfrac{\partial}{\partial q}G(\mathbf{r}_d-\mathbf{r}, t_d-t)}{\dfrac{\partial}{\partial q}G(\mathbf{r}_d-\mathbf{r}_s, t_d-t_s)}dt$$

$$I = I_- - I_+, \quad I_\pm = \frac{z}{\pi(4Dc)^{3/2} t_d^{1/2} z_s}\exp\left[\frac{x_d^2+y_d^2+z_s^2}{4Dct_d} - \left(\sqrt{p}+\sqrt{q_\pm}\right)^2\right]$$

$$\times\left(q_\pm^{-1/2} + 2p^{-1/2} + \frac{1}{2}p^{-3/2} + p^{-1}q_\pm^{1/2}\right),$$

$$p = \frac{(x-x_d)^2+(y-y_d)^2+z^2}{4Dct_d}, \quad q_\pm = \frac{x^2+y^2+(z\pm z_s)^2}{4Dct_d}$$

A.B. Konovalov, V.V. Vlasov, Quantum Electron. 44: 719 (2014)

A.B. Konovalov, V.V. Vlasov, Proc. PIERS Spring: 3487 (2017)

# Analytic representation for sensitivity function

$$W_{\mu_{af}}(\mathbf{r}_s, t_s, \mathbf{r}_d, t_d, \mathbf{r}) = \left(W_{\mu_{af}}\right)_- - \left(W_{\mu_{af}}\right)_+ ,$$

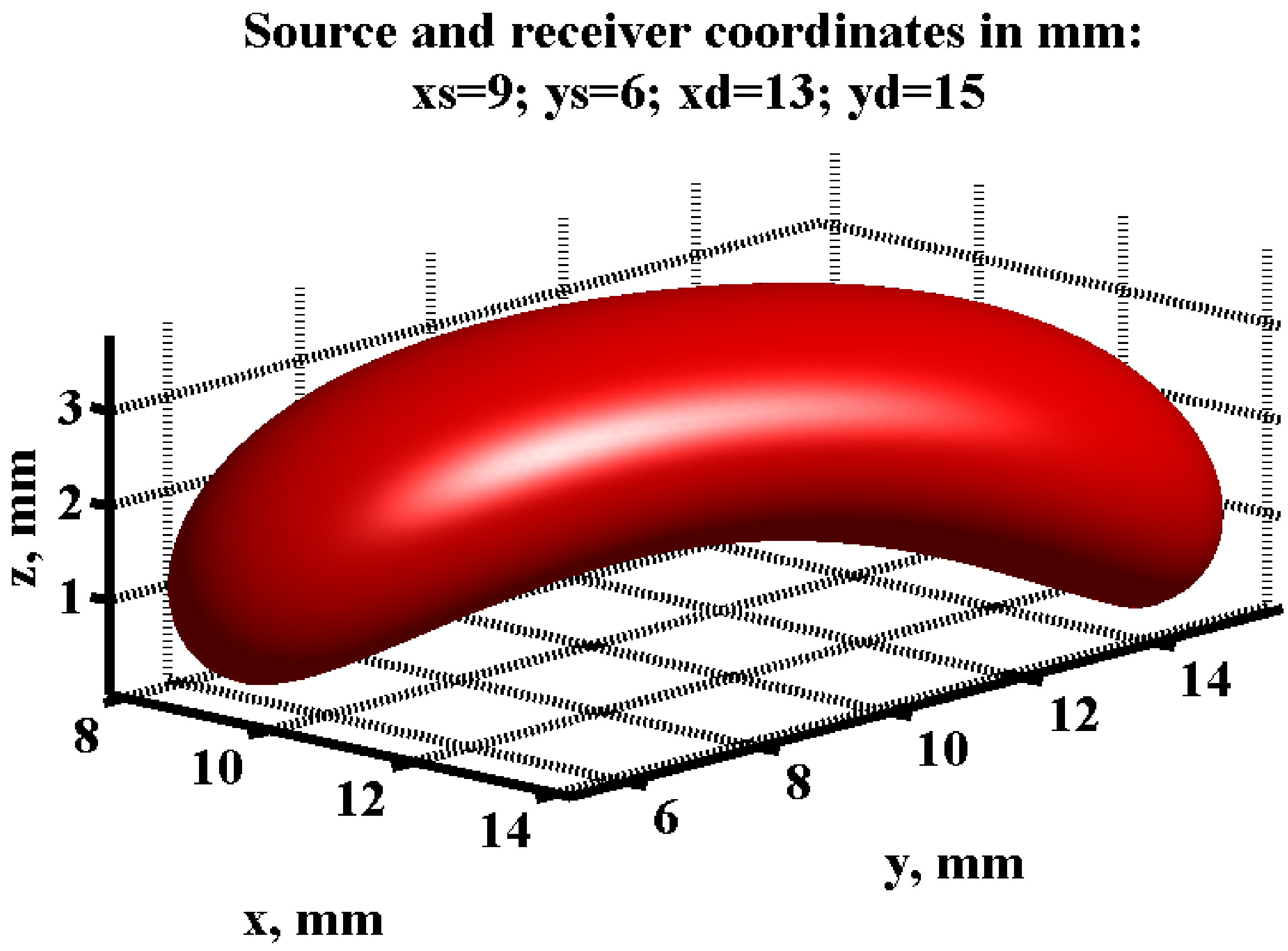
$$\left(W_{\mu_{af}}\right)_\pm = \frac{\gamma z}{24\pi D^{5/2}(ct_d)^{1/2}} \cdot \frac{4Dct_d^2}{\tau(x_d^2 + y_d^2) + 4Dct_d^2}$$

$$\times \exp\left[\frac{x_d^2 + y_d^2 + (3D)^2}{4Dct_d} - \left(\sqrt{p} + \sqrt{q_\pm}\right)^2\right]\left(q_\pm^{-1/2} + 2p^{-1/2} + \frac{1}{2}p^{-3/2} + p^{-1}q_\pm^{1/2}\right),$$

$$p = \frac{(x - x_d)^2 + (y - y_d)^2 + z^2}{4Dct_d}, \quad q_\pm = \frac{x^2 + y^2 + (z \pm 3D)^2}{4Dct_d}$$

# Example of sensitivity function visualization






$$c = 0.214 \text{ mm / ps} \qquad D = 0.194 \text{ mm} \qquad \gamma = 1 \qquad \tau = 1000 \text{ ps}$$

# Discretization of the fundamental equation

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$$g_{i,j}=\sum_{m=1}^{M}\sum_{n=1}^{N}\sum_{l=1}^{L}W_{m,n,l}^{i,j}\,f_{m,n,l}\qquad (\mathbf{g}=\mathbf{Wf})$$

$$\left(W_{m,n,l}^{i,j}\right)_{\pm}=\frac{\Delta^3\gamma z_l}{24\pi D^{5/2}(ct_d)^{1/2}}\cdot\frac{4Dct_d^2}{\tau(x_i^2+y_i^2)+4Dct_d^2}\cdot\exp\left[\frac{x_i^2+y_i^2+(3D)^2}{4Dct_d}\right.$$

$$\left.-\left(\sqrt{\frac{(x_n-x_i)^2+(y_m-y_i)^2+z_l^2}{4Dct_d}}+\sqrt{\frac{(x_n-x_j)^2+(y_m-y_j)^2+(z_l\pm 3D)^2}{4Dct_d}}\right)^2\right]$$

$$\times\left\{\left[\frac{(x_n-x_j)^2+(y_m-y_j)^2+(z_l\pm 3D)^2}{4Dct_d}\right]^{-1/2}+2\left[\frac{(x_n-x_i)^2+(y_m-y_i)^2+z_l^2}{4Dct_d}\right]^{-1/2}\right.$$

$$+\frac{1}{2}\left[\frac{(x_n-x_i)^2+(y_m-y_i)^2+z_l^2}{4Dct_d}\right]^{-3/2}+\left[\frac{(x_n-x_i)^2+(y_m-y_i)^2+z_l^2}{4Dct_d}\right]^{-1}$$

$$\left.\times\left[\frac{(x_n-x_j)^2+(y_m-y_j)^2+(z_l\pm 3D)^2}{4Dct_d}\right]^{1/2}\right\}$$

# Virtual fluorescent tomograph

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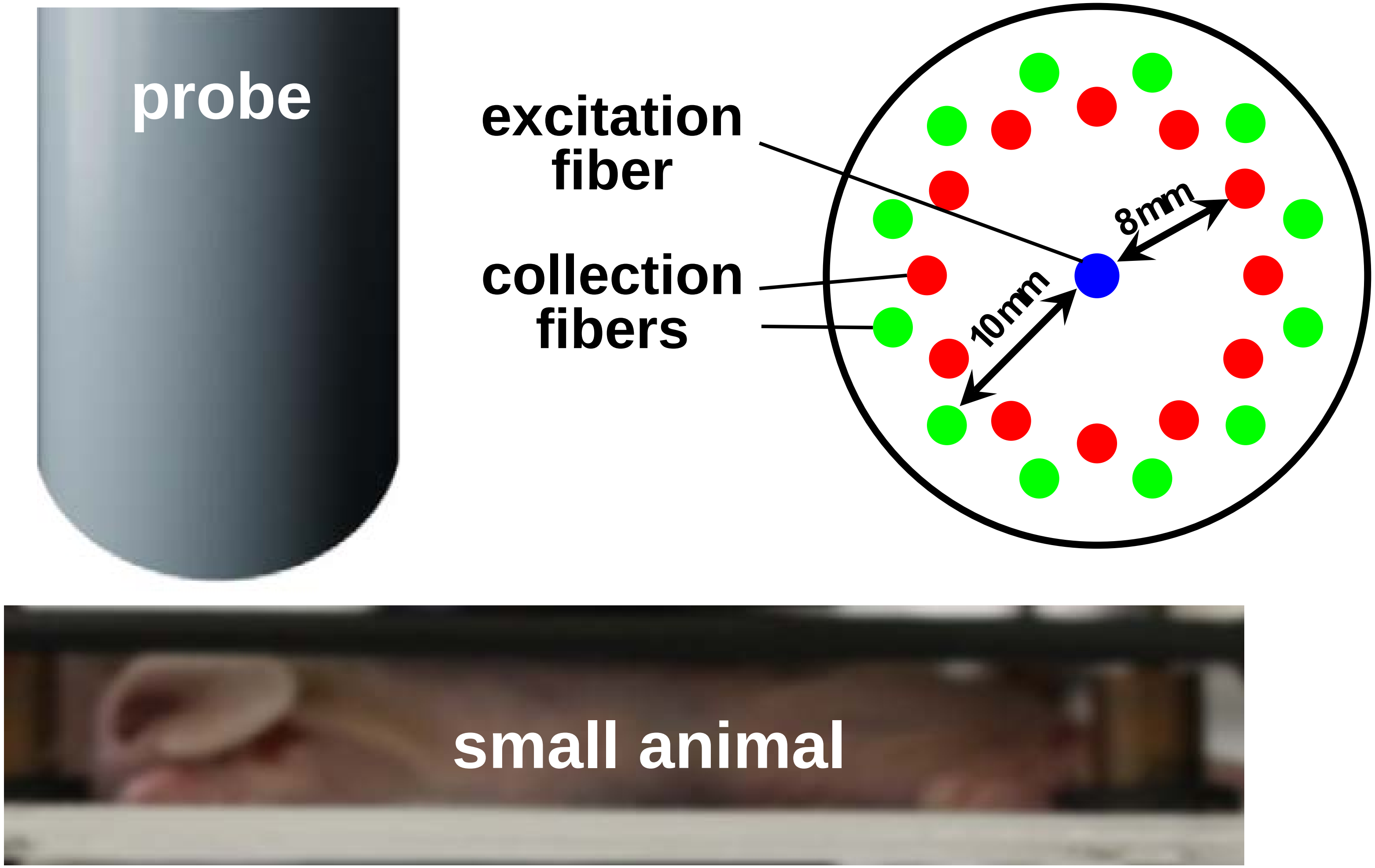
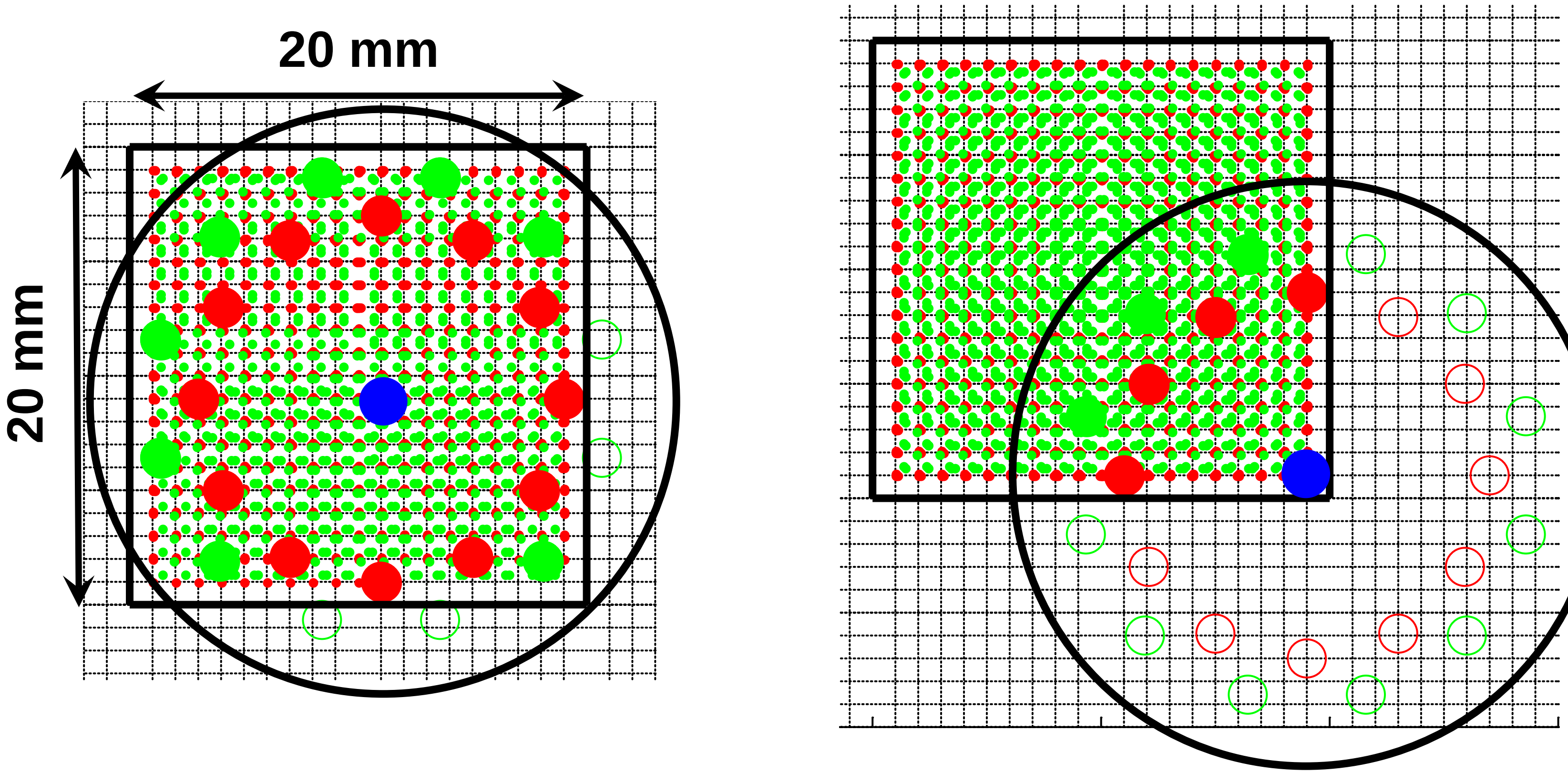


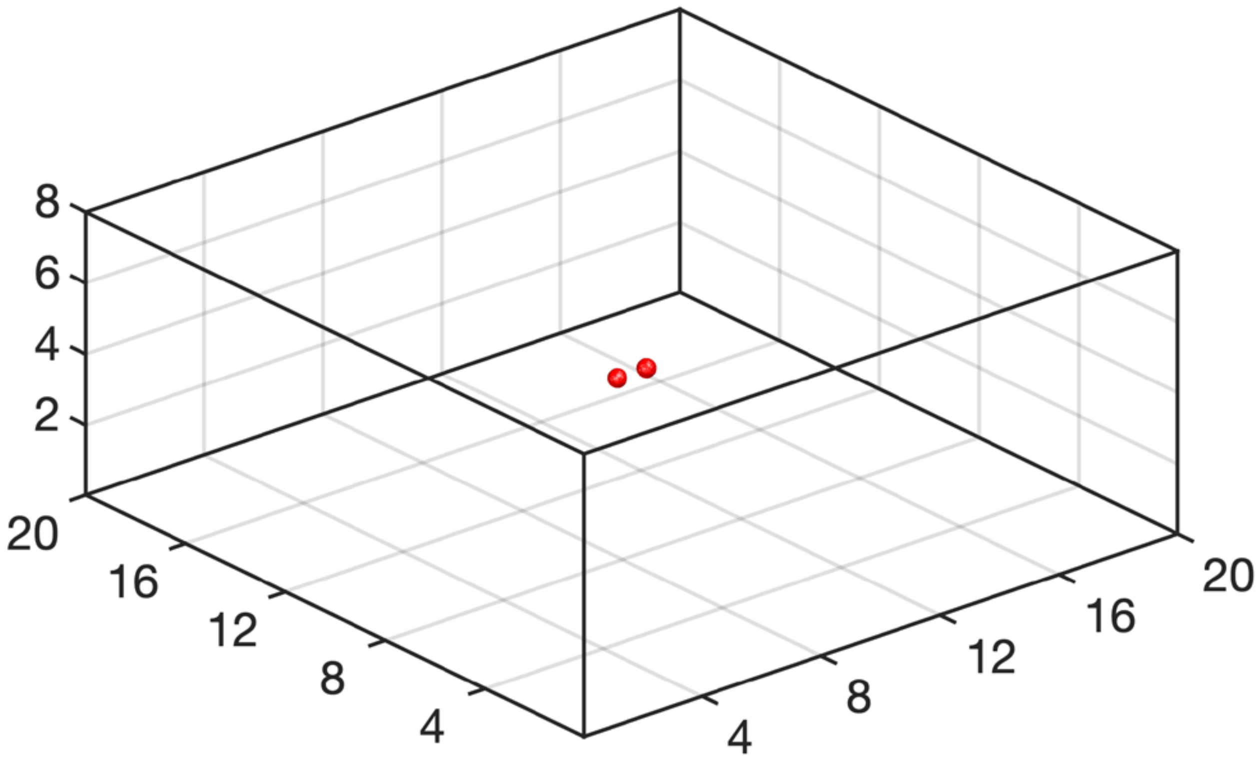

E. Cordero et al., J. Biomed. Opt. 23: 071210 (2018)

# Scanning of the object




**1419 useful source-receiver connections**

# The object to be reconstructed




$$c = 0.214\ \text{mm} / \text{ps}$$

$$D = 0.194\ \text{mm}$$

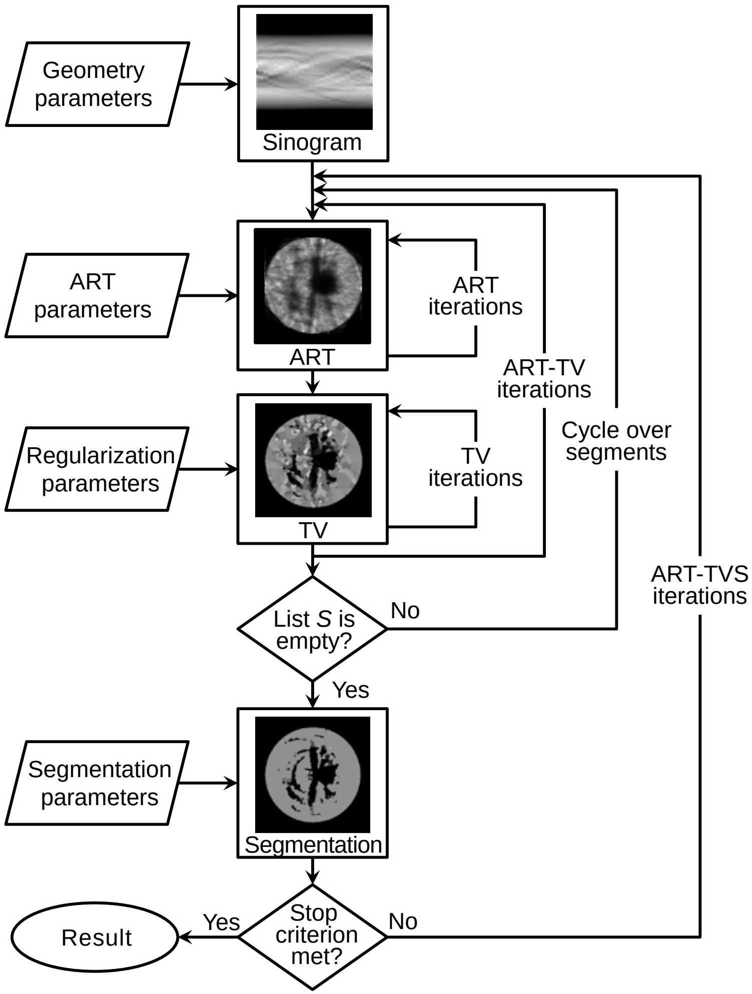
$$\gamma = 1$$

$$\tau = 1000\ \text{ps}$$

$$\mu_{af} = 0.01\ \text{mm}^{-1}$$

**The values of time gates are 100 and 150 ps. They correspond to the source-receiver separations of 8 and 10 millimeters, respectively.**

# The ART-TVS algorithm




**ART-TVS = ART-TV + S**

**Algebraic reconstruction with total variation regularization (ART-TV)**

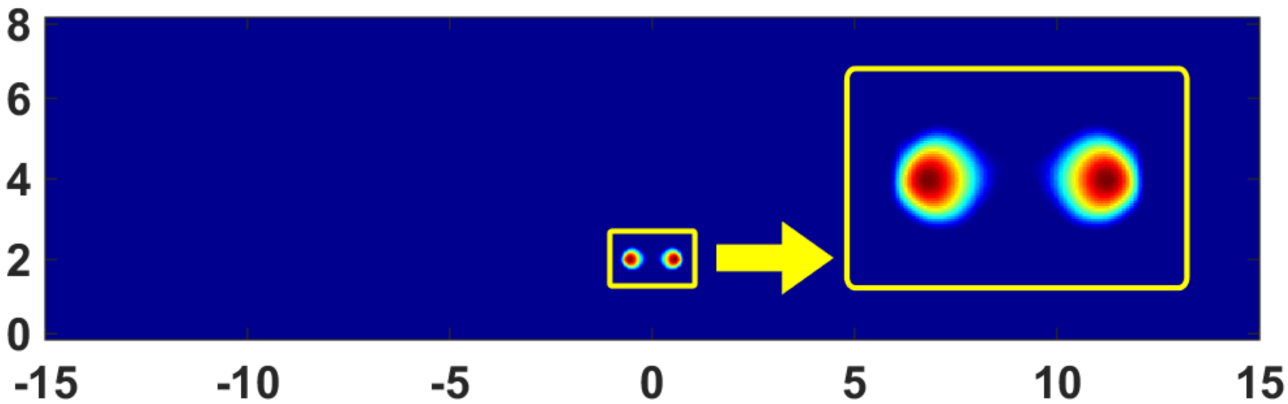
H. Yu, G. Wang, Phys. Med. Biol. 54, 2791 (2009)

**Adaptive segmentation (S) based on region growing**

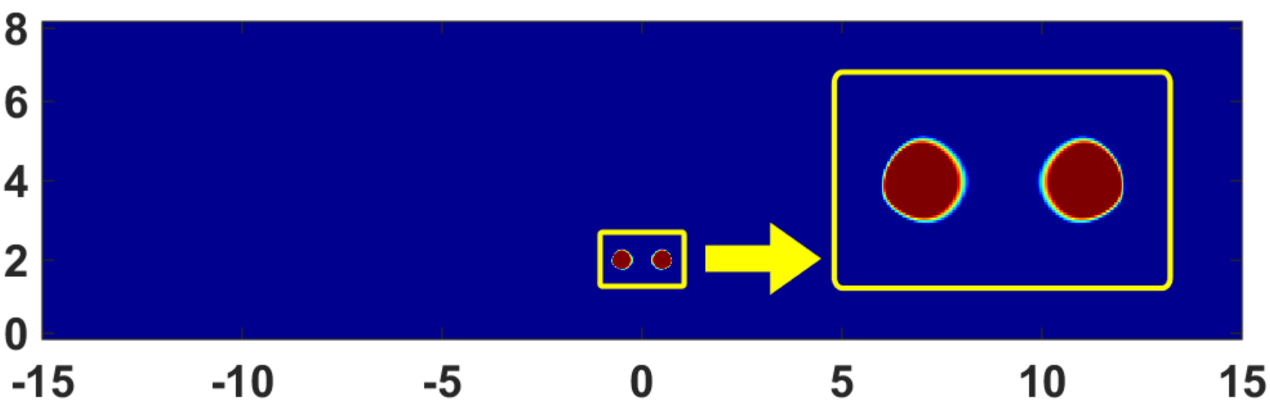
A. Mehnert, O. Jackway, Pattern Recognit. Lett. 18, 1065 (1997)

V.V. Vlasov et al., J. Electron. Imaging 27: 043006 (2018)

# The main advantage of ART-TVS




ART




ART-TVS

# The results of 3D reconstruction

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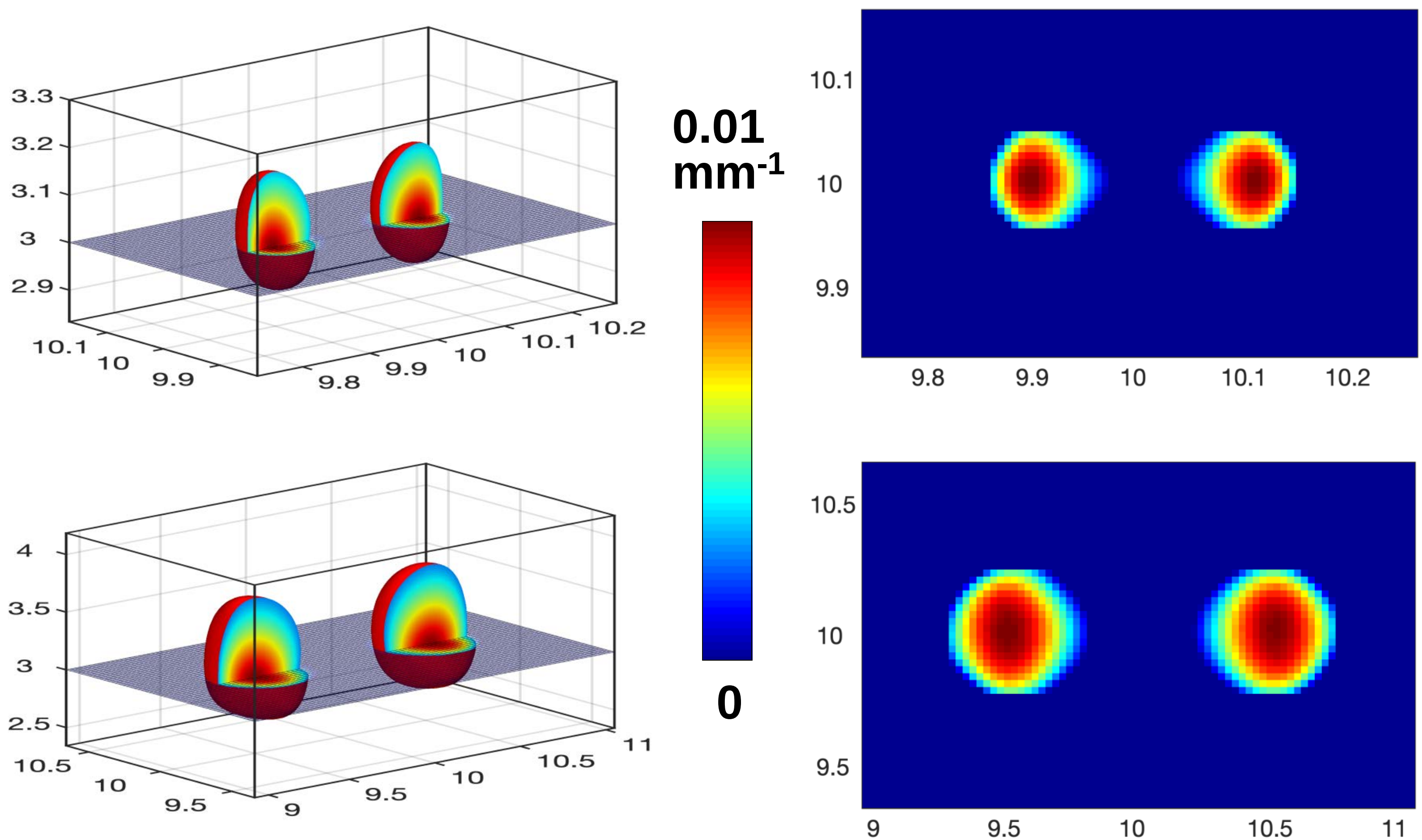
## depth of 3 mm

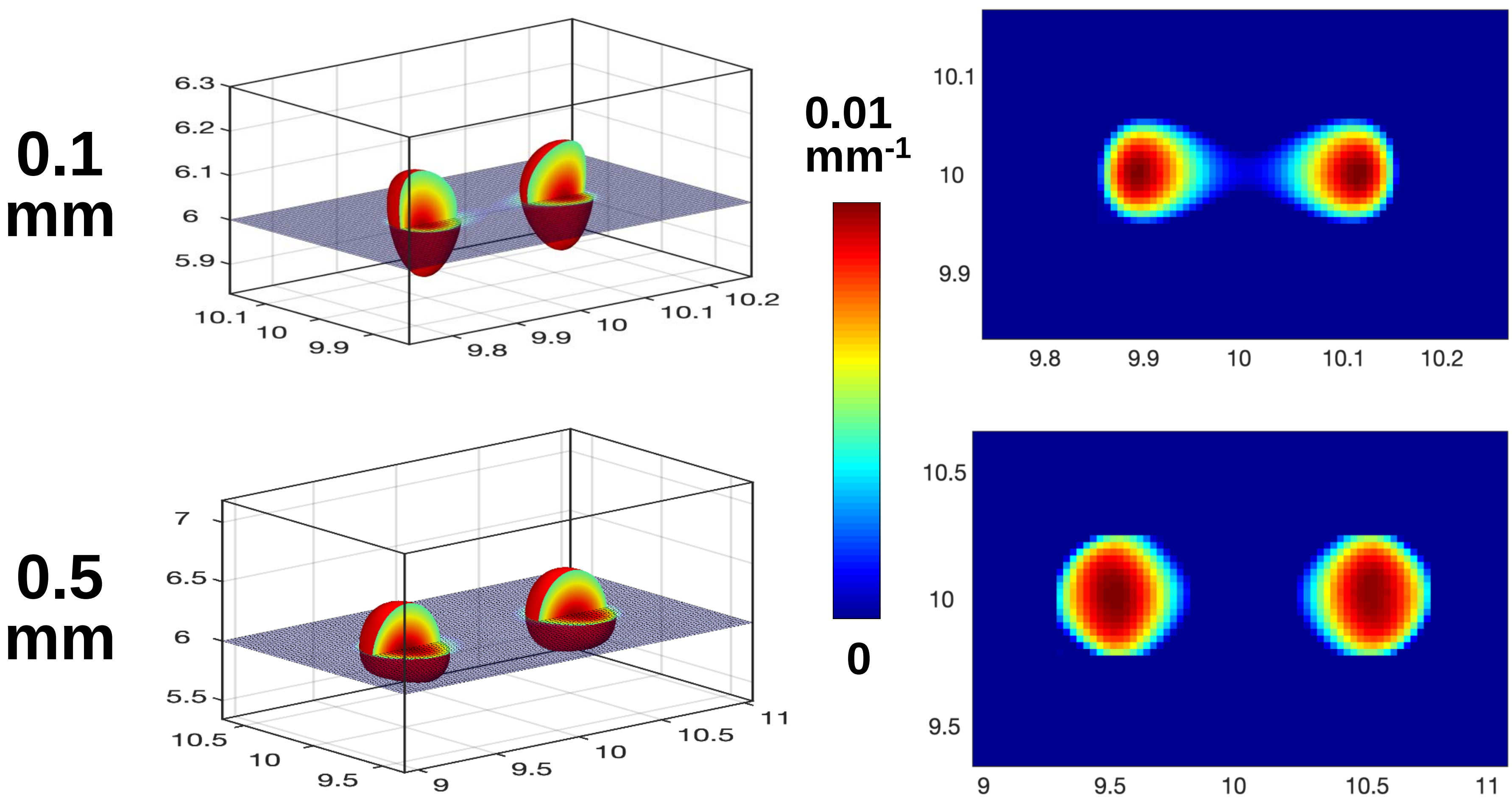
**0.1 mm**

**0.5 mm**



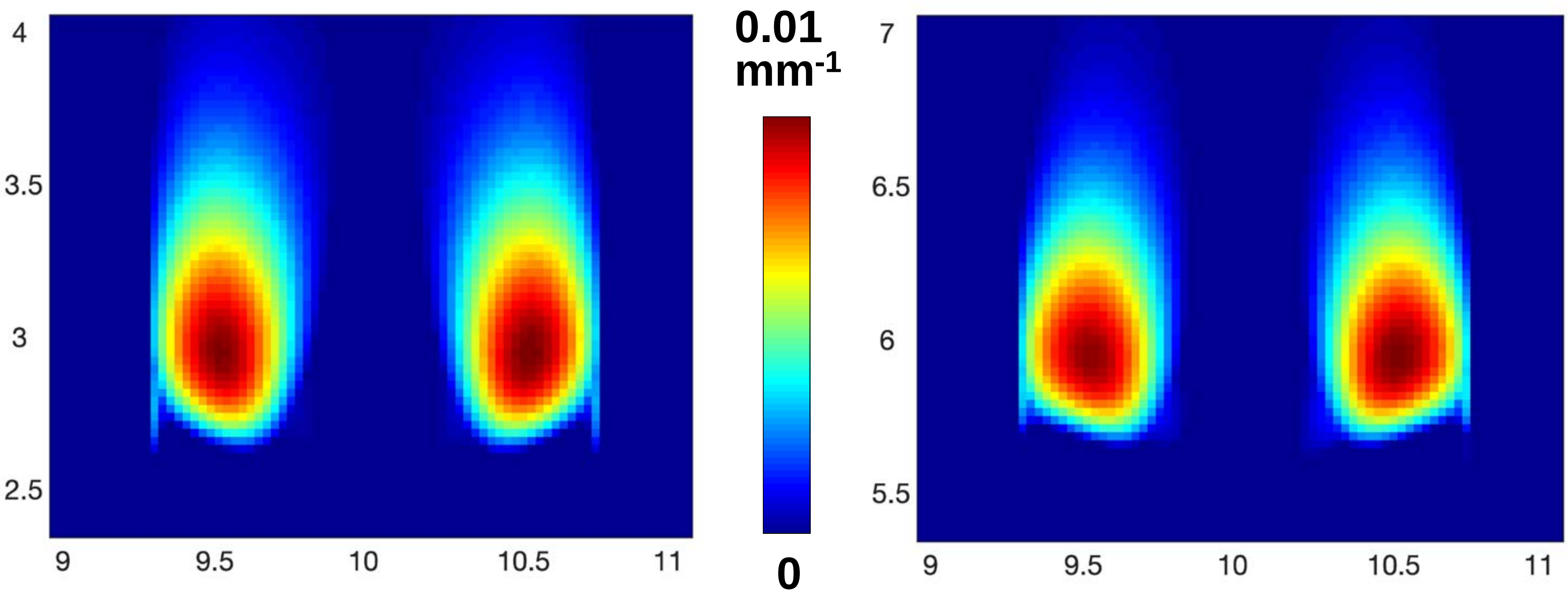
# The results of 3D reconstruction

## depth of 6 mm



# The results of 3D reconstruction

**depth of 3 mm** **depth of 6 mm**



# Conclusion and further research

- Our approach to macroscopic FMT allows the resolution of 100 micrometers to be obtained
- Our further research is aimed at developing a physical experiment to verify the results
- Of special interest to us is to adapt our approach to fluorescence lifetime tomography

# Thank you for your time!

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