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# Simultaneous reconstruction of absorption, scattering and anisotropy factor distributions in quantitative photoacoustic tomography

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**Abstract** We present for the first time the simultaneous reconstruction of three optical parameters distributions of biological tissues namely, the absorption  $\mu_a$  and scattering  $\mu_s$  coefficients, as well as the anisotropy factor  $g$  of the Henyey-Greenstein phase function as a new optical contrast. The 2D images are obtained from the simulation experiments and multi-source quantitative photoacoustic tomography with the radiative transfer equation (RTE) as light transport model. The image reconstruction method is based on a gradient-based optimization scheme. The adjoint method applied to the RTE is used to efficiently compute the gradient of the objective function. The results show simultaneous reconstructions of the three optical properties even with noisy data. The crosstalk problem between the three parameters is highlighted. Superior quality images are obtained for  $\mu_a$  compared to those of  $\mu_s$  and  $g$ . Moreover, our algorithm allows reconstructing inserts-like heterogeneities with very good spatial resolution and qualitative accuracy.

**Keywords** quantitative photoacoustic tomography, radiative transfer equation, inverse problem, image reconstruction, adjoint method, biological tissues.

## 24 Nomenclature

25	$A$	absorbed energy density field, $\text{W mm}^{-3}$
26	$M$	measured data of the absorbed optical energy density, $\text{W mm}^{-3}$
27	$N_s$	number of collimated sources
28	$g$	anisotropy factor of the Henyey-Greenstein phase function
29	$H$	observation equation
30	$J$	objective function
31	$\mathbf{n}$	outward unit vector normal to the medium boundary
32	$p$	scattering phase function
33	$\mathbf{r}$	spatial position ( $= x, y$ ), mm
34	$S$	source term in the RTE
35		
36	<i>Greek symbols</i>	
37	$\psi$	radiance, $\text{W mm}^{-2} \text{sr}^{-1}$
38	$\Delta\Omega$	control solid angle
39	$\mathcal{L}$	Lagrangian
40	$\mu_a$	absorption coefficient, $\text{mm}^{-1}$
41	$\mathbf{\Omega}$	direction vector
42	$\mu_t$	attenuation coefficient ( $= \mu_a + \mu_s$ ), $\text{mm}^{-1}$
43	$\psi$	radiance, $\text{W mm}^{-2} \text{sr}^{-1}$
44	$\mu_s$	scattering coefficient, $\text{mm}^{-1}$
45	$\rho$	directional reflection coefficient
46	$\mathcal{R}$	state equation
47	$\Theta$	angle between two directions, rad
48	$\theta$	parameter to be reconstructed
49	$\Upsilon$	intensity of the collimated laser beam, $\text{W mm}^{-2}$

50	$\Phi$	fluence rate, $\text{W mm}^{-2}$
51	$\phi$	adjoint variable
52	$\Sigma$	interval $[0, 2\pi]$
53	$\mathcal{D}$	domain of $\mathbb{R}^2$
54	$\partial\mathcal{D}$	boundary of the medium $\mathcal{D}$
55		
56	<i>Subscripts</i>	
57	$\mathcal{D}$	spatial
58	$\Omega$	angular
59	$\mathcal{D}\Omega$	spatial-angular
60	$c$	collimated
61	$s$	scattered
62	$sp$	specular
63	$x, y, z$	$(Ox)$ -axis, $(Oy)$ -axis, $(Oz)$ -axis
64	<i>Superscripts</i>	
65	*	adjoint operator
66	+	incoming boundary
67	−	outgoing boundary
68		

## 69 **1 Introduction**

70 Photoacoustic tomography (PAT) is an emerging technique for non-invasive imaging of biological tissues. It is  
71 based on the photoacoustic effect, which refers to the generation of acoustic waves by the absorption of the optical  
72 energy in the tissue illuminated by an ultrashort pulsed laser [1–13]. The hybrid modality of PAT combines the  
73 high tissue contrast of optical imaging methods and the good spatial resolution of ultrasound imaging methods.

74 PAT allows imaging at depths and resolutions unprecedented for optical methods. The optical part of PAT provides  
75 information on the distribution of chromophores, which are light-absorbing molecules within the tissue. The chro-  
76 mophores of interest are, for example, haemoglobin, melanin, collagen, and various contrast agents. PAT has been  
77 successfully applied to the visualization of different structures in biological tissues, such as microvasculature of  
78 tumors, human blood vessels, the cerebral cortex in small animals or breast cancer. However, this information is  
79 only a qualitative image and it does not give quantitative information on the concentrations of the chromophores.

80 Quantitative photoacoustic tomography (QPAT) is a technique aimed at estimating the absolute concentration of the  
81 chromophores from a reconstructed PAT image. It reconstructs the optical parameters of biological tissue from data  
82 describing the absorbed energy distribution inside the tissue (assumed to be known in this work). The development  
83 of improved image reconstruction algorithm in QPAT constitutes a challenging problem [2]. An accurate forward  
84 model is essential to meet the requirements of clinical applications and to obtain a good quality reconstruction.

85 There have been extensive studies on the optical inverse problem of QPAT, although most were using the Diffusion  
86 Equation (DE) in the diffusive regime typically assuming that the light propagation throughout the tissue is near-  
87 isotropic [7]. However, this model has well-known limitations [14–17]. In addition, the anisotropy factor also  
88 strongly affects the light propagation in tissue in the transport regime. Indeed, the biological tissues are highly  
89 forward scattering media where  $g$  is typically between 0.8 and 1 [9, 14, 18].

90 Although the absorption map is usually of the major clinic interest, it is necessary to reconstruct the scattering  
91 maps ( $\mu_s$ ,  $g$ ) as well in order to accurately reconstruct the absorption map when the scattering coefficient and  
92 the anisotropy factor are unknown. Some works have shown that  $g$  can be modified when the tissue is affected  
93 by a tumor because cells and cell nuclei change their size and shape. Therefore, the morphological modification  
94 of the tissue changes the scattering coefficient  $\mu_s$ . Since the anisotropy factor describes the anisotropy (angular  
95 distribution) of light scattering, this modification will also lead to a variation of  $g$  values between healthy and  
96 tumor tissues. For instance, quantitative phase imaging showed, on a prostate tissue biopsy with malignancy, that  
97 the anisotropy factor  $g$  can be a marker of disease [19]. Van Hillegersberg et al. [20] pointed that the anisotropy  
98 factor of rat liver decreases from 0.952 to 0.946 in a tumor at 633 nm. Germer et al. [21] reported experimentally  
99 that  $g$  was different for normal human liver tissue ( $g = 0.902$ ) and liver metastases ( $g = 0.955$ ) at three different

100 wavelengths. Consequently, the anisotropy factor can provide an additional intrinsic contrast for optical imaging.

101 To overcome the limitations of the DE, the Radiative Transfer Equation (RTE) has been addressed as a rigorous

102 model for light transport in biological tissues and has become a focus of investigations in QPAT [15–17, 22–35].

103 In the optical inverse problem of QPAT, it has been shown that the absorption coefficient  $\mu_a$  can be reconstruct if

104 one light source is used whereas the simultaneous reconstruction of  $(\mu_a, \mu_s)$  needs multiple optical illuminations,

105 so-called multi-source QPAT [16, 25, 36, 37]. Multiple measurements are often needed as well to eliminate non-

106 uniqueness of the reconstruction problem [7, 23].

107 To the best of our knowledge, the simultaneous reconstruction of  $(\mu_a, \mu_s, g)$  has not been presented so far while

108 the anisotropy factor is an important optical parameter [38]. In practical applications, the anisotropy factor is

109 usually not known while this factor should be known to better describe light propagation. Recovering  $(\mu_s, g)$  is

110 especially difficult due to the weak dependence of the absorbed optical energy density on scattering. To overcome

111 this problem, the approach has been to assume the anisotropy factor as known and estimate simultaneously  $(\mu_a, \mu_s)$

112 in QPAT based on the RTE [16, 17, 26, 29, 31–33]. However, this approach can bias the estimated value of  $\mu_s$  and also

113 of  $\mu_a$ . In this regard, we investigated the simultaneous reconstruction of  $(\mu_a, \mu_s, g)$  in multi-source QPAT based on

114 the RTE in the transport regime. For the inversion, a gradient-based scheme using the Lm-BFGS was considered

115 to update the spatial distribution of optical parameters. In such scheme, the major challenge is the computation

116 of the objective function gradient which is the most expensive step. Evaluating the gradient through perturbation

117 methods is daunting and prohibitively expensive with the RTE, especially in this case where the parameters are

118 spatially dependent. To overcome this difficulty, the adjoint method applied to the RTE [17, 26–28, 31, 35, 38–40]

119 was used to efficiently compute the objective function gradient with respect to the three optical parameters  $(\mu_a, \mu_s,$

120  $g)$  regardless the number of unknowns. In this work, a two-dimensional geometry was considered.

121 The inverse problem in QPAT is challenging since it is ill-posed due to the unsatisfying of both conditions unique-

122 ness and stability. The uniqueness is caused by the strong under-determination nature of the problem where the

123 spatially unknown number to retrieve is significantly higher than the spatially absorbed energy density data. This

124 implies that different spatial distributions of parameters can lead to identical absorbed energy density data. More-

125 over, the measured noise due to the experimental setup causes an instability of the solution where small noise level

126 is able to significantly amplify the estimation errors of optical coefficients. The crosstalk problem is an interesting  
127 example in QPAT which allows to highlight the robustness of the reconstruction algorithm versus the uniqueness  
128 condition. The improvement of the quality reconstruction is expected when increasing the source number where  
129 the amount of measured data becomes more important leading to reduce the under-determination character. Fur-  
130 thermore, the noise level is also assessed in our study in order to test the stability of our method.  
131 The remainder of this paper is organized as follows. Section 2 presents the optical forward model in QPAT. Section  
132 3 deals with the optical inverse problem of QPAT. A continuous Lagrangian formulation is used to rigorously deduce  
133 the adjoint RTE and an objective function gradient. The results obtained on 2D reconstructions are presented and  
134 discussed in section 4. Concluding remarks are finally offered in the final section.

## 135 2 Optical forward model in QPAT

### 136 2.1 Light transport model

137 We assumed that the convex domain  $\mathcal{D}$  of the medium is illuminated by a collimated laser beam of direction  $\boldsymbol{\Omega}_c$ .  
138 Then, the illuminated wall of the medium is defined by:

$$\partial\mathcal{D}_c = \left\{ \mathbf{r} \in \partial\mathcal{D}, \boldsymbol{\Omega}_c \cdot \mathbf{n}(\mathbf{r}) < 0 \right\}, \quad (1)$$

139 where  $\mathbf{n}$  is the outward unit vector normal to the medium boundary. Let  $\Sigma$  be the interval  $[0, 2\pi]$ . We also define  
140 the incoming and outgoing boundaries:

$$\Gamma^- = \left\{ (\mathbf{r}, \boldsymbol{\Omega}) \in \partial\mathcal{D} \times \Sigma, \boldsymbol{\Omega} \cdot \mathbf{n}(\mathbf{r}) < 0 \right\} \quad \text{and} \quad \Gamma^+ = \left\{ (\mathbf{r}, \boldsymbol{\Omega}) \in \partial\mathcal{D} \times \Sigma, \boldsymbol{\Omega} \cdot \mathbf{n}(\mathbf{r}) > 0 \right\}. \quad (2)$$

The light source  $\Upsilon(\mathbf{r})$ , given at any location point  $\mathbf{r} \in \partial\mathcal{D}$ , penetrates from the outgoing into the medium. Part  
of it propagates through the medium without being deviated, while the rest is scattered in all directions. It is  
thus convenient to split the radiance  $\psi$  into two components [41]. These are denoted  $\psi_c(\mathbf{r}) = \psi(\mathbf{r}, \boldsymbol{\Omega})\delta(\boldsymbol{\Omega} - \boldsymbol{\Omega}_c)$   
for  $\mathbf{r} \in \mathcal{D}$  ( $\delta$  is the Dirac-delta function and  $\boldsymbol{\Omega}_c$  is the direction of the collimated laser beam) and  $\psi_s(\mathbf{r}, \boldsymbol{\Omega})$  for

$(\mathbf{r}, \boldsymbol{\Omega}) \in \mathcal{D} \times \Sigma$ . They are respectively the collimated and scattered components of radiance [42]. The  $\psi_c(\mathbf{r})$  collimated radiance is governed by the Bouguer-Beer-Lambert equation with its boundary conditions [42]:

$$\left[ \boldsymbol{\Omega}_c \cdot \nabla + \mu_t(\mathbf{r}) \right] \psi_c(\mathbf{r}) = 0 \text{ for } \mathbf{r} \in \mathcal{D}, \quad (3)$$

$$\psi_c(\mathbf{r}) - \Upsilon(\mathbf{r}) = 0 \text{ for } \mathbf{r} \in \partial\mathcal{D}_c \text{ and } \psi_c(\mathbf{r}) = 0 \text{ for } \mathbf{r} \in \partial\mathcal{D} \setminus \partial\mathcal{D}_c. \quad (4)$$

141 where  $\mu_t$  is the sum of the absorption and scattering coefficients. The scattered radiance  $\psi_s(\mathbf{r}, \boldsymbol{\Omega})$  at location  
 142  $\mathbf{r} \in \mathcal{D} \subset \mathbb{R}^2$  in direction  $\boldsymbol{\Omega} \in \Sigma$  is solution of the steady state RTE:

$$\left[ \boldsymbol{\Omega} \cdot \nabla + \mu_t(\mathbf{r}) \right] \psi_s(\mathbf{r}, \boldsymbol{\Omega}) - \mu_s(\mathbf{r}) \int_{\Omega'=2\pi} p(\boldsymbol{\Omega}' \cdot \boldsymbol{\Omega}) \psi_s(\mathbf{r}, \boldsymbol{\Omega}') d\Omega' - S_c(\mathbf{r}, \boldsymbol{\Omega}) = 0, \quad (5)$$

143 for  $(\mathbf{r}, \boldsymbol{\Omega}) \in \mathcal{D} \times \Sigma$  where  $S_c$  is an additional radiation source term to the RTE due to the scattered part of the  
 144 collimated laser beam within the medium [42]:

$$S_c(\mathbf{r}, \boldsymbol{\Omega}) = \mu_s(\mathbf{r}) p(\boldsymbol{\Omega}_c \cdot \boldsymbol{\Omega}) \psi_c(\mathbf{r}). \quad (6)$$

145 The Henyey-Greenstein (H-G) phase function is the most widely-adopted scattering phase function of biomedical  
 146 optics [14] and this has been used here. This function depends only on the inner product between the incident  
 147 direction  $\boldsymbol{\Omega}'$  that scattered  $\boldsymbol{\Omega}$  and the anisotropy factor  $g$ . It is expressed for 2D media as:

$$p(\boldsymbol{\Omega}' \cdot \boldsymbol{\Omega}) = \frac{1}{2\pi} \frac{1 - g^2}{(1 + g^2 - 2g \boldsymbol{\Omega}' \cdot \boldsymbol{\Omega})}. \quad (7)$$

148 The tissue surfaces are assumed to be semi-transparent boundaries due to the refractive index mismatch between  
 149 air and tissue. Thus, the boundary conditions for the scattered radiance are [43]:

$$\psi_s(\mathbf{r}, \boldsymbol{\Omega}) - \frac{1}{\pi} \int_{\boldsymbol{\Omega}' \cdot \mathbf{n} > 0} \rho(\Theta') \psi_s(\mathbf{r}, \boldsymbol{\Omega}') \boldsymbol{\Omega}' \cdot \mathbf{n} d\Omega' = 0 \text{ with } \cos \Theta' = \boldsymbol{\Omega}' \cdot \mathbf{n} \text{ (scattered reflection),} \quad (8)$$



150 for  $(\mathbf{r}, \boldsymbol{\Omega}) \in \Gamma^-$ . The directional reflection coefficient  $\rho$  is given by Snell-Descartes laws assuming that the refrac-  
 151 tive index of the outside medium (air) is unity and that of tissue is equal to 1.4 [42, 43]. The specular reflection  
 152  $\boldsymbol{\Omega}_{sp} = \boldsymbol{\Omega} - 2(\boldsymbol{\Omega} \cdot \mathbf{n}) \mathbf{n}$  is defined as the direction from which a laser beam must hit the surface. Then, after a specular  
 153 reflection it travels in the direction of  $\boldsymbol{\Omega}$ .

154 Similarly as for the radiance, the fluence may be separated into its collimated ( $\Phi_c$ ) and scattered ( $\Phi_s$ ) components:

$$\Phi(\mathbf{r}) = \Phi_s(\mathbf{r}) + \Phi_c(\mathbf{r}) \text{ for } \mathbf{r} \in \mathcal{D} \text{ with } \Phi_c(\mathbf{r}) = \psi_c(\mathbf{r}) \text{ and } \Phi_s(\mathbf{r}) = \int_{\Omega=2\pi} \psi_s(\mathbf{r}, \boldsymbol{\Omega}) d\Omega. \quad (9)$$

155 The absorption of light in the tissue results in the absorbed energy density field:

$$A(\mathbf{r}) = \mu_a(\mathbf{r})\Phi(\mathbf{r}) = \mu_a(\mathbf{r})\psi_c(\mathbf{r}) + \mu_a(\mathbf{r})\Phi_s(\mathbf{r}). \quad (10)$$

156 The function  $\Phi(\mathbf{r})$  depends on the distribution of absorption and scattering within  $\mathcal{D}$ , as well as the light source.  
 157 The optical forward problem in QPAT is to compute (10) when the optical properties of the biological tissue and  
 158 the input light source are given.

### 159 **3 Optical inverse problem of QPAT**

#### 160 **3.1 The objective function and observation equation**

161 The optical inverse problem of QPAT is to estimate the optical parameters of the tissue when the absorbed energy  
 162 density  $H$  is given. In this work, we intended to reconstruct the absorption  $\mu_a$  and scattering  $\mu_s$  coefficients as  
 163 well as the anisotropy factor  $g$ . The spatial distribution of the vector of parameters  $\theta = (\mu_a, \mu_s, g)$  is reconstructed  
 164 by applying a nonlinear optimization technique to an objective function  $J$  that is an explicit function of  $\theta$ . The  
 165 real-value objective function describes the discrepancy between the measured absorbed energy density,  $M(\mathbf{r})$  and  
 166 the predicted numerical data,  $A(\mathbf{r})$  (given from Eq. (10)). The objective function to be minimized, writes

$$J(\theta) = \frac{1}{2} \sum_{s=1}^{N_s} \left\| \frac{A_s(\theta) - M_s}{M_s} \right\|_{\mathcal{D}}^2, \quad (11)$$

167 where  $A_s(\theta)$  and  $M_s$  are the predictions and measurements obtained with the  $s^{th}$  collimated source, respectively  
 168 while  $N_s$  is the number of collimated sources. In (11), the fraction uses point-wise division and the norm is  
 169 associated to  $L^2(\mathcal{D})$ , the space of real valued square-integrable functions on  $\mathcal{D}$ . In order to avoid round-off error  
 170 due to the low level of the readings of the forward model, the function  $J$  is normalized with respect to  $M_s$ . Note  
 171 that  $M_s$  can be small far away of the illuminated wall of the medium. But, this didn't affect the stability of the  
 172 algorithm for the simulations presented further.

It can be noticed that all the mathematical development presented further can be made for one fixed collimated source. Then, we can omit the index  $s$  for simplicity. The observation equation  $A(\theta)$  is defined as:

$$A(\theta)(\mathbf{r}) = (H \psi_{c,\theta})(\mathbf{r}) + (\tilde{H} \psi_{s,\theta})(\mathbf{r}) \text{ for } \mathbf{r} \in \mathcal{D}, \quad (12)$$

$$\text{with } (H \psi_{c,\theta})(\mathbf{r}) = \mu_a(\mathbf{r})\psi_c(\mathbf{r}) \text{ and } (\tilde{H} \psi_{s,\theta})(\mathbf{r}) = \mu_a(\mathbf{r}) \int_{\Omega=2\pi} \psi_s(\mathbf{r}, \mathbf{\Omega}) d\Omega. \quad (13)$$

173 To define compactly the state equation, we denote by  $\mathcal{R}_c(\cdot, \psi_c)$  and  $\mathcal{R}_s(\cdot, \psi_c, \psi_s)$  the right-hand sides in equations  
 174 (3) and (5). Then:

$$\mathcal{R}(\theta, \psi_c, \psi_s) = \left\{ \mathcal{R}_c(\theta, \psi_c), \mathcal{R}_s(\theta, \psi_c, \psi_s) \right\}. \quad (14)$$

175 The reconstruction algorithm consists of minimizing  $J$  when (14) is satisfied. The nonlinear optimization algorithm  
 176 chosen in this work requires knowledge of the objective function gradient with respect to unknown parameters. To  
 177 compute this gradient, the adjoint method (starting from the Lagrangian method) is introduced.

### 178 3.2 The Lagrangian and adjoint method

179 For one fixed collimated source, the Lagrangian is written in the  $L^2$  space as [44, 45]:

$$\mathcal{L}(\theta, \psi_c, \psi_s, \phi_c, \phi_s) = \frac{1}{2} \left\| \frac{(H \psi_c) + (\tilde{H} \psi_s) - M}{M} \right\|_{\mathcal{D}}^2 + \langle \phi_c | \mathcal{R}_c \rangle_{\mathcal{D}} + \langle \phi_s | \mathcal{R}_s \rangle_{\mathcal{D}\Omega}, \quad (15)$$

180 where the Lagrangian multipliers are:  $\phi_c = \phi_c(\mathbf{r})$  (with  $\mathbf{r} \in \mathcal{D}$ ) and  $\phi_s = \phi_s(\mathbf{r}, \mathbf{\Omega})$  (with  $(\mathbf{r}, \mathbf{\Omega}) \in \mathcal{D} \times \Sigma$ ). They  
 181 are real functions that represent the adjoint variables associated to  $(\psi_c, \psi_s)$ . The two last terms in (15) are the inner

182 products associated to  $L^2(\mathcal{D})$  and  $L^2(\mathcal{D}\Omega)$ . It can be noticed that (which is trivial in appearance) if  $(\psi_c, \psi_s)$  is the  
 183 solution of the state equation (14) for the true  $\theta$  parameter, then we have the identity:

$$\mathcal{L}(\theta, \psi_c(\theta), \psi_s(\theta), \phi_c, \phi_s) = J(\theta), \text{ for all } \phi_c, \phi_s. \quad (16)$$

184 By deriving this equation it yields:

$$J'(\theta) \delta\theta = \frac{\partial \mathcal{L}(\theta, \psi_c, \psi_s, \phi_c, \phi_s)}{\partial \theta} \delta\theta + \frac{\partial \mathcal{L}(\theta, \psi_c, \psi_s, \phi_c, \phi_s)}{\partial \psi_c} \frac{\partial \psi_c(\theta)}{\partial \theta} \delta\theta + \frac{\partial \mathcal{L}(\theta, \psi_c, \psi_s, \phi_c, \phi_s)}{\partial \psi_s} \frac{\partial \psi_s(\theta)}{\partial \theta} \delta\theta. \quad (17)$$

185 We denote the following independant quantities by:

$$\delta\psi_c = \frac{\partial \psi_c(\theta)}{\partial \theta} \delta\theta \text{ and } \delta\psi_s = \frac{\partial \psi_s(\theta)}{\partial \theta} \delta\theta. \quad (18)$$

186 Then, the adjoint variables are solutions to the following equation [44, 45]:

$$\frac{\partial \mathcal{L}(\theta, \psi_c, \psi_s, \phi_c, \phi_s)}{\partial \psi_c} \delta\psi_c + \frac{\partial \mathcal{L}(\theta, \psi_c, \psi_s, \phi_c, \phi_s)}{\partial \psi_s} \delta\psi_s = 0, \quad (19)$$

187 and Eq. (17) is reduced to:

$$J'(\theta) \delta\theta = \left\langle \nabla J(\theta) \middle| \delta\theta \right\rangle_{\mathcal{D}} = \frac{\partial \mathcal{L}(\theta, \psi_c, \psi_s, \phi_c, \phi_s)}{\partial \theta} \delta\theta. \quad (20)$$

Using (15) and (19) we deduce that:

$$\begin{aligned} & \left\langle \phi_c \middle| \frac{\partial \mathcal{R}_c}{\partial \psi_c} \delta\psi_c \right\rangle_{\mathcal{D}} + \left\langle \phi_s \middle| \frac{\partial \mathcal{R}_s}{\partial \psi_s} \delta\psi_s \right\rangle_{\mathcal{D}\Omega} + \left\langle \phi_s \middle| \frac{\partial \mathcal{R}_s}{\partial \psi_c} \delta\psi_c \right\rangle_{\mathcal{D}\Omega} \\ & + \left\langle \frac{(H \psi_c) + (\tilde{H} \psi_s) - M}{M} \middle| \frac{(H \delta\psi_c)}{M} \right\rangle_{\mathcal{D}} + \left\langle \frac{(H \psi_c) + (\tilde{H} \psi_s) - M}{M} \middle| \frac{(\tilde{H} \delta\psi_s)}{M} \right\rangle_{\mathcal{D}} = 0. \end{aligned} \quad (21)$$

188 Using (12), we change  $(H \psi_c) + (\tilde{H} \psi_s)$  by  $A$  in the second line of (21). As Eq. (21) has to be satisfied for all  
 189 sensitivity directions  $\delta\psi_c$  and  $\delta\psi_s$ , then it leads to the following set of equations (for each sensitivity directions):

$$\begin{aligned} & \left\langle \frac{A-M}{M} \left| \frac{\tilde{H} \delta\psi_s}{M} \right. \right\rangle_{\mathcal{D}} + \left\langle \phi_s \left| \frac{\partial \mathcal{R}_s}{\partial \psi_s} \delta\psi_s \right. \right\rangle_{\mathcal{D}\Omega} = 0, \\ & \left\langle \frac{A-M}{M} \left| \frac{H \delta\psi_c}{M} \right. \right\rangle_{\mathcal{D}} + \left\langle \phi_c \left| \frac{\partial \mathcal{R}_c}{\partial \psi_c} \delta\psi_c \right. \right\rangle_{\mathcal{D}} + \left\langle \phi_s \left| \frac{\partial \mathcal{R}_s}{\partial \psi_c} \delta\psi_c \right. \right\rangle_{\mathcal{D}\Omega} = 0. \end{aligned} \quad (22)$$

We denote  $\mathcal{A}^*$  the adjoint operator of  $\mathcal{A}$ . Using its definition and Appendix A, the equations of (22) lead to:

$$\begin{aligned} & \left\langle \left( \frac{\partial \mathcal{R}_s}{\partial \psi_s} \right)^* \phi_s \left| \delta\psi_s \right. \right\rangle_{\mathcal{D}\Omega} + \left\langle \frac{H(A-M)}{M^2} \left| \delta\psi_s \right. \right\rangle_{\mathcal{D}} = 0, \\ & \left\langle \left( \frac{\partial \mathcal{R}_c}{\partial \psi_c} \right)^* \phi_c \left| \delta\psi_c \right. \right\rangle_{\mathcal{D}} + \left\langle \left( \frac{\partial \mathcal{R}_s}{\partial \psi_c} \right)^{\bar{*}} \phi_s \left| \delta\psi_c \right. \right\rangle_{\mathcal{D}} + \left\langle \frac{H(A-M)}{M^2} \left| \delta\psi_c \right. \right\rangle_{\mathcal{D}} = 0, \end{aligned} \quad (23)$$

190 where  $\mathcal{A}^{\bar{*}} = 2\pi \mathcal{A}^*$ . As the equations of (23) have to be satisfied for all sensitivity directions  $\delta\psi_c$  and  $\delta\psi_s$ , the  
191 adjoint variables must be solutions to the following set of equations:

$$\left( \frac{\partial \mathcal{R}_s}{\partial \psi_s} \right)^* \phi_s + \frac{H(A-M)}{M^2} = 0 \quad \text{and} \quad \left( \frac{\partial \mathcal{R}_c}{\partial \psi_c} \right)^* \phi_c + \left( \frac{\partial \mathcal{R}_s}{\partial \psi_c} \right)^{\bar{*}} \phi_s + \frac{H(A-M)}{M^2} = 0. \quad (24)$$

Replacing  $\mathcal{R}_c$  and  $\mathcal{R}_s$  defined by (3) and (5) in Eq. (24), we obtain the following adjoint equations model:

$$\begin{aligned} & \left[ \boldsymbol{\Omega} \cdot \boldsymbol{\nabla} + \mu_t(\mathbf{r}) \right] \phi_s(\mathbf{r}, -\boldsymbol{\Omega}) = \mu_s(\mathbf{r}) \int_{\Omega'=2\pi} p(\boldsymbol{\Omega}' \cdot (-\boldsymbol{\Omega})) \phi_s(\mathbf{r}, \boldsymbol{\Omega}') d\Omega' - \mu_a(\mathbf{r}) \frac{(A(\mathbf{r}) - M(\mathbf{r}))}{M^2}, \\ & \left[ \boldsymbol{\Omega}_c \cdot \boldsymbol{\nabla} + \mu_t(\mathbf{r}) \right] \phi_c(\mathbf{r}) = \mu_s(\mathbf{r}) \int_{\Omega'=2\pi} p(\boldsymbol{\Omega}' \cdot (-\boldsymbol{\Omega}_c)) \phi_s(\mathbf{r}, \boldsymbol{\Omega}') d\Omega' - \mu_a(\mathbf{r}) \frac{(A(\mathbf{r}) - M(\mathbf{r}))}{M^2}. \end{aligned} \quad (25)$$

192 The directions  $\boldsymbol{\Omega}$  and  $\boldsymbol{\Omega}_c$  were changed to  $-\boldsymbol{\Omega}$  and  $-\boldsymbol{\Omega}_c$  for convenience.

193 If the tissue surfaces are assumed to be semi-transparent with specular reflection, the boundary conditions of the

194 first equation are given by [39]:

$$\phi_s(\mathbf{r}, \boldsymbol{\Omega}) = \rho(\Theta_{sp}) \phi_s(\mathbf{r}, -\boldsymbol{\Omega}_{sp}) \quad \text{for } (\mathbf{r}, \boldsymbol{\Omega}) \in \Gamma^+ \quad \text{with} \quad \cos \Theta_{sp} = \boldsymbol{\Omega}_{sp} \cdot \mathbf{n} \quad \text{and} \quad \cos \Theta = \boldsymbol{\Omega} \cdot \mathbf{n}. \quad (26)$$

195 The boundary conditions for the adjoint collimated radiance fulfill the condition:  $\phi_c(\mathbf{r}) = 0$  for  $\mathbf{r} \in \partial\mathcal{D}$ .

196 It can be seen that the adjoint equations model takes a similar form to the forward model. The adjoint equations  
 197 model can be solved in a similar manner to that used to solve the forward model. It also shows that the first equation  
 198 of (25) is solved to obtain  $\phi_s(\mathbf{r}, \boldsymbol{\Omega})$  which is bring into the second equation to obtain  $\phi_c(\mathbf{r})$ .

### 199 3.3 Gradient of the objective function

200 The differentiation of the Lagrangian (for one fixed collimated source) with respect to  $\theta$  in direction  $\delta\theta$  satisfies:

$$\frac{\partial \mathcal{L}(\theta, \psi_c, \psi_s, \phi_c, \phi_s)}{\partial \theta} \delta\theta = \frac{\partial J(\theta)}{\partial \theta} \delta\theta + \left\langle \phi_c \left| \frac{\partial \mathcal{R}_c}{\partial \theta} \delta\theta \right. \right\rangle_{\mathcal{D}} + \left\langle \phi_s \left| \frac{\partial \mathcal{R}_s}{\partial \theta} \delta\theta \right. \right\rangle_{\mathcal{D}\Omega}. \quad (27)$$

201 It should be noticed that the function  $J$  (see Eqs. (11,12)) depends explicitly on  $\theta$  only if  $\theta = \mu_a$ . For the other  
 202 optical coefficients,  $\frac{\partial J(\theta)}{\partial \theta} = 0$ . Using (10) and Eq. (20), Eq. (27) is reduced to:

$$\left\langle \nabla J(\theta) \left| \delta\theta \right. \right\rangle_{\mathcal{D}} = \left\langle \phi_c \left| \frac{\partial \mathcal{R}_c}{\partial \theta} \delta\theta \right. \right\rangle_{\mathcal{D}} + \left\langle \phi_s \left| \frac{\partial \mathcal{R}_s}{\partial \theta} \delta\theta \right. \right\rangle_{\mathcal{D}\Omega} \left( + \left\langle \frac{\Phi(A(\theta) - M)}{M^2} \left| \delta\theta \right. \right\rangle_{\mathcal{D}} \text{ if } \theta = \mu_a \right). \quad (28)$$

This is the expression that evaluates the gradient of the objective function. Applying respectively Eq. (28) to  
 $\theta = \mu_a$ ,  $\theta = \mu_s$  and  $\theta = g$  we deduce the objective function gradient, with respect to these parameters:

$$\nabla J(\mu_a) = \frac{\Phi(A(\mu_a) - M)}{M^2} + \phi_c \psi_c + \left\langle \phi_s \left| \psi_s \right. \right\rangle_{\Omega}, \quad (29)$$

$$\nabla J(\mu_s) = \phi_c \psi_c + \left\langle \phi_s \left| \psi_s \right. \right\rangle_{\Omega} - \left\langle \phi_s \left| \int_{\Omega'=2\pi} p(\boldsymbol{\Omega}' \cdot \boldsymbol{\Omega}) \psi_s(\mathbf{r}, \boldsymbol{\Omega}') d\Omega' + p(\boldsymbol{\Omega}_c \cdot \boldsymbol{\Omega}) \psi_c(\mathbf{r}) \right. \right\rangle_{\Omega}, \quad (30)$$

$$\nabla J(g) = - \left\langle \phi_s \left| \mu_s(\mathbf{r}) \left( \int_{\Omega'=2\pi} \frac{\partial p(\boldsymbol{\Omega}' \cdot \boldsymbol{\Omega})}{\partial g} \psi_s(\mathbf{r}, \boldsymbol{\Omega}') d\Omega' + \frac{\partial p(\boldsymbol{\Omega}_c \cdot \boldsymbol{\Omega})}{\partial g} \psi_c(\mathbf{r}) \right) \right. \right\rangle_{\Omega}. \quad (31)$$

203 It should be noticed that if more than one collimated sources are considered, the objective function gradient is  
 204 obtained by summing the objective function gradient for each collimated source.

### 205 3.4 Parameter and data scaling

206 In order to speed-up the iterative convergence to the local minimum, a scaling strategy of the optical parameters [16]  
 207 in the RTE based forward model was carried out in this work. Choosing an a priori function for each optical

208 parameters, say  $\mu_a^r, \mu_s^r, g_r$ , the parameters are searched that fluctuate about unity. This scaling leads to recover:

$$\sigma_a(\mathbf{r}) = \frac{\mu_a(\mathbf{r})}{\mu_a^r(\mathbf{r})}, \sigma_s(\mathbf{r}) = \frac{\mu_s(\mathbf{r})}{\mu_s^r(\mathbf{r})}, q(\mathbf{r}) = \frac{g(\mathbf{r})}{g_r(\mathbf{r})}, \quad (32)$$

for which magnitude is of order one approximately for all these three new parameters. It results that the considered objective function becomes  $J(\sigma_a, \sigma_s, q)$  (instead of  $J(\mu_a, \mu_s, g)$ ). In the results presented further, the a priori functions for each optical parameters were chosen as those of the background (homogeneous) medium. The objective function gradients with respect to  $\sigma_a, \sigma_s$  and  $q$  are:

$$\begin{aligned} \nabla J(\sigma_a) &= \mu_a^r(\mathbf{r}) \nabla J(\mu_a); \quad \nabla J(\sigma_s) = \mu_s^r(\mathbf{r}) \nabla J(\mu_s); \\ \nabla J(q) &= - \left\langle \phi_s \middle| \mu_s(\mathbf{r}) \left( \int_{\Omega'=2\pi} \frac{\partial p(\boldsymbol{\Omega}' \cdot \boldsymbol{\Omega})}{\partial q} \overline{\psi_s(\mathbf{r}, \boldsymbol{\Omega}')} d\Omega' + \frac{\partial p(\boldsymbol{\Omega}_c \cdot \boldsymbol{\Omega})}{\partial q} \overline{\psi_c(\mathbf{r})} \right) \right\rangle_{A\Omega}. \end{aligned} \quad (33)$$

209 A second scaling, as in [46], was necessary for the simultaneous reconstruction of three optical parameters dis-  
 210 tributions. Indeed, the optical coefficients to be reconstructed from the absorbed energy density are different in  
 211 nature, and their order of magnitude also differs. As a consequence, the objective function gradient parts associated  
 212 with these optical coefficients also differ by roughly the same order of magnitude, which is very bad for the con-  
 213 vergence in the optimization problem when using a gradient-based method. Then, the objective function gradients  
 214 with respect to  $\sigma_a, \sigma_s$  and  $q$  was scaled as:

$$\nabla J^{scaled}(\sigma_a) = c_{\sigma_a} \nabla J(\sigma_a); \quad \nabla J^{scaled}(\sigma_s) = c_{\sigma_s} \nabla J(\sigma_s) \quad \text{and} \quad \nabla J^{scaled}(q) = c_q \nabla J(q). \quad (34)$$

215 where  $c_{\sigma_a}, c_{\sigma_s}$  and  $c_q$  are empirical coefficients that are determined after the first inverse iteration such that the  
 216 largest element of the scaled gradient vector  $\nabla J^{scaled}(\sigma_a)$  equals 5% of the largest element of vector  $\sigma_a^0$ :

$$c_{\sigma_a} = 0.05 \frac{\max(\sigma_a^0)}{\max(|\nabla J(\sigma_a^0)|)}. \quad (35)$$

217 The same holds for  $c_{\sigma_s}$ . The results show that the best quality reconstruction are obtained when the largest element  
218 of  $\nabla J^{scaled}(q)$  equals 1.5% of the largest element of  $q^0$ . The scaling factors are kept constant during the recon-  
219 struction from the first iteration.

220 In QPAT, where the dynamic range of the measured light intensities can be very large, scaling of the data may be  
221 needed in order to ensure numerical stability of the optimization problem. Furthermore, in this work, the data space  
222 was scaled similarly as in [16], where we used the logarithm of amplitude as the data.

### 223 3.5 Implementation of the reconstruction algorithm

224 A Modified Finite Volume Method (MFVM) of high accuracy [42] was used for solving the equations of the  
225 forward and adjoint models. This MFVM can be applied to arbitrarily shaped geometries, by using unstructured  
226 triangular grids. The methodology of the employed method is not repeated here, we refer the reader to [42] for  
227 comprehensive details. The objective function  $J$  was iteratively minimized using the quasi-Newton algorithm with  
228 Lm-BFGS (limited-memory Broyden–Fletcher–Goldfarb–Shanno) [47]. It iteratively updates an initial estimate of  
229 the parameters distribution along a search descent direction denoted  $d$ . Once the minimum is found, the final result  
230 is the unknown parameters distribution. The updating procedure is formulated as:  $\theta^{k+1} = \theta^k + \alpha^k d (\nabla J(\theta^k))$  [47],  
231 where  $k$  is the current iteration of the inverse procedure and  $\alpha^k$  represents the step size obtained by the Armijo line  
232 search in order to provide a sufficient minimization of the objective function.

## 233 4 Results and discussion

234 We consider a 2D numerical phantom with a homogeneous background containing different inserts. In the first test  
235 case, the reconstruction were performed on a relatively large object of size  $20 \times 20 \text{ mm}^2$  while the other test cases  
236 use a phantom of  $10 \times 10 \text{ mm}^2$  (in all the simulations the length unit is the minimeter). The optical properties of  
237 the background are fixed to  $\mu_a = 0.05 \text{ mm}^{-1}$ ,  $\mu_s = 5 \text{ mm}^{-1}$  and  $g = 0.9$  expect for the final test case wherein  $\mu_s$   
238 and  $g$  are assigned the value  $6 \text{ mm}^{-1}$  and 0.8, respectively. The optical background values were used to start the  
239 optimization procedure by assuming a homogeneous medium. The geometry and positions of the inserts differ for  
240 each test in order to carry out different situations that highlight the main issues encountered in QPAT. The intensity

241 of the Laser beam has a spatial Gaussian distribution along the  $x$ - axis or  $y$ - axis ( $s = x$  or  $y$ ) such as:

$$\Upsilon(s) = \frac{1}{\sigma_s \sqrt{2\pi}} \exp\left(\frac{-(s - s_c)^2}{2\sigma_s^2}\right), \quad (36)$$

242 where  $\sigma_s = 1$  mm is the standard deviation of the Laser beam. The position  $s_c$  corresponds to the source location  
 243 at the center of the illuminated wall of the medium. The angular space was discretized with 32 control solid angles  
 244 whereas the number of nodes of the spatial mesh is given for each test case presented further. The quality of the  
 245 algorithm is assessed thanks to the relative estimation error  $\varepsilon$  between the retrieved  $\hat{\beta}$  and the exact vector  $\beta^*$ :

$$\varepsilon = 100\% \frac{\|\hat{\beta} - \beta^*\|_2}{\|\beta^*\|_2} \quad \text{where } \|\cdot\|_2 \text{ denotes Euclidian norm.} \quad (37)$$

#### 246 **4.1 Anisotropy factor reconstruction**

247 This case points out the ability of the QPAT to reconstruct, in the multiple scattering regime, the anisotropy factor  
 248 as an endogenous optical property of tissues. The spatial domain is discretized into 15,857 mesh nodes. Figure 1a  
 249 illustrates the reference medium including three circular inserts centered at (4 mm; -2 mm), (10 mm; 4 mm) and  
 250 (16 mm; -4 mm) with a radius of 2 mm. In this case, the absorption coefficient  $\mu_a = 0.05 \text{ mm}^{-1}$  is kept constant  
 251 while  $\mu_s$  and  $g$  are chosen so that their values lead to a constant value of  $\mu'_s = 0.5 \text{ mm}^{-1}$  in the whole phantom.  
 252 This configuration avoids attributing the spatial variation of  $g$  to  $\mu'_s = \mu_s(1 - g)$ . One Laser source was used to  
 253 illuminate the west surface ( $x = 0$  mm). Figure 1b shows the reconstructed image of the anisotropy factor. It can be  
 254 seen that the retrieved image presents a good agreement with the reference object. The three inserts were spatially  
 255 well fitted with their original positions. The estimated mean values inside the inclusions are correctly retrieved  
 256 with respect to their exact values, even though the red-insert presents a slightly over-estimated values  $\hat{g}_{max} = 0.96$   
 257 against  $g^* = 0.95$ . The circular shape is also well reconstructed. This result implies that the spatial variation of  $g$   
 258 cannot be caused by a variation of  $\mu'_s$  itself. The anisotropy factor can hence be independently reconstructed and  
 259 separated from  $\mu_s$  with our inverse algorithm.



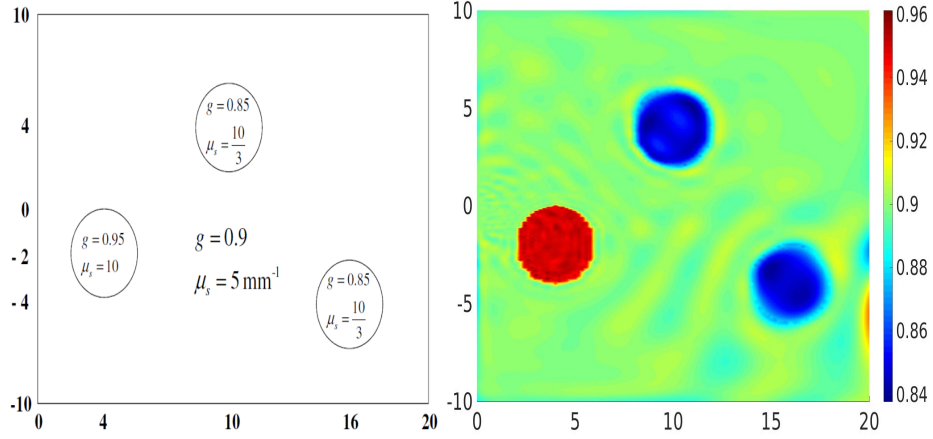


Figure 1: Reconstruction of the anisotropy factor: (a) the reference medium containing three inclusions at different spatial positions and (b) the reconstructed image of  $g$ .

## 260 4.2 Source number effect

261 After testing the capability of the proposed algorithm to reconstruct the anisotropy factor with one Laser source, we  
 262 attempt in this case to assess the robustness of the QPAT to simultaneously reconstruct the three optical properties  
 263  $\mu_a$ ,  $\mu_s$  and  $g$ . This task has not been reported in the previous optical imaging related works, for our best knowledge.  
 264 The original medium contains two circular inserts centered at (2 mm; 2 mm) and (-2 mm; -2 mm) with a radius  
 265 of 1 mm. The exact optical values of the top-right and bottom-left inclusions are assigned as  $\mu_a = 0.06 \text{ mm}^{-1}$ ,  $\mu_s$   
 266  $= 6 \text{ mm}^{-1}$ ,  $g = 0.85$  and  $\mu_a = 0.04 \text{ mm}^{-1}$ ,  $\mu_s = 4 \text{ mm}^{-1}$  and  $g = 0.95$ , respectively. The unstructured triangular  
 267 mesh used is composed of 2,821 nodes. Two illumination configurations were carried out: in the first one, the  
 268 west surface was illuminated with one Laser source while in the second, the phantom is sequentially illuminated  
 269 on its fourth tissue surfaces. The calculations were carried out with an Intel Xeon Processor E5-2683v4, 2.1GHz,  
 270 32 cores. This last uses Hyper-Threading and Intel C compiler. The computational time for the reconstruction in  
 271 the second configuration was 40 min. where 103 iterations were required. It can be noticed that, while keeping  
 272 the same quality of reconstruction, the logarithmic scaling allowed to reduce by about a factor four the number  
 273 of iterations and decreased the norms of the objective function gradients (with respect to each parameter to be  
 274 recover) by a factor  $10^4$ . The obtained results for the first and second configurations are depicted in the left and  
 275 right column of figure 2, respectively. Despite the critical inversion conditions concerning the large unknowns  
 276 number of parameters ( $3 \times 2,821$ ) with only one source, the algorithm was still able to reveal the heterogeneities

277 in the medium. In addition, the retrieved local values are close to their exact values even for the relatively deeper  
278 insert (top-right). The localization and the circular edge were achieved with a better quality reconstruction for  
279 the  $\mu_a$  coefficient compared to those of the  $\mu_s$  coefficient and anisotropy factor. This is due to the measured  
280 absorbed energy density used for fitting that is directly related to the  $\mu_a$  coefficient which explains, therefore, the  
281 superior quality estimation for  $\mu_a$  (see Eq.10). From the right column, the reconstructed images were significantly  
282 improved and the estimated values and the localization are in a good agreement with the real solution. The relative  
283 estimation errors for the top-right inclusion have been decreased from 8.9%, 10.45% and 3.65% to 0.17%, 2.37%  
284 and 0.75% for  $\mu_a$ ,  $\mu_s$  and  $g$  respectively when illuminating the medium with four Laser sources. Furthermore, the  
285 circular shape is correctly reconstructed for all the optical parameters. This configuration has led to increasing the  
286 amount of measured data in the inverse procedure which allows thus to better reconstruct the optical properties  
287 simultaneously.

288 This result highlights the potential interest of using multiple sources which indeed corresponds to real experimental  
289 scenarios with a tomographic context. It is worth noting that the simultaneous reconstruction of the three optical pa-  
290 rameters is not possible with the standard optical tomography since its inverse problem is usually under-determined  
291 and the measured data are collected on the tissue-surface.

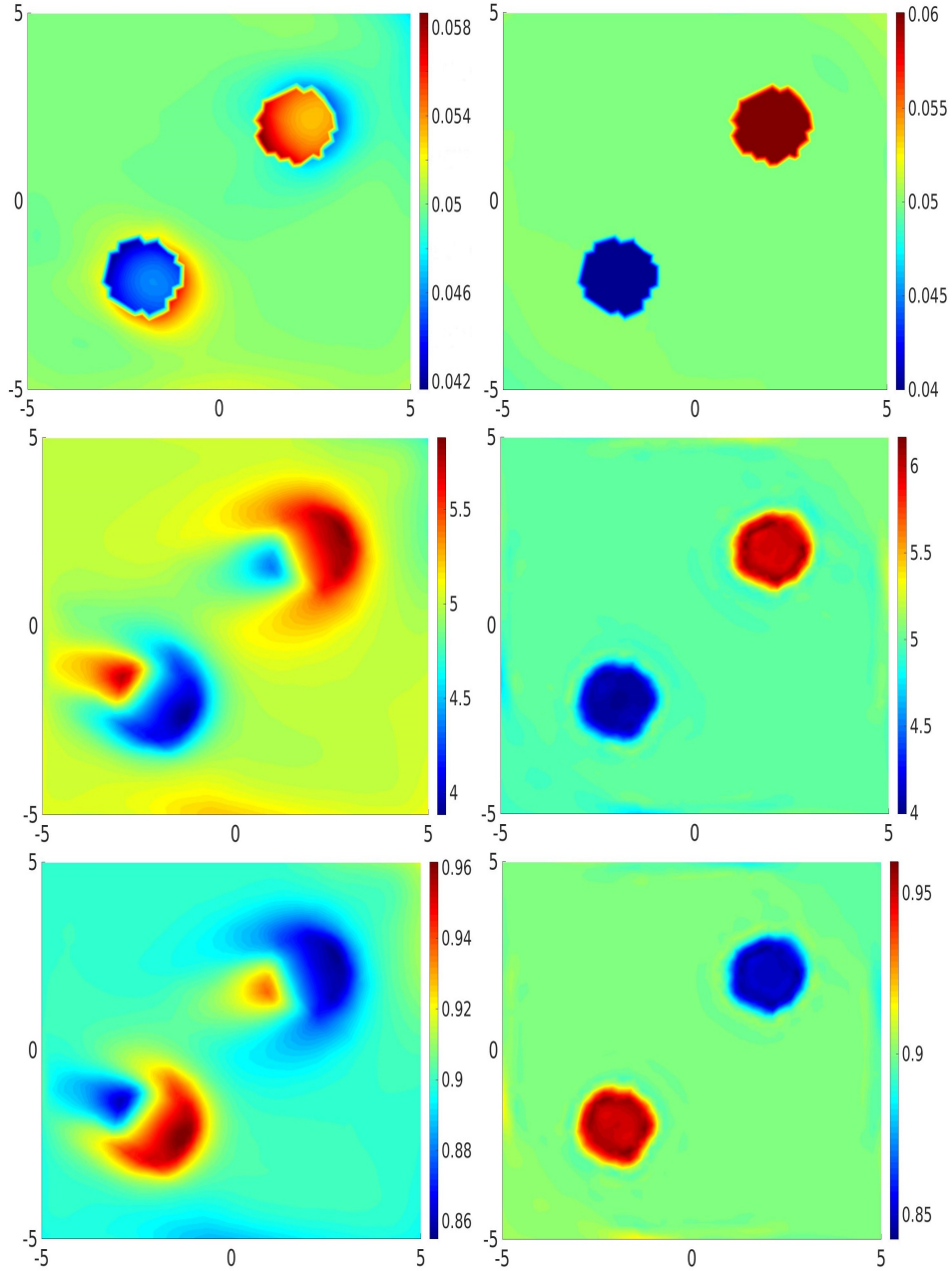


Figure 2: Simultaneous reconstruction of  $\mu_a$ ,  $\mu_s$  and  $g$  with: (left column) only one Laser source illuminating the west surface and (right column), four Laser sources illuminating sequentially the phantom, (top row) absorption coefficient  $\mu_a$ , (middle row) scattering coefficient  $\mu_s$  and (bottom row) anisotropy factor  $g$ .

### 292 4.3 Effect of anisotropy factor kept as a fixed constant

293 We consider the second configuration as in the previous test case by assuming that the two inclusions represent  
 294 heterogeneities only in  $\mu_a$  and  $\mu_s$  coefficients and the anisotropy factor  $g$  is fixed at a constant value in the whole  
 295 medium. The value of  $g$  is most often in the range  $[0.8 - 1]$ . We then chose four different values of  $g$  to represent this  
 296 interval  $(0.8, 0.85, 0.9 \text{ and } 0.95)$ . Figure 3 displays the reconstructed images of  $\mu_a$  and  $\mu_s$  for each fixed value of  $g$ .

297 The relative estimation errors of the two inclusions for  $\mu_a$  and  $\mu_s$  are shown in Table 1. Qualitatively, the inclusions  
298 in  $\mu_a$  and  $\mu_s$  are recovered with low contrast level for  $g = 0.8$  and  $g = 0.85$  (due to the high backscattering of  
299 light) while the reconstruction is relatively improved when the  $g$  values are increased to 0.9 and 0.95. This has  
300 an important realistic interest because the biological tissues are known to be highly forward scattering. Therefore,  
301 more pronounced local artifacts are appeared near to the detectors and in the background especially in the  $\mu_s$   
302 images. For the four values of  $g$ , the  $\mu_a$  coefficient is correctly retrieved with respect to the exact values of the two  
303 inclusions ( $\sim 0.06$  for the top-right and  $\sim 0.04$  for the bottom-left). However, the reconstructed  $\mu_s$  values become  
304 under- and over-estimated with respect to the inclusions-original values as the  $g$  is higher since the two scattering  
305 parameters ( $\mu_s$  and  $g$ ) are significantly correlated.

306 To assess the anisotropy factor effect, the obtained result in the previous test case (Fig. 2 right column) is compared  
307 with the present test case when  $g$  is fixed at 0.9 in order to be closer as possible to the simulation conditions. For  
308 both cases, the background medium in the  $\mu_a$  and  $\mu_s$  images is recovered with the same quality (clear and homo-  
309 geneous). The relative estimation errors for the inclusions of  $\mu_a$  (0.11 % for top-right and 0.13 % for bottom-left)  
310 is approximately similar while that of  $\mu_s$  (46.47 % for top-right and 45.64 % for bottom-left) has been increased.

$\varepsilon$ (%)	$g$ values			
	0.8	0.85	0.9	0.95
$\mu_a$ (top-right inclusion)	7.59	4.49	0.11	2.72
$\mu_a$ (bottom-left inclusion)	8.23	5.42	0.13	2.6
$\mu_s$ (top-right inclusion)	18.9	8.82	46.47	167.79
$\mu_s$ (bottom-left inclusion)	70.57	62.98	45.64	30.22

Table 1: The relative estimation errors  $\varepsilon$  of inclusions of  $\mu_a$  and  $\mu_s$  parameters for the four different values of  $g$ .

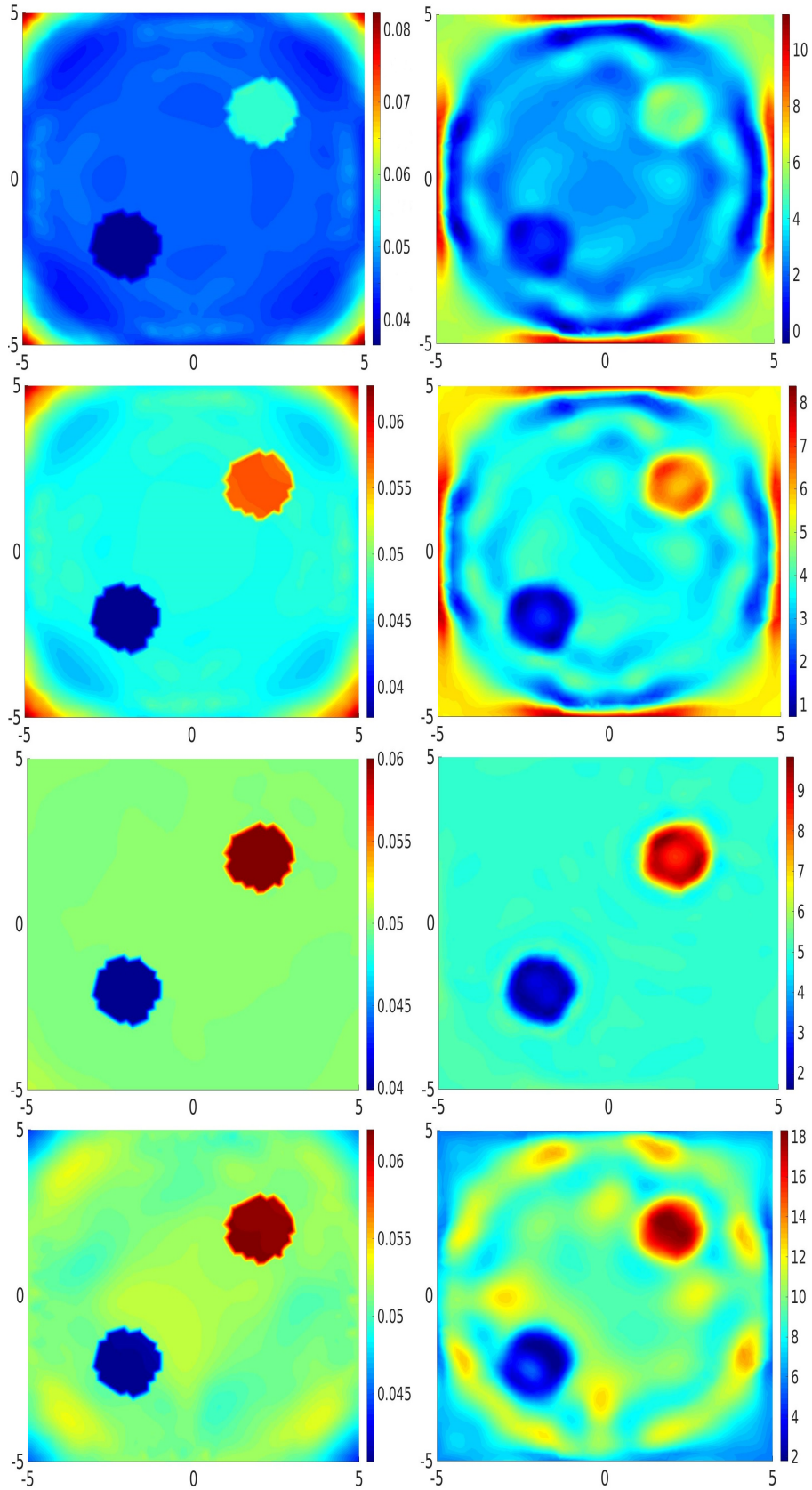


Figure 3: Simultaneous reconstruction of  $\mu_a$  and  $\mu_s$  when  $g$  is kept as a fixed constant in the reconstruction procedure: (left column) absorption coefficient and (right column), scattering coefficient, (first line)  $g = 0.8$ , (second line)  $g = 0.85$ , (third line)  $g = 0.9$  and (last line)  $g = 0.95$ .

#### 311 4.4 Noise level effect

312 In QPAT the measurements noise due to the experimental acquisition setup is unavoidable. To mimics real situa-  
313 tions, the simultaneous reconstructions of  $\mu_a$ ,  $\mu_s$  and  $g$  are performed using corrupted data at different noise levels  
314 of 1%, 3% and 6% added as a random Gaussian distribution on the exact predictions (absorbed energy density).  
315 The original phantom of section 4.2 illuminated by four Laser sources is used in this test case with the same spatial  
316 mesh. The used data (i.e. the absorbed energy density) with 6% of noise when the top wall is illuminated is depicted  
317 in Figure 4. The reconstructed images are shown in Figure 5.

318 The relative estimation errors of  $\mu_a$ ,  $\mu_s$  and  $g$  parameters are given in table 2 for the three noise levels with also  
319 the noiseless case for comparison. They were computed over the whole reconstructed image domain. The obtained  
320 results show that our QPAT algorithm is able to localize the spatial positions of the inserts for the three parameters  
321 even with noisy data. As expected, it is seen that the image quality (characterized by its relative error) is worse as  
322 the noise level increases (see Tab. 2). Qualitatively, the artifacts and local perturbations become more pronounced  
323 and the circular shape of the inserts is degraded especially for  $\mu_s$  and  $g$  images. It can be seen that the  $\mu_a$  images  
324 strongly handle the noise levels better than the scattering parameters  $\mu_s$  and  $g$ . This is again explained by the  
325 fact that the fitted data in the inverse problem of the QPAT are directly dependent on the absorption coefficient.  
326 Quantitatively, the estimated mean values for the top-right insert become slightly over-estimated for  $\mu_a$  and  $\mu_s$  and  
327 under-estimated for  $g$  with the noise level. Concerning the bottom-left insert, the retrieved mean values are slightly  
328 under-estimated for  $\mu_a$  and  $\mu_s$  and over-estimated for  $g$  when the noise increases.

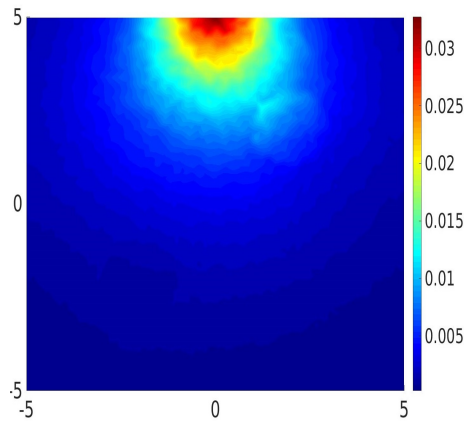


Figure 4: Used data (i.e. the absorbed energy density) with 6% of noise when the top wall is illuminated.



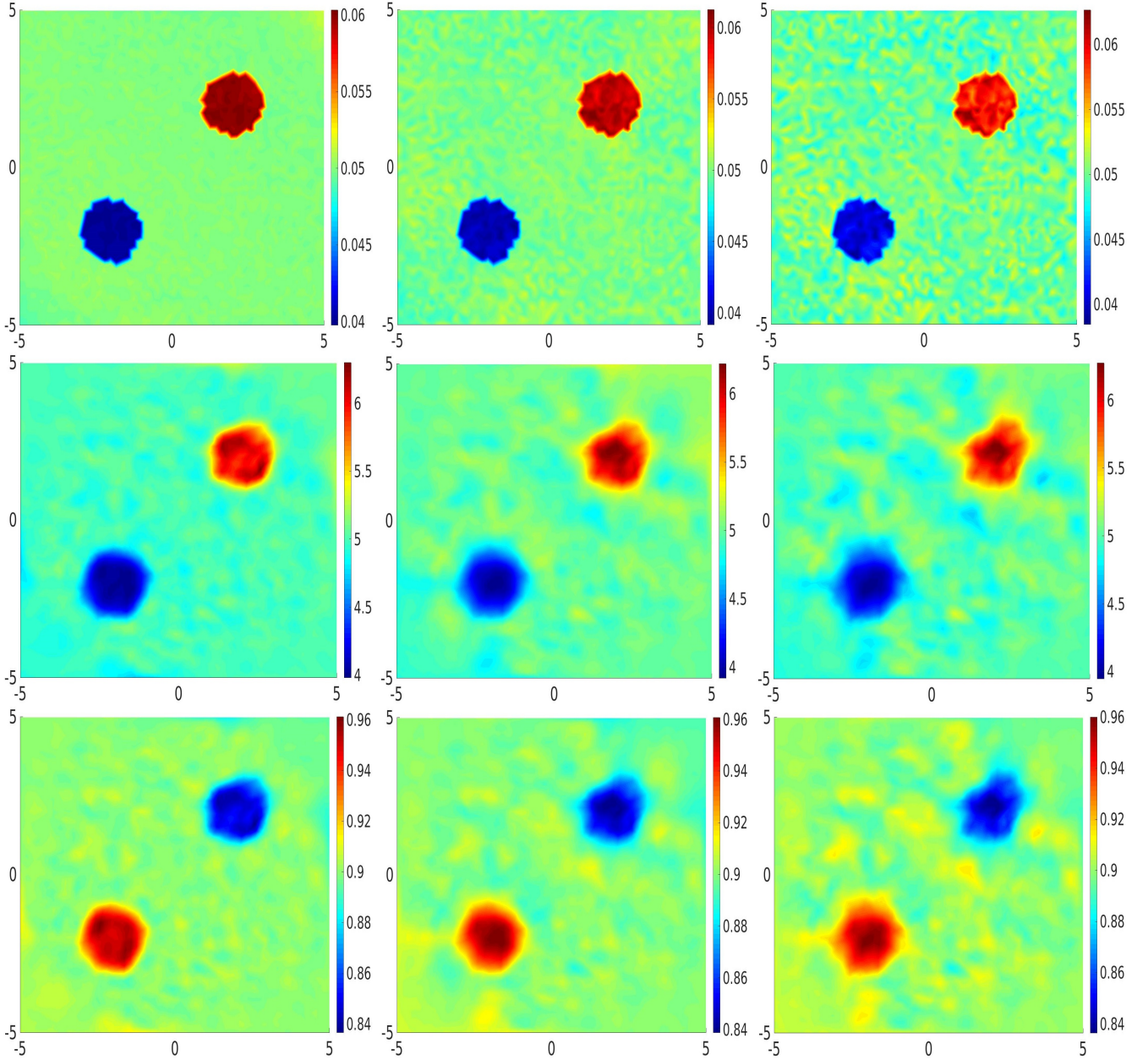


Figure 5: Simultaneous reconstruction with noisy data at different level of: (left column) 1%, (middle column) 3% and (right column) 6% for the absorption coefficient  $\mu_a$  (top row), the scattering coefficient  $\mu_s$  (middle row) and the anisotropy factor  $g$  (bottom row).

$\varepsilon$ (%)	Noise levels			
	0 %	1 %	3 %	6 %
$\mu_a$	0.54	1.53	3.83	8.26
$\mu_s$	7.63	10.50	13.03	14.24
$g$	1.79	2.63	3.33	3.60

Table 2: The relative estimation errors  $\varepsilon$  of  $\mu_a$ ,  $\mu_s$  and  $g$  parameters of the reconstruction algorithm for the four different noise levels on the absorbed density energy data.

## 329 4.5 Crosstalk effect

330 The crosstalk problem is often encountered in optical imaging when reconstructing simultaneously the  $\mu_a$  and  
331  $\mu_s$  coefficients. It is worth noting that the simultaneous reconstruction of  $\mu_a$ ,  $\mu_s$  and  $g$  parameters has not been  
332 previously reported in the literature, for authors' best knowledge. In this case the crosstalk problem and the inter-  
333 parameter effects become challenger in the recovered images. In this work, we highlight the interest of the QPAT  
334 to simultaneously reconstruct the three optical properties while the conventional optical imaging fails to perform  
335 this task. We present a test case that mimics a crosstalk problem between  $\mu_a$ ,  $\mu_s$  and  $g$  wherein their original  
336 images are depicted in Figs. 6a-c, respectively. The same spatial mesh that previously presented (2, 821 nodes)  
337 was used. The phantom was illuminated by four Laser sources. The corresponding recovered images are shown in  
338 Figs. 6d-e. The reconstructed results show that the crosstalk effect is only presented in the  $\mu_s$  and  $g$  images. The  
339 impact of the  $g$ -insert appears with a high contrast heterogeneity in the  $\mu_s$  image ( $\varepsilon_{\mu_s}^{\text{crosstalk}} = 12\%$ ) while the  $\mu_s$   
340 insert produces, in turn, a small contrast heterogeneity in the  $g$  image ( $\varepsilon_g^{\text{crosstalk}} = 1.56\%$ ). Therefore, the crosstalk  
341 error induced in the  $\mu_s$  coefficient is more pronounced than that obtained for the anisotropy factor. This is due to the  
342 high sensitivity of this factor on the light scattering. On the other hand, none crosstalk effect was found in the  $\mu_a$   
343 image which is reconstructed in a very good agreement with its original image. Moreover, the  $\mu_a$  inclusion has no  
344 impact on the  $\mu_s$  and  $g$  images. That can be explained by the fact the absorbed energy density is directly dependent  
345 on the  $\mu_a$  coefficient, which makes the fitted data more sensitive for  $\mu_a$  than the  $\mu_s$  and  $g$  parameters. Within the  
346 minimization scheme, when the algorithm is seeking to simultaneously reconstruct the three parameters ( $\mu_a$ ,  $\mu_s$   
347 and  $g$ ), the  $\mu_a$  image is accurately and quickly obtained after only few iterations of the convergence. Therefore,  
348 the  $\mu_s$  and  $g$  coefficients are reconstructed as in the case that assuming the  $\mu_a$  coefficient is fixed to its exact value.  
349 The superior quality reconstruction of  $\mu_a$ , under these crucial situations, implies that the QPAT has an important  
350 interest for pre-clinical applications because the  $\mu_a$  coefficient can lead to further physiological properties such as  
351 oxygen saturation, hemoglobin concentration, blood oxygenation, etc.

352 The crosstalk is a challenging problem in QPAT which has been reported in previous works related to optical imag-  
353 ing. The crosstalk is induced when the  $\mu_a$  coefficient is only changed for a particular tissue due to physiological



354 variation while its  $\mu_s$  coefficient remains unchanged. Its practical implications can mainly concern the blood tumors  
 355 or other tissues which not containing fibrous. The crosstalk assessment for cancer diagnosis can allow highlighting  
 356 the robustness of the imaging system to handle the false positive tumoral inclusions. In order to overcome its effect,  
 357 more data are needed in the reconstruction algorithm to reduce the uniqueness character of the inverse problem.

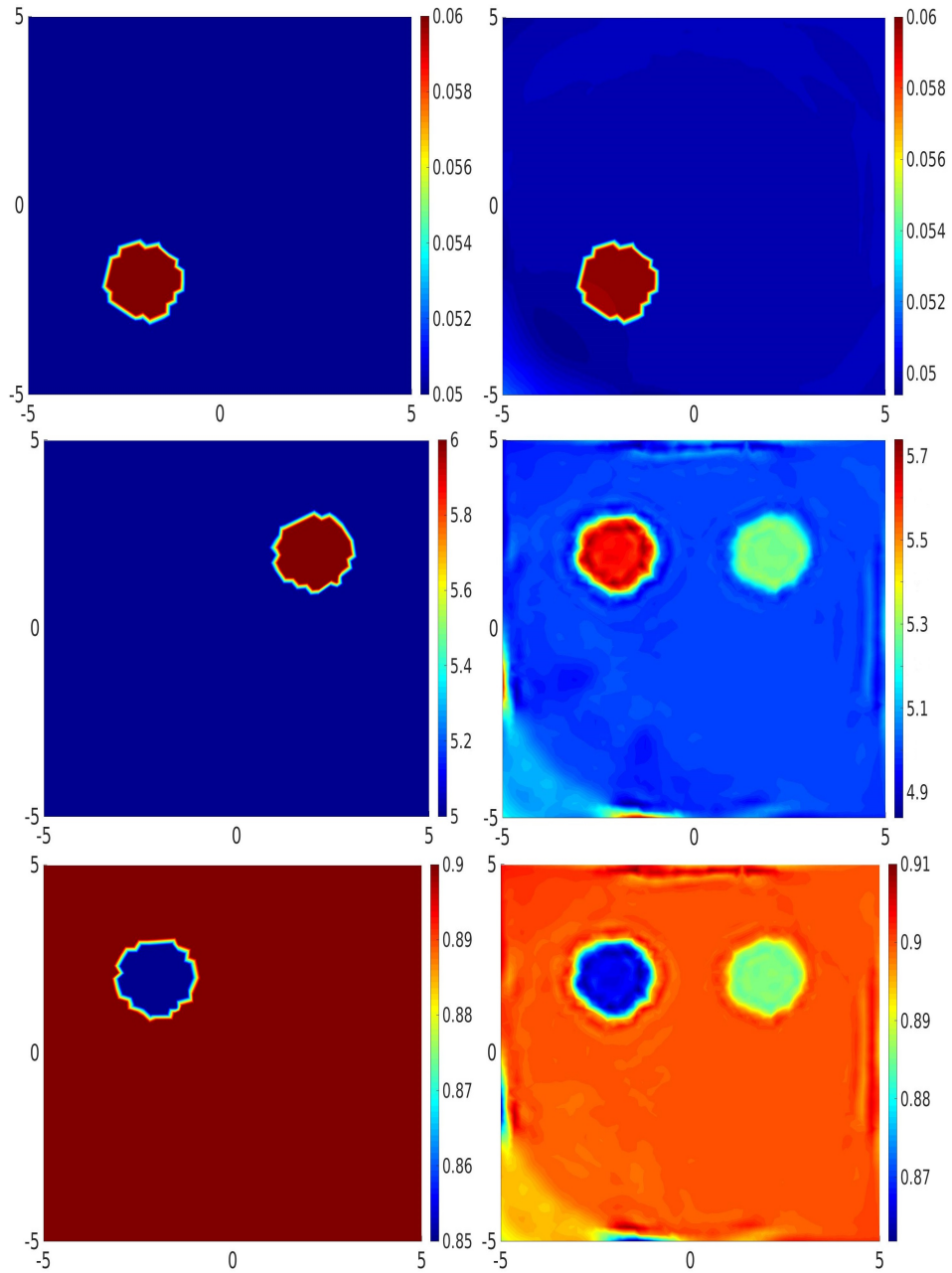


Figure 6: Simultaneous reconstruction of  $\mu_a$ ,  $\mu_s$  and  $g$  with a crosstalk problem: (left column) original images and (right column) reconstructed images, (top row) absorption coefficient  $\mu_a$ , (middle row) scattering coefficient  $\mu_s$  and (bottom row) anisotropy factor  $g$ .

358 **4.6 Slabs inserts reconstruction**

359 In this case, we assess the performance of the QPAT to reconstruct rectangular heterogeneities with different thick-  
 360 nesses and distance separations. To this end, two examples are studied. In the first example, four thin slabs of 200  
 361  $\mu\text{m}$  of thickness separated by 2 mm are inserted in the phantom (see Fig. 7 top-row). In the second example, three  
 362 slabs have 1 mm of thickness with 50  $\mu\text{m}$  of separation (see Fig. 7 bottom-row). The spatial mesh has been in-  
 363 creased to 33,025 nodes for both cases to suitably represent the thin inserts and the small separation. The phantoms  
 364 were illuminated by four Laser sources. The reconstructed results of the first and second example are shown in the  
 365 left and right column of Fig. 8, respectively. Also, the reconstructions were achieved without a crosstalk problem.

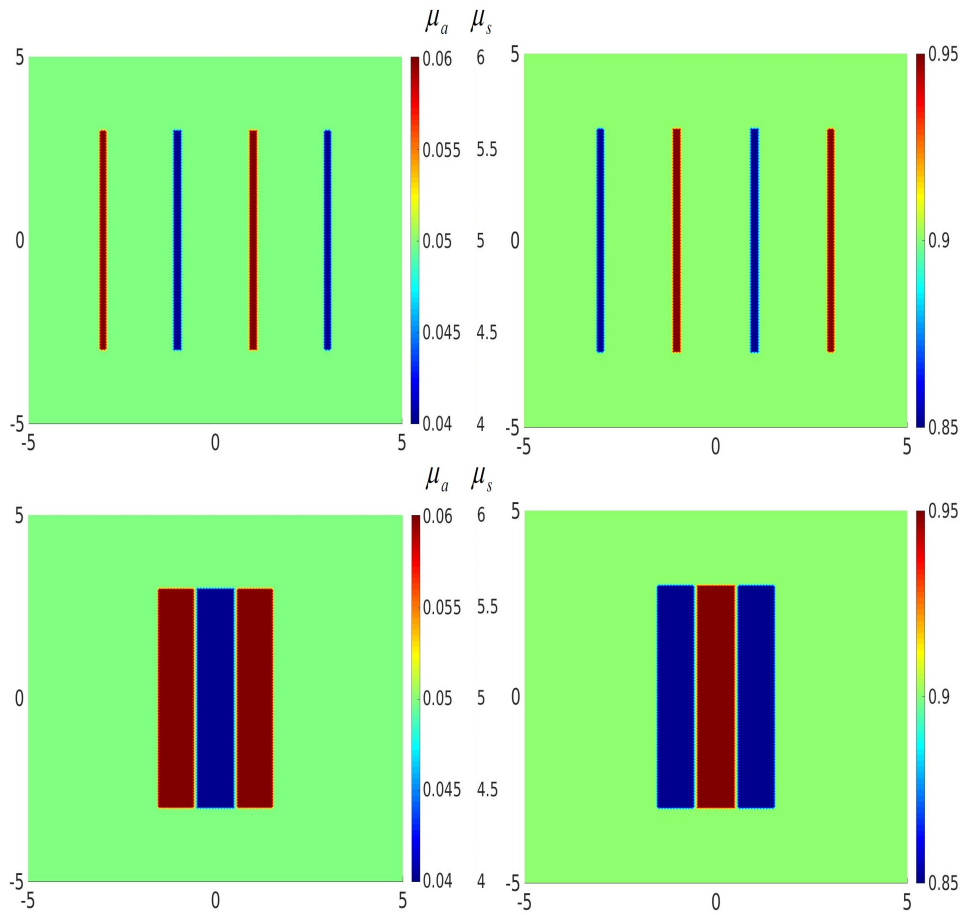


Figure 7: The original images containing the rectangular slabs inserts of the first example (top row) and the second example (bottom row). The right column shows the exact values of the anisotropy factor while the left column indicates the exact values for the  $\mu_a$  and  $\mu_s$  coefficients.

366 Figure 8 shows the robustness of our QPAT algorithm to accurately reconstruct the thin slabs heterogeneities (left  
 367 column in Fig. 8) and also to precisely separate the small-inter-distance thick inserts (right column in Fig. 8). The

368 algorithm is able to retrieve the localization, the size, the thicknesses and also the local optical values  $\mu_a$ ,  $\mu_s$  and  
 369  $g$  of the rectangular slabs inserts. Therefore, the reconstruct images were achieved with a good quantitative and  
 370 qualitative accuracy. For both examples, these slabs are recovered with a high contrast level, contrary to optical  
 371 imaging. The use of the local absorbed energy density, related to the initial acoustic pressure, has advantageously  
 372 provided a potential improvement of the spatial resolution to the optical properties images.

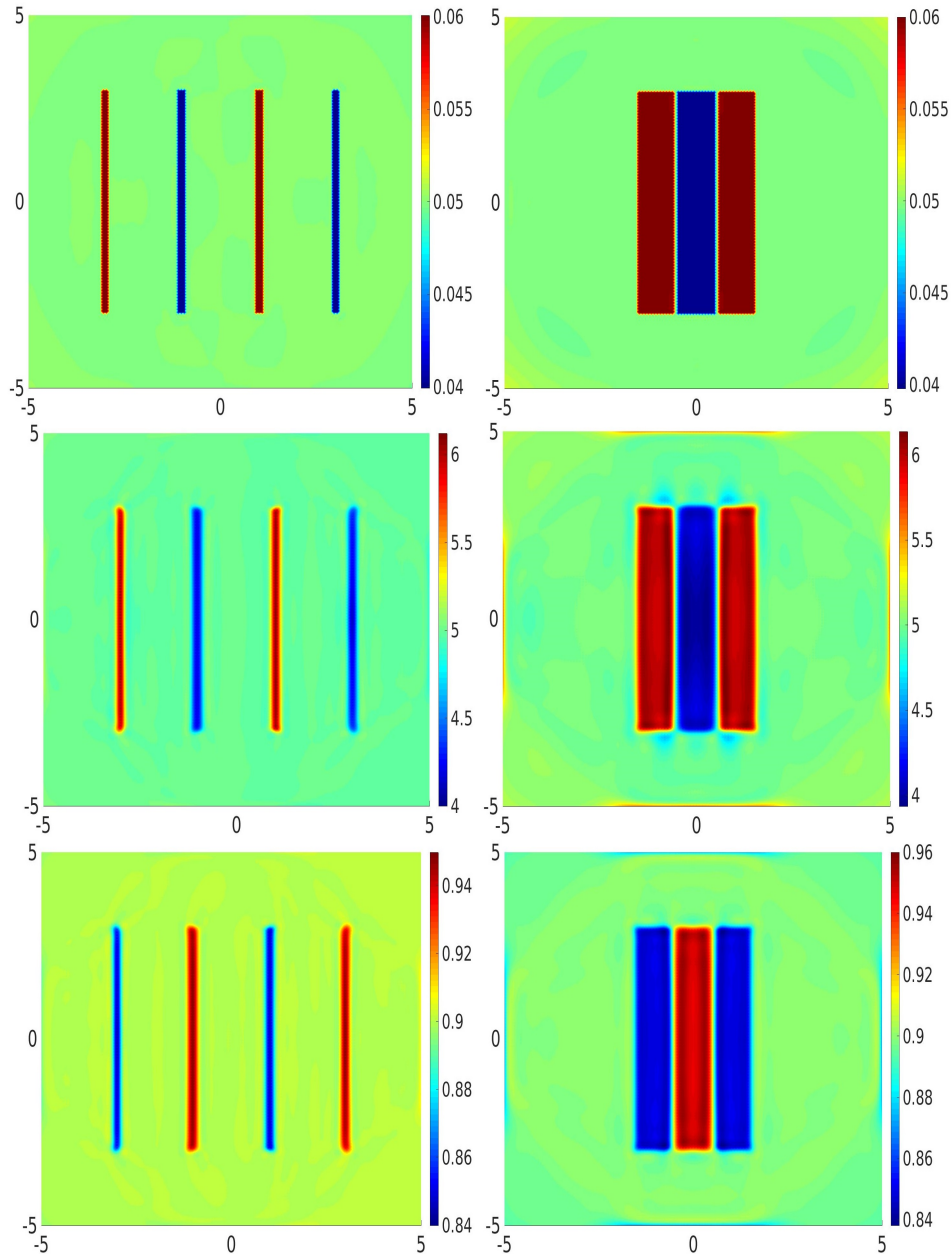


Figure 8: The reconstructed images of: (left column) the first example and (right column) the second example, (top row) the absorption coefficient  $\mu_a$ , (middle row) the scattering coefficient  $\mu_s$  and (bottom row) the anisotropy factor  $g$ .

## 373 5 Conclusion

374 The optical inverse problem of the QPAT using the RTE as light transport model was presented. The adjoint  
 375 method was applied to efficiently compute the gradient of the objective function where its expressions for  $\mu_a$ ,  $\mu_s$ ,  
 376 and  $g$  coefficients were explicitly obtained. For the first time, the simultaneous reconstruction of  $\mu_a$ ,  $\mu_s$ , and  $g$   
 377 was possible thanks to our QPAT algorithm that uses spatially absorbed energy density data. The results showed  
 378 that treating the anisotropy parameter as a fixed constant leads to low errors in the reconstructed images of the  
 379 absorbing coefficient and significant errors in the reconstructed images of the scattering coefficient. Also, they  
 380 showed that the  $\mu_a$  images are reconstructed with a better estimation quality than  $\mu_s$  and  $g$  images even with noisy  
 381 data or when only one Laser source was used. Furthermore, the  $\mu_a$  images are insensitive to the crosstalk issue  
 382 contrary to those of  $\mu_s$  and  $g$  parameters. The obtained results highlight the interest of the QPAT algorithm to  
 383 advantageously complete the conventional imaging modalities for cancer diagnosis. This work was a necessary  
 384 preliminary study to show that a complete optical imaging of tissue is possible through the QPAT modality. The  
 385 extension of our method to 3D geometries for real applications is a significant numerical challenge which is not  
 386 straightforward. We plan to investigate this problem.

387

## 388 Appendix A. Calculations of adjoint operators

It should be noted that in the calculations given below, the quantities are not divided by  $M^2$  as in (22) for the sake of simplicity. This does not change the result. From (12), we have:

$$\begin{aligned}
 \left\langle A - M \left| (\tilde{H} \delta\psi_s) \right\rangle_{\mathcal{D}} &= \int_{\mathcal{D}} (A - M)(\mathbf{r}) \mu_a(\mathbf{r}) \int_{\Omega=2\pi} \delta\psi_s(\mathbf{r}, \boldsymbol{\Omega}) d\Omega dr \\
 &= \int_{\mathcal{D}} \int_{\Omega=2\pi} (A - M)(\mathbf{r}) \mu_a(\mathbf{r}) \delta\psi_s(\mathbf{r}, \boldsymbol{\Omega}) d\Omega dr = \left\langle A - M \left| (H \delta\psi_s) \right\rangle_{\mathcal{D}\Omega} \\
 &= \int_{\mathcal{D}} \int_{\Omega=2\pi} \mu_a(\mathbf{r}) (A - M)(\mathbf{r}) \delta\psi_s(\mathbf{r}, \boldsymbol{\Omega}) d\Omega dr = \left\langle H^*(A - M) \left| \delta\psi_s \right\rangle_{\mathcal{D}\Omega}. \tag{38}
 \end{aligned}$$

Also,

$$\begin{aligned} \langle A - M | (H \delta\psi_c) \rangle_{\mathcal{D}} &= \int_{\mathcal{D}} (A - M)(\mathbf{r}) \mu_a(\mathbf{r}) \delta\psi_c(\mathbf{r}, \mathbf{\Omega}) dr \\ \int_{\mathcal{D}} \mu_a(\mathbf{r}) (A - M)(\mathbf{r}) \delta\psi_c(\mathbf{r}, \mathbf{\Omega}) dr &= \langle H^*(A - M) | \delta\psi_c \rangle_{\mathcal{D}}. \end{aligned} \quad (39)$$

389 Thus,  $H^* = H$ .

## 390 Bibliography

- 391 [1] Pinkert M A, Salkowski L R, Keely P J, Hall T J, Block W F and Eliceiri K W 2018 Review of quantitative  
392 multiscale imaging of breast cancer *J. Med. Imaging* **5**(1) 010901
- 393 [2] Anastasio M A, Beard P C and Zhu Q 2017 Photoacoustic imaging and sensing *J. Biomed. Opt.* **22**(4) 041001
- 394 [3] Wang L V and Yao J 2016 A practical guide to photoacoustic tomography in the life sciences *Nat. Meth.* **13**  
395 627-638
- 396 [4] Xia J and Wang L V 2014 Small-animal whole-body photoacoustic tomography: a review *Phys. Med. Biol.*  
397 **61**(5) 1380-1389
- 398 [5] Anastasio M A and Beard P C 2012 Photoacoustic imaging and sensing *J. Biomed. Opt.* **17**(6) 061201
- 399 [6] Wang L V and Hu S 2012 Photoacoustic tomography: in vivo imaging from organelles to organs *Science*  
400 **335**(6075) 1458-1462
- 401 [7] Cox B, Laufer J G, Arridge S R and Beard P C 2012 Quantitative spectroscopic photoacoustic imaging: a  
402 review *J. Biomed. Opt.* **17**(6) 061202
- 403 [8] Beard P 2011 Biomedical photoacoustic imaging *Interface Focus* **1**(4) 602-631
- 404 [9] Ntziachristos V 2010 Going deeper than microscopy: the optical imaging frontier in biology *Nat. Meth.* **7**(8)  
405 603
- 406 [10] Li C and Wang L V 2009 Photoacoustic tomography and sensing in biomedicine *Phys. Med. Biol.* **54**(19) R59

- 407 [11] Wang L V 2009 Photoacoustic imaging and spectroscopy, CRC Press, Florida
- 408 [12] Xu M and Wang L V 2006 Photoacoustic imaging in biomedicine *Rev. Scient. Instrum.* **77**(4) 041101
- 409 [13] Ntziachristos V, Ripoll J, Wang L V and Weissleder R 2005 Looking and listening to light: the evolution of  
410 whole-body photonic imaging *Nat. Biotechnol.* **23**(3) 313
- 411 [14] Ripoll J 2012 Principles of diffuse light propagation. Light propagation in tissues with applications in biology  
412 and medicine (Singapore: World Scientific)
- 413 [15] Yao L, Sun Y and Jiang H 2010 Transport-based quantitative photoacoustic tomography: Simulations and  
414 experiments *Phys. Med. Biol.* **55**(7) 1917-1934
- 415 [16] Tarvainen T, Cox B T, Kaipio J P and Arridge S R 2012 Reconstructing absorption and scattering distributions  
416 in quantitative photoacoustic tomography *Inverse Probl.* **28**(8) 084009
- 417 [17] Saratoon T, Tarvainen T, Cox B T and Arridge S R 2013 A gradient-based method for quantitative photoa-  
418 coustic tomography using the radiative transfer equation *Inverse Probl.* **29**(7) 075006
- 419 [18] Jacques S L 2013 Optical properties of biological tissues: a review *Phys. Med. Biol.* **58**(11) R37
- 420 [19] Wang Z, Tangella K, Balla A, Popescu G 2011 Tissue refractive index as marker of disease, *J Biomed. Opt.*  
421 **16**(11) 116017
- 422 [20] Hillegersberg R V, Pickering J W, Maurice A, and Beek J F 1993 Optical properties of rat liver and tumor at  
423 633 nm and 1064 nm: Photofrin enhances scattering *Lasers Surg. Med.* **13**(1) 31-39
- 424 [21] Germer G T, Andre R, Ritz J P, Christoph I, Dirk A, Gerhard M and Buhr H J 1998 Optical properties of  
425 native and coagulated human liver tissue and liver metastases in the near infrared range *Lasers Surg. Med.*  
426 **23**(4) 194-203
- 427 [22] Yao L, Sun Y and Jiang H 2009 Quantitative photoacoustic tomography based on the radiative transfer equa-  
428 tion *Opt. Lett.* **34**(12) 1765-1767

- 429 [23] Bal G, Jollivet A and Jugnon V 2010 Inverse transport theory of photoacoustics *Inverse Probl.* **26** 025011
- 430 [24] Xi L, Li X, Yao L, Grobmyer S and Jiang H 2012 Design and evaluation of a hybrid photoacoustic tomography  
431 and diffuse optical tomography system for breast cancer detection *Med. Phys.* **39**(5) 2584-2594
- 432 [25] Gao H, Osher S and Zhao H 2012 Quantitative photoacoustic Tomography *Lecture Notes Math.* **2035** 131-158
- 433 [26] Mamonov A V and Ren K 2013 Quantitative photoacoustic imaging in the radiative transport regime *Commun.*  
434 *Math. Sci.* **12**(2) 201-234
- 435 [27] Haltmeier M, Neumann L and Rabanser S 2015 Single-stage reconstruction algorithm for quantitative pho-  
436 toacoustic tomography *Inverse Probl.* **31**(6) 065005
- 437 [28] De Cezaro A, Travessini De Cezaro F and Seije Suarez J 2015 Regularization approaches for quantitative  
438 Photoacoustic tomography using the radiative transfer equation *J. Math. Anal. Appl.* **429**(1) 415-438
- 439 [29] Pulkkinen A, Cox B T, Arridge S R, Kaipio J P and Tarvainen T 2015 Quantitative photoacoustic tomography  
440 using illuminations from a single direction *J. Biomed. Opt.* **20**(3) 036015
- 441 [30] Li X, Heldermon C D, Yao L, Xi L and Jiang H 2015 High resolution functional photoacoustic tomography  
442 of breast cancer *Med. Phys.* **42**(9) 5321-5328
- 443 [31] Hochuli R, Powell S, Arridge S R and Cox B 2016 Quantitative photoacoustic tomography using forward and  
444 adjoint Monte Carlo models of radiance *J. Biomed. Opt.* **21**(12) 126004
- 445 [32] Tarvainen T, Pulkkinen A, Cox B T and Arridge S R 2017 Utilizing the radiative transfer equation in quan-  
446 titative photoacoustic tomography Proc. of SPIE Vol. 10064, Photons Plus Ultrasound: Imaging and Sensing,  
447 100643E-1
- 448 [33] Wang C and Zhou T 2017 On iterative algorithms for quantitative photoacoustic tomography in the radiative  
449 transport regime *Inverse Probl.* **33**(11) 115006



- 450 [34] Okawa S, Hirasawa T, Kushibiki T and Ishihara M 2017 Effects of the approximations of light propagation  
451 on quantitative photoacoustic tomography using two-dimensional photon diffusion equation and linearization  
452 *Opt. Rev.* **24**(6) 705-726
- 453 [35] Haltmeier M, Neumann L, Nguyen L and Rabanser S 2018 Analysis of the linearized problem of quantitative  
454 photoacoustic tomography *SIAM J. Appl. Math.* **78**(1) 457-478
- 455 [36] Bal G and Ren K 2011 Multi-source quantitative photoacoustic tomography in a diffusive regime *Inverse*  
456 *Probl.* **27** 075003
- 457 [37] Shao P, Cox B, and Zemp R J 2011 Estimating optical absorption, scattering, and Grueneisen distributions  
458 with multiple-illumination photoacoustic tomography *Appl. Opt.* **50**(19) 3145-3154
- 459 [38] Addoum A, Contassot-Vivier S and Asllanaj F 2019 Three-dimensional frequency-domain optical anisotropy  
460 imaging of biological tissues with near-infrared light *Med. Phys.* **46**(9) 4057-4069
- 461 [39] Asllanaj F, Addoum A and Roche J R 2018 Fluorescence molecular imaging based on the adjoint radiative  
462 transport equation *Inverse Probl.* **34** 075009
- 463 [40] Addoum A, Farges O and Asllanaj F 2018 Optical properties reconstruction using the adjoint method based  
464 on the radiative transfer equation *J. Quant. Spectrosc. Radiat. Transfer* **204** 179-189
- 465 [41] Saratoon T, Tarvainen T, Arridge S R and Cox B T 2013 3D quantitative photoacoustic tomography using  
466 the delta-Eddington approximation Proc. of SPIE Vol. 8581, Photons Plus Ultrasound: Imaging and Sensing,  
467 85810V
- 468 [42] Asllanaj F, Contassot-Vivier S, Liemert A and Kienle A 2014 Radiative transfer equation for predicting light  
469 propagation in biological media: comparison of a modified finite volume method, the Monte Carlo technique  
470 and an exact analytical solution *J. Biomed. Opt.* **19** 015002
- 471 [43] Klose A D 2009 Light Scattering. Reviews 4, Book Chapter: Radiative transfer of luminescence light in  
472 biological tissue (Berlin Heidelberg: Springer:293-345)

- 473 [44] Fiacco A V and McCormick G P 1968 Nonlinear Programming: Sequential Unconstrained Minimization  
474 Techniques (John Wiley and Sons)
- 475 [45] Bonnans J F, Gilbert J C, Lemarechal C and Sagastizabal C A 2016 Numerical Optimization Theoretical and  
476 Practical Aspects (Springer Sciences and Business Media)
- 477 [46] Klose A 2001 Optical tomography based on the radiative transfer equation. PhD thesis, Department of Physics  
478 Freie Universitat, Berlin Germany
- 479 [47] Klose A D, Ntziachristos V and Hielscher A H 2005 The inverse source problem based on the equation of  
480 radiative transfer in optical molecular imaging *J. Comp. Phys.* **202** 323-345