One-step fluorescence photoacoustic tomography with the optical radiative transfer model

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Abstract: We present adjoint-based Jacobian as well as gradient evaluations, and corresponding reconstruction schemes to solve the fully nonlinear, optical radiative transfer modeled one-step fluorescence photoacoustic tomographic (FPAT) problem which aims to reconstruct the map of absorption coefficient of the exogenous fluorophore from boundary photoacoustic data. Radiative transport equation (RTE) and frequency-domain photoacoustic equation (PAE) have been employed to model light and photoacoustic wave propagation respectively. Levenberg-Marquardt and BFGS reconstruction schemes have been used corresponding to the evaluated Jacobians and gradients respectively. Numerical reconstructions obtained from the two schemes have been validated for scattering-dominant as well as non-scattering-dominant media in two-dimensions. To the best of our knowledge, these are the first one-step FPAT reconstruction results in literature based upon the optical RTE model.

1. Introduction

A quantitative photoacoustic tomography (QPAT) [1–11] problem aims to reconstruct the map of optical parameters such as absorption and scattering coefficients, scattering anisotropy, exogenous marker concentration and quantum yield in the domain of interest, from boundary photoacoustic (PA) pressure measurements. Optical tomographic techniques such as diffuse and fluorescence optical tomography (DOT/FOT) yield poor resolution and penetration depth due to high scattering based attenuation of optical signals. Scattering of ultrasound is known to be 2-3 orders of magnitudes lesser as compared to light and hence QPAT which is based on acoustic detection provides better resolution and deeper penetration depths. A QPAT reconstruction problem is generically solved in two-steps: (1) reconstruction of the absorbed optical energy density (AOED, i.e. the PA-source) from boundary PA data, and (2) execution of an inversion algorithm based on light transport models to reconstruct the maps of desired optical parameters, considering the reconstructed AOED map as internal data. Two-step QPAT problems have been solved in [1–6, 8–10, 12, 13]. In such reconstruction schemes, the accuracy of the final reconstruction is highly dependent on the
first step PA reconstruction. Under limited data settings as well for noisy PA measurements, the PA reconstruction carries erroneous artifacts that cascade into the final optical parameter reconstructions. Therefore one-step QPAT algorithms have been developed [7, 11, 14–17], and have been reported to perform better as compared to the two-step schemes.

In the presence of fluorophores, fluorescent light also contributes to the PA signal, and if the fluorophores have high quantum efficiency, one needs to consider the contribution of the fluorescence light to the PA signal as well, in order to obtain quantitatively accurate reconstructions [18]; such a technique is known as fluorescence photoacoustic tomography (FPAT) [18–20]. Recently developed fluorophores [21, 22] with high quantum efficiency and low toxicity are requiring the use of FPAT reconstructions. The first reconstruction study of FPAT was carried out in [19] using the diffusion equation as the photon transport model. There, the full Newton’s method was used to reconstruct the optical parameters in the domain of interest from true internal AOED data. Similar Newton-based algorithms have also been developed in [20, 23] using radiative transfer.

The approaches in [19, 20, 23] deal only with the second step of the FPAT problem. However, reconstruction errors from the first step (the PA step) cannot simply be modeled as random noise, and a more practical reconstruction would be obtained, only after the complete two-step problem is solved. The first reconstruction results for the nonlinear full-FPAT problem in two-step [18] and one-step [18, 24] in Jacobian based frameworks were demonstrated by us using the diffusion equation as the photon transport model. The one-step algorithm was observed to produce superior reconstruction results as compared to the two-step algorithm in noisy and limited-data settings. Recently, we have also demonstrated one-step gradient based FPAT reconstruction algorithms with the diffusion photon transport model [25].

In our present work, we demonstrate Jacobian and gradient-based reconstruction schemes for the fully-nonlinear one-step FPAT problem using the full radiative transport equation (RTE) as the model for light transport, which to the best of our knowledge is the first such study.

Fully-nonlinear reconstruction problems can be solved using Jacobian-based (Gauss-Newton (GN) or Levenburg-Marquardt (LM) schemes [26]) as well as gradient-based techniques (such as the Broyden-Fletcher-Goldfarb-Shanno (BFGS) method). For QPAT, Jacobian-based reconstruction studies have been carried out in two-step [8–10] and one-step [11, 14] frameworks. The first complete FPAT Jacobian-based reconstructions from synthetic boundary PA measurements for the two-step and one-step schemes were reported in [18, 24]. Jacobian computation requires solving the corresponding adjoint problem $O(N)$ ($N$: number of nodes in the domain) times whereas computation of gradient needs to solve the corresponding adjoint problem $O(1)$ times. Therefore, although a gradient-based scheme generally can take a large number of iterations to converge (and in this work, is executed at a relatively higher mesh resolution), it is found to
be significantly faster as compared to the Jacobian-based scheme. Gradient-based reconstructions corresponding to the second-step of QPAT have been reported in [1–4, 6, 12, 13], while the complete two-step QPAT reconstruction results (from boundary PA data) were demonstrated in [5]. Single-step, gradient based schemes for QPAT have been reported in [7, 15–17] and [27] using the time-domain and frequency-domain PAE respectively. The reduced computational complexity with the gradient-based schemes better enables their potential scaling-up to three-dimensional as well as dynamic settings.

A majority of quantitative studies in photoacoustic tomography (PAT) employ the diffusion equation (DE) for modeling the light transport in tissue-like media. However, as is well known, the DE-model has drawbacks such as: 1. diffusion equation is an approximation to RTE for media with high optical scattering and low absorption properties; for tissues with comparable absorption and reduced scattering coefficients (such as hematoma and liver tissue), diffusion approximation does not hold; 2 diffusion approximation does not hold close to the excitation source, while a major contribution to the PA signal comes from its vicinity. Therefore, it necessary to develop such algorithms for quantitative PA reconstruction studies which employ the full RTE as the photon transport model [5]. The second step of RTE-based QPAT problems has been solved using Jacobian [10, 12] and gradient-based [6, 12, 13] schemes. In full-QPAT setting, gradient-based reconstructions using RTE as photon transport model have been demonstrated in [5, 13]. Corresponding one-step reconstructions using time-domain PAE have been demonstrated in [7, 17] respectively. To the best of our knowledge, the present work is the first study of Jacobian and gradient-based schemes for the complete FPAT problem in a one-step framework.

The rest of this manuscript is structured as follows. Section 2 gives the brief formulation of the FPAT forward and inverse problems. In section 3, we present the adjoint-based Jacobian and gradient evaluations, and the corresponding Levenberg-Marquardt (LM) and BFGS schemes to solve the one-step FPAT problem. Test cases considered in this study, along with corresponding reconstruction results and discussions have been provided in section 4. Section 5 contains the summary and conclusions of the present work. Appendix A contains FEM based computational model for the FPAT forward problem, and appendix B contains the 2D barycentric angular basis elements used in the RTE computations. Appendix C evaluates the adjoint based sensitivities for the composite frequency-domain PAE and coupled-RTE system, and appendix D gives their finite element evaluations.

2. Problem definition

A fluorescent photoacoustic tomography (FPAT) problem aims to recover the map of optical parameters such as absorption and scattering coefficients of chromophores and fluorophores, anisotropy factor etc.) in the region of interest from the measured PA pressure data. In this section, we briefly introduce the
forward and inverse problems of FPAT.

When biological markers are injected in the tissue-like medium, they get tagged with the cancerous tissues and fluoresce on excitation. Recovery of the sources of fluorescent emissions i.e. the spatial concentration map or the absorption coefficient map $\mu_{axf}(\vec{r})$ of the fluorescent markers reveal the size and location of tumors inside the tissue; this is the focus in the current work and is illustrated in the sequel.

2.1. Forward Model
2.1.1. Fluorescent light propagation

The RTE is accepted as the model for light transport in turbid media. In a turbid media consisting of chromophores as well as fluorophores, the excitation and fluorescence radiation transport \cite{28} in the domain $\Omega$ is given by,

$$\left(\hat{s} \cdot \nabla + \mu_{aq}(\vec{r}) + \mu_{sq}(\vec{r})\right) I_q(\vec{r}, \hat{s}) - \mu_{sq}(\vec{r}) \int_S I_q(\vec{r}, \hat{s}') P(\hat{s} \cdot \hat{s}') d\omega' = s_q(\vec{r}, \hat{s})$$

(1)

where subscript $q = x$ or $m$ corresponding to excitation and emission light respectively, and the internal source is,

$$s_q = \begin{cases} 0, & \text{for } q = x \\ \frac{1}{2n-1\pi} \eta(\vec{r}) \int_S I_x(\vec{r}, \hat{s}') d\omega', & \text{for } q = m \end{cases}$$

with $I_x$ (respectively $I_m$) being the excitation (respectively emission) radiance at position $\vec{r}$ in $\hat{s}$ direction, and $\mu_{a(x/m)} = \mu_{a(x/m)i} + \mu_{a(x/m)f}$, where $\mu_{axi}$ (respectively $\mu_{ami}$) is the absorption coefficient of the intrinsic chromophore at excitation (respectively emission) wavelength; and correspondingly $\mu_{a(x/m)f}$ being the excitation / emission absorption coefficients of the fluorophores (with their ratio $\gamma = \mu_{amf}/\mu_{axf}$). $\mu_{sx/m}$ denote the scattering coefficient at excitation / emission wavelengths, $\nabla$ is the gradient operator, $\eta (= \phi \mu_{axf})$ is the quantum yield, $\phi$ is fluorescence quantum efficiency. Phase function $P(\cos \theta)$ is probability density function of the as the angular distribution of scattered light intensity at a given wavelength. It is a function of the angle $\theta$ relative to the incident beam. A commonly used phase function is the "Henyey- Greenstein phase function", given as:

$$P(\cos \theta) = \frac{1}{2n-1\pi} \frac{1-g^2}{(1+g^2-2g \cos \theta)^{n/2}}$$

(2)

where $g \equiv < \cos \theta >$ is known as the anisotropy factor and $n$ takes the values 2 and 3 for 2D and 3D modeling respectively. The boundary condition with a boundary source $I_0(\vec{r}, \hat{s})$ at source position $\vec{r}_0$ is given as \cite{28},

$$I_x(\vec{r}, \hat{s}) = f(\vec{r}, \hat{s}) = \begin{cases} I_0(\vec{r}_0, \hat{s}) & \vec{r}_0 \in \partial \Omega, \hat{n} \cdot \hat{s} < 0 \\ 0 & \vec{r} \in \partial \Omega \setminus \vec{r}_0, \hat{n} \cdot \hat{s} < 0 \end{cases}$$

(3)
and

\[ I_m(\vec{r}, \hat{s}) = 0; \quad \vec{r} \in \partial \Omega, \quad \hat{n} \cdot \hat{s} < 0 \quad (4) \]

enforced of the domain boundary \( \partial \Omega \), where \( \hat{n} \) denotes the outward normal from the boundary. The excitation/emission fluences \( \Phi_{x/m} \) are related to the corresponding radiances by:

\[ \Phi_{x/m}(\vec{r}) = \int_S I_{x/m}(\vec{r}, \hat{s}) d\omega \quad (5) \]

The PA heat source (the total AOED) \( h(\vec{r}) \) at a location \( \vec{r} \) is given by,

\[ h(\vec{r}) = \mu_{ax}(\vec{r}) \Phi_x(\vec{r}) + \mu_{am}(\vec{r}) \Phi_m(\vec{r}) \quad (6) \]

Thus the PA equation in the frequency-domain can be written as [29]

\[ (\nabla^2 + k^2) p(\vec{r}, k) = ik \frac{\tilde{\beta}}{C_p} h(\vec{r}) \quad \text{in} \quad \Omega_p \quad (7) \]

with absorbing boundary condition

\[ \hat{n} \cdot \nabla p(\vec{r}) + i k p(\vec{r}) = 0 \quad \text{on} \quad \partial \Omega_p \quad (8) \]

where \( k \) is the acoustical wavenumber, \( v \) is the speed of sound, \( \tilde{\beta} \) is volumetric expansion coefficient, \( C_p \) is the specific heat at constant pressure. In the present work, the acoustic propagation domain \( \Omega_p \) is chosen to be larger than the optical transport domain \( \Omega \).

2.2. The measurement equation

In our work, we focus on the reconstruction of \( \mu_{ax f} \), the fluorophore absorption coefficient at excitation wavelength. The discretized heat source \( h \) for a nominal discretized distribution of fluorophore absorption coefficient \( \mu_{ax f} \) is given by:

\[ h \equiv \mathcal{H}(\mu_{ax f}) = \sum_{q=x,m} (\mu_{aq i} + \mu_{aq f}) \odot \Phi_q \quad (9) \]

where \( \mathcal{H} \) denotes the heat source operator, \( \odot \) represents the pointwise multiplication and \( \Phi_{q=x,m} \) are obtained by solving (51)(in Appendix C). The forward problem of FPAT, defined in the above subsection is discretized in our work in a finite element method (FEM) framework to yield a nonlinear relation between the PA pressure data vector \( p_{meas} \) measured at detector positions \( \vec{r}_d(i = 1, ..., M) \) at frequencies \( \omega_j(j = 1, ..., L) \), and the unknown fluorophore absorption coefficient vector \( \mu_{ax f} \) in the domain, and can be written as:

\[ p_{meas} = J_h \mathcal{H}(\mu_{ax f}) \equiv \mathcal{G}(\mu_{ax f}) \quad (10) \]
where the PA measurement operator $J_h$ which relates the PA measurements with the heat source $h$, and discrete-domain FPAT measurement operator $G = J_h H$ which relates the PA measurements with the fluorophore absorption coefficient $\mu_{axf}$, are explicitly given in [18], and mentioned in Appendix A (eq. (61)) for completeness.

2.3. Inverse problem

The FPAT inverse problem can be written as:

$$\hat{\mu}_{axf} = \arg \min_{\mu_{axf}} \varepsilon(\mu_{axf}) = \frac{1}{2} \| \tilde{p}_{\text{meas}} - G(\mu_{axf}) \|^2$$

(11)

where $\tilde{p}_{\text{meas}}$ denotes the PA measurement vector obtained from an unknown sample. We assume prior knowledge of $\mu_a(x/m)$ and $\mu'_s(x/m)$ which can be obtained in principle via QPAT at excitation and emission wavelengths [11, 30] before fluorophore injection.

3. Reconstruction algorithms

In this section, we discuss Jacobian and adjoint based reconstruction algorithms as well as detailed evaluations of corresponding Jacobian and gradient of the error functional $\varepsilon(\mu_{axf})$ defined in Eq. (11) to solve the full-FPAT problem.

3.1. Inversion schemes

3.1.1. Jacobian-based inversion scheme

We use the Levenberg-Marquardt (LM) scheme to solve the fully nonlinear one-step FPAT problem, with the update $\Delta \mu_{axf}$ being given as:

$$\Delta \mu_{axf, jac}^{(j)} = (J^T J + \kappa^2 I)^{-1} J^T (\tilde{p}_{\text{meas}} - G(\mu_{axf}))$$

(12)

where $J$ is the Jacobian for the one-step algorithm and is defined in Eq. (20). The damping parameter $\kappa$ is computed from the L-curve method [31]. The algorithm of Jacobian based one-step reconstruction scheme is provided in Algorithm 1, and the evaluation of Jacobian is provided in section 3.2.

3.1.2. Gradient-based inversion scheme

The gradient-based reconstructions were carried out using the BFGS algorithm [32], a quasi-Newton approach. The update direction $\Delta \mu_{axf}^j$ at iterate $j$ is computed by solving,

$$B^{(j)} \mu_{axf, grad}^{(j)} = g^{(j)}$$

(13)
where \( g^{(j)} \) is the gradient vector at present iterate, and \( B^{(j)} \) is an approximation to the Hessian matrix, which is initialized as identity matrix (of size \( N \times N \)) and updated at each iterate using

\[
B^{(j+1)} = B^{(j)} + \frac{y^{(j)}y^{(j)T}}{y^{(j)T}g^{(j)}} - \frac{B^{(j)}g^{(j)T}g^{(j)}B^{(j)T}}{2y^{(j)T}g^{(j)}}
\]

(14)

Here \( y^{(j)} = g^{(j+1)} - g^{(j)} \), and \( s^{(j)} = \alpha \Delta \mu^{(j)_{grad}} \) is the total update, where the steplength \( \alpha \) is computed using a line search algorithm [33]. To ensure no negative reconstructions, at each iteration of our iterative scheme, as is standard practice, we apply the lower (zero) bound constraint by setting to zero the negative values of the nominal absorption coefficient. The algorithm of BFGS reconstruction scheme is provided in Algorithm 2, and the evaluation of gradient is provided in section 3.3.

3.2. Evaluation of Jacobian

Using eq. (60) (of Appendix A), the first variation in the PA measurements \( \delta p_{\text{meas}} \) can be expressed as

\[
\delta p_{\text{meas}} = J_h \delta h
\]

(15)

Using Eq. (9), we can write

\[
\delta h = \sum_{q=x/m} \Phi_q \otimes \delta(\mu_{aq} + \mu_{a(f)}) + (\mu_{aq} + \mu_{a(f)}) \otimes \delta \Phi_q = \sum_{q=x/m} \text{diag}(\Phi_q) \delta \mu_{a(f)} + \text{diag}(\mu_{aq}) \delta \Phi_q
\]

(16)

The first variations \( \delta \Phi_{x/m} \) are found to be (Eq. (86), (87) of Appendix C)

\[
\delta \Phi_x = J_x \delta \mu_{axf}; \quad \delta \Phi_m = J_m \delta \mu_{amf}
\]

(17)

where,

\[
J_x = \left[ L_{xx}(\psi_{xx}^{(1)})^T, \ldots, L_{xx}(\psi_{xx}^{(N)})^T \right]^T
\]

\[
J_m = \left[ L_{xm}(\psi_{xm}^{(1)}) + L_{mm}(\psi_{mm}^{(1)})^T, \ldots, L_{xm}(\psi_{xm}^{(N)}) + L_{mm}(\psi_{mm}^{(N)})^T \right]^T
\]

(18)

with \( \psi_{xx}, \psi_{xm}, \psi_{mm} \) being the adjoints that solve Eq. (84) (from Appendix D) and \( L_{xx}, L_{mm}, L_{xm} \) are the operators defined in Eqs. (86), (87). Since \( \mu_{amf} = \gamma \mu_{axf} \), and using Eq. (17), Eq. (16) can be written as

\[
\delta h = J_\mu \delta \mu_{axf}; \quad J_\mu = [\text{diag}(\Phi_x) + \gamma \text{diag}(\Phi_m) + \text{diag}(\mu_{ax}) J_x + \text{diag}(\mu_{am}) J_m]
\]

(19)

And Eq. (10) is expressed as

\[
\delta p_{\text{meas}} = J \delta \mu_{axf}; \quad J = J_h J_\mu
\]

(20)
3.3. Evaluation of gradient

The first variation of the error functional \( \varepsilon(\mu_{axf}) \) can be written (using Eq. (9),(10)) as:

\[
\delta \varepsilon(\mu_{axf}) = -(p_{meas} - G(\mu_{axf}))^T \delta(G(\mu_{axf}))
\]

\[
= -(p_{meas} - G(\mu_{axf}))^T J_h \delta H(\mu_{axf})
\]

\[
\equiv -v^T \delta H(\mu_{axf}) = -(\delta H(\mu_{axf}))^T v
\]

\[
= -(\mu_{ax} \odot \delta \Phi_x + \Phi_x \odot \delta \mu_{ax} + \mu_{am} \odot \delta \Phi_m + \Phi_m \odot \delta \mu_{am})^T v
\]

\[
\equiv \delta \varepsilon_1 + \delta \varepsilon_2 + \delta \varepsilon_3 + \delta \varepsilon_4 \quad (21)
\]

where \( v := J_h^T(p_{meas} - G(\mu_{axf})) \). Also since \( \mu_{ax} = \mu_{ax i} + \mu_{ax f} \implies \delta \mu_{ax} = \delta \mu_{ax f} \) and \( \mu_{am} = \mu_{ami} + \gamma \mu_{ax f} \implies \delta \mu_{am} = \gamma \delta \mu_{ax f} \), we obtain,

\[
\delta \varepsilon = -(\mu_{ax} \odot \delta \Phi_x + \Phi_x \odot \delta \mu_{ax} + \mu_{am} \odot \delta \Phi_m + \Phi_m \odot \delta \mu_{am})^T \nu
\]

\[
\equiv \delta \varepsilon_1 + \delta \varepsilon_2 + \delta \varepsilon_3 + \delta \varepsilon_4 \quad (22)
\]

The second and fourth terms (\( \delta \varepsilon_2 \) and \( \delta \varepsilon_4 \) respectively of Eq. (22) can be written as:

\[
\delta \varepsilon_2 = -(\Phi_x \odot \delta \mu_{ax f})^T \nu = (\delta \mu_{ax f})^T (\nu \odot \Phi_x) \quad (23)
\]

and

\[
\delta \varepsilon_4 = (\Phi_m \odot \delta \mu_{ax f})^T (-\gamma \nu) = (\delta \mu_{ax f})^T (-\gamma \nu \odot \Phi_m) \quad (24)
\]

The first term of Eq. (22) is written as:

\[
\delta \varepsilon_1 = -\nu^T (\mu_{ax} \odot \delta \Phi_x) = - \sum_{w=1}^N v_w \mu_{axw} \delta \Phi_{x}^{(w)}
\]

(25)

where \( w \) denotes the nodes in the domain. The relation between \( \delta \Phi_x \) and adjoint \( \psi_{xx} \) is linear (Eq. (86) in Appendix C), and can be written in the form,

\[
\delta \Phi_{x}^{(w)} = L_{xx}(\psi_{xx}^{(w)}) \delta \mu_{ax f}
\]

(26)

where \( \psi_{xx}^{(w)} \) is the solution to the adjoint problem with Dirac source at the \( w \)th node (\( \Delta_{w}^{(w)} \)): \( \tilde{A}_{w} \psi_{xx}^{(w)} = \Delta_{w}^{(w)} \), and \( L_{xx} \) is defined in Eq. (86) (in Appendix C). Therefore,

\[
\delta \varepsilon_1 = - \sum_{w=1}^N v_w \mu_{axw} L_{xx}(\psi_{xx}^{(w)}) \delta \mu_{ax f} = - L_{xx}(\sum_{w=1}^N v_w \mu_{axw} \psi_{xx}^{(w)}) \delta \mu_{ax f}
\]

\[
= - L_{xx}(\tilde{A}_{x}^{-1} \sum_{w=1}^N v_w \mu_{axw} \Delta_{w}) \delta \mu_{ax f} \equiv L_{xx}(\Psi_{xx}) \delta \mu_{ax f} = (\delta \mu_{ax f})^T g
\]

(27)
with \( g_x \equiv [\mathcal{L}_{xx}(\Psi_{xx})]^T \), and adjoint \( \Psi_{xx} \) is solution to:

\[
\tilde{A}_x \Psi_{xx} = S_x
\]

(28)

where \( S_x = -\sum_{w=1}^{N} v_w \mu_{axw} \Delta^{(w)} \). Similarly, using Eqs. (84) and (87) of Appendix D, the third term of Eq. (22) can be written as:

\[
\delta \varepsilon_3 = -\sum_{w=1}^{N} v_w \mu_{amw} \left[ \mathcal{L}_{mm}(\psi_{mm}^{(w)}) + \mathcal{L}_{xm}(\psi_{xm}^{(w)}) \right] \delta \mu_{axf}
\]

\[
= -\mathcal{L}_{mm} \left( \sum_{w=1}^{N} v_w \mu_{amw} \Delta^{(w)} \right) - \mathcal{L}_{xm} \left( \sum_{w=1}^{N} v_w \mu_{amw} \psi_{xm}^{(w)} \right) \delta \mu_{axf}
\]

\[
= -\mathcal{L}_{mm} \left( \tilde{A}_m^{-1} \sum_{w=1}^{N} v_w \mu_{amw} \Delta^{(w)} \right) - \mathcal{L}_{xm} \left( \tilde{A}_x^{-1} V \tilde{A}_m^{-1} \sum_{w=1}^{N} v_w \mu_{amw} \Delta^{(w)} \right) \delta \mu_{axf}
\]

\[
\equiv \mathcal{L}_{mm}(\Psi_{mm}) + \mathcal{L}_{xm}(\Psi_{xm}) \delta \mu_{axf} = (\delta \mu_{axf})^T g_x \]

(29)

with \( g_m \equiv [\mathcal{L}_{mm}(\Psi_{mm}) + \mathcal{L}_{xm}(\Psi_{xm})]^T \), and adjoints \( \Psi_{mm} \), \( \Psi_{xm} \) are solutions of,

\[
\tilde{A}_m \Psi_{mm} = S_m, \quad \tilde{A}_x \Psi_{xm} = V \Psi_{mm}
\]

(30)

with \( S_m = -\sum_{w=1}^{N} v_w \mu_{amw} \Delta^{(w)} \). Therefore, using Eqs. (23)-(29) in Eq. (22), we can write:

\[
\delta \varepsilon = (\delta \mu_{axf})^T (g_x - v \odot \Phi_x + g_m - \gamma v \odot \Phi_m) \equiv (\delta \mu_{axf})^T g
\]

(31)

where the gradient \( g \) is given as:

\[
g_x = [\mathcal{L}_{xx}(\Psi_{xx})]^T - v \odot \Phi_x + [\mathcal{L}_{mm}(\Psi_{mm}) + \mathcal{L}_{xm}(\Psi_{xm})]^T - \gamma v \odot \Phi_m
\]

(32)

4. Numerical Studies

4.1. Test cases

Numerical studies in this work are carried out for scattering-dominant as well as non-scattering-dominant media.

4.1.1. Scattering-dominant media

For scattering-dominant media, the absorption coefficient (\( \mu_a \)) is much smaller than the reduced scattering coefficient (\( \mu_s(1-g) \)), and the diffusion approximation
Algorithm 1 One-step Jacobian-based FPAT algorithm

1: procedure ONE-STEP JACOBIAN-BASED FPAT RECONSTRUCTION
2: \[ \mu_{\text{axf}} = \text{zeros}(N_F \times 1) \]
3: \[ \text{Predict absorbed optical energy density on FOT-grid } h^s_F \]
4: \[ \text{Compute FOT-grid to PAT-grid interpolation matrix } \Xi_{F \rightarrow P} \]
5: \[ h^s_P \leftarrow \Xi_{F \rightarrow P} h^s_F \]
6: \[ \text{Compute PAT measurement matrix on PAT grid } J_h \]
7: \[ \text{Predict boundary PA data } p^s_P \]
8: \[ \text{Compute } \varepsilon \leftarrow ||p^{o} - p^s_P||_2^2 \]
9: \[ \text{while } \varepsilon \leq \text{tol} \text{ or the residual is unchanging do} \]
10: \[ \mu_{\text{axf}} \leftarrow \mu_{\text{axf}} \]
11: \[ J = J_h\Xi_{F \rightarrow P}J_{\mu} \]
12: \[ \text{Compute } \alpha \text{ using L-curve} \]
13: \[ \text{Compute the LM update } \Delta \mu_{\text{axf}} \]
14: \[ \text{Compute steplength } \alpha \text{ using line search} \]
15: \[ \mu_{\text{axf}} \leftarrow \mu_{\text{axf}} + \alpha \Delta \mu_{\text{axf}} \]
16: \[ \text{Predict absorbed optical energy density on FOT-grid } h^s_f \]
17: \[ h^s_P \leftarrow \Xi_{F \rightarrow P} h^s_F \]
18: \[ \text{Predict boundary PA data } p^s_f \]
19: \[ \text{Compute } \varepsilon \leftarrow ||p^{o} - p^s_f||_2^2 \]
20: \[ \text{end while} \]
21: \[ \text{return } \mu_{\text{axf}} \]
22: \[ \text{end procedure} \]

Background optical properties of the RTE domain are considered to be homogeneous, with \( \mu_{\text{axi}} = 0.023 \text{cm}^{-1}, \mu_{\text{ami}} = 1.2565 \cdot \mu_{\text{axi}}, \mu_{sx} = 98.4 \text{cm}^{-1}, \)
Algorithm 2 One-step, gradient-based FPAT algorithm

1: procedure ONE-STEP, GRADIENT-BASED FPAT RECONSTRUCTION
2: \( \mu_{axf} \) = zeroes\((N \times 1)\) (Initialization by zero)
3: Predict absorbed optical energy density \( h^s \)
4: Compute PAT measurement matrix \( J_h \)
5: Predict boundary PA data \( p^s \)
6: \( B = \text{eye}(N \times N) \) (Initialization by identity)
7: \( g_0 = \text{zeros}(N \times 1) \) (Initialization by zero)
8: Compute \( \varepsilon \leftarrow ||p^o - p^s||^2_2 \)
9: while \( \varepsilon \leq \text{tol} \) or the residual is unchanging do
10: Compute gradient \( g \)
11: Compute the update direction \( \Delta \mu_{axf} \)
12: update \( \mu_{axf} \leftarrow \mu_{axf} + \delta \)
13: Predict absorbed optical energy density \( h^s \)
14: Predict boundary PA data \( p^s \)
15: \( y = g - g_0 \)
16: \( g_0 \leftarrow g \)
17: \( B \leftarrow B + \frac{y y^T}{\sum z^2} - \left( \frac{B x x^T B^T}{\sum z y^2} \right) \)
18: Compute \( \varepsilon \leftarrow ||p^o - p^s||^2_2 \)
21: end while
22: return \( \mu_{axf} \)
23: end procedure

\( \mu_{sm} = \mu_{sx}, \ g = 0.9, \ \Phi = 0.4, \ R_{x,m} = 0.431, \ \mu_{axf} = 0.005 cm^{-1} \) and \( \mu_{amf} = 0.1012 \cdot \mu_{axf} \) [18,34,35]. The phantoms we aim to reconstruct are: (i) **phantom 1**: a circular fluorescent inhomogeneity \( \mu_{axf} = 0.05 \: cm^{-1} \) (Fig. 2a) and (ii) **phantom 2**: a concave \( \mu_{axf} = 0.04 \: cm^{-1} \) as well as a circular inhomogeneity \( \mu_{axf} = 0.05 \: cm^{-1} \) (Fig. 2b). The acoustic properties of the PAE modeling domain are also chosen to be homogeneous: \( \eta = 4 \times 10^{-4} K^{-1} \) and \( C_p = 4000 JK g^{-1} K^{-1} \) [18,36]. Equations involved in this work have been solved using

![Fig. 2: Scattering-dominant media: true maps of \( \mu_{axf} \) (a) phantom 1 and (b) phantom 2.](image-url)
the finite element method. The PA data are computed at 100 frequencies between 9.6kHz to 960kHz, at 160 and 41 detector locations for full and limited data cases respectively, with detector separation of $1/16\text{ cm}$. The experimental PA measurements are simulated at a mesh resolution of $1/128\text{ cm}$, and for the angular discretization to model RTE, a unit circle is uniformly divided into 32 angular elements.

To carry out the Jacobian-based reconstructions, the iterative forward RTE solvers were executed at a mesh resolution of $1/32\text{ cm}$, and the optical Jacobians ($J_\mu$) were also computed on the same grid. PA modeling, as well as the measurement matrix ($J_h$), were computed at a mesh resolution of $1/64\text{ cm}$. In the gradient-based inversion scheme all the forward solvers, as well as gradient computations, were executed at a mesh resolution of $1/64\text{ cm}$.

4.1.2. Non-scattering-dominant media

In non-scattering-dominant media, the absorption coefficient ($\mu_a$) is comparable to (or greater than) the reduced scattering coefficient ($\mu_s(1-g)$), and the diffusion approximation to the RTE does not hold. We consider the domain of interest to be of dimension $1\text{ cm} \times 1\text{ cm}$, with the overall computational domain set at $3\text{ cm} \times 3\text{ cm}$ for PA modeling. The coupled-RTE (Eq. (1)) is solved in $1\text{ cm} \times 1\text{ cm}$ domain to obtain the heat source, followed by solving the frequency-domain PAE (Eq. (7)) in the overall $3\text{ cm} \times 3\text{ cm}$ domain. The set-ups considered in our numerical studies are depicted in Fig. 4. We consider smaller domain sizes for photon propagation in non-scattering-dominant media because owing to high absorption and low-scattering properties of the domain, majority of the heat source is confined within the $1\text{ cm} \times 1\text{ cm}$ domain.

Background optical properties of the RTE domain are considered to be homogeneous, with $\mu_{axi} = 0.45 \text{ cm}^{-1}$, $\mu_{ami} = \mu_{axi}$, $\mu_{sx} = 20 \text{ cm}^{-1}$, $\mu_{sm} = \mu_{sx}$, $g = 0.9$, $\Phi = 0.4$, $\mu_{ax f} = 0.005 \text{ cm}^{-1}$ and $\mu_{am f} = 0.1012 \cdot \mu_{ax f}$ [18,34,35]. The phantoms we aim to reconstruct are: (i) **phantom 3**: [low contrast] a concave ($\mu_{ax f} = 0.10 \text{ cm}^{-1}$) as well as a circular inhomogeneity ($\mu_{ax f} = 0.08 \text{ cm}^{-1}$) (Fig. 3a).(ii) **phantom 4**: [high contrast] a concave ($\mu_{ax f} = 0.40 \text{ cm}^{-1}$) as well as a circular inhomogeneity ($\mu_{ax f} = 0.30 \text{ cm}^{-1}$) (Fig. 3b).

The acoustic properties of the PAE modeling domain are also chosen to be homogeneous: $\eta = 4 \times 10^{-4} \text{ K}^{-1}$ and $C_P = 4000 \text{ JK}^{-1} \text{ K}^{-1}$ [18,36]. Equations involved in this work have been solved using the finite element method. The PA data are computed at 100 frequencies between 9.6kHz to 960kHz, at 160 and 41 detector locations for full and limited data cases respectively, with detector separation of $1/16\text{ cm}$. The experimental PA measurements are simulated at a mesh resolution of $1/256\text{ cm}$, and for the angular discretization to model RTE, a unit circle is uniformly divided into 32 angular elements.

To carry out the Jacobian-based reconstructions, the iterative forward RTE solvers were executed at the at a mesh resolution of $1/64\text{ cm}$ and the optical Jacobians ($J_\mu$) were also computed on the same grid. PA modeling, as well as the
measurement matrix \((J_h)\) were computed at a mesh resolution of 1/128 cm. In
the gradient-based inversion scheme all the forward solvers, as well as gradient
computations, were executed at a mesh resolution of 1/128 cm.

4.2. Reconstruction studies

Reconstruction procedure starts with an initial guess for \(\mu_{\text{axf}}\) which we choose
to be a zero vector. Algorithms 1 and 2 are executed to obtain the Jacobian and
gradient-based reconstructions in full and limited-data settings, for all the test
cases, and have been displayed in Fig. 5 - 12. Accuracy of the reconstructions
thus obtained has been quantified on the basis of the error measures: correlation
coefficient\((\rho)\) and deviation factor \((\delta)\) defined as [37]:

\[
\rho = \frac{\sum_{i=1}^{N} (p_i - \bar{p})(p_i' - \bar{p}')}{(N-1)\Delta p' \Delta p}; \quad \delta = \frac{\sqrt{\sum_{i=1}^{N} (p_i' - p_i)^2 / N}}{\Delta p'}
\]  

(33)

where \(N\) is the total number of spatial nodes in the reconstruction domain, \(\Delta p'\)
and \(\Delta p\) are the standard deviations and \(\bar{p}'\) and \(\bar{p}\) are the mean values of the true
and reconstructed values of the parameter respectively. The error measures \((\rho, \delta)\)
obtained for these reconstructions are tabulated in Table 1 and 2.
4.2.1. Scattering-dominant media

Fig. 5 and 6 depict the Jacobian-based reconstructions in the full and limited data settings, respectively, obtained in scattering-dominant media. Corresponding gradient-based reconstructions are shown in Fig. 7 and 8. Table 1 contains the error measures corresponding to the reconstructions thus obtained.

In full data setting, both, the Jacobian as well as the gradient-based schemes locate the inhomogeneities and able to reconstruct the shapes accurately for noiseless as well as noisy PA data. With computational budgets in mind, the Jacobian based reconstructions have been executed at the least resolution that yielded acceptable reconstructions. Since the gradient computations, as well as iterative forward RTE solvers, were executed at a better spatial resolution for the gradient-based scheme, it was found to yield quantitatively more accurate reconstructions. Consequently, as compared to the Jacobian-based scheme, gradient-based scheme yields higher correlation coefficients for PA data with $SNR \geq 10dB$. Under limited data settings, the Jacobian and gradient-based reconstructions carry characteristic directional artifacts. Both the schemes were found to reconstruct the inhomogeneities well but the reconstruction artifacts are more prominent than corresponding full data counterparts. It was also observed that in limited data settings, Jacobian-based reconstructions were relatively more accurate and carry fewer artifacts as compared to the gradient-based reconstructions as justified by error metrics observed in Table 1.

![Image of reconstructions](image-url)
Fig. 6: [Scattering-dominant media] Jacobian-based reconstructions: Limited-data setting

Fig. 7: [Scattering-dominant media] Gradient-based reconstructions: Full-data setting
Fig. 8: [Scattering-dominant media] Gradient-based reconstructions: Limited-data setting

Table 1: [Scattering-dominant media] Correlation coefficients $\rho$ and deviation factors $\delta$ for one-step Jacobian and gradient-based reconstructions

<table>
<thead>
<tr>
<th>Phantom</th>
<th>SNR</th>
<th>Jacobian-based</th>
<th>Gradient-based</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\rho$</td>
<td>$\delta$</td>
<td>$\rho$</td>
</tr>
<tr>
<td>Full data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phantom-1</td>
<td>Noiseless</td>
<td>0.70</td>
<td>0.96</td>
</tr>
<tr>
<td></td>
<td>15dB</td>
<td>0.68</td>
<td>0.95</td>
</tr>
<tr>
<td></td>
<td>10dB</td>
<td>0.67</td>
<td>0.98</td>
</tr>
<tr>
<td></td>
<td>5dB</td>
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<td>1.04</td>
</tr>
<tr>
<td>Phantom-2</td>
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<td>0.80</td>
</tr>
<tr>
<td></td>
<td>15dB</td>
<td>0.79</td>
<td>0.76</td>
</tr>
<tr>
<td></td>
<td>10dB</td>
<td>0.78</td>
<td>0.77</td>
</tr>
<tr>
<td></td>
<td>5dB</td>
<td>0.76</td>
<td>0.81</td>
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<td>Limited data</td>
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<td></td>
<td></td>
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<tr>
<td>Phantom-1</td>
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<td></td>
<td>30dB</td>
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<tr>
<td></td>
<td>20dB</td>
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<td>10dB</td>
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<td>0.82</td>
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<td>20dB</td>
<td>0.71</td>
<td>0.85</td>
</tr>
<tr>
<td></td>
<td>10dB</td>
<td>0.65</td>
<td>0.90</td>
</tr>
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</table>
4.3. Non-scattering-dominant media

Between the two phantoms considered for this part of the study, phantom-3 has a lower inhomogeneity to background contrast as compared to phantom-4. Fig. 9 and 10 depict the Jacobian-based reconstructions in the full and limited data settings, respectively, obtained in non-scattering-dominant media, and corresponding gradient-based reconstructions are demonstrated in Fig. 11 and 12. Corresponding error measures are tabulated in Table 2.

Although the $\mu_{\text{ax}}/f$ contrast (inhomogeneity to background) for phantom-3 and phantom-4 are 20 : 1 and $\sim 80 : 1$ respectively, their total absorption coefficient ($\mu_a$) contrast are $\sim 1.2 : 1$ and $\sim 1.8 : 1$. To accurately reconstruct such subtle changes in the absorption property (especially in the case of phantom-3) needs the Jacobian/gradient computation, as well as iterative forward modeling needs to be done at a highly resolved grid. Keeping computational budgets in mind, we have executed the Jacobian computations at the least resolution that yielded acceptable reconstructions; the Jacobians have been thus computed on a coarser grid than the gradients. Therefore, while in full data settings, Jacobian and gradient-based schemes yield comparable reconstructions for phantom-4, the gradient-based scheme performs significantly better than the Jacobian-based scheme for phantom-3, a low contrast phantom. The difference
Fig. 10: [Non-scattering-dominant media] Jacobian-based reconstructions: Limited-data setting. (a-c) low-contrast phantom 3 and (d-f) high-contrast phantom 4.

Table 2: [Non-scattering-dominant media] Correlation coefficients $\rho$ and deviation factors $\delta$ for one-step Jacobian and gradient-based reconstructions

<table>
<thead>
<tr>
<th>Phantom</th>
<th>SNR</th>
<th>Jacobian-based $\rho$</th>
<th>Jacobian-based $\delta$</th>
<th>Gradient-based $\rho$</th>
<th>Gradient-based $\delta$</th>
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<tr>
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<td>0.70</td>
</tr>
<tr>
<td></td>
<td>15dB</td>
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<td>0.96</td>
<td>0.71</td>
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<td>1.21</td>
<td>0.63</td>
<td>0.84</td>
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<td>0.78</td>
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</tr>
<tr>
<td></td>
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<td>0.64</td>
</tr>
<tr>
<td></td>
<td>10dB</td>
<td>0.73</td>
<td>0.70</td>
<td>0.74</td>
<td>0.68</td>
</tr>
<tr>
<td></td>
<td>5dB</td>
<td>0.69</td>
<td>0.76</td>
<td>0.61</td>
<td>0.85</td>
</tr>
<tr>
<td>Limited data</td>
<td>Phantom-3</td>
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<td>0.51</td>
<td>1.27</td>
<td>0.58</td>
</tr>
<tr>
<td></td>
<td>30dB</td>
<td>0.50</td>
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<td>0.91</td>
</tr>
<tr>
<td></td>
<td>20dB</td>
<td>0.48</td>
<td>0.94</td>
<td>0.56</td>
<td>0.91</td>
</tr>
<tr>
<td>Phantom-4</td>
<td>Noiseless</td>
<td>0.72</td>
<td>0.69</td>
<td>0.71</td>
<td>0.71</td>
</tr>
<tr>
<td></td>
<td>30dB</td>
<td>0.68</td>
<td>0.75</td>
<td>0.70</td>
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</tr>
<tr>
<td></td>
<td>20dB</td>
<td>0.66</td>
<td>0.76</td>
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</tr>
<tr>
<td></td>
<td>10dB</td>
<td>0.61</td>
<td>0.80</td>
<td>0.68</td>
<td>0.75</td>
</tr>
</tbody>
</table>
in the reconstruction quality is manifested in the high $\rho$ values and low $\delta$ values, for the gradient-based reconstructions as compared to the Jacobian-based reconstructions for phantom-3, whereas the error measures are comparable for the phantom with relatively higher contrast (phantom-4).

In limited data setting, Jacobian-based reconstructions for phantom-3 display a lot of artifacts as compared to corresponding gradient-based reconstructions, which is clearly indicated in corresponding $\rho$ and $\delta$ values. For the higher contrast phantom, the reconstructions obtained from both the schemes carry much lesser artifacts. While both the schemes were able to locate the inhomogeneities and reconstruct their shapes accurately, the Jacobian-based scheme provided a better quantitative estimate.

### 4.4. Further discussion

In our work, keeping computational budgets in mind, after initial experimentation, we have chosen the least reconstruction grid resolution that was able to accurately compute the forward problem and yield acceptable reconstructions; these resolutions have been already mentioned in the numerical studies section.

In our present work, taking into account the wide-spectrum of numerical test cases considered, for brevity and clarity, we have demonstrated only single-
grid reconstructions across all the test cases. The algorithms presented in this manuscript can be extended to a dual grid based reconstruction framework as demonstrated in our previous paper [18]; in our computational experience in FPAT reconstructions [18], the dual-grid scheme, while saving on computational resources, is expected to give similar reconstructions as the single-grid scheme in these settings.

However, higher spatial resolution offers the ability to probe higher frequencies (since for a stable acoustic wave propagation, the resolution should be at least one-tenth of the lowest acoustic wavelength [38]) and can be used to reconstruct smaller absorbers than what have been considered in our cases.

We mention that in our work, we have directly reconstructed the absorption coefficient at excitation frequency $\mu_{axf}$, in a one-step method that does not reconstruct the photoacoustic signal (the absorbed optical energy density (AOED)) as an intermediate quantity. However, as an example of a visualization of the difference in the absorbed optical energy density (AOED; the photoacoustic signal) due to the different $\phi$ used, we depict in Fig. 13, calculated (from reconstructions of $\mu_{axf}$) maps ($H_m$) and the true maps of the fluorescence contribution ($H_m^{true}$) to the AOED for $\phi = 0.4$ and $\phi = 0.6$. Here:

$$H_m^{true} = (\mu_{ami} + \gamma \mu_{axf}^{true}) \odot \Phi_m(\mu_{axf}^{true})$$

and

$$H_m = (\mu_{ami} + \gamma \mu_{axf}^{recn}) \odot \Phi_m(\mu_{axf}^{recn}).$$
We have also performed gradient based reconstruction for a relatively higher quantum efficiency ($\phi = 0.6$) fluorophores. The reconstruction results as well as the error measures for the $\phi = 0.6$ case are found to be similar to those obtained for $\phi = 0.4$ already presented, and hence are not included in the paper for the sake of brevity.

![Image](image.png)

Fig. 13: (a,d) Maps of true $H_m$ for $\phi = 0.4, 0.6$, (b,e) maps of $H_m$ computed from the reconstructed $\mu_{axf}$ maps obtained from PA data with SNR=15dB for $\phi = 0.4, 0.6$ and (c,f) SNR=10dB for $\phi = 0.4, 0.6$.

In order to briefly relate the specifications of the detector configuration considered, to experimental realization, we mention that earlier works such as say those carried out by the group of Dr. Huabei Jiang utilize 50 frequencies from 50 up to 540 kHz to carry out QPAT reconstructions [8,11,39] . More recent works by this group [40,41] utilize a transducer with 1 MHz central frequency and bandwidth range from 0.65 to 1.18 MHz in multispectral QPAT reconstructions. The work in [40] used a total of 120 detectors equally distributed along the boundary of the circular background of 3cm diameter, which implies a detector separation of $\sim 0.8$ mm. DAQ cards corresponding to such frequencies have been mentioned in literature such as in [42,43].

As a simple demonstration of reconstructions using a modified (smaller) frequency range than what we have considered, we carried out the gradient based reconstruction of phantom 2 considering 83 equispaced frequencies between
105.6 and 892.8 kHz for scattering dominant media in full data setting using the PA data with 15dB SNR. The reconstruction obtained is provided in Fig 14 and yielded correlation coefficient $\rho = 0.85$ and deviation factor $\delta = 0.93$.

![Fig. 14: (a) True and (b) reconstructed $\mu_{axf}$ maps for phantom-2 with PA data in a smaller frequency band: 105.6 to 892.8 kHz](image)

Moreover, development of all optical detection of ultrasonic signal facilitates low detector pitch and broadband PA data collection. A recent publication [44] used a Fabrey-Perot based PA scanner (in planar detection geometry) which offers flat acoustic frequency response from 50 kHz to 20 MHz and the measurements were made in the increments of 110 $\mu m$.

In our work, we have set up our numerical test cases by considering point detectors with unlimited bandwidth, since our aim is to present a basic detailed validation of the reconstruction framework. Specific detector configurations and sensitivities can be incorporated as needed via their spatial and electrical impulse responses, into the forward model [45,46].

For any detector specifications, the measured pressure signal can be obtained from the point-detector evaluations by its temporal convolution with the spatial and electrical impulse responses (corresponding to finite-size/shape and bandwidth specifications respectively) of the detector-configuration of choice [45]. This convolution can be incorporated into a the forward model of the photoacoustic process by the use of FFTs [46]. We note that while the forward model in [46] is in the time domain, in our frequency-domain PA-equation modeled setting, the corresponding Fourier-domain multiplication is similarly straightforwardly applicable.

5. Conclusion

We solve the complete one-step FPAT problem of reconstructing the absorption coefficient of the exogenous fluorophore from boundary photoacoustic measurements in a Levenberg-Marquardt (Jacobian-based) and BFGS (gradient-based) frameworks, using the radiative transport equation as the photon transport model. To the best of our knowledge, these are the first such results in literature.
Reconstruction studies have been carried out in scattering-dominant (where diffusion approximation holds) as well as non-scattering-dominant media under full and limited data settings. Over the test cases considered, we observed comparable reconstruction results for Jacobian and gradient based schemes. Noting that keeping computational budgets in mind, we have computed Jacobians at the least resolutions that yielded acceptable reconstructions. We observed the gradient based reconstructions to be slightly better than their Jacobian counterparts in full-data settings. However, under limited data settings, while both the schemes were able to locate the inhomogeneities and reconstruct their shapes accurately, the Jacobian-based scheme provided a better quantitative estimate.

Jacobian computation requires solving the corresponding adjoint problem $O(N)$ ($N$: number of nodes in the domain) times whereas computation of gradient needs to solve corresponding adjoint problem $O(1)$ times. Therefore, although the gradient-based scheme took more iterations to converge, and in this work, was executed at a relatively higher mesh resolution, overall it was found to be significantly faster as compared to the Jacobian-based scheme. The reduced computational complexity with the gradient-based schemes better enables their potential scaling-up to three-dimensional as well as dynamic settings.

Disclosures
The authors declare no conflicts of interest.

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Appendix A: Finite element formulation of FPAT forward problem

.1. Finite element formulation of coupled radiative transport equations

We are using the Galerkin’s approach to solve the RTE using finite element method (FEM). In order to obtain the weak form of Eq. (1) ($q = x, m$), we multiply both the sides by a trial function $\phi(\vec{r}, \hat{s})$ and integrate it over the complete spatial and angular domain $\Omega \times S^d$, ($d = 1, 2$). Using the scalar product definition,

$$ (\mathcal{F}, \mathcal{G}) = (\mathcal{F}, \mathcal{G})_{\Omega \times S^2} = \int_\Omega \int_S \mathcal{F}(\vec{r}, \hat{s}) \mathcal{G}(\vec{r}, \hat{s}) d\omega d^3x = \int_V \mathcal{F}(\vec{r}, \hat{s}) \mathcal{G}(\vec{r}, \hat{s})dV $$

(34)

we can write operator form of the weak formulation as,

$$ (\mathcal{A}I, \phi) = (q, \phi). $$

(35)

In the low scattering environment, the RTE behaves as a hyperbolic equation, which yield spurious oscillations in the solution, obtained from standard FEM.
The stability has been proposed to be achieved by the streamline diffusion modification [5]:

$$(\mathcal{A}I, \phi + \delta \hat{s} \hat{V} \phi) = (q, \phi + \delta \hat{s} \hat{V} \phi)$$  \hspace{1cm} (36)$$

where $\delta$ is the smoothing parameter [47, 48], a spatially varying constant that depends on the local absorption and scattering in addition to the mesh resolution or distance from source. Therefore, in our further calculations, we replace $\phi(\vec{r})$ by $\phi(\vec{r}) + \delta \hat{s} \hat{V} \phi(\vec{r})$.

Using Eq. (3), the first term on the L.H.S. of Eq. (37) can be written as

$$\int_{\Omega} \int_{S} \hat{s} \hat{V} I(\vec{r}, \hat{s})[\phi(\vec{r}, \hat{s}) + \delta \hat{s} \hat{V} \phi(\vec{r}, \hat{s})]d\omega d^3x = - \int_{\Omega} \int_{S} \hat{s} \nabla \phi(\vec{r}, \hat{s}) I(\vec{r}, \hat{s}) d\omega d^3x$$

$$+ \int_{\partial \Omega \cup} \int_{S} (\hat{s} \hat{n})_+ \phi(\vec{r}, \hat{s}) I(\vec{r}, \hat{s}) d\omega dl + \int_{\partial \Omega \cup} \int_{S} (\hat{s} \hat{n})_- \phi(\vec{r}, \hat{s}) f(\vec{r}, \hat{s}) d\omega dl$$

$$+ \int_{\Omega} \int_{S} \hat{s} \nabla I(\vec{r}, \hat{s})[\delta \hat{s} \hat{V} \phi(\vec{r}, \hat{s})] d\omega d^3x$$  \hspace{1cm} (37)$$

Substituting Eq. (38) into Eq. (37) we get:

$$- \int_{\Omega} \int_{S} \hat{s} \nabla \phi(\vec{r}, \hat{s}) I(\vec{r}, \hat{s}) d\omega d^3x + \int_{\partial \Omega \cup} \int_{S} (\hat{s} \hat{n})_+ \phi(\vec{r}, \hat{s}) I(\vec{r}, \hat{s}) d\omega dl$$

$$+ \int_{\Omega} \int_{S} \hat{s} \nabla I(\vec{r}, \hat{s})[\delta \hat{s} \hat{V} \phi(\vec{r}, \hat{s})] d\omega d^3x$$

$$+ \int_{\Omega} \int_{S} \mu_a(\vec{r}) + \mu_s(\vec{r}) + \frac{i \omega}{c} I(\vec{r}, \hat{s})[\phi(\vec{r}, \hat{s}) + \delta \hat{s} \hat{V} \phi(\vec{r}, \hat{s})] d\omega d^3x +$$

$$\int_{\Omega} \int_{S} \mu_s(\vec{r}) P(\hat{s}', \hat{s}) I(\vec{r}, \hat{s}')[\phi(\vec{r}, \hat{s}) + \delta \hat{s} \hat{V} \phi(\vec{r}, \hat{s})] d\omega' d^3x$$

$$= \int_{\Omega} \int_{S} s_q(\vec{r}, \hat{s})[\phi(\vec{r}, \hat{s}) + \delta \hat{s} \hat{V} \phi(\vec{r}, \hat{s})] d\omega d^3x - \int_{\partial \Omega \cup} \int_{S} (\hat{s} \hat{n})_- \phi(\vec{r}, \hat{s}) f(\vec{r}, \hat{s}) d\omega dl$$  \hspace{1cm} (39)$$

The spatial and angular domains are discretized, and using finite element
formulation, the radiance $I_q$ at a point $\vec{r}$ and in direction $\hat{s}$ can be expressed as

$$I_q(\vec{r}, \hat{s}) \equiv \sum_{k=1}^{N} \sum_{i=1}^{M} N_k(\vec{r}) Q(\hat{s}) I_{qi} = [Q \otimes N] L_q$$  \hspace{1cm} (40)$$

where $L_q$ denotes the discrete radiance vector of size $MN \times 1$, constructed as:

$$L_q = (I_{q11} \cdots I_{q1N}, I_{q21} \cdots I_{q2N}, \cdots, I_{qMN})^T$$

where $I_{qk}$ denotes the nodal value of excitation/emission radiance at $k^{th}$ spatial node in $i^{th}$ angular nodal direction.

Using Galerkin’s FEM, the discretized form of the RTE can be expressed as,

$$A_q L_q = b_q$$  \hspace{1cm} (41)$$

The excitation source-vector is given as $b_q = -(A_4 \otimes S_3) f$, where $f$ is the discretized concatenation of the excitation source function $f(\vec{r}, \hat{s})$, constructed similar to the discrete radiance vector $L_q$.

The system matrix $A_q$ (size: $MN \times MN$) is given as:

$$A_q = -A_1 \otimes S_1 + A_2 \otimes S_2 + A_3 \otimes S_3 + A_5 \otimes S_4 + A_6 \otimes S_5 + A_6 \otimes S_6 + A_7 \otimes S_7 + A_8 \otimes S_8(\mu_i) + A_9 \otimes S_9(\mu_i) + A_2 \otimes S_{10}(\mu_i) - A_9 \otimes S_8(\mu_s) - A_{10} \otimes S_9(\mu_s) - A_{11} \otimes S_{10}(\mu_s).$$  \hspace{1cm} (42)$$

Here $S_1, \cdots, S_7$ are assembled form of elemental matrices $S_1, \cdots, S_7$, and $S_8(\mu_{s/j}), S_9(\mu_{s/j}), S_{10}(\mu_{s/j})$ are the assembled form of $S_8(\mu_{s/j}), S_9(\mu_{s/j}), S_{10}(\mu_{s/j})$ respectively, defined as:

$$S_1 = \left[ \int_{\Omega_e} (\nabla_x [N])^T [N] \right], \quad S_2 = \left[ \int_{\Omega_e} (\nabla_y [N])^T [N] \right], \quad S_3 = \left[ \int_{\partial\Omega_e} [N]^T [N] \right],$$

$$S_4 = \left[ \int_{\Omega_e} \delta^e (\nabla_x [N])^T \nabla_x [N] \right], \quad S_5 = \left[ \int_{\Omega_e} \delta^e (\nabla_y [N])^T \nabla_y [N] \right],$$

$$S_6 = \left[ \int_{\Omega_e} \delta^e (\nabla_y [N])^T \nabla_x [N] \right], \quad S_7 = \left[ \int_{\Omega_e} \delta^e (\nabla_y [N])^T \nabla_y [N] \right],$$

$$S_8(\mu) = \left[ \sum_{j=1}^{3} \int_{\Omega_e} N_j \mu_j [N]^T [N] \right] = \int_{\Omega_e} [N]^T [N] \mu_j [N],$$

$$S_9(\mu) = \left[ \sum_{j=1}^{3} \int_{\Omega_e} \delta^e N_j \mu_j (\nabla_x [N])^T [N] \right], \quad S_{10}(\mu) = \left[ \sum_{j=1}^{3} \int_{\Omega_e} \delta^e N_j \mu_j (\nabla_y [N])^T [N] \right]$$  \hspace{1cm} (43)$$

and $A_1, \cdots, A_8$ are assembled form of angular elemental matrices $A_1, \cdots, A_8$.
we get:

\[
\mathcal{A}_1 \hat{x} + \mathcal{A}_2 \hat{y} = \int_{S_e} \hat{s} [Q]^T [Q], \quad \mathcal{A}_3 = \int_{S_e} (\hat{s} \hat{n})_x [Q]^T [Q], \quad \mathcal{A}_4 = \int_{S_e} (\hat{s} \hat{n})_y [Q]^T [Q],
\]

(44)

\[
\mathcal{A}_5 = \int_{S_e} \cos^2 \theta [Q]^T [Q], \quad \mathcal{A}_6 = \int_{S_e} \sin \theta \cos \theta [Q]^T [Q], \quad \mathcal{A}_7 = \int_{S_e} \sin^2 \theta [Q]^T [Q]
\]

(45)

\[
\mathcal{A}_8 = \int_{S_e} [Q]^T [Q]
\]

(46)

Matrices \( \mathbf{A}_9, \mathbf{A}_{10}, \mathbf{A}_{11} \) are the assembled form of the elemental matrices \( \mathcal{A}_9, \mathcal{A}_{10}, \mathcal{A}_{11} \). Elements of these angular elemental matrices involve double integrations, and are computed as:

\[
[\mathbf{A}_9]_{ii}^{\ell_1, \ell_2} = \int_{r_1} Q_1(\hat{s}) \int_{r_2} Q_1(\hat{s}') P(\hat{s}, \hat{s}') d\omega' d\omega 
\]

(47)

\[
[\mathbf{A}_{10}]_{ii}^{\ell_1, \ell_2} \hat{x} + [\mathbf{A}_{11}]_{ii}^{\ell_1, \ell_2} \hat{y} = \int_{r_1} \hat{s} Q_1(\hat{s}) \int_{r_2} Q_1(\hat{s}') P(\hat{s}, \hat{s}') d\omega' d\omega
\]

(48)

and stored into corresponding elemental matrices of size \( 2 \times 2 \times M^2 \), and then assembled into \( M \times M \) matrices. \( [\mathbf{N}] = [N_1 N_2 N_3] \) being the linear basis function (size: \( 1 \times 3 \)) for a triangular element \( e \), and \( \nabla (x/y) [\mathbf{N}] \) denotes its derivative matrix with respect to \( (x/y) \) (size: \( 1 \times 3 \)). Index \( j (= 1, 2, 3) \) corresponds to the nodes in element \( e \). The parameters \( C \in \{\mu_r, \mu_s\} \) are represented in nodal basis, i.e. the value of coefficient \( C \) at any point in an element can be expressed as \( C = \sum_{j=1}^{3} N_j C_j = [\mathbf{N}] \bar{C} \), where \( \bar{C} = [C_1 C_2 C_3]^T \) (size: \( 3 \times 1 \)) denotes the nodal values of parameter \( C \) in element \( e \). \( [\mathbf{Q}] = [Q_1 Q_2] \) are the angular basis functions (size: \( 1 \times 2 \)) for a circular arc \( e \). The angular integrals over a circular (arc) element \( (e) \) are calculated using rectangular rule (with \( \approx 1000 \) intervals).

Since there are no excitation sources inside the domain, \( s_{q=x} = 0 \). For emission (fluorescence) light, the source is given as \( s_{q=m} = \frac{1}{2\pi} \eta(\mathbf{r}) \int_S I_8(\mathbf{r}, \hat{s}') d\omega' \) and \( b_{q=m} = \mathbf{V} I_{x'} \), where \( \mathbf{V} = [\mathbf{A}_{12} \otimes S_8(\eta) + \mathbf{A}_{13} \otimes S_9(\eta) + \mathbf{A}_{14} \otimes S_{10}(\eta)] \) and \( \mathbf{A}_{12}, \mathbf{A}_{13}, \mathbf{A}_{14} \) are the assembled form of the elemental matrices \( \mathbf{A}_{12}, \mathbf{A}_{13}, \mathbf{A}_{14} \), whose elements are computed as:

\[
[\mathbf{A}_{12}]_{ii}^{\ell_1, \ell_2} = \int_{S_e} Q_1(\hat{s}) \int_{S_e} Q_1(\hat{s}') d\omega' d\omega 
\]

(49)

\[
[\mathbf{A}_{13}]_{ii}^{\ell_1, \ell_2} \hat{x} + [\mathbf{A}_{14}]_{ii}^{\ell_1, \ell_2} \hat{y} = \int_{S_e} \hat{s} Q_1(\hat{s}) \int_{S_e} Q_1(\hat{s}') d\omega' d\omega
\]

(50)

The fluence at a position \( \mathbf{r} \) is defined as: \( \Phi_q(\mathbf{r}) = \int_S I_q(\mathbf{r}, \hat{s}) d\omega \). Using Eq. (40) we get:

\[
\Phi_q \equiv [\mathbf{N}][\hat{Q}]^T \quad \Phi_q = [\hat{Q}]^T
\]

(51)
where $\tilde{Q} = [\int_S Q_1, \cdots, \int_S Q_M]$ and $\tilde{I} = [I_{11}, \cdots, I_{M1}]^T \cdots, [I_{1N}, \cdots, I_{MN}]^T]$. The integrations $\int_S Q_i$ ($i = 1 \cdots M$) are computed elementwise using rectangular rule. The discretized photoacoustic heat source (AOED) for a nominal distribution of fluorophore absorption coefficient is computed as:

$$h = \mathcal{H}(\mu_{\text{axf}}) = \sum_{q=i,m} (\mu_{aqi} + \mu_{aqf}) \odot \Phi_q$$

(52)

.2. Finite element formulation of photoacoustic equation

Weak formulation of the frequency-domain PAE [29,49] is discussed in this section. We express the heat source and the complex PA pressure variables using linear basis functions as:

$$p \approx \hat{p} = NP; \quad h \approx \hat{h} = Nh$$

(53)

Galerkin formulation yields the weighted residual forms of eq. (7) as:

$$\int_{\Omega} [N]^T (\nabla^2 + k^2) \hat{p} = \int_{\Omega} [N]^T ik \frac{v_B}{Cp} \hat{h}$$

(54)

which for the $j^{th}$ frequency yields the matrix equation [49]:

$$A^j p = B^j h$$

where,

$$A^j = -K_s + k_j^2 K_m - i k_j K_b; \quad B^j = i k_j \frac{v_B}{Cp} K_m.$$  

(56)

The kernels $K_s$, $K_m$ and $K_b$ are defined as:

$$K_s = \left[ \int_{\Omega_s} \nabla^2 [N] \nabla^2 [N] \right], \quad K_m = \left[ \int_{\Omega_s} [N]^T [N] \right],$$

$$K_b = \left[ \int_{\partial \Omega_s} [N]^T [N] \right]$$

(57)

and $k_j$ denotes the wavenumber corresponding to the $j^{th}$ frequency.

.3. measurement matrix

The complex PA measurement $p_{\text{comp}}^j$ on M detector nodes can be expressed as

$$p_{\text{comp}}^j = \mathcal{D} \hat{p} = \mathcal{D}(A^j)^{-1}B^j \hat{h} = J^j \hat{h}$$

(58)

where $\mathcal{D}$ is the binary detection matrix operator of size $M \times N$ and $J^j$ is the complex measurement operator for $j^{th}$ frequency. Each row of $\mathcal{D}$ is constructed of $N$ elements where all but one element corresponding to the detector node number are zero.
The measurement operator $J_h$ is written as

$$J_h = \begin{bmatrix} [Re\{J\}]^T, [Im\{J\}]^T \end{bmatrix}^T$$

(59)

where, $J = [[J_1]^T, [J_2]^T, ...[J_L]^T]^T$ and the complete PA measurement equation can be expressed as the linear system

$$p_{meas} = J_h \hat{h}$$

(60)

Combining eq. (52) and eq.(60), the discrete FPAT measurement equation can be written as:

$$p_{meas} \equiv J_h \mathcal{H}(\mu_{ax f}) \equiv \mathcal{G}(\mu_{ax f})$$

(61)

where $\mathcal{G} = J_h \mathcal{H}$ is the discrete measurement operator, with $\mathcal{H}$ being defined in (52).

Appendix B: Discretization of angular domain and corresponding basis functions

While solving the RTE in two dimensions, unit circle is uniformly discretized (figure 15) to express the angular distribution of radiance at spatial nodes.

Fig. 15: Circle Discretisation

The value of a quantity $\zeta$ at an angular location $\hat{s}$ in a circular element $\epsilon$ is expressed in terms of its nodal values and angular basis functions as,

$$\zeta(\hat{s}) = \sum_{m=1}^{2} \zeta_m Q_m(\hat{s}) = [Q] \zeta$$

(62)
, where \( \tilde{\zeta} = [\zeta_1 \quad \zeta_2]^T \) (size: 2 \( \times \) 1) denotes the nodal values of quantity \( \zeta \) at the two nodes of element \( \epsilon \). Basis functions for a circular element are given as,

\[
Q_m(\hat{s}) = \frac{1}{\langle \hat{s}, \hat{s}_m \rangle} \hat{\phi}_m(\hat{s})
\]

(63)

where, \( \hat{\phi}_m(\hat{n}) \) is the basis functions for projected tangential linear element. The one dimension linear interpolation functions for the linear element \( \hat{\phi}_m(\hat{y}) \) can be written as,

\[
\hat{\phi}_1(\hat{s}) = \frac{|\hat{s}_2 - \hat{s}|}{|\hat{s}_2 - \hat{s}_1|} = \frac{\tan(\alpha - \beta)}{\tan(\alpha - \beta) + \tan\beta}
\]

(64)

\[
\hat{\phi}_2(\hat{s}) = \frac{|\hat{s} - \hat{s}_1|}{|\hat{s}_2 - \hat{s}_1|} = \frac{\tan\beta}{\tan(\alpha - \beta) + \tan\beta}.
\]

(65)

Using (63), we obtain the basis functions on the circular (arc) element as,

\[
Q_1(\hat{s}) = \frac{\tan(\alpha - \beta)}{\cos(\beta)(\tan(\alpha - \beta) + \tan\beta)}
\]

(66)

\[
Q_2(\hat{s}) = \frac{\tan\beta}{\cos(\alpha - \beta)(\tan(\alpha - \beta) + \tan\beta)}.
\]

(67)

**Appendix C: Calculation of coupled fluence sensitivities**

Denoting by \( 'p' \) and \( 'p'_\delta \) an optical parameter needing to be reconstructed and its perturbation respectively, if \( p \mapsto (I_x, I_m) \) is the forward operator, then \( p + p^\delta \mapsto (I_x + I^\delta_x, I_m + I^\delta_m) \), with \( I_{x/m} \) being excitation (and emission) radiances and \( I^\delta_{x/m} \) being corresponding first variations. We can write the equations for perturbed radiances as:

\[
(\hat{s} \cdot \nabla + \mu_{sx}(\hat{r})) I^\delta_x(\hat{r}, \hat{s}) - \mu_{sx}(\hat{r}) \int_S I^\delta_x(\hat{r}, \hat{s}')P(\hat{s} \cdot \hat{s}')d\omega' = -\frac{\partial \mu_{sx}}{\partial p} p^\delta(\hat{r}, \hat{s}) I_x(\hat{r})
\]

\[
+ \frac{\partial \mu_{sx}}{\partial p} p(\hat{r}) \int_S I_x(\hat{r}, \hat{s}')P(\hat{s} \cdot \hat{s}')d\omega'
\]

(68)

and

\[
(\hat{s} \cdot \nabla + \mu_{tm}(\hat{r})) I^\delta_m(\hat{r}, \hat{s}) - \mu_{sm}(\hat{r}) \int_S I^\delta_m(\hat{r}, \hat{s}')P(\hat{s} \cdot \hat{s}')d\omega' = -\frac{\partial \mu_{tm}}{\partial p} p^\delta(\hat{r}, \hat{s}) I_m(\hat{r})
\]

\[
+ \frac{\partial \mu_{sm}}{\partial p} p^\delta(\hat{r}) \int_S I_m(\hat{r}, \hat{s}')P(\hat{s} \cdot \hat{s}')d\omega' + \frac{1}{2^{n-1}\pi} \frac{\partial \eta}{\partial p} p^\delta(\hat{r}) \int_S I_x(\hat{r}, \hat{s}')d\omega'
\]

\[
+ \frac{1}{2^{n-1}\pi} \eta(\hat{r}) \int_S I^\delta_x(\hat{r}, \hat{s}')d\omega'
\]

(69)
with the boundary conditions,

\[ I_{x/m}^\delta(\vec{r}, \hat{s}) = 0; \vec{r} \in \partial \Omega, \hat{n} \cdot \hat{s} < 0 \quad (70) \]

Eq. (68) is multiplied by \( \psi_{xx}(\vec{r}, \hat{s}) \) and integrated over \( \Omega \times S \) as.

\[
\int_\Omega \int_S \psi_{xx}(\vec{r}, \hat{s}) \left((\hat{s} \cdot \nabla + \mu_{tx}(\vec{r})) I_x^\delta(\vec{r}, \hat{s}) - \mu_{sx}(\vec{r}) \right) \int_S I_x^\delta(\vec{r}, \hat{s}') P(\hat{s} \cdot \hat{s}') d\omega' d\vec{r} \\
= \int_\Omega \int_S \psi_{xx}(\vec{r}, \hat{s}) - \frac{\partial \mu_{tx}}{\partial p} P(\hat{s}, \hat{s}') d\omega' d\vec{r} + \frac{\partial \mu_{sx}}{\partial p} P(\hat{s}, \hat{s}') d\omega' d\vec{r} \\
= \int_\Omega \int_S I_x^\delta(\vec{r}, \hat{s}) \hat{s} \cdot \nabla \psi_{xx}(\vec{r}, \hat{s}) d\omega' d\vec{r} \\
(71)
\]

We will treat each term of this equation separately. Using the divergence theorem, the first term on the L.H.S. of Eq. (71) can be written as:

\[
\int_\Omega \int_S \psi_{xx}(\vec{r}, \hat{s}) \hat{s} \cdot \nabla I_x^\delta(\vec{r}, \hat{s}) d\omega' d\vec{r} = \int_\Omega \int_S \psi_{xx}(\vec{r}, \hat{s}) I_x^\delta(\vec{r}, \hat{s})(\hat{s} \cdot \hat{n}) d\omega' d\vec{a} \\
- \int_\Omega \int_S I_x^\delta(\vec{r}, \hat{s}) \hat{s} \cdot \nabla \psi_{xx}(\vec{r}, \hat{s}) d\omega' d\vec{r} \\
(72)
\]

Using the B.C. on the perturbed radiance, (Eq. (70)),

\[
\int_\Omega \int_S \psi_{xx}(\vec{r}, \hat{s}) \hat{s} \cdot \nabla I_x^\delta(\vec{r}, \hat{s}) d\omega' d\vec{r} = \int_\Omega \int_S \psi_{xx}(\vec{r}, \hat{s}) I_x^\delta(\vec{r}, \hat{s})(\hat{s} \cdot \hat{n}) d\omega' d\vec{a} \\
- \int_\Omega \int_S I_x^\delta(\vec{r}, \hat{s}) \hat{s} \cdot \nabla \psi_{xx}(\vec{r}, \hat{s}) d\omega' d\vec{r} \\
(73)
\]

The third term on the L.H.S. of Eq. (71), using variable transformation \( \hat{s}' \leftrightarrow \hat{s} \) can be written as:

\[
\int_\Omega \int_S \psi_{xx}(\vec{r}, \hat{s}) \mu_{sx}(\vec{r}) I_x^\delta(\vec{r}, \hat{s}') P(\hat{s} \cdot \hat{s}') d\omega' d\vec{r} \\
= \int_\Omega \int_S I_x^\delta(\vec{r}, \hat{s}) \psi_{xx}(\vec{r}, \hat{s}') P(\hat{s} \cdot \hat{s}') d\omega' d\vec{r} \\
(74)
\]

Using Eq. (73) and 74, Eq. (71) can be written as:

\[
\int_\Omega \int_S I_x^\delta(\vec{r}, \hat{s}) \left(-\hat{s} \cdot \nabla \psi_{xx}(\vec{r}, \hat{s}) + \mu_{tx}(\vec{r}) \psi_{xx}(\vec{r}, \hat{s}) - \mu_{sx}(\vec{r}) \right) \psi_{xx}(\vec{r}, \hat{s}') P(\hat{s} \cdot \hat{s}') d\omega' d\vec{r} \\
+ \int_\Omega \int_S \psi_{xx}(\vec{r}, \hat{s}) I_x^\delta(\vec{r}, \hat{s})(\hat{s} \cdot \hat{n}) d\omega' d\vec{a} \\
- \int_\Omega \int_S \psi_{xx}(\vec{r}, \hat{s}) \frac{\partial \mu_{tx}}{\partial p} P(\vec{r}, \hat{s}) I_x(\vec{r}) d\omega' d\vec{r} \\
+ \int_\Omega \int_S \psi_{xx}(\vec{r}, \hat{s}) \frac{\partial \mu_{sx}}{\partial p} P(\vec{r}, \hat{s}) I_x(\vec{r}) d\omega' d\vec{r} \\
(75)
\]
Multiplying Eq. (69) by $\psi_{nm}(\vec{r}, \tilde{s})$ and Eq. (68) by $\psi_{xm}(\vec{r}, \tilde{s})$, and then adding the two and integrating over $\Omega \times S$, we get:

$$
\int_{\Omega} \int_{S} \psi_{xm}(\vec{r}, \tilde{s}) \left( (\tilde{s} \cdot \nabla + \mu_{tx}(\tilde{r})) I_{x}^{\delta}(\vec{r}, \tilde{s}) - \mu_{sx}(\tilde{r}) \int_{S} I_{x}^{\delta}(\vec{r}, \tilde{s}') P(\tilde{s} \cdot \tilde{s}') d\omega' \right) d\omega d\vec{r}
$$

$$
+ \int_{\Omega} \int_{S} \psi_{mm}(\vec{r}, \tilde{s}) \left( (\tilde{s} \cdot \nabla + \mu_{tm}(\tilde{r})) I_{m}^{\delta}(\vec{r}, \tilde{s}) - \mu_{sm}(\tilde{r}) \int_{S} I_{m}^{\delta}(\vec{r}, \tilde{s}') P(\tilde{s} \cdot \tilde{s}') d\omega' \right) d\omega d\vec{r}
$$

$$
\quad \quad - \frac{1}{2n-1} \eta(\tilde{r}) \int_{S} I_{x}^{\delta}(\vec{r}, \tilde{s}') d\omega' d\vec{r}
$$

$$
= \int_{\Omega} \int_{S} \psi_{xm}(\vec{r}, \tilde{s}) \left( \begin{array}{c}
- \frac{\partial \mu_{tx}}{\partial p} \rho^{\delta}(\tilde{r}, \tilde{s}) I_{x}(\tilde{r}) + \frac{\partial \mu_{sx}}{\partial p} \rho^{\delta}(\tilde{r}) \int_{S} I_{x}(\tilde{r}, \tilde{s}') P(\tilde{s} \cdot \tilde{s}') d\omega' \\
+ \frac{\partial \mu_{sm}}{\partial p} \rho^{\delta}(\tilde{r}) \int_{S} I_{m}(\tilde{r}, \tilde{s}') P(\tilde{s} \cdot \tilde{s}') d\omega' + \frac{1}{2n-1} \frac{\partial \eta}{\partial p} \rho^{\delta}(\tilde{r}) \int_{S} I_{x}(\tilde{r}, \tilde{s}') d\omega'
\end{array} \right) d\omega d\vec{r}
$$

(76)

Adjoint $\psi_{xm}$ and the addition above is required to compute the fluorescence sensitivity because of the coupled nature of the fluorescence RTE. Following the steps similar to Eq. (72)-(74) and arranging terms with $I_{x}^{\delta}$ and $I_{m}^{\delta}$,

$$
\int_{\Omega} \int_{S} I_{x}^{\delta}(\vec{r}, \tilde{s}) \left( (\tilde{s} \cdot \nabla + \mu_{tx}(\tilde{r})) \psi_{xm}(\vec{r}, \tilde{s}) - \mu_{sx}(\tilde{r}) \int_{S} \psi_{xm}(\vec{r}, \tilde{s}') P(\tilde{s} \cdot \tilde{s}') d\omega' \right)
$$

$$
\quad \quad - \frac{1}{2n-1} \eta(\tilde{r}) \int_{S} \psi_{mm}(\vec{r}, \tilde{s}') d\omega' d\vec{r}
$$

$$
+ \int_{\Omega} \int_{S} I_{m}^{\delta}(\vec{r}, \tilde{s}) \left( (\tilde{s} \cdot \nabla + \mu_{tm}(\tilde{r})) \psi_{mm}(\vec{r}, \tilde{s}) - \mu_{sm}(\tilde{r}) \int_{S} \psi_{mm}(\vec{r}, \tilde{s}') P(\tilde{s} \cdot \tilde{s}') d\omega' \right) d\omega d\vec{r}
$$

$$
= \int_{\Omega} \int_{S} \psi_{xm}(\vec{r}, \tilde{s}) \left( \begin{array}{c}
- \frac{\partial \mu_{tx}}{\partial p} \rho^{\delta}(\tilde{r}, \tilde{s}) I_{x}(\tilde{r}) + \frac{\partial \mu_{sx}}{\partial p} \rho^{\delta}(\tilde{r}) \int_{S} I_{x}(\tilde{r}, \tilde{s}') P(\tilde{s} \cdot \tilde{s}') d\omega' \\
+ \frac{\partial \mu_{sm}}{\partial p} \rho^{\delta}(\tilde{r}) \int_{S} I_{m}(\tilde{r}, \tilde{s}') P(\tilde{s} \cdot \tilde{s}') d\omega' + \frac{1}{2n-1} \frac{\partial \eta}{\partial p} \rho^{\delta}(\tilde{r}) \int_{S} I_{x}(\tilde{r}, \tilde{s}') d\omega'
\end{array} \right) d\omega d\vec{r}
$$

(77)
With the objective of obtaining fluence sensitivities, let us define the adjoint variables \( \psi_{xx}(\vec{r}, \hat{s}) \), \( \psi_{mm}(\vec{r}, \hat{s}) \) and \( \psi_{xm}(\vec{r}, \hat{s}) \) such that,

\[
-\hat{s} \cdot \nabla \psi_{xx}(\vec{r}, \hat{s}) + \mu_{tx}(\vec{r})\psi_{xx}(\vec{r}, \hat{s}) - \mu_{sx}(\vec{r}) \int_{S} \psi_{xx}(\vec{r}, \hat{s}') P(\hat{s} \cdot \hat{s}') d\omega' = \delta(\vec{r} - \vec{r}_d) 
\]

(78)

\[
-\hat{s} \cdot \nabla \psi_{mm}(\vec{r}, \hat{s}) + \mu_{tm}(\vec{r})\psi_{mm}(\vec{r}, \hat{s}) - \mu_{sm}(\vec{r}) \int_{S} \psi_{mm}(\vec{r}, \hat{s}') P(\hat{s} \cdot \hat{s}') d\omega' = \delta(\vec{r} - \vec{r}_d) 
\]

(79)

and

\[
-\hat{s} \cdot \nabla \psi_{xm}(\vec{r}, \hat{s}) + \mu_{tx}(\vec{r})\psi_{xm}(\vec{r}, \hat{s}) - \mu_{sx}(\vec{r}) \int_{S} \psi_{xm}(\vec{r}, \hat{s}') P(\hat{s} \cdot \hat{s}') d\omega' \\
= \frac{1}{2^{n-1}\pi} \eta(\vec{r}) \int_{S} \psi_{mm}(\vec{r}, \hat{s}') d\omega' 
\]

(80)

with boundary conditions

\[
\psi_{xx}(\vec{r}, \hat{s}) = \psi_{mm}(\vec{r}, \hat{s}) = \psi_{xm}(\vec{r}, \hat{s}) = 0 \text{ for } \vec{r} \in \partial \Omega, \hat{n} \cdot \hat{s} > 0, 
\]

(81)

The fluence sensitivities can thus be written as

\[
\int_{S} I_{x}^{\delta}(\vec{r}_d, \hat{s}_d) d\omega \equiv \Phi_{x}^{\delta}(\vec{r}_d) = \int_{S} \int_{S} \psi_{xx}(\vec{r}, \hat{s}) \frac{\partial \mu_{sx}}{\partial p} p^{\delta}(\vec{r}, \hat{s}) \int_{S} I_{x}(\vec{r}, \hat{s}') P(\hat{s} \cdot \hat{s}') d\omega' d\omega'd\vec{r} \\
- \int_{S} \int_{S} \psi_{xx}(\vec{r}, \hat{s}) \frac{\partial \mu_{tx}}{\partial p} p^{\delta}(\vec{r}, \hat{s}) I_{x}(\vec{r}) d\omega' d\omega' d\vec{r} 
\]

(82)

\[
\int_{S} I_{m}^{\delta}(\vec{r}_d, \hat{s}_d) d\omega \equiv \Phi_{m}^{\delta}(\vec{r}_d) = - \int_{S} \int_{S} \psi_{xm}(\vec{r}, \hat{s}) \frac{\partial \mu_{mx}}{\partial p} p^{\delta}(\vec{r}, \hat{s}) I_{x}(\vec{r}) d\omega' d\omega' d\vec{r} \\
+ \int_{S} \int_{S} \psi_{xm}(\vec{r}, \hat{s}) \frac{\partial \mu_{sx}}{\partial p} p^{\delta}(\vec{r}, \hat{s}) \int_{S} I_{x}(\vec{r}, \hat{s}') P(\hat{s} \cdot \hat{s}') d\omega' d\omega' d\vec{r} \\
- \int_{S} \int_{S} \psi_{mm}(\vec{r}, \hat{s}) \frac{\partial \mu_{sm}}{\partial p} p^{\delta}(\vec{r}, \hat{s}) I_{m}(\vec{r}) d\omega' d\omega' d\vec{r} \\
+ \psi_{mm}(\vec{r}, \hat{s}) \frac{1}{2^{n-1}\pi} \frac{\partial \eta}{\partial p} p^{\delta}(\vec{r}, \hat{s}) \int_{S} I_{x}(\vec{r}, \hat{s}') d\omega' d\omega' d\vec{r} 
\]

(83)

It is noteworthy, that while \( I_{x}^{\delta} \) depends on just one adjoint \( \psi_{xx} \), \( I_{m}^{\delta} \) depends on \( \psi_{mm} \) as well as the coupling adjoint \( \psi_{xm} \). This reveals the asymmetry in the coupled-RTE for modeling the fluorescence propagation, where the emission radiance \( I_{m} \) is dependent on the excitation radiance \( I_{x} \), but \( I_{x} \) is independent of \( I_{m} \).
Appendix D: Finite element formulation of adjoints and sensitivities

.4. Finite element formulation for adjoints’ computation

Applying Galerkin’s formulation on Eq. (78), (79), and (80) and using boundary conditions Eq. (81), the discrete-domain adjoint equations can be expressed as:

\[ \tilde{A}_x \psi^{(w)}_{xx} = \Delta_{(w)}; \quad \tilde{A}_m \psi^{(w)}_{mm} = \Delta_{(w)}; \quad \tilde{A}_x \psi^{(w)}_{xm} = V \psi^{(w)}_{mm} \] (84)

where

\[ \tilde{A}_q = A_1 \otimes S_1 - A_3 \otimes S_3 + A_8 \otimes S_8(\mu t_q) - A_9 \otimes S_8(\mu s_q). \] (85)

and \( \Delta_{(w)} \) denotes the source vector corresponding to an isotropic point source with unit strength at \( w^{th} \) node.

.5. Finite element formulation for computation of fluence sensitivities

\[ \delta \Phi^{(w)}_{x} = -\int_{\Omega} \int_{S} ([Q \otimes N] \psi^{(w)})^T [Q \otimes N] L_x [N] \delta \mu_{ax f} \]

\[ = -\psi^{(w)}_{xx}^T \left[ \int_{\Omega} \int_{S} ([Q \otimes N])^T [Q \otimes N] L_x [N] \right] \delta \mu_{ax f} = L_{xx}(\psi^{(w)}) \delta \mu_{ax f} \] (86)

\[ \delta \Phi^{(w)}_{m} = -\int_{\Omega} \int_{S} ([Q \otimes N] \psi^{(w)})^T [Q \otimes N] L_m [N] \delta \mu_{ax f} \]

\[ + \frac{\eta}{2\pi} \int_{\Omega} \int_{S} ([Q \otimes N] \psi^{(w)})^T \Phi_x [N] \delta \mu_{ax f} \]

\[ = -\psi^{(w)}_{xm}^T \left[ \int_{\Omega} \int_{S} ([Q \otimes N])^T [Q \otimes N] L_m [N] \right] \delta \mu_{ax f} \]

\[ -\psi^{(w)}_{mm}^T \left[ \int_{\Omega} \int_{S} ([Q \otimes N])^T [N] \Phi_x [N] \right] \delta \mu_{ax f} \]

\[ + \psi^{(w)}_{mm}^T \left[ \frac{\eta}{2\pi} \int_{\Omega} \int_{S} ([Q \otimes N])^T [N] \Phi_x [N] \right] \delta \mu_{ax f} \]

\[ = L_{xm}(\psi^{(w)}) \delta \mu_{ax f} + L_{mm}(\psi^{(w)}) \delta \mu_{ax f} \] (87)

References


