Inverse Problems in Optical Tomography

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Analytic and Geometric Methods in Medical Imaging
Light propagation through tissue used for mammographic investigations (Cutler 1929)
Introduction
Optics in BioPhysics

Light propagation through tissue used for mammographic investigations (Cutler 1929)

Jösis 1977, used optical radiation in the near-infrared band as a method for studying cerebral haemodynamics on the exposed cortex of a cat.

Noninvasive, Infrared Monitoring of Cerebral and Myocardial Oxygen Sufficiency and Circulatory Parameters

Abstract. The relatively good transparency of biological materials in the near infrared region of the spectrum permits sufficient photon transmission through organs in situ for the monitoring of cellular events. Observations by infrared transillumination in the exposed heart and in the brain in cephalo without surgical intervention show that oxygen sufficiency for cytochrome $a,a_3$ function, changes in tissue blood volume, and the average hemoglobin-oxyhemoglobin equilibrium can be recorded effectively and in continuous fashion for research and clinical purposes. The copper atom associated with heme $a_3$ did not respond to anoxia and may be reduced under normoxic conditions, whereas the heme-a copper was at least partially reducible.
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From the attenuation of the light changes in the concentrations of chromophores such as oxygenated (HbO₂) and deoxygenated haemoglobin (HbR), and cytochrome oxidase can be calculated.

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Introduction

Functional Near Infrared Spectroscopy (fNIRS) refers to the application of NIRS to the haemodynamic response to an external stimulus; this is a direct analogy to the term Functional Magnetic Resonance Imaging (fMRI) as distinguished from strustructural or “static” MRI. Thus fNIRS is a dynamic modality (compare fMRI).
**Introduction**

**functional Near Infra Red Spectroscopy**

*Functional Near Infrared Spectroscopy* (fNIRS) refers to the application of NIRS to the haemodynamic *response* to an external stimulus; this is a direct analogy to the term *Functional Magnetic Resonance Imaging* (fMRI) as distinguished from structural or “static” MRI. Thus fNIRS is a *dynamic* modality (compare fMRI).
Introduction

Comparison of Modalities

- OT is faster than fNIRS
- OT gives a *spectral* contrast

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Figure taken from S. Lloyd-Fox, Neuroscience and BioBehavioral Reviews 2009.
Quantitative Near Infra Red Spectroscopy: time-resolved measurements

Quantitative relation between measured intensity changes are confounded by light scattering
Quantitative Near Infra Red Spectroscopy: time-resolved measurements

Quantitative relation between measured intensity changes are confounded by light scattering.

Time of flight information is related to *pathlength* of light in tissue.
Quantitative relation between measured intensity changes are confounded by light scattering
Time of flight information is related to *pathlength* of light in tissue

Optical Tomography
Neonatal imaging

Figure 1. A fibre holder helmet on the head of an infant during an imaging scan.

Figure 2. Ultrasound image of infant with haemorrhage in left ventricle.

Figure 3. Absorption images of infant brain with left-side haemorrhage: a) Coronal and b) sagittal views.

a) 0.005  

b) 0.015 mm\(^{-1}\)
Optical Tomography
Breast imaging
Optical Tomography

Breast imaging

Right breast

Left breast

Subtracted MRI image
Outline

1 Introduction

2 Modelling in Optical Tomography

3 Inverse Problems in Optical Tomography

4 Imaging with CCD arrays

5 PhotoAcoustics

6 Summary

7 Acknowledgements
Medical imaging methods are generally classified as *indirect imaging* methods in the sense that the sort-for image $x$ has to be inferred from data $y$ through the inversion of a forward model

$$y = A(x)$$  \hspace{1cm} (1)$$

In many problems, eq.(1) is a linear process. In optical imaging, in general, it is a non-linear process, although for some problems, a linear approximation is sufficient. In both the linear and non-linear cases, the forward model represents the measurement of a photon distribution $U$, which is the result of a propagator (Green’s operator) that depends on the image $x$ and a source term $q$

$$y = MU = MG(x)q$$  \hspace{1cm} (2)$$

In emission tomography problems, the source $q$ is also part of the inverse problem.
The Radiative Transfer Equation (RTE) is a natural description of light considered as photons. It represents a balance equation where photons in a constant refractive index medium, in the absence of scattering, are propagated along rays \( l := r_0 + l \hat{s} \)

\[
\hat{s} \cdot \nabla U + \mu_a U = 0 \quad \equiv \quad T_{\mu_a} U = 0
\]  

(3)

whose solution

\[
U = U_0 \exp \left[ - \int_l \mu_a (r_0 + l \hat{s}) dl \right]
\]  

(4)

is the basis for the definition of the Ray Transform

\[
g_{\hat{s}}(p) := - \ln \left[ \frac{U}{U_0} \right] = \int_{-\infty}^{\infty} \mu_a (p \hat{s}_\perp + l \hat{s}) dl \quad \equiv \quad g_{\hat{s}} = R_{\hat{s}} \mu_a
\]  

(5)
In the presence of scattering, and with source terms $q$, eq.(3) becomes

$$\left[ T_{\mu_{tr}} - \mu_sS \right] U = q$$

(6)

where $\mu_{tr} = \mu_s + \mu_a$ is the attenuation coefficient and $S$ is the scattering operator, which is local (non propagating).

A series solution for eq.(6) can be formally written as

$$U = \left[ T_{\mu_{tr}}^{-1} + T_{\mu_{tr}}^{-1} \mu_sS T_{\mu_{tr}}^{-1} + \ldots \left( T_{\mu_{tr}}^{-1} \mu_sS \right)^k T_{\mu_{tr}}^{-1} \ldots \right] q$$

(7)

This is the method of successive approximation (Sobolev 1963). The first term may be found from the Ray Transform, giving an alternative equation for the collided flux

$$\left[ T_{\mu_{tr}} - \mu_sS \right] U_{\text{collided}} = \mu_sS \left( T_{\mu_{tr}}^{-1} q \right)_{\text{uncollided}}$$

(8)
Modelling in Optical Tomography

RTE solutions
Modelling in Optical Tomography

RTE solutions
Modelling in Optical Tomography

RTE solutions
Modelling in Optical Tomography

RTE solutions
In the Diffusion Approximation (DA), the radiance is approximated by first order spherical harmonics only ($\hat{\mathbf{s}} \equiv [Y_1,-1, Y_1,0, Y_1,1]$), giving

$$U(r, \hat{s}) \approx \frac{1}{4\pi} \Phi(r) + \frac{3}{4\pi} \hat{s} \cdot J(r) \quad (9)$$

where $\Phi(r)$ and $J(r)$ are the photon density and current defined as

$$\Phi(r) = \int_{S^{n-1}} U(r, \hat{s}) d\hat{s} \quad (10)$$

$$J(r) = \int_{S^{n-1}} \hat{s} U(r, \hat{s}) d\hat{s}. \quad (11)$$

Inserting the approximation (9) into equation (6) results in a second order PDE in the photon density

$$- \nabla \cdot D \nabla \Phi(r) + \mu_a \Phi(r) = q_0(r) \equiv D\Phi = q_0, \quad (12)$$

with $D = \frac{1}{\mu_a + (1-g)\mu_s}$. Equation(12) and its associated frequency and time domain versions, including the Telegraph Equation, are the most commonly used in DOI.
Optical Tomography can be done in the time or frequency domains. If intensity only measurements are used, non-uniqueness theorem indicates that recovery of both absorption and scattering is not possible.

The Green’s operator $G(x)$ in eq. 2 is the inverse of an operator $L(x)$. If the form of $G(x_0)$ is available for some state $x_0$ then we can consider a perturbation in parameters to define a potential operator

$$V(\delta x) = L(x_0 + \delta x) - L(x_0), \quad (13)$$

Under this notation, a series solution for a perturbed state $x_0 + \delta x$ is given by

$$A(x_0 + \delta x) = M [I - G(x_0)V(\delta x)]^{-1} U$$

$$= A(x_0) + M \left[ G(x_0)V(\delta x) + (G(x_0)V(\delta x))^2 + \ldots \right] U, \quad (14)$$

where $I$ is the identity operator. Eq. (14) is a general Born series for forward problems based on PDEs.

More generally, the appropriate transform can be based on considerations of the appropriate likelihood model of the forward model in a Bayesian framework.
In the finite element method (FEM) the field $U$ and parameters $x$ are represented in bases

$$U(r) \simeq \sum_j U_j u_j(r) \quad x(r) \simeq \sum_i x_i b_i(r)$$  \hspace{1cm} (15)$$

The basis $\{u_j\}$ is chosen to reflect the stability and accuracy of the forward model, whereas the basis $\{b_i\}$ is chosen to reflect the expected accuracy of the inverse problem.

The PDE $\mathcal{L}(x)$ is discretised to a matrix $K(x)$ parameterised by $x$ and with matrix elements (in the Galerkin approximation) $\langle u_j, \mathcal{L}u_{j'} \rangle$ and the forward map eq. 2 becomes the matrix equation

$$y = MU = MK^{-1}(x)q$$ \hspace{1cm} (16)$$
By considering the decomposition

\[ K = \sum x_i K^{(i)} \]  \hspace{1cm} (17)

where \( K^{(i)} \) is the discretisation of the potential operator \( \psi_i \) representing the perturbation \( b_i(r) \). From properties of matrix inverses we see

\[ \frac{\partial y}{\partial x_i} = M K^{-1}(x) \frac{\partial K}{\partial x_i} K^{-1}(x) q = \left\langle U^*, K^{(i)} U \right\rangle =: [A']_i \]  \hspace{1cm} (18)

where \( U^* \) is the *adjoint field*
Reconstruction in Optical Tomography

Regularised output least squares

Reconstruction methods follow similar strategies to classical tomography problems such as CT and SPECT, or to related soft-field imaging methods such as EIT and microwave tomography.

Regularised output least squares method → model-fitting problem

\[
\hat{x} = \arg\min_x \left[ E(y, A(x)) = \|y - A(x)\|_e^2 + \Psi(x) \right]
\]

(19)

where \( E(y, A(x)) \) is the sum of a negative log likelihood term for a multivariate Gaussian noise model with covariance \( \Gamma_e \) and a negative log prior term \( \Psi(x) \).

For nonlinear forward operators, or for non-Gaussian prior densities, eq. 19 needs to be solved iteratively through the normal equations

\[
x_{n+1} = x_n + \left( A'(x_n)\Gamma_e^{-1} A'(x_n) + H_n \right)^{-1} \left( A'(x_n)\Gamma_e^{-1}(y - A(x_n)) - \Psi'(x) \right)
\]

(20)

where \( H_n \) is the Hessian of \( \Psi(x_n) \) and \( A', A'^* \) are the forward and adjoint Fréchet derivatives, given by the representation in eq. 18.
Reconstruction Methods
Matrix Free methods

For large scale problems the inversion step in eq. 20 is a limiting step. Instead the Krylov method constructs only a few terms in the series

$$v_{k+1} = \Gamma_n A'* (x_n) \Gamma_e^{-1} A'(x_n) v_k$$

(21)

where \(\{v_k\}\) are the Krylov basis vectors, and \(\Gamma_n = H_n^{-1}\) is a smoothing operator representing the correlation of the prior. Eq. (21) involves forward and back projections and filtering in the data and solution spaces. It can be implemented in a matrix-free framework without the need to construct the memory intensive derivative matrices \(A'\).
Non-linear reconstruction

\[ x \equiv \{ \mu_a, D \} \text{ or } x \equiv \{ \mu_a, \mu'_s \} \text{ and } \]

\[
A'_i \left( \frac{\mu_a}{D^{\delta}} \right) = - \int_{\Omega} \left( \nabla U_i^* \cdot \nabla U_i \right) \cdot \left( \frac{\mu_a}{D^{\delta}} \right) 
\]
Bio-Luminescence tomography (BLT) is the optical analogue of SPECT.
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Spontaneous emission of optical radiation from within tissues from administered lumiphore $y = \mathcal{M}\mathcal{G}(x)q$. 

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*Source Identification Problems in Optical Tomography*

Bioluminescence

- **Bio-Luminescence tomography** (BLT) is the optical analogue of SPECT.
- Spontaneous emission of optical radiation from within tissues from administered lumiphore $y = \mathcal{M}\mathcal{G}(x)q$. 

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S.Arridge (University College London)  
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Diffuse regime $\Rightarrow$ no collimation $\Rightarrow$ non-uniqueness, (cf. EEG).
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- Measurement fields are still *highly correlated*.
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![Fig. 7. Left, a BLT target, and its reconstruction below. Right the internal photon density fields for different wavelengths of emitted light.](image-url)
In Fluorescence Optical Tomography (FOT), fluorophores are promoted by an excitation field, followed by Poisson decay.
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The inverse problem is linear in \( \eta \) in simplest form:

\[ y^{(f)} = A \eta \]
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**Fig. 8.** Left, a fluorescence target, and its reconstruction below. Right the internal emission photon density fields for different excitation sources.
Accuracy of FDOT depends on knowledge of the background.

- reconstruct fluorescence and absorption simultaneously

\[
y^{(e)} = A(x) \quad \text{non-linear}
\]
\[
y^{(f)} = A \eta \quad \text{linear}
\]
Case 1: Reconstruction of 2 fluorochrome rods, one of which is shadowed by an absorbing rod.

Geometry:

Absorption reconstruction:  Fluorochrome reconstruction:

Top view:

Front view:

17 mm
In Fluorescence Lifetime Optical Tomography (FLOT), we use frequency, or time-domain, data and look for both the density and lifetime of the fluorophores.

Lifetime can be affected by molecular environment (compare spin-lattice effect in MRI).

In the frequency domain we represent the parameter of interest as

$$\eta(r, \omega) = \eta_0(r) \frac{1}{1 + i\omega \tau(r)}$$

(22)

where $\eta_0$ is concentration and $\tau$ is lifetime.

Reconstruction strategies

1. Reconstruct complex $\eta$ from complex $y$ and complex $A$; followed by solving (22)
2. Fit directly for $\eta_0, \tau$ from data

Second approach is more general
Fluorescence Lifetime Reconstruction

Phantom results

Fig. 1. (a) Phantom; (b) Surface mesh; (c) Mesh slice showing internal mesh structure.

Fig. 4. Reconstruction results. First, second, and third rows show slices at $y = 40\,\text{mm}$, $50\,\text{mm}$, and $60\,\text{mm}$ respectively. First column shows reconstructed reduced scattering coefficient $\mu_s'$, second column shows the absorption coefficient $\mu_a$, third - the fluorescence efficiency $\eta \mu_a$, and fourth - the lifetime $\tau$. 
Förster Resonant Energy Transfer (FRET) is the radiationless transfer of energy from an excited donor fluorophore to an appropriate acceptor in close proximity and is accompanied by a reduction of the donor fluorescence lifetime and quantum yield.
Exploit well characterised spectral dependence $\varepsilon$ 

$$\mu_a(\lambda_j) = \sum_i \varepsilon_i(\lambda_j) c_i \rightarrow \mu_a(\lambda) = \varepsilon c$$

spectral dependence of scattering (quasi-Mie theory) 

$$\mu'_s(\lambda) = a\lambda^{-b}$$

reparameterise uncoupled inverse problems at each spectral sample into a problem in recovery of 
{$a, b, c_k; k = 1 \ldots K$}. 

 LASER ABSORPTION AND TISSUE PENETRATION

<table>
<thead>
<tr>
<th>PROTEIN</th>
<th>MELANIN</th>
<th>HEMOGLOBIN</th>
<th>WATER</th>
</tr>
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<tbody>
<tr>
<td>SCATTER</td>
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WAVELENGTH (MICRONS)
Fig. 9. Simultaneous reconstruction of chromophore and scattering parameter distributions from frequency domain measurement data at two wavelengths. Top row: target distributions, left to right: chromophore 1, chromophore 2, scattering parameters $a$ and $b$. Middle row: resulting absorption coefficients (left two images), and resulting scattering coefficients at the two wavelengths (right two images). Bottom row: reconstructed distributions for chromophore 1, 2, and scattering parameters $a$ and $b$. 
Combined X-Ray CT and fluorescence tomography system (courtesy of V.Ntziachristos)
Regularisation using structured prior

\[ \Psi(x) = \int_{\Omega} \psi(|w \nabla x|) \, dr \]

Anisotropic Diffusion Denoising

\[ \Psi'(x) \equiv \mathcal{L} x \]
\[ = \nabla \cdot \kappa(x) \nabla x \]
\[ \kappa(x) = w \frac{\psi'(|\nabla x|)}{|\nabla x|} \]
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5 PhotoAcoustics
6 Summary
7 Acknowledgements
A typical rotating-projection geometry.

We consider a localised spot illumination, which may be scanned through a number $n_s$ positions, and a camera detector digitised into $n_x \times n_y$ pixels. The whole geometry may be rotated through $n_\theta$ angles. The resultant total amount of data is potentially $n_{tot} = n_x \times n_y \times n_s \times n_\theta$ in size. In a typical system $n_{tot} \approx 5 \times 10^7$. The reconstructed parameters are represented on $n_v$ voxels, with $n_v = 10^6$ typical.
The reconstruction problem in fDOT may be posed as the inversion

\[ \hat{y} = \frac{y_{obs}^f}{y_{obs}^e} = \frac{1}{y_{calc}^e} A h = \hat{A} h \]  

(23)

where for each excitation source field \( U_i^e \) the forward model is given by

\[ \hat{y}_{i,j} = \left\langle w_j, SPG^f[h U_i^e] \right\rangle_\Sigma = \left\langle G^f[*P^* S w_j], h U_i^e \right\rangle_\Omega \]  

(24)

where \( G^f \) is the Green’s operator at the fluorescence wavelength, \( P \) is the free-space propagation mapping from the physical domain boundary \( \partial \Omega \) to the detector \( \Sigma \), \( S = \text{diag} \left[ 1/y_i^e \right] \) is the rescaling by the excitation data, and \( w_j \) is the area integration function representing the support of pixel \( j \) on \( \Sigma \).

Operator \( P^* \) is the adjoint to \( P \) representing backprojection from the camera to \( \partial \Omega \), and \( G^{f*} \) is the adjoint Green’s operator generating an adjoint internal field from a function defined on \( \partial \Omega \).
Let $\mathbf{z}_{k,i}, k \in [1 \ldots n_z]$ be a basis vector of the transformation of the image resulting from source $i$

$$\tilde{\mathbf{y}}_i = \mathbf{Z}_i \hat{\mathbf{y}}_i \quad (25)$$

To obtain the corresponding row of the compressed Jacobian $\tilde{\mathbf{A}}$, replace $w_j$ with $z_{k,i}$ in (24)

$$\tilde{\mathbf{y}} = \tilde{\mathbf{A}} \mathbf{h} \quad (26)$$

where the number of rows of $\tilde{\mathbf{A}}$ has been reduced to $n_z \times n_s \times n_\theta$. 

Fig. 2: Simulated data from one projection. The images are (a) excitation data $y^e$, (b) fluorescence data $y^f$, (c) normalized data $y^f/y^e$ masked in the region $y_e > 1\% \text{max}(y_e)$ to reduce noise amplification, and (d) normalized masked data compressed with 256 Battle–Lemarie wavelet coefficients—some artifacts can be seen in the background.
Data Compression

Reconstruction Results
Imaging with CCD arrays

Structured Light

- Change from point sources to illumination patterns.
- Use compression basis (e.g. wavelets) in source space
- Digital Micromirror Device (DMD) 1024 × 768 tiltable micromirrors, independently controlled.
Imaging with CCD arrays
Structured Light

Fig. 1. (a) Illumination (right) and detection (left) area; (b) Example of three illumination patterns (first row); Born normalized fluorescence images (second row); compressed images with $K=64$ (third row).

Fig. 2. Section at different depths (top), at step of 1.5 mm, and 3D rendering (bottom) of the fluorochrome concentration: expected (a); reconstructed with 8 views (b).
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PhotoAcoustic Tomography

Outline

- ns laser pulses
- "tissue"
- array of ultrasound detectors
- \( \lambda = 670 \text{nm}, \phi = 6.7 \text{mJ/cm}^2 \)
- 20 mm x 20 mm x 6 mm
  - \( dx = dy = 250 \mu \text{m} \)
Aim: to extract distributions of chromophores from multiwavelength PAT images

How are chromophores and PAT images related?

Tissue physiology, pathology, etc → Distributions of chromophores and scattering → Optical absorption and scattering coefficient distributions → Scattered light transport → Absorbed optical energy distribution → Initial acoustic pressure distribution → Acoustic propagation → Acoustic pressure measurements

[slide courtesy of Ben Cox]
Aim: to extract distributions of chromophores from multiwavelength PAT images

How are chromophores and PAT images related?

[slide courtesy of Ben Cox]
PAT images $\propto$ absorbed energy distribution $h(r, \lambda)$

$h(r, \lambda)$ is related to absorption coefficient $\mu_a(r, \lambda)$ via the fluence, $U(r, \lambda)$:

$$h(r, \lambda) = \mu_a(r, \lambda) U(r, \lambda)$$

$\mu_a$ is related to chromophores concentrations $C^{(k)}$ via specific absorption coefficients $\epsilon_k$:

$$\mu_a(r, \lambda) = \sum_{k=1}^{K} \epsilon_k(\lambda) C^{(k)}(r)$$

Inverse problem is non-linear but well-posed. Solve using diffusion or transport methods
Quantitative PhotoAcoustic Tomography
Diffusion and RTE reconstructions

Left: iterations of QPAT using diffusion approximation. Right: iterations of QPAT using RTE.
Optical Tomography is of interest because of its spectral contrast that relate to functional activity of tissues.

- Low resolution but relatively fast.
- Analysis can be based on Diffusion or Transport.
- Systems based on time-of-flight or frequency modulated.
- Linear and non-linear inverse problems.
- Large data sets can be compressed.
- Quantitative PhotoAcoustics allow high resolution and high contrast.
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