The strengths and weaknesses of the optoacoustic method: is combining light and sound always beneficial?

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What is so good about imaging with light?

(+) Rich intrinsic molecular and functional contrast

(+) Versatility of contrast approaches - nanoparticles, fluorescent proteins, reporter genes, cell-, receptor- targeting, enzyme activation

(+) Low entry and maintenance cost

(+) Simple to use

(++) Versatility of excitation mechanisms - multispectral, life-time, FRET, MSOT

(++) Safe, non-ionizing
Optoacoustic imaging utilizes absorption of ultrashort pulses of light in order to generate ultrasonic responses from biological tissues. Therefore, imaging contrast is optical but spatial resolution is determined by ultrasonic diffraction.
Optoacoustic imaging is a complex inverse problem

An accurate optoacoustic forward model has to accommodate for a number of parameters, e.g. multiple chromophores in tissue, light transport at multiple wavelengths, acoustic wave propagation effects, detectors’ properties

Headache #1: Acoustic inversion
Image formation (1994)

Tissue phantoms

Optoacoustic source equation:

\[ \nabla^2 p(\vec{r}, t) - \frac{1}{v_s^2} \frac{\partial^2 p(\vec{r}, t)}{\partial t^2} = -\rho_\text{m} \beta \frac{\partial^2 T(\vec{r}, t)}{\partial t^2} = \frac{\beta}{C} \frac{\partial H(\vec{r}, t)}{\partial t} \]

Detected pressure variation

(laser absorption)

Spherical Radon (spherical mean) transform

\[ p(\vec{r'}, t) = \frac{\beta v_s}{4\pi C} \frac{\partial}{\partial t} \int_{R=r'} \frac{H_x(\vec{r})}{R} dA \]

RA Kruger et al., Med Phys, 1994, 1995
Y Xu et al, IEEE Trans Med Imag, 2002

In-vivo mouse images (2002)

X Wang et al, Nature Biotech, 2003

In-vivo mouse brain
Tomographic detection using Fabry-Perot resonances

The excitation light is focused

Scanning optical resolution microscopy

Ultrasound linear array detection


Optoacoustic endoscope

Three dimensional tomography

Brecht et al., JBO (2009)

Ultrasound imaging in 1950’s

The "pan scanner“ of Douglas Howry in University of Colorado

First US images of human leg, 1954
Tomographic detection approaches

- Detection approaches

Inversion in 2D

Filtered back-projection

Reconstructed source

Detected pressure variation

\[
\hat{H}_r(\hat{r}) = \frac{C}{4\pi R_2^2} \int \left[ \frac{\hat{p}(\hat{r}', t)}{t} - \frac{\partial \hat{p}(\hat{r}', t)}{\partial t} \right] dA'
\]

Model-based inversion

Forward model (Poisson-type integral)

\[
p(\hat{r}, t) = \frac{\beta v_s}{4\pi C} \frac{\partial}{\partial t} \int_{R-v_t} H_r(\hat{r}) R dA
\]

Discretized model

\[
p = Mf
\]

Inversion (LSQR)

\[
\hat{f}_{sol} = \arg \min \|p - Mf\|_2^2
\]

Inversion (SVD)

\[
\hat{f}_{sol} = M^T p
\]

\[
M^T = (M^T M)^{-1} M^T
\]


Dean Ben et al., IEEE Trans. Med. Imag. 31(10), 2012.
Headache #2:

*Light transport in tissues*

\[ H = \mu_a(r)U(r) \]

Correction using numerical FEM solution

<table>
<thead>
<tr>
<th>Initial optoacoustic image</th>
<th>Light distribution</th>
<th>Normalized image</th>
</tr>
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<tbody>
<tr>
<td><img src="image1.png" alt="Initial image" /></td>
<td><img src="image2.png" alt="Light distribution" /></td>
<td><img src="image3.png" alt="Normalized image" /></td>
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<tr>
<td><img src="image4.png" alt="Iteration 1" /></td>
<td><img src="image5.png" alt="Iteration 3" /></td>
<td><img src="image6.png" alt="Iteration 10" /></td>
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</table>

Light diffusion equation

\[-\nabla D(\vec{r}) \nabla U(\vec{r}) + \mu_a(\vec{r}) U(\vec{r}) = q_0\]

Iterative normalization

\[
\mu_i = \frac{H^i}{U_i + \sigma}
\]


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Blind separation approach

- Our function \( H = \mu_a U \) is a product of two distinct functions

- Taking the log of the signal, we get a sum:
  \( \log[\mu_a] + \log[U] \)

- Can one separate the signal into its components?

Sparse representation

Fluence is a smooth and slow function

\[ \log[U(x, y)] = \sum_{m=1}^{\infty} d_m \psi_m(x, y). \]

Can be fitted by a small number of smooth functions therefore will be represented by polynomials or 2D discrete Fourier basis

Absorption coefficient is quickly varying with strong local properties

\[ \log[\mu_a(x, y)] = \sum_{n=1}^{\infty} c_n \phi_n(x, y), \]

Will be represented by 2D discrete Haar wavelet basis that can successfully represent discontinuities


Finding the coefficients

The problem now becomes a problem of finding a minimal amount of coefficients \(c_n\) and \(d_m\) that can sparsely represent the optoacoustic image:

\[ \log[h(x, y)] = \sum_{n=1}^{N} c_n \phi_n(x, y) + \sum_{m=1}^{M} d_m \psi_m(x, y) \]

Experimental results

Photograph of cylindrical tissue mimicking phantom $\mu_a=0.2\text{cm}^{-1}$, $\mu_s=10\text{cm}^{-1}$. Two insertions have $\mu_a=0.6\text{cm}^{-1}$.

Initial optoacoustic image

Decomposed light fluence

Decomposed optical absorption


Headache #3: Extracting chromophore distribution
Multi-Spectral Optoacoustic Tomography (MSOT)

\[
\mu_a(\lambda) = \alpha_a(\lambda) c_b + \alpha_p(\lambda) c_p \\
\mu_s(\lambda) = \alpha_s(\lambda) c_s + \alpha_p(\lambda) c_p
\]

\[
R_{\text{pinv}} = M S + S^T (S S^T)^{-1}
\]

Inversion
linear regression, PCA, ICA


Headache #4:
Modeling imperfections and image artifacts
Statistical correction for strong acoustic heterogeneities

**Standard discretized back-projection**

\[
H(r_j^i) = \sum_i \left[ p\left(r_i, t_{ij}\right) - t_{ij} \frac{\partial p\left(r_i, t_{ij}\right)}{\partial t} \right]
\]

**Probability that the generated signal arrived via reflection**

\[
P_r^i(t_{ij}) = \int_{A_{ij}} P_r^i(t_{ij} | r') f_E(r') dr' = \int_{A_{ij}} f_E(r') dr' = \frac{P_r^i(t_{ij} | r') A_{ij}}{A}
\]

**Probability for detection of direct propagation**

\[
P_d^i(t_{ij}) = 1 - P_r^i(t_{ij}) = 1 - \frac{A_{ij}}{A}
\]

**Corrected version of the back-projection algorithm**

\[
H(r_j^i) = \sum_i \left( 1 - \frac{A_{ij}}{A} \right) \left[ p\left(r_i, t_{ij}\right) - t_{ij} \frac{\partial p\left(r_i, t_{ij}\right)}{\partial t} \right]
\]


Out-of-plane artifacts

Cylindrically-focused detector

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Buehler et al., in review, 2012
Optoacoustics with linear (array) scanning

US image of a mouse tumor superimposed with distribution of carbon nanoparticles (in color) resolved by optoacoustics

US image of a mouse superimposed with distribution of Hb (in color) resolved by optoacoustics

Courtesy of Visualsonics Inc. De la Zerda et al., Nature Nanotech. 2008

Limited-view tomographic problem

Model-based unregularized
Model-based PLSQR
Model-based TGSVD
Back-projection

Buehler et al., Med. Phys. 2011
k-means clustering algorithms seek to minimize the sum of the distances from each data point to the mean of the cluster it is assigned to.

Examples of in-vivo imaging results
Whole-body video-rate MSOT scanner

Razansky et al., Nature Prot., 6(8), 2011
Buehler et al., Optics Letters, 35(14), 2010

Blood oxygenation in tumors

Herzog et al., Radiology, 2012
Whole-body video-rate MSOT imaging

- Kidney perfusion imaging with ICG
- Buehler et al., Optics Letters, 2010
- Razansky et al., Nature Prot., 6(8), 2011
- Buehler et al., Optics Letters, 35(14), 2010

Pharmacokynetics and metabolism

- CW800 NIR dye (Li-Cor Biosciences)
- 20nmol tail vein injection
- peak absorption at 774nm

- Signal level (normalized)

- Injection

- Time after injection [minutes]

- Left renal pelvis
- Left renal cortex

Taruttis et al., PLoS ONE, 2012
Handheld real-time tomographic imaging


Hand-held real-time 3D scanner

Dean-Ben et al., IEEE Trans. Med. Imag., 2013
Dean-Ben et al., Opt. Exp., 2013

512 simultaneously acquired channels
Real-time tracking of deep human vasculature

Dean-Ben & Razansky, Opt. Exp., 2013

Real-time rendering of 3D images is enabled with graphics processing unit (GPU)-based reconstruction

5D optoacoustic imaging

Volumetric (3D) real-time (4D) spectrally-enriched (5D) tomography

Noninvasive real-time 3D tracking of probe biodistribution in mouse brain following tail vein injection of ICG

Dean-Ben & Razansky, Light Science and Applications, 3, e137 (2014)
5D optoacoustic imaging

Volumetric real-time spectrally enriched tomography

Dean-Ben & Razansky, Light Science and Applications, 3, e137 (2014)