

the **abdus salam** international centre for theoretical physics

SMR 1495 - 16

WINTER COLLEGE ON BIOPHOTONICS: Optical Imaging and Manipulation of Molecules and Cells (10 - 21 February 2003)

Optical Diffusion Tomography

Ulf L. ÖSTERBERG

Thayer School of Engineering Dartmouth College, New Hampshire, 03755-8000 Hanover, USA

These are preliminary lecture notes, intended only for distribution to participants.

OPTICAL DIFFUSION TOMOGRAPHY

Ulf Österberg

Thayer School of Engineering

Trieste, February 10-22, 2003 - p.1/5

1

Acknowledgements

Brian Pogue Dartmouth College
Rick Trebino Georgia Tech
Peter Anderson Risø Natl. Lab.
Imaging Group University College London

OPTICAL



y i 0-23, 2003 – p.2/17

DIFFUSION



TOMOGRAHY



Trieste, February 10-23, 2003 - p.4/17

Tumors viewed optically, macroscopically and microscopically

fibroadenoma: benign





High stromal content Lower blood vessel density invasive ductal carcinoma: malignant



High epithelial content high blood vessel density

http://korb1.sote.hu/KKK/KKK_E.HT

Red and near-infrared are dominated by multiple scattering



Diffusion of photons in tissue

appears as a 'glowing'

Electromagnetic Radiation Attenuation Spectrum in Tissue



Data source: NIST http://physics.nist.gov/PhysRefDa

Spectral Information from Tissue



9

Typcal Values

Breast Tissue	$\lambda[nm]$	$\mu_a[mm^{-1}]$	$\mu_s'[mm^{-1}]$
benign (in vitro)	700-900	0.022-0.75	0.53-1.42
malign (in vitro)	700-900	0.045-0.050	0.89-1.18
benign (in vivo)	800	0.002-0.003	0.72-1.22

References: In vitro data [Peters (1990)], in vivo data [Mitic (1994)]





Attenuation = Absorption + Scattering

11

Tissue Characterization



Tissue is characterized by.

scattering, absorption, refractive index

Scattering is due to,

cell membranes, cell nuclei, capillary walls, hair follicles ...

Absorption is due to,

hemoglobin and melanin (400 nm - 800 nm), molecular vib./rot. states (> $1\mu m$)...

Light propgation in random media

Incident light

> Diffuse reflectance



random media

"Snake" component

Ballistic component

Diffuse transmittance

> Center for Biomedical Optics and New Laser Systems

P. E. Andersen - 4/14/2002



Optics and Fluid Dynamics Department RISØ

General considerations

The *impinging* field excites a *secondary* field radiated from the scatterer

The scatterer is excited as a dipole

Maxwell's equations describing the electro-magnetic wave propagation

 to be solved for the geometry at hand.



Center for Biomedical Optics and New Laser Systems

Maxwell's Equations

$$\nabla \cdot \mathbf{D} = \rho_f \qquad \nabla \cdot \mathbf{B} = 0$$
$$\nabla \times \mathbf{E} = -\frac{\partial \mathbf{B}}{\partial t} \qquad \nabla \times \mathbf{H} = \mathbf{J}_f + \frac{\partial \mathbf{D}}{\partial t}$$

where

$$\mathbf{D} = \epsilon_0 \mathbf{E} + \mathbf{P}$$

$$\mathbf{H} = \frac{\mathbf{B}}{\mu_0} - \mathbf{M}$$

Trieste, February 10-22, 2003 - p.4/5



$\begin{aligned} \mathbf{J}_f &= \sigma \mathbf{E} \\ \mathbf{B} &= \mu \mathbf{H} \\ \mathbf{P} &= \epsilon_0 \chi \mathbf{E} \end{aligned}$

$$\mathbf{D} = \epsilon_0 \mathbf{E} + \mathbf{P} = \epsilon_0 \underbrace{(1+\chi)}_{\epsilon_r} \mathbf{E} = \epsilon_0 \epsilon_r \mathbf{E} = \epsilon \mathbf{E}$$

Constitutive Relations

Trieste, February 10-23, 2003 - p.10/15

E-field — absorption

$$\mathbf{E}_i = \mathbf{E}_0 \exp(i\mathbf{k} \cdot \mathbf{r} - \omega t)$$

$$\mathbf{k} = \frac{\omega}{c} n(\omega) = \frac{\omega}{c} \sqrt{\epsilon_r(\omega)} = \frac{\omega}{c} \sqrt{\epsilon'_r(\omega) + i \cdot \epsilon''_r(\omega)}$$
$$|\mathbf{k}| = k' + i \cdot k'' = \mathbf{n} + i \cdot \mathbf{k}$$
$$\mathbf{E}_t = \mathbf{E}_0 \exp(-\frac{2\pi kz}{\lambda}) \exp(\frac{i \cdot 2\pi nz}{\lambda} - i \cdot \omega t)$$

assuming $\mathbf{k} \cdot \mathbf{r} = kz$.

Trieste, February 10-23, 2003 - p.11/15

Optics and Fluid Dynamics Department

RISØ

General considerations

Four important quantities

Cross sections

- absorption,
- scattering,
- extinction

= scattering + absorption.

Angular dependence

scattering phase function.



Center for Biomedical Optics and New Laser Systems

Lambert - Beer's Law

 $I = I_0 e^{-\alpha z}$ $\alpha = \frac{4\pi k}{\lambda}$

Trieste, February 10-23, 2003 - p.12/15

Scattering Regimes



Assume that d is a characteristic length for the scattering object

Rayleigh

 ${\tt d}\ll \lambda$

Mie

 ${\tt d}pprox\lambda$

Frauenhofer

 ${\tt d}\gg\lambda$

Scattering Regimes

ACTUALLY, *Mie scattering* is valid for all regimes but is only necessary to use in the transition region.

Propagation in matter



- In a homogeneous medium the dipoles cancel each other except in the forward direction.
- Inhomogeneities scatter the light and thus the dipoles do not cancel each other.

Basic Scattering.



- Particle excited by E&M wave vibrates:
 - special frequencies absorbs
 - other frequencies scatters

Absorption and Scattering — same origin?

 $\sigma_t = \sigma_a + \sigma_s$ — extinction cross section

σ_t — Extinction Cross Section

The formula below lets you compute the total cross section for an electromagnetic field interacting with a dielectric medium.

 $\sigma_t = \sigma_a + \sigma_s$

σ_t — Extinction Cross Section

The formula below lets you compute the total cross section for an electromagnetic field interacting with a dielectric medium.

$$\sigma_t = \sigma_a + \sigma_s$$

where

$$\sigma_a = \frac{\int_V k\epsilon_r''(r') |\mathbf{E}(r')|^2 \,\mathrm{d}V'}{|\mathbf{E}_i|^2}$$

Trieste, February 10-23, 2003 - p.17/18

σ_t — Extinction Cross Section

The formula below lets you compute the total cross section for an electromagnetic field interacting with a dielectric medium.



$\epsilon_r(\mathbf{r'})$ — Dielectric Function

BOTH ABSORPTION and SCATTERING DEPEND ON THE DIELECTRIC FUNC-TION $\epsilon_r(\mathbf{r}')$.

Cross Sections



Far-field limit: $R > \frac{d^2}{\lambda}$ $\mathbf{E}_s = \mathbf{f}(\mathbf{o}, \mathbf{i}) \frac{e^{ikR}}{R}$

Differential scattering cross section

$$\sigma_d = \frac{R^2 S_s}{S_i} \Big|_{R \to \infty} = |\mathbf{f}(\mathbf{o}, \mathbf{i})|^2 = \frac{\sigma_t}{4\pi} p(\mathbf{o}, \mathbf{i})$$

 $p(\mathbf{o}, \mathbf{i})$ is the scattering phase function.

Definitions

Power Flux Density — $[W/m^2]$ $\mathbf{S}_i = \frac{1}{2} (\mathbf{E}_i \times \mathbf{H}_i^*) = \frac{|E_i|^2}{2\eta_0} \hat{\mathbf{i}}$ $\mathbf{S}_s = \frac{1}{2} (\mathbf{E}_s \times \mathbf{H}_s^*) = \frac{|E_s|^2}{2\eta_0} \hat{\mathbf{o}}$ Scattering Cross Section — $[m^2]$ $\sigma_s = \int_{4\pi} \sigma_d \, d\omega = \frac{\sigma_t}{4\pi} \int_{4\pi} p(\mathbf{o}, \mathbf{i}) \, d\omega$ Albedo

$$W_0 = \frac{\sigma_s}{\sigma_t}$$

Scattering Phase Function - p(o, i)



Angle θ between incoming and scattered light $\mathbf{o} \cdot \mathbf{i} = \cos \theta$ Normalized — $\int_{4\pi} p(\mathbf{o}, \mathbf{i}) d\omega = 1$

Scattering Phase Function - $p(\theta)$



Anisotropy factor $g = \langle \cos \theta \rangle = \int_{4\pi} p(\theta) \cos \theta \, d\theta$ g = 0 — isotropic scattering g = 1 — forward scattering

<u>Applications...</u> Time scales for light-tissue interaction



Ultrafast Ballistic-Photon Imaging

Since scattering is probabilistic, there will usually be some photons that experience no scattering and pass straight through the medium.

Note that rays that travel straight through a medium take the least time. A tortuous path with many scatterings takes much longer.



So illuminate the medium with an ultrashort pulse and time-gate the transmitted beam, detecting only the photons that arrive earliest (i.e., that pass straight through).
Ultrafast Ballistic-Photon Imaging

The transmitted light will have a fast "ballistic" component of unscattered photons, followed by a slower diffuse scattered component.



Using ultrafast time-gating to detect only the ballistic component will yield an image of absorption vs. transverse position.

Optics and Fluid Dynamics Department

RISØ

Example: Diffusion tomography



Optics and Fluid Dynamics Department

RISØ

Example: Diffusion tomography

Solving the inverse problem

- light in one fiber all others detect,
- then change.



Optics and Fluid Dynamics Department

Transport theory – basic quantities

Specific intensity

- intensity with direction $[Watt/(m^2 sr)]$,
- often referred to as 'intensity'.



Center for Biomedical Optics and New Laser Systems

The equation of transfer

Derivation in *chapter 7-3*

- describes the transport using 'heuristic' arguments



Center for Biomedical Optics and New Laser Systems

Scattering – one direction

From one direction

 $\left|\mathbf{f}\left(\mathbf{s},\mathbf{s}'\right)\right|^{2}I\left(\mathbf{r},\mathbf{s}'\right) = \frac{\sigma_{t}}{4\pi}p\left(\mathbf{s},\mathbf{s}'\right)I\left(\mathbf{r},\mathbf{s}'\right)$



Reduction of incident light

Incident intensity reduced by

 $\rho(\sigma_a + \sigma_s) ds = \rho \sigma_t ds$

note the recurrence of the cross sections.



unit cross section

Scattering – all directions

All directions and all particles in the volume contribute

$$ds \frac{\rho \sigma_{t}}{4\pi} \int_{4\pi} p(\mathbf{s}, \mathbf{s}') I(\mathbf{r}, \mathbf{s}') d\omega'$$



RISØ

Equation of transfer

Adding all contributions from previous slides yields

$$\frac{dI(\mathbf{r},\mathbf{s})}{ds} = -\rho\sigma_t I(\mathbf{r},\mathbf{s}) + \varepsilon(\mathbf{r},\mathbf{s}) + \frac{\rho\sigma_t}{4\pi} \int_{4\pi} p(\mathbf{s},\mathbf{s}') I(\mathbf{r},\mathbf{s}') d\omega'$$

which is the equation of transfer.

P. E. Andersen - 4/14/2002

Reduced and diffuse quantities

To ease computations (without loss of rigor), the intensity is split into two components

- the reduced incident (ballistic) I_{ri}
- the diffuse intensity I_d .

Therefore, we have

$$I(\mathbf{r},\mathbf{s}) = I_{ri}(\mathbf{r},\mathbf{s}) + I_d(\mathbf{r},\mathbf{s})$$

The ballistic component is found from $dI_{ri}(\mathbf{r},\mathbf{s}) = -\rho\sigma_t I_{ri}(\mathbf{r},\mathbf{s}) ds$

Reduced and diffuse quantities

Using the reduced intensity yields a new equation of transfer

$$\frac{dI_{d}(\mathbf{r},\mathbf{s})}{ds} = -\rho\sigma_{t}I_{d}(\mathbf{r},\mathbf{s}) + \varepsilon_{ri}(\mathbf{r},\mathbf{s}) + \varepsilon(\mathbf{r},\mathbf{s})$$

$$+\frac{\rho\sigma_{t}}{4\pi}\int_{4\pi}p(\mathbf{s},\mathbf{s}')I_{d}(\mathbf{r},\mathbf{s}')d\omega'$$

The reduced intensity now acts as a source

$$\varepsilon_{ri}(\mathbf{r},\mathbf{s}) = \frac{\rho\sigma_{t}}{4\pi} \int_{4\pi} p(\mathbf{s},\mathbf{s}') I_{d}(\mathbf{r},\mathbf{s}') d\omega'$$

Center for Biomedical Optics and New Laser Systems

Average intensity

Introduction of new quantity – average intensity U_d

- average of specific intensity in a single point,
- basic quantity in 'diffusion theory'.

$$U_d(\mathbf{r}) = \frac{1}{4\pi} \int_{4\pi} I(\mathbf{r}, \mathbf{s}) d\boldsymbol{\omega} \propto \text{ absorbed power / m}^3$$

Average intensity

Diffuse intensity as a series expansion

 $I_d(\mathbf{r},\mathbf{s}) = \operatorname{constant}(\mathbf{r}) + c_1 \mathbf{F}_d \cdot \mathbf{s} + c_2 \mathbf{F}_d^2 \cdot \mathbf{s}^2 + \dots$

Only one term is retained in the Taylor expansion

$$I_d(\overline{r}, \hat{s}) = U_d(\overline{r}) + c\overline{F}_d \cdot \hat{s}$$

Using a bit of math, yields $c = \frac{3}{4\pi} \implies I_d(\mathbf{r}, \mathbf{s}) = U_d(\mathbf{r}) + \frac{3}{4\pi} \mathbf{F}_d \cdot \mathbf{s}$

P. E. Andersen - 4/14/2002

RISØ

Diffusion equation

Assume

$$p(\mathbf{s},\mathbf{s'}) = p(\theta)$$



Integrate the equation of transfer over 4π , and insert

$$I_{d}(\mathbf{r},\mathbf{s}) = U_{d}(\mathbf{r}) + \frac{3}{4\pi}\mathbf{F}_{d} \cdot \mathbf{s}$$

We then get the diffusion equation

$$\nabla^{2} U_{d}(\mathbf{r}) - \kappa_{d}^{2} U_{d}(\mathbf{r}) = -Q(\mathbf{r})$$

note similarity to wave equation!

Center for Biomedical Optics and New Laser Systems

RISØ

New quantities (averaged over volume)

Transport-reduced scattering cross section [m²]

 $\sigma_s' = \sigma_s (1-g)$

Transport attenuation cross section [m²]

 $\sigma_{tr} = \sigma'_s + \sigma_a$

Diffusion coefficient [m] $D = 1/(3\rho\sigma_{tr})$

Propagation coefficient [m⁻¹]

$$\kappa_d^2 = 3\rho\sigma_a\rho\sigma_{tr}$$

= $3\rho\sigma_a\rho[\sigma_s(1-g)+\sigma_a]$

Asymmetry parameter

 $\overline{\mu} = g$

Scattering coefficient

 $\mu_s = \rho \sigma_s$

Transport-reduced scattering coefficient [m⁻¹] $\mu'_{s} = \mu_{s} (1-g)$

Absorption coefficient [m⁻¹] $\mu_a = \rho \sigma_a$

Source term

The complex source term is then

$$Q(\mathbf{r}) = 3\rho\sigma_{s}\rho\left[\sigma_{s}(1-g) + \sigma_{a}\right]U_{ri}(\mathbf{r})$$
$$+\frac{3}{4\pi}\rho\left[\sigma_{s}(1-g) + \sigma_{a}\right]\int_{4\pi}\varepsilon(\mathbf{r},\mathbf{s})d\omega$$
$$-\frac{3}{4\pi}\nabla\cdot\int_{4\pi}\varepsilon_{ri}(\mathbf{r},\mathbf{s})\mathbf{s}d\omega - \frac{3}{4\pi}\nabla\cdot\int_{4\pi}\varepsilon(\mathbf{r},\mathbf{s})\mathbf{s}d\omega$$

Note the importance of the transport-reduced scattering coefficient

Diffusion approximation

Diffusion approximation to the equation of transfer

- the diffuse intensity undergoes many scattering events, hence, it is uniform in all directions;
 - » note: angular dependence cannot be constant because then there would no power propagation.

Limitation:

- not valid close to surface or sources;
 - » because the light has not undergone many scattering events.

Usually referred to as 'diffusion theory'

Boundary conditions

Boundary condition(s) needed to solve differential equation

Boundary condition

no scattered light reenters the medium;

$$I_d(\mathbf{r},\mathbf{s}) = 0 \text{ for } \mathbf{n} \cdot \mathbf{s} > 0$$

- if the medium extends to infinity, I_d must vanish at infinity.



Center for Biomedical Optics and New Laser Systems

Boundary condition

The boundary condition for diffusion theory

the *total* diffuse intensity entering from the outside should be zero.

$$\int_{2\pi} I_d(\mathbf{r}, \mathbf{s}) \mathbf{s} \cdot \mathbf{n} d\omega = 0, \quad (\text{so that } \mathbf{n} \cdot \mathbf{s} > 0)$$

Approximate boundary condition

• In mathematical terms the boundary condition becomes

$$U_{d}(\mathbf{r}_{0}) - h \frac{\partial}{\partial n} U_{d}(\mathbf{r}_{0}) + \frac{2}{4\pi} \mathbf{n} \cdot \mathbf{Q}_{1}(\mathbf{r}_{0}) = 0$$

$$h = \frac{2}{3\rho\sigma_{tr}}$$
$$\mathbf{Q}_{1}(\mathbf{r}) = \frac{\sigma_{t}}{\sigma_{tr}} \int_{4\pi} I_{ri}(\mathbf{r}, \mathbf{s}') \int_{4\pi} \frac{1}{4\pi} p(\mathbf{s}, \mathbf{s}') \mathbf{s} d\omega d\omega'$$

Diffusion equation

$$\nabla \cdot D(\mathbf{r})U_d - \mu_a U_d = -S(\mathbf{r})$$

Diffusion constant: $D = \frac{1}{3[\mu_a(\mathbf{r}) + \mu'_s(\mathbf{r})]}$ [m]

Source term: $S = S_0 \cdot \delta(\mathbf{r} - \mathbf{r}_0)$ Point source.

Interrogating Tissue with Frequencydomain tomographic Projections





Diffuse light field as source rotates

$$\nabla \cdot D(r) \nabla \Phi(r, \omega) - \left(\mu_a(r) + \frac{i\omega}{c}\right) \Phi(r, \omega) = -S_o(\omega) \delta(r - r_o)$$

Projections from source to each detector

 $\left[\Phi(r,\omega)(\Delta\mu_a)\Gamma(r,\omega) \right] dr$

Inverse Problem - x-rays



 $y_{i} = x_{1}\mu_{1} + x_{2}\mu_{2} + \dots x_{M}\mu_{M} \text{ where}$ $y=\ln(I_{o}/I)$ $y_{i} = \sum x_{ij} \mu_{j}$ $y = A \mu \text{ (matrix equation)}$



A is matrix describing the projection geometry in (x,y) μ is the image of attenuation coefficients to be calculated

Non-linear Inverse Problem reconstruction from projection measurements y_i

$y = \Phi(\mu) + r$

 $\Phi(\mu)$ is the solution to the diffusion equation μ is the image of attenuation coefficients to be calculated r is the residual due to measurement error



Inverse Problem - reconstructionfromprojection

measurements

Minimize: $\chi^2 = (y - \Phi(\mu))^T (y - \Phi(\mu)) + F(\mu)$

taking derivative of χ^2 and expand in a Taylor's series about $(\chi^2)' = 0$,

$$0 = \Phi^{/T} (y - \Phi) + \Delta \mu \Phi^{/T} \Phi^{/} + \dots$$
$$\Delta \mu = (\Phi^{/T} \Phi)^{-1} \Phi^{/T} y$$

so solve iteratively where,

$$\mu^{k+1} = \mu^k + \Delta \mu^k$$

Model-based Image Reconstruction



Simulated measurements diffusion theory finite element to measurements

3-D Model-based Image Reconstruction



Finite element mesh generation

MRI scan

FEM mesh

Absorption coeff. map





Frequency-domain detection system





Figure 3.1: (a) Phantom geometry for the off-centered target case. The centered target case is identical except that the center of the internal heterogeneity is concentric with the background region. (b) Photograph of the phantom system used in this study. On the top of the phantom, a target suspension system has been incorporated into a rotatable stage (scaled precisely with less than 0.5° error) which provided accurate manipulations during the data collection procedures.

Experimental Setup



Variable diameter fiber optic array



10 cm diameter

5 cm diameter

Imaging with Intralipid coupling or with direct Contact between tissue and fibers

Direct contact between 65 mm phantom and optical fibers





Imaging with Intralipid coupling between phantom and optical fibers



breast no object



breast & object homogenous 1st estimate





breast & object using homogenous breast to normalize the data
Maging different diameter sized breast phantoms

91 mm 72 mm Jer, a r. bras b 82 mm 65 mm

Note: Image quality is NOT limited by the diffusion approximation for low contrast objects. Noise limited.

System Calibration in solid phantoms

Accuracy testing versus position within phantom



Simultaneous reconstruction of absorption and scattering objects



McBride et al., Optics Letters 26(11), 822 (2001).

Spectral imaging of Absorption Coefficient for water using .5% Intralipid



Clinical System





translation stages

fiber optics

bed and console

Computer

Controllers

Laser Sources

Frequency Generators



Patient Interface



Photographs of detection array





Photographs of detection array

Top view of first round plate mounted on rotary stage

16 PMTs



16 electrical mixers



New Fiber Array - 3 simultaneous layers



Breast position in imaging array



Breast pendent in NIR array



Plane 1



Plane 2



Plane 3

Reconstruction : Statistical Image Analysis



Absorption

Scattering

Bias

Standard Deviation



*based upon Wray *et. al.* (1988) Biochemica Biophysica Acta 933, pp184-192 assuming 156 mg/L hemoglobin content

Experimental demonstration of imaging hemoglobin concentration and oxygen saturation



Normal Breast Changes with Age





from <u>Breast Imaging</u> by D. Kopans. Lippencott-Raven Publ

Near-Infrared Imaging provides a means to image hemoglobin and angiogenesis.



Patient 1044 - normal breast



Patient 5 - 3.5 cm fibroadenoma





Pogue et al., Radiology, 218(1) p.261 (2001)

Patient 6 - 0.8 cm invasive ductal carcinoma



Pogue et al., Radiology, 218(1) (Jan 2001).

Where does NIR fit within medical imaging ?

