Diffuse Optical Spectroscopy: Analysis of Biophotonics Signals

2013 Short Course in Computational Biophotonics
Albert Cerussi
Day 4/Lecture #2
Disclosures

- No financial conflicts to disclose
Learning Objectives

- **Control of optical pathlength \((s)\)**
  - Wavelength \((\lambda)\), Space \((\rho, z)\), Time \((t)\)/Frequency \((f)\)

- **Controlling path length enables optical property measurement**
  - Absorption Coefficient \((\mu_a)\)
  - Reduced Scattering Coefficient \((\mu_s')\)

- **Quantify molecular absorbers**
  - Use of models to optimize information
Why do we care about modeling light transport in tissues?

Some examples from this morning
Why Modeling Matters

- Optical property change from pressor drug
- Absorption and/or scattering?
- Brain and/or skull/skin?

Why Modeling Matters

- Long term R(λ) changes related to tumor pathology

- How do we know changes are true tumor metabolism?

Tissue Optical Index (TOI) = (HHb x H₂O)/lipid

Why Modeling Matters

• Clinical outcome tied to optical measurement (threshold)

• Can better modeling improve this?

M. Heringlake et al., Anesthesiology V 114 (2011).
Why Modeling Matters

ANCIENT SCRIPT ➔ MODERN SCRIPT

BIOPHYSICAL STRUCTURE & FUNCTION ➔ OPTICAL MEASUREMENTS
What then is our goal?
What is Our Goal?

Quantitative absorption/scattering NIR spectroscopy in turbid tissues

purely absorbing

with scatter

Beer-Lambert Law

$$\log\left(\frac{I_0}{I}\right) = \varepsilon c s$$

$\varepsilon = \text{molar extinction}$

$c = \text{absorber concentration}$

$s = \text{photon path length (or L)}$
What is Our Goal

Need to know & control photon path length (s)  
To get accurate molecular concentrations and states...

Cerussi A, et al. J. Biomed Optics 10(5); 2005
The Key: Control Photon Pathlength

• Noted in the Previous lecture
  – Control of pathlength key to diffuse optical imaging and spectroscopy
Some Scales to Remember

<table>
<thead>
<tr>
<th></th>
<th>SCATTERING</th>
<th>ABSORPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SPACE</strong></td>
<td>$l_{sc} \sim 30 , \mu m$</td>
<td>$l_{abs} \sim 100 , mm$</td>
</tr>
<tr>
<td><strong>TIME</strong></td>
<td>$\tau_{sc} \sim 0.1 , ps$</td>
<td>$\tau_{abs} \sim 0.2 , ns$</td>
</tr>
</tbody>
</table>
• Diffuse Optical Spectroscopy for deep tissue
  – Depths > 5mm

• Clinical Examples (non-invasive)
  – Brain
  – Breast Tumors
  – Muscle
Models to consider …

- Transport theory
- Analytic (e.g., diffusion)
- Numerical (NIRFAST, COMSOL)
- Monte Carlo (VP, MCML)
CW Intensity Characteristics
CW Light Distribution

"HOMOGENEOUS" TISSUE

\[ I_0 \]

\[
\mu_a = 0.01 \text{ mm}^{-1} \\
\mu_s' = 1.0 \text{ mm}^{-1}
\]
CW Light Distribution

Diffusion Theory (INF)

\[ \Phi(\mu_a, \mu_s', r) \sim \frac{1}{4\pi Dr} e^{-r\mu_{eff}} \]

\[ D = \frac{1}{3(\mu_a + \mu_s')} \]  
Optical Diffusion Coefficient (mm)

\[ \mu_{eff} = \sqrt{3\mu_a(\mu_a + \mu_s')} \]  
Effective Attenuation Coefficient (mm⁻¹)

\[ \delta = \sqrt{\frac{D}{\mu_a}} \]  
Optical Penetration Depth (mm)
CW Light Distribution

\[ R(\rho) \]

\[ \mu_a = 0.01 \text{ mm}^{-1} \]

\[ \mu_s' = 1.0 \text{ mm}^{-1} \]

https://virtualphotonics.codeplex.com/releases
CW Light Distribution

https://virtualphotonics.codeplex.com/releases
CW Light Distribution

https://virtualphotonics.codeplex.com/releases

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Question:

• What wavelengths should we use for deep tissue penetration?
Modeling Light Penetration

- Consider homogeneous “brain-like” media:

<table>
<thead>
<tr>
<th>λ (nm)</th>
<th>μₐ (mm⁻¹)</th>
<th>μₛ’ (mm⁻¹)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>450</td>
<td>1.38</td>
<td>1.56</td>
<td>1.4</td>
</tr>
<tr>
<td>750</td>
<td>0.017</td>
<td>0.93</td>
<td>1.4</td>
</tr>
<tr>
<td>1200</td>
<td>0.25</td>
<td>.58</td>
<td>1.4</td>
</tr>
</tbody>
</table>
Modeling Light Penetration

Fluence of $\rho$ and $z \sim 450\text{nm}$

LOG $\Phi$

$z$ [mm]

$\rho$ [mm]
Modeling Light Penetration

Fluence of $\rho$ and $z$ ~ 450nm

Fluence range: 10 mw in $10^{-5}$ atto-W to $10^{-2}$ zepto-W to 10 yocto-W.

LOG $\Phi$ scale: -60 to 0.

Parameters:
- $\rho$ [mm]
- $z$ [mm]
Modeling Light Penetration

Fluence of $\rho$ and $z \sim 450\text{nm}$
Modeling Light Penetration

Fluence of $\rho$ and $z \sim 750\text{nm}$

$\rho$ [mm]  
-20  0  20

$z$ [mm]  
-6  -4  -2  0  2  10  20  30

LOG $\Phi$

-6  -4  -2  0
Modeling Light Penetration

Fluence of $\rho$ and $z \sim 1200\text{nm}$
Modeling Broadband Light Penetration

Question:

• How much will different NIR wavelengths penetrate tissues?
Modeling Broadband Light Penetration

Optical Penetration Depth from Diffusion theory:

$$\delta = \sqrt{\frac{D}{\mu_a}}$$

= 4.35 ± 0.68 mm
Modeling Broadband Light Penetration

Fluence of $\rho$ and $z$ @650 nm

<table>
<thead>
<tr>
<th>$\lambda$ (nm)</th>
<th>$\delta$ (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>650</td>
<td>3.5</td>
</tr>
<tr>
<td>700</td>
<td>4.97</td>
</tr>
<tr>
<td>750</td>
<td>4.76</td>
</tr>
<tr>
<td>800</td>
<td>4.99</td>
</tr>
<tr>
<td>850</td>
<td>4.56</td>
</tr>
<tr>
<td>900</td>
<td>4.3</td>
</tr>
<tr>
<td>950</td>
<td>3.37</td>
</tr>
<tr>
<td>1000</td>
<td>3.3</td>
</tr>
</tbody>
</table>
Optical Property Recovery (CW)

Question:

• How can we use this information to recover the optical properties of the tissue?
Optical Property Recovery (CW)

Diffusion Theory (INF)

\[ \Phi(\mu_a, \mu_s', r) \sim \frac{1}{4\pi D r} e^{-r \mu_{eff}} \]

\[ D = \frac{1}{3(\mu_a + \mu_s')} \]

\[ \mu_{eff} = \sqrt{3\mu_a(\mu_a + \mu_s')} \]
Optical Property Recovery (CW)

\[ \mu_{eff} = 0.174 \text{ mm}^{-1} \]

\[ \Phi(\mu_a, \mu'_s, r) \sim \frac{1}{4\pi Dr} e^{-r \mu_{eff}} \]

\[ D = \frac{1}{3(\mu_a + \mu'_s)} \]

\[ \mu_{eff} = \sqrt{3\mu_a(\mu_a + \mu'_s)} \]

Diffusion Theory (INF)

- \( \Phi(\mu_a, \mu'_s, r) \) is the radiative flux at a distance \( r \) from the source.
- \( D \) is the diffusion coefficient.
- \( \mu_{eff} \) is the effective attenuation coefficient.

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Spatially-Resolved Not always applicable

SCATTER DOMINATED
Optical Property Recovery

Question:

- Can we improve measurement sensitivity to the tissue optical properties?
  - Want to separate absorption from scattering in thick tissues (>5mm)
Optical Property Measurement: Time Domain
Time Domain: How it Works

Narrow FWHM Pulse (ps): Hi repetition rate (MHz) broadens (ns)
Time Domain: How it Works

Real World:
Detector responses broaden

Convolution of IRF and Tissue Response
\[ \phi(r,t) = cQ \frac{\exp[-r^2/(4cDt)]}{(4\pi cDt)^{3/2}} \exp(-\mu_a ct). \]

- Diffusion Theory (Inf Med)
Time Domain (Diffusion Theory)

\[
\rho = 20 \text{ mm} \\
\mu_a = 0.01 \text{ mm}^{-1} \\
\mu_s' = 1.0 \text{ mm}^{-1}
\]
Time Domain (Diffusion Theory)

\[ \rho = 20 \text{ mm} \]
\[ \mu_a = 0.01 \text{ mm}^{-1} \]
\[ \mu_s' = 1.0 \text{ mm}^{-1} \]
Time Domain (Diffusion Theory)

\[ L \approx 85 \text{ mm} \]
Time Domain (Diffusion Theory)
Question:

- My data never looks like that...
Time Domain Models: Monte Carlo

\[ \rho = 20 \text{ mm} \]
\[ \mu_a = 0.01 \text{ mm}^{-1} \]
\[ \mu_s' = 1.0 \text{ mm}^{-1} \]

https://virtualphotonics.codeplex.com/releases/view/108048
Question:

- How can we exploit temporal dependence to measure optical properties?
Optical Property Measurement (TD)

Sample and discriminate short/long paths

$t_1 = 200 \text{ ps}$
$t_2 = 600 \text{ ps}$
$t_4 = 1400 \text{ ps}$
Optical Property Measurement (TD)

\[ \rho = 20 \text{ mm} \]
Optical Property Measurement (TD)

\[ \rho = 20 \text{ mm} \]
Shortcut: Theory of Moments

- I hate fitting ...
- Theory of moments
  - Analytical
  - Easy to include IRF

\[ m_k = \langle t^k \rangle = \frac{\int_{-\infty}^{+\infty} t^k g(t) dt}{\int_{-\infty}^{+\infty} g(t) dt} \]

\[ V = \langle t^2 \rangle - \langle t \rangle^2 \]

\[ \mu_a = \frac{m_1^3}{2\nu V (m_1^2 + V)} \]

\[ \mu_s' = \frac{2m_1 \nu (m_1^2 + V)}{3\rho^2 V} \]

Liebert et al., Appl Opt 42(28) 2003.
Question:

- How can we exploit temporal dependence to control penetration depth?
Time Domain: Time Gating

PATH LENGTH ~ 15 - 1387 mm

COUNTS (LOG)

TIME (ns)
Time Domain: Time Gating

Layered Phantom Measurement (830 nm)

ρ = 5 mm

Mainly Top Layer

Mainly Bottom Layer
Optical Property Measurement: Frequency Domain
Frequency-Domain Measurements

SOURCE

TISSUE

DETECTED

stuff happens

$\phi \sim \text{time}$

$M \sim \text{AC/DC}$
Frequency-Domain Measurements

Frequency Sweeps (50 to 500 MHz)
Calibration of IRF: No Convolution

**Graphs:**

- **Amplitude (au):**
  - Y-axis: \(10^{-3}\) to 7
  - X-axis: 50 to 500 MHz

- **Phase (Deg):**
  - Y-axis: \(10^{-7}\) to 10
  - X-axis: 0 to 500 MHz

**Legend:**

- **FREQUENCY (MHz):**
- **AMPLITUDE**
- **PHASE** (Deg)
• Time & Frequency Domain are Fourier equivalents
• Experimental considerations dictate choice
Frequency Domain Light Propagation (SI)

\[ A_{si}(\rho, \omega) = \frac{S(\omega)}{4\pi vD} \sqrt{\xi^2 + \eta^2} \quad \text{Photon density amplitude} \]

\[ \Theta_{si}(\rho, \omega) = k_{\text{imag}}(\omega) r_0 - \arctan \left( \frac{\eta}{\xi} \right) + \phi_0(\omega) \quad \text{Photon density phase} \]

where ...

\[ \xi = \frac{1}{r_o} \exp[-k_{\text{real}}(\omega)r_0] - \cos[k_{\text{imag}}(\omega)(r_{0b} - r_0)] \frac{1}{r_{0b}} \exp[-k_{\text{real}}(\omega)r_{0b}] \]

\[ \eta = \sin[k_{\text{imag}}(\omega)(r_{0b} - r_0)] \frac{1}{r_{0b}} \exp[-k_{\text{real}}(\omega)r_{0b}] \]

Frequency Domain: Diffusion Theory

\[ \rho = 20 \text{ mm} \]
\[ \mu_a = 0.01 \text{ mm}^{-1} \]
\[ \mu_s' = 1.0 \text{ mm}^{-1} \]
Question:

- My data never looks like that ...
Frequency Domain Models: Monte Carlo

Graph 1: PHASE (deg) vs. FREQUENCY (GHz)
- 2M
- 10M
- 24M
- 50M

Graph 2: PHASE (deg) vs. FREQUENCY (GHz)
- 2M
- 10M
- 24M
- 50M
Optical Property Recovery

Question:

• Can we improve measurement sensitivity to the tissue optical properties?
  – Want to separate absorption from scattering in thick tissues (>5mm)
Frequency Domain: Evolution in $f$
Frequency Domain: Evolution in Rho

FDM MULTI-R PLOTS: LAMBDA = 850nm  FREQ =204MHz

- PHASE (deg)
- DISTANCE (mm)

- LN(A) (au)
- DISTANCE (mm)

- ΔPHASE (deg.)
- DISTANCE (mm)

57.75 MHz
200 MHz

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Frequency Domain: Evolution in Rho

![Graphs showing FLUENCE (RHO = 0) with Z (mm) on the x-axis and FLUENCE (au) on the y-axis. The graphs display exponential decay curves with varying colors.]
Question:

- How can we exploit frequency dependence to measure optical properties?
Optical Property Measurement: Frequency Domain
Frequency Domain: Optical Properties

\[ \rho = 20 \text{ mm} \]

\[ MOD = \frac{AC(f)}{DC(f = 0)} \]
Frequency Domain: Optical Properties

\[ \rho = 20 \text{ mm} \]

\[ \text{MOD} = \frac{AC(f)}{DC(f = 0)} \]
Frequency Domain: Optical Properties

\[ \rho = 20 \text{ mm} \]

\[ MOD = \frac{AC(f)}{DC(f = 0)} \]
Frequency Domain: Multi R, Single S

\[ \mu_a = \frac{2\pi f}{2\nu} \left( \frac{S_\varphi}{S_{AC}} - \frac{S_{AC}}{S_\varphi} \right) \]

\[ \mu_s' = \frac{S_{AC}^2 - S_\varphi^2}{3\mu_a} \]

S. Fantini et al., Optical Engineering 34 (1996)
Optical Property Measurement: Imaging and Spectroscopy
Cant We all Just Get Along

• CW Spectroscopy:
  – Many wavelengths
  – Hard to quantify at depth with single $\rho$

• FD/TD Spectroscopy
  – Easy to quantify at depth with single $\rho$
  – Tougher for many wavelengths
Harmony of $\lambda$ and $f$ ...

- modulation
- 401 frequency sweep
- 50-500 MHz (~ 200 ms)

Graph:
- TIME (ns) on the x-axis
- INTENSITY on the y-axis
- 100 MHz
- ~ .5 ms
Harmony of $\lambda$ and $f$ ...
Harmony of $\lambda$ and $f$ ...

- modulation
- diffusion model
- global fit
Harmony of $\lambda$ and $f$ ...

- modulation
  - diffusion model
    - global fit
      - optical properties
Harmony of $\lambda$ and $f$ ...

- Modulation
- Diffusion model
- Absorption & scattering
Harmony of $\lambda$ and $f$ ...

modulation

diffusion model

absorption & scattering

power law

scattering = $SA \times \lambda^{-SP}$
Harmony of $\lambda$ and $f$ ...

- modulation
- diffusion model
- absorption & scattering
- broadband reflectance
Harmony of $\lambda$ and $f$ ...

- modulation
  - diffusion model
  - absorption & scattering
    - broadband reflectance
  - scale w FDPM

**Graphs:**
- Absorption vs. Wavelength
  - Wavelength (nm): 650, 700, 750, 800, 850, 900, 950, 1000
  - Absorption (nm$^{-1}$): 0.000, 0.003, 0.006, 0.009, 0.012

- Reflectance vs. Wavelength
  - Wavelength (nm): 650, 700, 750, 800, 850, 900, 950, 1000
  - Reflectance (a.u.): 2, 4, 6, 8, 10
modulation

diffusion model

absorption & scattering

broadband reflectance

scale w FDPM
Harmony of λ and f ...

modulation

diffusion model

absorption & scattering

broadband reflectance

FDPM

BROADBAND

FOUR COMPONENT FIT

ABSORPTION (mm⁻¹)

WAVELENGTH (nm)
Harmony of $\lambda$ and $f$ ...

modulation

- diffusion model
- absorption & scattering
- broadband reflectance

- chromophore fit

![Graph showing absorbance and wavelength relationship with points and line segments labeled FDPM, broadband, and four component fit.](image)
Harmony of $\lambda$ and $f$ ... and $\rho$

Two-layer phantom spectrum at different Source-Detector separations
Harmony of $\lambda$ and $f$ ... and $\rho$

A. Li et al, Applied Optics 46(21) 2007
Harmony of $\lambda$ and $f \ldots$ and $\rho$

3D TUMOR PHANTOM (SINGLE $\lambda$)

RECONSTRUCTION WITH NIRFAST

2cm TARGET @ 11mm depth

http://www.dartmouth.edu/~nir/nirfast/

Learning Objectives

• **Control of optical pathlength** ($s$)
  - Wavelength ($\lambda$), Space ($\rho, z$), Time ($t$)/Frequency ($f$)

• **Controlling path length enables optical property measurement**
  - Absorption Coefficient ($\mu_a$)
  - Reduced Scattering Coefficient ($\mu_s'$)

• **Quantify molecular absorbers**
  - Use of models to optimize information
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http://www.bli.uci.edu

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