Time domain diffuse optical imaging and spectroscopy for biomedical diagnostics

Rinaldo Cubeddu

SIF, Pisa, September 22-26, 2014
Introduction:
Time-Resolved Diffuse Optical Spectroscopy

- Time – Resolved Diffusion Equation for Homogeneous Media

\[ R(\rho,t) = \Phi(\rho,\mu'_s,t)\exp(-\mu_a vt) \]

Reflectance and Transmittance geometry

\[ \mu'_s, \mu_a \]
**Spectroscopy Clinical Set-up**

- Fully automated set-up
- Time resolution: 300 ps FWHM

---

![Diagram of spectroscopy clinical set-up](image-url)
Spectral analysis

\[ \mu_a(\lambda) = \sum_i c_i \varepsilon_i(\lambda) \]

\[ \mu_s = a \left( \frac{\lambda}{\lambda_0} \right)^b \]

IL (solid fraction) = 10

- a (cm\(^{-1}\)) = 4.69
- b = 1.08
- \( r_s (\mu\text{m}) \) = 0.24
- g = 0.75

Absorption coefficient (cm\(^{-1}\))

Wavelength (nm)

HbO\(_2\) [43 uM]
Hb [22 uM]
Water [34%]
Lipid [53%]
Breast absorption and scattering spectra

<table>
<thead>
<tr>
<th>T</th>
<th>PT-40</th>
<th>DC-29</th>
<th>EL-34</th>
<th>LT-23</th>
<th>FM-50</th>
<th>KE-31</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>9.3</td>
<td>8.9</td>
<td>6.8</td>
<td>11.7</td>
<td>11.0</td>
<td>9.6</td>
</tr>
<tr>
<td>b</td>
<td>2.0</td>
<td>1.4</td>
<td>2.0</td>
<td>0.7</td>
<td>0.7</td>
<td>0.7</td>
</tr>
</tbody>
</table>

Water: 62% 32% 53% 23% 16% 12%
Lipids: 16% 37% 20% 68% 77% 68%
tHb/\(\mu\)M: 13.5 21 8 18 15 15
SO\(_2\): 55% 77% 43% 77% 68% 79%

<table>
<thead>
<tr>
<th>T</th>
<th>PT-40</th>
<th>DC-29</th>
<th>EL-34</th>
<th>LT-23</th>
<th>FM-50</th>
<th>KE-31</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>9.3</td>
<td>8.9</td>
<td>6.8</td>
<td>11.7</td>
<td>11.0</td>
<td>9.6</td>
</tr>
<tr>
<td>b</td>
<td>2.0</td>
<td>1.4</td>
<td>2.0</td>
<td>0.7</td>
<td>0.7</td>
<td>0.7</td>
</tr>
</tbody>
</table>

Absorption (cm\(^{-1}\))

Reduced scattering (cm\(^{-1}\))
EXAMPLE 1: Non-invasive Quantification of Collagen in the Breast

BACKGROUND
- non-invasive quantification of collagen could lead to dedicated diagnostic procedures and higher survival

BASIC CHARACTERIZATION
- measurement absorption spectrum of collagen in the 600-1100 nm range

→ Explore Spectral Region beyond 1100 nm by Time-Domain Diffuse Spectroscopy

IN VIVO MEASUREMENT
- first absorption spectra of the breast in the 600-1100 nm range
# Breast tissue composition and scattering parameters

<table>
<thead>
<tr>
<th>Subject ID</th>
<th>tHb (µM)</th>
<th>SO₂ (%)</th>
<th>Lipid (mg/cm³)</th>
<th>Water (mg/cm³)</th>
<th>Collagen (mg/cm³)</th>
<th>a (cm⁻¹)</th>
<th>b</th>
<th>Tabàr classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>18.6</td>
<td>75</td>
<td>0</td>
<td>736</td>
<td>93</td>
<td>15.1</td>
<td>1.29</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>24.3</td>
<td>80</td>
<td>173</td>
<td>615</td>
<td>107</td>
<td>17.6</td>
<td>1.16</td>
<td>IV: Fibrous</td>
</tr>
<tr>
<td>3</td>
<td>24.1</td>
<td>84</td>
<td>428</td>
<td>302</td>
<td>60</td>
<td>16.1</td>
<td>0.71</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>15.0</td>
<td>58</td>
<td>528</td>
<td>298</td>
<td>48</td>
<td>20.7</td>
<td>0.93</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>18.5</td>
<td>84</td>
<td>621</td>
<td>200</td>
<td>89</td>
<td>18.1</td>
<td>0.86</td>
<td>I: Mixed</td>
</tr>
<tr>
<td>6</td>
<td>19.2</td>
<td>82</td>
<td>467</td>
<td>253</td>
<td>63</td>
<td>14.6</td>
<td>0.69</td>
<td>I: Mixed</td>
</tr>
<tr>
<td>7</td>
<td>16.3</td>
<td>42</td>
<td>500</td>
<td>237</td>
<td>51</td>
<td>17.8</td>
<td>0.75</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>12.8</td>
<td>83</td>
<td>728</td>
<td>99</td>
<td>34</td>
<td>12.4</td>
<td>0.52</td>
<td>II: Adipose</td>
</tr>
<tr>
<td>9</td>
<td>11.2</td>
<td>71</td>
<td>567</td>
<td>87</td>
<td>54</td>
<td>12.4</td>
<td>0.62</td>
<td>II: Adipose</td>
</tr>
<tr>
<td>10</td>
<td>10.0</td>
<td>71</td>
<td>737</td>
<td>111</td>
<td>24</td>
<td>13.4</td>
<td>0.69</td>
<td>III: Adipose with ducts</td>
</tr>
</tbody>
</table>

**Density**
- Water: 1.00 g/cm³
- Lipid: 0.91 g/cm³
- Collagen: 1.30 g/cm³

**System Development: Experimental Set-up**

- **Fiber laser**
  - Sync
  - Fully automated

- **Time-gated InGaAs/InP Single Photon Avalanche Diode**, Dipartimento di Elettronica e Informazione, Politecnico di Milano
  - 450-1750 nm
  - 40 MHz

- **TCSPC**

- **SPAD InGaAs/InP**
  - $\phi=25 \mu m$
  - $V_e (V)$
  - $T (K)$

- **Adjustable slit**
  - L1, L2, L3

- **ND**
  - $\phi=100 \mu m$

- **FC**

- **Sample**

- **NIR spectrometer**

Specifications:
- Sensor size: 25 $\mu m$
- Temporal response: ~100 ps
- Efficiency > 20% over the range 800-1700 nm
Spectroscopy Beyond 1100 nm: Validation on Lipid Sample (pig fat)

- First characterization of lipids up to 1700 nm

Data fitted with Monte Carlo simulations

Bargiglia et al., Appl. Spectrosc. 66, 2012.
Collagen Type I

Dried bone
Spectroscopy Beyond 1100 nm

Arm

Breast
- Optical Mammography
- NIRS Functional Imaging
Absorption of tissue constituents

- HbO2
- Hb
- Lipid
- Water
- Collagen

Absorption (cm^-1)

Wavelength (nm)
**Time domain multi-wavelength optical mammograph**

**Laser driver:** “Sepia” (PicoQuant)
- Repetition rate: 20 MHz
- Pulse duration: 150-400 ps
- Max incident power: 1.1 – 4.7 mW

**Photomultipliers** (Hamamatsu, KK):
- **RED:** R5900U-01-L16, 150 ps TTS, \( \lambda < 850 \text{ nm} \)
- **NIR:** H7422P-60, 450 ps TTS, \( \lambda < 1100 \text{ nm} \)
Time domain multi-wavelength optical mammograph

- Fiber bundle
- Laser fibers
POLIMI-#043 (CC): Tumor (L) + Cysts (R)

Age: 41 y
Thickness = 4.7/4.6 cm

Late gated intensity

Scattering

cysts

tumor
POLIMI2-#013 (L_CC): Phylloid Tumor

Lesion size = 45 mm

Tissue composition

Late gated intensity
POLIMI2-#099 (L_CC): Invasive Ductal Carcinoma

Lesion size = 25 mm

### Late gated intensity

<table>
<thead>
<tr>
<th>X-ray</th>
<th>Ref</th>
<th>635</th>
<th>685</th>
<th>785</th>
</tr>
</thead>
</table>

### Tissue composition

<table>
<thead>
<tr>
<th>Hb</th>
<th>HbO₂</th>
<th>tHb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipid</td>
<td>Water</td>
<td>Collagen</td>
</tr>
</tbody>
</table>
Breast Density: Background and aims

**Background**
- Breast density is a strong independent risk factor for developing breast cancer
  - At present, assessed from x-ray mammograms
  - Not widely used in screening programs and clinical practice

**Aim**
- Non-invasive optical assessment of breast density
  ⇒ Personalized diagnostic path
  ⇒ Interventions for density reduction
- Identification of high-risk subjects
- Direct assessment of cancer risk
Effect of tissue heterogeneity

- 52 subjects (with recent x-ray mammograms)
- Estimate of average properties
  - RCC and LCC images
  - 5 areas (5 x 5 mm²)
- Correlation with BI-RADS categories

1: Outer
2: Chest
3: Inner
4: Nipple
5: Middle

[Taroni et al, BOE 2012]
Area 5 (Middle): Correlation with breast density

$$OI2 = \frac{([Water] + [Collagen]) \times b}{[Lipid]}$$

⇒ **Good correlation** between OI2 from a small area and breast density
Functional imaging gives information about how an organ works and not only about its morphological structure. In particular FI of the Brain is used to determine where and in which manner an activation takes place in the cerebral cortex.
DOI – Time domain Functional near-infrared spectroscopy

Time-resolved:
Depth sensitivity

Haemodynamic Response

TG-MLB

Rest Task Recovery

$\Delta$O$_2$Hb & $\Delta$HHb (µM)

$\Delta$HHB (Intra) $\Delta$O$_2$Hb (Intra) $\Delta$HHB (Extra) $\Delta$O$_2$Hb (Extra)
PoliMi multi-channel time-resolved fNIRS system

- Laser driver
- variable ND
- 690 nm
- 820 nm
- sync
- variable ND
- delay
- 2x2 fused splitter
- 50%
- 50%
- 1x9 fiber switch
- 2x4 fused splitter
- Piezojena F-SM19
- OZOptics VISNIR5050
- clock

- PicoQuant PDL800
- Laser driver
- variable ND
- 690 nm
- 820 nm
- sync
- variable ND
- delay
- 2x2 fused splitter
- 50%
- 50%
- 1x9 fiber switch
- 2x4 fused splitter
- Piezojena F-SM19
- OZOptics VISNIR5050
- clock

- TCSPC-1
- 4 ch router-1
- 8 ch amp-1
- 4 anodes PMT-1
- Hamamatsu R5900-20-M4

- TCSPC-2
- 4 ch router-2
- 8 ch amp-1
- 4 anodes PMT-2

- TCSPC-3
- 4 ch router-3
- 8 ch amp-2
- 4 anodes PMT-3

- TCSPC-4
- 4 ch router-4
- 8 ch amp-2
- 4 anodes PMT-4

- Becker & Hickl, SPC-134, HRT-41, HAFC-26

- Microchip Technology dsPIC30F6014

- PicoQuant PDL800
fNIRS results
Topographic maps: healthy subject 1

Right vs. Void

Low density, brunette, <3cm
**Brain activation monitoring during a motor task**

**Haemodynamic changes: GLM maps**

**Protocol:** 20 s baseline, 20 s task (finger tapping with right hand at ≈2Hz), 40 s recovery, 9 repetitions, acquisition time 1s

**O$_2$Hb** (p-val < 0.05)

**HHb** (p-val < 0.05)
Simultaneous fMRI and DOI

Time-resolved Oxymeter with capability of simultaneous activation of 16 source channels and 64 detector channels.

Maps of brain activation during a motor task with the right hand: increase in blood oxygenation on the left hemisphere.
Multimodality approach
Towards data fusion

- $O_2$Hb and HHb maps (NIRS-SPM)
- BOLD map (SPM8)
- fMRI max over 10/20 System

- $\alpha$ ERD maps
- TMS CoG
- TMS CoG over 10/20 System
Thank you