Brain Monitoring with Diffuse Optics Techniques

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Light Propagation

- Reflected light
- Incident light
- Propagation through the medium
- Transmitted light
- Absorption
- Scattering
- Re-emission (fluorescence)
- Heat
- Transference (resonance)
Light Propagation

LASER SCATTERING COEFFICIENT

Low High

LASER ABSORPTION COEFFICIENT

Low High

LASER SCATTERING COEFFICIENT

Low High
**Diffuse Optics**

**High Scattering (turbid) medium**
- Light can be detected few centimeters away from the source
- *Detected light carries information about the medium*
- Physical model for the propagation of light can recover optical properties of the medium: *diffusion approximation*

\[
\nabla \cdot (D(\vec{r}) \nabla \Phi(\vec{r}, t)) - v \mu_a(\vec{r}) \Phi(\vec{r}, t) + v S(\vec{r}, t) = \frac{\partial \Phi(\vec{r}, t)}{\partial t}
\]

\(\Phi(\vec{r}, t) \equiv \text{Light Fluence (W/cm}^2\text{)}\)

- High temporal resolution (~100 ms)

**Spatial resolution**

Distance between the source and the detector determines the volume (and depth) of tissue probed

\[\max(z) \simeq \frac{\rho}{2}\]
Biological Tissue is a turbid medium in the near infrared (NIR, 650 - 900 nm) range
Absorption in the NIR is primarily due to oxy- and deoxy-hemoglobin
Scattering is primarily due to red blood cells (RBCs)

Diffuse Optics can be used to probe tissue
Diffuse Optical Techniques

Near-Infrared Spectroscopy (NIRS, DOS)
- Measures the ‘static properties’ of tissue
- Provides information about tissue oxygenation
- More robust, more developed
- Commercially available

Diffuse Correlation Spectroscopy (DCS)
- Measures the ‘dynamic properties’ of tissue
- Provides information about blood flow
- Lower SNR due to signal acquisition
- Pioneered at Penn
- Not commercial yet
Near-Infrared Spectroscopy (NIRS)

Detected intensity is static, and proportional to absorption:

\[
\mu_a(\lambda) = \varepsilon_{HbR}(\lambda)[HbR] + \varepsilon_{HbO}(\lambda)[HbO]
\]

Same idea of the pulse oximeter

NIRS provides information about oxygenation in the tissue probed

\[
[HbT] = [HbO] + [HbR] \propto BV
\]

\[
S_{tO2} = \frac{[HbO]}{[HbT]}
\]

Absolute or relative values can be measured, depending on how one shines light into tissue
Source-detector distance of 2.5 - 3.0 cm can reach the most external surface of the cortex

NIRS can be used to probe and monitor cortical changes with high temporal resolution and low spatial resolution

It also carries information about ‘everything’ in between the scalp and the cortex (systemic physiological noise)
**Functional Activation in Brain**

**Median nerve stimulation**

- **Electric stimulation**
  - 4 Hz, 1-4 s, motion threshold
  - (N = 14)

**NIRS** can quantify parametric changes (in duration) due to median-nerve stimulation in the brain with high-temporal resolution.

RC Mesquita et al., In: HBM (2008)
### Functional Activation in Brain

#### Median nerve stimulation

- **Electric stimulation**
  - 4 Hz, 1-4 s, motion threshold
  - \((N = 14)\)

- **Optode mapping with MRI** allows for spatial localization with high spatial resolution (creation of an optical atlas)

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**A Custo, RC Mesquita et al., NeuroImage (2010)**
1. Pick a seed channel
2. Compute the Pearson’s correlation coefficient from each seed with all other channels
3. Project the correlation values on a distance-weighted SD map

Vascular Connectivity Map
**Resting State Connectivity**

Resting state connectivity of the whole head

Diffuse Optical Techniques

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Diffuse Correlation Spectroscopy (DCS)

Dynamic motion of scatterers

Motion of red blood cells cause intensity of scattered light to fluctuate quickly in time.

Fluctuations can be quantified with a statistical measure of the autocorrelation function for the detected light

$$g_2(r,\tau) = \frac{\langle I(t)I(t+\tau) \rangle}{\langle I(t) \rangle^2}$$

Biophysical model can relate the temporal intensity correlation function to the motion of red blood cells (i.e. blood flow)

A Blood Flow Index (BFI) can be derived and associated to blood flow in biological tissues

BFI is sensitive to relative changes in blood flow.
## DCS Validation Studies

<table>
<thead>
<tr>
<th>Sample</th>
<th>Perturbation</th>
<th>Modality</th>
<th>Correlation Coefficient</th>
<th>Slope DCS/Mod</th>
<th>References</th>
<th>Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse</td>
<td>Femoral Artery Occlusion</td>
<td>Laser Doppler</td>
<td>&gt; 0.8</td>
<td>0.96-1.07</td>
<td>Mesquita RC et al., Biomed. Opt. Expr. 2010</td>
<td>UPenn</td>
</tr>
<tr>
<td>Mouse Tumor</td>
<td>Antivascular therapy</td>
<td>Contrast Enhanced Ultrasound</td>
<td>N/A</td>
<td>Agreement</td>
<td>Sunar U et al., Opt. Expr., 2007</td>
<td>UPenn</td>
</tr>
<tr>
<td>Mouse Tumor</td>
<td>PDT</td>
<td>Doppler ultrasound</td>
<td>N/A</td>
<td>Agreement</td>
<td>Yu G et al., Clin. Cancer Res., 2005</td>
<td>UPenn</td>
</tr>
<tr>
<td>Rat</td>
<td>Hypercapnia</td>
<td>ASL-MRI</td>
<td>0.81 - 0.86</td>
<td>0.75</td>
<td>Carp S et al, Biomed. Opt. Expr. 2010</td>
<td>MGH</td>
</tr>
<tr>
<td>Rat</td>
<td>Hypocapnia</td>
<td>Laser Doppler</td>
<td>0.94</td>
<td>1.3</td>
<td>Durduran T. PhD Dissertation, University of Pennsylvania, 2004</td>
<td>UPenn</td>
</tr>
<tr>
<td>Neonatal Piglet</td>
<td>Traumatic Brain Injury</td>
<td>Fluorescent Microspheres</td>
<td>0.63</td>
<td>0.4</td>
<td>Zhou C et al., J. Biomed. Opt., 2009</td>
<td>UPenn</td>
</tr>
<tr>
<td>Premature Neonates</td>
<td>Absolute Baseline</td>
<td>TCD (velocity)</td>
<td>0.53</td>
<td>N/A</td>
<td>Roche-Labarbe N et al., Human Brain Map., 2010</td>
<td>MGH</td>
</tr>
<tr>
<td>Term Neonate</td>
<td>Hypercapnia</td>
<td>ASL-MRI</td>
<td>0.7</td>
<td>0.85</td>
<td>Durduran T et al., J. Biomed. Opt., 2010</td>
<td>UPenn</td>
</tr>
<tr>
<td>Premature Infant</td>
<td>Absolute Baseline</td>
<td>TCD (velocity)</td>
<td>0.91</td>
<td>0.9</td>
<td>Buckley EM et al., Opt. Expr., 2009</td>
<td>UPenn</td>
</tr>
<tr>
<td>Infants</td>
<td>Hypercapnia</td>
<td>MRI (velocity mapping)</td>
<td>0.9</td>
<td>0.86-0.99</td>
<td>Buckley EM et al., unpublished</td>
<td>UPenn</td>
</tr>
<tr>
<td>Human Muscle</td>
<td>Cuff inflation/deflation</td>
<td>ASL-MRI</td>
<td>&gt;0.77</td>
<td>1.5-1.7</td>
<td>Yu G et al., Opt. Expr., 2007</td>
<td>UPenn</td>
</tr>
<tr>
<td>Adult Human</td>
<td>Pressors &amp; Hyperventilation</td>
<td>Xenon-CT</td>
<td>0.73</td>
<td>1.1</td>
<td>Kim MN et al., Neurocrit. Care, 2010</td>
<td>UPenn</td>
</tr>
<tr>
<td>Adult Human</td>
<td>Acetazolamide</td>
<td>TCD (velocity)</td>
<td>N/A</td>
<td>Agreement</td>
<td>Zirak et al., Biomed. Opt. Expr., accepted</td>
<td>ICFO (Spain)</td>
</tr>
<tr>
<td>Adult Human</td>
<td>Hypercapnia/Hyperoxia</td>
<td>ASL-MRI</td>
<td>0.95</td>
<td>0.3</td>
<td>Durduran T et al., unpublished</td>
<td>UPenn</td>
</tr>
<tr>
<td>Adult Human</td>
<td>Breath-Holding</td>
<td>TCD (velocity)</td>
<td>0.83</td>
<td>1.13</td>
<td>Mesquita RC et al., unpublished</td>
<td>UPenn</td>
</tr>
<tr>
<td>Adult Human</td>
<td>Head-of-Bed</td>
<td>TCD (velocity)</td>
<td>0.85-0.87</td>
<td>2.3-2.9</td>
<td>Mesquita RC et al., unpublished</td>
<td>UPenn</td>
</tr>
</tbody>
</table>

### NOT fully understood, but it WORKS!

Red: clinical studies  
Black: pre-clinical/healthy population
DCS for Functional Activation

Cerebral Oxygen Metabolism: CMRO$_2$

\[ rCMRO_2 \approx \left( 1 + \frac{\Delta Hb}{Hb_o} \right) \left( 1 + \frac{\Delta THC}{THC_o} \right)^{-1} \cdot rBF \]

\( \downarrow \quad \uparrow \)

from DOS/NIRS \hspace{1cm} from DCS
Translation into the clinic

Is there an opportunity for NIRS/DCS into the clinic?

Currently, there is no available instrument to monitor tissue blood flow/oxygenation at the bedside
Acute Ischemic Stroke (AIS)

Types of Stroke

- About 80% of all strokes are ischemic strokes
- First 72 hours (acute phase) are critical to outcome
- Major goal in the care is optimization of cerebral blood flow to prevent additional damage
Acute Ischemic Stroke (AIS)

- Unilateral acute MCA cortical infarction (N = 17)

DCS has the potential to individualize stroke management, at the bedside.
Relative changes in CBF normalized by 30°

Increased CBF demonstrates impaired autoregulation in the brain following AIS
Relative changes in CBF normalized by 30°

Approximately 20% of the patients did not improve CBF at flat HOB

Also reported in patients with traumatic head injury

Elevated ICP, autonomous dysfunction
Traumatic Brain Injury (TBI)

- Sudden trauma causes damage to the brain
- Can be open or close skull injury
- 1.5 million TBIs per year in the US, with 17% hospitalized

Subarachnoid Hemorrhage (SAH)

- Bleeding in the subarachnoid space
- 85% caused by ruptured aneurysms
- Fatality rate about 50%, with 40% dead within 1 month of hospitalization
Neuro-ICU Injuries

DCS monitoring during Xe-CT in SAH patient (ruptured aneurysm at right MCA bifurcation which was later clipped)

On phenylephrine drip: vasopressor for regulating blood pressure

<table>
<thead>
<tr>
<th>Relative CBF Comparison, Patient 13</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mmHg)</td>
<td>-35</td>
</tr>
<tr>
<td>DCS, rCBF</td>
<td>Relative CBF (%)</td>
</tr>
<tr>
<td>Left (%)</td>
<td>-41.8</td>
</tr>
<tr>
<td>Right (%)</td>
<td>-27.0</td>
</tr>
<tr>
<td>Xenon-CT, rCBF</td>
<td>Relative CBF (%)</td>
</tr>
<tr>
<td>Left (%)</td>
<td>-39.7</td>
</tr>
<tr>
<td>Right (%)</td>
<td>-28.7</td>
</tr>
</tbody>
</table>
Comparison DCS vs. Xe-CT (N = 8)

- 8 patients (5M/3F) with 10 episodes of measurement.
- Good correlation observed ($r_s = 0.73, p = 0.010$).
- Linear fit has slope of 1.1 and intercept of 9.3%.

**EXAMPLE PATIENT: CBF**

- XeCT\textsubscript{BL}: 200 mcg/min.
- XeCT\textsubscript{IN}: 26 mcg/min.
- Lowered CBF for XeCT\textsubscript{IN}.

**Slope = 1.1; Intercept = 9.3%**

Good correlation, good agreement

*MN Kim et al., Neurocrit. Care (2010)*
Head-Of-Bed intervention in brain-injured patients (30o to flat bed, N = 9)

**RESULTS, NIRS**
- Brain-injured: THC, HbO\(_2\) \(\uparrow\)
- Healthy: THC no change, HbO\(_2\) \(\uparrow\)
- Significant difference in THC and HbO\(_2\) between brain-injured vs. healthy \((p<0.001)\).

**RESULTS, DCS**
- Brain-injured: CBF no change, but large variance.
- Healthy: CBF \(\uparrow\).
- Significant difference in CBF between brain-injured vs. healthy \((p<0.001)\).
- Sometimes large hemispheric disparity in brain-injured.

**Large CBF variability in brain-injured population: individualization**

**Large THC and HbO\(_2\) responses in brain-injured population**
Other On-going Clinical Studies

- Long-term monitoring of patients in the Neuro-ICU (Kofke)

- Assessment of DCS-based autoregulation indexes for patient’s real-time evaluation (Kofke)

- Monitoring of AIS patients during induced hypertension (Mullen)

- Post-surgery monitoring of neonates with congenital heart defects (Licht)
DCS in the Clinic

Cerebral Diseases
  Stroke
  Neuro-ICU

Treatment
  TMS
  PDT

Cardiology
  Congenital heart defects

Anesthesiology
  Spinal cord injuries

Muscle
  Peripheral Artery Disease

Cancer
  Head & Neck
  Breast
  Pleural
  Prostate

Genetics
  Angiogenesis
  HIF-expressions
Diffuse Optics probes physiology of deep tissues
- Brain, breast tumors, muscle, ...

- Non-invasively
- High-temporal resolution
- At the bedside (portability)
- Relatively cheap

Further development is needed
- Improve spatial resolution/coverage
- Extra-cortical contributions
- Influence of systemic physiology
- Real-time bedside monitor in the clinic

Many applications, developments, opportunities...
THANK YOU!

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