Why & How?

Near Infrared Spectroscopy and Diffuse Optical Imaging

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Director: David A. Boas
http://www.nmr.mgh.harvard.edu/PMI/

- Microscopy for Cerebro-Vascular Physiology
- Diffuse Optical Imaging of the Human Brain
- Optical Breast Imaging for Cancer Applications
Why Optical Imaging of the Brain?

But also: **Novel contrast** that spans all other methods!

Suitable for sensitive studies (children, neurocritical care, movement)

Non-invasive, low-cost, transportable
Optical Contrasts: Intrinsic & Extrinsic

**Hemodynamic**
- Oxy- & deoxy-hemoglobin
- Blood volume
- Blood flow

**Metabolic**
- Cytochrome oxidase
- NADH-FADH
- CMR$_{\text{Glucose}}$
- CMRO$_2$

**Neuronal - Electrical**
- Voltage sensitive dyes
- Calcium green
- Scattering

Invasive: high spatial resolution, more contrast parameters

Non-invasive: routine continuous and real-time use in animals & humans
Near Infrared Spectroscopy (NIRS)

Pulse oximeter

Global brain oxygenation monitoring

2 wavelengths

Light Propagation in Biological Tissues
Light – Tissue Interaction

What happens when light travels through a biological tissue?

Absorption + Scattering
Absorption

Main chromophore (absorber) = Hemoglobin

Two or more wavelengths enable spectroscopy of oxy-/deoxy-hemoglobin

HbO, HbR
Cheong et al., IEEE J. Quantum Electron 26, 1990

Water
Hale and Querry, Appl Opt 12, 1973
Scattering

Scatterers (Cell nuclei, mitochondria, whole cells, ...)

Scattering coefficient
\[ \mu_s = \frac{1}{l_s} \]
\( l_s \) = Average distance between two scattering events (mostly forward scattering)

Reduced scattering coefficient
\[ \mu'_s = \frac{1}{l^*} \]
\( l^* \) = Distance after which diffusion is isotropic (same in all directions)

In tissues

\(~ 100 \, \mu m\)

After \(~1\text{mm} \) depth, photons have lost all information about their initial direction

Note: Microscopy techniques also use optical contrast but work at shallow depths where photons have not or little scattered ⇒ Can only achieve a few \(~100 \, \mu m\) depth sensitivity.

DOI work in the diffusive regime at several cm depth using only diffuse photons.
Tissue Penetration

Absorption

Average propagation distance after which a photon is absorbed

$\lambda_a \sim 10 \text{ cm}$

Scattering

Average propagation distance after which a photon loses memory of its original direction

$\lambda_s \sim 1 \text{ mm}$
Light Propagation in the Head

- Diffuse light reaches the brain
- Source + detector probing a volume of a few cm$^3$ (Superficial + cerebral)
- Sensitive to superficial cortex only (5-8 mm)
Different NIRS modalities

**Continuous wave**
- Source
- Detector
- Attenuation

**Frequency domain**
- Source
- Detector
- Attenuation (AC, DC)
- Phase Shift

**Time domain**
- Source
- Detector
- Whole Temporal Point Spread Function
  or moments of TPSF
  or gated TPSF
NIRS modalities: Continuous Wave

- Least expensive
- High temporal resolution (25Hz)
- Not possible to distinguish between absorption and scattering changes
- Sensitive only to changes in hemoglobin
  - Functional studies (fNIRS)
  - Physiological oscillations

![Image of NIRS signal with Oxy-Hb and Total-Hb (volume) indicating changes over time.](image)
Modified Beer-Lambert Law

Beer-Lambert Law

\[ I(\lambda) = I_0(\lambda) \exp[- \mu_a(\lambda) \cdot L] \]

\[ \mu_a = \frac{1}{L \ln(I/I_0)} \]

Absorption

Optical Density

OD = \log(I/I_0)

Modified Beer-Lambert Law

\[ I(\lambda) = I_0(\lambda) \exp[- \mu_a(\lambda) \cdot DPF(\lambda) \cdot L + G] \]

DPF = Differential Pathlength Factor

G = Losses due to Geometry

\[ \mu_a = \frac{1}{DPF \cdot L} \ln\left(\frac{I}{I_0}\right) - G \]
Modified Beer-Lambert Law

Beer-Lambert Law

\[ I(\lambda) = I_0(\lambda) \exp[-\mu_a(\lambda) L] \]

Absorption

\[ \mu_a = \frac{1}{L} \ln \left( \frac{I}{I_0} \right) \]

Optical Density

\[ \text{OD} = \log \left( \frac{I}{I_0} \right) \]

Modified Beer-Lambert Law

\[ I(t) = I(t=0) \exp[-\Delta \mu_a(\lambda) \text{DPF}(\lambda) L + G] \]

DPF = Differential Pathlength Factor

\[ \Delta \mu_a(t) = \frac{1}{(\text{DPF} L)} \ln \left[ \frac{I(t)}{I(t=0)} \right] \]
Near Infrared Spectroscopy

\[ \Delta OD(\lambda_1) = \left( \varepsilon_{HbR}^{\lambda_1} \Delta[HbR] + \varepsilon_{HbO}^{\lambda_1} \Delta[HbO] \right) \times L_{eff} \]

\[ \Delta OD(\lambda_2) = \left( \varepsilon_{HbR}^{\lambda_2} \Delta[HbR] + \varepsilon_{HbO}^{\lambda_2} \Delta[HbO] \right) \times L_{eff} \]

Change in intensity

Chromophore extinction coefficient at each wavelength

Changes in concentration

\[ L_{eff} = SD \times DPF \]

Multi-wavelength measurements of optical absorption

Changes in oxy-hemoglobin and deoxy-hemoglobin

Changes in oxygenation and total hemoglobin
To Summarize: How does NIRS work?

Measurements of changes in detected light intensity

Changes in absorption at multiple wavelengths

Changes in **Oxy-hemoglobin** \([HbO]\)

**Deoxy-hemoglobin** \([HbR]\)

Changes in Total hemoglobin \([HbT] = [HbO] + [HbR]\) (blood volume) & Oxygen saturation

\[\text{SO2} = \frac{HbO}{HbT}\]

Arrays of sources and detectors

Hemoglobin maps
Different NIRS geometries

Local

Topography (2D)

Global

Tomography (3D)

Selb, *Pour la Science* (2005), in French
Instrumentation
Instrument evolution - CW

32 channel CW system: CW6

- 32 laser diode sources (690 & 830nm), frequency encoded in 200 Hz steps between 4.0 kHz and 7.4 kHz
- 32 parallel APD detectors
- Real-time display of time courses of intensity changes and ΔOD
- Acquisition time per image (32x32 channels) can be as short as 10ms!!!
Probe development
Probe Considerations

Adapt probe design to experiment!!!

Number of optodes? (= “optical electrode”)
- Local
- Whole head

Location?
Obviously over the studied cortical region(s)…
Need for control optodes elsewhere?

Combination with other modalities
- MRI compatible (non-magnetic material)
  compatible + space constraint
- ICU: other headgear?
- Co-registration!! (10-20 system, fiducial markers, 3D-digitizer)
Probe Considerations

Adapt probe design to experiment!!!

Trade-off subject comfort / signal quality / time to setup

Tolerance for movement?
  Infants, Children
  Clinical
  Postural changes, gait experiment
  Speech

Probe secured:
Chin strap (problem if speech)
Fiber weight (support fibers to avoid weight on the head)
fNIRS (functional NIRS)
What does fNIRS measure?

**Neuronal Activity**

- **Arteriole Dilation**
  - Increases in blood flow, volume, and oxygenation

- **Increased Oxygen Consumption**
  - Decrease in oxygenation

- **Hemodynamic Changes:**
  - $\downarrow [\text{HbR}]$
  - $\downarrow [\text{HbO}]$
  - $\uparrow \text{CBF}$
  - $\uparrow \text{CBV}$

- **NIRS signal**
  - Increase in blood flow exceeds increase in $O_2$ consumption
fNIRS - Sensorimotor

Moving average of 5 points
acquisition time 800 ms

Franceschini et al, Optics Express 6, 2000
fNIRS - Sensorimotor

Moving average of 5 points
acquisition time 800 ms

Franceschini et al, Optics Express 6, 2000
fNIRS - Sensorimotor

Hemoglobin maps

- Finger opposition
- Finger tactile
- Electrical median nerve

Franceschini et al. 
Functional NIRS (fNIRS)

fNIRS has been applied to a very broad range of studies

- Cortical regions
  - Sensorimotor
  - Visual
  - Auditory
  - Cognitive

- Population
  - Infants, Children, Adults, Healthy aging
  - Normal / pathological: schizophrenia, depression, Alzheimer, Parkinson’s…

- Methodology
  - Stand-alone
  - Multimodality (+ fMRI, EEG, MEG, TCD, …)
fNIRS - Language Processing in Infants

Heather Bortfelt (Univ Connecticut, Texas A&M at the time)

Infants 6-9 months

Audiovisual (animation + speech)
Visual (animation only)

Single trial

Robust patterns of activation in left temporal and primary visual regions of neocortex


Bortfeld et al., *Developmental Neuropsychology*, 34:1, 52-65 (2009)
Multimodality fNIRS

NIRS + fMRI
- Cross-validation
- Cerebral metabolic rate of oxygen

NIRS + MEG
- Neuro-vascular coupling

NIRS + EEG
- Epilepsy

Hoge et al, NeuroImage 2005
Huppert et al, NeuroImage 2006
Huppert et al, J Biomed Opt 2006

NIRS - 90%, 75%, 50% of max $\Delta[HbR]$ at t= 3-5s

Ou et al, NeuroImage 2009

MG - Neural activation at t=35 ms

Rob Cooper
Meryem Ayse Yucel
David Boas
Limitations
Spatial Resolution and Localization

- Poor lateral resolution ~ source-detector separation
- Overlapping measurements
- Very dense probe


Spatial resolution and localization

- Localization (laterally and in depth)
  - Overlapping measurements

MRI structural constraint

True subject anatomy

Atlas standard head

**Motion Artifacts Removal**

- **Visual identification (not objective!!)**

- **Principal component analysis**
  
  Principal or independent component analysis filters can be used to separate and remove motion artifacts from physiology.

- **Threshold on magnitude of intensity change**

  Works well in infants but tends to remove too much of the activation signal in adults.

implemented in HomER
Systemic Physiology Contamination

NIRS signal very sensitive to spontaneous physiological fluctuations arising from cardiac pulse, respiration, heart rate variability, blood pressure spontaneous oscillations, both of systemic and cerebral origins

Real biological signals, but hinder our capacity to measure cerebral activation ("physiological noise")

Various approaches to remove this physiological contamination from activation response
Other Diffuse Optical Modalities
NIRS modalities: Frequency Domain

- Absolute baseline properties (absorption AND scattering)
  → **Baseline oxygenation and CBV**
    (Multi-distance FD method)

- Some depth resolution

\[
\ln(r, I_{dc}) = \text{intercept (}\mu_s'\text{)} + \text{slope (}\mu_a, \mu_s'\text{)}
\]

\[
\text{slope (}\mu_a, \mu_s'\text{)}
\]

NIRS modalities: Time Domain

- Most information content vs. most expensive
- Absolute optical properties
  - Baseline oxygenation and CBV
- Depth sensitivity
  - fNIRS with depth resolution
- 3D tomography
**Diffuse Correlation Spectroscopy**

- **Coherent light**
- **Moving scatterers (Red Blood Cells)**

- **Blood Flow Index** (relative value)
- Sensitive to microvasculature
- Alone or combined with NIRS modalities

**Intensity autocorrelation**

- Increased velocity
- Static solution

**Correlation time (s)**

## Summary Diffuse Optical Modalities

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Baseline Measurements: Brain Metabolism in Infants
Cerebral Development in Healthy Infants


47 healthy infants
Age: 0-50 wks
Gestational age: 27.0-41.5 wks

Simple Probe / Measurement

- Frequency-Domain (Imagent ISS)
- 7 wavelengths (670 to 830 nm)
- 6-11 locations
- ~10 s / location

Relative cerebral metabolic rate of oxygen (rCMRO$_2$)

\[
CMRO_2 = CBF \cdot (SaO_2 - SvO_2)
\]

\[
rCMRO_2 = \frac{CMRO_2}{CMRO_{2o}} = \frac{HGB}{HGB_o} \cdot \left( \frac{CBV}{CBV_o} \right)^\beta \cdot \left( \frac{SaO_2 - StO_2}{SaO_{2o} - StO_{2o}} \right)
\]
Cerebral Development in Healthy Infants

Cerebral Blood Volume

CBV increases over the first year of life
⇒ Developing vasculature

Cerebral Oxygen Saturation

StO\textsubscript{2} ~ constant with age
⇒ Supply matches metabolic demand

Cerebral Metabolic Rate of Oxygen

CMRO\textsubscript{2} increases over the first year of life
⇒ Consistent with increase in glucose metabolism (PET)
Brain Development in Infants

Grubb flow-volume relationship from adults not valid in newborns

⇒ Need to measure blood flow

**DCS**: CBF index

**FD-NIRS**: CBV and StO$_2$

11 premature neonates (28-34.5 wGA)

Evolution $rCMRO_2$ with age

with CBF deduced from CBV

Combination of two DOI modalities enables much more accurate estimation of oxygen consumption!

Roche-Labarbe et al
Human Brain Mapping
31(3) (2010)
Brain Injury in Infants

Not statistically significant elevated StO$_2$ in brain injured with respect to healthy group

CBV significantly higher in brain injured than in all other groups

rCMRO$_2$ significantly higher in brain injured than in all other groups

Cerebral perfusion may adapt to normalize StO$_2$ after injury

Elevation in CBV is consistent with a hyperperfusion state

Increased CMRO$_2$ suggests post-injury excitotoxic mechanisms
Brain Injury in Infants

sensitivity & specificity
CBV vs. rCMRO$_2$ by clinical group

- sensitivity: 78.6%
- specificity: 96.6%

- brain injured
- stable
- unstable
- healthy
Cerebral Health and Development in Infants

StO$_2$ has been the most commonly used parameter to evaluate hemodynamics in infants

but

StO$_2$ relatively insensitive to brain maturation age or brain condition

It is the wrong parameter to look at.
Probable reason why NIRS failed to be implemented in the clinic in the '90s

Fortunately, NIRS provide additional measures:
- Cerebral Blood Volume
- Cerebral Blood Flow
- Cerebral Metabolic Rate of Oxygen
Summary
NIRS principle

Measurements of changes in detected light intensity

Changes in absorption at multiple wavelengths

Changes in Oxy-hemoglobin [HbO] Deoxy-hemoglobin [HbR]

Changes in Total hemoglobin [HbT] (blood volume) & Oxygen saturation

Measurement or estimation of Cerebral Blood Flow (CBF)

CMRO2

Novel contrast: hemodynamics + metabolic

Suitable for sensitive studies (children, neurocritical care, movement)

Non-invasive, low-cost, transportable

High temporal resolution (~ 10ms)

Relatively low spatial resolution (~ 1cm)
## Summary

### Diffuse Optical Imaging

- **NIRS:** Intrinsic absorption of oxy- and deoxy-hemoglobin
- **DCS:** Sensitive to motion of red blood cells
- Sensitive to microvasculature (as opposed to large vessels)
- Continuous Wave: Relative changes in Hb
  - Functional imaging
- Frequency-Domain and Time-Domain: Absolute Hb content
  - Longitudinal studies, Measurements over minutes to hours

### Advantages

- Low cost
- Non-ionizing
- Transportable
- Functional contrast: HbO & HbR
- High temporal resolution

### Limitations & difficulties

- Modest spatial resolution
- Limited penetration depth
- Superficial contamination
- Probe design
- Motion artifacts
Summary

Applications:

• Functional brain imaging:
  • Infants, children, adults, healthy aging
  • Sensorimotor (gait, pain studies); Developmental studies in infants (language processing, number processing, object processing (shape/color), etc…); Psychiatric studies (cognitive side effects in depression)

• Combination with other modalities: cross-validation, neurovascular coupling, CMRO$_2$

• Baseline measurements: brain monitoring during surgery and anesthesia, healthy and pathological infant cerebral development

• Applications to other parts of the body:
  • Muscle oxygenation
  • Breast imaging (tumor characterization, treatment monitoring)
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| Breast Imaging                                   |                                               |
| Stefan Carp                                      |                                               |
| Qianqian Fang                                    |                                               |
| Mark Martino                                     |                                               |
| Bernhard Zimmermann                              |                                               |