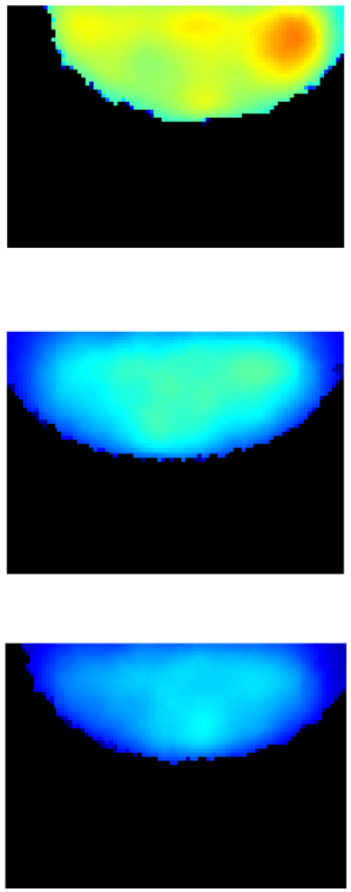
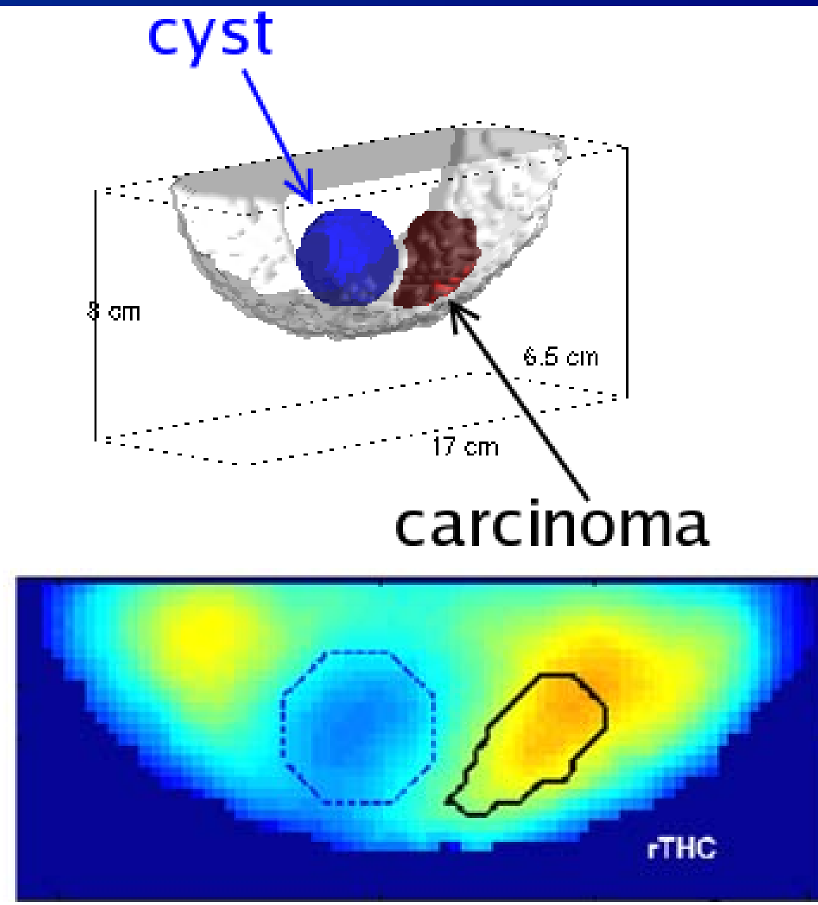
Diffuse Optics for Breast Cancer Imaging & Monitoring

Pre-chemotherapy



Post-chemotherapy

THC(microM)



Acknowledgement: NIH, ARMY, NSF

Recent comprehensive review: Durduran, T., Choe, R., Baker, W.B, and Yodh, A.G., Diffuse optics for tissue monitoring and tomography. *Reports on Progress in Physics*, 73, 076701 (2010).

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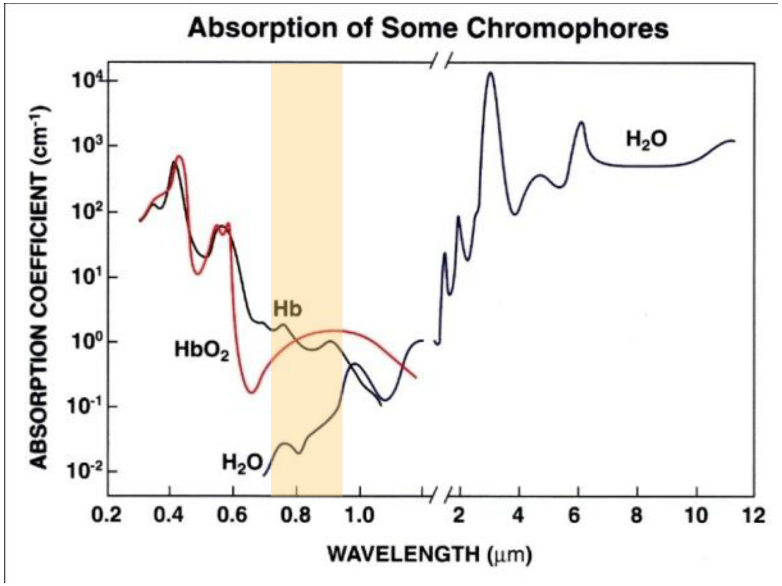
The Dream.

from: *Star Trek*

from: *Minority Report*

In-Vivo Optical Biopsy

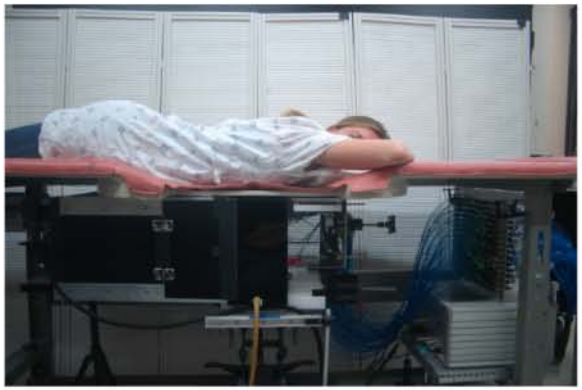
- **Near Infrared Light Penetrates Tissue**
- **Sensitivity to Tissue Physiology**
- **Unique Contrasts are Complementary to Other Medical Diagnostics**

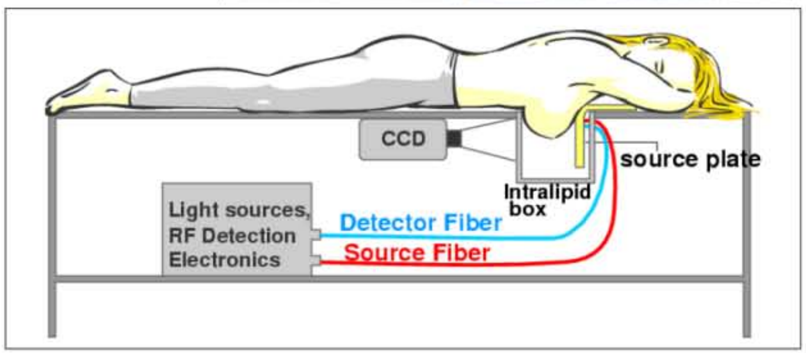


- **Non-invasive, safe, rapid, portable, continuous, inexpensive ...**

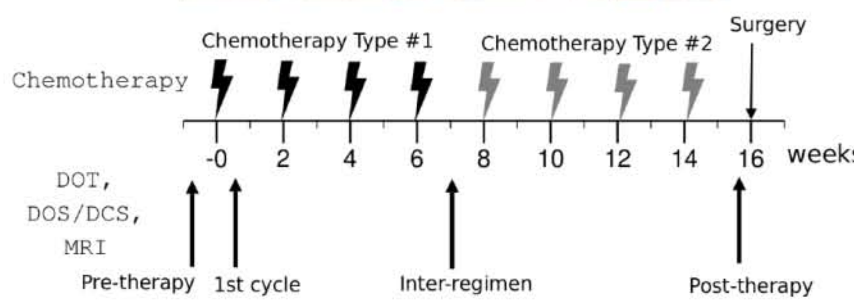
Imaging & Monitoring

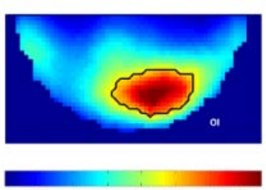
Tomography Approach

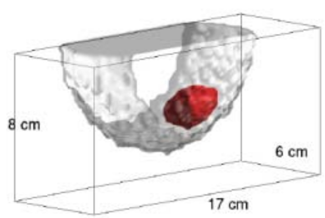


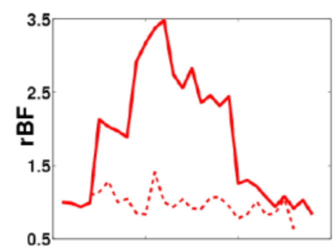


Hand-held Approach





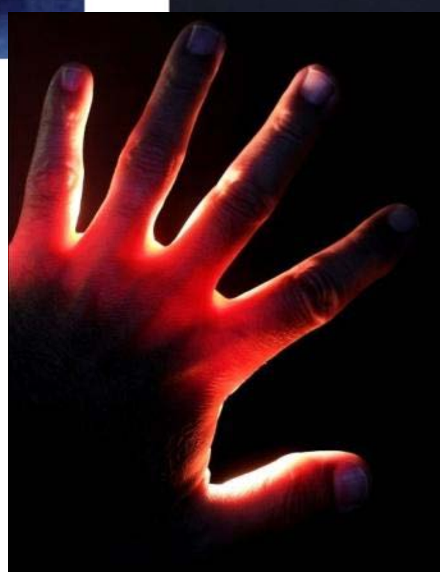


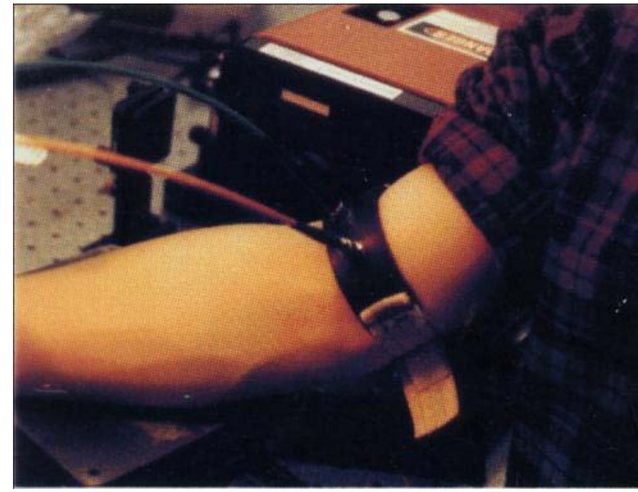


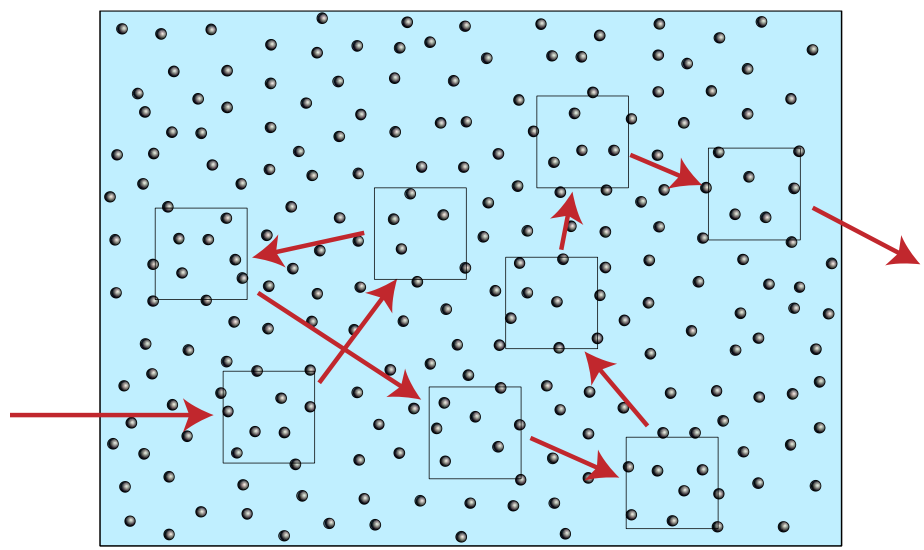
Outline

- The basic measurement techniques (DOS, DCS, DOT, FDOT)
- Breast Cancer Imaging
- Breast Monitoring (Cancer Therapy)

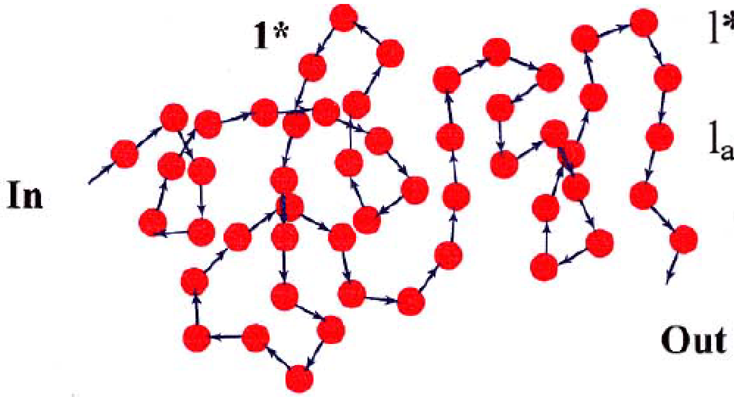
Problem of Tissue: Multiple Scattering







Individual Photons Undergo A Random Walk (with loss)



$l^* \leftrightarrow 1/\mu_s'$ (Scattering)

$l_a \leftrightarrow 1/\mu_a$ (Absorption)

1* - random walk step of photon

Photon Fluence Rate, $\Phi(r,t)$ (in J/cm^{2}sec), Obeys a Diffusion Equation:

$$\frac{\partial \Phi(r,t)}{\partial t} = D\nabla^2\Phi(r,t) - \upsilon\mu_a\Phi(r,t) + \upsilon S(r,t)$$

S = Light Source term

υ = Speed of Light in tissue

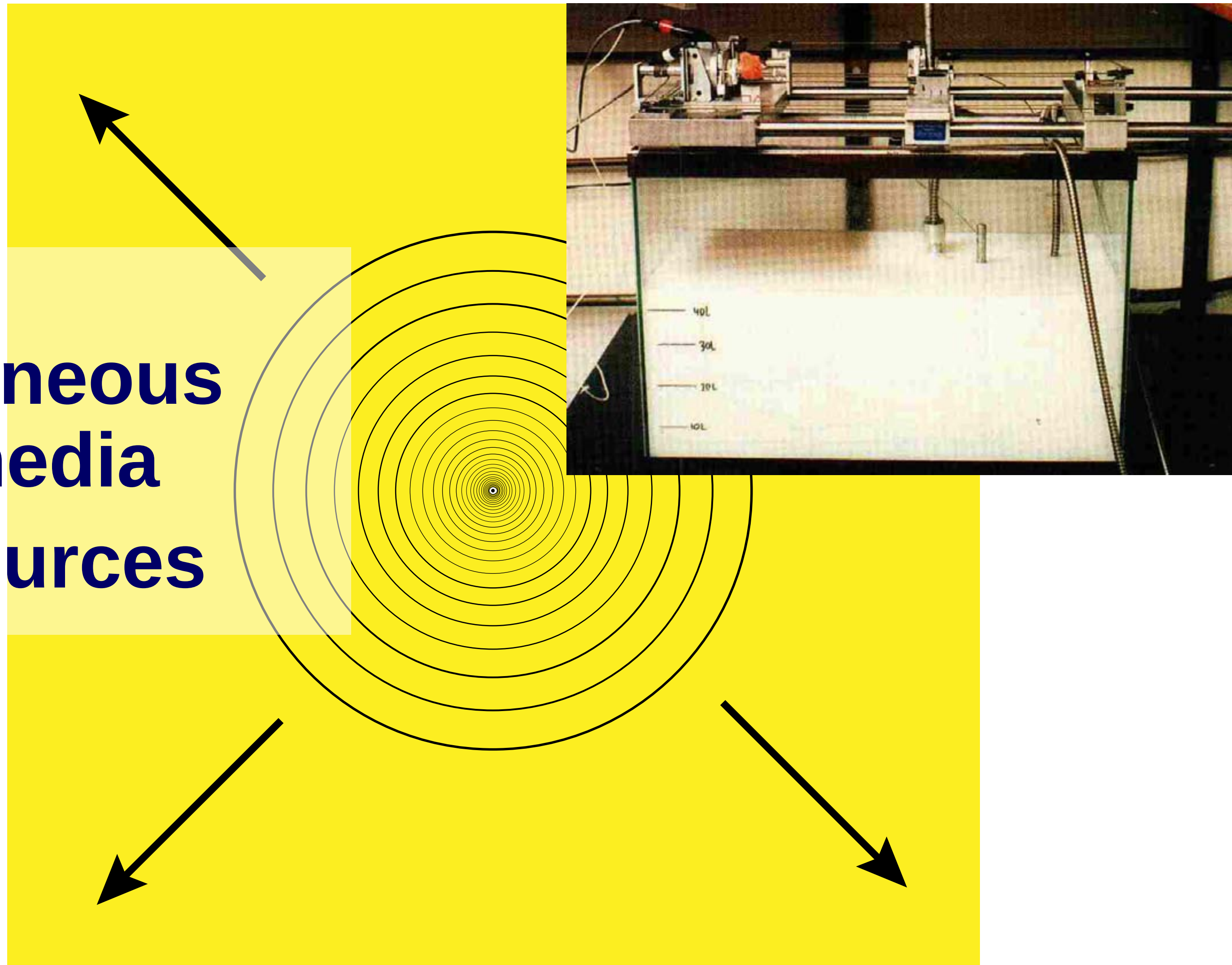
μ_a = Absorption Coefficient (cm^{-1})

$D = \frac{\upsilon}{3\mu_s'}$ = Photon Diffusion Coefficient

μ_s' = Scattering Coefficient (cm^{-1})

Diffusive Waves: Ideal samples, solutions

- **Infinite homogeneous turbid media**
- **Point sources**



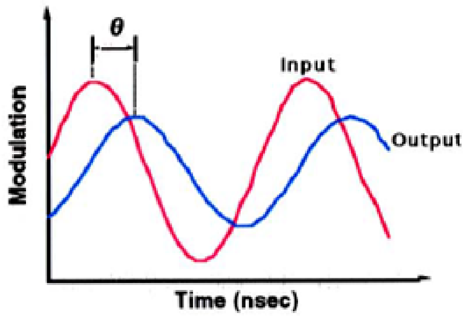
Frequency Domain: Diffuse Photon Density Waves*

$$\Phi_\omega(\vec{r},t) \equiv \Phi(\vec{r},\omega)\mathrm{e}^{i\omega t}, \text{ and } S_\omega(\vec{r},t) \equiv S(\vec{r})\mathrm{e}^{i\omega t}$$

$$\nabla \cdot (D(\vec{r})\nabla\Phi(\vec{r},\omega)) - (v\mu_a(\vec{r}) + i\omega)\Phi(\vec{r},\omega) + vS(\vec{r}) = 0$$

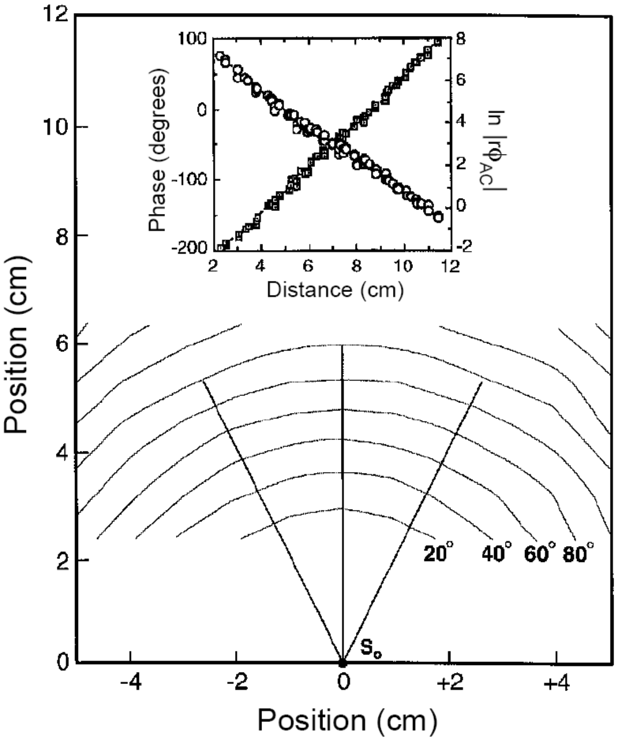
$$\nabla^2\Phi(\vec{r},\omega) - k_0^2\Phi(\vec{r},\omega) = -S(\vec{r})v/D,$$

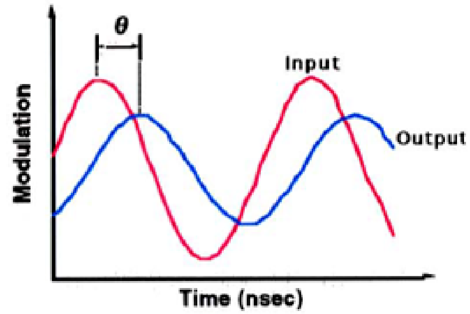
$$\text{with } k_0^2 \equiv \frac{v\mu_a + i\omega}{D}$$

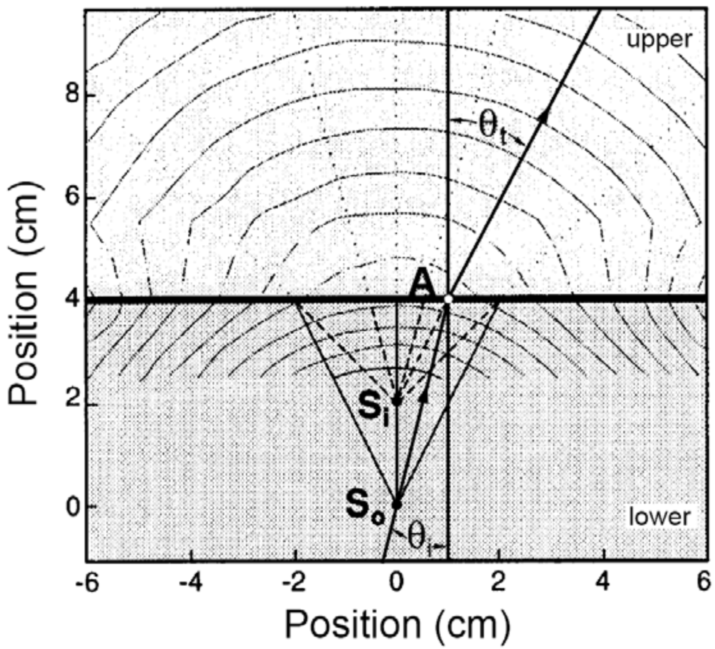


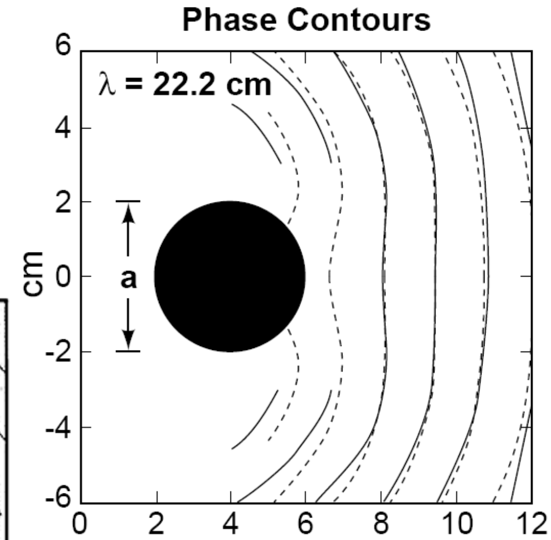
*first suggested by Enrico Gratton

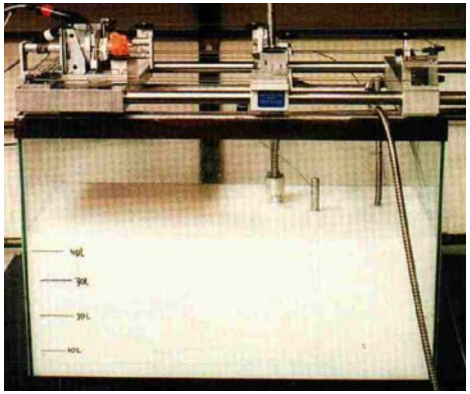
Diffusive Wave Optics







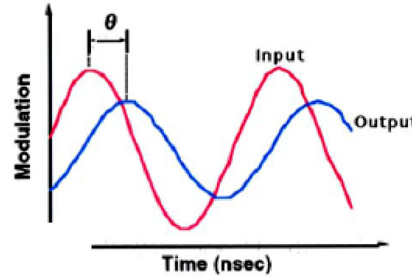


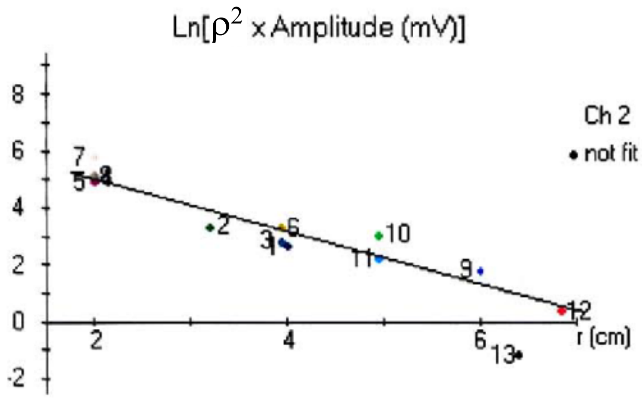


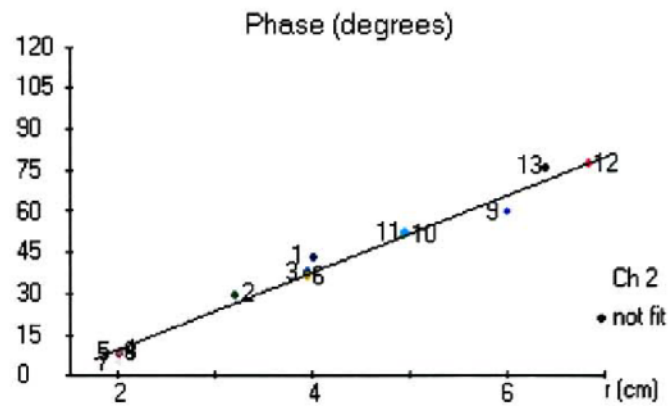
Boas, Oleary, Chance, Yodh. *Physical Review E*, **47(5)** 1993.
Oleary, Boas, Chance, Yodh. *Physical Review Letters*, **69** 1992.

Solutions: Semi-infinite Medium

$$\Phi(\rho, z) \approx \frac{S_0 v}{4\pi D} \boxed{\frac{e^{-k_0 \rho}}{\rho^2}} \left[2k_0\left(L_s \ell_t + L_s^2\right)\right]$$

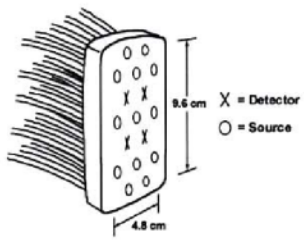






$k_i = 1.124 \pm 0.07\ \text{cm}^{-1}$ $k_r = 0.924 \pm 0.085\ \text{rads cm}^{-1}$

Age ~ 2 months old
Modulation frequency = 200 MHz
Probe placed on left side of forehead



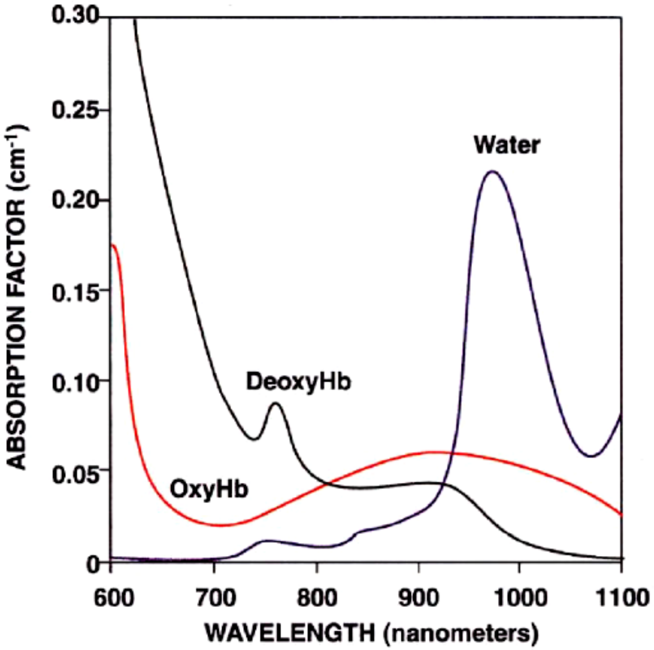
Optical properties: $\mu_a = 0.10\ \text{cm}^{-1}$, $\mu_s' = 2.6\ \text{cm}^{-1}$.

Danen, R.M., Wang, Y., Li, X.D., Thayer, W.S., and Yodh, A.G., *Photochemistry and Photobiology.* 67, 33-40 (1998)

What has been gained?

- Scattering separated from absorption.
- Absorption can be measured in turbid media.
- Scattering (photon random walk step) can be measured in turbid media.

Spectroscopy: Absorption Coefficients vs. λ



$$\mu_a(\lambda_1{=}780\text{ nm}) = \varepsilon_{Hb}(\lambda_1)\,[Hb] + \varepsilon_{HbO_2}(\lambda_1)\,[HbO2]$$

$$\mu_a(\lambda_2{=}805\text{ nm}) = \varepsilon_{Hb}(\lambda_2)\,[Hb] + \varepsilon_{HbO_2}(\lambda_2)\,[HbO2]$$

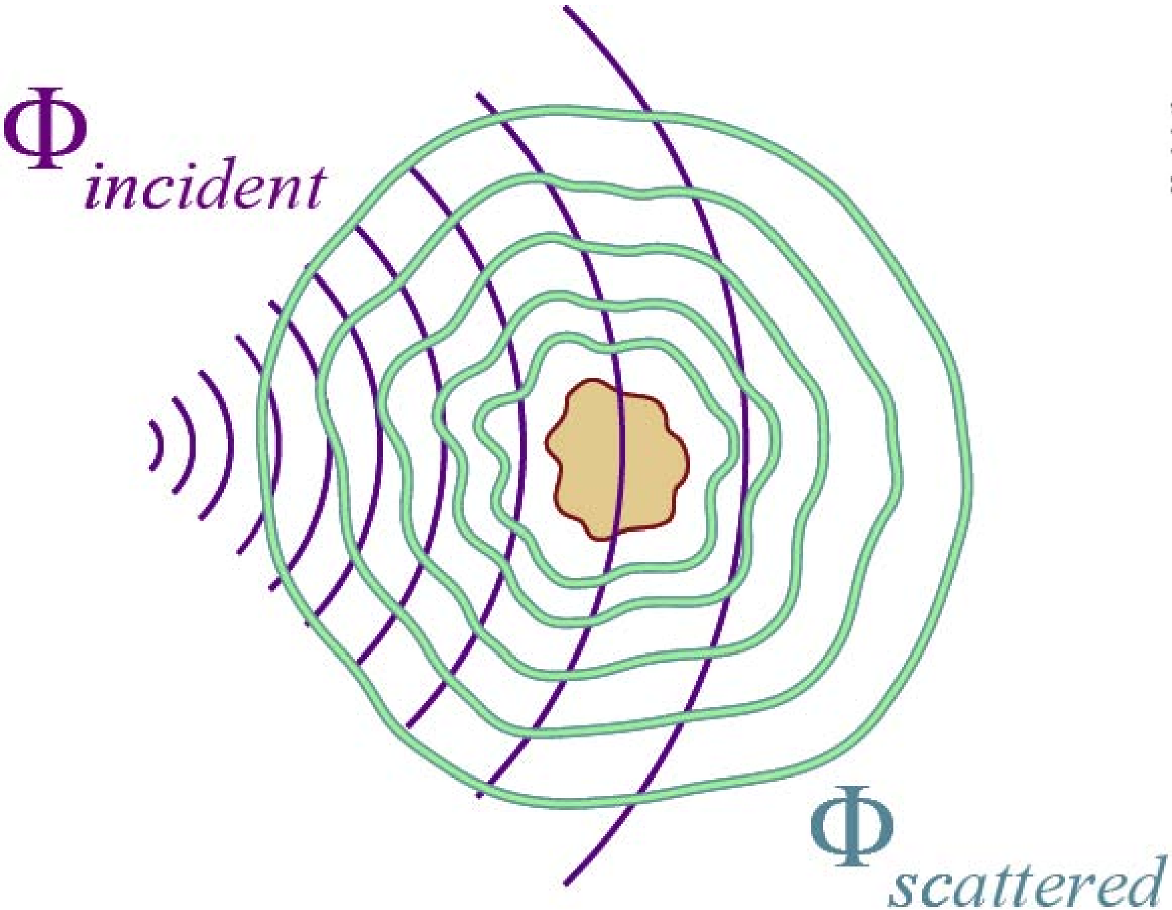
2 Equations, 2 Unknowns ([Hb], [HbO_2])

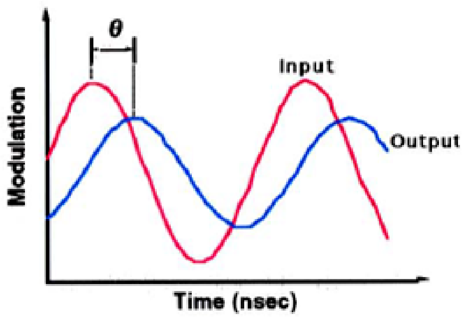
Total Hemoglobin Concentration = [HbO_2] + [Hb] = THC

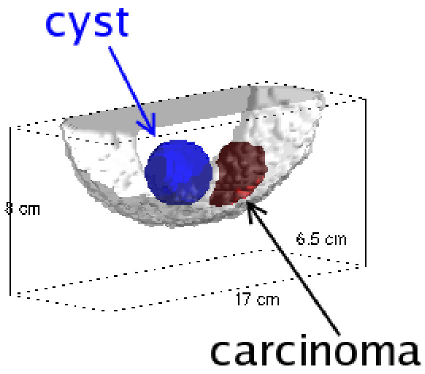
THC = $\mu_a(\lambda_1)[\varepsilon_{HbO_2}(\lambda_2)-\varepsilon_{Hb}(\lambda_2)] - \mu_a(\lambda_2)[\varepsilon_{HbO_2}(\lambda_1)-\varepsilon_{Hb}(\lambda_1)]$

Tissue Oxygen Saturation = [HbO_2] / THC = StO_2

Image Reconstruction: Diffuse Optical Tomography

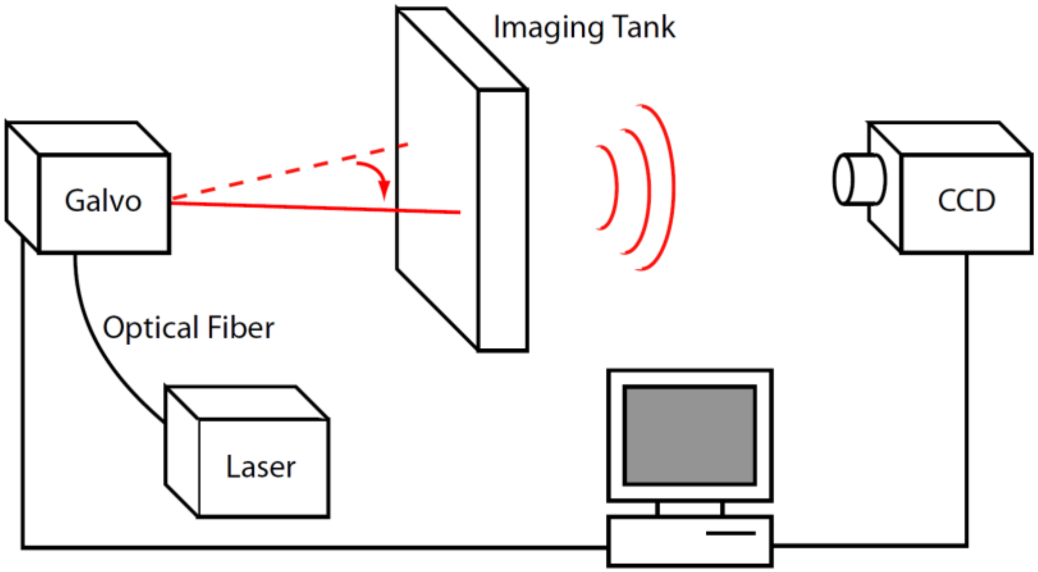


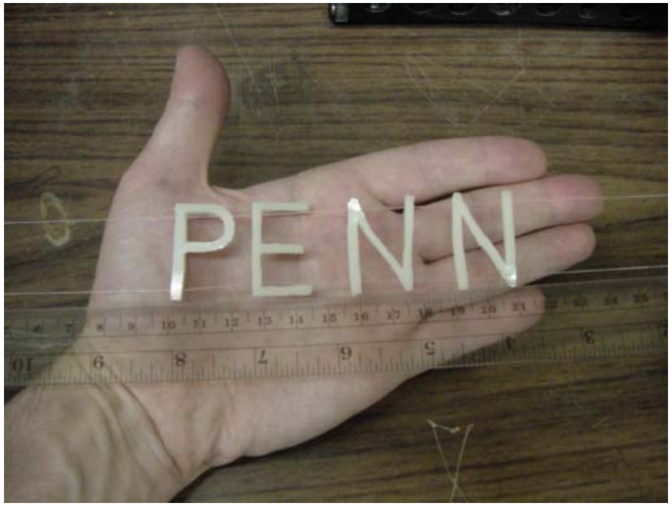


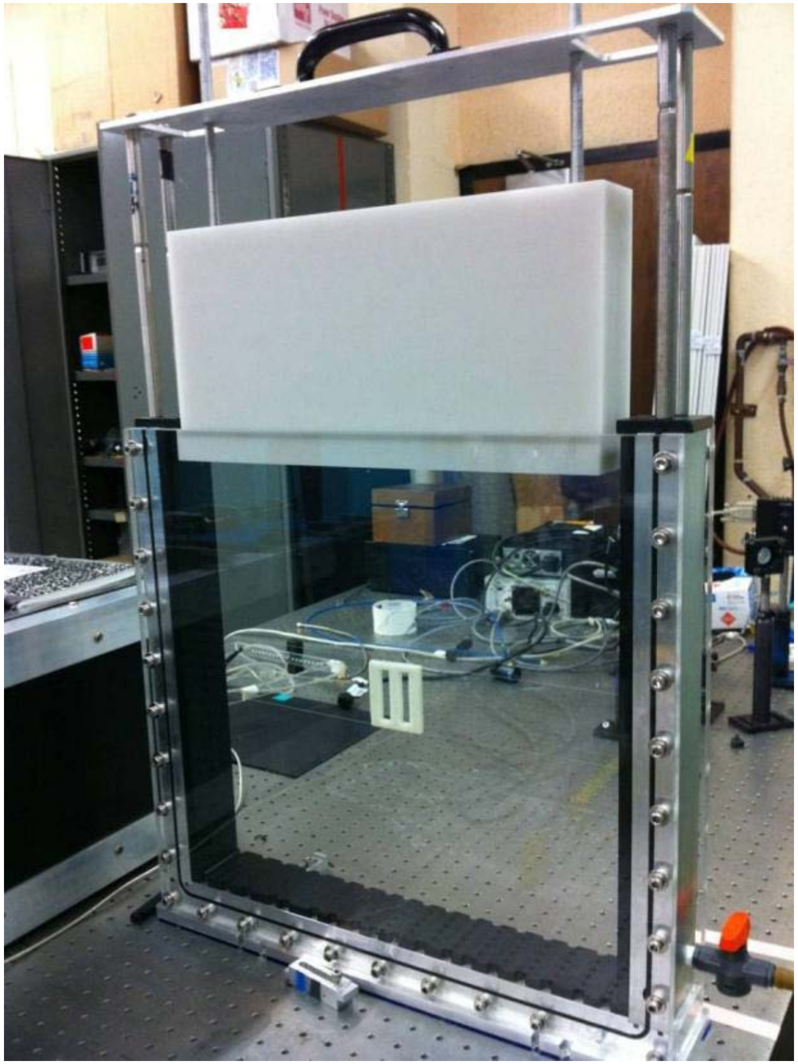


Arridge SR, Optical tomography in medical imaging, *Inverse Problems* **15**, R41-R93, 1999

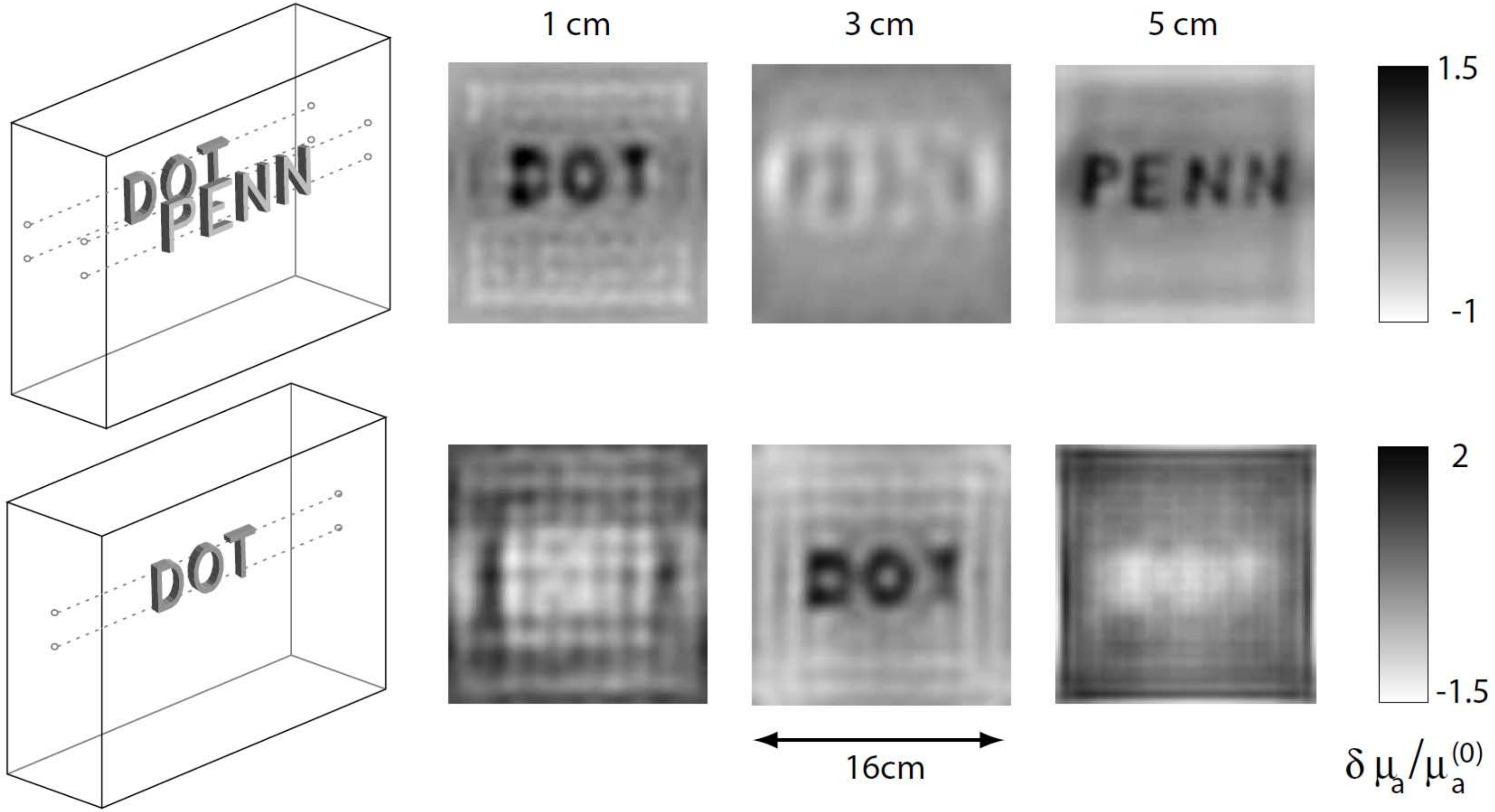
Tomography of Tissue Phantom







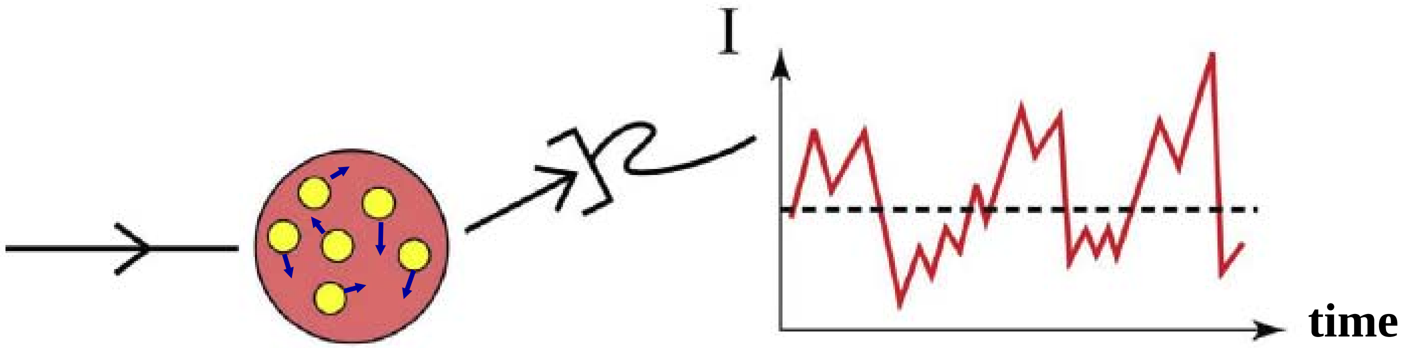
Reconstructed Images



Top: Letters “DOT” and “PENN” 1 cm from surfaces.
Bottom: Letters “DOT” in center of tank.

Konecky, S.D., Panasyuk, G.Y., Lee, K., Markel, V., Yodh, A.G., and Schotland J.C., Imaging complex structures with diffuse light. *Optics Express* 16, 5048-5060 (2008).

Diffuse Light from Tissue Fluctuates in Time



$$g_1(\tau) = \frac{\langle E^*(t+\tau)\, E(t)\rangle}{\langle |E(t)|^2 \rangle}$$

- **What is moving?**

  (organelles, red blood cells, …)

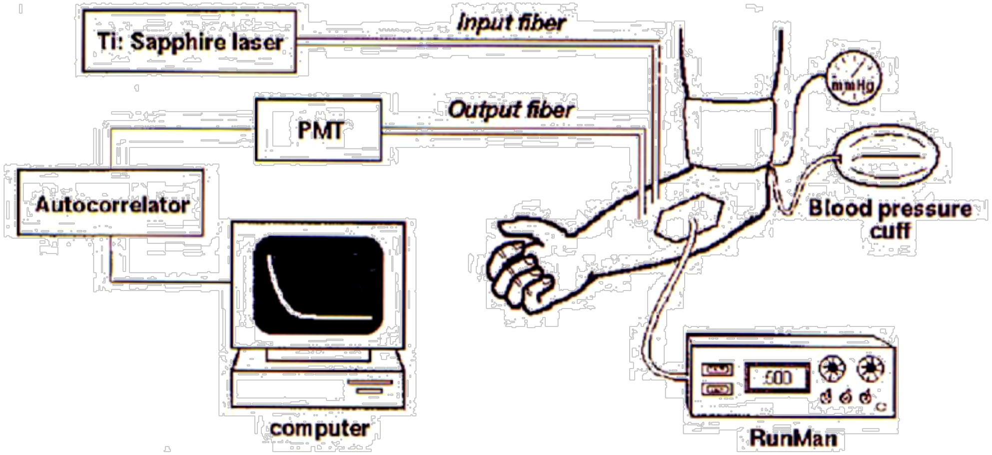
- **How much is moving, how fast & what is the manner of motion?**

  (Blood flow)

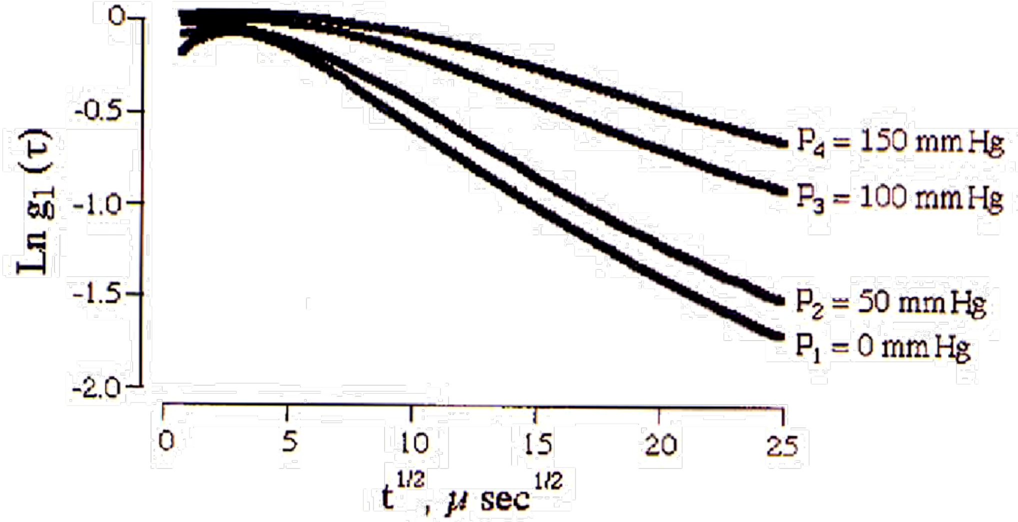
Boas, D.A., Campbell, L.E., and Yodh, A.G., Scattering and imaging with diffusing temporal field correlations, *Physical Review Letters* 75, 1855-1858 (1995).

Boas, D.A., and Yodh, A.G., Spatially varying dynamical properties of turbid media probed with diffusing temporal light correlation, *Journal of the Optical Society of America* A 14, 192-215 (1997).

Blood Flow in Tissues: Cuff Ischemia

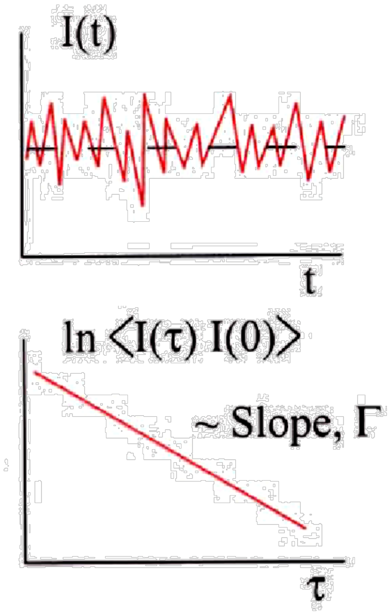


$$g_1(\tau) = \frac{\langle E^*(t+\tau)\, E(t)\rangle}{\langle |E(t)|^2\rangle}$$



Correlation Function is complex, but clearly 'something' is working!

Blood Flow Index (BFI)



Γ, exponential approximation, give $\alpha\langle\Delta r^2(\tau)\rangle$

$$\langle\Delta r^2(\tau)\rangle \sim D_b\,\tau$$

$$\alpha D_b = \text{BFI}$$

α = fraction of scatterers moving

D_b = ***effective*** diffusion constant

rBFI = **relative** blood flow change

Sensitivity to Tissue Physiology

1. Absorption Variations [$\mu_a(\lambda)$]

- Access to tissue chromophore concentrations
- **Hemoglobin Concentration (Hb), Blood Volume**
- **Blood Oxygen Saturation (HbO_2/[Hb + HbO_2])**
- Water, Lipids

2. Exogenous Contrast Agents **

- Absorption Contrast, Drugs,… [$\mu_a(\lambda)$]
- Fluorescence [c], $\tau_{lifetime}$
- Uptake & Clearance [$\mu_a(\lambda)$], [c(t)]

3. Scattering Variations [$\mu_{s'}(\lambda)$]

- Organelle Concentrations (mitochondria,…)
- Background fluids, n(λ,t).

4. Motions of Scatterers [$\langle \Delta r^2(\tau) \rangle$], Γ, BFI

- **Average Blood Flow Density**
- Brownian Dynamics

Relevant Clinical Scenarios

- **Cancer Imaging and Diagnosis**
- **Cancer Therapy monitoring**
- **Stroke detection and monitoring**
- **Mitochondial diseases**
- **Epilepsy**
- **Brain Activation**
- **Muscle Activation**
  (Peripheral Vascular Disease)

[Hb] , [HbO$_2$] , THC, StO$_2$, BFI , rBFI

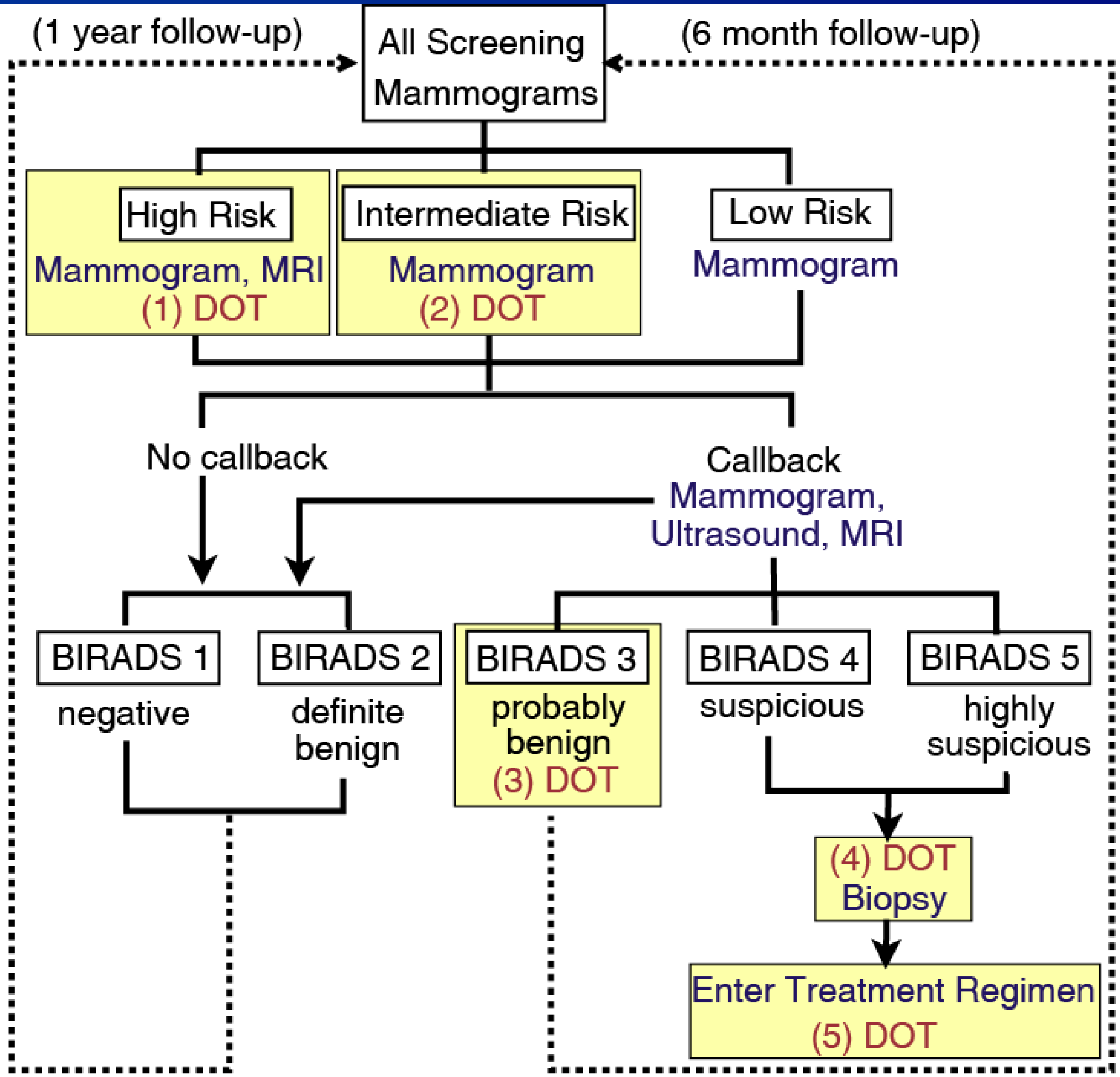
Outline

- The basic measurement techniques (DOS, DCS, DOT, FDOT)
- Breast Cancer Imaging
- Breast Monitoring (Cancer Therapy)

Potential niches for DOT in Breast Cancer

- Non-invasive
- Relatively portable, rapid and inexpensive
- Complementary contrasts (hemodynamics, water, lipid, contrast agents,…)
- Radiographically dense breasts
- Combine with other modalities

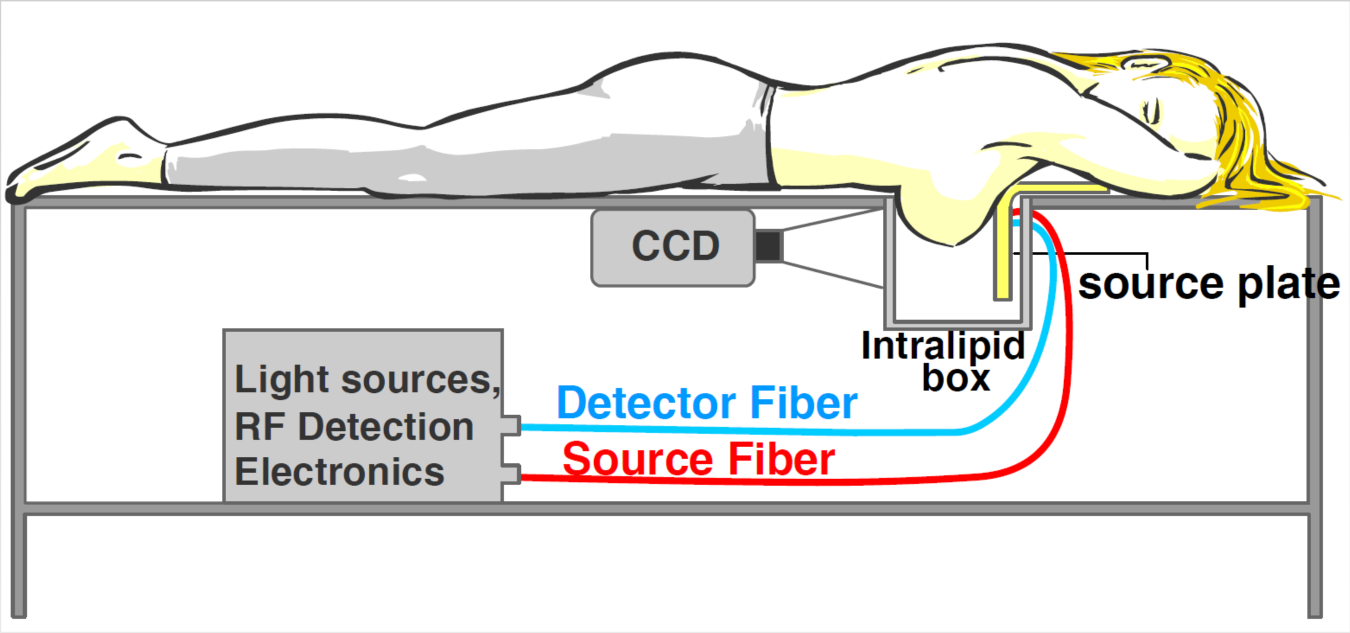
Potential niches for DOT in Breast Cancer



Diffuse Optical Tomography of Breast

Regine Choe, Soren D. Konecky, Alper Corlu, Kijoon Lee, Turgut Durduran, David R. Busch, Saurav Pathak, Brian J. Czerniecki, Julia Tchou, Douglas L. Fraker, Angela DeMichele, Britton Chance, Simon R. Arridge, Martin Schweiger, Joseph P. Culver, Mitchell D. Schnall, Mary E. Putt, Mark A. Rosen, and Arjun G. Yodh, *Journal of Biomedical Optics*, **14(2)**:024020, 2009.

Parallel-Plane DOT Instrument



Light sources
- 45 source
- 690, 750, 786, 830 nm
- 650, 905 nm

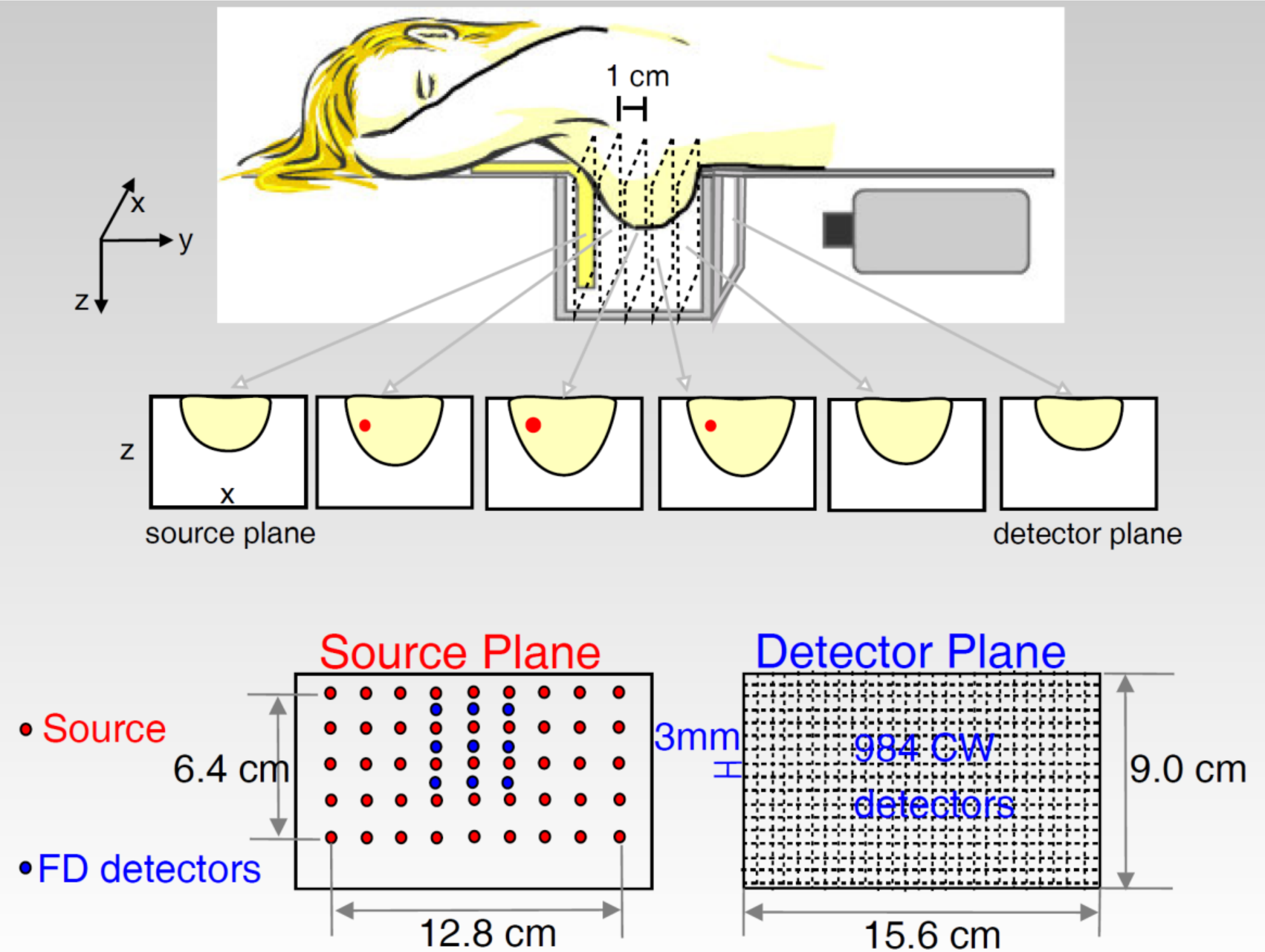
Detectors
- CCD CW Transmission
- 9 FD Remission

Other features
- matching fluid
- soft compression

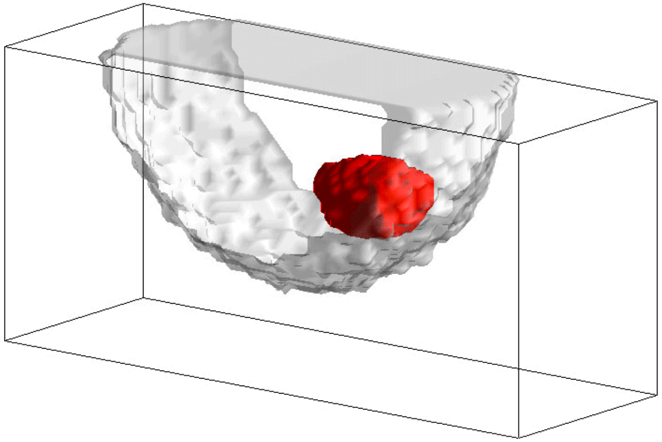
Data set : 45 x 984 x 6 ~ 250,000   Acquisition time = 8 minutes

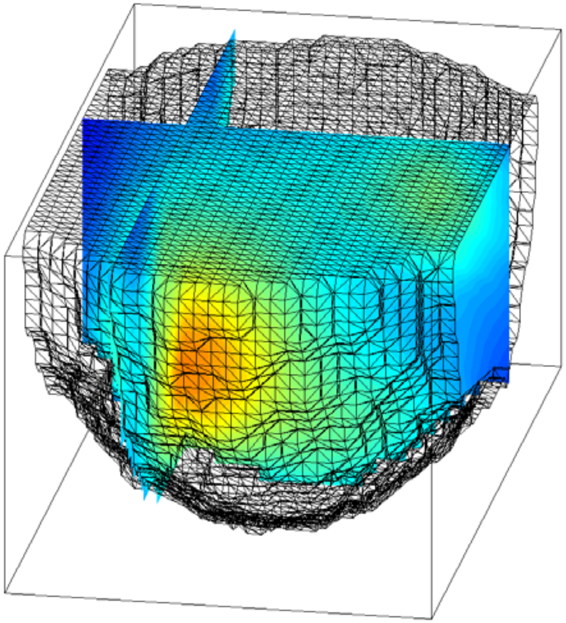
Culver, Choe, Holboke, Zubkov, Durduran, Slemp, Ntziachristos, Chance, Yodh, *Medical Physics* **30** 2003

Parallel-Plane DOT Instrument

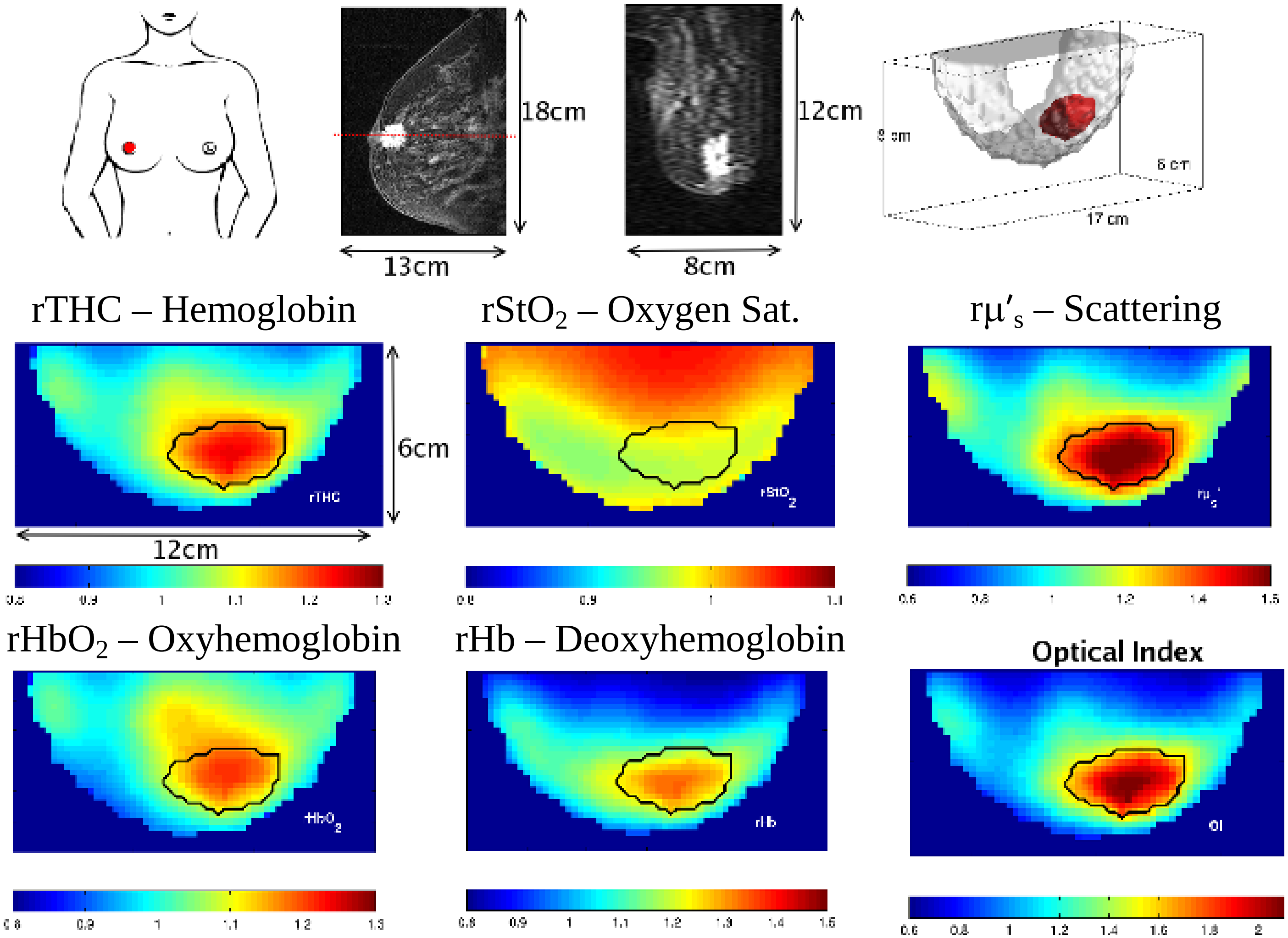


DOT image: 3D



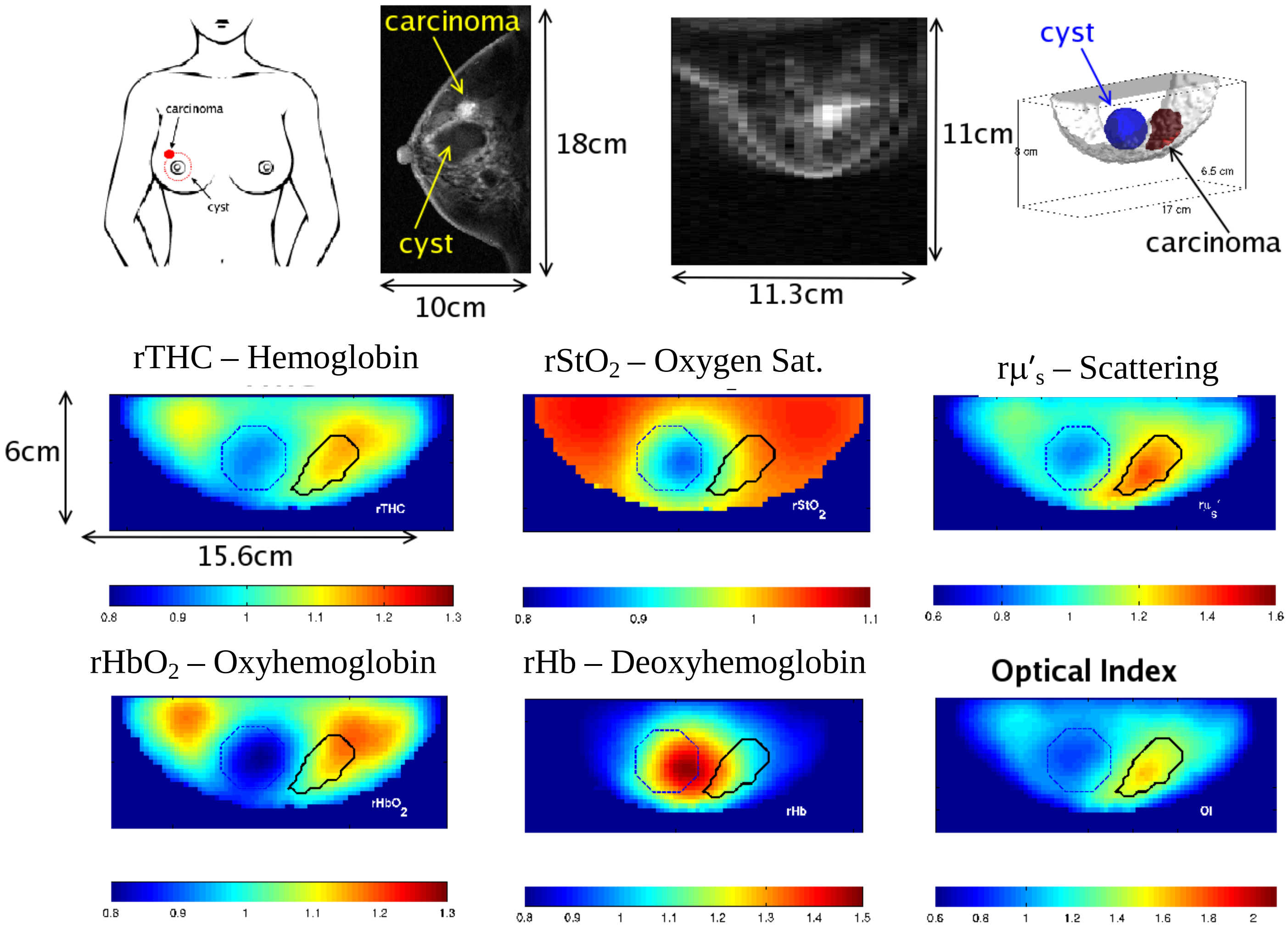


Invasive Ductal Carcinoma



- 53-year-old post-menopausal female, 2.2 cm invasive ductal carcinoma

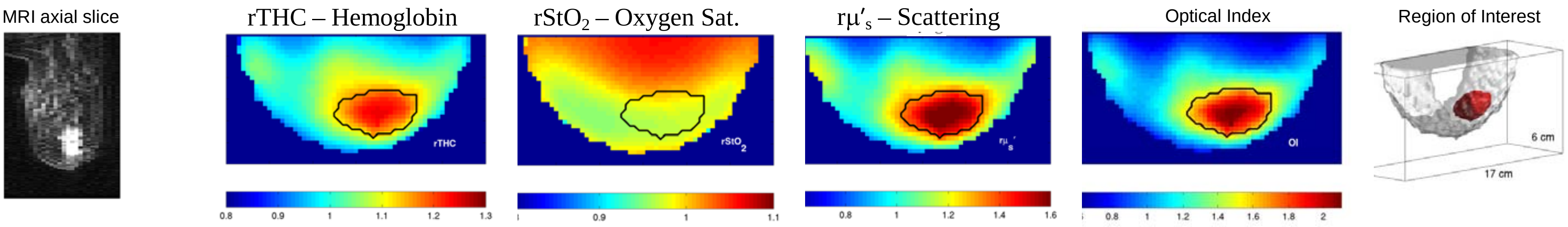
Cyst & Invasive Ductal Carcinoma



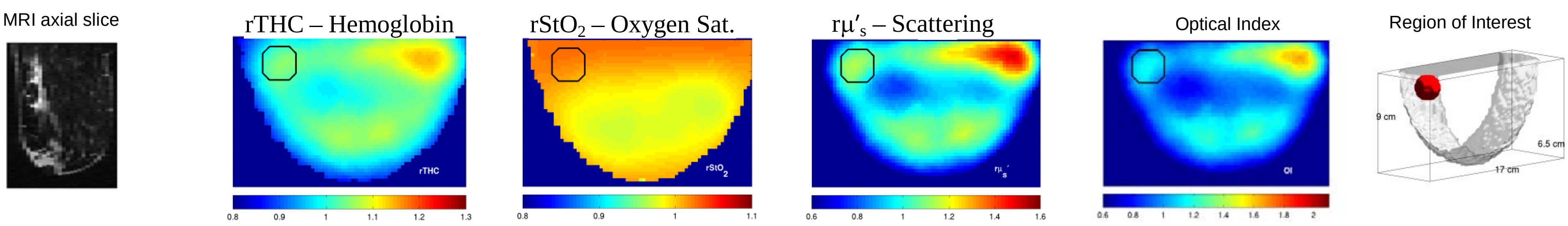
- 47-year-old pre-menopausal female, 6 cm cyst & 1.3 cm invasive ductal carcinoma

Example: Malignant vs Benign

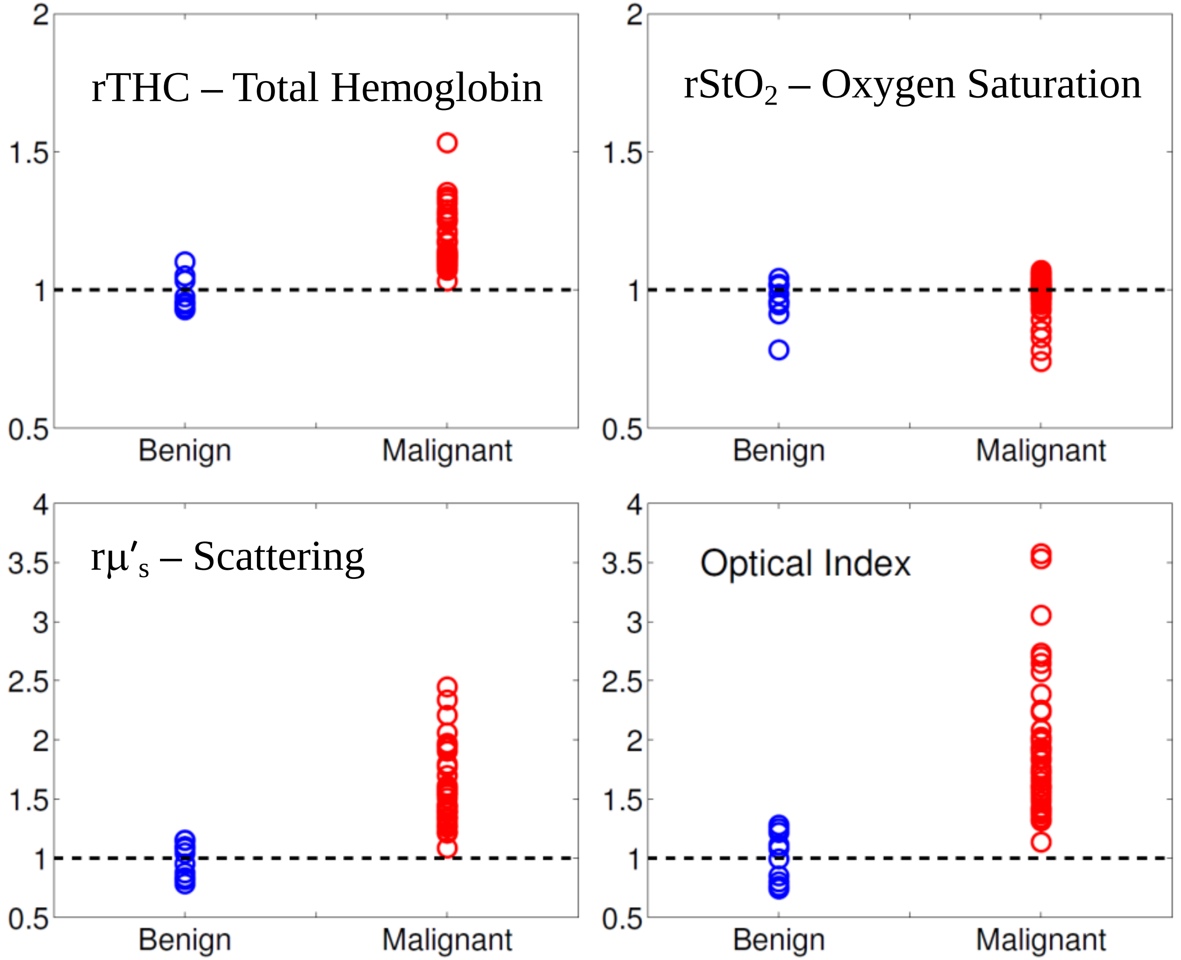
Malignant: Invasive Ductal Carcinoma



Benign: Fibroadenoma

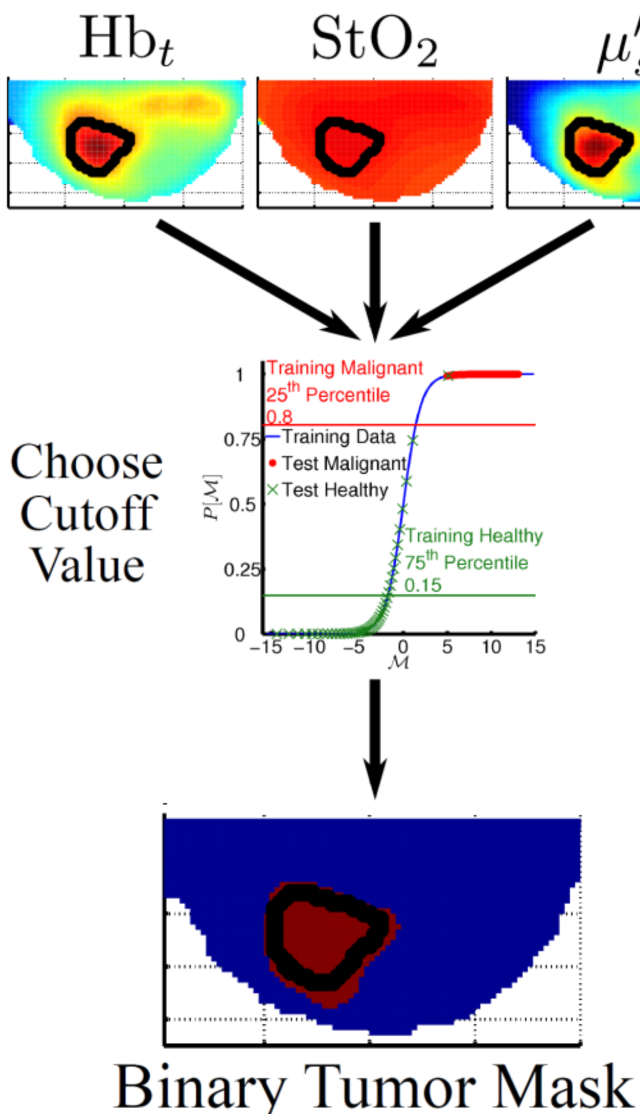


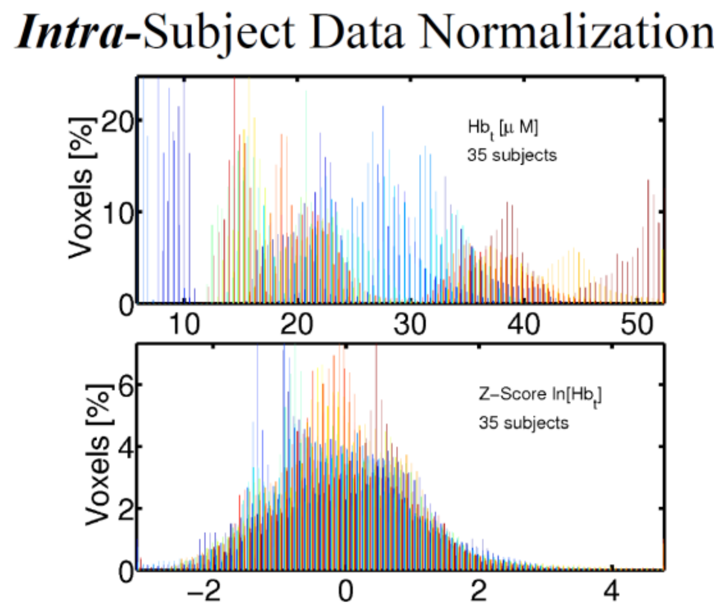
Endogenous Contrast: Benign vs Malignant (N=51)

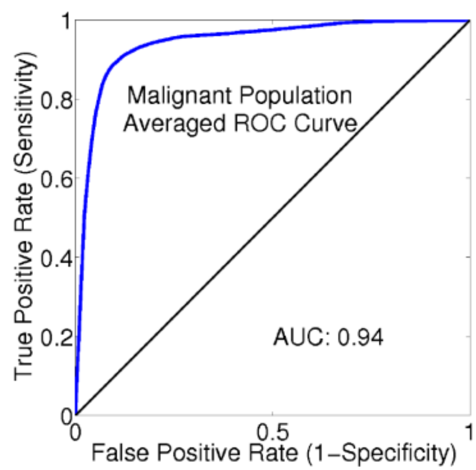


Choe, R., Konecky, S.D., Corlu, A., Lee, K., Durduran, T., Busch, D.R., Pathak,S., Czerniecki, B.J., Tchou, J., Fraker, D.L., DeMichele, A., Chance, B., Arridge, S.R., Schweiger, M., Culver, J.P., Schnall, M.D., Putt, M.E., Rosen, M.A., and Yodh, A.G., *Journal of Biomedical Optics* 14, 024020 (2009)

Future: Automated Computer Aided Cancer Detection





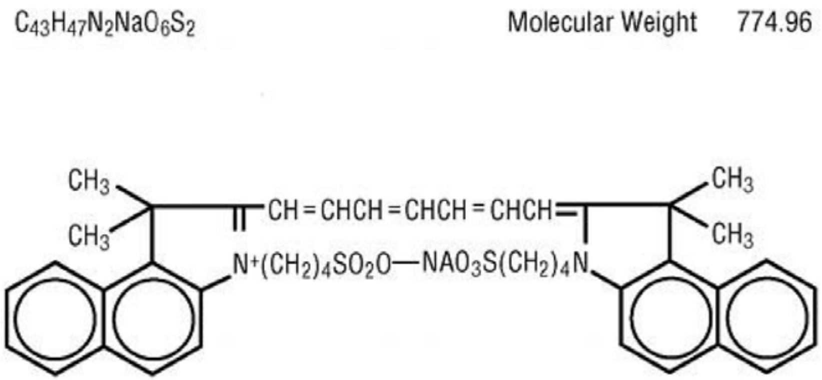


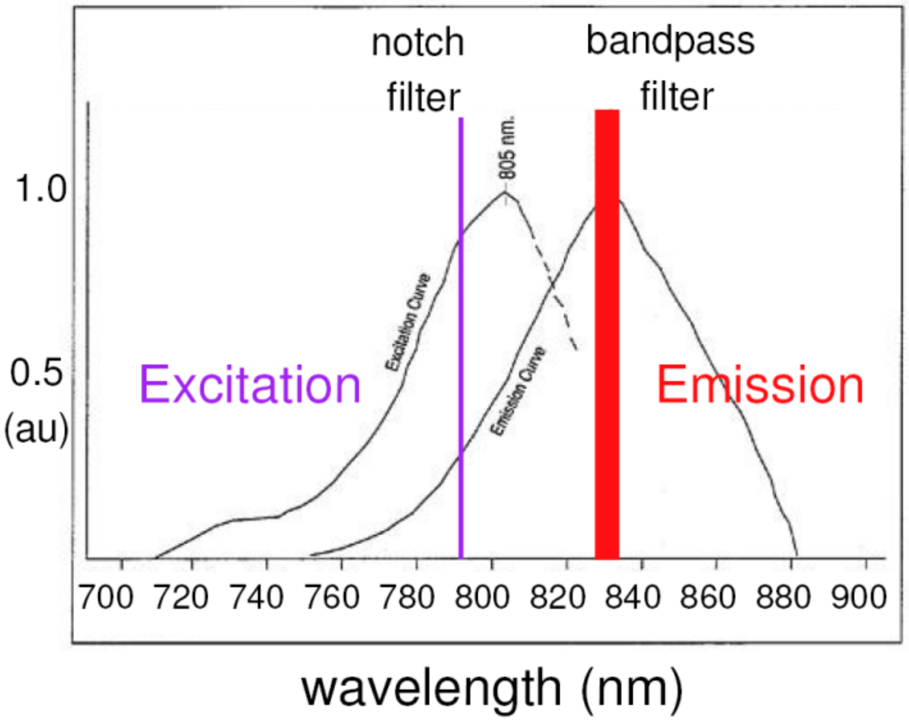
Exogenous Contrast: Fluorescence DOT

- Fluorescence signals can provide **greater detection** sensitivity and specificity compared to absorption signals.
- Access to new information: tissue pO_2, pH, intracellular calcium concentration
- Precursor to detecting cancer-targeted **molecular imaging probes** *in vivo* (e.g. dyes, molecular beacons, nanoparticles).
- Challenge: *In Vivo* Fluorescence Imaging of **Human Breast Cancer**

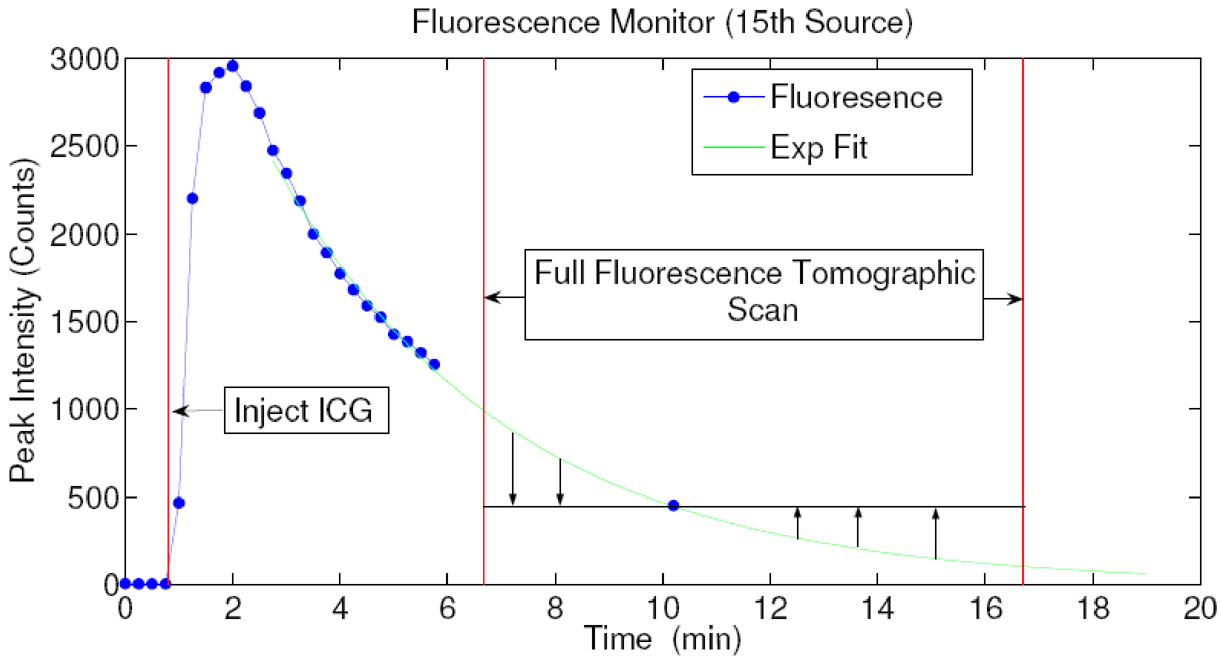
Corlu, Choe, Durduran, Rosen, Schweiger, Arridge, Yodh, *Optics Express*, **15**(11) (2007)

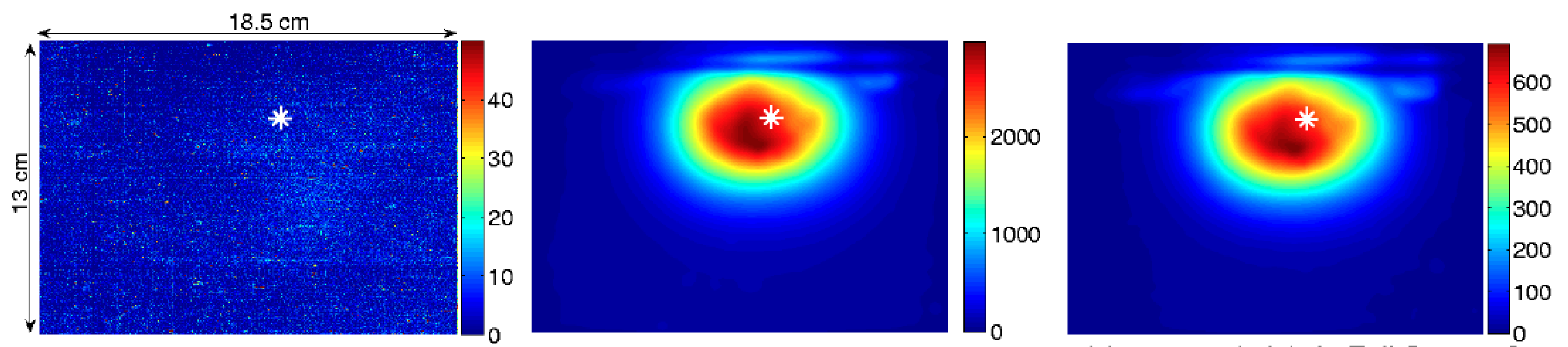
Indocyanine Green (ICG)





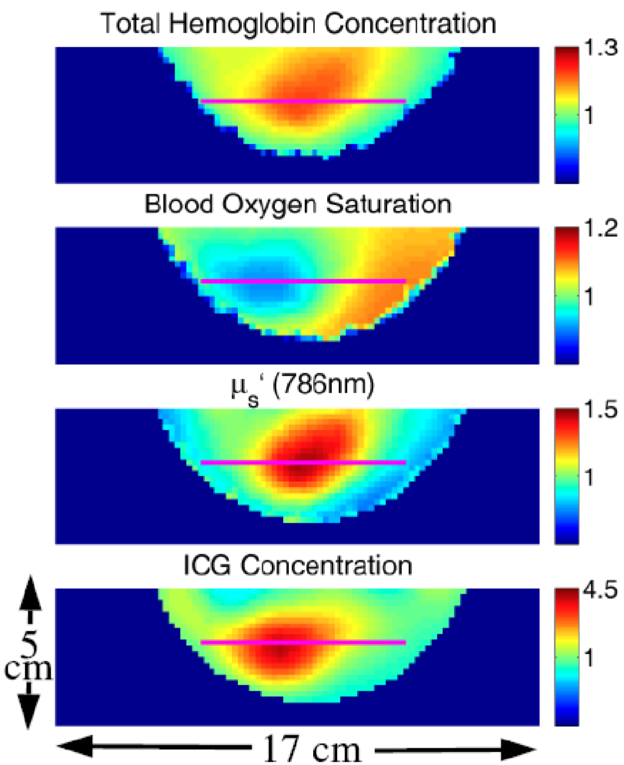
ICG Kinetics



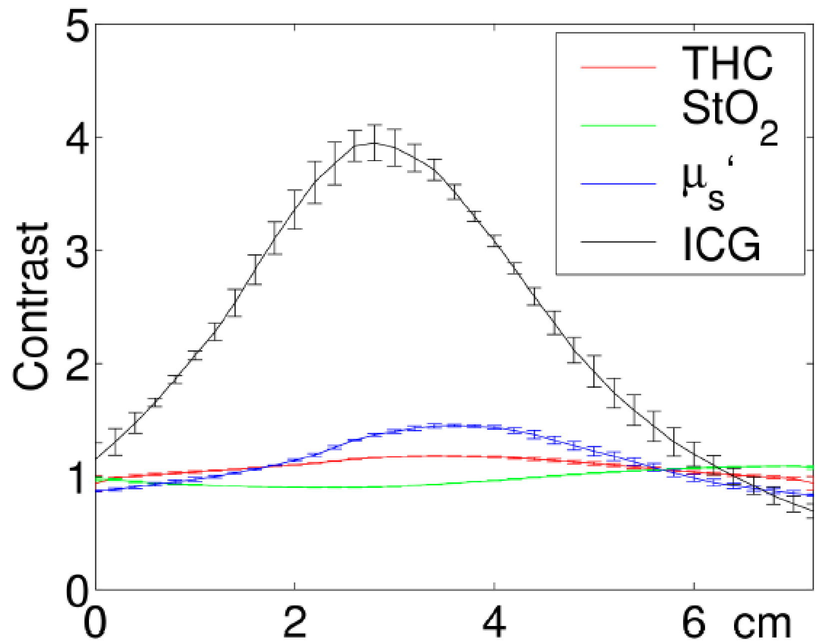


(a) t = 0 (min), No ICG Injection (b) t = 2(min), ICG Injection Peak (c) t = 10.2 (min), in Full Scan

FDOT Reconstruction (Large Contrast)



DOT Slices at y = 5 cm



- 4-fold increase in ICG concentration.
- Difference between hypervascularized and leaky regions.

$rTHC$	$rStO_2$	$r\mu_s'$	$rICG$
1.09 ± 0.03	0.91 ± 0.02	1.82 ± 0.93	3.74 ± 0.77

Future/Ongoing Improvements

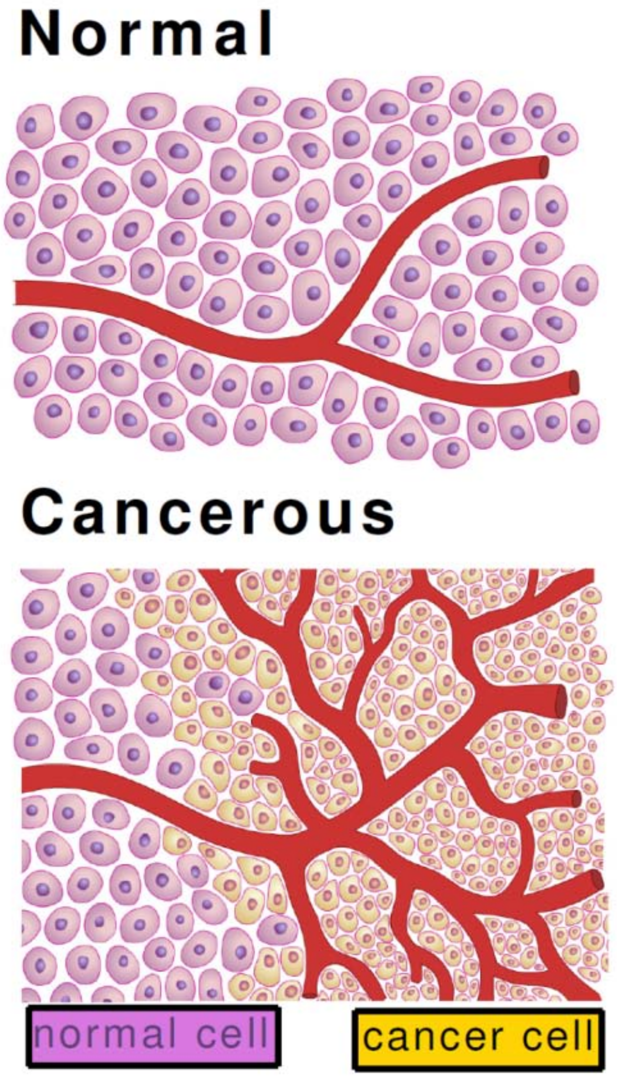
- **Image Reconstruction**
  (large data sets)
- **Image/Data Processing**
  (composite indices, automated segmentation)
- **Flow plus Oxygen gives Metabolism**
- **Contrast Agents**
  (fluorescence, nanoparticles, targeting, . . .)
- **Multi-modal Imaging & Diagnosis**
  - X-Ray
  - MRI
  - Ultrasound
  - PET

Outline

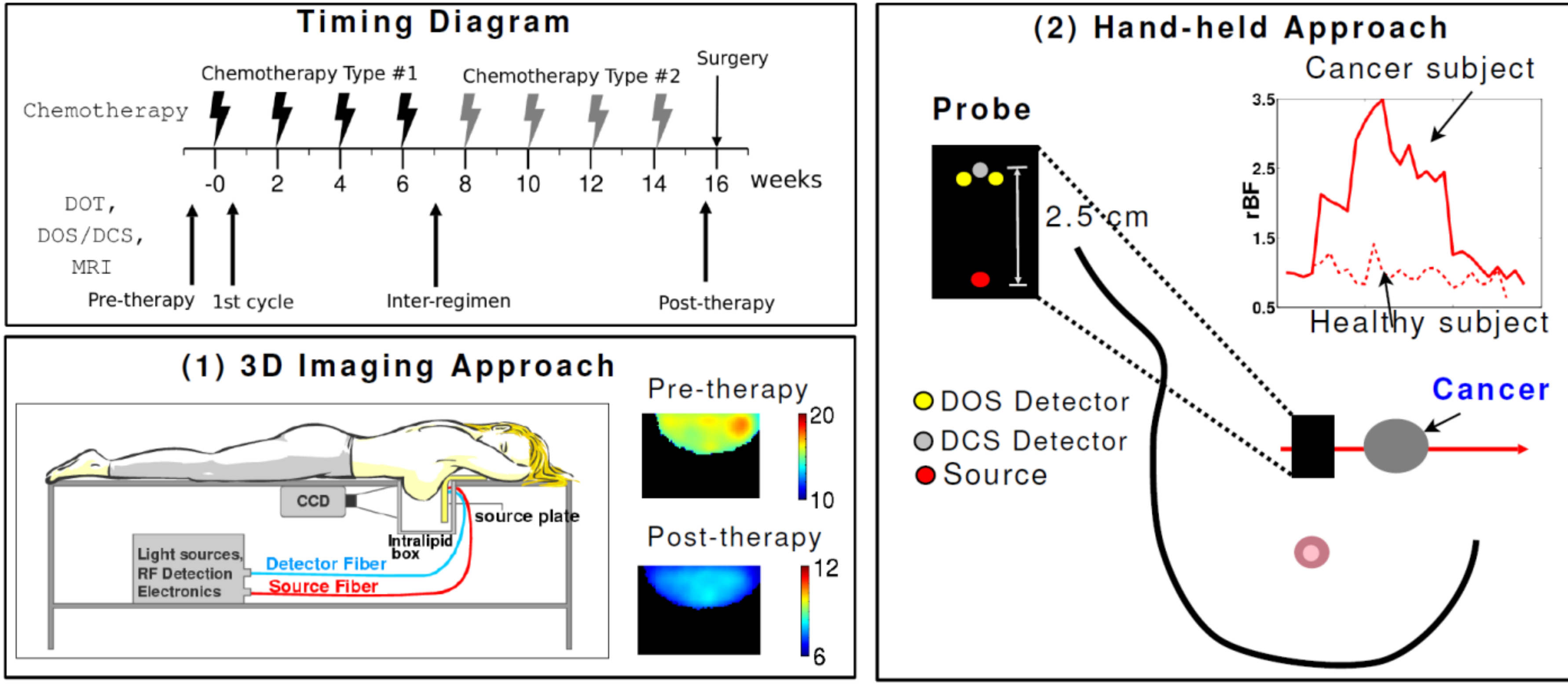
- The basic measurement techniques (DOS, DCS, DOT, FDOT)
- Breast Cancer Imaging
- Breast Monitoring (Cancer Therapy)

Cancer Therapy & Diffuse Optics

- **Cancer therapy efficacy is closely related with vascular physiology (e.g. blood flow, hypoxia).**
- **Diffuse Optics:**
  - Total hemoglobin concentration (THC),
  - Blood oxygen saturation (StO_2),
  - Microvascular blood flow (BF).
  - Inexpensive, Portable, Nonionizing radiation
  - Frequent monitoring
- **Can we predict the treatment efficacy early?**
- **Individualized therapy monitoring?**



Chemotherapy Monitoring

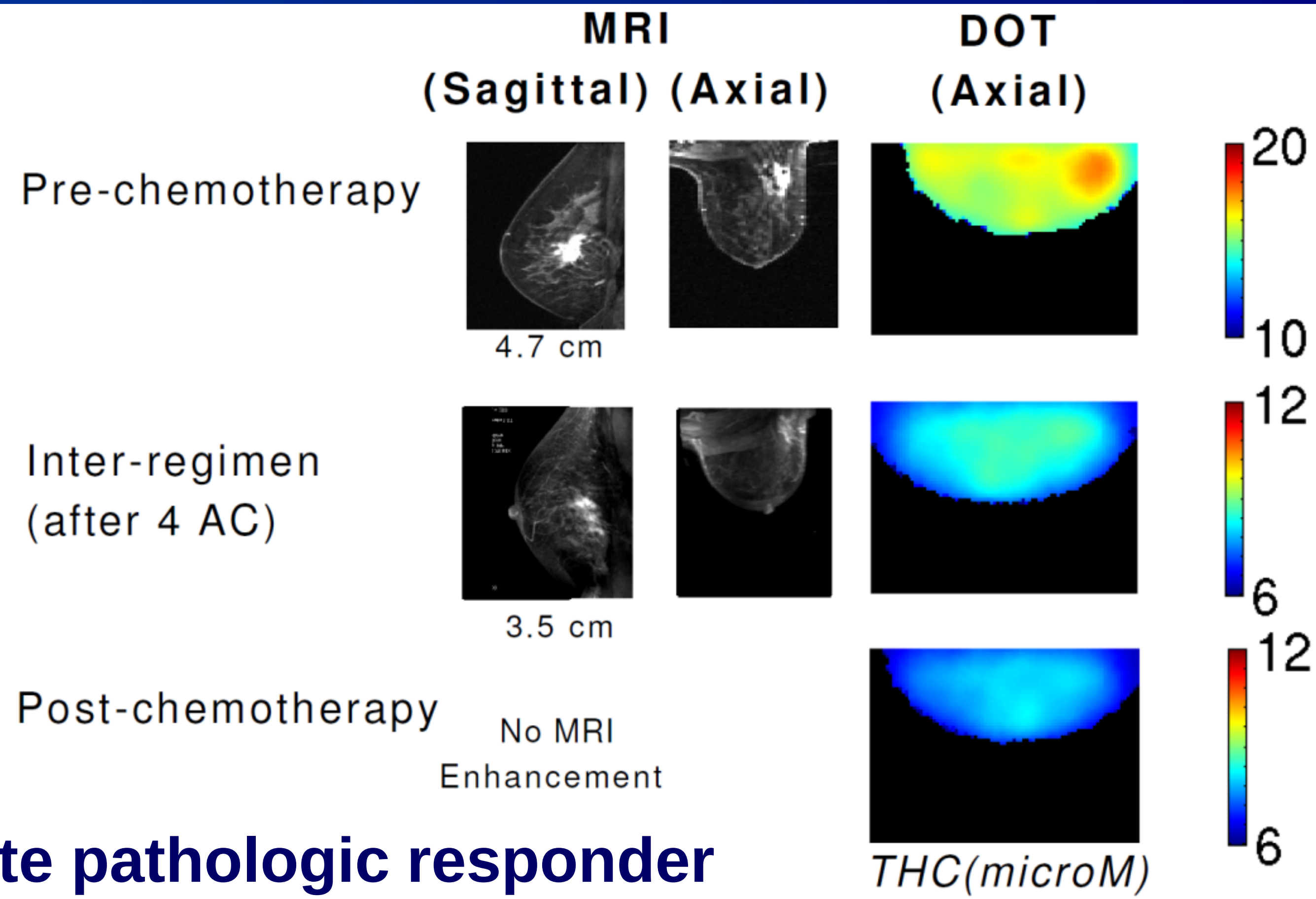


Neoadjuvant (i.e. Pre-surgical) Therapies

DOT: Diffuse Optical Tomography, DOS: Diffuse Optical Spectroscopy,

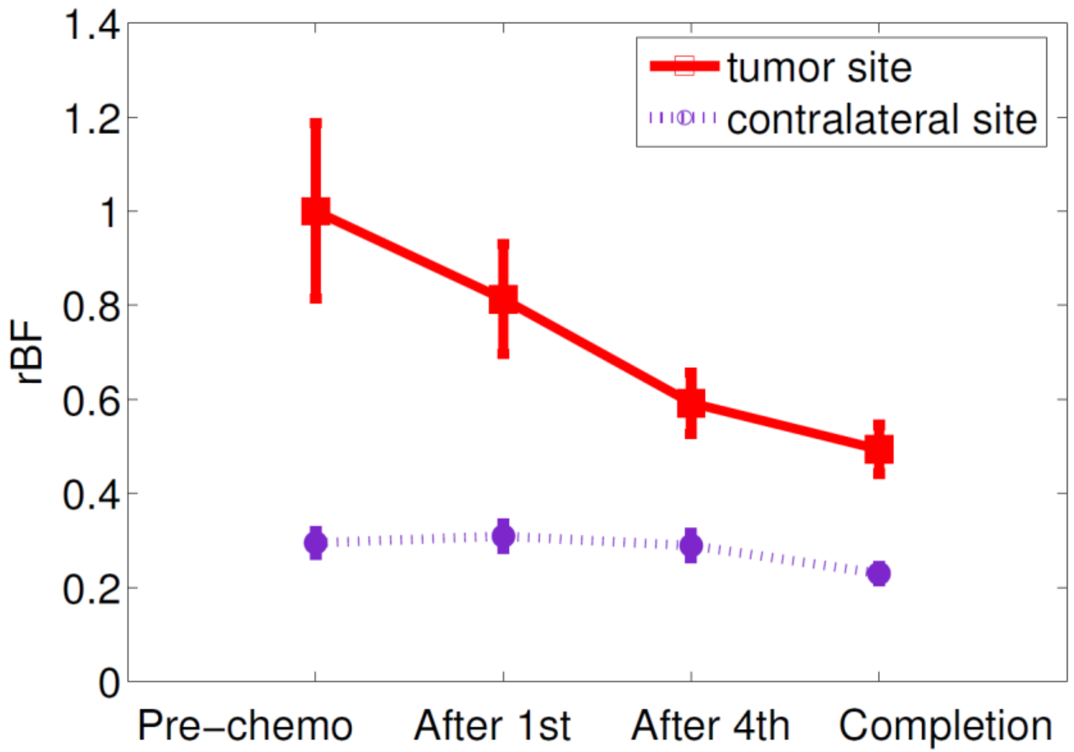
DCS: Diffuse Correlation Spectroscopy

Long Time Response (DOT, THC)



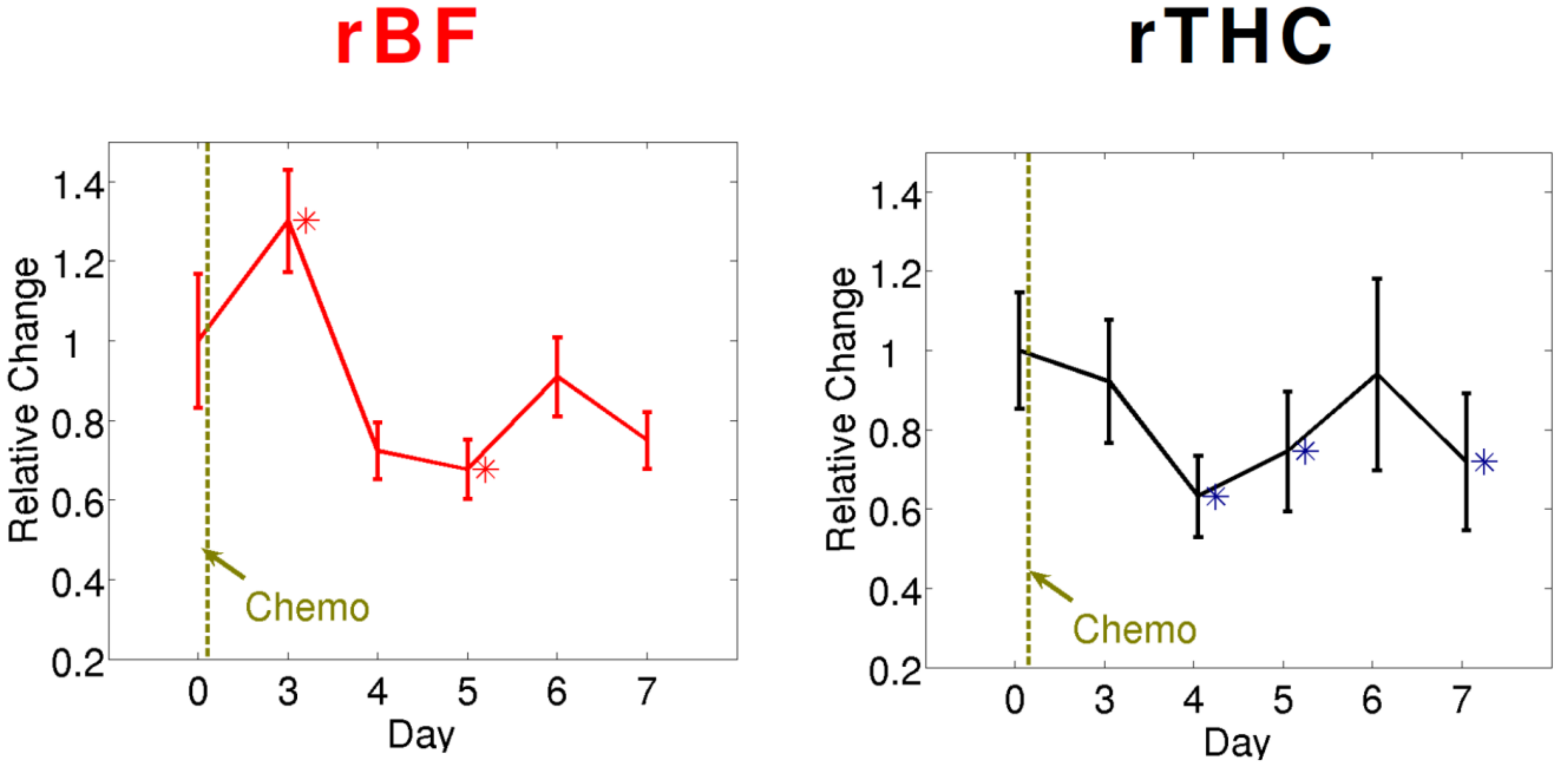
- **Complete pathologic responder**
- **Total hemoglobin concentration (THC) distribution became homogeneous**

Long Time Response (DCS, Blood Flow)



- **Relative Blood flow (rBF) = *BF/BF*$_{\textit{tumor,pre}}$**
- **Antivascular effects of chemotherapy → Blood flow decreased**

Short Time Response (N=1)



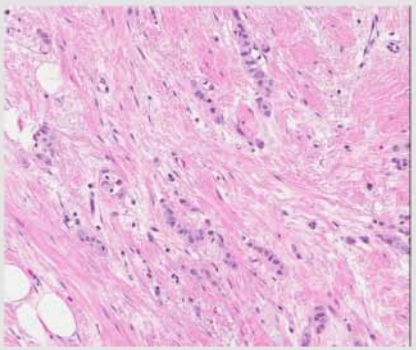
- Collaboration with UCI (Tromberg group)
- Partial responder with good response: residual carcinoma with extensive fibrosis

C. Zhou *et al.*, *Journal of Biomedical Optics*, ***12* p.051903 (2007)**

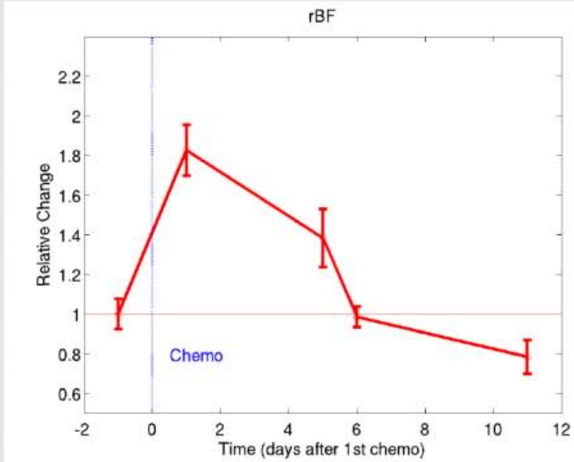
Short Time Response (N=2)

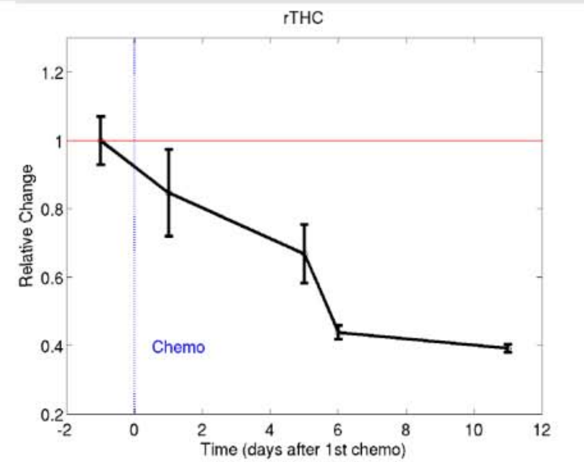
Surgical Pathology | rBF | rTHC

Good Response

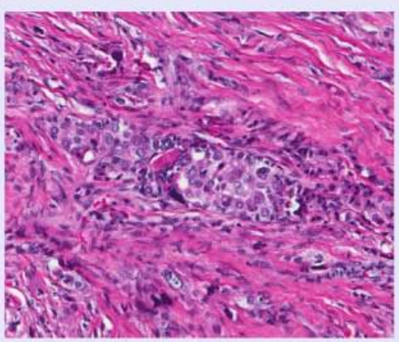


microscopic foci, fibrosis

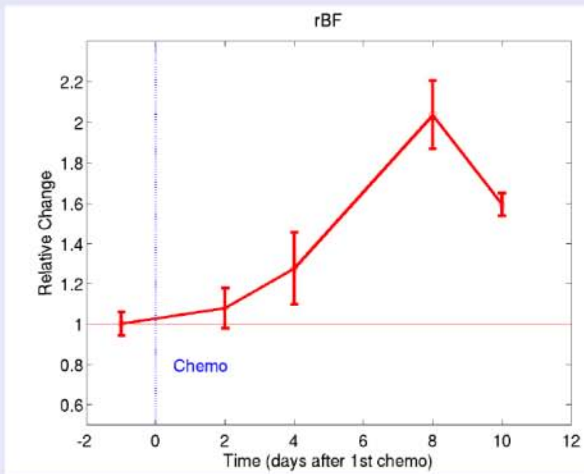


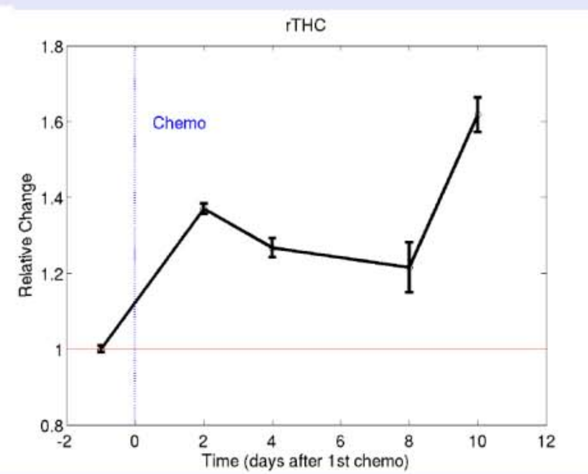


Bad Response



6cm tumor still present





Early Therapy Response

- **Good response**: rBF overshoot followed by significant ↓, rTHC ↓
- **Bad response**: rBF ↑, rTHC ↑
- ***Inflammation response followed by cancer cell death?***

Summary/Future

- **Diffuse Optics Probes Physiology of Deep Tissues.**
- **Breast Tumors, Brain, Head & Neck Tumors, Muscle ...**
- **Animal Model Research (Pre-clinical)**