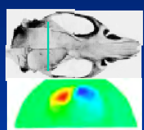
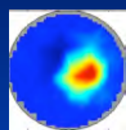
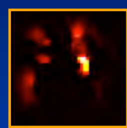
Optical Tomographic Imaging of Small Animals







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Dept. of Biomedical Engineering
Dept. of Radiology

Overview

- **Introduction**
  X-Ray Tomography vs Optical Tomography
- **Model-based iterative image reconstruction**
  Basic concepts and mathematical background
- **Instrumentation**
  General optical imaging modalities
  Dynamic optical tomography system
- **Applications**
  Brain Imaging
  Tumor Imaging
  Fluorescence Imaging

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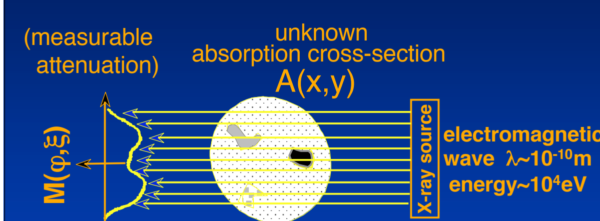
X-Ray Imaging

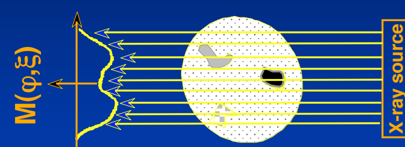
Uses X-rays to generate shadowgrams M(φ,ξ).



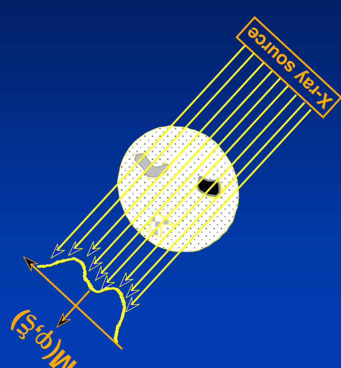
Energy propagates on straight lines through medium

X-Ray Shadowgram

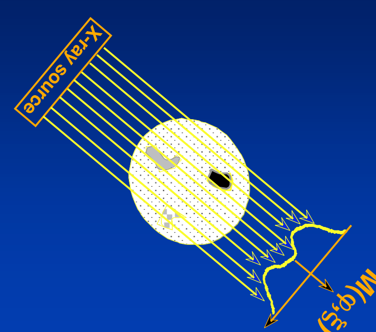
X-Ray Tomography



X-Ray Tomography

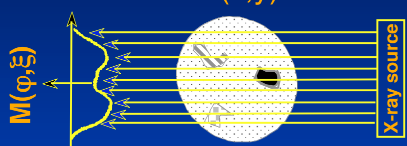


X-Ray Tomography



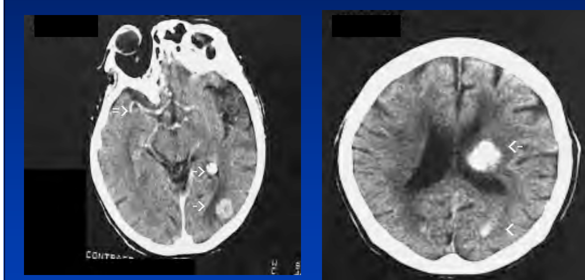
X-Ray Tomography

unknown
absorption cross-section
A(x,y)



=>Simple image reconstruction scheme: backprojection of M on lines of transmission. (Inverse Radon Transform)

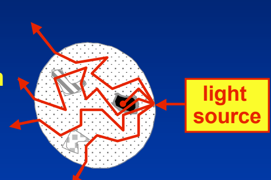
2D Scan of Head



Optical Imaging

Uses near-infrared light (700< λ<900nm)

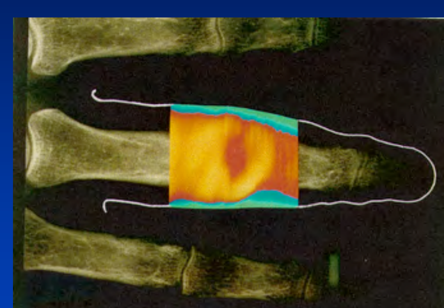
A(x,y) {unknown absorption & scattering profile}



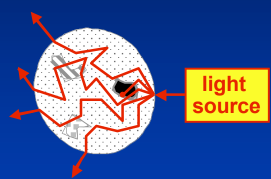
EM - wave
λ ~ 800•10^{-9}m
energy ~ 1 eV

Energy does not propagate on straight line between source and detector (light is strongly scattered)

Optical Shadowgram



Optical Tomography



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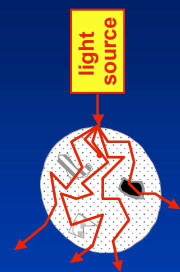

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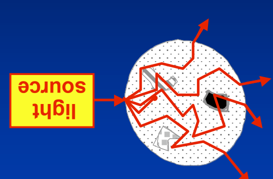
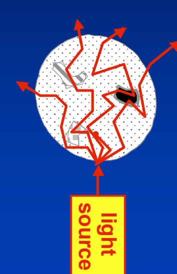


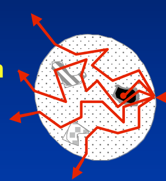
Optical Tomography



Optical Imaging

Uses near-infrared light (700< λ<900nm)

A(x,y)
{unknown
absorption
&
scattering
profile}



light source

EM - wave
$\lambda \sim 800 \cdot 10^{-9}$m
energy ~ 1 eV

How to reconstruct cross-sectional images A(x,y) from measurement on surface?
(Inverse Problem)

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Model-Based Iterative Image Reconstruction

Experiment

sources ? detectors

measured
detector readings $I_{M,i}$

Theory:
initial
guess

sources D = 1 cm²ns detectors

Forward Model, F ( )
depends on NxN unkowns

predicted
detector reading $I_{P,i}$( )

Forward Model I

3D-Time-Resolved Diffusion Equation

$$\frac{\partial U}{\partial t} = \frac{\partial}{\partial x} D \frac{\partial U}{\partial x} + \frac{\partial}{\partial y} D \frac{\partial U}{\partial y} + \frac{\partial}{\partial z} D \frac{\partial U}{\partial z} - c\mu_a U + S$$

with **c** := speed of light in medium, **S** = Source,

and **diffusion coefficient** : $D = c / (3 [\mu_a + \mu_{s'}])$

with μ_a = absorption coefficient and

$\mu_{s'}$ = reduced scattering coefficient .

Diffusion vs Transport Model

diffusion equation

$$\frac{\partial U}{\partial t} = \nabla c/(3\mu_a+3\mu_s')\,\nabla U - c\mu_a U + S$$

discretize into N spacial variables
leads to N finite-difference equations

↑ approximation

equation of radiative transport

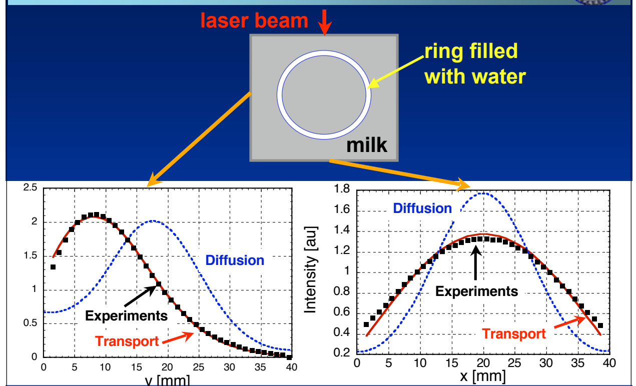
$$\partial\Psi/c\partial t = S - \Omega\nabla\Psi - (\mu_a+\mu_s)\Psi + \int_{4\pi}\Psi(\Omega')\,p(\Omega * \Omega')\,d\Omega'$$

with $U=\int_{4\pi}\Psi(\Omega')\,d\Omega'$ and $\mu_s' = (1\text{-}g)\,\mu_s$

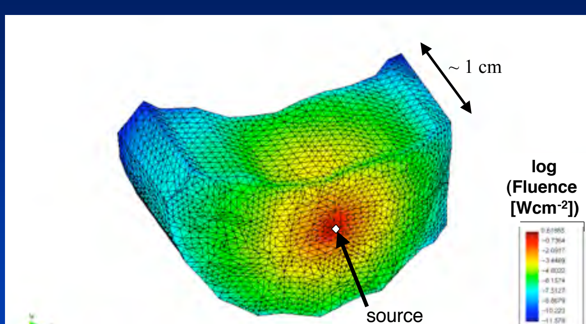
discretization into N spacial and A angular variables
leads to N x A coupled finite-difference equations

slower by factor ~A

Limits of Diffusion Model

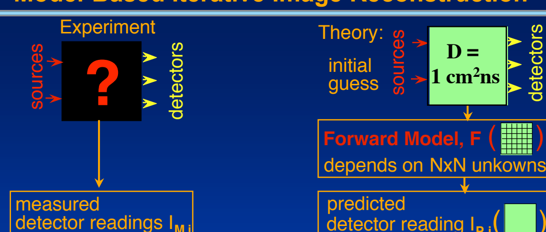


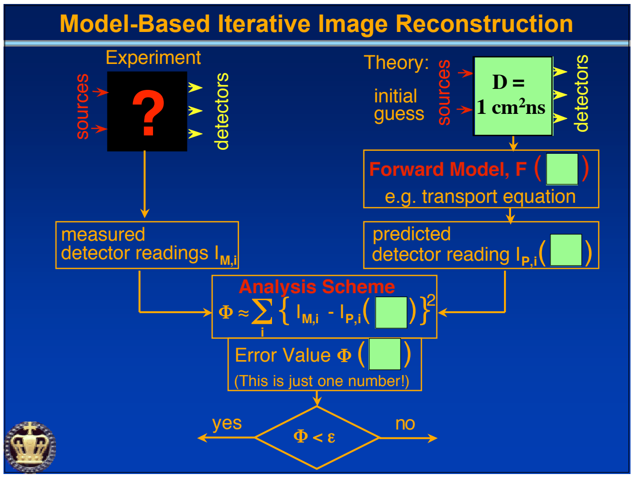
Forward Model applied to Mouse Head

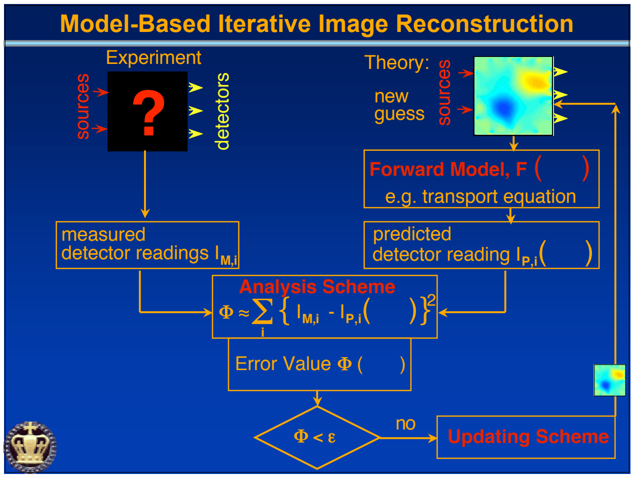


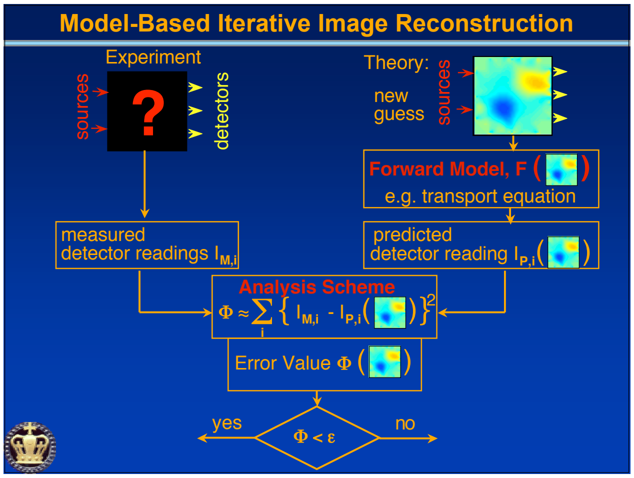
μ_a=0.1 cm^{-1} , μ_s =10 cm^{-1} ; 14781 nodes, 24 ordinates

Model-Based Iterative Image Reconstruction




Model-Based Iterative Image Reconstruction
Experiment
sources
?
detectors
Theory:
initial guess
sources
D = 1 cm²ns
detectors
Forward Model, F ( )
e.g. transport equation
measured detector readings I_M,i
predicted detector reading I_P,i( )
Analysis Scheme
Φ ≈ Σ { I_M,i - I_P,i( )}²
Error Value Φ ( )
(This is just one number!)
yes
Φ < ε
no


Model-Based Iterative Image Reconstruction
Experiment
sources
?
detectors
Theory:
new guess
sources
Forward Model, F ( )
e.g. transport equation
measured detector readings I_M,i
predicted detector reading I_P,i( )
Analysis Scheme
Φ ≈ Σ { I_M,i - I_P,i( )}²
Error Value Φ ( )
Φ < ε
no
Updating Scheme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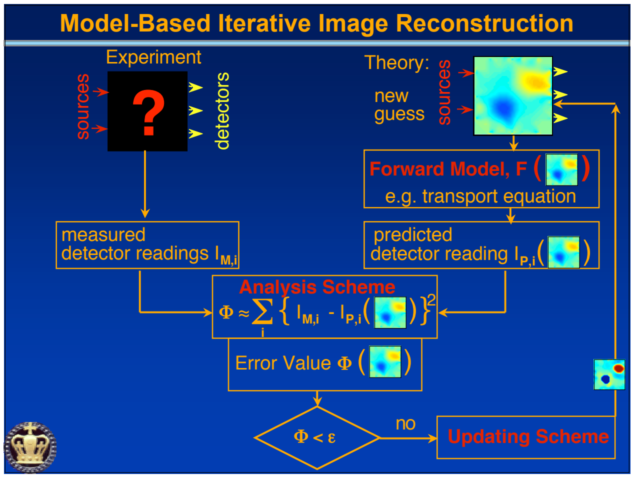
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Φ < ε
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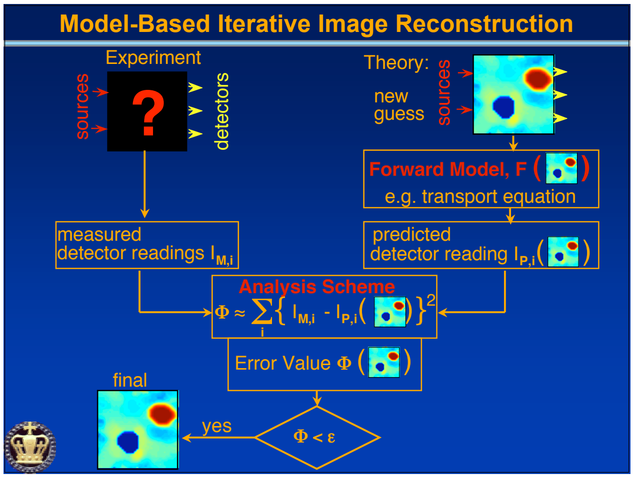
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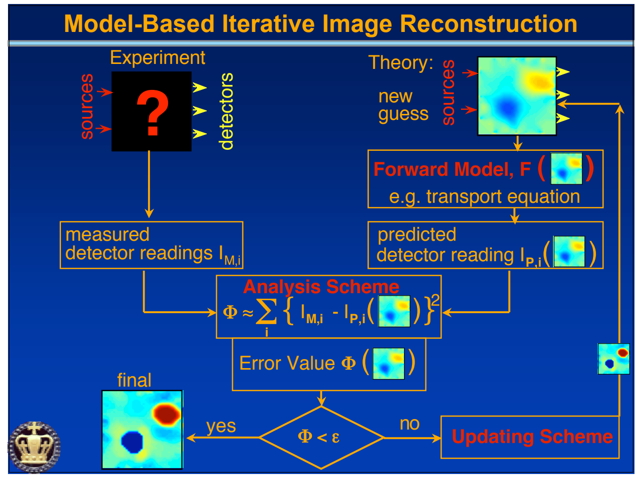
Experiment
sources
detectors
?
Theory:
new guess
sources
Forward Model, F ( )
e.g. transport equation
measured detector readings $I_{M,i}$
predicted detector reading $I_{P,i}$( )
Analysis Scheme
$\Phi \approx \sum \{ I_{M,i} - I_{P,i}( ) \}^2$
Error Value Φ ( )
final
yes
Φ < ε


Model-Based Iterative Image Reconstruction
Experiment
sources
detectors
?
Theory:
new guess
sources
Forward Model, F ( )
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no
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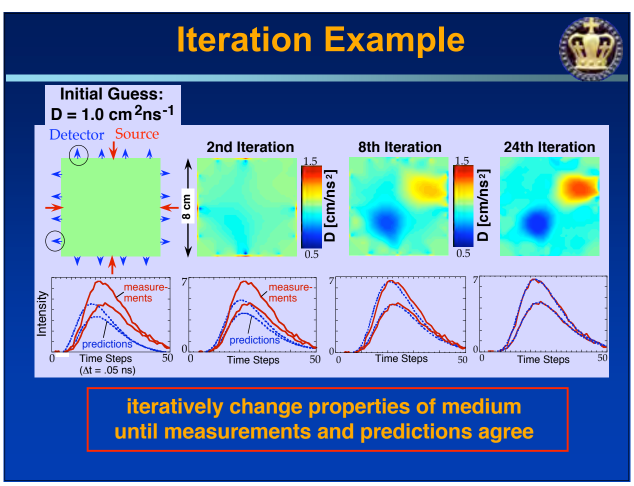

Iteration Example
Initial Guess:
D = 1.0 cm^2ns^{-1}
Detector
Source
2nd Iteration
8th Iteration
24th Iteration
8 cm
1.5
0.5
D [cm/ns2]
Intensity
measure-ments
predictions
Time Steps
(Δt = .05 ns)
0
50
7
iteratively change properties of medium
until measurements and predictions agree

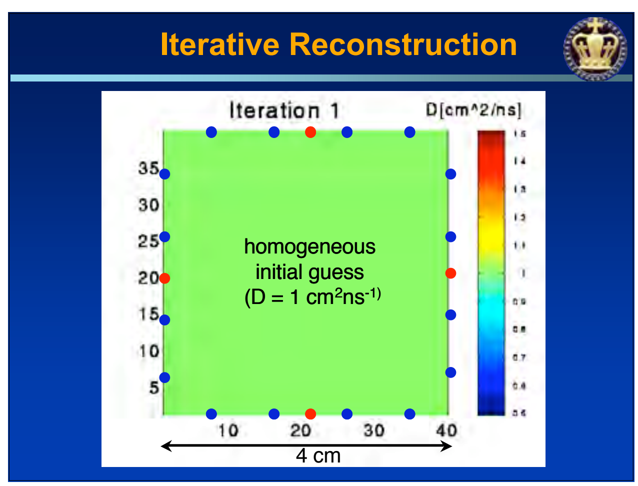
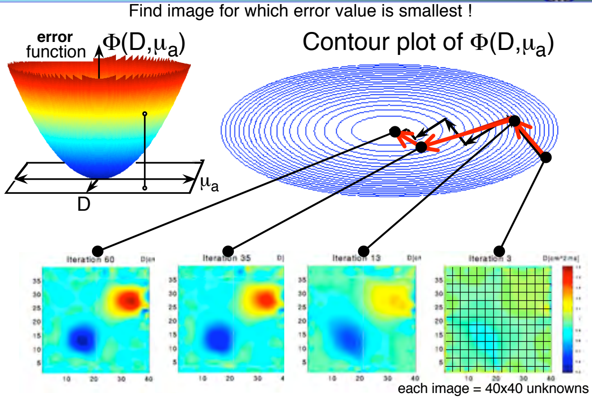

Iterative Reconstruction
Iteration 1
D[cm^2/ns]
35
30
25
20
15
10
5
10
20
30
40
4 cm
homogeneous
initial guess
(D = 1 cm^2ns^{-1})

Image Reconstruction as an Optimization Problem

Find image for which error value is smallest !



Data Analysis Scheme

Measurement Data **Y** Predicted data **U**

$$\Phi(\mu_a,D) = \sum_s \sum_d \sum_t \frac{(Y_{sdt} - U_{sdt}(\mu_a,D))^2}{2\sigma^2_{sdt}}$$

Objective Function = χ^2 Error Function

Goal : Find minimum of $\Phi(\mu_a,D)$

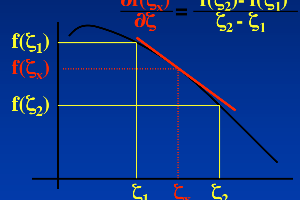
Employ minimization technique that uses information about gradient $\frac{d\Phi(\mu_a,D)}{d(\mu_a,D)}$.

Gradient Calculation

Divided Difference

1 variable: 2 forward calculations needed to get gradient

$$\frac{\partial f(\zeta_x)}{\partial \zeta} = \frac{f(\zeta_2) - f(\zeta_1)}{\zeta_2 - \zeta_1}$$



Therefore,
For problem with N unknowns one needs 2N forward calculations to find gradient.

Gradient Calculation

Divided Difference

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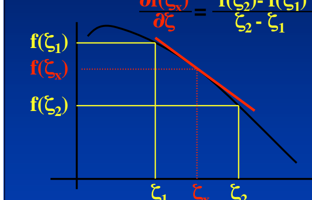

Therefore,
For problem with N unknowns one needs 2N forward calculations to find gradient.

Adjoint Differentiation

The evaluation of a gradient requires never more than five times the effort of one forward calculation!

A. Griewank, "On Automatic Differentiation," in Mathematical Programming, M. Iri, K. Tanabe, eds., Kluwer Academic Publishers, 1989, pp.83-107.

Therefore, adjoint differentiation method is 2N/5 times faster than "traditional" divided difference scheme!

For more details see:

G. Abdoulaev, K. Ren, A.H. Hielscher, "Optical tomography as a constrained optimization problem," accepted for publication in *Inverse Problems*.

K. Ren, G. Abdoulaev, G. Bal, A.H. Hielscher, "Frequency-domain optical tomography based on the equation of radiative transfer," accepted for publication in *SIAM Journal of Scientific Computing*.

K. Ren, G. Abdoulaev, G. Bal, A.H. Hielscher, "An algorithm for solving the equation of radiative transfer in the frequency domain," *Optics Letters* 29(6), pp. 578-580 (2004).

G. Abdoulaev and A.H. Hielscher, "Three-dimensional optical tomography with the equation of radiative transfer," *Journal of Electronic Imaging* 12(4), pp. 594-60 (2003).

A.H. Hielscher, A.D. Klose, U. Netz, J. Beuthan, "Optical tomography using the time-independent equation of radiative transfer. Part 1: Forward model," *Journal of Quantitative Spectroscopy and Radiative Transfer*, Vol 72/5, pp. 691-713, 2002.

A.D. Klose, A.H. Hielscher, "Optical tomography using the time-independent equation of radiative transfer. Part 2: Inverse model," *Journal of Quantitative Spectroscopy and Radiative Transfer*, Vol 72/5, pp. 715-732, 2002.

A.D. Klose and A.H. Hielscher, "Iterative reconstruction scheme for optical tomo-graphy based on the equation of radiative transfer," *Medical Physics*, vol. 26, no. 8, pp. 1698-1707, 1999.

A.H. Hielscher, A.D. Klose, K.M. Hanson, "Gradient-based iterative image recon-struction scheme for time-resolved optical tomography," *IEEE Transactions on Medical Imaging* 18, pp. 262-271, 1999.

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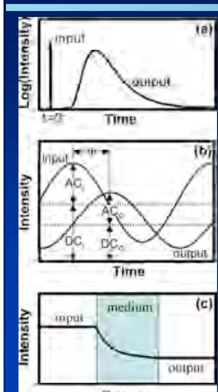
Optical Imaging Modalities



TIME DOMAIN

FREQUENCY DOMAIN

STEADY-STATE DOMAIN

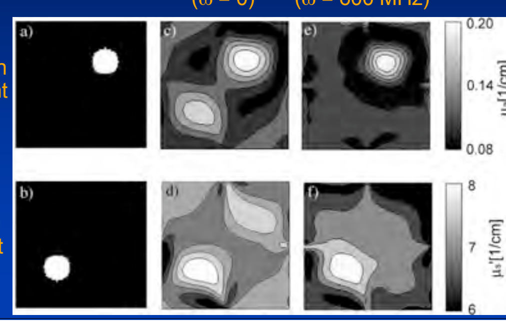
information content ↑

complexity/price of system ↑ (100k → 1 M)

data acquisition rate ↓ (1 image /min → 10 images /sec)

Frequency vs Steady-State Domain

	target	steady-state domain reconstruction ($\omega = 0$)	frequency domain reconstruction (ω = 600 MHz)
absorption coefficient μ_a			
scattering coefficient μ_s'			



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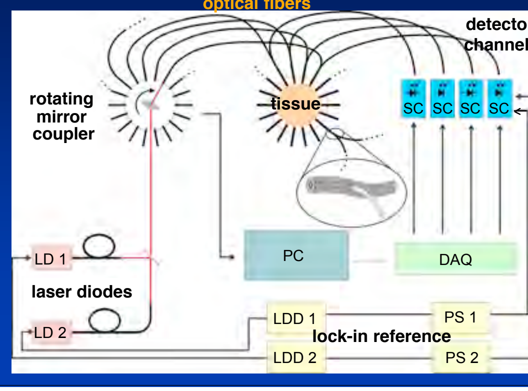
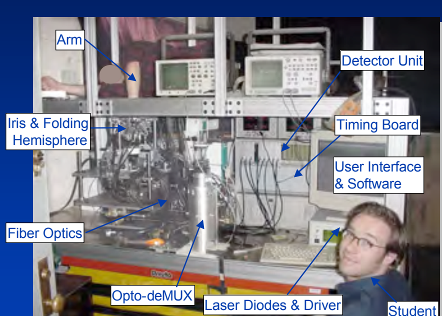
Instrument Diagram



Dynamic Optical Tomography System (DYNOT)



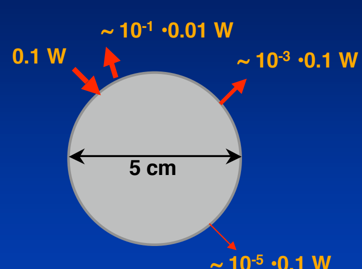
Up to 10 full tomographic images per second!

Dynamic Optical Tomography System (details)

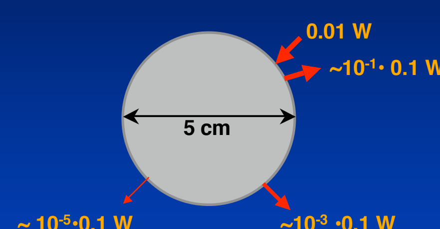
Detector and Timing Boards

Dynamic Optical Tomography System (DYNOT)

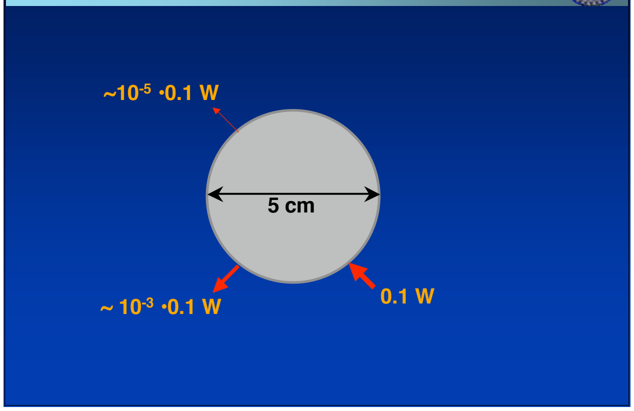
Dynamic Range of Measurement



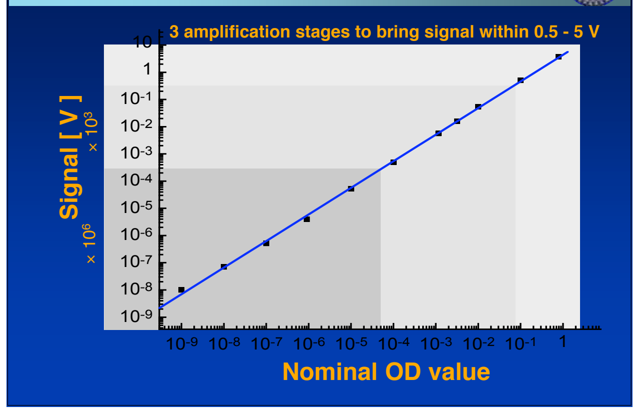
Dynamic Range of Measurement



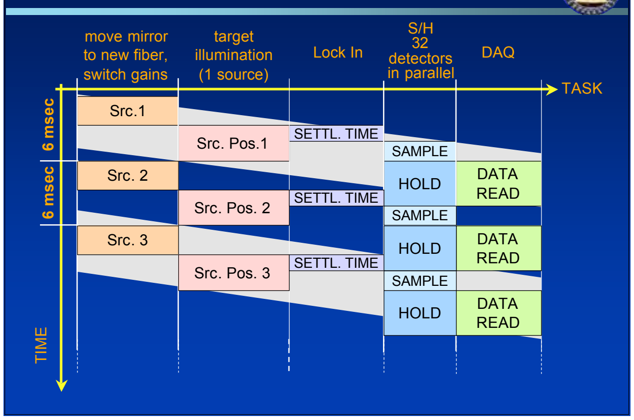
Dynamic Range of Measurement



Dynamic Range of Detectors



Timing Scheme



Performance Overview

Parameter	Value
Modulation frequency	5-10 kHz
Data acquisition rate	~150 Hz
Settling time	1-2 ms
Noise equivalent power	10 pW (rms)
Dynamic range	1:10^9 (180 dB)
Long term bias drifts	~1% over 30 min
Background light reject	~100 dB

For more details see:

A.H. Hielscher, A.Y. Bluestone, G.S.Abdoulaev, A.D. Klose, J. Lasker, M. Stewart, U. Netz, J. Beuthan, "Near-infrared diffuse optical tomography," *Disease Markers* 18(5-6), pp. 313-337 (2002).

C.H. Schmitz, M. Löcker, J.M. Lasker, A.H. Hielscher, R.L. Barbour, "Instrumentation for fast functional optical tomography," *Rev. of Scientific Instrumentation* 73(2), pp. 429-439 (2002).

C.H. Schmitz, Y. Pei, H.L. Graber, J.M. Lasker, A.H. Hielscher, R.L. Barbour, "Instrumentation for real-time dynamic optical tomography," in *Photon Migration, Optical Coherence Tomography, and Microscopy*, S. Andersson-Engels, M.F. Kaschke, eds., SPIE-The International Society for Optical Engineering, Proc. 4431, pp. 282-291, 2001.

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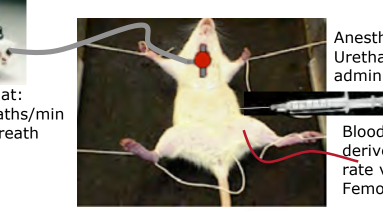
Animal Model

Ventilated at:
40-60 breaths/min
1-1.5 cc/breath

Regulate inspired $[O_2]$ and $[CO_2]$

325 gm
Sprague Dawley Rats

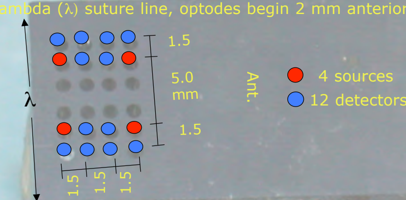


Anesthesia: Urethane administered *i.p.*

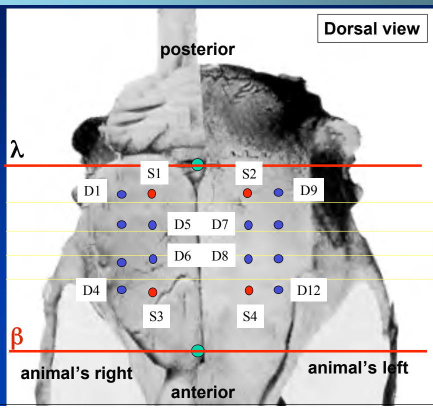
Blood Pressure and derived respiratory rate via Femoral catheter

Probe Geometry

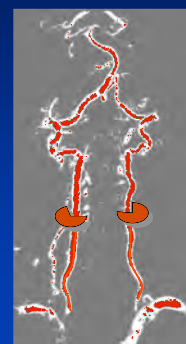
- Forehead shaven
- Animal's head fixed in place using stereotaxic
- Optical probe with fixed geometry positioned in line with lambda (λ) suture line, optodes begin 2 mm anterior to λ.



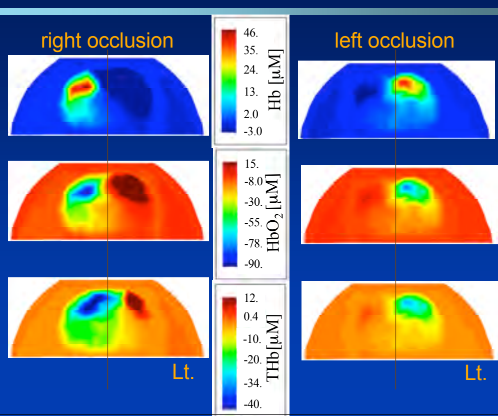
Probe Location



Carotid Occlusion

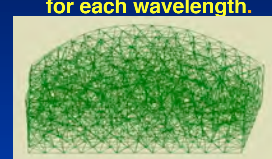


Carotid Occlusion



Two Wavelengths (λ_1, λ_2)

Reconstruction algorithm provides $\Delta\mu_a$ for each volume element (voxel) of finite element mesh for each wavelength.



For each voxel we get two equations:

$$\Delta\mu_a^{\lambda 1} = \varepsilon_{Hb}^{\lambda 1}\ \Delta[Hb] + \varepsilon_{HbO_2}^{\lambda 1}\ \Delta[HbO_2]$$

$$\Delta\mu_a^{\lambda 2} = \varepsilon_{Hb}^{\lambda 2}\ \Delta[Hb] + \varepsilon_{HbO_2}^{\lambda 2}\ \Delta[HbO_2]$$

ε := extinction coefficient (from literature)

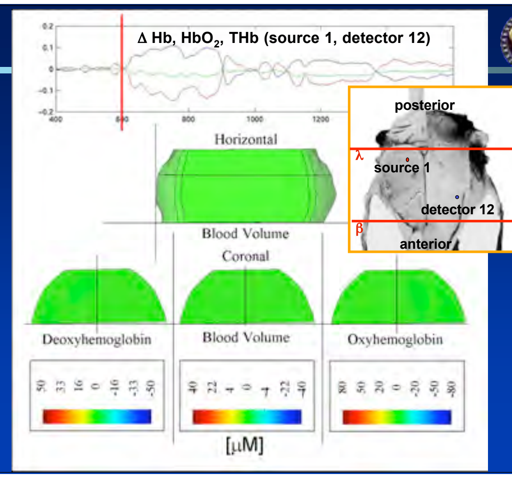
Two Wavelengths

Reconstruction algorithm provides $\Delta\mu_a$
for each volume element (voxel) of finite element mesh
for each wavelength.

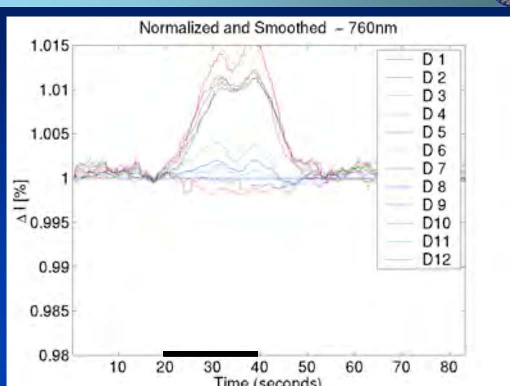
From this we can calculate changes in concentrations of oxy-hemoglobin, $\Delta[Hb]$, and dexoy-hemoglobin, $\Delta[HbO_2]$, for each voxel.

$$\Delta[Hb] = \frac{\varepsilon_{HbO_2}^{\lambda 2}\Delta\mu_a^{\lambda 1} - \varepsilon_{HbO_2}^{\lambda 1}\Delta\mu_a^{\lambda 2}}{\varepsilon_{Hb}^{\lambda 1}\,\varepsilon_{HbO_2}^{\lambda 2} - \varepsilon_{Hb}^{\lambda 2}\,\varepsilon_{HbO_2}^{\lambda 1}}$$

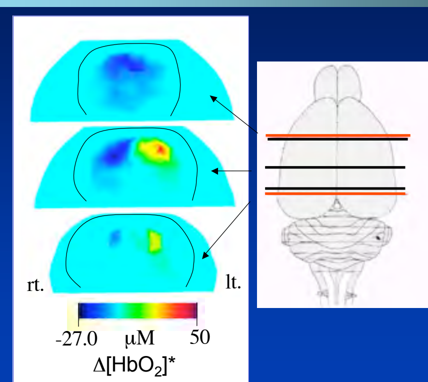
$$\Delta[HbO_2] = \frac{\varepsilon_{Hb}^{\lambda 1}\Delta\mu_a^{\lambda 2} - \varepsilon_{Hb}^{\lambda 2}\Delta\mu_a^{\lambda 1}}{\varepsilon_{Hb}^{\lambda 1}\,\varepsilon_{HbO_2}^{\lambda 2} - \varepsilon_{Hb}^{\lambda 2}\,\varepsilon_{HbO_2}^{\lambda 1}}$$



Forepaw Stimulation

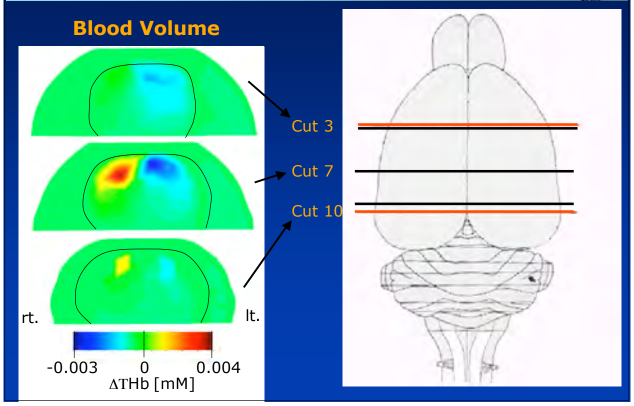


Right Forepaw Stimulation



*Oxyhemoglobin

Reconstruction



For more details see:

A.Y. Bluestone, M. Stewart, B. Lei, I.S. Kass, J. Lasker, G.S. Abdoulaev, A.H. Hielscher, "Three-dimensional optical tomographic brain imaging in small animals, Part I: Hypercapnia," *Journal of Biomedical Optics* 9(5), pp. 1046-1062 (2004).

A.Y. Bluestone, M. Stewart, J. Lasker, G.S. Abdoulaev, A.H. Hielscher, "Three-dimensional optical tomographic brain imaging in small animals, Part II: Unilateral Carotid Occlusion," *Journal of Biomedical Optics* 9(5), pp. 1063-1073 (2004).

A.Y. Bluestone, Kenichi Sakamoto, A.H. Hielscher, M. Stewart, "Three-Dimensional Optical Tomographic Brain Imaging during Kainic-Acid-Induced Seizures in Rats," in *Physiologu, Function, and Structure from Medical Images,* A. Amini, A. Manduca, eds., SPIE-The International Society for Optical Engineering, Proc. 5746, pp. 58-66 (2005).

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Overview

- **Introduction**
  - X-ray vs optical tomography
- **Model-based iterative image reconstruction**
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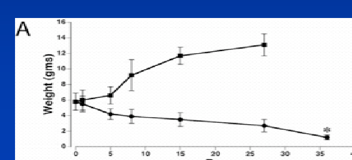
- **Instrumentation**
  - Static Measurements
  - Dynamic Measurements
- **Applications**
  - Brain Imaging
  - Tumor Imaging
  - Fluorescence Imaging

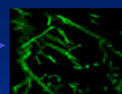
Tumors in Mice

- **Tumor is injected into mouse left kidney.**
- **Tumor continues to grow unless treated.**
- **Treatment with VEGF antagonist seeks to stop angiogenesis and reverse tumor growth.**

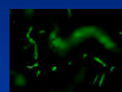


Tumors in Mice

- Untreated tumors: highly vascularized



- Treated tumors: much less vascularized



Fluorescent staining with Lectin (10 x)

- Currently:
  Many mice are sacrificed to get tumor data
- Only 1 time point per mouse
- We propose to use MRI and OT to study tumor size and vasculature in vivo

More Information:

Frischer JS, Huang JZ, Serur A, Kadenhe-Chiweshe A, McCrudden KW, O'Toole K, Holash J, Yancopoulos GD, Yamashiro DJ, Kandel JJ "Effects of potent VEGF blockade on experimental Wilms tumor and its persisting vasculature" INTERNATIONAL JOURNAL OF ONCOLOGY 25 (3): pp. 549-553 (2004).

Huang JZ, Frischer JS, Serur A, Kadenhe A, Yokoi A, McCrudden KW, New T, O'Toole K, Zabski S, Rudge JS, Holash J, Yancopoulos GD, Yamashiro DJ, Kandel JJ "Regression of established tumors and metastases by potent vascular endothelial growth factor blockade" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA 100 (13): 7785-7790 (2003)

Glade-Bender J, Kandel JJ, Yamashiro DJ, "VEGF blocking therapy in the treatment of cancer" EXPERT OPINION ON BIOLOGICAL THERAPY 3 (2): 263-276 APR 2003

fMRI vs Optical Tomography

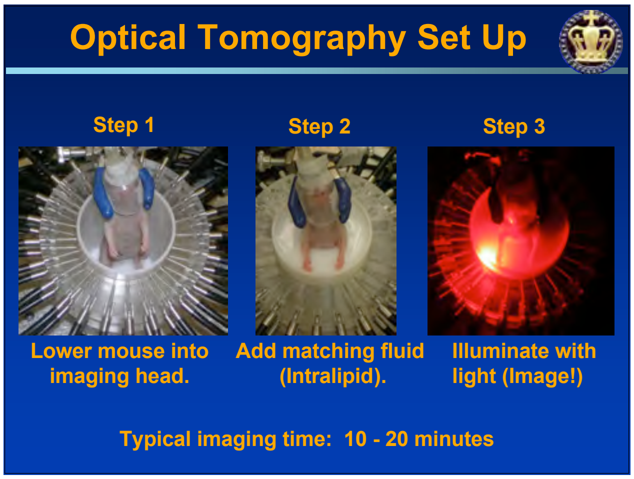
	fMRI	Optical Tomography
Spatial Resolution	0.1mm- 1mm	2mm - 10mm
Sensitive to	Hb (paramag.)	Hb, HbO_2, cytochrome, etc, blood volume, scattering properties
Speed	0.1 - 1Hz	~50 Hz
Cost	> $500.000	~ $100.000
Portability	no	yes
Continuous Monitoring	no	yes

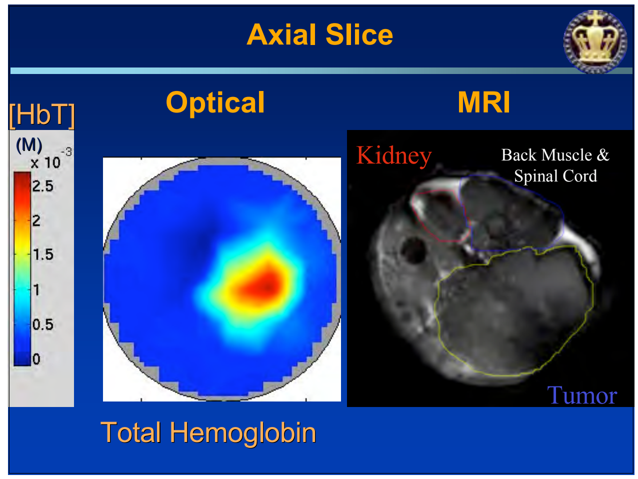
Combine high spatial resolution of fMRI and high speed and sensitivity of optical tomography!

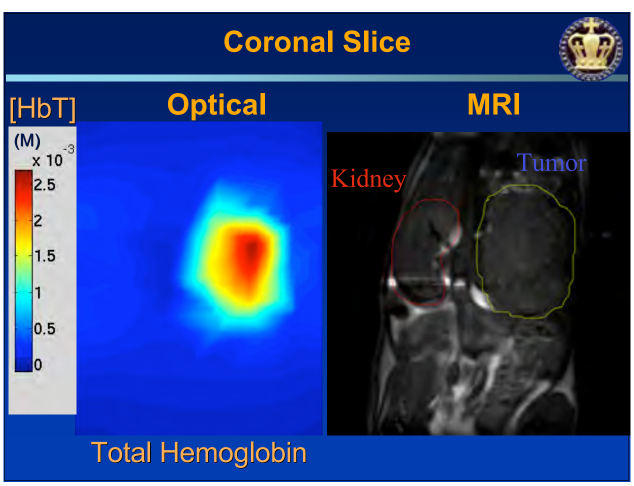
9.4 Tesla MRI (Bruker Avance 400)

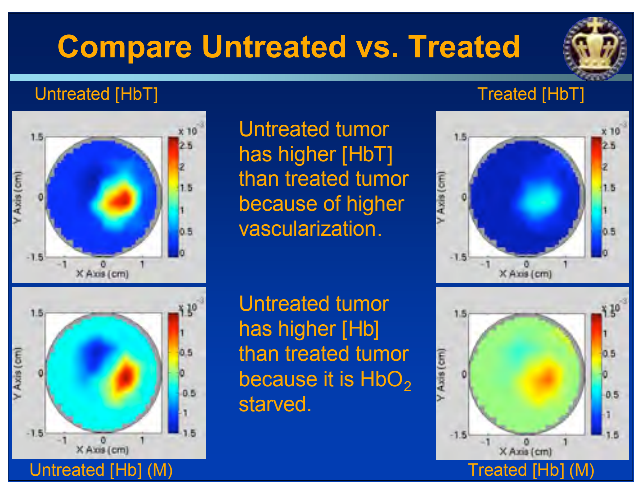
Micro2.5 Imaging set
35mm diameter
Linearly polarized
Birdcage coil

Typical imaging time: 30 - 60 minutes (T1 sequence)


Optical Tomography Set Up
Step 1
Step 2
Step 3
Lower mouse into imaging head.
Add matching fluid (Intralipid).
Illuminate with light (Image!)
Typical imaging time: 10 - 20 minutes


Axial Slice
[HbT]
(M)
x 10^-3
2.5
2
1.5
1
0.5
0
Optical
MRI
Kidney
Back Muscle & Spinal Cord
Tumor
Total Hemoglobin


Coronal Slice
[HbT]
(M)
x 10^-3
2.5
2
1.5
1
0.5
0
Optical
MRI
Kidney
Tumor
Total Hemoglobin


Compare Untreated vs. Treated
Untreated [HbT]
Treated [HbT]
Untreated tumor has higher [HbT] than treated tumor because of higher vascularization.
Untreated tumor has higher [Hb] than treated tumor because it is HbO2 starved.
Untreated [Hb] (M)
Treated [Hb] (M)

For more details see:

J. Masciotti, G. Abdoulaev, J. Hur, J. Papa, J. Bae, J. Huang, D. Yamashiro, J. Kandel, A.H. Hielscher, "Combined optical tomographic and magnetic resonance imaging of tumor bearing mice," in *Optical Tomography and Spectroscopy of Tissue VII*, B. Chance, R.R. Alfano, B.J. Tromberg, M. Tamura, E.M. Sevick-Muraca, eds., SPIE-The International Society for Optical Engineering, Proc. 5693, pp. 74-81 (2005).

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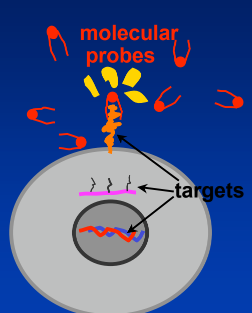
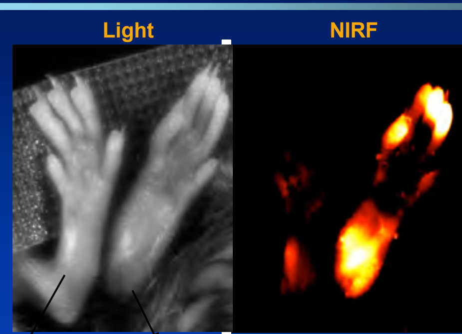
  - Tumor Imaging
  - Molecular Fluorescence Imaging

Molecular Imaging



Rheumatoid Arthritis



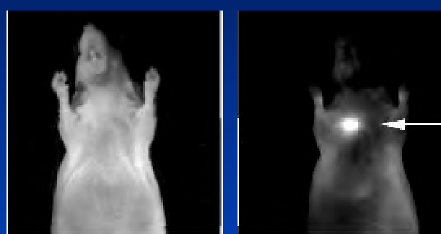
mouse without RA

transgenic mouse with RA

Antigen: glucose-6-phosphate isomerase (GPI)

Mahmood, Weissleder et al MGH-CMIR

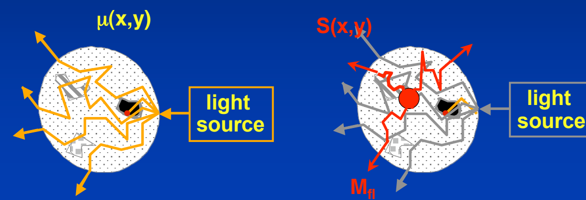
Cancer Detection



Fluorescence Tomography

reconstruction of absorption and scattering profile μ(x,y)

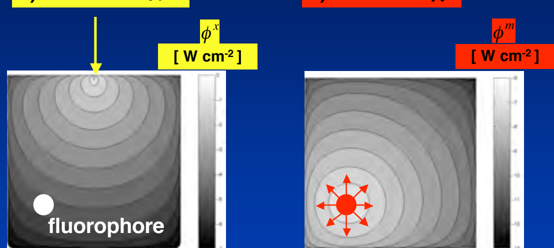
reconstruction of fluorescence source profile S(x,y)



Fluorescence Tomography

1) Excitation λ^x

2) Emission λ^m



$\mu_a^{x\to m}$ absorption of fluorophore

η quantum yield of fluorophore

Inverse Source Problem

$$\Omega \cdot \nabla\Psi(r,\Omega) + (\mu_a + \mu_s)\Psi(r,\Omega) = S(r,\Omega) + \mu_s \int_{4\pi} p(\Omega,\Omega')\Psi(r,\Omega')d\Omega'$$

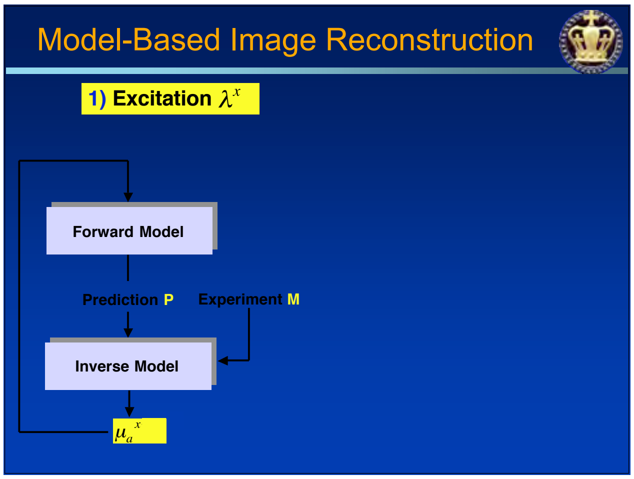
1) Excitation λ^x

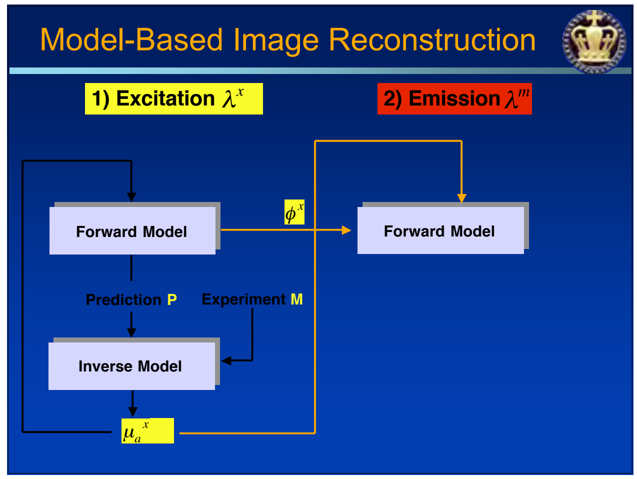
$$\Omega \cdot \nabla\Psi^x + \left(\mu_a^{x\to} + \mu_a^{x\to m} + \mu_s^x\right)\Psi^x = S^x + \mu_s^x \int_{4\pi} p(\Omega,\Omega')\Psi^x(\Omega')d\Omega'$$

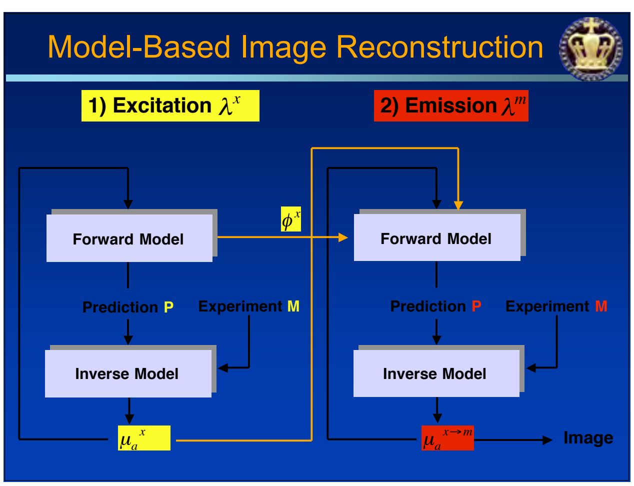
$$\phi^x = \int_{4\pi} \Psi^x(\Omega')d\Omega'$$

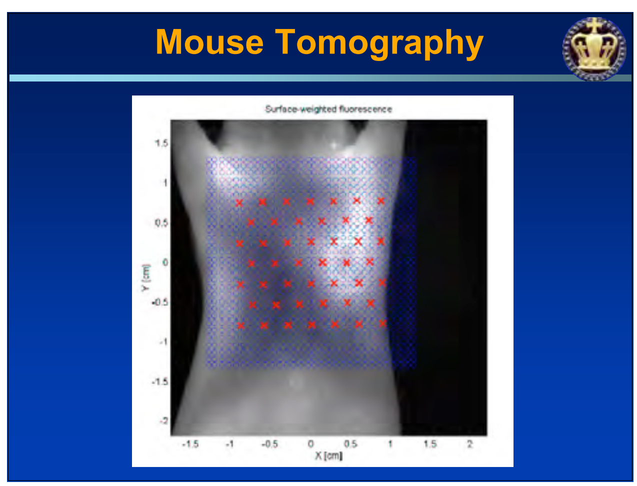
2) Emission λ^m

$$\Omega \cdot \nabla\Psi^m + \left(\mu_a^m + \mu_s^m\right)\Psi^m = \frac{1}{4\pi}\eta\mu_a^{x\to m}\phi^x + \mu_s^m \int_{4\pi} p(\Omega,\Omega')\Psi^m(\Omega')d\Omega'$$

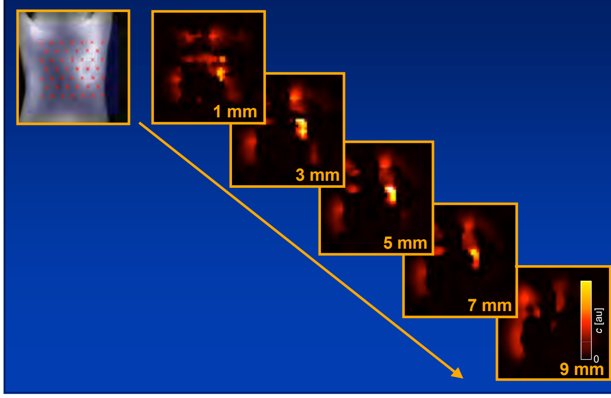

Model-Based Image Reconstruction
1) Excitation λ^x
Forward Model
Prediction P
Experiment M
Inverse Model
μ_a^x


Model-Based Image Reconstruction
1) Excitation λ^x
2) Emission λ^m
Forward Model
ϕ^x
Forward Model
Prediction P
Experiment M
Inverse Model
μ_a^x


Model-Based Image Reconstruction
1) Excitation λ^x
2) Emission λ^m
Forward Model
ϕ^x
Forward Model
Prediction P
Experiment M
Prediction P
Experiment M
Inverse Model
Inverse Model
μ_a^x
$\mu_a^{x \to m}$
Image


Mouse Tomography
Surface-weighted fluorescence
X [cm]
Y [cm]

Mouse Tomography



For more details see:

A.K. Klose, V. Ntziachristos, A.H. Hielscher, "The inverse source problem based on the radiative transfer equation in molecular optical imaging," *J. of Computational Physics* 202, pp. 323-345 (2005).

A.K. Klose, A.H. Hielscher, "Fluorescence tomography with the equation of radiative transfer for molecular imaging," *Optics Letters* 28(12), pp. 1019-1021 (2003).

A.K. Klose, A.H. Hielscher, " Optical fluorescence tomography with the equation of radiative transfer for molecular imaging," in *Optical Tomography and Spectroscopy of Tissue V*, B. Chance, R.R. Alfano, B.J. Tromberg, M. Tamura, E.M. Sevick-Muraca, eds., SPIE-The International Society for Optical Engineering, Proc. 4955, pp. 219-225 (2003).

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  Fluorescence Imaging

Acknowledgements I

- **Students:**
  J. Masciotti, X. Gu, J. Hur, F. Provenzano, J. Lasker, A. Bluestone, B. Moa-Anderson
- **Postdoctoral Fellows:**
  A. Klose, G. Abdoulaev, J. Papa
- **Collaborators:**
  Columbia
  - J. Kandel (Pediatrics & Surgery, Columbia)
  - D. Yamashiro (Pediatrics & Surgery, Columbia)
  - G. Bal (Applied Mathematics)

  SUNY - Downstate
  - Mark Steward (Physiology & Pharmacology)
  - R.L. Barbour (Pathology)
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- Schering Research Foundation (PI: Klose)

More Information

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