Optical Molecular Imaging

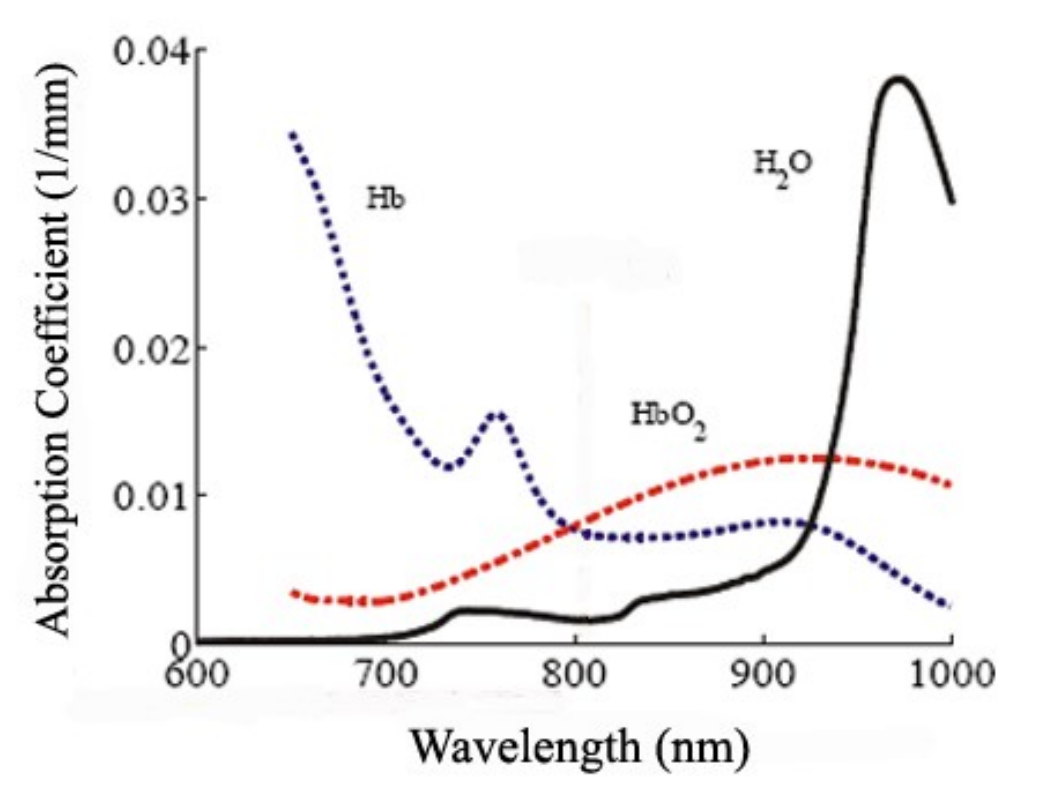
Fluorescence and Bioluminescence Tomography

Alexander D. Klose

Department of Radiology

Columbia University
New York

Optical Window Of Biological Tissue



Levels of Optical Imaging

Optical Imaging

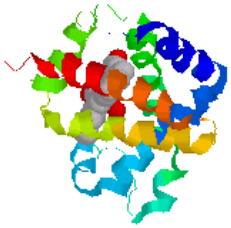
imaging of non-specific changes related to morphology and physiology

endogeneous chromophores or

non-specific contrast agents

developed disease

Optical Molecular Imaging



imaging of location and expression levels of

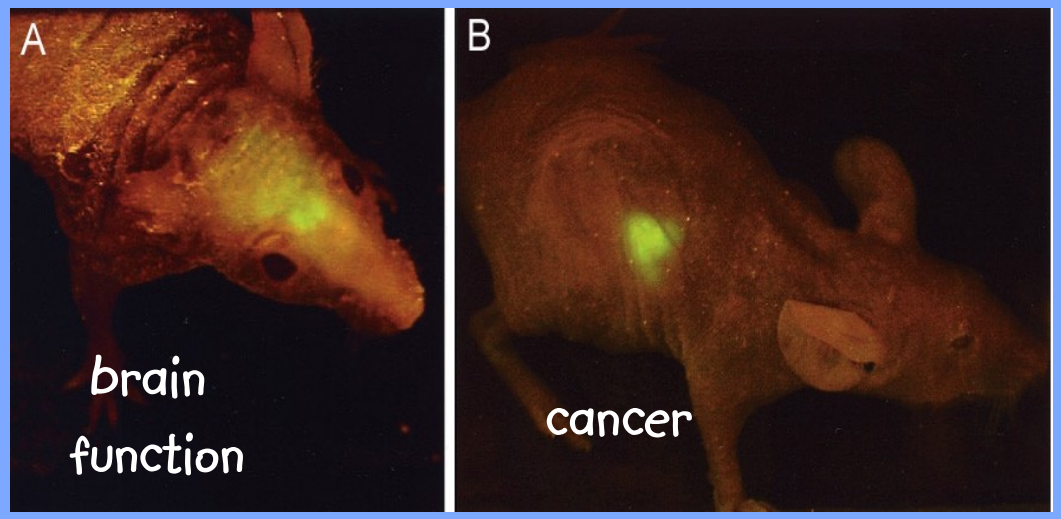
specific genes and proteins that are part in the molecular pathways of disease

targeted fluorescent probes

early disease

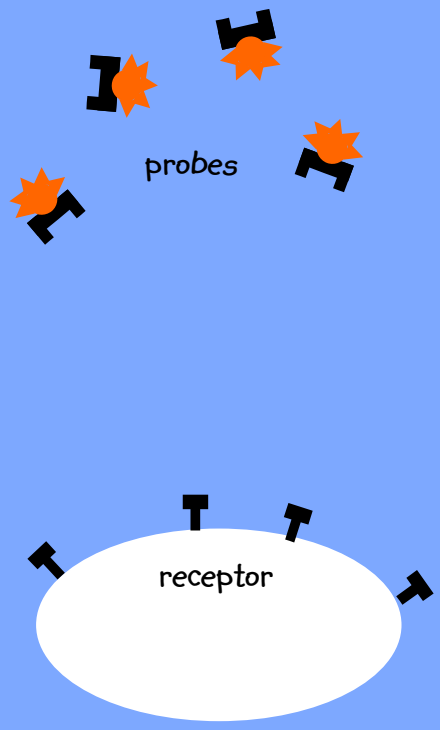
Optical Molecular Imaging

Fluorophore concentration?

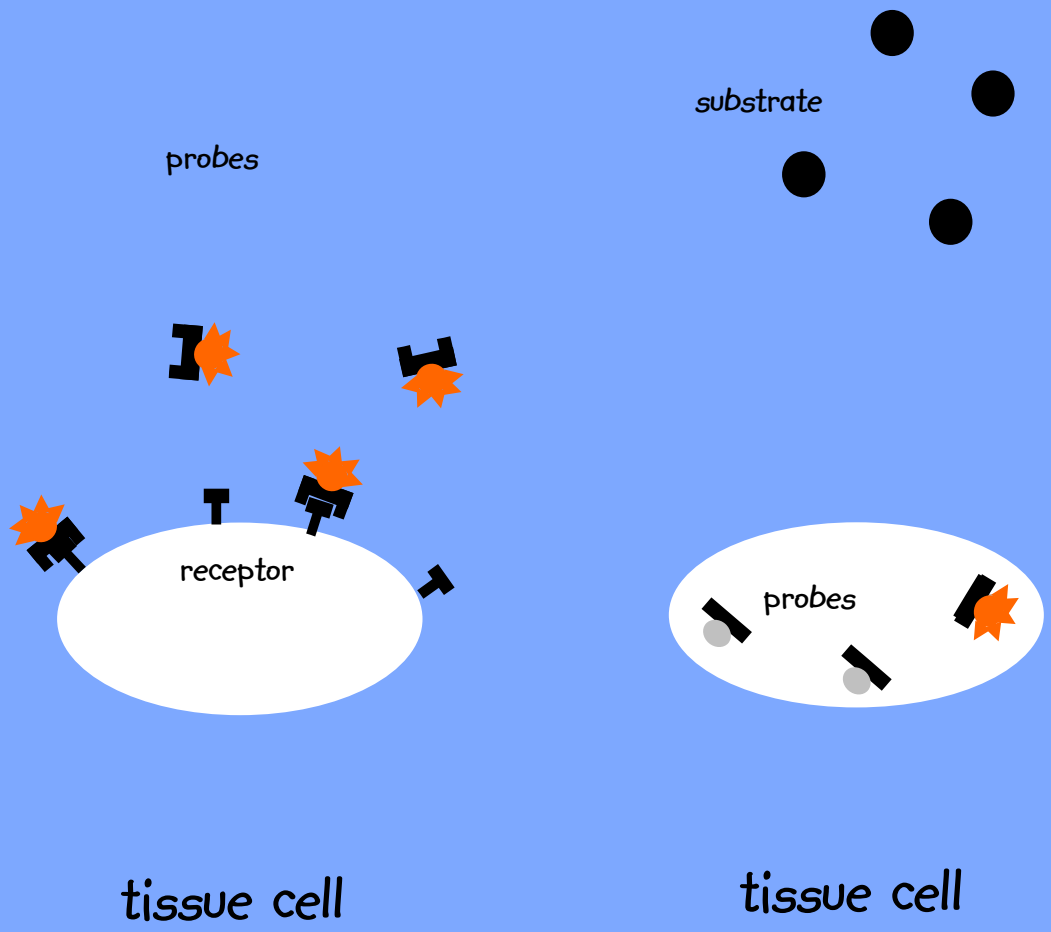


fluorescence light on tissue surface

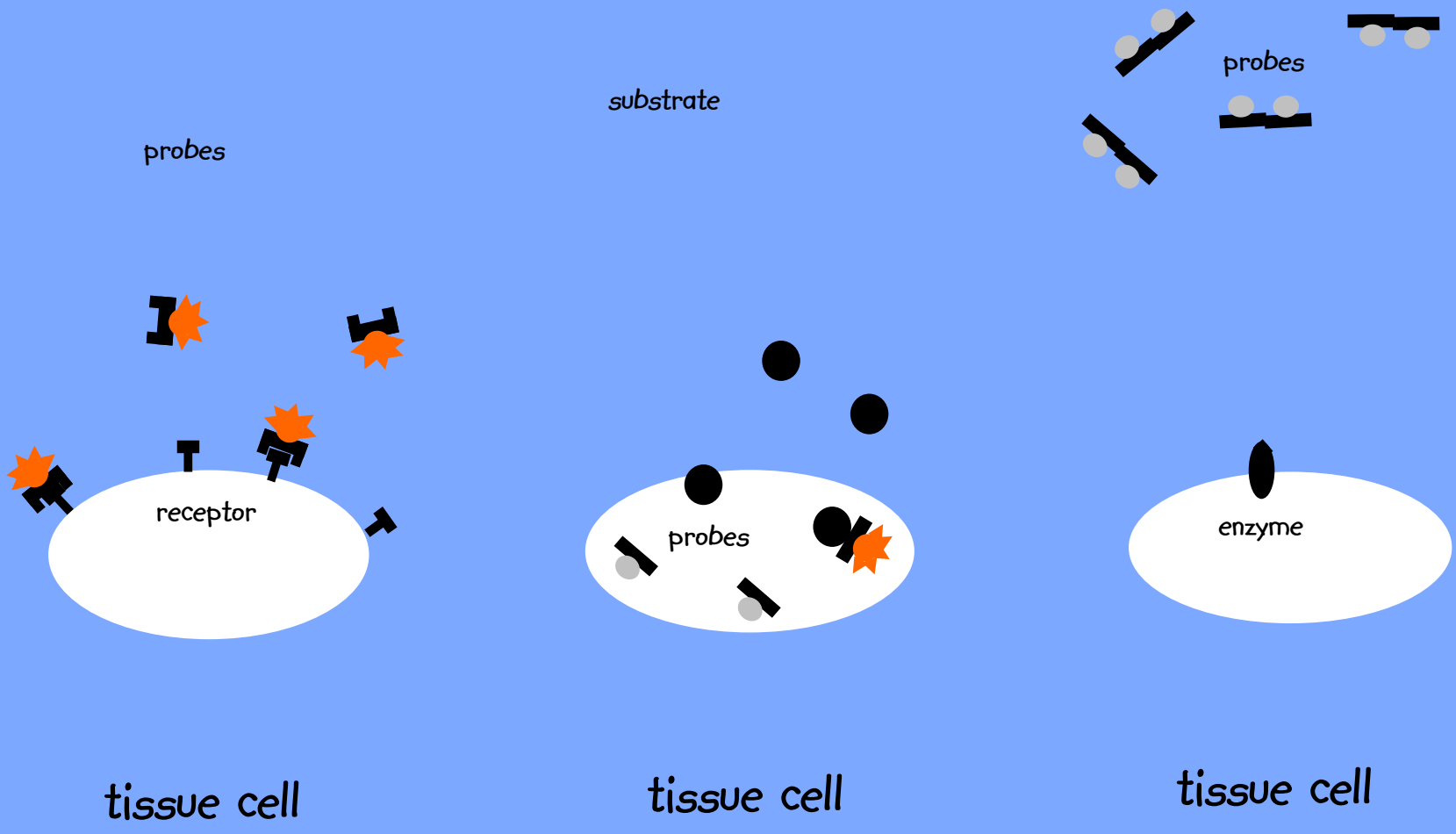
Optical Molecular Imaging



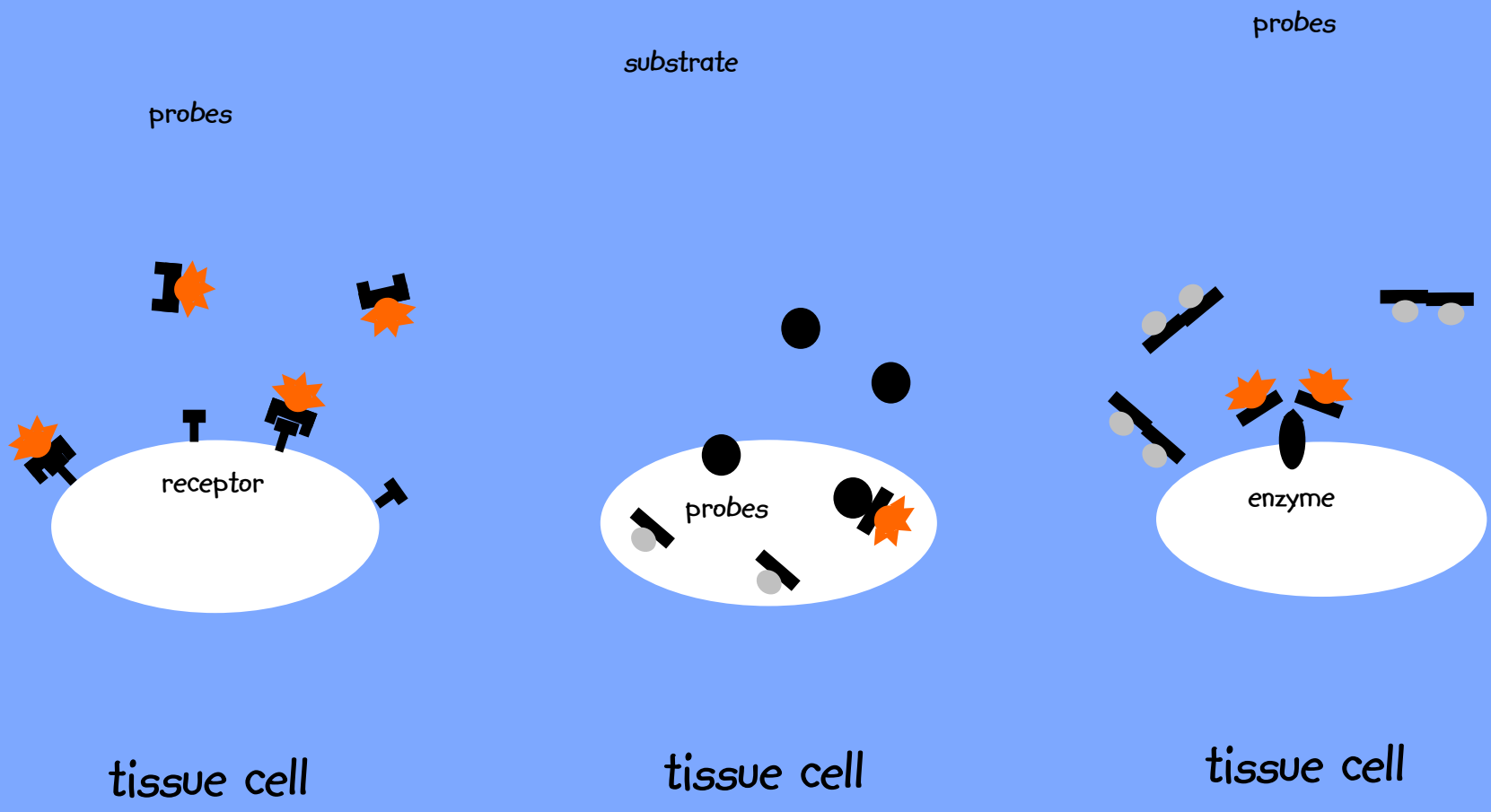
Optical Molecular Imaging



Optical Molecular Imaging



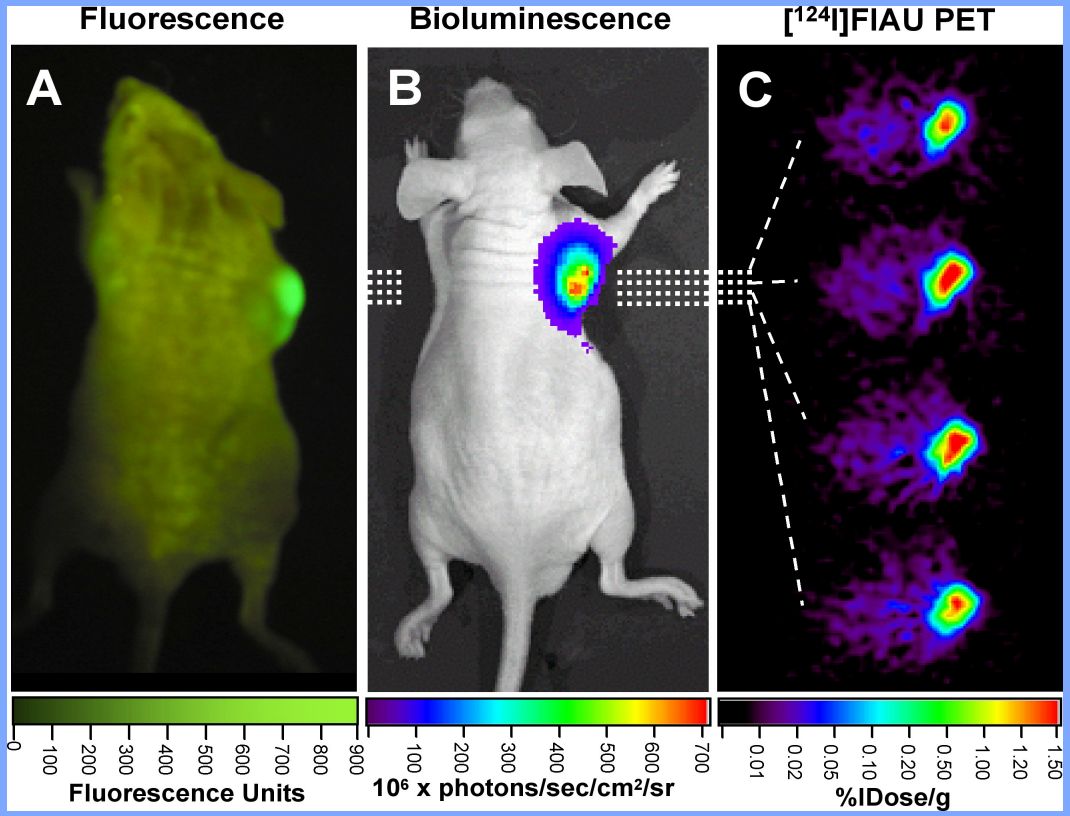
Optical Molecular Imaging



Optical Reporter Probes

Agent	Excitation [nm]	Emission [nm]	Extinction [cm^{-1} M^{-1}]	Quantum Yield
Dye:				
Cy5	649	670	250,000	0.28
Cy5.5	675	694	250,000	0.28
Cy7	743	767	200,000	0.29
Protein:				
GFP	489	508	55,000	0.6
DsRed	558	583	57,000	0.79
Catalyst-Substrate:				
Luciferase/ Luciferin	N.A.	560	N.A.	0.88

Optical Molecular Tomography?

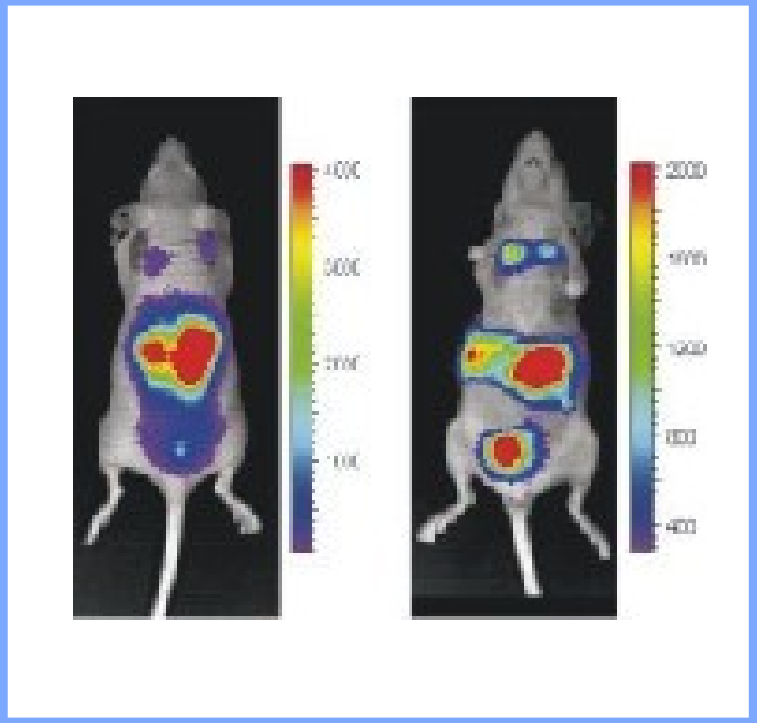


Mouse bearing two subcutaneous xenografts
(U87-NES-HSV1-tk/GFPcmvFluc – right shoulder)

Dr. Blasberg, Memorial Sloan Kettering Cancer Center, New York

Inverse Source Problem

measured light intensity



boundary current J^+

[Watts cm^{-2}]

[photons s^{-1} cm^{-2}]

reconstructed source

source power density Q

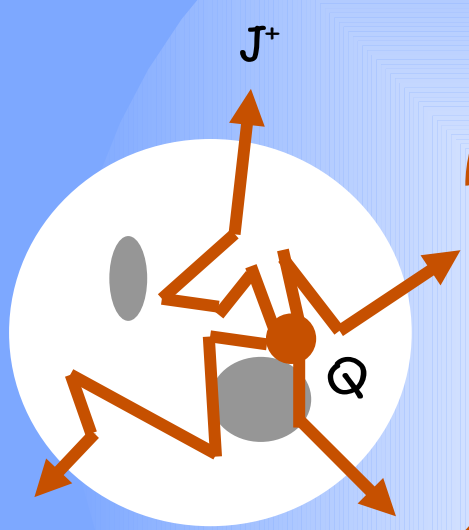
[Watts cm^{-3}]

[photons s^{-1} cm^{-3}]

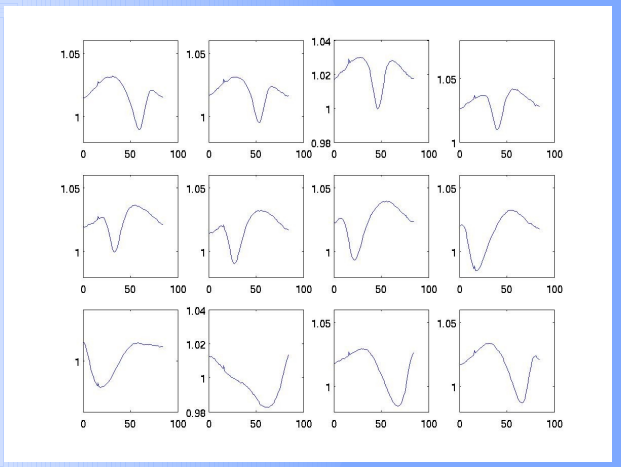
Inverse Source Problem

$J^+=F(Q)$

J^+



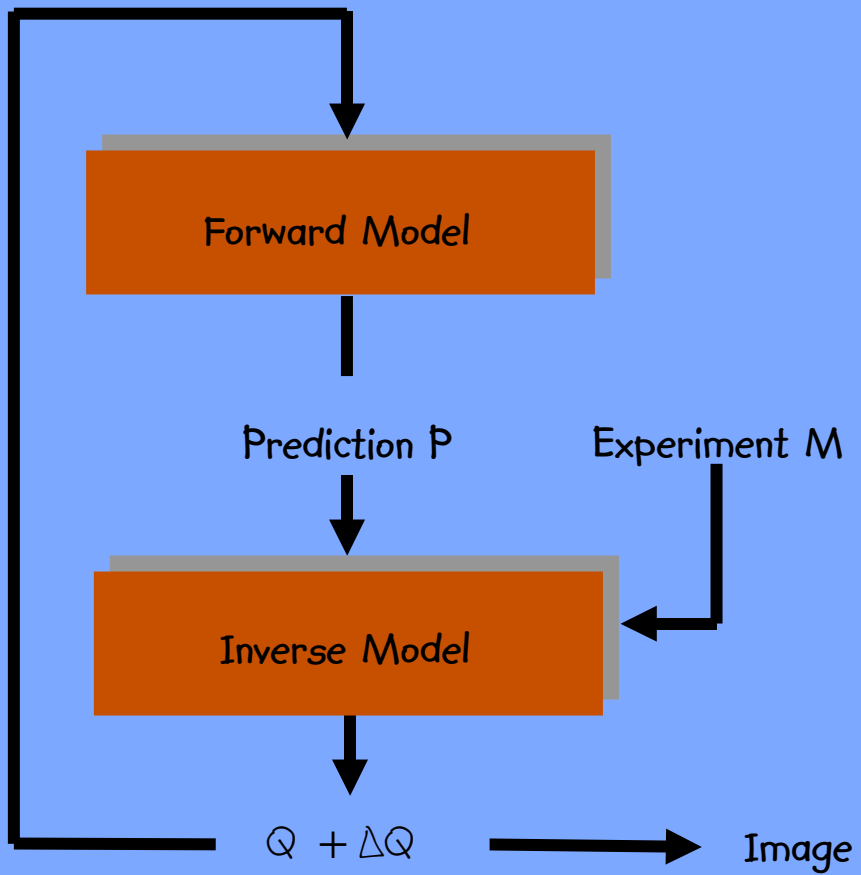
J^+



5 ... 100 mfp

$Q=F^{-1}(J^+)$

Optimization Problem – Error Function



Error Function:

$$\phi(Q) = \frac{1}{N}\sum_{n}^{N}\frac{\left(M_n - P_n(Q)\right)^2}{\sigma_n^2}$$

Overview

Forward Model

Inverse Model

Fluorescence Molecular Tomography

Bioluminescence Tomography

Overview

Forward Model

Inverse Model

Fluorescence Molecular Tomography

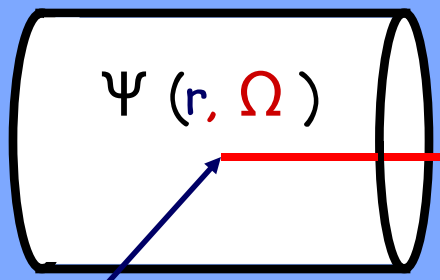
Bioluminescence Tomography

Radiative Transfer Model

volume element

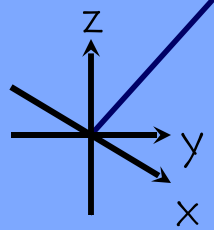
Radiance Ψ

[W cm^{-2} sr^{-1}]

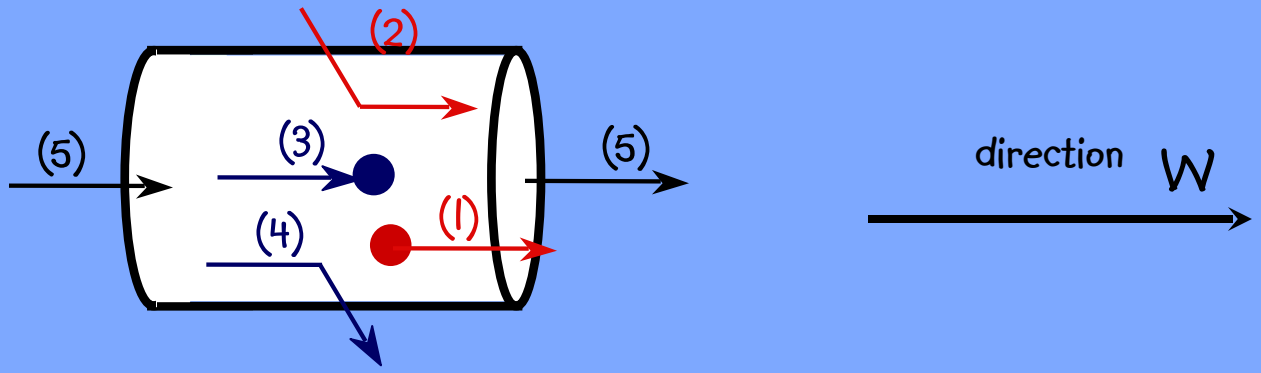


direction Ω

position r



Radiative Transfer Model



(1) gain - source

(3) loss - absorption

(2) gain - scattering

(4) loss - scattering

(5) loss / gain - stream

$$\Omega \cdot \nabla \psi(r, \Omega) + \mu_t \psi(r, \Omega) = Q(r) + \mu_s \int_{4\pi} p(\Omega, \Omega') \psi(r, \Omega') d\Omega'$$

(5) (3+4) (1) (2)

balance equation

Radiative Transfer Model

transport equation:

$$\Omega \cdot \nabla \psi(r, \Omega) + \mu_t \psi(r, \Omega) = Q(r) + \mu_s \int_{4\pi} p(\Omega, \Omega') \psi(r, \Omega') d\Omega'$$

attenuation coefficient:

$$\mu_t = \mu_a + \mu_s$$

partial-reflective boundary condition:

$$\psi(\Omega) = R(\Omega' \cdot n) \psi(\Omega') + S(\Omega) \qquad \text{for} \quad \Omega \cdot n < 0$$

partial current at boundary:

$$J = \int_{\Omega \cdot n > 0} (n \cdot \Omega) \psi d\Omega$$

flux (fluence):

$$\phi = \int_{4\pi} \psi(\Omega) d\Omega$$

Radiative Transfer Model - Approximations

Diffusion Equation:

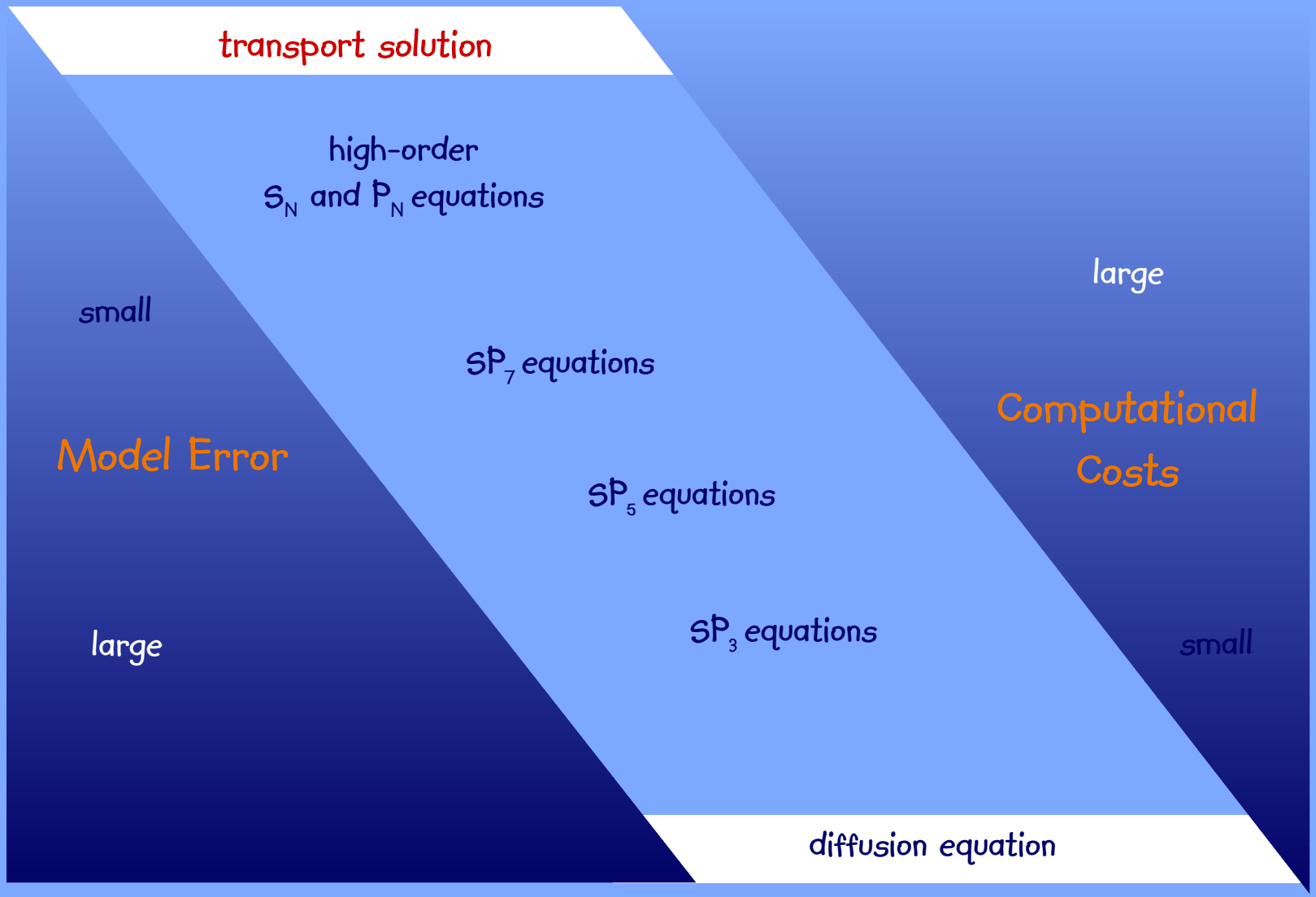
$$-\nabla \cdot \frac{1}{3\mu_{a1}} \nabla \varphi_1 + \mu_a \varphi_1 = Q$$

SP_3 Equations:

$$-\nabla \cdot \frac{1}{3\mu_{a1}} \nabla \varphi_1 + \mu_a \varphi_1 = Q + \left(\frac{3}{2} \mu_a \right) \varphi_2$$

$$-\nabla \cdot \frac{1}{7\mu_{a3}} \nabla \varphi_2 + \left(\frac{4}{9} \mu_a + \frac{5}{9} \mu_{a2} \right) \varphi_2 = -\frac{2}{3} Q + \left(\frac{3}{2} \mu_a \right) \varphi_1$$

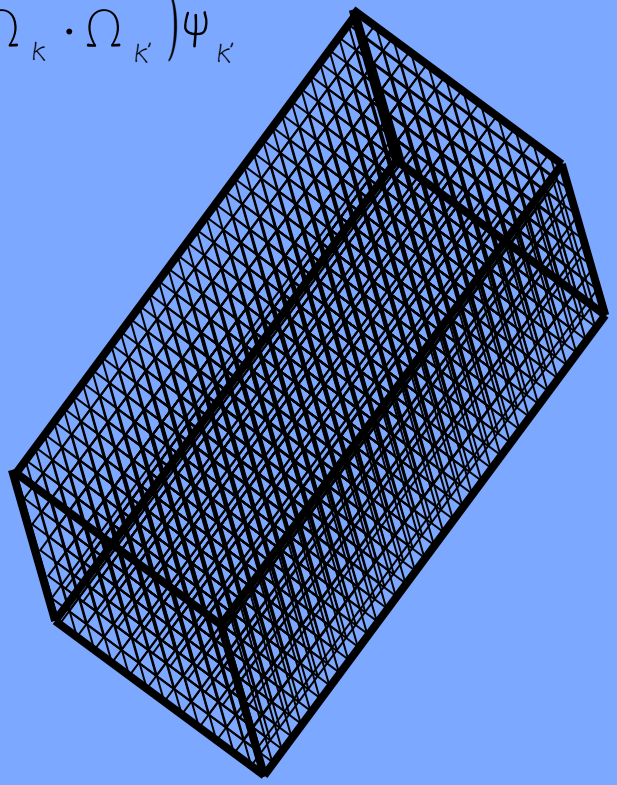
Radiative Transfer Models - Benefits vs. Costs



Finite-Difference Discrete-Ordinates (S_N)

$$\Omega_k \cdot \delta_k \psi_k + (\mu_a + \mu_s)\psi_k = Q_k + \mu_s \sum_{k'} w_{k'} p(\Omega_k \cdot \Omega_{k'})\psi_{k'}$$

- Upwind FD
- S_8 and 40x40x80 grid
- 10 Million coupled equations
- Source Iteration
  (Gauss-Seidel, SOR, etc.)



3D Cartesian grid

Overview

Forward Model

Inverse Model

Fluorescence Molecular Tomography

Bioluminescence Tomography

Inverse Problems

Non-Optical

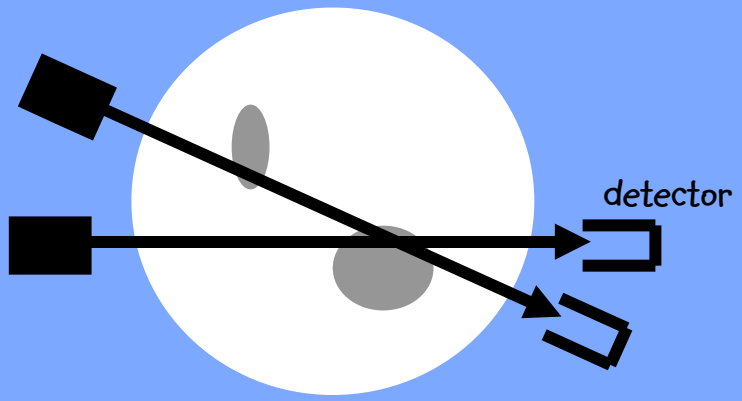
- X-Ray Computed Tomography (CT)
- Positron Emission Tomography (PET)
- Single Photon Emission Computed Tomography (SPECT)

Optical

- Diffuse Optical Tomography (DOT)
- Fluorescence Molecular Tomography (FMT)
- Bioluminescence Tomography (BLT)

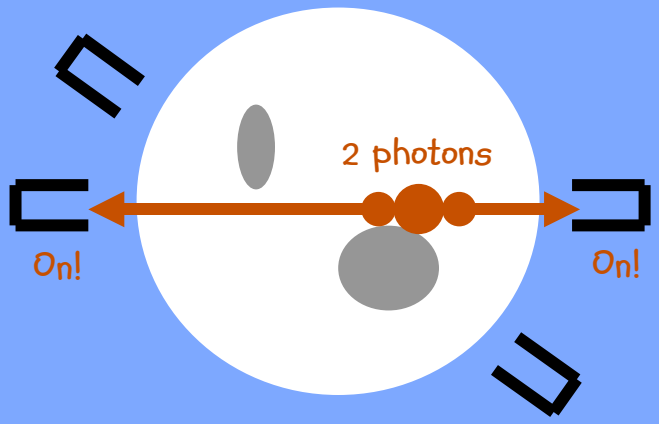
Inverse Problems – Non-Optical

X-Ray CT



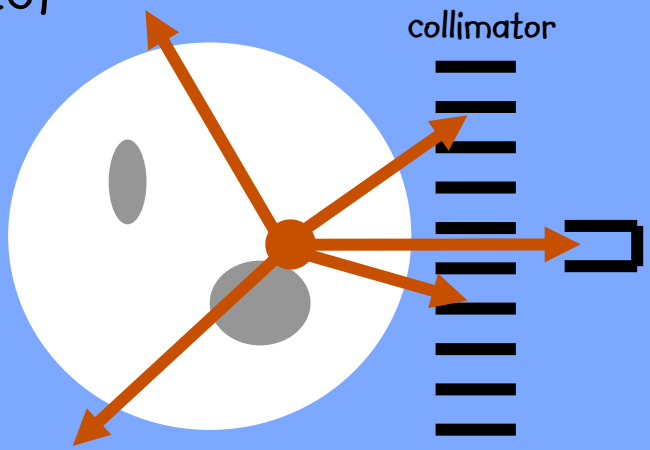
10-100 keV

PET



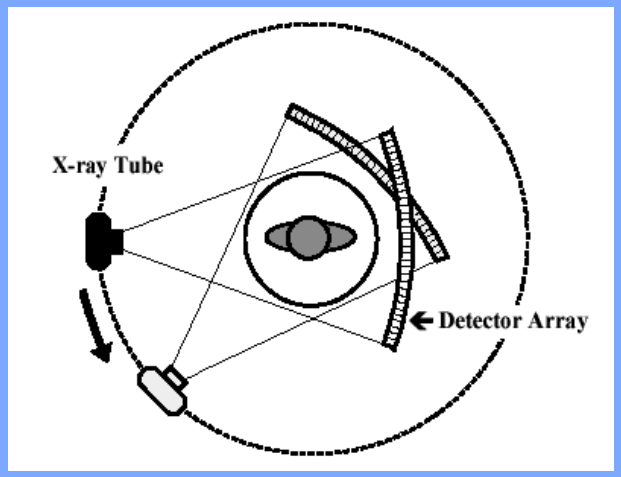
511 keV

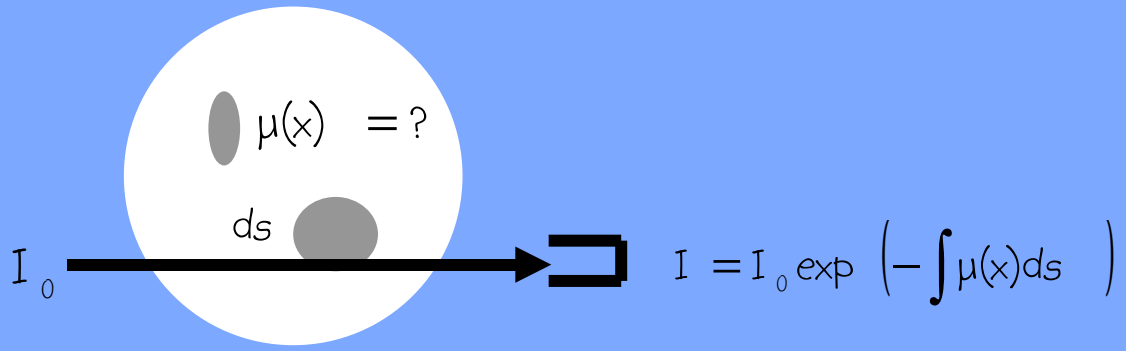
SPECT



27-245 keV

Inverse Problems – Non-Optical





Radon Transform

$$g = \ln(I_0/I) = \int \mu(x)ds$$

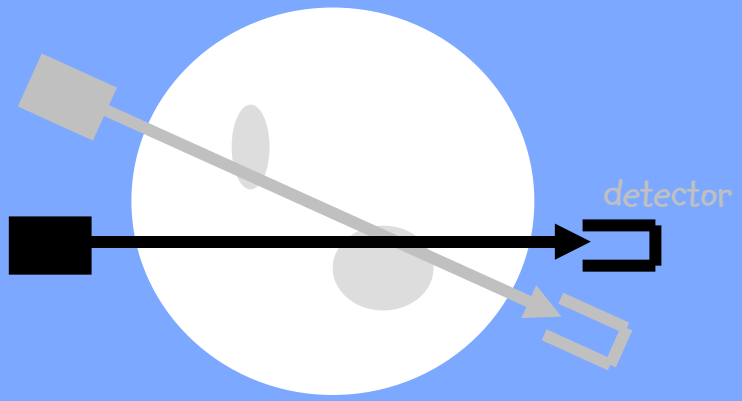
$$g = \Re\mu$$

Inverse Radon Transform

$$\mu = \Re^{-1} g$$

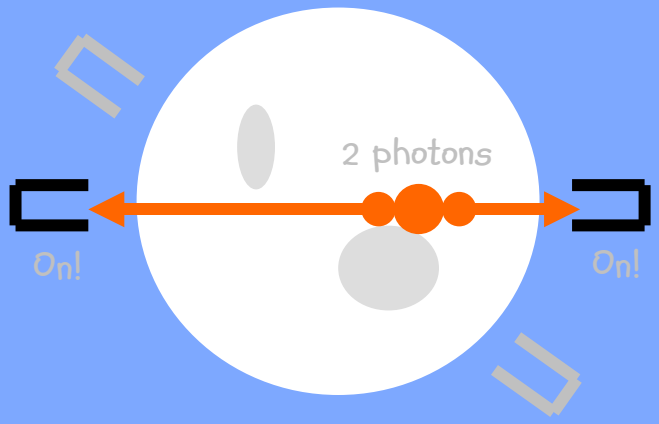
Inverse Problems - Optical

X-Ray CT



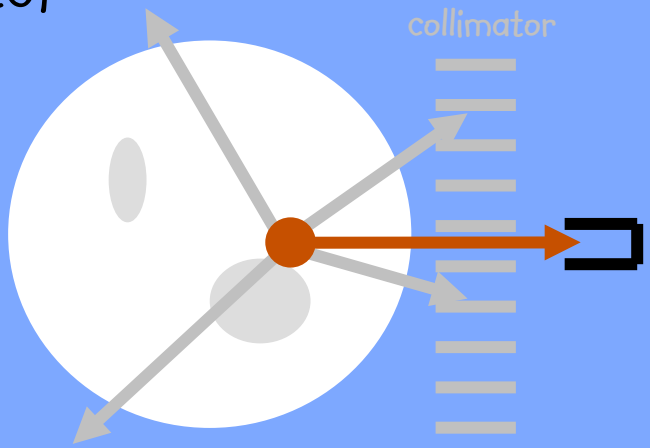
10-100 keV

PET



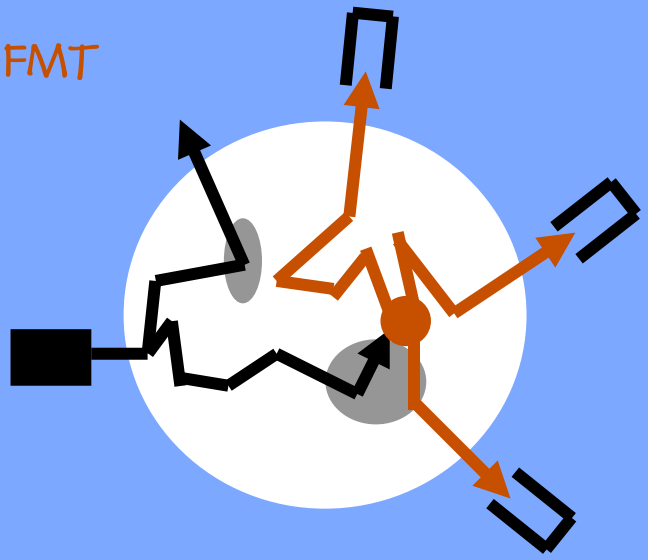
511 keV

SPECT



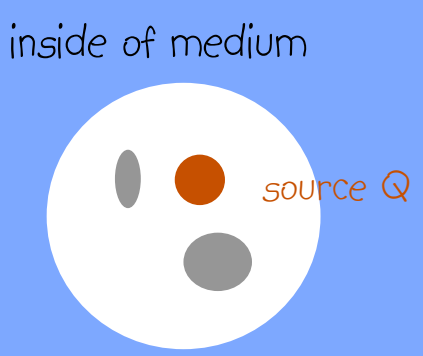
27-245 keV

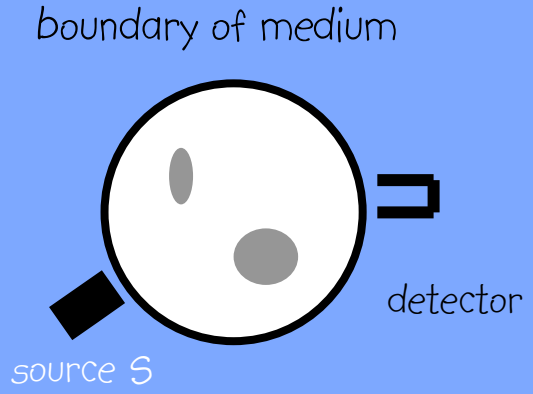
BLT,FMT



1-3 eV

Inverse Problems – Radiative Transfer



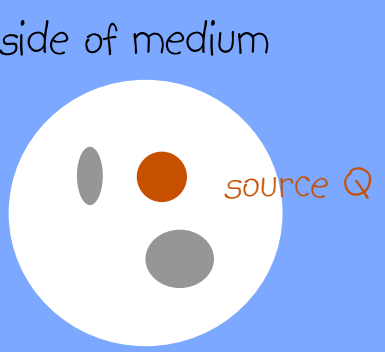


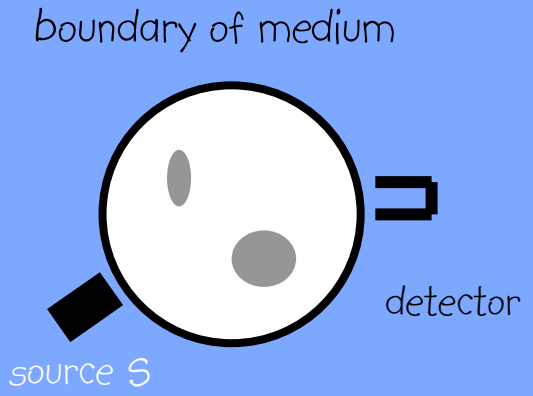
X-Ray CT

PET
SPECT

BLT
FMT

Inverse Problems – Radiative Transfer



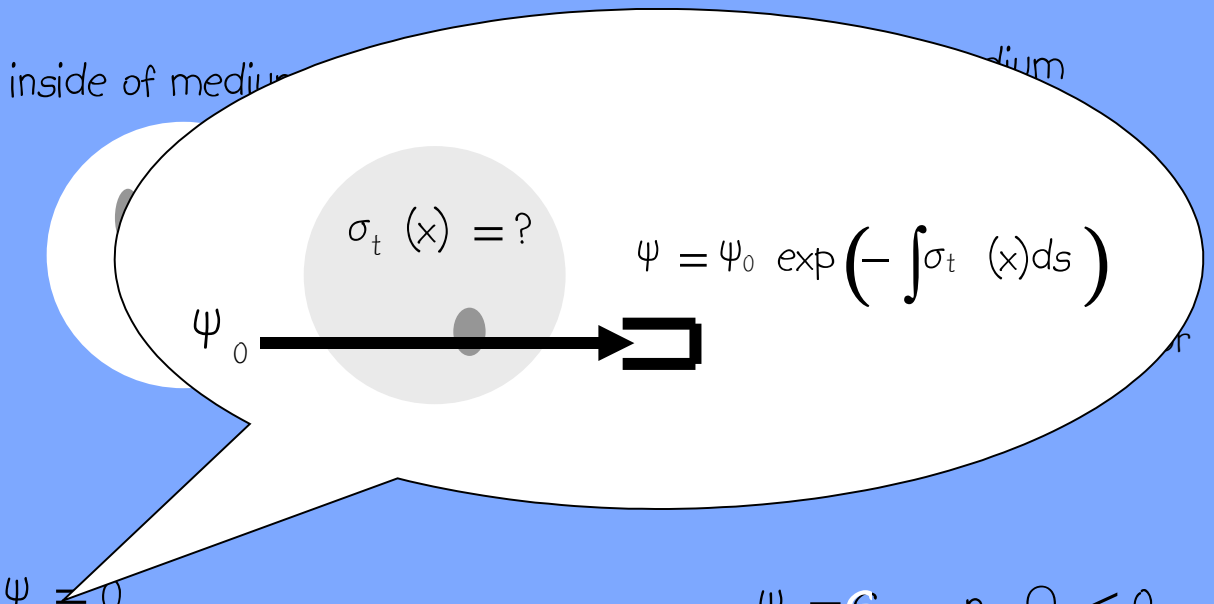


X-Ray CT $\quad \Omega \cdot \nabla \psi + \sigma_t \psi = 0 \qquad \psi = S, \quad n \cdot \Omega < 0$

PET
SPECT $\quad \Omega \cdot \nabla \psi + \sigma_t \psi = Q \qquad \psi = 0, \quad n \cdot \Omega < 0$

BLT
FMT $\quad \Omega \cdot \nabla \psi + \sigma_t \psi = Q + \sigma_s \int_{4\pi} p(\Omega \cdot \Omega') \psi d\Omega' \qquad \psi = S, \quad n \cdot \Omega < 0$

Inverse Problems – Radiative Transfer



X-Ray CT $\quad \Omega \cdot \nabla\psi + \sigma_t \psi = 0 \qquad \psi = s, \quad n \cdot \Omega < 0$

PET
SPECT $\quad \Omega \cdot \nabla\psi + \sigma_t \psi = q \qquad n \cdot \Omega < 0$

?

BLT
FMT $\quad \Omega \cdot \nabla\psi + \sigma_t \psi = q + \sigma_s \int_{4\pi} p(\Omega \cdot \Omega')\psi d\Omega' \qquad \psi = s, \quad n \cdot \Omega < 0$

Overview

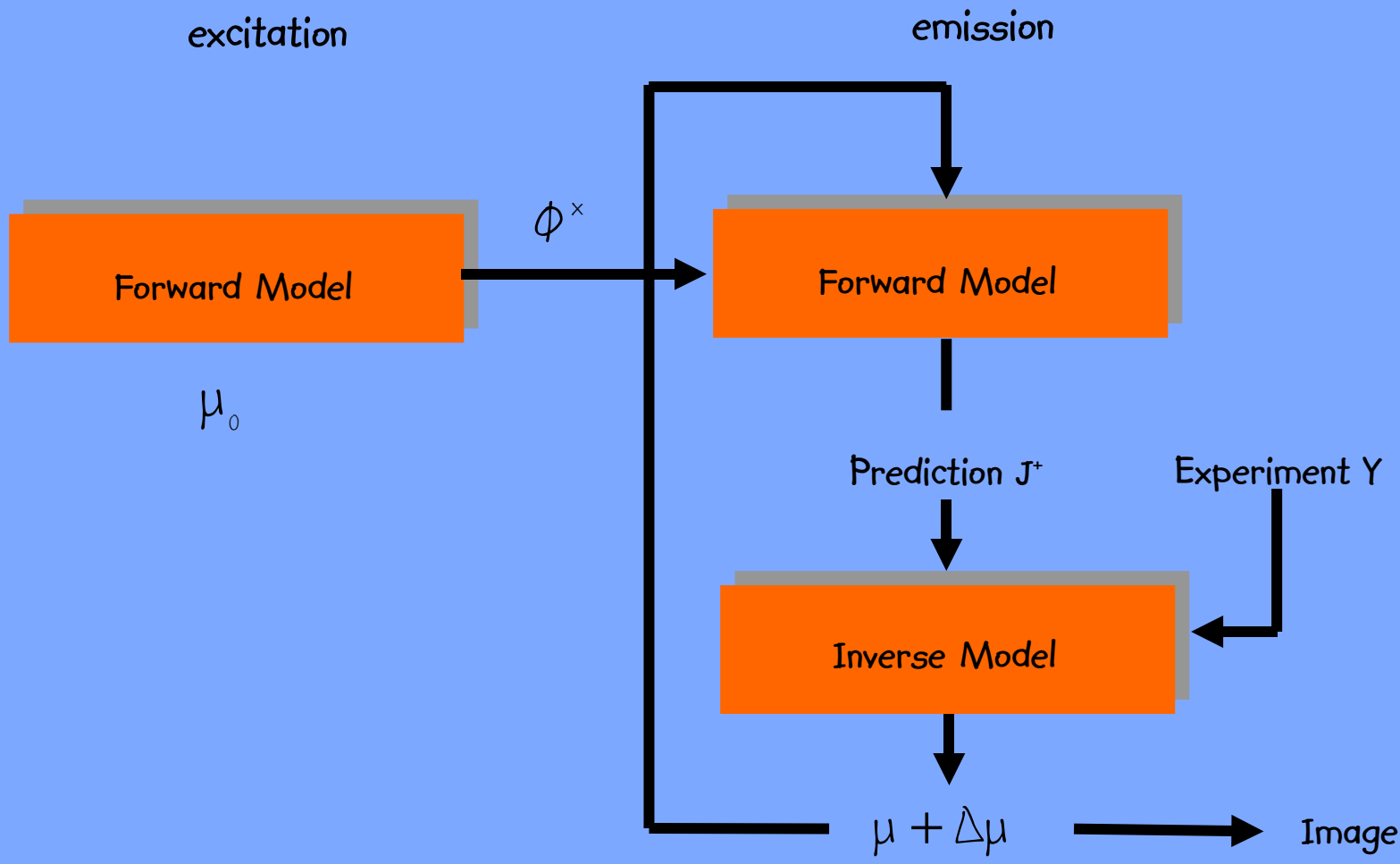
Forward Model

Inverse Model

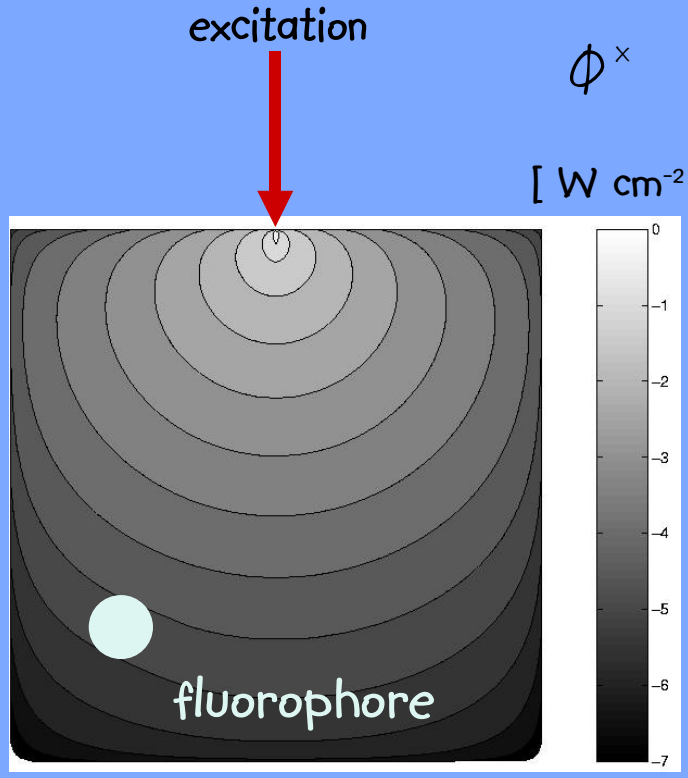
Fluorescence Molecular Tomography

Bioluminescence Tomography

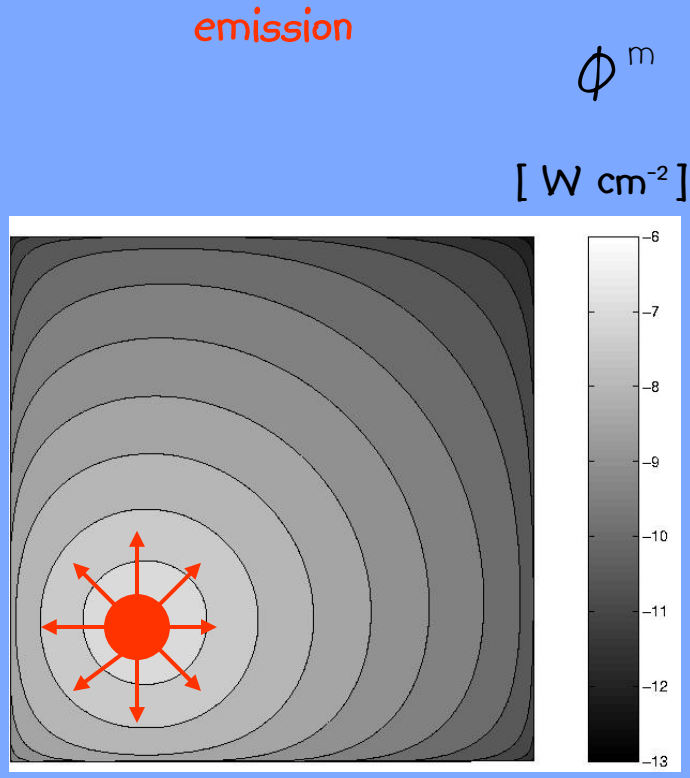
Fluorescence Molecular Tomography



Radiative Transfer Model - Fluorescence



light absorption by fluorophore



light emission by fluorophore

$$\mu_a^{x \to m} = c \cdot \varepsilon$$

$$Q^m = \frac{1}{4\pi} \eta \mu_a^{x \to m} \phi^x$$

Radiative Transfer Model - Fluorescence

excitation

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

$$\psi^{x} = S, \qquad n \cdot \Omega < 0$$

excitation field

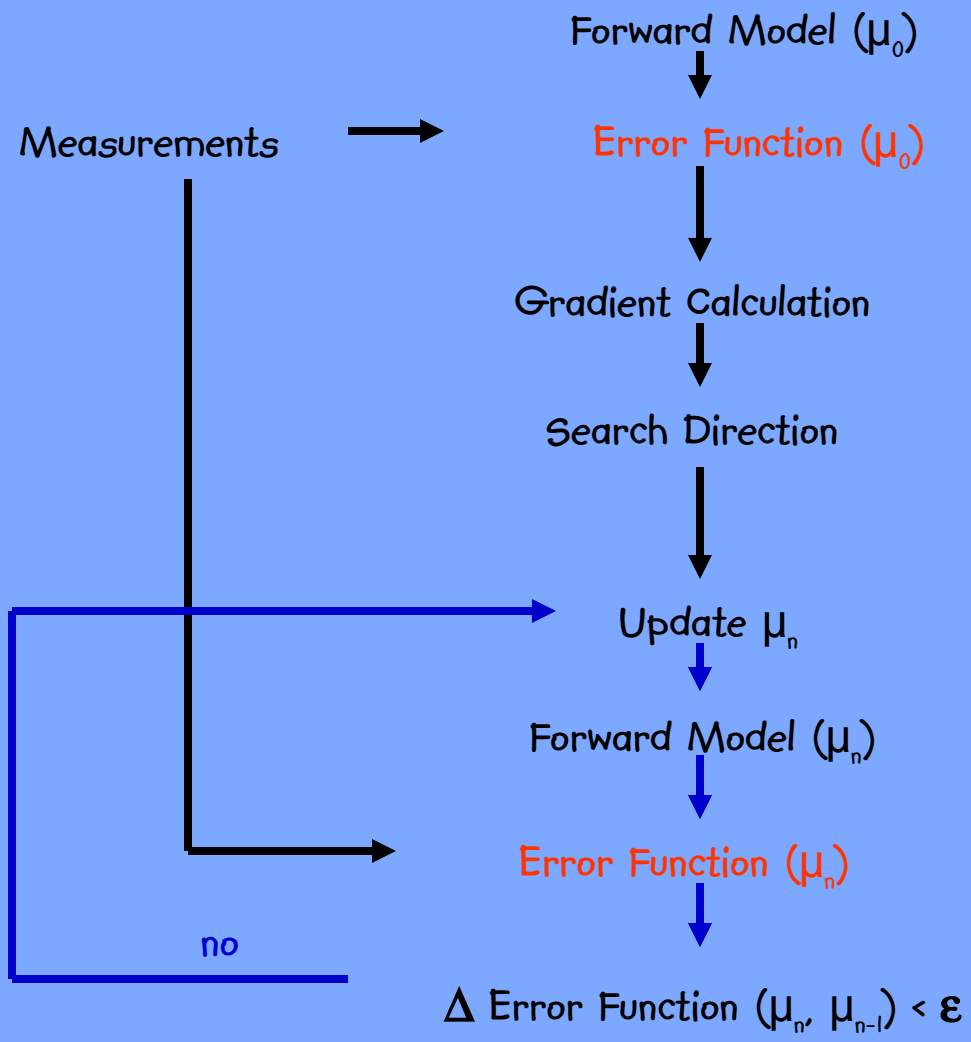
$$\phi^{x} = \int_{4\pi} \psi^{x} d\Omega$$

emission

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

$$\psi^{m} = 0, \qquad n \cdot \Omega < 0$$

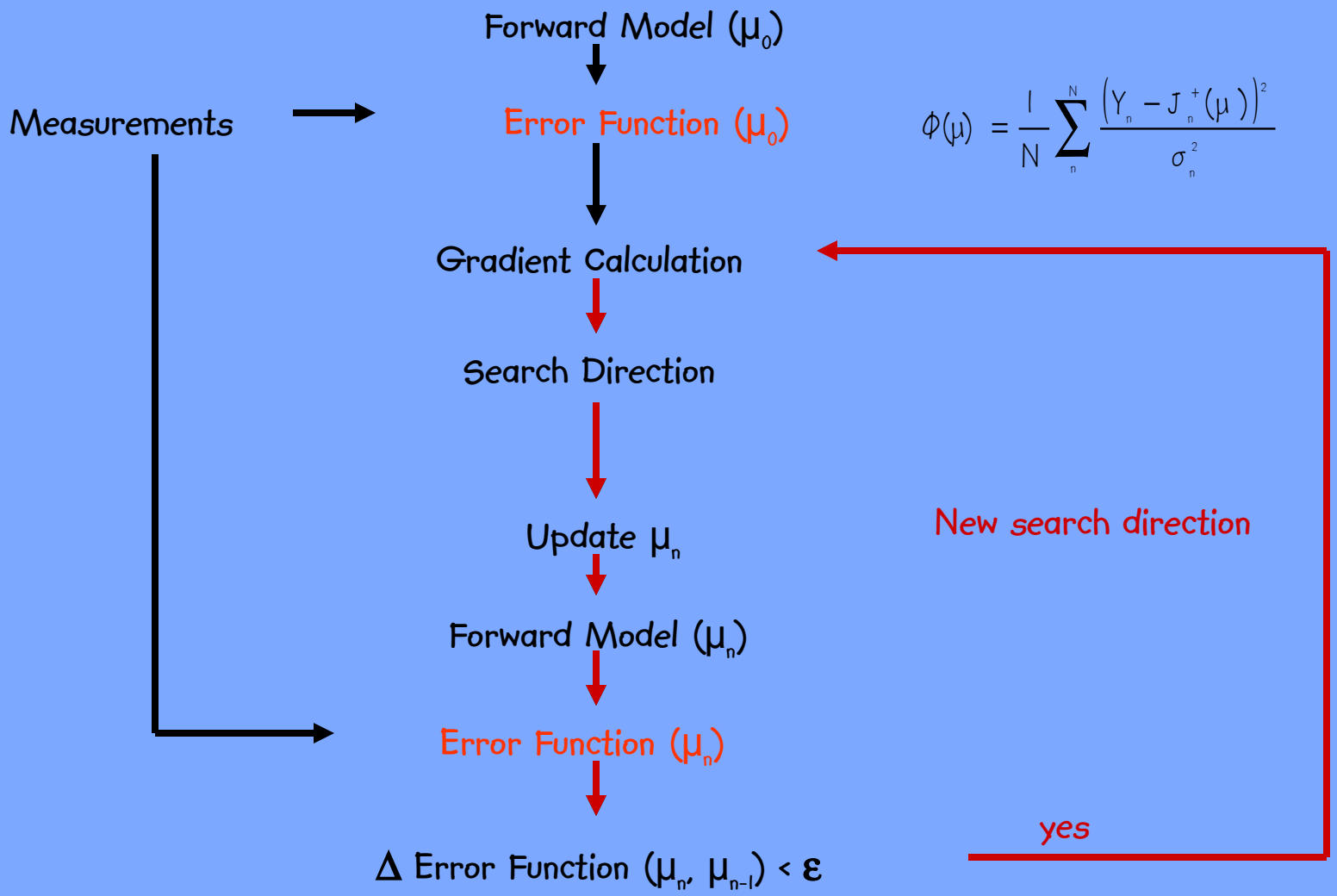
Local Optimization



$$\Phi(\mu) = \frac{1}{N}\sum_{n}^{N}\frac{\left(Y_n - J_n^{+}(\mu)\right)^2}{\sigma_n^2}$$

Search algorithm

Local Optimization



Computation Of Search Direction

$$\frac{\partial \phi}{\partial \mu_a} = \left(\frac{\partial \phi}{\partial \mu_{a1}}, \frac{\partial \phi}{\partial \mu_{a2}}, \ldots, \frac{\partial \phi}{\partial \mu_{aN}} \right)$$

amount of image voxels

Adjoint Differentiation

error function Φ is split up into subfunctions given Ψ^z by the radiative transfer model

$$\phi(\mu) = \left(\tilde{\phi} \circ \psi^z \circ \ldots \circ \psi^{z+1} \circ \psi^z \circ \ldots \circ \psi^2 \circ \psi^1\right)(\mu)$$

source iteration:
(sub-functions)

$$A\psi^0 = Q$$

$$A\psi^1 = B\psi^0 + Q$$

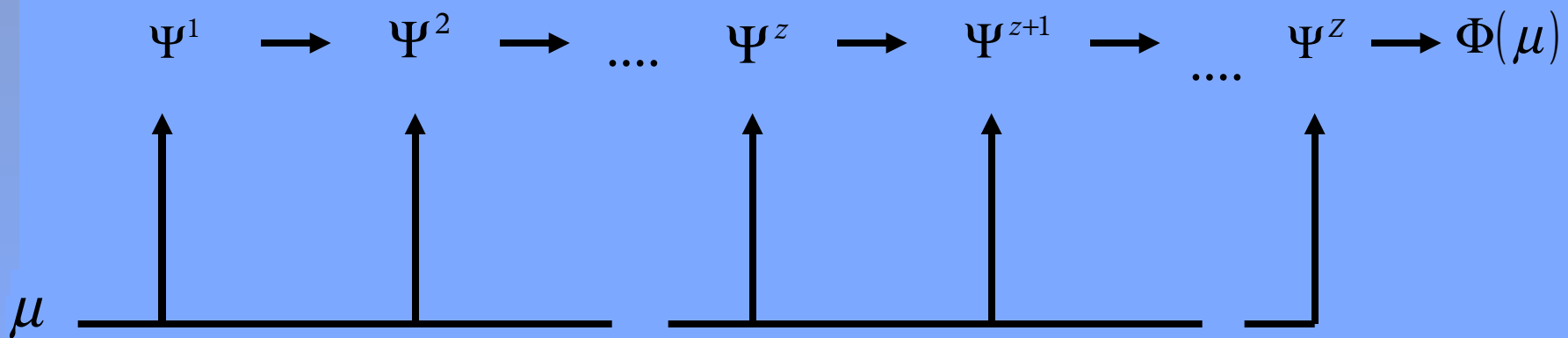
$$A\psi^2 = B\psi^1 + Q$$

Adjoint Differentiation

error function Φ is split up into subfunctions given Ψ^z by the radiative transfer model

$$\phi(\mu) = \left(\tilde{\phi} \circ \psi^{z} \circ \ldots \circ \psi^{z+1} \circ \psi^{z} \circ \ldots \circ \psi^{2} \circ \psi^{1}\right)(\mu)$$

forward direction

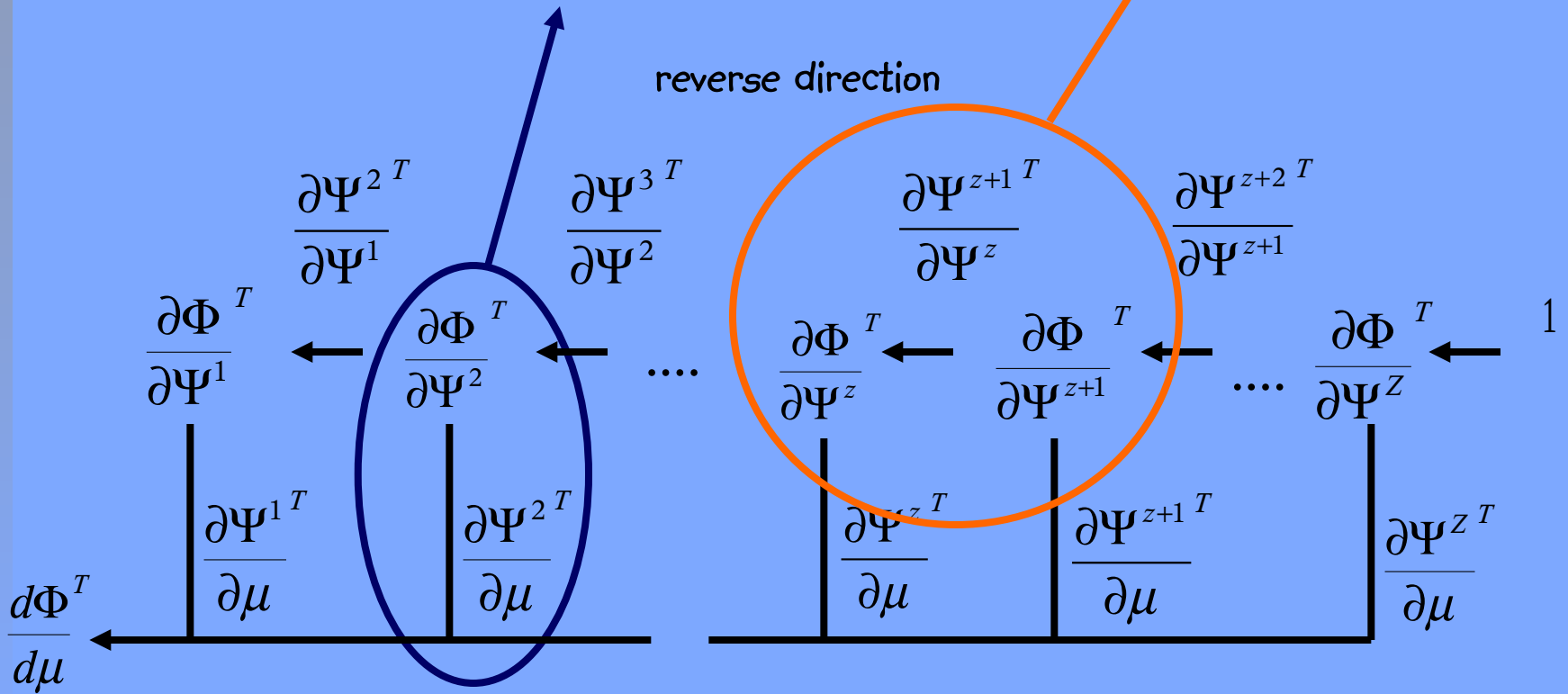


Adjoint Differentiation

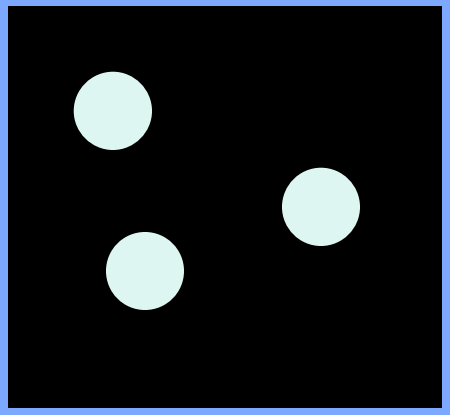
chain rule of differentiation

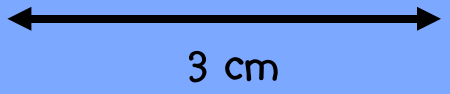
$$\frac{d\Phi}{d\mu}^T = \sum_z \frac{\partial \Psi^z}{\partial \mu}^T \frac{\partial \Phi}{\partial \Psi^z}^T$$

$$\frac{\partial \Phi}{\partial \Psi^z}^T = \frac{\partial \Psi^{z+1}}{\partial \Psi^z}^T \frac{\partial \Phi}{\partial \Psi^{z+1}}^T$$



Phantom Experiment





1) Excitation

solid phantom:

μ_s = 11.6 cm^{-1}

μ_a = 0.01 cm^{-1}

fluorophore:

η = 0.06

$\mu_a^{x \to m}$ = 0.013 cm^{-1}

wavelength:

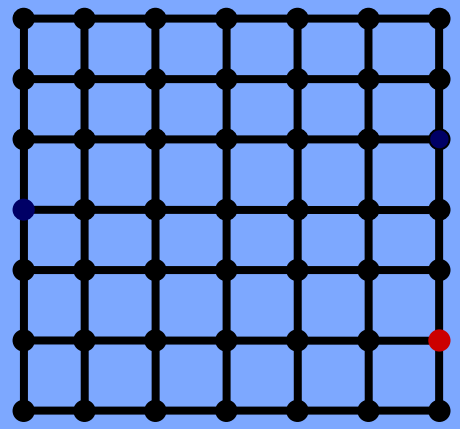
λ^x = 740 nm

λ^m = 802 nm

Phantom Experiment

24 discrete ordinates

61 x 61 grid points



4 sources

88 detectors

3 cm

1) Excitation

solid phantom:

μ_s = 11.6 cm^{-1}

μ_a = 0.01 cm^{-1}

fluorophore:

η = 0.06

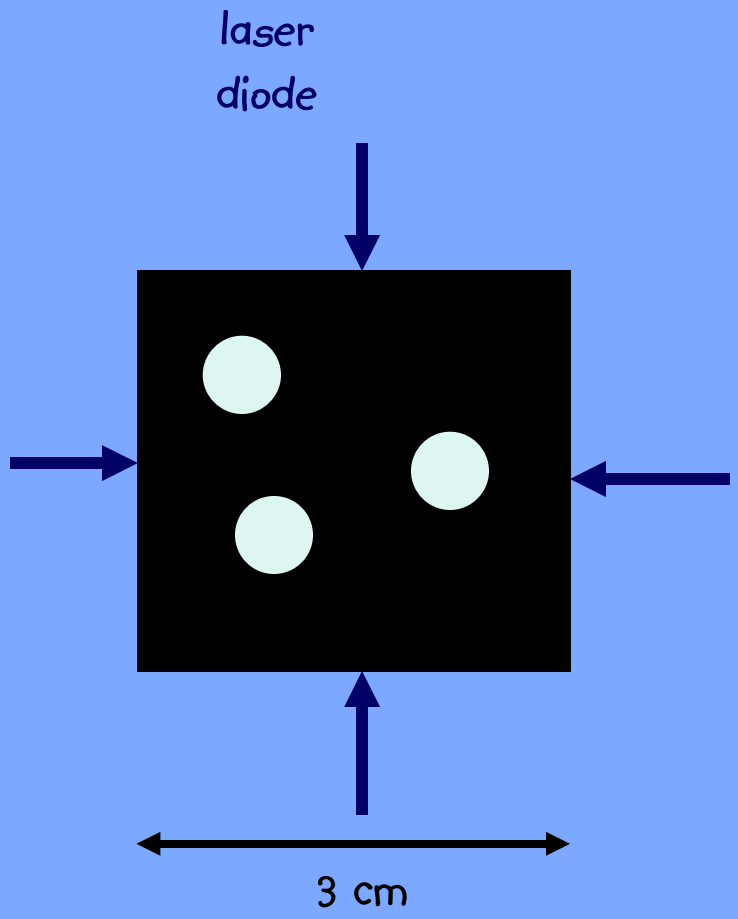
$\mu_a^{x \to m}$ = 0.013 cm^{-1}

wavelength:

λ^x = 740 nm

λ^m = 802 nm

Phantom Experiment



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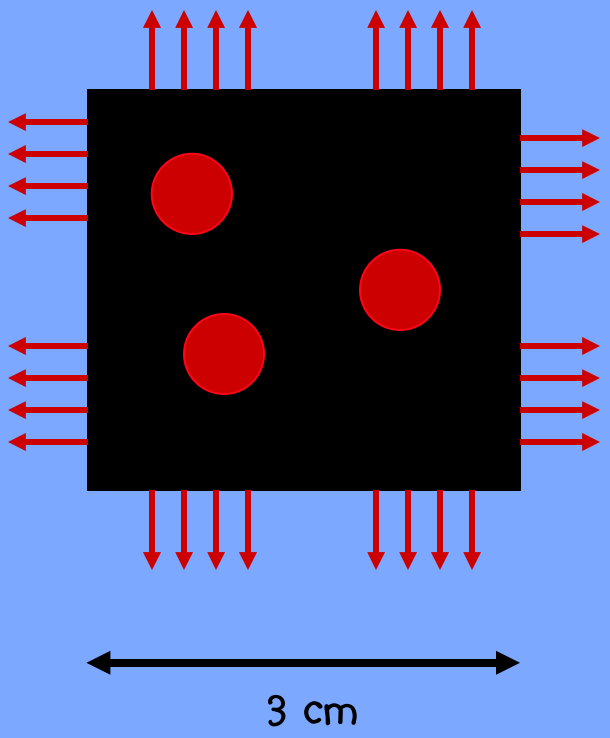

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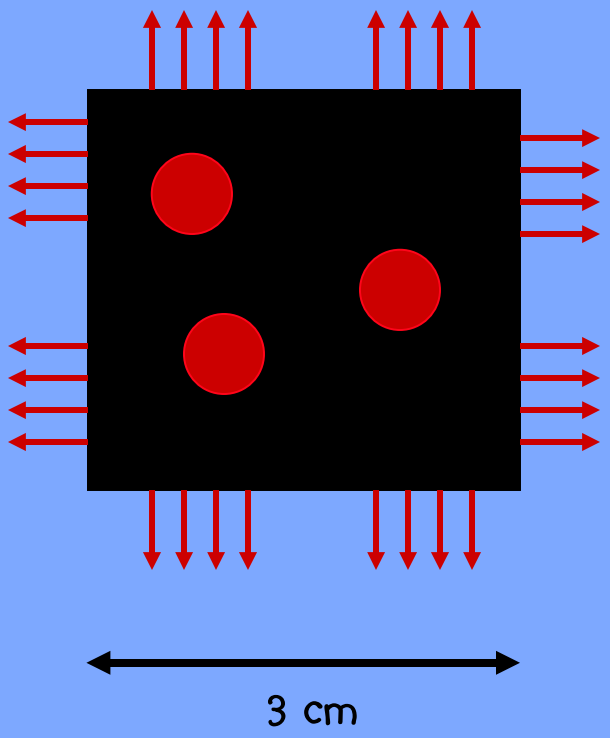
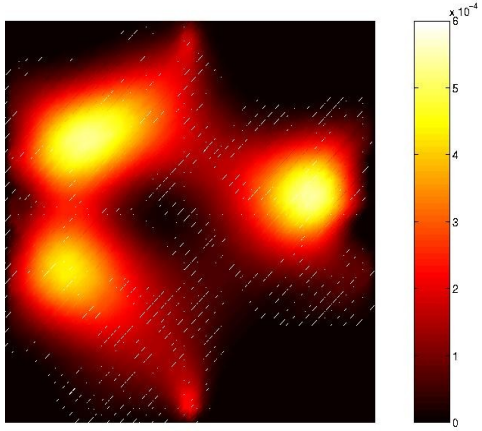
2) Emission

Phantom Experiment



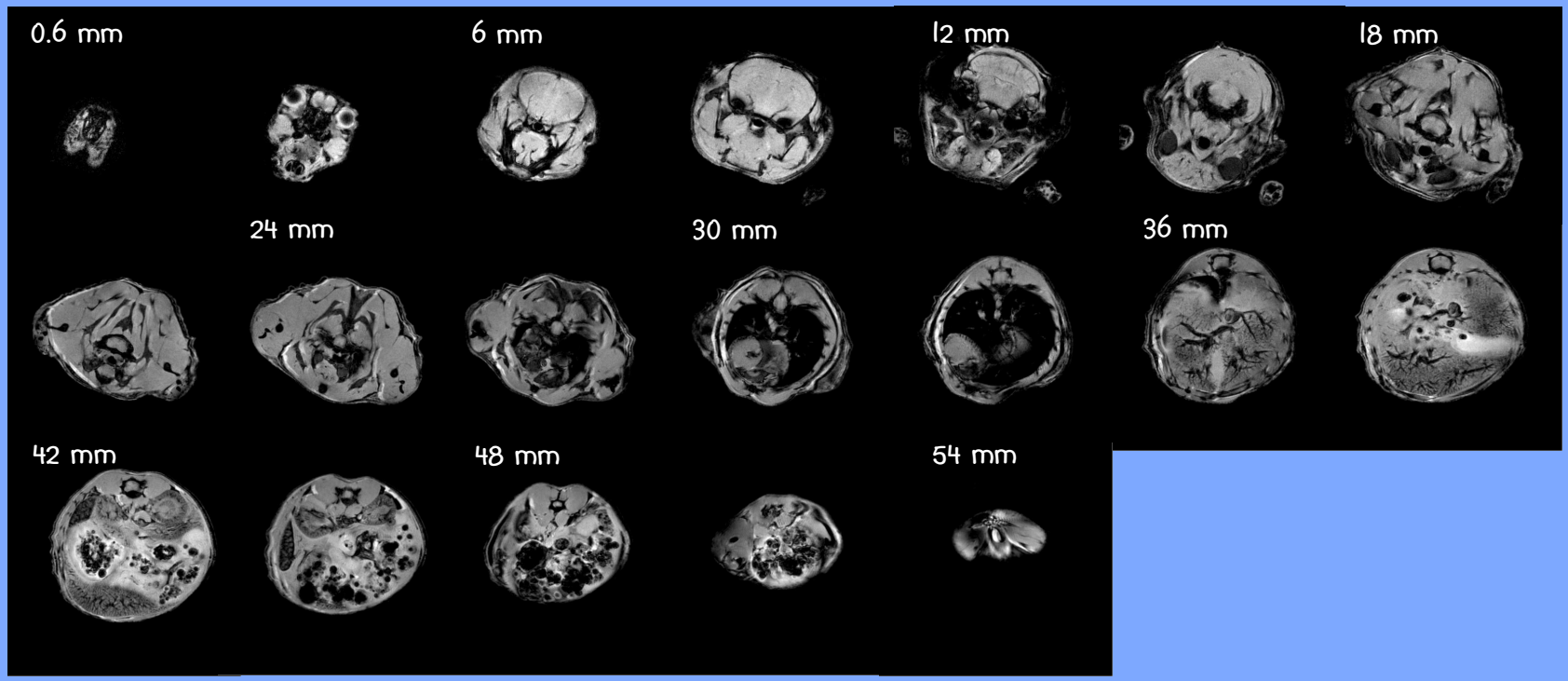
$\eta\mu_a$ = 0.0006 cm^{-1}



2) Emission

3D Numerical Mouse Model

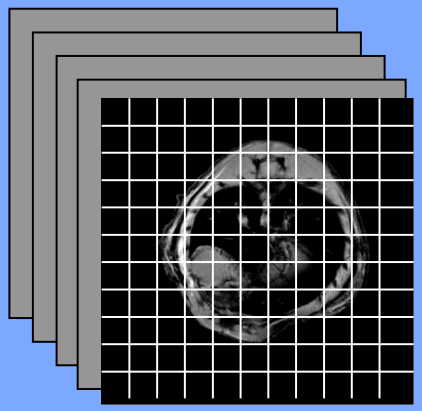
head



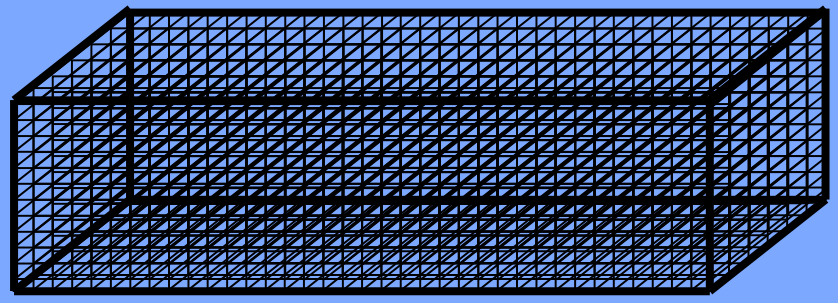
tail

3D Numerical Mouse Model

91 whole-body MRIs of mouse

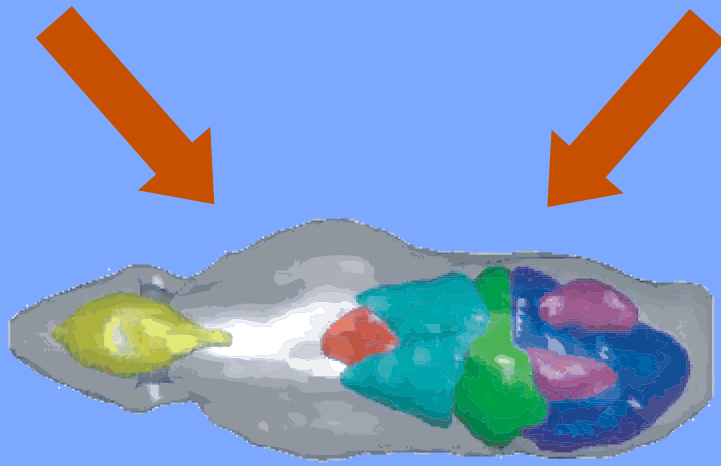


Cartesian grid with 80,000 points



0 mm

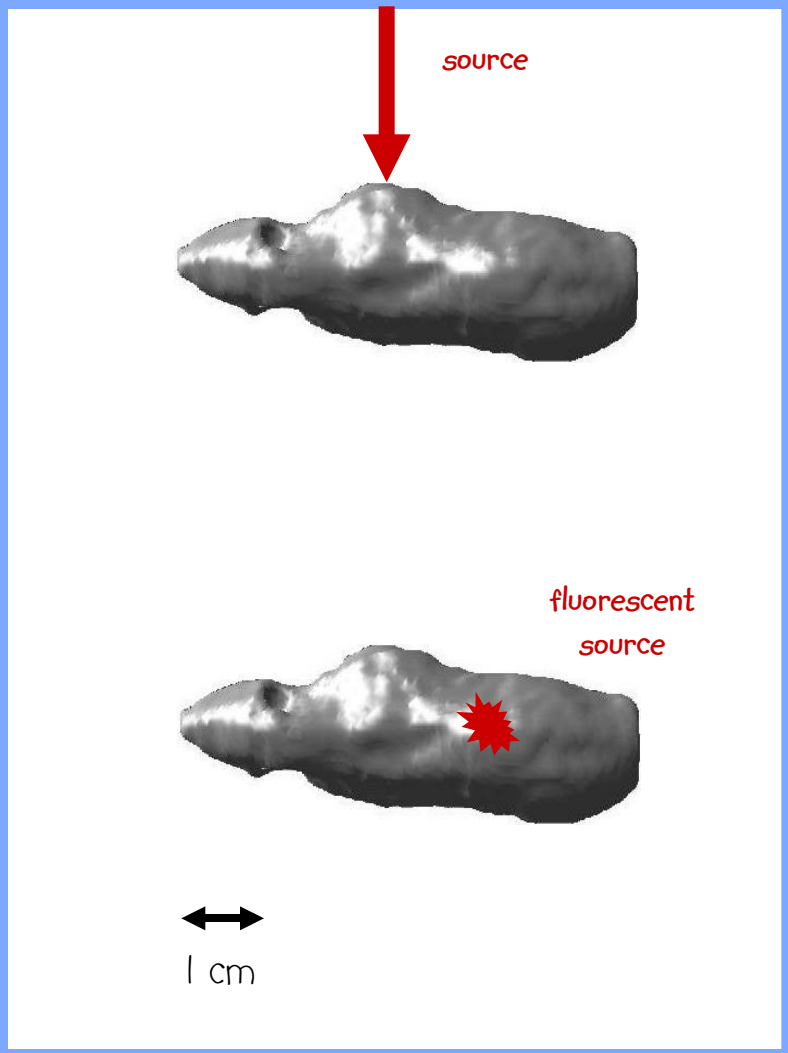
54 mm



Numerical Example

excitation

fluorescence

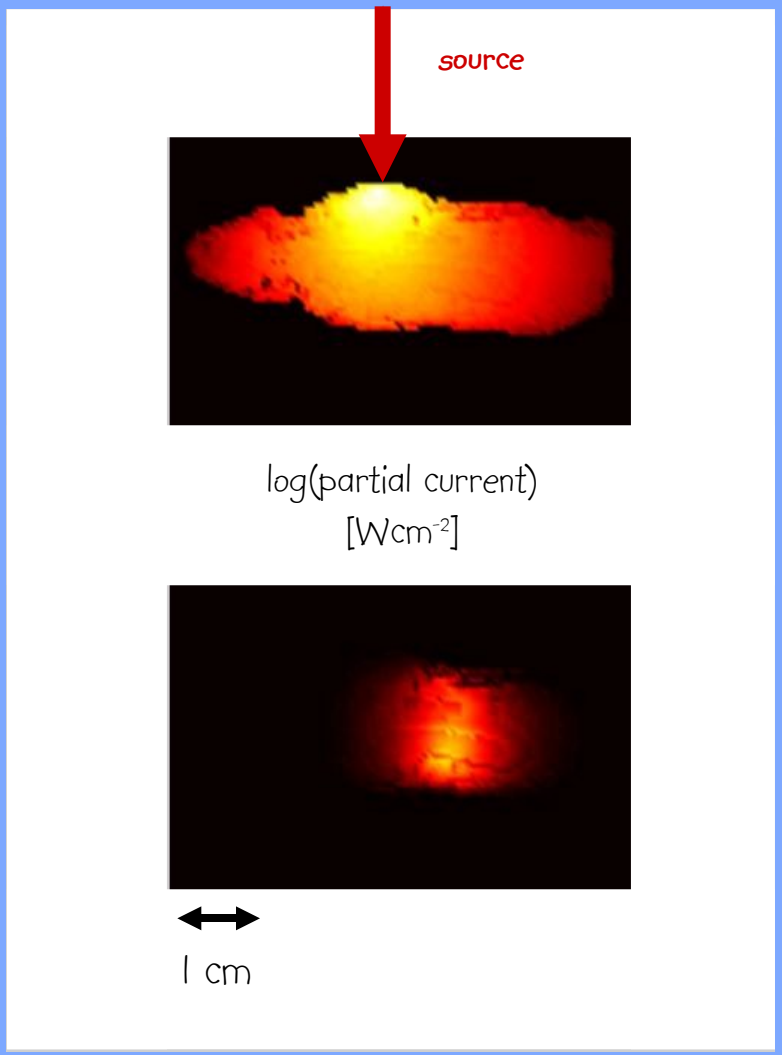


1.8 mm^3, 400nM Cy5.5

Calculated Boundary Flux

excitation

fluorescence



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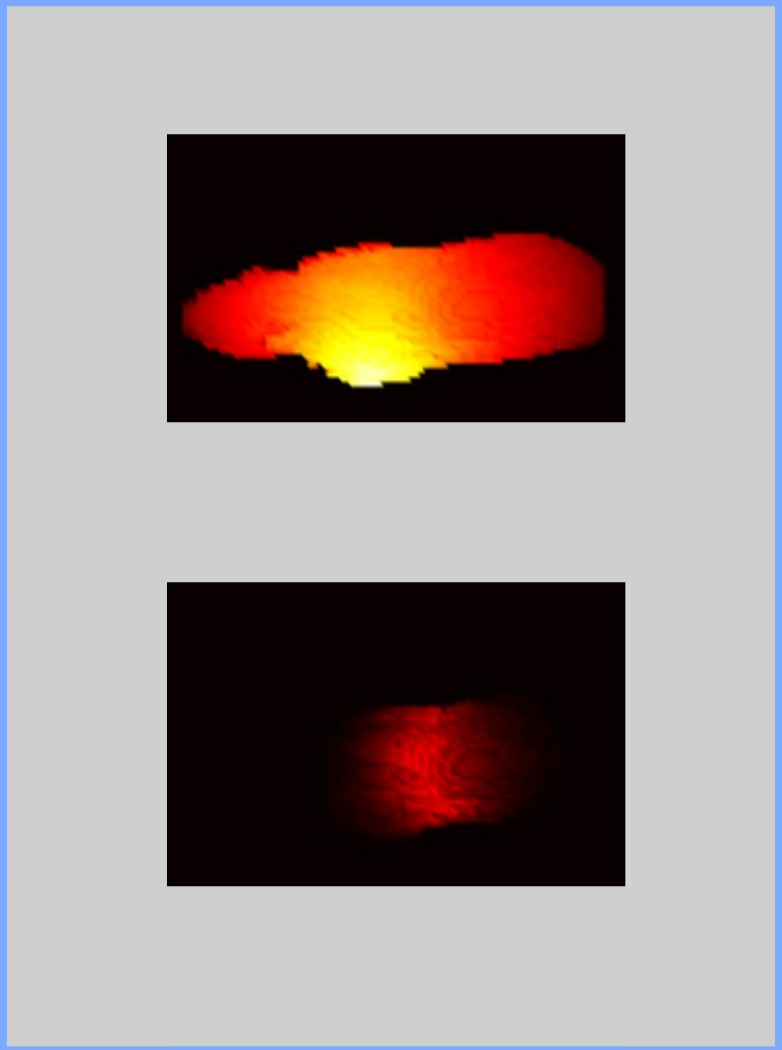
Calculated Boundary Flux

excitation

fluorescence



log(partial current)
[Wcm^{-2}]

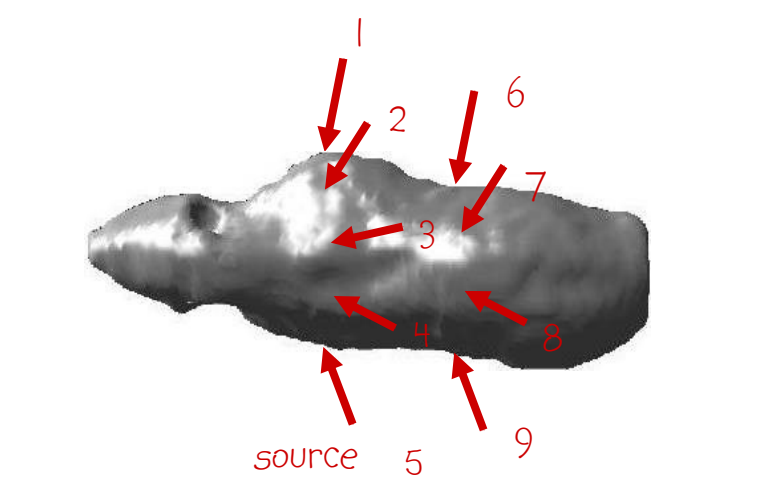
0

-7

-6

-7

Image Reconstruction



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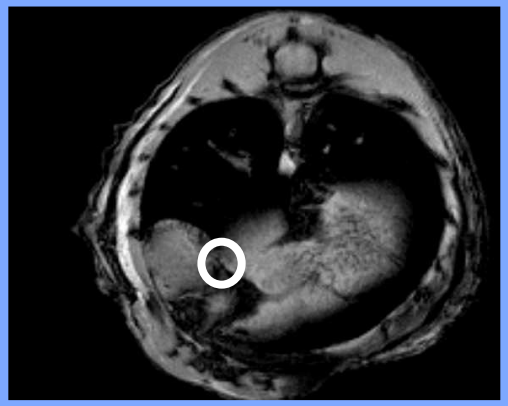
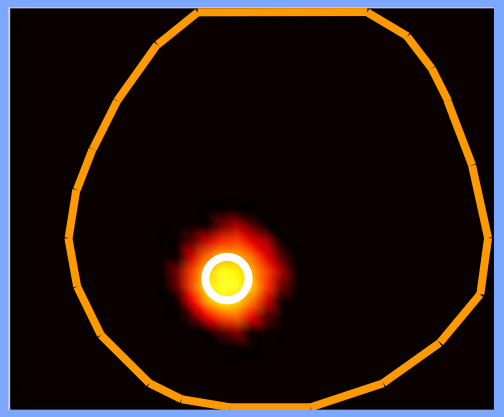
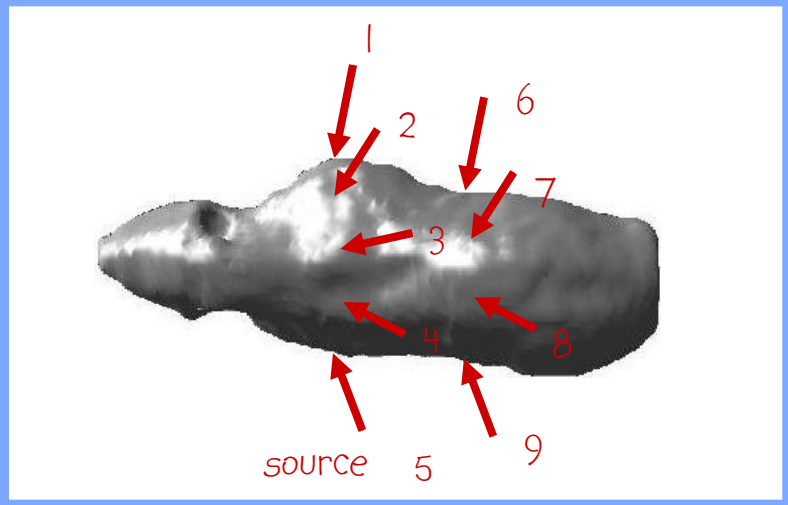


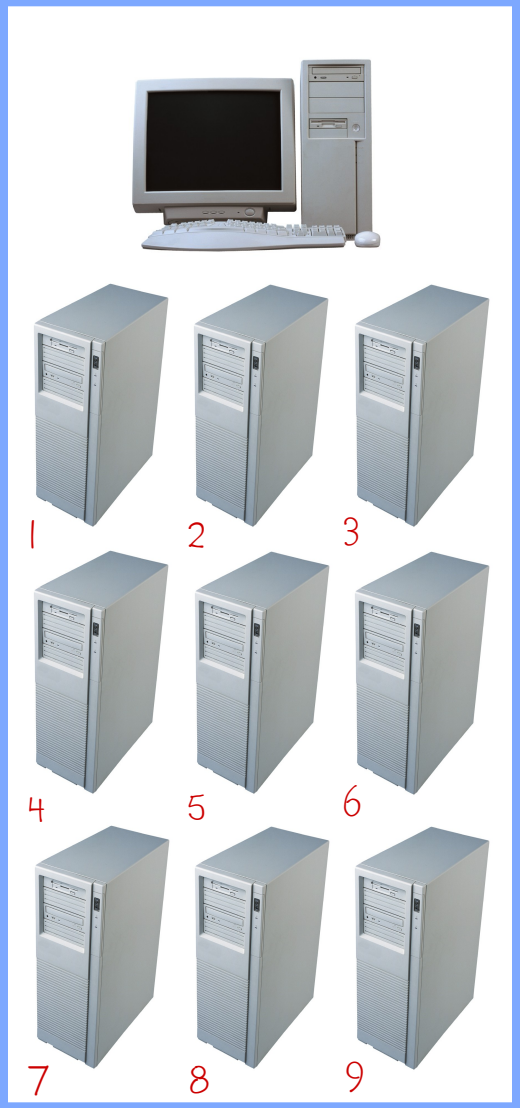


0.5 cm

Parallel Computing – Beowulf Cluster

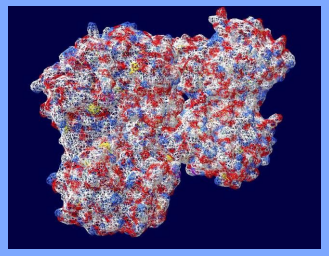


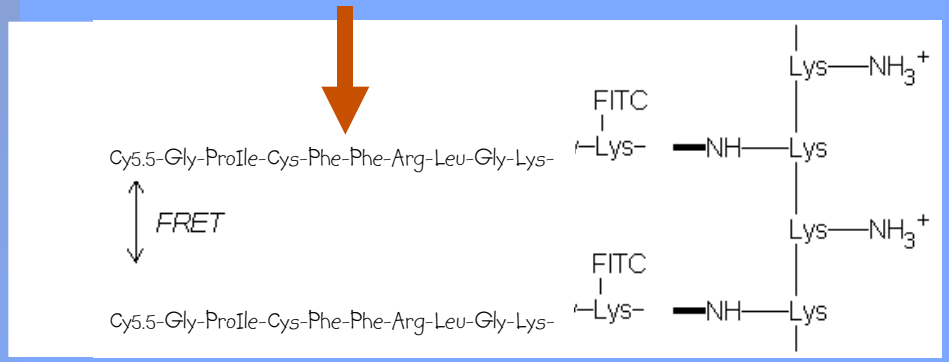
radiatve transfer model is solved
for all source positions on # processors



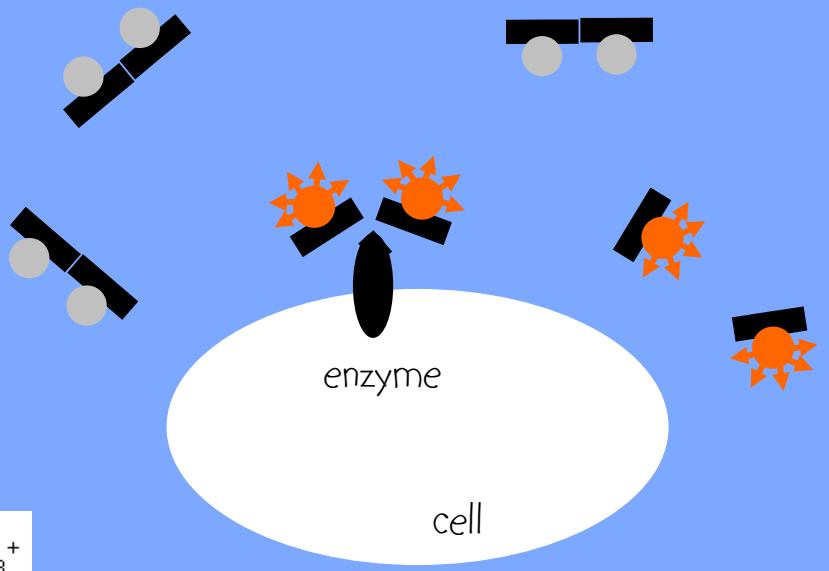
In Vivo Experiments

Fluorescent probe is activated through interaction with a molecular target, e.g. enzyme (Cathepsin D)





fluorescent probe

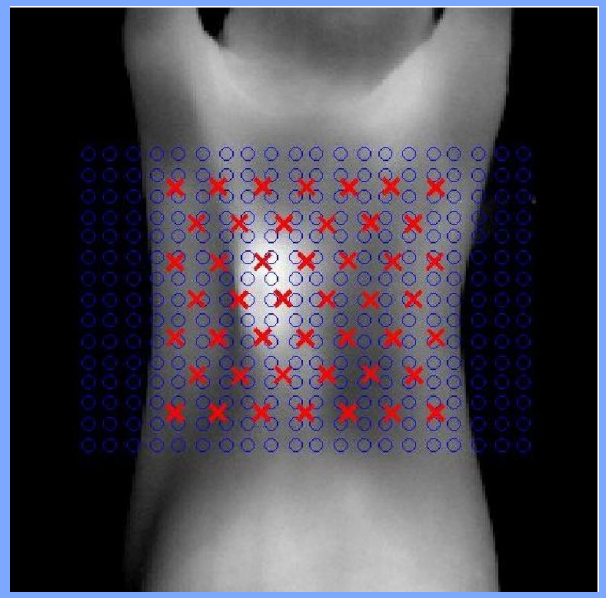


Tung et al, Bioconjugate Chemistry 10, (1999)

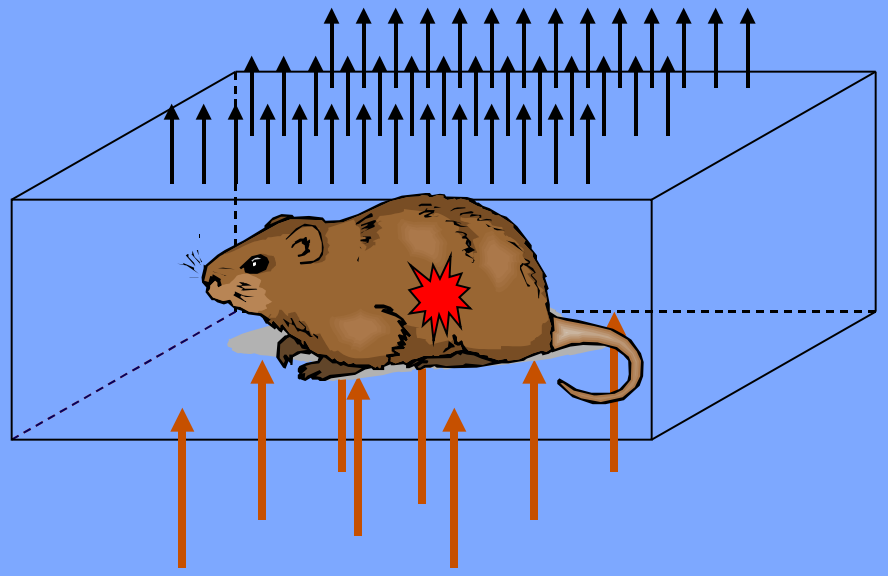
Weissleder et al, Nature Biotechnology 17, (1999)

In Vivo Experiments

Mouse with Lewis Lung Carcinoma (LLC)

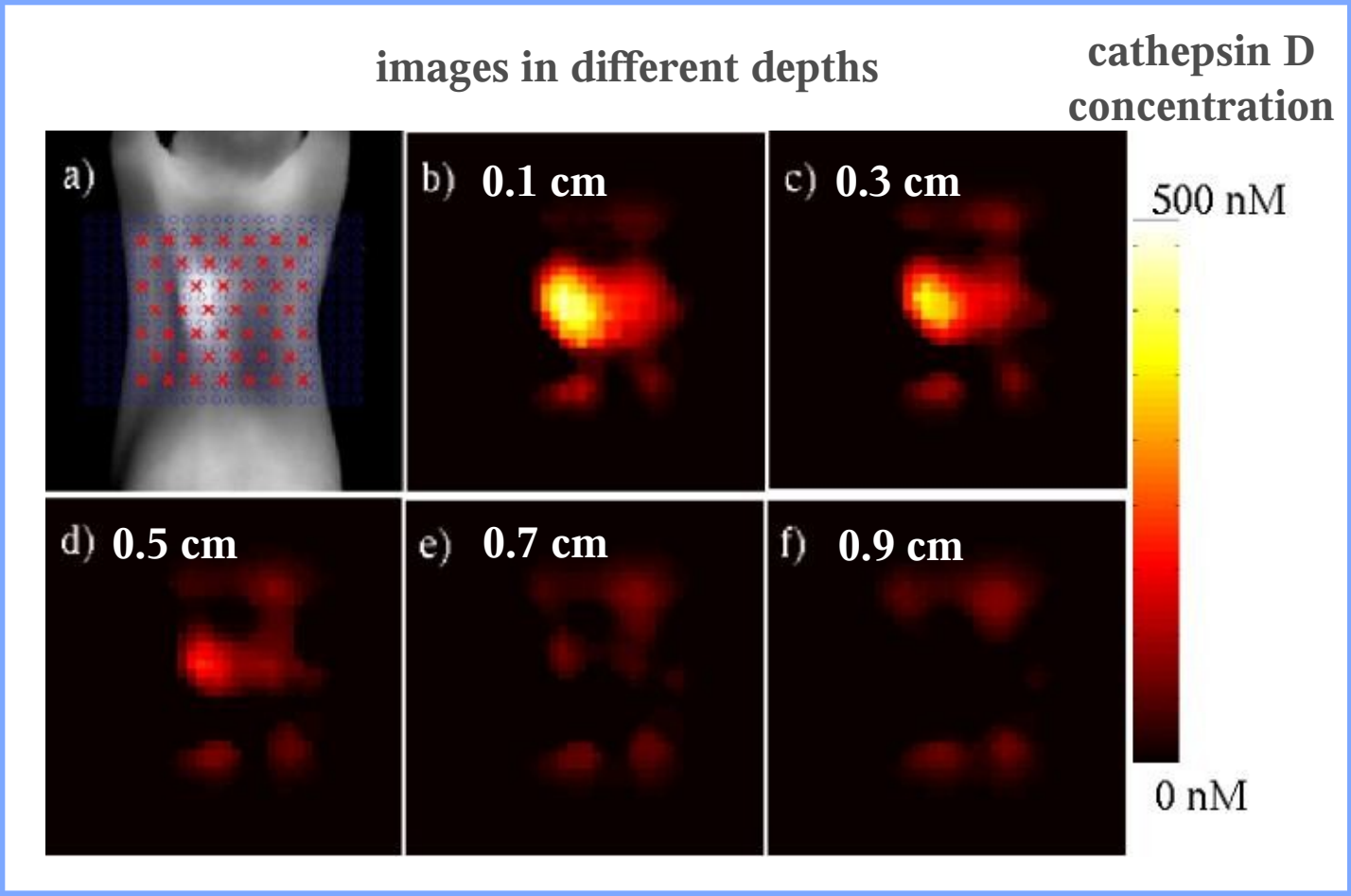


surface-weighted image



Experimental data were provided by V. Ntziachristos, MGH

In Vivo Experiments



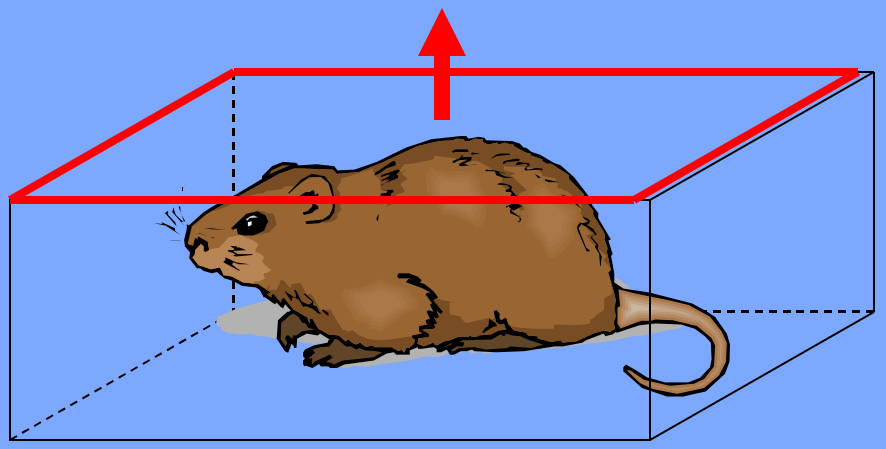
Beowulf Cluster

24 CPUs

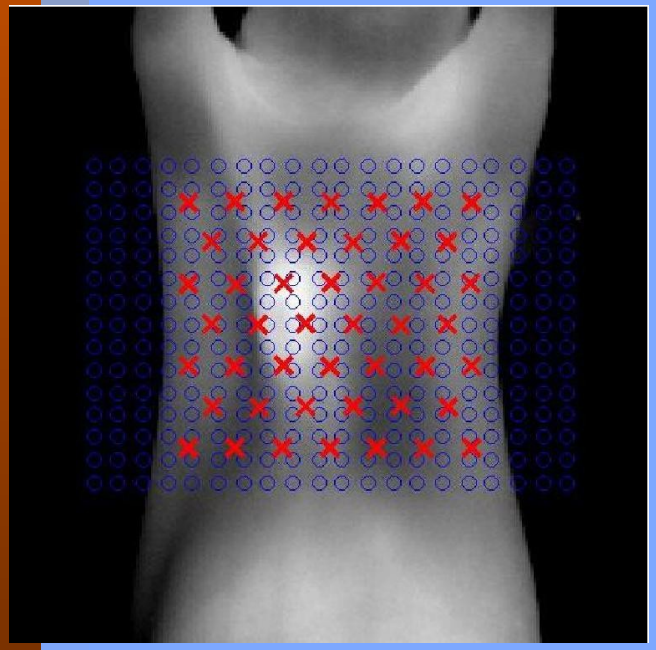
Parallel Processing (MPI)

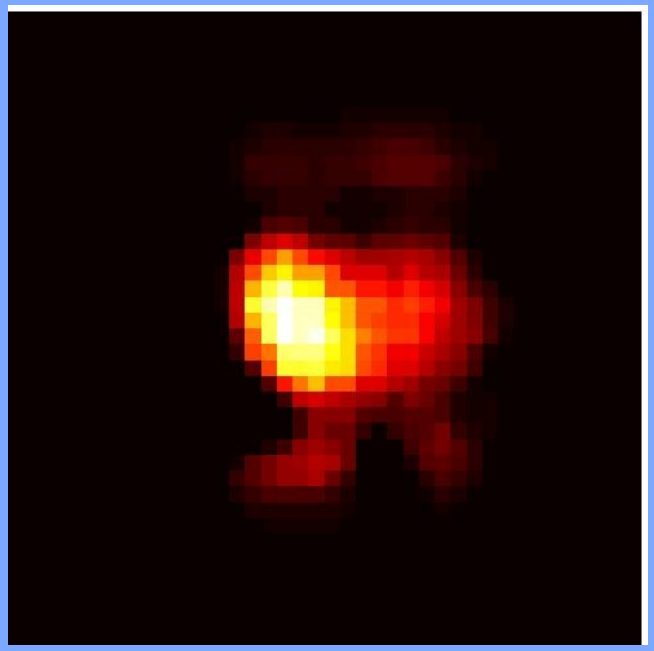
current reconstruction time
3 to 48 hours

In Vivo Experiments



top view



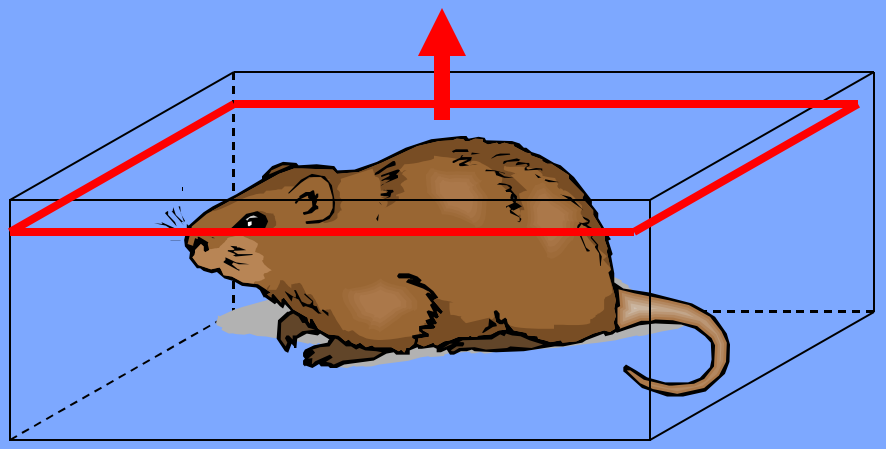


fluorophore
absorption = 0 - 0.032 cm^{-1}

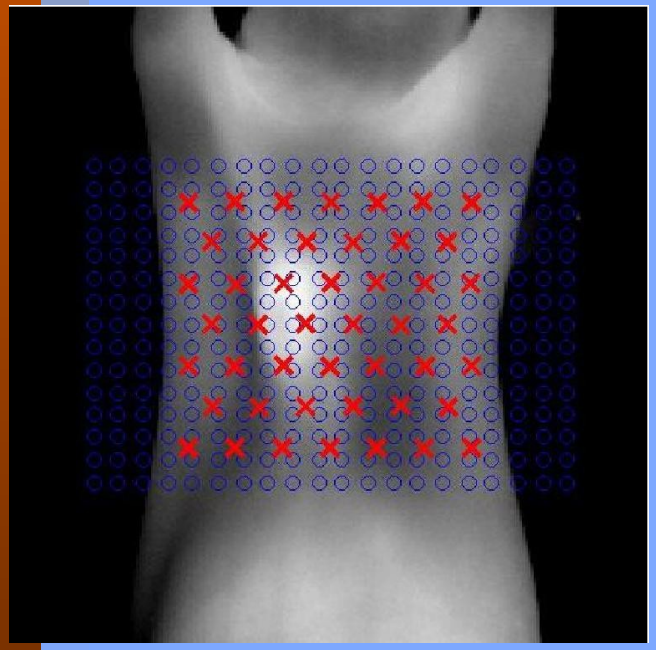
In Vivo Experiments

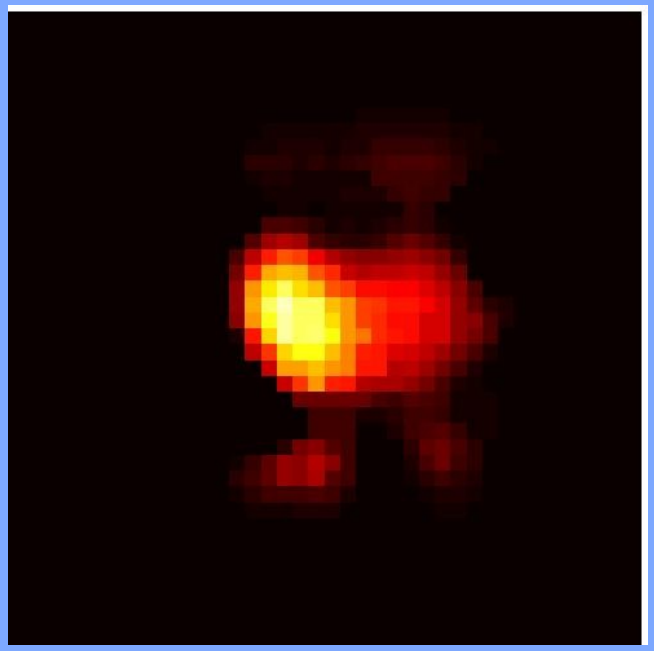
depth

0.1 cm



top view



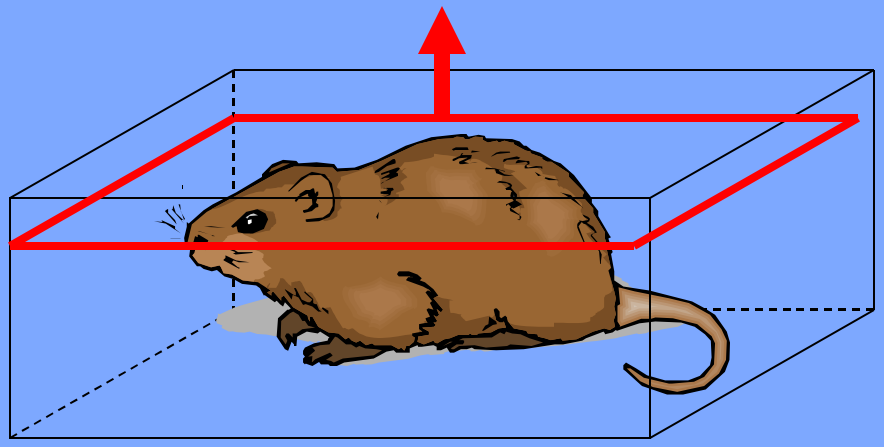


fluorophore
absorption = 0 - 0.032 cm^{-1}

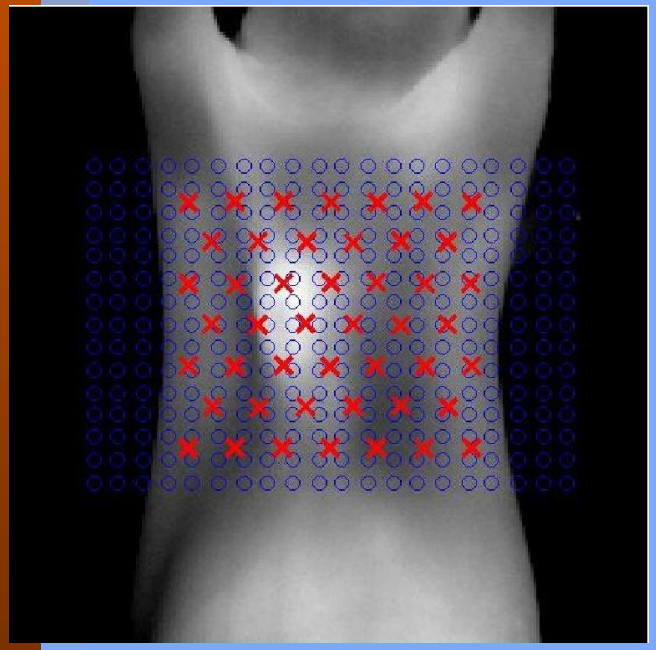
In Vivo Experiments

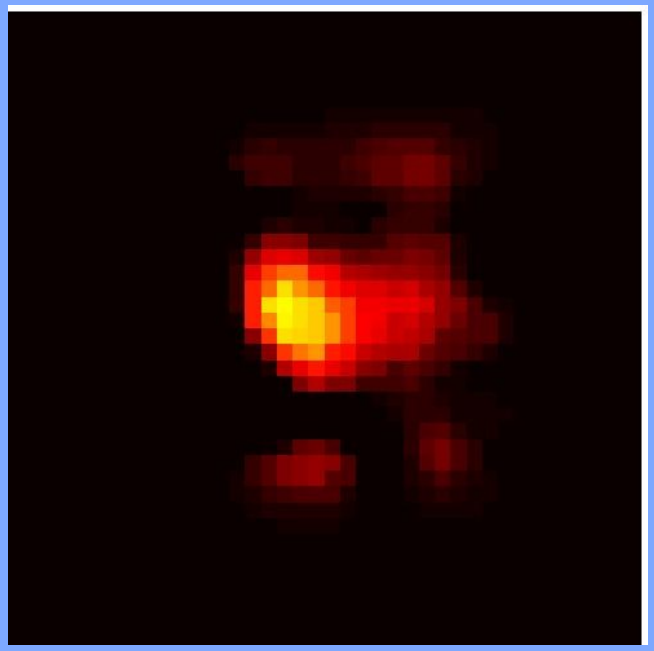
depth

0.2 cm



top view

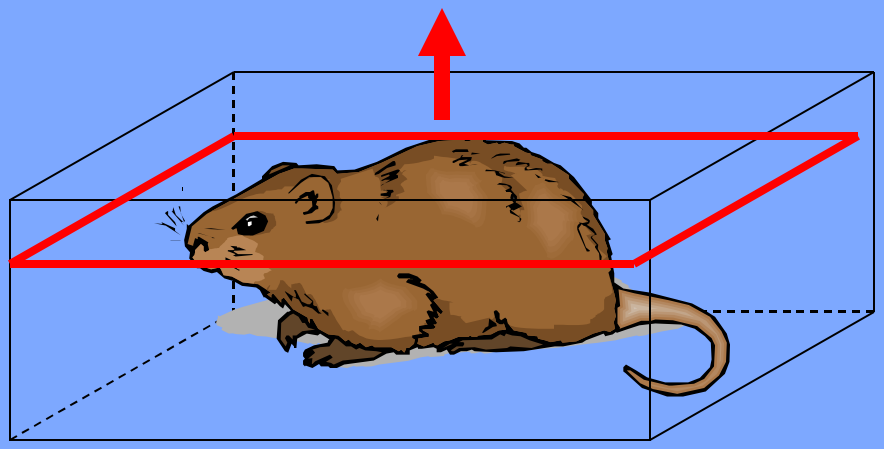




fluorophore
absorption = 0 - 0.032 cm^{-1}

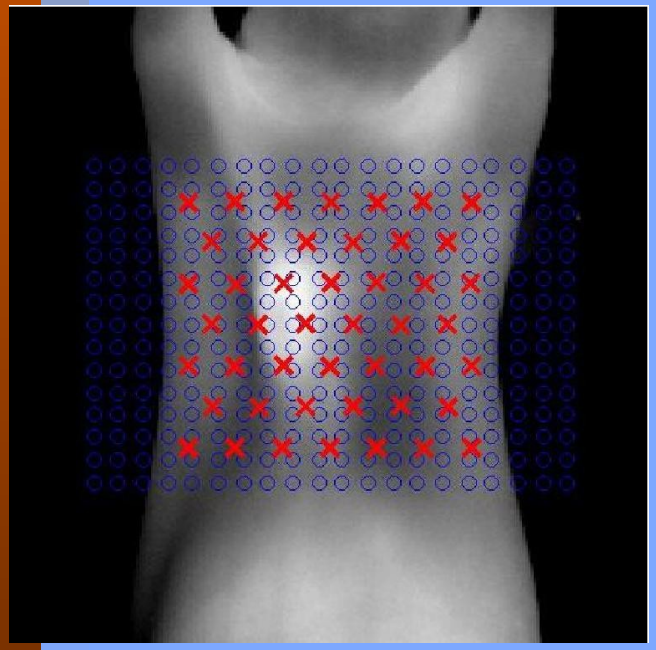
In Vivo Experiments

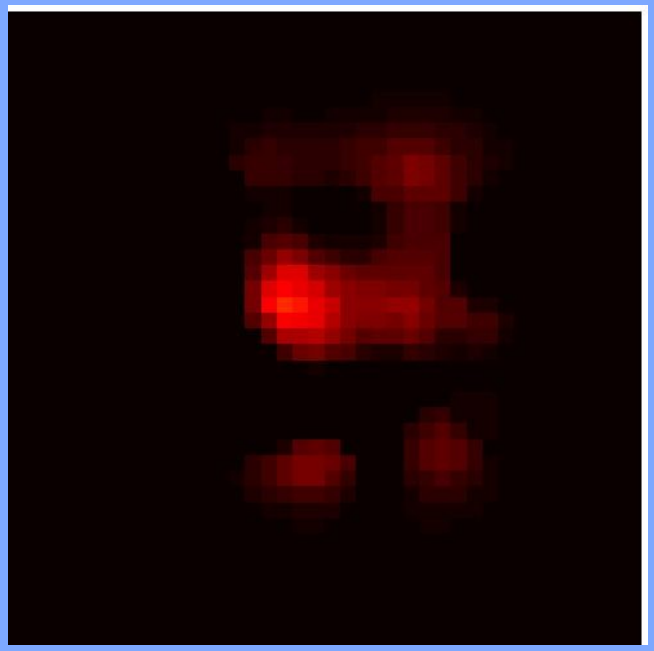
depth



0.3 cm

top view

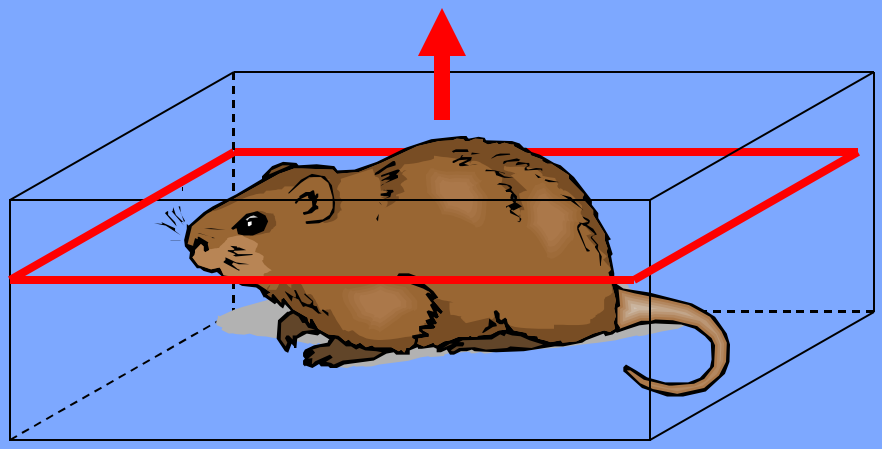




fluorophore
absorption = 0 - 0.032 cm^{-1}

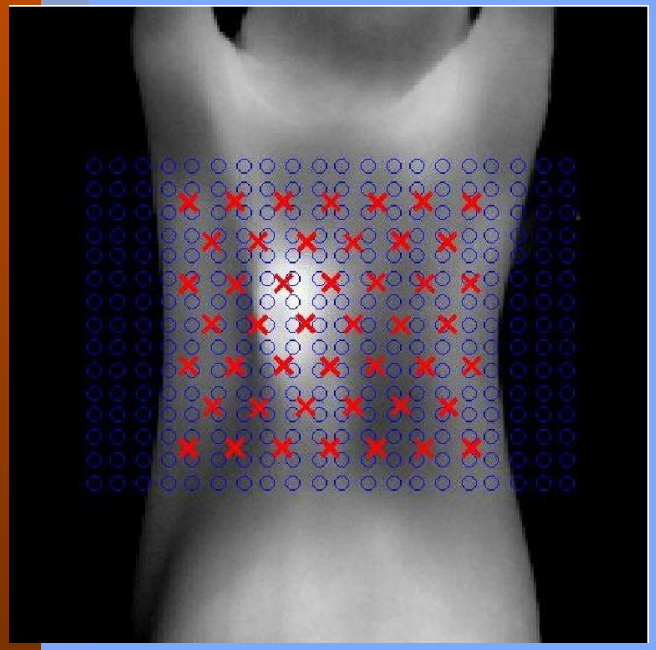
In Vivo Experiments

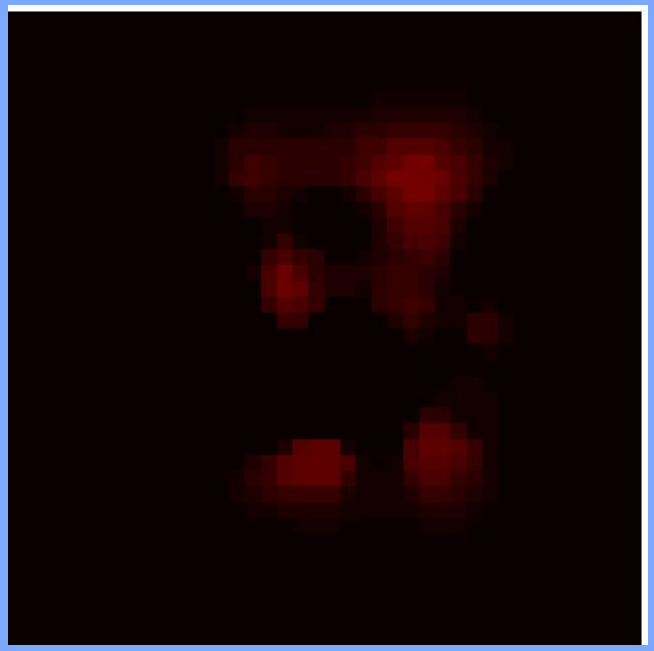
depth



0.4 cm

top view

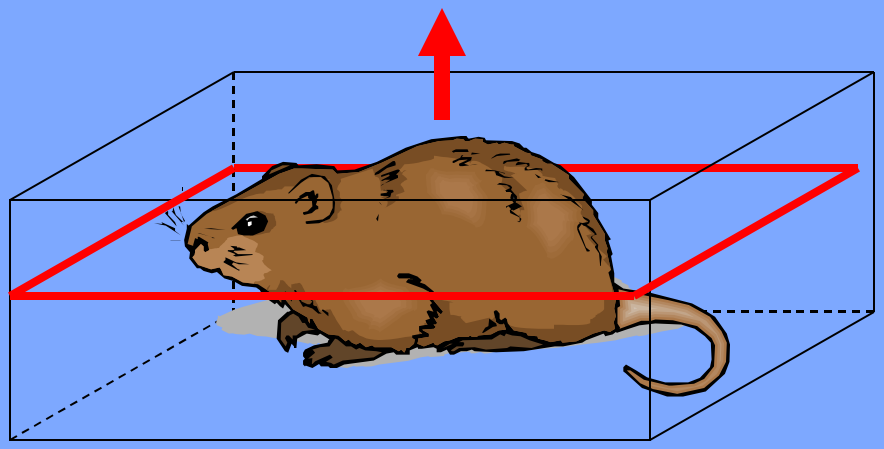




fluorophore
absorption = 0 - 0.032 cm^{-1}

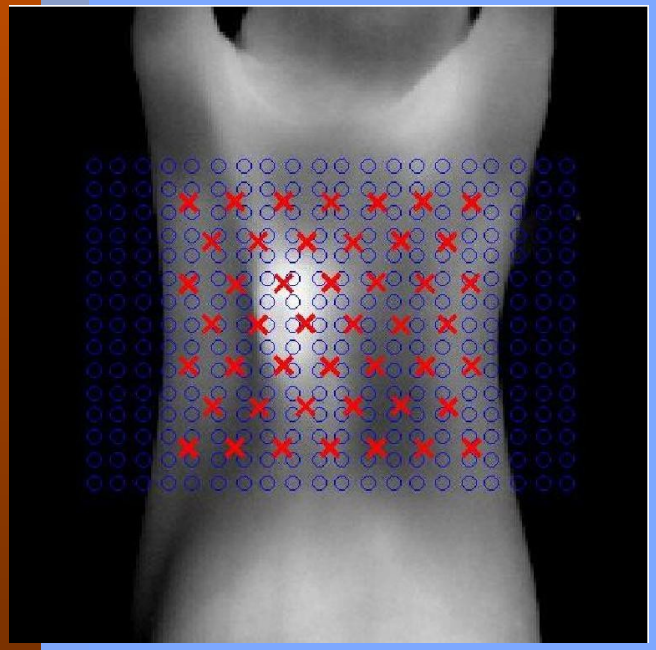
In Vivo Experiments

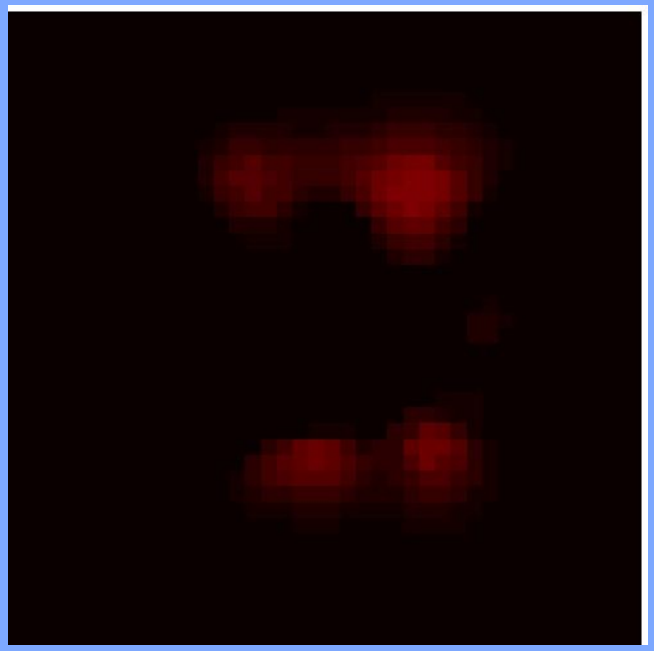
depth



0.5 cm

top view

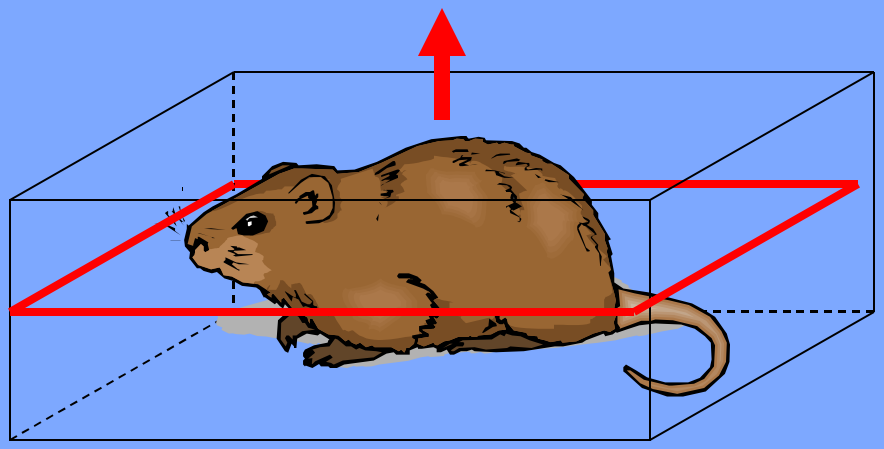




fluorophore
absorption = 0 - 0.032 cm^{-1}

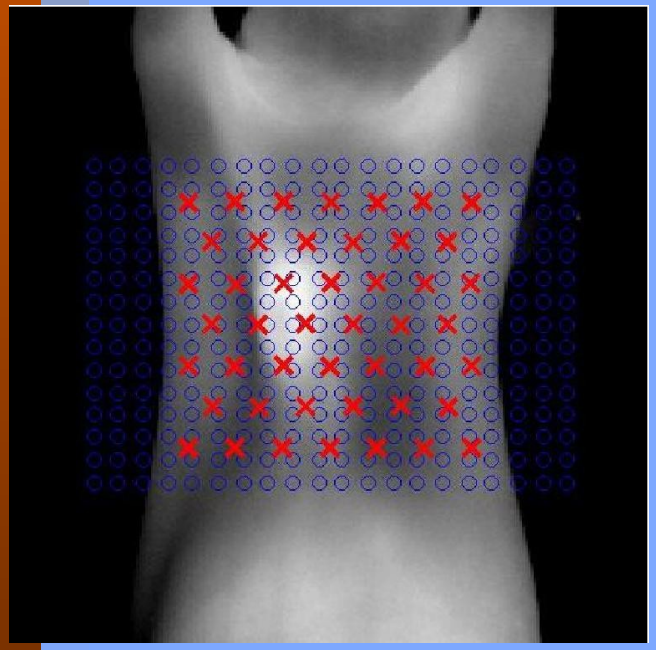
In Vivo Experiments

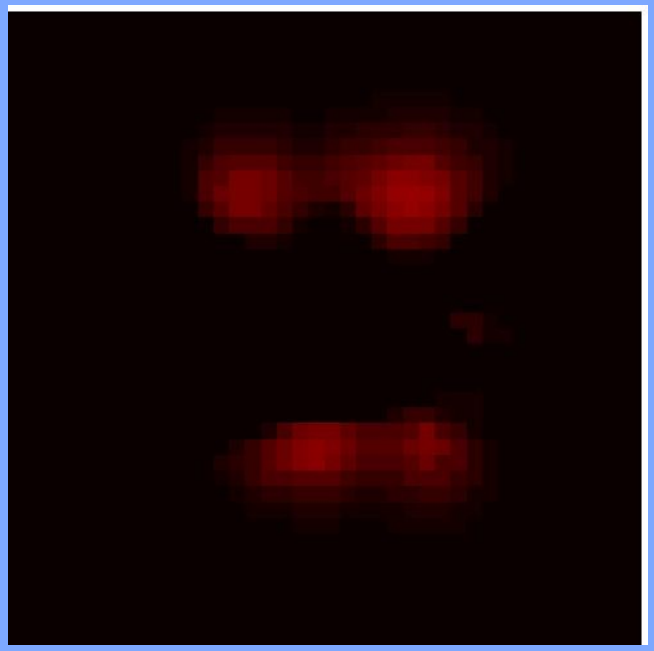
depth



0.6 cm

top view

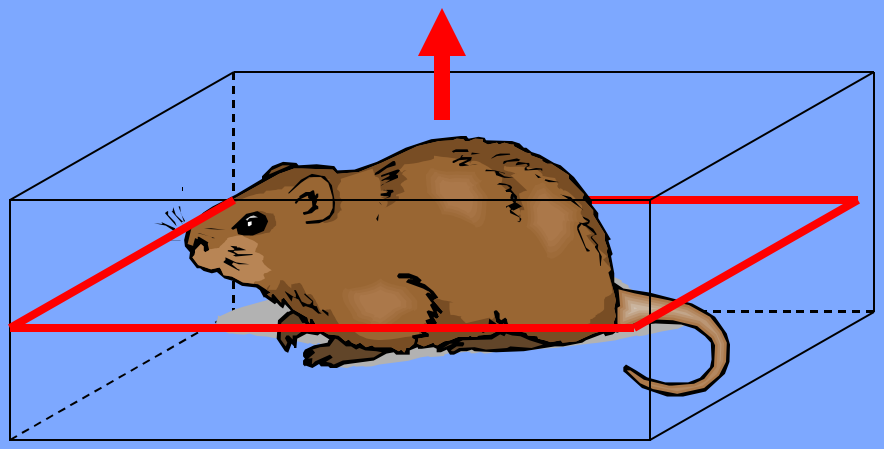




fluorophore
absorption = 0 - 0.032 cm^{-1}

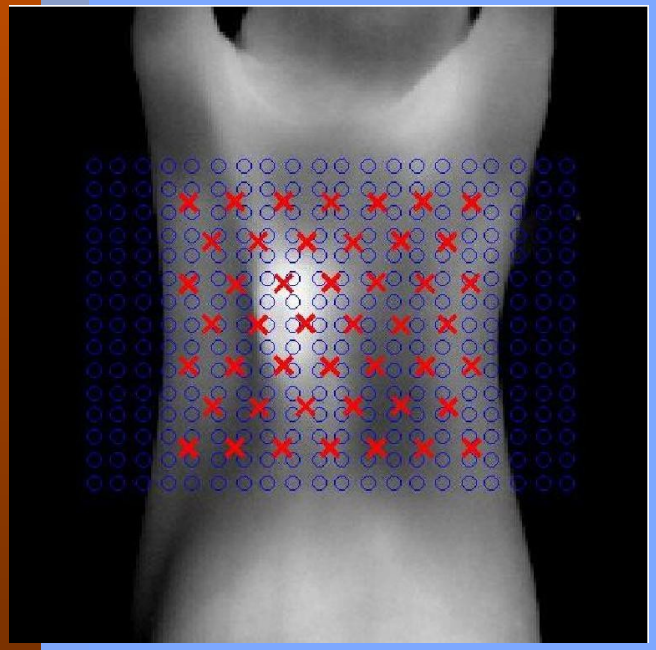
In Vivo Experiments

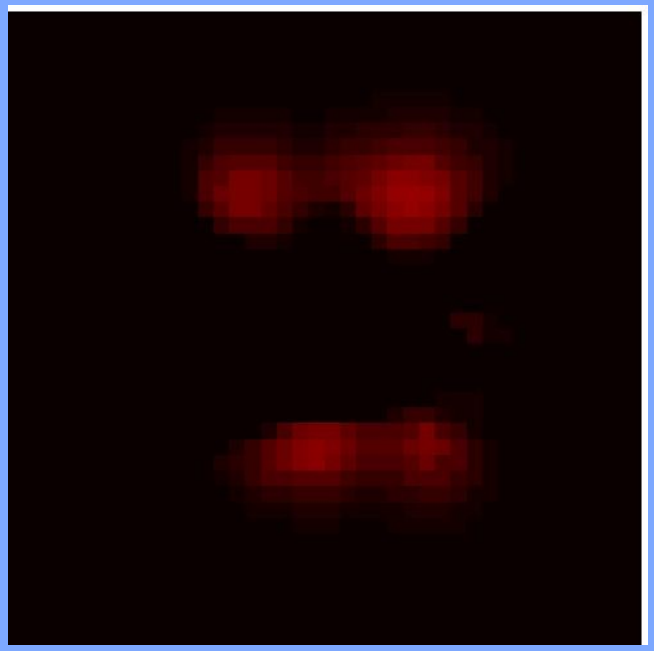
depth



0.7 cm

top view

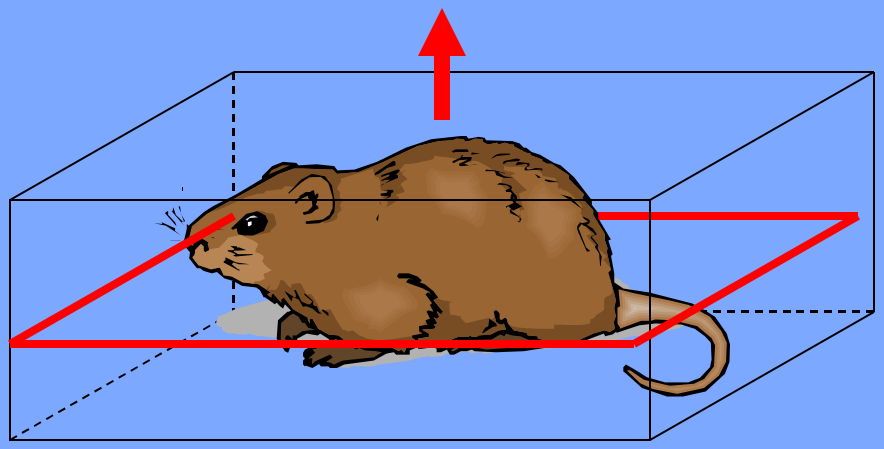




fluorophore
absorption = 0 - 0.032 cm^{-1}

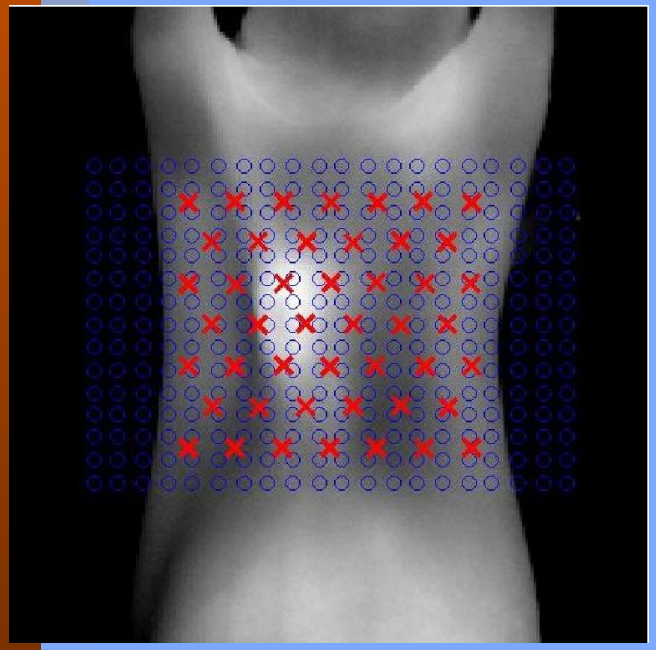
In Vivo Experiments

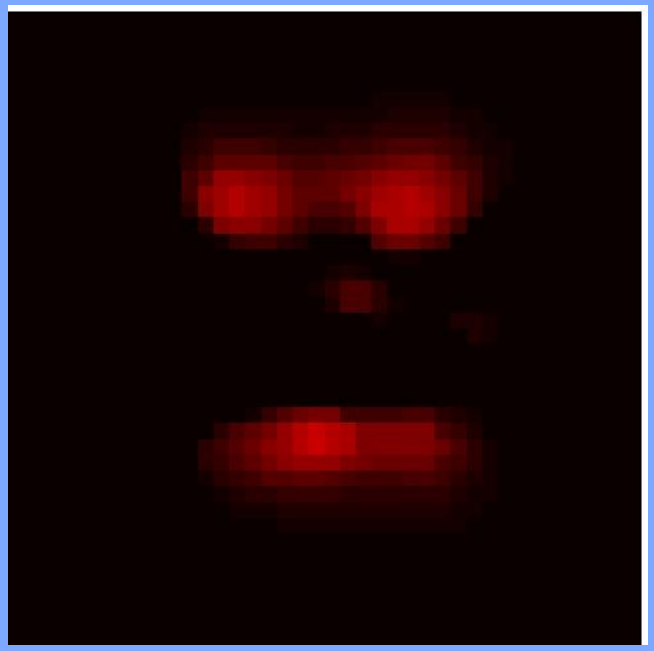
depth



0.8 cm

top view

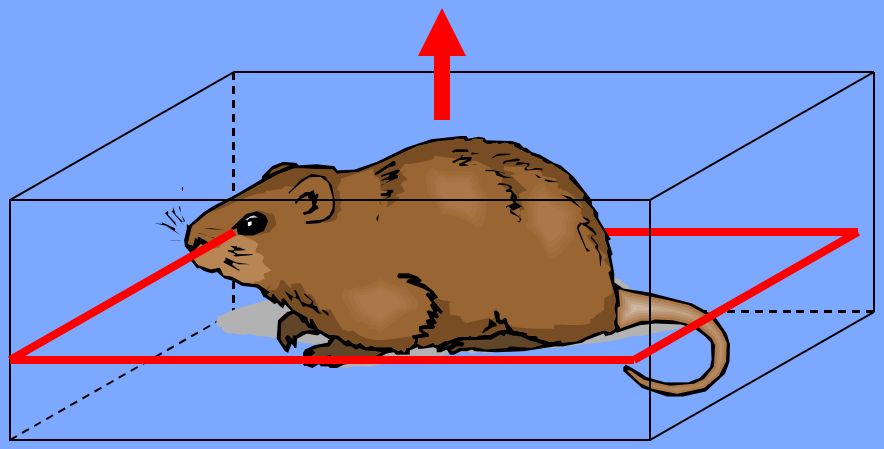




fluorophore
absorption = 0 - 0.032 cm^{-1}

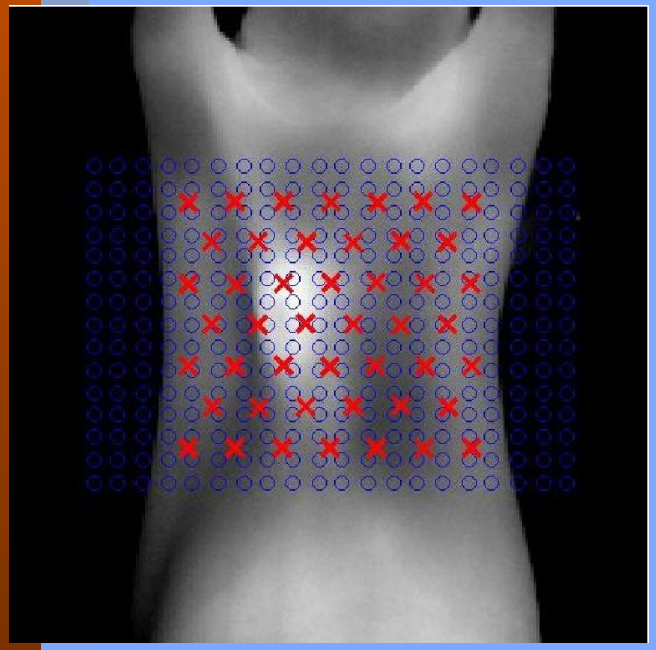
In Vivo Experiments

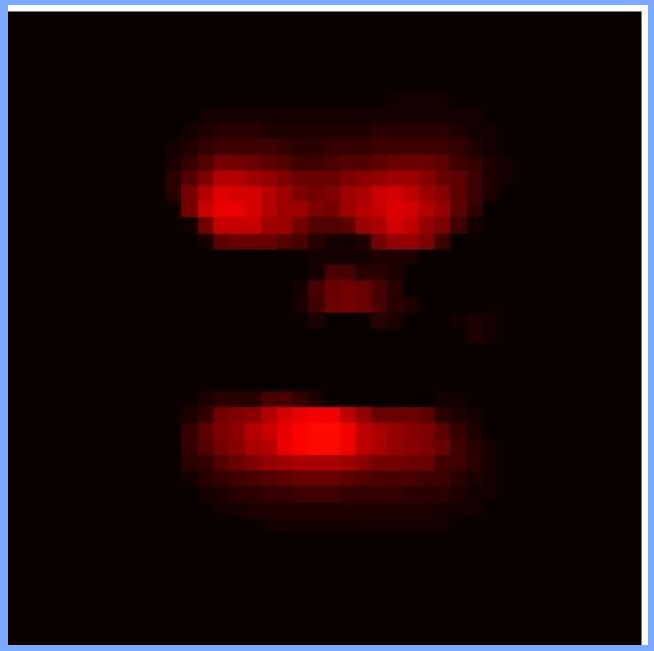
depth



0.9 cm

top view

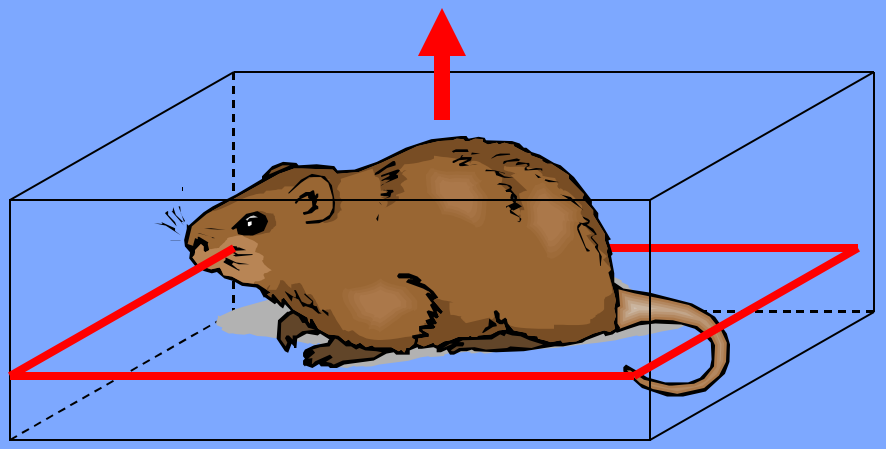




fluorophore
absorption = 0 - 0.032 cm^{-1}

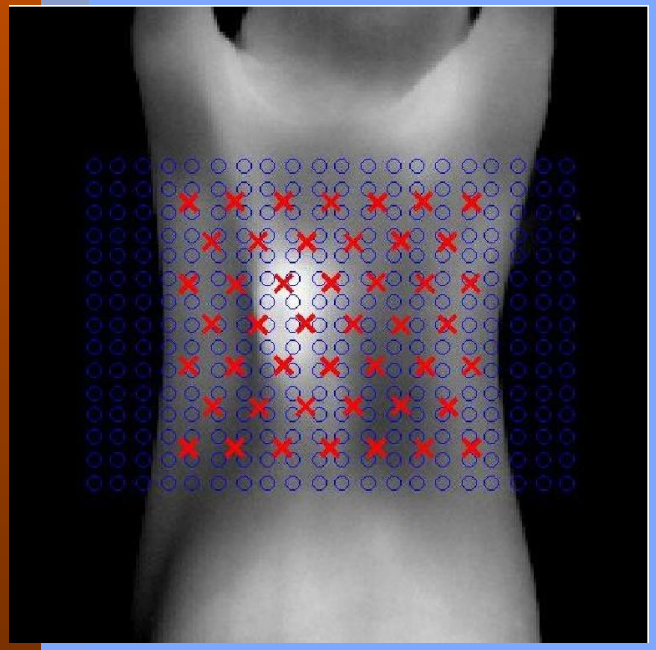
In Vivo Experiments

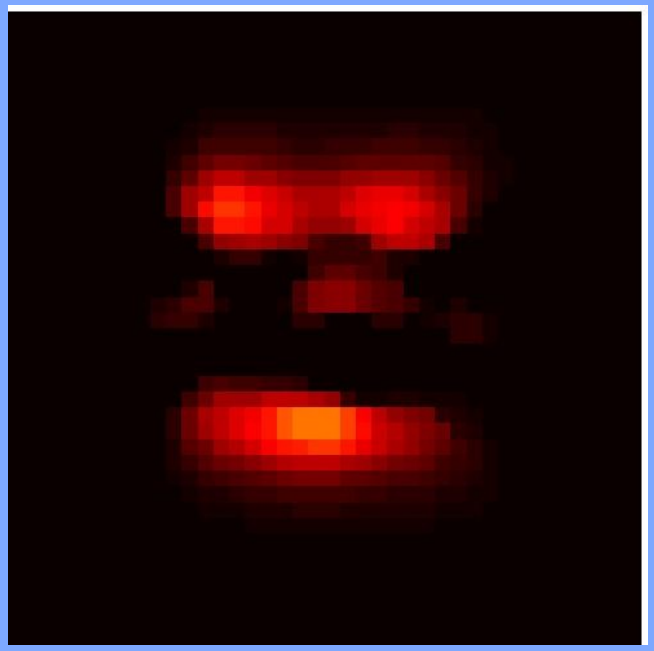
depth



1.0 cm

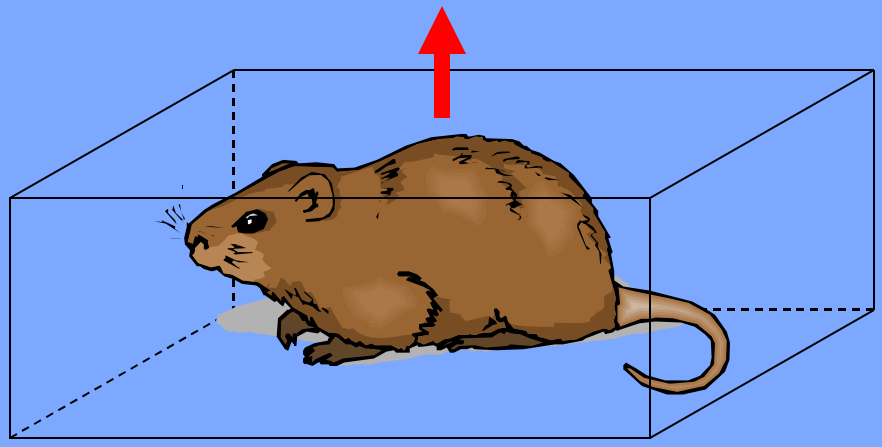
top view



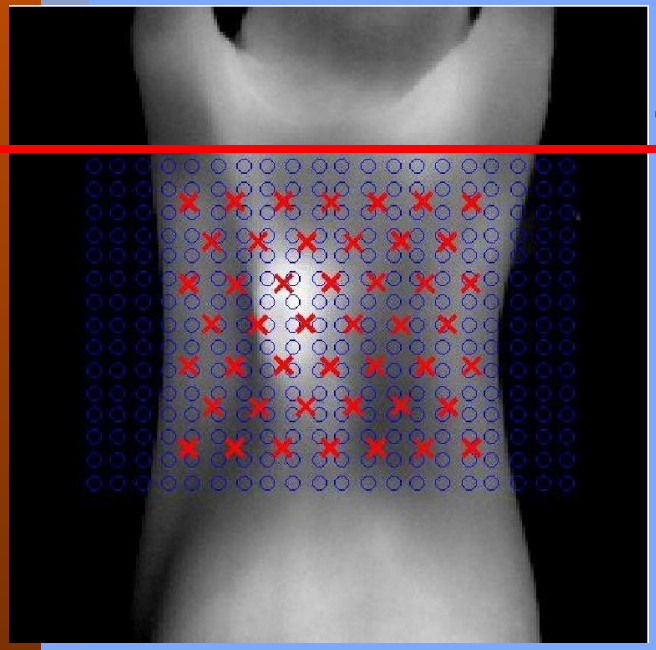


fluorophore
absorption = 0 - 0.032 cm^{-1}

In Vivo Experiments



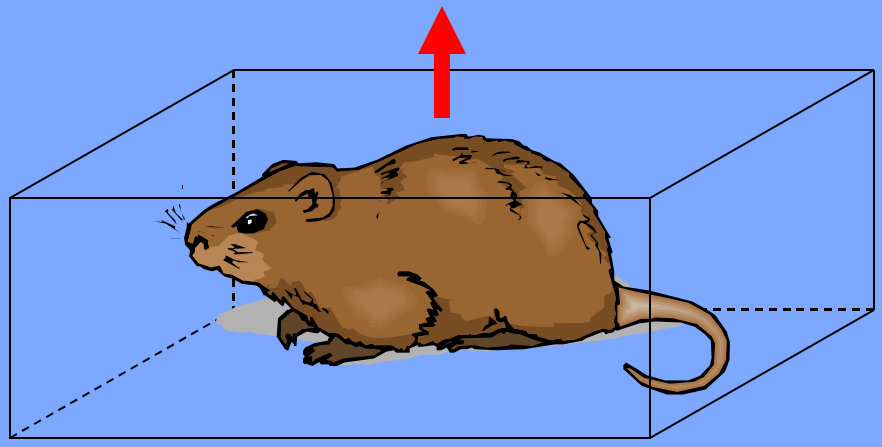
top view



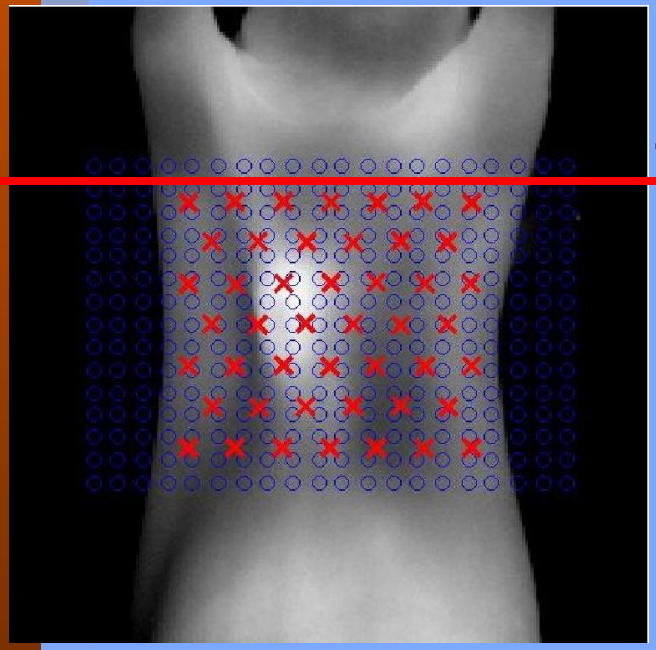
+1.0 cm

fluorophore
absorption = 0 - 0.032 cm^{-1}

In Vivo Experiments



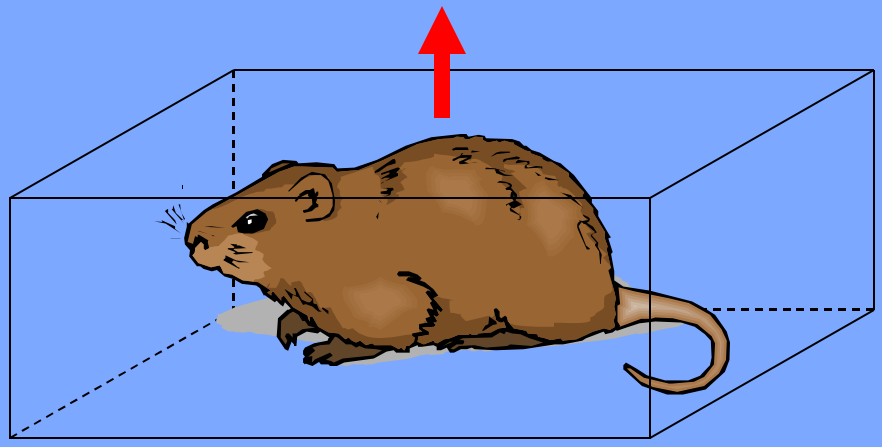
top view



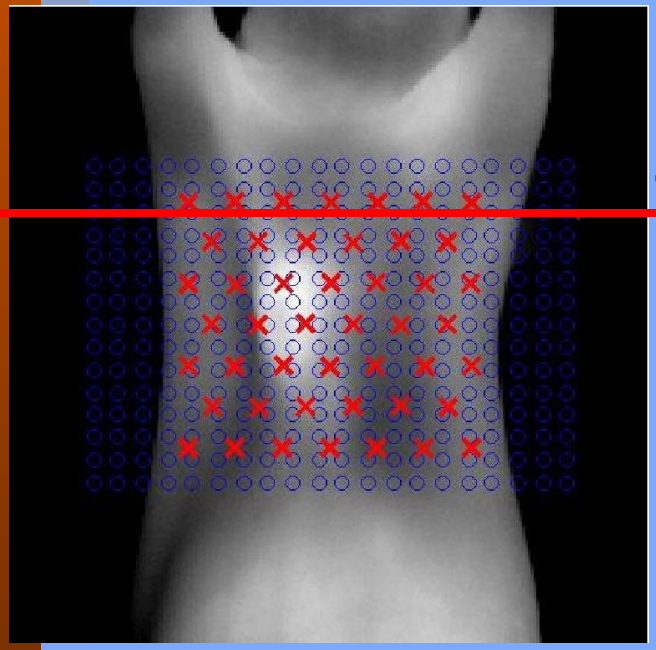
+0.8 cm

fluorophore
absorption = 0 - 0.032 cm^{-1}

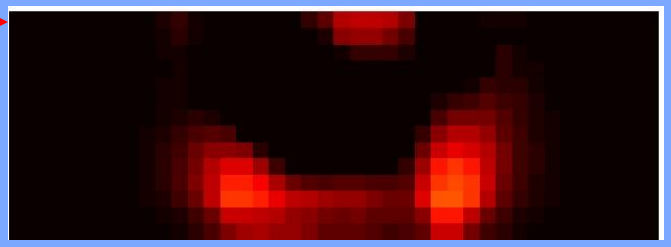
In Vivo Experiments



top view

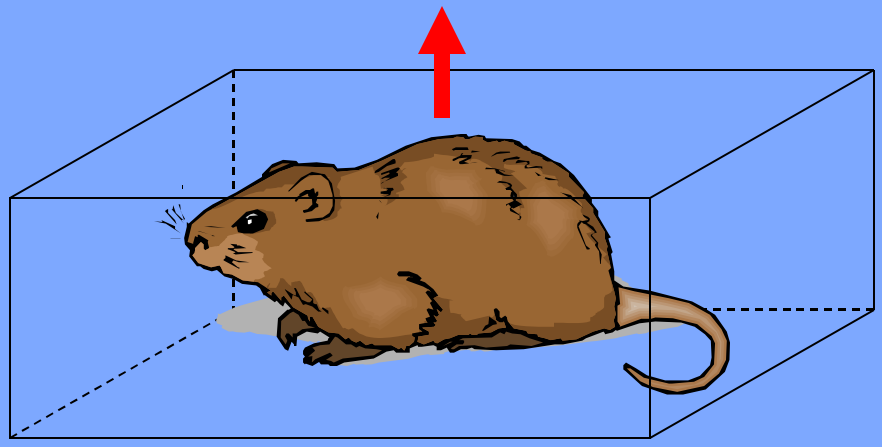


+0.6 cm

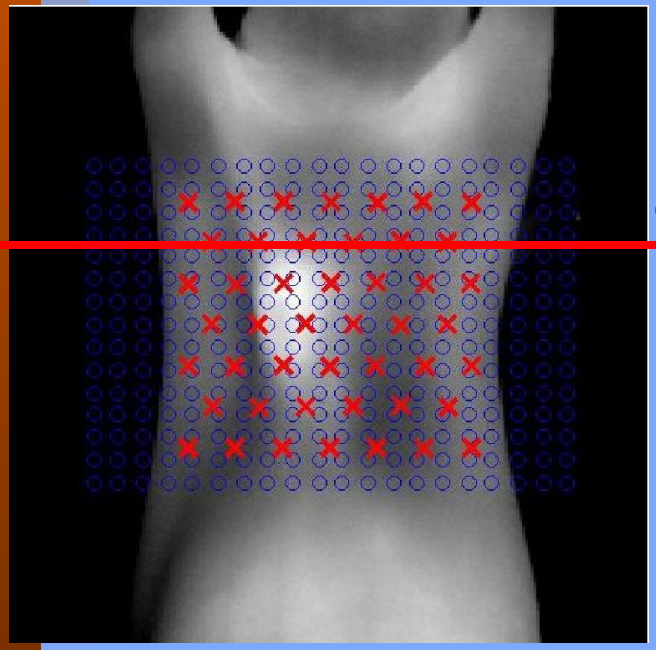


fluorophore
absorption = 0 - 0.032 cm^{-1}

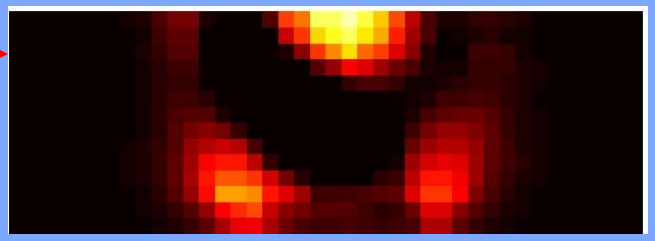
In Vivo Experiments



top view

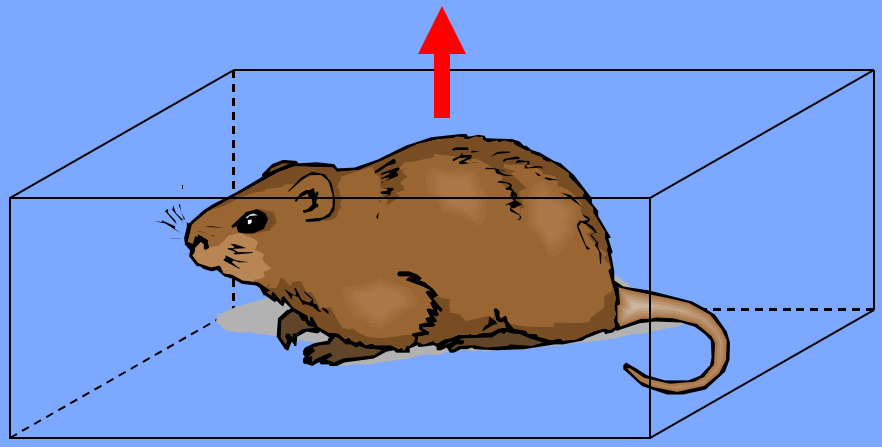


+0.4 cm

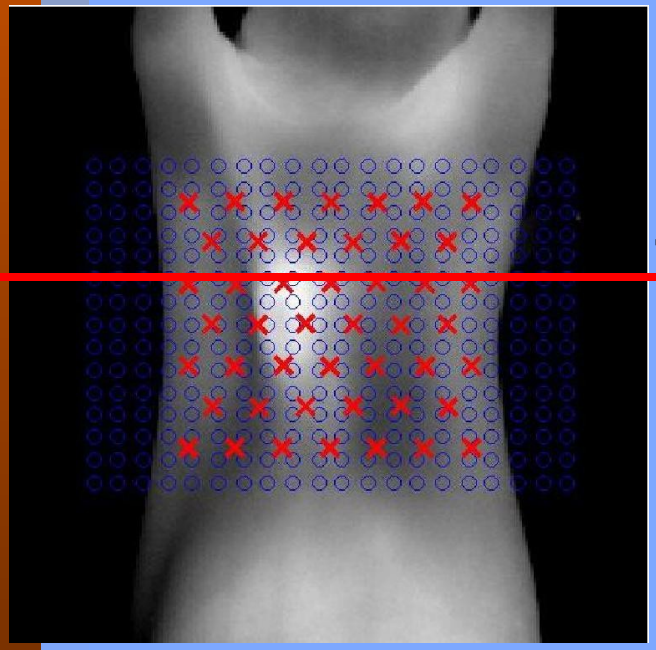


fluorophore
absorption = 0 - 0.032 cm^{-1}

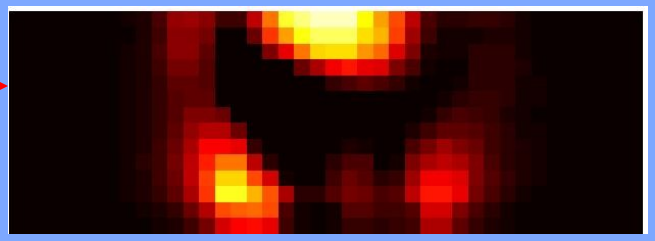
In Vivo Experiments



top view

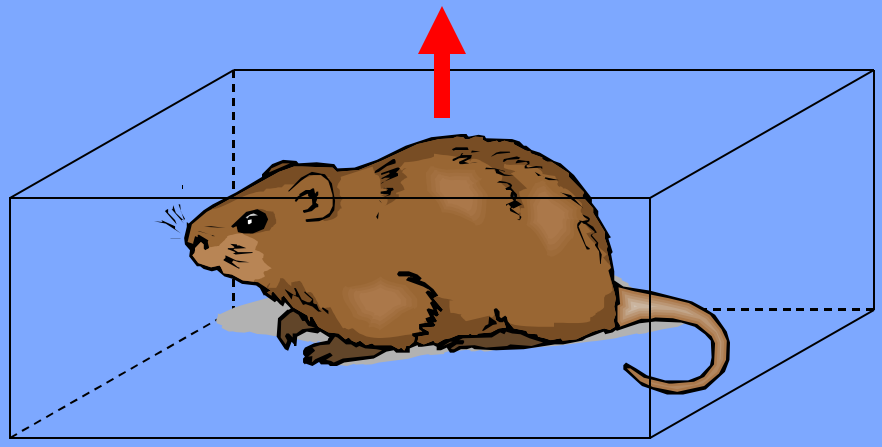


+0.2 cm

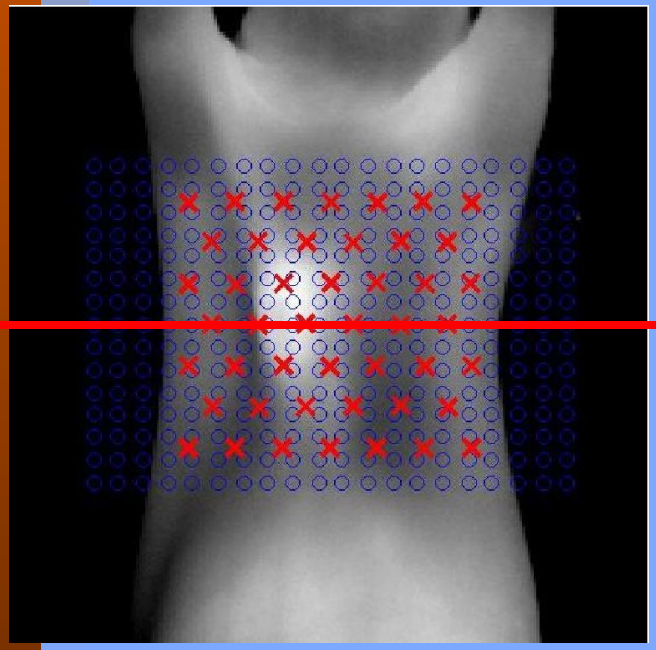


fluorophore
absorption = 0 - 0.032 cm^{-1}

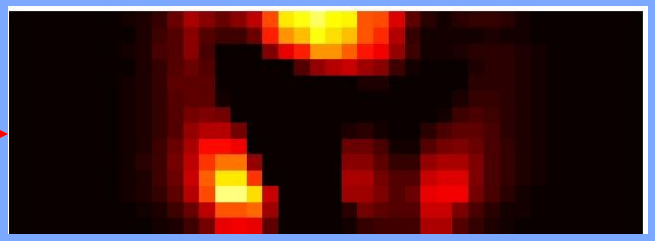
In Vivo Experiments



top view

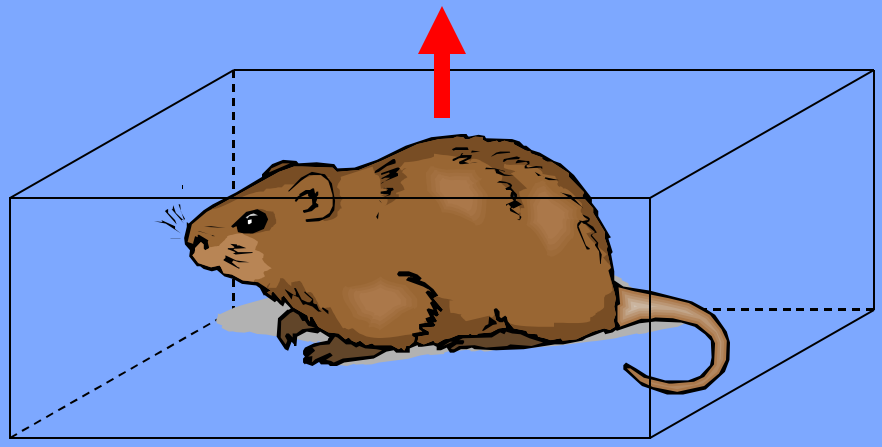


0 cm

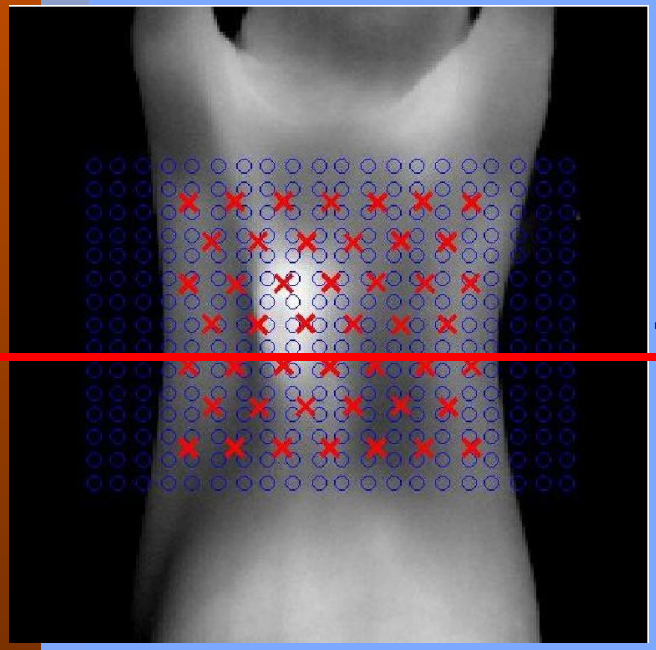


fluorophore
absorption = 0 - 0.032 cm^{-1}

In Vivo Experiments



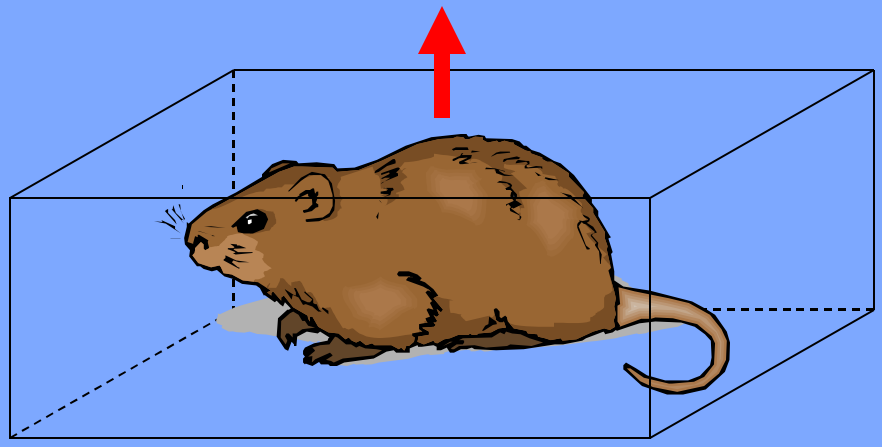
top view



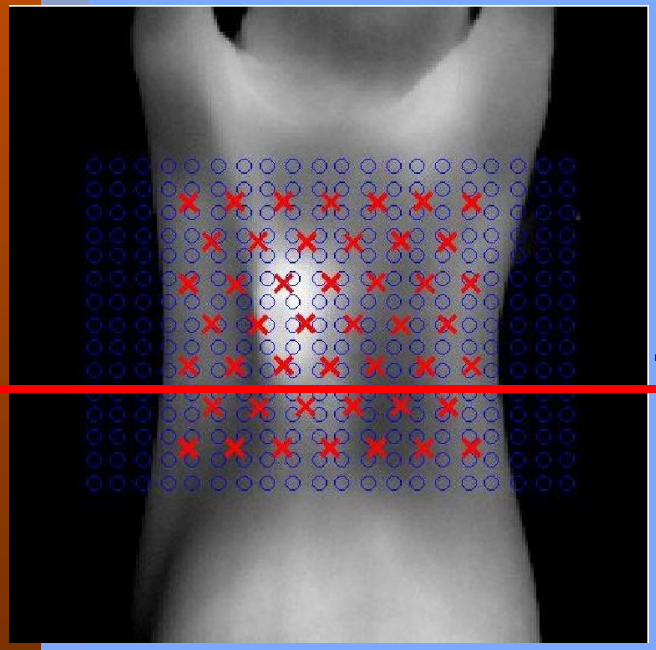
-0.2 cm

fluorophore
absorption = 0 - 0.032 cm^{-1}

In Vivo Experiments



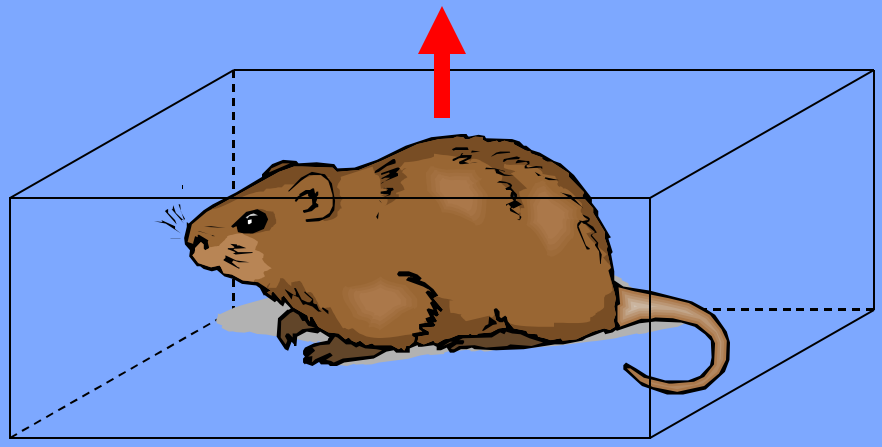
top view



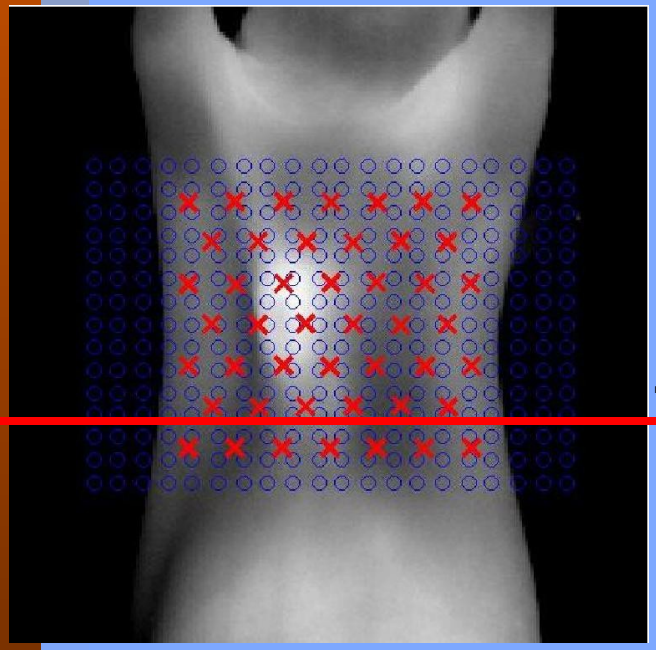
-0.4 cm

fluorophore
absorption = 0 - 0.032 cm^{-1}

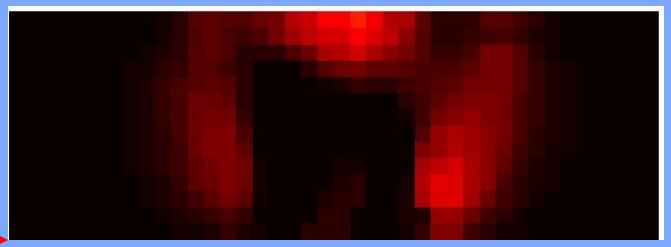
In Vivo Experiments



top view

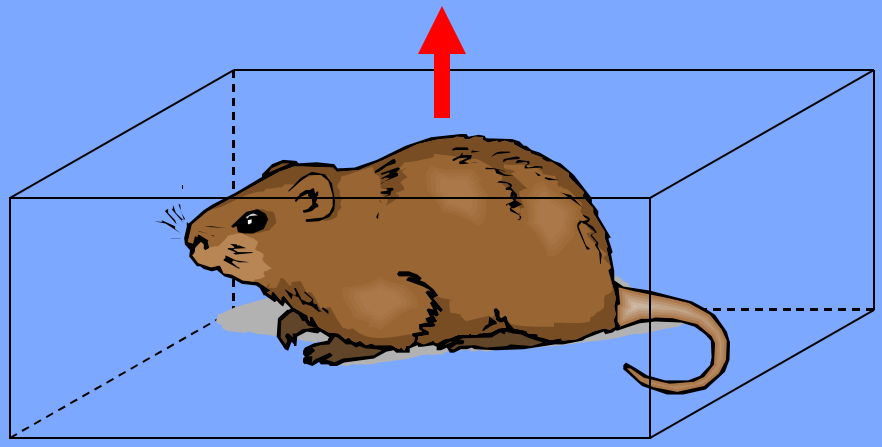


-0.6 cm

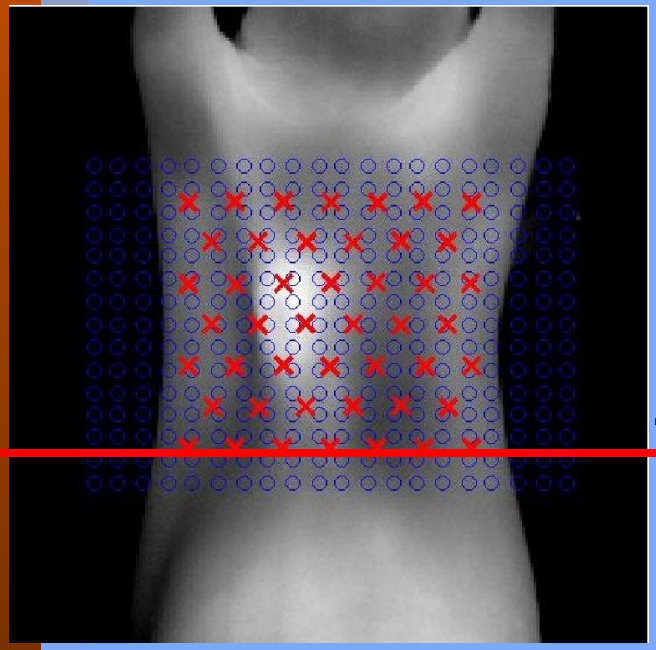


fluorophore
absorption = 0 - 0.032 cm^{-1}

In Vivo Experiments



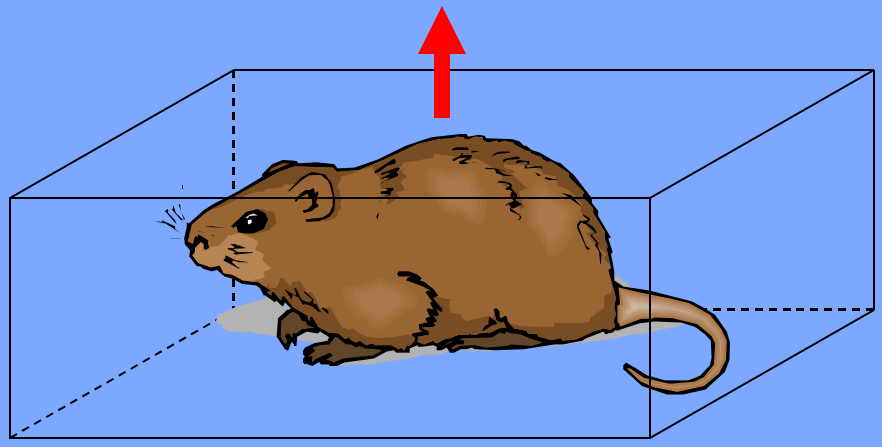
top view



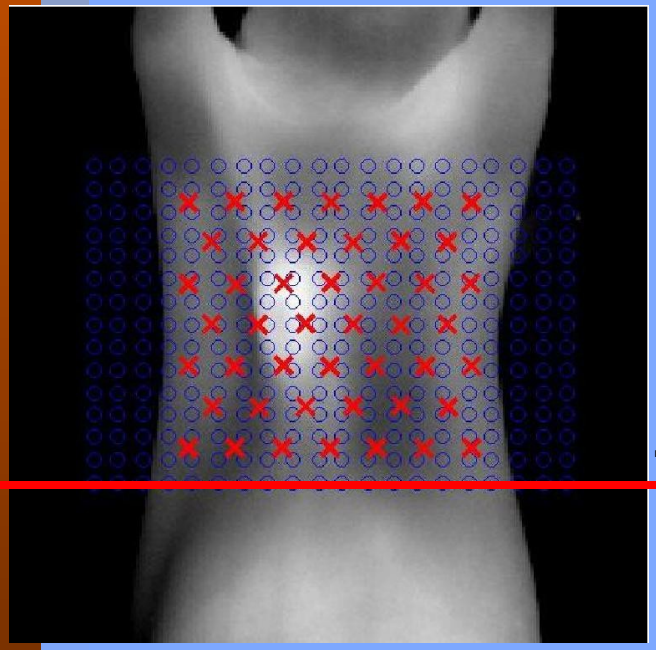
-0.8 cm

fluorophore
absorption = 0 - 0.032 cm^{-1}

In Vivo Experiments



top view



-1.0 cm

fluorophore
absorption = 0 - 0.032 cm^{-1}

Overview

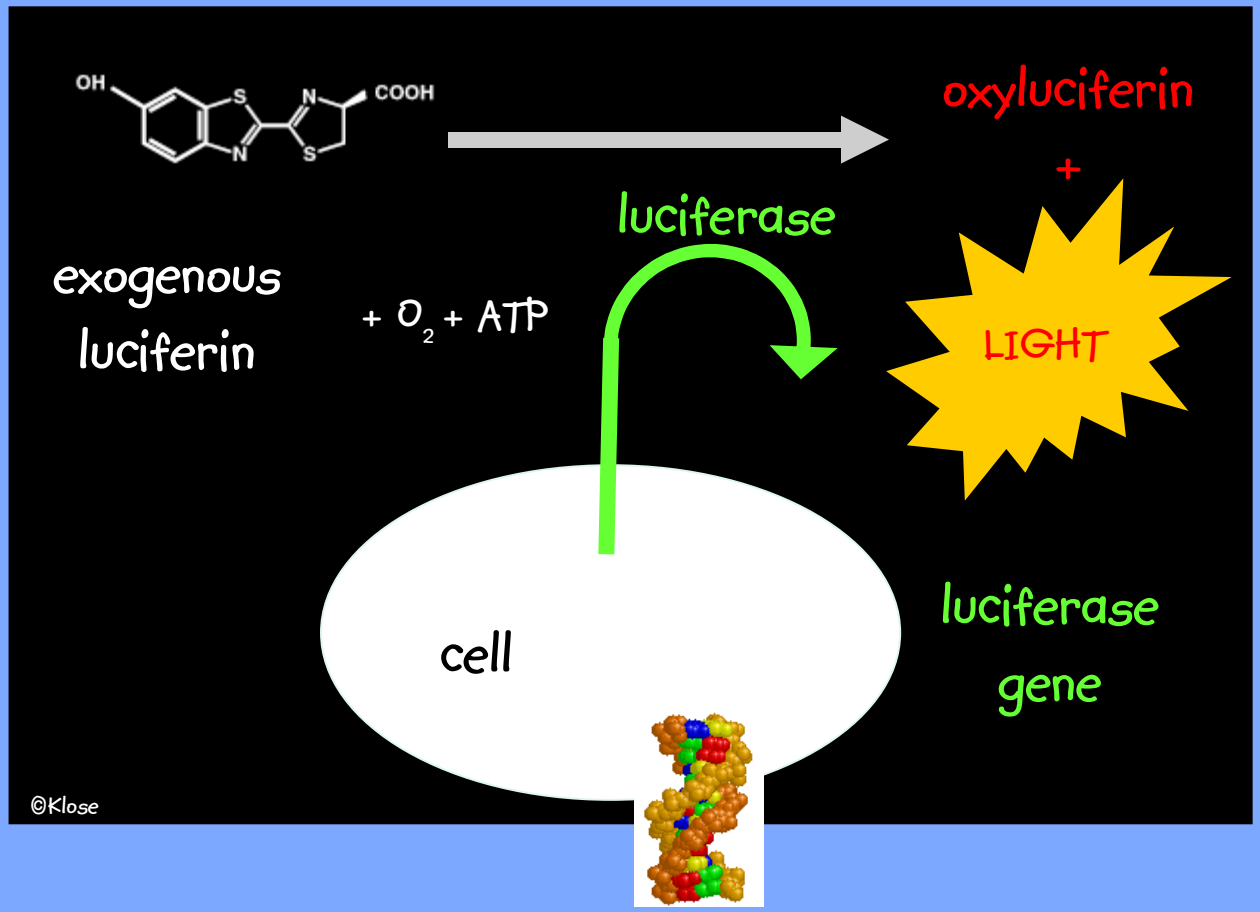
Forward Model

Inverse Model

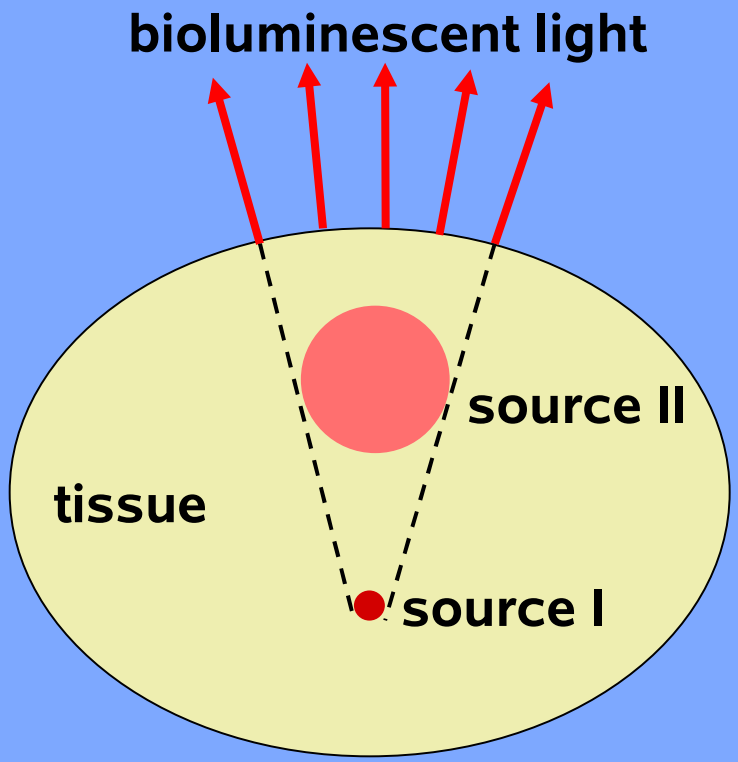
Fluorescence Molecular Tomography

Bioluminescence Tomography

Bioluminescence Tomography



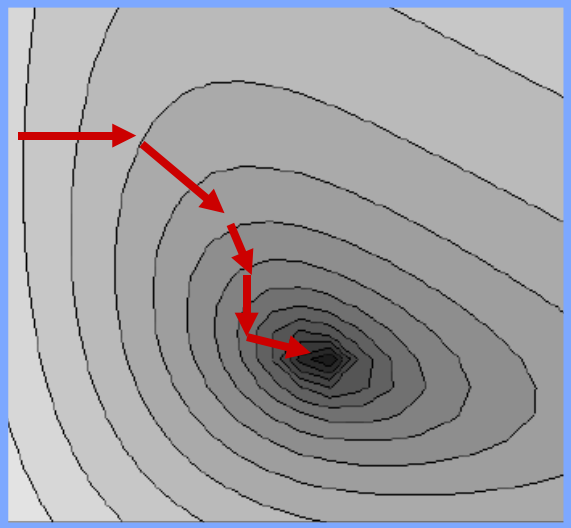
Multiple Solutions



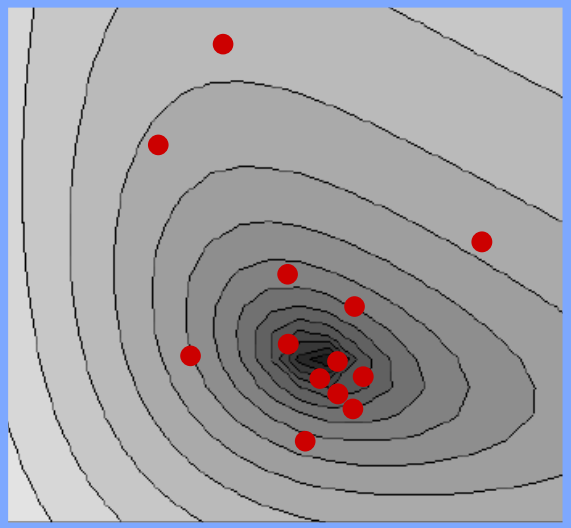
$$\Phi(\theta) = \frac{1}{N}\sum_{n}^{N}\frac{\left(Y_n - J_n^{+}(\theta)\right)^2}{\sigma_n^2}$$

Optimization of $\phi(\theta) = \frac{1}{N}\sum_{n}^{N}\frac{\left(Y_n - J_n^{+}(\theta)\right)^2}{\sigma_n^2}$

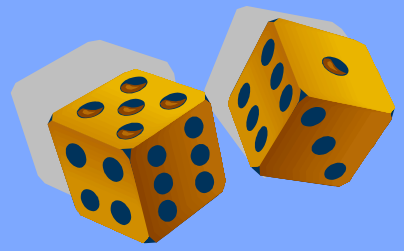
deterministic



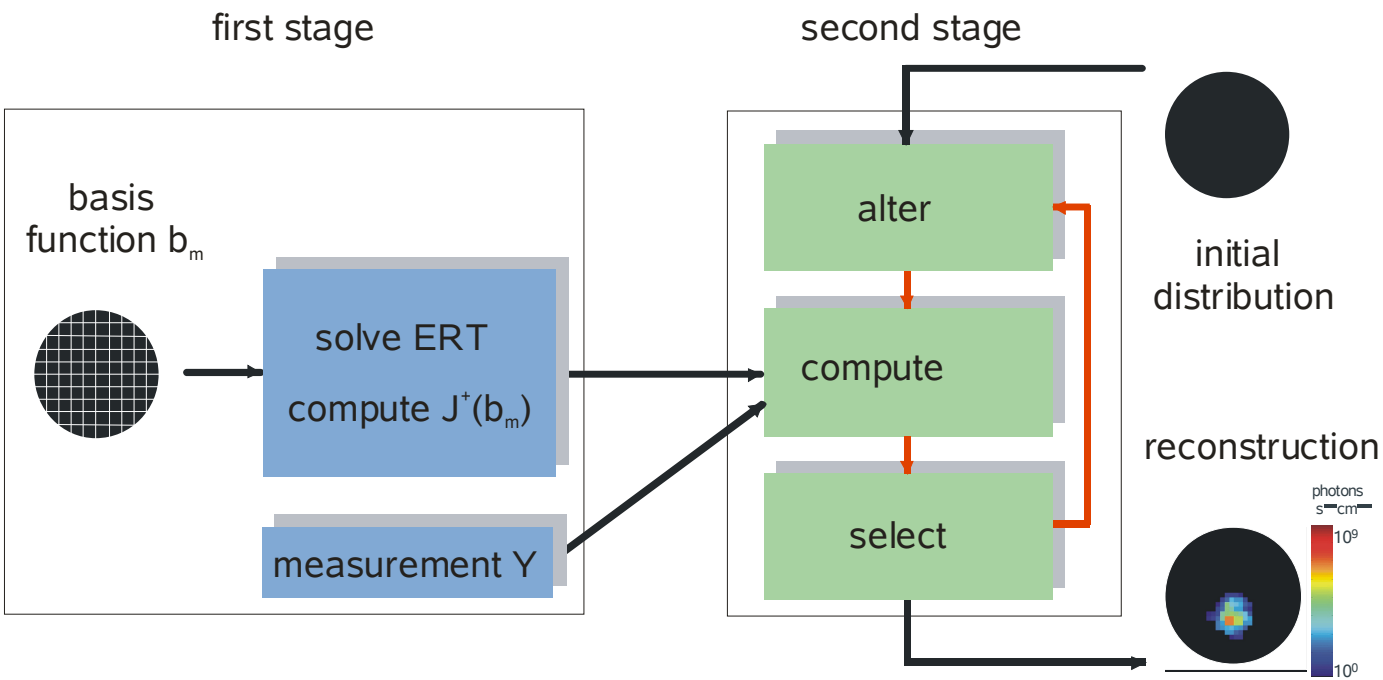
stochastic



$$\nabla\phi = \frac{(J^{+} - Y)}{2\sigma^2}\frac{\partial J^{+}}{\partial Q}$$



Stochastic Image Reconstruction (SIR)



First Stage - Linear Source problem

source power density is decomposed into source basis functions b_m

$$Q(r) = \sum_{m=0}^{M} \theta_m b_m(r)$$

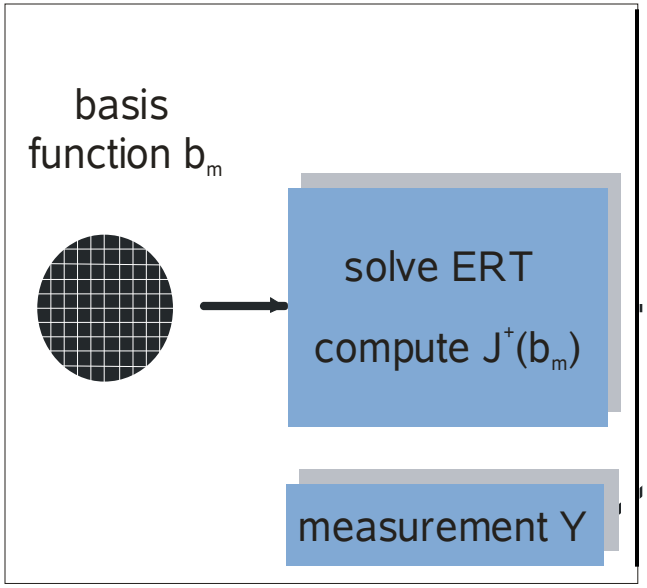
$$\Omega \cdot \nabla \psi(r, \Omega) + \mu_t \psi(r, \Omega) = \frac{b_m(r)}{4\pi} + \mu_s \int_{4\pi} p(\Omega, \Omega') \psi(r, \Omega') d\Omega'$$

boundary flux as function of unknown data variables θ_m

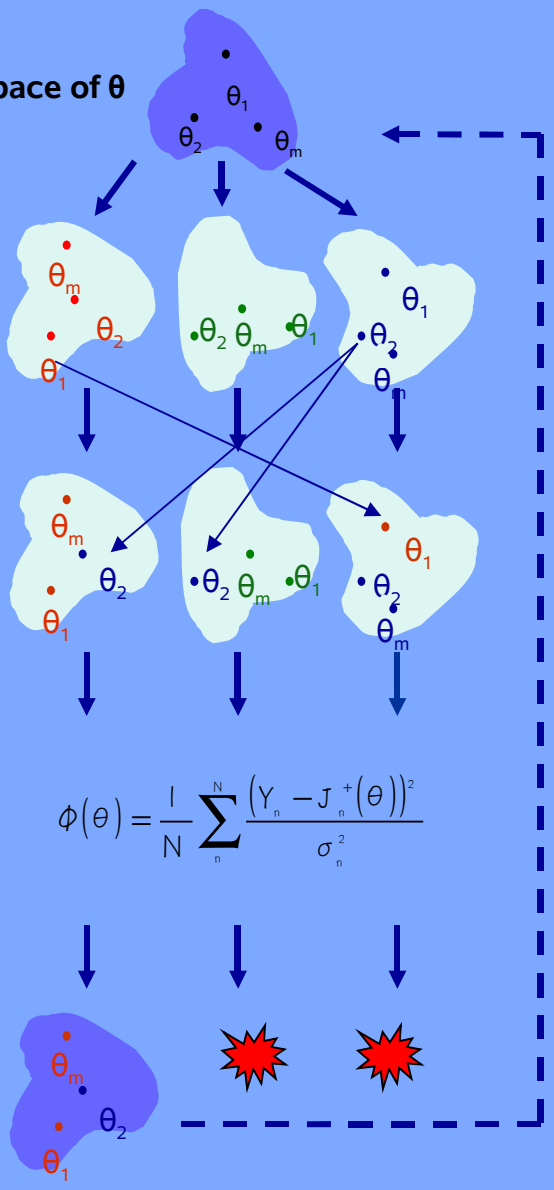
$$J_n(\theta) = \sum_{m=0}^{M} \theta_m J_n(b_m)$$

Stochastic Image Reconstruction (SIR)

first stage



Second Stage – Evolution Strategy



population of μ parents

population of λ offspring

recombination
self-adaptation
mutation

$$\theta_m^{new} = \theta_m^{old} + N(0, \sigma_m)$$

$$\phi(\theta) = \frac{1}{N}\sum_{n}^{N} \frac{(Y_n - f_n(\theta))^2}{\sigma_n^2}$$

select smallest Φ

"survival of the fittest"

NEW
population of μ parents

Second Stage – Evolution Strategy

- Recombination:

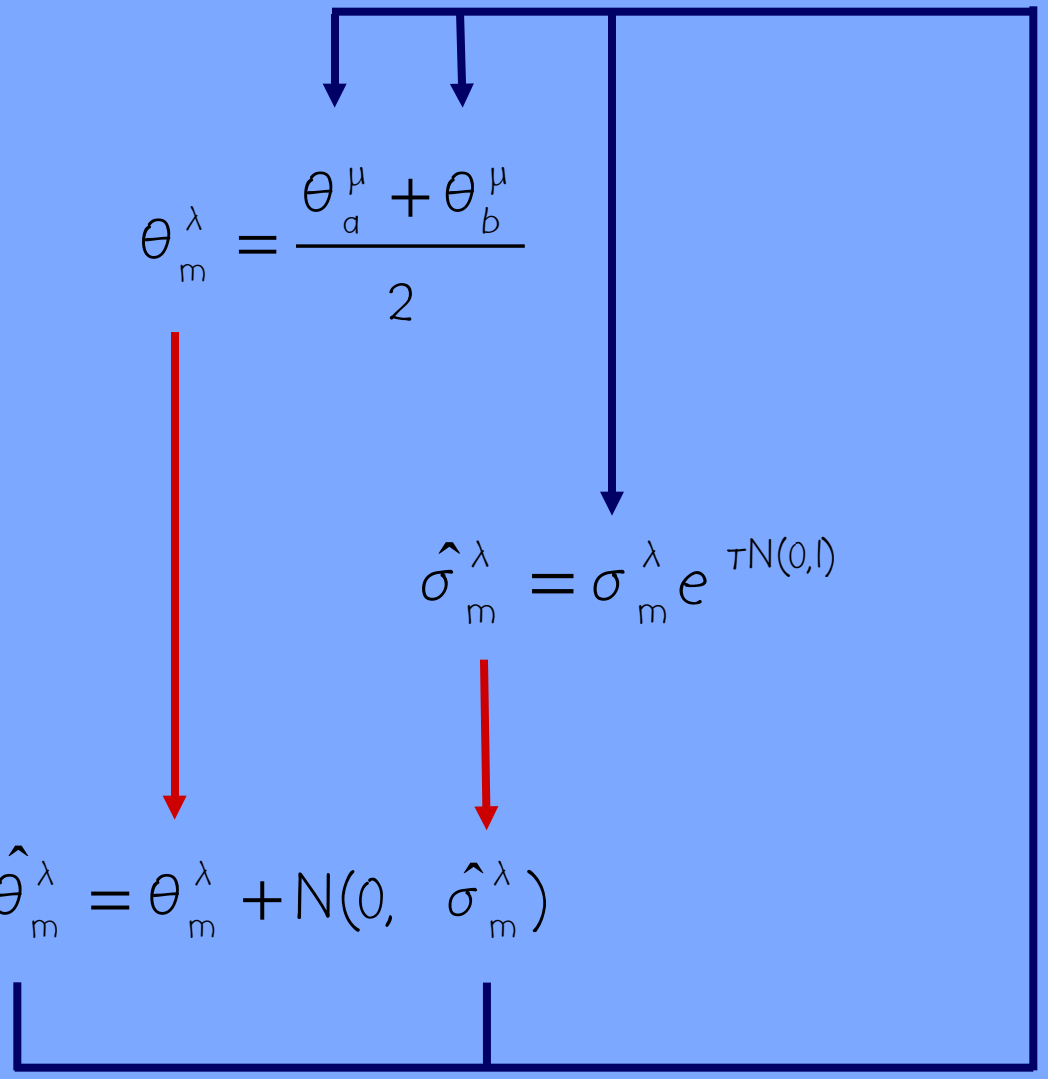
$$\theta_m^{\lambda} = \frac{\theta_a^{\mu} + \theta_b^{\mu}}{2}$$

- Self-Adaptation:

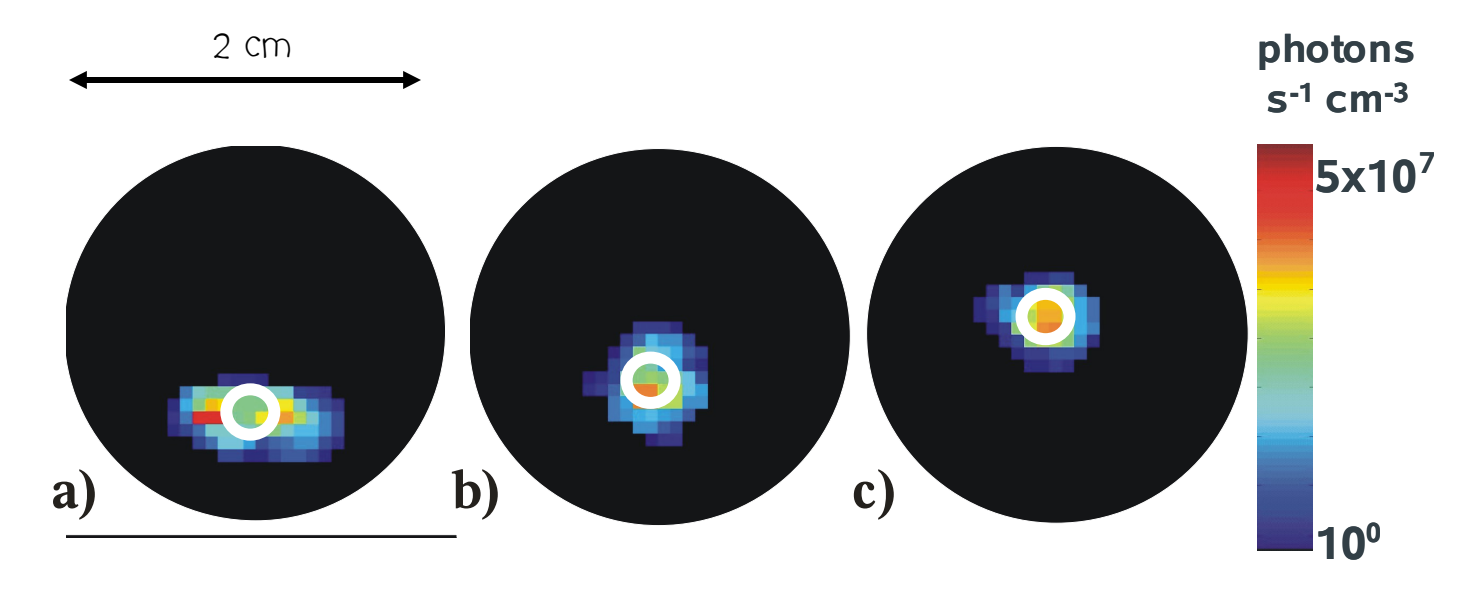
$$\hat{\sigma}_m^{\lambda} = \sigma_m^{\lambda} e^{\tau N(0,1)}$$

- Mutation:

$$\hat{\theta}_m^{\lambda} = \theta_m^{\lambda} + N(0, \hat{\sigma}_m^{\lambda})$$



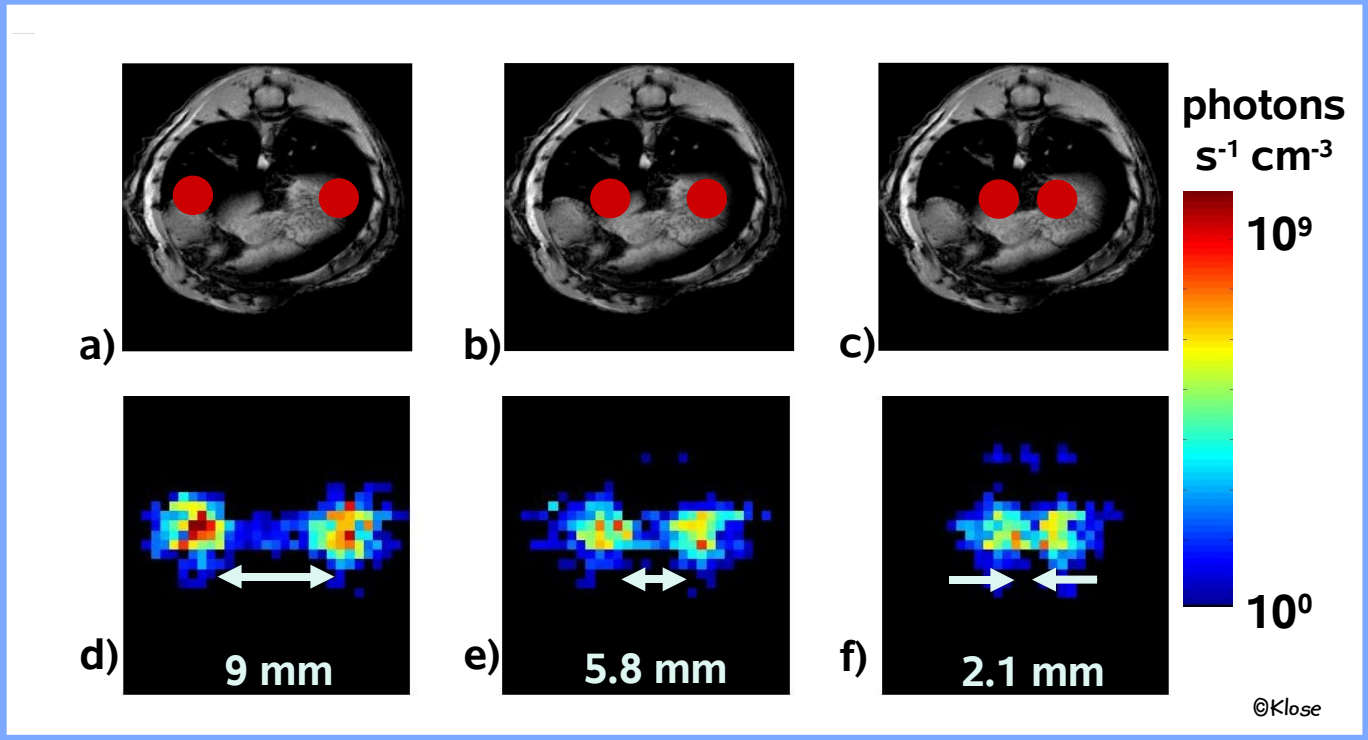
Results - Simulations



675 unknown vector elements θ_m (image)

μ = 3,000 parent members; λ = 18,000 offspring members
900 generations

Results – Simulations



Tomographic reconstruction of two bioluminescent sources.
Optical property maps are based on MRIs.

Summary

Optical Molecular Imaging

- fluorescent/bioluminescent probes

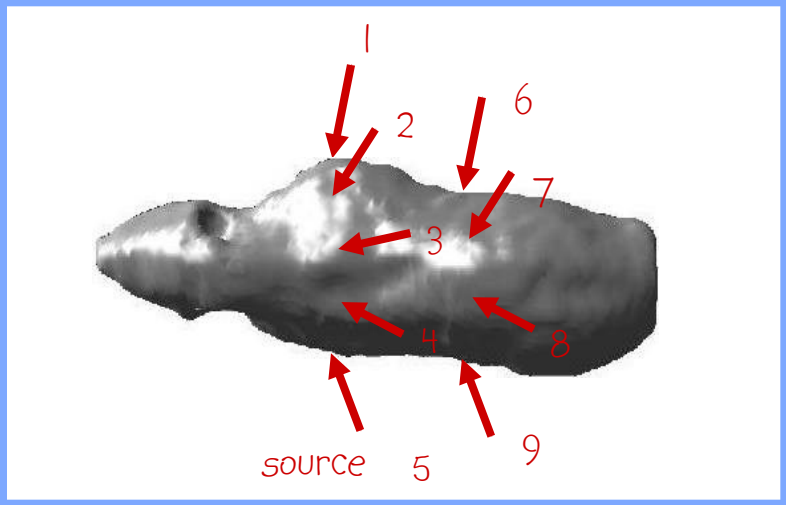
Biological tissue is highly scattering

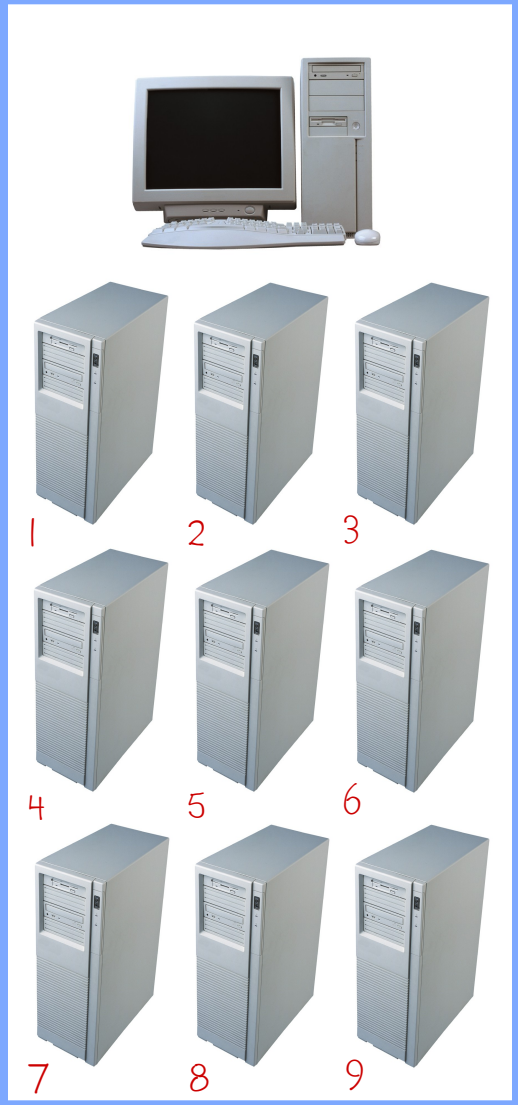
- Equation of Radiative Transfer
- Finite-Difference Discrete-Ordinates (FD-S_N)

Inverse source problem

- optimization methods
  - gradient techniques (Adjoint Differentiation)
  - Evolution Strategy

Future Work





Field Programming Gate Array (FPGA) ?

Acknowledgments

- Edward Larsen (University of Michigan)
- Ken Hanson (Los Alamos National Lab)
- Vasilis Ntziachristos (Harvard Medical School)

www.columbia.edu/~ak2083/publications.htm