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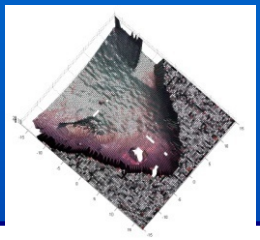
Time-Resolved Optical Tomography in Preclinical Studies: Propagation of Excitation and Fluorescence Photons.

F. Nouizi[1], R. Chabrier[1], M. Torregrossa[2], P. Poulet[1]

[1]Laboratoire d'Imagerie et de Neurosciences Cognitives,
[2]Laboratoire des Sciences de l'Image, de l'Informatique et de la Télédétection
4 rue Kirschleger, 67085 Strasbourg Cedex, France.



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Région Alsace

Introduction

- **WHY DOING OPTICAL IMAGING ?**
  - **New contrast: optical properties of tissues**
    - **Functional information (perfusion, oxygenation)**
  - **Fluorescent probes**
    - **Localization and activation of fluorochromes**
- **HOW DOING OPTICAL IMAGING ? (3D, volume, *in vivo*)**
  - **Pulsed light sources and time resolved detection**
  - **Reconstruction methods taking into account the diffuse photons**
- **SIMULATED AND EXPERIMENTAL RESULTS**
  - **Phantoms**
  - **Small animals**

The challenge of optical imaging

X – ray photons are transmitted with low scattering:
image reconstruction is easy.

Red and near-infrared photons are transmitted by tissues.
They are highly scattered: image reconstruction is difficult.

Absorption and scattering

- Expression:

  L_a: propagation length before absorption

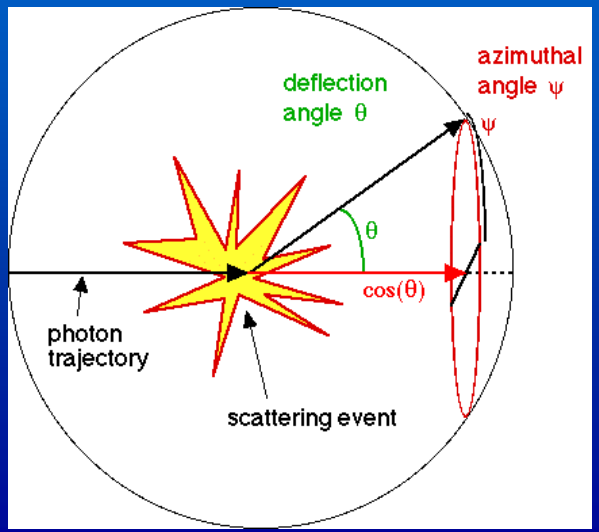
  $\mu_a = 1/L_a$: absorption coefficient (cm^{-1})

  L_s: propagation length between 2 scattering events

  $\mu_s = 1/L_s$: scattering coefficient (cm-1)

  θ: mean scattering angle, $g = \cos(\theta)$

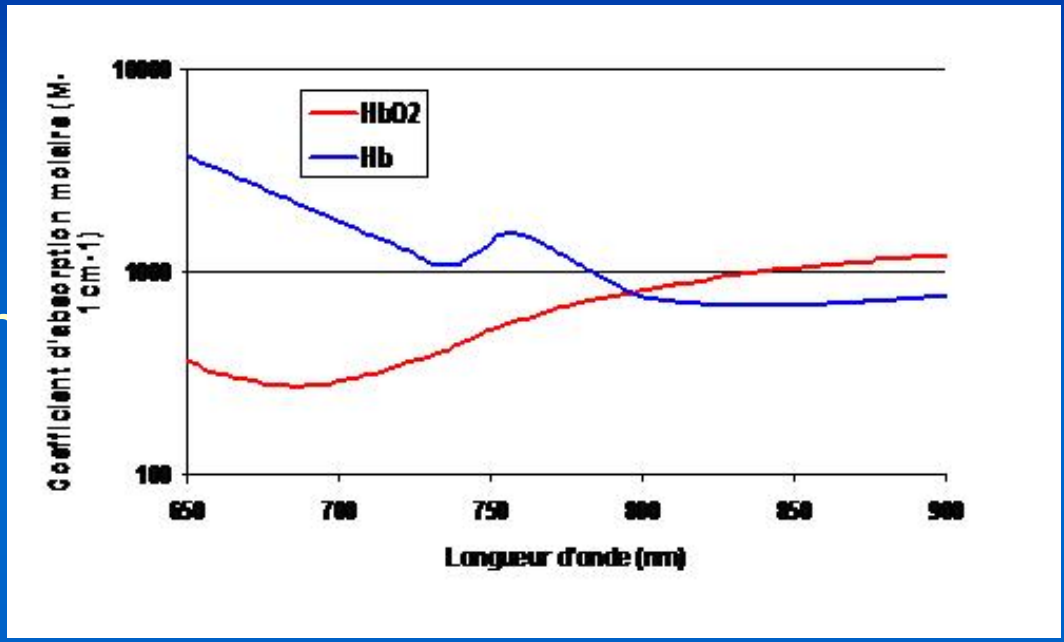
  $\mu's = (1-g).\mu s$: reduced scattering coefficient

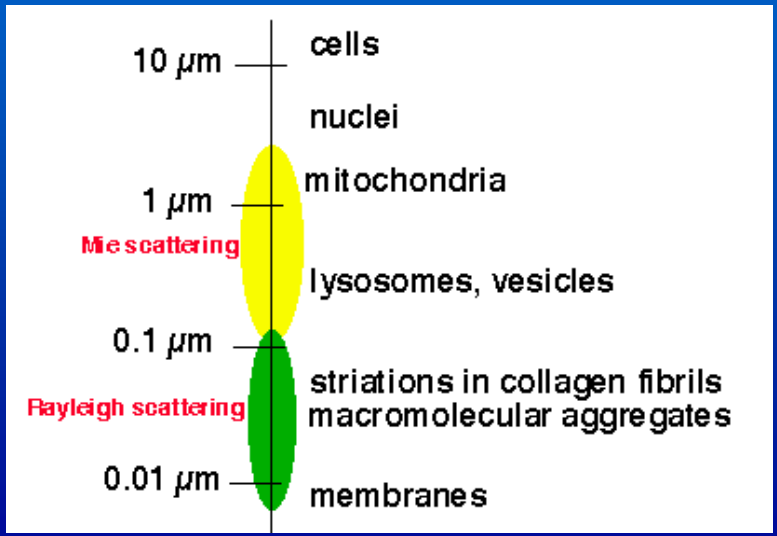


$1/\mu's = L's$: propagation length before forgetting the initial direction of the photon

Diffusion and absorption properties of tissues

- Main absorbers:
  - UV: proteins, DNA
  - Vis.: hemoglobin, melanin
  - NIR: water, lipids
- Main scatterers:
  - cells, nuclei,mitochondria, fibers, membranes …





$600 < \lambda < 1000$ nm

$100 < \mu_s < 1000\ cm^{-1}$ $0,8 < g < 1$

$0,1 < \mu_a < 1\ cm^{-1}$

Diffusion regime

Optical imaging of small animals

Principles of usual methods

Use of highly sensitive CCD camera: imaging of the light at the surface (skin) of the animals.

Limitations

Detection of visible light: small depth of analysis.
The volume sensed by irradiation photons and the true localization of light sources (in volume) remains unknown

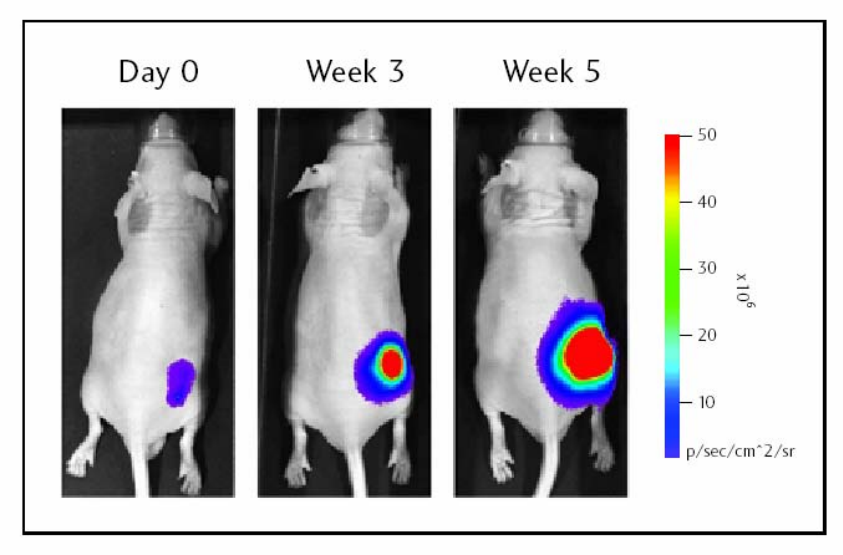
Solution

Near infrared photons

Tomographic approach

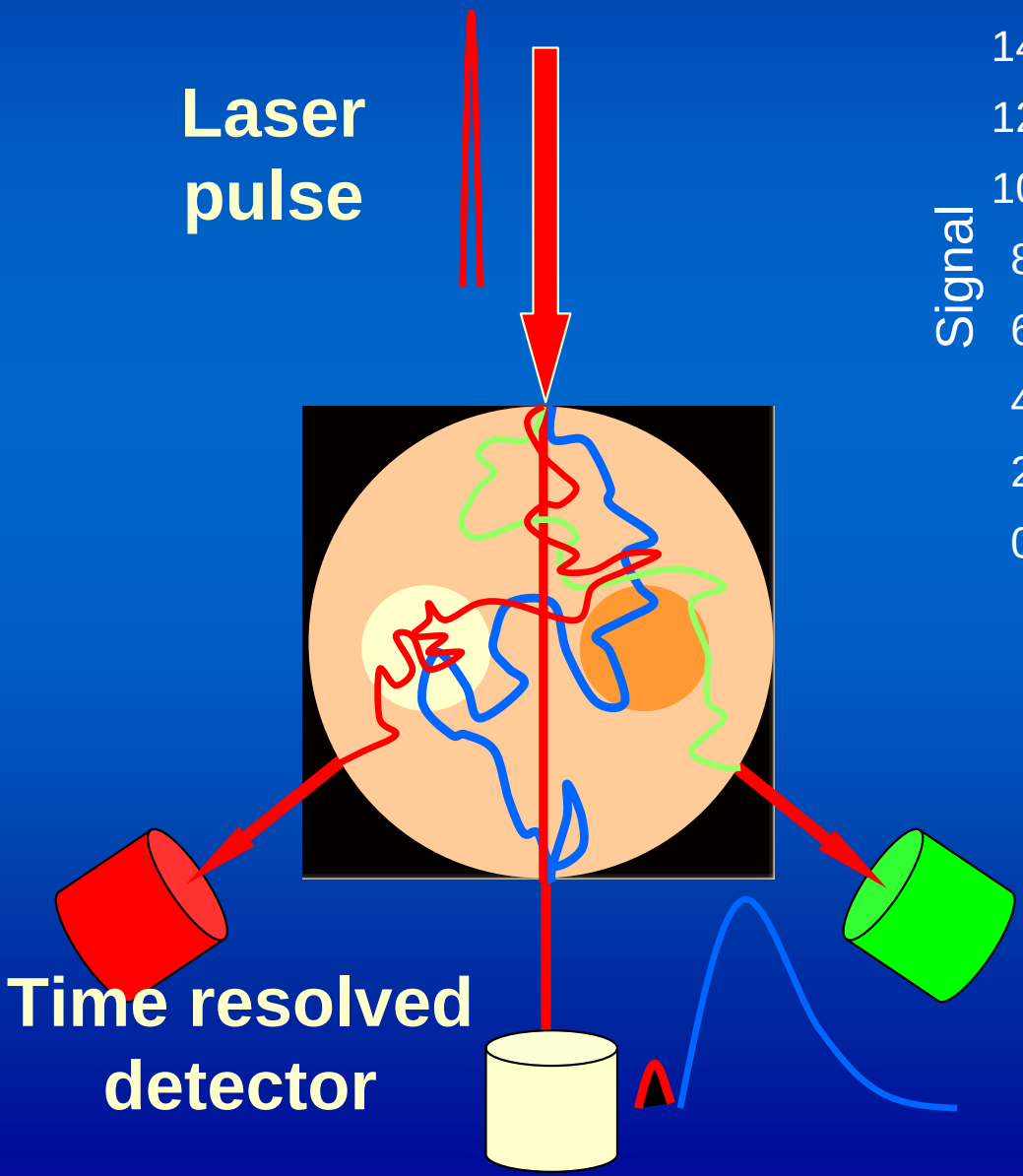
Diffuse propagation of photons

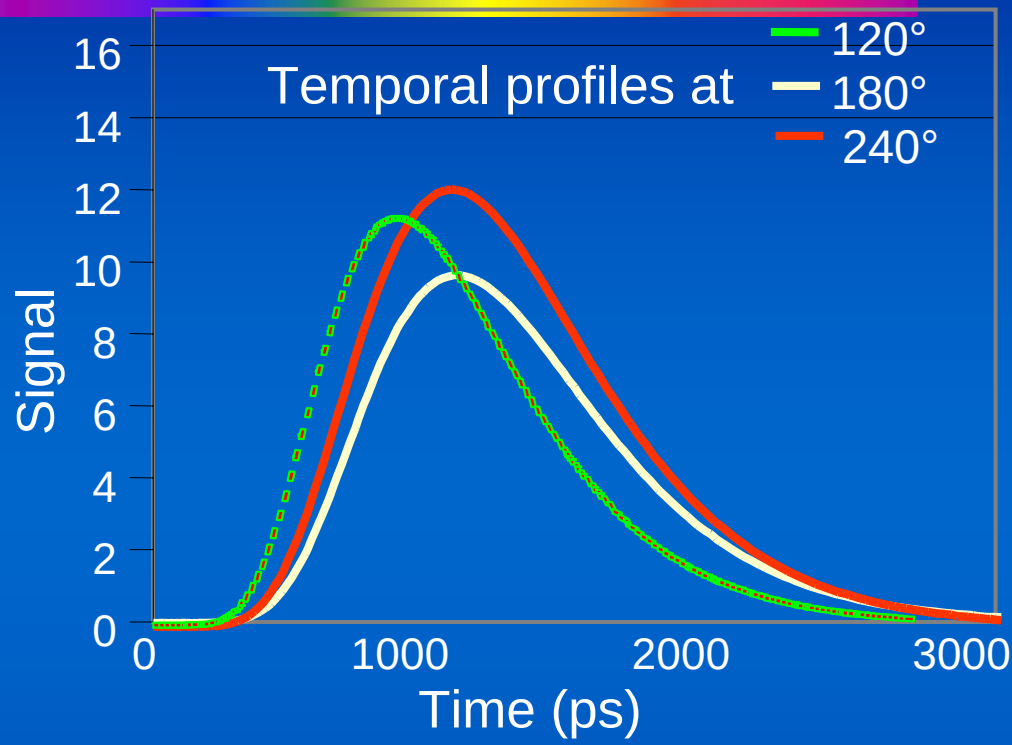
Time resolved detection



From Xenogen Corp.

Time resolved diffuse optical tomography



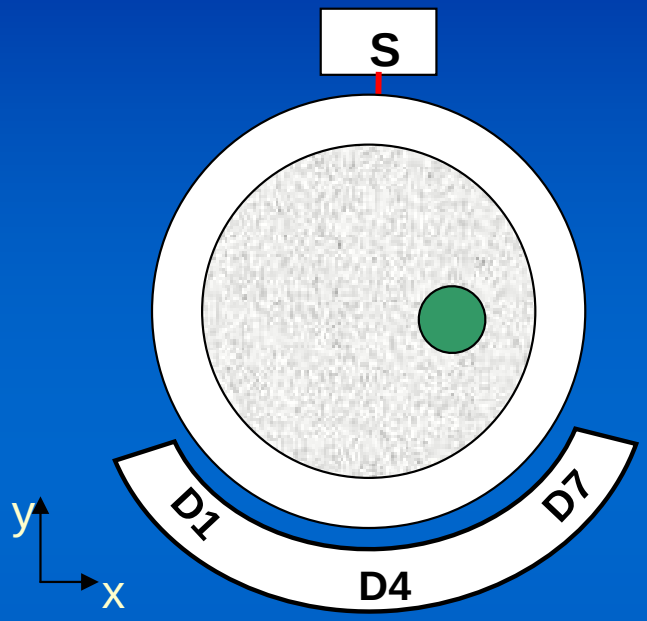


Temporal profiles (TPSF)

balistics

multi-scattered

General process of data acquisition and image reconstruction



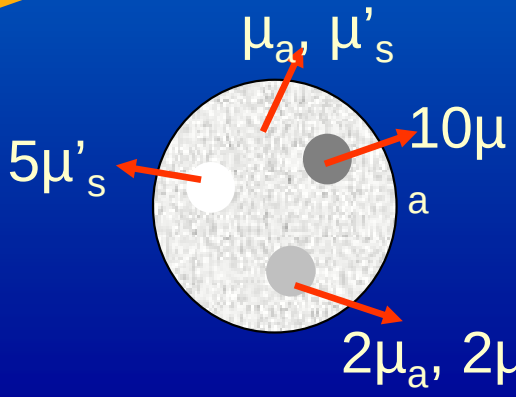
Measurements

(1 source - 7 detectors)
x 16 positions

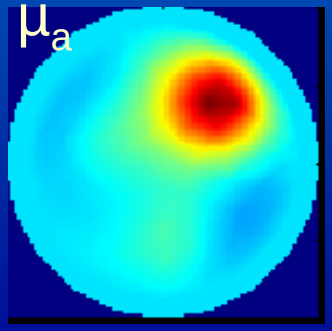
Inverse Problem

Direct problem

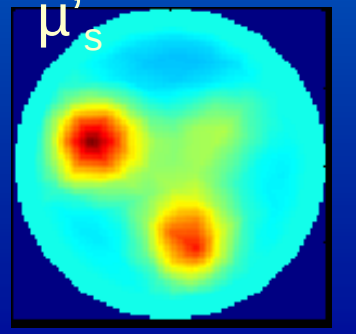
Finite Element Methods
(Matlab ⟶ Comsol)



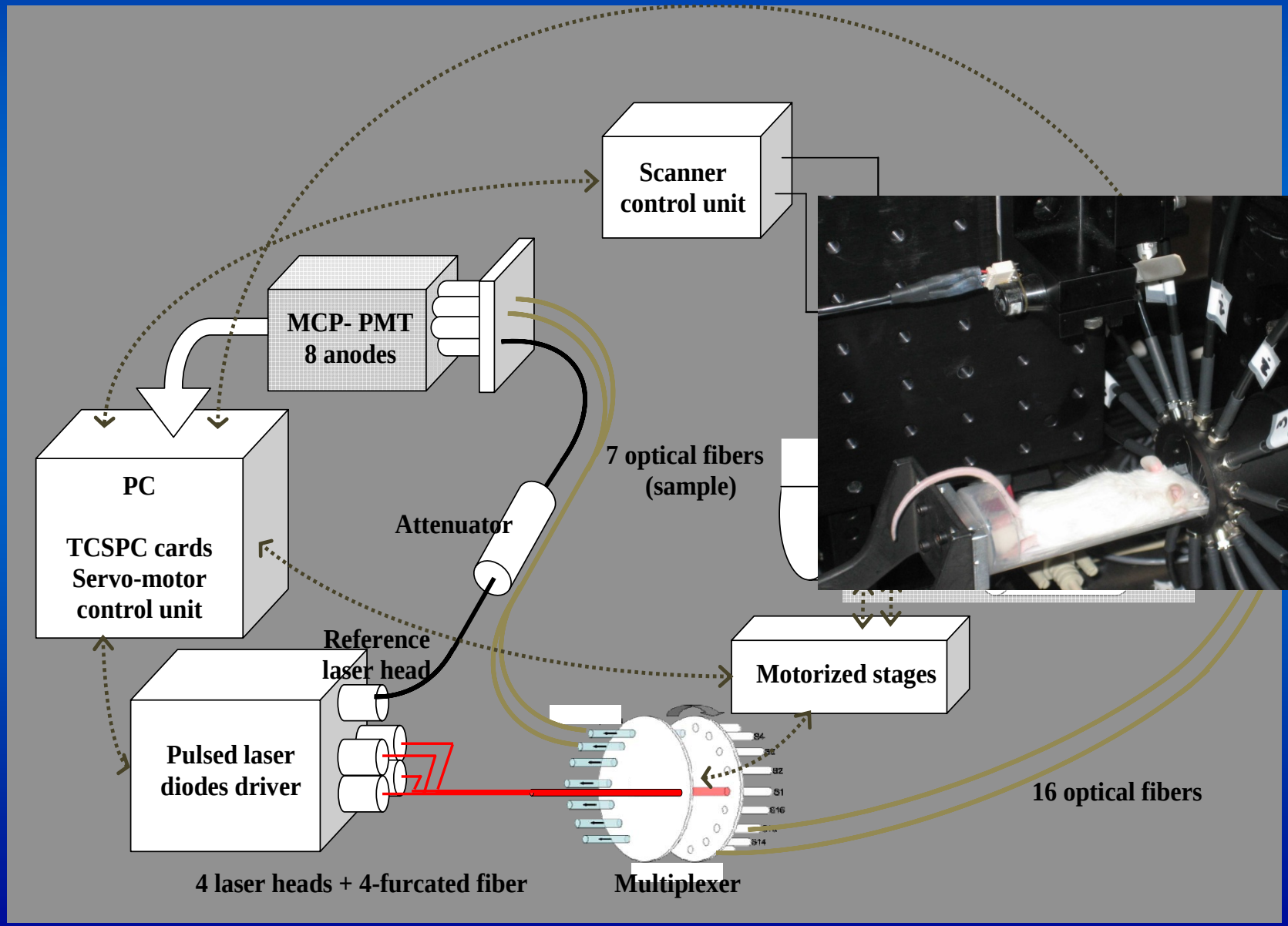
Absorption μ_a



Diffusion μ'_s

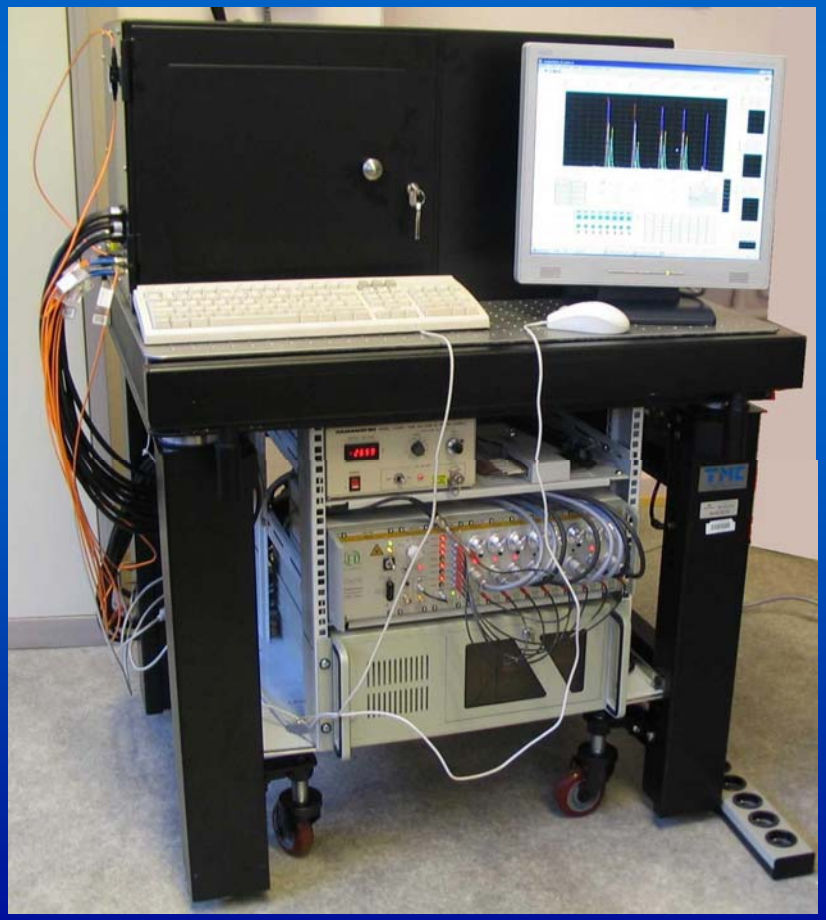


Time-resolved DOT system



Time-resolved DOT system

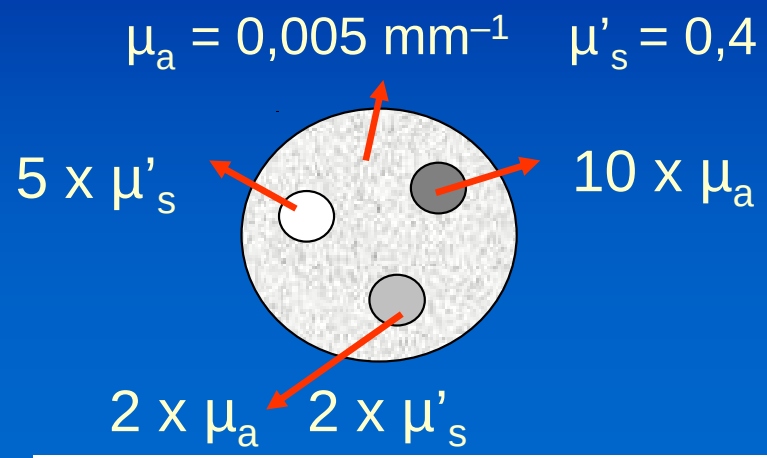
Instrumentation on a mobile optical table top

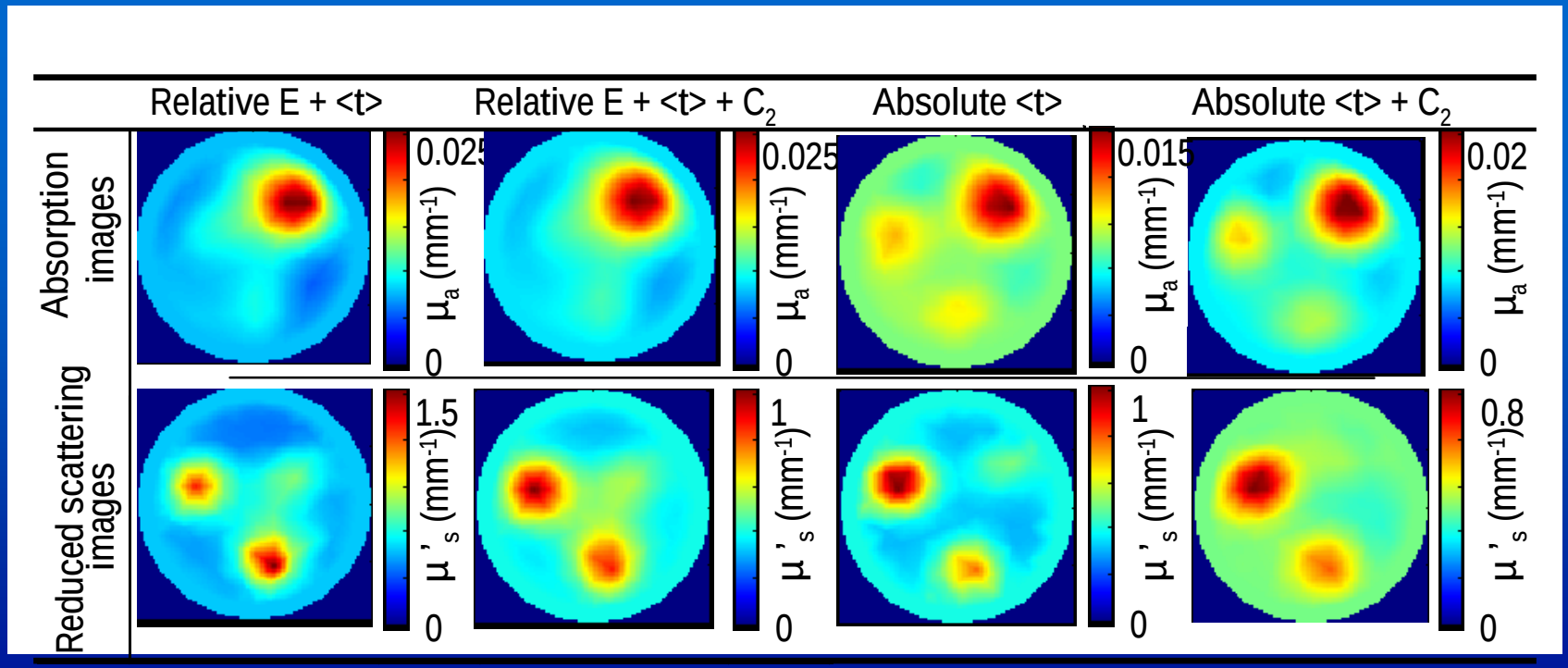


Main characteristics

Impulse response function (FWHM)		~ 260 ps
Mean incident power		< 1 mW
Sensitivity	max count rate	10^5 cps
	dark count rate	~ 0.6 cps
Temporal stability (meantime)		< 5 ps
Temporal stability (intensity)		2%
Crosstalk		< 1%

DOT of solid phantoms





Reconstruction using a 2D simulation of TPSF first moments

3D Modelisation of whole TPSF

- Radiative Transfer Equation

  ⇝ Diffusion Approximation

  - $\mu'_s >> \mu_a$ *Numerous scattering events before* detection

Photon Density $\Phi(r,t)$

- Diffusion Equation:

$$\frac{\partial \Phi}{\partial t} - \nabla \kappa \nabla \Phi + \mu_a c \Phi = -q(t, r_0)$$

q_0 : Isotropic source at $1/\mu'_s$ $\kappa = c/3(\mu_a + \mu'_s)$: difffusion coefficient

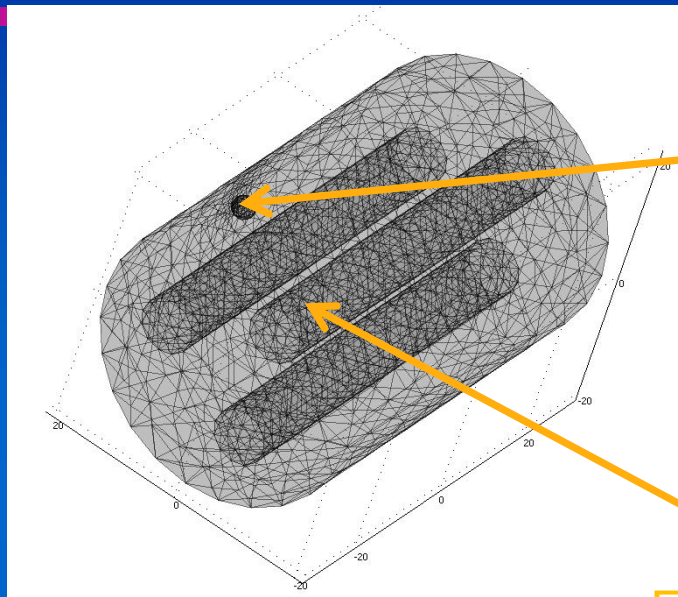
- Fluorescence:

$$\frac{\partial \Phi_2}{\partial t} - \nabla \kappa \nabla \Phi_2 + \mu_a c \Phi_2 = -\frac{\eta c}{\tau}(\Phi \otimes e^{-t/\tau})$$

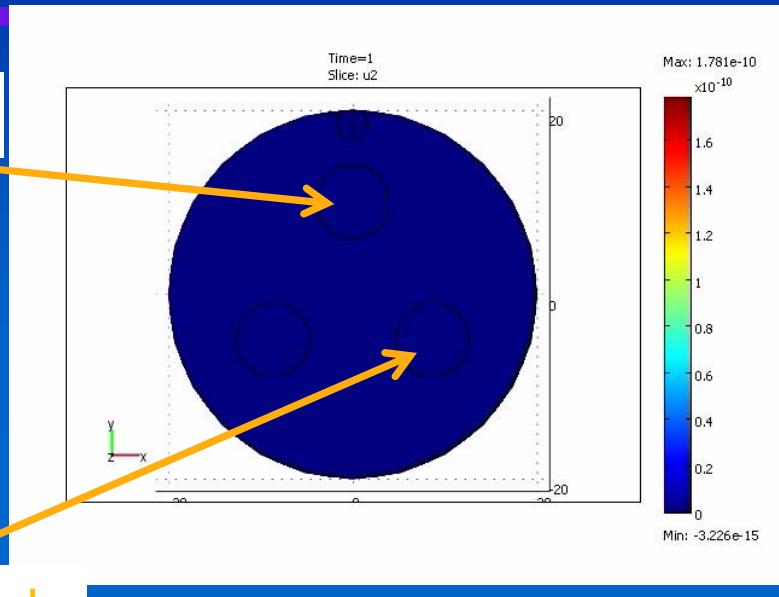
η : fluorophore concentration, τ : fluorescence lifetime

- Boundary Conditions (Robin conditions)
- Measurements: Exitance = $\Phi(r_d, r_s, t)/2A$

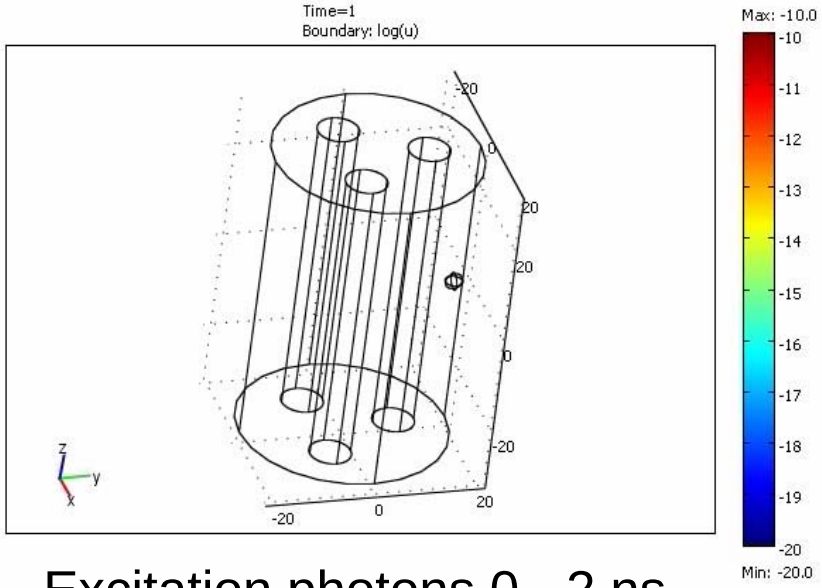
Excitation and fluorescence photons propagation



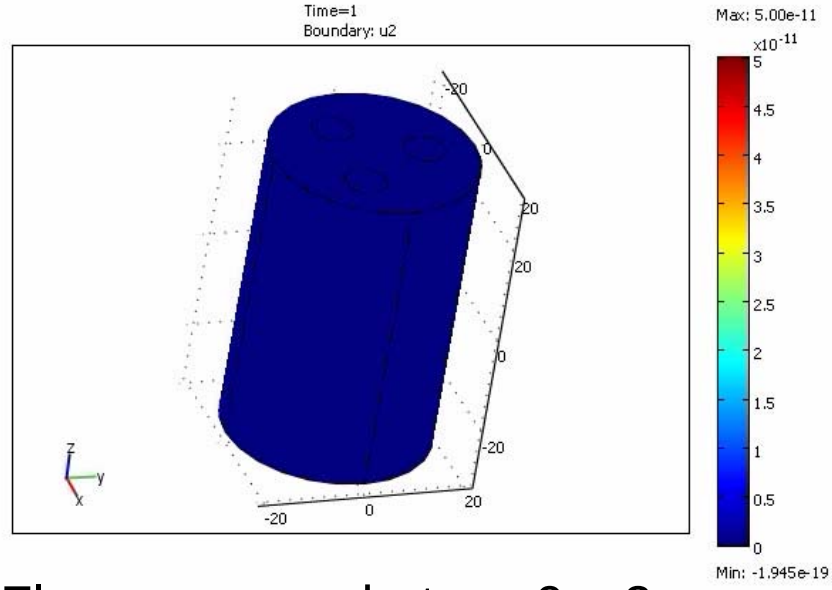
Source



Fluorescent rod

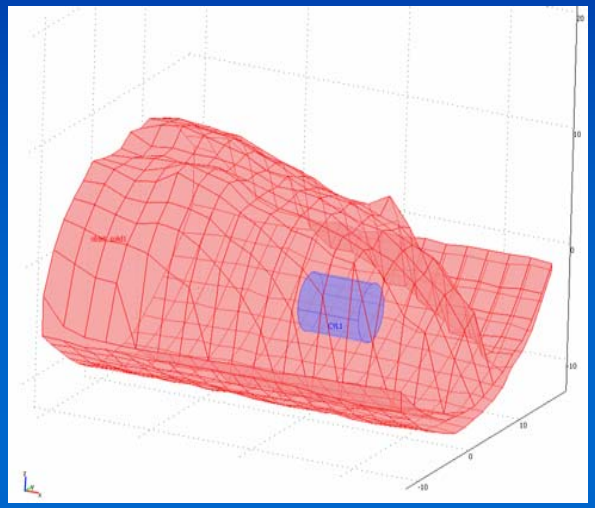


Excitation photons 0 - 2 ns

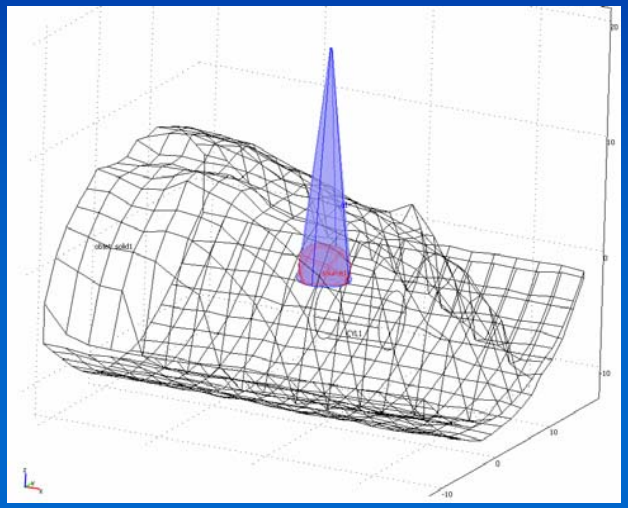


Fluorescence photons 0 – 2 ns

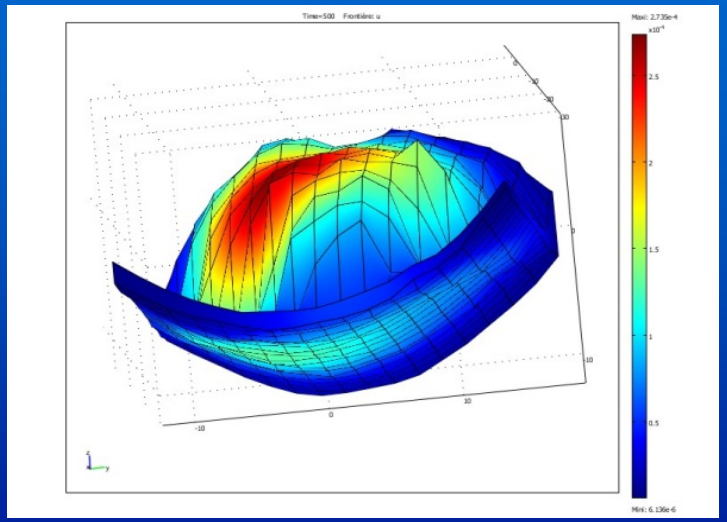
Excitation and fluorescence photons propagation



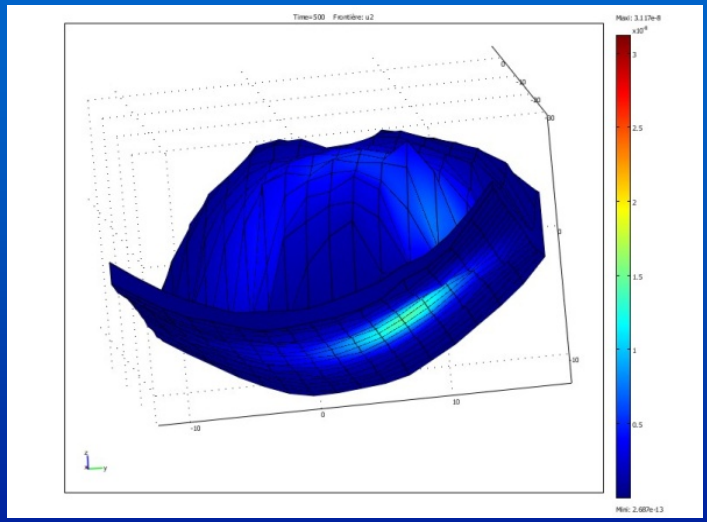
Mouse model with fluorescent volume



Irradiation from an optical fibre

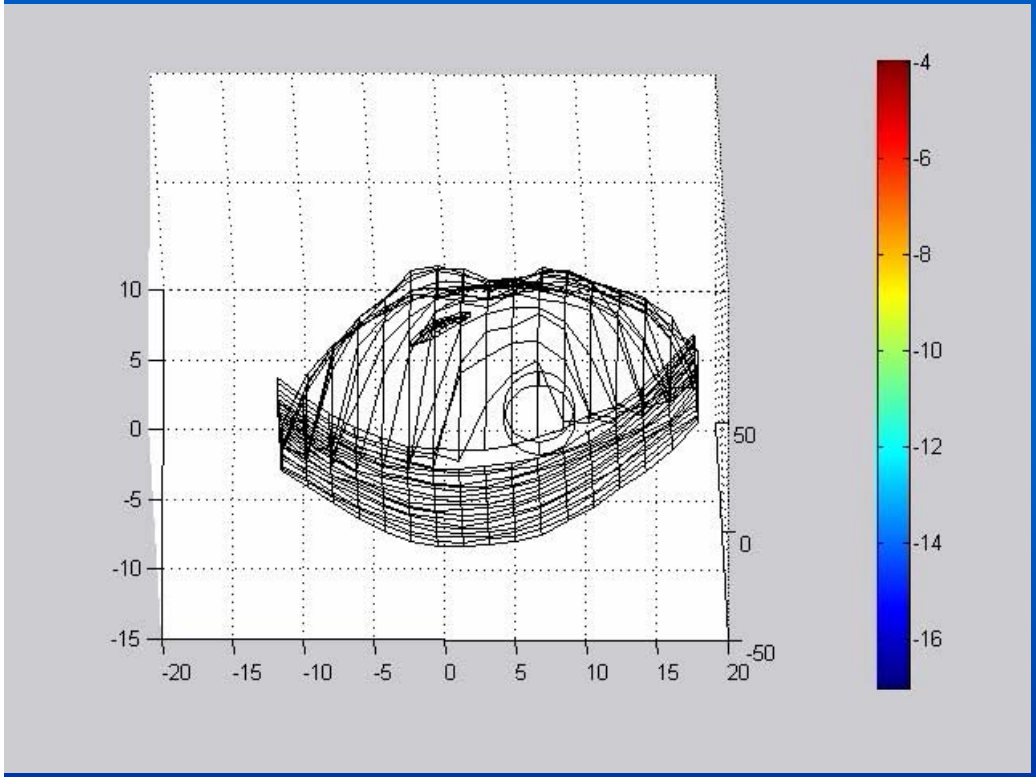


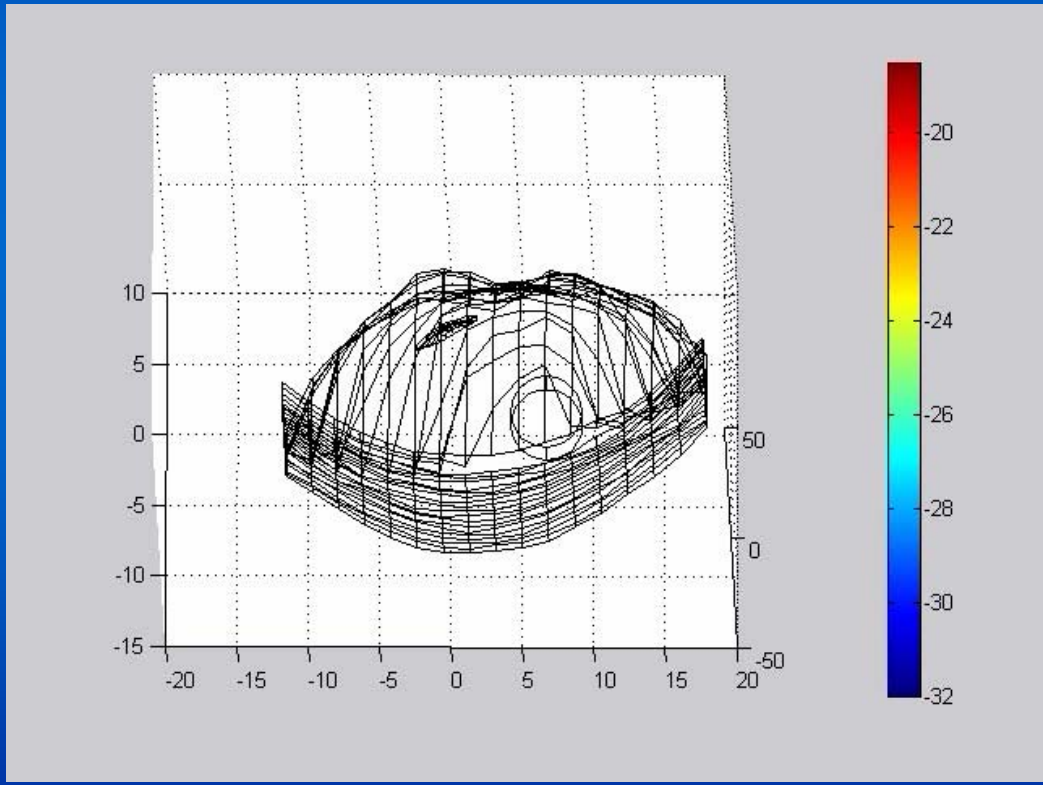
Excitation photons 500 ps post pulse



Fluorescence photons 500 ps post pulse

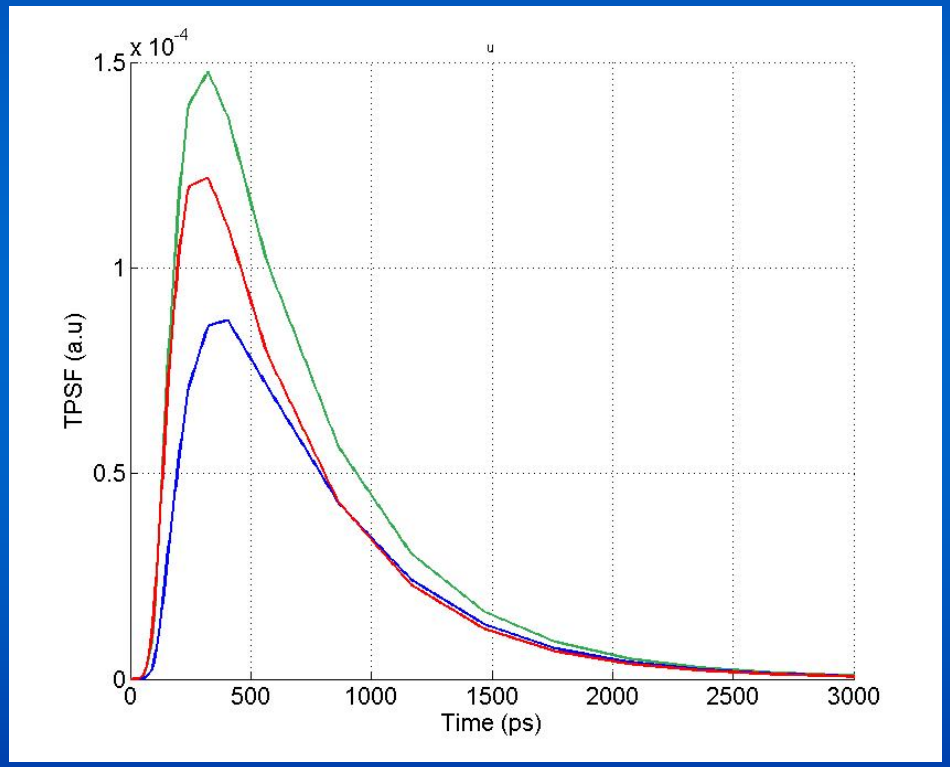
Excitation and fluorescence photons propagation

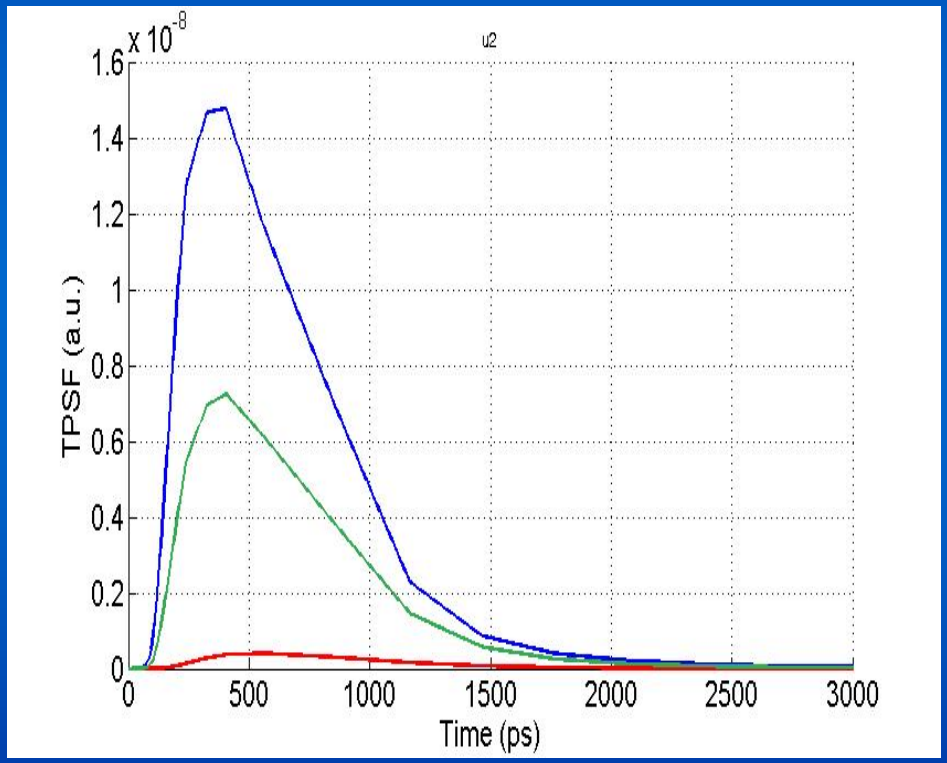




Excitation and Fluorescence photons 0 – 1 ns

Temporal profiles of excitation and fluorescence photons





Excitation (left) and fluorescence (right) photons detected at 180° (green), - 120° (blue) and + 120° (red) from the illumination fiber.

Conclusion

- **Time resolved optical tomography:**
  - **Absorption, scattering and fluorescence images**
- **Preclinical applications under progress:**
  - **Instrumentation for MRI +TODF coregistration**
  - **Image reconstruction: inverse problem**
    - **whole temporal profiles of excitation and fluorescence photons**
    - **a priori information from MRI**

Application perspectives

Clinical imaging

Mammography

Neurology: epilepsy, brain activation (oximetry)

Muscular pathology: myopathies

Preclinical imaging

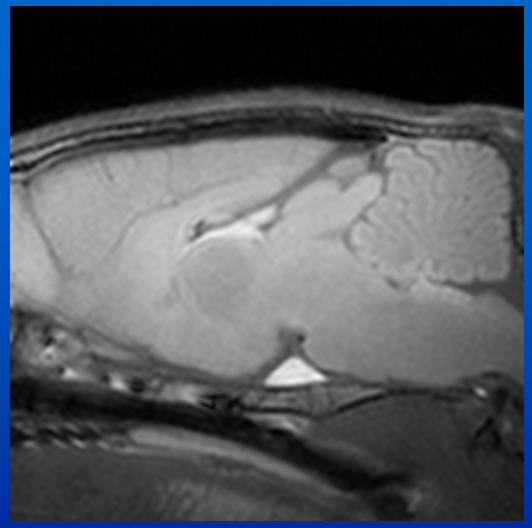
CNS deseases

Cancer therapy

MRI + TOD Coregistration

Technological Plateform

MRI + TOD



Sprag-Dawley rat.

T_1 MRI: 16h after $MnCl_2$ 0.8mmole/kg