Time-Resolved Diffuse Optical Tomography for tumour detection

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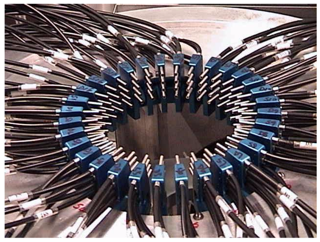
What are the objectives ?



(rf. wikipedia picture)

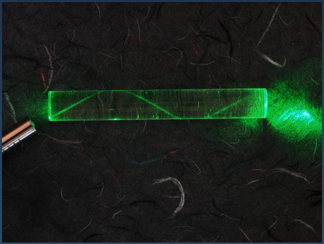
Objectives:

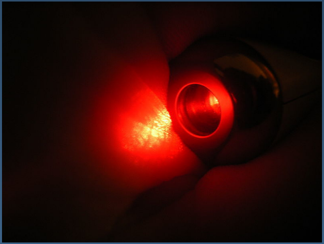
- Provide cheap and safe preclinical tool for tumours diagnosis.
  - Create a machine (tomograph).
  - Develop the associated software.
- Extend information provided by other technics (MRI,MRT...).
- Generalize optical tomography in hospitals.

IR light solution ?

Advantages:

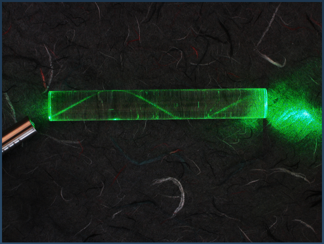
- Non invasive technic (contact and non contact measures).
- Non ionizing (contrary to Xrays).
- Low cost (contrary to MRI).
- Physiological information (MRI, Xrays provide an anatomical information).





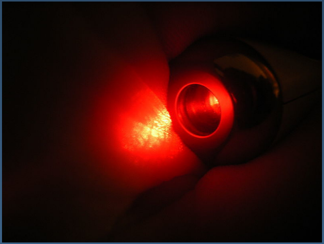
(rf. wikipedia pictures)

IR light solution ?



Drawbacks:

- Does not propagate in straight line (complex reconstruction).
- Small objects only (small animals, brain, breast, hand...).
- Image resolution (improve contrast using fluorescence markers,...).



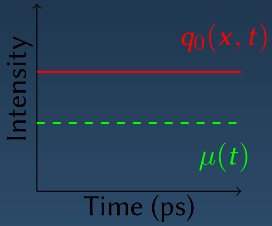
(rf. wikipedia pictures)

Summary

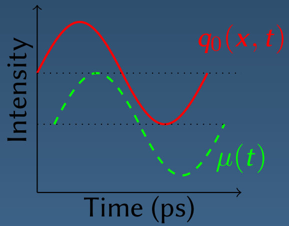
Type of DOT measure ?

3 classic methods:

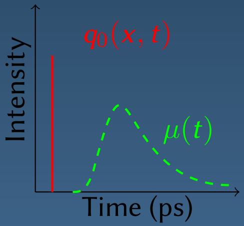
- Continuous-wave(CW).
- Frequency domain (FD).
- Time-Resolved (TR).



CW-measure.



FD-measure.

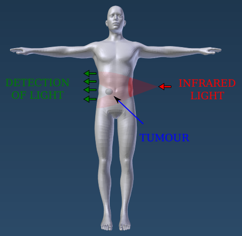


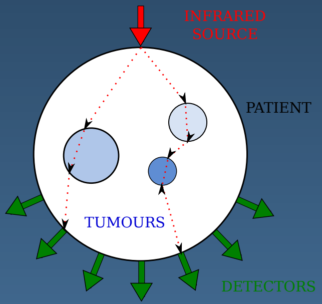
TR-measure.

How does it work ?

Principle:

- Pulse an IR light on the skin of a patient (or object boundary).
- Measure the photon density diffused though the turbid medium (7 TPSF per sources).
- Restart the previous step from different directions around the object.
- Reconstruct images of internal optic/fluorescence properties using cross-checking measures.

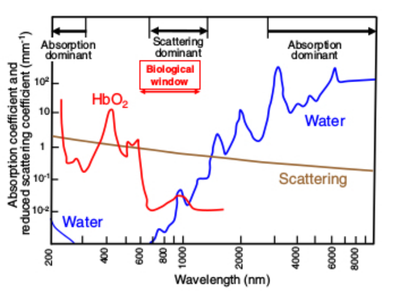




Why does it work ?

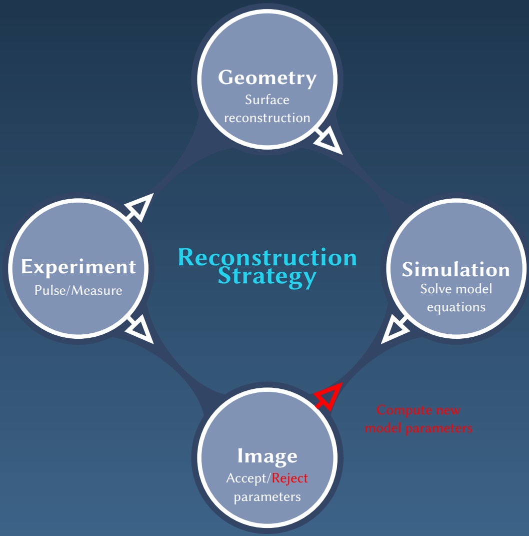
Biological properties:

- Main chromophores of biological tissues in near IR spectrum range are: Water and Hemoglobin.
- Hemoglobin absorption spectra strongly depends on its oxygenation.
- Tumour is characterized by a dense vascular network and high blood flow.



Light spectrum in biological tissues (ref [3])

Image reconstruction strategy



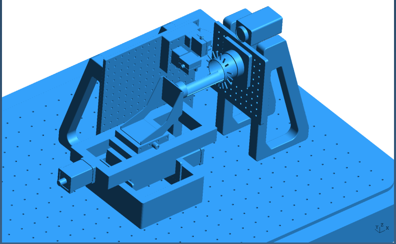
- The image reconstruction consists in determining the optical and fluorescence input parameters such that the error between the computed and real data is sufficiently small

$$||\phi_\ell^{\text{sim}} - \phi_\ell^{\text{real}}|| < \varepsilon.$$

- The inverse problem is highly non linear! Known data on a subset of $\delta\Omega$ does not necessary ensure the unicity of the solutions in Ω.
- The number of detectors and the setting strongly influence the convergence and the stability of the solutions.

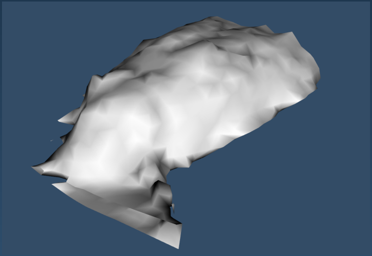
Tomograph setup and acquisition

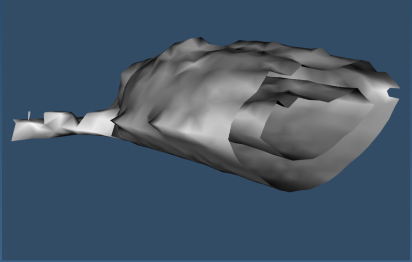
- 16 fibers ring (8 diodes, 7 TPSF/source) in a plane section.
- Surfacic acquisition (conoscop).
- Each fiber has two working mode:
    - $\delta(\partial\Omega)$-pulsing,
    - $\delta(\partial\Omega)$-detection.
- Two measure types:
    - Contact,
    - Non contact.



Geometry retrieving

- Conoscop acquires a data grid from the top (3D points).
- Surfacic reconstruction:
  - Poisson reconstruction (VTK),
  - Anysothropique reconstruction ?



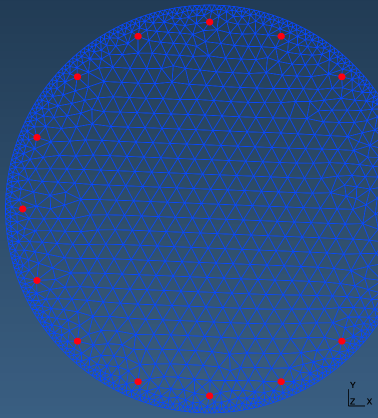


- Geometrical errors:
  - Measure artifacts
  - Mechanical noise
  - Bound holes due to top measures

Contact mode

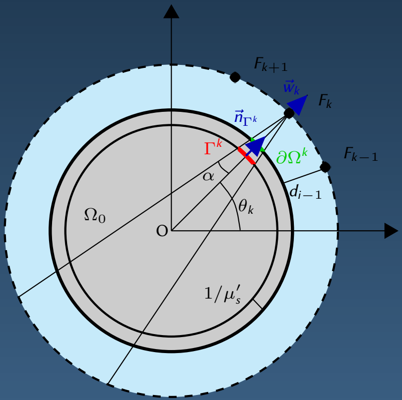
- Pointwise sources (red points) are located at a distance $1/\mu_s'$ from the boundary (free mean path distance).
- Measure modes:
  - Source: $q_0^k = \delta_{x_k}$ pointwise source where x_k is the source node in $\mathcal{T}(\Omega)$ for $k \in [1, N_s]$
  - Detector: $\mu^k\big|_{x_k}$ pointwise measure where x_k is the detector node in $\mathcal{T}(\partial\Omega)$ for $k \in [1, N_s]$
- $\phi^k \in \Omega \times [0, T]$, $T > 0$ the photon fluence rate, then the pointwise measure is

$$\mu^k(t) = \phi^k(x_k, t)$$



Non contact mode

- Surfacic sources located at a distance $1/\mu_s'$ from the boundary (corresponding to the free mean path).
- Measure modes:
  - Source:
    $q_0 = \delta_{\Gamma^k}$ surfacic source (In the fiber cone of vision Γ^k)
  - Detector:
    $\mu^k|_{\partial\Omega^k}$ surfacic measure (In the fiber cone of vision $\partial\Omega^k$)

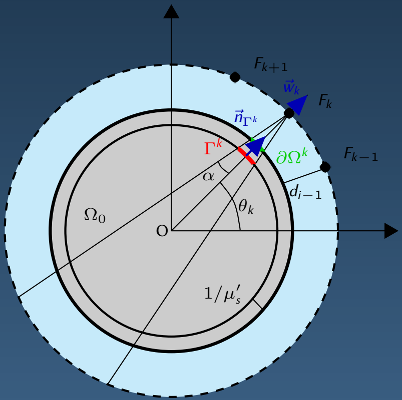


Non contact mode

- The measure is a weighted mean which depends on the angle α_j of the fiber with the j^{th} element in the cone of vision. ($\alpha = \max_{j<|\bar{\Gamma}^k|}(\alpha_j)$) and the mean value of the photon fluence rate per element $\hat{\phi}_j^k(t)$ taken at their barycentre.

$$\mu^k(t) = \int_{K_j \in \partial\bar{\Omega}^k} \hat{\phi}_j^k(t) * cos(\alpha_j)$$

$$\hat{\phi}_j^k = \frac{1}{|K_j|} \int_{K_j} \phi^k(\mathbf{r}, t)$$



Diffusion approximation

- Radiative transfer equation (RTE) [1, 3]: $L(\mathbf{r}, \mathbf{s}, t)$ the radiance, p the scattering phase function, Ω the solid angle, q the light source, μ_a, mu_s absorption and scattering coefficient.

$$\left\{\frac{1}{c}\frac{\partial}{\partial t} + \mathbf{s}\cdot\nabla + [\mu_a(\mathbf{r}) + \mu_s(\mathbf{r})]\right\} L(\mathbf{r}, \mathbf{s}, t) = \mu_s(\mathbf{r}) \int_{4\pi} p(\mathbf{s}', \mathbf{s}) L(\mathbf{r}, \mathbf{s}', t) d\Omega(\mathbf{s}') + q(\mathbf{r}, \mathbf{s}', t)$$

- L can expanded by the spherical harmonics (P_1 approximation). One introduce the fluence rate ϕ and the radiative flux J such that

$$L(\mathbf{r}, \mathbf{s}, t) = \frac{1}{4\pi}\left(\phi(\mathbf{r}, t) + 3\mathbf{J}(\mathbf{r}, t)\right), \quad \phi(\mathbf{r}, t) = \int_{4\pi} \mathbf{s} L(\mathbf{r}, \mathbf{s}, t) d\mathbf{s}, \quad \mathbf{J}(\mathbf{r}, t) = \int_{4\pi} L(\mathbf{r}, \mathbf{s}, t) d\mathbf{s},$$

- Derive the Fick law

$$\mathbf{J}(\mathbf{r}, t) = -\kappa(\mathbf{r})\nabla\phi(\mathbf{r}, t), \qquad \kappa(\mathbf{r}) = \frac{1}{3(\mu_a(\mathbf{r}) + \mu_s'(\mathbf{r}))}$$

- The previous equations lead to the photon diffusion equation.

Diffusion model

- Let's consider $k \in [1, Ns]$ fibers and Ω a domain of $\mathbb{R}^d$ ($d = 2$ or 3), $T > 0$ then the diffusion equation for the k^{th} fiber is given by

$$\begin{cases} -\text{div}(\kappa_x \nabla \phi_x^k) + c_e \mu_{a,x} \phi_x^k + \dfrac{\partial \phi_x^k}{\partial t} = q_0^k & \text{on } \Omega \times [0, T], \\ \phi_x^k + 2\text{A}\kappa_x \nabla \phi_x^k \cdot \mathbf{n} = 0 & \text{on } \partial\Omega \times [0, T]. \end{cases}$$

- $\mu_{a,x}$ absorption coefficient.
- $\mu'_{s,x}$ scattering coefficient.
- $\kappa_x = c_e/(3(\mu_{a,x} + \mu'_{s,x}))$ diffusion coefficient.
- c_e light speed in the turbid medium.
- q_0^k light source (Dirac delta-function).
- A internal refraction coefficient.
- $\mathbf{n}$ outward unit normal vector.

input:

- $\mu_{a,x}$, κ_x

output:

- ϕ_x^k

Diffusion model

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- Choose a regularized source q_0:

$$q_0^{\text{reg}} = \begin{cases} \frac{1+\cos(\pi d(\mathbf{r}))}{2\epsilon} & \text{if } d(\mathbf{r}) < \epsilon = O(h) , \\ 0 & \text{else} \end{cases}$$

- $q_0^{(k)}$, $\phi_x^{(k)}$ depends on contact/non contact acquisition modes

Fluorescence coupling model

- Let's consider $k \in [1, Ns]$ fibers and Ω a domain of $\mathbb{R}^d$ ($d = 2$ or 3), $T > 0$ and $\ell \in \{x, m\}$.

$$\begin{cases} -\operatorname{div}(\kappa_x \nabla \phi_x^k) + c_e \mu_{a,x} \phi_x^k + \dfrac{\partial \phi_x^k}{\partial t} = q_0^k & \text{on } \Omega \times [0, T], \\ -\operatorname{div}(\kappa_m \nabla \phi_m^k) + c_e \mu_{a,m} \phi_m^k + \dfrac{\partial \phi_m^k}{\partial t} = \dfrac{\gamma}{\tau} \displaystyle\int_0^t \phi_x^k e^{(\frac{t-s}{\tau})}\, ds & \text{on } \Omega \times [0, T], \\ \phi_\ell^k + 2A\kappa_\ell \nabla \phi_\ell^k \cdot \mathbf{n} = 0 & \text{on } \partial\Omega \times [0, T]. \end{cases}$$

- $\mu_{a,\ell}$ absorption coefficients.
- $\mu'_{s,\ell}$ scattering coefficients.
- $\kappa_\ell = c_e/(3(\mu_{a,\ell} + \mu'_{s,\ell}))$ diffusion coefficients.
- $\gamma = \eta\sigma\xi$ fluorophor coefficient
- ξ flurorophor concentration
- σ fluorophor molar extinguishing coefficient
- η fluorophor yield
- τ fluorophor average lifetime

input:

- $\mu_{a,\ell}, \kappa_\ell, \xi, \tau$

output:

- ϕ_ℓ^k

Weak formulation

- We multiply the previous equation by a test function $v \in H^1(\Omega)$, integrate by parts and use a BDF strategy of order 1 to deduce the weak formulation:

$$\int_\Omega (\kappa \nabla \phi^{k,n+1} : \nabla v + c\mu_a \phi^{k,n+1} \cdot \mathbf{v}) + \int_{\partial\Omega} \frac{1}{2A} \phi^{k,n+1} \cdot \mathbf{v} + \int_\Omega \frac{\phi^{k,n+1}}{\Delta t} \cdot \mathbf{v}$$
$$= \int_\Omega \mathbf{q}^k(\phi_x^k) \cdot \mathbf{v} + \int_\Omega \frac{\phi^{k,n+1}}{\Delta t} \cdot \mathbf{v} \,, \qquad (1)$$

- where $\phi^k = (\phi_x^k, \phi_m^k)$ and the source term is,

$$\mathbf{q}^k(\phi_x^{k,n}) = \begin{pmatrix} q_0^k \\ \frac{\gamma(\mathbf{r})}{\tau} \int_0^t \phi_x^k(\mathbf{r}, s) e^{\left(\frac{t-s}{\tau}\right)} ds \end{pmatrix} . \qquad (2)$$

Fluorescence source term

- The convolution integral can be developped such that,

$$\frac{\gamma(\mathbf{r})}{\tau}\int_0^{t_{n+1}} \phi_x^k(\mathbf{r},s)e^{\left(\frac{t_{n+1}-s}{\tau}\right)}ds = B_n^k(\mathbf{r}) + R_n^k(\mathbf{r})$$

- Where the buffer term B_n^k and the remaining term R_n^k are

$$B_n^k(\mathbf{r}) = \frac{\gamma(\mathbf{r})}{\tau}\int_0^{t_n} \phi_x^k(\mathbf{r},s)e^{\left(\frac{t_{n+1}-s}{\tau}\right)}ds \ , \tag{3}$$

$$R_n^k(\mathbf{r}) = \frac{\gamma(\mathbf{r})}{\tau}\int_{t_n}^{t_{n+1}} \phi_x^k(\mathbf{r},s)e^{\left(\frac{t_{n+1}-s}{\tau}\right)}ds \ . \tag{4}$$

- The recursive formula is,

$$\begin{cases} B_n^k(\mathbf{r}) & = & e^{\frac{\Delta t}{\tau}}\left(B_{n-1}^k(\mathbf{r}) + R_{n-1}^k(\mathbf{r})\right) , \\ B_0^k & = & R_0^k . \end{cases} \quad (5)$$

- The remaining term can be calculated. Indeed ϕ_x^k is time polynomial of order 1 in $[t_n, t_{n+1}]$,

$$R_n^k(\mathbf{r}) = \gamma(\mathbf{r})\left(C_1\phi_x^{k,n+1} + C_2\phi_x^{k,n}\right) , \quad (6)$$

- where C_1 and C_2 are constants.

Forward algorithm for the coupled system in Feel++

Require: mesh (**or** geometry)
Mark sources **and** detectors
assembly bilinear form a_x **and** a_m
assembly linear form l_x **and** l_m
for all time step **do**
  for all k marked sources **do**
    update $l_x \leftarrow q^k_{0,x}$
    $R_n \leftarrow \phi_x^{k,n}$
    $\phi_x^{k,n+1} \leftarrow A_x \phi_x^{k,n+1} = L_x$
    $R^k_n \leftarrow \phi_x^{(n+1)}$
    $B^k_{n+1} \leftarrow B^k_n$ **and** R^k_n
    update $l_m \leftarrow q^k_{0,m}$
    $\phi^k_m \leftarrow A^k_m \phi^k_m = L_m$
    shift ϕ_x **and** ϕ_m for next step
  end for
end for

- Feel++ a C++ library for finite elements methods,
- Support arbitrary order Galerkin methods 1D, 2D, 3D,
- Interface to large scale linear/nonlinear solvers (PETSc, Trilinos...),
- Interface to optimisation libraries (IPopt,Nlopt),
- Wide range of post-processing format (Paraview, GMSH, Ensight, ...).

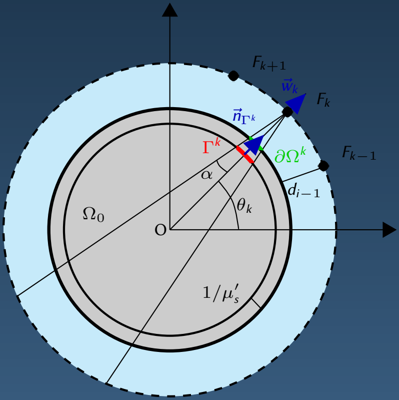
Level Set Methods

- The method retrieves a distance function φ from the interface Γ of two regions Ω_1, Ω_2 $\Gamma(t) = \{(\mathbf{r}, t) | \varphi(\mathbf{r}, t) = 0\}$ and

$$\varphi(\mathbf{r}, t) = \begin{cases} -d(\mathbf{r}(t), \Gamma(t)) & x \in \Omega_1 \times [0, T] \\ 0, & x \in \Gamma \times [0, T] \\ d(\mathbf{r}(t), \Gamma(t)) & x \in \Omega_2 \times [0, T] \end{cases} \qquad \mathbf{n} = \frac{\nabla \varphi}{|\nabla \varphi|} \qquad \kappa = \nabla \cdot \mathbf{n}$$

- where d is the signed distance function $d = \inf_{y \in \Gamma}(d(x, y)), \forall x \in \Omega$. φ verify the property $|\nabla \varphi| = 1$. $\mathbf{n}$ the unit outward normal to the interface and κ curvature,
- The Fast marching method (FMM) is a fast (O(N)) and robust algorithm to reinitialize φ to a distance function (solve the eikonal equation $|\nabla \varphi|$=1).
- Feel++ provides a parallel implementation for FMM methods [2].

Create markers for sources and detectors

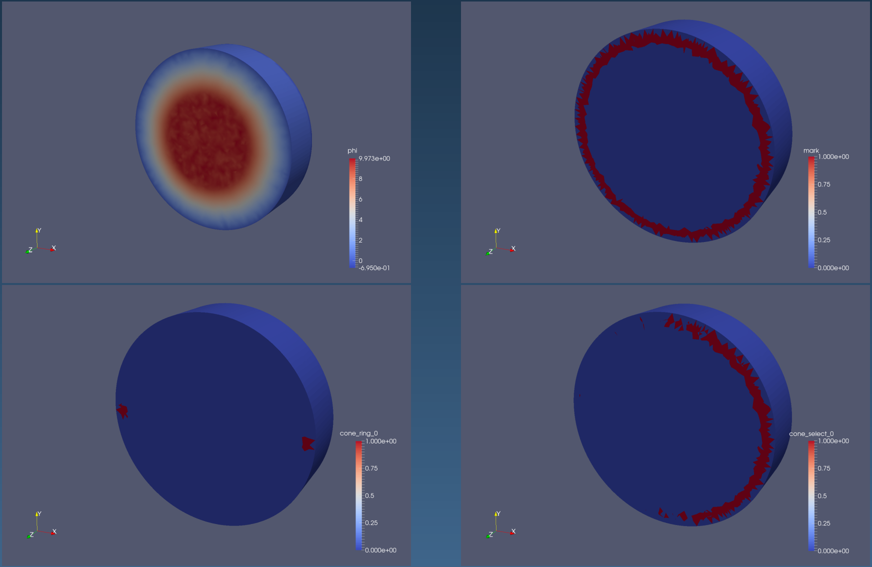


- $\mathcal{C}^k$ cone projection on Γ^k, $\mathcal{N}^k$ positive normals in the k^{th} fiber space system.

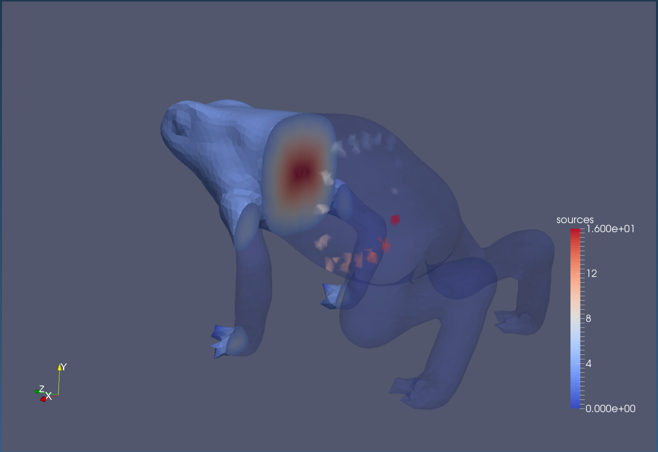
- Feel++ markers are contructed from $\mathbb{P}_0$ discontinuous functions such that values correspond to marker indices.

Require: mesh2D
$\varphi \leftarrow$ **FMM**
$\overline{\Gamma} \leftarrow d(\varphi, 1/\mu_s') < \epsilon$
for all fibers i **do**
$\overline{\mathcal{C}^k} \leftarrow \Pi_{\text{cone}}(\overline{\Gamma})$
$\overline{\mathcal{N}^k} \leftarrow \{K_j | \mathbf{n}_{K_j} \cdot \mathbf{w}_k > 0, \forall K_j \in \overline{\Gamma}\}$
$\overline{\Gamma^k} \leftarrow \overline{\mathcal{N}^k} \cap \overline{\mathcal{R}^k}$
end for
$\rightarrow$ *repeat loop on* $\overline{\partial\Omega}$ *instead of* $\overline{\Gamma}$ *to get* $\overline{\partial\Omega_K}$

Numerical example



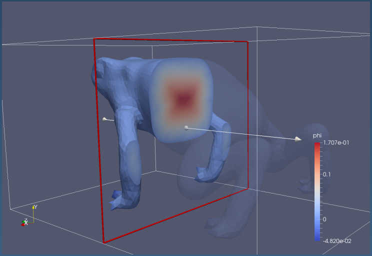
Pseudo real geometry markers

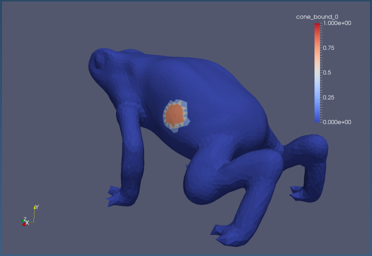


All sources Γ^k (transparent part) and the function φ (head part) marked using the fast marching method. The legend represents marker indices.

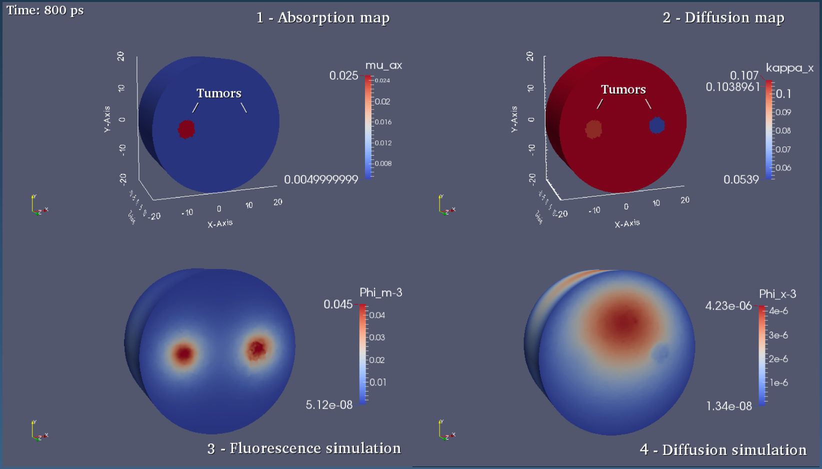
Pseudo real geometry example

- This method lets handle complex geometries.
- This method has currently some limitation especially for non-convex shape (for example, the frog's head, or shoulder parts)

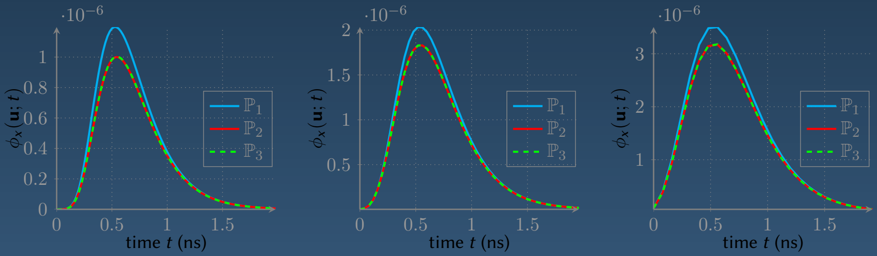




Numerical solution for diffusion and fluorescence



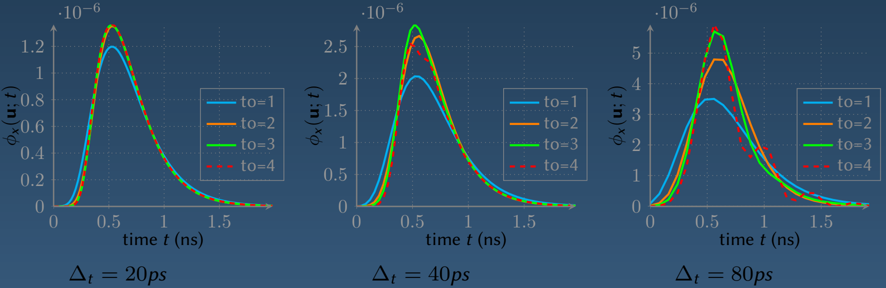
TPSF polynomial order comparison



$\Delta_t = 20ps$ $\Delta_t = 40ps$ $\Delta_t = 80ps$

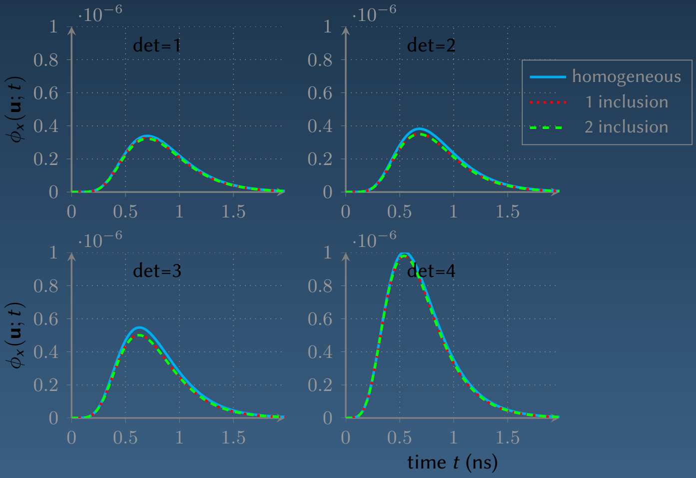
Comparison between $\mathbb{P}_1$,$\mathbb{P}_2$ and $\mathbb{P}_3$ approximation with fixed mesh size and varying time step for time order 1.

TPSF time order comparison



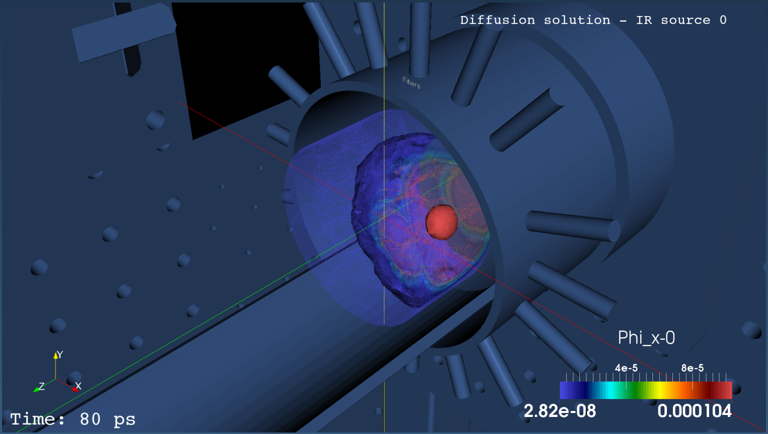
Comparison time orders for different time step for an $\mathbb{P}_1$ approximation.

TPSFs and Inclusions Influence



TPSFs a phantom with 1 and 2 inclusions inserted.

Forward problem simulation



Contour comparison for different sources.

Movie Player YouTube

Conclusion & Overview

- Solve each problem in parallel (using MPI group of communicators)
- Inverse problem analysis
- Reduced order models (Certified reduced basis,...)
- Uncertainty quantification (Sensitivity analysis,...)
- New coupling models (Photoacoustic,...)

Thank you!

See also:

- DOT Project page at: www.cemosis.fr
- Feel++ library: www.feelpp.org
- Movie DOI: 10.5281/zenodo.11641

Slides references:

- Wikipedia pictures:
  - Axial Tomograph
  - Fiber rings
  - Laser refraction
  - infrared scattering

- Farouk Nouizi.
  Tomographie optique diffuse et de fluorescence préclinique : instrumentation sans contact, modélisation et reconstruction 3D résolue en temps.
  PhD thesis, Université de Strasbourg, 2011.
  [link].
- Doyeux V.
  Modeling and simulation of multi-fluid systems. Application to blood flows.
  PhD thesis, Université de Grenoble, 2014.
  [link].
- Y. Yamada and S. Okawa.
  Diffuse optical tomography: Present status and its future.
  Optical Review, 21(3):185–205, 2014.