Modeling of Hyperthermia Therapy and Heat Diffusion using GATE

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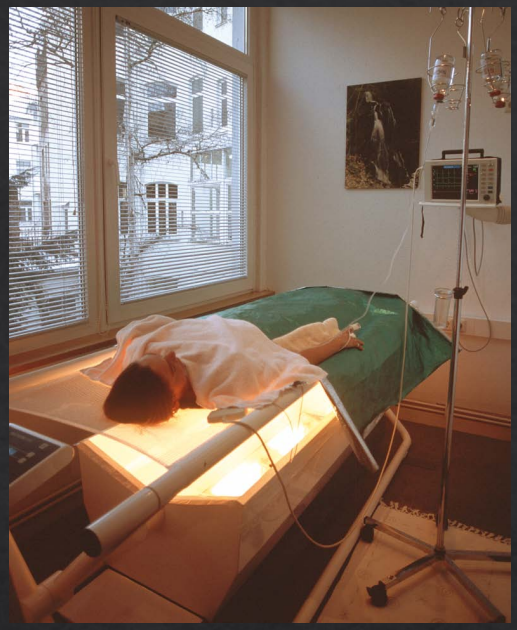
THERMAL THERAPY

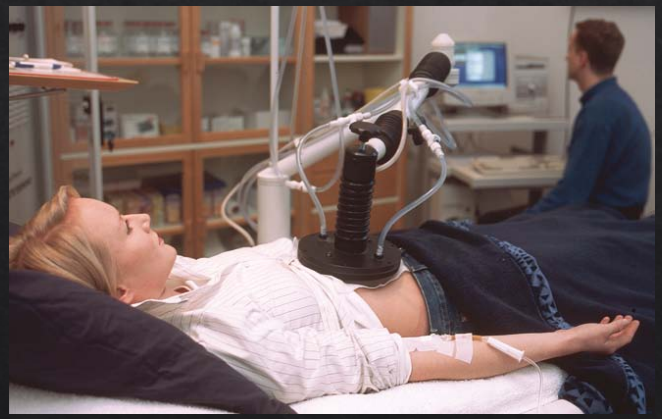
- Hyperthermia therapy is a treatment in which body tissue is exposed to **higher temperatures** to kill cancer cells or to make cancer cells more sensitive to the effects of radiation or anti-cancer drugs.

- Hyperthermia has demonstrated the ability to **increase the effectiveness** of other treatments.

- Current research focuses on how one might **precisely distribute heat** within a target tissue (i.e. nanoparticles).



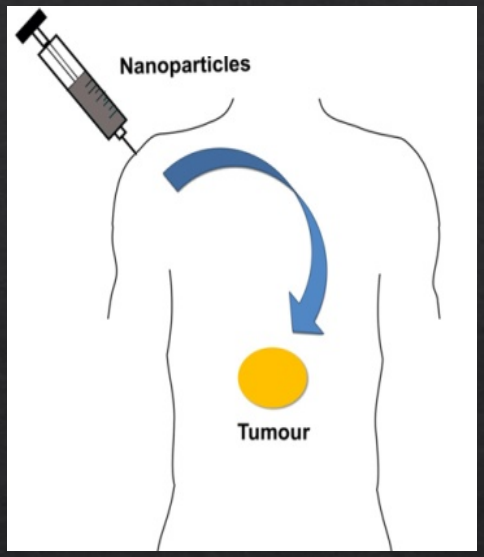
Whole-body hyperthermia during chemotherapy

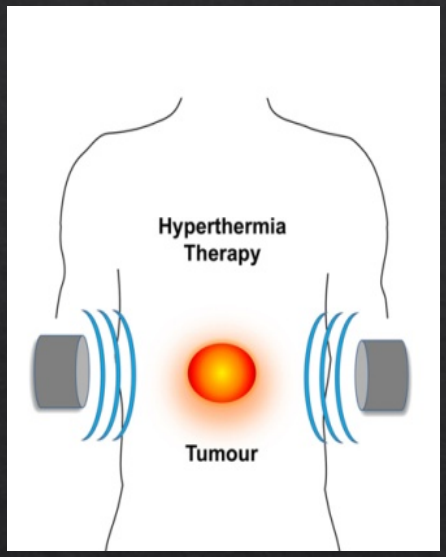


Local hyperthermia
using short-wave radiofrequency radiations

NANOPARTICLE mediated HYPERTHERMIA

Nanoparticles (NP) are injected into the patient bloodstream or directly into the tumor.





NP in the tumor site are activated by NIR light or by a magnetic field.

- Minimally invasive technique
- Heat is concentrated within the tumor
- Damage to healthy cells is reduced
- Potential to image and treat tumors (i.e. theranostic)

THERMAL MODULE in GATE

- Nanoparticle photothermal treatment is under study in clinical trials (Nanospectra Biosciences, Rice University, TX, USA).
- Investigate the influence of **nanoparticle properties** on the heat spatial distribution in the tumor and healthy tissues :
  - Simulations are required
- **Extend GATE** to model thermal therapies as well as simple heat diffusion in biological tissues.
- **Combine** this new therapy with optical imaging to show a proof of concept of **theranostic** scenario simulation.

Nanospectra

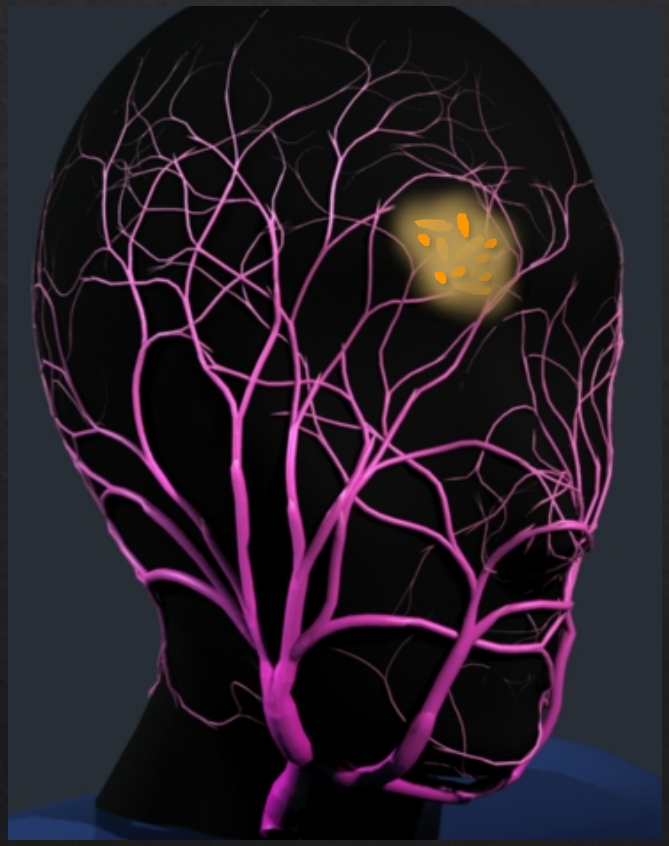
AuroLase® therapy – clinical studies

Determination of any adverse device effects attributable to AuroShell particle administration

- ❑ primary and/or metastatic lung tumors – **currently performed**
- ❑ head and neck refractory or recurrent tumors - **completed**

1. The NPs are delivered intravenously
2. Accumulate in the tumor by EPR effect
3. Tumor is illuminated with a NIR laser
4. The particles selectively absorb the laser energy, converting the light into heat
5. The heat thermally destroy the tumor and the blood vessels supplying it
6. Surrounding healthy tissue are not significantly damaged

HEAT DIFFUSION : PENNES MODEL



Thermal diffusivity (m^2/s)

Perfusion term (s^{-1})

$$\frac{\partial T(x,y,z,t)}{\partial t} = \nabla.[K\,\nabla T(x,y,z,t)] + \sigma[T_{Blood} - T(x,y,z,t)]$$

Blood temperature from the main arteries

Tissue thermal conductivity W/(mxK)

$$K = \frac{k}{\rho c}$$

Tissue density (kg/m^3)

Tissue thermal capacity J/(kgxK)

Blood density

Blood thermal capacity

$$\sigma = \frac{\rho_{Blood}\, c_{Blood}}{\rho c}\,\omega_{Blood}$$

Tissue density

Tissue thermal capacity

Blood perfusion rate (s^{-1})

ANALYTICAL SOLUTION to the HEAT DIFFUSION EQUATION

The analytical solution to the heat equation was obtained via Fourier transformations and convolution theorem :

$$T(x,y,z,t) = [T(x,y,z,0) - T_{Blood}] \otimes \left(\frac{1}{(4\pi K t)^{\frac{3}{2}}} e^{-\frac{x^2+y^2+z^2}{4Kt}} \right) e^{-\sigma t} + T_{Blood}$$

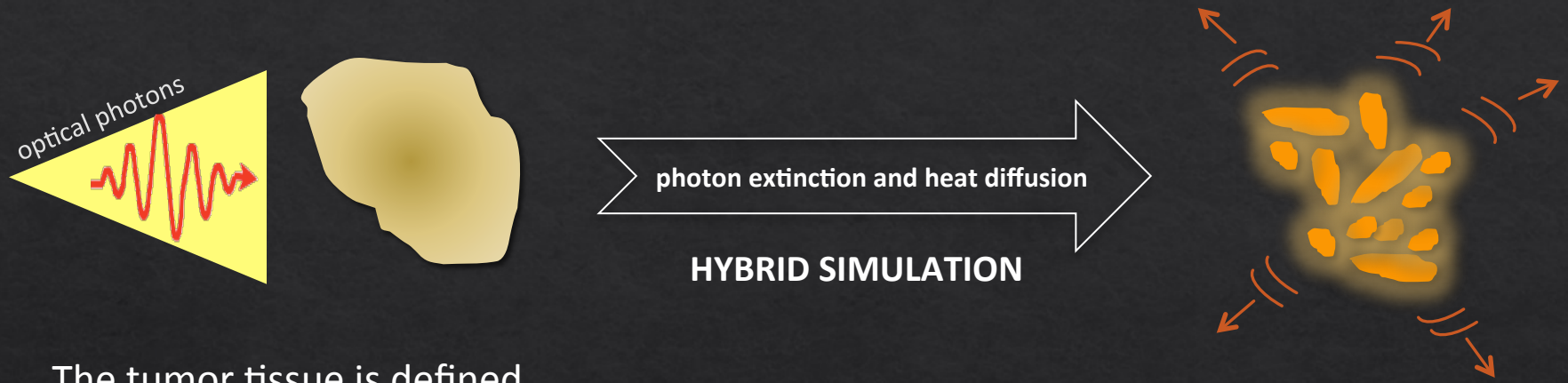
Voxelised images

Convolution with a Gaussian

Blood perfusion term

The analytical simulation is implemented in GATE using the Insight Segmentation and Registration Toolkit platform.

HYPERTHERMIA THERAPY MODELISATION using GATE



The tumor tissue is defined with an absorption length that is a function of the density of nanoparticles and the nanoparticle absorption cross-section area :

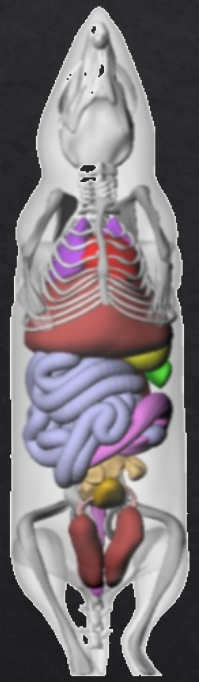
$$\mu_{absorption} = N \times C_{absorption}$$

Ex: C_{abs} = 3.8x10^{-14} m^2 at 820 nm (gold nanoshell)

- **MONTE-CARLO simulation:** During light illumination, optical photons are absorbed by the nanoparticle infused tumor.
- **ANALYTICAL simulation:** The diffusion of the deposited photon energy is implemented through an analytical simulation in which we solve the heat diffusion equation.

This process is **dynamic**.
Heat diffusion occurs during light irradiation.

THERMAL ACTOR : How To



Digital phantom

Phantom material properties (Materials.xml):

- Nanoparticle (NP) infused tissue absorption coefficient depends on the concentration of NP and the NP absorption cross-section area.

$$\mu_{absorption} = N \times C_{absorption}$$

C_{abs} = 3.8x10^{-14} m^2 at 820 nm (gold nanoshell)

- Tissue optical absorption coefficient
- Tissue Rayleigh and/or Mie diffusion coefficient
- Fluorescence properties for diagnosis

Thermal Actor GATE command lines (macro) :

```
/gate/actor/addActor ThermalActor                    MyActor
/gate/actor/MyActor/save                             3DMap.hdr
/gate/actor/MyActor/attachTo                         phantom
/gate/actor/MyActor/stepHitType                      random
/gate/actor/MyActor/setPosition                      0. 0. 0. cm
/gate/actor/MyActor/setVoxelSize                     0.5 0.5 0.5 mm

/gate/actor/MyActor/setThermalDiffusivity            0.32 mm2/s

/gate/actor/MyActor/setBloodDensity                  1.06E-6
/gate/actor/MyActor/setBloodHeatCapacity             3.6E6
/gate/actor/MyActor/setTissueDensity                 1.04E-6
/gate/actor/MyActor/setTissueHeatCapacity            3.65E6
/gate/actor/MyActor/setBloodPerfusionRate            0.004

/gate/actor/MyActor/setDiffusionTime                 5 s
```

Output : 3D voxelised image

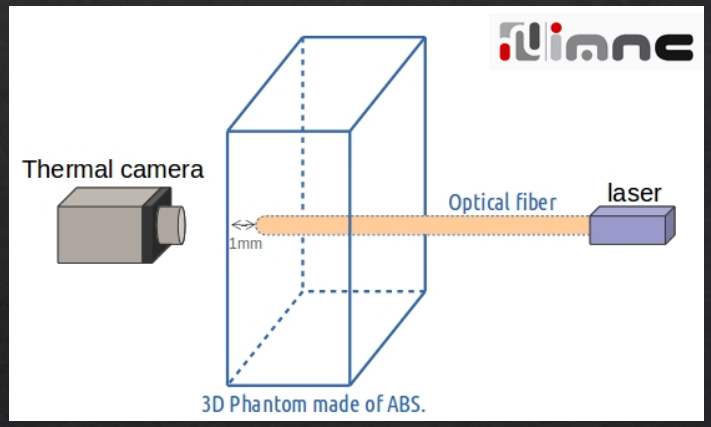
Output image voxel size

Heat conduction term

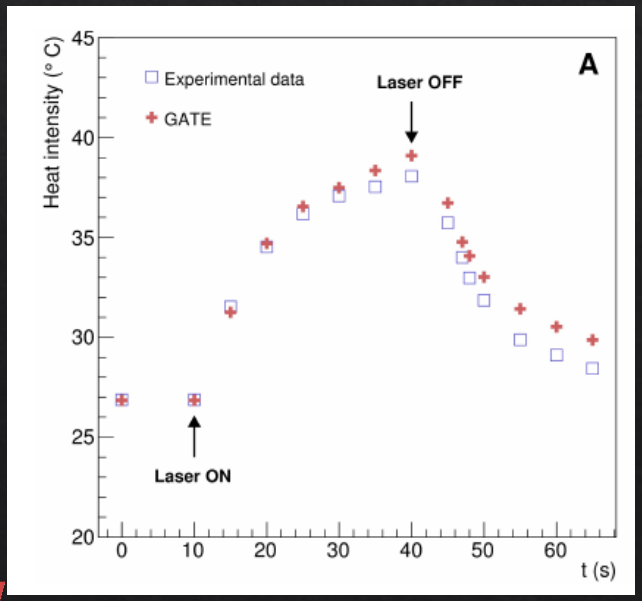
Blood perfusion term

VALIDATION: LOCAL HYPERTHERMIA

Experimental set-up

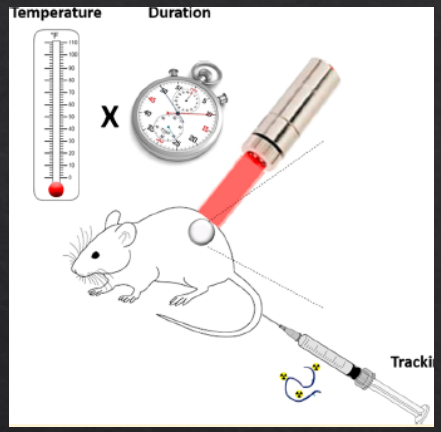


- Box phantom made of acrylonitrile butadiene styrene (ABS)
- Laser optical fiber inserted into the phantom
- Thermal camera recording 3 thermal images per second



- The simulation does not model the thermal camera nor its reponse
- For absolute comparison, the simulation was calibrated using the data
- Good agreement between data and simulation

VALIDATION : NANOSHELL THERAPY



Nanoshell-mediated near-infrared thermal therapy of tumors under magnetic resonance guidance

L. R. Hirsch*, R. J. Stafford†, J. A. Bankson†, S. R. Sershen*, B. Rivera‡, R. E. Price‡, J. D. Hazle†, N. J. Halas§, and J. L. West*¶

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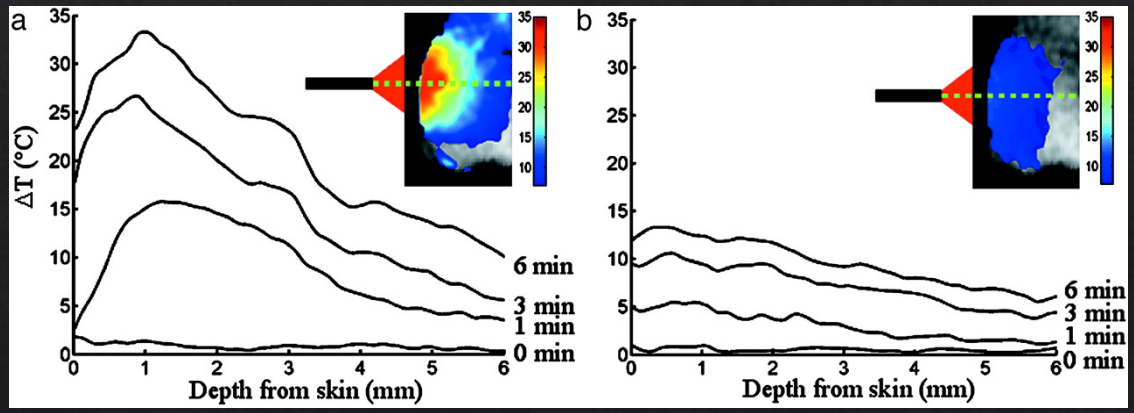
Canine transmissible venereal tumor cells were inoculated in 5 mice and grown to a tumor of 1cm diameter. Gold-silica nanoshells were injected into the tumor. Tumor sites were exposed to NIR light. Temperature profiles were monitored by MRI.

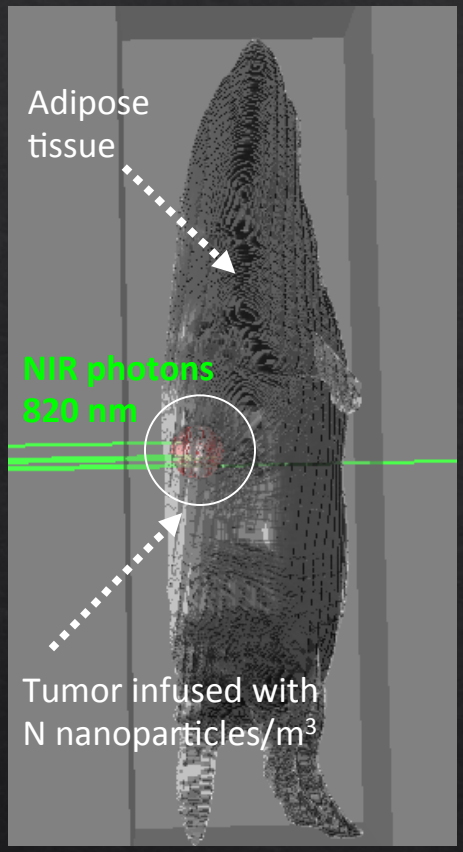
Nanoshell treatment



Control treatment

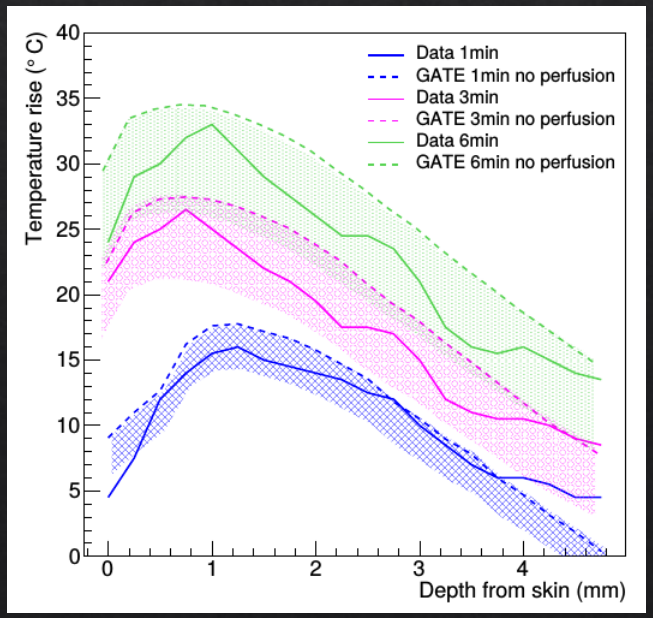
Measured temperature rise plotted as a function of depth from skin.

In Vivo NANOSHELL THERAPY: BENCHMARK and HEAT GENERATION



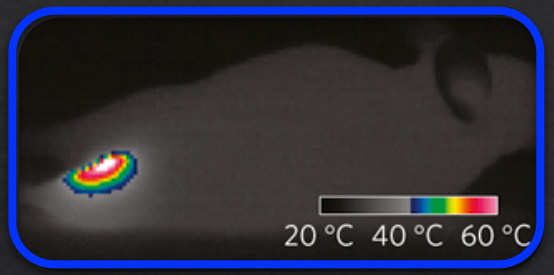
MOBY digital mouse

- Tumor absorption coefficient : N x C_{abs} = 1.7 cm^{-1}
- Thermal diffusivity (mouse skin and tumor) : 0.17 mm^2/s
- Tissue (adipose) scattering coefficient : 2 mm^{-1}
- Tissue (adipose) absorption coefficient : 0.05 mm^{-1}
- Blood perfusion rate : 0.004 and 0.0004 s^{-1}
- Diffusion time : 1, 3 and 6 minutes
- Source : 1.51 eV, 2.5mm optical fiber radius, aperture 0.48

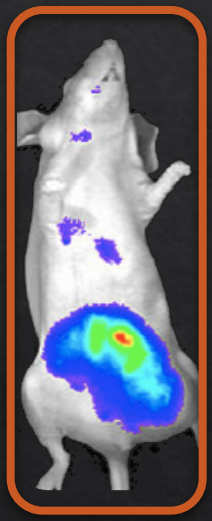


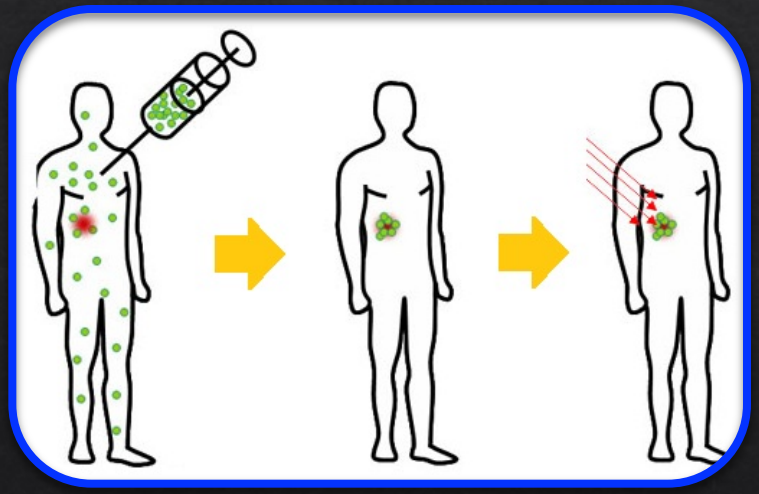
- Hashed temperature rise bands illustrate the effect of the blood perfusion term :
  - Upper limit = 0.0004 s^{-1}
  - Lower limit = 0.004 s^{-1}
- The comparison between in-vivo mouse data and the GATE simulation is good.

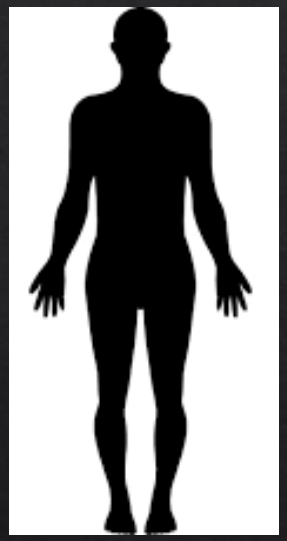
THERANOSTIC SIMULATION
THERApeutic and diagNOSTIC

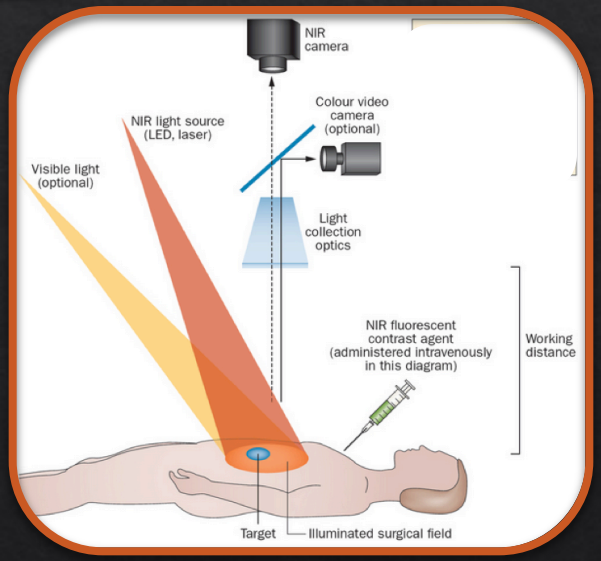


Theranostic probes









Hyperthermia using nanoparticles
GATE Thermal Actor

Fluorescence imaging
GATE Optical system

Conclusion

- The GATE code for the thermal therapy is validated :
  - Local hyperthermia in a plastic (collaboration with IMNC, Orsay)
  - In vivo nanoshell hyperthermal therapy in mice (Hirsch *et al*.)
- The simulation of theranostic scenario is possible : hyperthermia coupled with fluorescence imaging.
- The Thermal Therapy module will be released to the public in early 2017.
- Poster presentation this afternoon starting at 16:30 in the Etoile hall on the first floor of the Convention Center.