



AMISSA

Développement d'une plate-forme d'imagerie multimodale dédiée au petit animal



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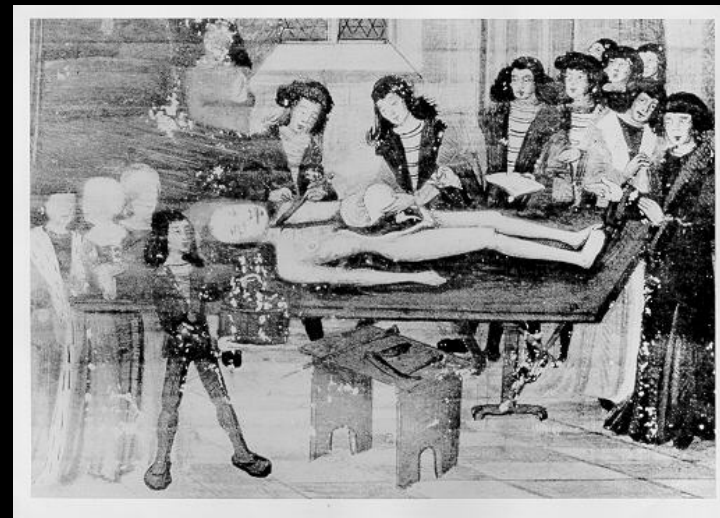
IN₂P₃

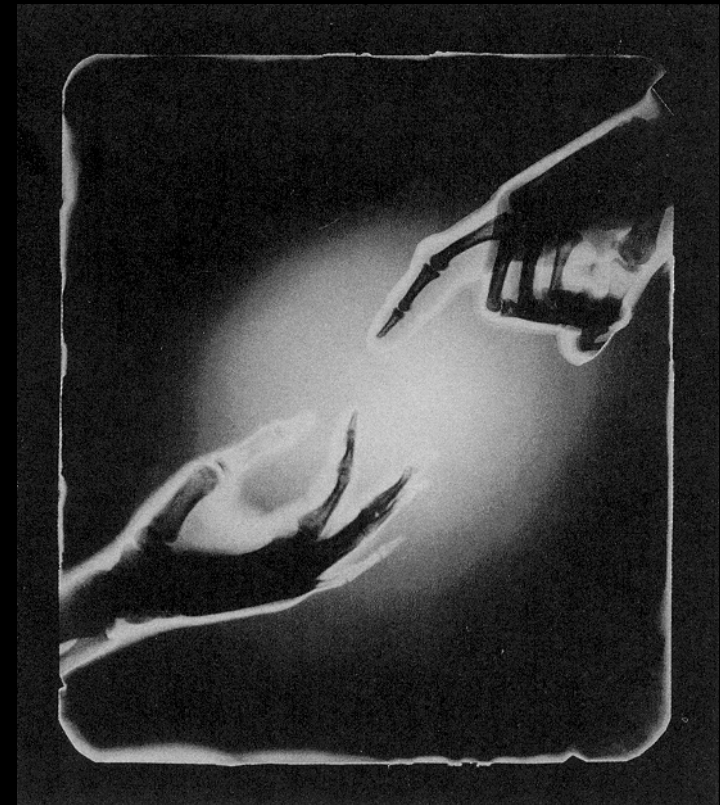
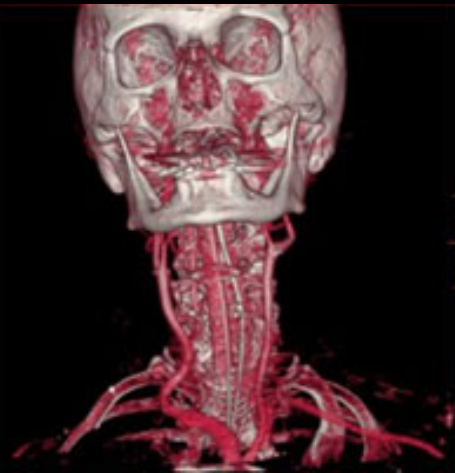


Nous sommes curieux de savoir
comment nous sommes à l'intérieur...



...mais nous n'aimons pas être meurtris!



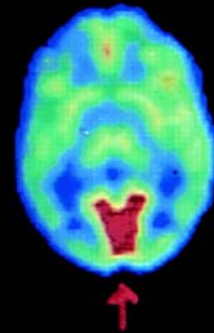


David Teplica, *Birth of man with homage to Michelangelo* (1987)

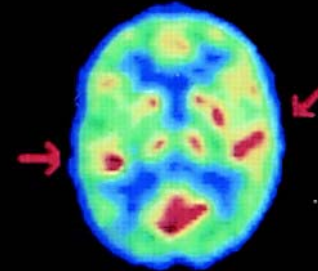
Nous sommes également curieux
de comment...



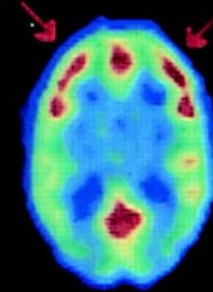
Regarder



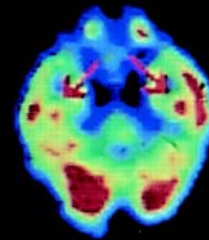
Ecouter



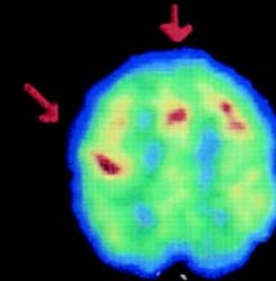
Penser



Se souvenir

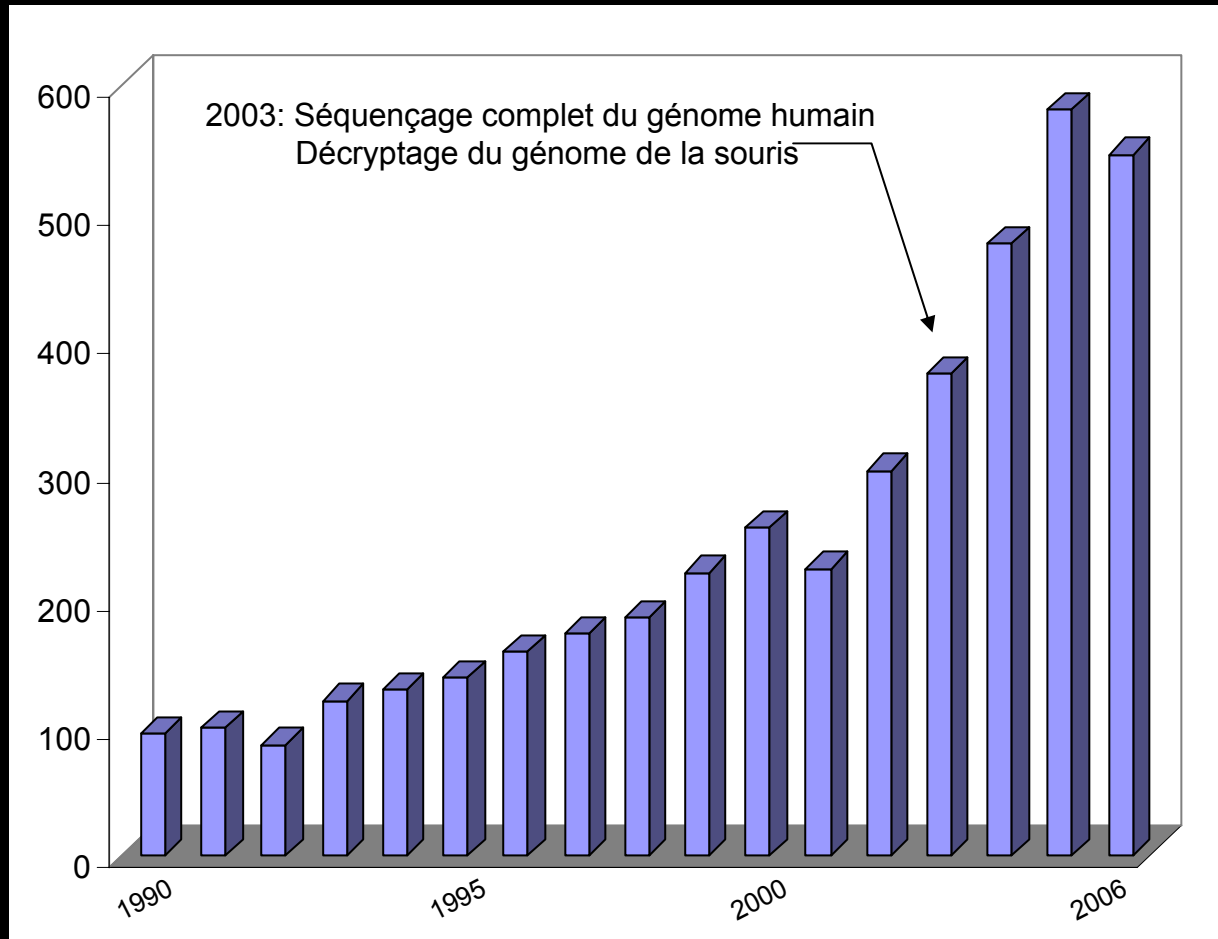


Travailler



...nos organes fonctionnent

Recherche pubmed: « small animal imaging »



Environ 30 000 gènes chacun
Seul 300 gènes différents

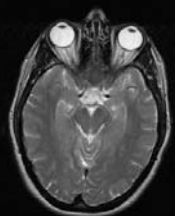
↪ Outil fabuleux
pour la recherche médicale

L'imagerie in vivo du petit animal: un défi certain

Homme



70-80 kg



1450 cm³

Rat



100-500 g

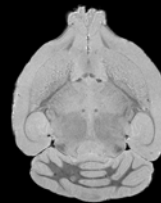


1,2 cm³

Souris



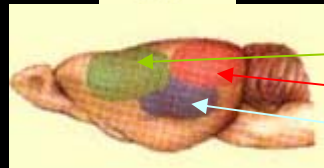
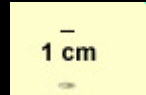
15-30 g



0,5 cm³



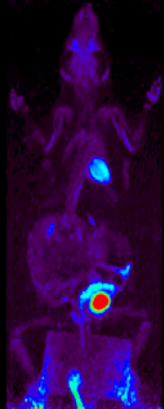
Homme / Souris -- FDG
ECAT HR+ – 45 minutes



Aire sensorimotrice
Aire visuelle
Aire auditive

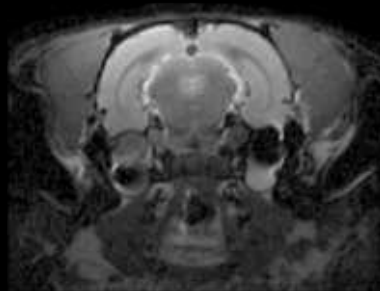
Imagerie Moléculaire

Unregistered HyperCam



Manchester institute

Système TEP



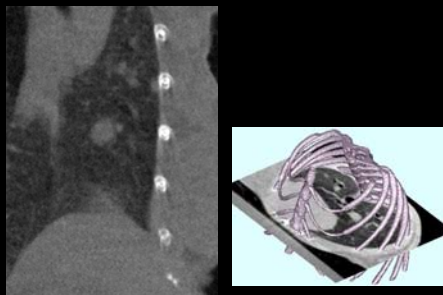
Système IRM



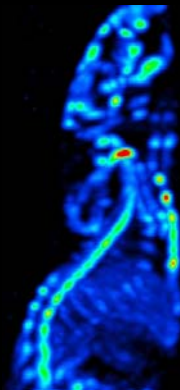
Autoradiographie



Système Ultrason



Tomodensitomètre X



Julich Research center

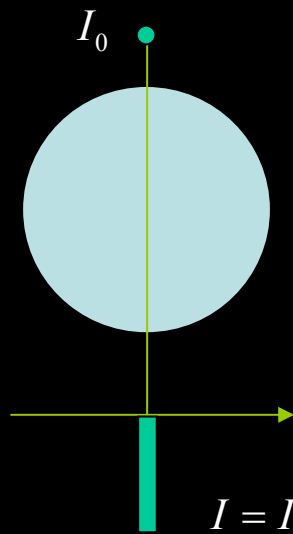
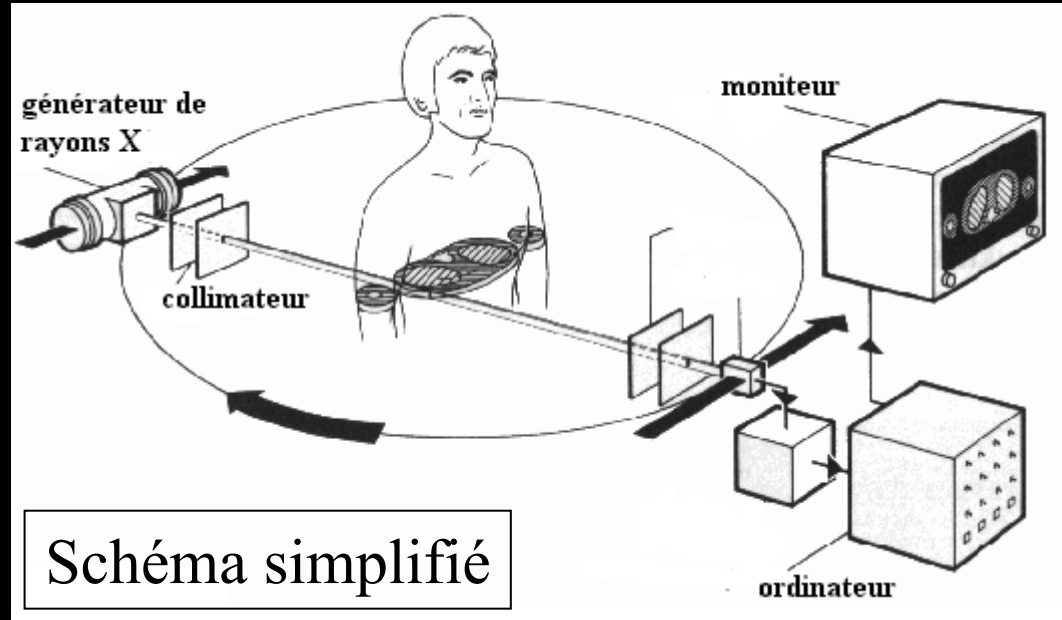
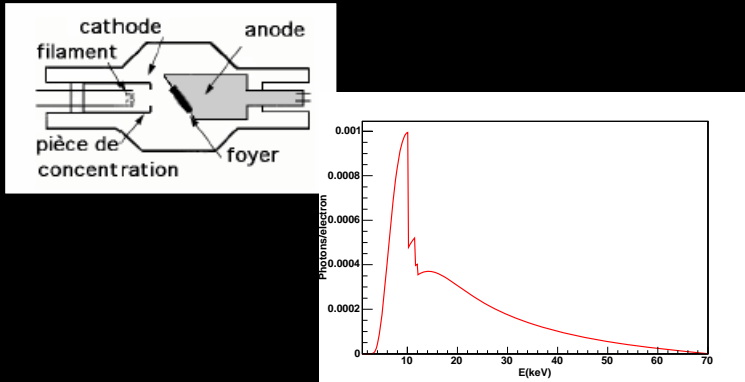
Système TEMP



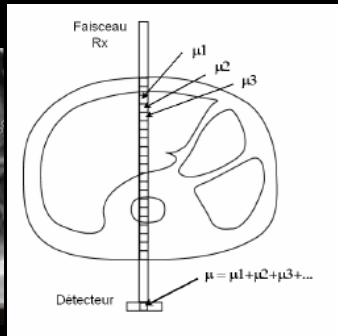
Systèmes optiques

Bioluminescence
fluorescence

Imagerie par transmission



$$I = I_0 e^{-\mu d}$$



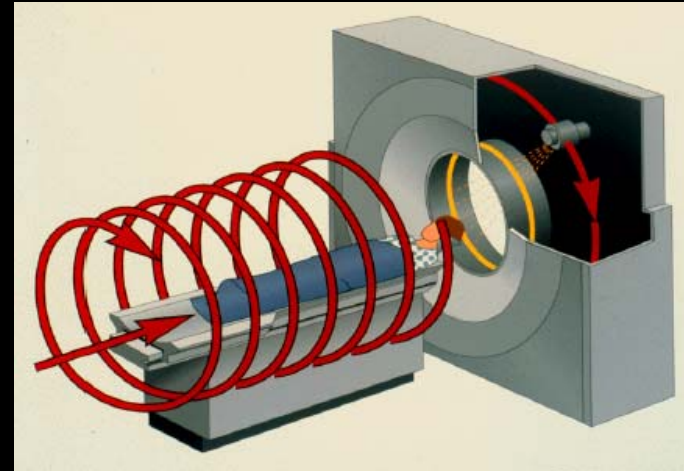
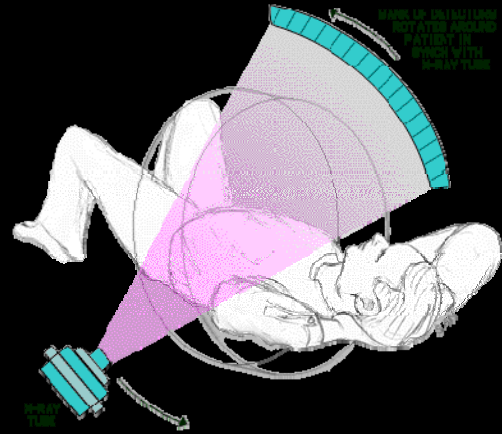
$$I = I_0 e^{-\int_L \mu_E(x,y,z) dL}$$

$$\int_L \mu_E(x,y,z) dL = \ln \frac{I_0}{I}$$

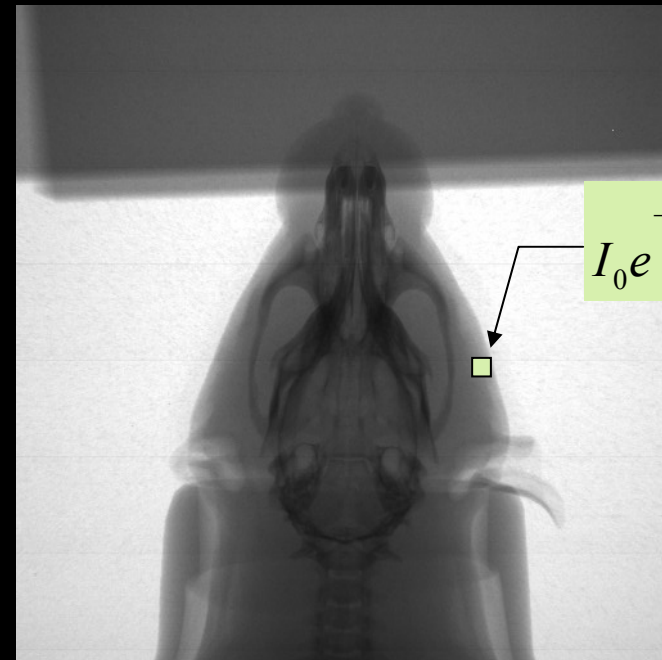
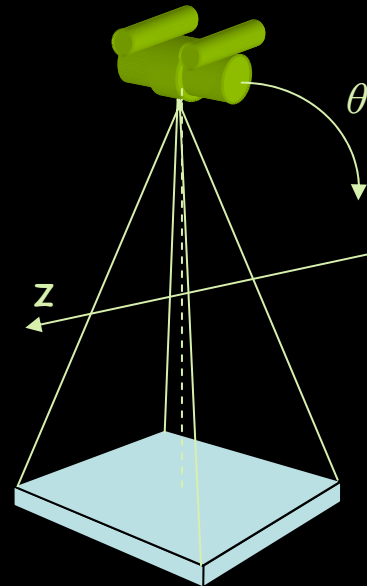
Hypothèse: E constante

Principe du tomographe

Système
homme

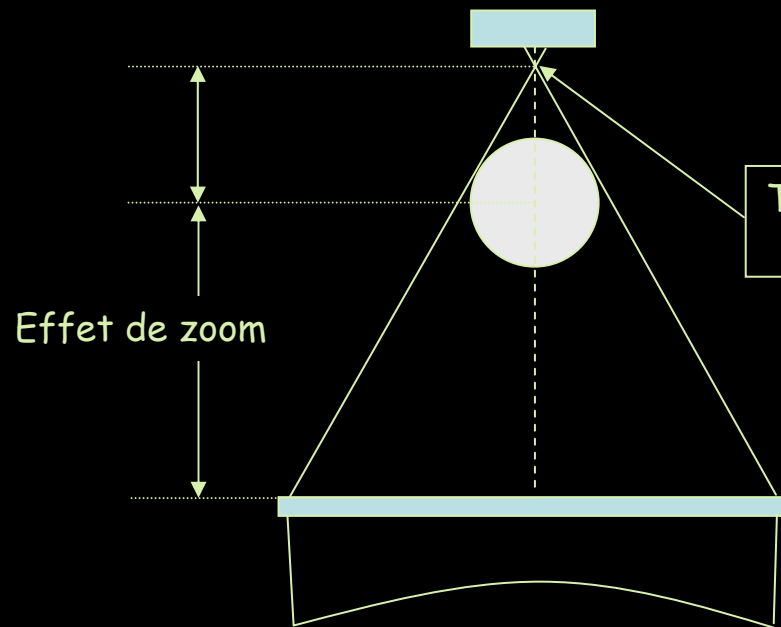


Système
animal



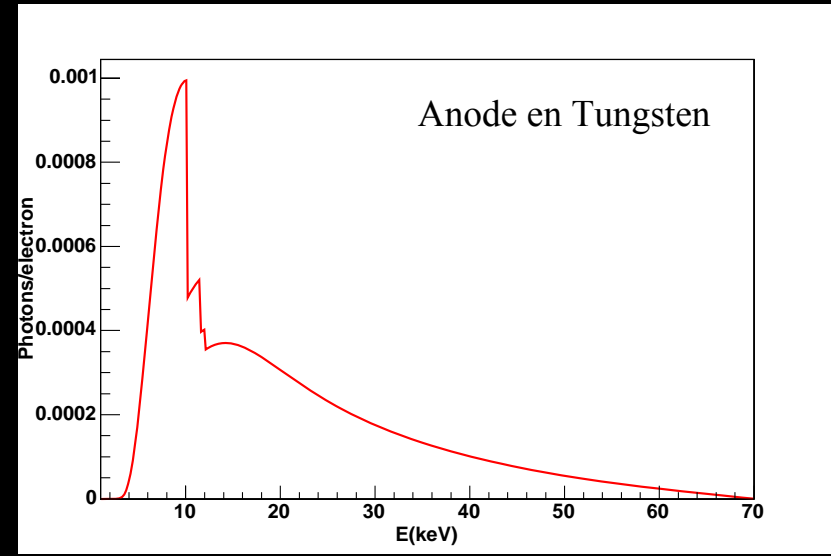
Paramètres importants

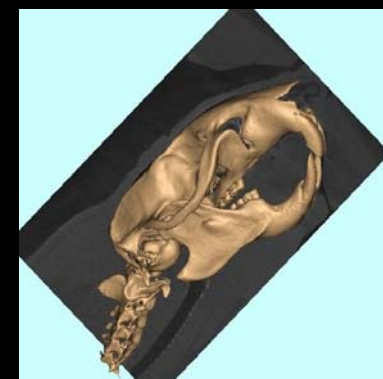
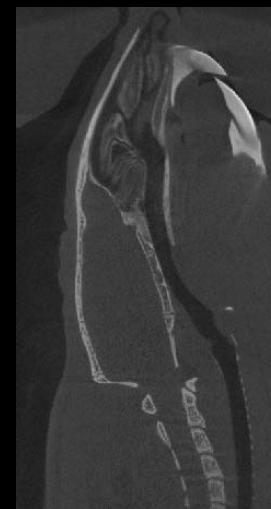
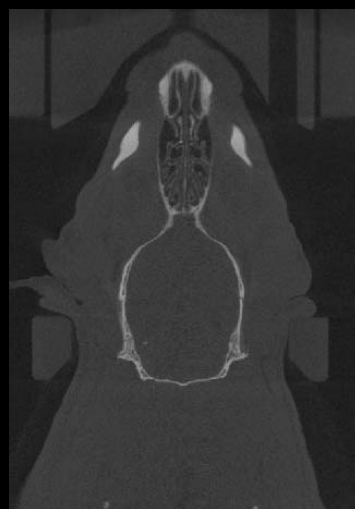
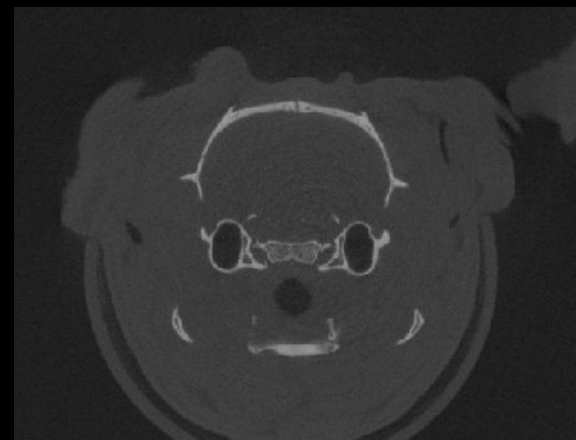
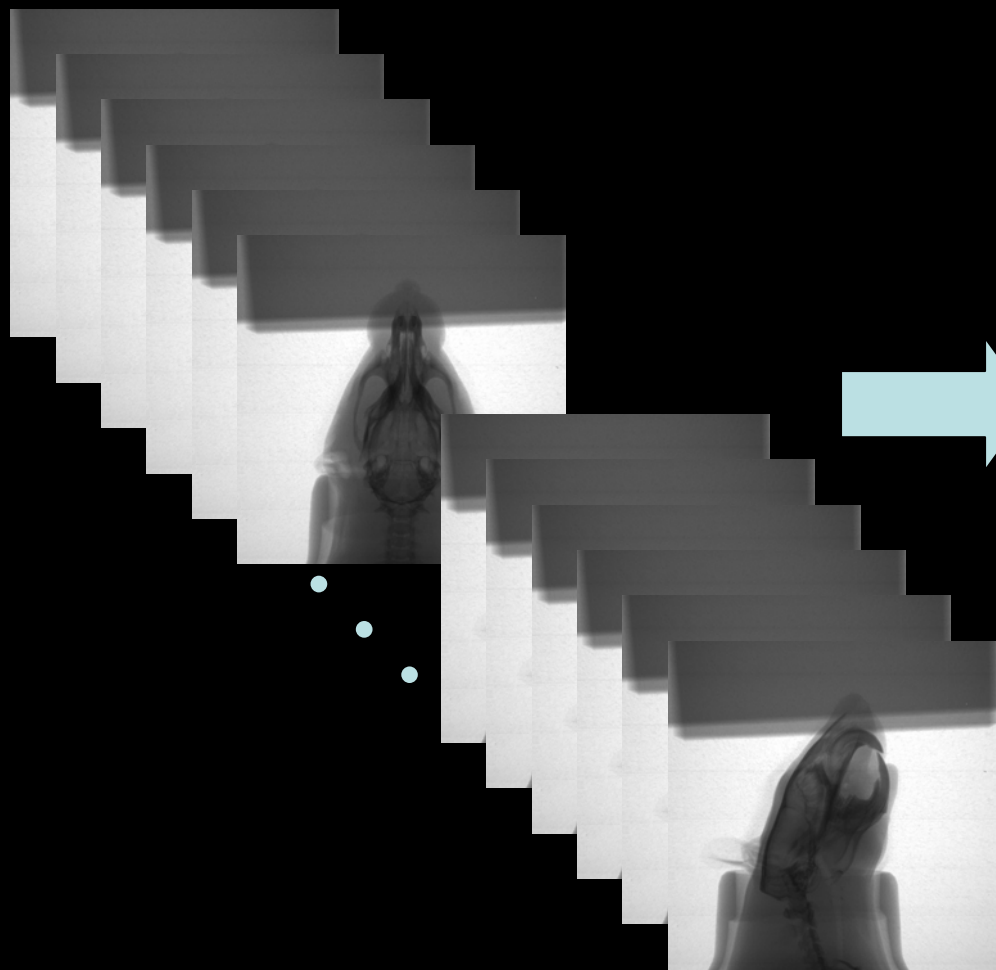
Source X
Idéalement monochromatique
 $I < 2\text{mA}$
 $T < 100\text{kV}$



Très petit point focal
 $\mu\text{foyer} (< 100\ \mu\text{m})$

Efficacité importante
Temps de lecture rapide

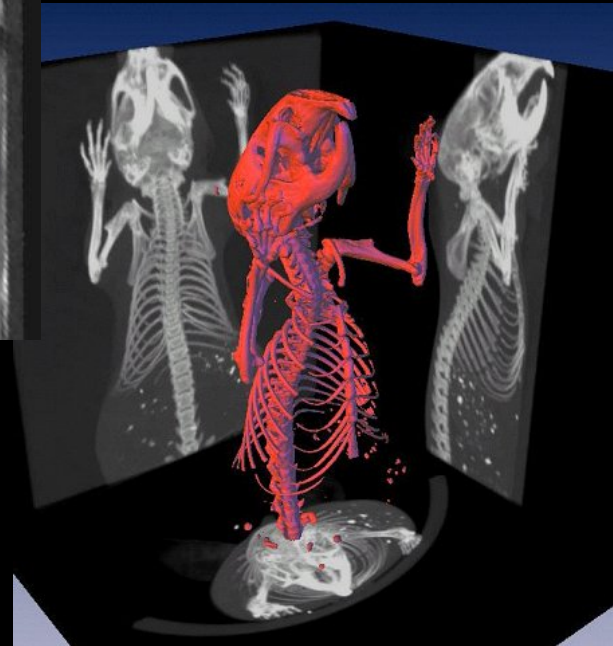
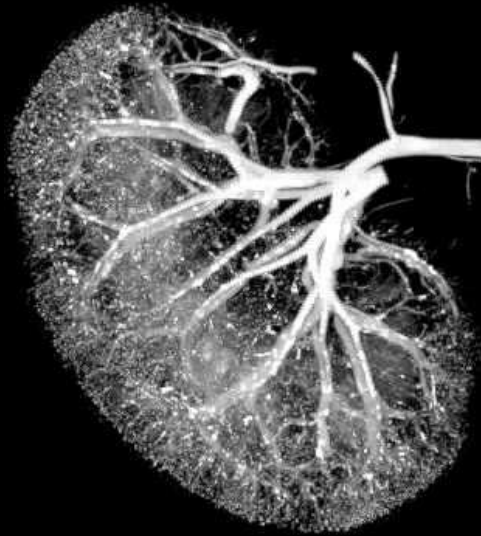




Quelques images



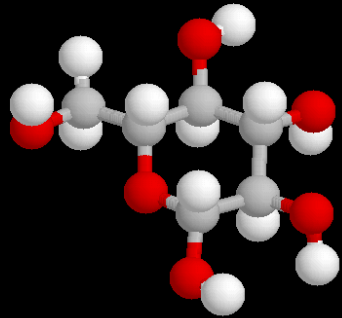
*Imtek:
microCAT*



GE: eXplore

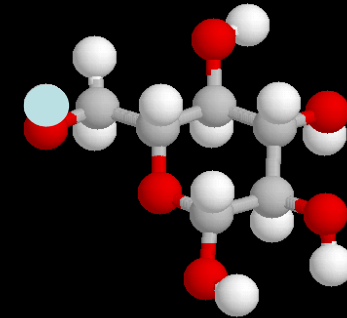
Imagerie d'émission: principe

Acte I



Traceur caractéristique d'une
fonction métabolique ou
physiologique

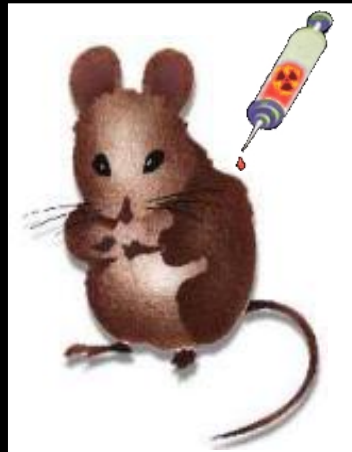
Acte II



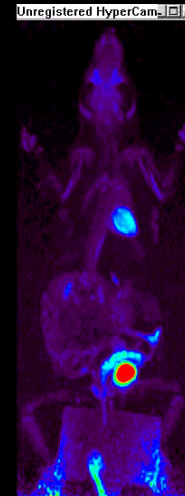
Marquage de la molécule

radiotraceur

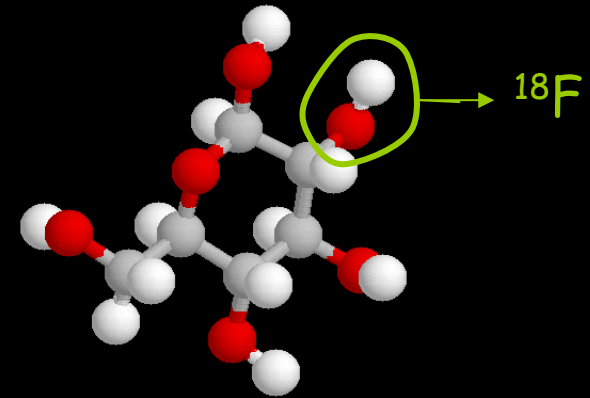
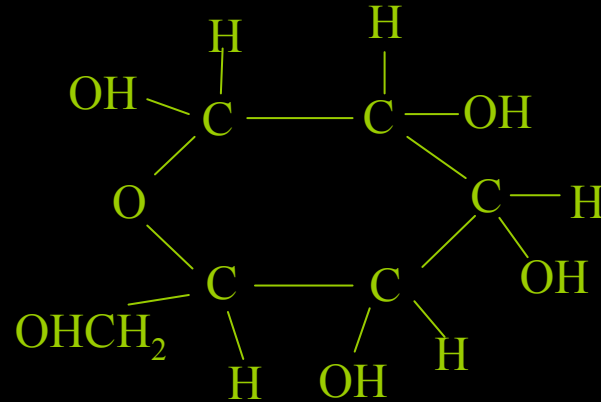
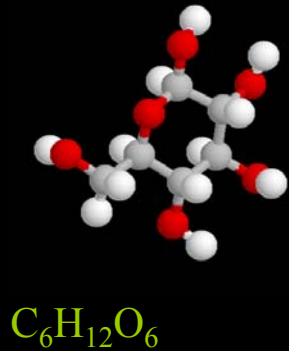
Acte III



Injection et étude
de la répartition de
la molécule marquée



Exemple du FDG



glucose

Phosphorylation
par l'enzyme hexokinase

Glucose-6-phosphate

Isomérisation
=
Réarrangement du groupe carbonyle

Fructose-6-phosphate

FDG

Phosphorylation
par l'enzyme hexokinase

FDG-6-phosphate

Par manque d'atome d'oxygène
sur le groupe carbonyle

Ce composé est bloqué au sein de la cellule et permet donc d'étudier la captation du glucose par les cellules.

Isotopes couramment utilisés

Isotope

Energie

Période

Emetteurs γ

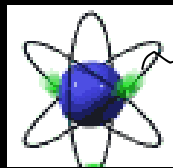
Technétium 99m	140 keV (89%)	6,02 heures
Iode 123	27 (71%) 159 keV (83%)	13,2 heures
Thallium 201	71 keV (47%)	73 heures

Emetteurs β^+

Oxygène 15	1738 keV	2,1 minutes
Carbone 11	960 keV	20,4 minutes
Fluor 18	634 keV	109,8 minutes
Brome 76	3980 keV	972 minutes

Technique d'imagerie associée

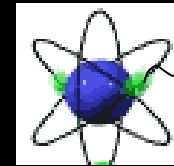
Emetteurs γ



γ

Tomographie par
émission monophotonique
(TEMP)

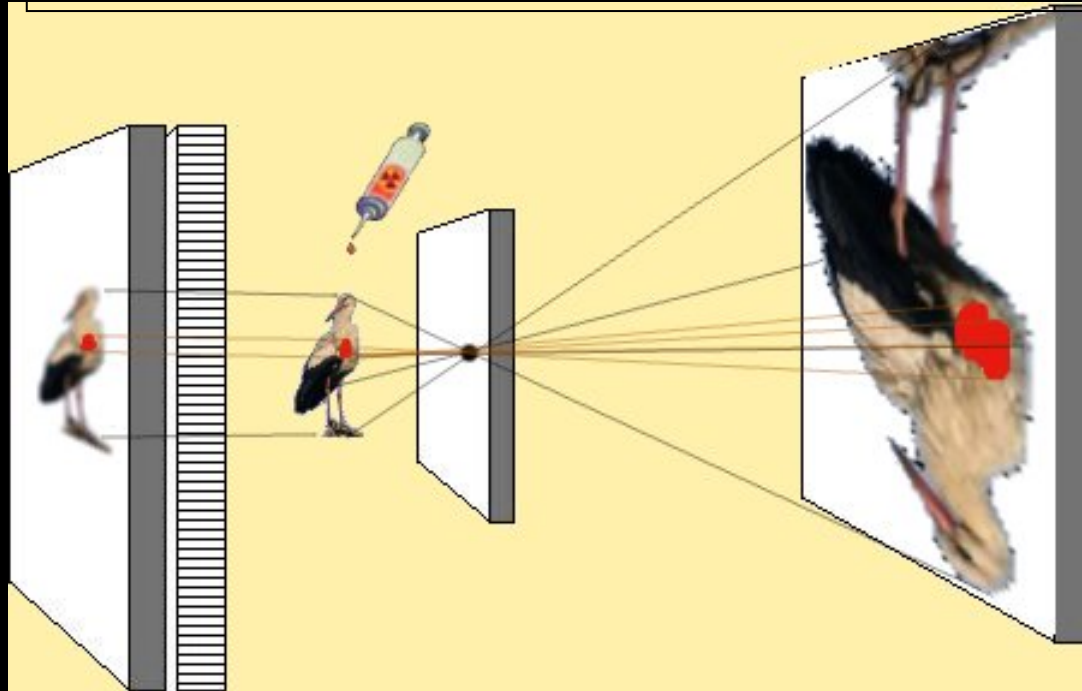
Emetteurs β^+



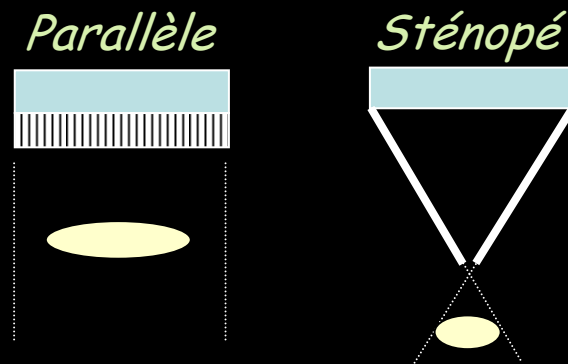
β^+

Tomographie par
émission de positons
(TEP)

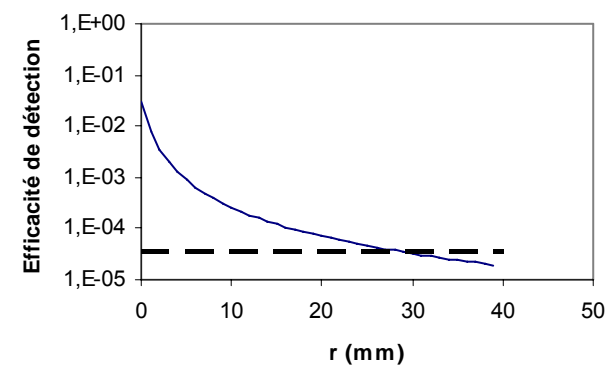
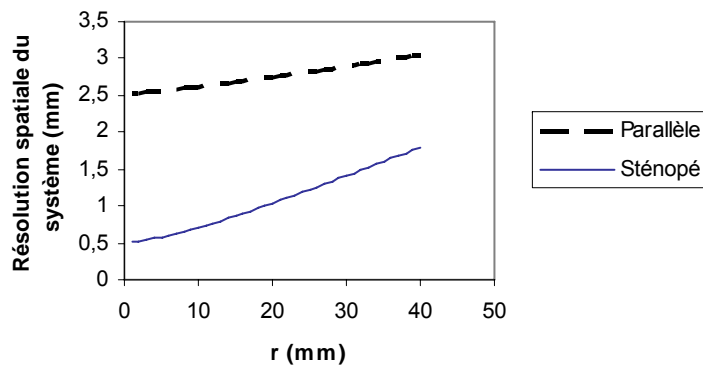
Principe de la TEMP

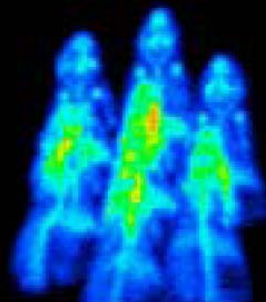
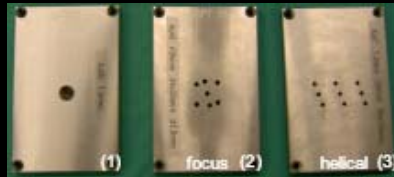


Injection du radiotracteur
Emission isotrope
1ère étape:
Sélection du rayonnement

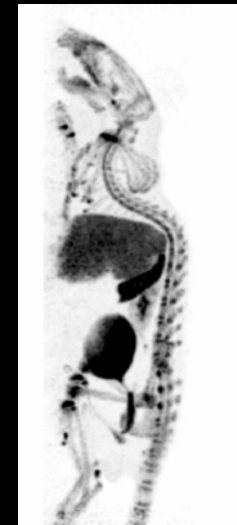
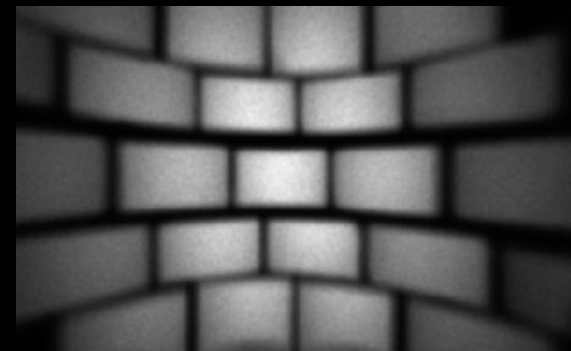
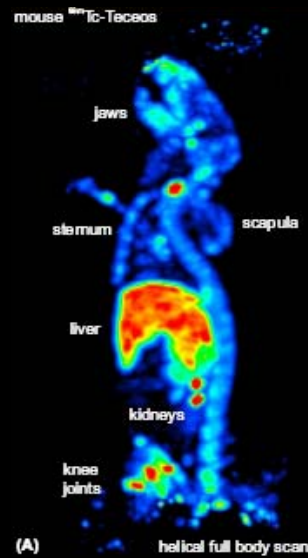


$$R_i = 2,3 \text{ mm}$$



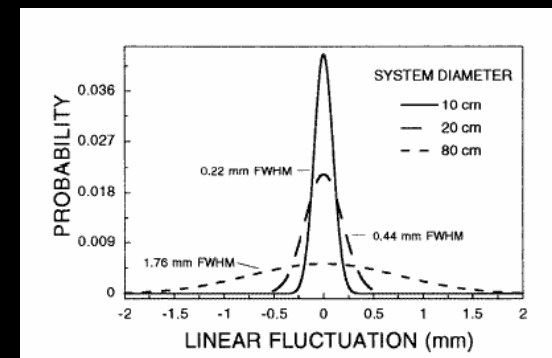
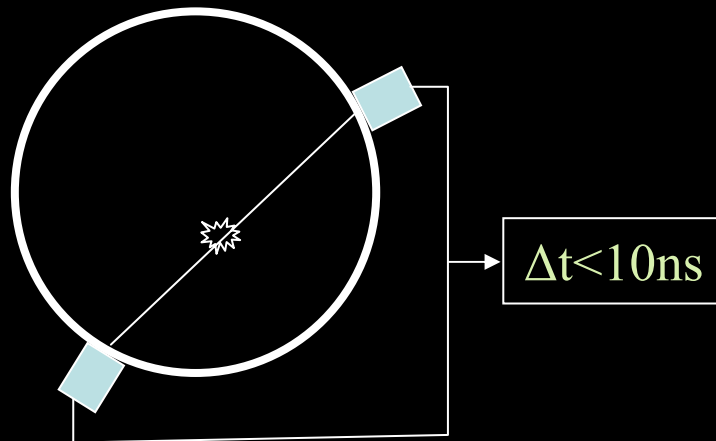
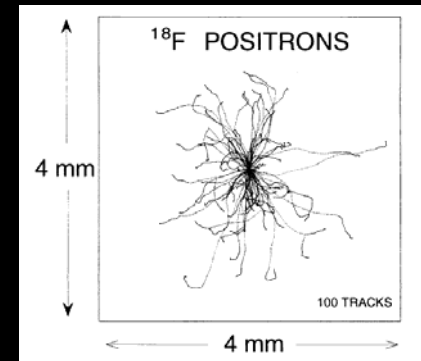
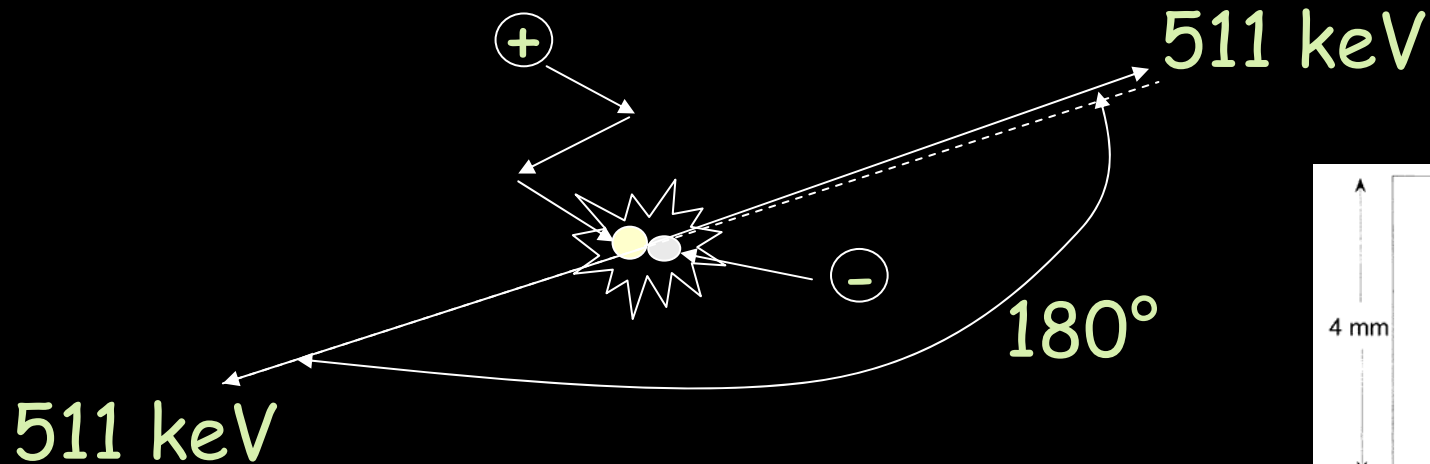


NanoSPECT @ Bioscan

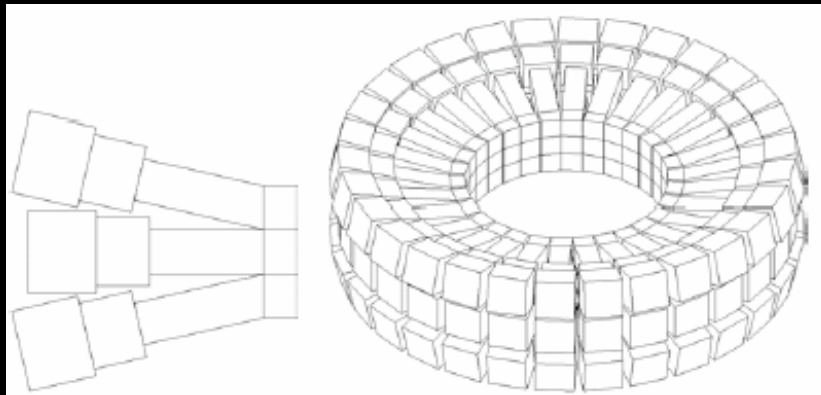


U-SPECT @ MILabs

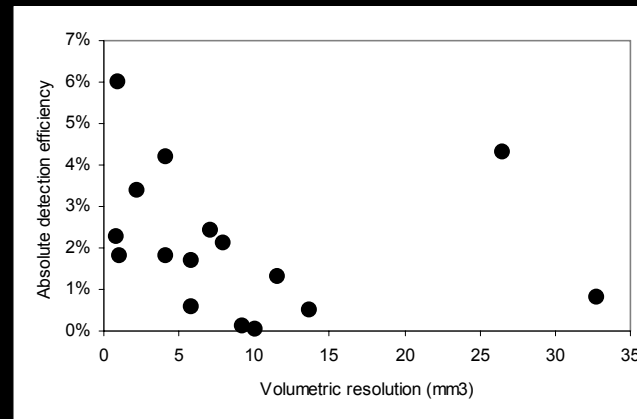
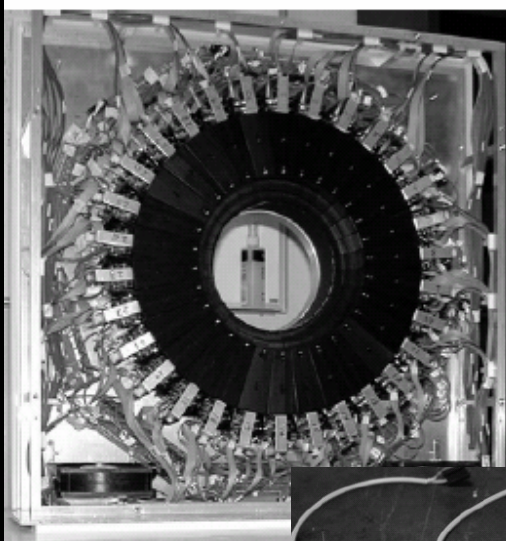
Principe de la TEP



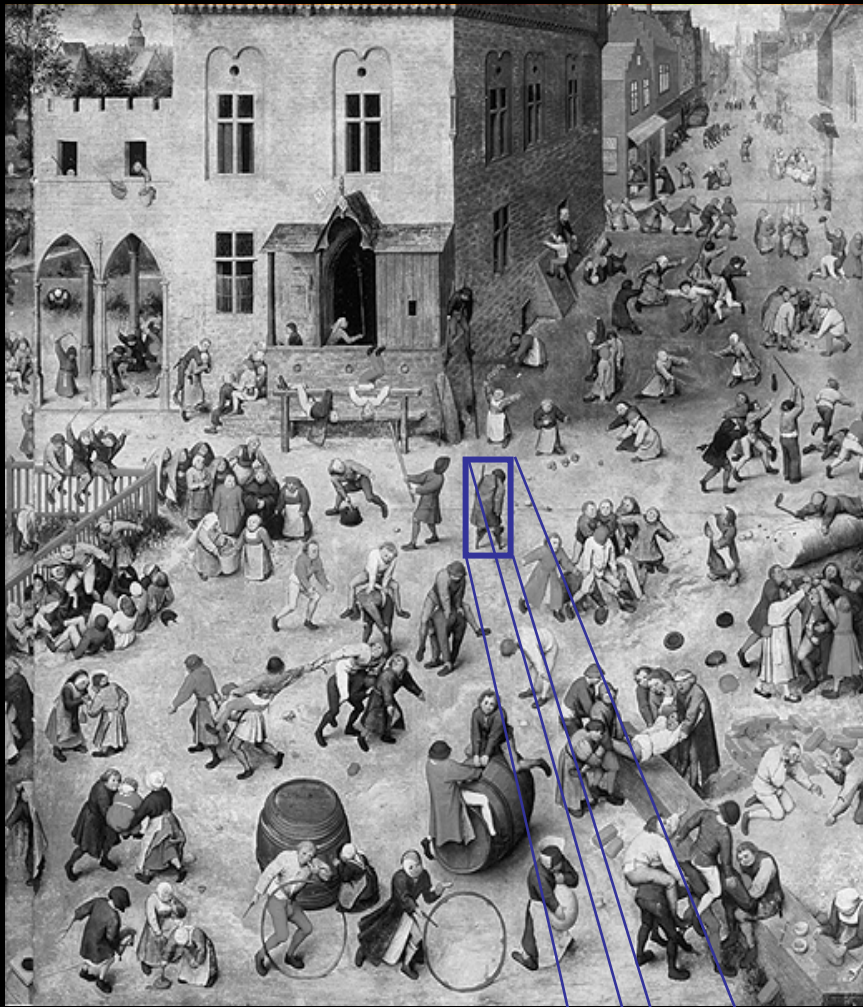
Exemple de microTEP: microPET II @ UCLA



Diamètre du détecteur: 160 mm
 Diamètre FOV: 80 mm
 FOV axial: 49 mm (3D)
 Type: 90 modules (3 couronnes) de 14 x 14 cristaux
 Cristal: LSO
 Photo détecteur : MA-PMT
 Taille du cristal: 0,975 x 0,975 x 12,5 mm³
 Efficacité absolue: 2,26 % (> 250 keV)
 Résolution tr (@centre): 0,83 mm
 Résolution axiale: 1,25 mm

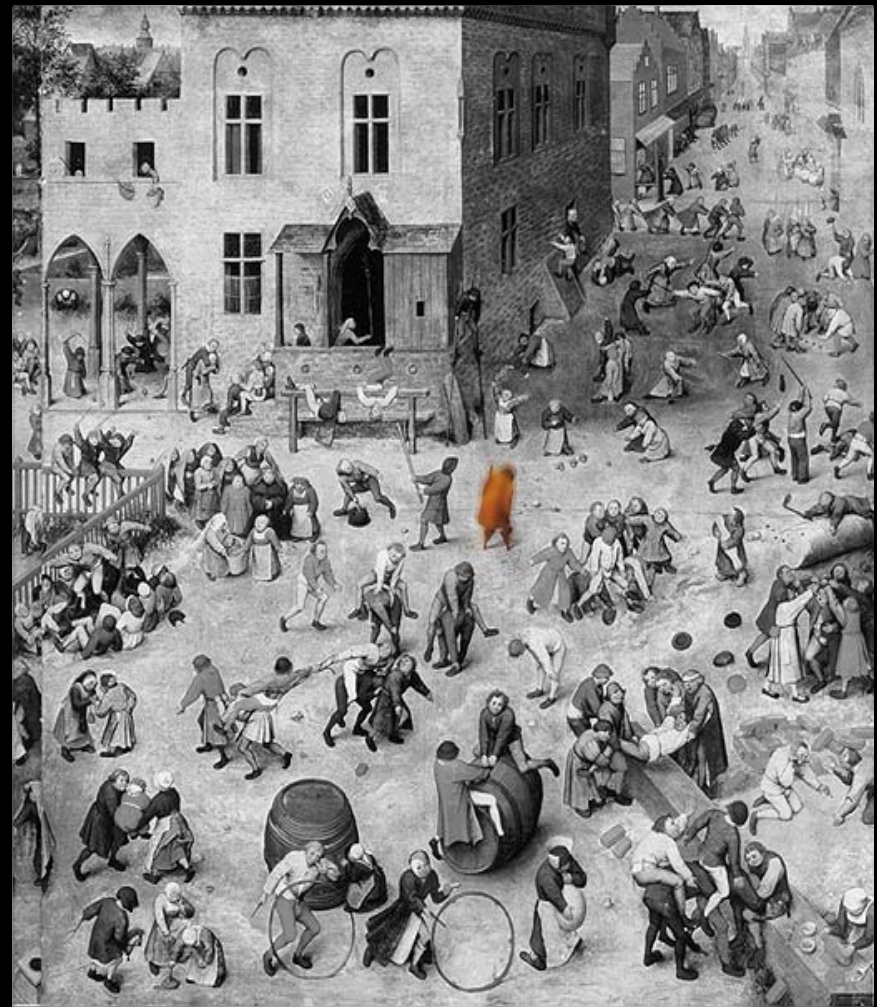


Crump institute

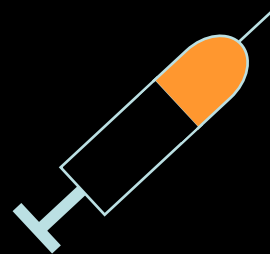


P. Brueghel

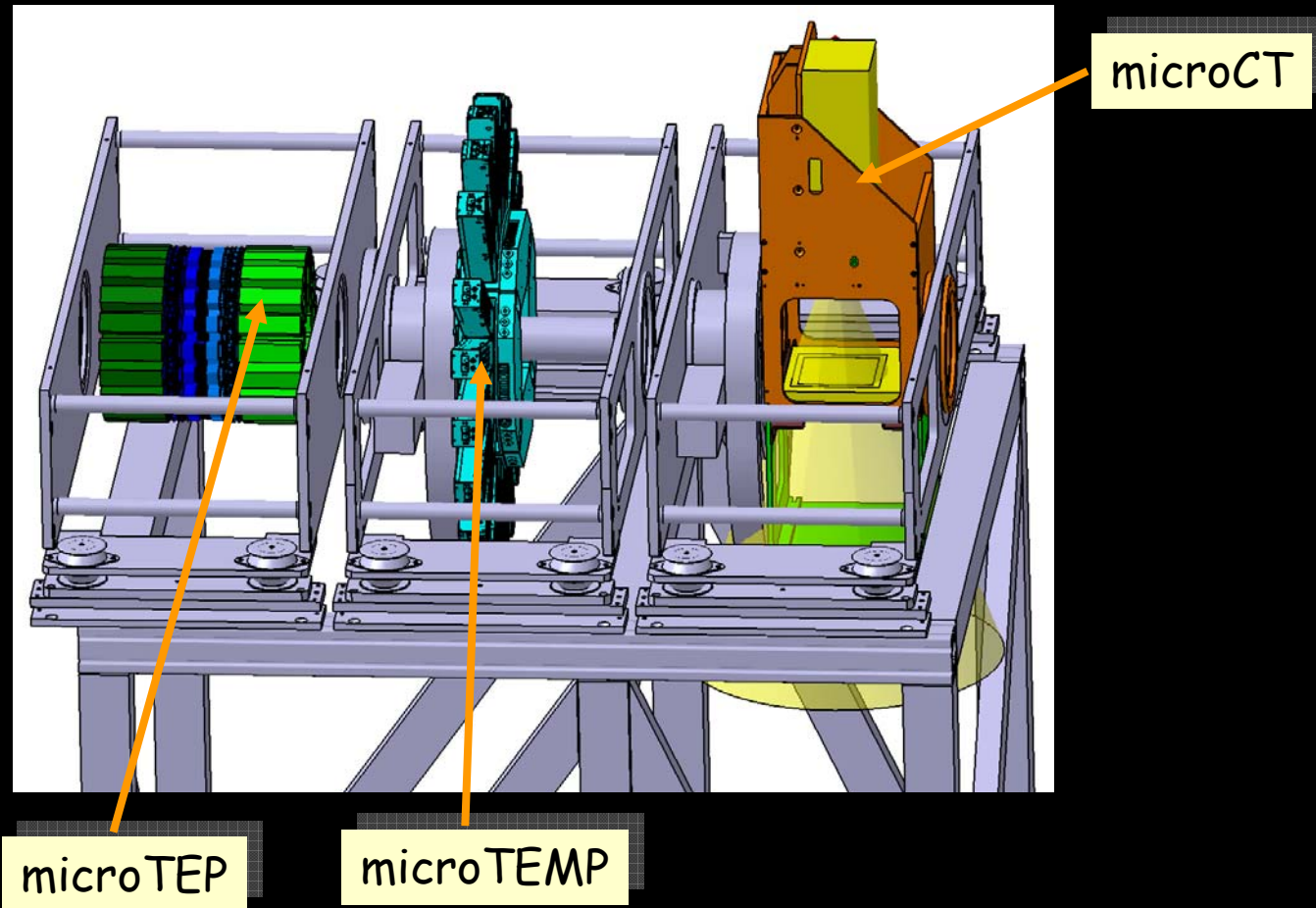
Anatomie

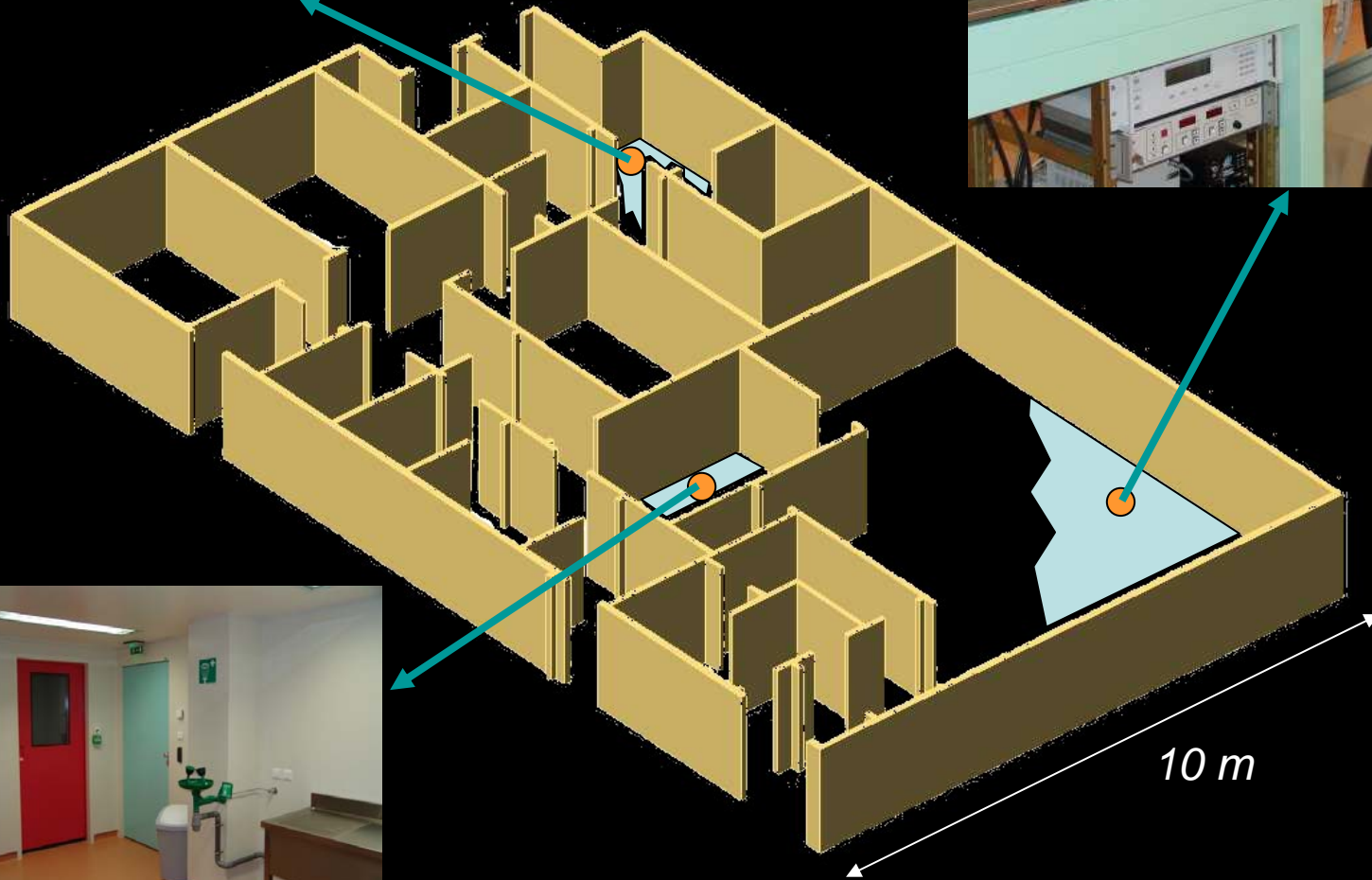
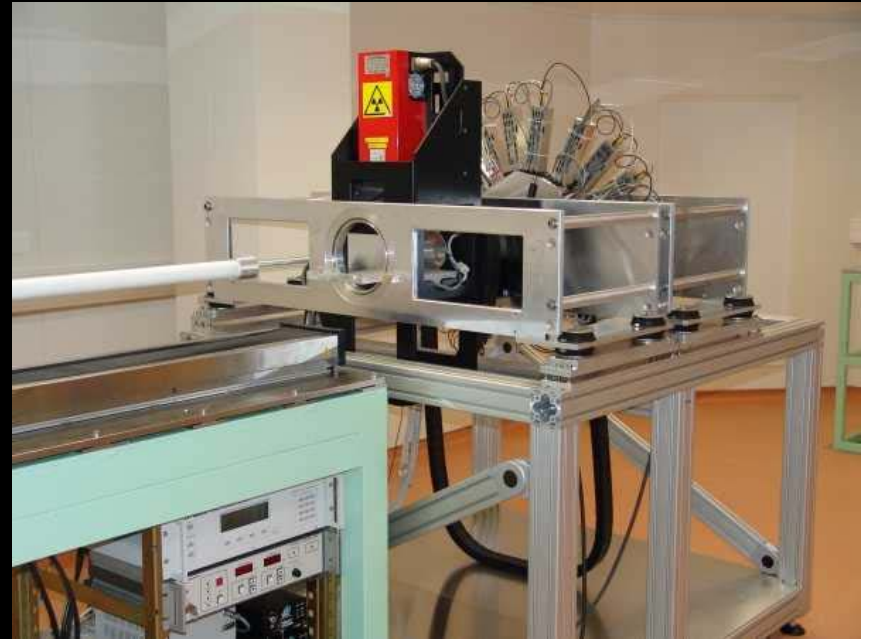


Fonction



A Multimodality Imaging System for Small Animal





Physiologie de l'animal

Rythme respiratoire

Ventilations pulmonaire par minute

Souris

136 à 216

Rat

66 à 114

Rythme cardiaque

Pulsations par minute

520 à 780

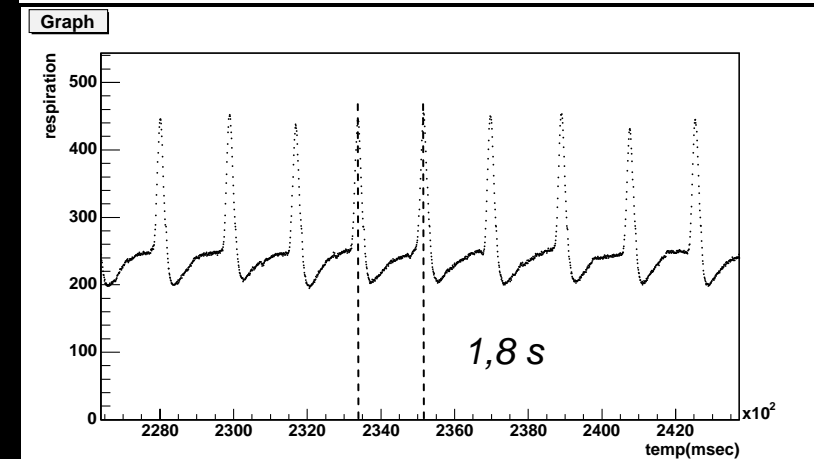
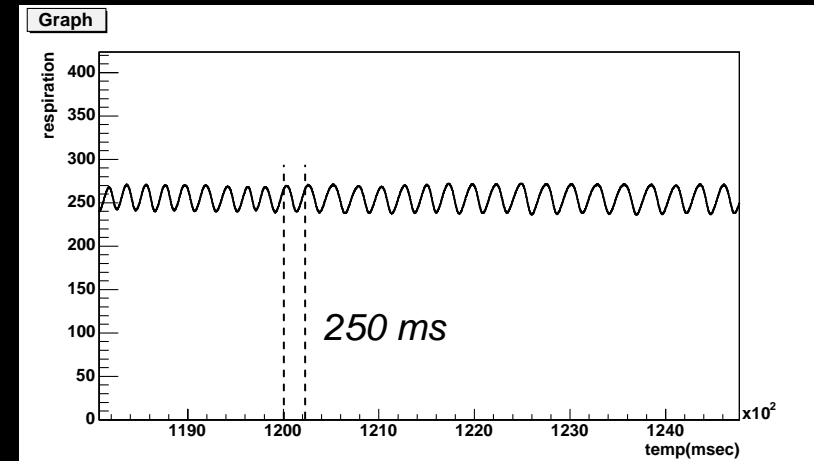
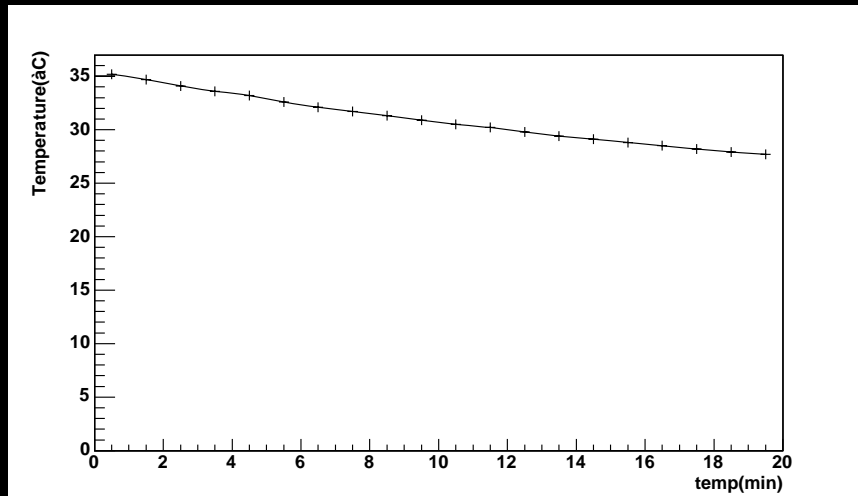
270 à 350

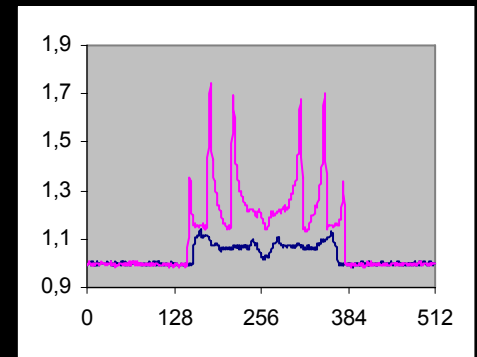
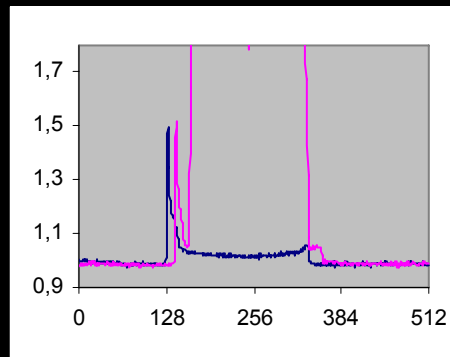
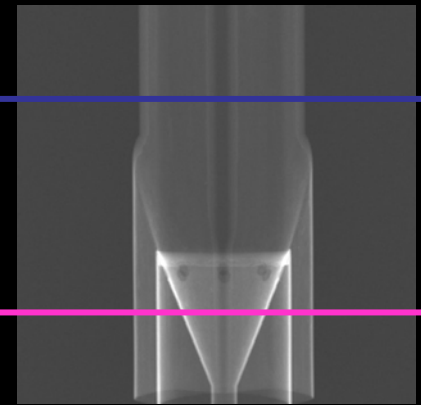
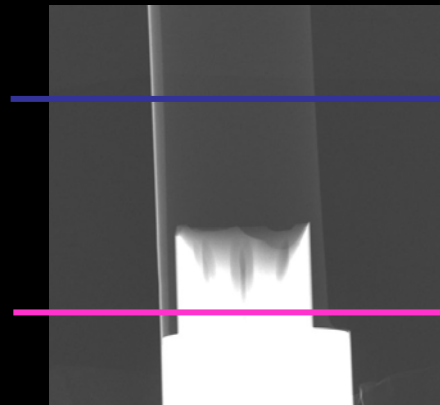
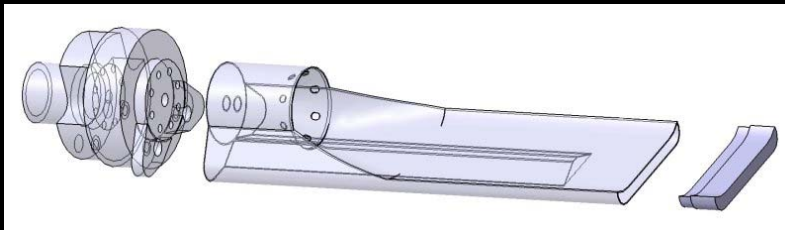
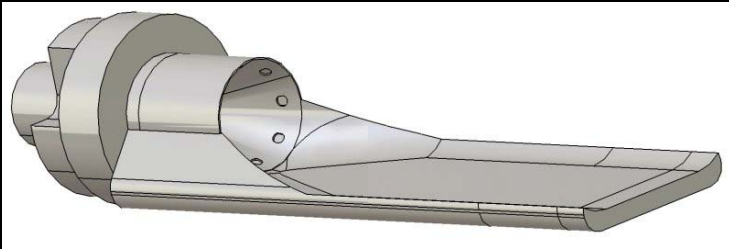
Volume sanguin

(70 ml/kg)

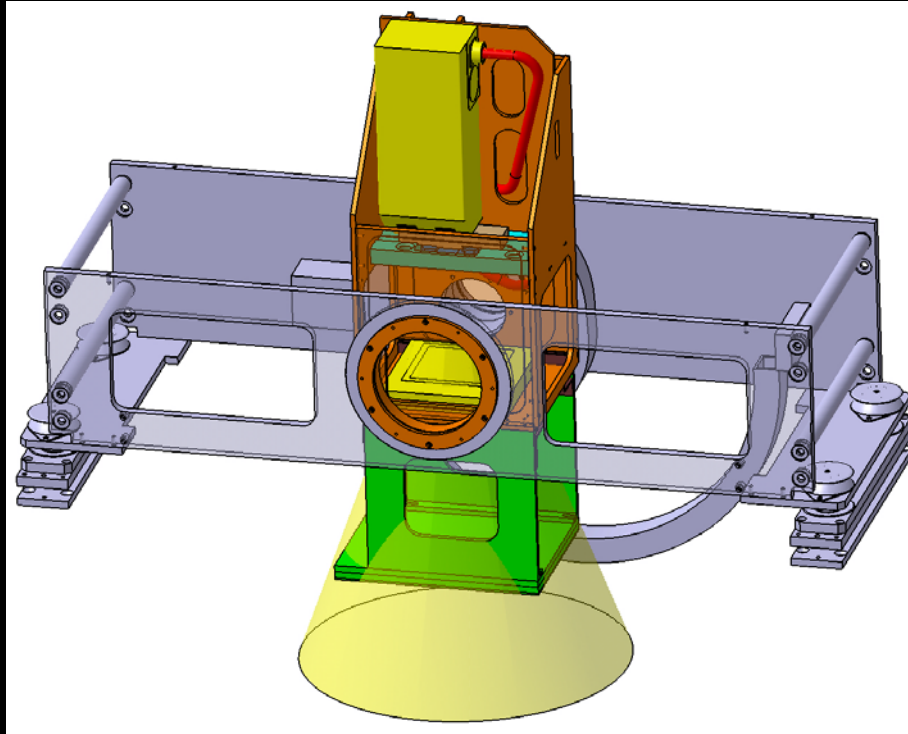
~1,4 ml

~20 ml





Micro Tomodensitomètre X

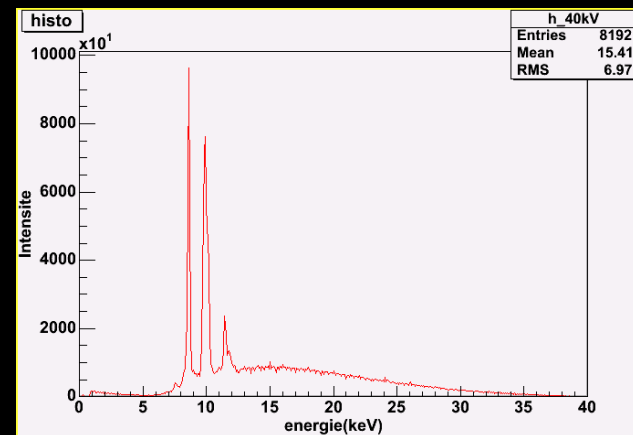


Composants du microCT: Source X

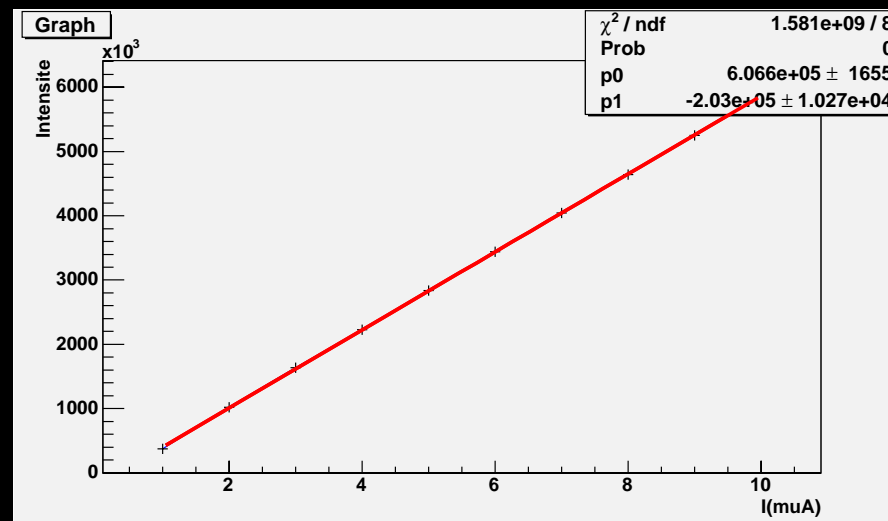
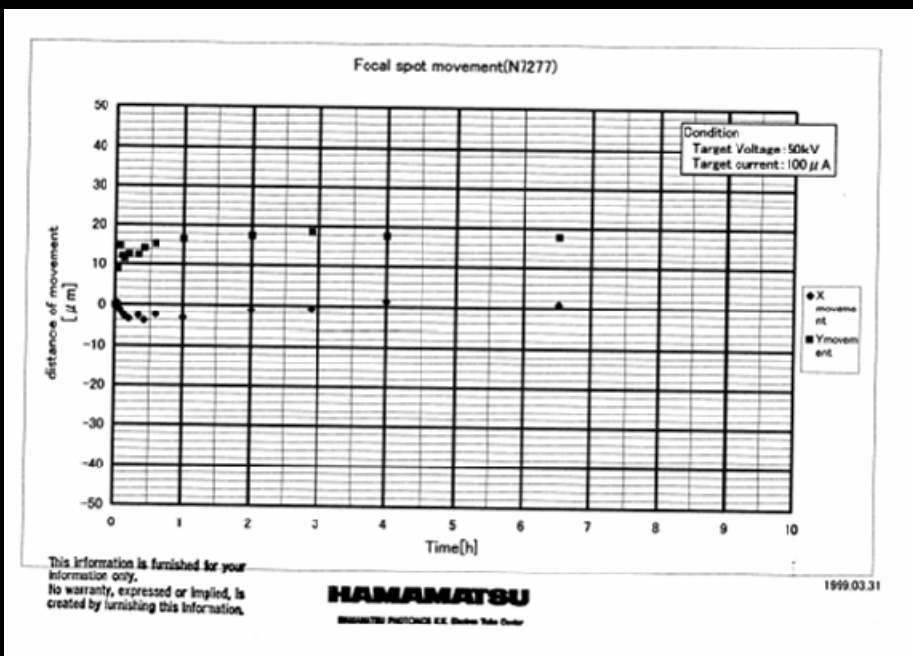


Hamamatsu, L8601-01

Micro foyer X ($7\mu\text{m}$)
 Voltage: 20 à 90 kV
 Intensité: 0 à 250 μA
 P_{max} : 10 W
 Ouverture: 39°
 Fonctionne en continu
 Anode: Tungstène



Travaux effectués en collaboration avec le groupe RAMSES (IReS, Strasbourg)

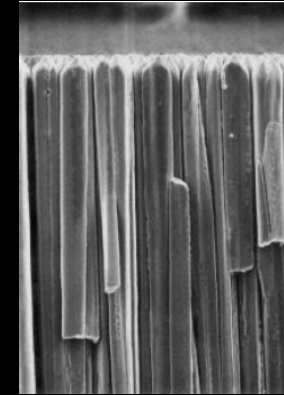
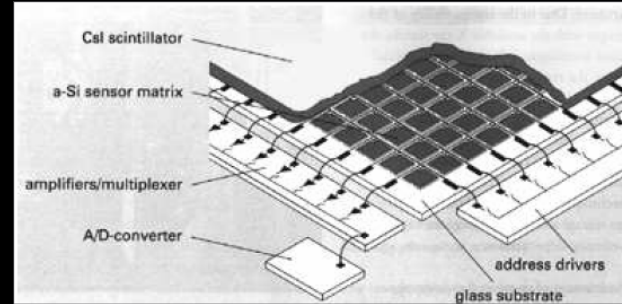


Composants du microCT: Détecteur

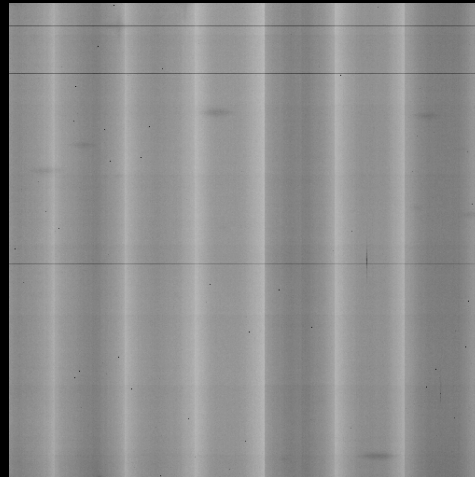


Hamamatsu, C7942

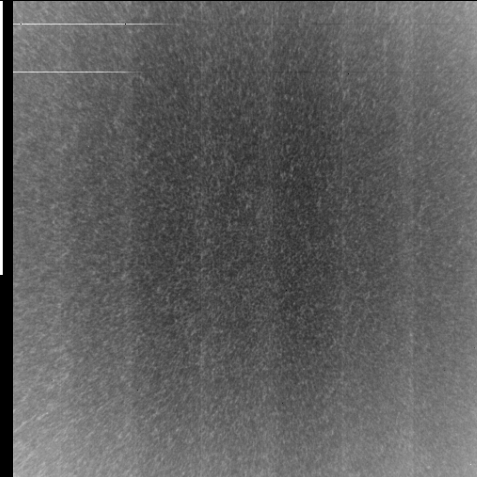
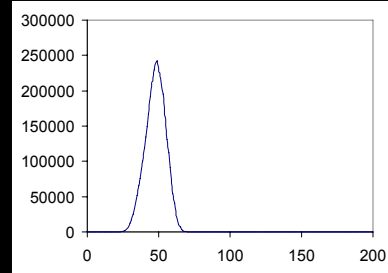
CsI / photodiode
120 x 120 mm²
2400 x 2400 pixels
Pixel de 50µm
470ms/projection
Mode binning:
2x2 (4 images/s)
4x4 (9 images/s)



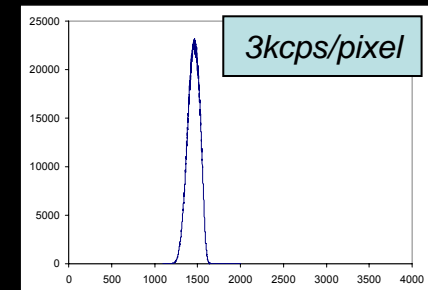
Aiguille de CsI



Bruit électronique



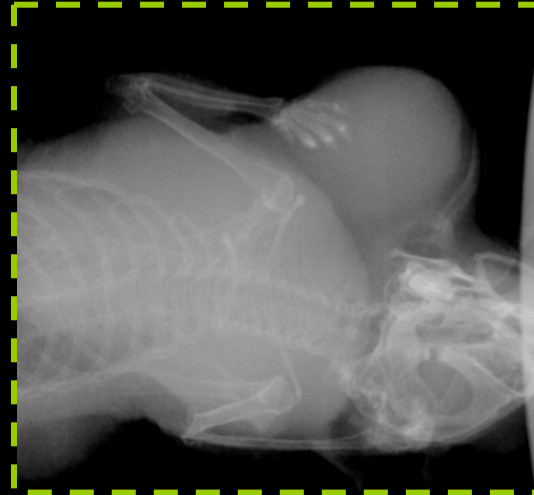
Plein flux (40kV, 250µA, 0,5mm Al, 470ms)



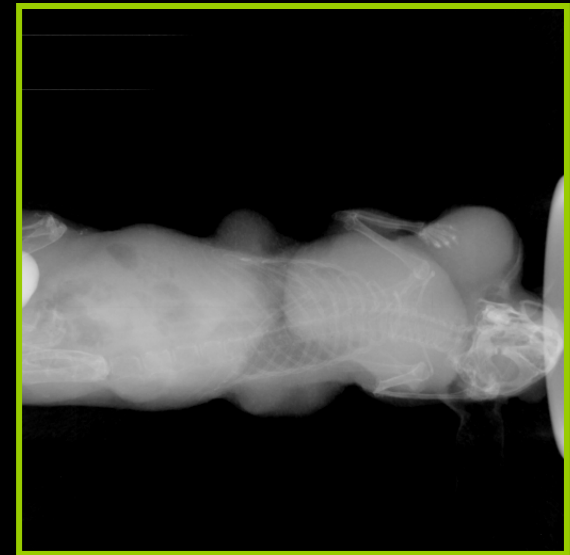
Exemple de binning



2048x2048, 50 μ m, 470ms



1024x1024, 100 μ m, 250ms

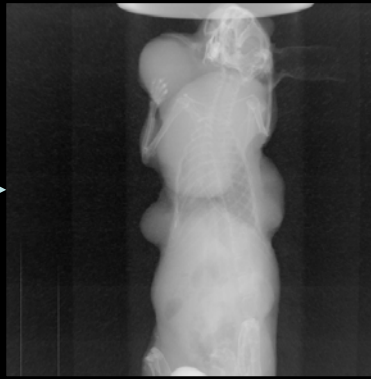


512x512, 200 μ m, 110ms

Acquisition et Reconstruction en ligne

470 ms

Acquisition



X-ray detector

12 bits

FPGA

64 bits

CPU

64 bits

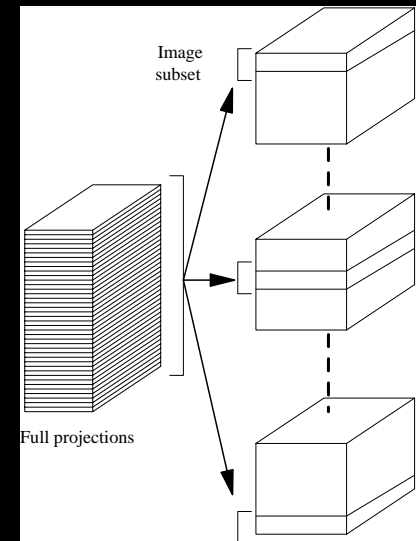
First PC

470 ms

$$R_{\beta}(p, \xi) = \ln \left(\frac{I_0(p, \xi) - I_D(p, \xi)}{I(p, \xi) - I_D(p, \xi)} \right)$$

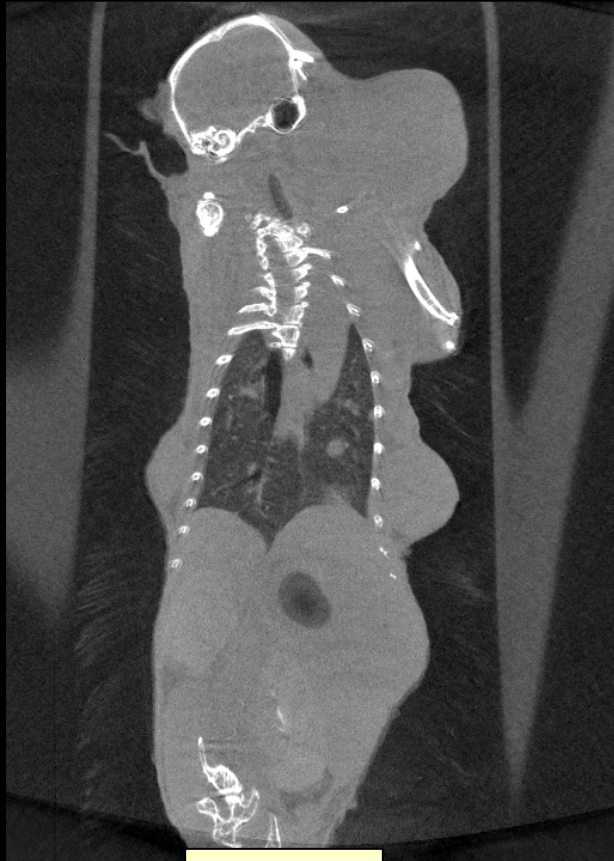
$$Q_{\beta}(p, \xi) = \frac{D_{SO}}{\sqrt{D_{SO}^2 + p^2 + \xi^2}} R_{\beta}(p, \xi) * \frac{1}{2} h(p)$$

$$f(x, y, z) = \int_0^{2\pi} \frac{D_{SO}^2}{(D_{SO} + x \sin \beta - y \cos \beta)^2} \cdot Q_{\beta} \left(\frac{D_{SO} x \cos \beta + D_{SO} y \sin \beta}{D_{SO} + x \sin \beta - y \cos \beta}, \frac{D_{SO} z}{D_{SO} + x \sin \beta - y \cos \beta} \right) d\beta$$

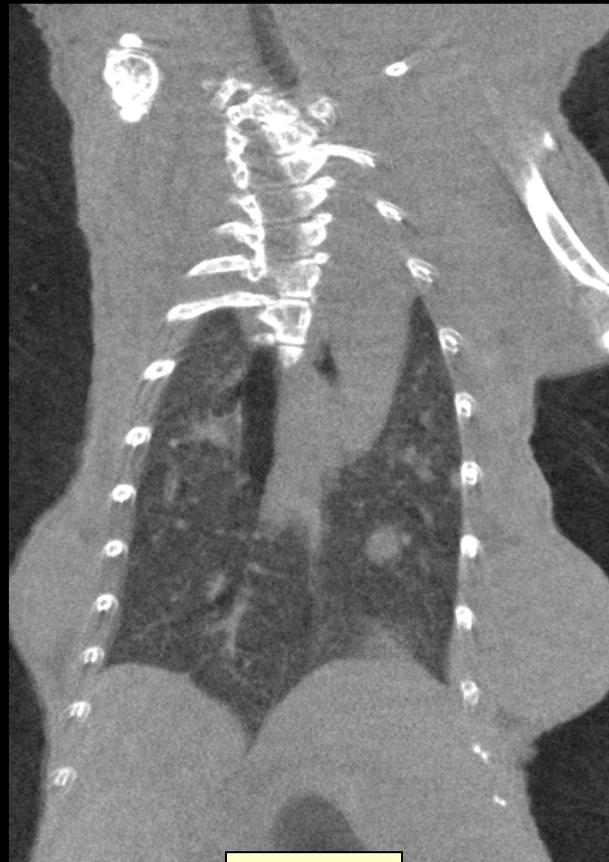


Taille du voxel de l'image

40kVp, 250 μ A, 0,5 mm Al, 470 ms



100 μ m



50 μ m



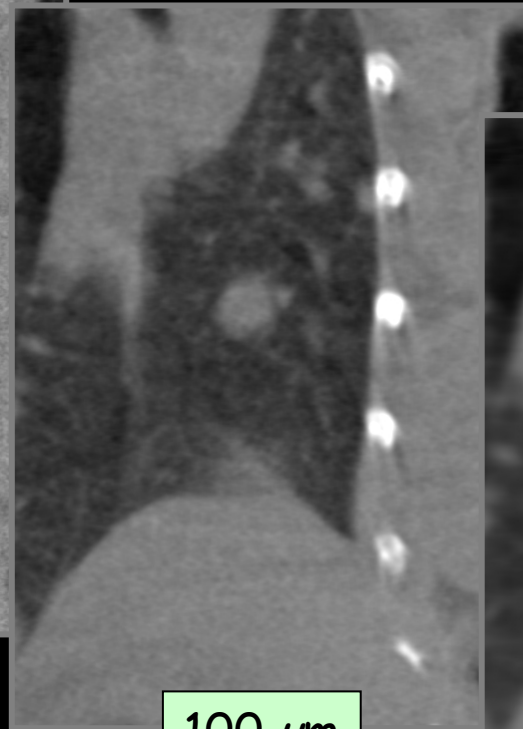
25 μ m

Temps de reconstruction identique

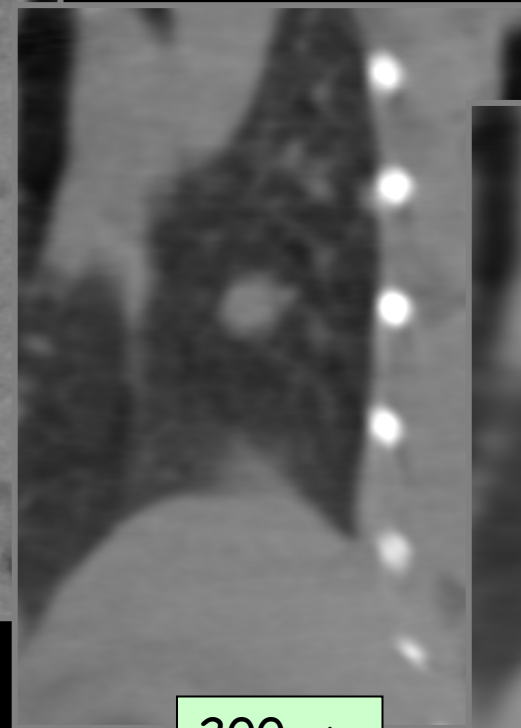
Taille du pixel de projection



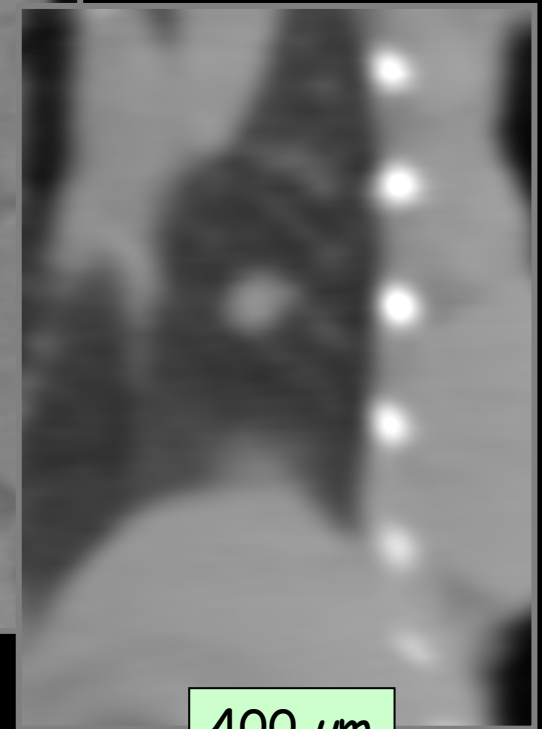
50 μm



100 μm



200 μm

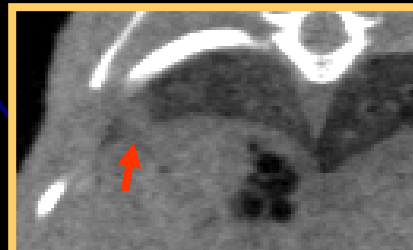
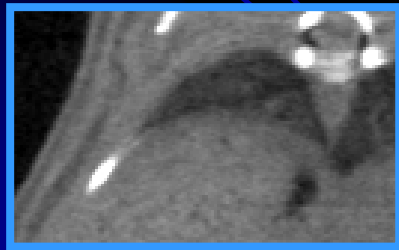


400 μm

Modèle murin du cancer du sein

11 Juillet 2005

12 Août 2005



Injection de cellules cancéreuses

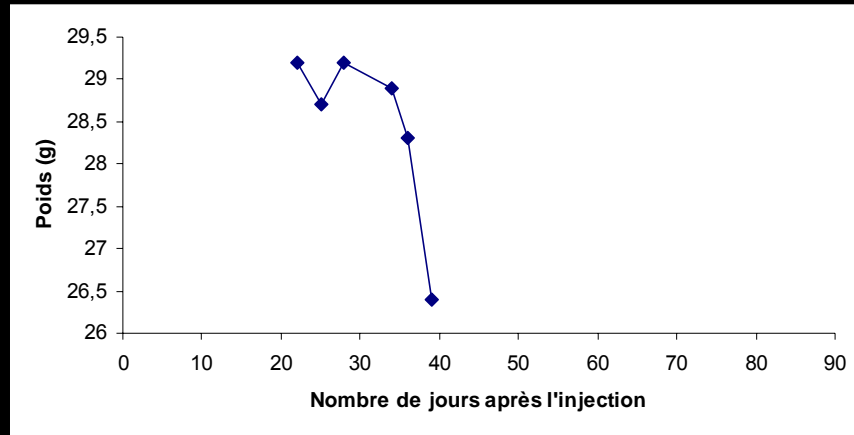
Souris normales

Déficiance en stromélysine-3

Développement de métastases

Influence de la stromélysine-3

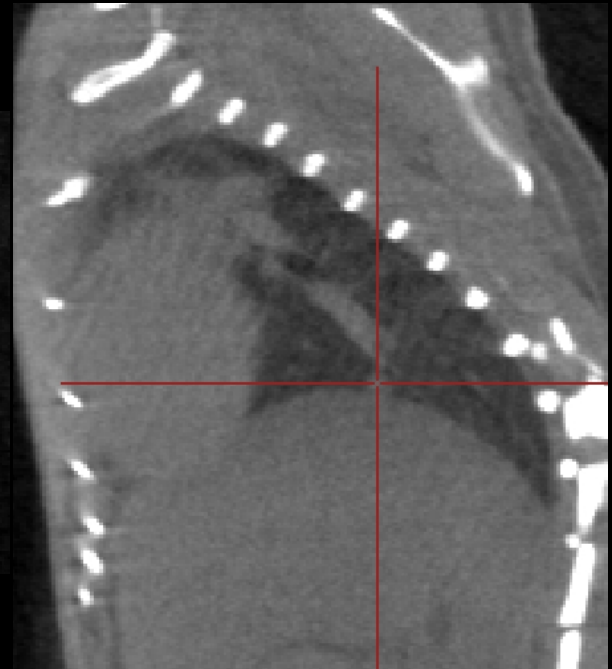
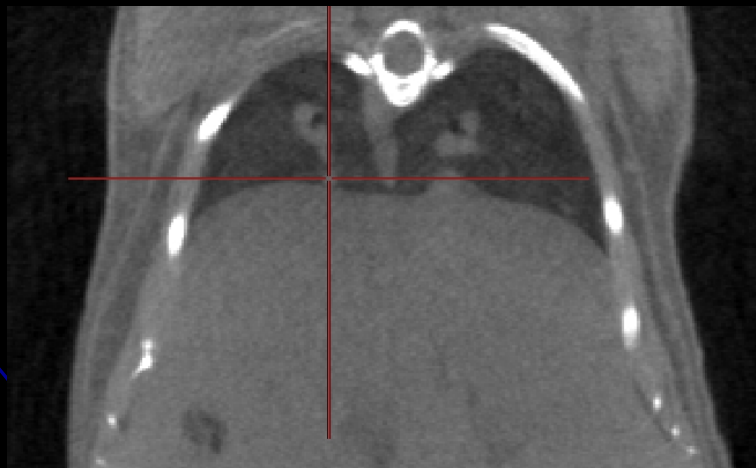
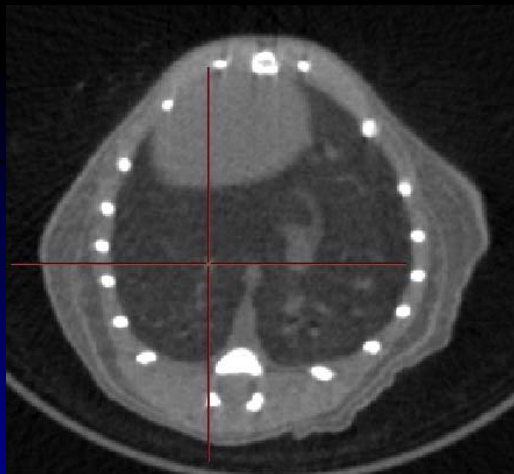
Modèle murin du cancer du sein



07/04 (+22) : RAS

13/04 (+28) : RAS

19/04 (+34) :



T28: RAS



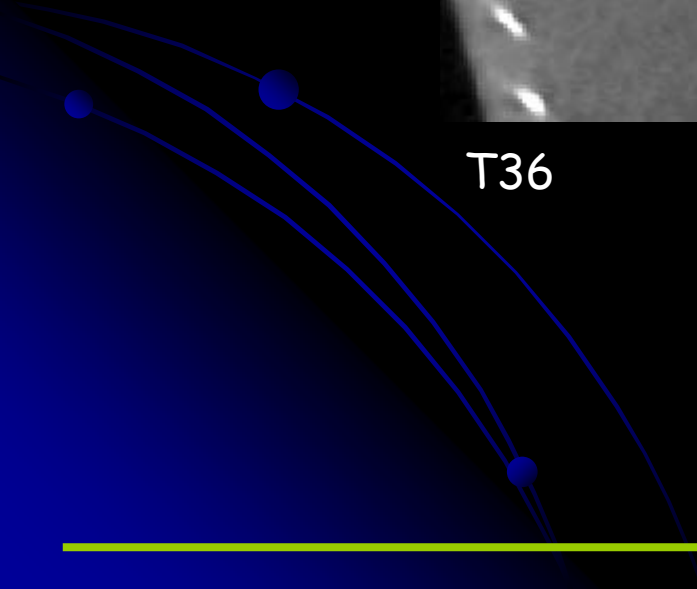
T34

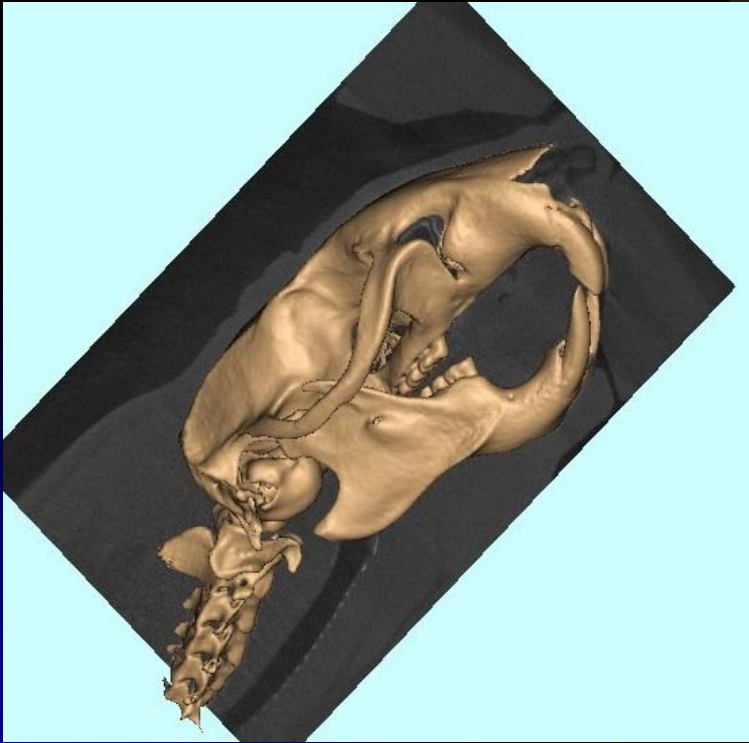
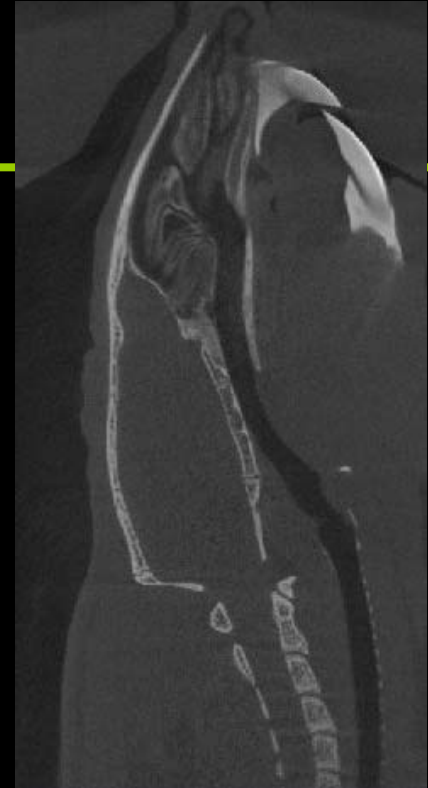
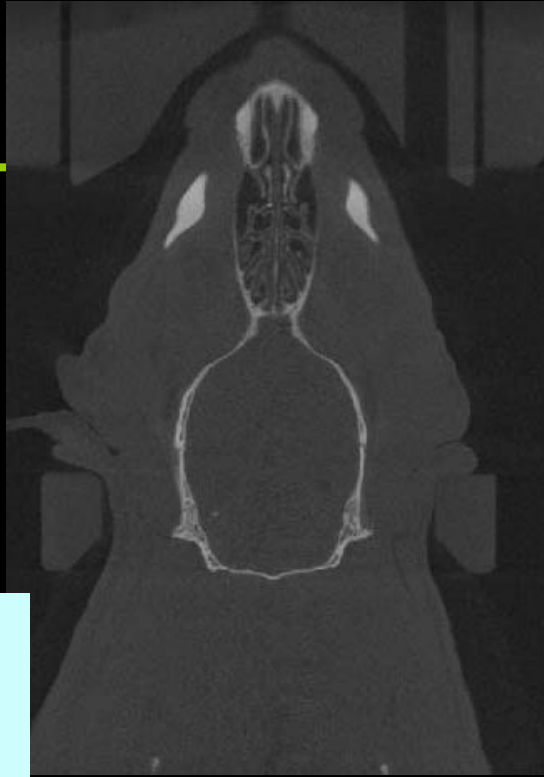


T36

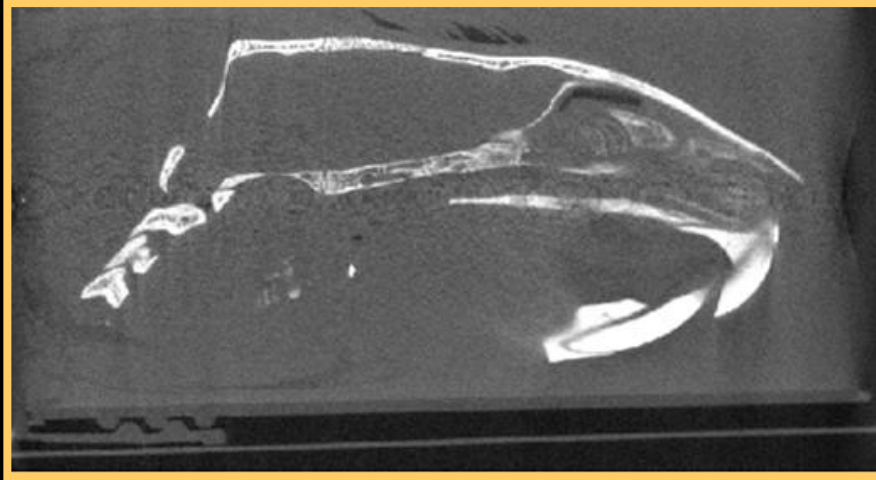


T39



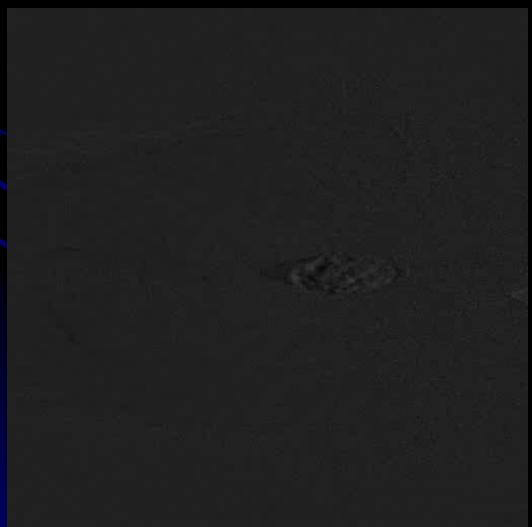
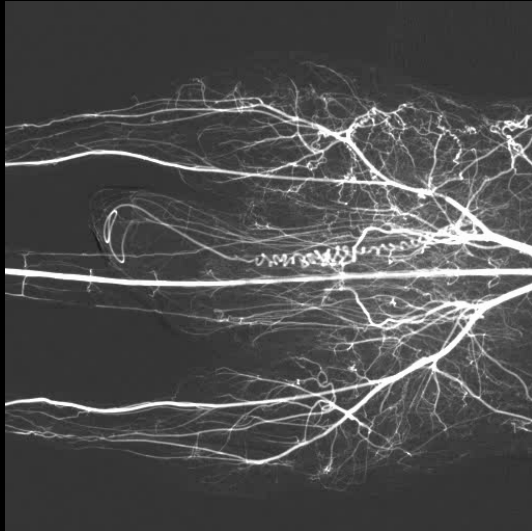


Produit de contraste

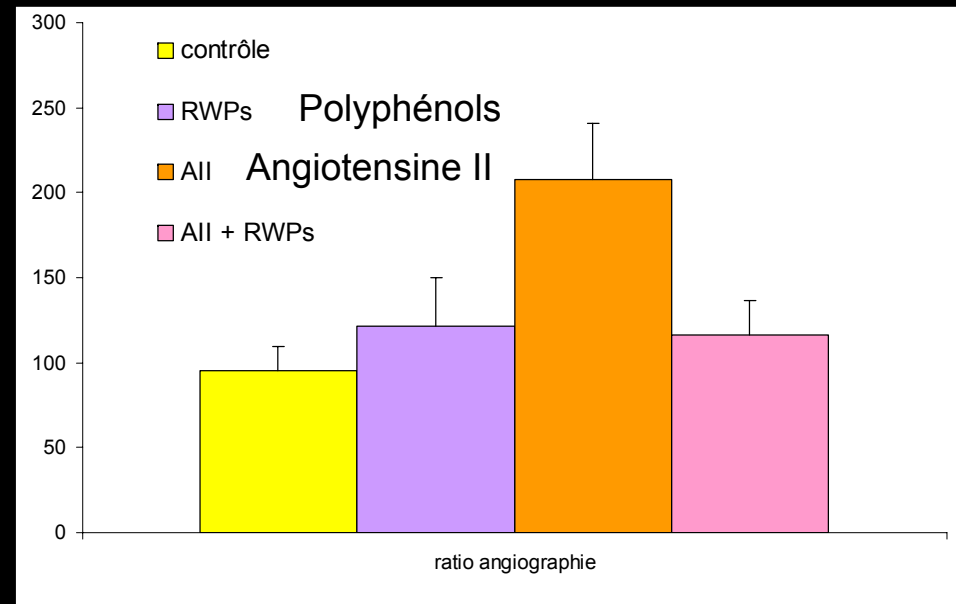


Produit de contraste Argenté

Étude de l'angiogénèse



Ligature de l'artère fémorale chez le rat
Injection d'un produit de contraste



Travaux réalisés en collaboration avec la Faculté de Pharmacie de Strasbourg (N Etienne)

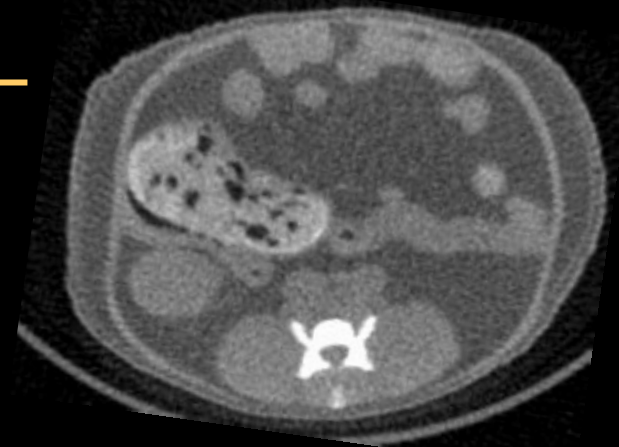
Cinétique 3D



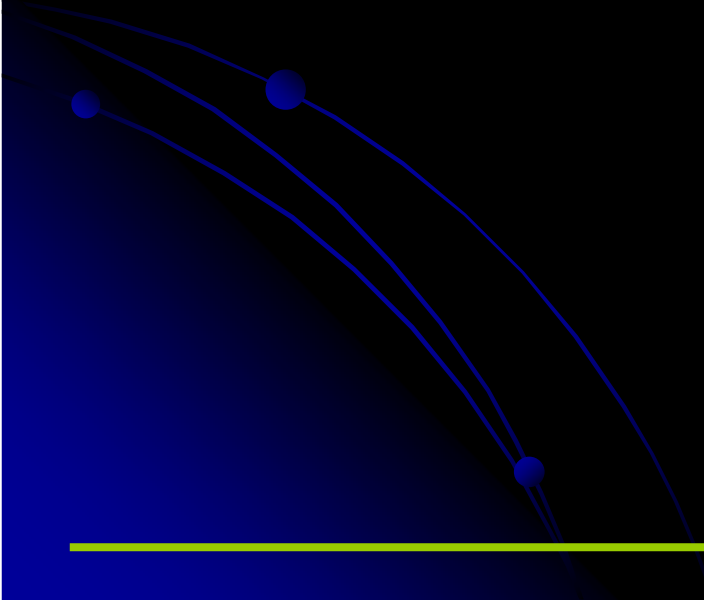
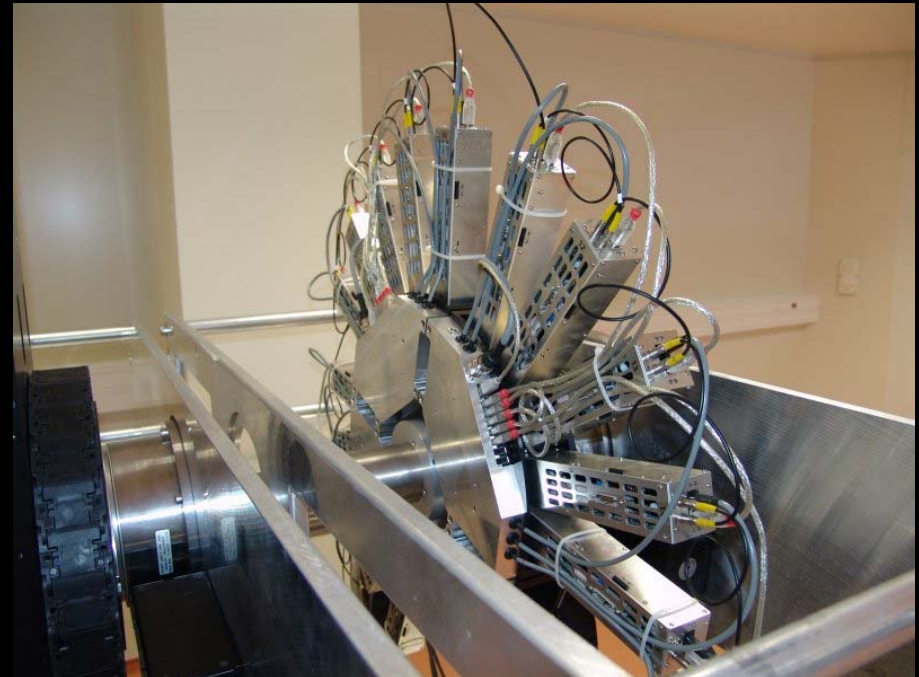
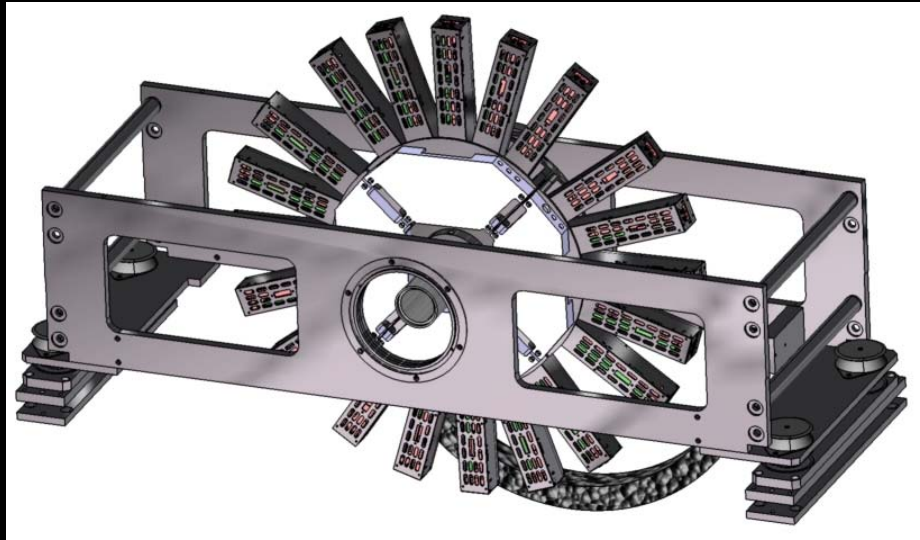
6 minutes



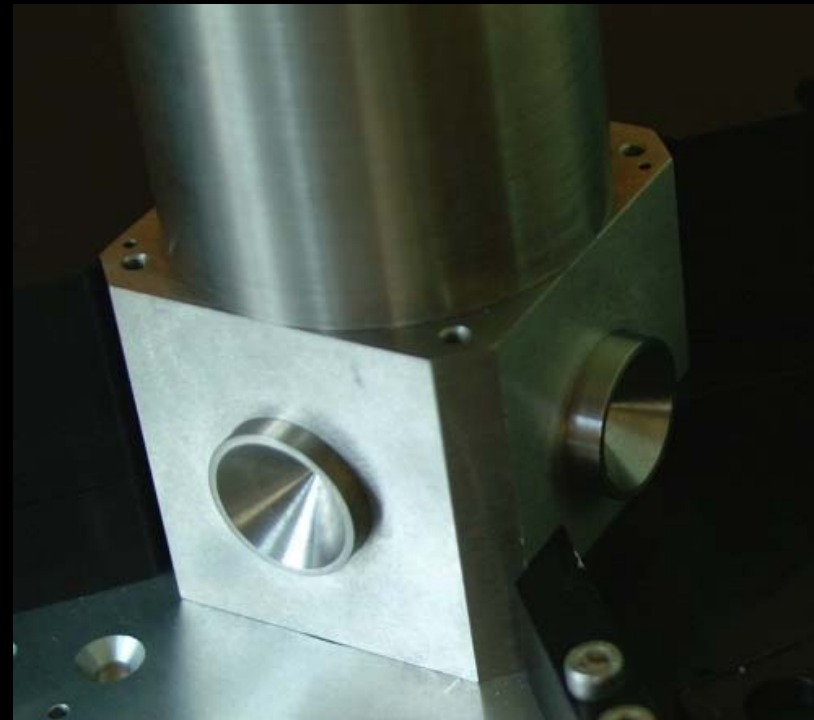
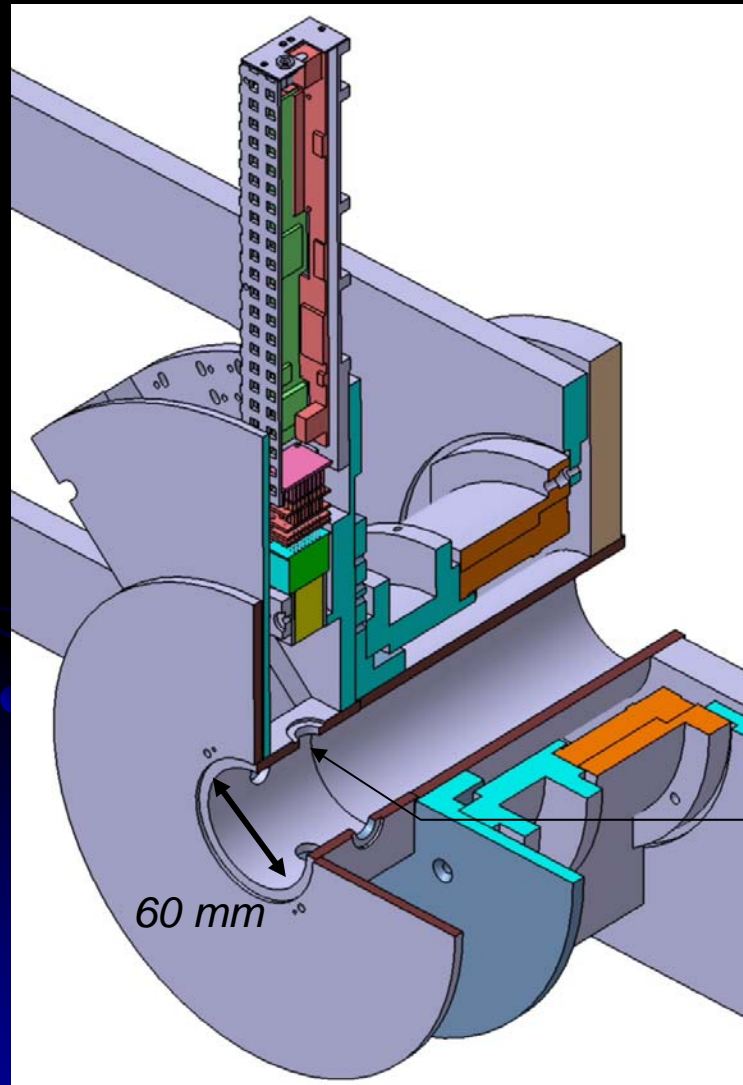
42 secondes



micro Tomographie d'Emission MonoPhotonique



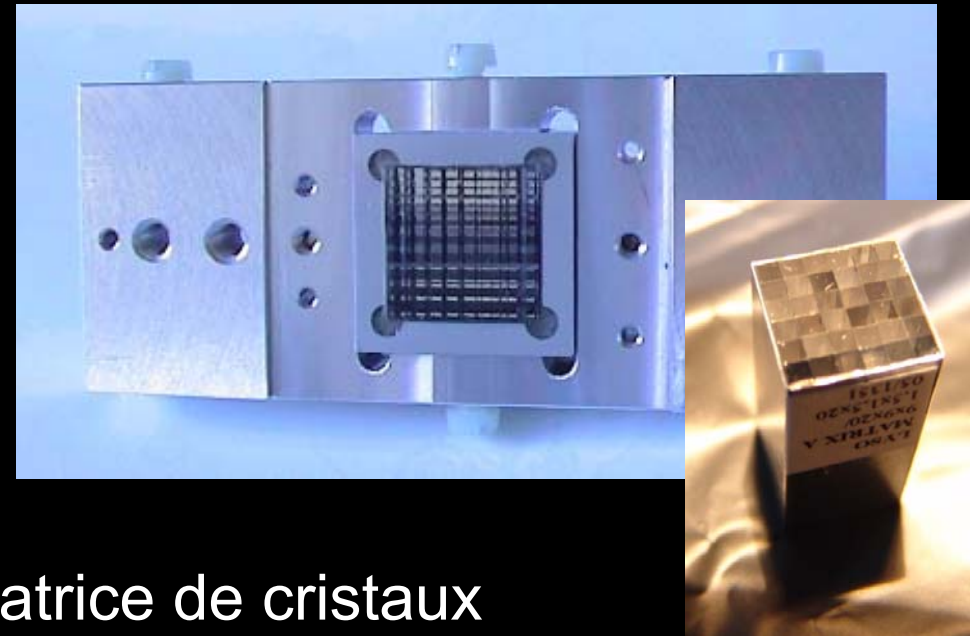
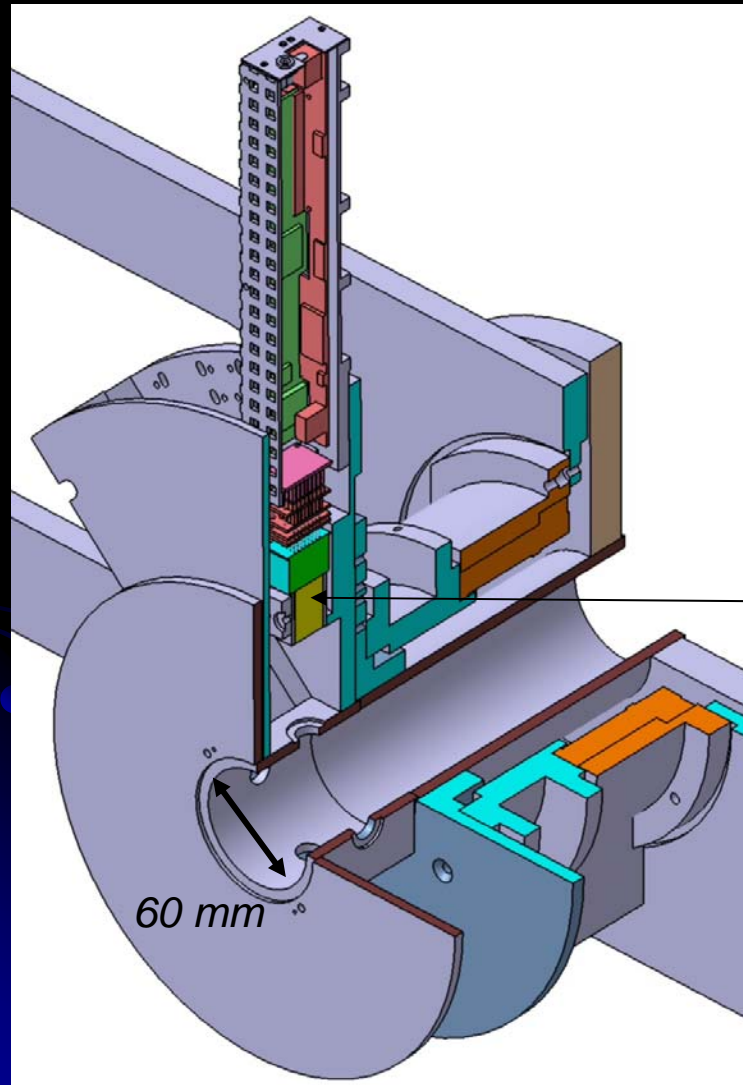
Anatomie d'un module de détection



Collimateur sténopé

Tungsten material
Keel edge shape
Aperture ranging from 0.5 mm to 1.5 mm
Magnification of 2.1

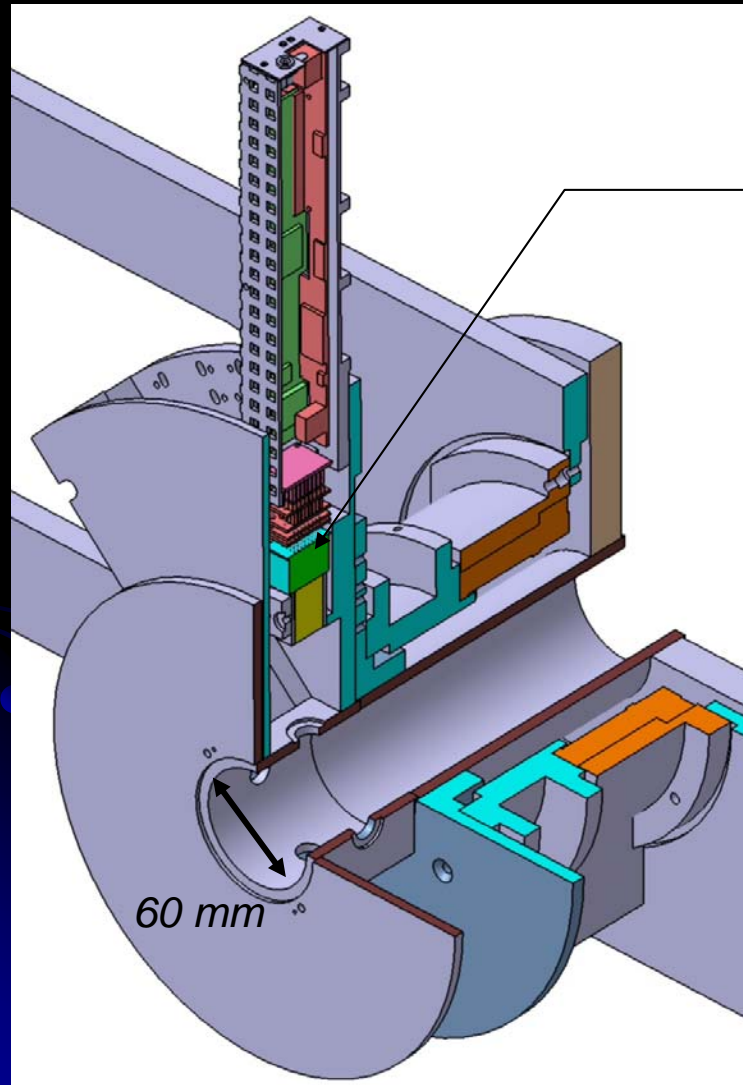
Anatomie d'un module de détection



Matrice de cristaux

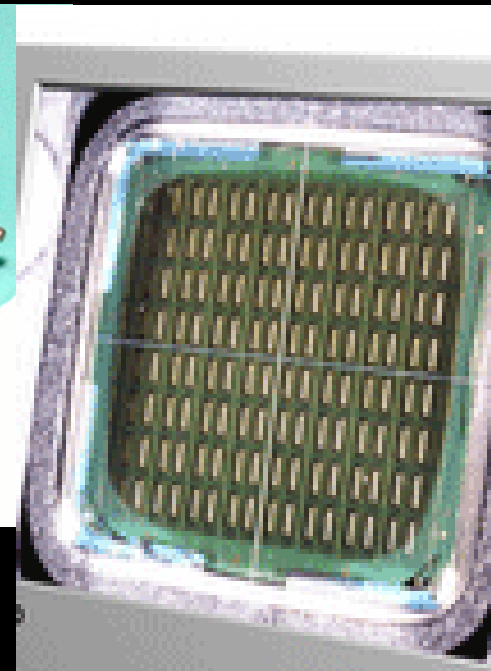
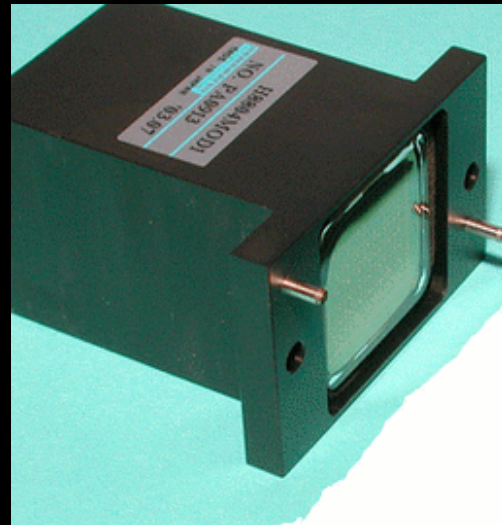
8 x 8 array of YAP:Ce crystals
Crytur, Turnov, CZ
Crystal size: $2.3 \times 2.3 \times 28 \text{ mm}^3$
Optically glued to the PMT

Anatomie d'un module de détection

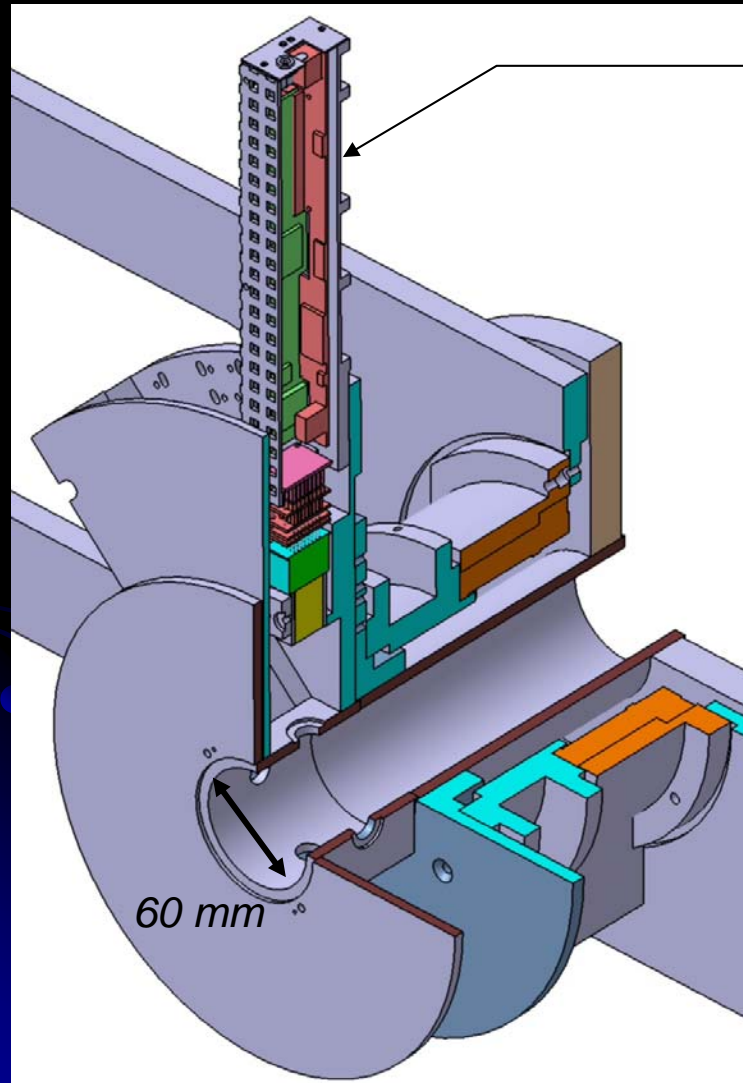


Tube photomultiplicateur

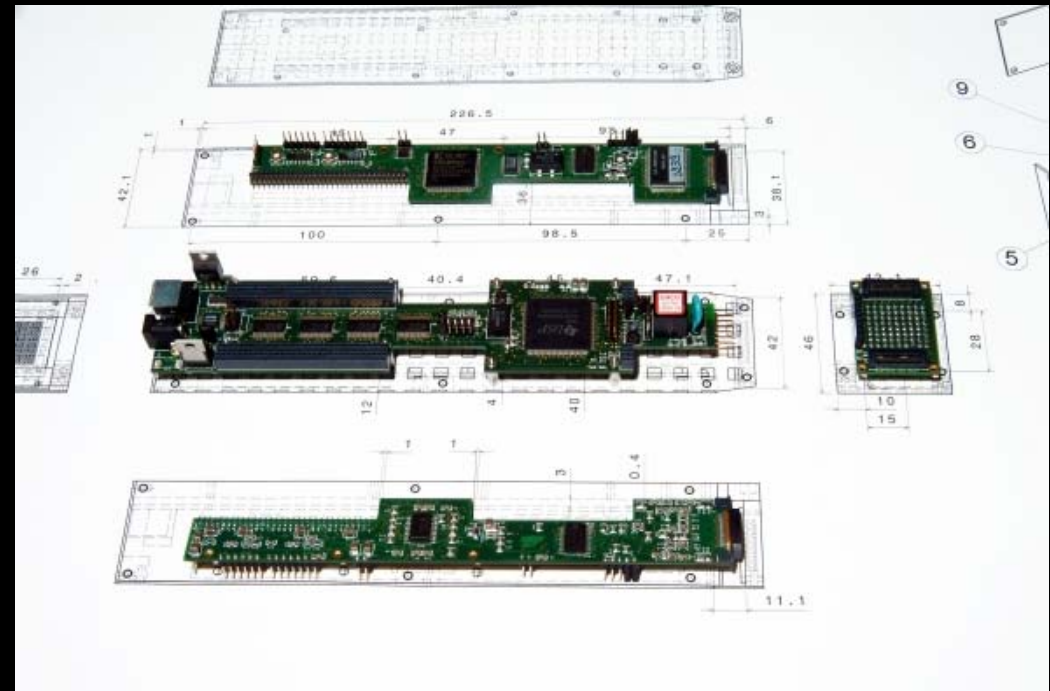
multi anodes (H8804, Hamamatsu Corp.)
64 anodes
Anode size: $2.3 \times 2.3 \text{ mm}^2$



Solution retenue



Électronique compacte

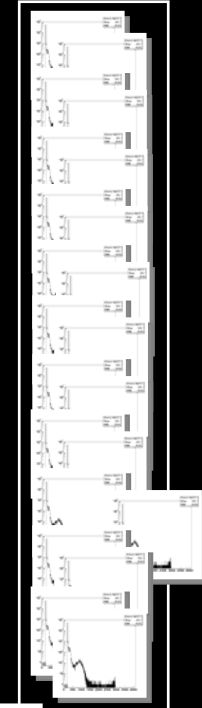


Analyse des données

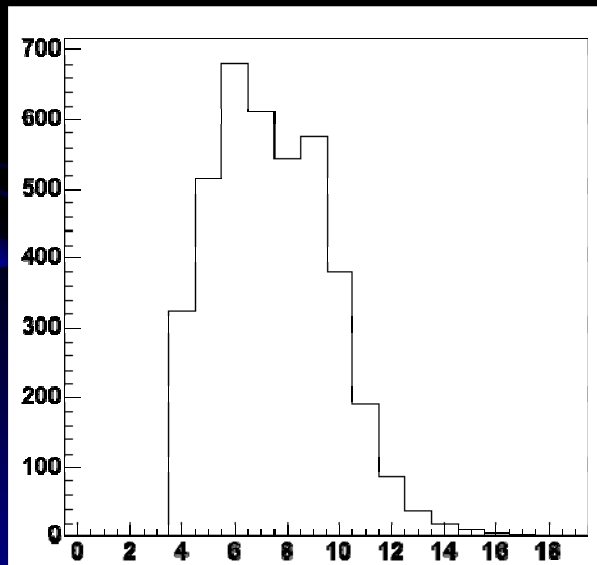


Lien USB

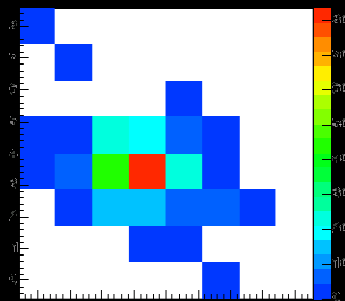
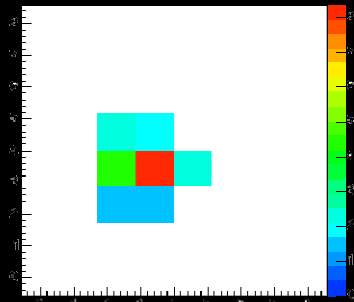
64 canaux



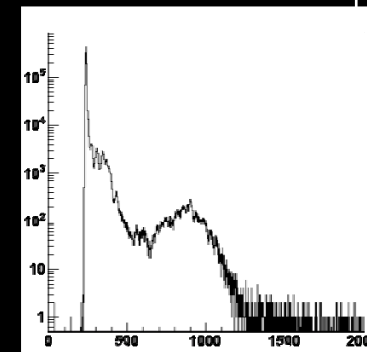
Counts



Clusters response

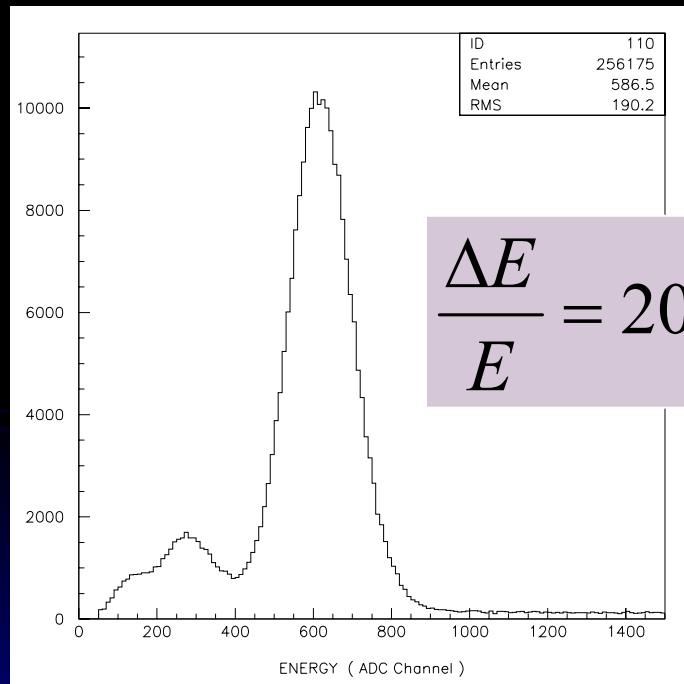


1 événement



Coups ADC

Performances intrinsèques



à 122 keV

$$\overline{cell}/cluster \cong 7$$

Résolution intrinsèque

$$R_i = 2,3 \text{ mm}$$

Résolution image

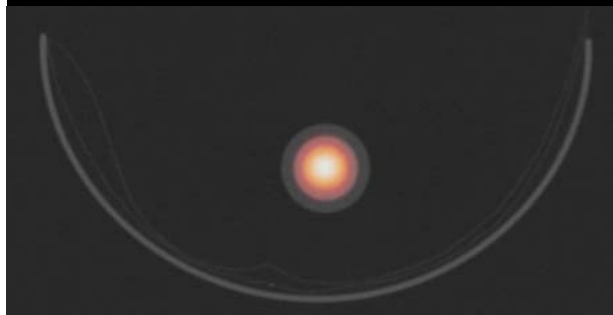
$$R = 1,3 \text{ mm (pinhole } 0,5\text{mm)}$$

Efficacité de détection

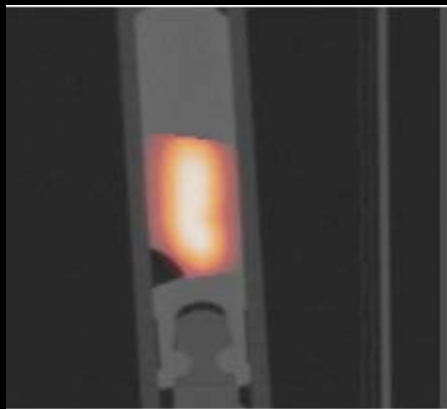
$$E_{ff} = 35 \text{ cps/MBq / caméra}$$

Recalage CT/TEMP

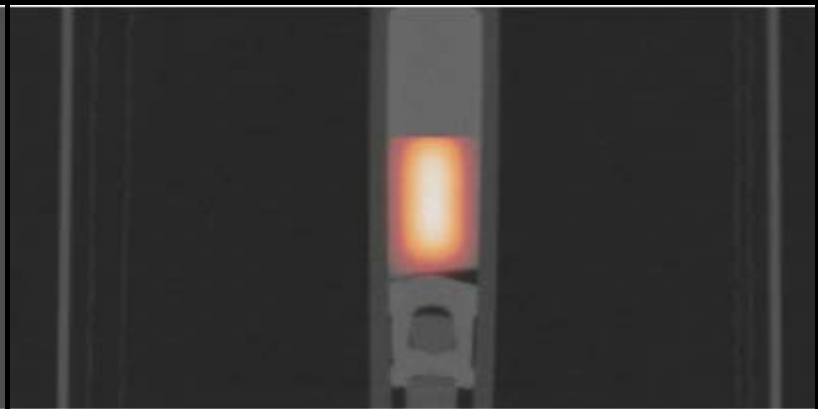
- ▶ Simple fantôme pour tester la fusion CT/TEMP



Transverse



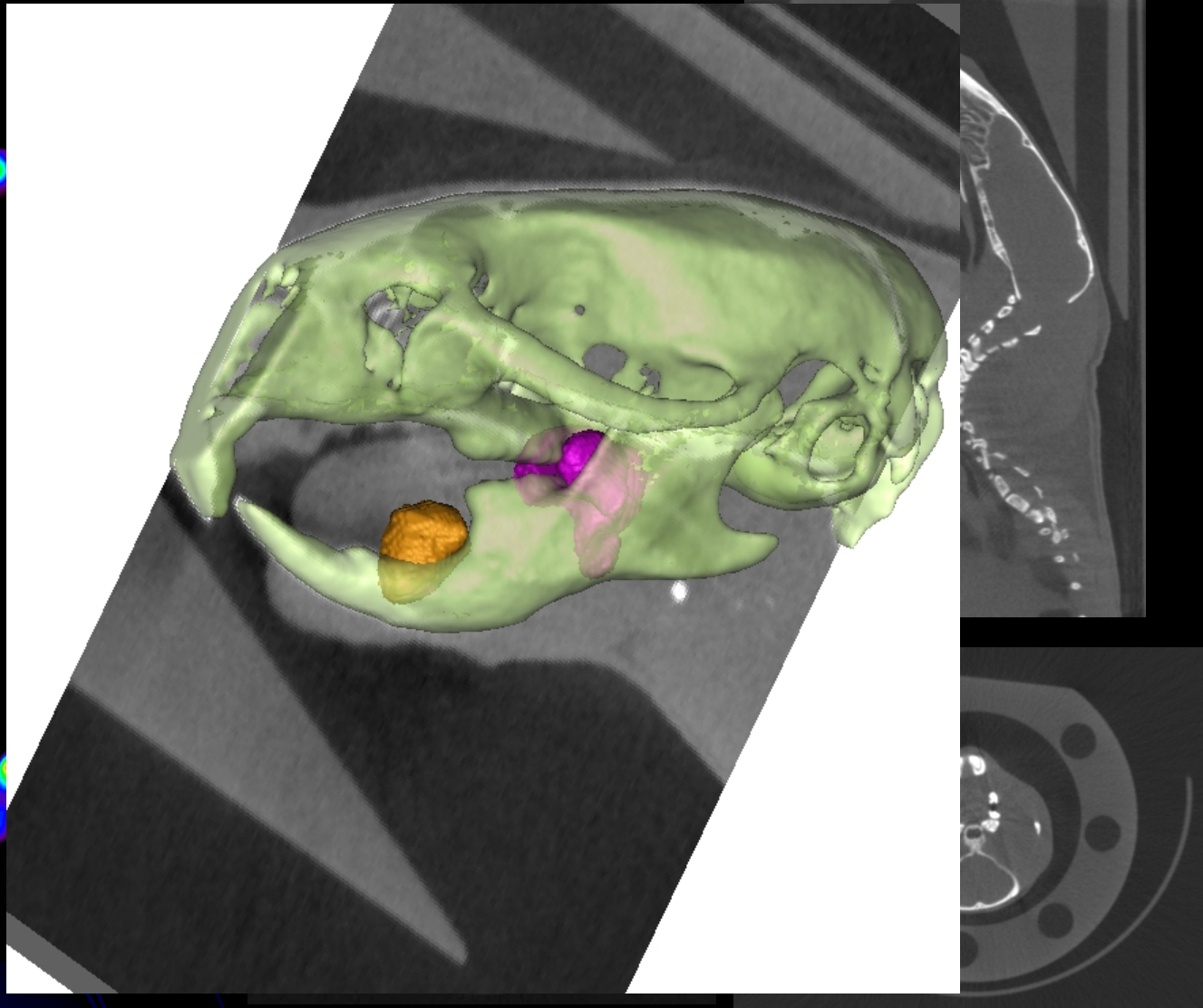
Sagittale



Coronale

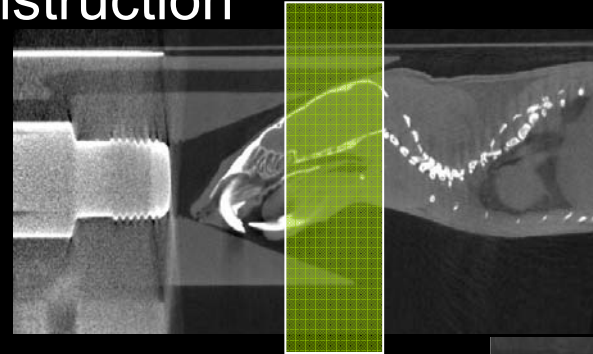


Couplage Fonction / Anatomie

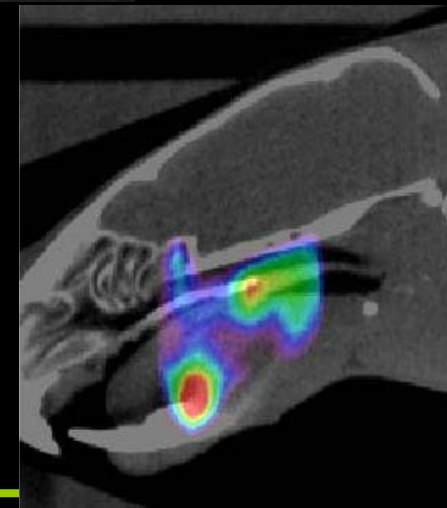


Protocole d'acquisition

- ◇ Injection de 2.5 mCi de $^{99m}\text{TcO}_4^-$
- ◇ Acquisition microCT
768 projections sur 360° , binning 2x2, 4 projections/s
3 minutes acquisition/reconstruction



- ◇ Acquisition microSPECT (1 caméra)
128 projections sur 360° , 15s/projection



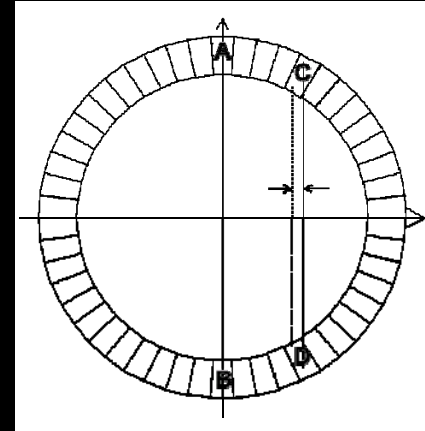
Troisième modalité: R&D TEP

Cahier des charges:

- Efficacité de détection élevée ($>10\%$)
- Résolution spatiale élevée (1mm^3)

Problème de parallaxe:

- \uparrow Efficacité de détection = \downarrow Résolution spatiale

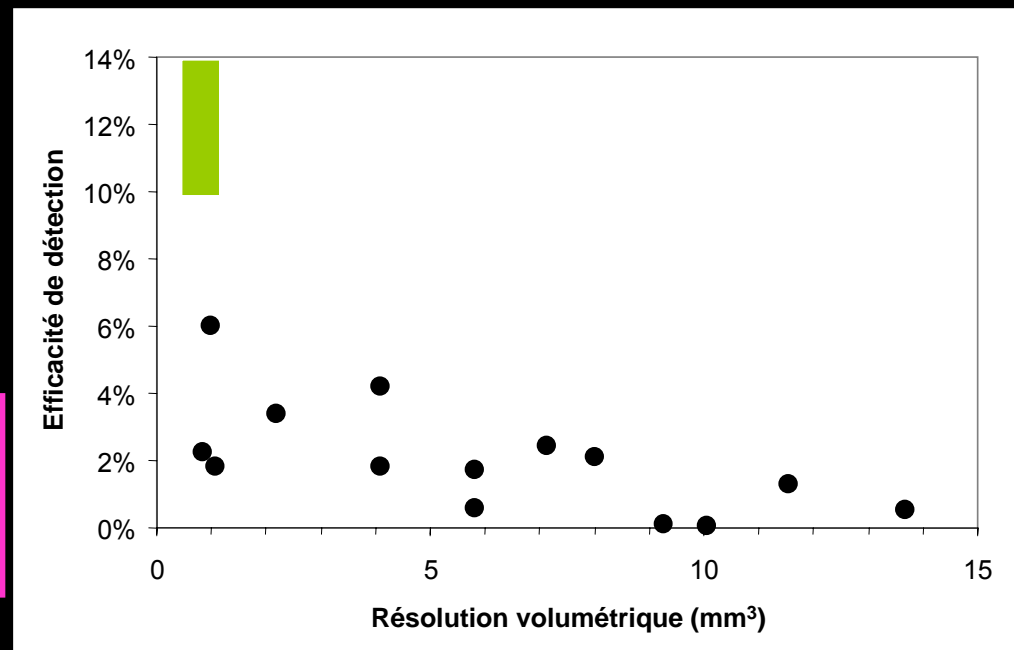


Objectifs:

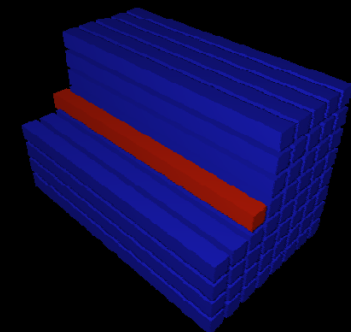
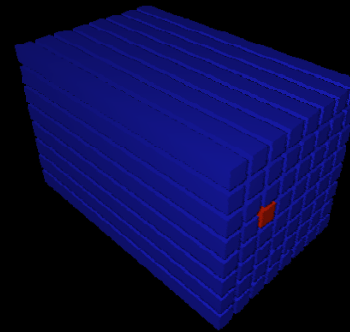
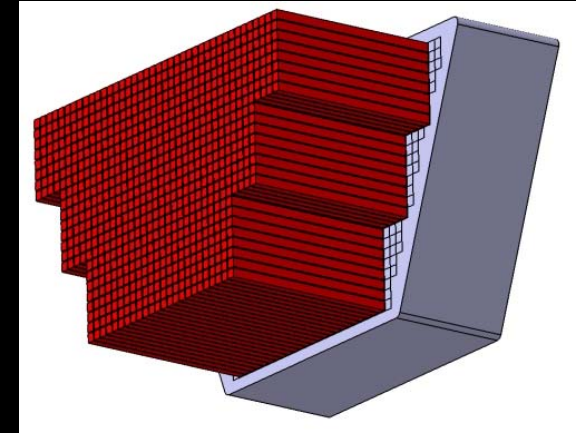
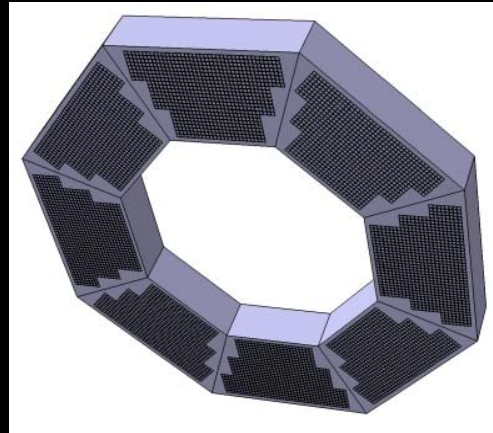
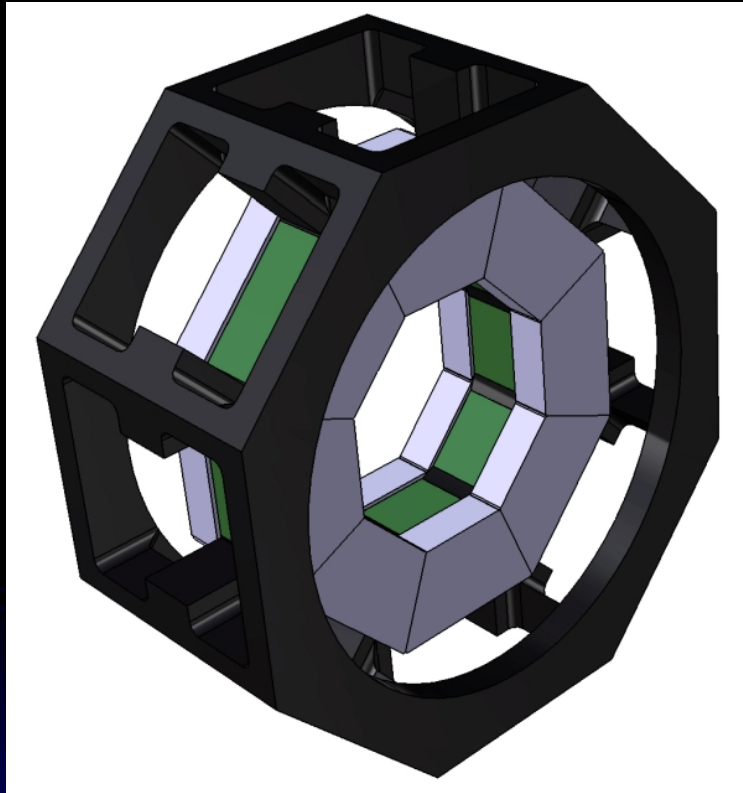
- Résolution spatiale: 1 mm
- Efficacité de détection: $> 10\%$
- Résolution en temps: $< 1\text{ ns}$

Solution:

- Mesurer la profondeur d'interaction
- Cristaux orientés axialement



Nouvelle géométrie



Résolution transverse

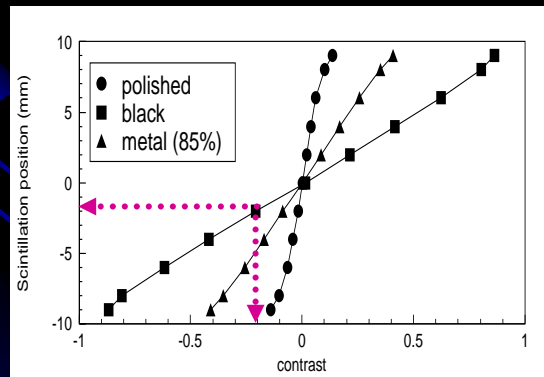
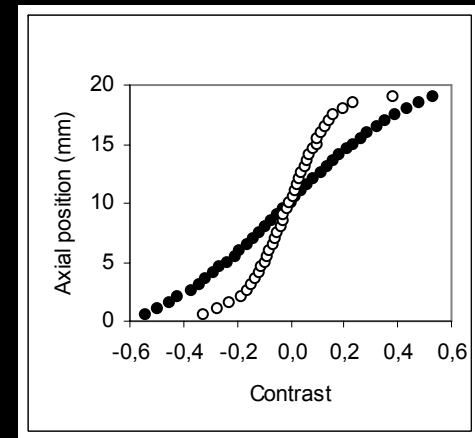
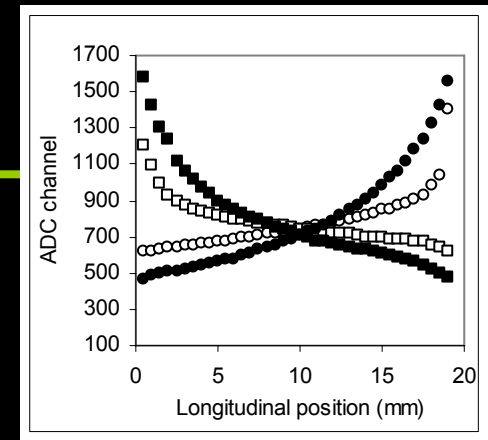
$$LTMH_T = k \sqrt{\left(\frac{d}{2}\right)^2 + (0,0022D)^2 + r_p^2 + b^2}$$

Résolution axiale

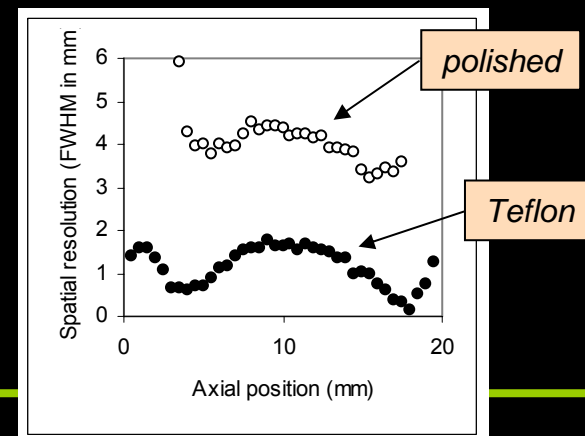
$$C = \frac{S_R - S_L}{S_R + S_L} = f(z)$$

Résolution axiale

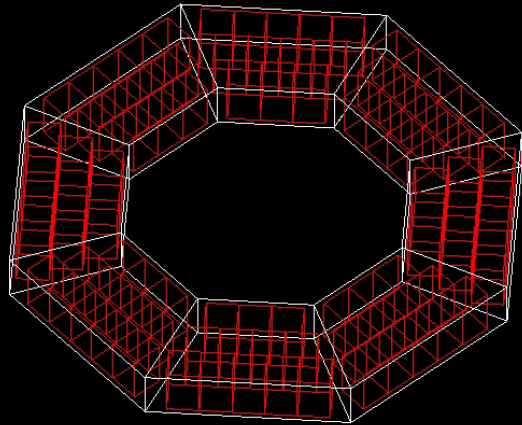
	YAP:Ce	LaBr ₃ :Ce	LYSO
Density (g.cm ⁻³)	5.35	5.29	7.11
Light yield (ph/MeV)	18000	61000	33800
λ_{max} (nm)	370	380	420
Refractive index	1.93	1.9	1.81
Absorption length (cm)	2→14	14	14



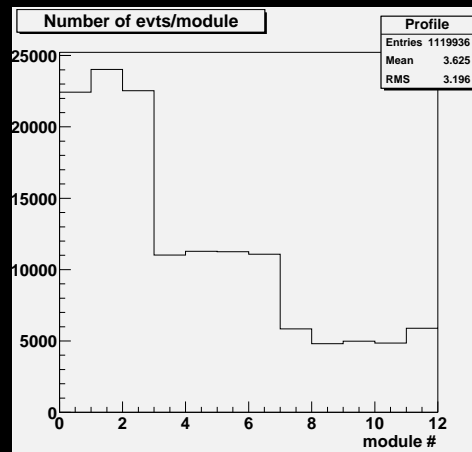
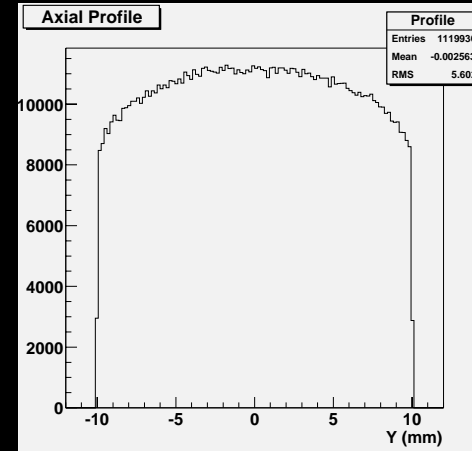
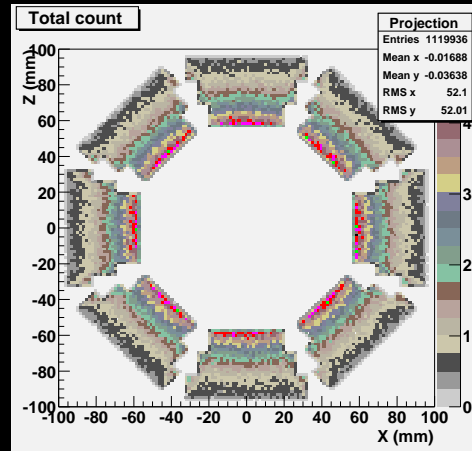
Contrast vs point d'interaction



Efficacité de détection



Simulation avec openGate



Efficacité de détection: 13%

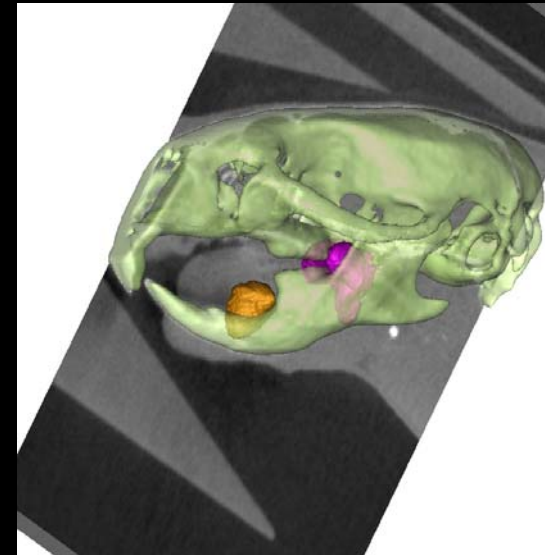
Remerciements

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David Bonnet
Hubert Friedmann
Christian Fuchs
Jean-Michel Gallone
Bernard Humbert
Richard Igersheim
Bruno Jessel
Marc Krauth
Ali Ouali
Damien Vintache
Jacques Wurtz

Jean Daniel Berst
Claude Colledani
Yann Hu
Christine Hu-Guo
Ndeye awa Mbow
Nicolas Ollivier-Henry



Nelly Etienne (UMR 7034)
Carole Mathelin (HUS)
Marie-Christine Rio (IGBMC)
Jérôme Steibel (IPB)