

Exemple of **SMALL-ANIMAL-PET** in biomedical research

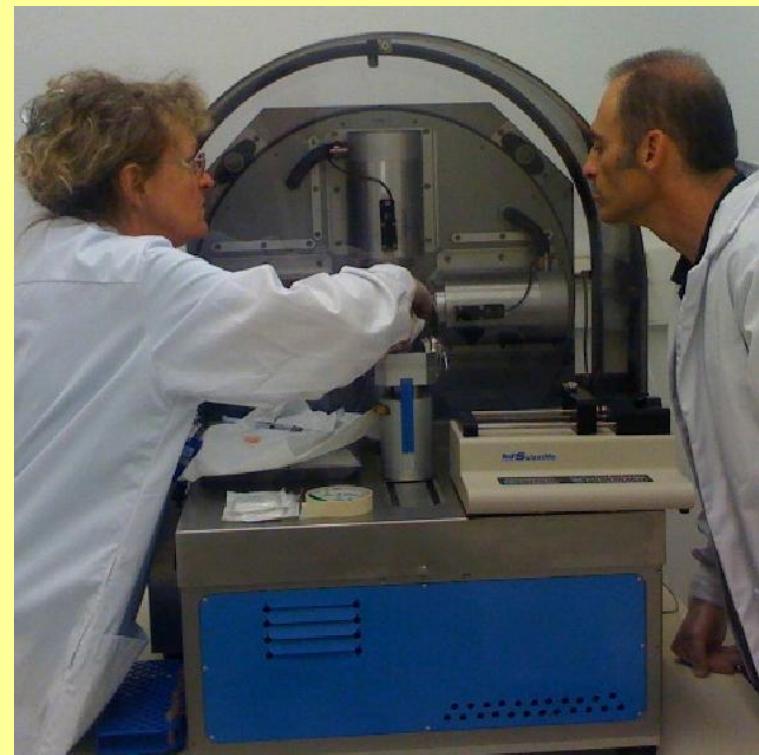
Example of a Micropet (YAPPET) experiments performed in collaboration with Neuro imaging unit of Geneva Hospital

☞ Goal: Quantify 5-HT_{1A} receptors interactions

- Need Better QUANTIFICATION than SUV coefficient
- Pharmacokinetics models

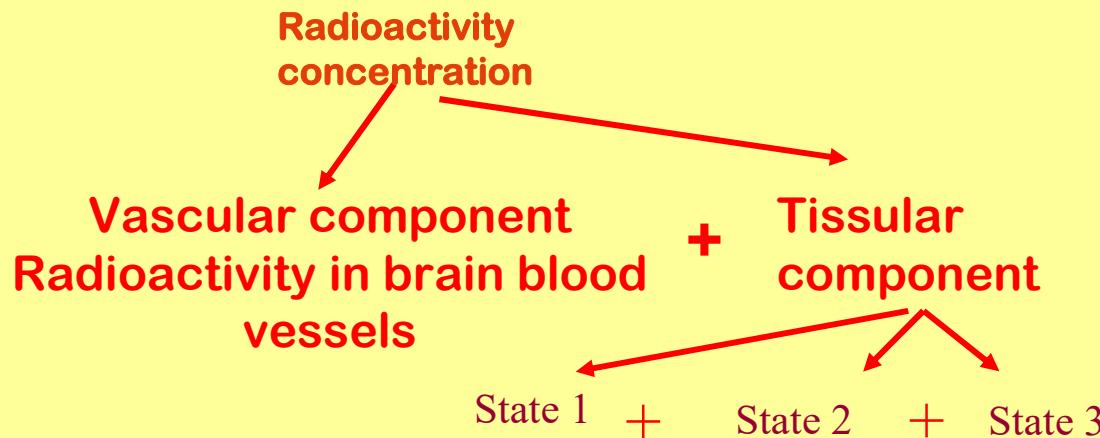
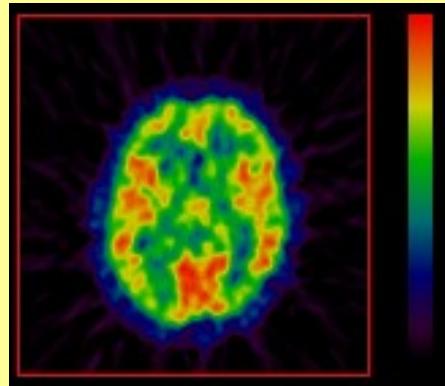
Part 1 : Backgrounds about mathematical modelling

Part 2 : Analysis of data obtained with the YAPPET.

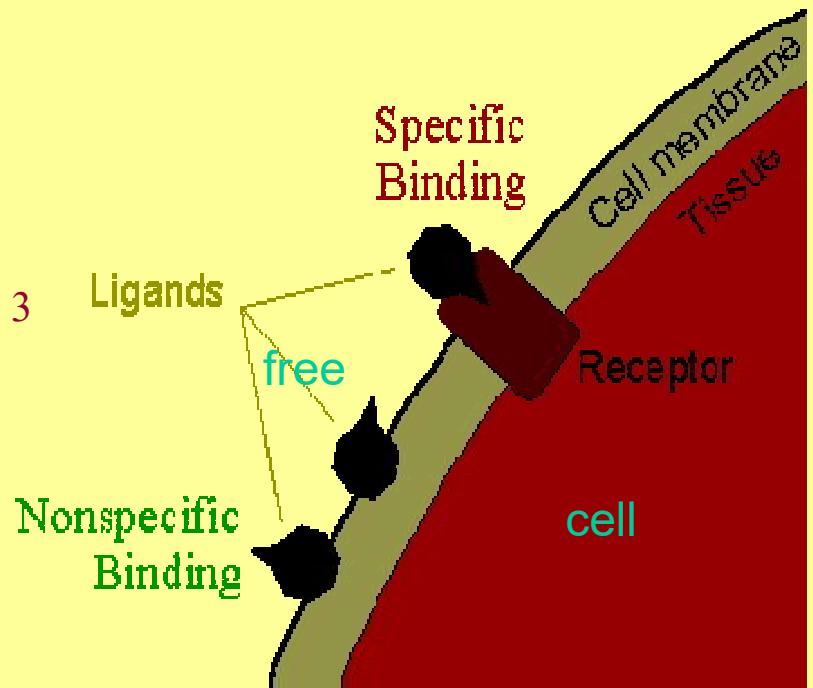


M. Moulin, P. Millet, *Neuroimaging Unit, HCU,
Geneva-CH*

What is modeling used for ?

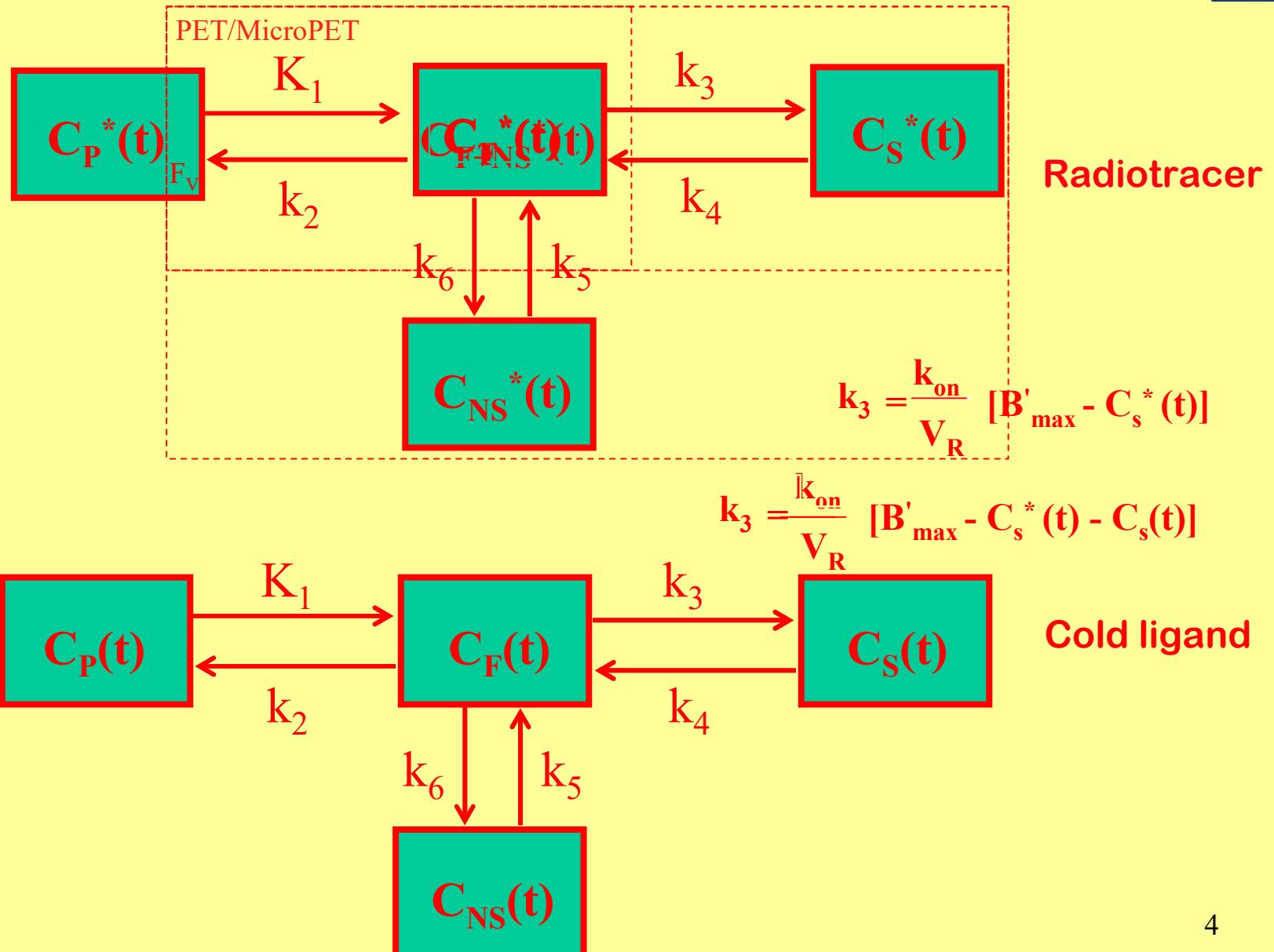


PET images represent
radioactivity concentrations
**Not directly the biological
parameters !!**



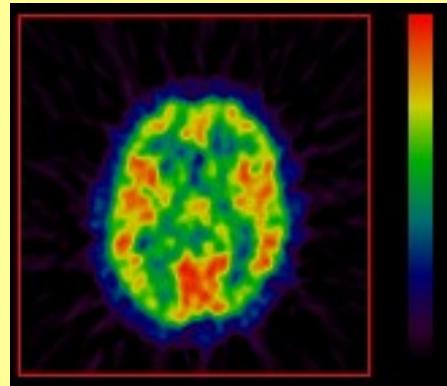
**Mathematical modeling allows to
extract biological parameters
from whole PET data**

Compartment model

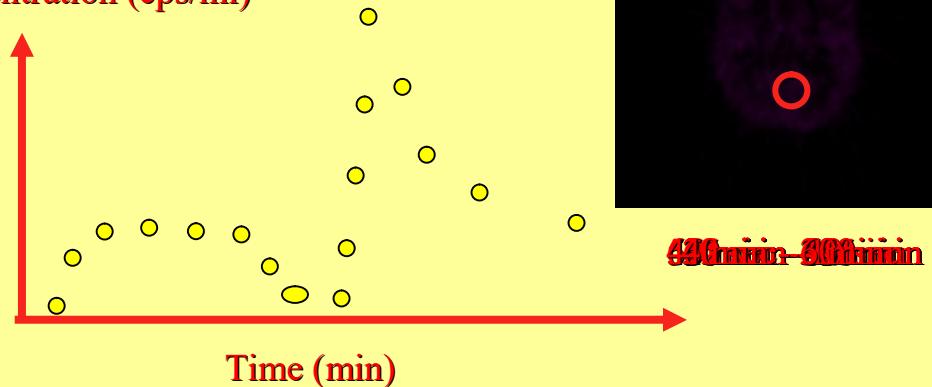


Static or Dynamic images

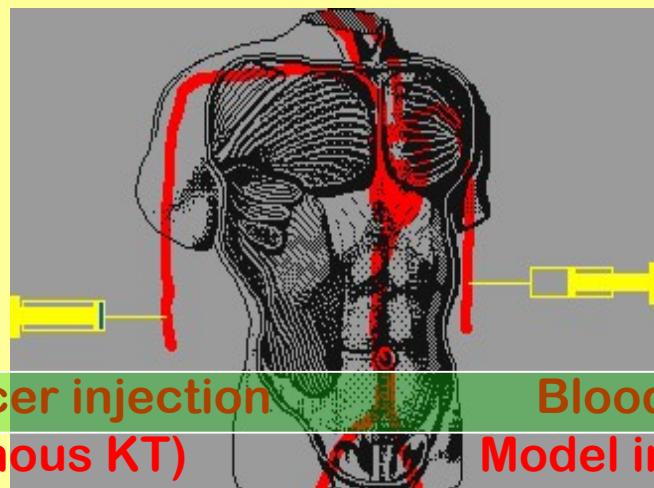
Static image



Concentration (cps/ml)



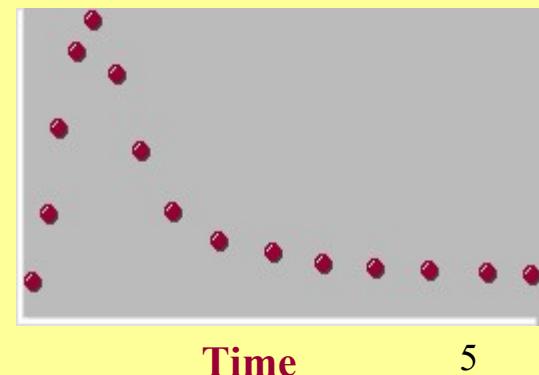
Plasmatic concentration



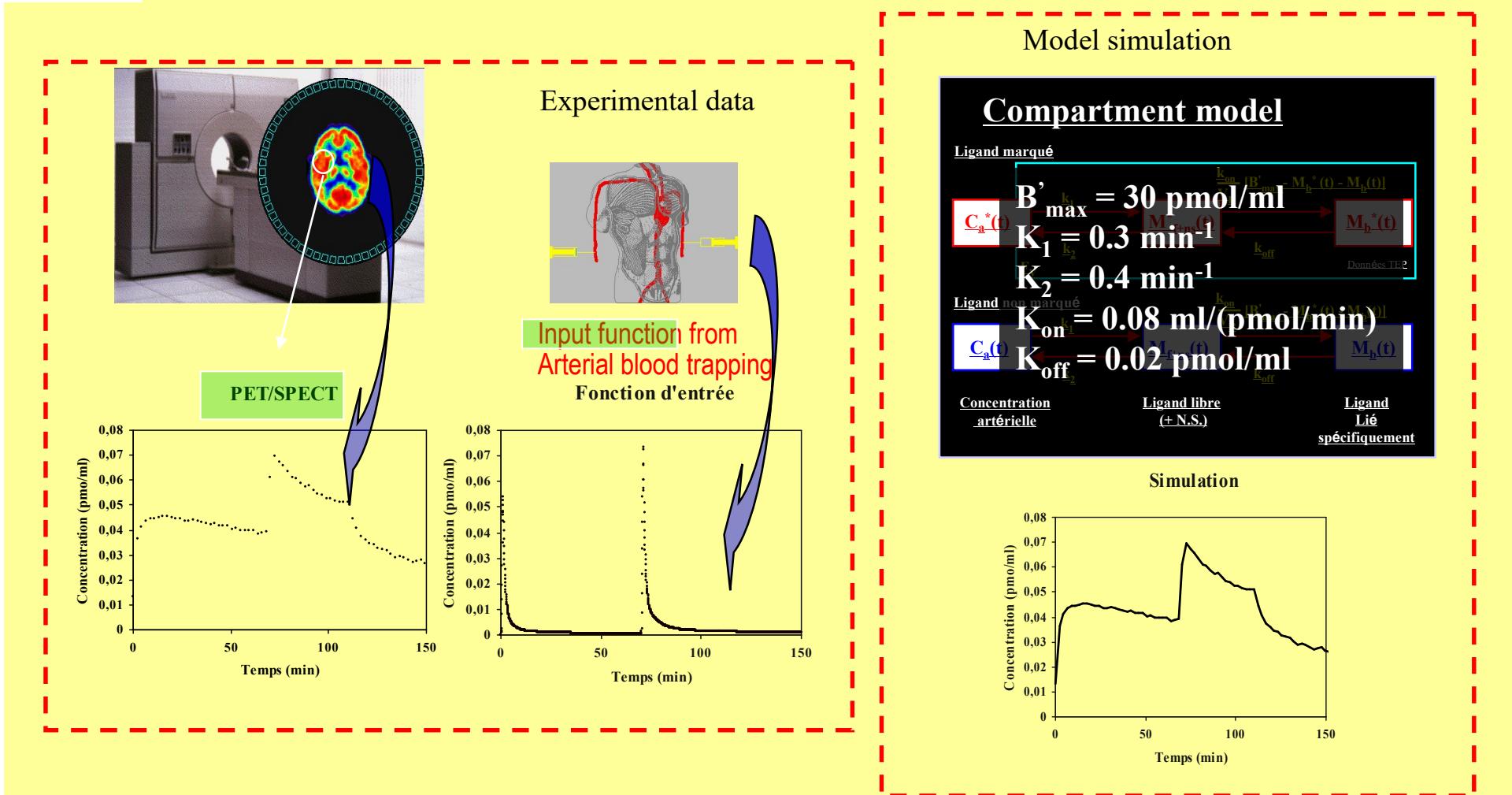
Tracer injection
(Venous KT)

Blood sampling
Model input function
(Arterial KT)

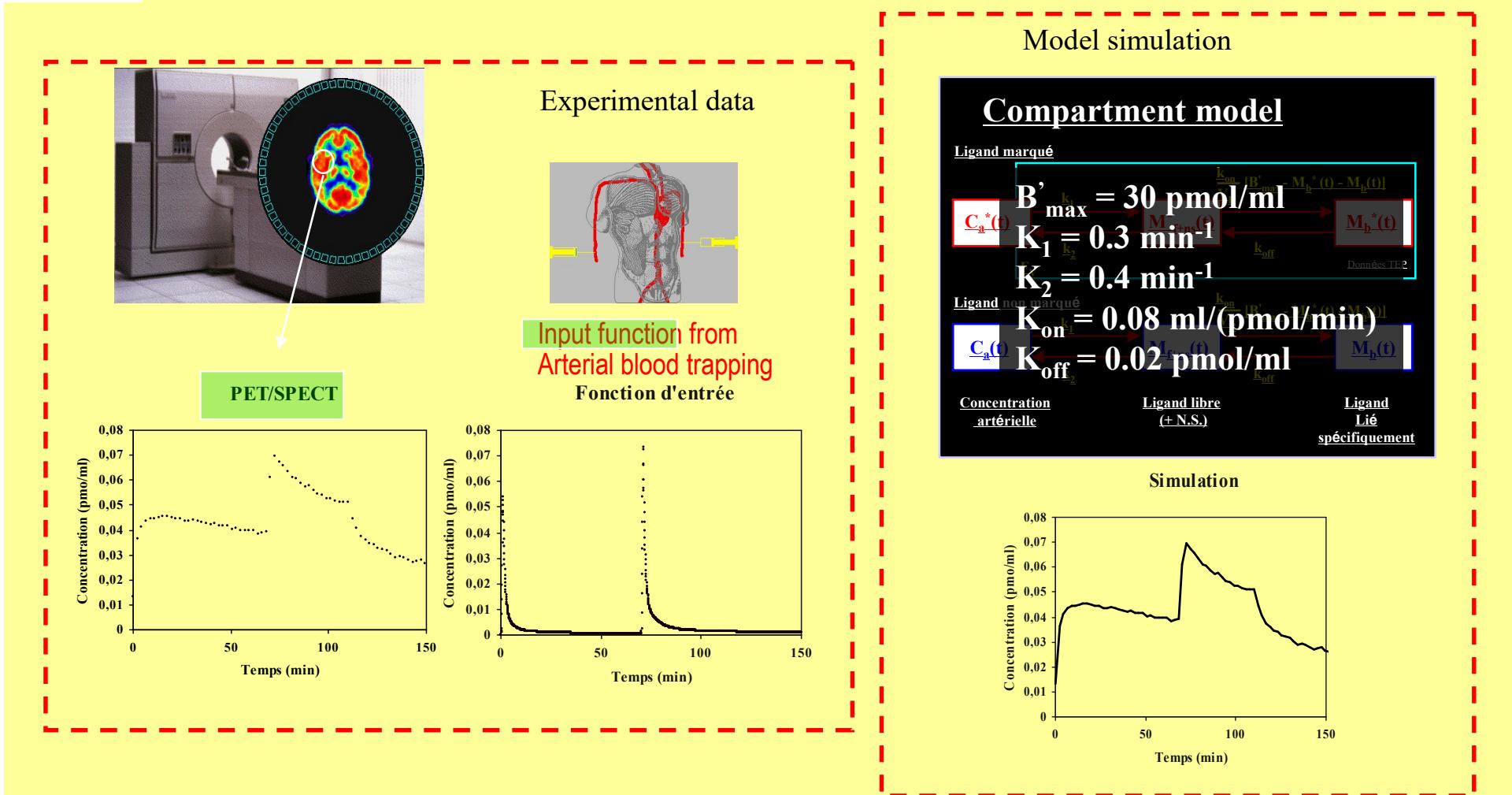
Time-concentration curve



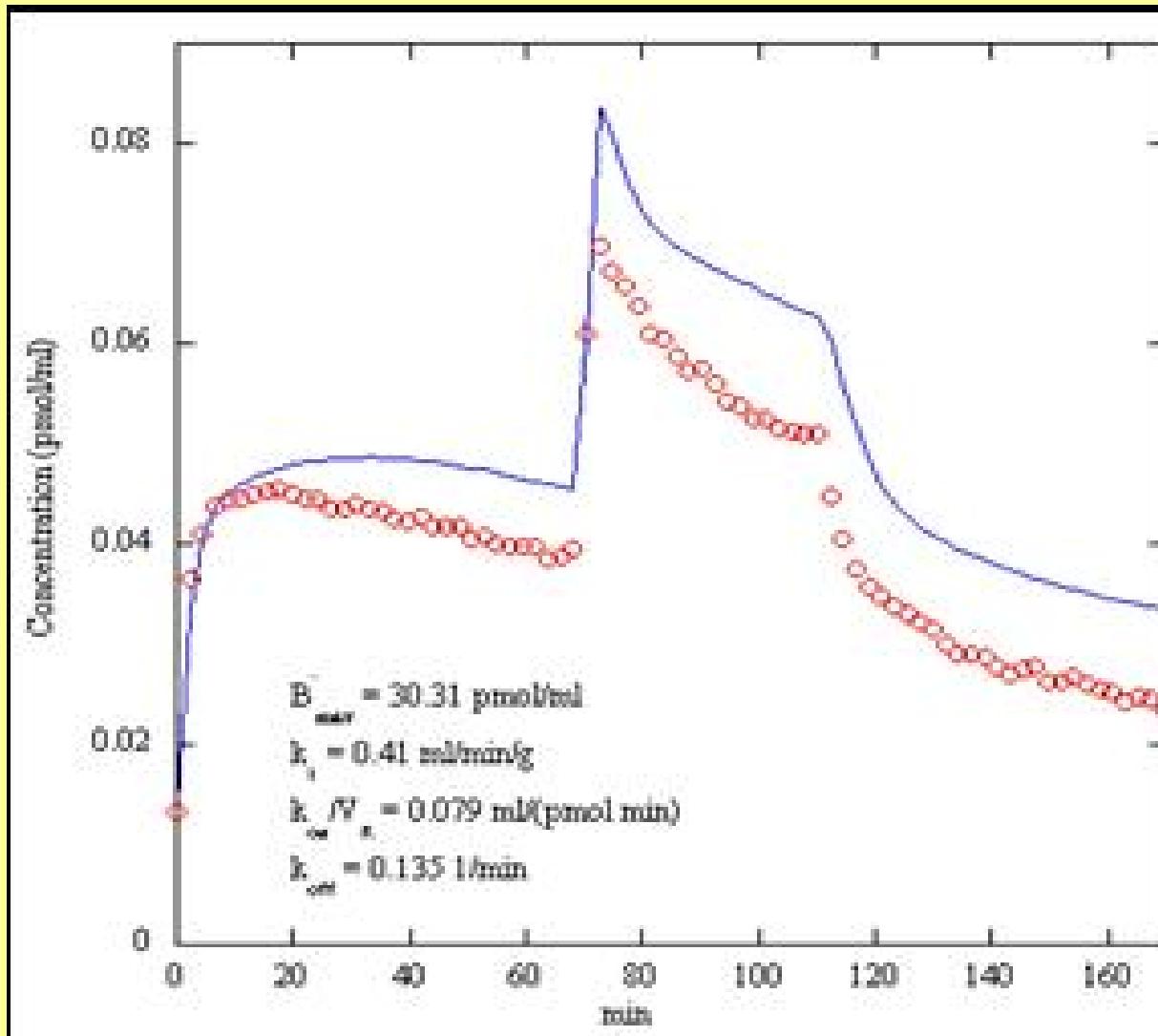
Parameter estimate



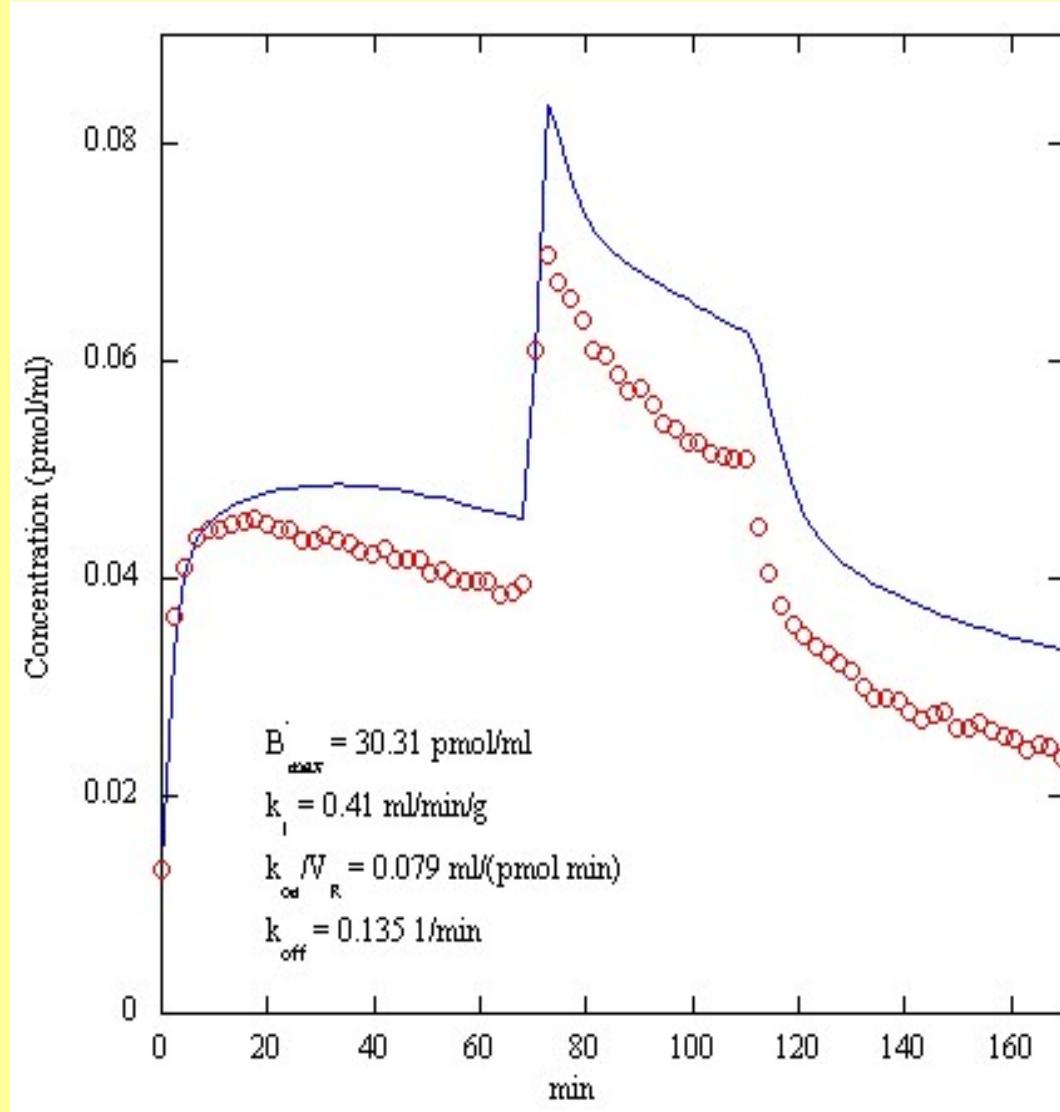
Parameter estimate



Parameter estimate Identification Adjustment



Parameter estimate Identification Adjustment



Modeling of ligand-receptor interactions

Application to $5HT_{1A}$ receptors

Receptor

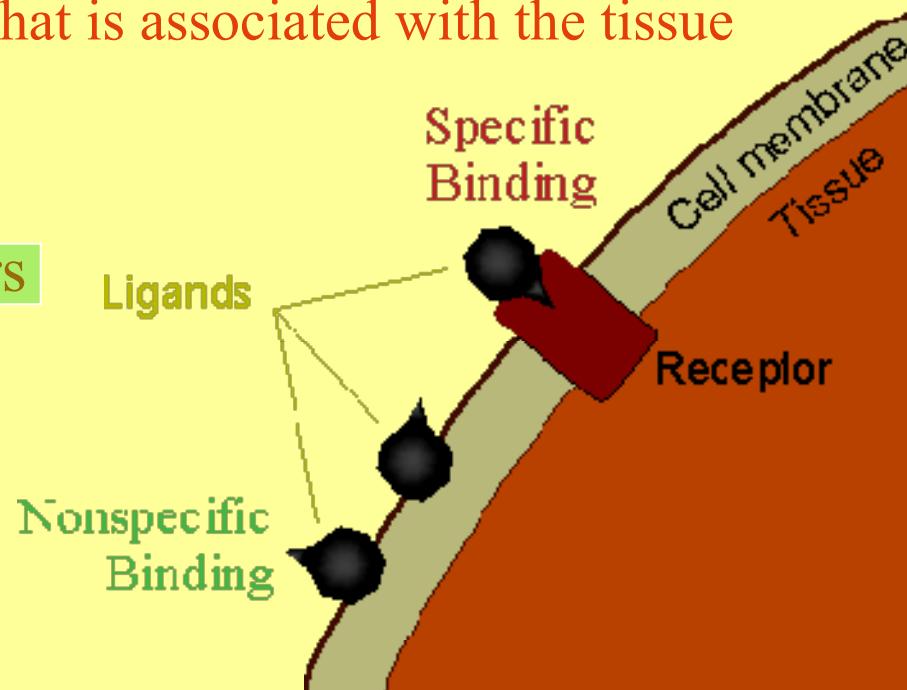
A molecule inside or on the surface of a nerve cell that binds to a specific substance (neurotransmitter or ligand) and causes a specific physiologic effect in the cell

Both specific binding (ie. ligand binding to receptor) and nonspecific binding (ie. Absorption to the tissue) contribute to the radioactivity that is associated with the tissue

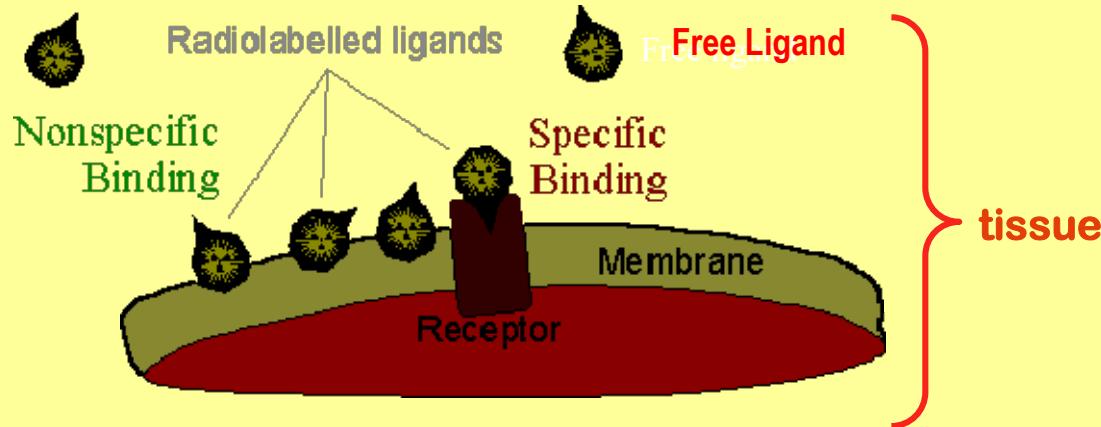
To be measured :

B_{max} : number of receptors

$1/K_d$: Affinity of ligand



Positron Emission Tomography



→ Bound radioactivity = Nonspecific + Specific binding

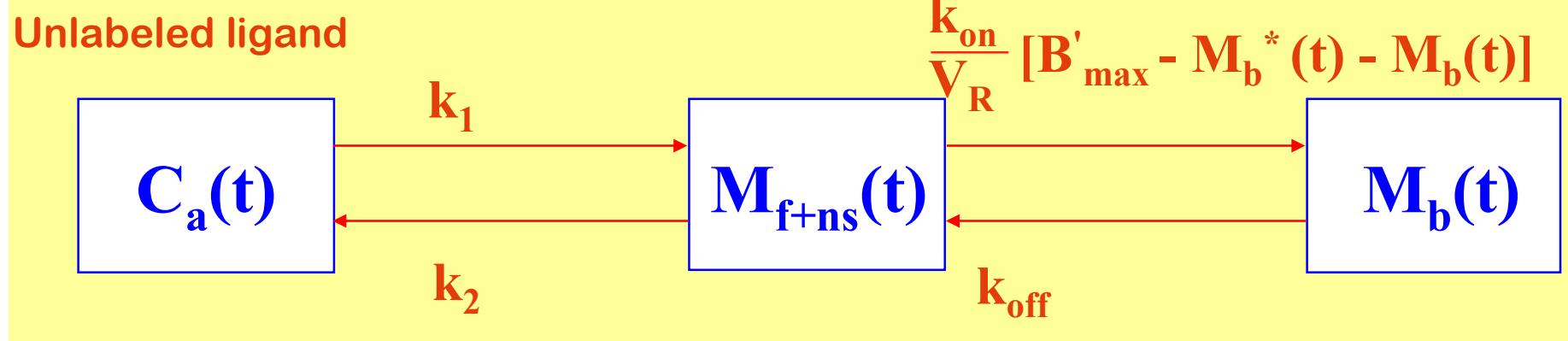
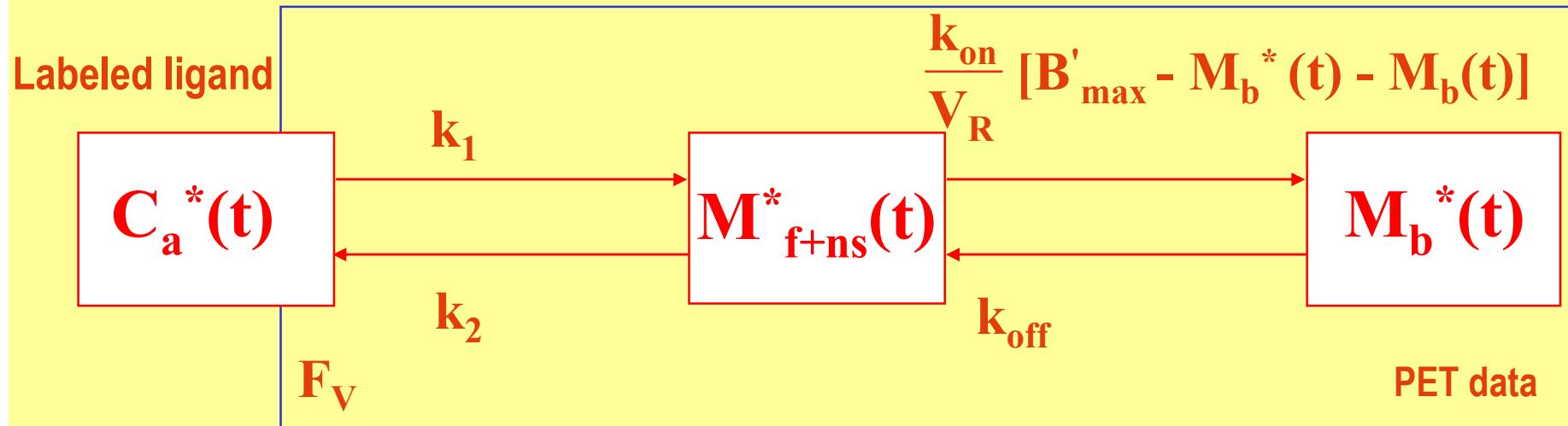
$$\text{PET} = C_{\text{radiolabeled ligand}} = C_{\text{tissular}} + C_{\text{vascular}}$$

$$C_{\text{specifically bound ligand}} + C_{\text{free ligand}} + C_{\text{non-specifically bound ligand}}$$

Goal: B'_{\max} and $1/K_d$



Model



**Arterial
concentration**

**Free ligand
(+ N.S. binding)**

**Specifically bound
ligand** ₁₃

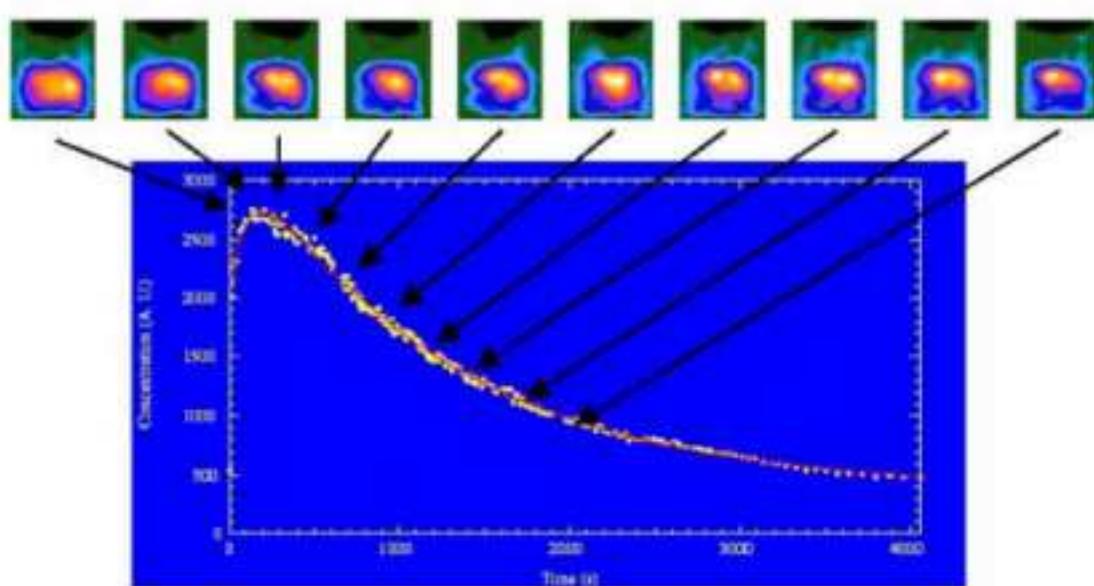
YAP-(S)PET

An integrated PET/SPECT small animal scanner

Scanner configuration

Configuration:	Four rotating heads
Scintillator:	YAlO ₃ :Ce (YAP:Ce)
Photodetector:	Position Sensitive PMT
Readout method:	Resistive chain (4 channels)
FoV size:	4 cm axial × 4 cm Ø
Collimators: (SPECT)	Lead (parallel holes)
Animal bed:	Motorized, PC controlled

*In vivo dynamic imaging of Rat Brain - 500 µCi of ¹¹C-Flumazenil.
Sagittal section through Center Brain (Nose left).*



Goal :

To study the effect of antidepressant treatments on 5-HT_{1A} receptors

Quantification of ligand-receptor interactions in vivo
using
[¹⁸F]MPPF (2'-Methoxyphenyl-(N-2'-pyridinyl)-p-18F-fluoro- Benzamidoethylpiperazine)
Which is a specific serotonin 5-HT_{1A} antagonist PET tracer

...

Mesure B' _{max}, (density of receptors) **inside the Hypocampus**

K_{on} =association constant,

Product Affinity K_{on}/K_{off}

Full Scenario

Radiochemistry



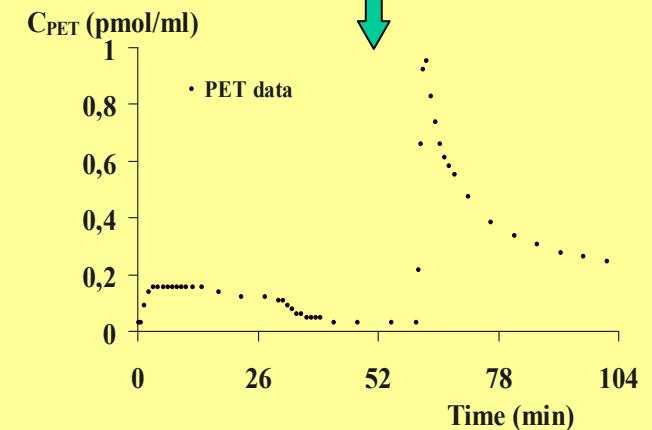
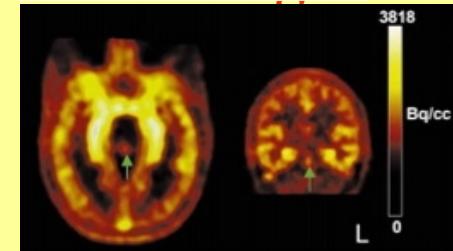
Fluor 18
 - Positron emitter
 - $T = 109$ min
Ligand
 - MPPF

YAPPET



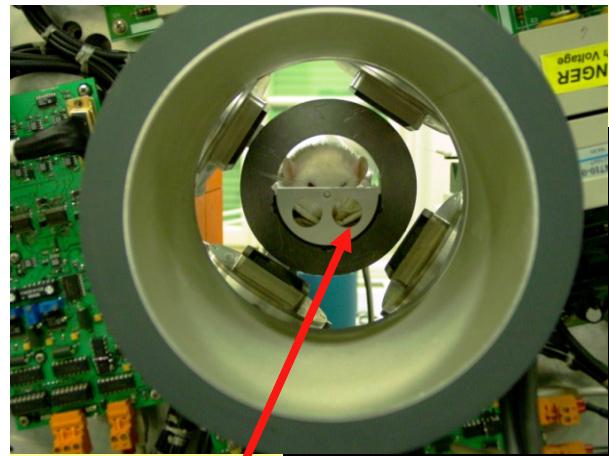
Radioligand
 $[^{18}\text{F}]\text{MPPF}$
 Injected
 to the Rat

PET Images



Analysis

Activation studies



MPPF MicroPET (YAPPET) Images

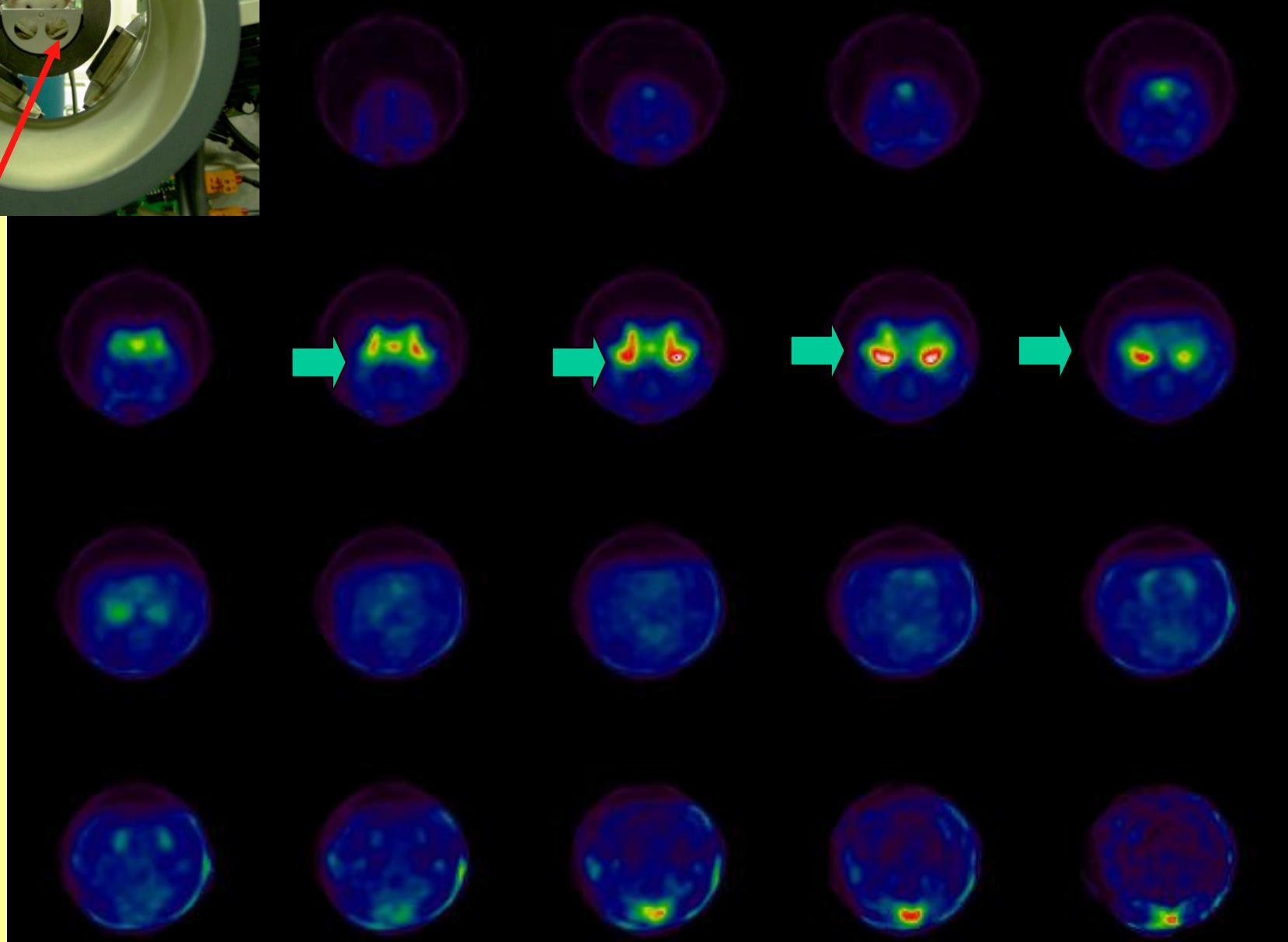


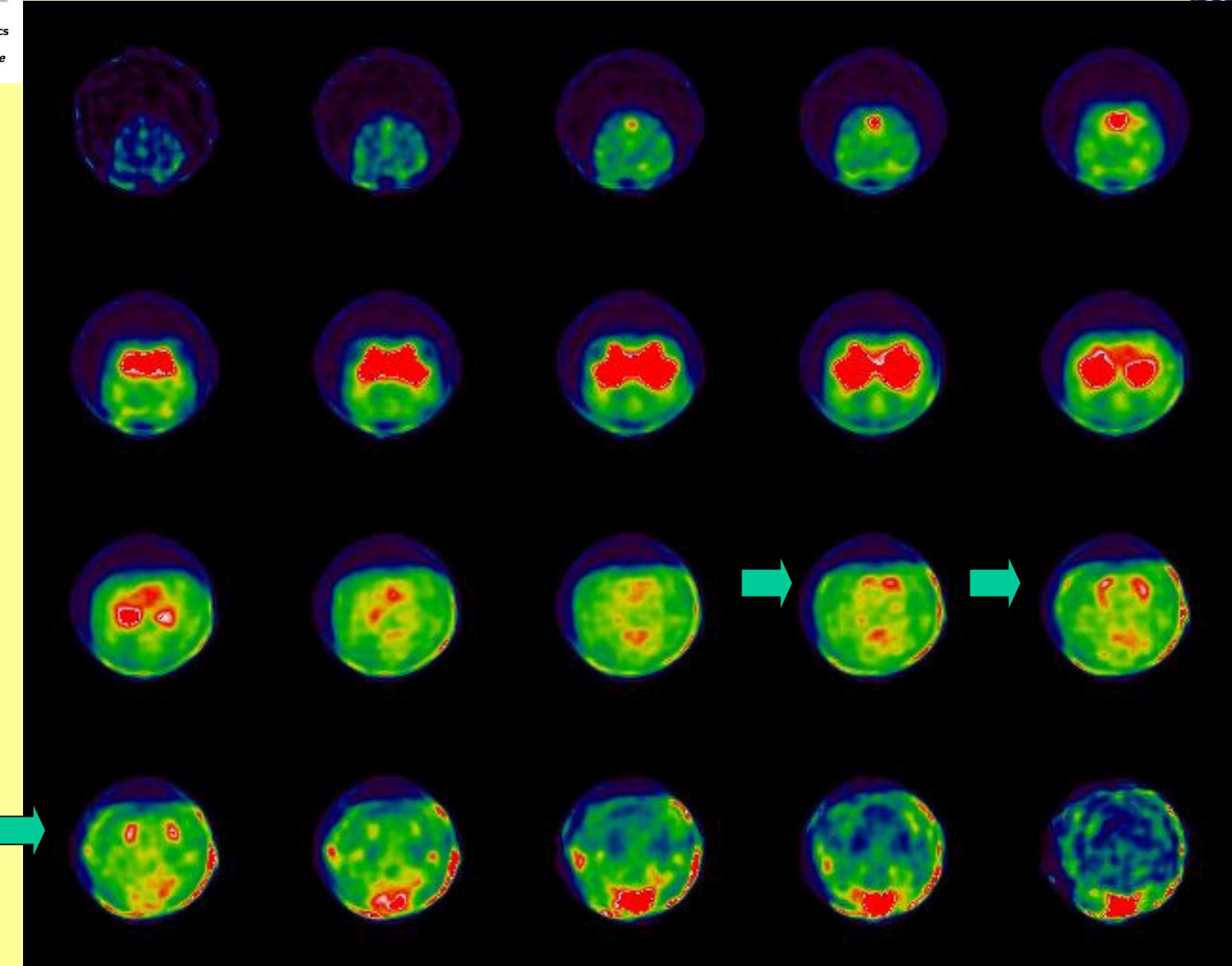
The Rat

The YAPPET
gave us a lot
of images
divided in 20
slides of 2
mm every 5
mn (for
example)

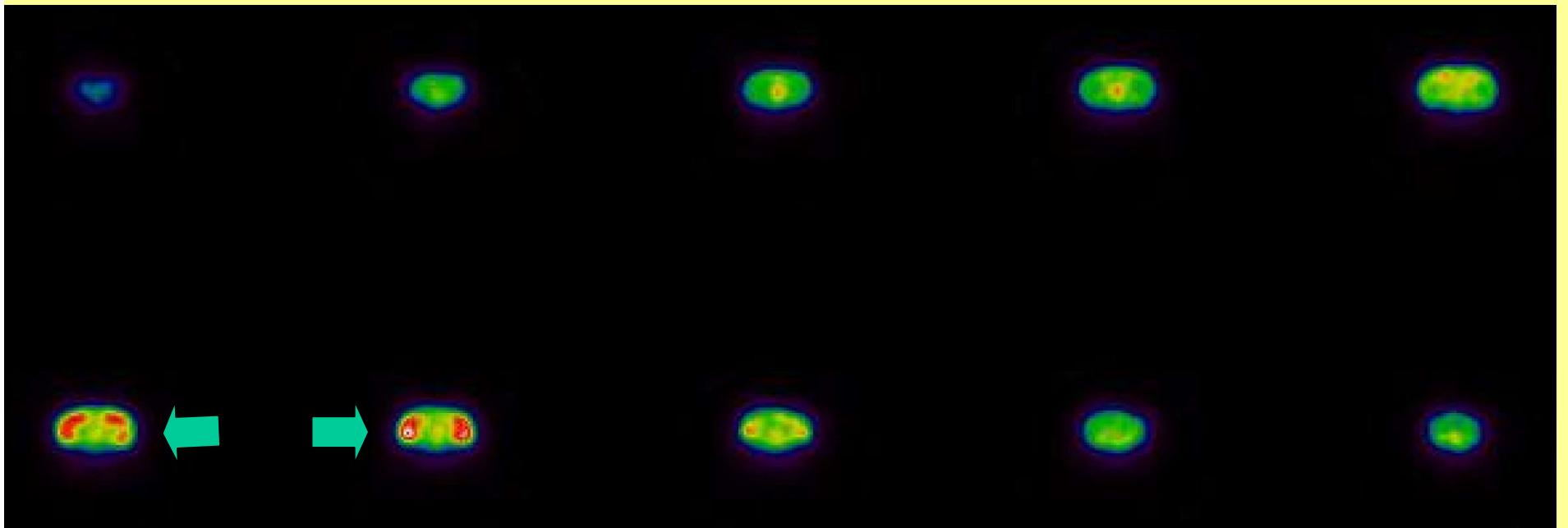
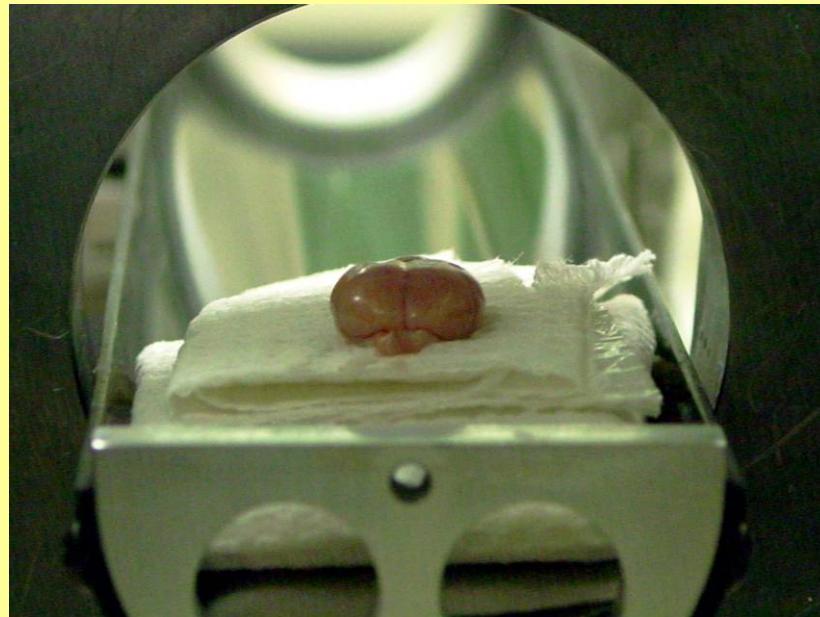
Spurious
effect of
Harderian
glands !!

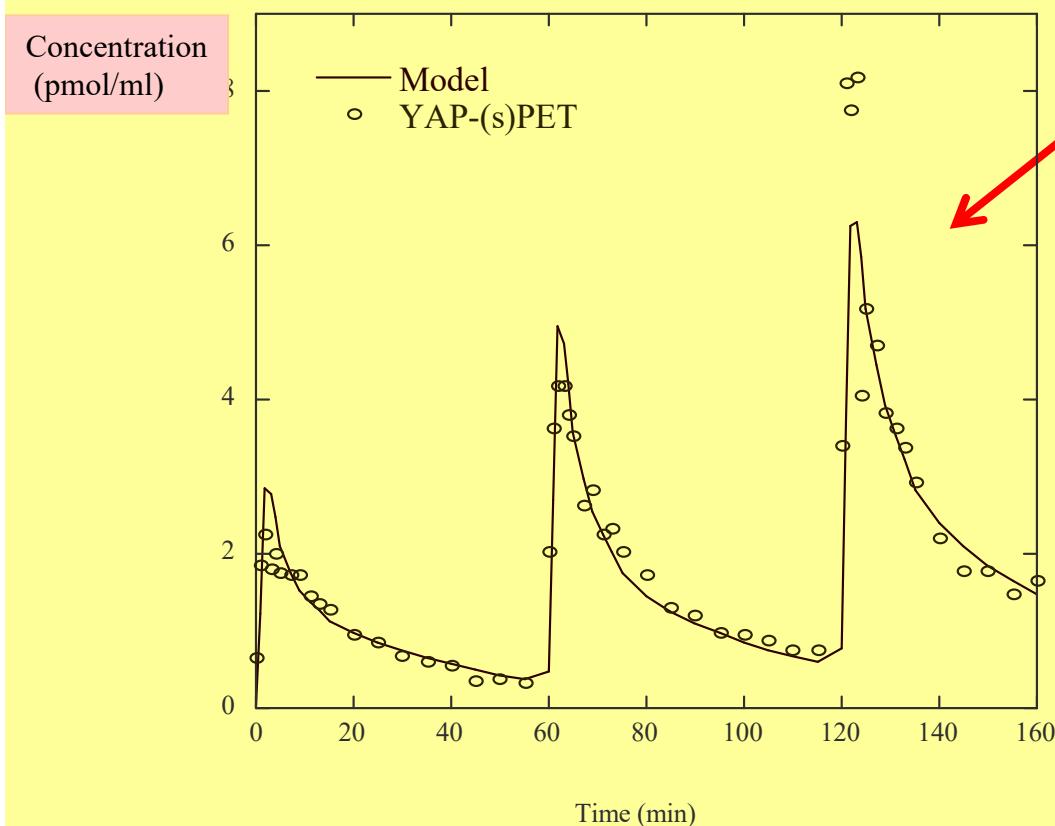
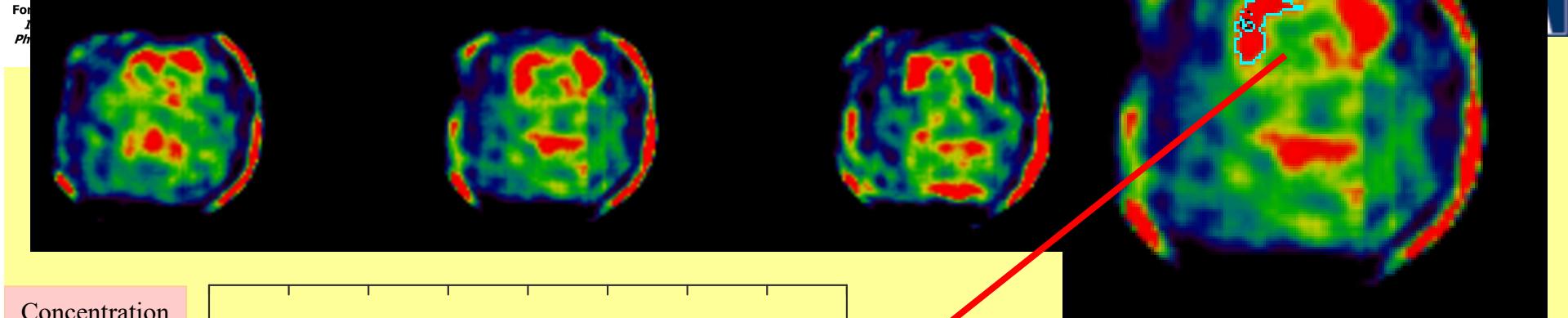
Ohrid Work





To get rid of Harderian glands, the Rat was sacrificed, th brain extracted and put bak inside the YAPPET for static images



MPPF 5-HT_{1A} receptors using [¹⁸F]

6 Parameters estimate:

$$B'_{\max} = 1.94 \pm 0.56 \text{ pmol/ml}$$

$$K_1 = 0.306 \pm 0.022 \text{ min}^{-1}$$

$$k_2 = 0.257 \pm 0.019 \text{ min}^{-1}$$

$$k_{on}/V_R = 0.024 \text{ ml/(pmol min)}$$

$$k_{off} = 0.053 \text{ min}^{-1}$$

$$K_d V_R = 2.13 \text{ pmol/ml}$$

From YAPPET Images, the density of 5-HT_{1A} receptors $B' = 1.94 \pm 0.56 \text{ pmol/ml}$

Conclusion

- Due to their high sensitivity PET Cameras are a powerful imaging tool (Oncology, Neurology...).
- Modelling is needed to understand phenomena...
- Both they allow Quantification so useful in Biomedical research (Small-Animal-PET...). Enormous progress in research!
- Clinical PET camera, now combined with CT-scanners (and MRI) have increased hospital capabilities.
- Pre-clinical PET combined with CT and MRI cameras are now in use enlarging sizeably their possibilities for research....
- Further improvement can be experimented (new crystals, new electronics...) to reduce the deadtime and imaging cost (to treat more than half a dozen patients a day-PET !)



**Thanks a lot for
the gentle attention!**

Parameter estimate

