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EXEMPLE OF

SMALL-ANIMAL-PET

IN BIOMEDICAL RESEARCH

Yves LEMOIGNE / Institute for Medical Physics – Armbilly,74100, France

Small Animal PET in Biomedical research

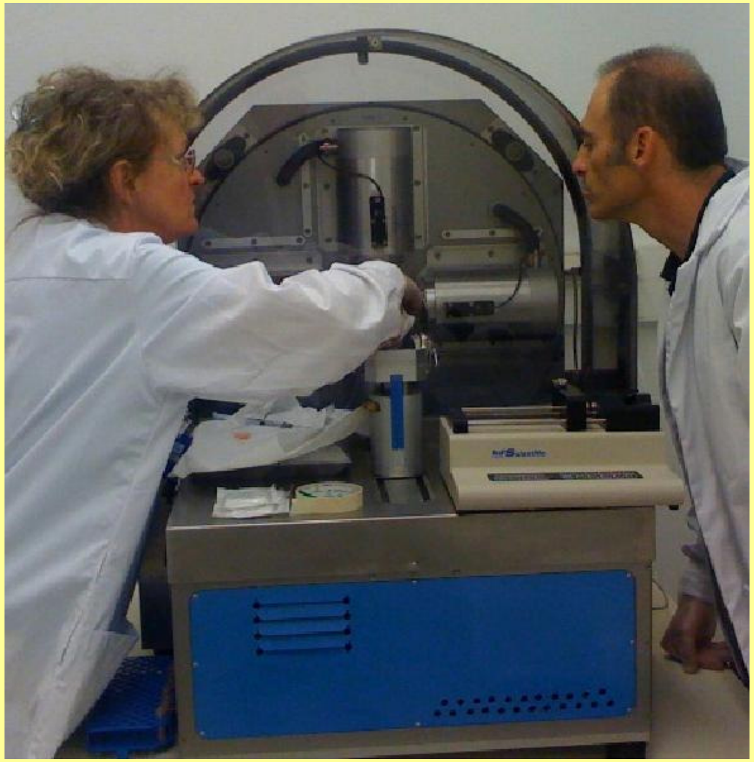
Example of a Micropet (YAPPET) experiments performed in collaboration with Neuro imaging unit of Geneva Hospital

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

- **Need Better QUANTIFICATION than SUV coefficient**
- **Pharmacokinetics models**

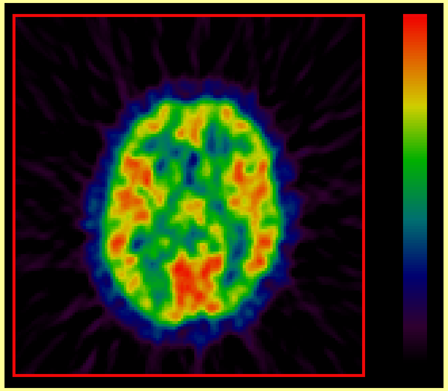
Part 1 : Backgrounds about mathematical modelling

Part 2 : Analysis of data obtained with the YAPPET.



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

What is modeling used for ?



Radioactivity concentration

PET images represent radioactivity concentrations

Not directly the biological parameters !!

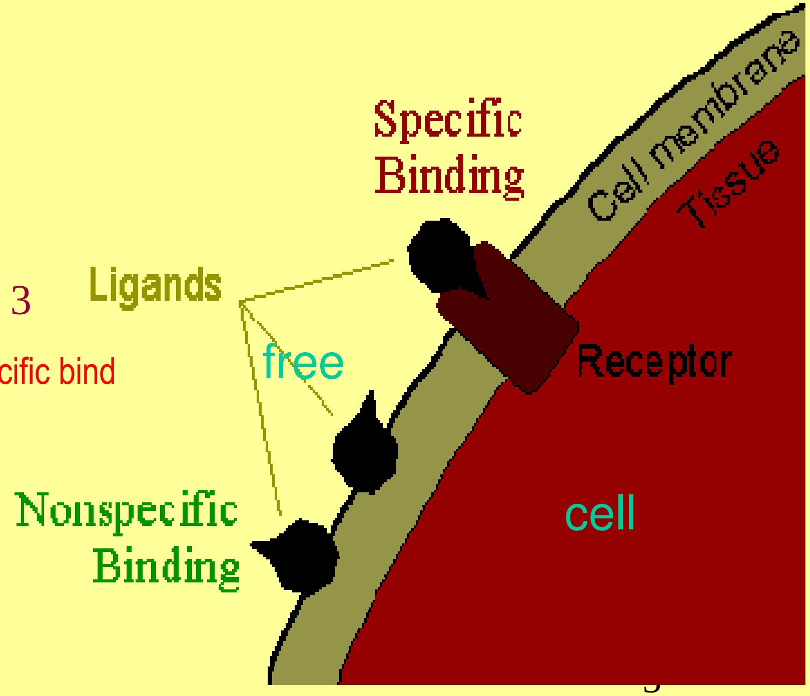
Vascular component
Radioactivity in brain blood vessels

\+

Tissular component

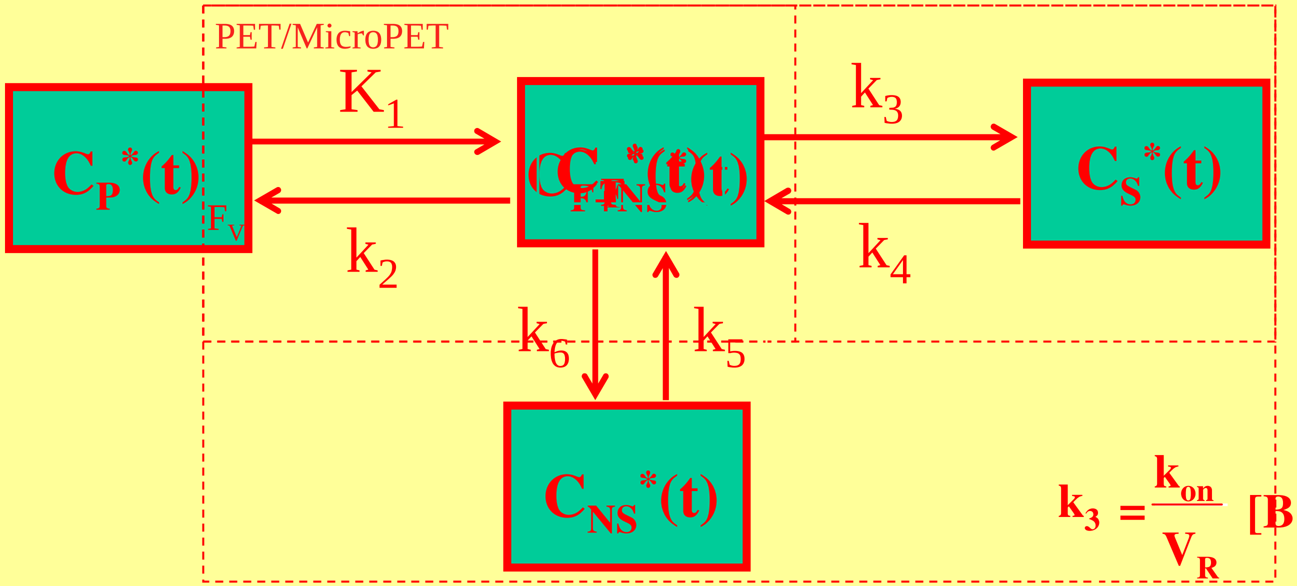
State 1 + State 2 + State 3

Ligands could have : Free Specific Bind Nonspecific bind



Mathematical modeling allows to extract biological parameters from whole PET data

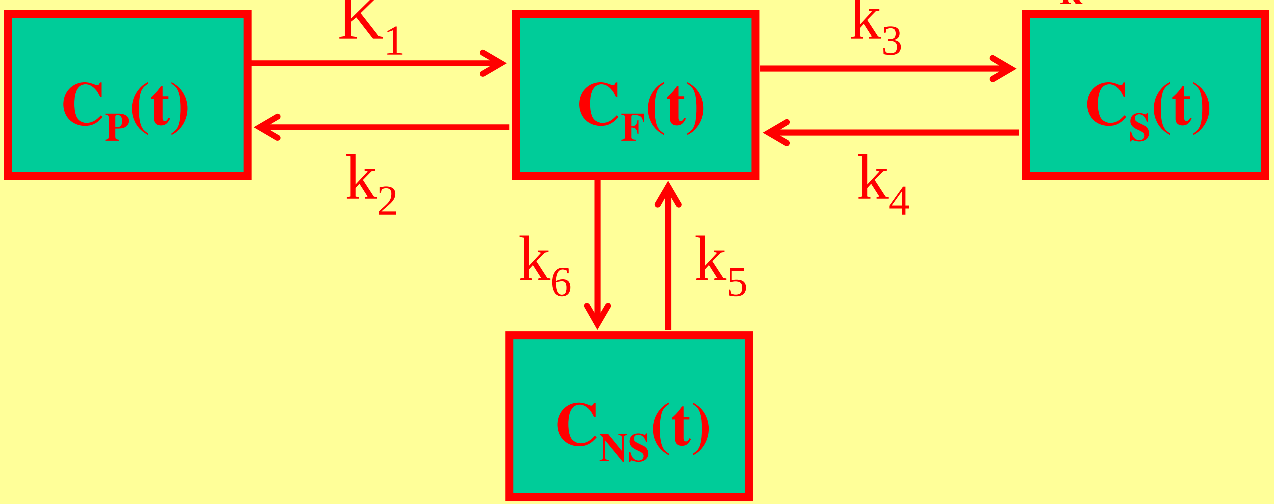
Compartment model



Radiotracer

$$k_3 = \frac{k_{on}}{V_R}\left[B'_{max} - C_s^*(t)\right]$$

$$k_3 = \frac{k_{on}}{V_R}\left[B'_{max} - C_s^*(t) - C_s(t)\right]$$

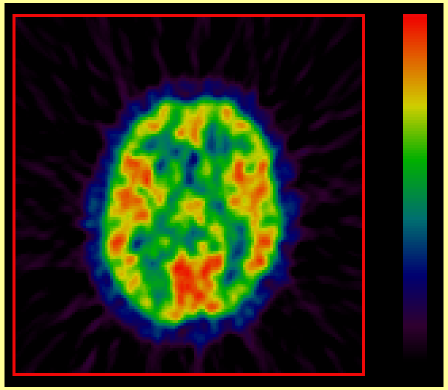


Cold ligand

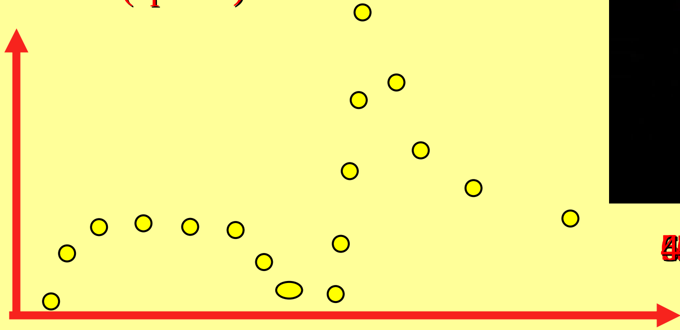
PET Can provide two types of images

Static or Dynamic images

Static image

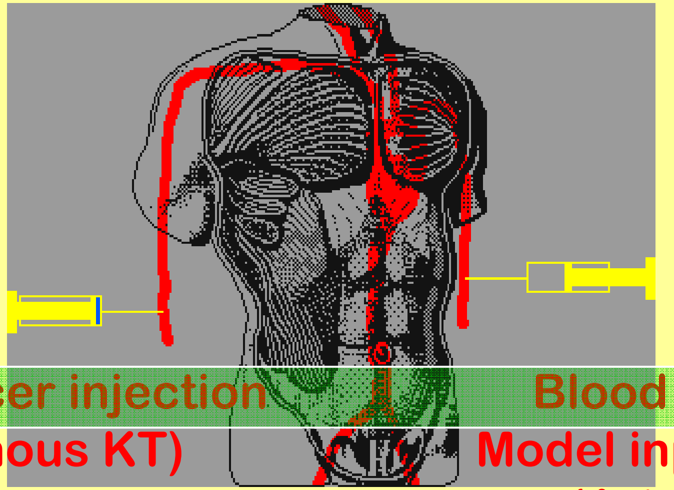


Concentration (cps/ml)



Time (min)

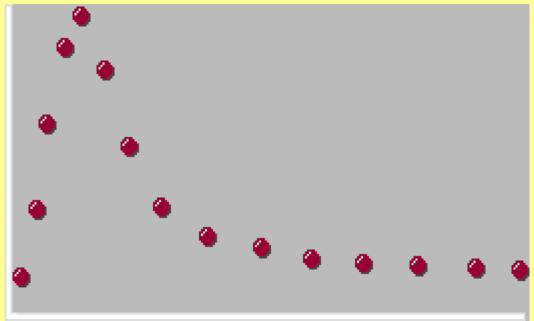
Plasmatic concentration



Tracer injection
(Venous KT)

Blood sampling
Model input function
(Arterial KT)

Time-concentration curve



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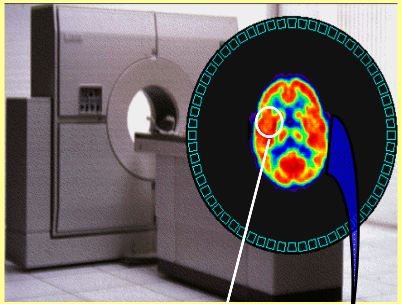
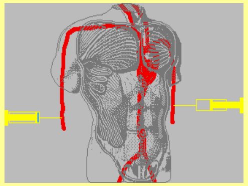
Parameter estimate

Experimental data

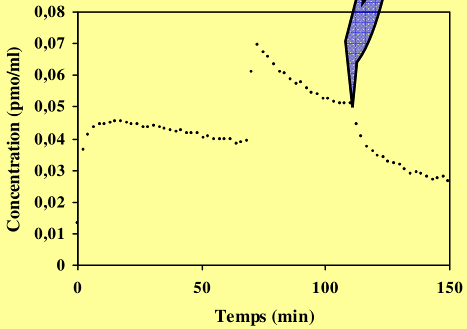


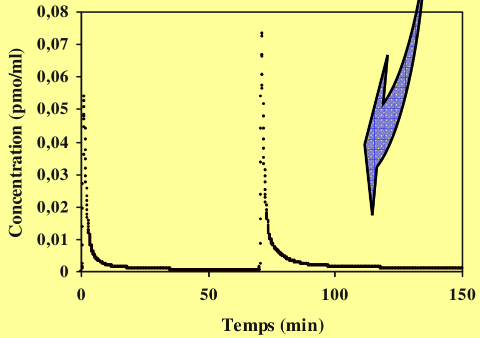


Input function from
Arterial blood trapping

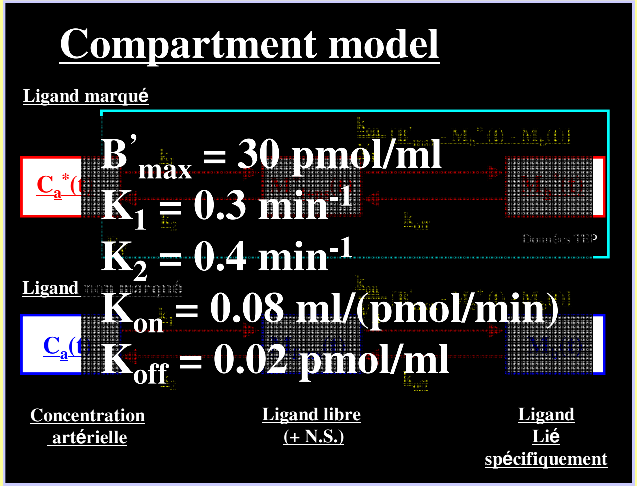
PET/SPECT

Fonction d'entrée

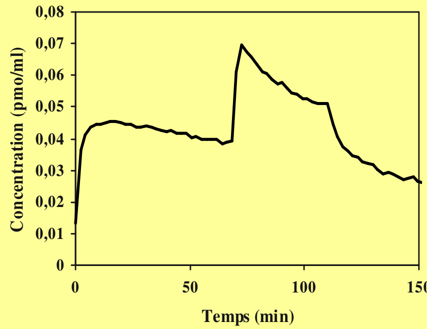




Model simulation

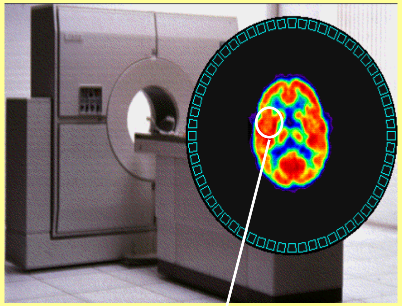


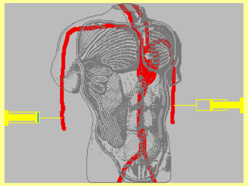
Simulation



Parameter estimate

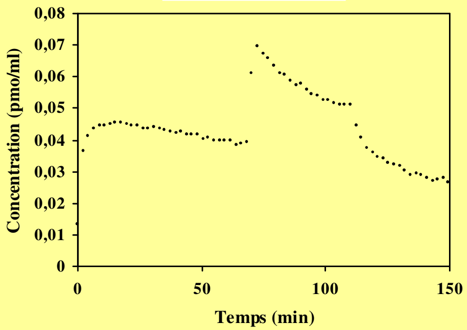
Experimental data



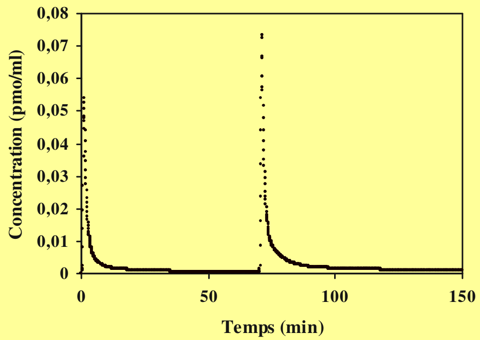


Input function from
Arterial blood trapping

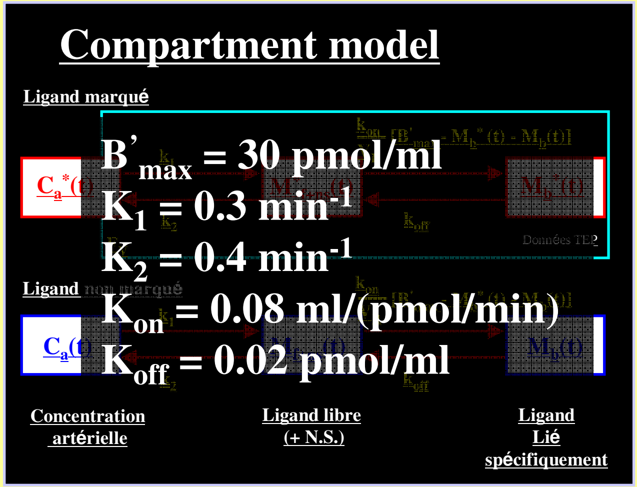
PET/SPECT



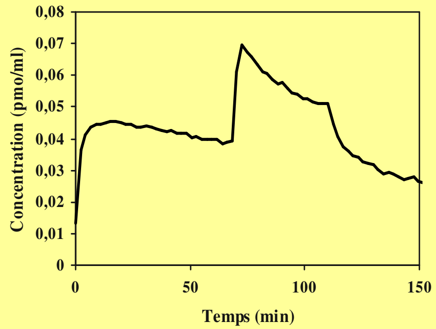
Fonction d'entrée



Model simulation



Simulation



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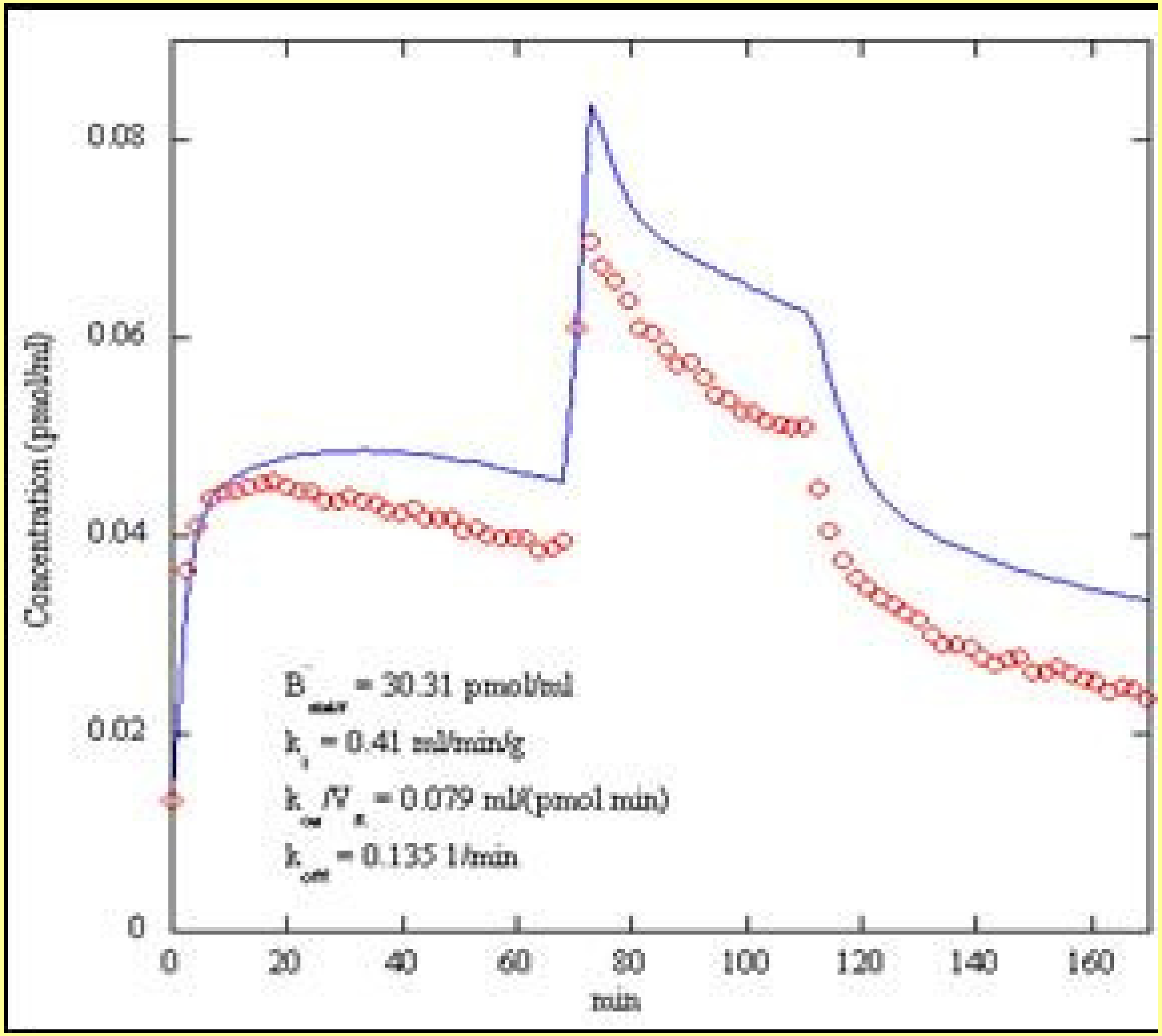
Parameter estimate

Identification Adjustment



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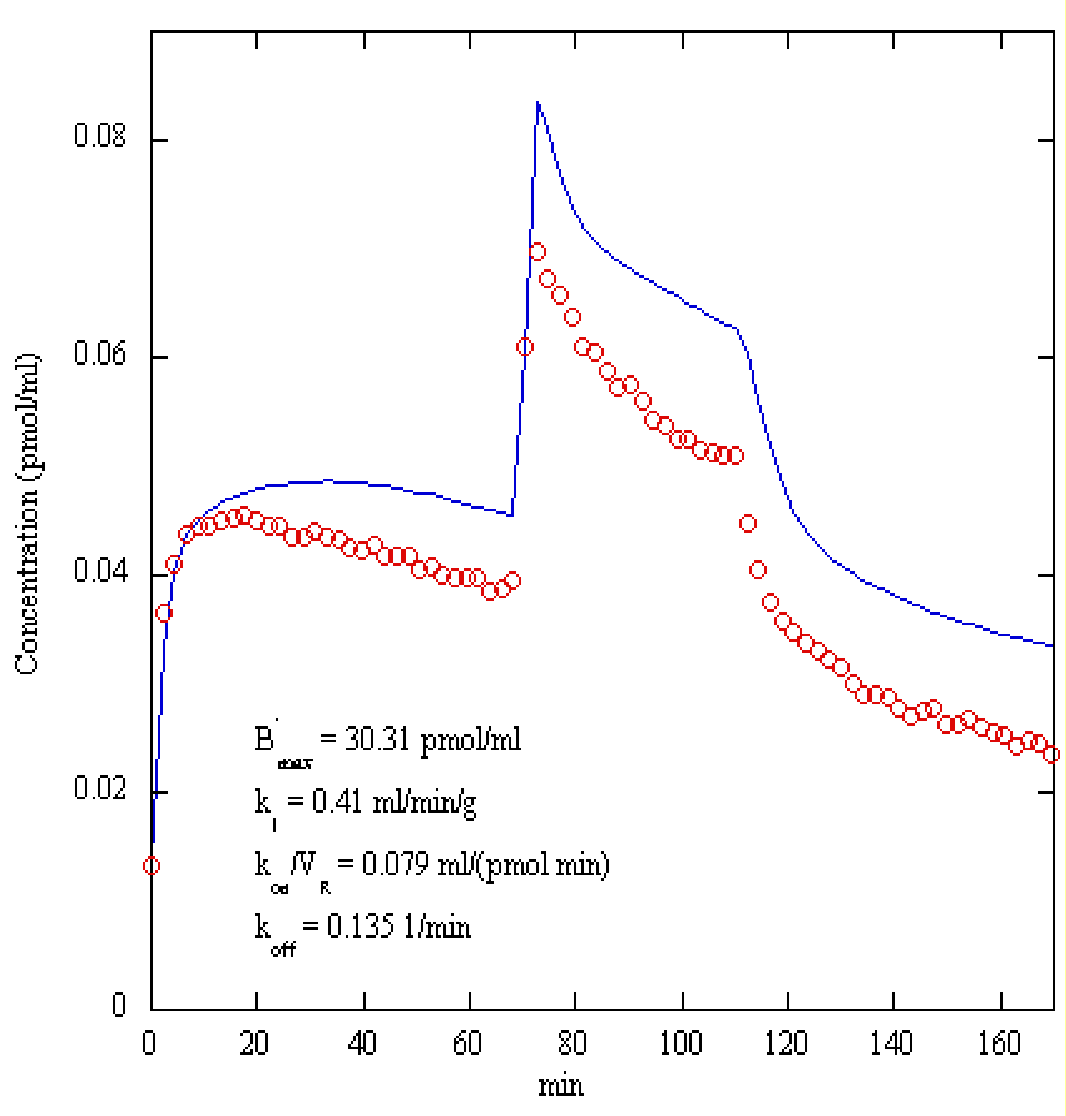
Parameter estimate
Identification Adjustment



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Modeling of ligand-receptor interactions

Application to $5HT_{1A}$ receptors

Receptor

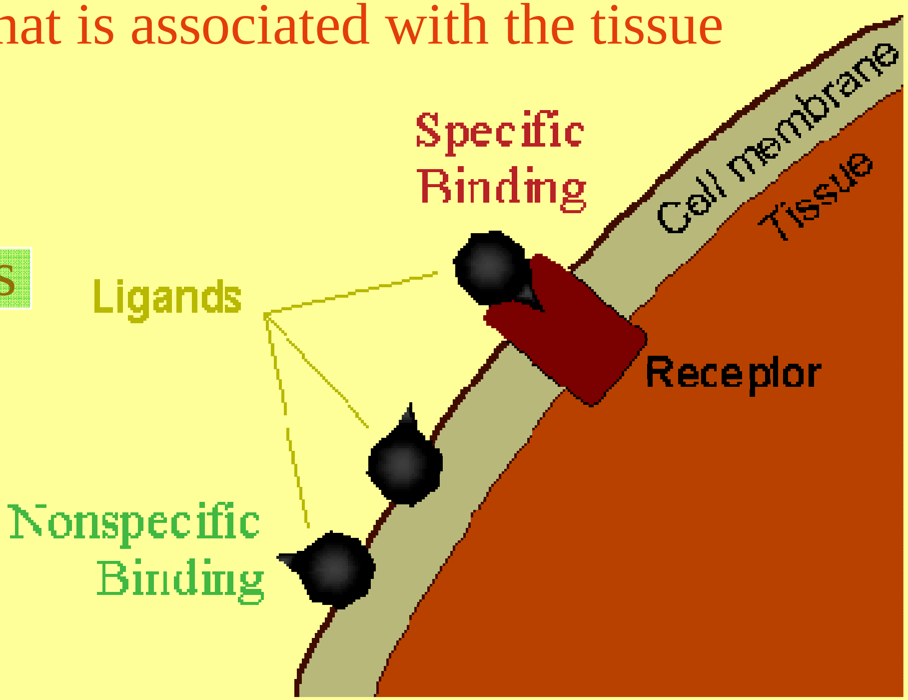
A molecule inside or on the surface of a nerve cell that binds to a specific substance (neurotransmitter or ligand) and causes a specific physiologic effect in the cell

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

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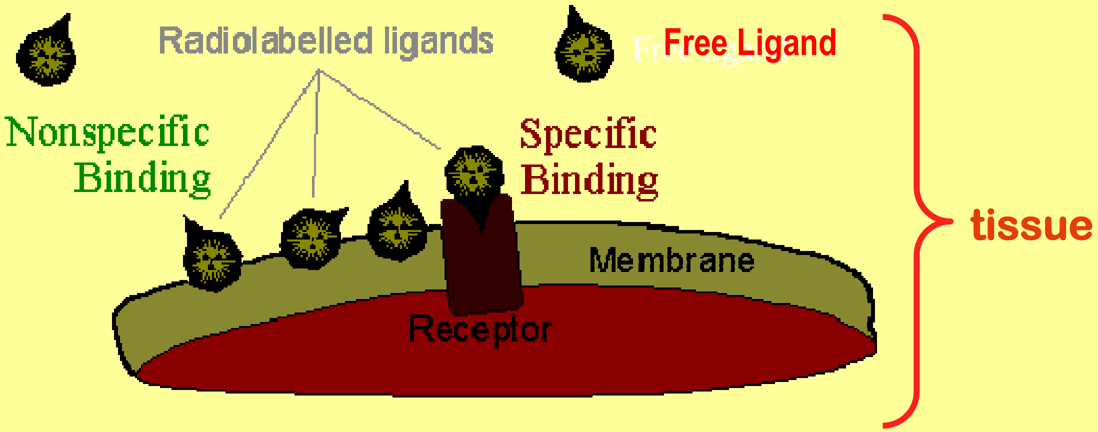

➡ Bound radioactivity = Nonspecific + Specific binding

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

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

Goal: B'_{max} and $1/K_d$ ⟶ **Model**

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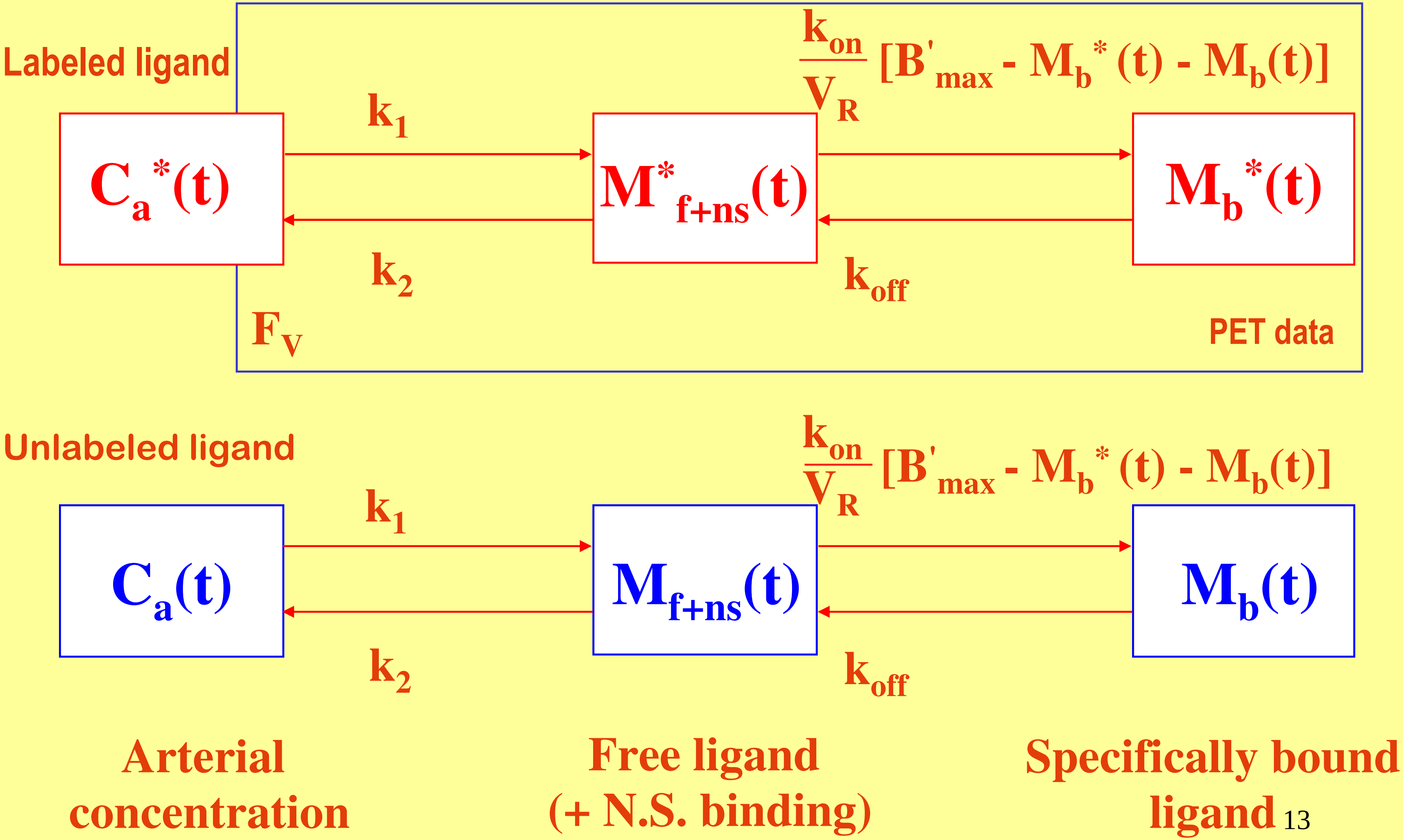
Ligand-receptor model



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In vivo **dynamic imaging of** Rat Brain - 500 µCi of ^{11}C-Flumazenil.

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5-HT$_{1A}$ receptor study

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Goal :

To study the effect of antidepressant treatments on 5-HT$_{1A}$ receptors

Quantification of ligand-receptor interactions in vivo using
[^{18}F]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}

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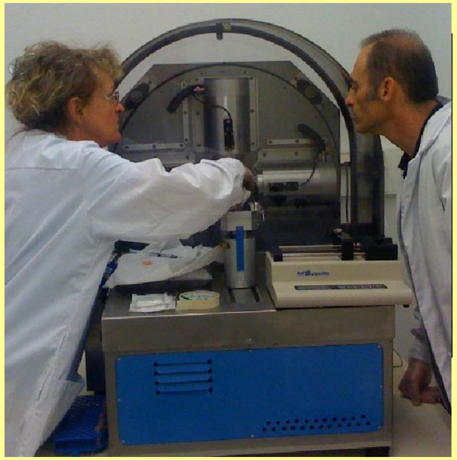
Full Scenario

Radiochemistry

Fluor 18
- Positron emitter
- T = 109 min

Ligand
- MPPF

YAPPET

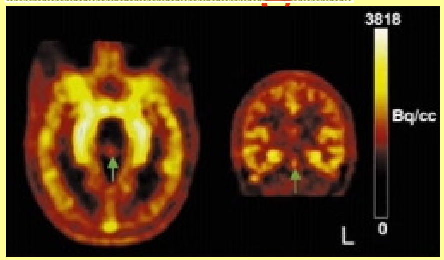


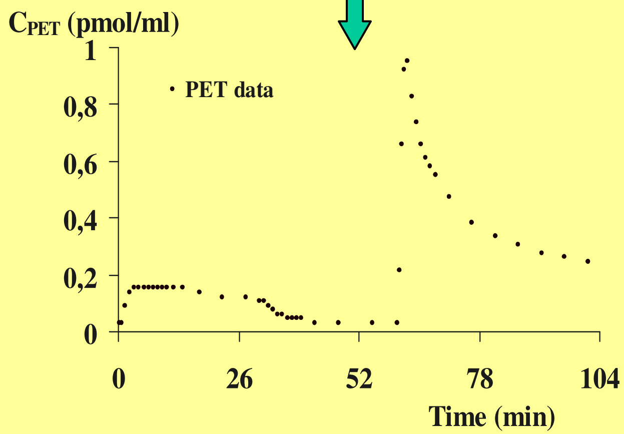
Radioligand

$[^{18}F]MPPF$

Injected
to the Rat

PET Images





Analysis

Activation studies

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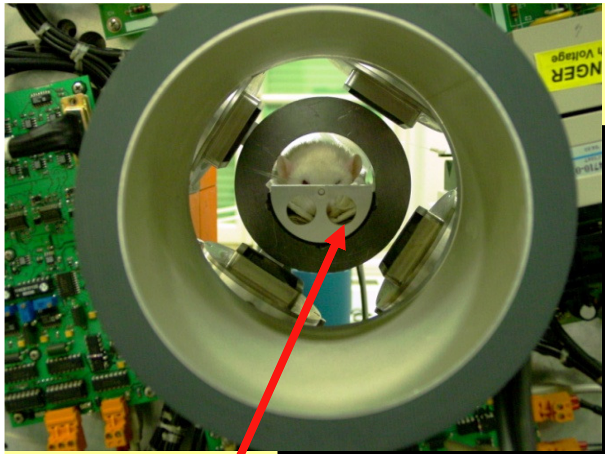
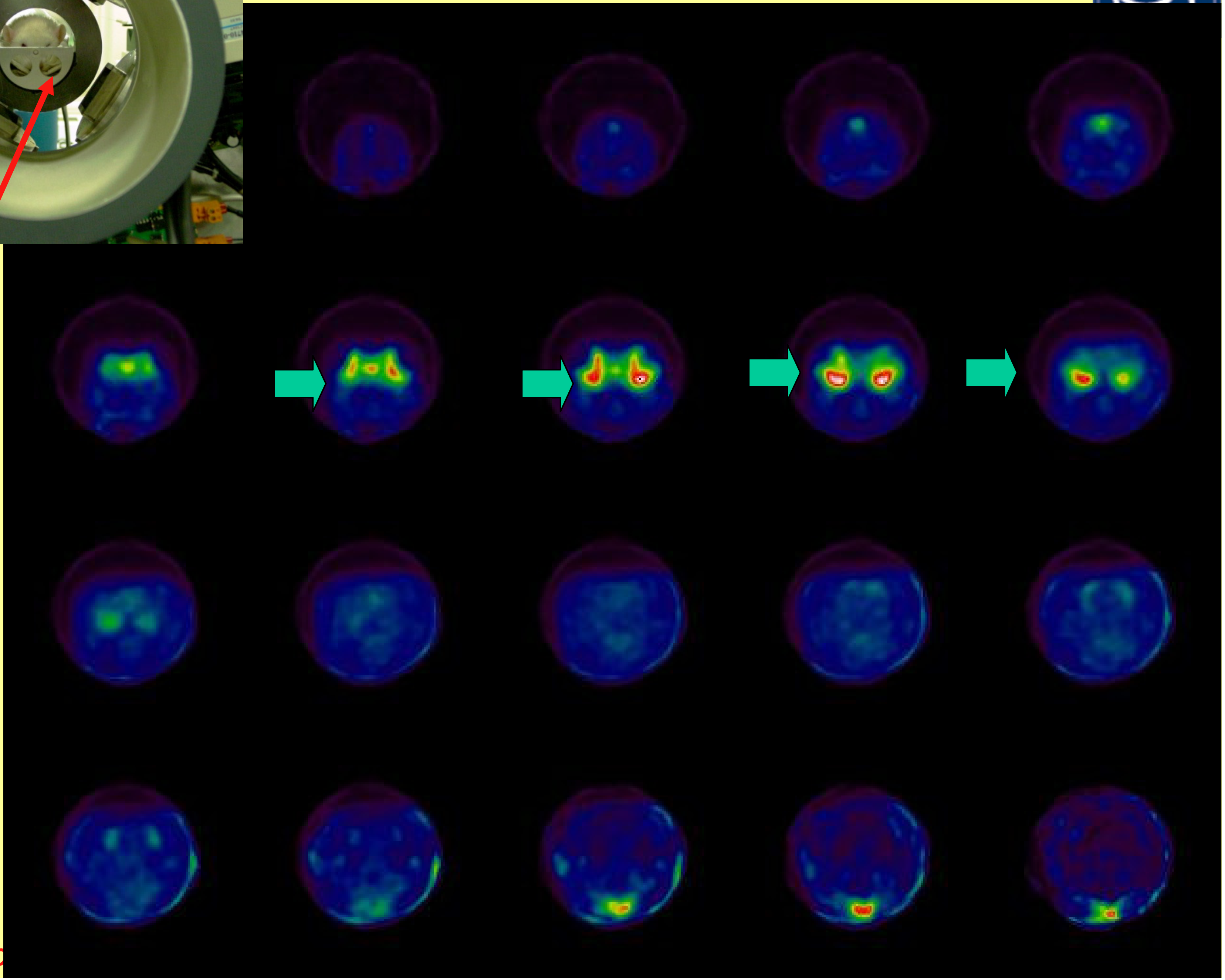
MPPF MicroPET (YAPPET) Images



The Rat

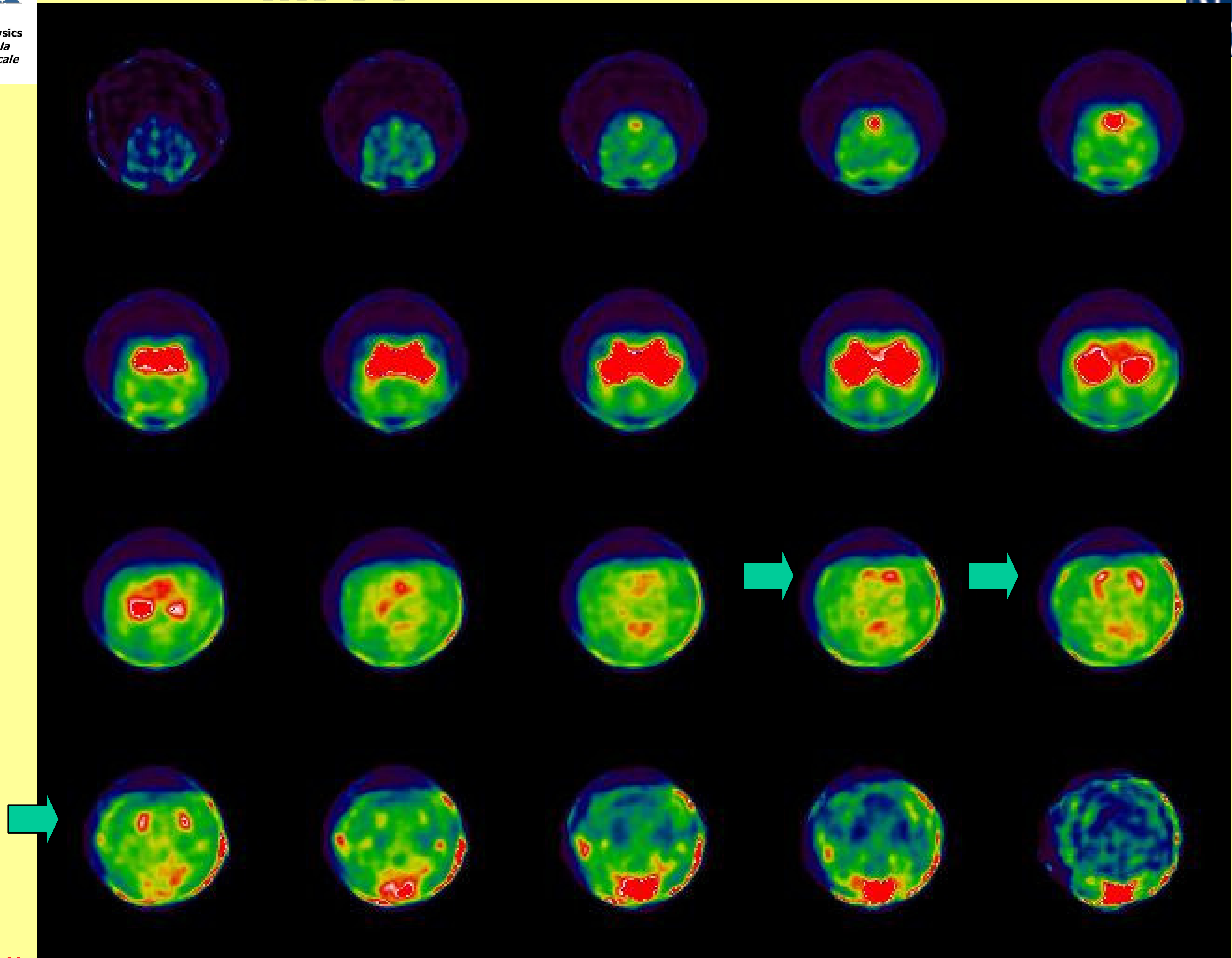


The YAPPET gave us a lot of images divided in 20 slides of 2 mm every 5 mn (for example)

Spurious effect of Harderian glands !!

MPPF

MicroPET (YAPPET) Images



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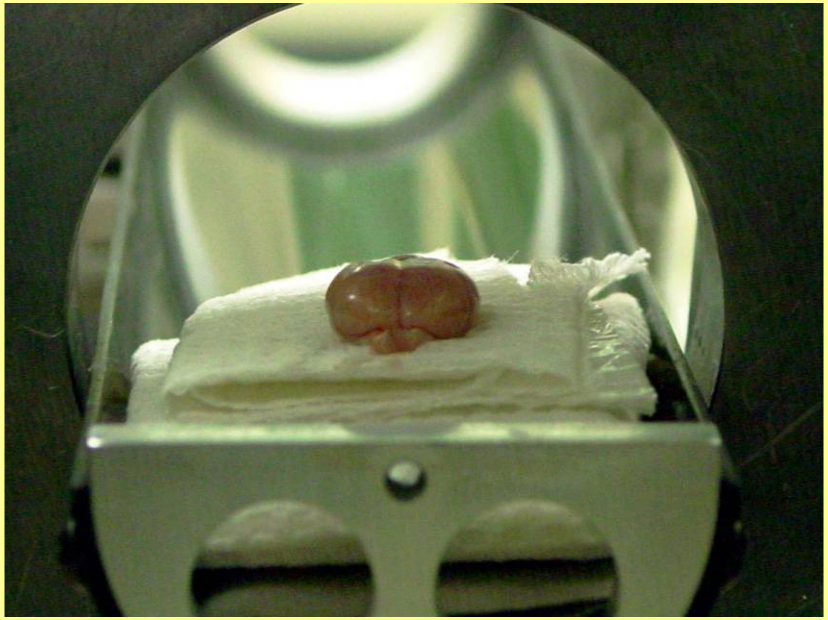
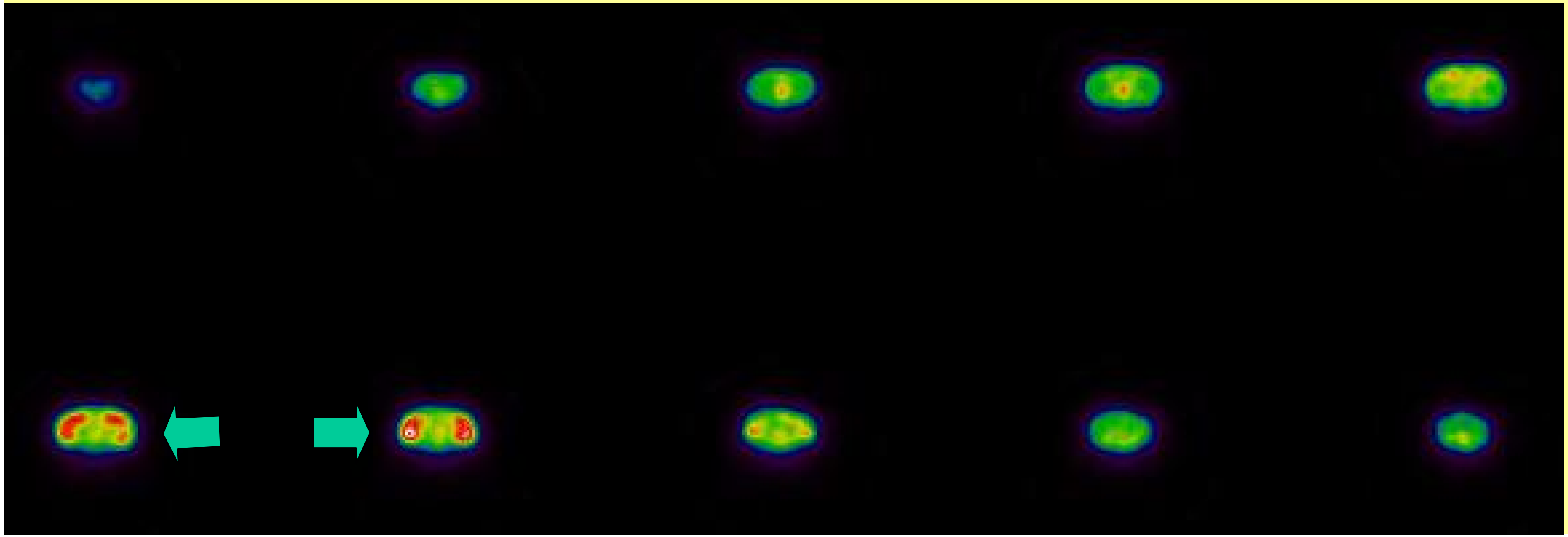
MPPF

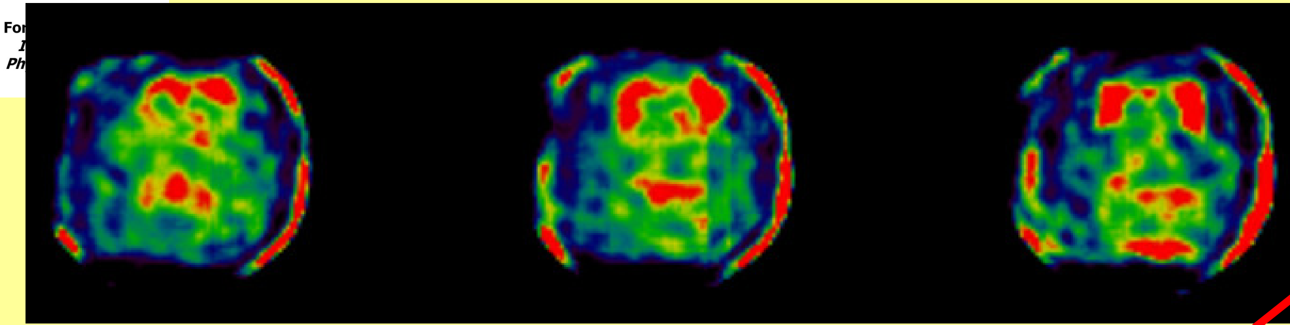
MicroPET (YAPPET) Images

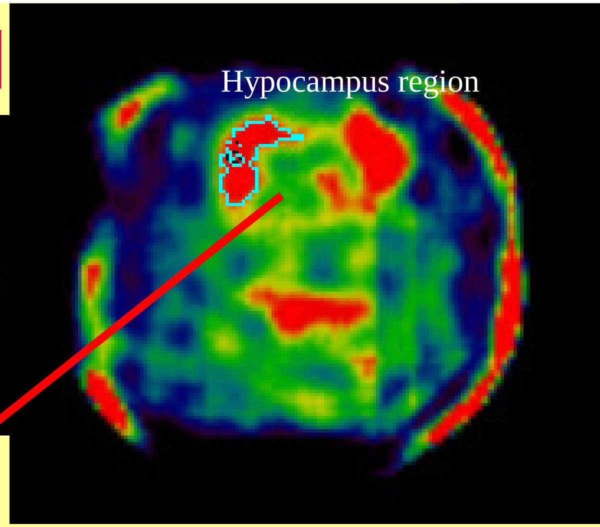
To get rid of Harderian glands, the Rat was sacrified, th brain extracted and put bak inside the YAPPET for static images

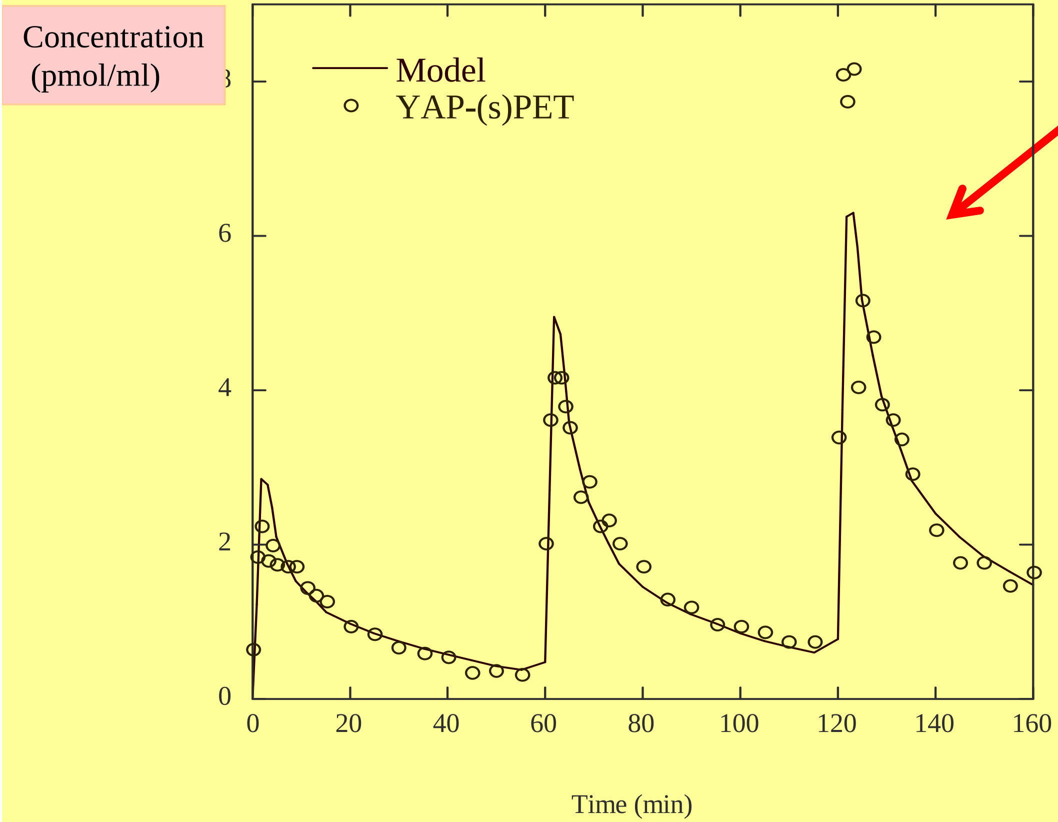




MPPF 5-HT$_{1A}$ receptors using [^{18}F]







6 Parameters estimate:

B'_{max} = 1.94 ± 0.56 pmol/ml

K_1 = 0.306 ± 0.022 min^{-1}

k_2 = 0.257 ± 0.019 min^{-1}

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

k_{off} = 0.053 min^{-1}

$K_d V_R$ = 2.13 pmol/ml

From YAPPET Images, the density of 5-HT$_{1A}$ receptors B'= 1.94 ± 0.56 pmol/ml

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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 !)

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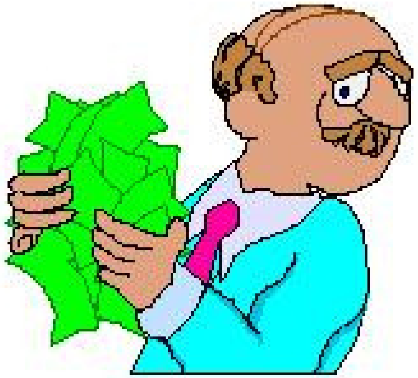
CERN



Thanks a lot for the gentle attention!