Neurotransmitter Systems Studied with Positron Emission Tomography

By Lauri Tuominen

Outline of talk

1. Neurotransmission – what is it?
2. Basic principles
3. Examples of study designs

Why PET?

- PET imaging allows the study of neurotransmission in the living brain

Example:
Dopamine synthesis is increased in schizophrenia

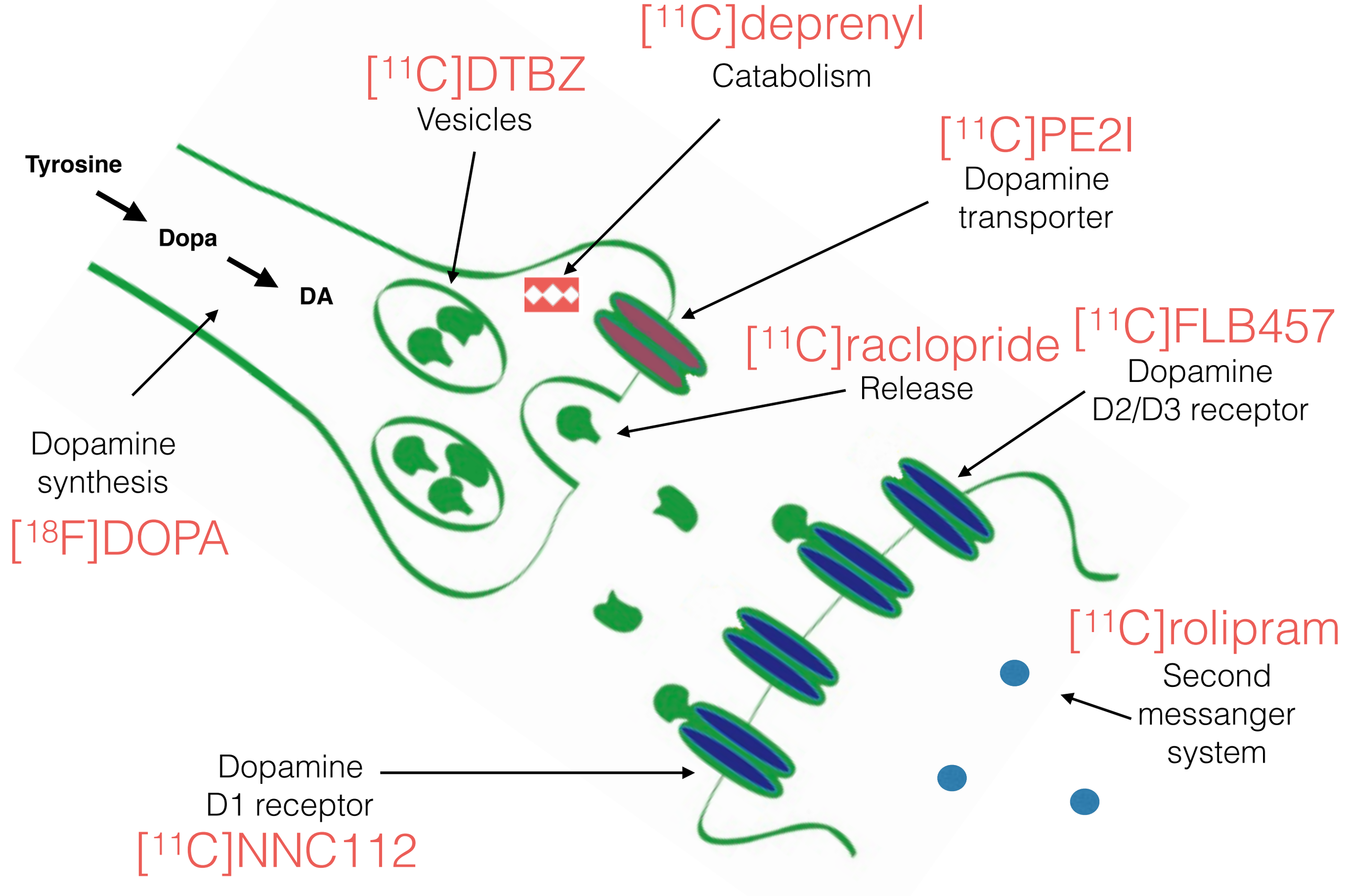
Neurotransmission

Wikipedia: the process by which signaling molecules called neurotransmitters are released by a neuron, and activate the receptors of another neuron

Neurotransmission

- Communication between neurons in brain
- Along the signaling pathway
  - Neurotransmitter synthesis and storage
  - Neurotransmitter release
  - Postsynaptic receptors
  - Second messenger systems and other downstream effects
  - Reuptake and catabolism

Neurotransmission



Neurotransmitter system

- Dopamine
- Glutamate
- Gamma-amino butyric acid (GABA)
- Serotonin
- Opioid
- Cannabinoid

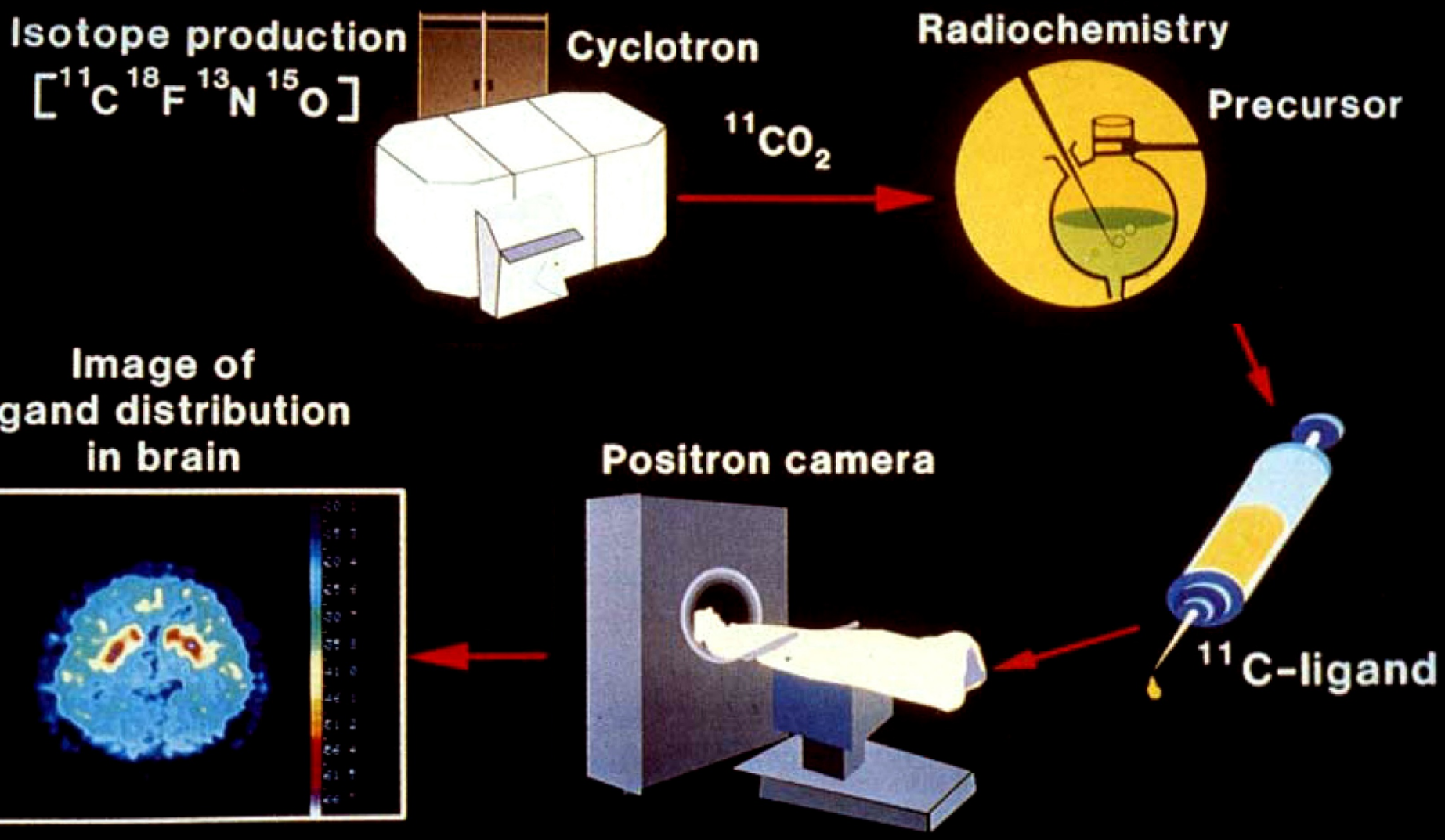
How PET

- PET imaging is based on detecting radioactively labelled compounds in the tissue
- Carbon-11 and fluorine-18 are the most commonly used isotopes for radioactive labelling
- Isotopes are used to label ligands that bind to biologically interesting targets in the tissue
- PET scanner measures changes in radioactivity concentration over time
- Mathematical models are used to derive index of the target density from the radioactivity concentration

Positron emission tomography: pros and cons

- **Pros**
  - Molecule level phenomena in living tissue
  - Minimally invasive
  - Chemical resolution (specificity)
  - Chemical Sensitivity (up to 10^{-9} mol/L)
- **Cons**
  - Modest spatial resolution (up to 2–3 mm)
  - Poor time resolution (minutes)
  - Ionizing radiation (typically about 3 mSv per injection)
  - Limited availability
  - High cost

POSITRON EMISSION TOMOGRAPHY



Cyclotron is a particle accelerator that is used to produce carbon-11

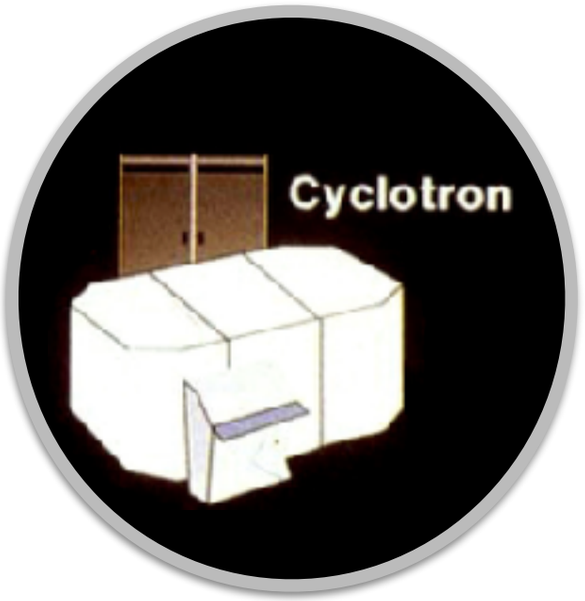
- A beam of charged particles is accelerated into a spiral path using alternating voltage

- Carbon-11 is produced by bombarding gaseous nitrogen-14 with protons, which induces an alpha decay:

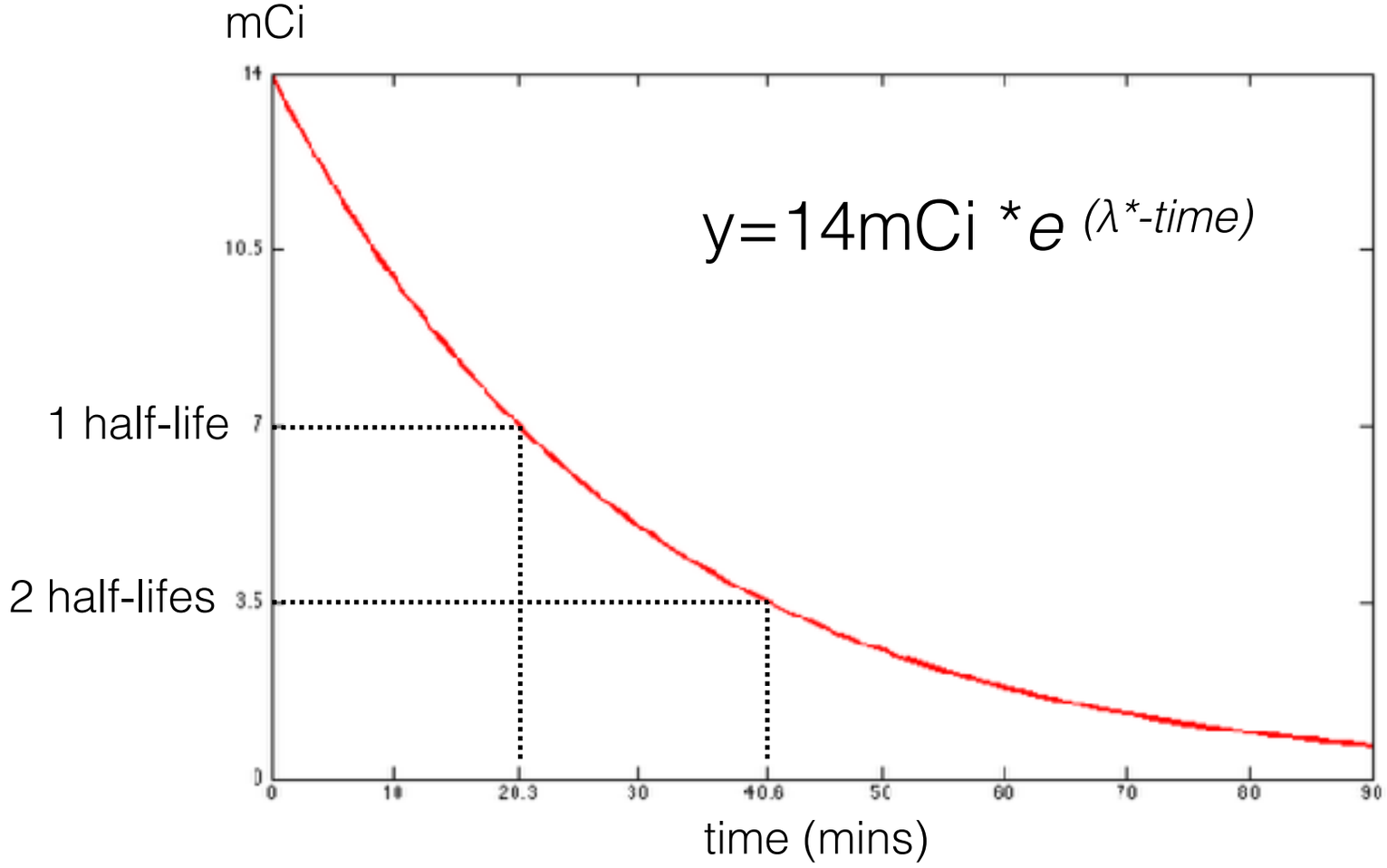
    - $^{14}N(p,\alpha)^{11}C$

18 MeV CC18/9 Cyclotron at the Turku PET Centre

Carbon-11 decays to Boron-11 through positron emission



- $^{11}C \longrightarrow {}^{11}B + e^{+} + \nu$
- Half-life of ^{11}C is 20.3 minutes



λ = decay constant

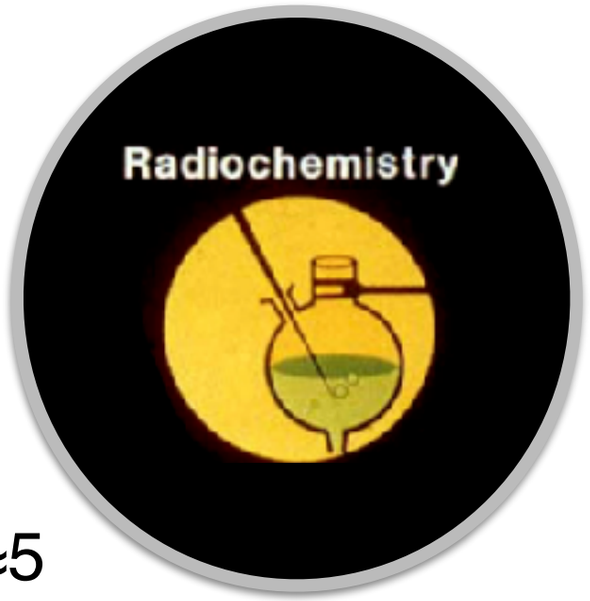
Different ligands are used to study different biological processes

Radioligands produced at the Martinos center:

- [^{11}C]Raclopride
- [^{11}C]Diprenorphine
- [^{11}C]PBR28
- [^{11}C]Martinostat
- [^{11}C]DASB
- [^{11}C]NNC112
- [^{11}C]Temozolomide
- [^{18}F]Fallypride
- [^{18}F]FLT
- [^{18}F]T807
- [^{18}F]FMISO
- [^{18}F]FDG
- [^{68}G]DOTATOC

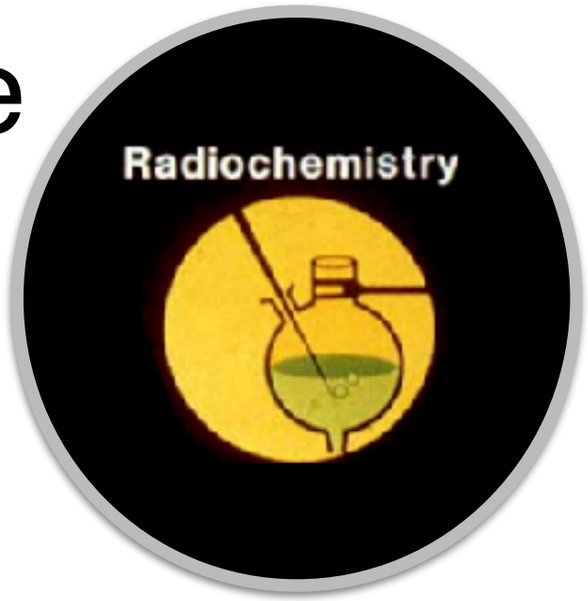
Creating new ligands is an active field of research

What makes a good radioligand?

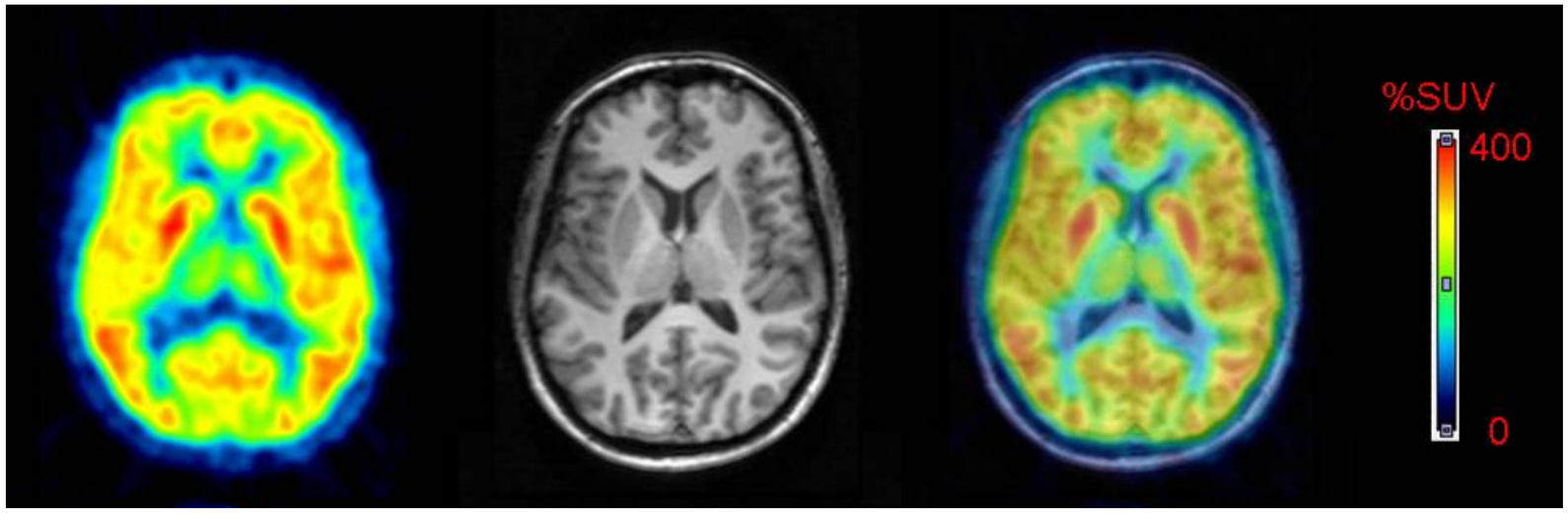


- Optimal target density and ligand affinity: Density x Affinity ≈5
- High brain uptake
- Optimal lipophilicity (*LogP*=2.5–4)
  - Sufficiently high to cross blood-brain barrier
  - Not too high to cause non-specific binding
- Not substrate for efflux transporters at BBB (*e.g.*, P-gp)
- No brain-penetrant radiometabolites
- High pharmacological selectivity
- Quantifiable plasma protein binding / have a refence region
- Amenability to rapid labelling with high specific activity
- Fast enough kinetics to allow measurement in a few hours

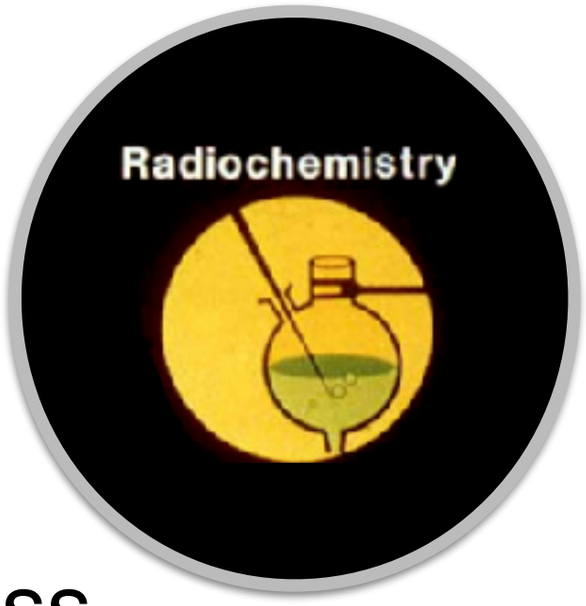
^{18}F-FMPEP-d_2: high brain uptake despite high lipophilicity



- ^{18}F-FMPEP-d_2 for cannabinoid CB_1 receptor
- Very lipophilic (*LogP*= 4.8)
  high protein binding and high non-specific binding
- High brain uptake and specific binding because CB_1 receptor is the highest density GPCR in the brain

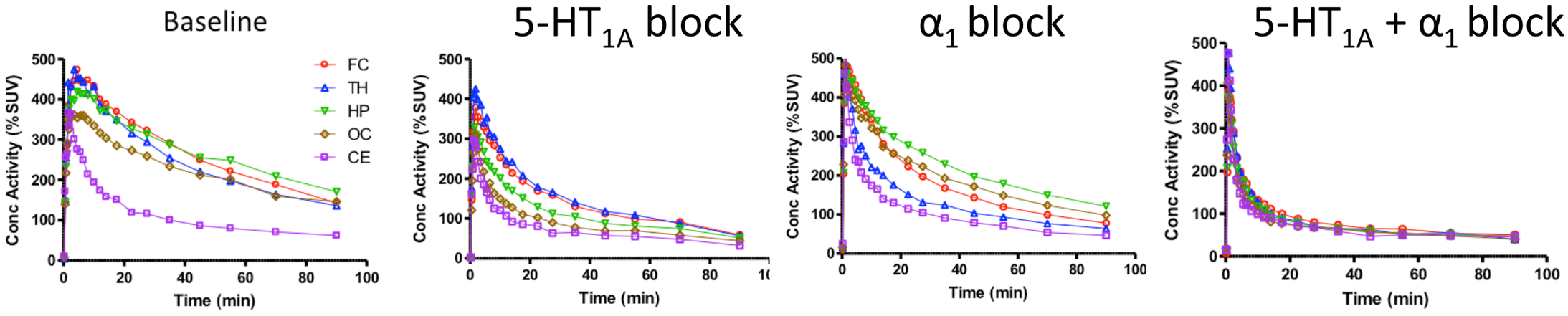


Target selectivity

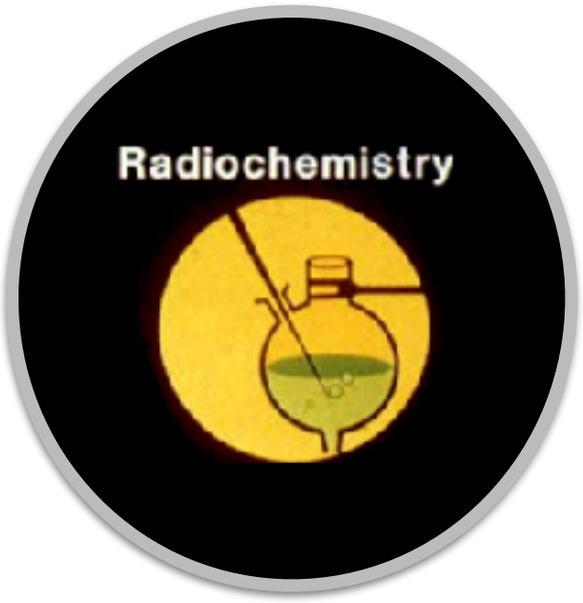


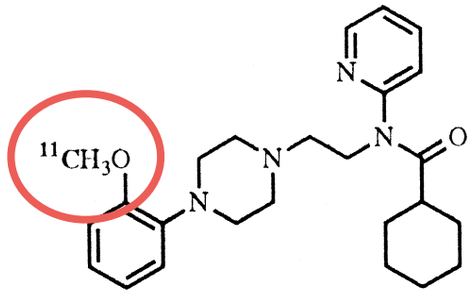
- Ligand should bind to target only to avoid cross-contamination
  - PET scanner measures only radioactivity
- Pharmacological screening prior to clinical studies

^{11}C-CUMI-101: a 5-HT$_{1A}$ receptor agonist contaminated with α_1 receptors

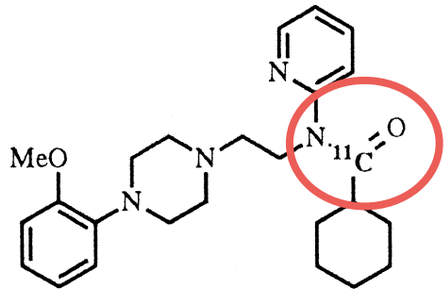


Radiometabolites





[*O-methyl*-^{11}C]WAY-100635



[*carbonyl*-^{11}C]WAY-100635

Enters the brain

Does not enter the brain

PET scanner measures only radioactivity

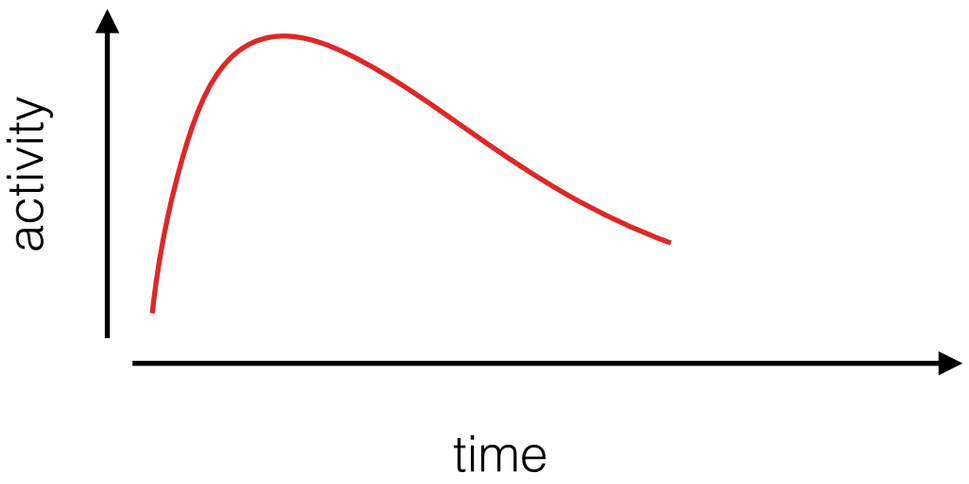
Osman et al. *Nucl Med Biol* 1998;25:215–223

Radioligand can be given as a bolus or bolus+infusion

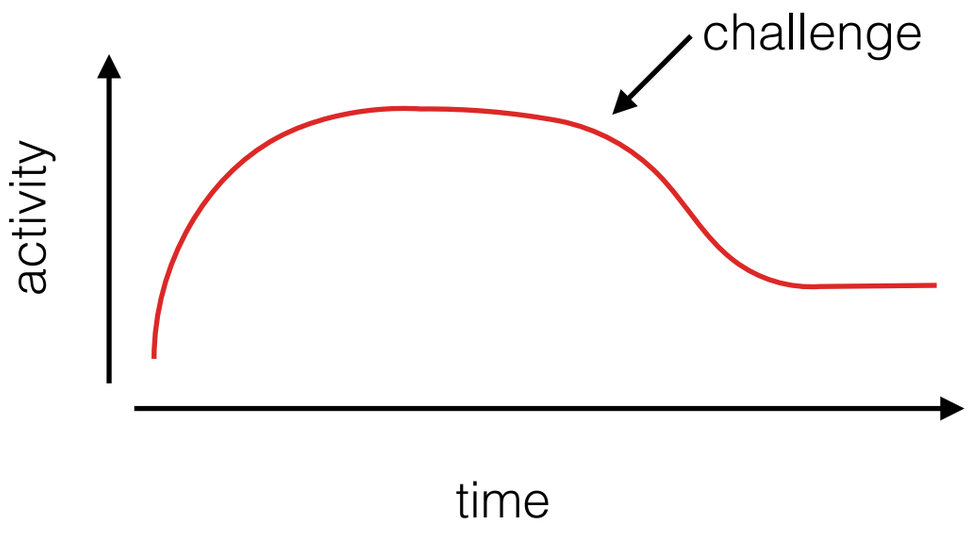
- Bolus = the whole dose is given at once

- Bolus+infusion = part of the dose is given as a bolus and the remaining radioligand is infused slowly during the rest of the scan

Bolus



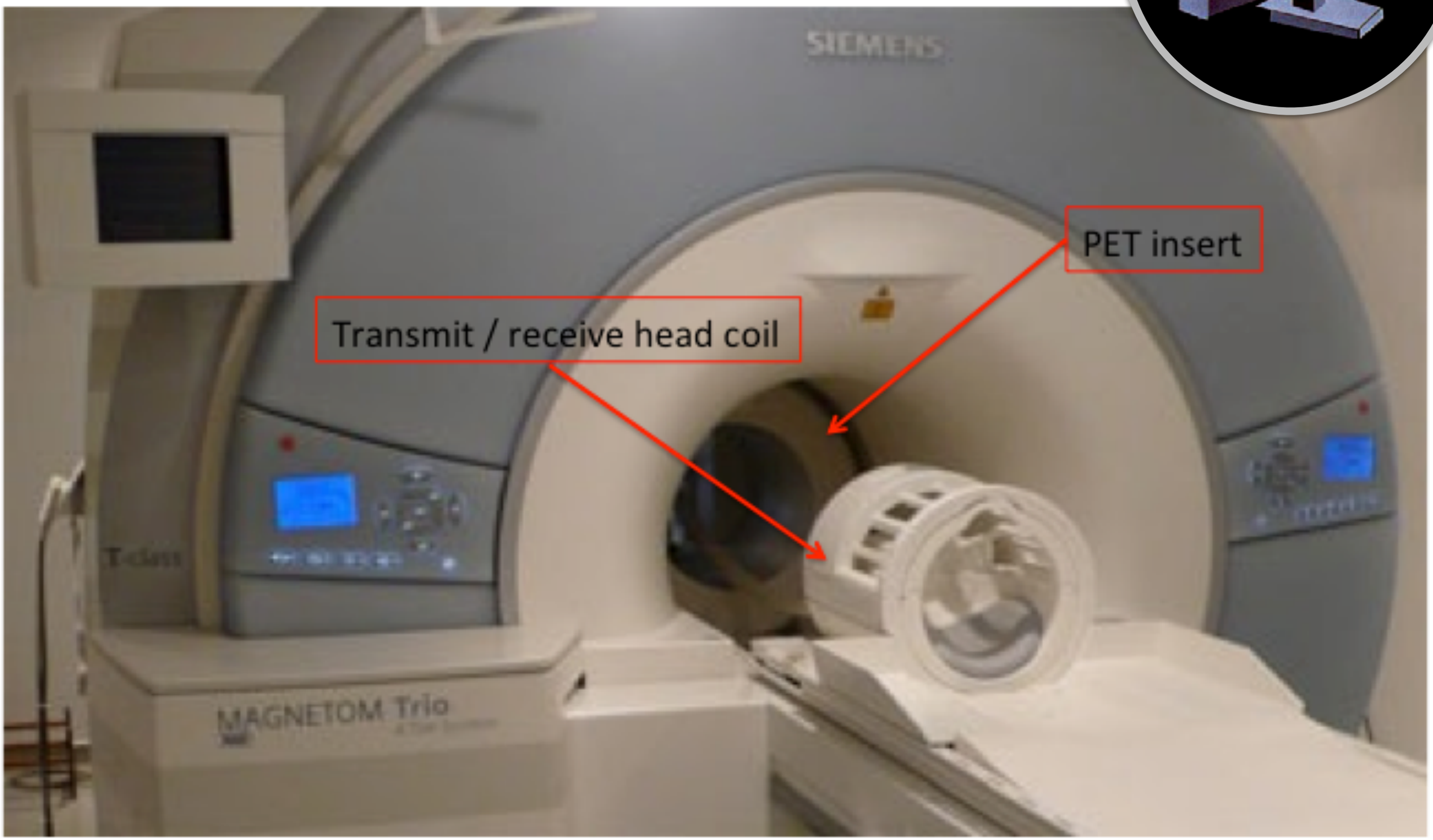
Bolus+infusion



Bolus vs. bolus+infusion

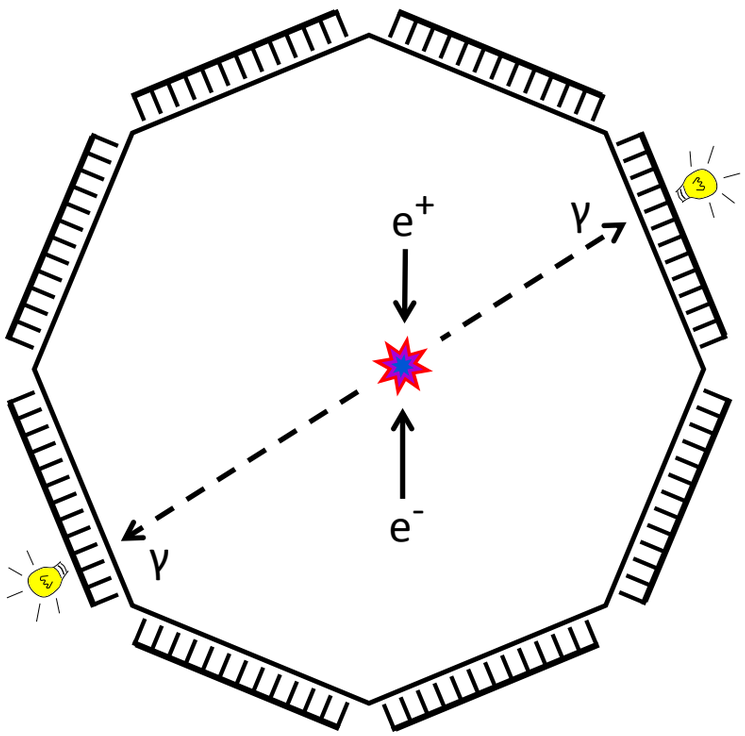
	Required dose	Scan time	scans required for a challenge	Counterbalancing stimulus	Requires Kbol estimation	Modelling
Bolus	low	short	1-2	yes	no	complex
Bolus+infusion	high	long	1	no	yes	simple/ complex

Bay 6 PET/MRI scanner



Kolb et al., molecular imaging 2012

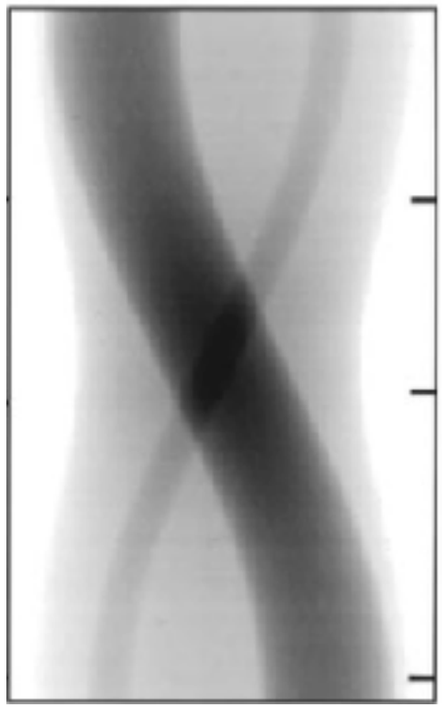
How PET scanner works?

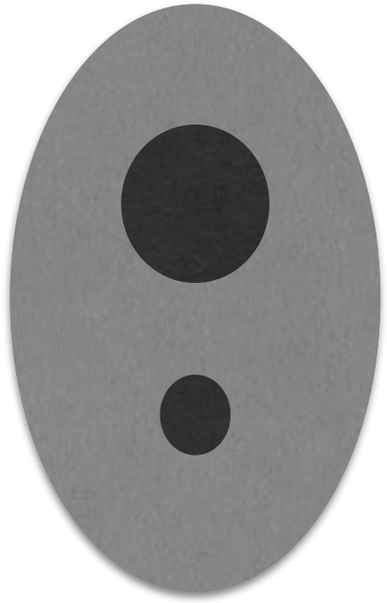


Coincidental detection of two photons emitted in annihilation of positron and electron

LOR: distance from the center & angle

Sinogram



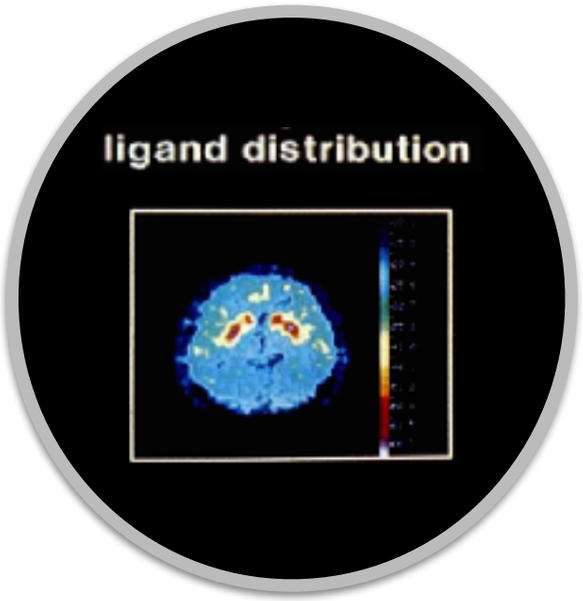


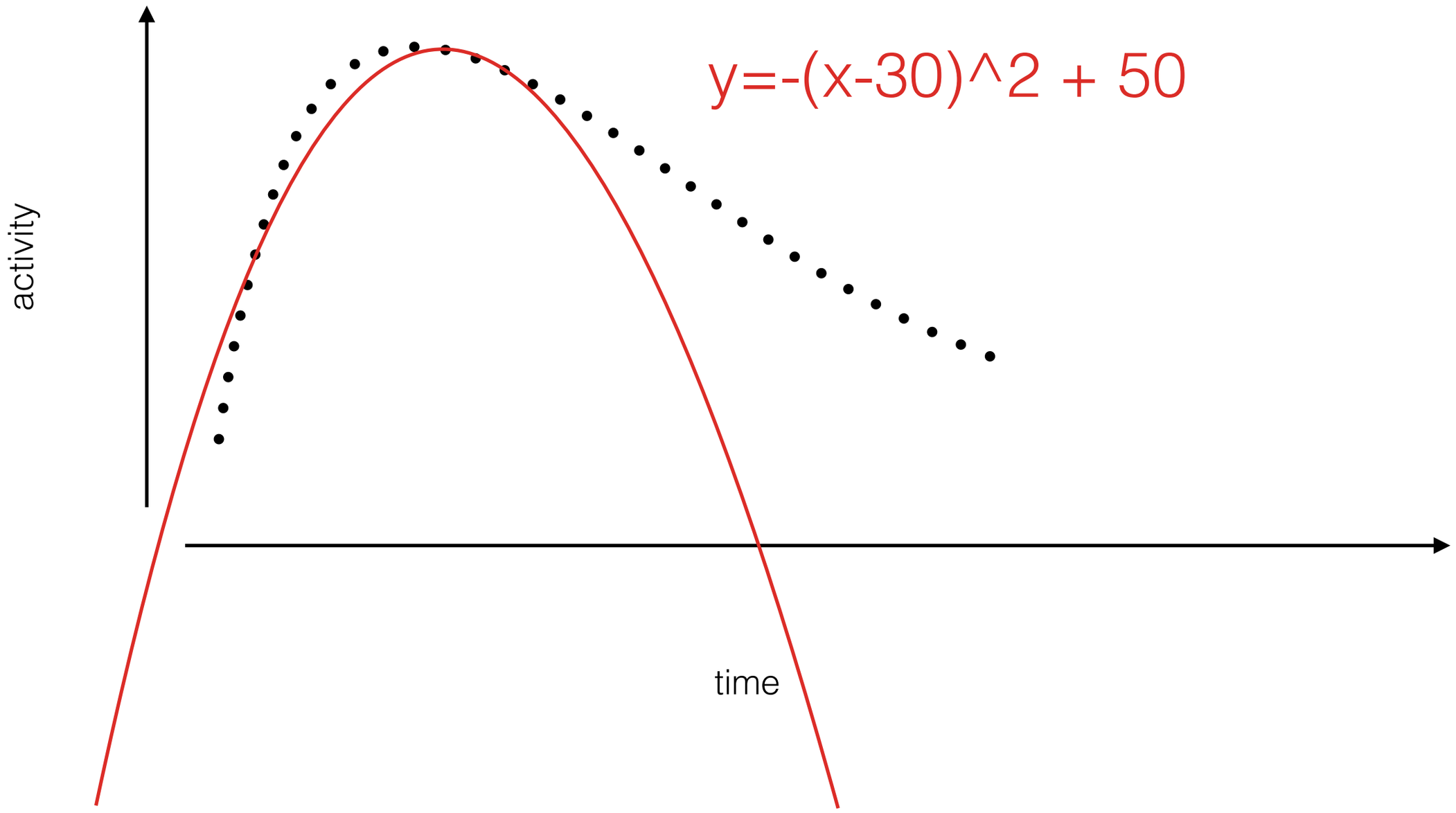
Fahey, J Nucl Med Technol 2002

Resolutions - spatial, temporal and chemical

- Spatial resolution ~ 3 mm fwhm of point spread function
- Temporal resolution ~ minutes to 20 minutes
- Chemical resolution ~ K_i 100x lower than for closest resembling molecules
- Chemical sensitivity 10^{-12} – 10^{-9} mol (~MRS sensitivity 10^{-4} mol)

Modelling means fitting a function to the data





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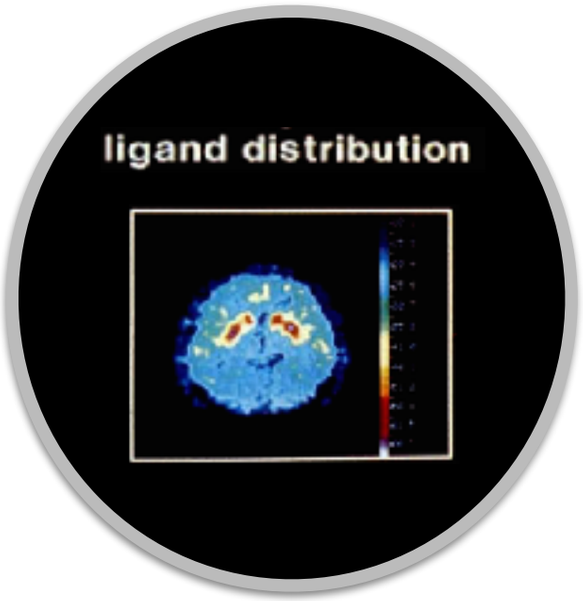
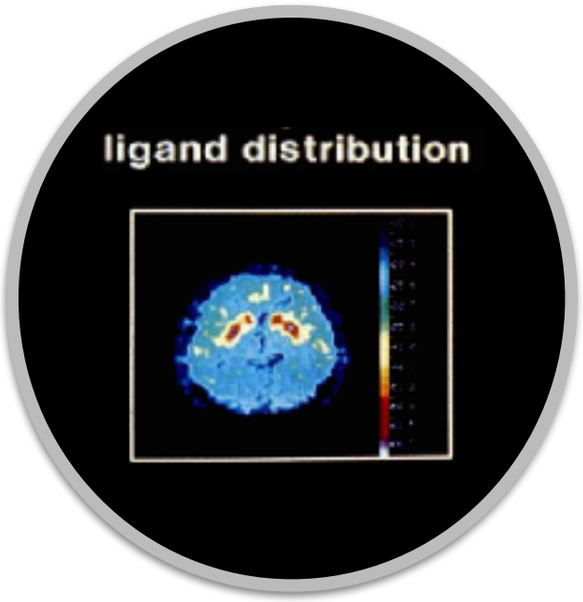


$$y = K_1 e^{-k2t} + k_3 e^{-k4t}$$

activity

time

What is this thing called Binding Potential?

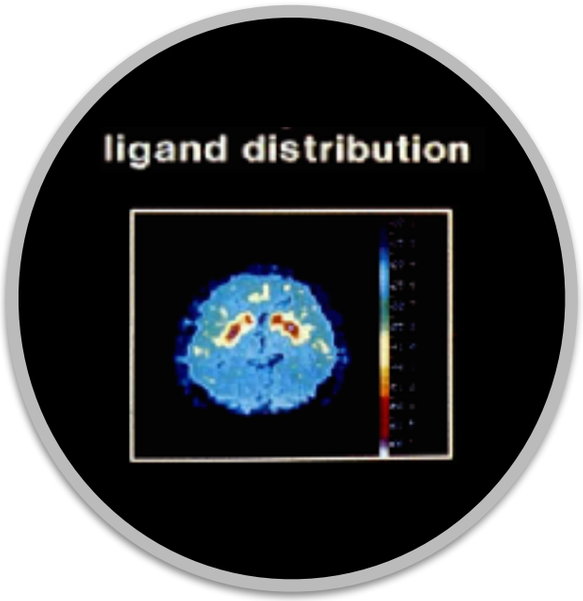


BP = k3 / k4 = affinity x density

How can we get k3/k4 from this:

$$y=K_1 e^{-k2t} + k_3 e^{-k4t}$$

Reference tissue model



Region of interest

C_P

K1’

k2a

C_{F+NS}

k3

k4

C_B

K1’

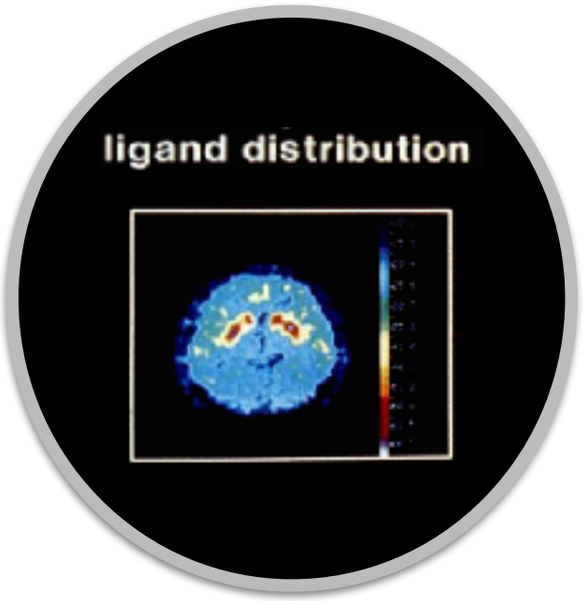
k2’

C_{ref}

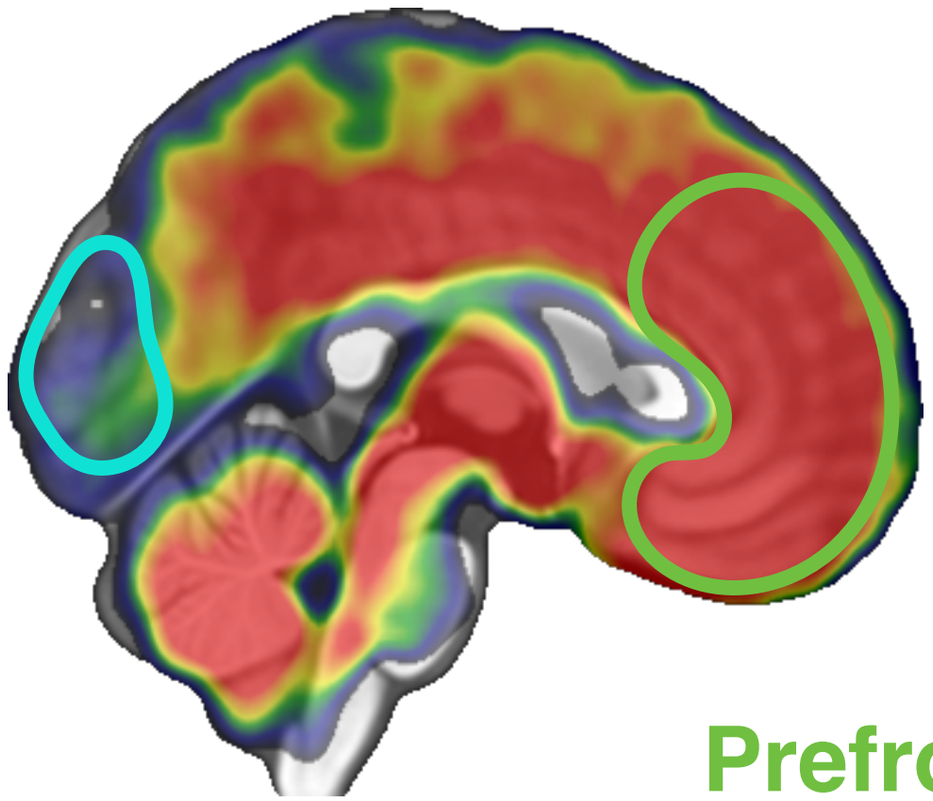
Reference region

$$C_{F+NS} = C_{ref}$$

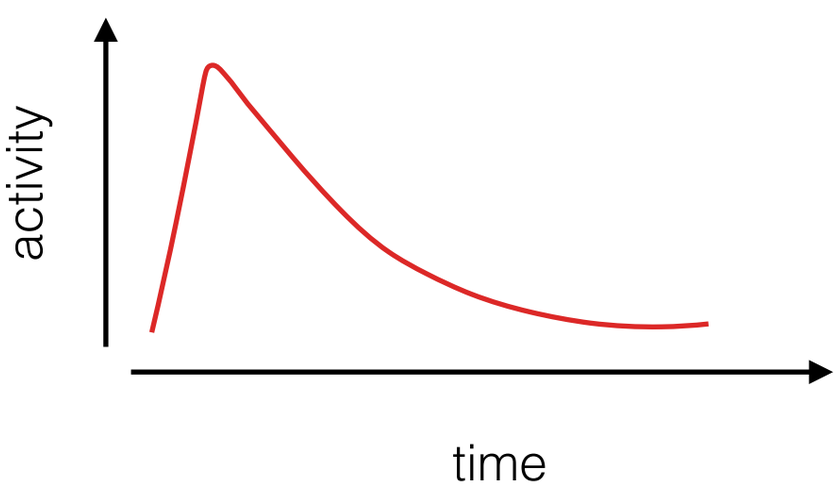
Reference region is devoid of target molecule



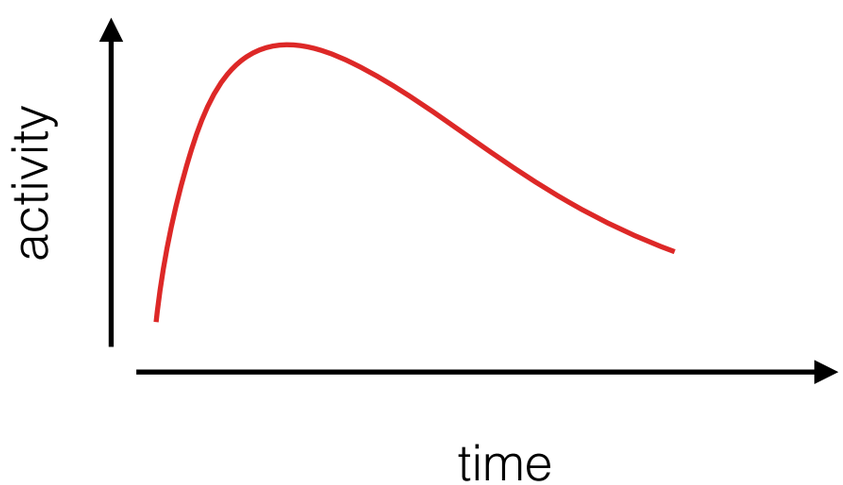
μ-opioid receptor



Occipital cortex



Prefrontal cortex



How PET data-analysis in practice

- Reconstructed PET data consist of several volumes, one for each timeframe
- Volumes are realigned to correct for motion
- Obtain time-activity curves from volumes of interest
- Each time activity curve is modelled to derive binding potential in each ROI