Translational Research in Molecular Imaging and Radionuclid Therapy

August 30 – September 1, 2018

Quantitative Imaging and Tracer Kinetic Modelling

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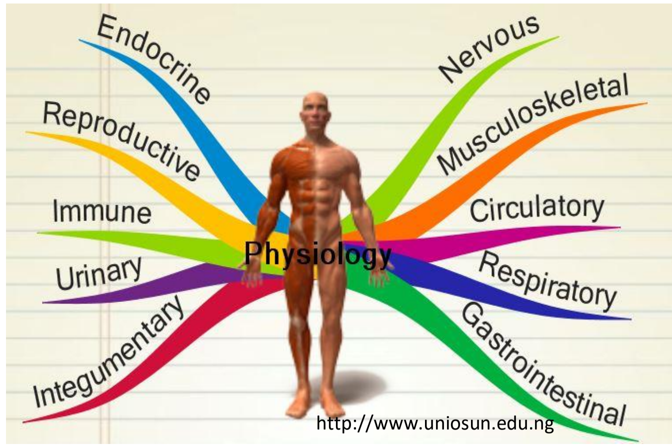
Aim of tracer kinetic modelling is….

in vivo characterization of tissues / organs

with respect to physiological / biophysical parameters

using SPECT / PET imaging



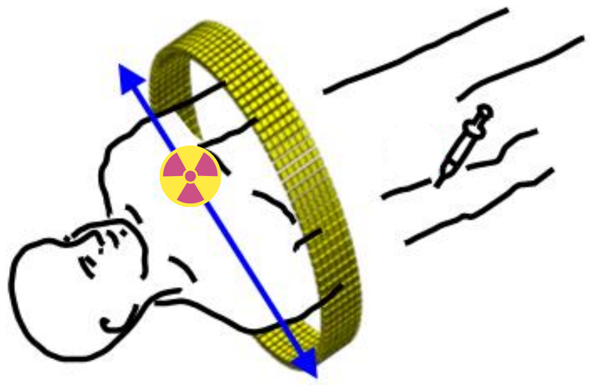
- metabolic rates (micromol substrate / g tissue / min)
- perfusion (ml blood / g tissue / min)
- receptor density (fmol / mg)
- affinity of tracer for target (nM)
- density of pathological targets, e.g. Aß-plaques, tau-tangles…

Contents

- basic principle of PET and SPECT radionuclide imaging & tracer principle
- tracer kinetic modelling
  - application in medical research
  - how it works

chironomus plumosus larvae

PET and SPECT radionuclide imaging: basic principle



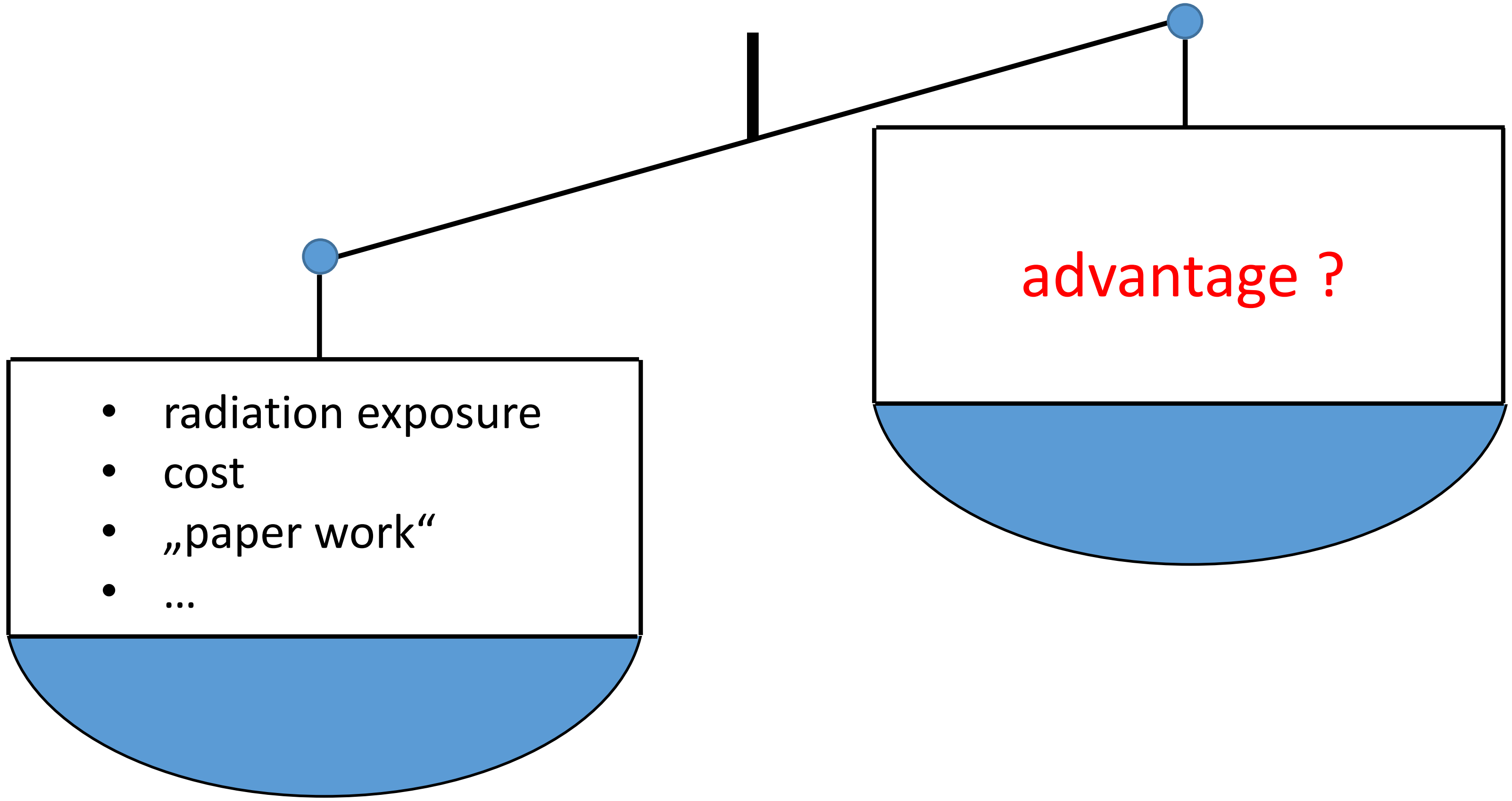
1. function / (patho)physiological process / target

↓

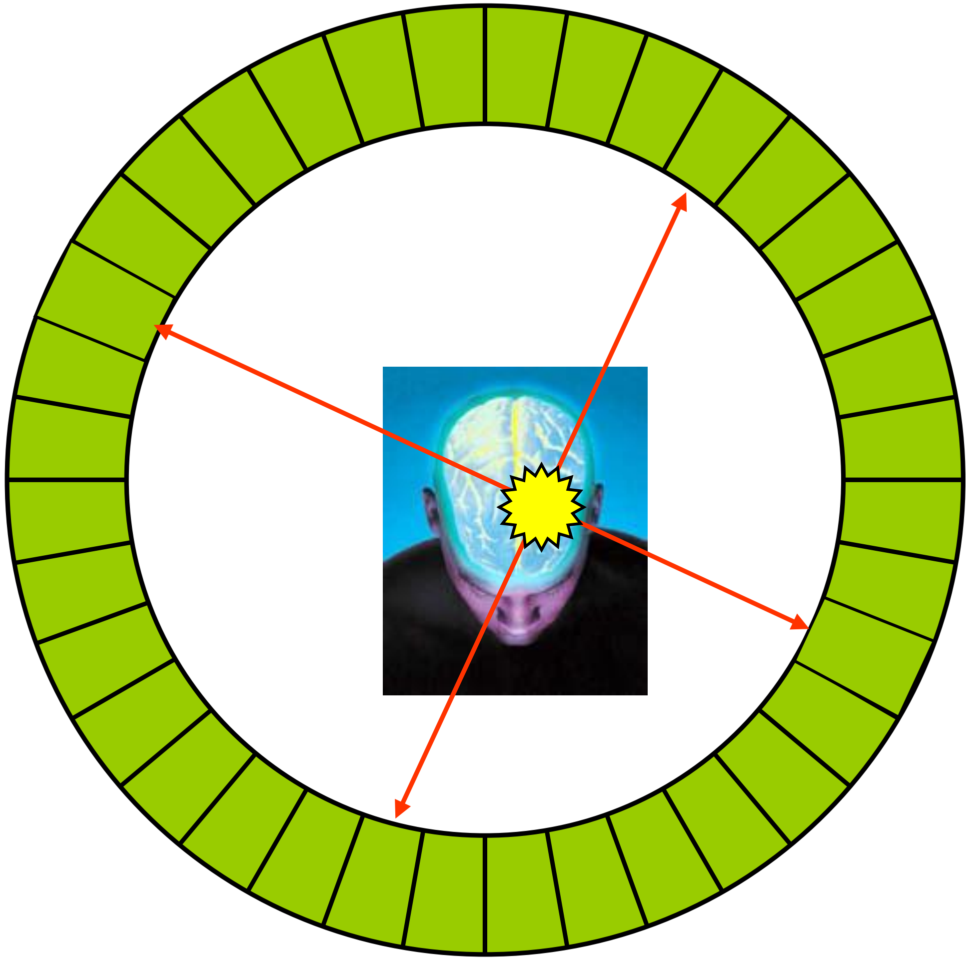
2. relevant molecule / ligand + 3. radionuclide ← labeling

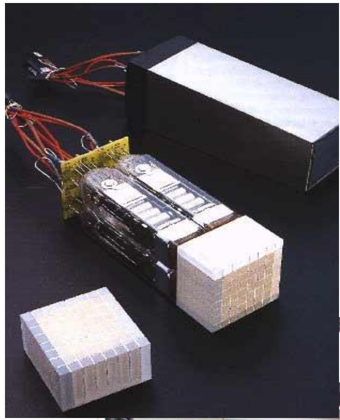
relevant molecule / ligand + radionuclide = tracer

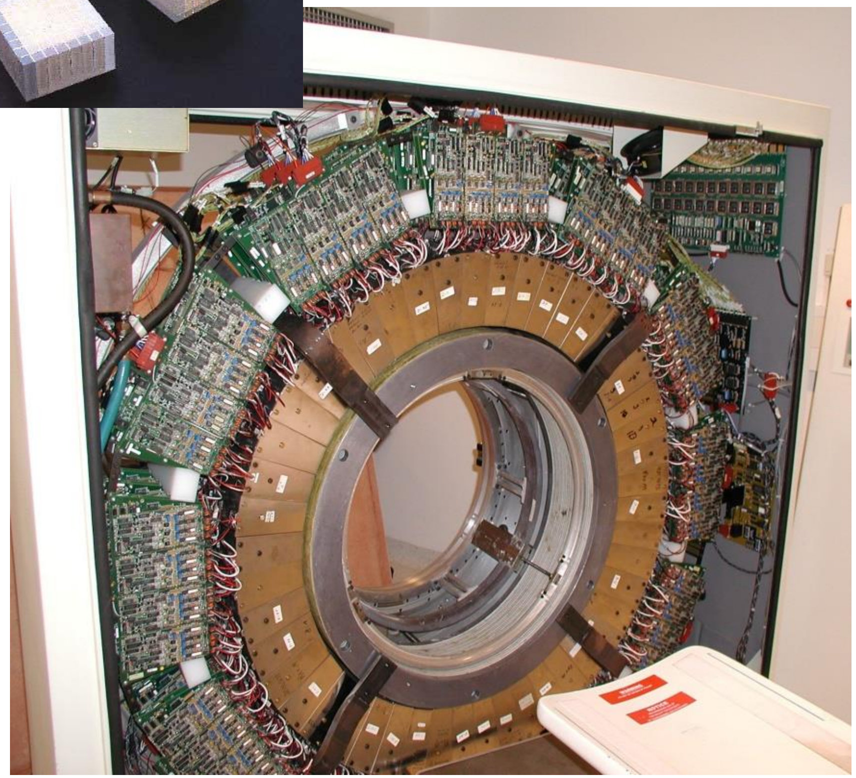
radioactive labeling



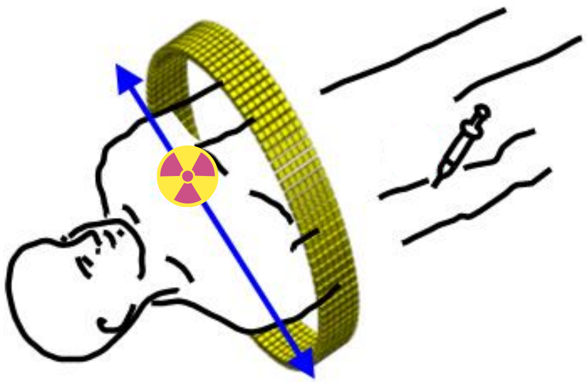
PET: high sensitivity for detection of positron decays







PET and SPECT radionuclide imaging: basic principle



1. function / (patho)physiological process / target — labeling

2. relevant molecule / ligand + 3. radionuclide

→ tracer

typical mass dose

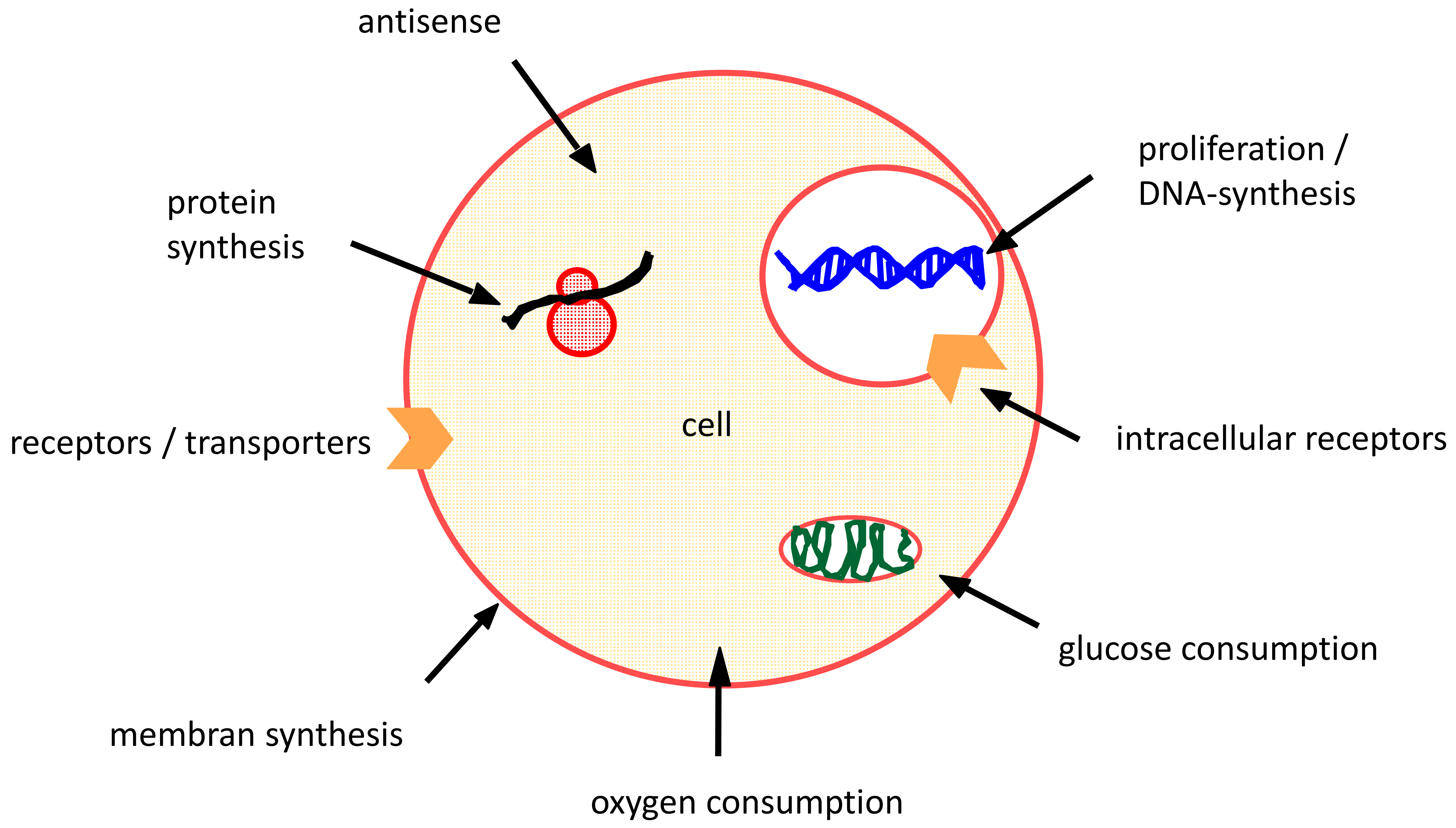
μg - ng

1. no toxic effects → no toxicological restrictions in the selection of relevant molecules

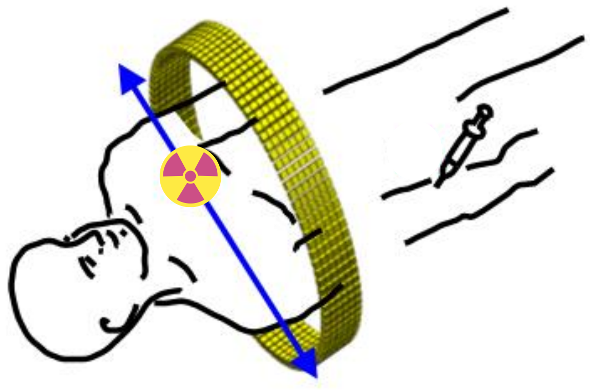
Functions / Targets

Tracer: Iwata, Reference Book for PET Radiopharmaceuticals

Molecular Imaging & Contrast Agent Database (NIH)



PET and SPECT radionuclide imaging: tracer principle



1. function / (patho)physiological process / target → 2. relevant molecule / ligand

labeling → 3. radionuclide

relevant molecule / ligand + radionuclide = tracer

typical mass dose

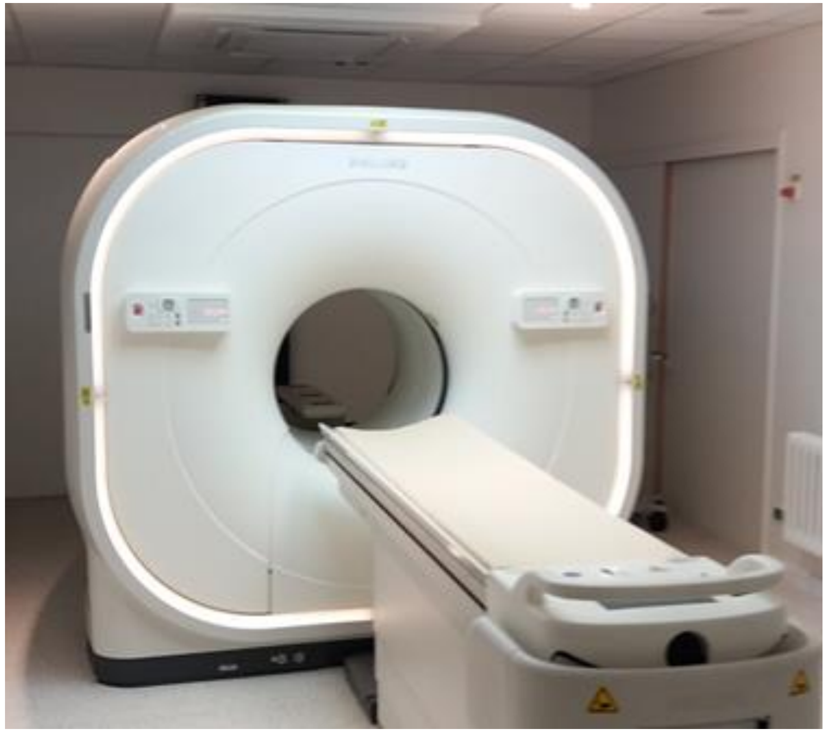
µg - ng

1. no toxic effects → no toxicological restrictions in the selection of relevant molecules
2. no pharmacological effects → no interference of the tracer with function/target of interest

tracer principle

State of the art PET image quality

2005

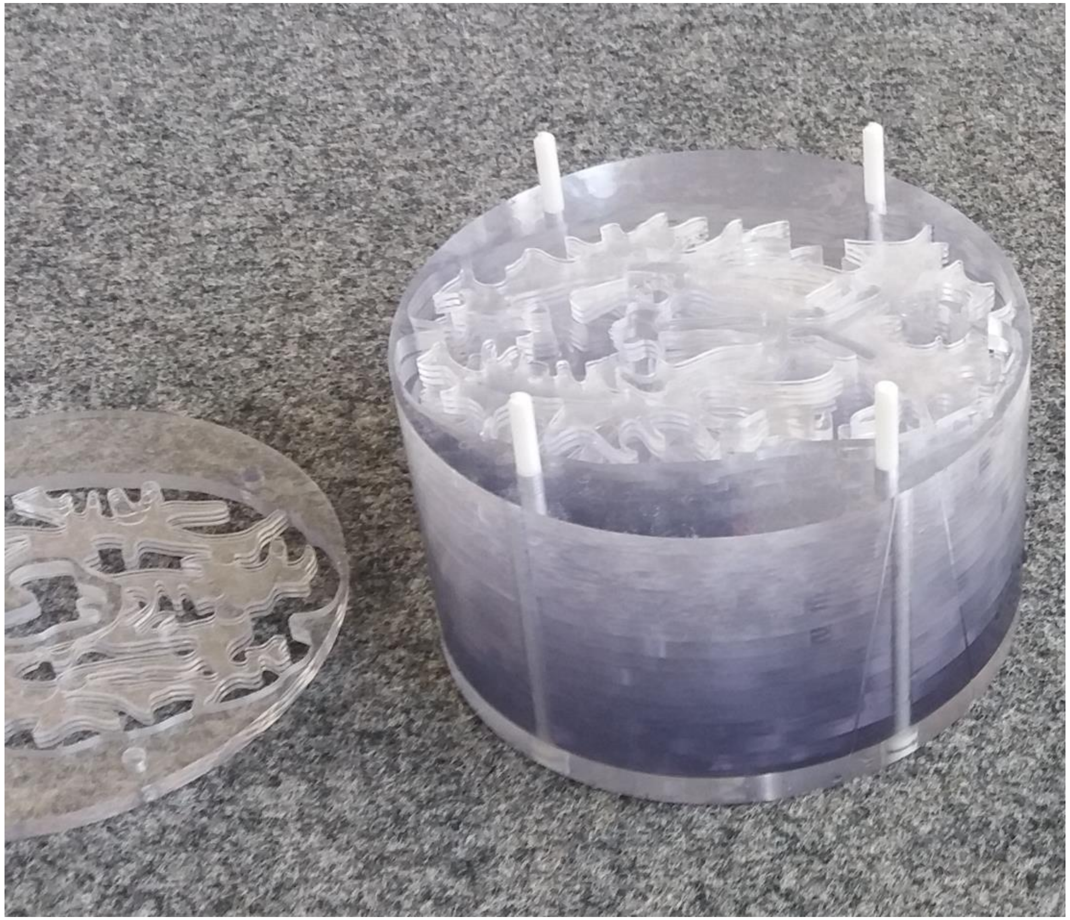


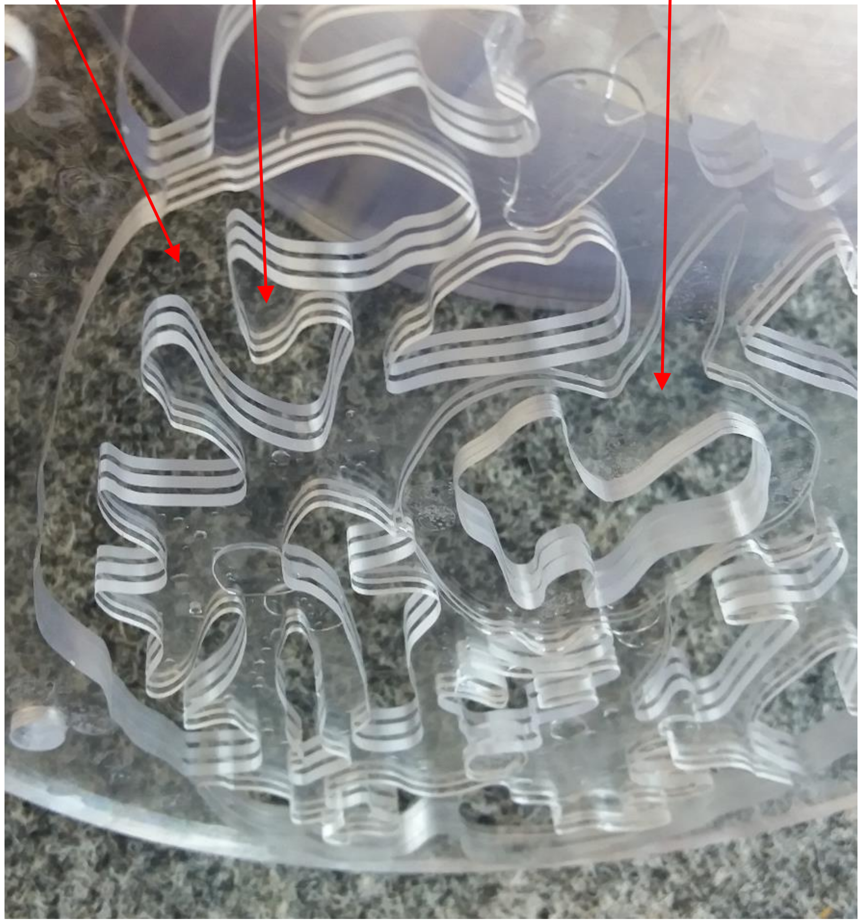
2018

(dSiPM → improved TOF → improved SNR)

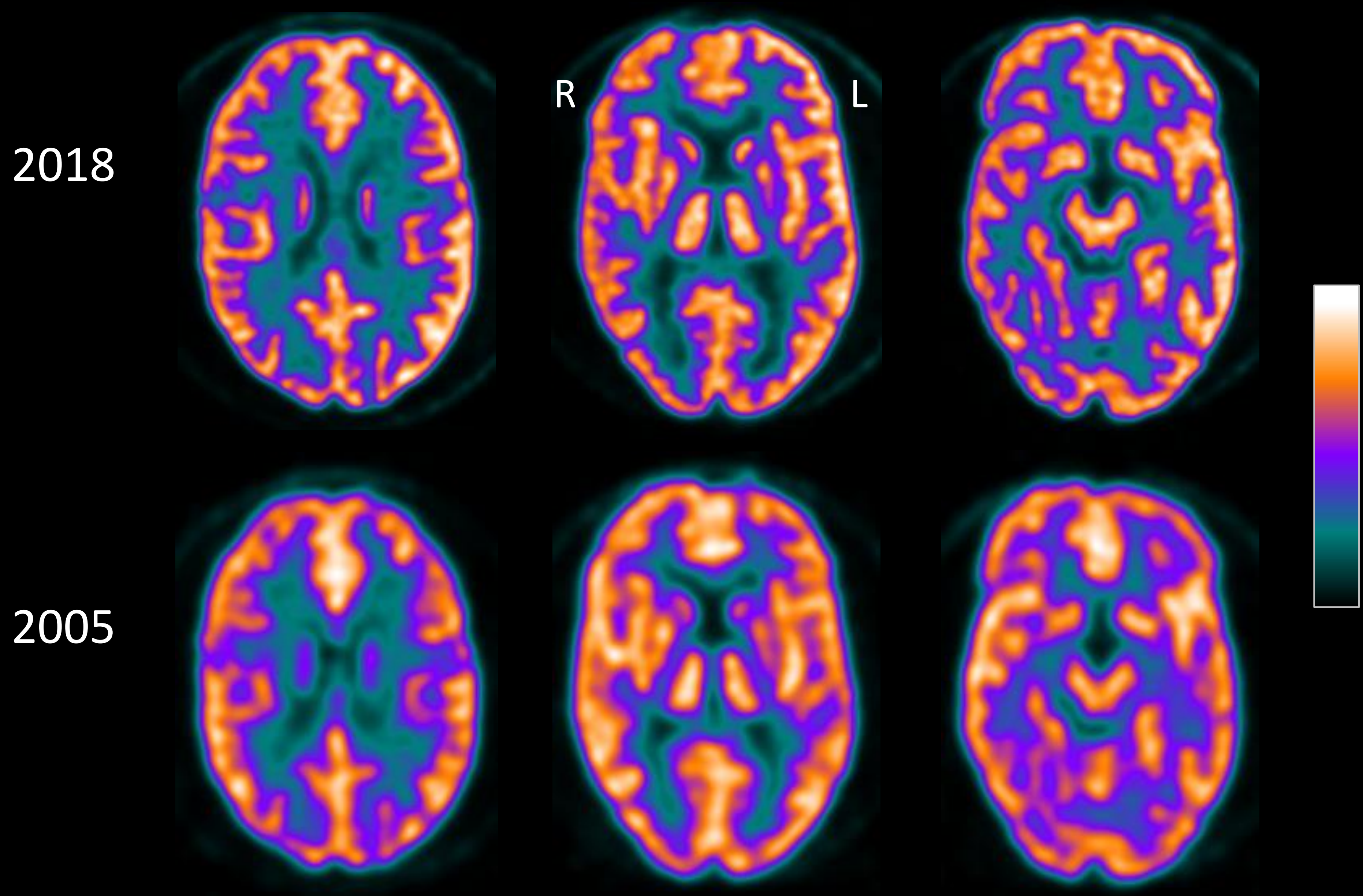
Hoffman 3D phantom

19 acrylic glass inserts made up of 5 slices

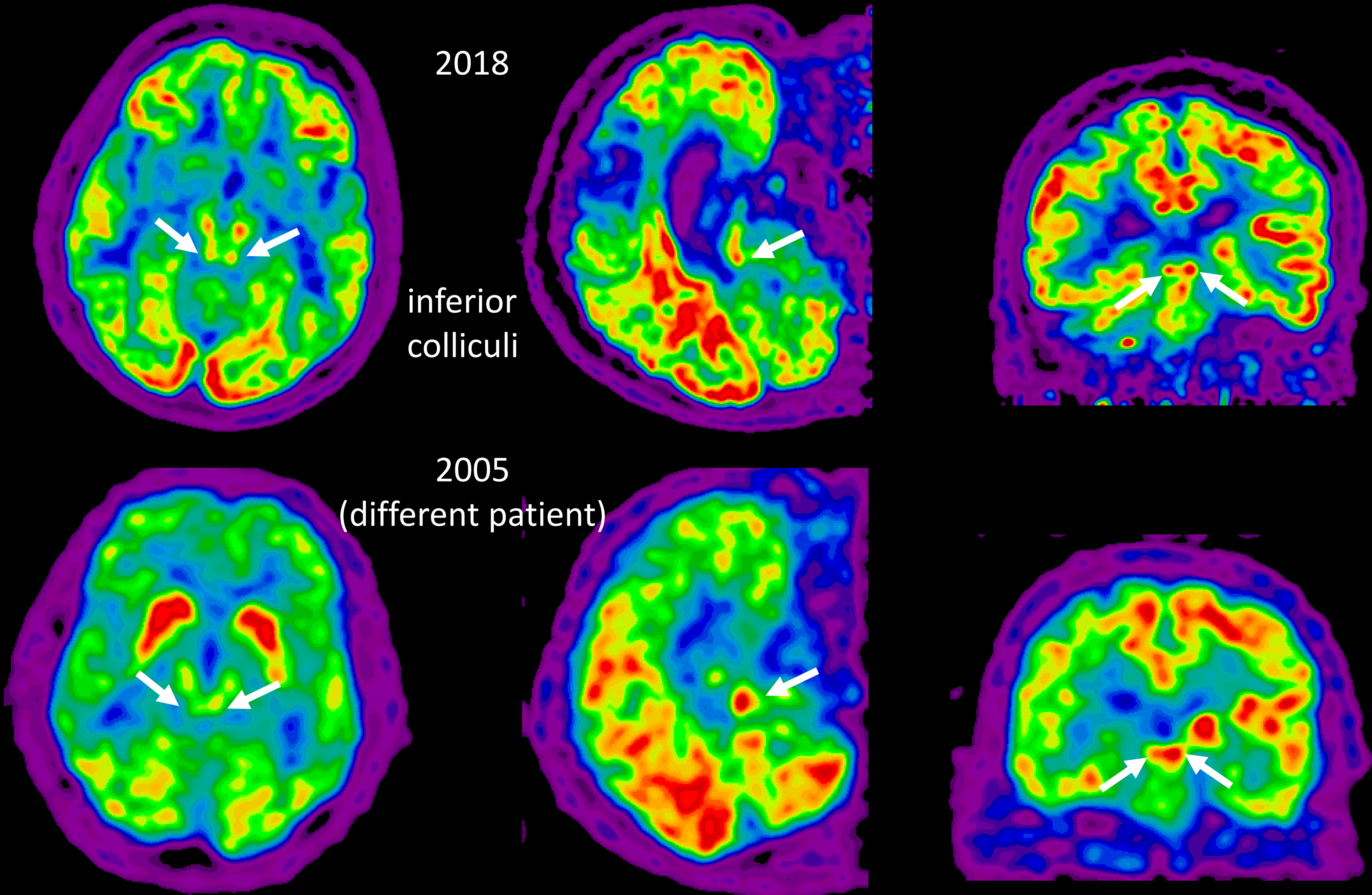




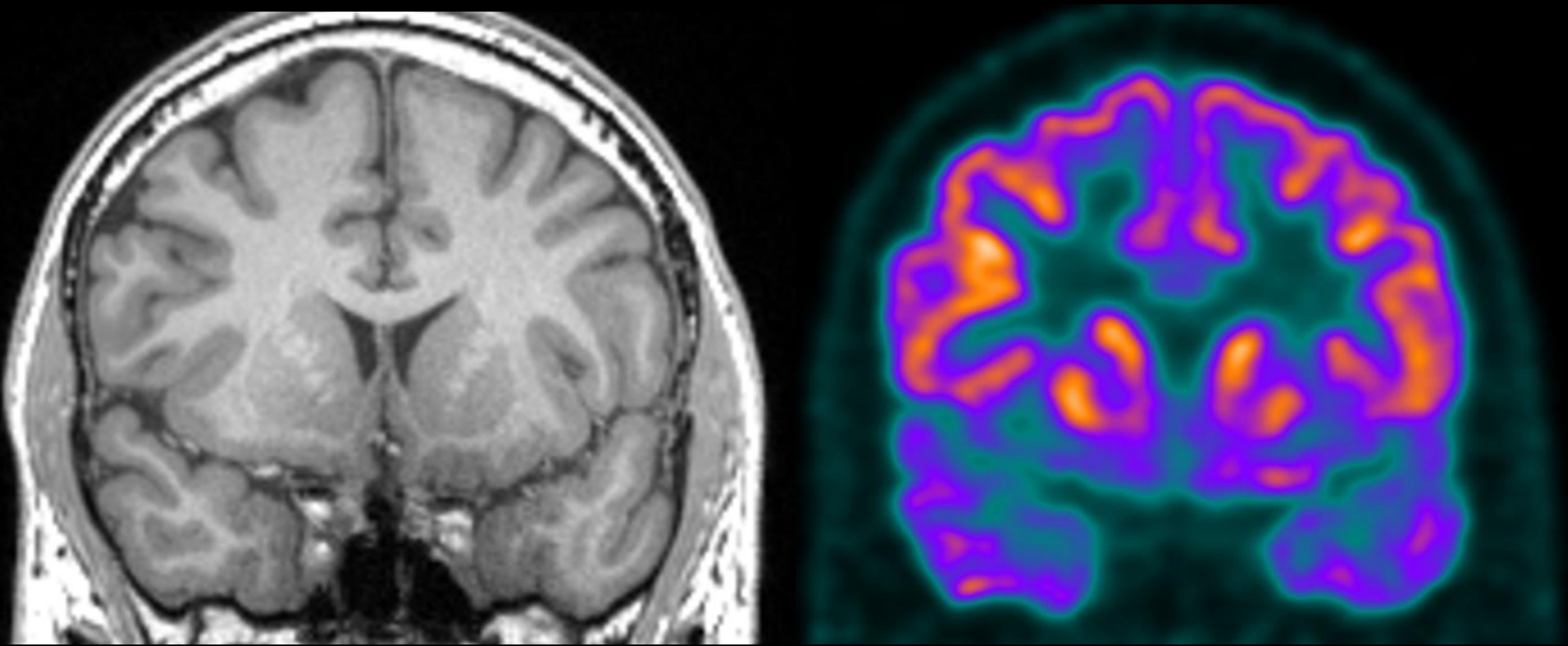
Hoffman 3D phantom



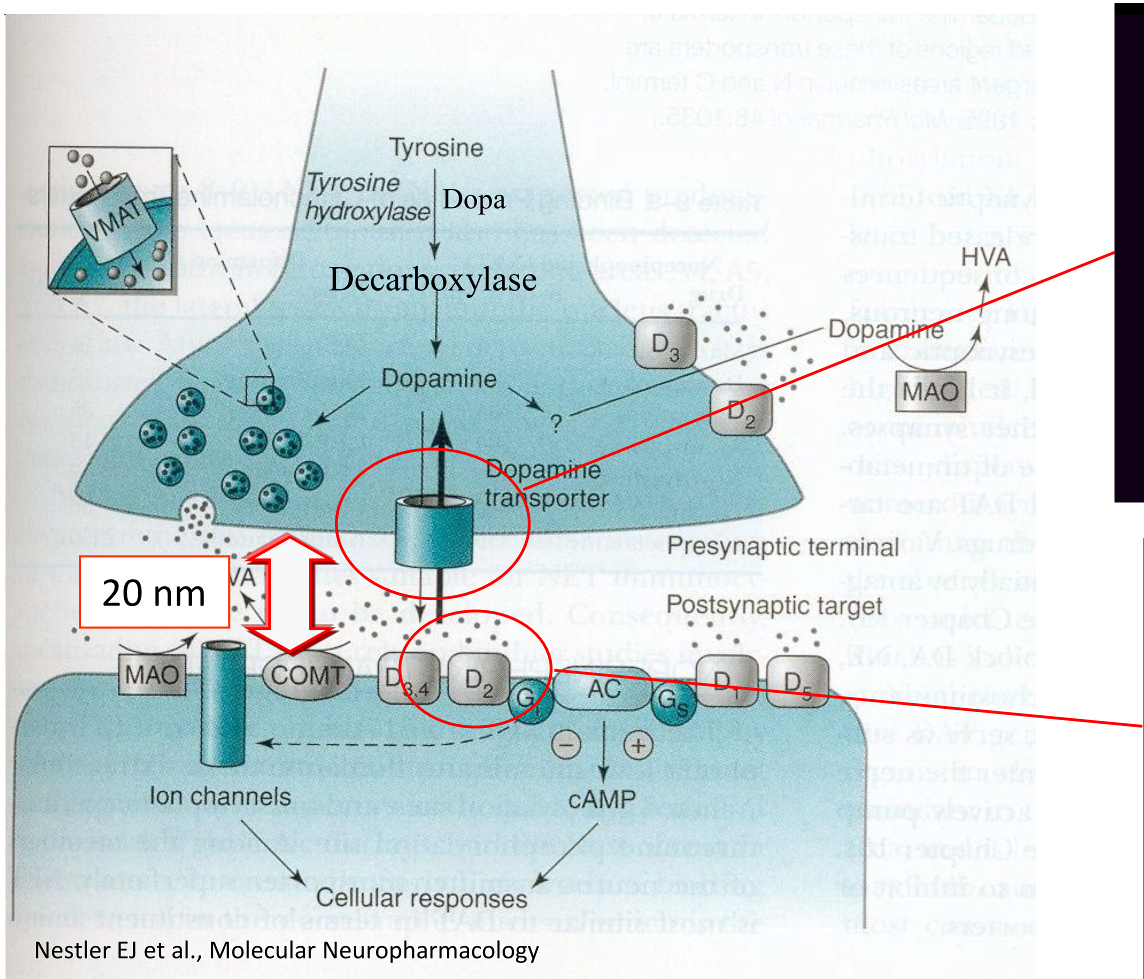
Patient FDG PET scans



PET vs MRI

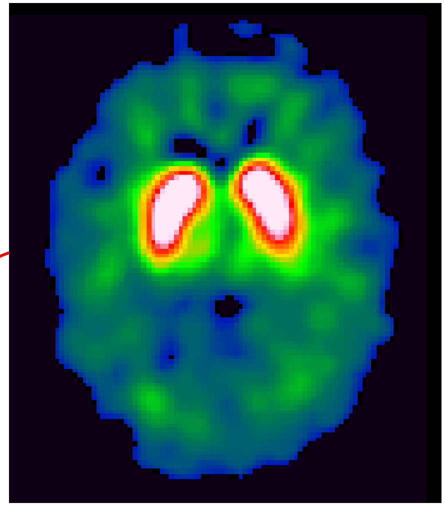


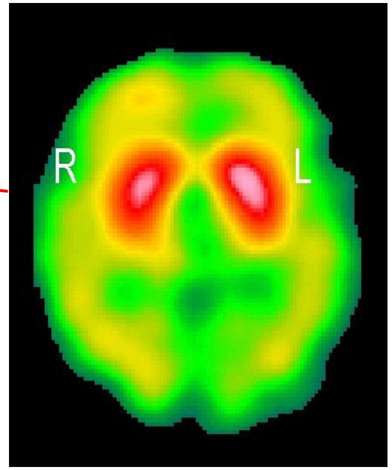
high „intrinsic“ spatial resolution



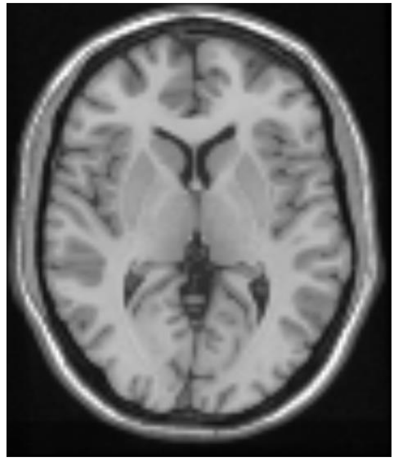
Nestler EJ et al., Molecular Neuropharmacology

dopamine transporter
I-123-FP-CIT





dopamine D2 receptor
I-123-IBZM



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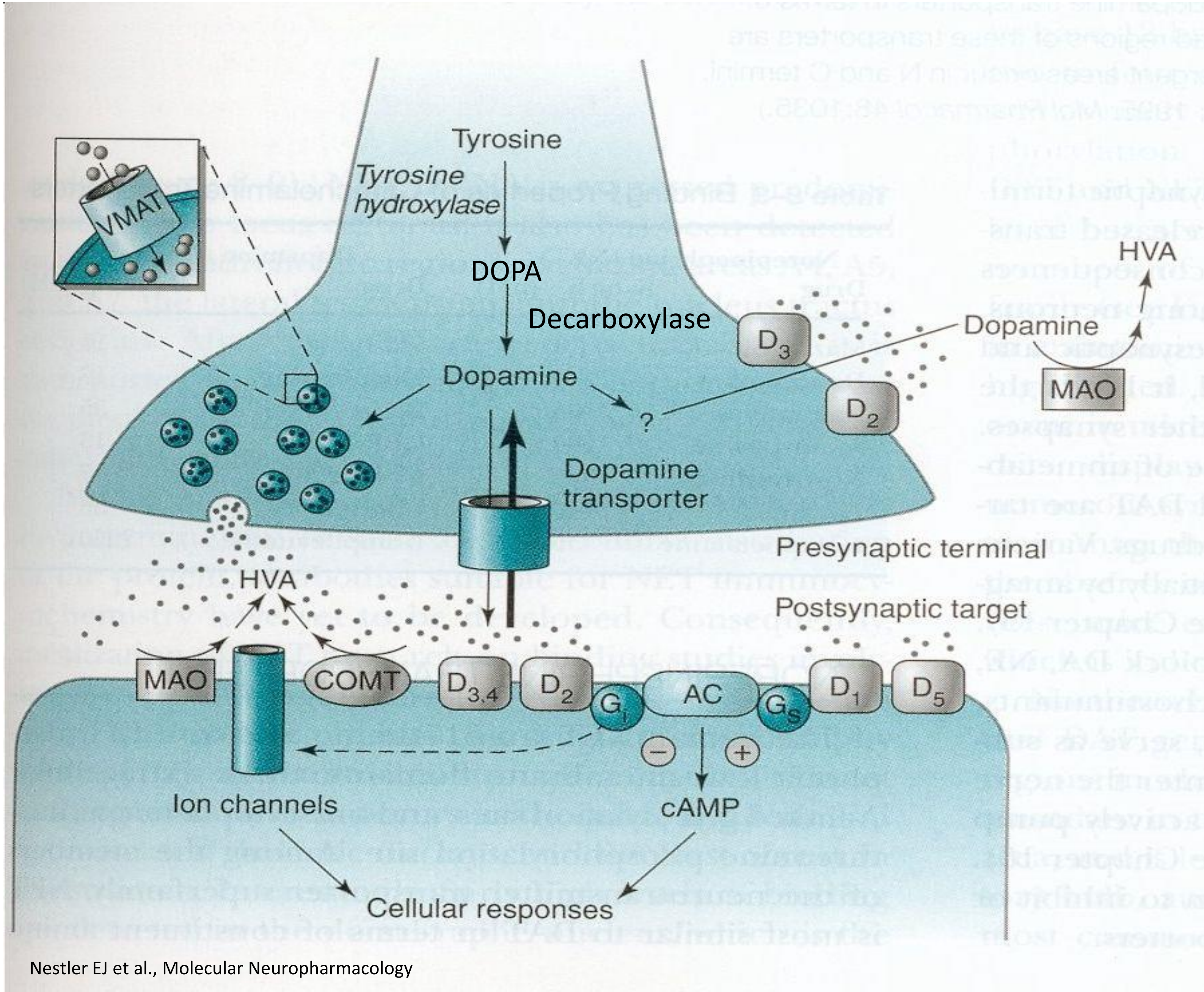
chironomus plumosus larvae

F-18-DOPA PET: dopamine synthesis versus dopamine storage



Nestler EJ et al., Molecular Neuropharmacology

Parkinson's disease

Zeichnung R. Gowers 1886

reward processing

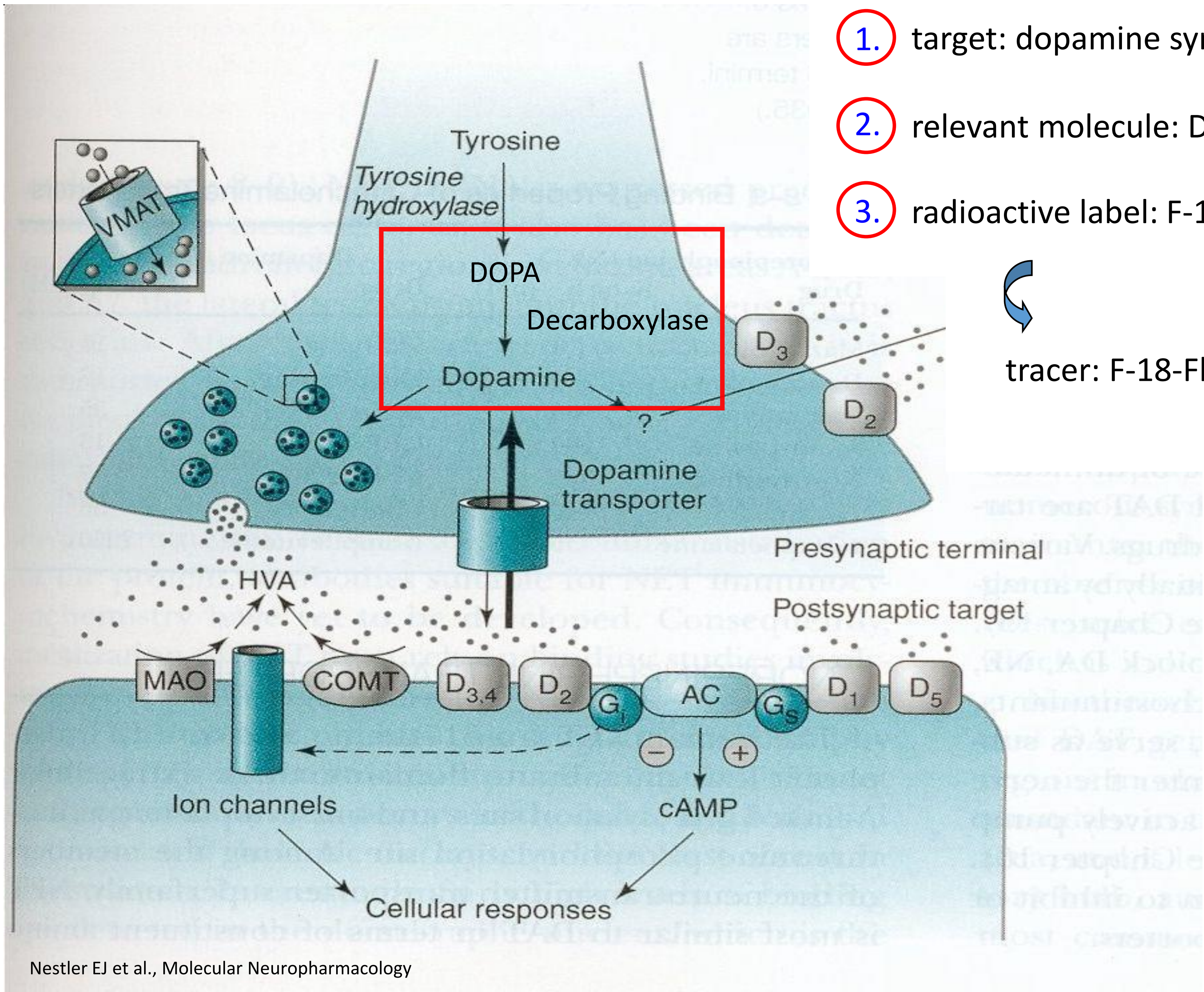
addictction

drugsdetails.com

memory

littlethingz.be

F-18-DOPA PET: dopamine synthesis versus dopamine storage

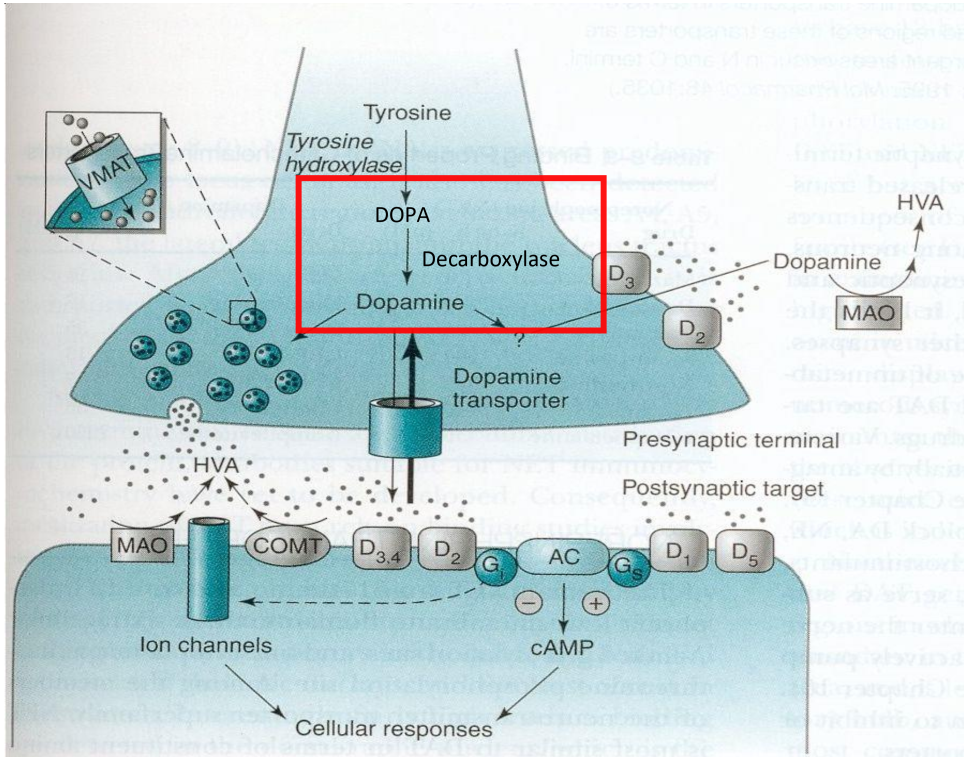


Nestler EJ et al., Molecular Neuropharmacology

1. target: dopamine synthesis
2. relevant molecule: DOPA
3. radioactive label: F-18

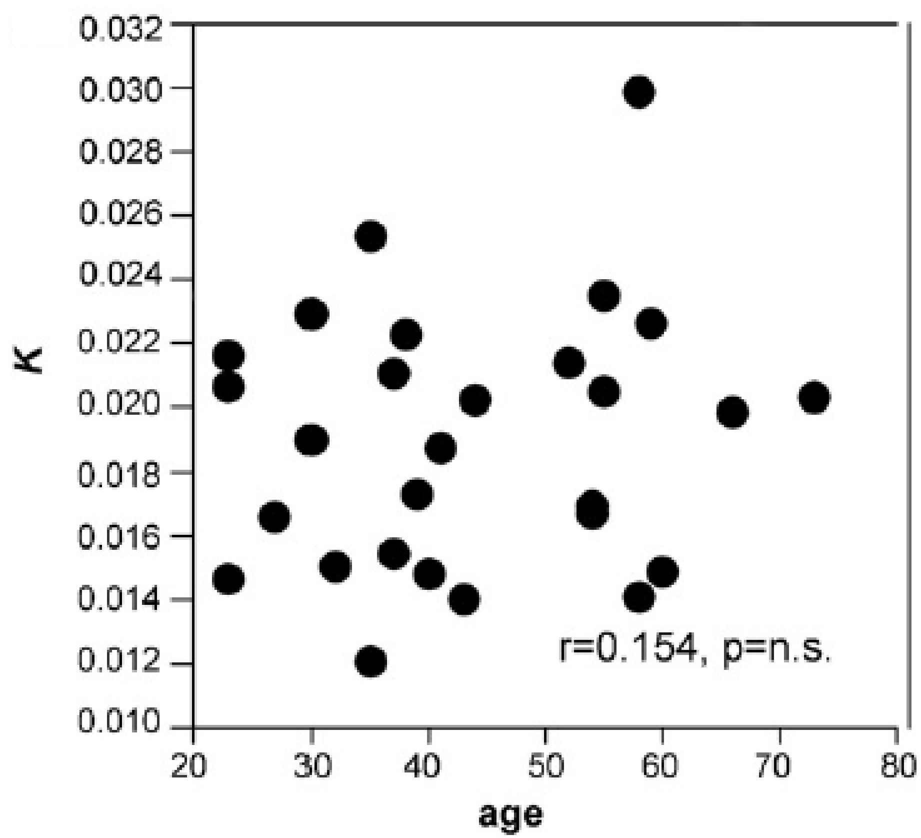
tracer: F-18-Fluoro-L-DOPA (FDOPA)

F-18-DOPA PET: dopamine synthesis versus dopamine storage

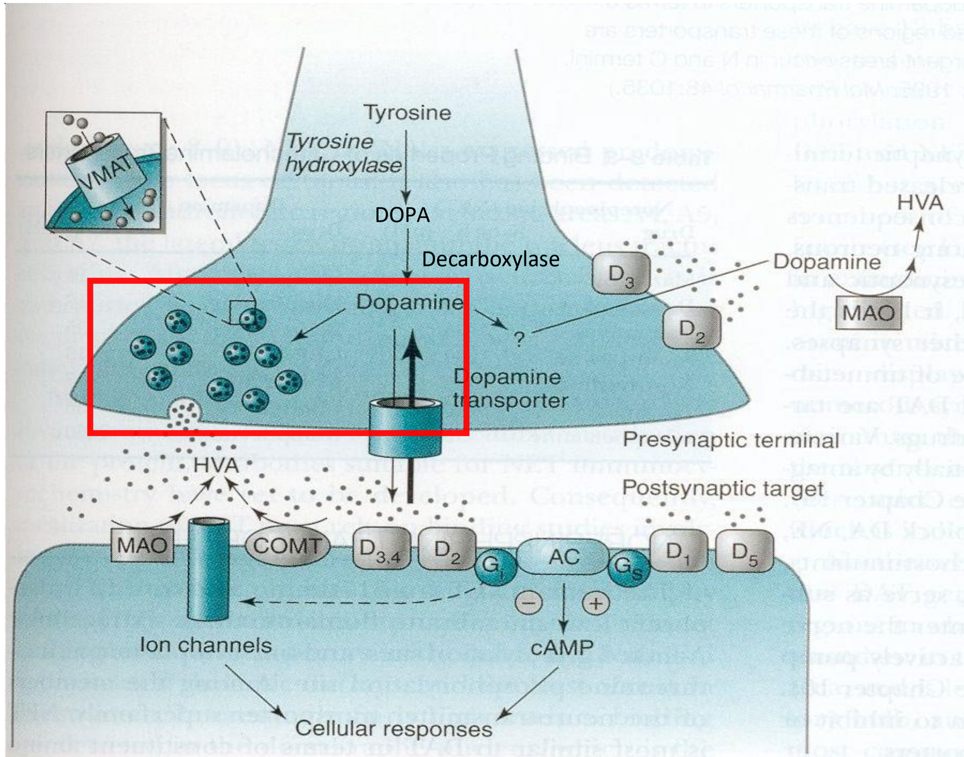


Nestler EJ et al., Molecular Neuropharmacology

Kumakura et al., Neurobiol of Aging 2010, 31: 447-63

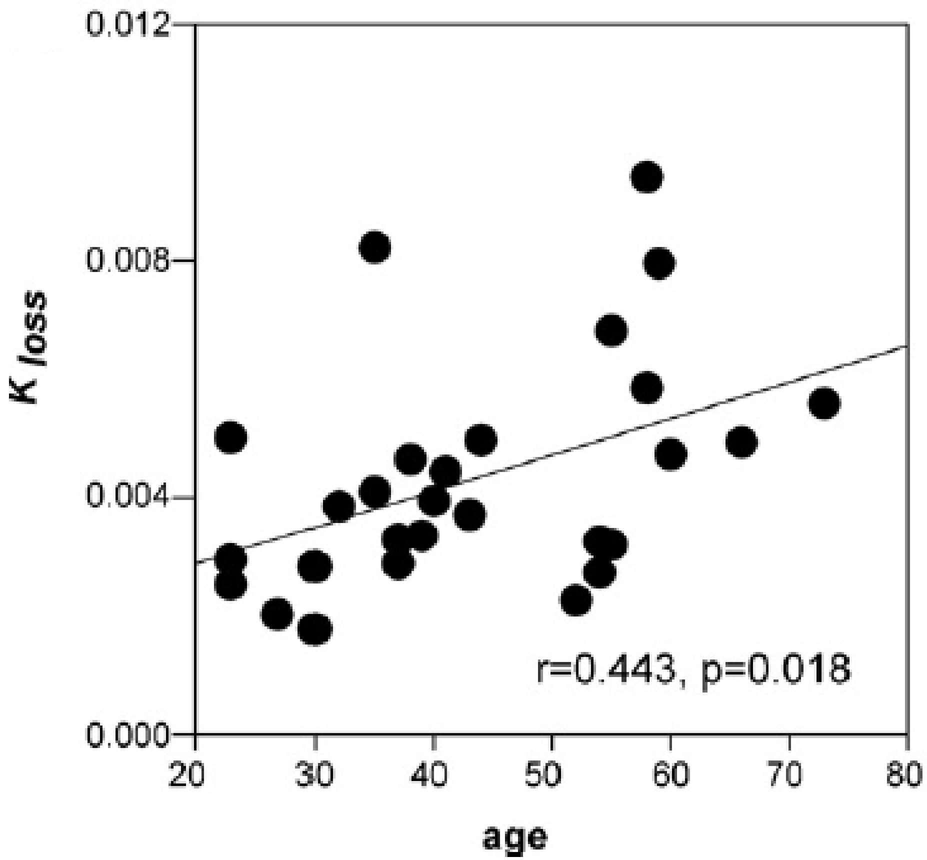


F-18-DOPA PET: dopamine synthesis versus dopamine storage



Nestler EJ et al., Molecular Neuropharmacology

Kumakura et al., Neurobiol of Aging 2010, 31: 447-63



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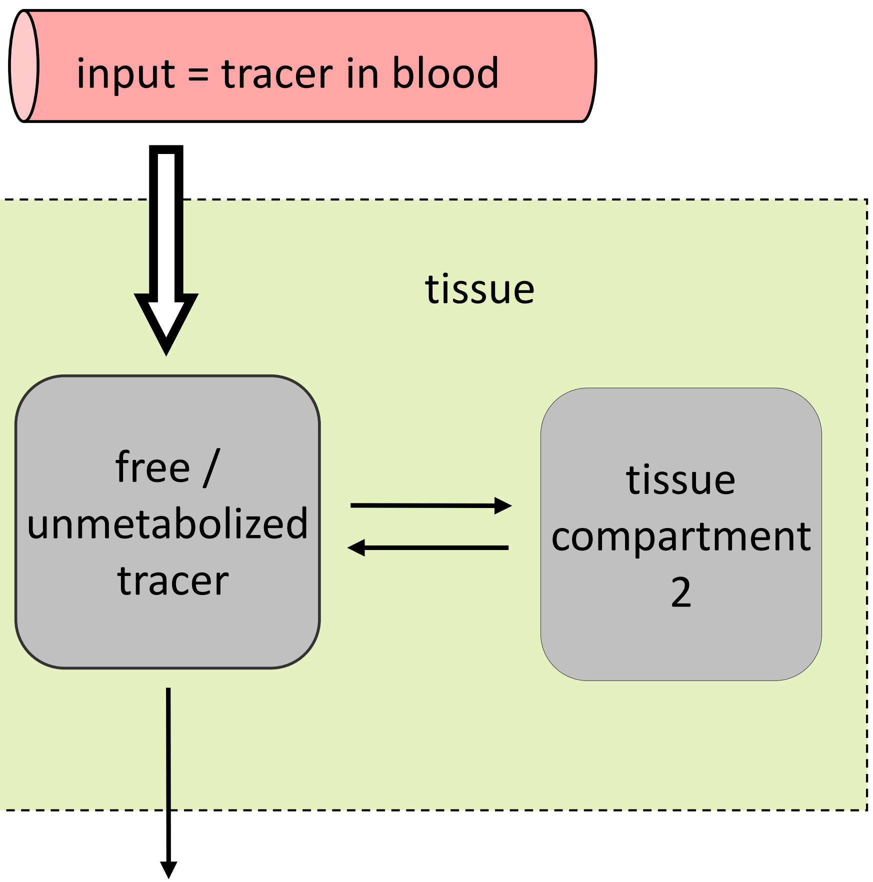
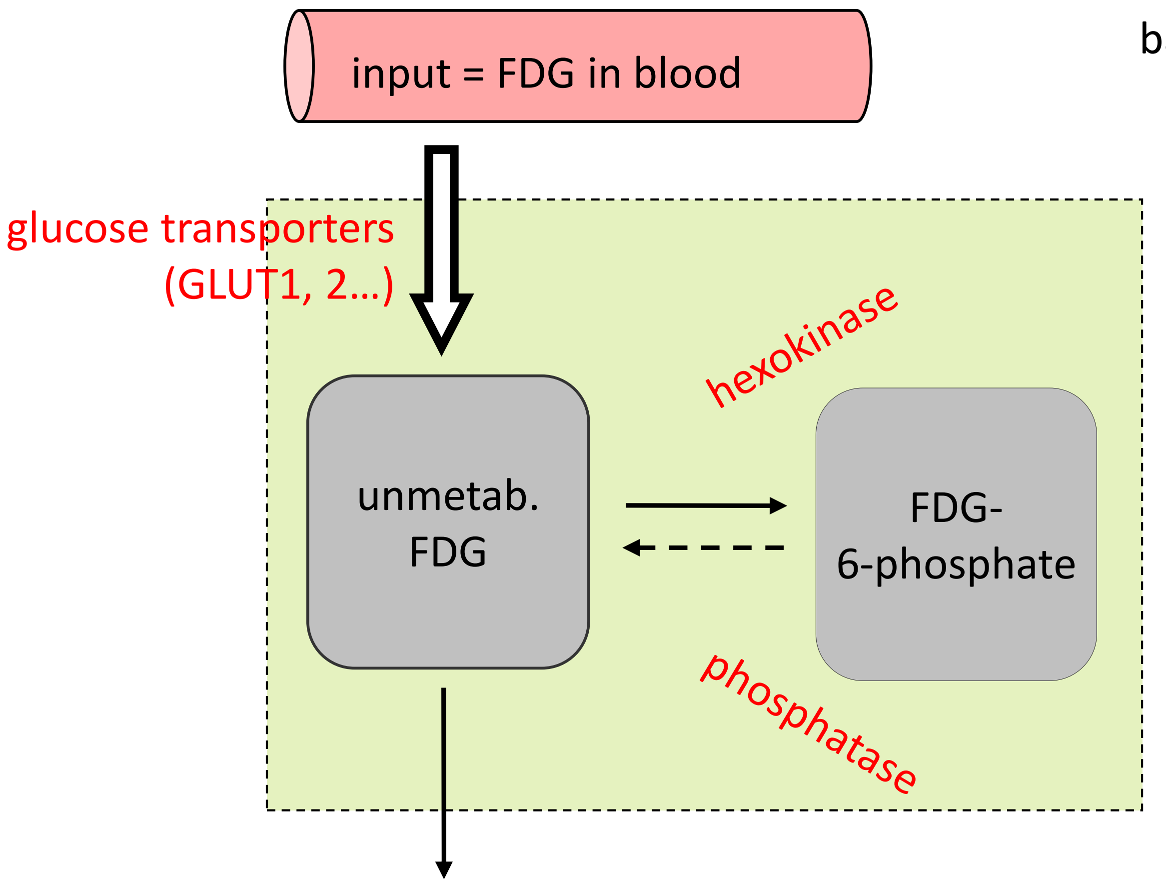
chironomus plumosus larvae

Tracer kinetic modelling: compartment models

2-tissue compartment model



Tracer kinetic modelling: compartment models



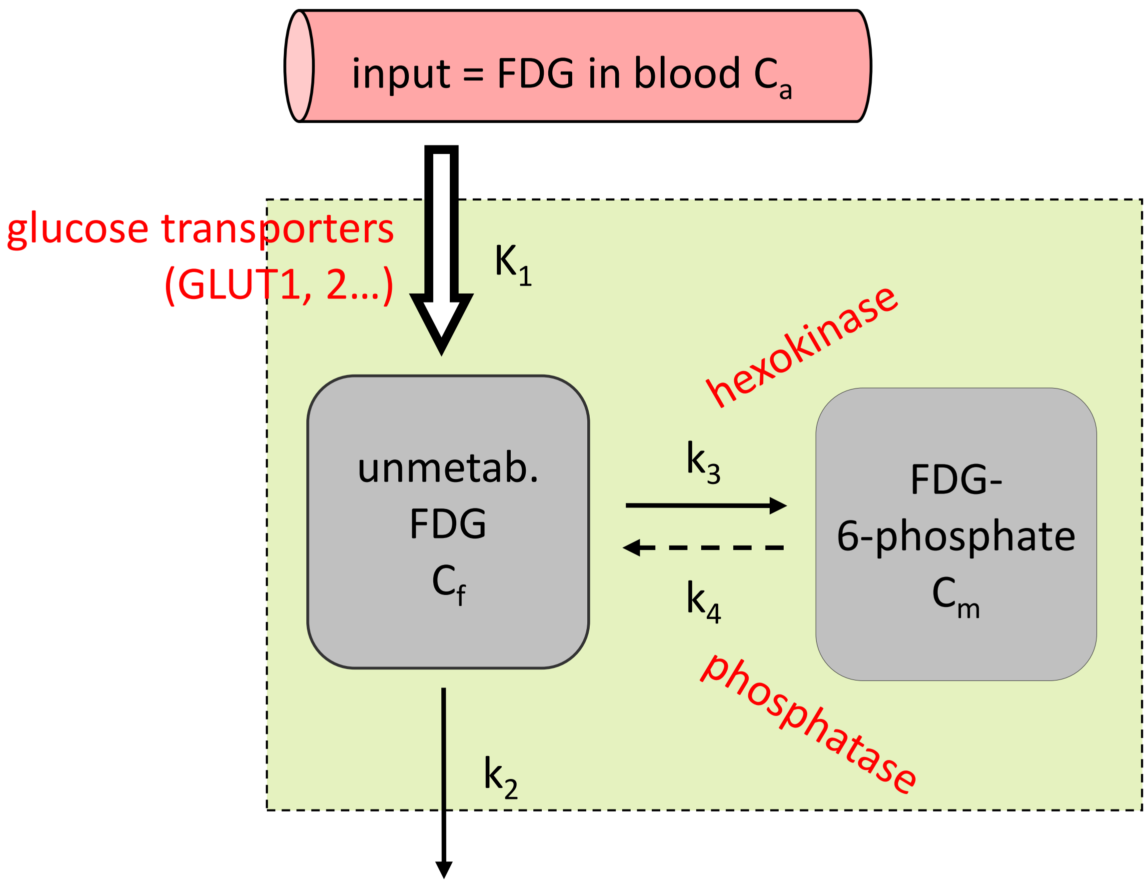
F-18-fluorodeoxyglucose (FDG)

based on known pharmacokinetics*

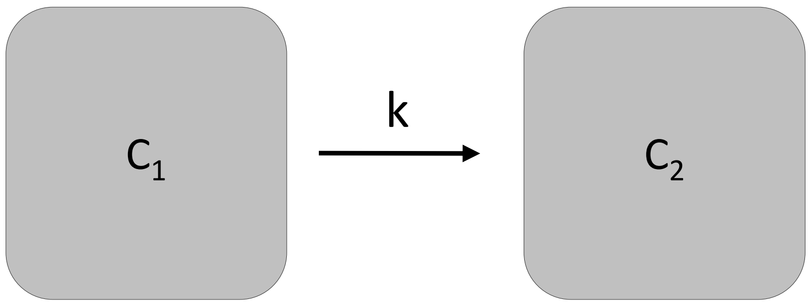
* Bidder TG, Hexose translocation across the blood-brain interface: configurational aspects, J Neurochem 1968, 15: 867-874
Sols A, Crane RK, Substrate specificity of brain hexokinase, J Biol Chem 1954, 210: 581-595
Sokoloff L et al., The [14C]deoxyglucose method…, J Neurochem 1977, 28: 581-595

Tracer kinetic modelling: compartment models

FDG



Tracer kinetic modelling: translation graphical representation → equations

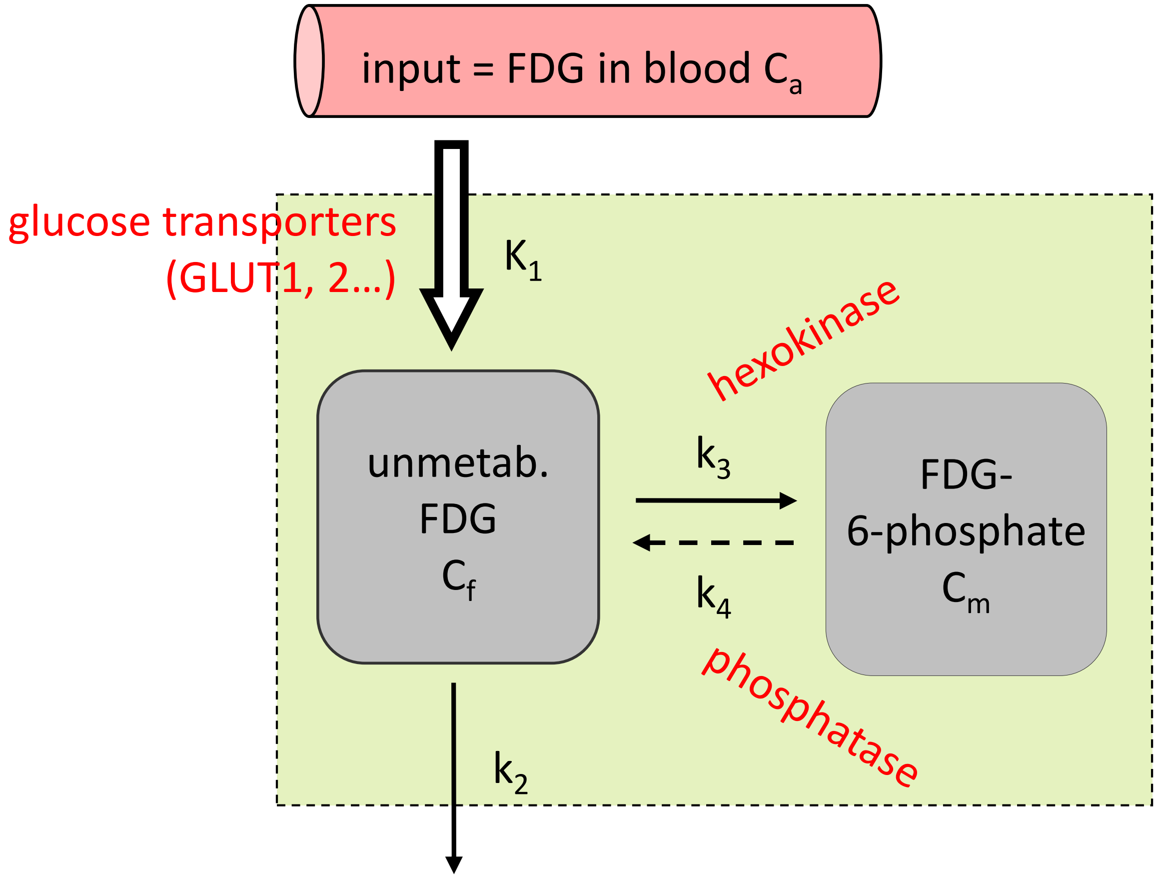


$$dC_1/dt = -k * C_1$$

$$dC_2/dt = k * C_1$$

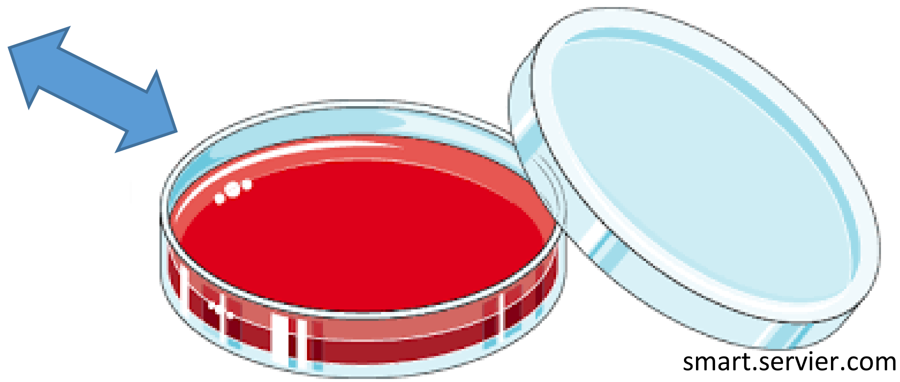
Tracer kinetic modelling: compartment models

FDG



$$dC_f/dt = K_1 * C_a - k_2 * C_f - k_3 * C_f + k_4 * C_m$$

$$dC_m/dt = k_3 * C_f - k_4 * C_m$$



Michaelis-Menten model

Michaelis-Menten model of enzyme kinetics (in vitro)

enzyme-mediated reaction

$$\text{substrate (S)} + \text{enzyme (E)} \underset{q_2}{\overset{q_1}{\rightleftharpoons}} \text{complex (ES)} \xrightarrow{q_3} \text{product (R)} + \text{E}$$

substrate (S)	enzyme (E)		product (R)
FDG/glucose	hexokinase		FDG-6-P O_4
FDG/glucose extracellular	GLUT		FDG/glucose intracellular

Operational equations

(1a) $dC_{ES}/dt = q_1 * C_E * C_S - (q_2 + q_3) * C_{ES}$

(1b) $V = dC_R/dt = q_3 * C_{ES}$ reaction rate

(1c) $\text{total } C_E = C_E + C_{ES}$

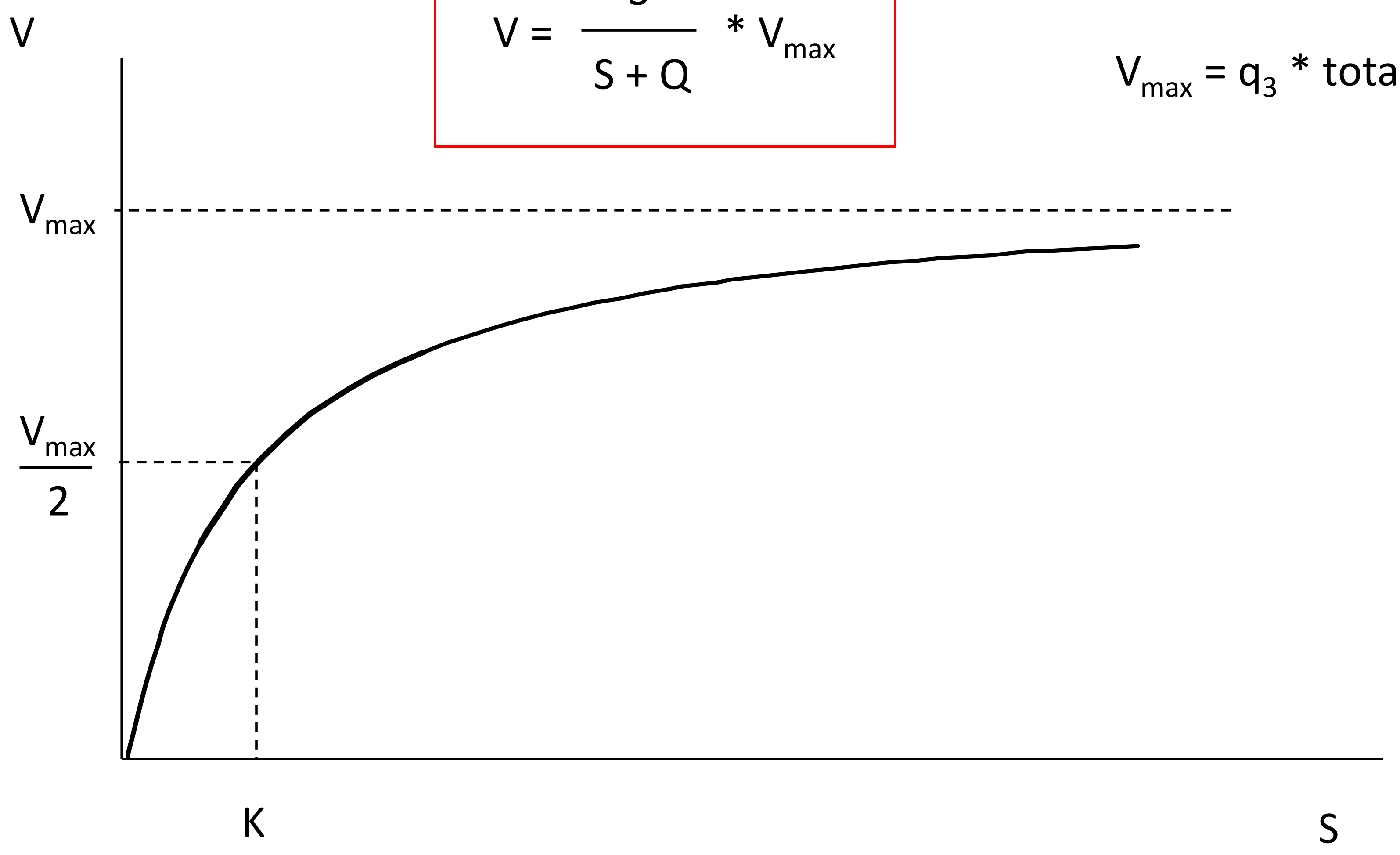
Michaelis-Menten model of enzyme kinetics II

steady state ($dC_{ES}/dt = 0$)

$$V = \frac{S}{S + Q} * V_{max}$$

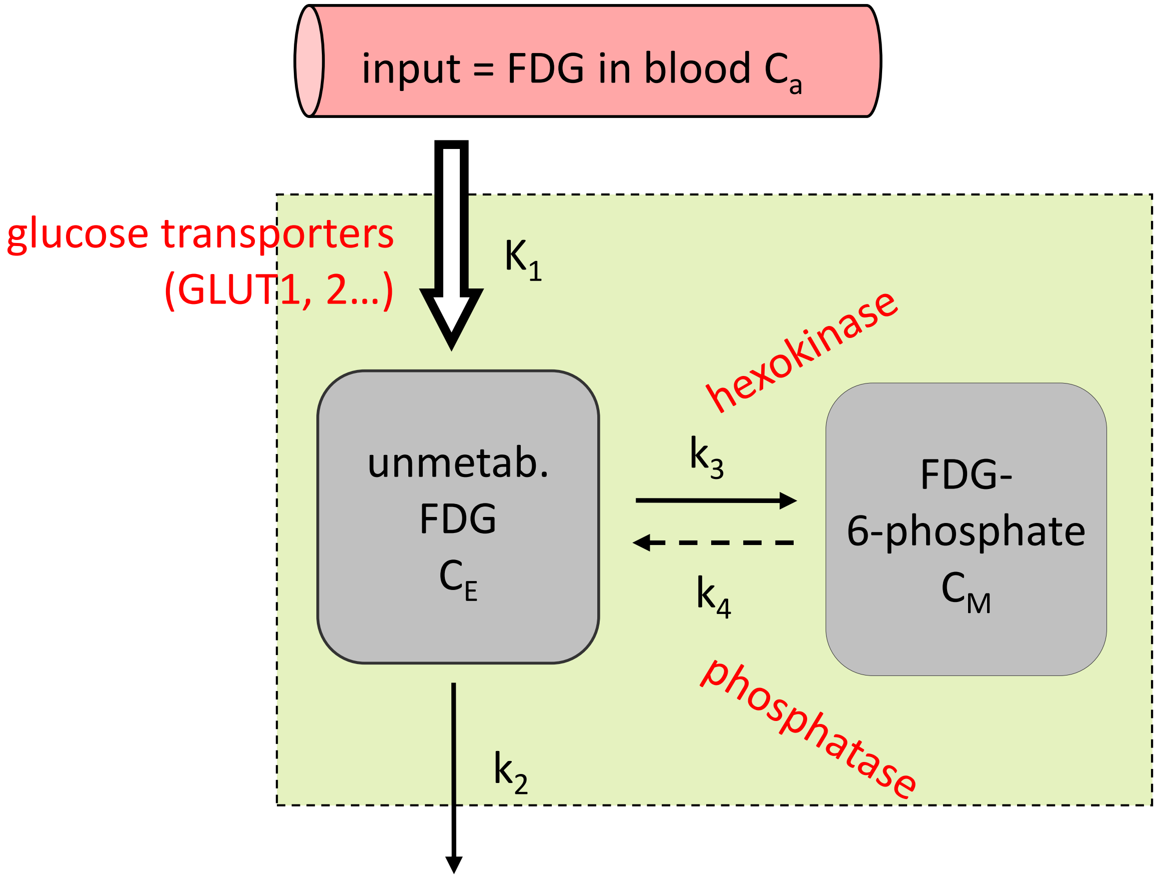
$$Q = \frac{q_2 + q_3}{q_1}$$

$$V_{max} = q_3 * \text{total } E$$



Tracer kinetic modelling: compartment models

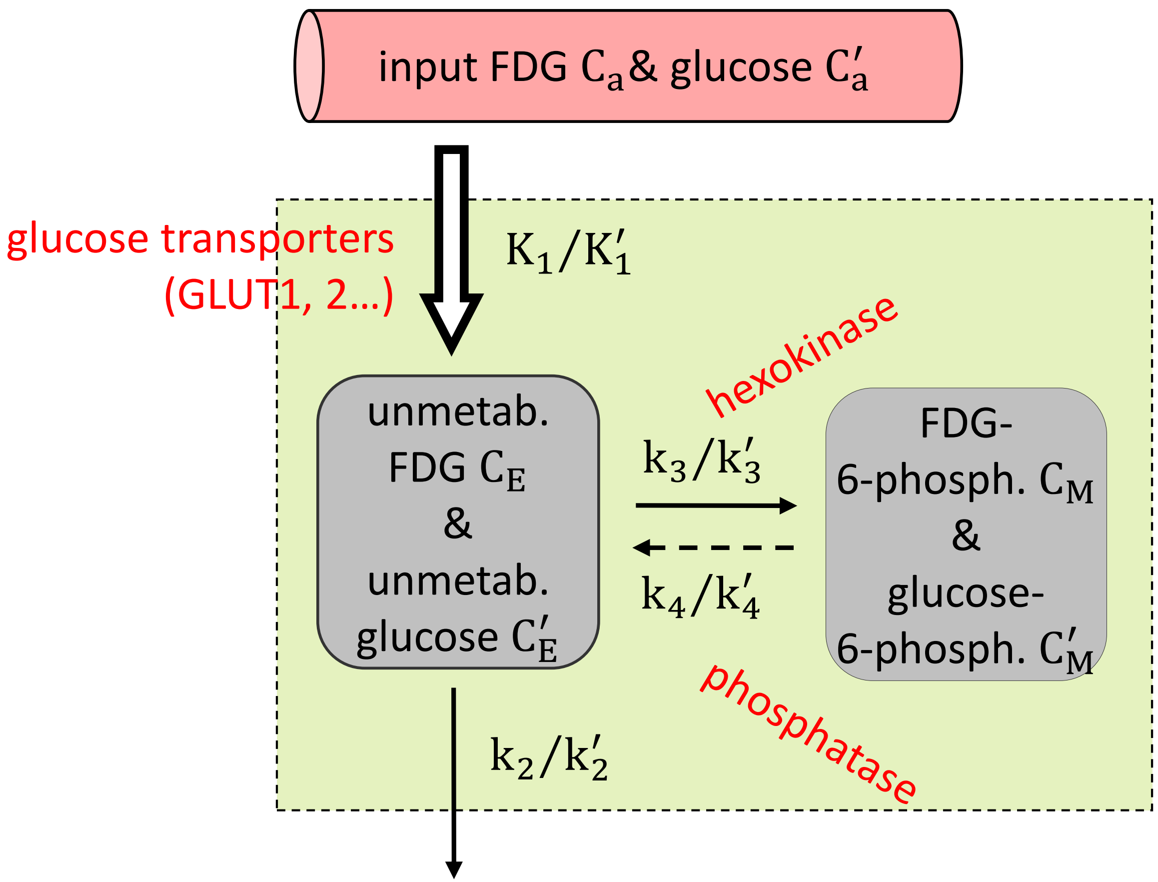
	compartment model	Michaelis-Menten
transport	K_1, k_2	Q_T, V_T
phosporylation	k_3, k_4	Q_M, V_M



Tracer kinetic modelling: competing substrates

Buchert et al., Nuklearmedizin 2009; 48: 44-54

	compartment model	Michaelis-Menten
transport	K_1, k_2	Q_T, V_T
phosporylation	k_3, k_4	Q_M, V_M



primed: glucose

unprimed: FDG

$$K_1 = \frac{V_T}{Q_T * (1 + C'_a/Q'_T) + C_a}$$

$$k_3 = \frac{V_M}{Q_M * (1 + C'_E/Q'_M) + C_E}$$

if tracer principle fulfilled, i.e.

$$C_a \ll Q_T * (1 + C'_a/Q'_T)$$

$$C_E \ll Q_M * (1 + C'_E/Q'_M)$$

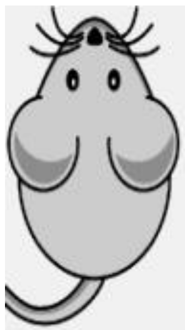
$$K_1 \approx \frac{V_T}{Q_T * (1 + C'_a/Q'_T)}$$

$$k_3 \approx \frac{V_M}{Q_M * (1 + C'_E/Q'_M)}$$

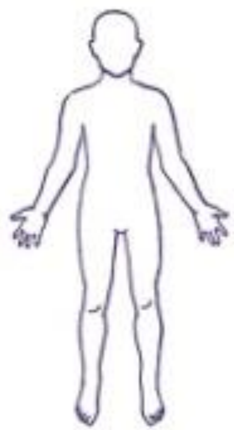
Tracer principle: Cave!

1. total tracer, both labelled and unlabelled → specific activity

2.

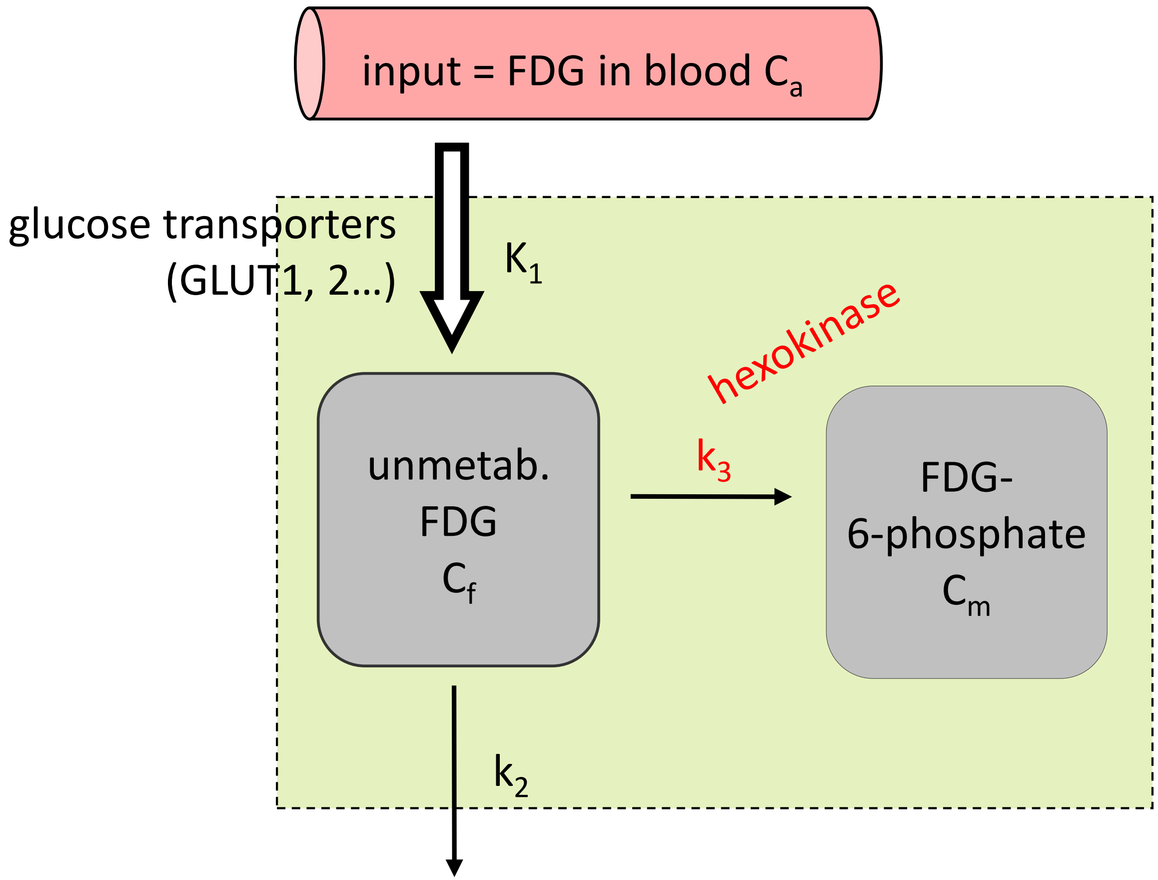


1.5 ml blood



5 L blood

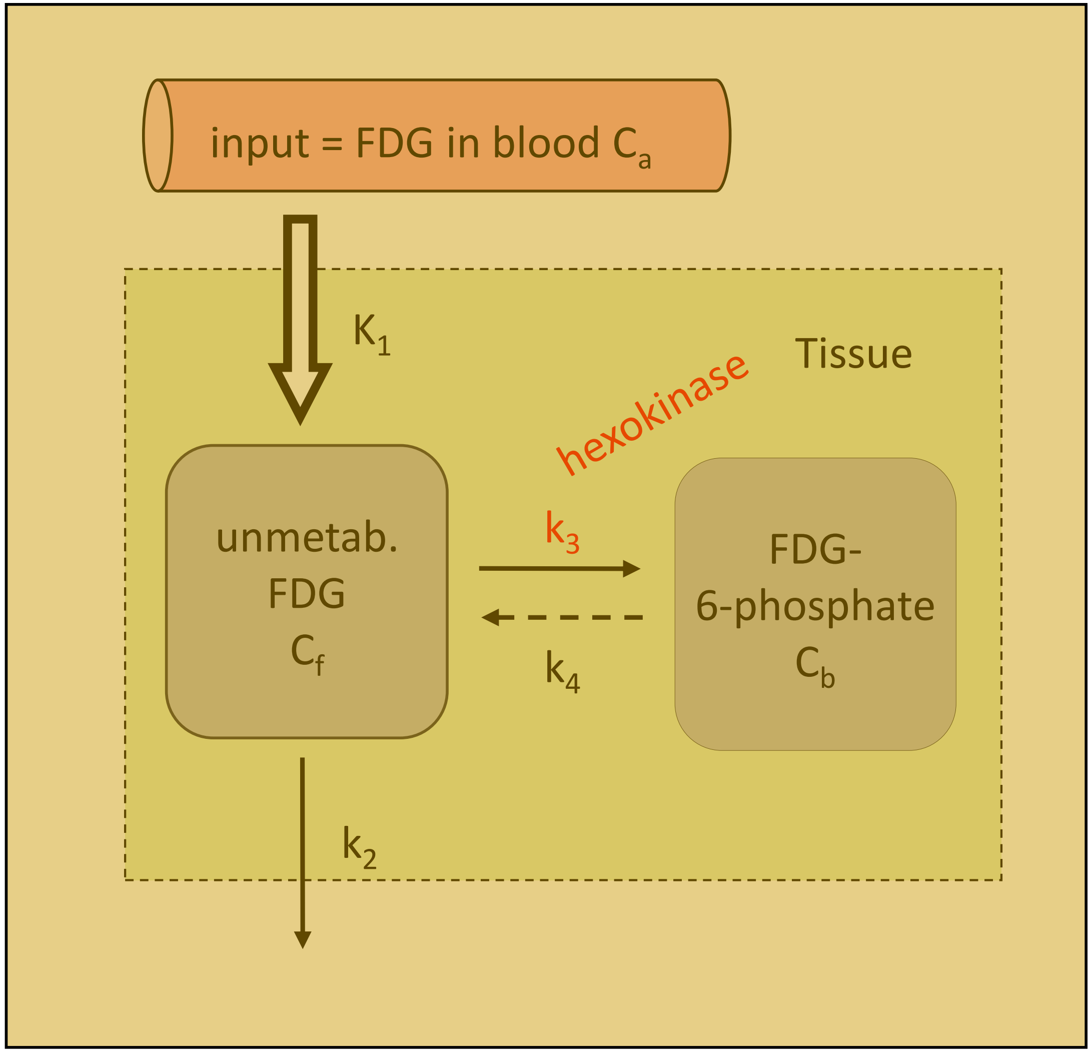
Tracer kinetic modelling: compartment models



$dC_m/dt = k_3 * C_f$

$k_3 = (dC_m/dt) / C_f$

Tracer kinetic modelling: problem



compartments defined

by function, not localization

PET image volume element

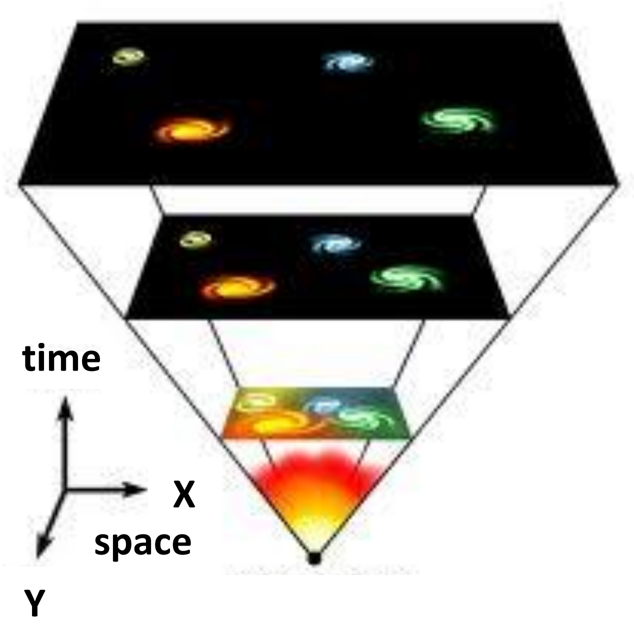
(voxel) =

sum of signals

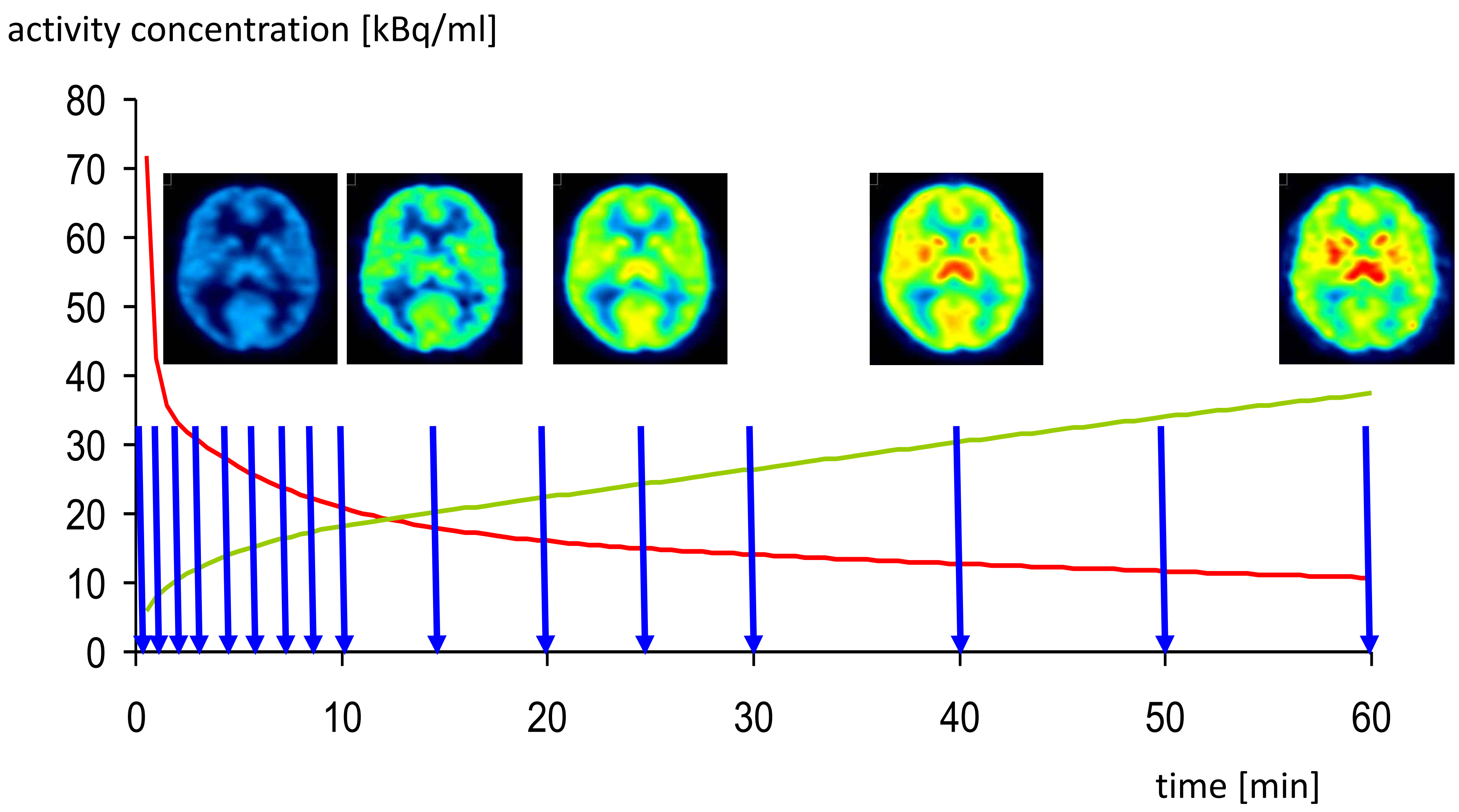
from all compartments

Tracer kinetic modelling: solution

functional compartments might be separated in **time** (rather than space)

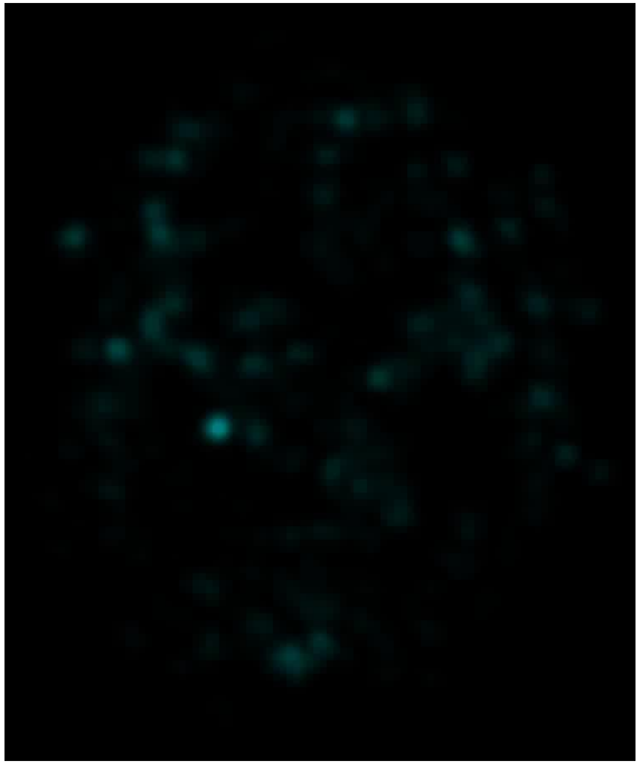


Static imaging → dynamic imaging



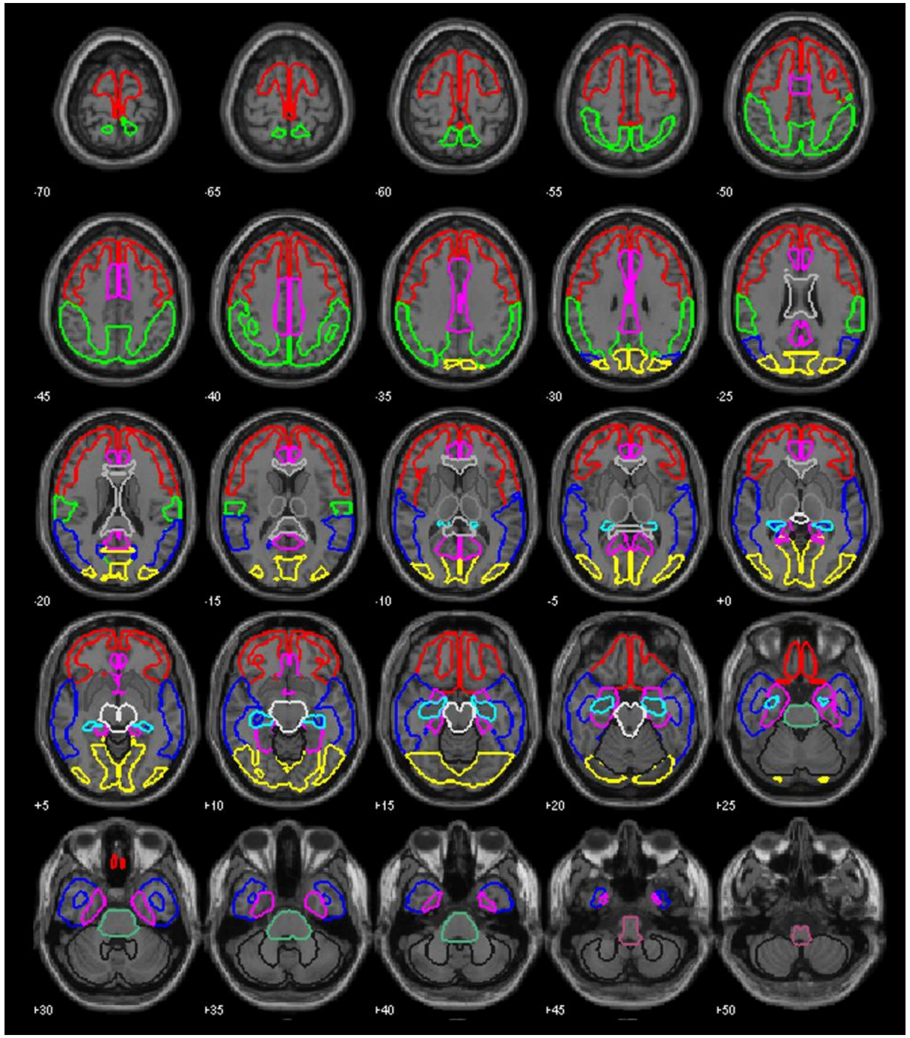
dynamic imaging

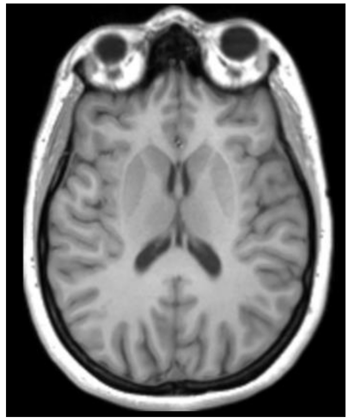
F-18-Fallypride



motion correction!

dynamic imaging: region-of-interest (ROI) based time activity curves

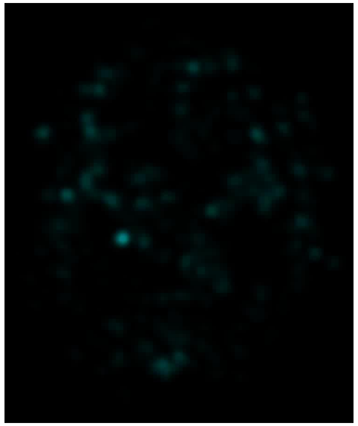


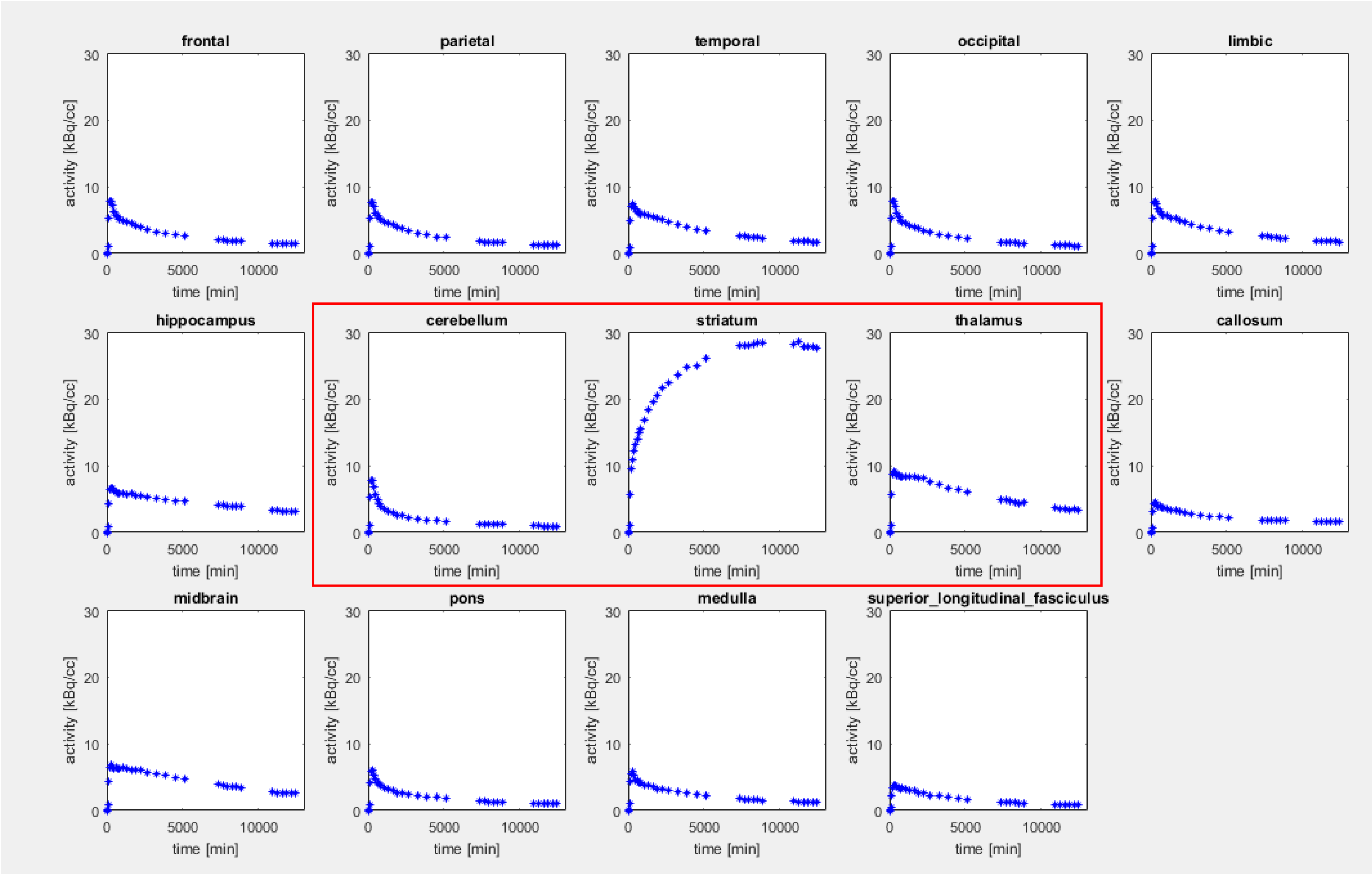


stereotactical normalization

dynamic imaging: region-of-interest (ROI) based time activity curves

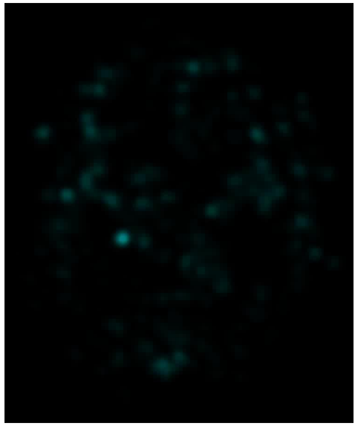
F-18-Fallypride

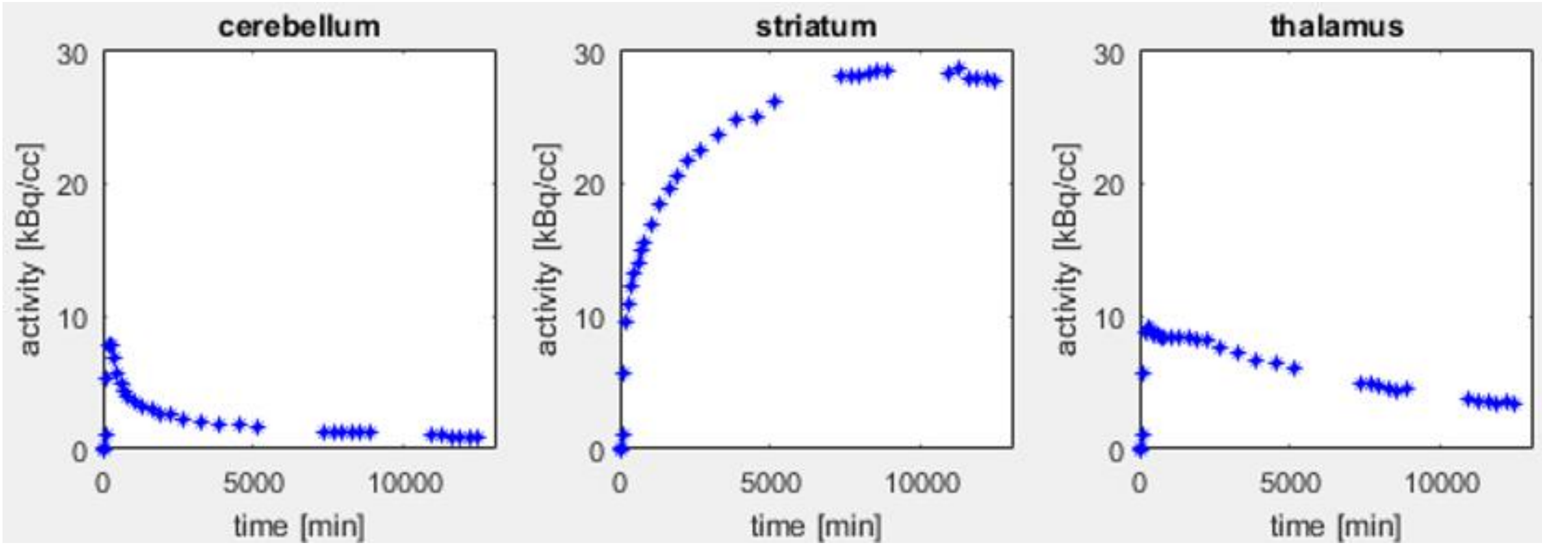




dynamic imaging: region-of-interest (ROI) based time activity curves

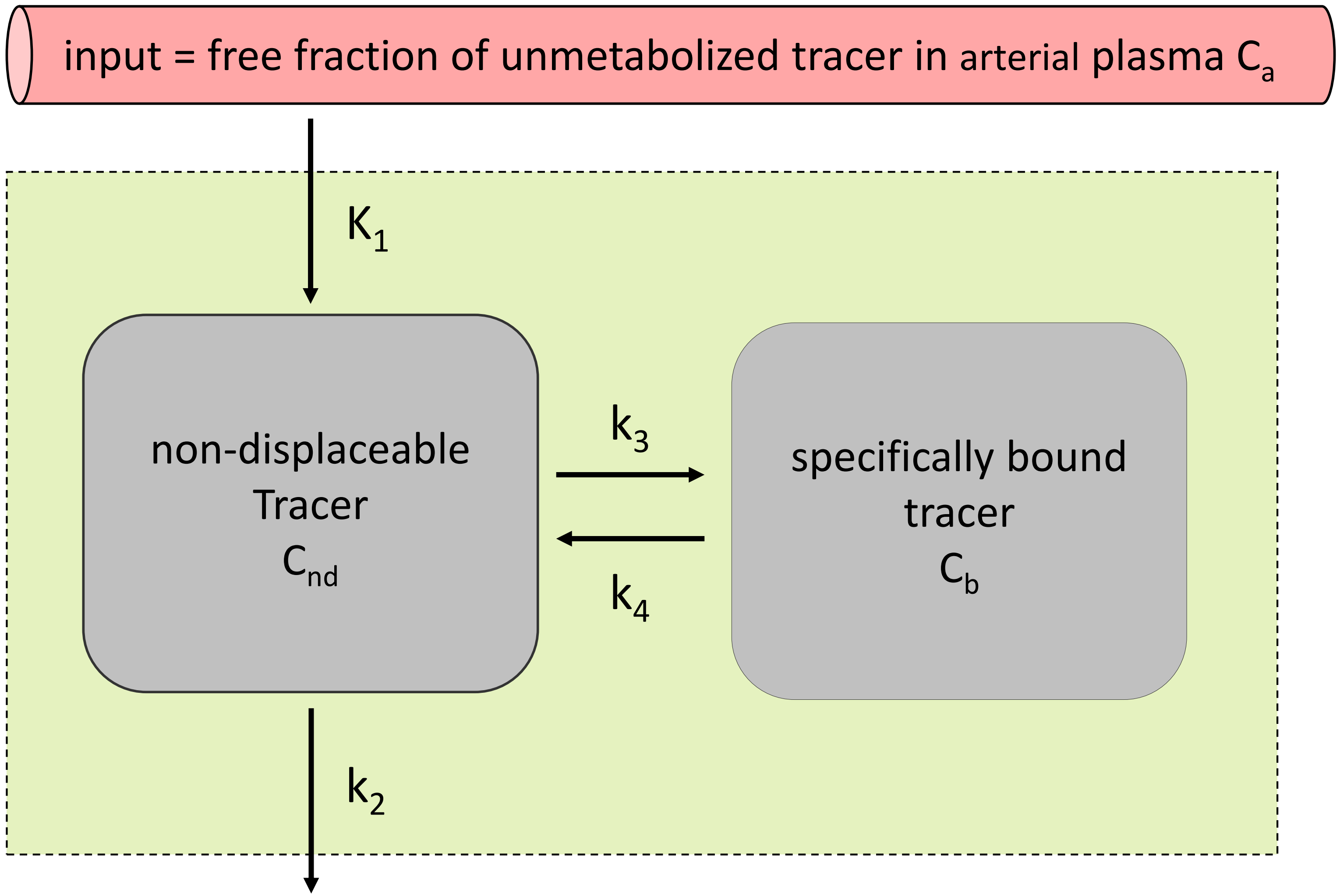
F-18-Fallypride





dynamic imaging: compartment model for F-18-fallypride

mathematically same model as for FDG



$$dC_{nd}/dt = K_1 * C_a - (k_2 + k_3) * C_{nd} + k_4 * C_b$$

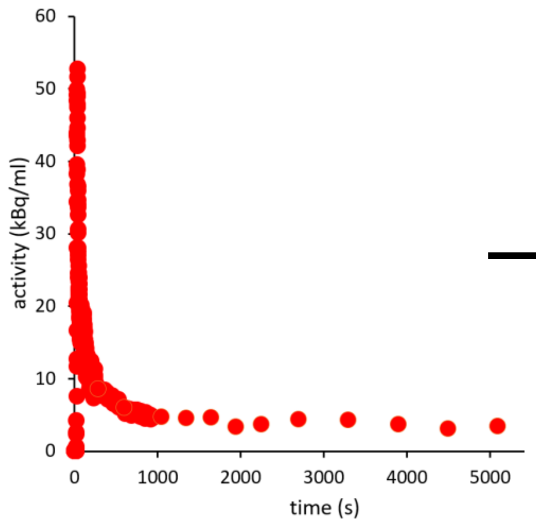
$$dC_b/dt = k_3 * C_{nd} - k_4 * C_b$$

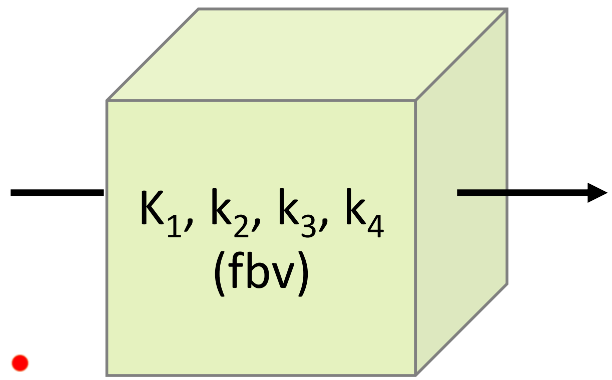
$$C_t = C_{nb} + C_b \quad (+ fbv * C_{blood})$$

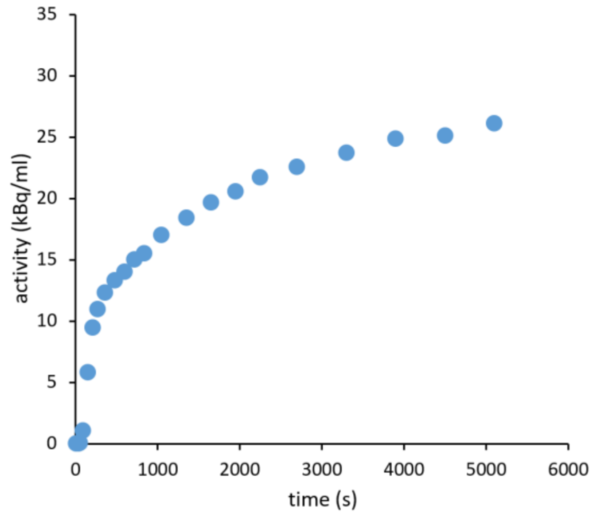
linear system

PET ROI

compartment model







input

unmetabolized tracer in arterial plasma (t)

Output = C_t

linear function(input; K_1,k_2, k_3, k_4, fbv, t)

=

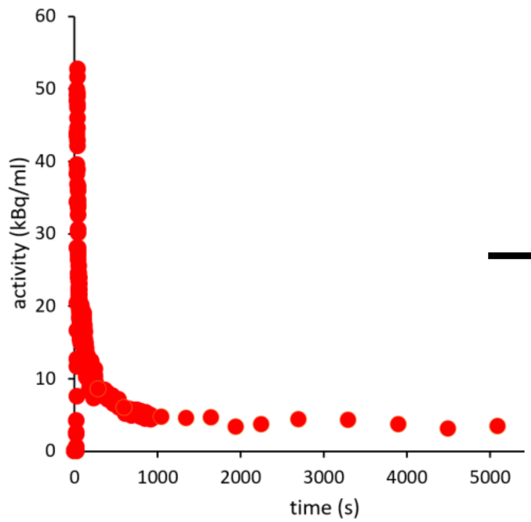
PET time activity curve

noise, systematic errors → no exact solution

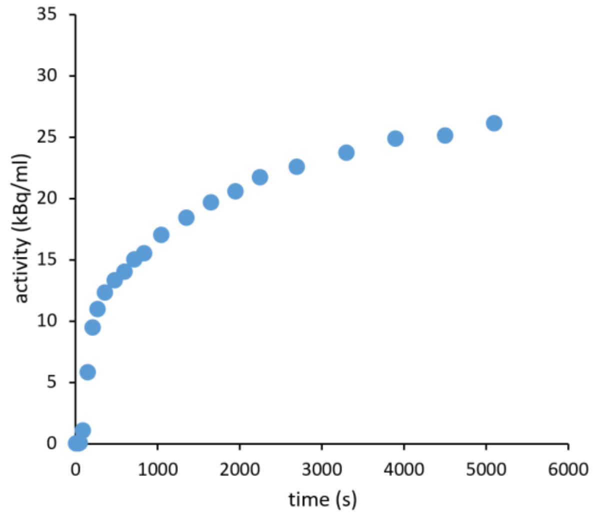
linear system

PET ROI

compartment model



K_1, k_2, k_3, k_4
(fbv)



improved estimate

input

output

unmetabolized tracer in arterial plasma (t)

function(input; K_1,k_2 k_3, k_4, fbv, t)

difference

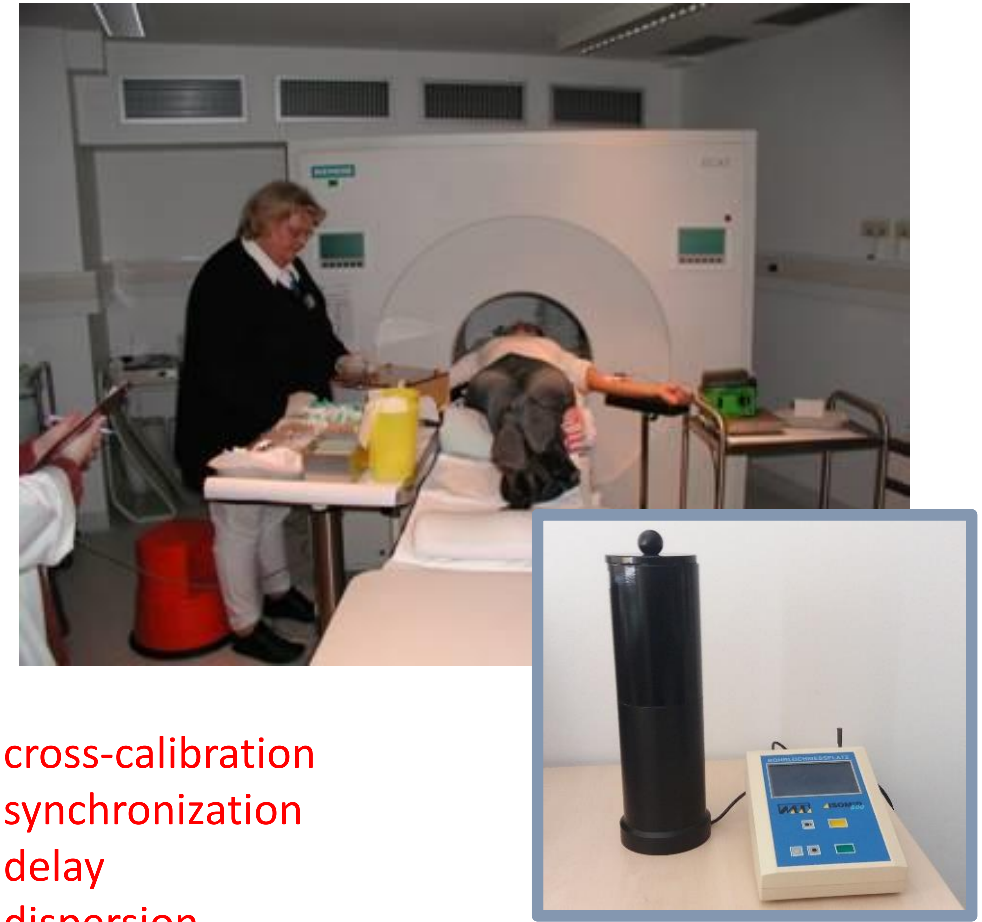
PET time activity curve

approximate solution

arterial blood sampling

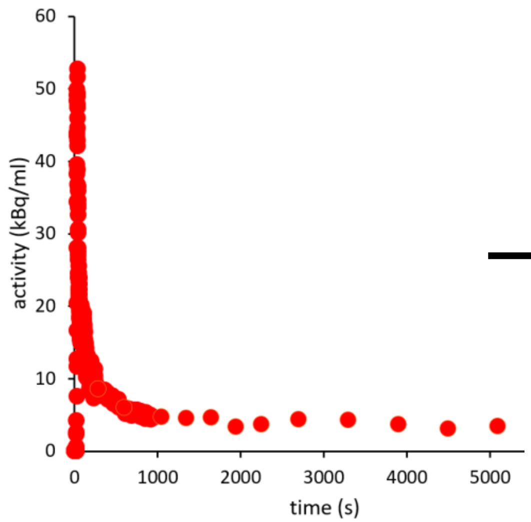
automatic

manual



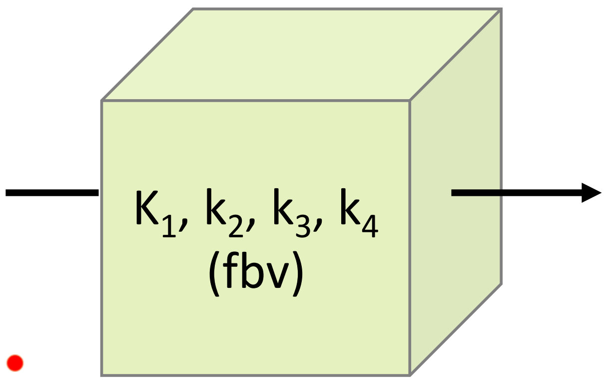
- cross-calibration
- synchronization
- delay
- dispersion

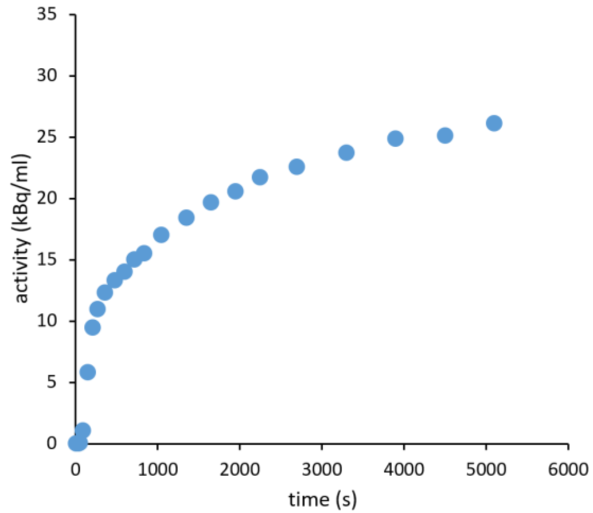
linear system



PET ROI

compartment model





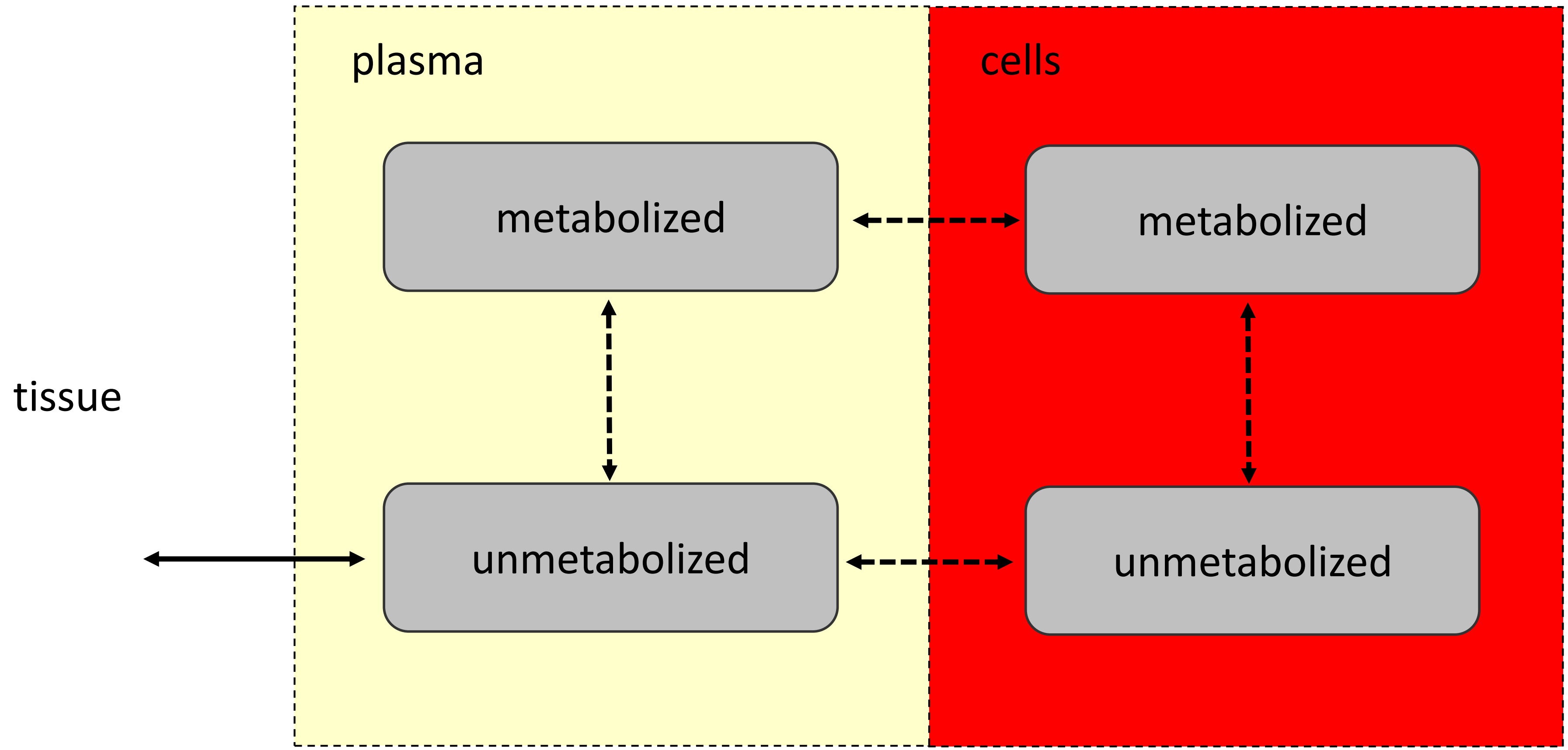
input

unmetabolized tracer in arterial plasma (t)

output

function(input; K_1,k_2 k_3, k_4, fbv, t)

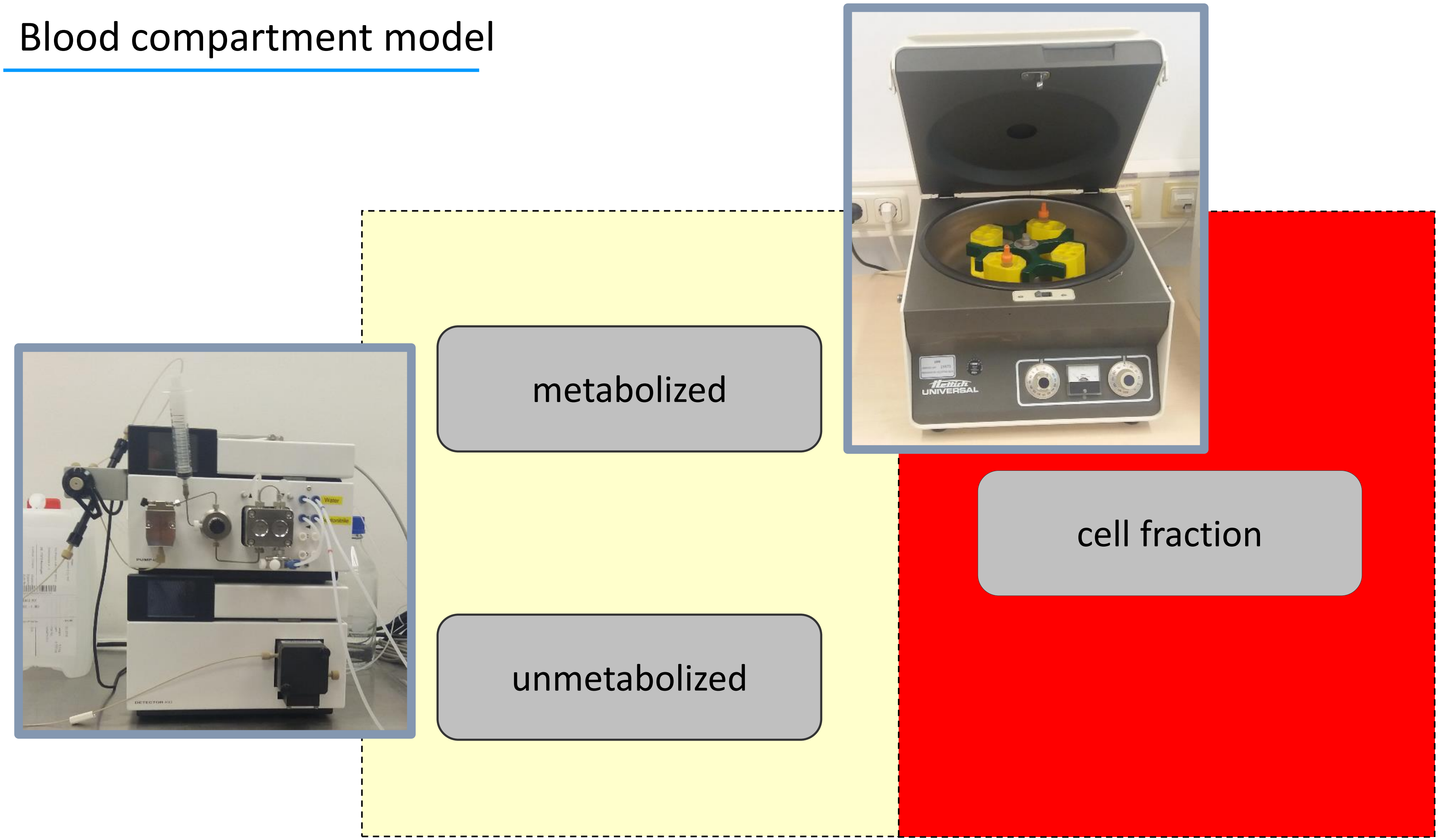
Blood compartment model



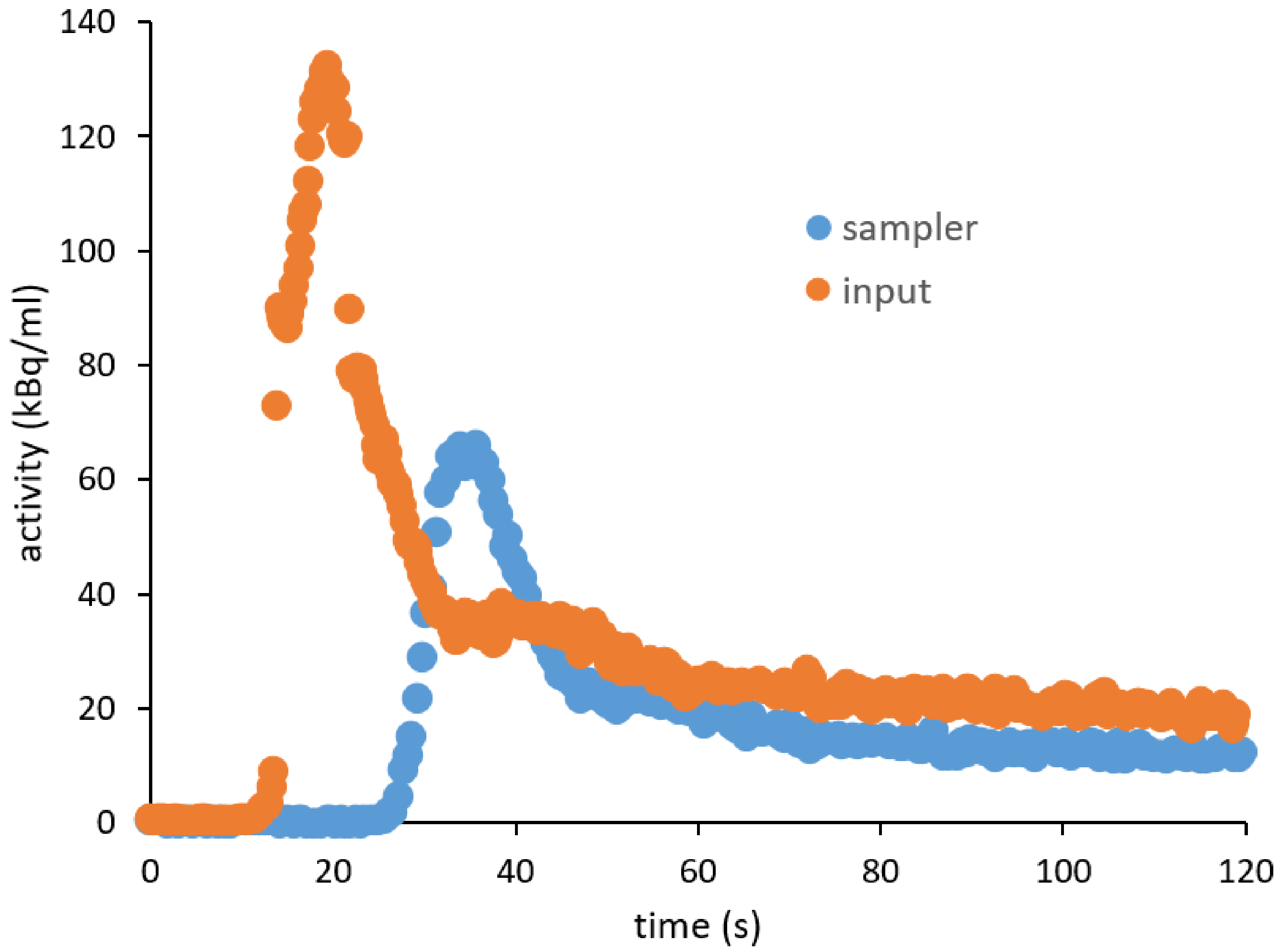
neglected

- uptake of metabolized tracer
- binding to plasma proteins

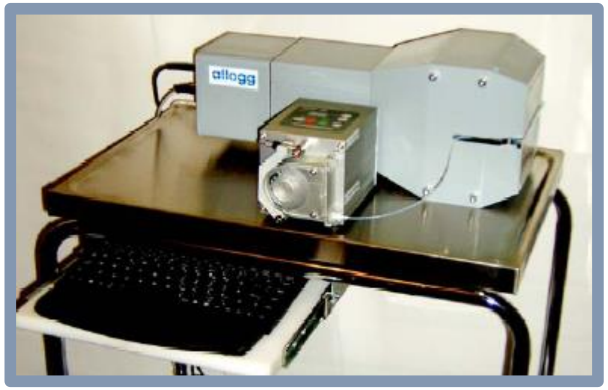
Blood compartment model

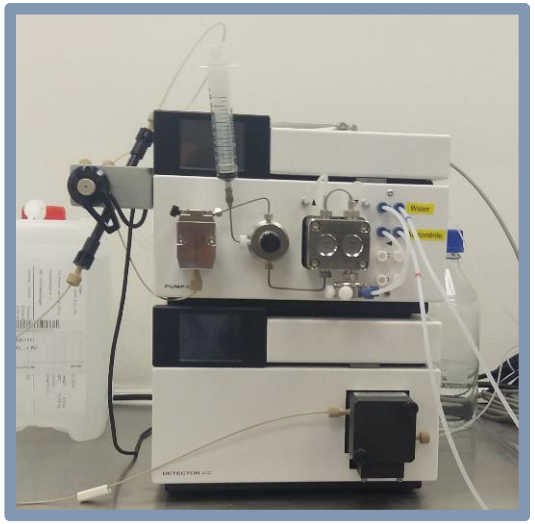


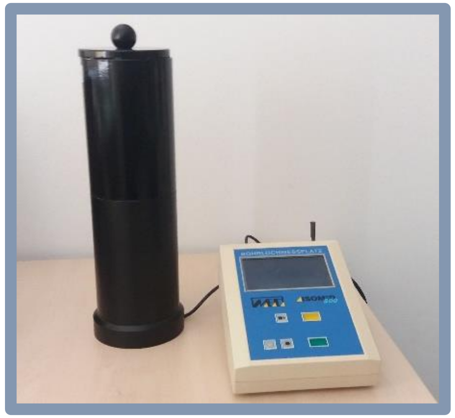
Input function



Tracer kinetic modelling: technical requirements







Tracer kinetic modelling: staff



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physician technician radiochemist physicist


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Contents

- basic principle of PET and SPECT radionuclide imaging & tracer principle
- tracer kinetic modelling
  - application in medical research
  - how it works

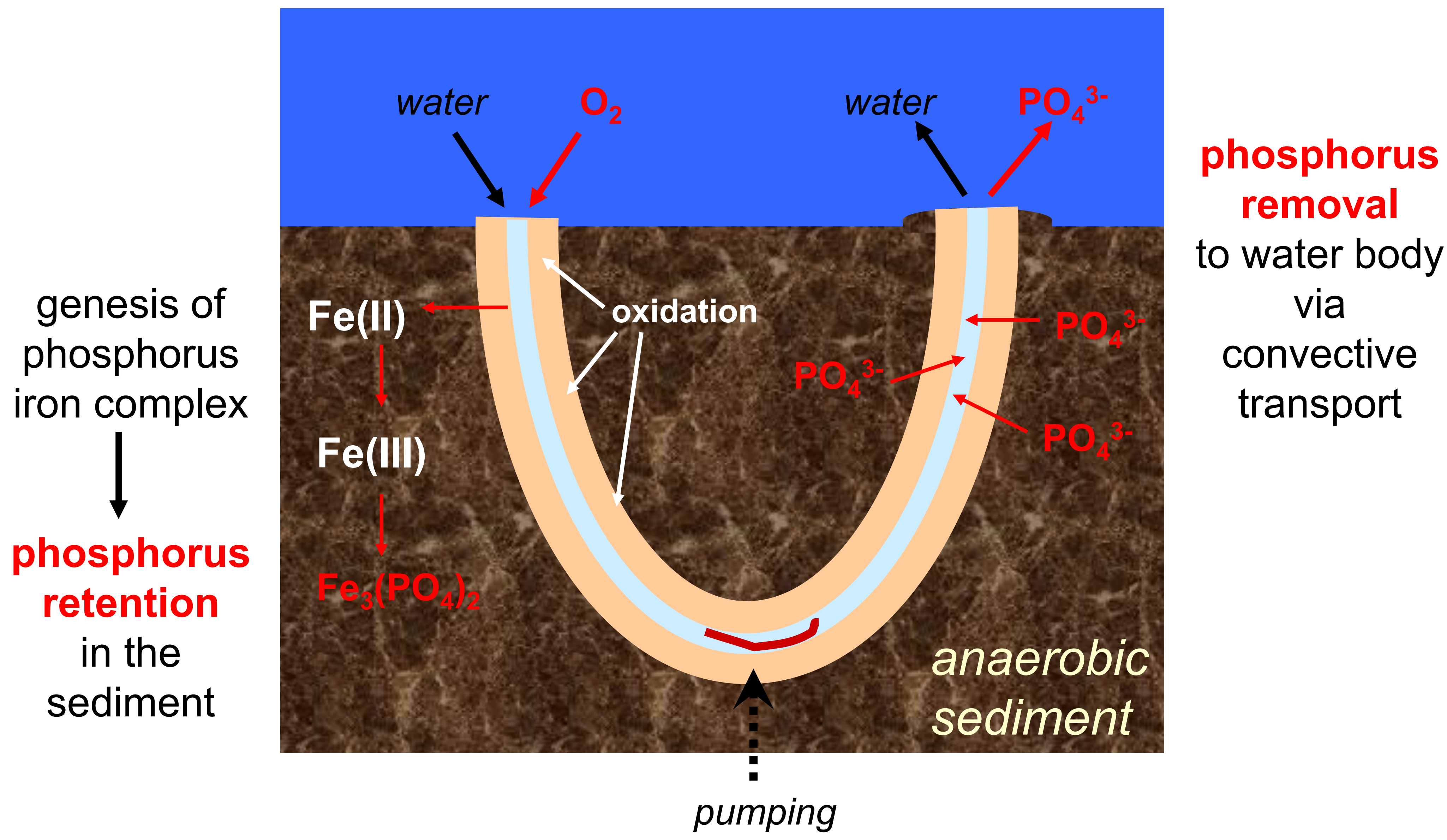
chironomus plumosus larvae

Chironomus plumosus larvae

up to 10.000 per m^2 lake sediment

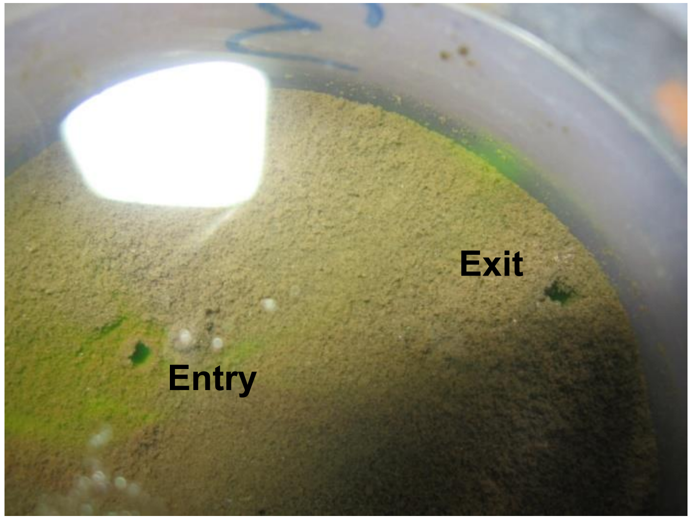
building u-shaped burrows (15 cm deep) inside lake sediments

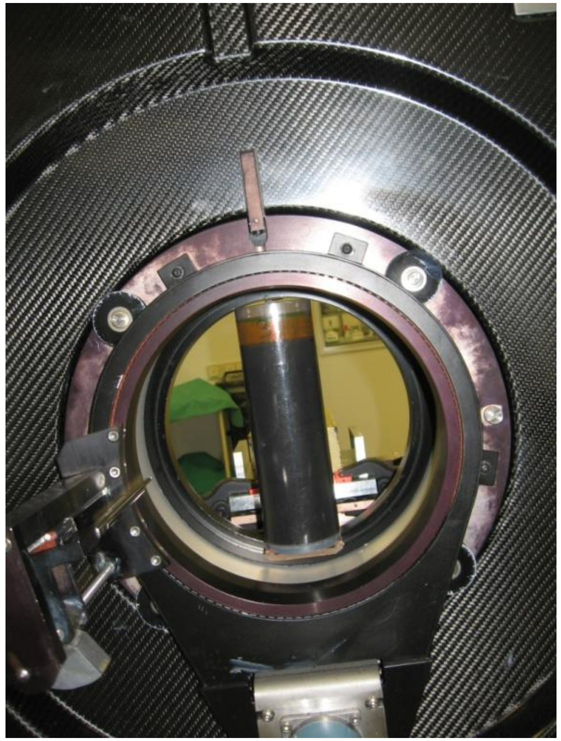
Chironomus plumosus larvae



Chironomus plumosus larvae: dynamic small animal PET

Roskosch A et al., Appl Radiat Isot 2010; 68:1094-7.





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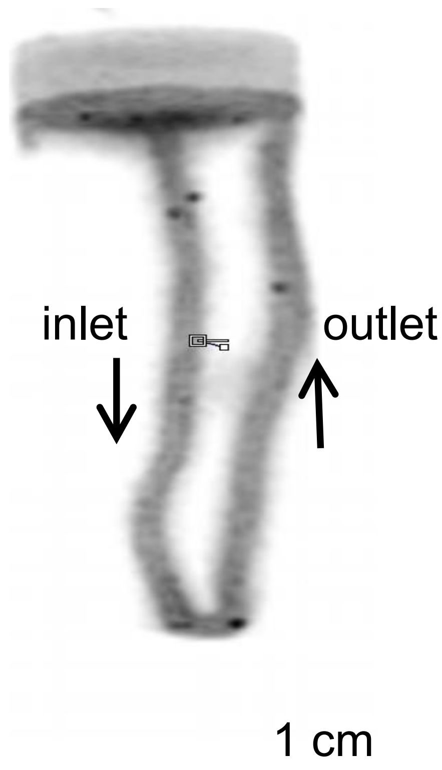

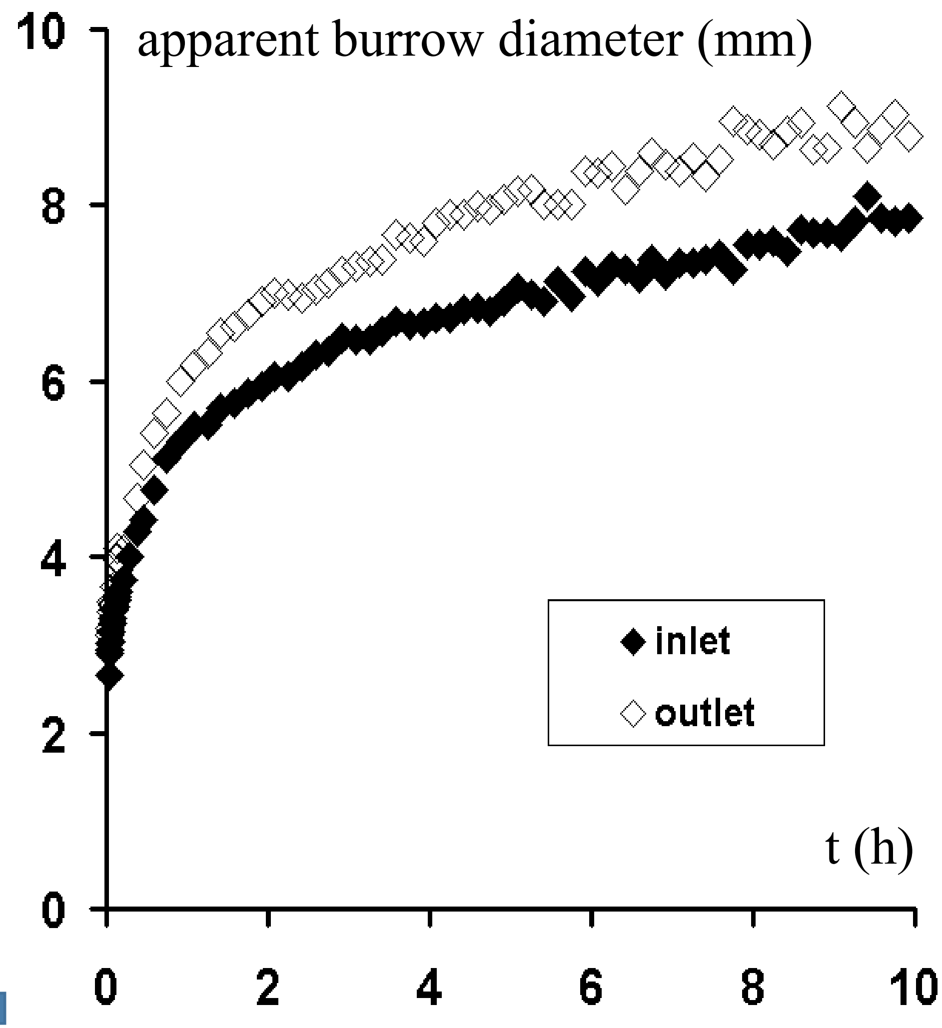

advection (diffusion, convection)

Further reading

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