ETH zürich
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Biomedical Imaging

Nuclear Imaging (II)

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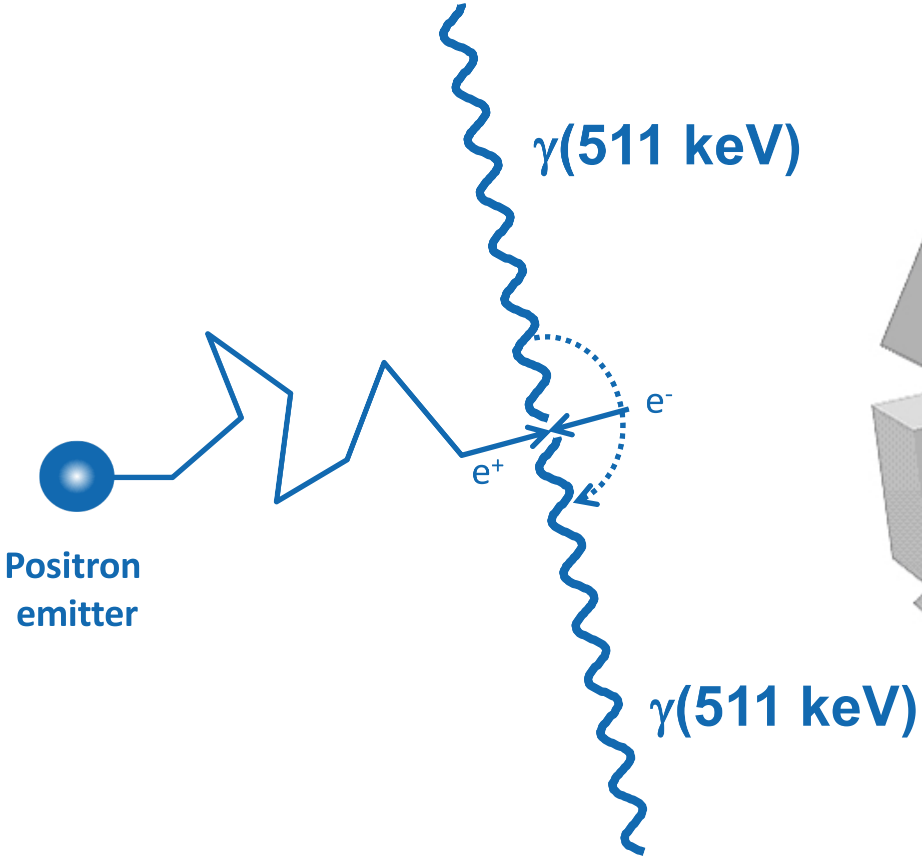
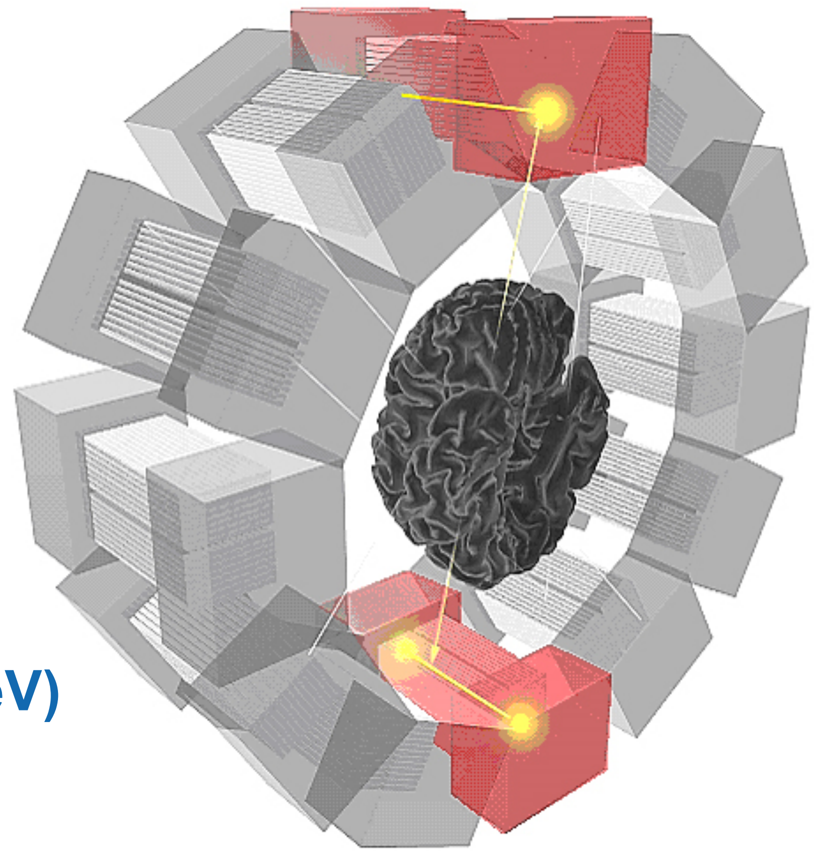
Today's Learning Objectives

- **Explain various PET coincidence events and corrections thereof**
- **Describe SPECT radioisotope production (Technetium generator)**
- **Describe PET radioisotope production (cyclotron)**
- **Derive basic kinetic models for PET tracer quantification**
- **Implement kinetic modeling for PET** (Exercise)

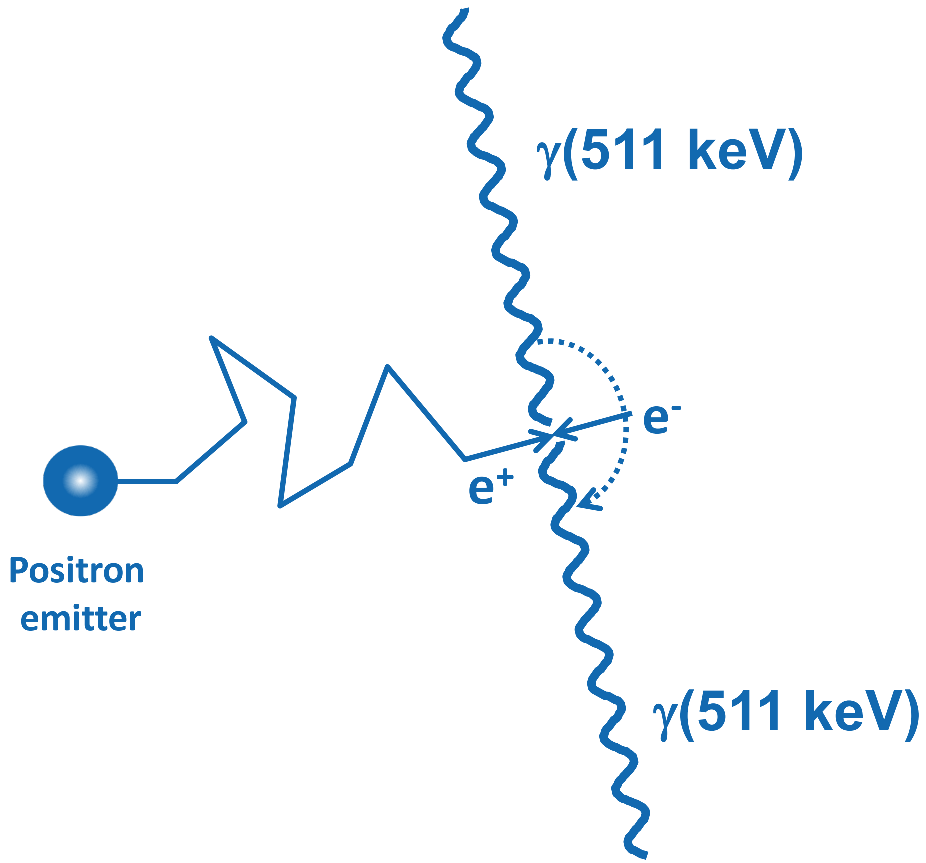
Positron Emission Tomography

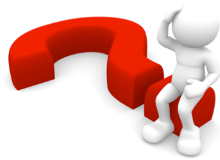




Activity (5 min)

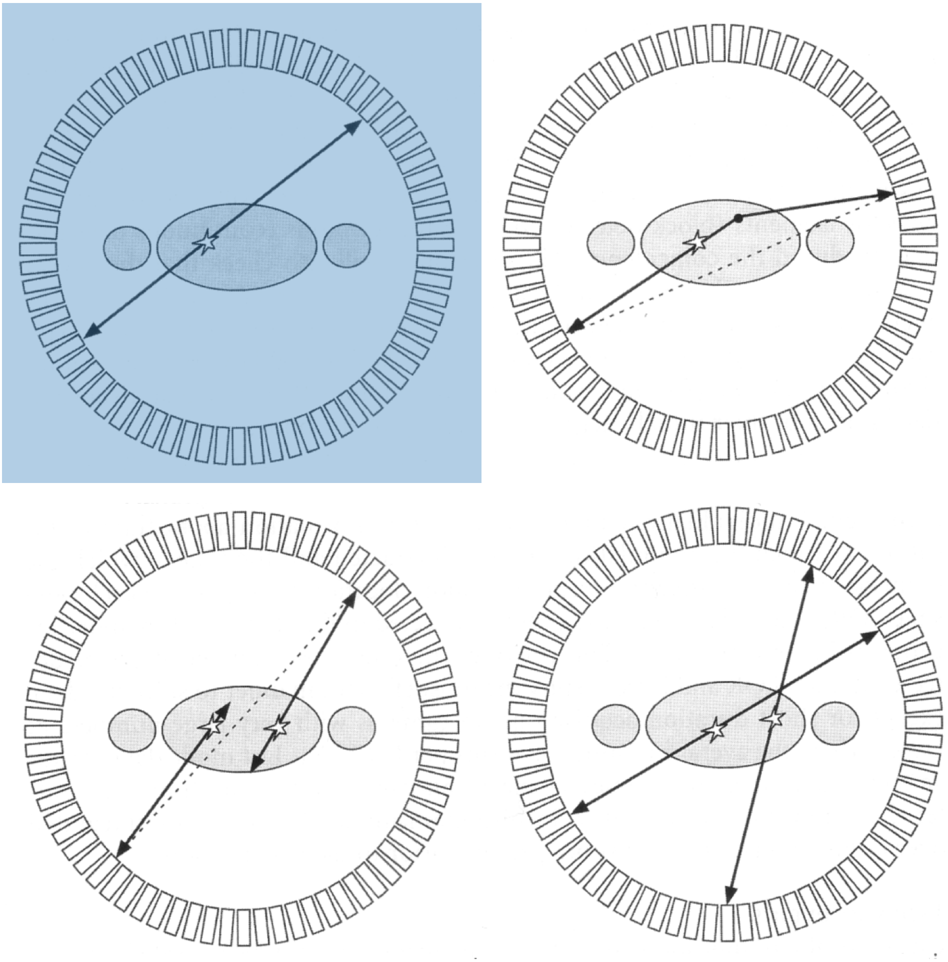
Using the mass of positron/electron, show that the energy of γ-photons is indeed 511 keV ($m_{p,e} = 9.11 \cdot 10^{-31}$ kg; 1 eV = $1.6 \cdot 10^{-19}$ J)**!**





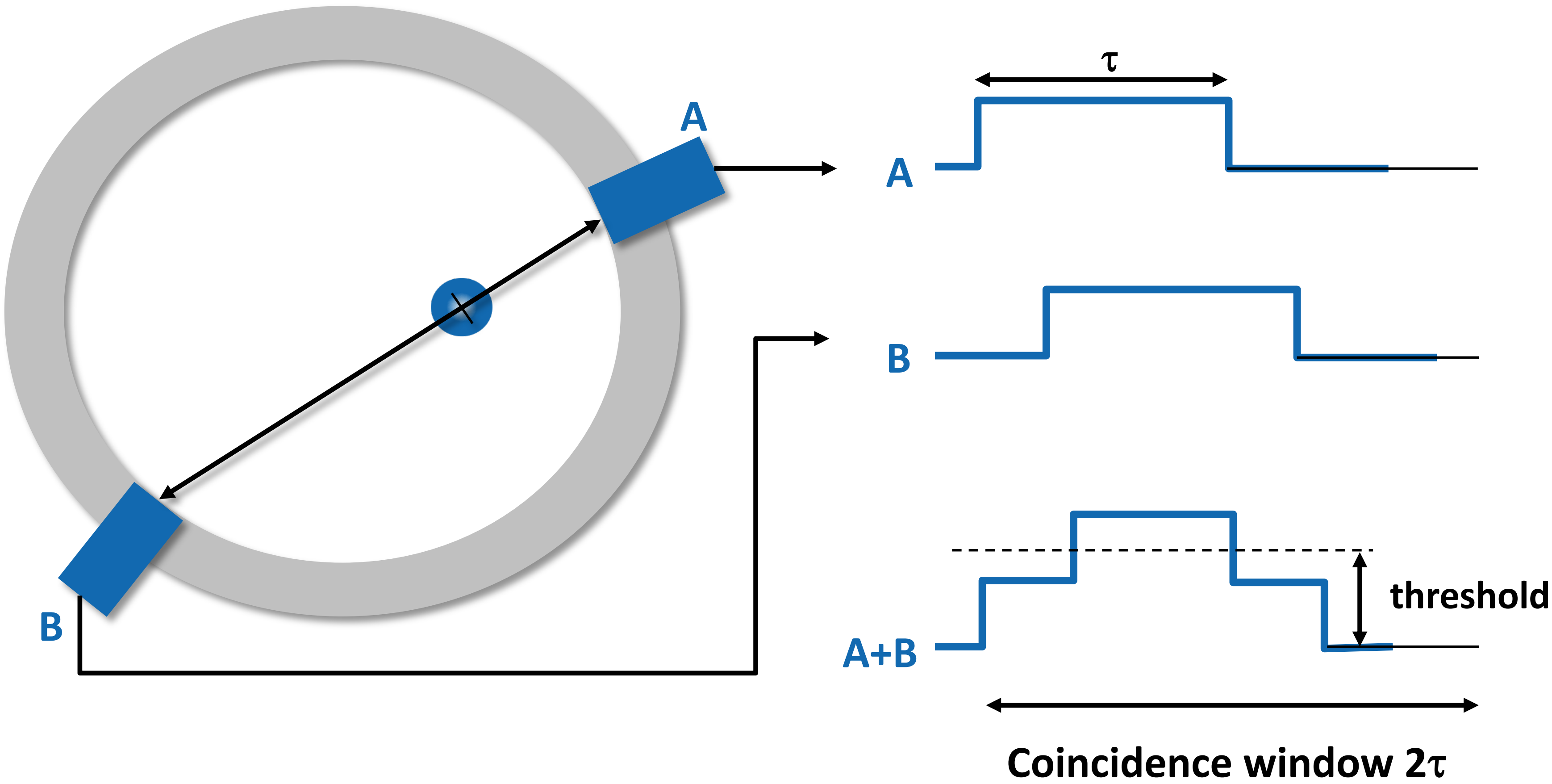
Coincidence types

true coincidence **scattered coincidence**



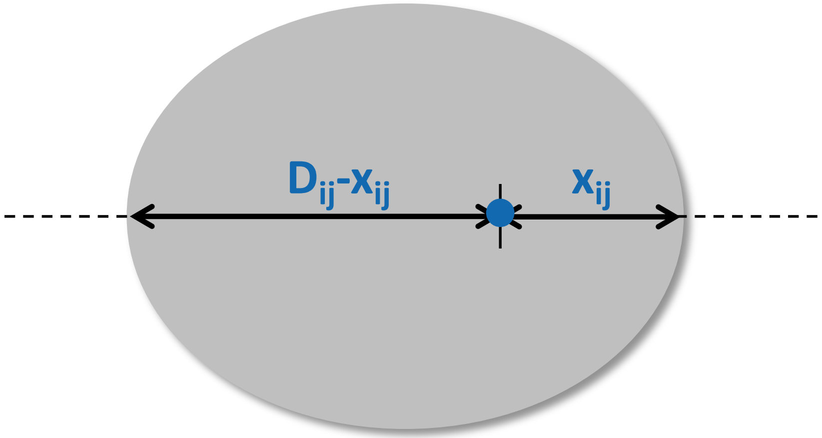
random coincidence **multiple coincidence**

Coincidence detection



Attenuation correction

- **Loss of γ-photons due to Compton scattering**



$$p_{1ij} = e^{-\mu \cdot x_{ij}}$$

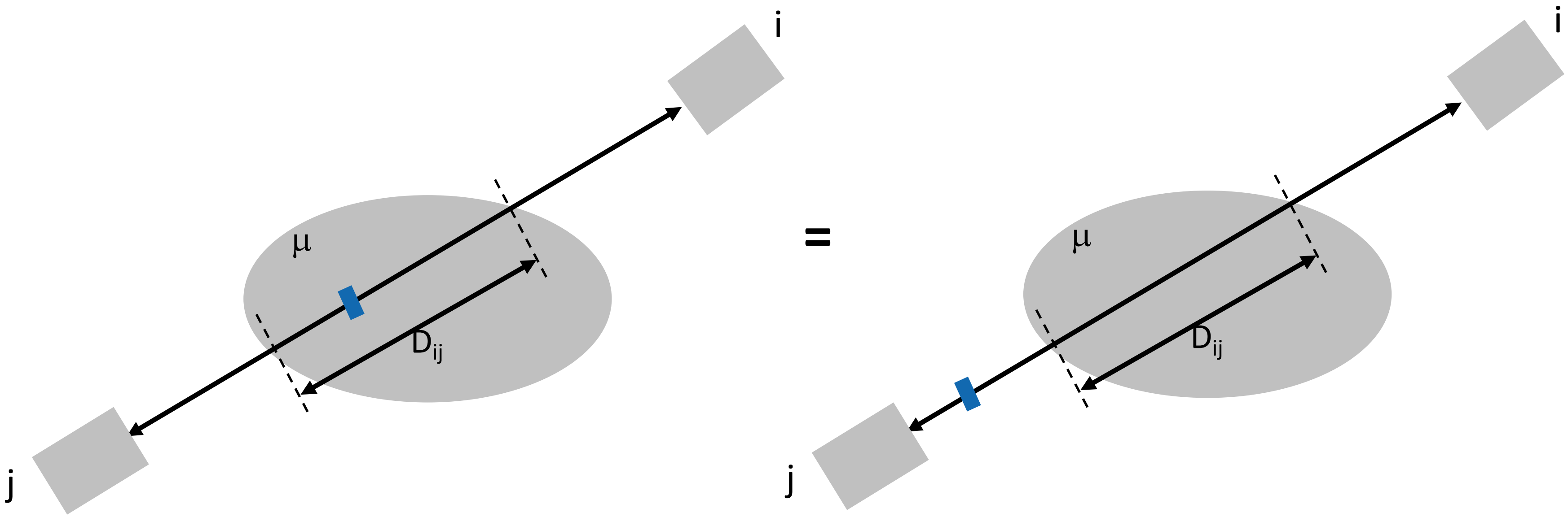
$$p_{2ij} = e^{-\mu \cdot (D_{ij} - x_{ij})}$$

- **Total scattering probability**

$$\boxed{p_{ij} = p_{1ij} \cdot p_{2ij} = e^{-\mu \cdot D_{ij}}}$$

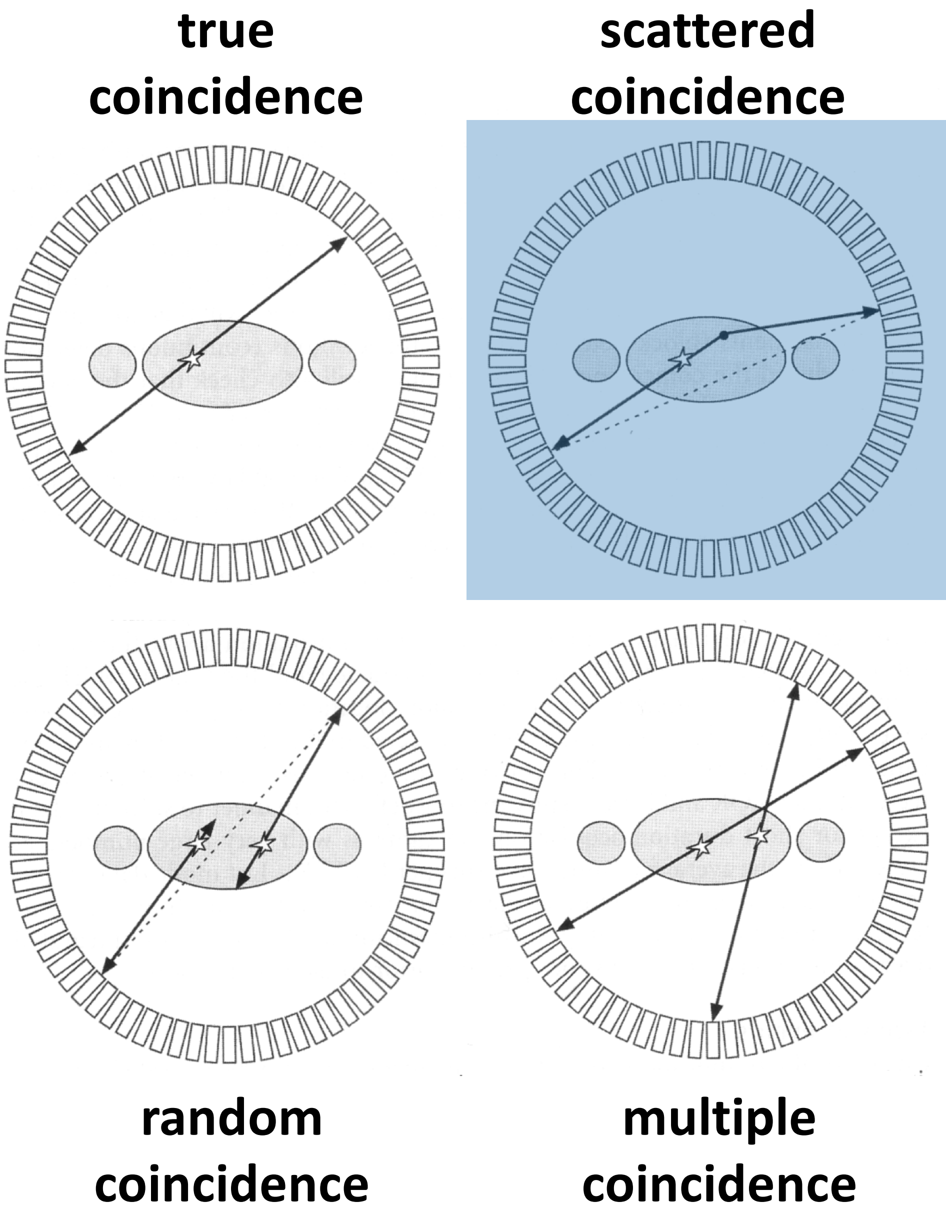
Attenuation correction

$$\mathbf{a_{ij}} = \frac{\mathbf{1}}{\mathbf{p_{ij}}} = \mathbf{e^{\mu \cdot D_{ij}}}$$



internal PET source **external PET source**

Coincidence types

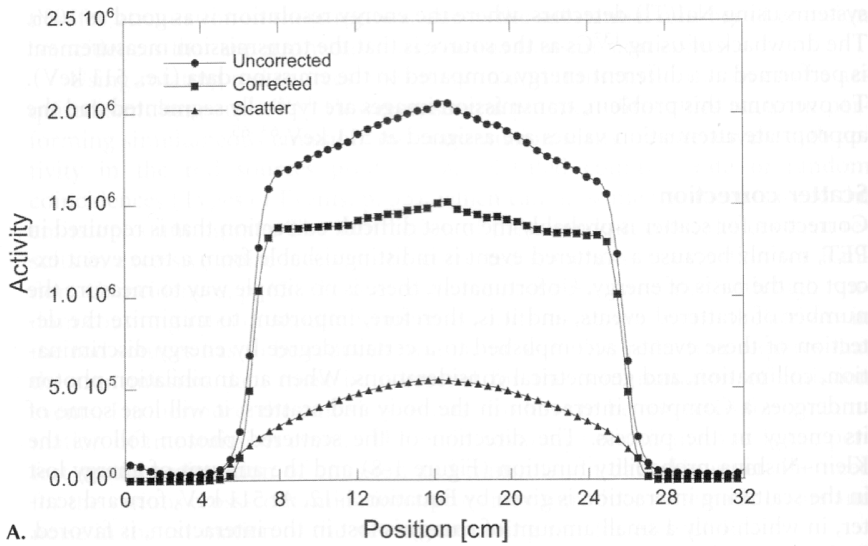


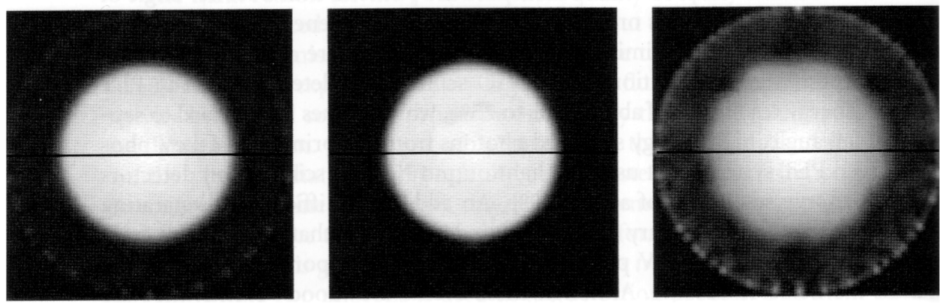
Scatter correction

Analytical method
- assumption: scatter distribution varies slowly across scattering medium
- use phantom data to correct for scattered events

Dual energy method
- Energy range 400-600 keV: scattered and true events
- Energy range 200-400 keV: only scattered events

Simulation method
- Reconstruction without scattering correction
- Estimation of scattering correction

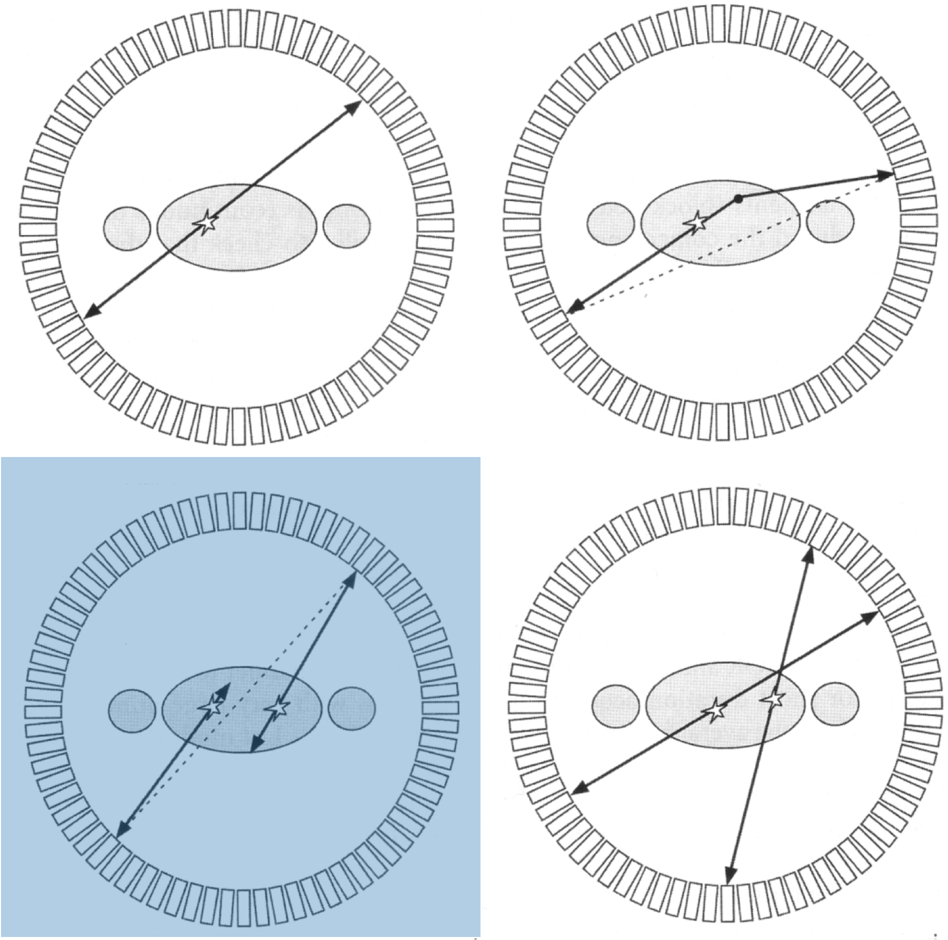




Coincidence types

true coincidence

scattered coincidence



random coincidence

multiple coincidence

Random coincidences

Frequency of random events

Individual photon detection rates of a pair of detectors: $\mathbf{N_A, N_B}$

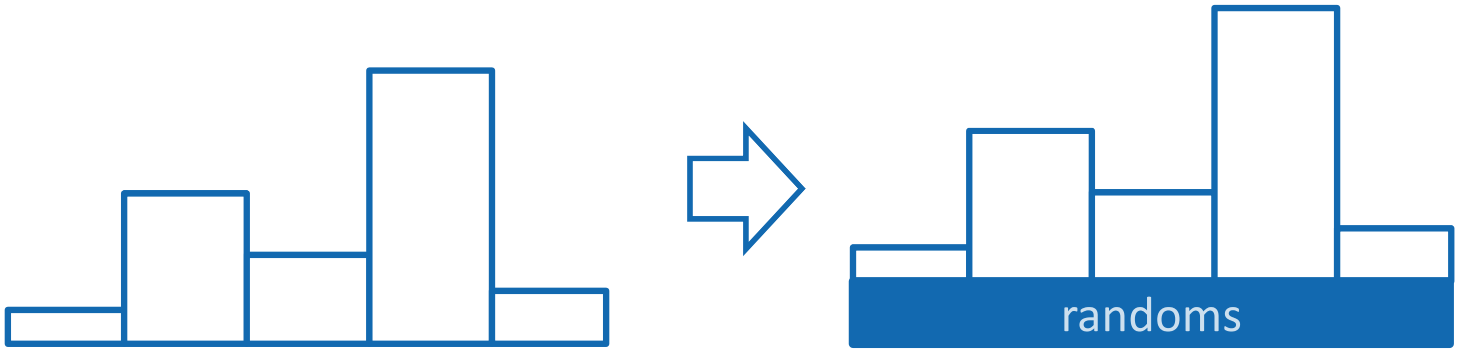
Coincidence window: $\mathbf{2\tau}$

Frequency of random events: $\mathbf{N_R = N_A \cdot N_B \cdot 2\tau}$

‚Randoms'

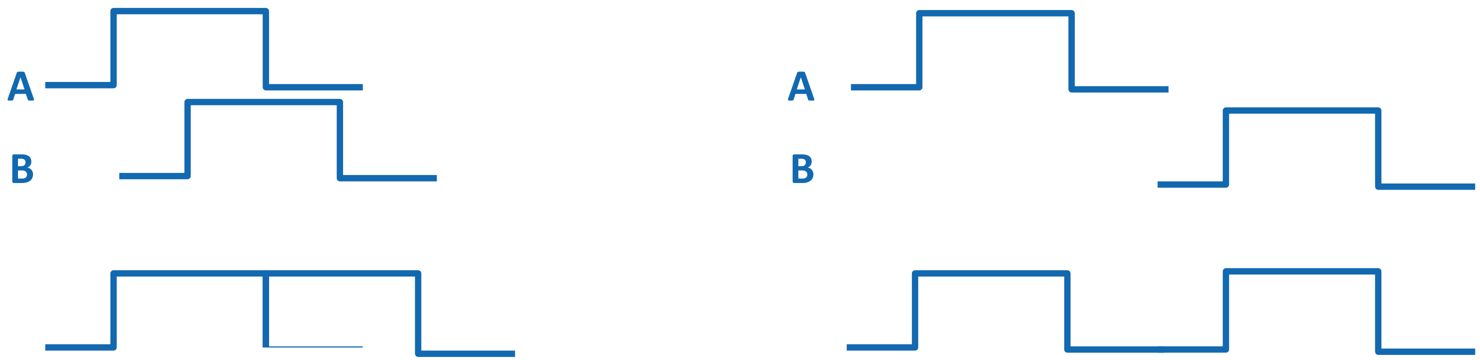
- no geometrical information
- almost uniform distribution across field-of-view

  $\rightarrow$ **reduced contrast-to-noise ratio**



Correction of random coincidences

- Estimate number of ‚randoms’ for each detector pair: N_1, N_2, 2τ must be known
- Measure/estimate number of ‚randoms‘ by adding parallel coincidence circuit



Coincidence window 1 → ‚trues‘ and ‚randoms‘ N_{actual}

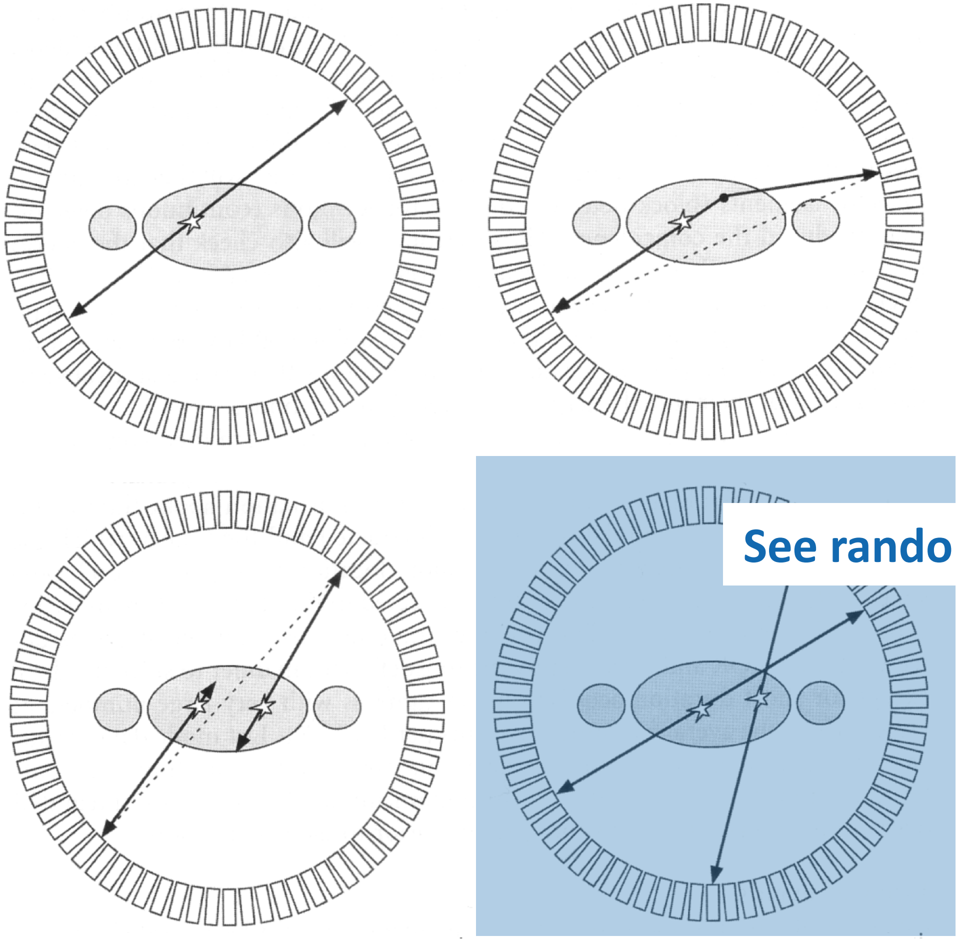
Coincidence window 2 → ‚randoms‘ $N_{randoms}$

Estimation of number of true events:

$$\boxed{N_{true} = N_{actual} - N_{randoms}}$$

Coincidence types

true coincidence **scattered coincidence**



random coincidence **multiple coincidence**

See random coincidence

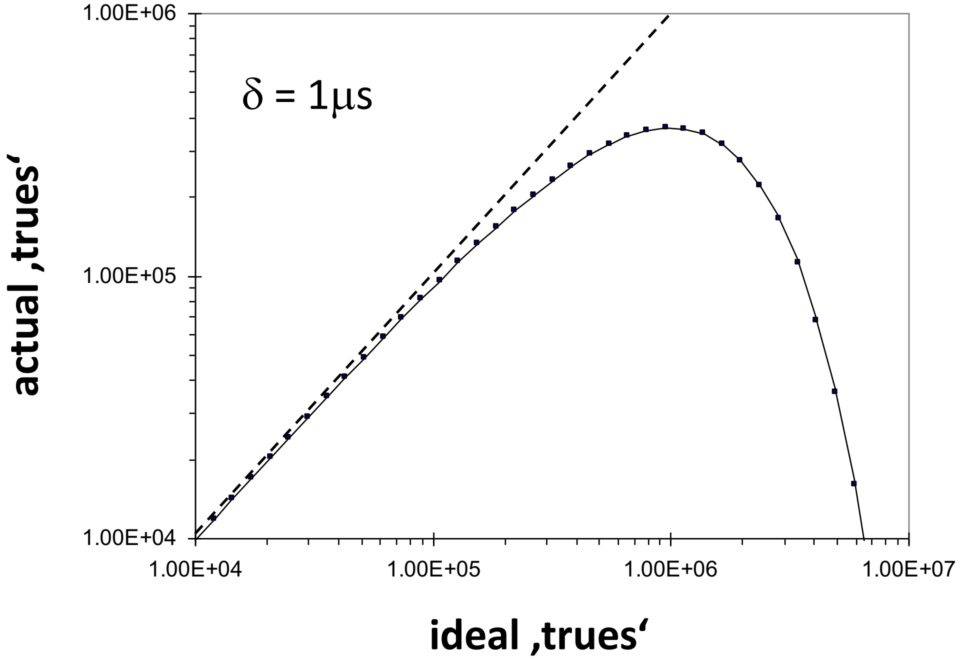
Dead time correction

Detector dead time: **number of events measured < number of true events**

Effect more severe for high activities → high count rate, high fraction of missed events:

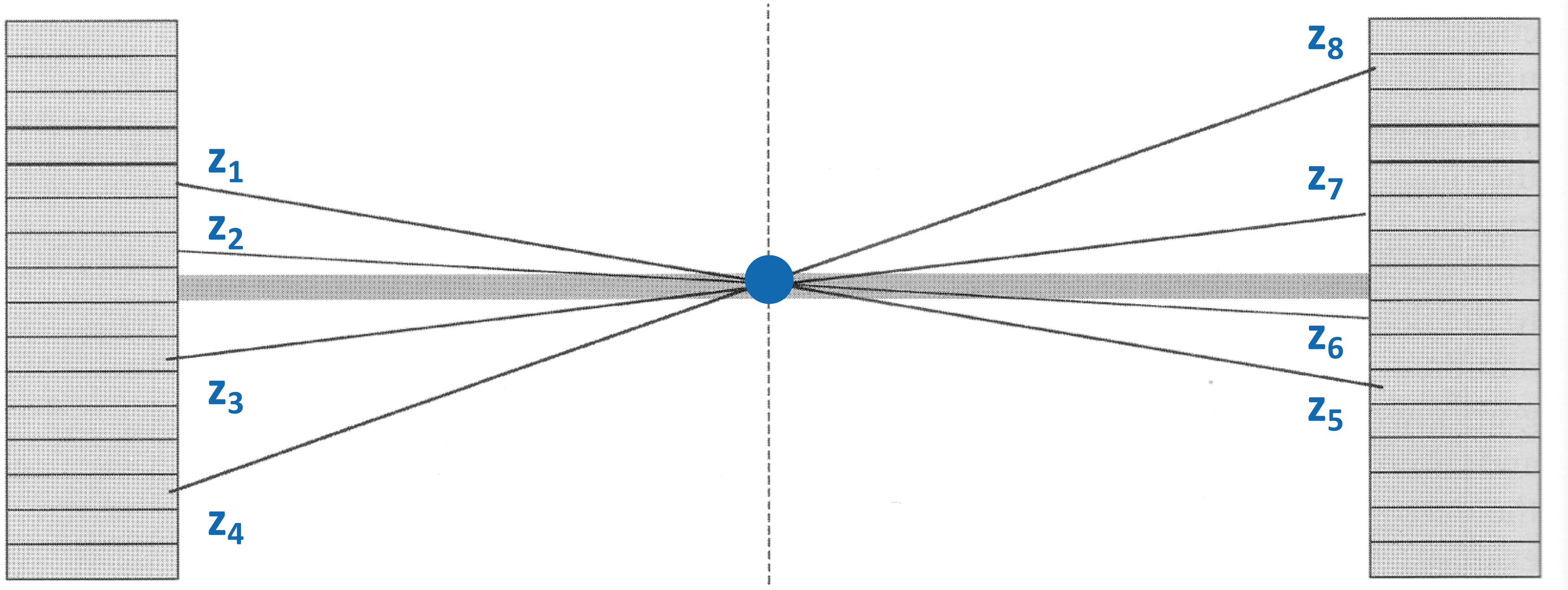
$$\boxed{N_{actual} = N_{true} \cdot e^{-N_{true} \cdot \delta}}$$

δ…dead time



3D image reconstruction

Data are reduced to a set of **parallel 2D sinograms** by rebinning all sinograms with same z value into the same sinogram



$$\boxed{\mathbf{z}_1 + \mathbf{z}_5 = \mathbf{z}_2 + \mathbf{z}_6 = \mathbf{z}_3 + \mathbf{z}_7 = \mathbf{z}_4 + \mathbf{z}_8}$$

▸ **Reconstruction of N 2D sinograms**

3D image reconstruction

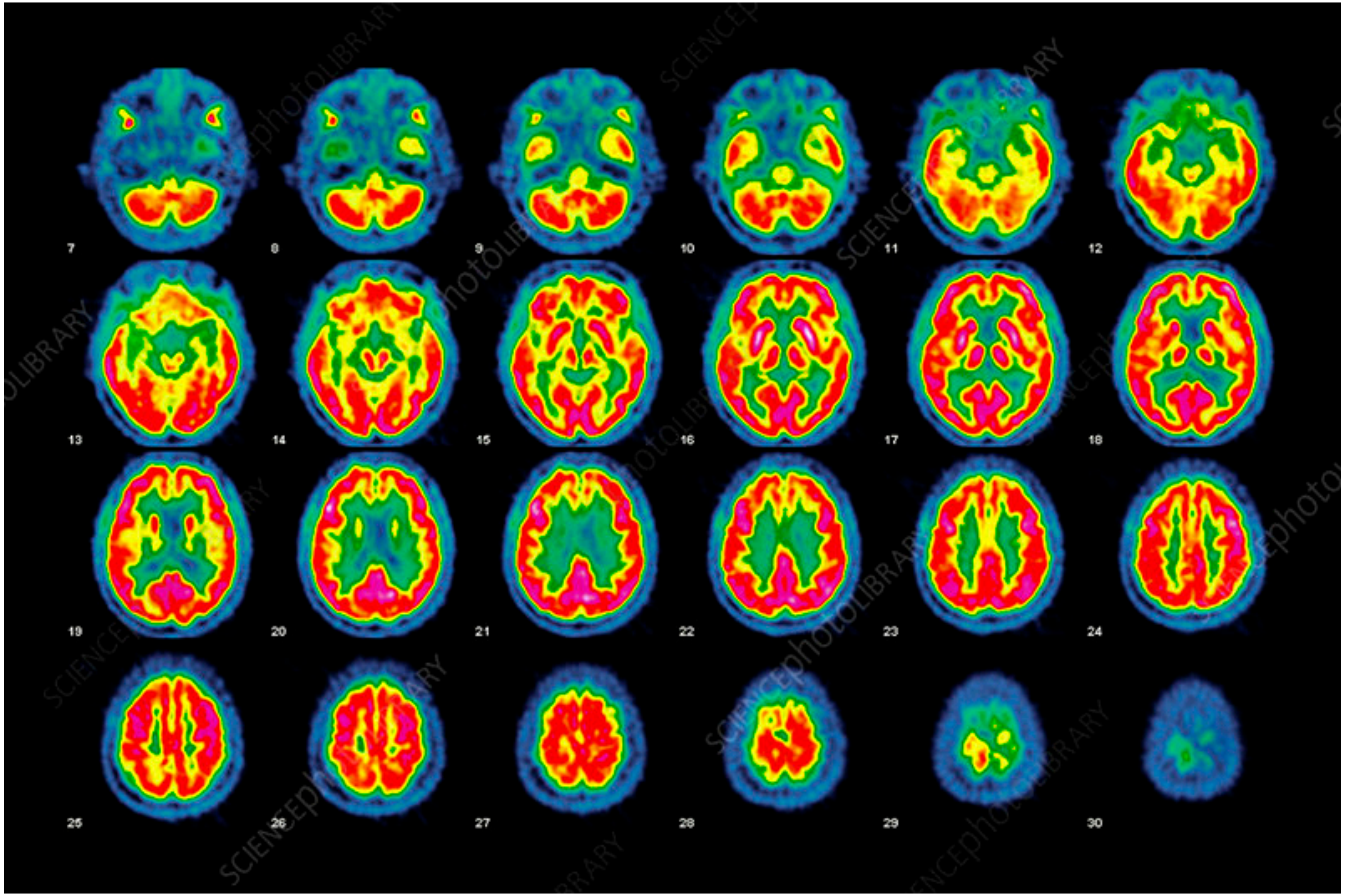
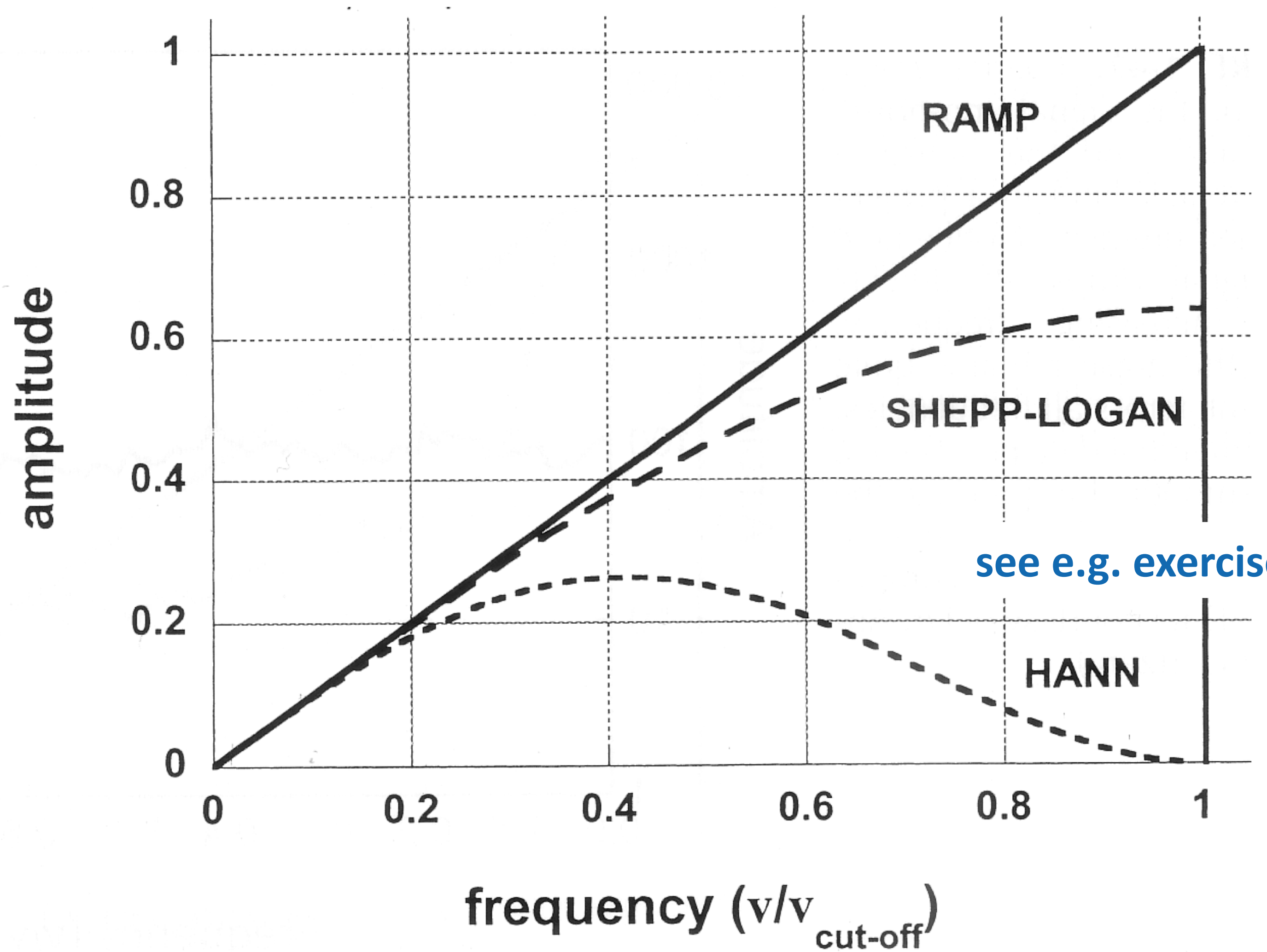
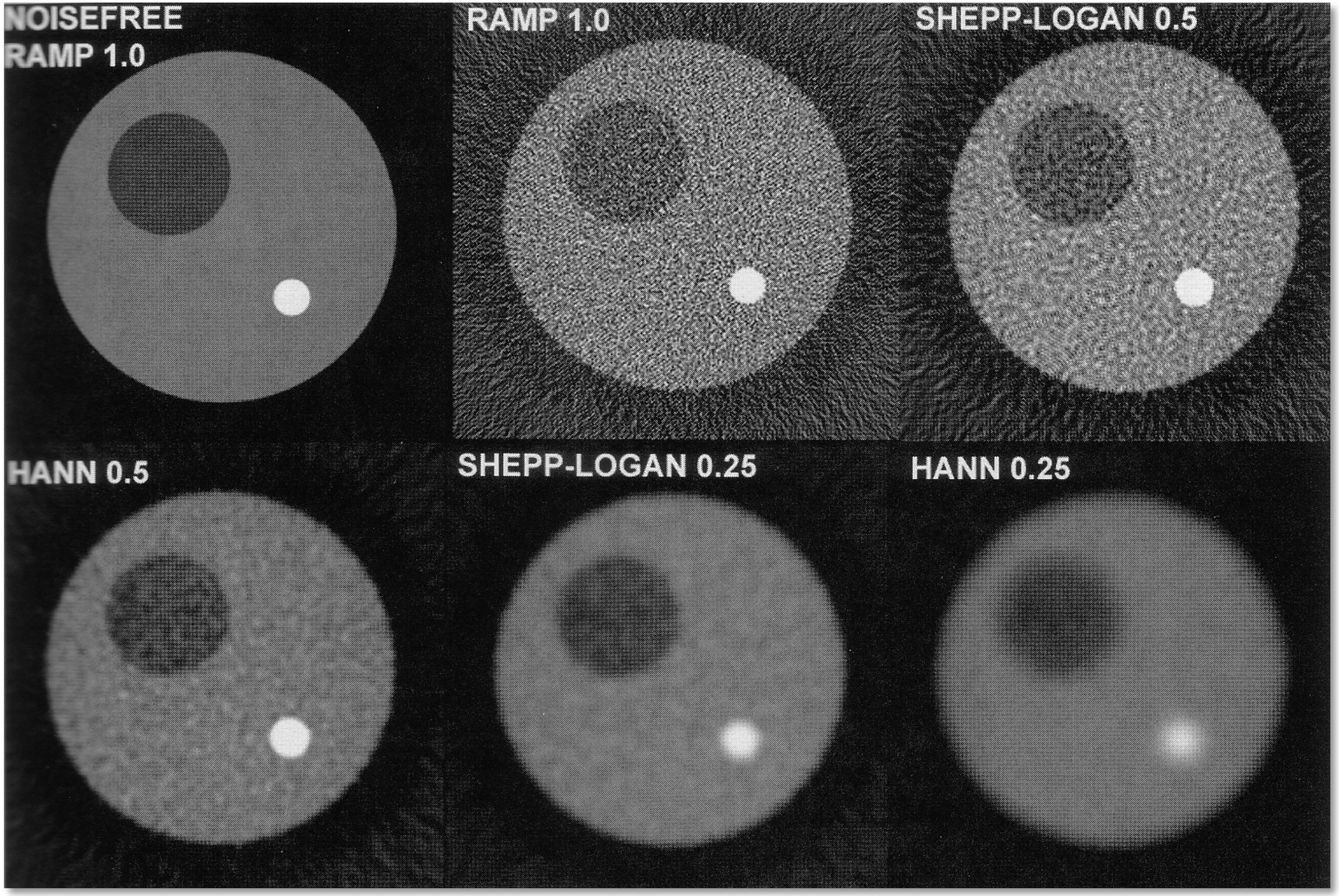


Image noise reduction



see e.g. exercise XCT #2

Image noise reduction

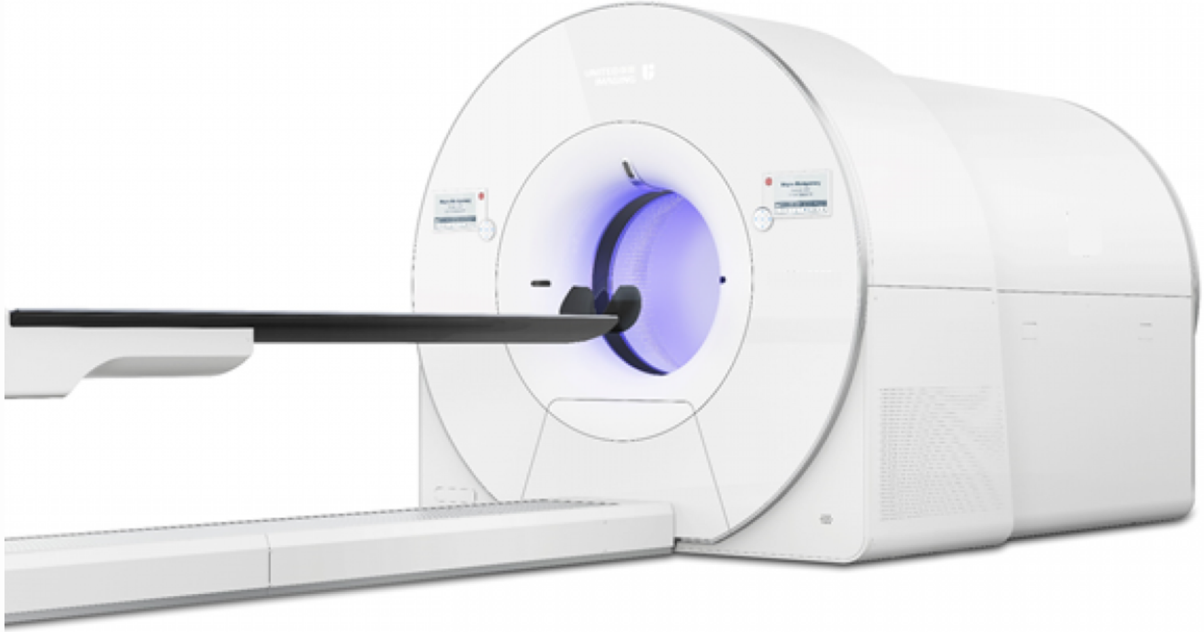


Clinical PET scanner

Animal PET scanner

PET/CT scanner

Total body PET scanner

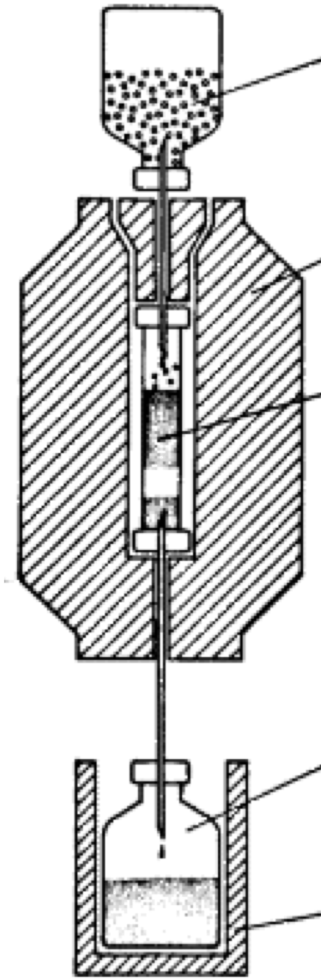


Radiotracer Production

SPECT radioisotopes

Radioisotope	Energy (keV)	Half-life	Production
^{67}Ga	93, 185, 300	3.3d	cyclotron
^{99m}Tc	140	6h	generator
^{111}In	173, 247	67h	cyclotron
^{123}I	160	13h	cyclotron
^{133}Xe	81	5.2d	reactor
^{201}Tl	60, 83	73h	cyclotron

Technetium generator



Eluate: NaCl

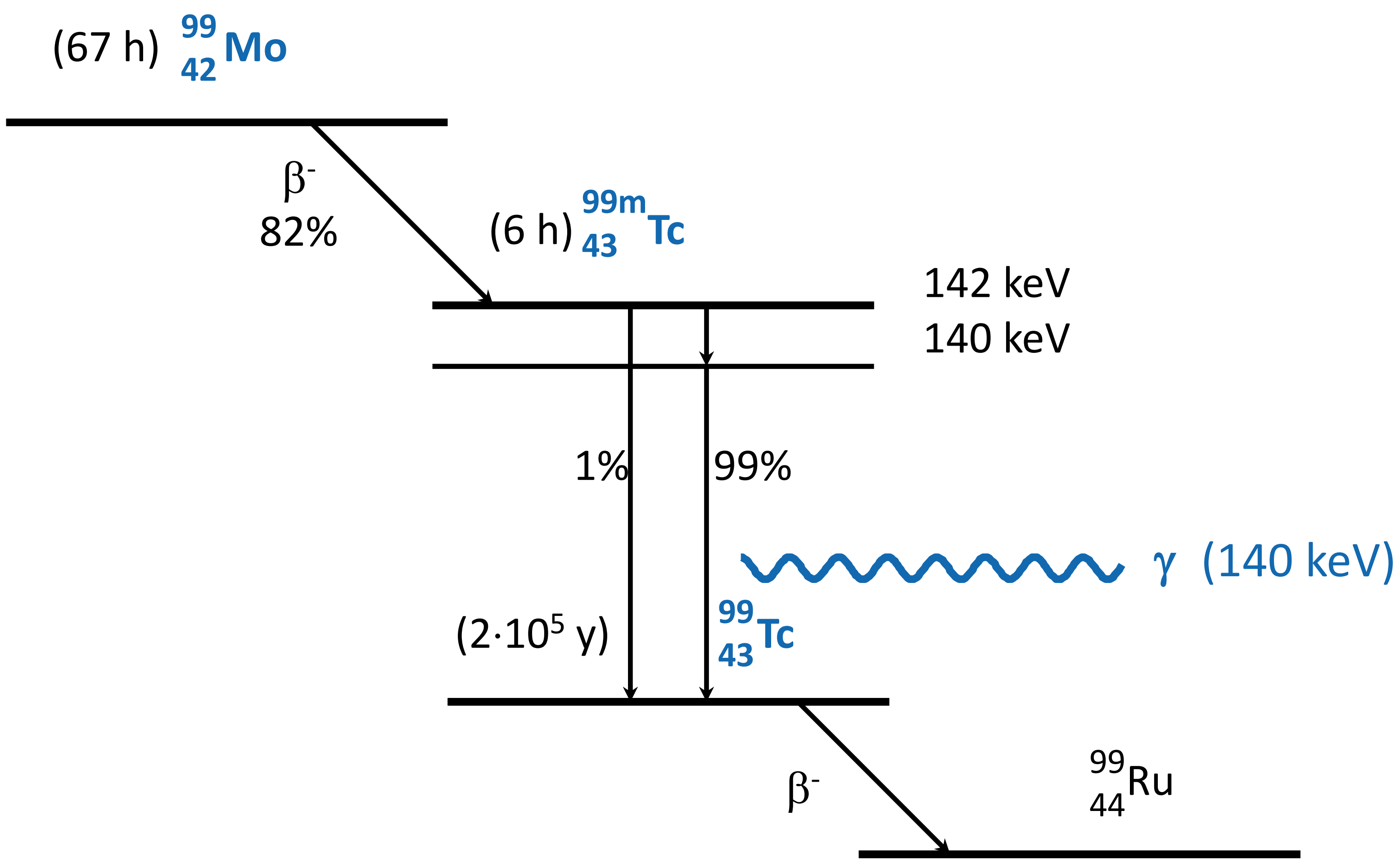
Lead screen

Generator:
Mother nuclide **(^{99}Mo)**
Immobilized on alumina
(Al_2O_3)

Collection vial for
daughter nuclide
(^{99m}Tc)

Lead screen

Technetium generator



Technetium generator

$$^{99}_{42}Mo \xrightarrow[2.90\cdot10^{-6}s^{-1}]{k_{Mo}} {}^{99m}_{43}Tc \xrightarrow[3.20\cdot10^{-5}s^{-1}]{k_{Tc}} {}^{99}_{44}Ru$$

Kinetic equations:

$$\frac{d}{dt}N_{^{99}Mo} = -k_{Mo}\cdot N_{^{99}Mo}$$

$$\frac{d}{dt}N_{^{99m}Tc} = +k_{Mo}\cdot N_{^{99}Mo} - k_{Tc}\cdot N_{^{99m}Tc}$$

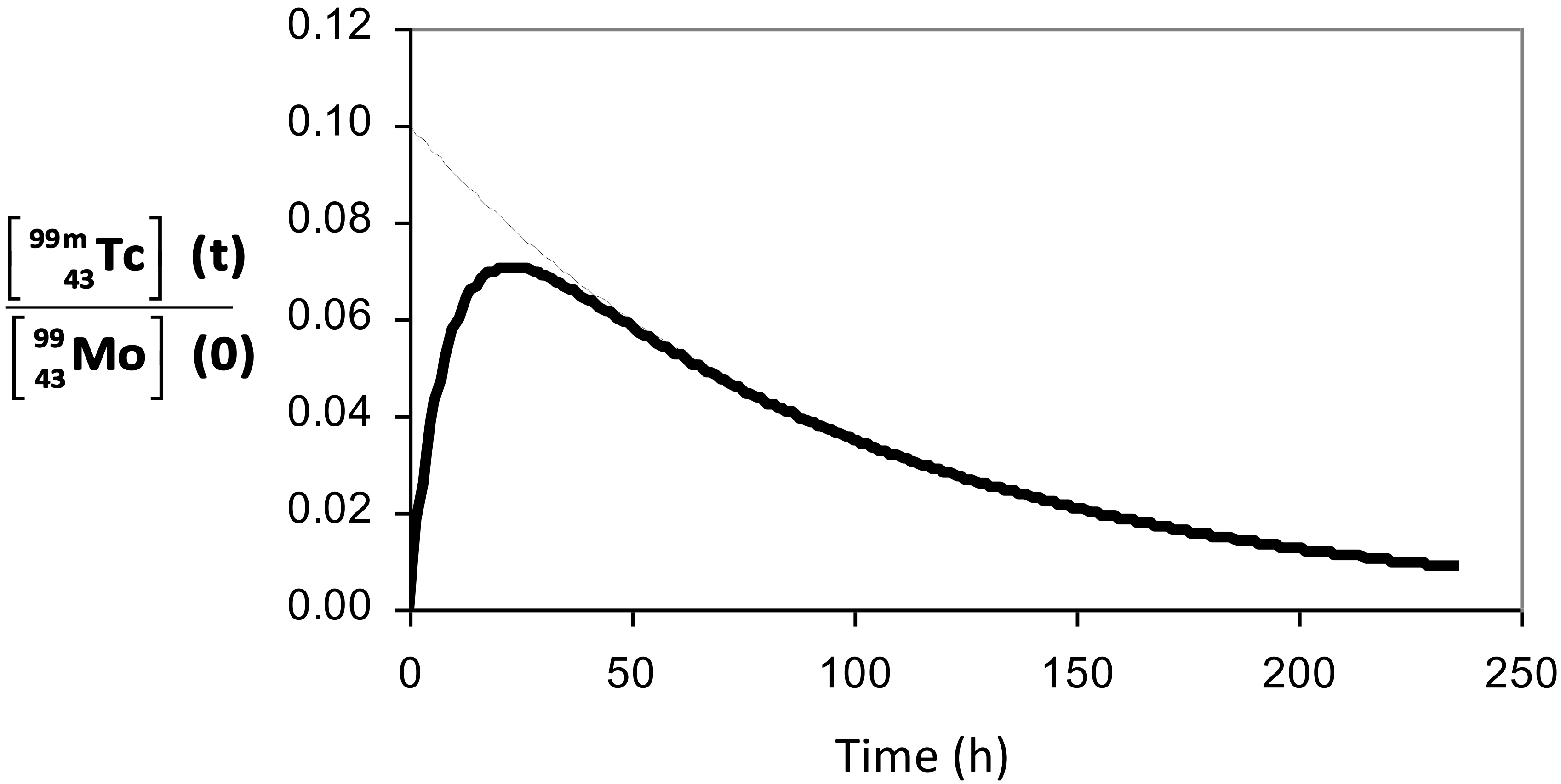
Solution:

$$N_{^{99m}Tc}(t) = N_{^{99}Mo}(0)\cdot\frac{k_{Mo}}{k_{Tc}-k_{Mo}}\cdot\{\exp(-k_{mo}\cdot t)-\exp(-k_{Tc}\cdot t)\}$$

Radioactivity of ^{99m}Tc:

$$Q_{^{99m}Tc}(t) = k_{Tc}\cdot N_{^{99m}Tc}(t) = N_{^{99}Mo}(0)\cdot\frac{k_{Mo}\cdot k_{Tc}}{k_{Tc}-k_{Mo}}\cdot\{\exp(-k_{mo}\cdot t)-\exp(-k_{Tc}\cdot t)\}$$

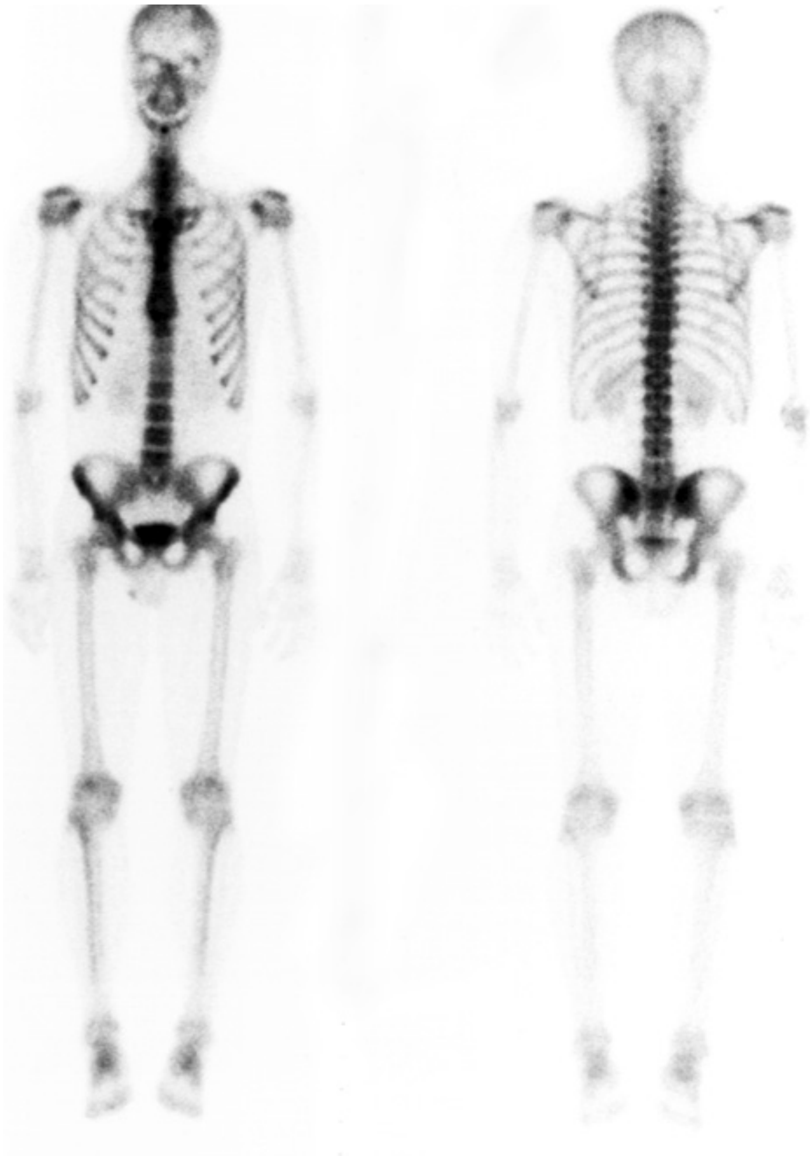
Technetium generator



Technetium tracers

Radiolabel	Ligand	Application
$^{99m}TcO_4$-Na	Sodium pertechnate	Thyroid function
^{99m}Tc-HSA	Human serum albumine	Blood pool, cardiac function
^{99m}Tc-HSA	Human serum albumine (microspheres)	Regional perfusion, vascular patency
^{99m}Tc-MIBI	2-methoxy-isobutylisonitril	Myocardial function
^{99m}Tc-HMPAO	Hexamethyl-propylenaminoxim	Cerebral perfusion
^{99m}Tc-HEDP	Hydroxyl-ethylene-diphosphonate	Bone metabolism / formation
^{99m}Tc-MDP	Methylene-diphosphonate	Bone metabolism / formation
^{99m}Tc-DTPA	Diethylene-triamine-tetraacetate	Kidney function, lung function

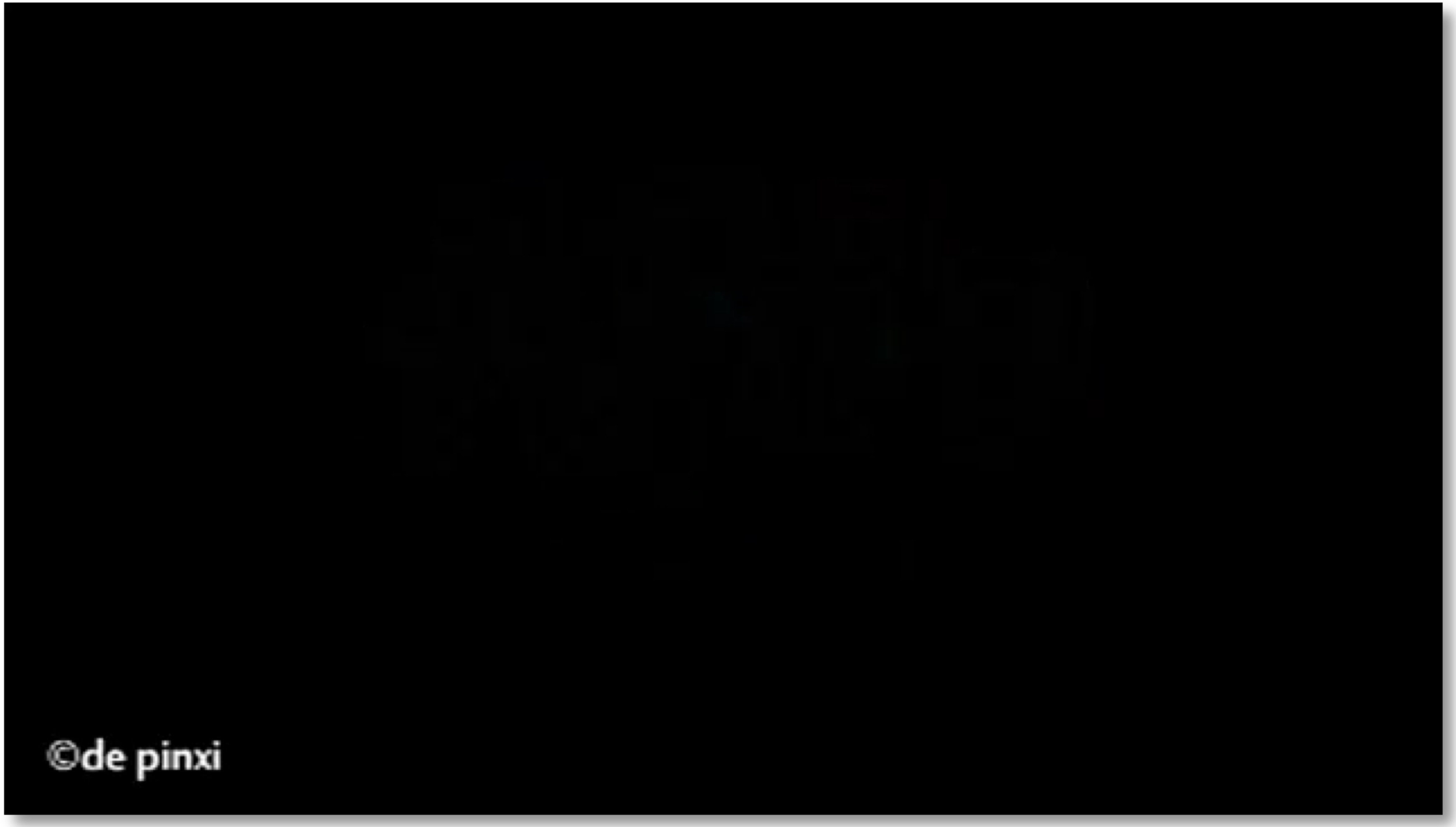
SPECT imaging of bone



PET radioisotopes

Radionuclide	Half-life	E_{max} (MeV)	e^+ decay (%)
^{11}C	20.4 min	0.96	100
^{13}N	10 min	1.20	100
^{15}O	2 min	1.73	100
^{18}F	110 min	0.63	97
^{22}Na	2.6 y	0.55	90
^{62}Cu	9.7 min	2.93	97
^{64}Cu	12.7 h	0.65	29
^{68}Ga	67.6 min	1.89	89
^{76}Br	16.2 h	Various	56
^{82}Rb	1.3 min	2.60, 3.38	96
^{124}I	4.2 d	1.53, 2.14	23

Production of ^{18}F radionuclide



https://www.youtube.com/watch?v=zD1fnNAmAPk

Properties of ^{18}F radionuclides

- Lifetime 110 min
- Lifetime reasonably long for chemical synthesis
- Lifetime long enough to allow for shipping of labeled compound
- ^{18}F PET does not require on-site cyclotron
- Studies can be repeated in relatively short time intervals

but

- Pharmacokinetics different from native, endogenous compound

PET radioisotopes

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Production of ^{11}C radionuclide

α
(2p, 2n)

^{14}N + p → [^{15}F] → ^{11}C → e^+ + ν
(7p, 7n) (8p, 7n) (6p, 5n)

<< 1s

20 min → ^{11}B
(5p, 6n)

Proton capture
Proton source: cyclotron

Metastable nucleus
($t_{1/2} << 1\,\mathrm{s}$)

Positron emitter
Stabilization by positron emission

Stable nucleus

Stabilization by emission of α-particle

Chemical synthesis

Properties of ^{11}C radionuclides

- All organic compounds contain C and can be labeled in principle
- Pharmacokinetic properties identical to that of ‚cold' parent compound
- Studies of drug biodistribution / PK
- Receptor affinity identical to that of parent compound

but

- Short half life (20 min)
- Chemical synthesis difficult due to time constraints

Quantitative PET Analysis

Quantitative PET – definitions

Injected dose per gram of tissue:

$$\boxed{\%ID / g = \frac{c_t \cdot v_t}{D_{inj}} \cdot \frac{1}{m_t} \cdot 100\%}$$

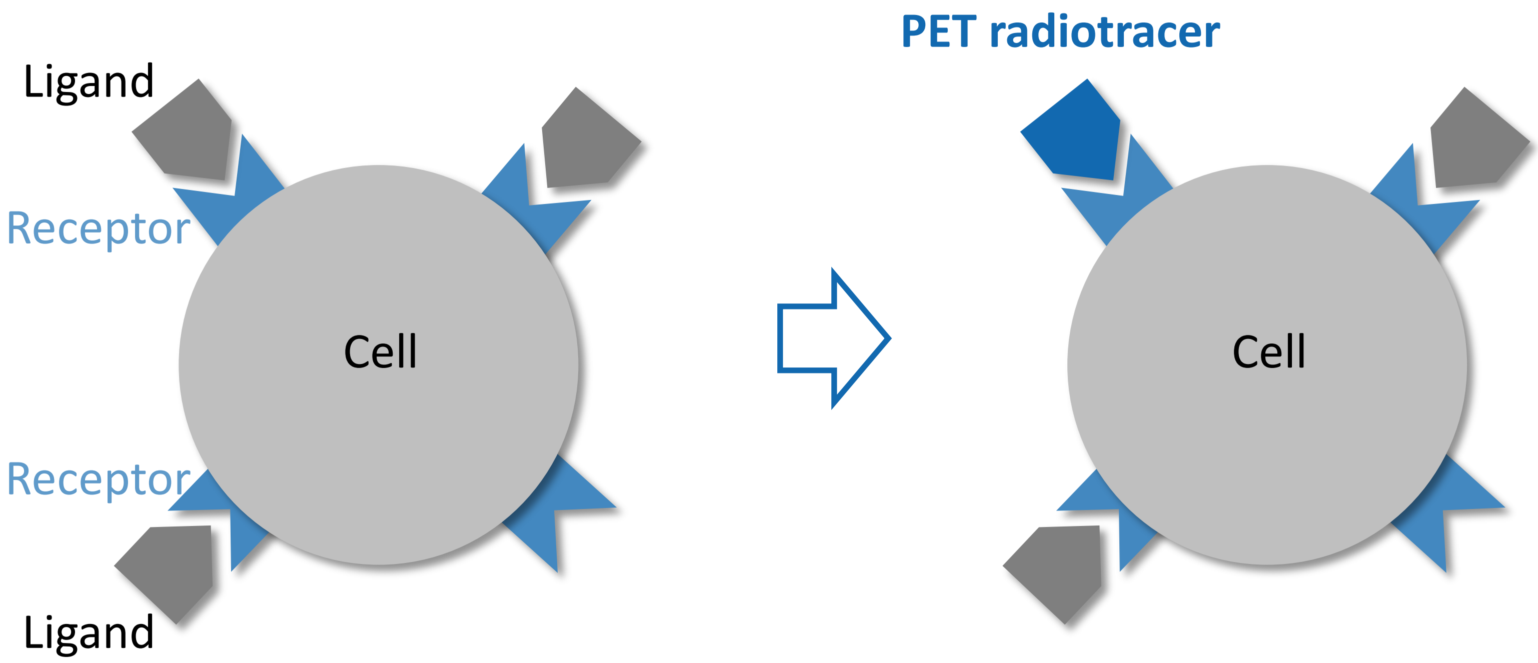
c_t tissue concentration
v_t volume of tissue ROI
m_t mass of tissue ROI
D_{inj} injected dose

Standardized Uptake Value (SUV):

$$\boxed{SUV = [\%ID / g] \cdot M / 100 = \frac{c_t \cdot v_t}{D_{inj}} \cdot \frac{1}{m_t} \cdot M}$$

M : Body mass

Quantitative PET – receptor binding



Quantitative PET – receptor binding

Receptor Binding: $L + R \leftrightarrow RL$ (*L:* Ligand, *R:* Receptor)

Equilibrium constant: $K_d = \frac{k_{off}}{k_{on}} = \frac{[L]\cdot[R]}{[RL]}$ $\quad k_{off}\cdot[RL] = k_{on}\cdot[R]\cdot[L]$

(principle of microreversibility)

Mass conservation for receptor: $[R_T] = [R] + [RL]$

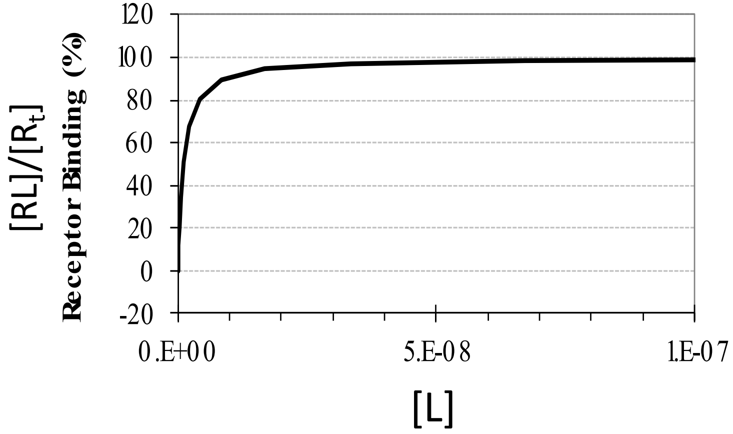
yields $K_d = \frac{[L]}{[RL]}\cdot([R_T]-[RL])$

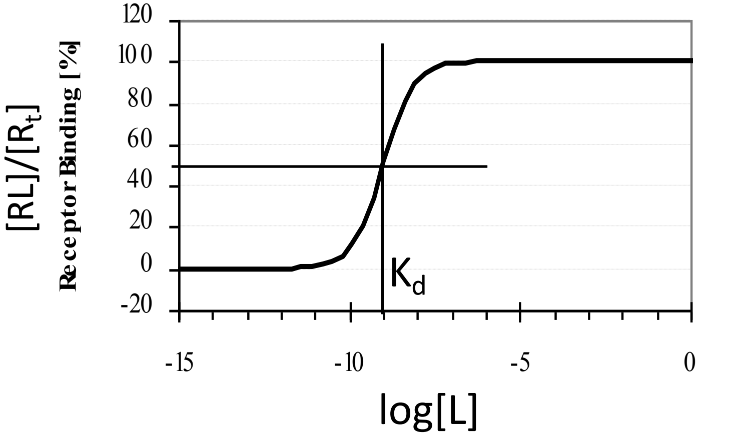
or the receptor binding $\frac{[RL]}{[R_t]} = \frac{[L]}{K_d + [L]}$

and the Scatchard equation $$\boxed{\frac{[RL]}{[L]} = -\frac{1}{K_d}\cdot[RL] + \frac{[R_T]}{K_d}}$$

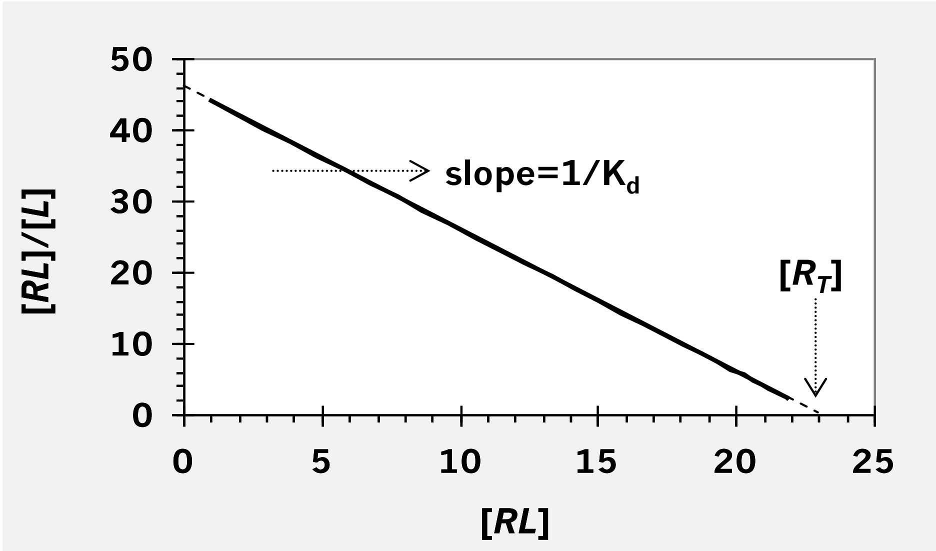
Quantitative PET – receptor binding

Binding plot





Scatchard plot



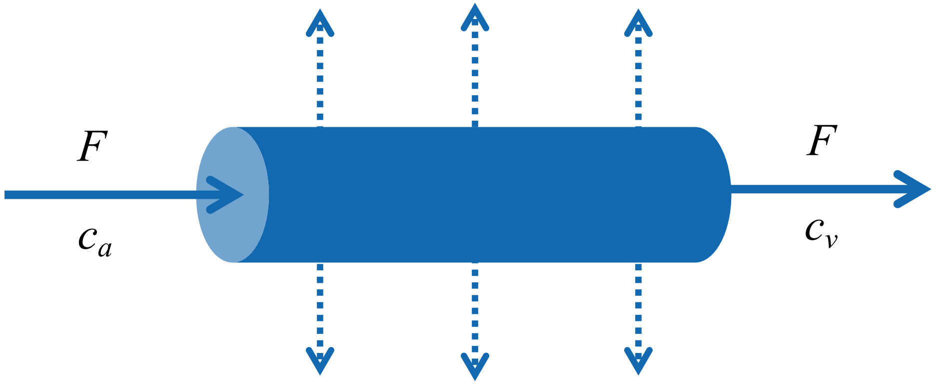
$$\boxed{\frac{[RL]}{[L]} = -\frac{1}{K_d}\cdot[RL] + \frac{[R_T]}{K_d}}$$

for $[RL] \ll [R_T]$ $$\frac{[RL]}{[L]} = \frac{[R_T]}{K_d} = \frac{B_{max}}{K_d}$$

B_{max}: maximum binding capacity

Quantitative PET – tracer extraction

Tracer extraction from capillaries

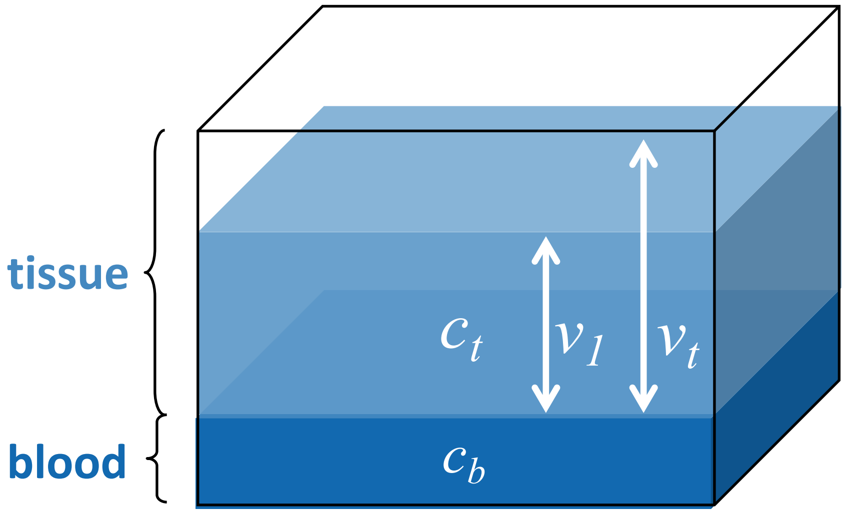


The amount of tracer extracted from capillaries depends on capillary surface S, the vascular permeability P and the blood flow F:

$$\boxed{E = 1 - \exp(-P \cdot S / F)}$$

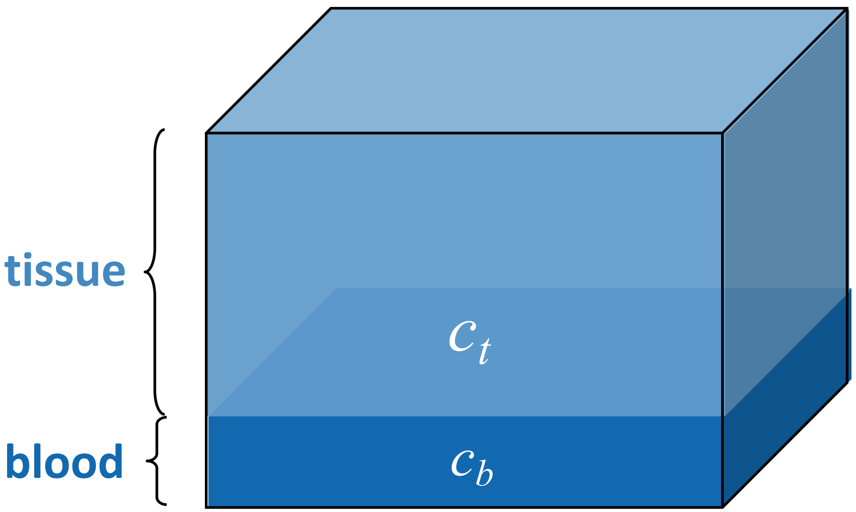
Renkin-Crone equation

Quantitative PET – volume distribution



Distribution volume

$$V_d = V_1 + V_b = V_t \cdot \frac{c_t}{c_b} + V_b$$



Tracer experiment

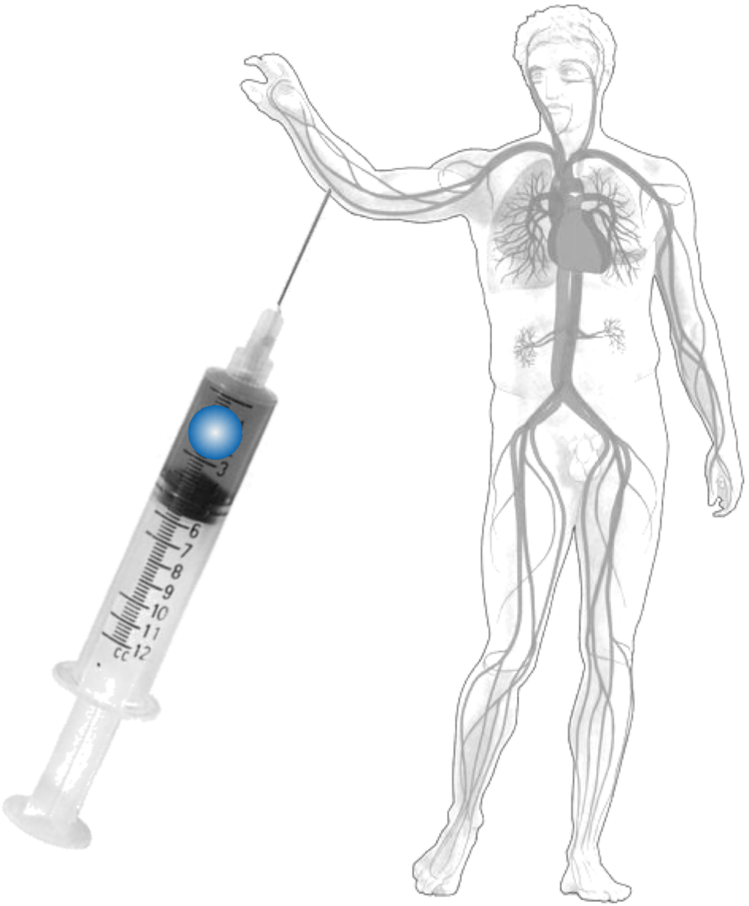
$$V_d = \frac{M}{c_b}$$

M: total amount of tracer

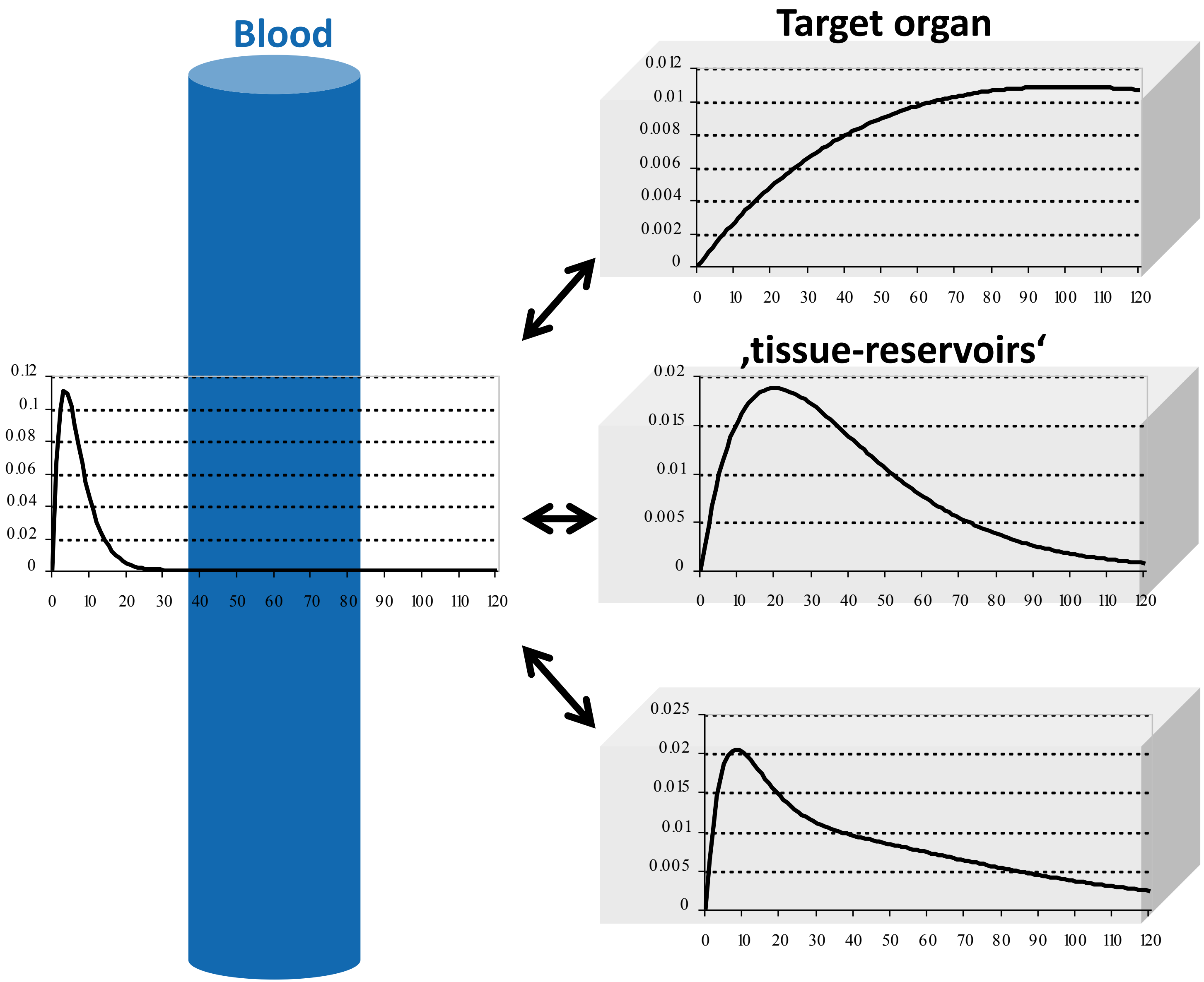
Clicker Activity (5 min)

After administration of 1 µg/kg of a tracer into a patient of 70 kg body mass, an average blood concentration of 1.4 µg/l is measured. What is the distribution volume?

- 5 l
- 500 ml
- 50 l
- 10 l



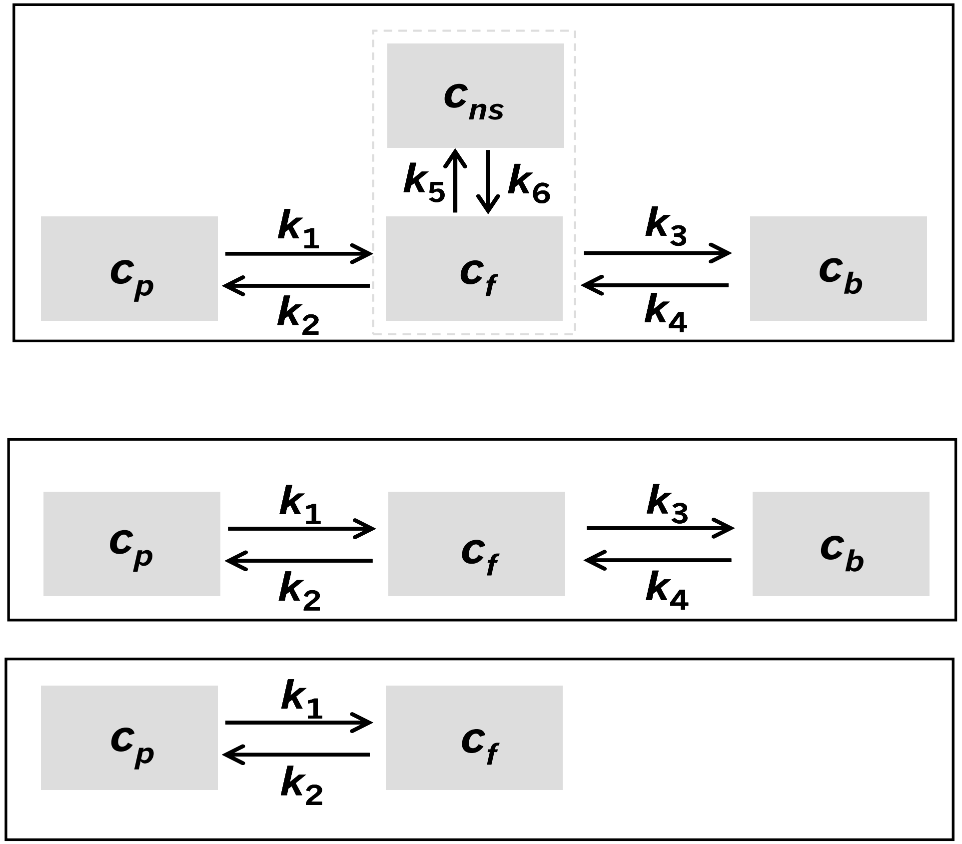
Quantitative PET – compartment modeling



Quantitative PET – modeling of receptor binding

Tracer fraction in tissue compartments

p: plasma
f: free (in tissue)
ns: non-specific bound
b: bound

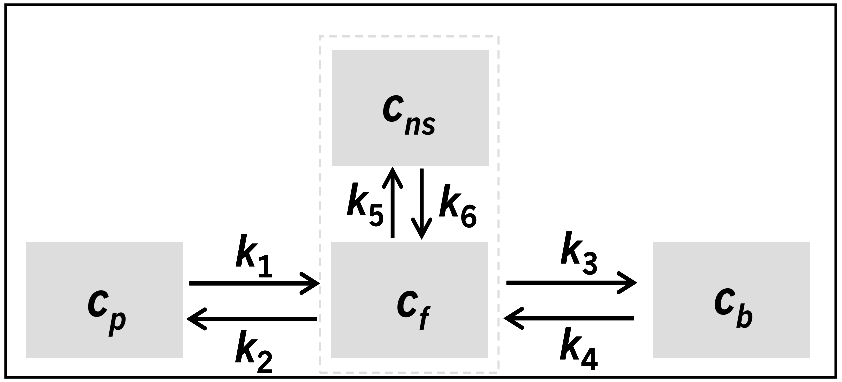


PET activity at time *t*:

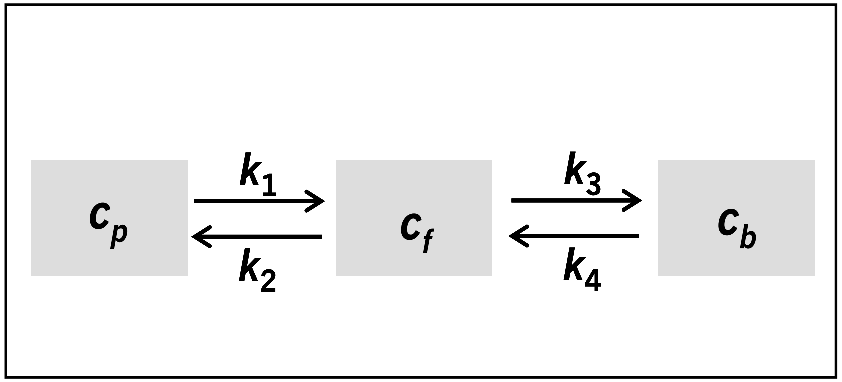
$$c_t^*(t) = \sum_i v_i \cdot c_i^*(t)$$

i = *p, f, ns, b*
v_i fractional volume of compartment

Quantitative PET – modeling of receptor binding



$\approx$



Equilibrium free / non-specifically bound tracer instantaneous: $c_f = f_2 \cdot (c_f + c_{ns})$

Kinetic equations:

$$\frac{dc_f}{dt} = k_1 \cdot c_p - (k_2 + k_3) \cdot c_f + k_4 \cdot c_b$$

$$\frac{dc_b}{dt} = k_3 \cdot c_f - k_4 \cdot c_b$$

with rate constants:

$$k_3 = k_{on} \cdot [R] \qquad k_1 = F \cdot (1 - \exp(-P \cdot S / F))$$

$$k_4 = k_{off} \qquad k_2 = k_1 \cdot c_p / c_f$$

Renkin-Crone: $\boxed{E = 1 - \exp(-P \cdot S / F)}$

Quantitative PET – tracer kinetics for receptor binding

Solution for compartment expressing receptor:

$$\boxed{c_t(t) = c_f(t) + c_b(t) = k_1 \cdot \sum_{i=1}^{2} a_i \cdot \exp(-\alpha_i \cdot t) \otimes c_p(t)}$$

with coefficients

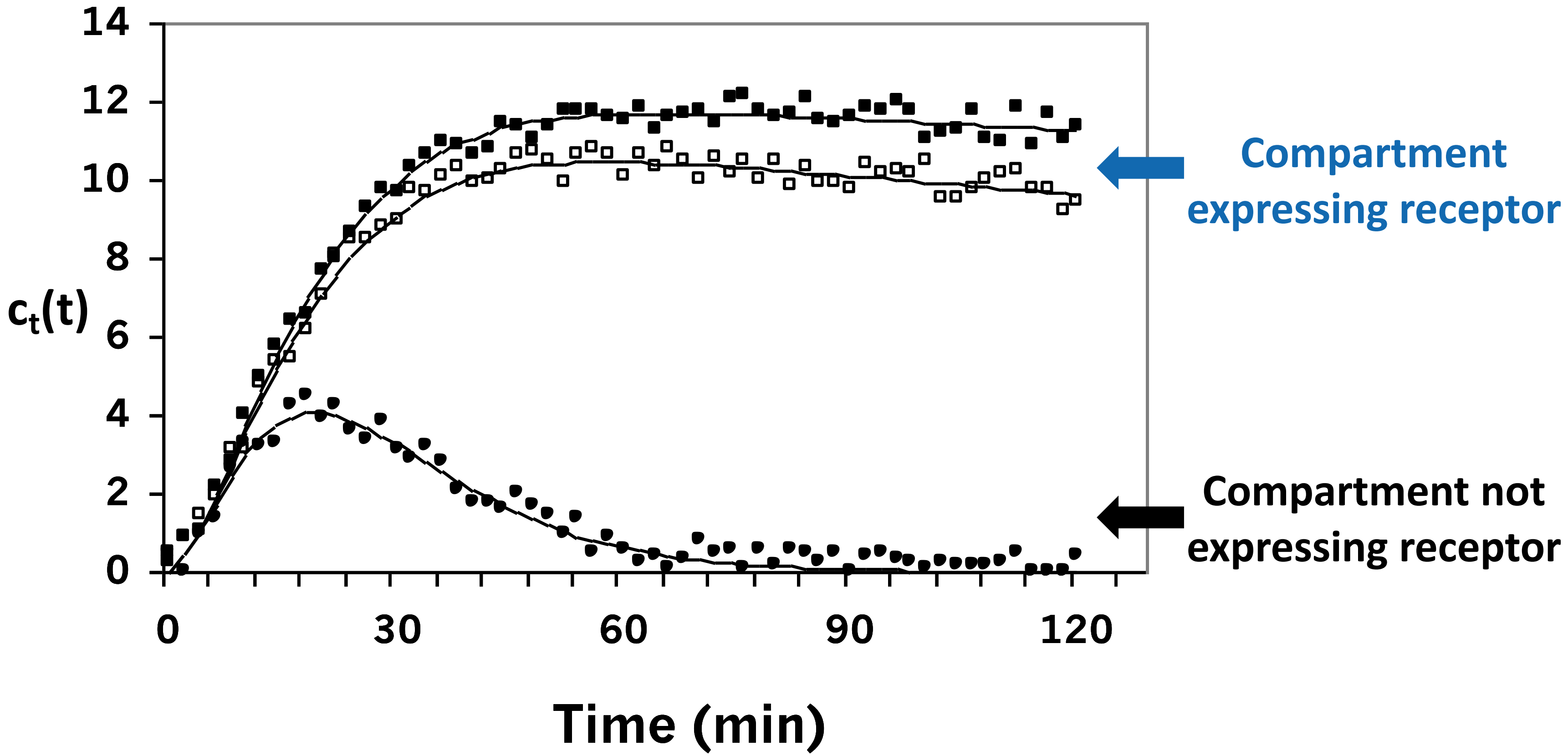
$$a_1 = \frac{k_3 + k_4 - \alpha_2}{\alpha_2 - \alpha_1}$$

$$a_2 = -\frac{k_3 + k_4 - \alpha_1}{\alpha_2 - \alpha_1}$$

Solution for compartment not expressing receptor:

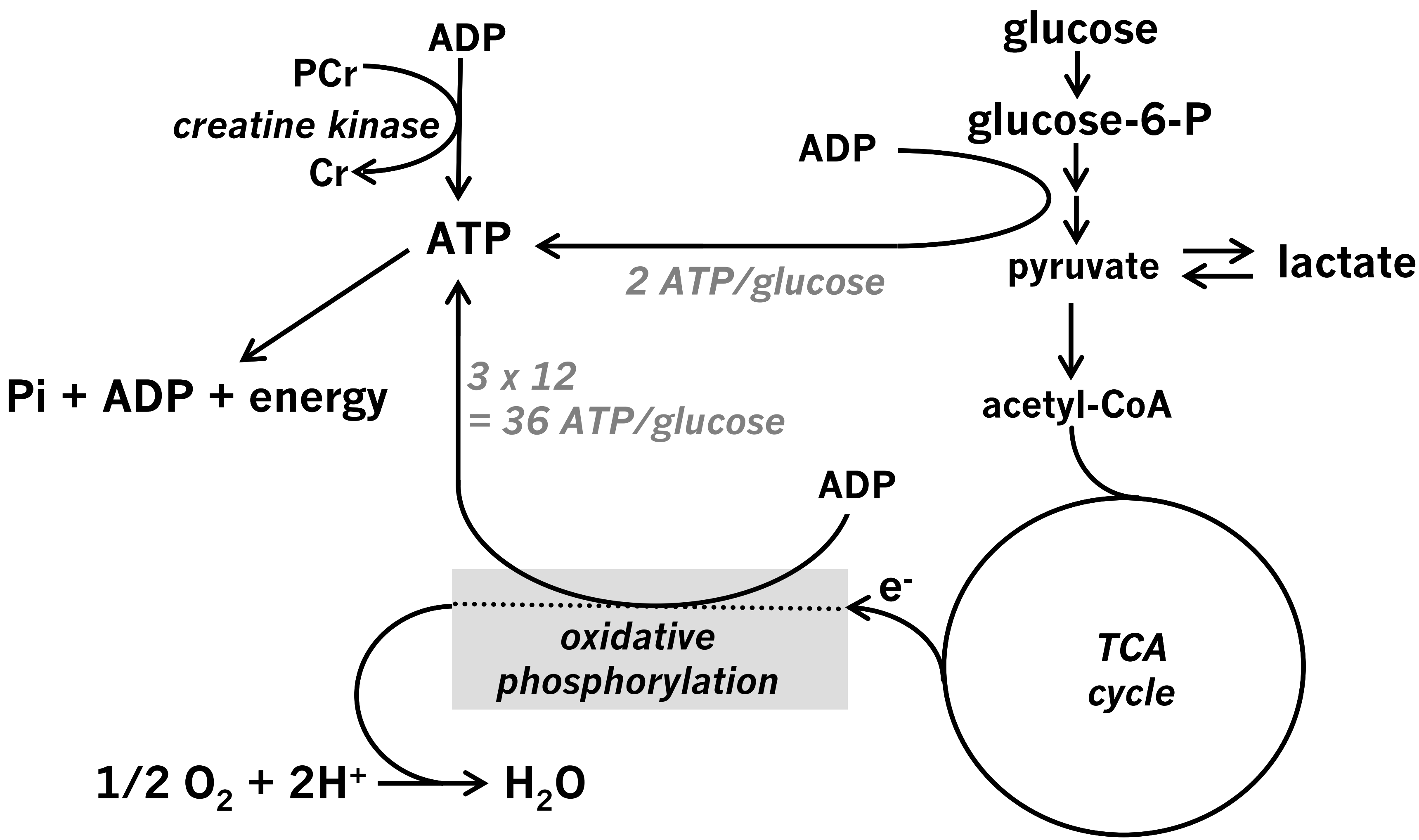
$$\boxed{c_t(t) = c_f(t) = k_1 \cdot \exp(-k_2 \cdot t) \otimes c_p(t)}$$

Quantitative PET – tracer binding example



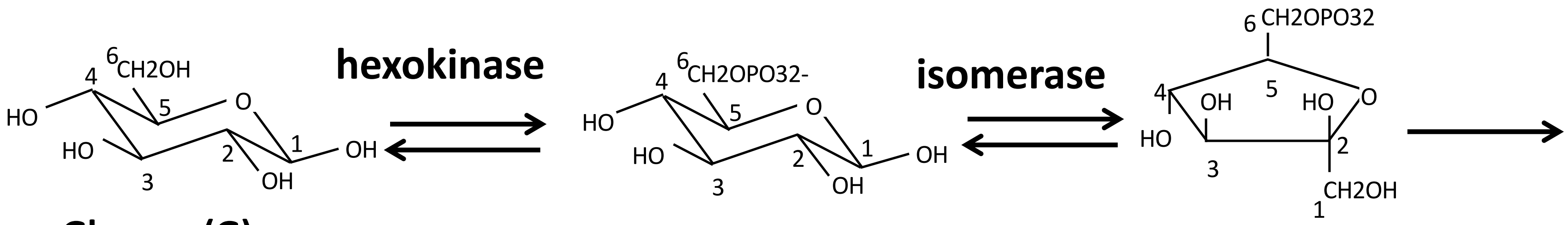
k_1=1min^{-1}, k_2=0.1min^{-1}, k_3=1min^{-1} and 0.5min^{-1}, k_4=0.01min^{-1}

Quantitative PET – cell energy metabolism



Quantitative PET – cell energy metabolism

Native glucose utilization

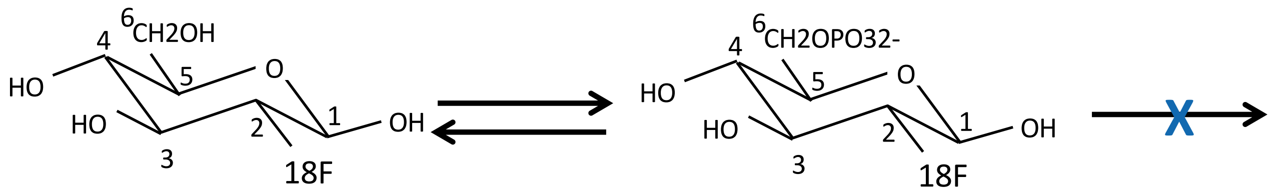


Glucose (G)

Glucose -6-phosphate(G6P)

Fructose-6-phosphate(G6P)

FDG PET deoxyglucose utilization

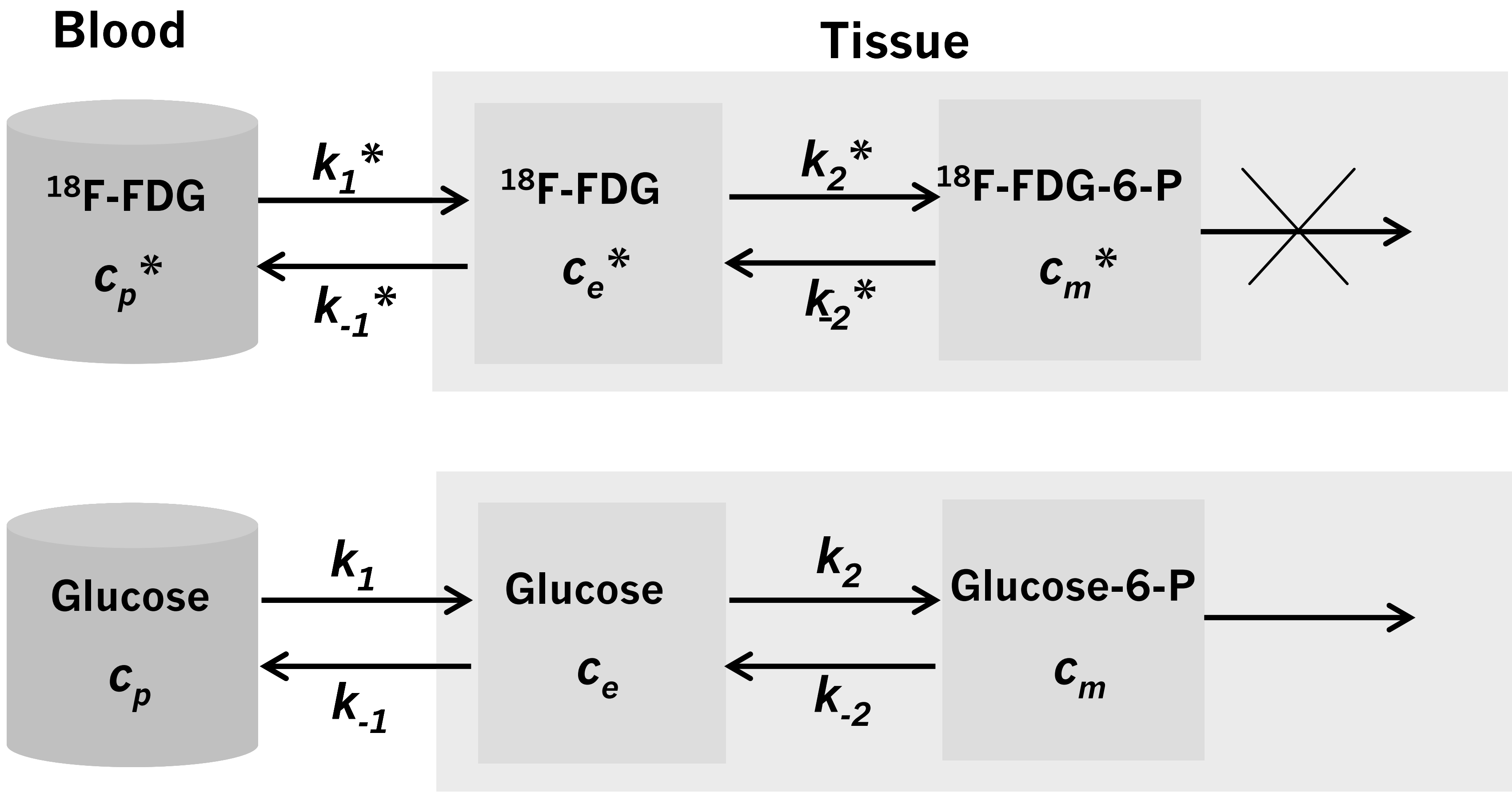


[18F]-2-fluoro-2-deoxyglucose (FDG)

FDG6P

Ligand trapped in cells as FDG6P

Quantitative PET – FDG compartment models



Quantitative PET – FDG compartment models

Total tracer concentration in tissue

$$c_t^* = \frac{1}{V}(v_p \cdot c_p^* + v_t \cdot (c_e^* + c_m^*)) \approx \frac{1}{V}(V \cdot c_e^* + V \cdot c_m^*) = c_e^* + c_m^*$$

(assume $v_p \ll v_t \approx V$)

Kinetic equations for tracer:

$$\frac{dc_e^*}{dt} = k_1^* \cdot c_p^* - (k_{-1}^* + k_2^*) \cdot c_e^* + k_{-2}^* \cdot c_m^*$$

$$\frac{dc_m^*}{dt} = k_2^* \cdot c_e^* - k_{-2}^* \cdot c_m^*$$

Solution:

$$\boxed{c_e^*(t) = k_1^* \cdot \int_0^t c_p^*(t') \cdot \exp\{-(k_{-1}^* + k_2^*) \cdot (t - t')\} \cdot dt' = k_1^* \cdot \exp\{-(k_{-1}^* + k_2^*) \cdot t\} \otimes c_p^*(t)}$$

Quantitative PET – FDG compartment models

Metabolic rate of FDG:

$$\boxed{v_{FDGMR} = k^{*}{}_{2} \cdot c_e^{*}(t) \approx \frac{k_1^{*} \cdot k_2^{*}}{k_{-1}^{*} + k_2^{*}} \cdot c_p^{*}(t)}$$

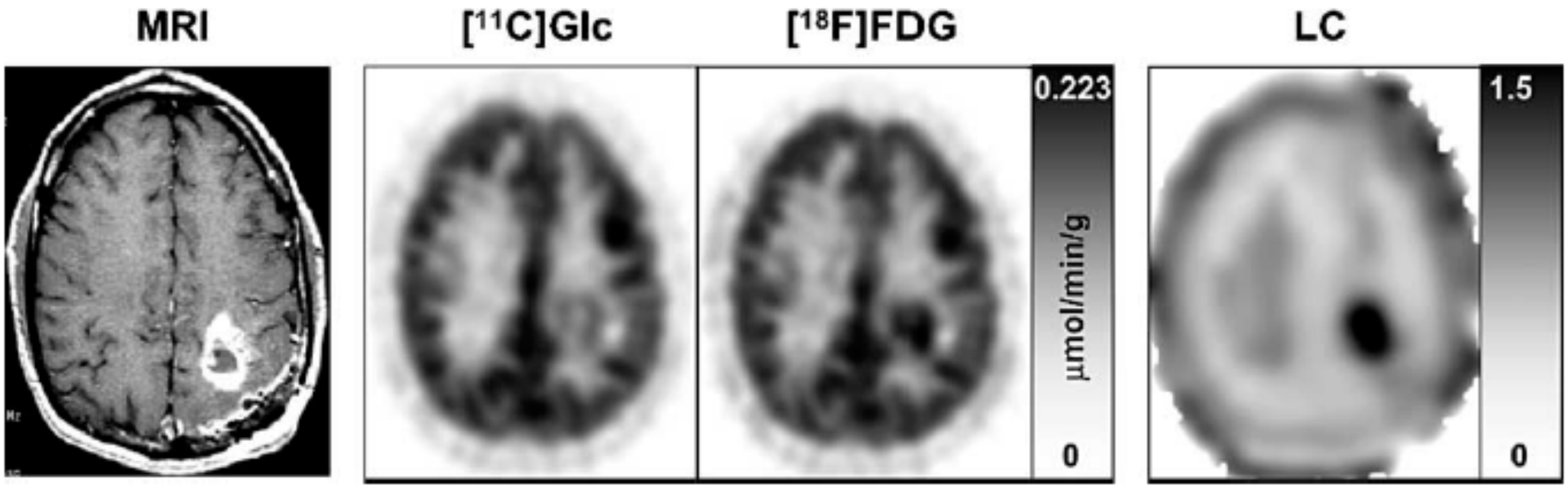
Metabolic rate of glucose (glucose utilization):

$$\boxed{v_{GluMR} \approx \frac{k_1 \cdot k_2}{k_{-1} + k_2} \cdot c_p(t) \approx \frac{1}{LC} \cdot \frac{k_1^{*} \cdot k_2^{*}}{k_{-1}^{*} + k_2^{*}} \cdot c_p(t)}$$

Lumped constant (ca. 0.6 in humans)

Correction factor to translate measured reaction rate for FDG to that for glucose

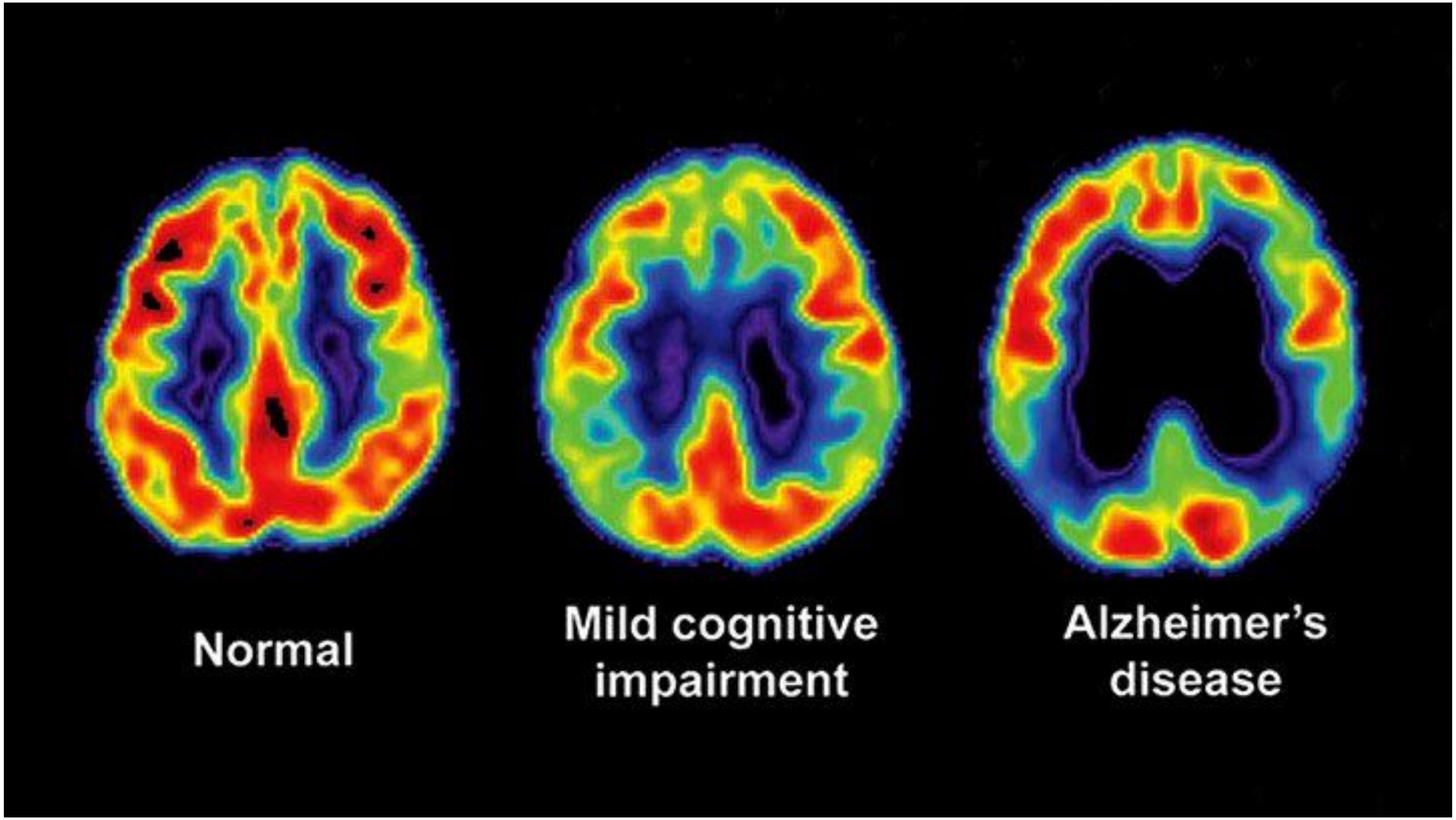
Quantitative PET – FDG lumped constant



Patient with brain glioma. The panels include calculated metabolic rate for the true tracer [1-^{11}C]glucose and the analog FDG. The two PET images were divided (PET_{FDG}/PET_{glc}) on a pixel-by-pixel basis to provide an image of regional variation of the lumped constant LC.

Krohn et al (2005) Nucl Med Biol. 32:663

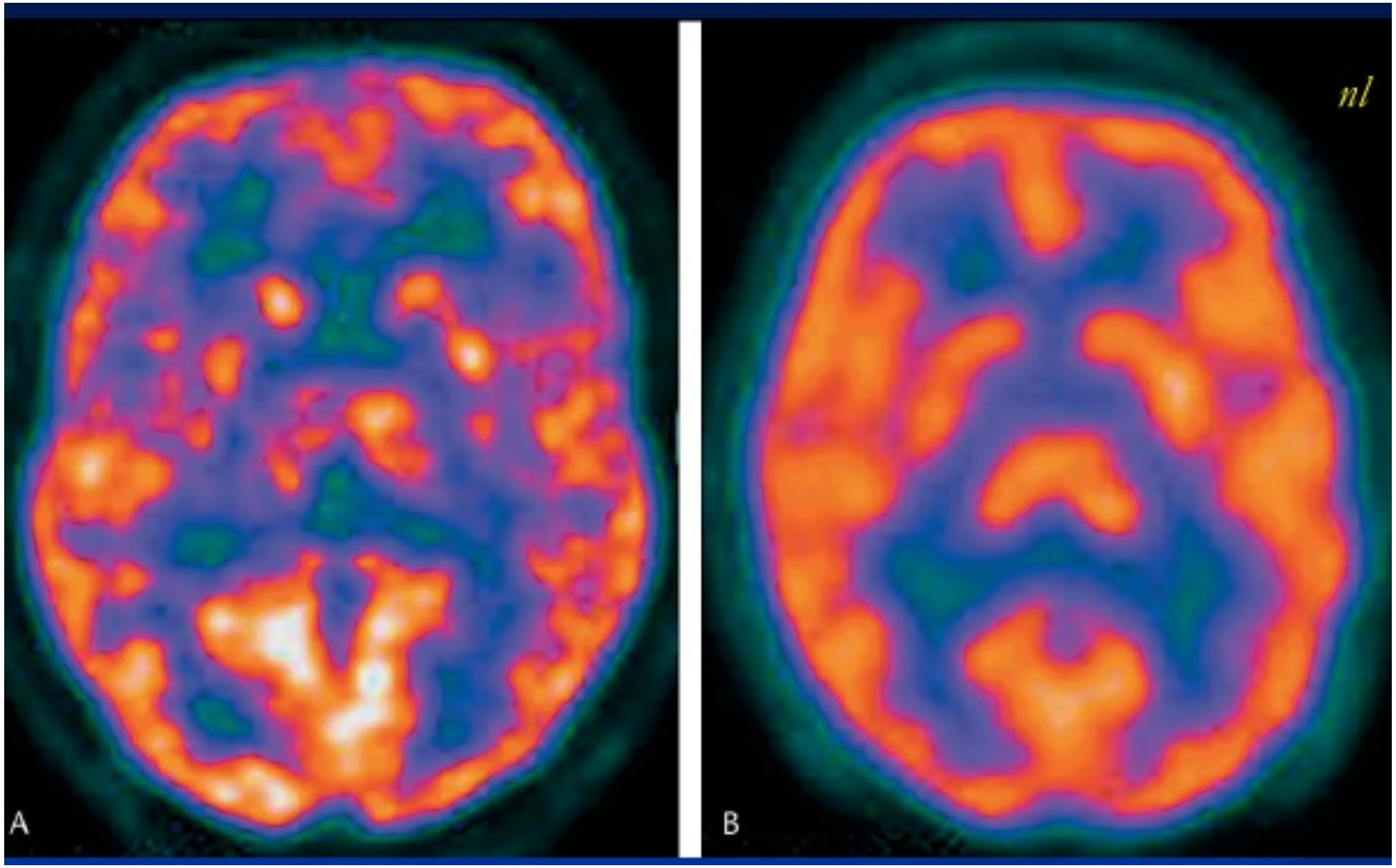
Application – FDG PET of Alzheimer disease



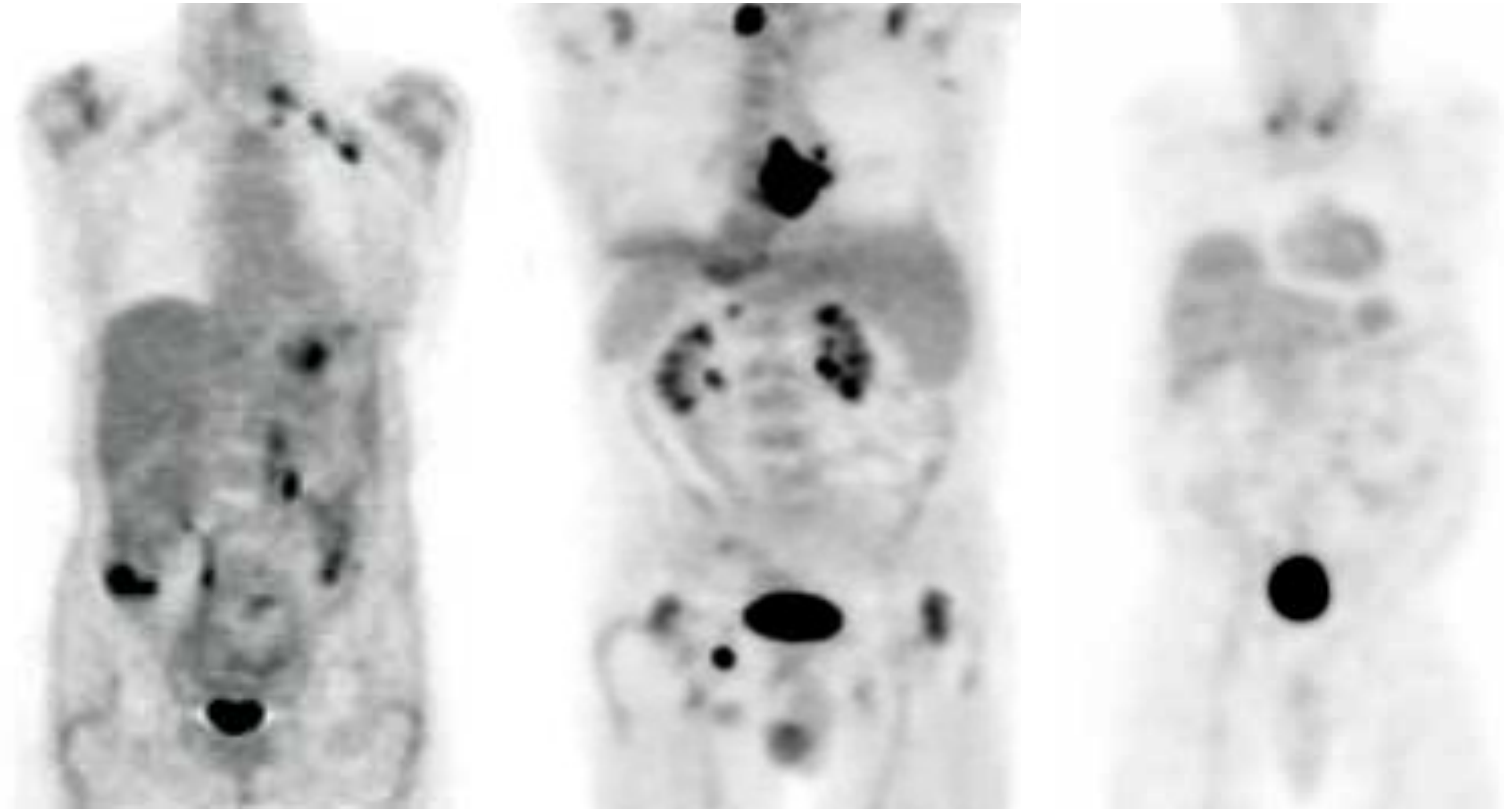
Reduced FDG PET activity in Alzheimer patient compared to age-matched control

Application – FDG PET of cocaine abuse

Cocaine abuse **Normal**



Application – FDG PET of cancer metastases



“The most important slides”