Receptor kinetics

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Copenhagen University Hospital

Overview

- What goes on in the blood?
- What goes on in the brain?
  - Some useful concepts from biochemistry
- Kinetic modeling of PET / SPECT data
- Compare outputs from our kinetic models to in vitro analyses
- Emphasize on some assumptions – please don't violate.

Established nomenclature for PET / SPECT

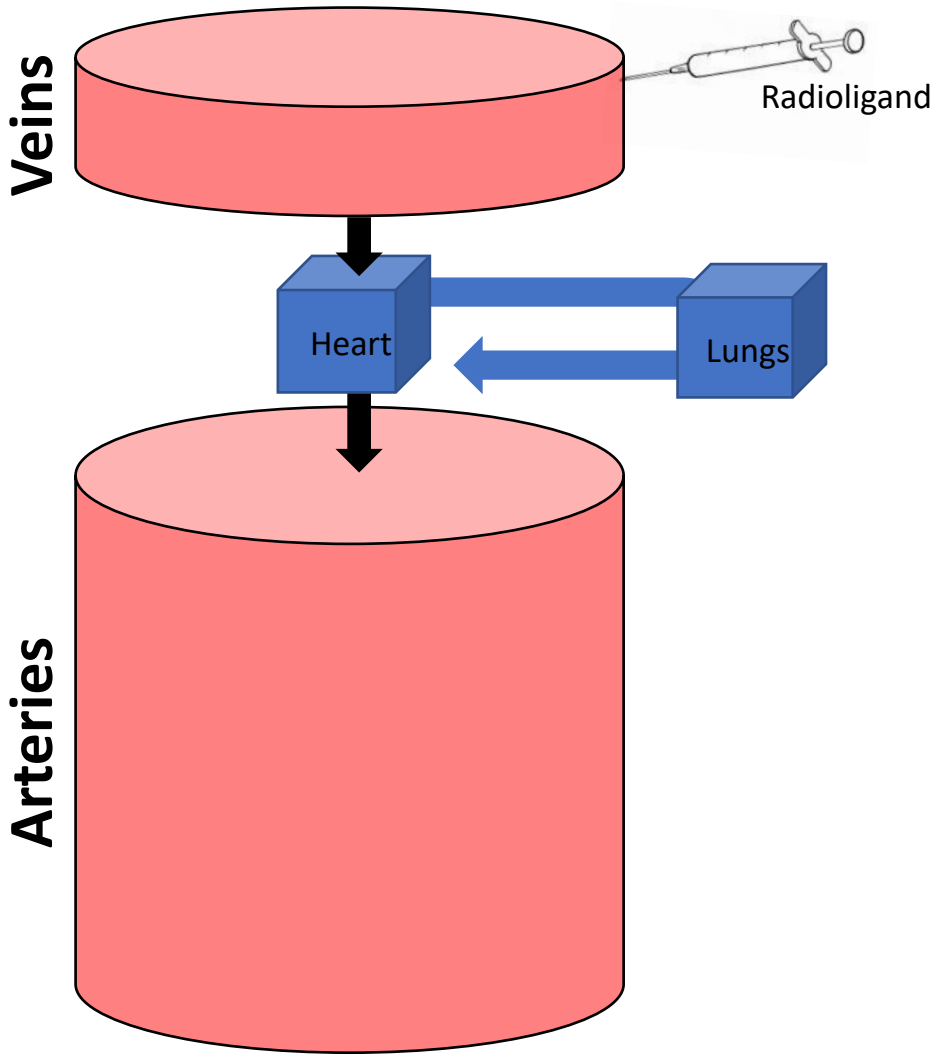
Journal of Cerebral Blood Flow & Metabolism (2007) 27, 1533–1539

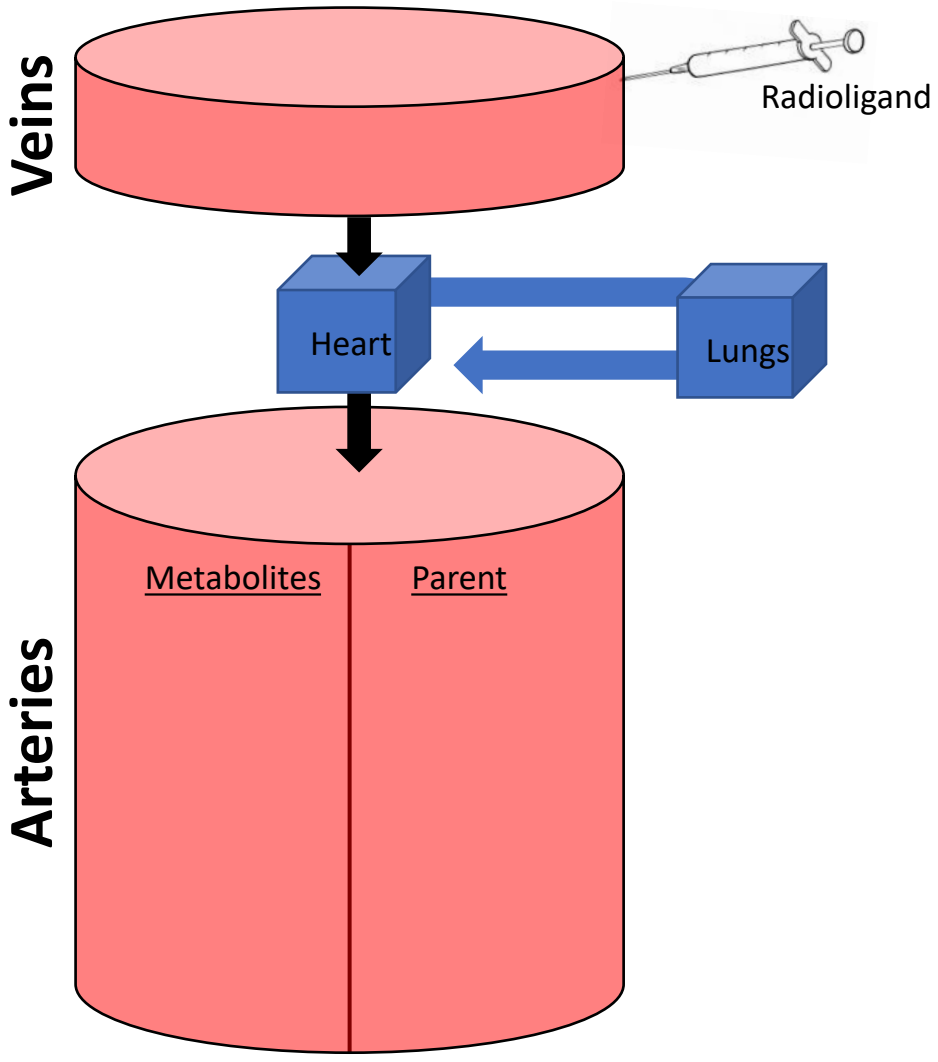
www.jcbfm.com

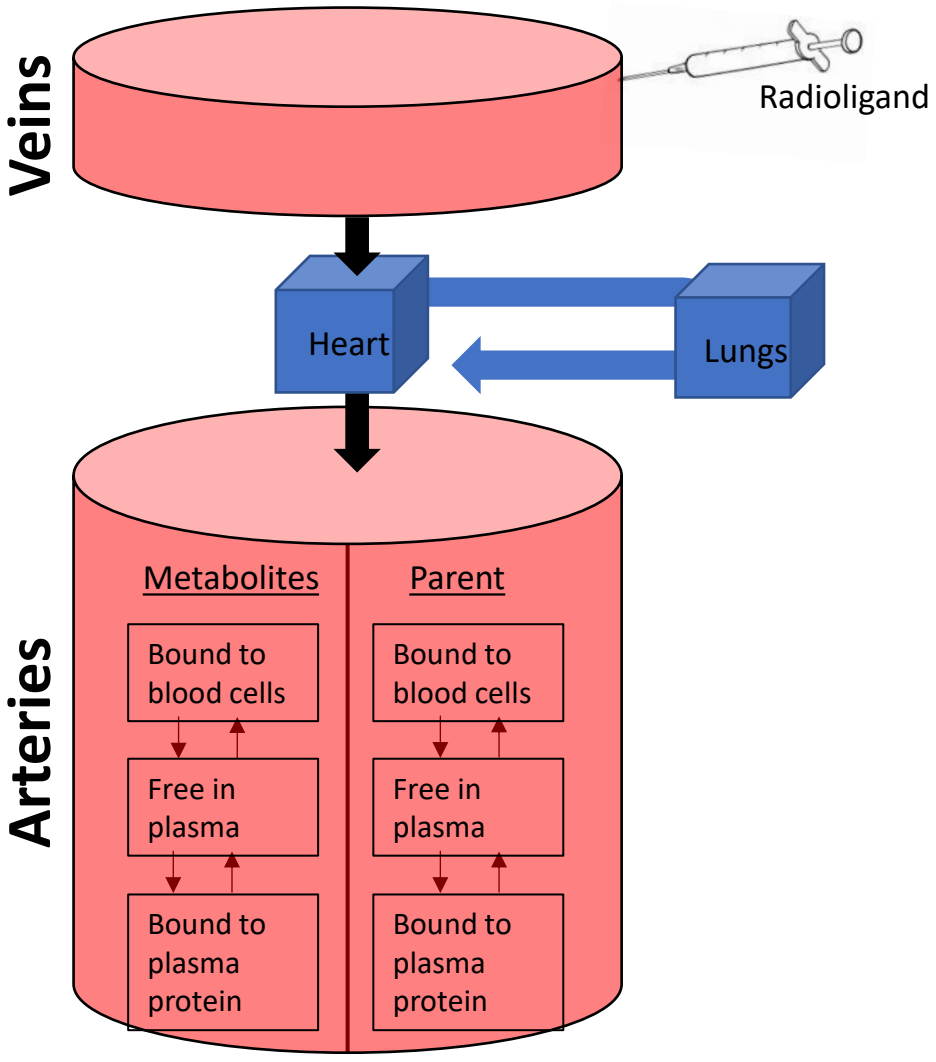
Review Article

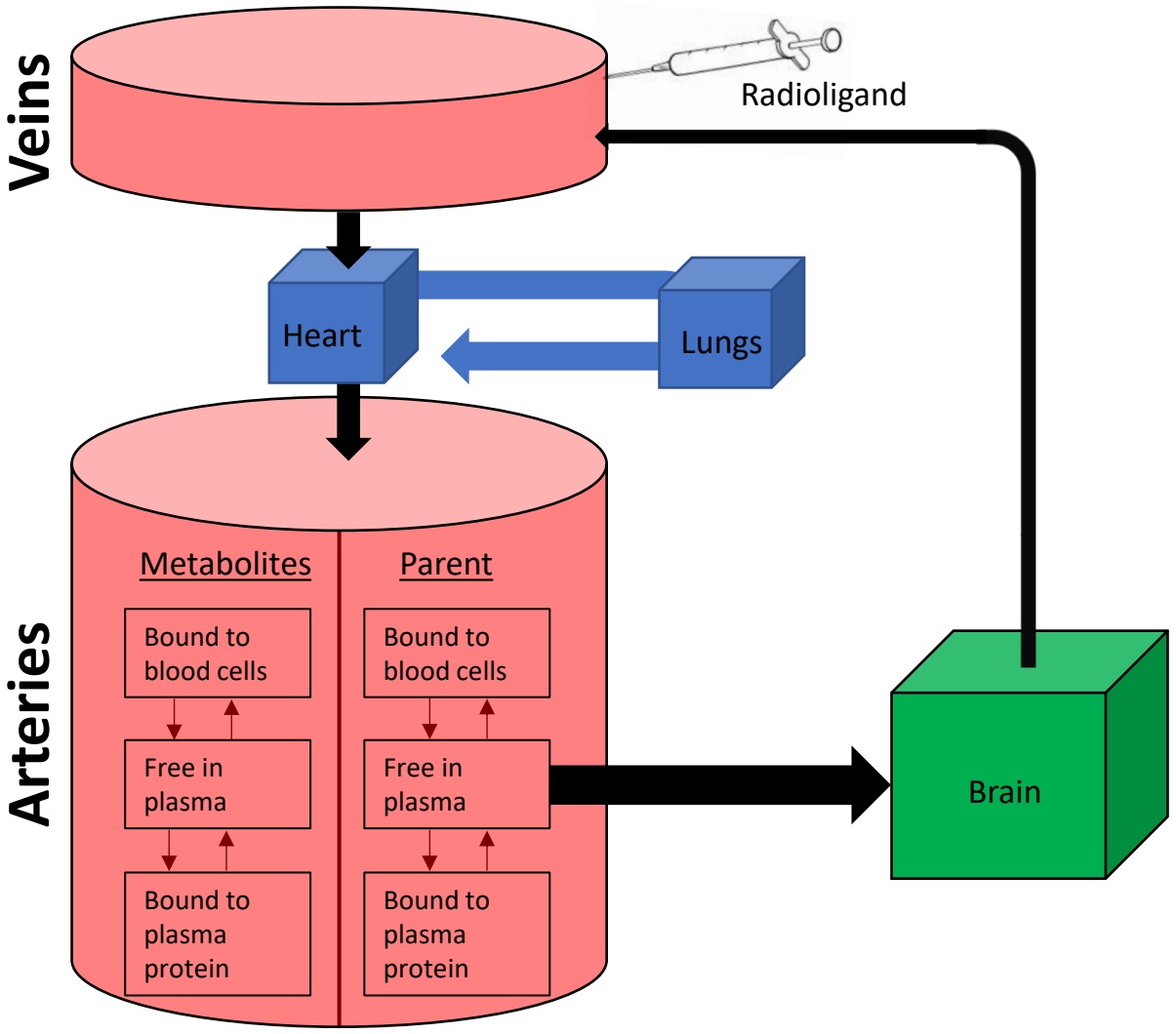
Consensus nomenclature for *in vivo* imaging of reversibly binding radioligands

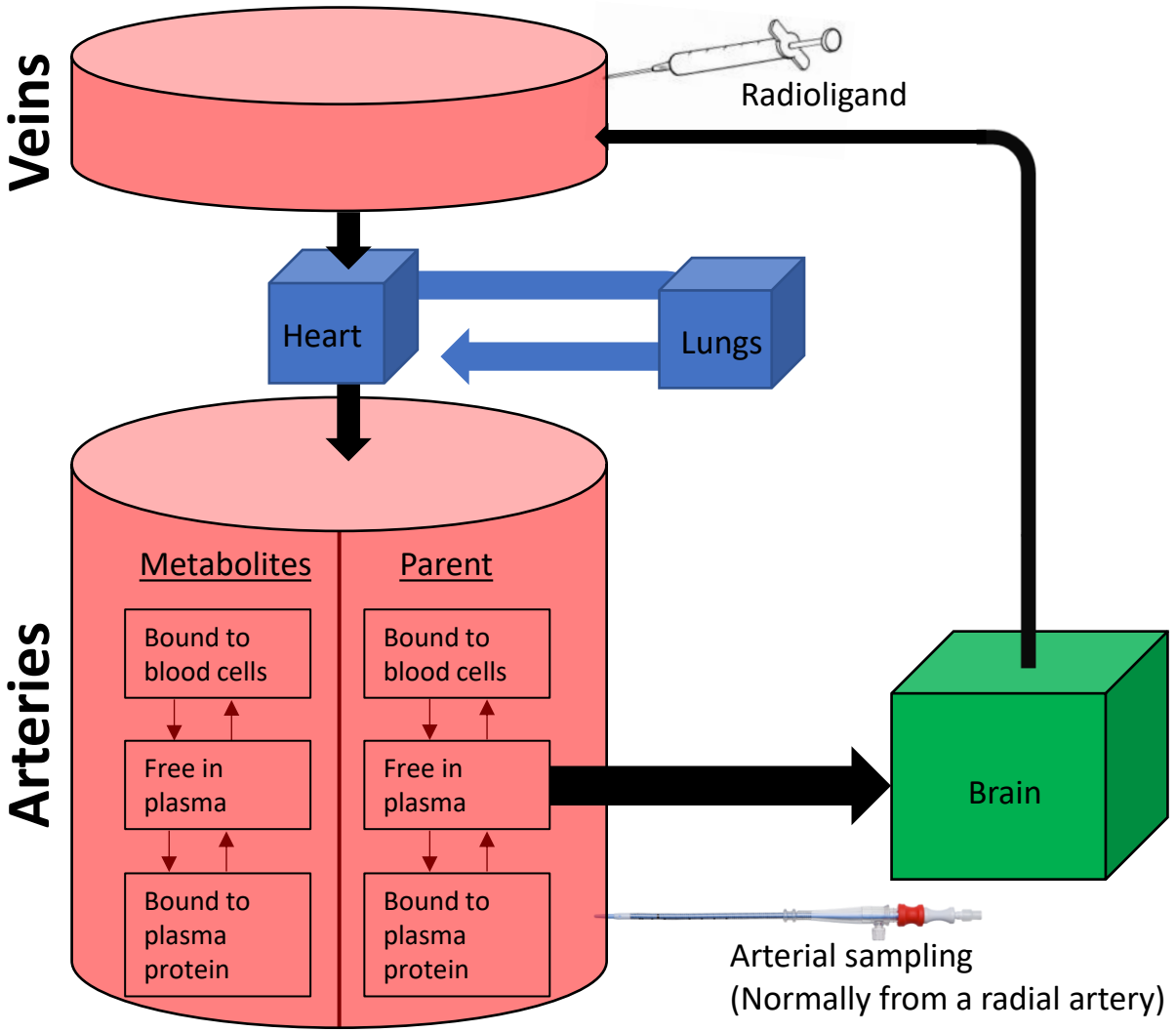
Robert B Innis[1], Vincent J Cunningham[2], Jacques Delforge[3], Masahiro Fujita[1], Albert Gjedde[4], Roger N Gunn[5], James Holden[6], Sylvain Houle[7], Sung-Cheng Huang[8], Masanori Ichise[9], Hidehiro Iida[10], Hiroshi Ito[11], Yuichi Kimura[12], Robert A Koeppe[13], Gitte M Knudsen[14], Juhani Knuuti[15], Adriaan A Lammertsma[16], Marc Laruelle[2], Jean Logan[17], Ralph Paul Maguire[18], Mark A Mintun[19], Evan D Morris[20], Ramin Parsey[9], Julie C Price[21], Mark Slifstein[9], Vesna Sossi[22], Tetsuya Suhara[11], John R Votaw[23], Dean F Wong[24] and Richard E Carson[25]


Veins
Radioligand
Heart
Lungs
Arteries


Veins
Radioligand
Heart
Lungs
Arteries
Metabolites
Parent


Veins
Radioligand
Heart
Lungs
Arteries
Metabolites
Parent
Bound to blood cells
Free in plasma
Bound to plasma protein
Bound to blood cells
Free in plasma
Bound to plasma protein


Veins
Radioligand
Heart
Lungs
Arteries
Metabolites
Parent
Bound to blood cells
Free in plasma
Bound to plasma protein
Bound to blood cells
Free in plasma
Bound to plasma protein
Brain


Veins
Radioligand
Heart
Lungs
Arteries
Metabolites
Parent
Bound to blood cells
Free in plasma
Bound to plasma protein
Bound to blood cells
Free in plasma
Bound to plasma protein
Brain
Arterial sampling
(Normally from a radial artery)

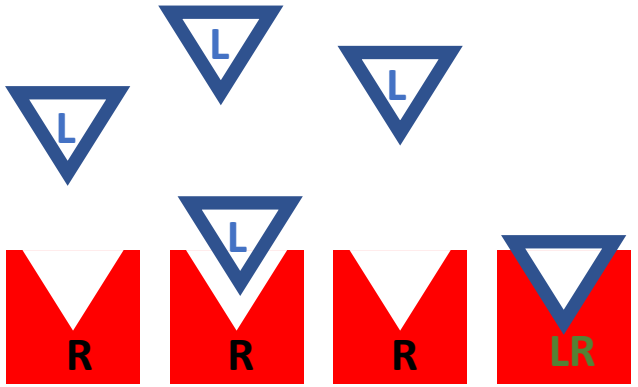
Some useful concepts from biochemistry

Single binding site model

[RL]: Conc. of bound receptor-ligand complexes

[L] : Conc. of free ligand

$$[L] + [R] \underset{k_{off}}{\overset{k_{on}}{\rightleftarrows}} [RL]$$



Dissociation constant

$$K_D = \frac{k_{off}}{k_{on}} \qquad \text{Affinity} = 1/K_D$$

Binding potential

$$BP = \frac{[RL]}{[L]} = \frac{"bound"}{"free"}$$

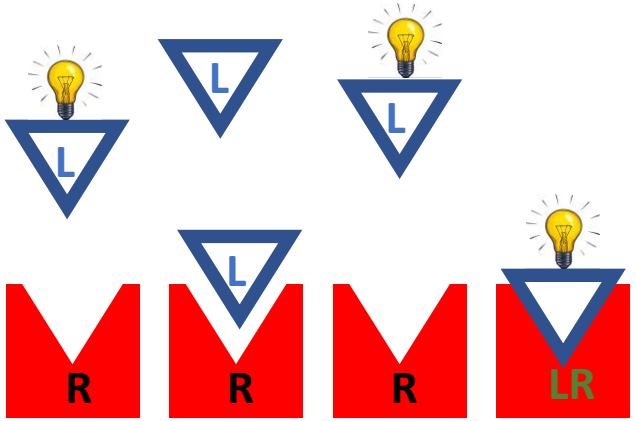
Some useful concepts from biochemistry

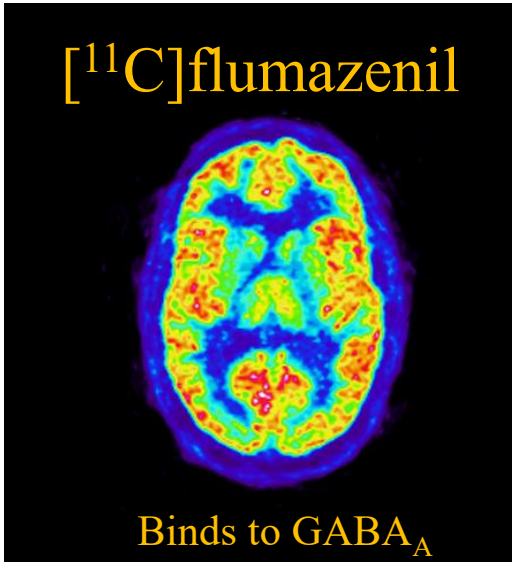
Single binding site model

$$[L] + [R] \underset{k_{off}}{\overset{k_{on}}{\rightleftarrows}} [RL]$$

$$K_D = \frac{k_{off}}{k_{on}} \qquad BP = \frac{[RL]}{[L]}$$

What would we ideally want from a PET experiment?





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Some useful concepts from biochemistry

Single binding site model

$$[L] + [R] \underset{k_{off}}{\overset{k_{on}}{\rightleftarrows}} [RL]$$

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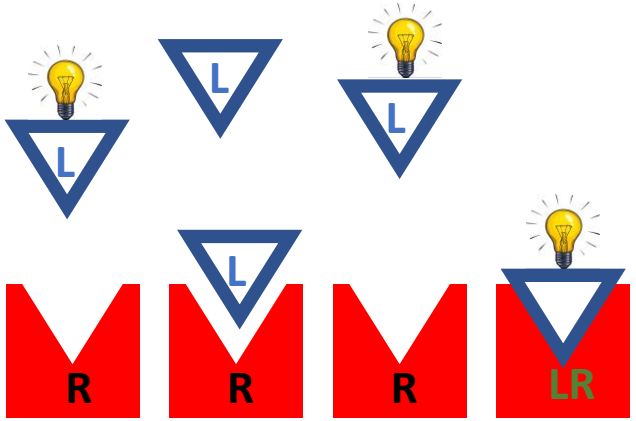
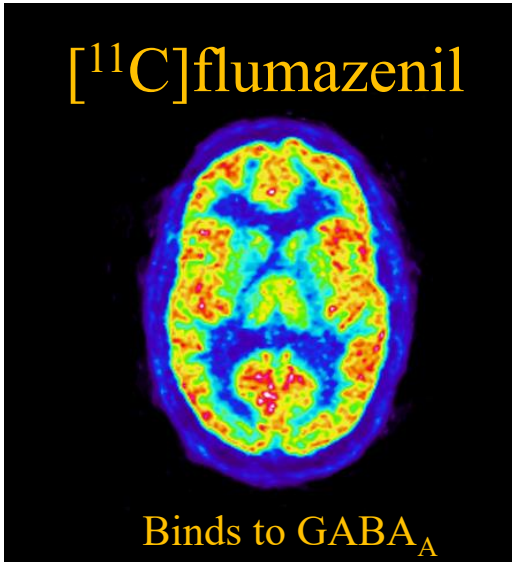


What would we ideally want from a PET experiment?

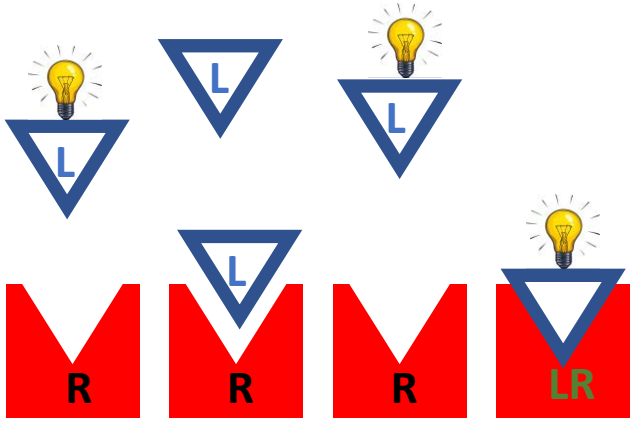
Probably we want to estimate the number of receptors, [R] (B_{max} or B_{avail})



Some useful concepts from biochemistry

Single binding site model

We want to estimate the number of receptors, [R]
(B_{max} or B_{avail})



$$[L] + [R] \underset{k_{off}}{\overset{k_{on}}{\rightleftarrows}} [RL]$$

$$K_D = \frac{k_{off}}{k_{on}}$$

Michelis-Menten equation

$$[RL] = \frac{[R][L]}{[L] + K_D}$$

$$BP = \frac{[RL]}{[L]}$$

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Some useful concepts from biochemistry

Single binding site model

We want to estimate the number of receptors, [R]
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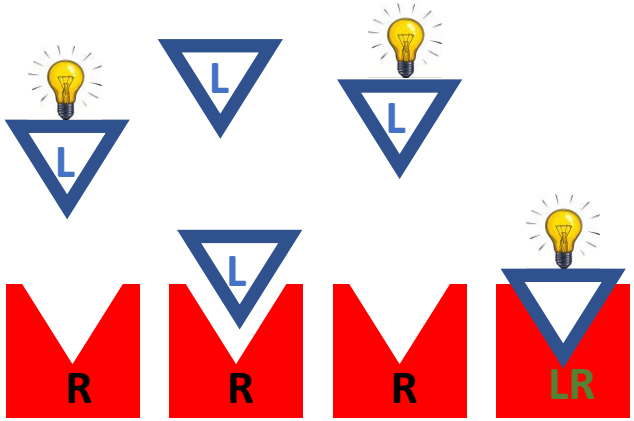

$$[L] + [R] \underset{k_{off}}{\overset{k_{on}}{\rightleftarrows}} [RL] \qquad K_D = \frac{k_{off}}{k_{on}}$$

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$$BP = \frac{[RL]}{[L]} = \frac{[R][L]}{[L]\,([L] + K_D)}$$

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Some useful concepts from biochemistry

Single binding site model

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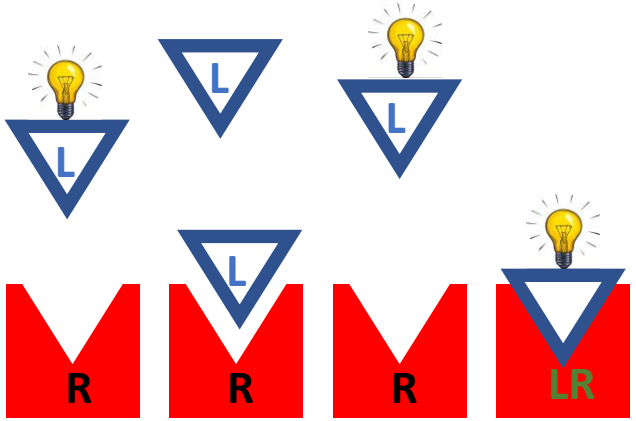

$$[L] + [R] \underset{k_{off}}{\overset{k_{on}}{\rightleftarrows}} [RL]$$

$$K_D = \frac{k_{off}}{k_{on}}$$

Michelis-Menten equation

$$[RL] = \frac{[R][L]}{[L] + K_D}$$

$$BP = \frac{[RL]}{[L]} = \frac{[R][L]}{[L]\,([L] + K_D)}$$

Tracer doses: $([L] \ll K_D)$

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Some useful concepts from biochemistry

Single binding site model

We want to estimate the number of receptors, [R]
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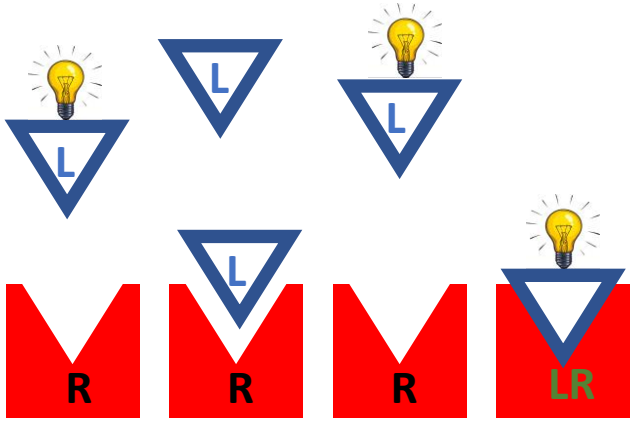


$$[L] + [R] \underset{k_{off}}{\overset{k_{on}}{\rightleftarrows}} [RL] \qquad K_D = \frac{k_{off}}{k_{on}}$$

Michelis-Menten equation

$$[RL] = \frac{[R][L]}{[L] + K_D}$$

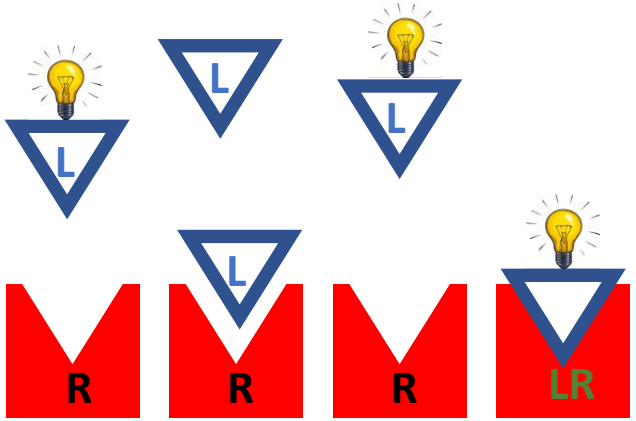
$$BP = \frac{[RL]}{[L]} = \frac{[R][L]}{[L]\,([L] + K_D)} \quad \left[\text{Tracer doses: } ([L] \ll K_D)\right] = \frac{B_{max}}{K_D}$$

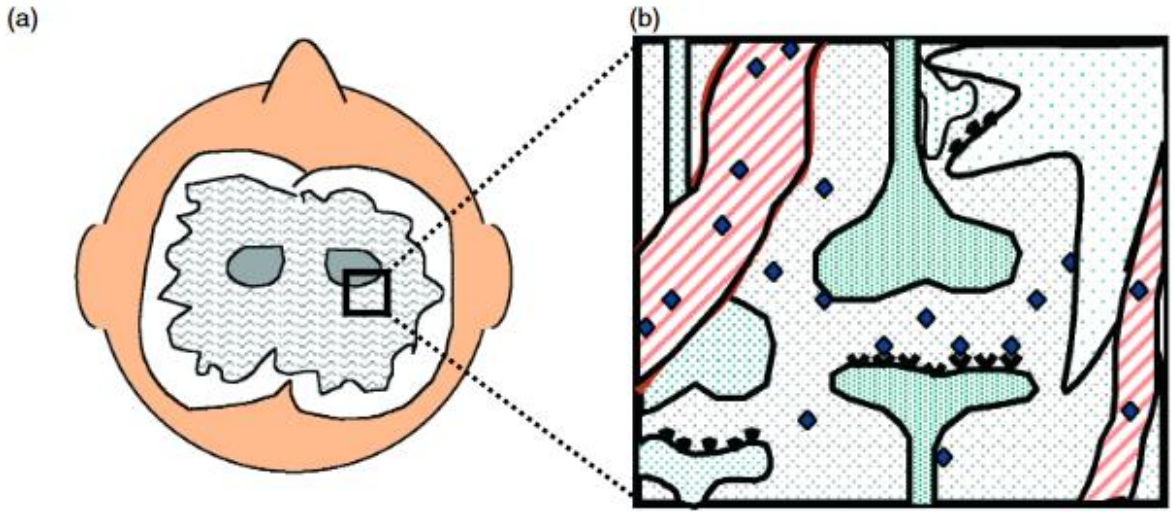
Some useful concepts from biochemistry

Single binding site model

What would we ideally want from a PET experiment?

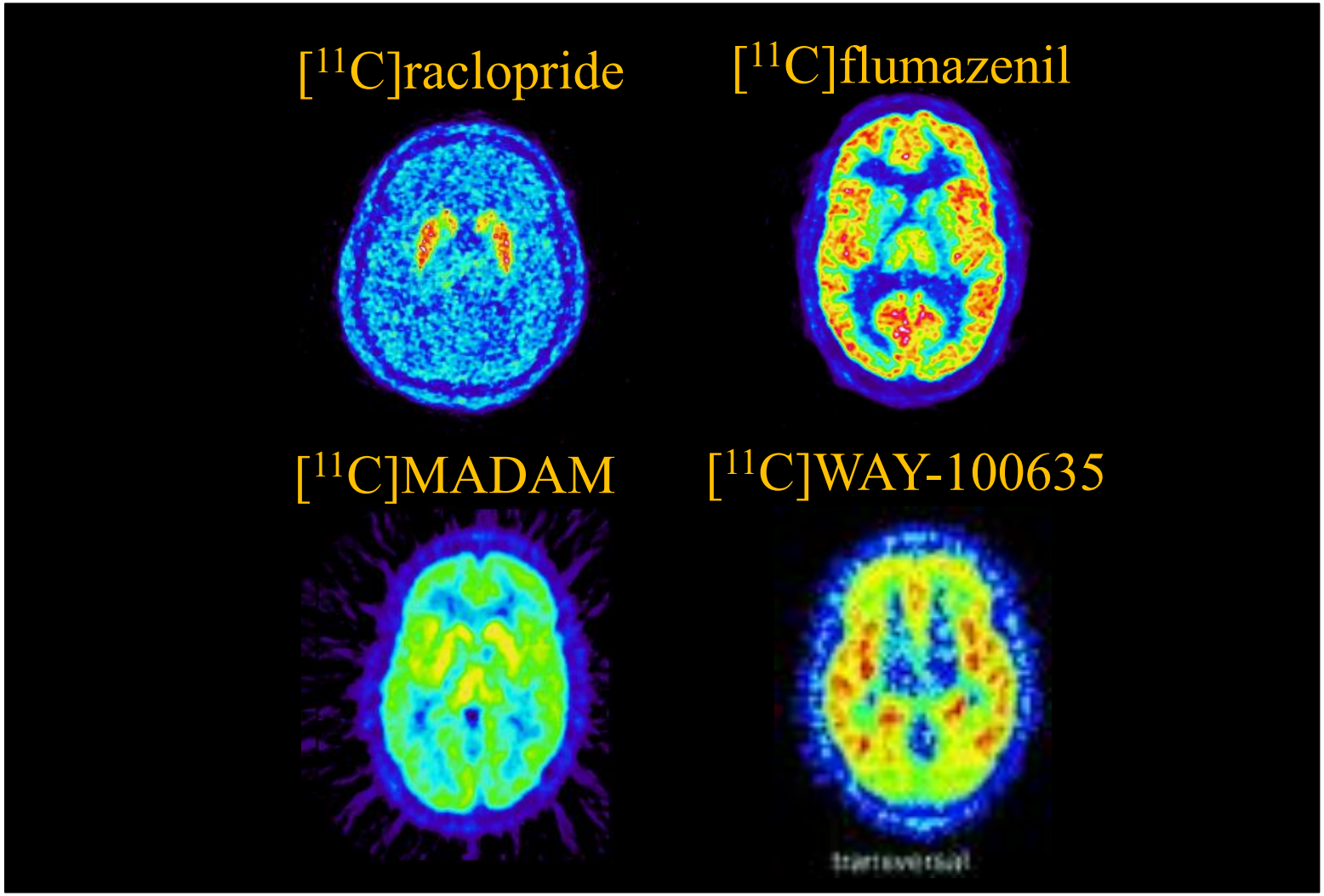
$$BP = \frac{bound}{free} = \cdots = \frac{B_{max}}{K_D}$$





Morris et al., Emission Tomography, Elsevier 2004

PET/SPECT data quantification



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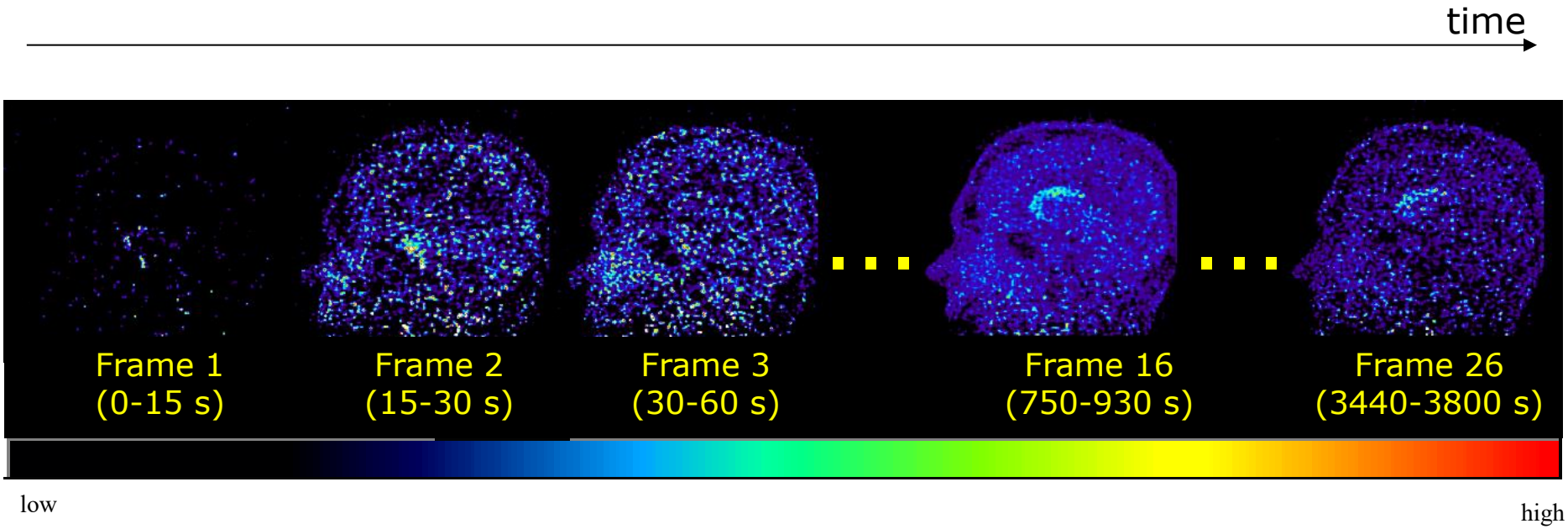
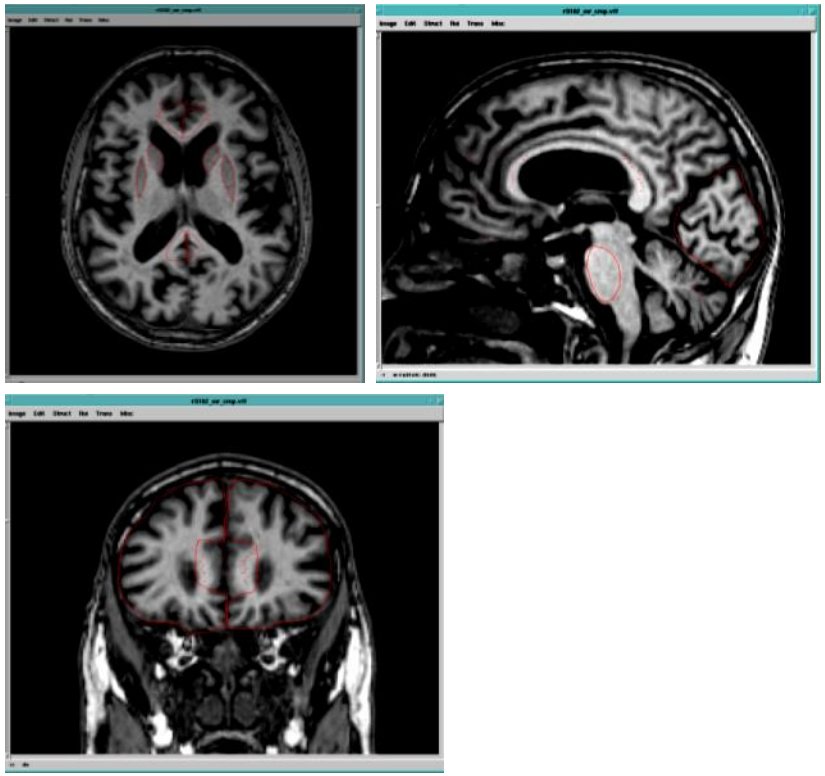
Time frames of a PET image



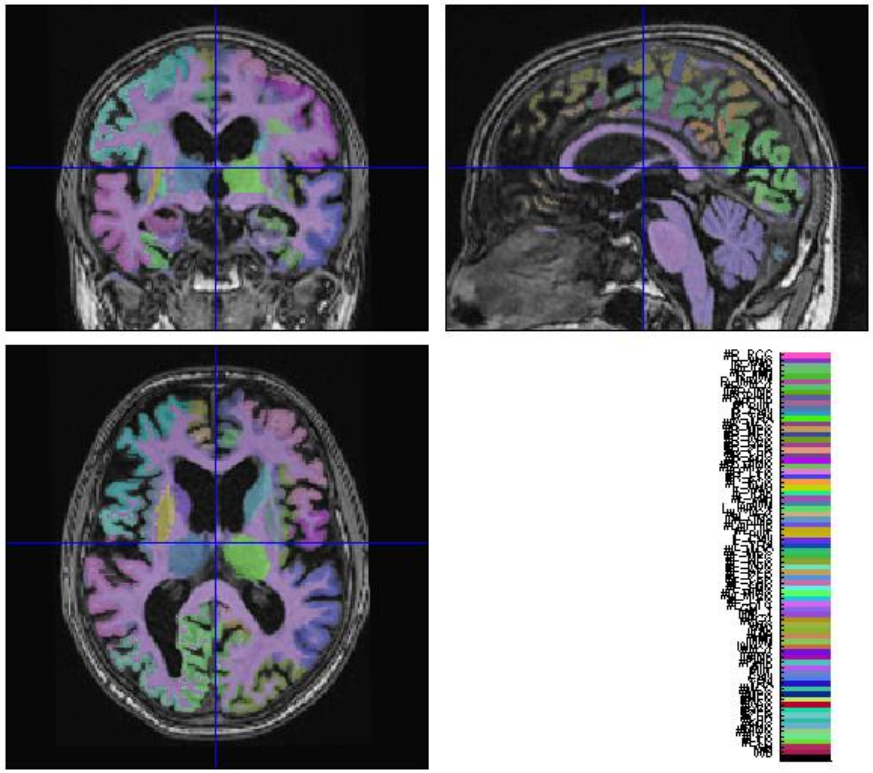
Increasing frame durations (why?)
Each voxel (pixel) has a value, what's the unit?
Very noisy
Very little spatial information

Regions of Interests (ROI)

Manual ROIs



Automatic ROIs



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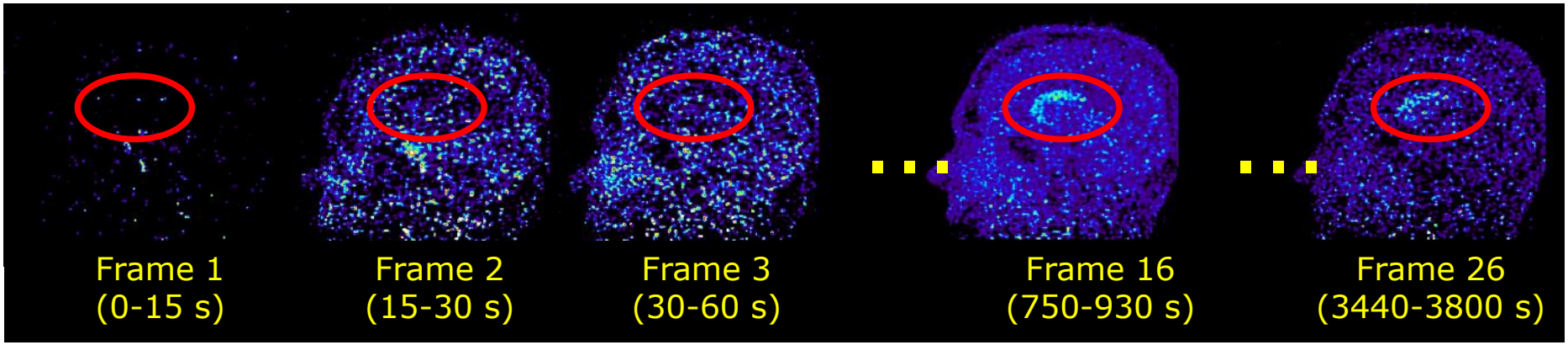
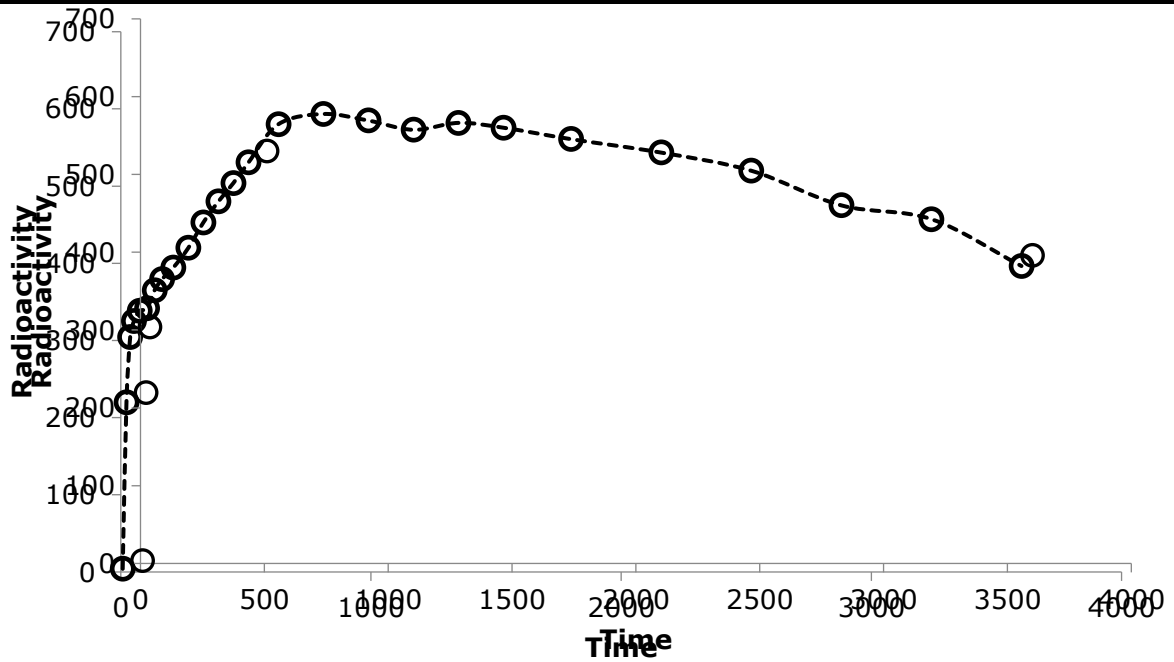
Time frames of PET / SPECT images



Time activity curve (TAC)



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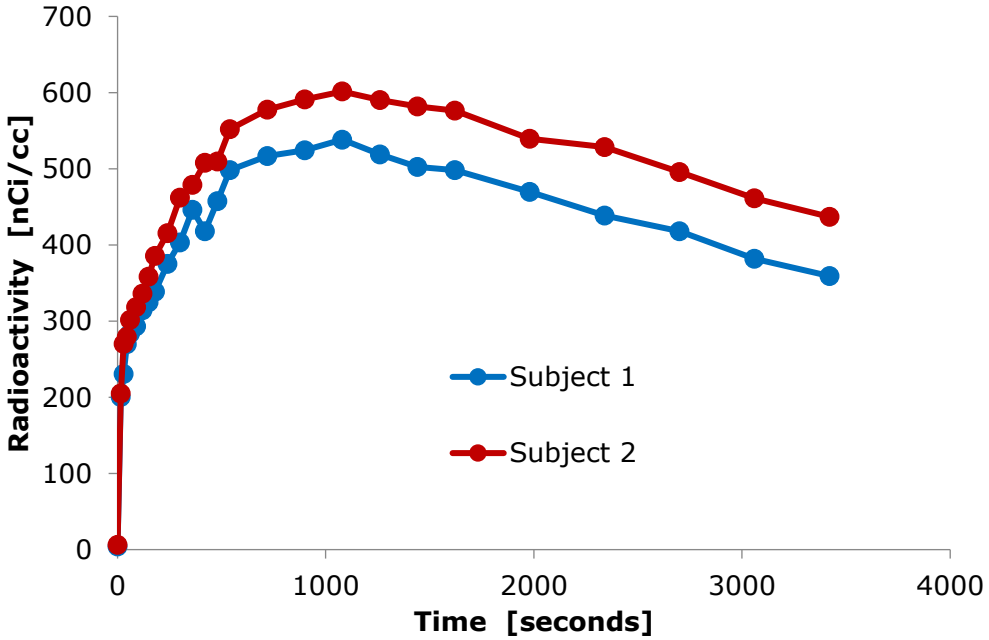
Quantification of dynamic PET / SPECT data



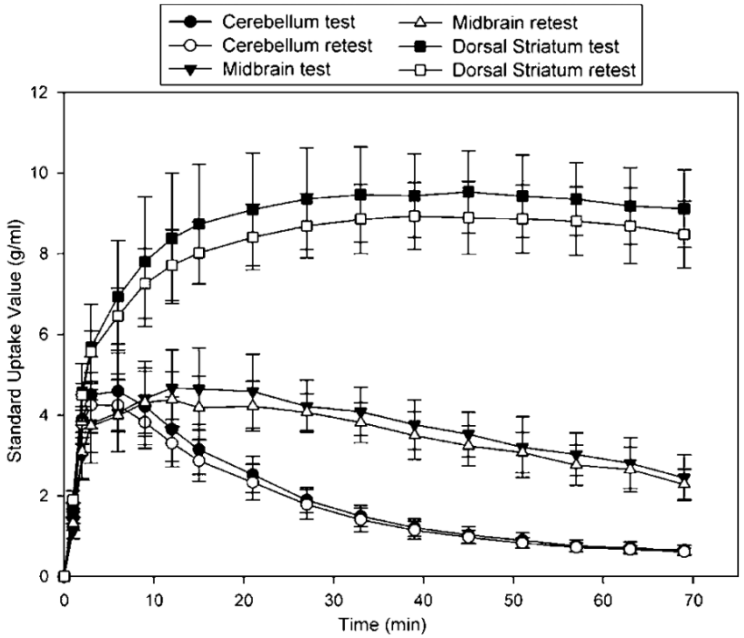
Subject 2 has a higher density of Dopamine D2 receptors ⁉

Was the same amount of radioactivity injected both subjects?
Did they have the same body weight?
Did the radioligand metabolise in the exact same way?
Did they have the same degree of non-specific binding?
Etc...

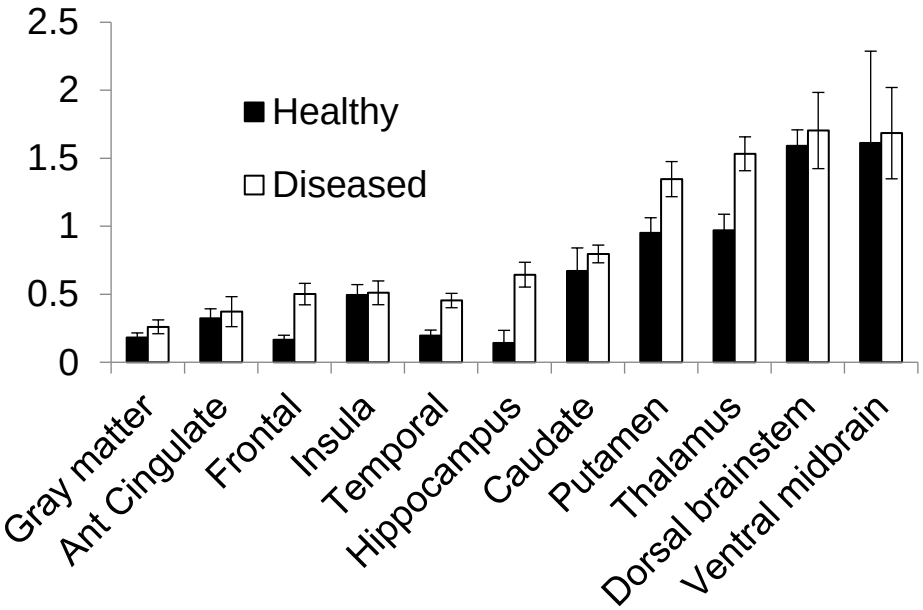
Standardized uptake value

$$SUV(t) = \frac{TAC(t)}{ID / weight}$$

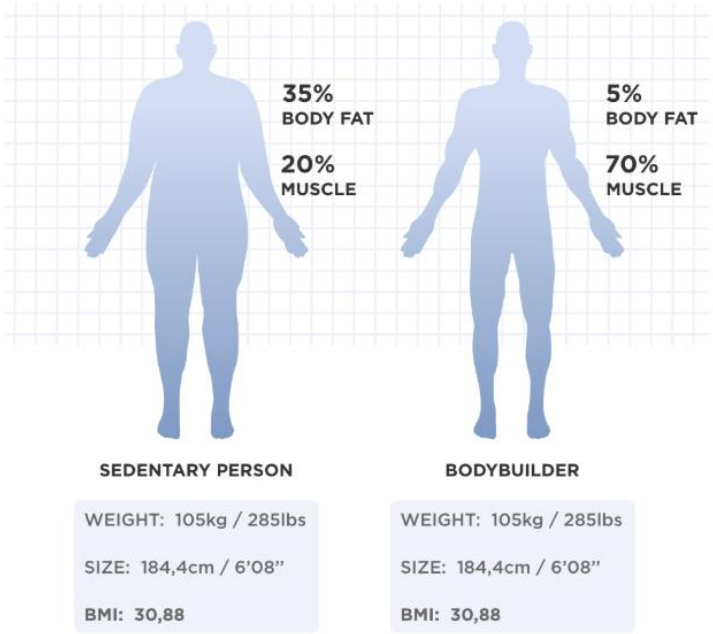
$$AUC_{SUV} = \int_0^{t_{end}} SUV(t)dt$$



SUV curves, [11C]PE2I.
Hirvonen et al., JCBFM 2008



Example where SUV may be inappropriate



https://bodysculptdoc.co.za/bmi-calculator/

Revisiting Weight-Normalized SUV and Lean-Body-Mass–Normalized SUV in PET Studies

Ismet Sarikaya[1], Ahmed N. Albatineh[2], and Ali Sarikaya[3]

[1]*Department of Nuclear Medicine, Faculty of Medicine, Kuwait University, and Mubarak Al-Kabeer Hospital, Jabriya, Kuwait;*
[2]*Department of Community Medicine and Behavioral Sciences, Faculty of Medicine, Kuwait University, Safat, Kuwait; and*
[3]*Department of Nuclear Medicine, Faculty of Medicine, Trakya University, Edirne, Turkey*

- Inject 105 MBq in each
- 5x more uptake in brain than in "background"

- Volume in which tracer is distributed
  - Sedentary: 105kg*0.65 = 68.25kg
  - Bodybuilder: 105kg*0.95 = 99.75kg

- Amount of "background" radioactivity per kilo lean mass
  - Sedentary: 105MBq/68.25kg = 1.5 MBq/kg
  - Bodybuilder: 105Mbq/99.75kg = 1.05 MBq/kg

- Uptake in brain
  - Sedentary = 5*1.5MBq/kg = 7.5 MBq/kg
  - Bodybuilder = 5*1.05MBq/kg = 5.25 MBq/kg

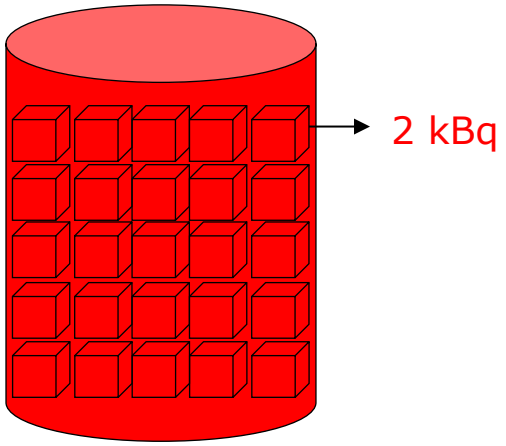
- SUV:

$$SUV = \frac{Uptake\ in\ brain}{injected\ dose / bodyweight}$$

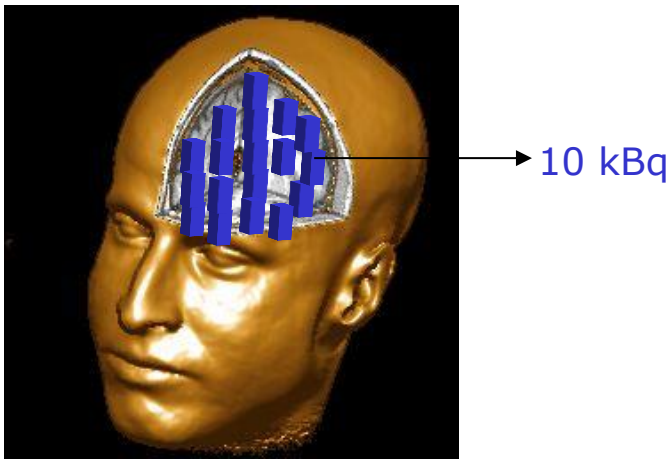
  - Sedentary: 7.5 / 105MBq/105kg = 7.5
  - Bodybuilder: 5.25 / 105MBq / 105kg = 5.25

Total distribution volume, V_T

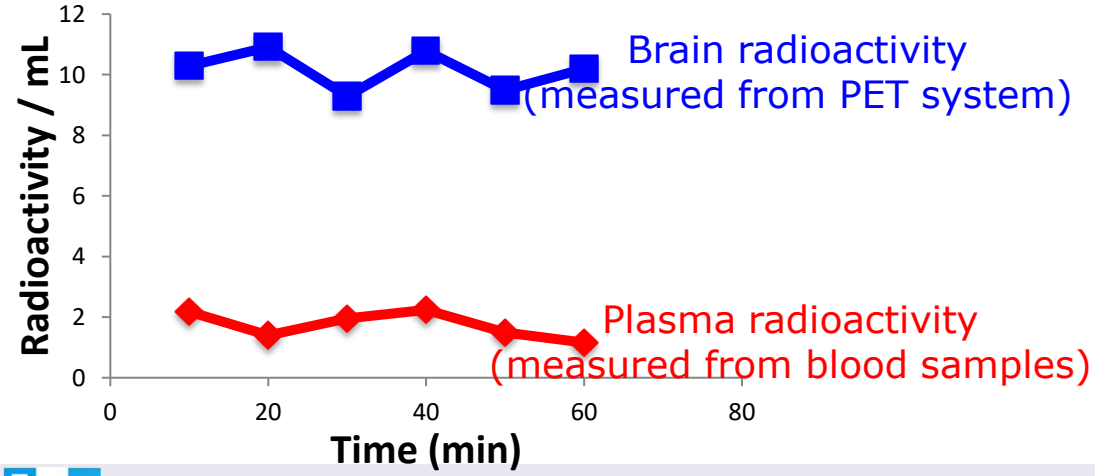
Parent radioligand in plasma



Radioactivity in brain



If equilibrium:



While at equilibrium,
V_T = brain / plasma

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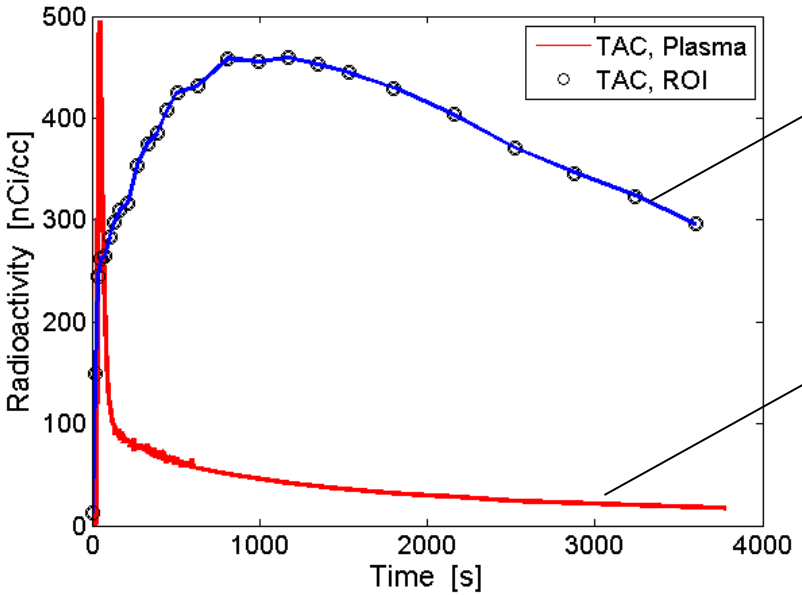
Distribution volume, V_T

The volume of plasma required to account for the measured radioactivity in tissue.

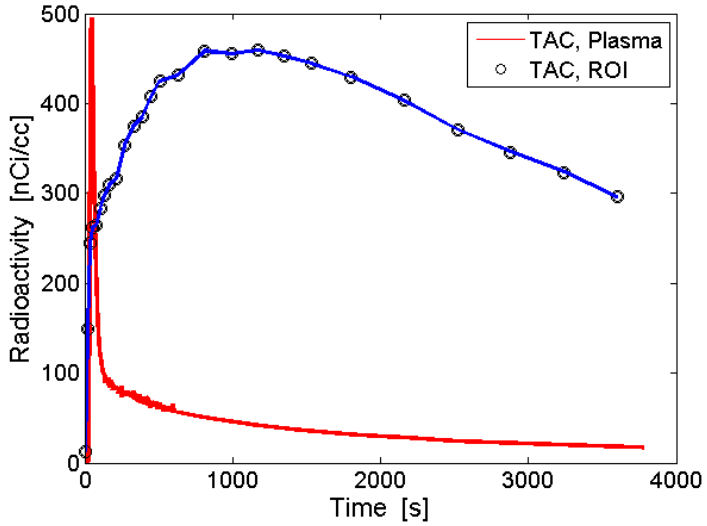


Concentration of radioligand in a brain region

Concentration of unchanged radioligand in plasma

Distribution volume, V_T

The volume of plasma required to account for the measured radioactivity in tissue.

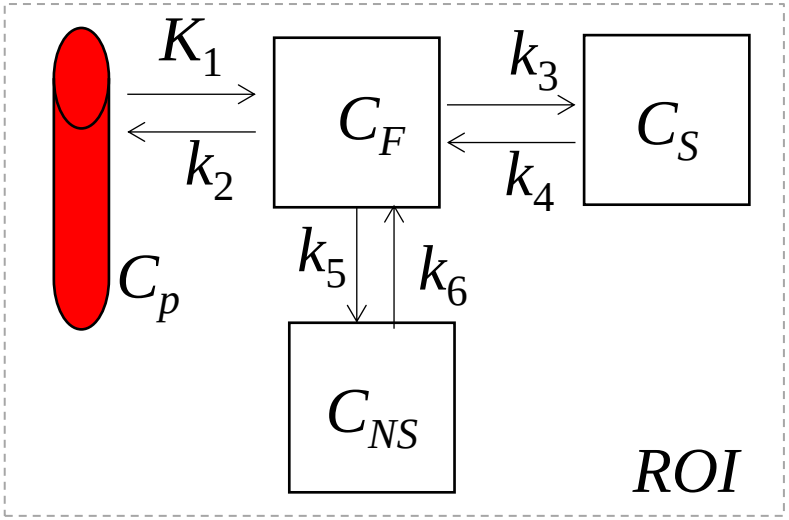


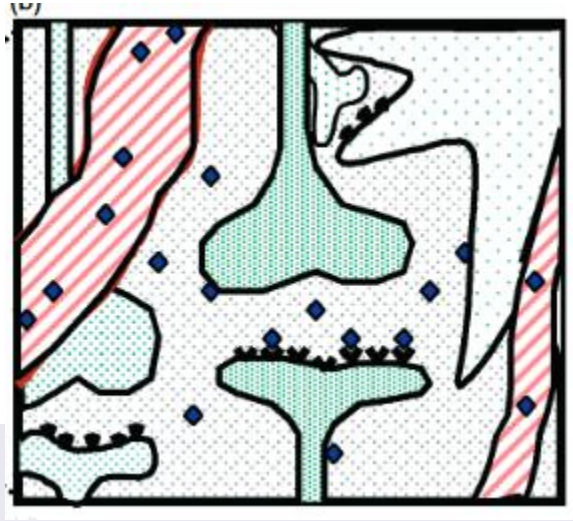
$$V_T = \frac{\int_0^\infty TAC(t)dt}{\int_0^\infty plasma(t)dt}$$

Distribution volume, V_T

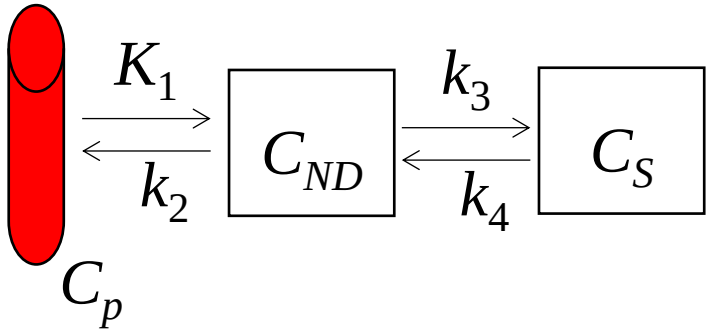
What can we assume about the kinetic behaviour of the tracer?

3 tissue compartment model

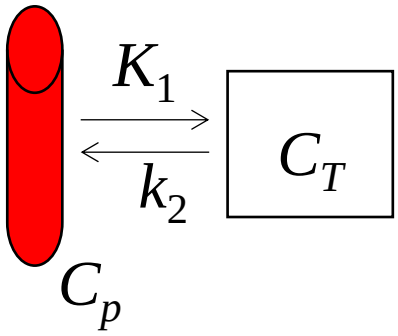




2 tissue compartment model

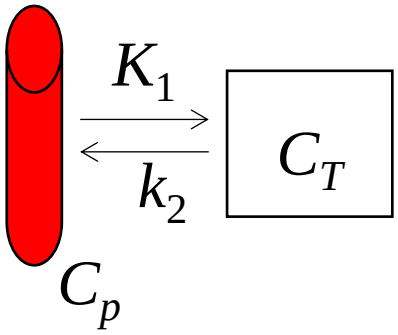


1 tissue compartment model



Distribution volume, V_T

What can we assume about the kinetic behaviour of the tracer?



Mass balance

"Rate of change"
= influx - outflux

$$\frac{dC_T(t)}{dt} = K_1 C_p(t) - k_2 C_T(t)$$

Solving dif. Eq...

$$C_T(t) = C_p(t) \otimes K_1 e^{-k_2 t}$$

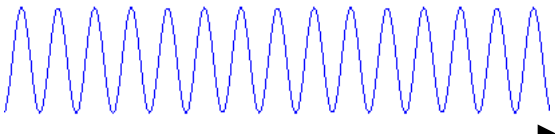
$$V_T = \frac{\int_0^\infty TAC(t)dt}{\int_0^\infty plasma(t)dt} = \frac{\int_0^\infty C_T(t)dt}{\int_0^\infty C_p(t)dt} = \cdots = \frac{K_1}{k_2}$$

Linear Time Invariant (LTI) Systems

Linear Time Invariant (LTI) Systems

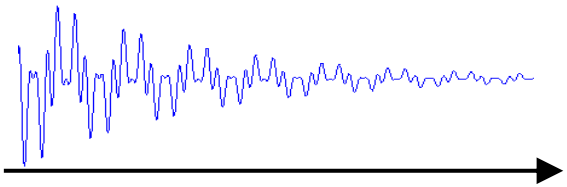
Synthesizer

Electric current,
sinus wave...



Input
signal

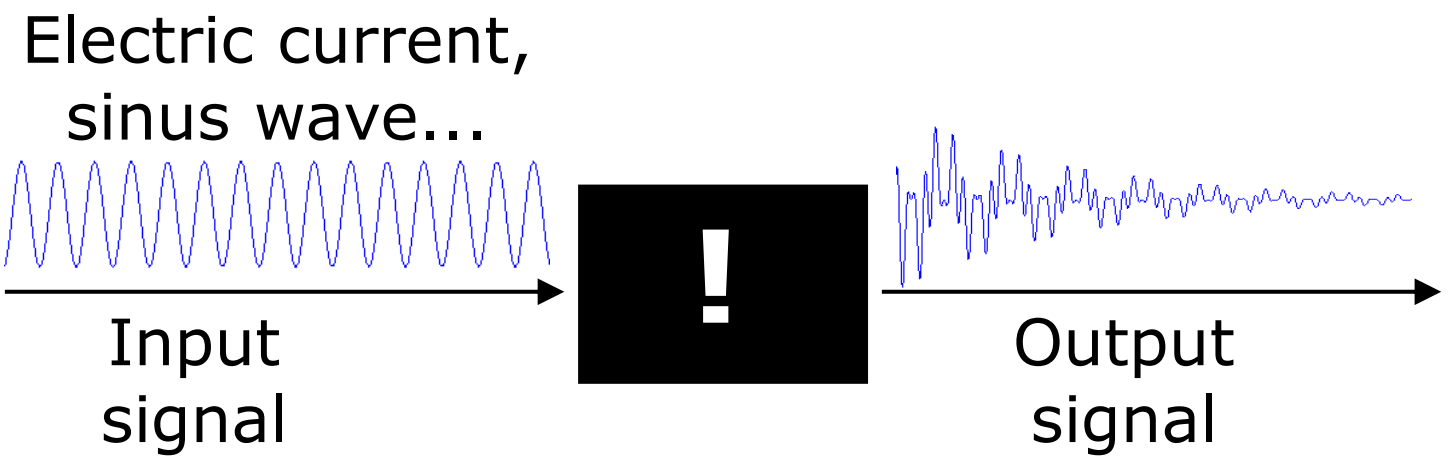
?



Output
signal

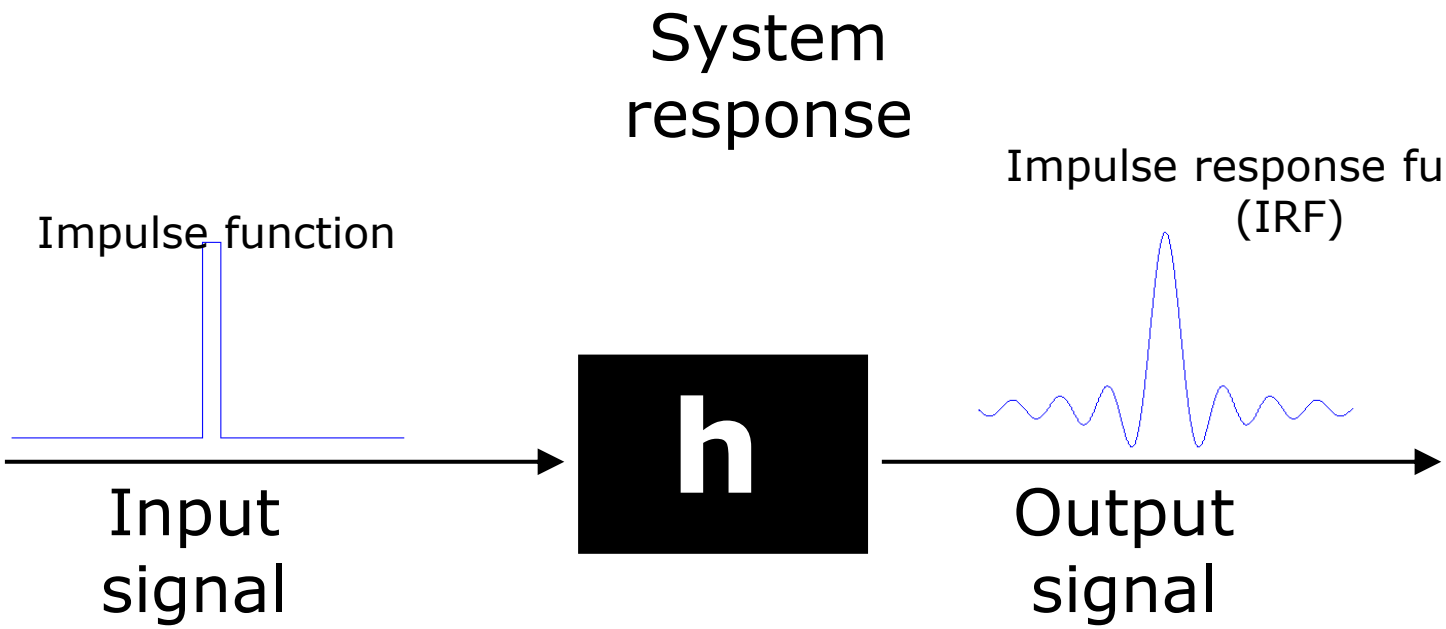
Linear Time Invariant (LTI) Systems

Synthesizer



Modify input signal + Study output signal →
Understand the system (!)

Linear Time Invariant (LTI) Systems



Impulse response function ”defines” the system!

For any input signal $f_i(t)$, the corrsponding output signal $f_o(t)$ is given by

$$f_o(t) = f_i(t) \otimes IRF$$

Convolution

Convolution of two square functions. The convolution (black line) at any time is the size of the joint area (yellow field) of the two functions at that time.

Convolution of a square input function and a ”response function”. The convolved signal will be the output in this ”model”.

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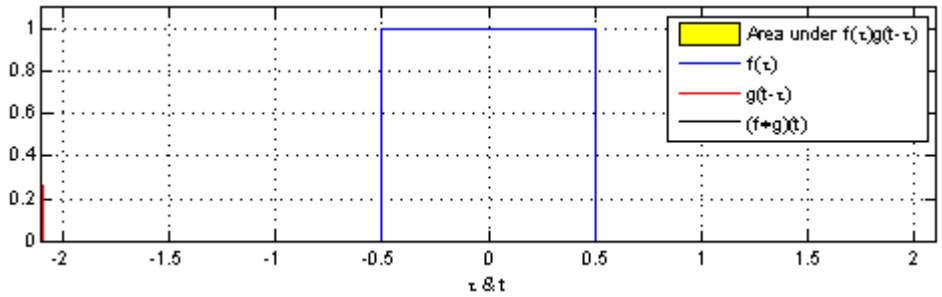

Convolution of a square input function and a ”response function”. The convolved signal will be the output in this ”model”.

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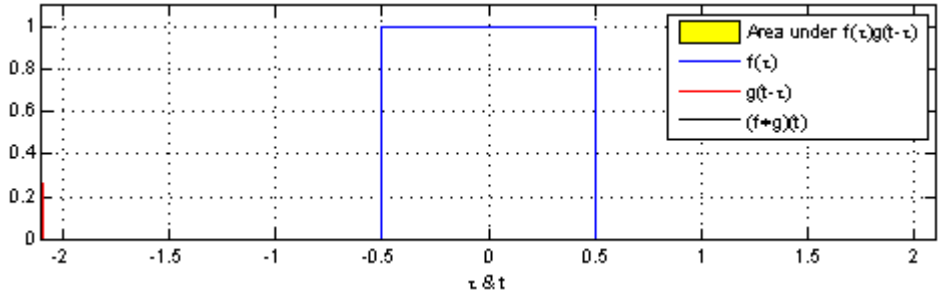
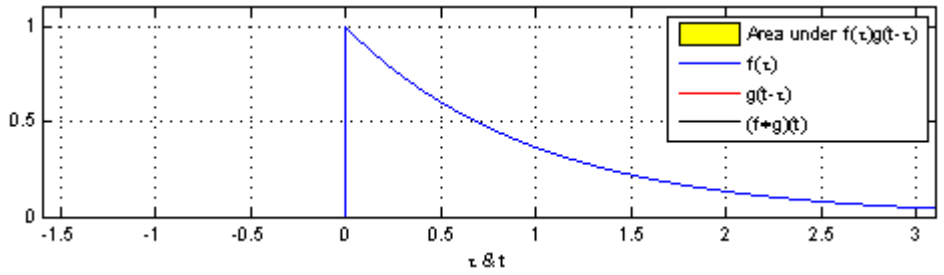


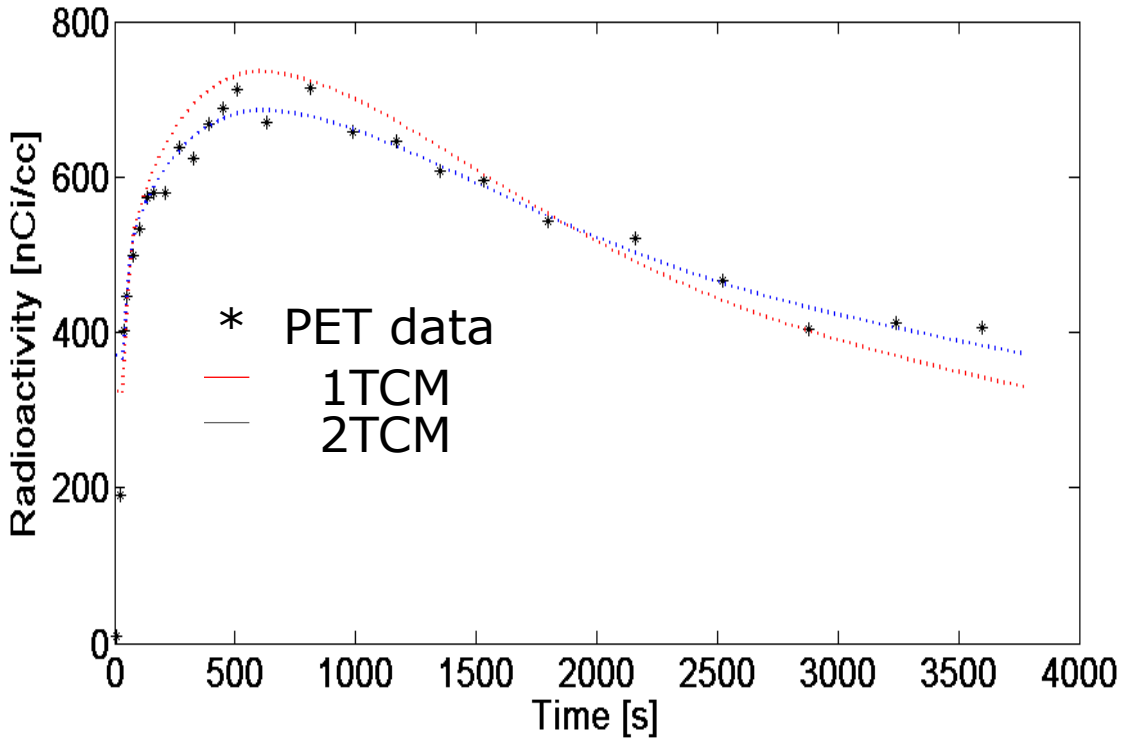
Convolution of a square input function and a "response function". The convolved signal will be the output in this "model".

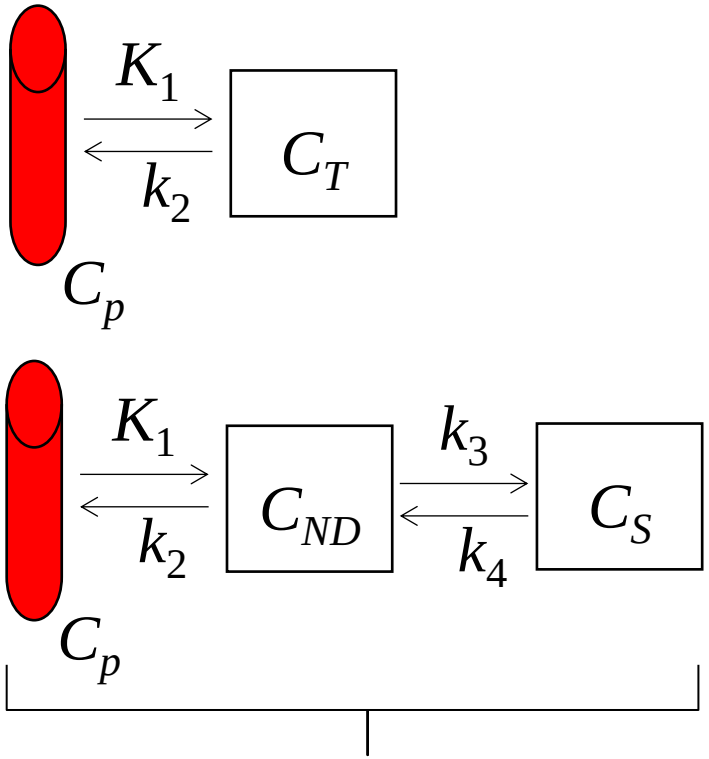


Distribution volume, V_T

$$C_T(t) = C_p(t) \otimes K_1 e^{-k_2 t}$$

$$V_T = \frac{\int_0^\infty C_T(t)dt}{\int_0^\infty C_p(t)dt} = \ldots = \frac{K_1}{k_2}$$





$$V_T = \frac{K_1}{k_2}\left(1 + \frac{k_3}{k_4}\right)$$

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Distribution volume, V_T

Question?
What if you think that the fits obtained from 1TCM and 2TCM are equally good?

Occam's razor
Parsimony Principle

Distribution volume, V_T

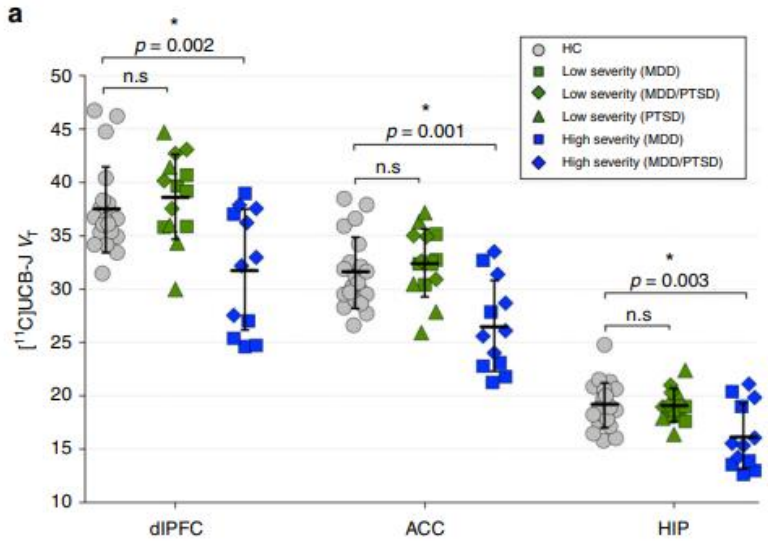
Example I

ARTICLE

https://doi.org/10.1038/s41467-019-09562-7 OPEN

Lower synaptic density is associated with depression severity and network alterations

Sophie E. Holmes[1], Dustin Scheinost[2], Sjoerd J. Finnema[1], Mika Naganawa[2], Margaret T. Davis[1], Nicole DellaGioia[1], Nabeel Nabulsi[2], David Matuskey[1,2], Gustavo A. Angarita[1], Robert H. Pietrzak[1,3], Ronald S. Duman[1], Gerard Sanacora[1], John H. Krystal[1,3], Richard E. Carson[2] & Irina Esterlis[1,3]



Discussion

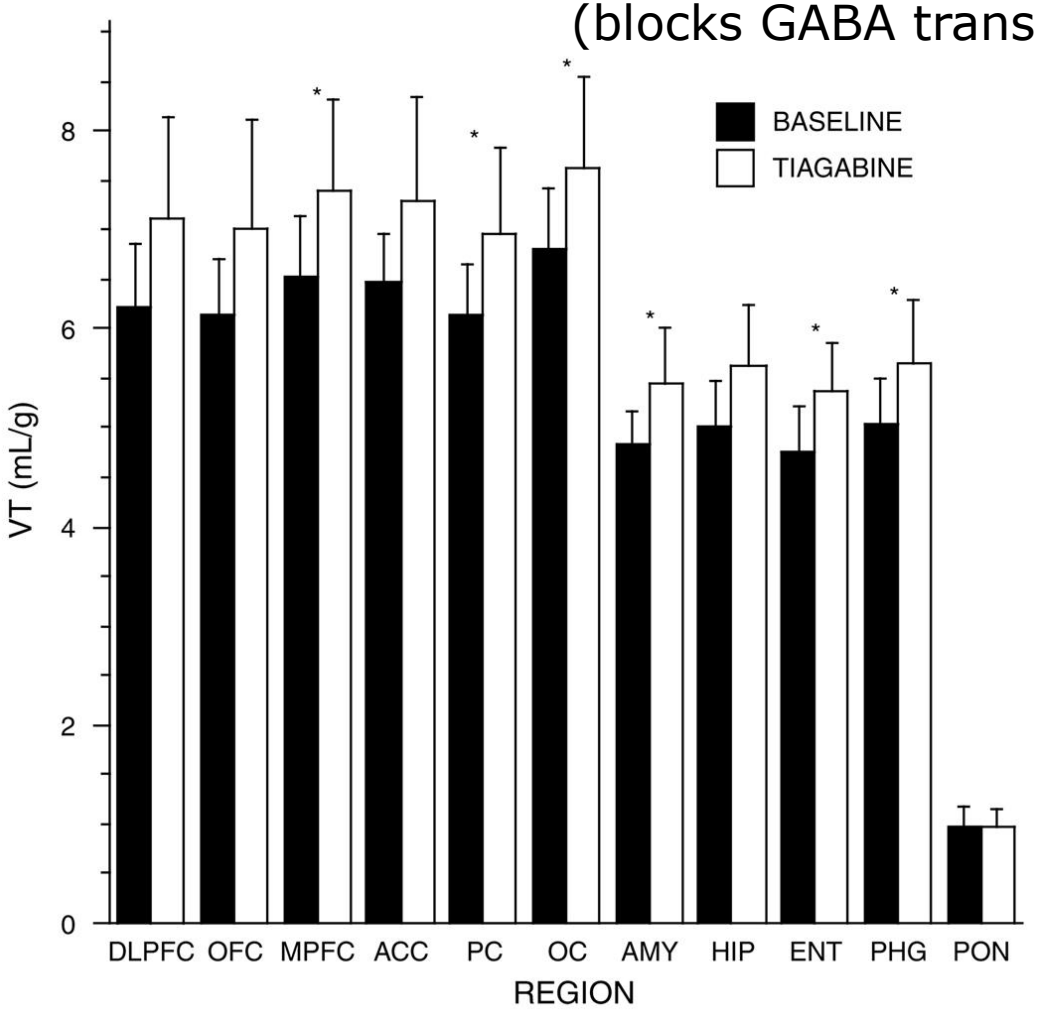
This is the first study to investigate radioligand binding to SV2A in MDD and PTSD, and the first in vivo evidence of lower synaptic density in association with depressive symptoms in these disorders. Findings suggest that lower synaptic density con-

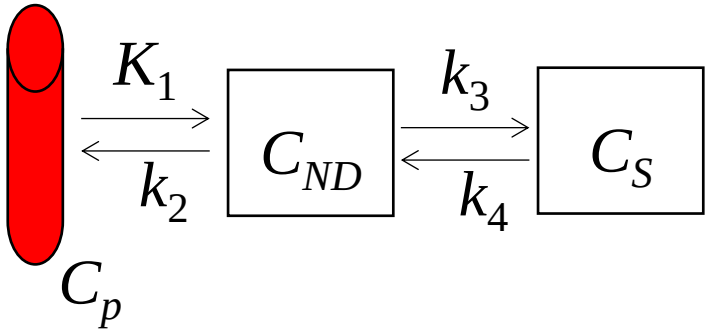
PET image analysis. The primary outcome measure was total volume of distribution (V_T), computed parametrically using the 1 tissue (1T) compartment model and a metabolite-corrected arterial input function, as validated previously[70]. Distribution volume (V_T) is the tissue-to-plasma concentration ratio at equilibrium and reflects total uptake (specific plus nonspecific binding) of the radioligand.

Distribution volume, V_T

Example II

[^{11}C]Flumazenil V_T before and after treatment with Tiagabine (blocks GABA transporter).

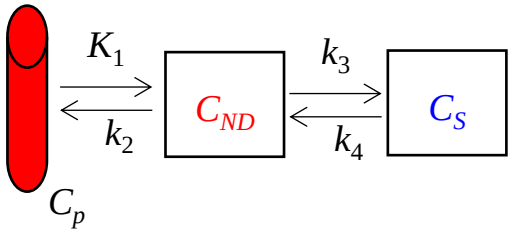




Frankle et al, *Neuropsychopharmacology* (2009)

Distribution volume, V_T

$V_T = V_{ND} + V_S$



Total binding
($C_T(t)$, observed)

Total binding
(modeled)

$$V_T = \frac{K_1}{k_2}\left(1 + \frac{k_3}{k_4}\right)$$

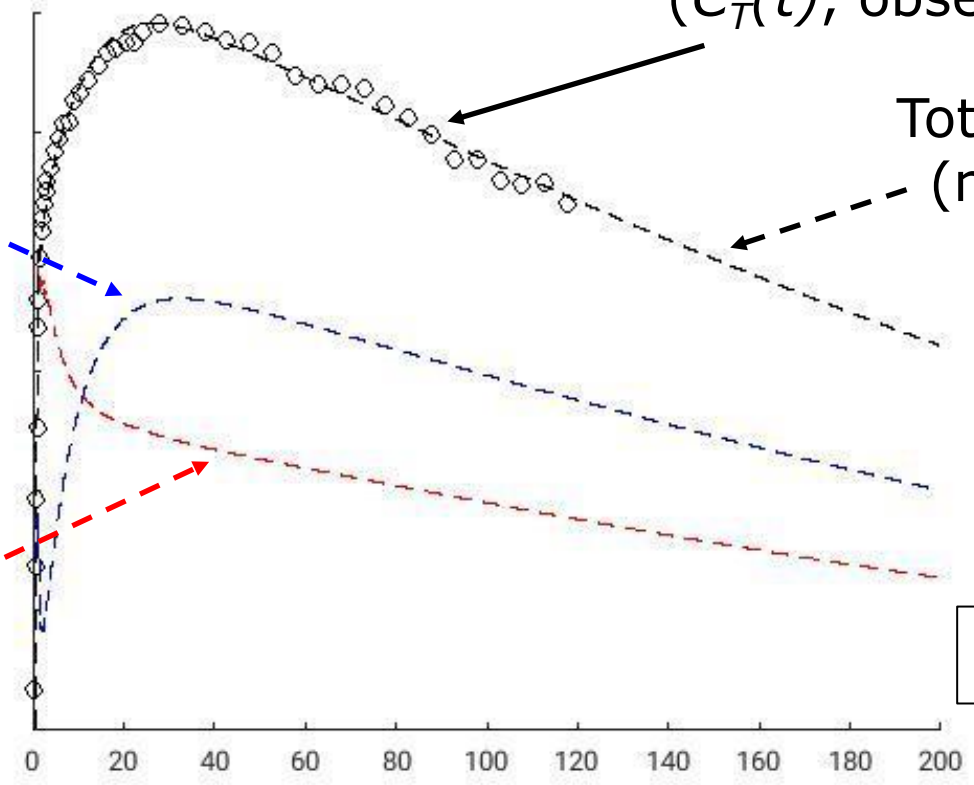
$$V_T = \frac{C_S + C_{ND}}{C_p}$$

Specific binding
($C_S(t)$, modeled)

$$V_S = \frac{C_S}{C_p}$$

Non-displaceable binding
($C_{ND}(t)$, modeled)

$$V_{ND} = \frac{C_{ND}}{C_p}$$



$$V_T = V_{ND} + V_S$$

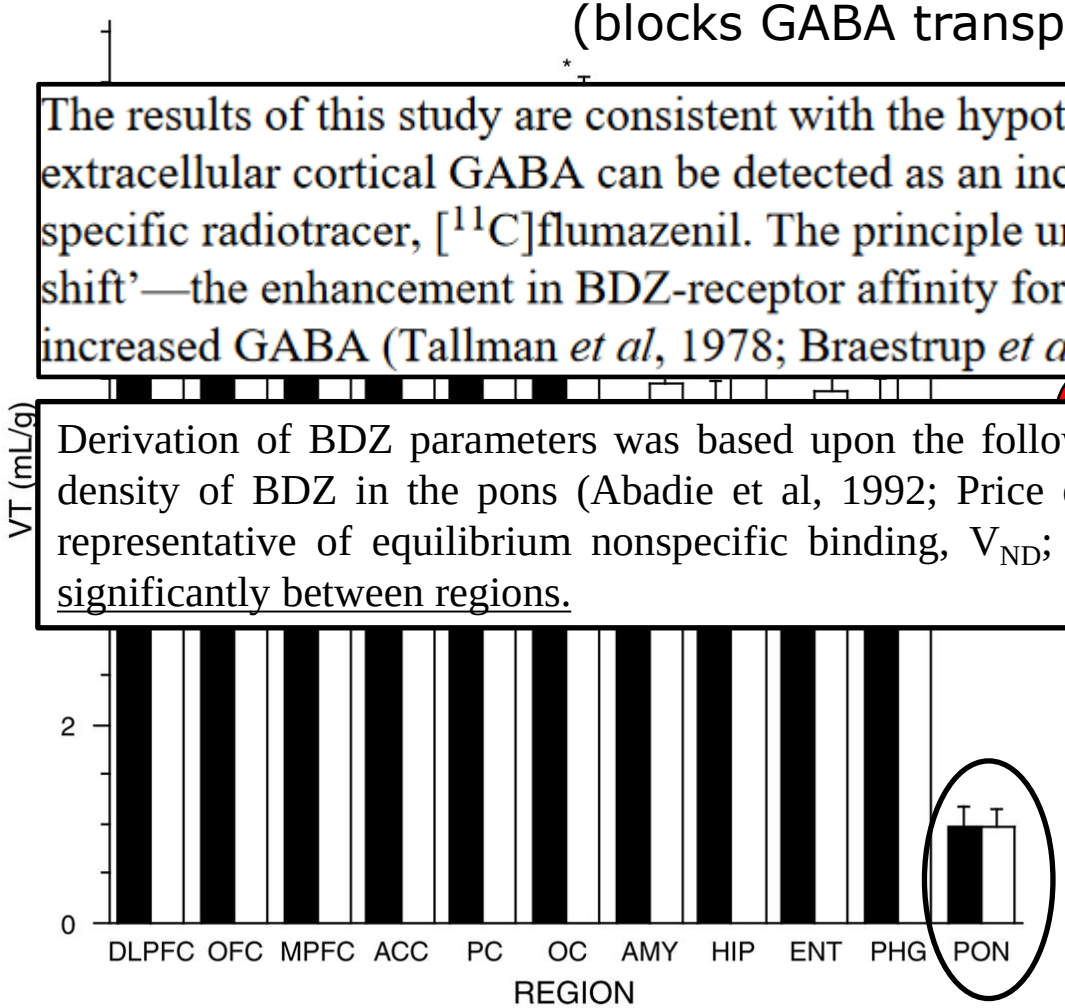
Distribution volume, V_T

Example II

[^{11}C]Flumazenil V_T before and after treatment with Tiagabine (blocks GABA transporter).

The results of this study are consistent with the hypothesis that the acute increases in extracellular cortical GABA can be detected as an increase in the binding of the BDZ site-specific radiotracer, [^{11}C]flumazenil. The principle underlying this hypothesis is the 'GABA shift'—the enhancement in BDZ-receptor affinity for BDZ site substrates resulting from the increased GABA (Tallman *et al*, 1978; Braestrup *et al*, 1982). It is widely accepted that

Derivation of BDZ parameters was based upon the following assumptions: (1) because of the low density of BDZ in the pons (Abadie et al, 1992; Price et al, 1993), pons V_T was assumed to be representative of equilibrium nonspecific binding, V_{ND}; (2) the nonspecific binding did not vary significantly between regions.



Frankle et al, *Neuropsychopharmacology* (2009)

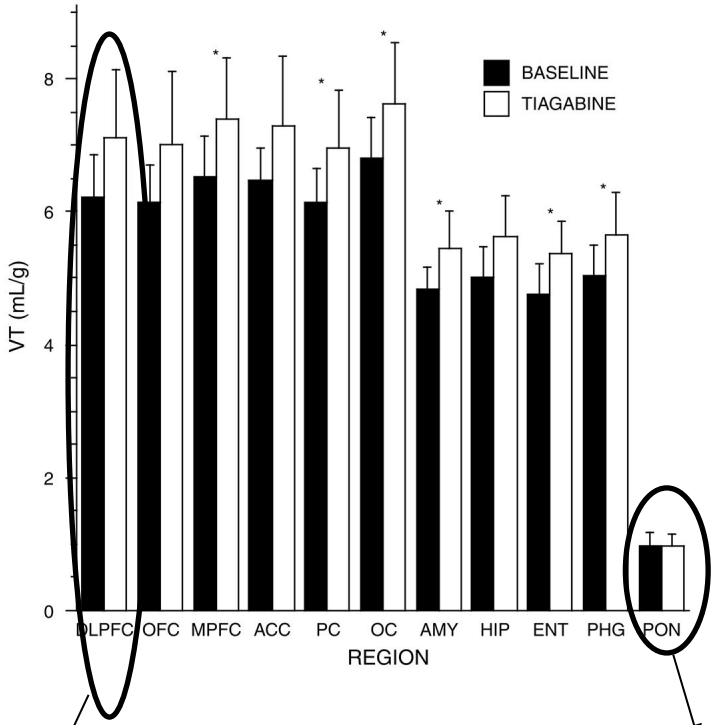
C_p

Reference region – negligible density of target

$C_S=0$

Fundamental assumption of PET:
V_{ND} doesn't change

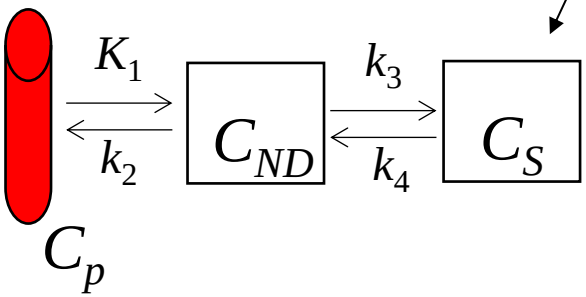
$$V_T = V_S + V_{ND}$$

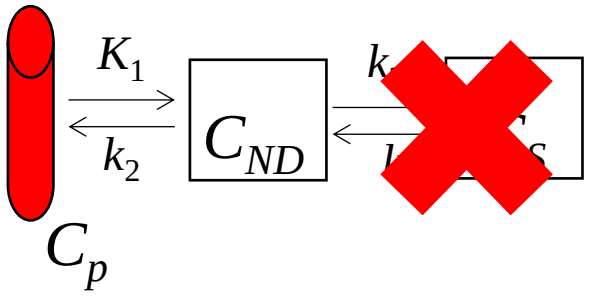


V_S

V_{ND}

V_T





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How can we estimate V_{ND}?

If there is a reference region:

Your answer here...

If there is not a reference region:

Your answer here...

How can we estimate V_{ND}?

If there is a reference region:

Apply your kinetic model to the reference region TAC.
The V_T you get will be V_{ND}

If there is not a reference region:

Your answer here...

How can we estimate V_{ND}?

If there is a reference region:

Apply your kinetic model to the reference region TAC.
The V_T you get will be V_{ND}

If there is not a reference region:

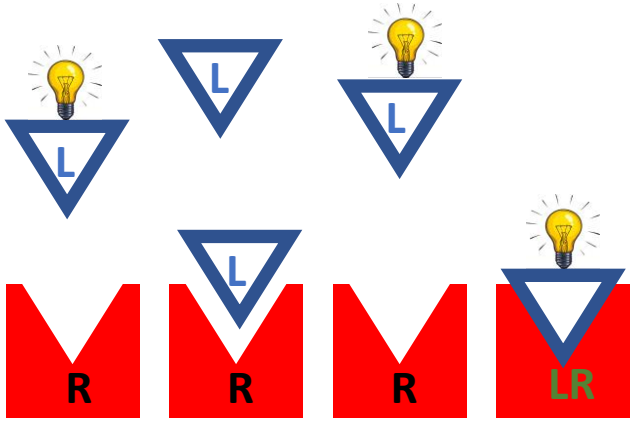
No established way exists...

Some useful concepts from biochemistry

Single binding site model (equilibrium)

$$[L] + [R] \underset{k_{off}}{\overset{k_{on}}{\rightleftarrows}} [RL]$$

$$K_D = \frac{k_{off}}{k_{on}} \qquad BP = \frac{[RL]}{[L]} = \frac{B_{max}}{K_D}$$

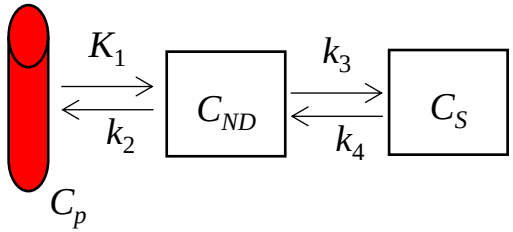


f_{ND}: fraction of free tracer in ND compartment
f_p : fraction of free tracer in plasma

$[RL]: C_S$

$[L]: f_{ND} C_{ND}$

$[L]: f_p C_p$



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Three approaches to estimate in vitro BP

Approach 1a (relative to free conc in plasma)

$$BP = \frac{[RL]}{[L]} = \frac{B_{max}}{K_D}$$

$[RL]: C_S$

$[L]: f_{ND} C_{ND}$

$[L]: f_p C_p$

f_{ND}: fraction of free tracer in ND compartment
f_p : fraction of free tracer in plasma
C_p : Concetration of tracer in plasma

Approach 1a: ”Free” means ”free in plasma”
(i.e., conc. of free in plasma = conc. of free in tissue)

$$BP = \frac{[RL]}{[L]} = \frac{C_S}{f_p C_p} = \frac{C_S/C_p}{f_p C_p/C_p} = \frac{V_S}{f_p} = \frac{V_T - V_{ND}}{f_p} = \frac{B_{max}}{K_D} = BP_F$$

Three approaches to estimate in vitro BP

Approach 1b (relative to concentration in plasma)

$$BP = \frac{[RL]}{[L]} = \frac{B_{max}}{K_D}$$

$[RL]: C_S$

$[L]: f_{ND} C_{ND}$

$[L]: f_p C_p$

f_{ND}: fraction of free tracer in ND compartment
f_p : fraction of free tracer in plasma
C_p : Concetration of tracer in plasma

Approach 1b: ”Free” means ”total in plasma”
(Conc. of free in tissue = conc. of total in plasma – e.g., f_p doesn’t change across groups)

$$BP = \frac{[RL]}{[L]} = \frac{C_S}{C_p} = V_S = V_T - V_{ND} = f_p \frac{B_{max}}{K_D} = BP_P$$

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Three approaches to estimate BP
Approach 2 (relative to ND)

$$BP = \frac{[RL]}{[L]} = \frac{B_{max}}{K_D}$$

$[RL]: C_S$
$[L]: f_{ND} C_{ND}$
$[L]: f_p C_p$

f_{ND}: fraction of free tracer in ND compartment
f_p : fraction of free tracer in plasma
C_p : Concetration of tracer in plasma

Approach 2: ”Free” means ”free in non-displaceable compartment”

$$\frac{[RL]}{[L]} = \frac{C_S}{f_{ND} C_{ND}} = \frac{{C_S}/{C_p}}{f_{ND} {C_{ND}}/{C_p}} = \frac{V_S}{f_{ND} V_{ND}} \rightarrow \frac{V_T - V_{ND}}{V_{ND}} = f_{ND} \frac{B_{max}}{K_D} = BP_{ND}$$

Binding potential!

PET

B_{max}: Total number of receptors

K_D : Affinity of the radioligand

f_p: Free fraction of radioligand in plasma

f_{ND}: Free fraction of radioligand in non-displaceable compartment

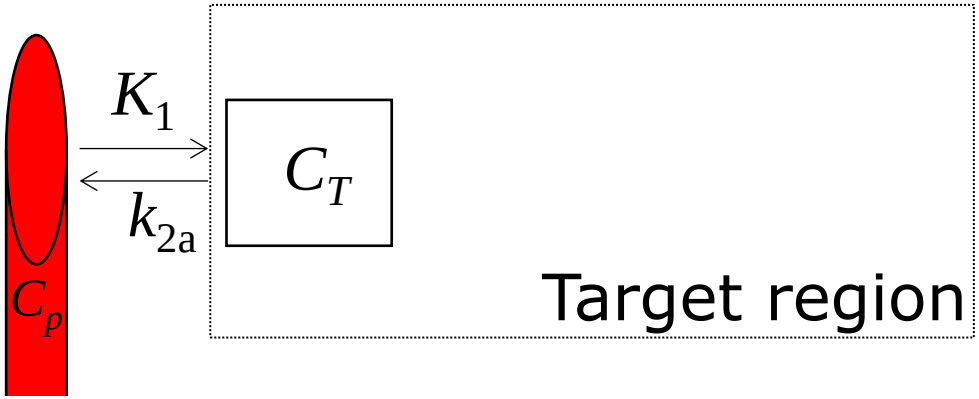
$$BP = \frac{B_{max}}{K_D}$$

$$\frac{V_T - V_{ND}}{f_p} = \frac{B_{max}}{K_D} = BP_F$$

$$V_T - V_{ND} = \frac{B_{max}}{K_D} f_p = BP_P$$

$$\frac{V_T - V_{ND}}{V_{ND}} = \frac{B_{max}}{K_D} f_{ND} = BP_{ND}$$

Simplified Reference Tissue Model



$$C_T(t) = C_p(t) \otimes K_1 e^{-k_2 t}$$

Summary of (some) assumptions

If you use 2TCM to estimate V_T:

- Assume that the model describes the data well
- Assume that V_{ND} is not different between the groups

If you use 2TCM to estimate BP_{ND} $(V_T-V_{ND})/V_{ND}$:

- Assume that the model describes the data well
- Assume that V_{ND} is the same in all brain regions
- Assume that V_{ND} is not different between the groups

If you use reference tissue modeling to estimate BP_{ND}

- Assume that the model describes the data well
- Assume that V_{ND} is the same in all brain regions
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Summary of (some) assumptions

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Possible to estimate V_{ND} without reference region?

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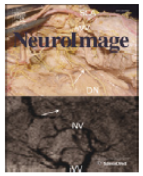

Estimation of in vivo nonspecific binding in positron emission tomography studies without requiring a reference region

R. Todd Ogden [a,b,*], Francesca Zanderigo [b], Ramin V. Parsey [c]

[a] Department of Biostatistics, Columbia University, 10032, New York, NY, USA
[b] Department of Molecular Imaging and Neuropathology, New York State Psychiatric Institute, 10032, New York, NY, USA
[c] Departments of Psychiatry and Radiology, Stony Brook University, Stony Brook, 11794, NY, USA

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Accuracy and reliability of [11C]PBR28 specific binding estimated without the use of a reference region

Pontus Plaven-Sigray[a, *], Martin Schain[b], Francesca Zanderigo[b, c], Karolinska [11C]PBR28 study groupIlan Rabiner[d], Roger Gunn[d, e], Todd Ogden[b, c, f], Simon Cervenka[a]

[a] Department of Clinical Neuroscience, Center for Psychiatry Research, Karolinska Institutet and Stockholm County Council, SE-171 76, Stockholm, Sweden
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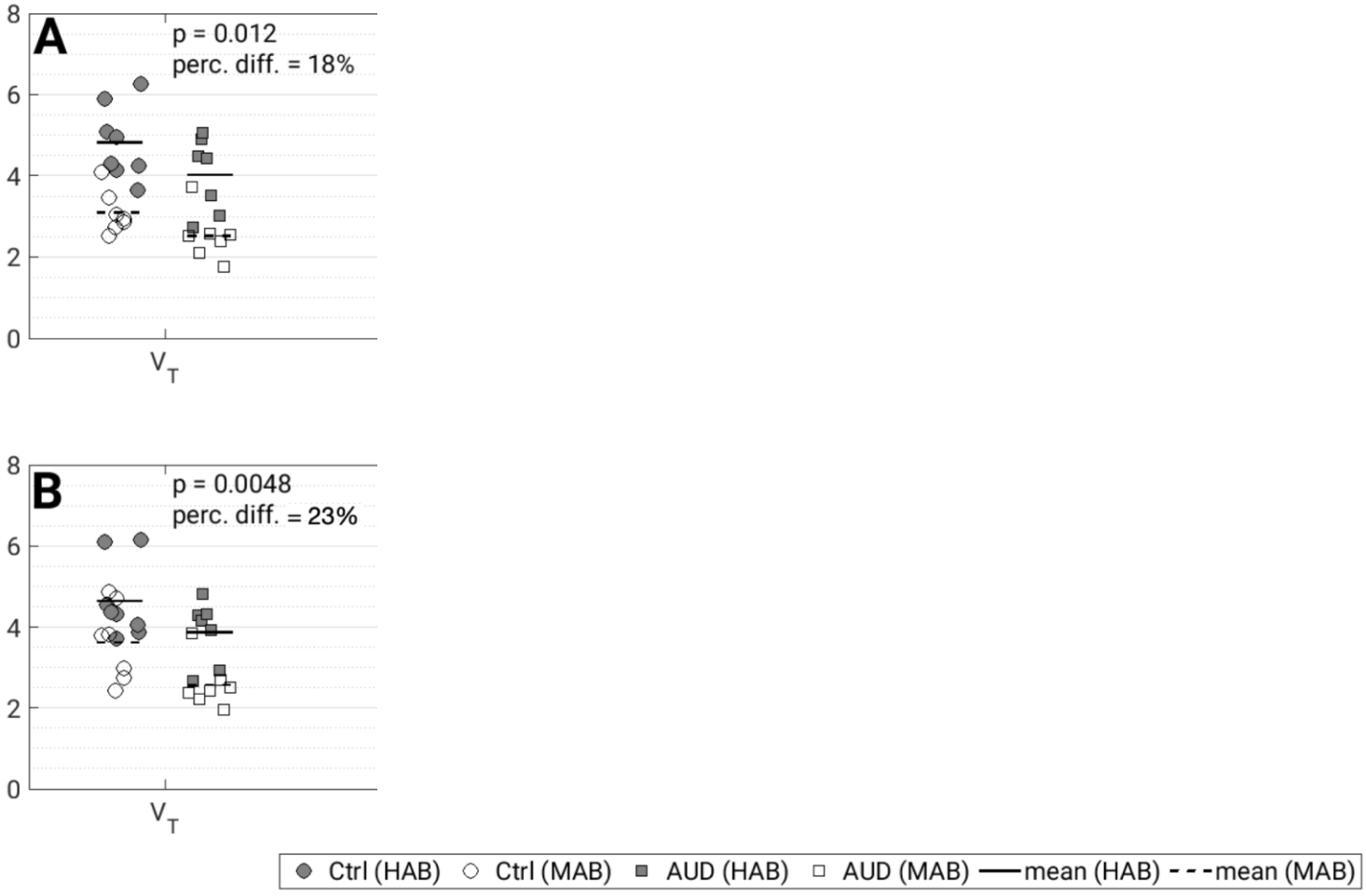
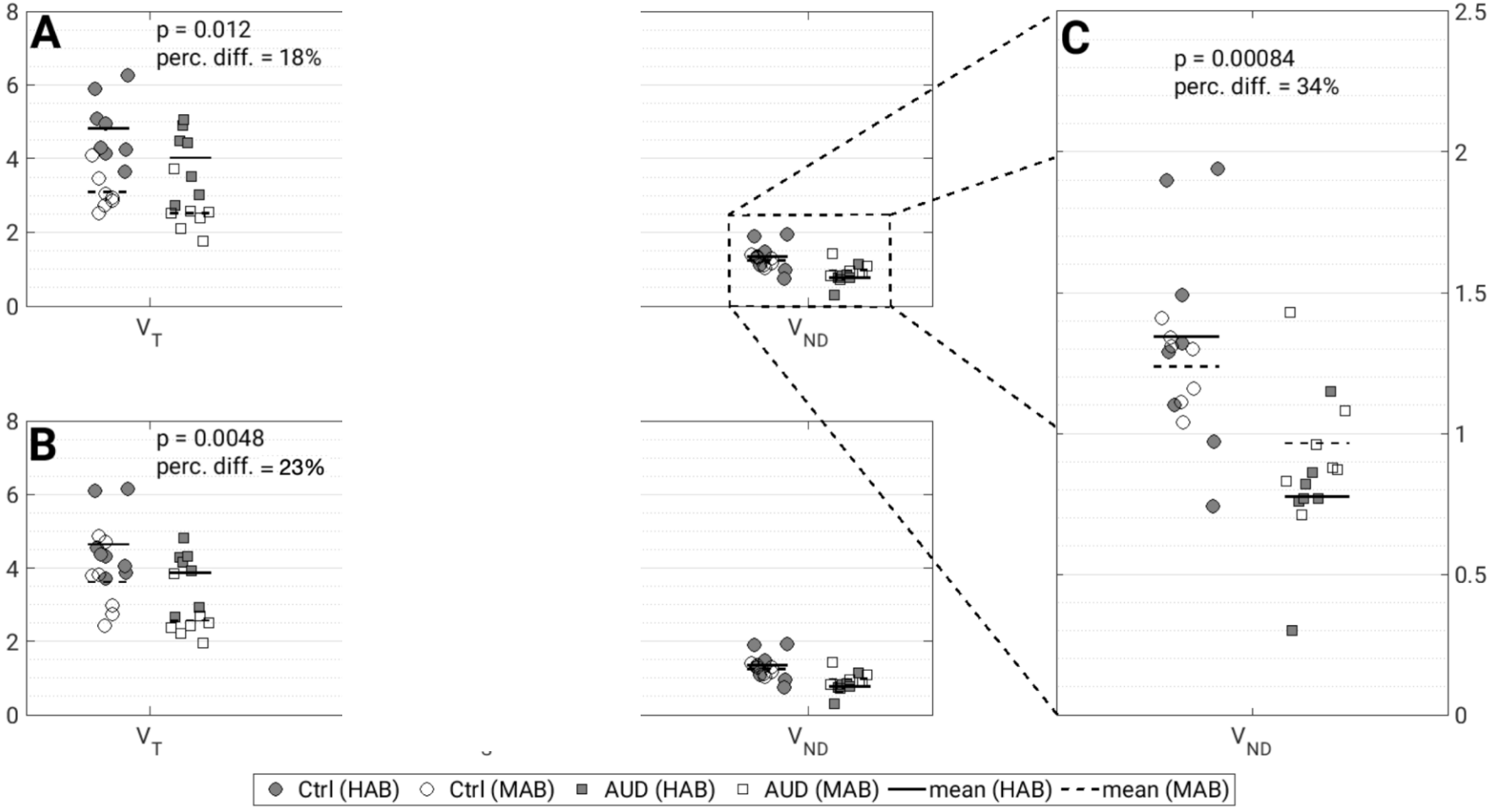
[e] Division of Brain Sciences, Imperial College London, London, UK
[f] Department of Biostatistics, Mailman School of Public Health, Columbia University, New York, USA

Example where V_{ND} may confound



Laurell et al., in Review

Example where V_{ND} may confound



Laurell et al., in Review

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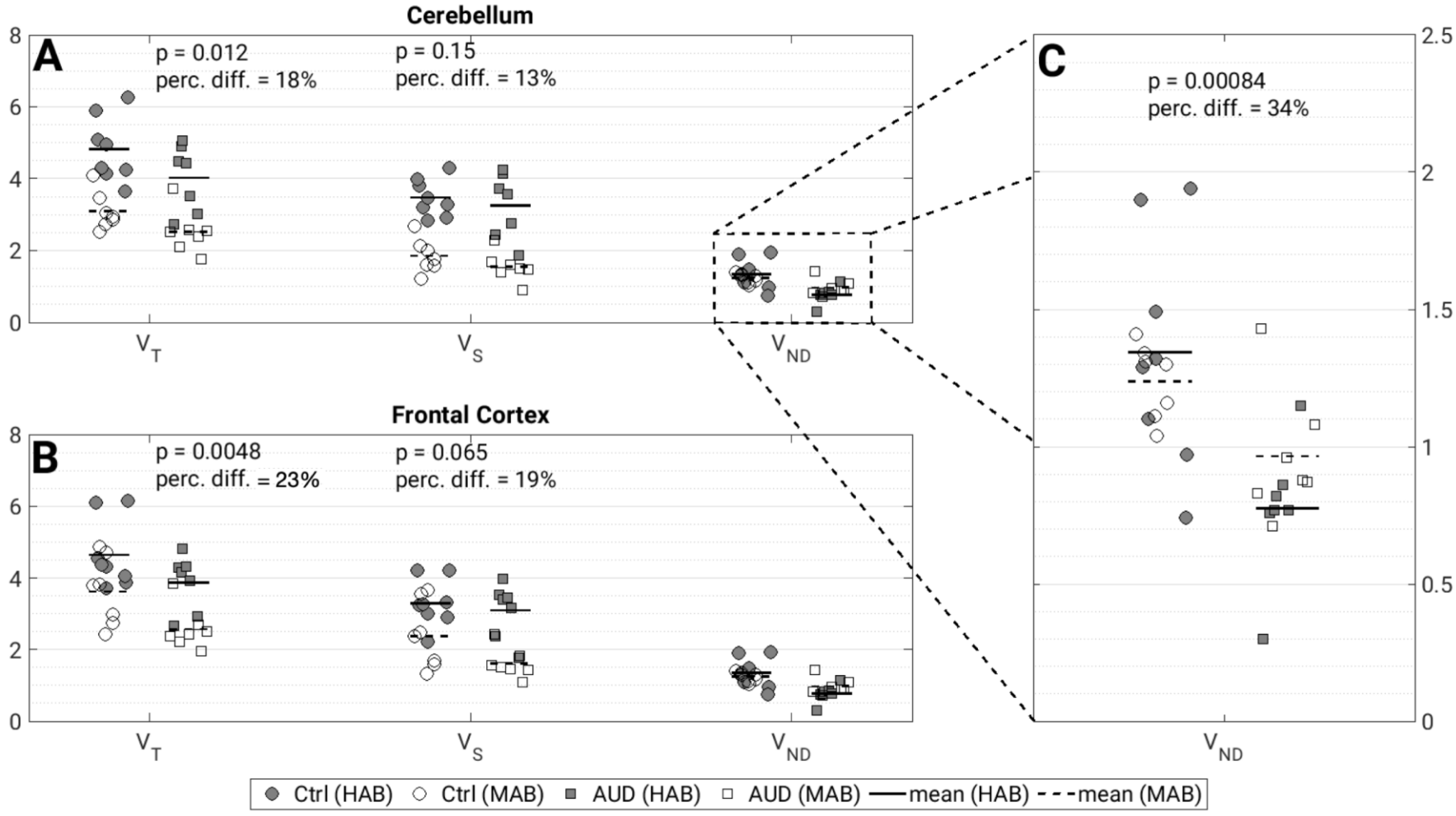

Laurell et al., in Review

Summary

- Dynamic PET data = Acquired over time → time activity curves
- Most (not all) radioligands can be described by 1TCM or 2TCM
- 1TCM and 2TCM requires arterial input functions (cumbersome measurement)
- With a TCM, non-linear regression is used to estimate rate constants, which are combined into total distribution volume (V_T)
- If a reference region exist, non-displaceable distribution volume (V_{ND}) can be estimated → estimation of BP
- BP_{ND}, BP_F and BP_P are thought to represent estimates of B_{max}. This relies on a number of assumptions.