Reference Tissue Models

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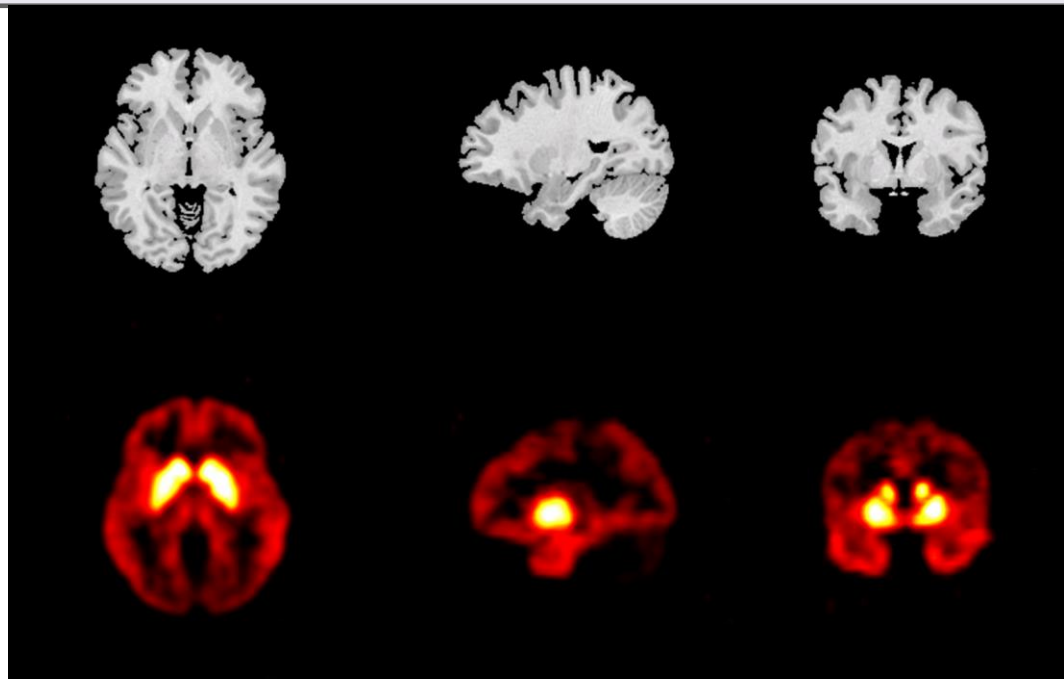

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Overview

- Outcome parameters
- Reference tissue
- Reference tissue models
- Linearisations
  - Irreversible models
  - Reversible models

Outcome parameters

- The term **distribution volume** originates from clinical pharmacology
- In PET:
  - The distribution volume $\boldsymbol{V_T}$ refer to the volume of plasma needed to account for the radioligand in a brain region when tracer is evenly distributed between brain and plasma

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    - No differentiation between specific and non-specific binding
    - Arterial plasma necessary

Binding Potentials

Binding potential quantifies the ratio of receptor density to the dissociation constant (inverse affinity); the specific type of binding potential is designated according to the chosen reference tissue concentration Innis et al., 2007, JCBFM 27: 1533-9

- Free plasma concentration: $BP_F = \frac{B_{max}}{K_D}$
- Total plasma concentration: $BP_P =$
- Non-displaceable uptake: $BP_{ND} =$

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Reference tissue models

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Advantages:

- No invasive arterial cannulation
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- Less noise from plasma measurements

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Advantages:

- No invasive arterial cannulation
- No labor-intensive measuring of radiolabeled metabolites
- Less noise from plasma measurements

Limitations:

- Only BP_{ND} can be achieved, thus not useful when non-displacable binding could be affected:
  - Biased if radiolabeled metabolites cross the blood-brain-barrier
  - Changes in tissue composition due to illness

A True Reference Region

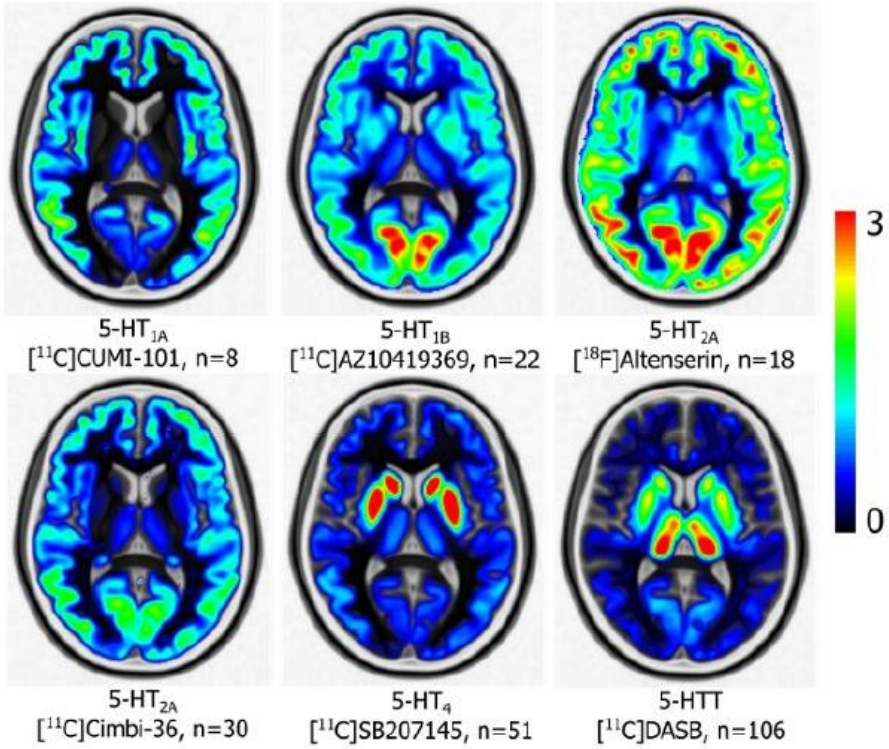


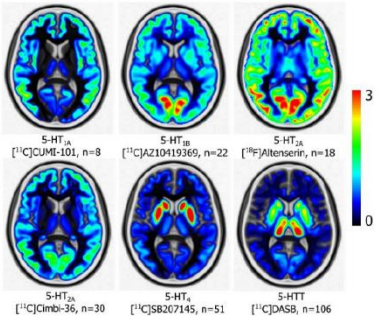
Figure 4. Average BP_{ND} and BP_P maps for all tracers mapped on to the MNI152 space (horizontal view). Color scaling is constant across images.

BP maps created using 6 different tracers that binds to serotonin receptors and the transporter

Vincent Beliveau, NRU

A True Reference Region

- Demonstrably devoid of specific binding
  - *In vitro*
  - *In vivo*
- Similar non-specific binding as the rest of the brain



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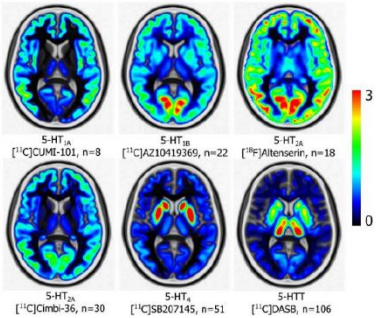

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This should be tested with a blocking study. The blocking agent should:

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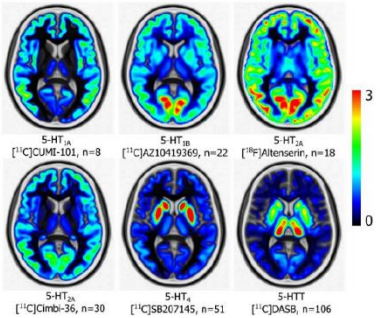
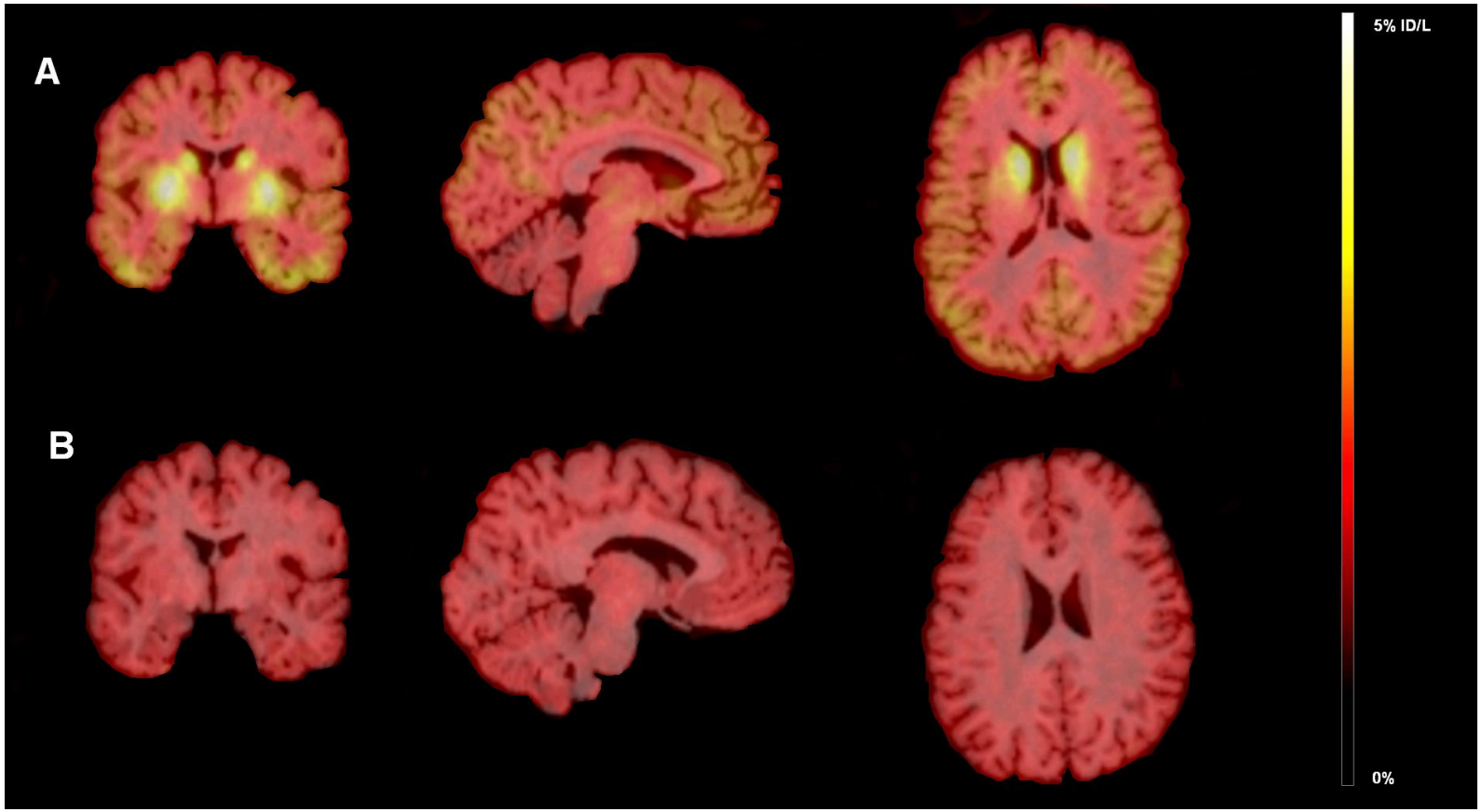


- Demonstrably devoid of specific binding
  - *In vitro*
  - *In vivo*
- Similar non-specific binding as the rest of the brain

This should be tested with a blocking study. The blocking agent should:

- Selectively bind to the same receptor with high affinity
- Be structurally dissimilar
- Non-toxic in high doses
- Cross the blood-brain-barrier

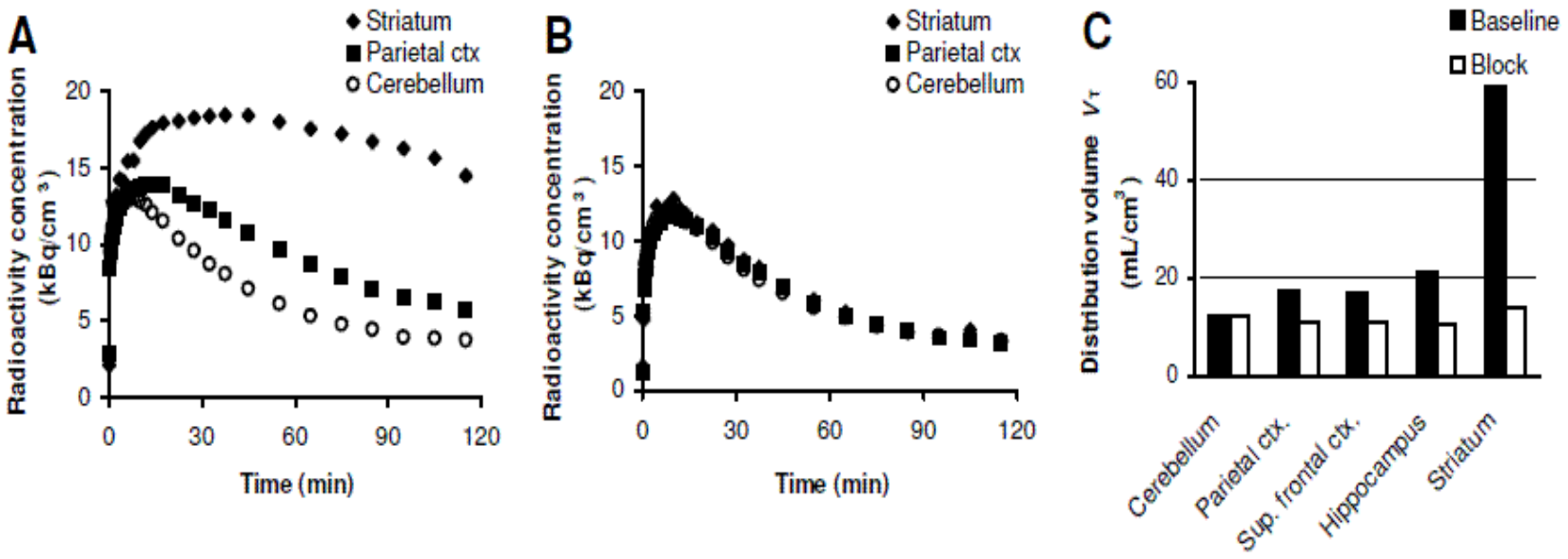
Blocking Study – part 1



Baseline (A) and a blocked (B) [^{11}C]SB207145 scan (male, 29 years) before and after oral administration of 150 mg Piboserod, an inverse agonist for 5-HT_4 (SB207266), structurally dissimilar to [^{11}C]SB207145.

(Marner et al., 2009 JNM 50(6):900-8)

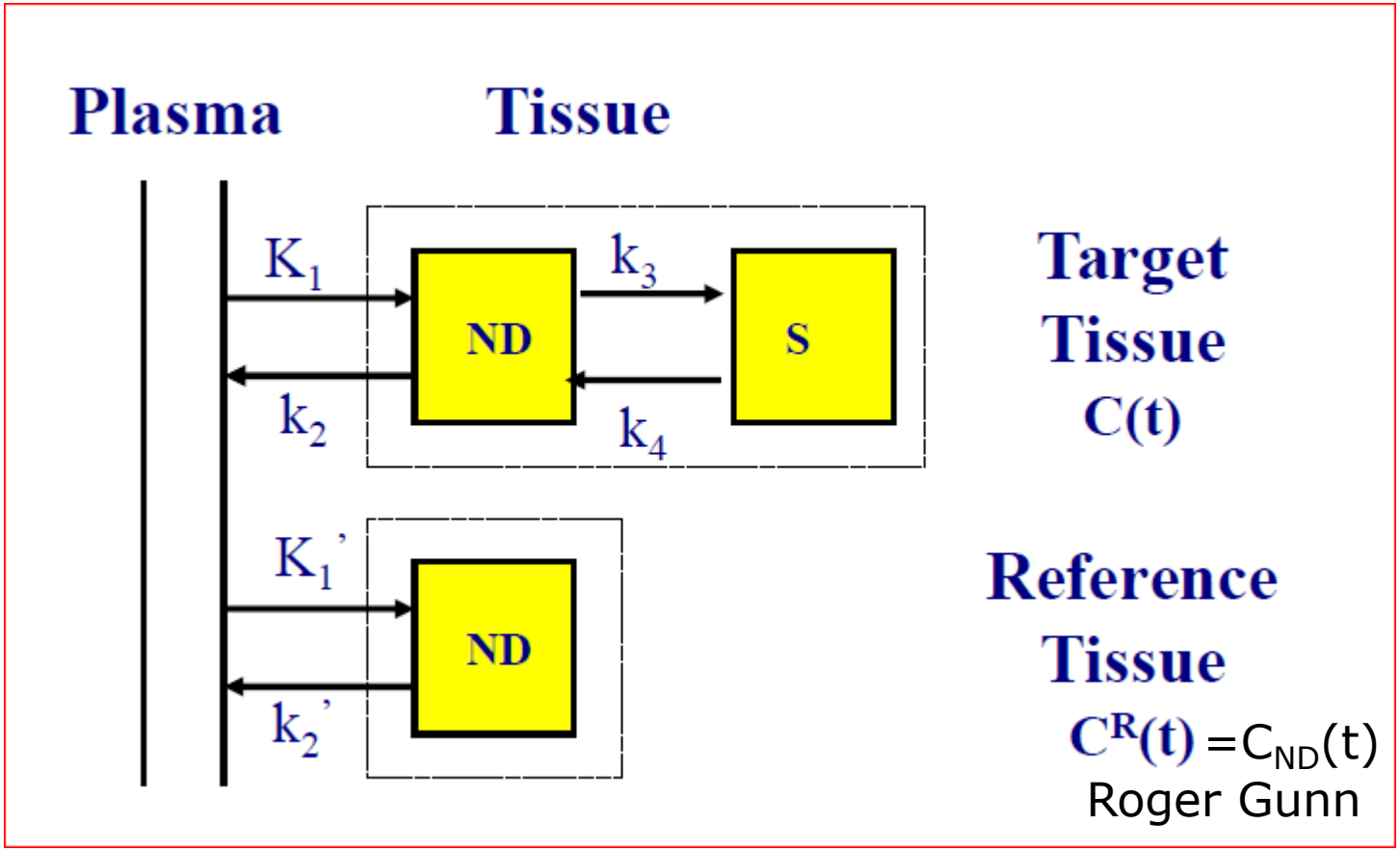
Blocking Study – part 2



Time activity curves for the baseline (A) and the blocked (B) scans. After administration of Piboserod, the [^{11}C]SB207145 distribution volumes (C) are reduced to the level of cerebellum at baseline (n=2).

(Marner et al., 2009 JNM 50(6):900-8)

Full Reference Tissue Model



Assumption: $\frac{K_1}{k_2} = \frac{K_1'}{k_2'}$ non specific binding the same

ND: Non-Displacable binding, S: Specific binding

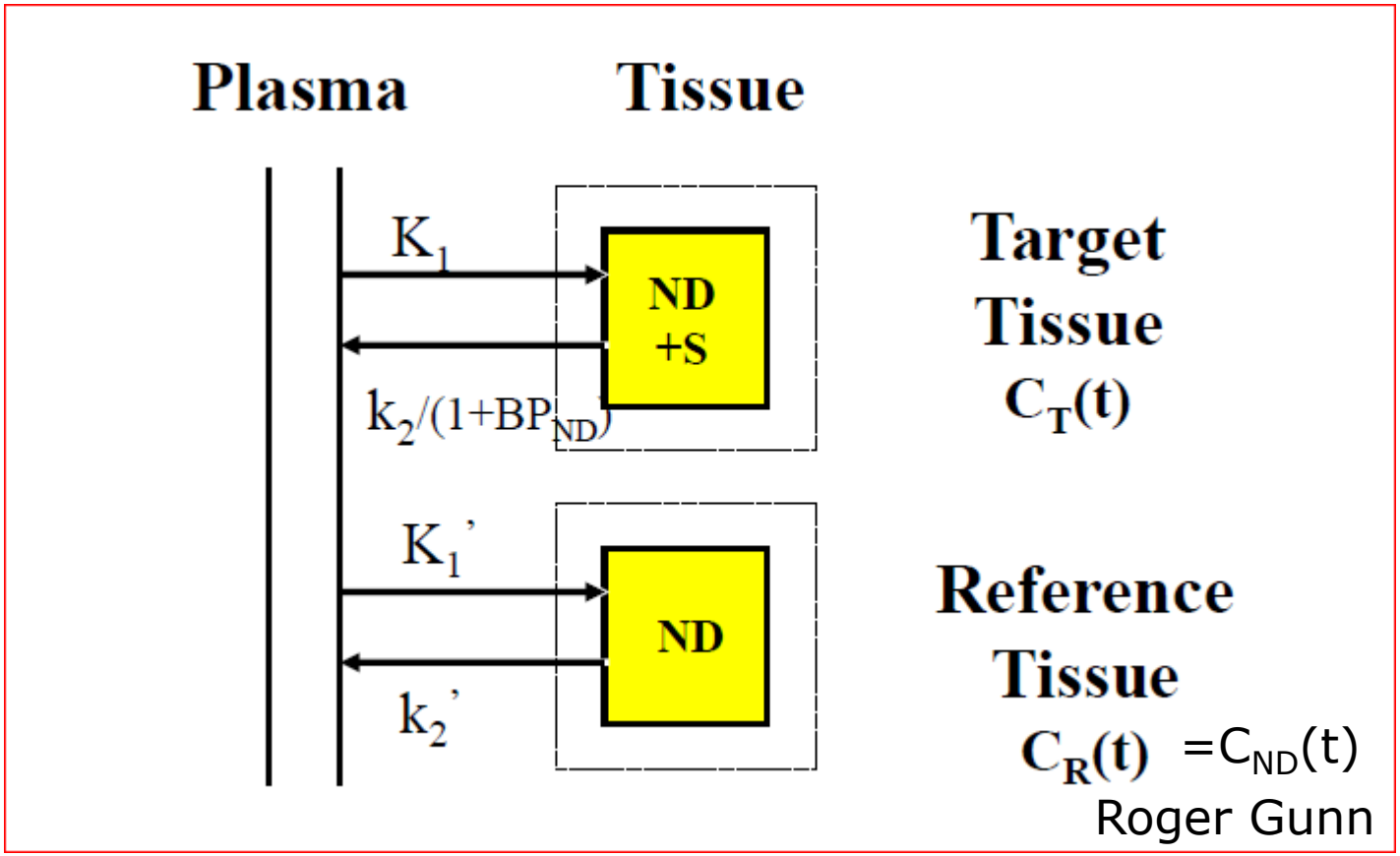
Full/Simplified Reference Tissue Model

- Full: Four parameter model (Cunningham et al., 1991, JCBFM)
  - $R_1=K_1/K_1'$, k_2, k_3, k_4
  - Slow convergence
  - Sometimes unstable

- Simplified: Three parameter model (Lammertsma and Hume, 1996, Neuroimage)
  - $R_1=K_1/K_1'$, k_2 (or k_2^{app}), BP_{ND} (k_3/k_4)
  - Assumption: ND+S equilibrate rapidly (target ROI is 1 tissue comp. kinetics)

Roger Gunn

Simplified Reference Tissue Model



Assumption: $\frac{K_1}{k_2} = \frac{K_1'}{k_2'}$ non specific binding the same

$k_2^{app} = \frac{k_2}{1 + BP_{ND}}$ rapid exchange in target tissue

Full Reference Tissue Model

- Reference tissue: $\frac{dC_{ND}(t)}{dt} = K_1' C_P(t) - k_2' C_{ND}(t)$

- Target tissue:

$$\frac{dC_{FT}(t)}{dt} = K_1 C_P(t) - k_2 C_{FT}(t) - k_3 C_{FT}(t) + k_4 C_S(t)$$

$$\frac{dC_S(t)}{dt} = k_3 C_{FT}(t) - k_4 C_S(t)$$

- $C_{FT}(t)$ is the concentration time course of free ligand in tissue water
- $C_S(t)$ is the concentration time course of specific bound ligand in tissue
- $C_{ND}(t)$ is the concentration time course in the reference region

- K_1 is the influx rate constant from plasma
- k_2 is the efflux rate constant from the tissue
- k_3 is the influx rate constant to specific bound compartment
- k_4 is the efflux rate constant from specific bound compartment
- R_1 is the ratio of the delivery in the tissue region to the reference region

- Assumption: $K_1/k_2 = K'_1/k'_2$

Roger Gunn

Simplified Reference Tissue Model

Reference tissue: $\frac{dC_{ND}(t)}{dt} = K_1' C_p(t) - k_2' C_{ND}(t)$

Target tissue: $\frac{dC_{FT}(t)}{dt} = K_1 C_p(t) - k_{2,app} C_{FT}(t)$

Solution: $C_T(t) = R_1 C_{ND}(t) + \left(k_2 - \frac{R_1 k_2}{1 + BP_{ND}}\right) C_{ND}(t) \otimes e^{\frac{-k_2}{1+BP_{ND}}t}$

Where: $R_1 = K_1/K_1', BP_{ND} = k_3/k_4, k_{2,app} = k_2/(1 + BP_{ND})$

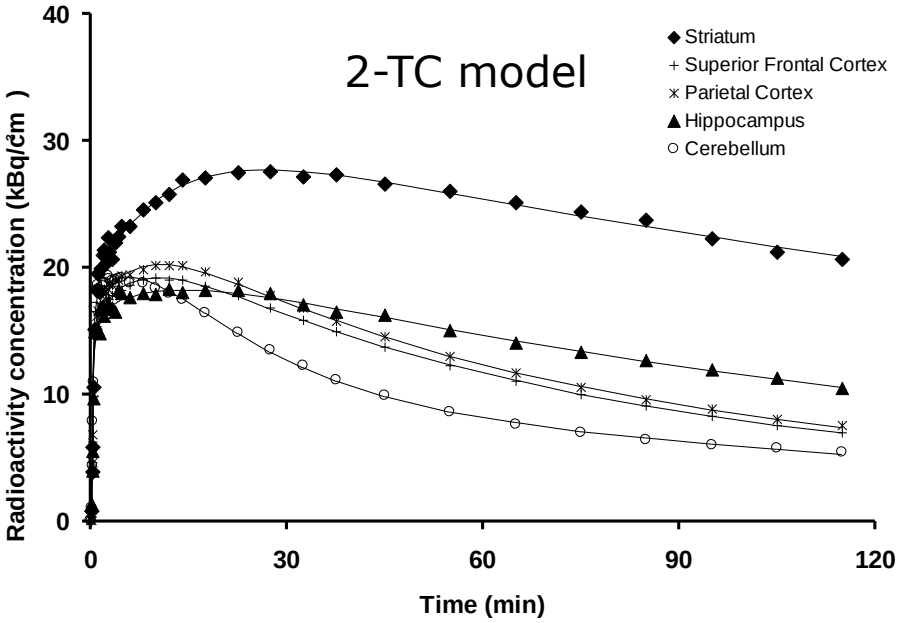
- $C_{FT}(t)$ is the concentration time course in the tissue (region of interest)
- $C_{ND}(t)$ is the concentration time course in the reference region

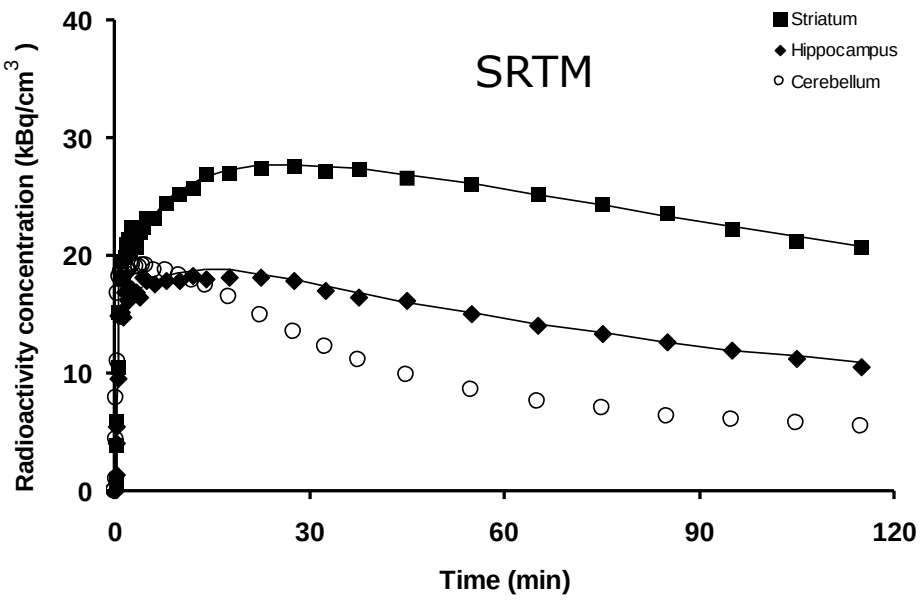
- k_2 is the efflux rate constant from the tissue
- R_1 is the ratio of the delivery in the tissue region to the reference region (K_1/K'_1)
- BP_{ND} is the binding potential

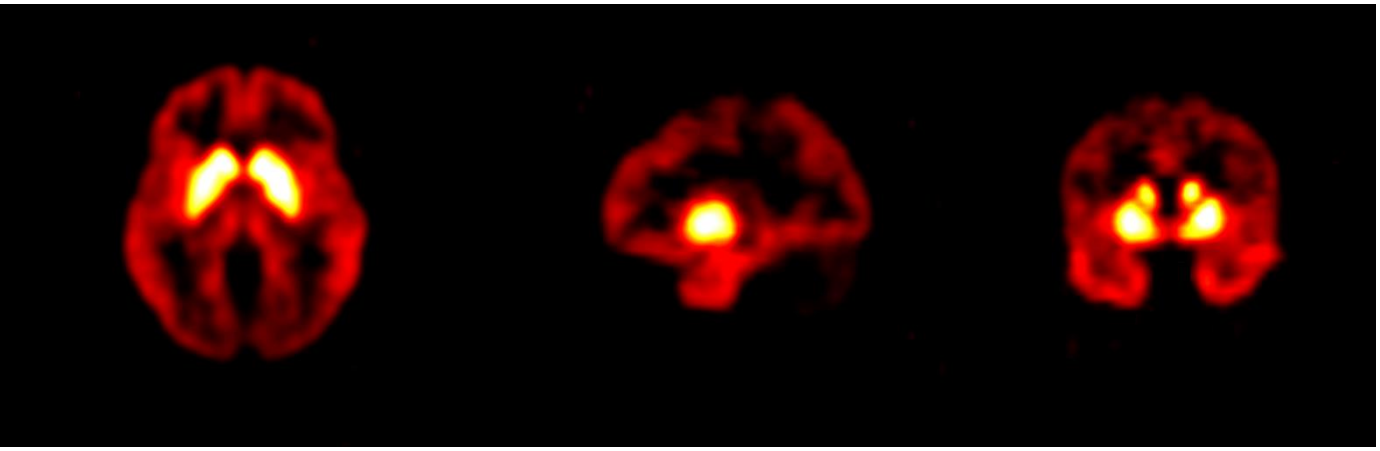
- Assumption: $K_1/k_2 = K'_1/k'_2$

Roger Gunn

Example: [^{11}C]SB207145 imaging 5-HT$_4$ receptors







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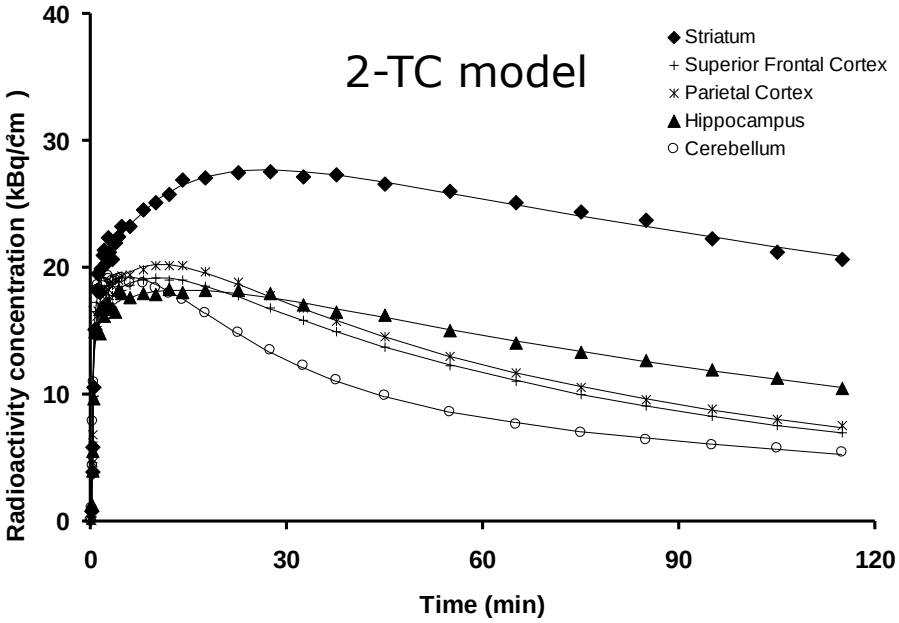

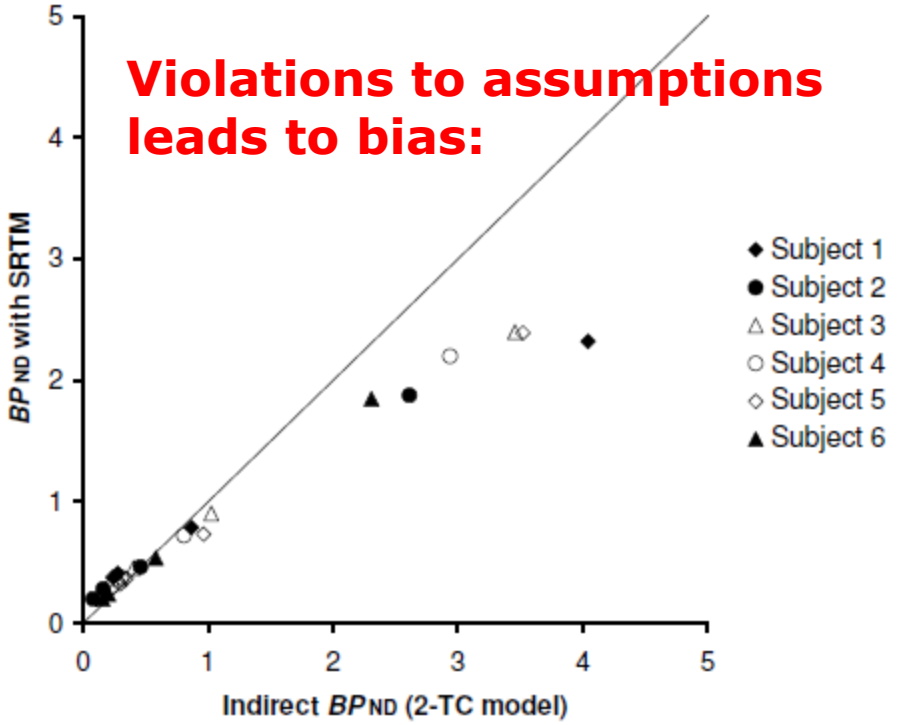

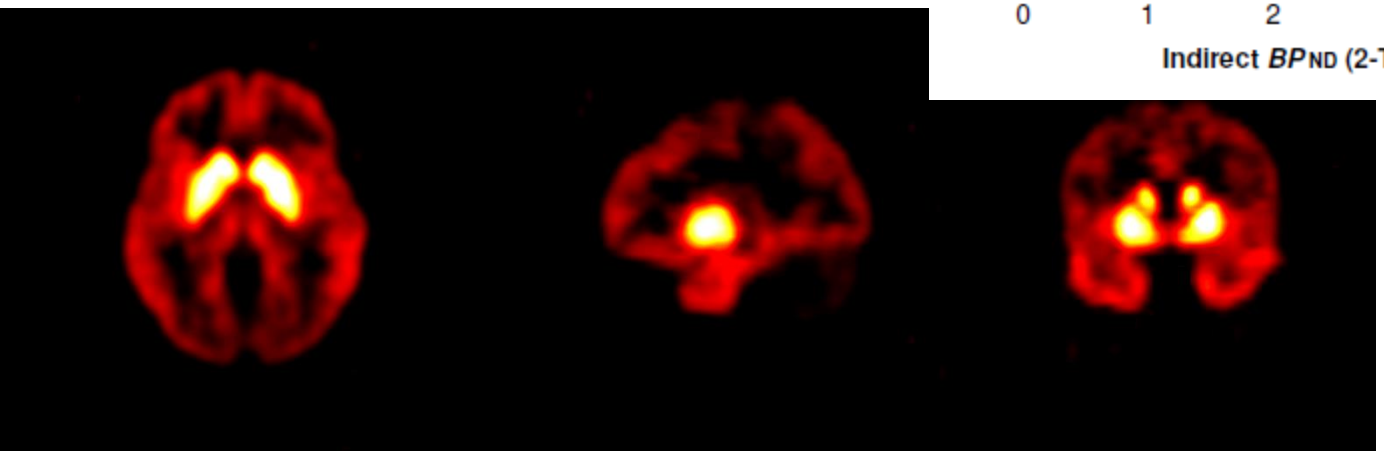

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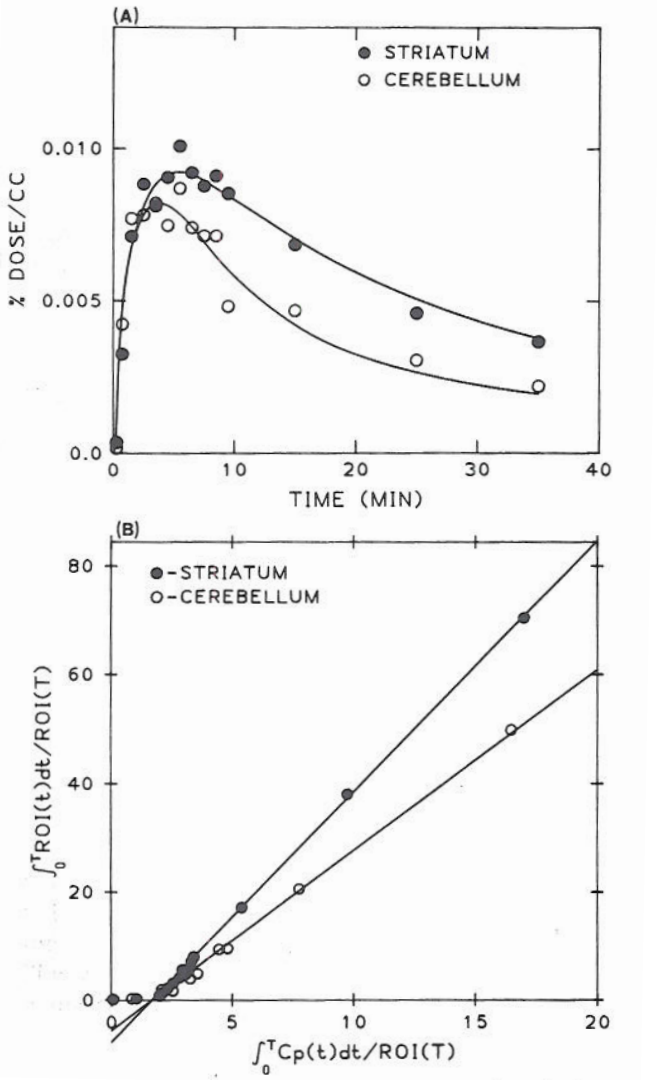
Logan plot



Graphical analysis of reversible radioligand binding:

- At time t^*, the **integrated tissue** activity divided by the tissue activity **as a function of** the **integrated plasma** activity divided by the tissue activity becomes linear with the slope $1+BP_P$
- Plasma input can be substituted with the reference tissue input function

(Logan et al.,1990, JCBFM 10:740-7)

Linearized (Reference) Models

In comparison to Simplified Reference Tissue Model

- Advantage:
  - Fast linear calculation especially important for parametric images
- Limitation:
  - Dependence on choosing a proper t^*
  - Noise-induced bias due to $C_T(T)$ on both sides of the equation
    - Overcome by the derivations by Ichise, of the MRTM and the MRTM2 with fixed k_2'

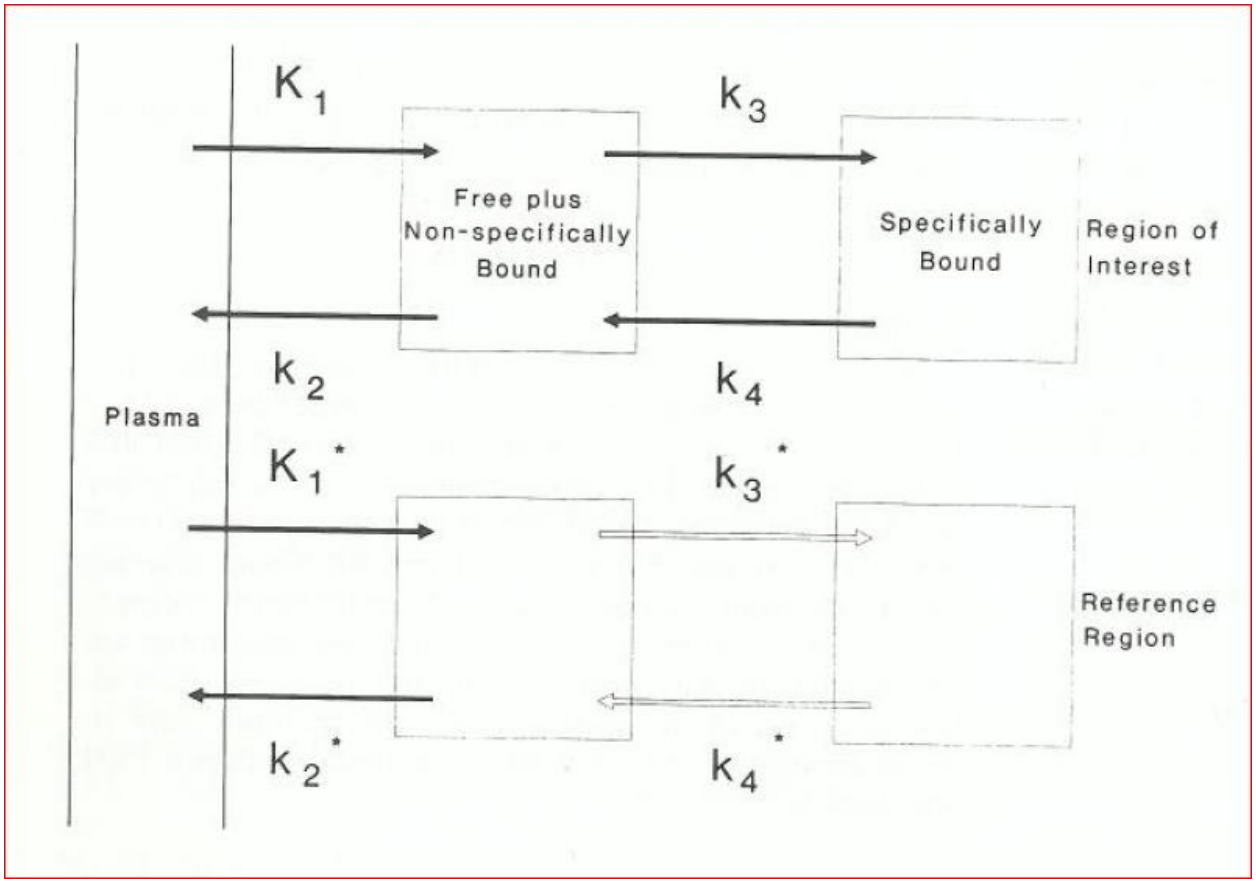
SRTM has by Roger Gunn been implemented as linear fitting using a library of basic functions (basic pursuit functions), which also makes SRTM fast!

Overview of linearized models

- Irreversible models
  - Patlak model (require arterial samples)
- Reversible models
  - Logan model (require arterial samples)
  - Logan reference model
  - Multilinear Reference tissue model (MRTM)

Model of receptor binding

$C_p(t)$ $C_T(t)$



$C_{ND}(t)$

Cunningham et al., 1991, JCBFM

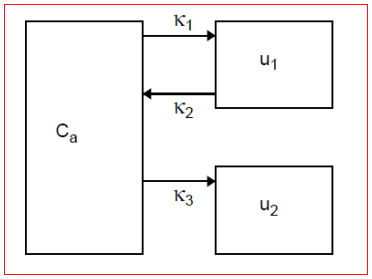
Patlak plot (irreversible models, k_4=0)

From page 45-48 in the Pharmacokinetic book (Blomquist):

- The solution to a two-tissue compartment model (FDG, K_4=0) is:

$$C_T = \frac{K_1}{k_2 + k_3}\left(k_2 e^{-(k_2+k_3)t} + k_3\right) \otimes C_P$$

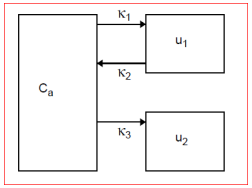
- From this analytic solution a two tissue compartment model can be written with the following rate constants:



$$\kappa_1 = \frac{K_1 k_2}{k_2 + k_3}, \quad \kappa_2 = k_2 + k_3 \quad and \quad \kappa_3 = \frac{K_1 k_3}{k_2 + k_3}$$

Patlak plot (irreversible models, k_4=0)

- This can be written as the two differential equations:



$$\frac{du_1}{dt} = \kappa_1 C_P - \kappa_2 u_1 \quad and \quad \frac{du_2}{dt} = \kappa_3 C_P$$

- Linearization of this leads to the following equations:

$$u_1 = \kappa_1 \int_0^t C_P \, d\tau - \kappa_2 \int_0^t u_1 \, d\tau$$

$$u_2 = \kappa_3 \int_0^t C_P \, d\tau$$

- The measured signal from the brain scanner is:

$$C_T = u_1 + u_2$$

Patlak plot (irreversible models, $k_4=0$)

- From the late time points (stable) where $\frac{du_1}{dt}$ can be assumed to be close to zero, we get the following approximation (Patlak-Gjedde):

$$0 = \kappa_1 C_p - \kappa_2 u_1 \rightarrow u_1 = \frac{\kappa_1}{\kappa_2} C_P$$

- and therefore by substituting:

$$C_T = \frac{\kappa_1}{\kappa_2} C_P + \kappa_3 \int_0^t C_P \, d\tau$$

- which by dividing by C_P gives (Patlak plot):

$$\frac{C_T}{C_P} = \frac{\kappa_1}{\kappa_2} + \kappa_3 \frac{\int_0^t C_P \, d\tau}{C_P}$$

Patlak plot (irreversible models, k_4=0)

- From the fitted line we therefore have:
  - The metabolic rate $K_i = \frac{K_1 k_3}{k_2 + k_3}$ is therefore the same as the slope κ_3
  - The distribution volume $V_T = \frac{K_1 k_2}{(k_2 + k_3)^2}$ is therefore the same as the intercept κ_1/κ_2

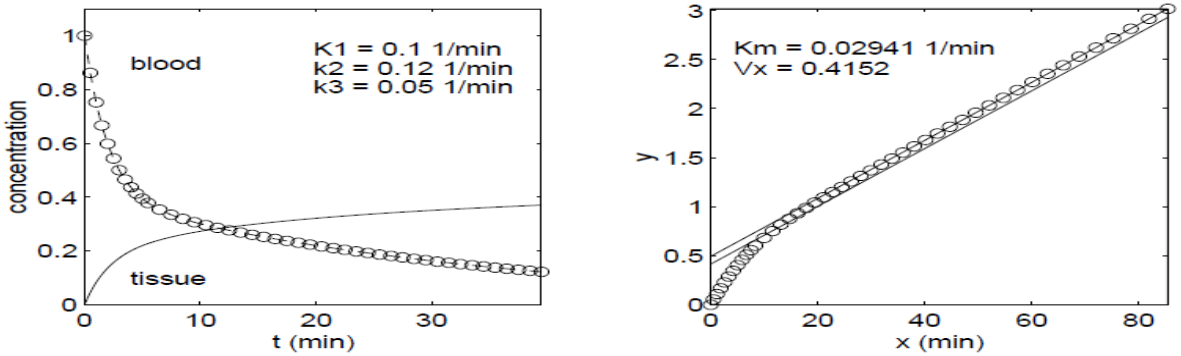


Figure 6-3. Time activity curves (left) and Patlak-plot (right). In the Patlak-plot two straight lines are indicated. The first one results from a least squares fit to the linear portion of the data points. The second one is the straight line expected from Eq. (6.16). The shift of the data points relative to the theoretically expected behaviour is explained by the rather rapid variations of c_a during the late phase.

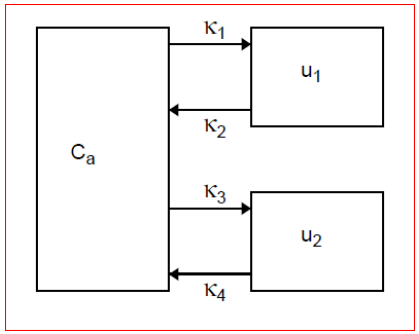
$K_m = K_i$

$V_x = V_T$

Pharmacokinetic book, p 48

Logan plot (reversible model)

- From page 49-50 in the Pharmacokinetic book:
- For a decoupled two-tissue compartment model:



$$\frac{du_1}{dt} = C_P\kappa_1 - u_1\kappa_2 \text{ and } \frac{du_2}{dt} = C_P\kappa_3 - u_2\kappa_4$$

$$C_T = u_1 + u_2 = \kappa_1 e^{-\kappa_2 t} + \kappa_3 e^{-\kappa_4 t}$$
$$C_a = C_P$$

- If k_4 is large (reversible system) the decoupled constants can be approximated as:

$$\kappa_1 = K_1, \kappa_2 = \frac{k_2 k_4}{k_2 + k_3 + k_4}$$

$$\kappa_4 = (k_2 + k_3 + k_4) - \kappa_2$$

- In the case with a high k_4 the concentration in u_2 approaches zero, and the total system response is approximately coming from u_1

Logan plot (reversible model)

- The system can therefore be approximated by:

$$\frac{dC_T}{dt} = \kappa_1 C_P - \kappa_2 C_T$$

- And in this case the distribution volume can be calculated as (k_4 assumed to be much larger than k_2):

$$V_T = \frac{\kappa_1}{\kappa_2} \approx \frac{K_1}{k_2}\frac{k_3 + k_4}{k_4}$$

- Linearization in the Logan approximation therefore gives:

$$C_T = \kappa_1 \int_0^t C_P d\tau - \kappa_2 \int_0^t C_T d\tau$$

$$\frac{\int_0^t C_T\, d\tau}{C_T} = -\frac{1}{\kappa_2} + V_T \frac{\int_0^t C_P\, d\tau}{C_T}$$

- The slope of the fitted line therefore describe the distribution volume, V_T.

Logan plot (reversible model)

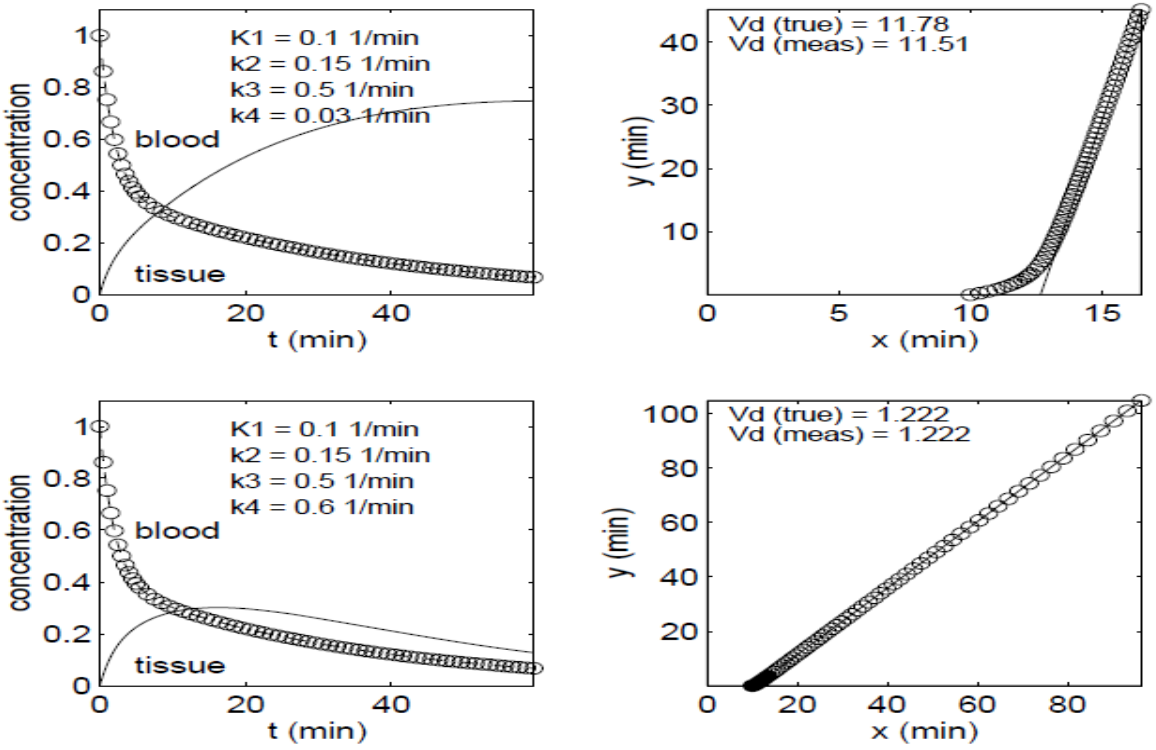


Figure 6-5. Logan plot for small k_4 (upper graph) and large k_4 (lower graph).

$$x = \frac{\int_0^t C_P \, d\tau}{C_T}$$

$$y = \frac{\int_0^t C_T \, d\tau}{C_T}$$

$$V_d = V_T$$

Pharmacokinetic book, p 51

Logan reference plot (reversible model)

- The linearized equation for the Logan model with plasma input is:

$$\frac{\int_0^T C_T(t)dt}{C_T(t)} = DV\frac{\int_0^T C_p(t)dt}{C_T(t)} + b$$

$$\text{with } DV = 1 + BP_P \qquad DV = V_T$$

- With a reference region we have:

$$\frac{dC_{ND}(t)}{dt} = K_1^{'}C_p(t) - k_2^{'}C_{ND}(t)$$

$$\int_0^T C_p(t)dt = \frac{1}{\lambda}\left[\int_0^T C_{ND}(t)dt + \frac{C_{ND}(t)}{k_2^{'}}\right]$$

$$\text{with } \lambda = K_1^{'}/k_2^{'}$$

- And substituting this into the first equations we get:

$$\frac{\int_0^T C_T(t)dt}{C_T(t)} = DVR\frac{\int_0^T C_{ND}(t)dt + \frac{C_{ND}(t)}{k_2^{'}}}{C_T(t)} + b$$

$$\text{with } DVR = DV/\lambda \qquad DVR = \frac{V_T}{V_T'}$$

- Estimation of k'_2 has to come from another method, or a population based value

Logan et al., 1996, JCBFM 16(5):834-40

Logan reference plot (reversible model)

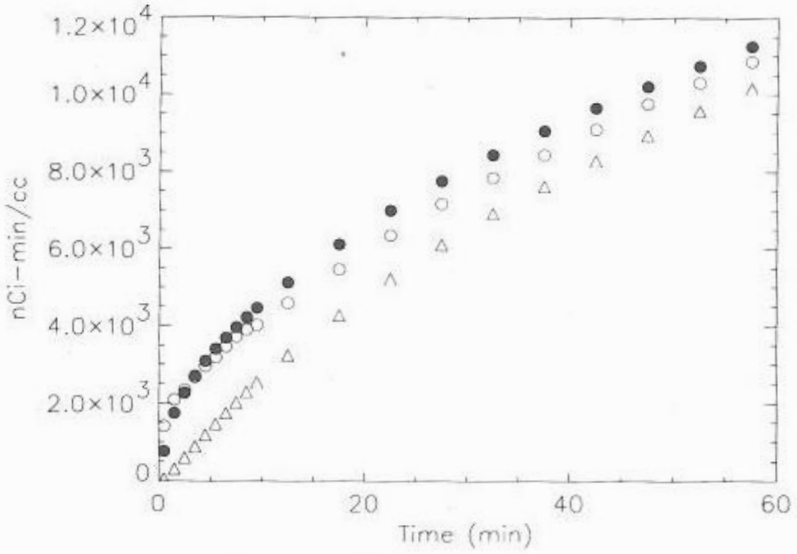


FIG. 1. Comparison of $\int_0^T C_p(t)dt$ (filled circles), $(1/\lambda)[\int_0^T CB(t)dt + CB(T)/\bar{k}_2]$ (open circles), and $(1/\lambda)\int_0^T CB(t)dt$ (triangles) for raclopride ($\lambda = 0.418$ was determined graphically using the measured plasma input function).

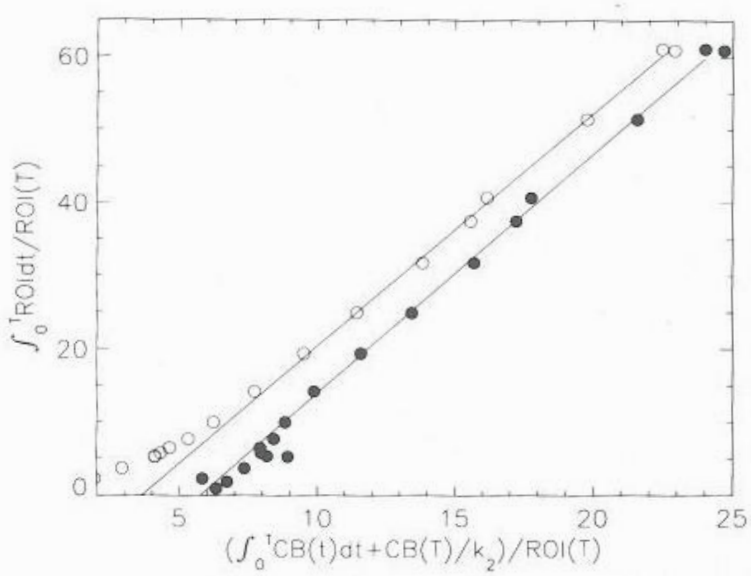


FIG. 3. Comparison of DVR for BG/CB of a [^{11}C]raclopride study, $\bar{k}_2 = 0.163$ (filled circles, DVR = 3.24), and DVR calculated using Eq. 7 so that $CB(T)/\bar{k}_2$ was not included (open circles, DVR = 3.17). For comparison, DVR with plasma is 3.25. See text for abbreviations.

Logan et al., 1996, JCBFM 16(5):834-40

Multilinear reference tissue models

From Ichise et al., 1996, JCBFM:

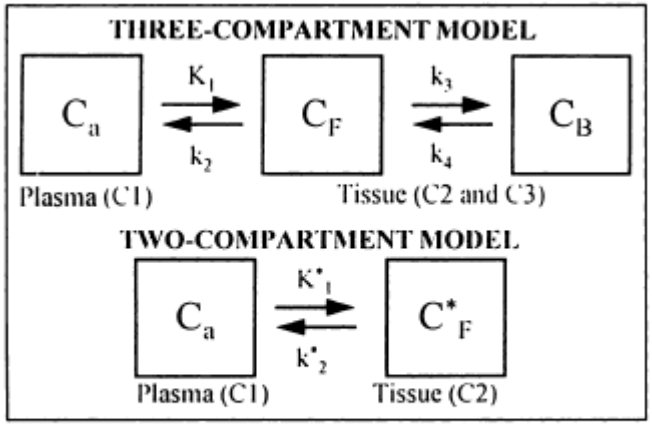


FIGURE 1. Three- and two-compartment models used to describe IBF kinetics. C_a = arterial plasma concentration; C_F, C^*_F = free tissue concentration in the basal ganglia and the frontal cortex, respectively; C_B = specifically bound tissue concentration in the basal ganglia.

Linearization of both tissue and ref tissue models separately:

$$\frac{\int_0^t C_{BG}(t)dt}{C_{BG}(t)} = a\frac{\int_0^t fC_a(t)dt}{C_{BG}(t)} + b, \qquad \text{Eq. 5}$$

$$\frac{\int_0^t C_{FC}(t)dt}{C_{FC}(t)} = a'\frac{\int_0^t fC_a(t)dt}{C_{FC}(t)} + b', \qquad \text{Eq. 6}$$

Slope $a=V_T$
$C_a=C_P$
$C_{BG}=C_T$
$C_{FC}=C_{ND}$

Linear Model Summary (slides from Ichise)

$MRTM_O$

Ichise et al., 1996, JCBFM

$$\frac{\int_0^t C_T(t)dt}{C_T(t)} = \frac{V_T}{V_T'}\frac{\int_0^t C_T'(t)dt}{C_T(t)} + \frac{V_T}{V_T'k_2'}\frac{C_T'(t)}{C_T(t)} + b$$

$$BP_{ND} = \frac{V_T}{V_T'} - 1 = \gamma_1 - 1$$

1T tracers: $t > 0$
2T tracers: $t > t^*$

MRTM

Ichise et al., 2002, JCBFM

- Improvement to noise:
  - C_T is no longer present in independent variables
  - Correlation between noise in dependent and independent variables reduced

$$C(T) = -\frac{V}{V'b}\int_0^T C'(t)dt + \frac{1}{b}\int_0^T C(t)dt - \frac{V}{V'k_2'b}C'(T)$$

$$BP_{ND} = -(\gamma_1/\gamma_2 + 1)$$

2T tracers: $t > t^*$

$$C(T) = R_1k_2'\int_0^T C'(t)dt - k_2\int_0^T C(t)dt + R_1C'(T)$$

$$BP_{ND} = -(\gamma_1/\gamma_2 + 1) \qquad R_1 = \gamma_3 \qquad k_2' = \gamma_1/\gamma_3$$

1T tracers: $t > 0$

γ's: regression coefficients

Linear Model Summary (slides from Ichise)

MRTM2

Ichise et al., 2003, JCBFM

In MRTM k'_2 is estimated independtly for each voxel, but there is only one reference region, so to take care of that it could be fixed to a common value and the equations reduces to:

$$C(T) = -\frac{V}{V'b}\left(\int_0^T C'(t)dt + \frac{1}{k'_2}C'(T)\right) + \frac{1}{b}\int_0^T C(t)dt$$

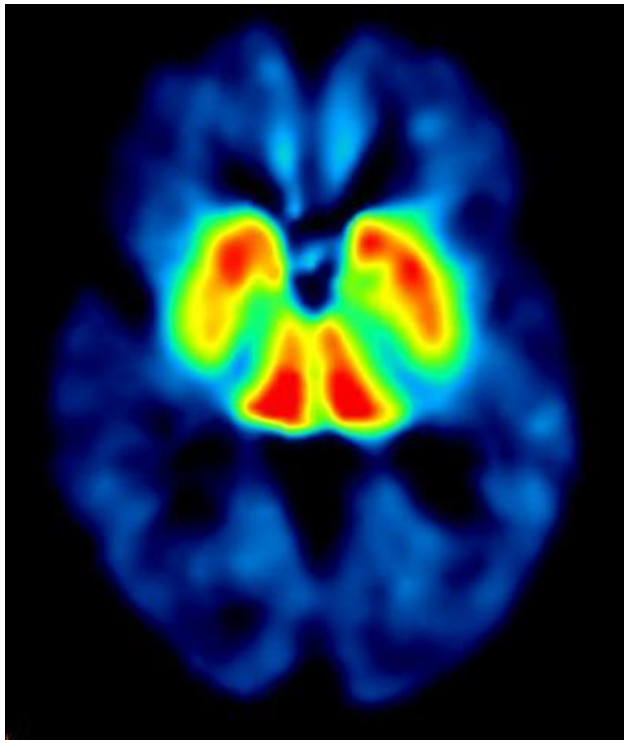
$$BP_{ND} = -(\gamma_1 / \gamma_2 + 1)$$

2T tracers: $t > t^*$

$$C_T(T) = R_1\left(k_2'\int_0^T C'_T(t)dt + C'_T(T)\right) - k_2\int_0^T C_T(T)dt$$

$$BP_{ND} = -(\gamma_1 / \gamma_2 + 1) \qquad R_1 = \gamma_1$$

1T tracers: $t > 0$



Parametric image of the serotonin transporter using [^{11}C]DASB

γ's: regression coefficients