Analysis of quantitative PET neuroreceptor studies

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Lecture at the Imanet Academy Course

"PET in Drug Development"

13 October 2004
Uppsala, Sweden

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Contents

1. Introduction: examples of brain PET ligands

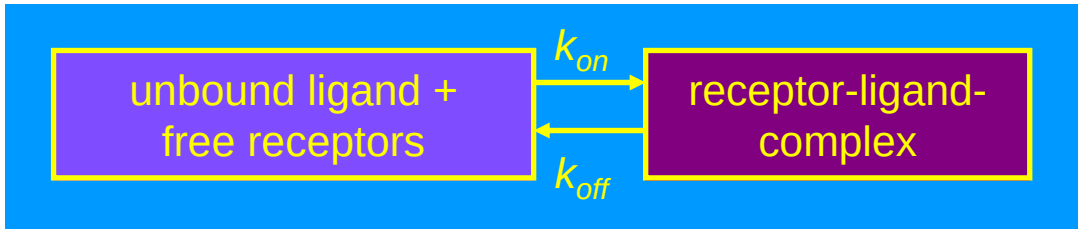
Name:	*Target(s):*
[^{11}C]SCH23390	*dopamine D_1 receptors*
[^{11}C]raclopride	*striatal dopamine D_2/D_3 receptors*
[^{11}C]FLB 457	*extrastriatal dopamine D_2/D_3 receptors*
[^{18}F]fallypride	*striatal and extrastriatal D_2/D_3 receptors*
[^{11}C]flumazenil	*GABA receptors*
[^{11}C]Ro5-4864, [^{11}C]PK11195	*peripheral benzodiazepine binding site*
[^{11}C]carfentanil, [^{11}C]diprenorphine, [^{18}F]cyclofoxy	*opiate receptors*
[^{11}C]WAY-100635, [^{18}F]FPWAY, [^{11}C]DWAY	*serotonin 5-HT_{1A} receptors*
[^{18}F]setoperone, [^{18}F]altanserin, [^{11}C]MDL 100,907	*serotonin 5-HT_{2A} receptors*
[^{11}C](+)McN5652, [^{11}C]DASB	*serotonin 5-HT transporter*
[^{18}F]SPA-RQ, [^{11}C]GR205171 (example)	*neurokinin NK_1 receptors*

and many more ...

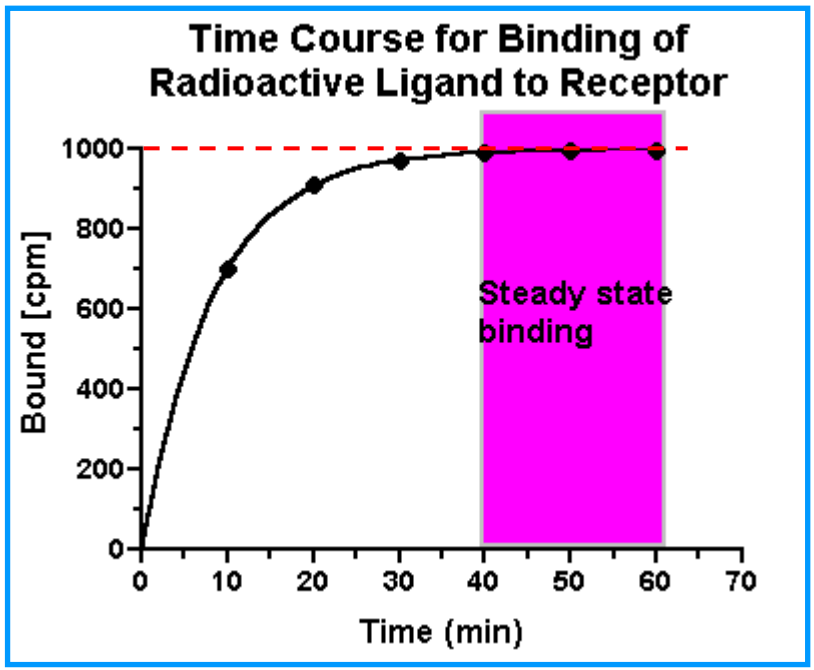
What is the basic methodology of these studies?

1. Introduction: receptor autoradiography

Reversible binding of a ligand to a receptor (in vitro binding assay):



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



law of mass action:

$$\frac{d\,[RL]}{d\,t} = k_{on} \cdot [L] \cdot [R] - k_{off} \cdot [RL]$$

dissociation constant: $K_D = \frac{k_{off}}{k_{on}}$

maximum binding capacity (total number of receptors): $B_{max} = [R] + [RL]$

$$\frac{d\,[RL]}{d\,t} = k_{on} \cdot [L] \cdot (B_{max} - [RL]) - k_{off} \cdot [RL]$$

in PET: k_3 in PET: k_4

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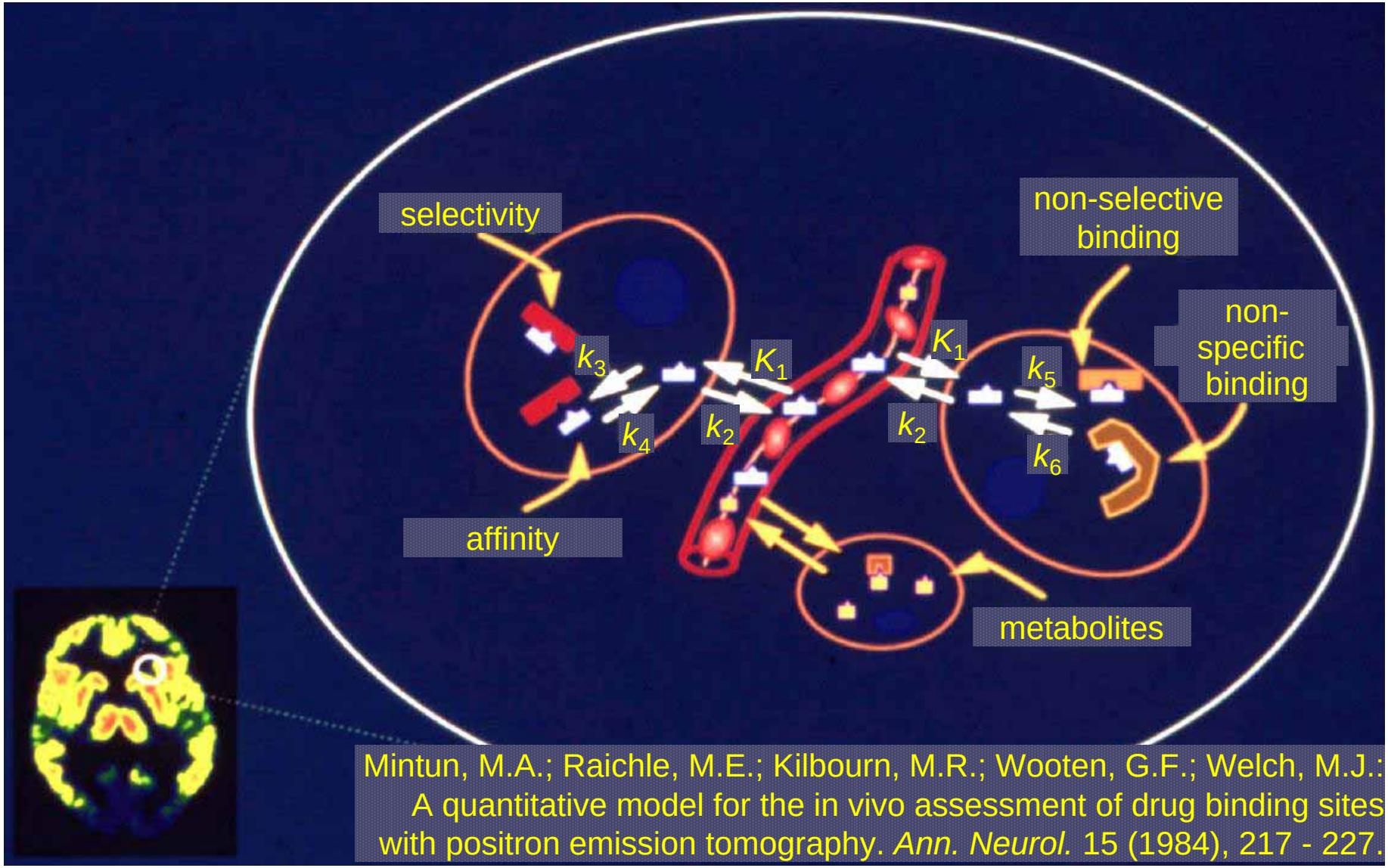
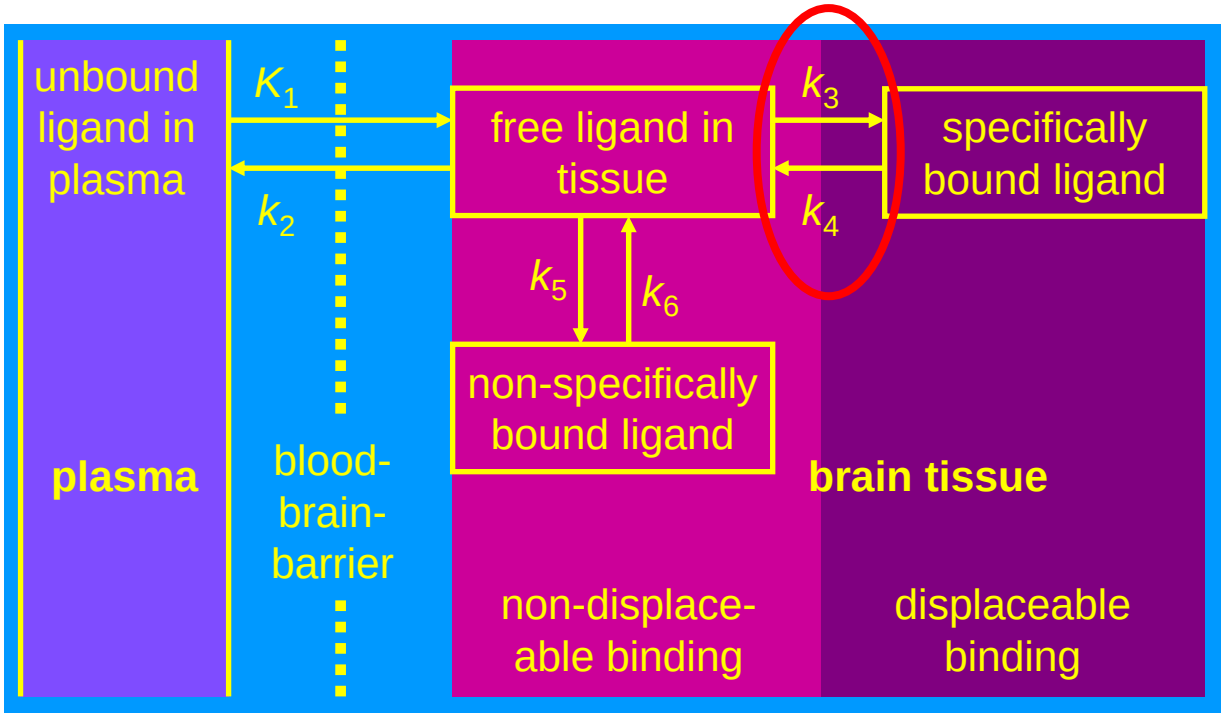
2. The standard model for receptor studies with PET



Mintun, M.A.; Raichle, M.E.; Kilbourn, M.R.; Wooten, G.F.; Welch, M.J.: A quantitative model for the in vivo assessment of drug binding sites with positron emission tomography. *Ann. Neurol.* 15 (1984), 217 - 227.

2. The standard model for receptor studies with PET



binding potential:

$$BP = \frac{B_{max} - [RL]}{K_D} = \frac{k_3}{k_4}$$

volume of distribution:

$$VD_F = \frac{K_1}{k_2}$$

$$VD_{F+NS} = \frac{K_1}{k_2} \cdot \left(1 + \frac{k_5}{k_6} \right)$$

$$VD_{tot} = \frac{K_1}{k_2} \cdot \left(1 + \frac{k_3}{k_4} + \frac{k_5}{k_6} \right)$$

$$VD_{tot} = VD_{F+NS} \cdot (1 + f_2 \cdot BP)$$

free fraction in plasma: f_1

free fraction in brain tissue: $f_2 = \frac{1}{1 + \frac{k_5}{k_6}}$

at thermodynamic equilibrium: $\frac{f_1}{f_2} = \frac{K_1}{k_2}$

influx rate constant: $K_1 = F \cdot E$

blood flow F

extraction $E = 1 - e^{-\frac{PS}{F}}$

product of permeability and capillary surface area PS

rate constants: $k_2 \ldots k_6$

$$f_2 \cdot BP = \frac{VD_{tot}}{VD_{F+NS}} - 1$$

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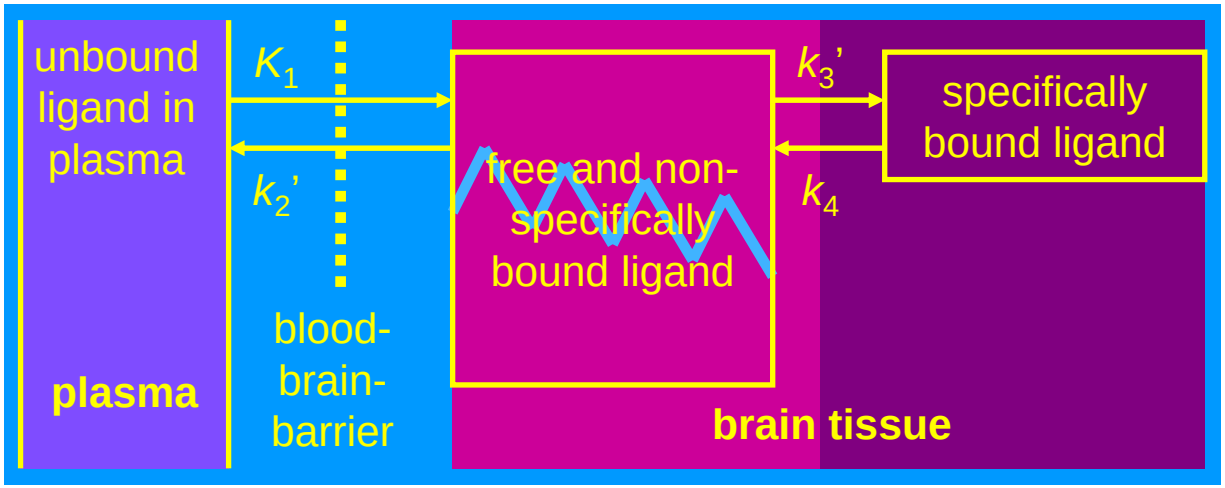
2. The standard model for receptor studies with PET

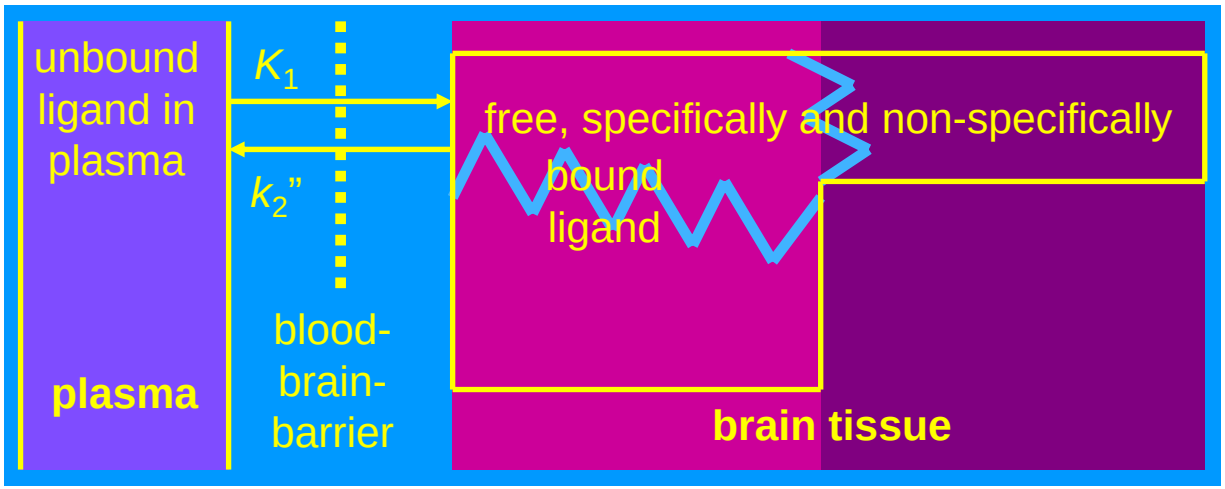


Two-tissue compartment model:

$$k_2' = k_2 \cdot f_2 \qquad k_3' = k_3 \cdot f_2$$

$$VD_{F+NS} = \frac{K_1}{k_2'}$$

$$VD_{tot} = \frac{K_1}{k_2'} \cdot \left(1 + \frac{k_3'}{k_4} \right)$$



One-tissue compartment model:

$$k_2'' = \frac{k_2'}{1 + \frac{k_3'}{k_4}}$$

$$VD_{tot} = \frac{K_1}{k_2''}$$

Koeppe, R.A.; Holthoff, V.A.; Frey, K.A.; Kilbourn, M.R.; Kuhl, D.E.: Compartmental analysis of [^{11}C]flumazenil kinetics for the estimation of ligand transport rate and receptor distribution using positron emission tomography. *J. Cereb. Blood Flow Metab.* 11 (1991), 735 - 744.

3. Simplified analysis of receptor studies with PET

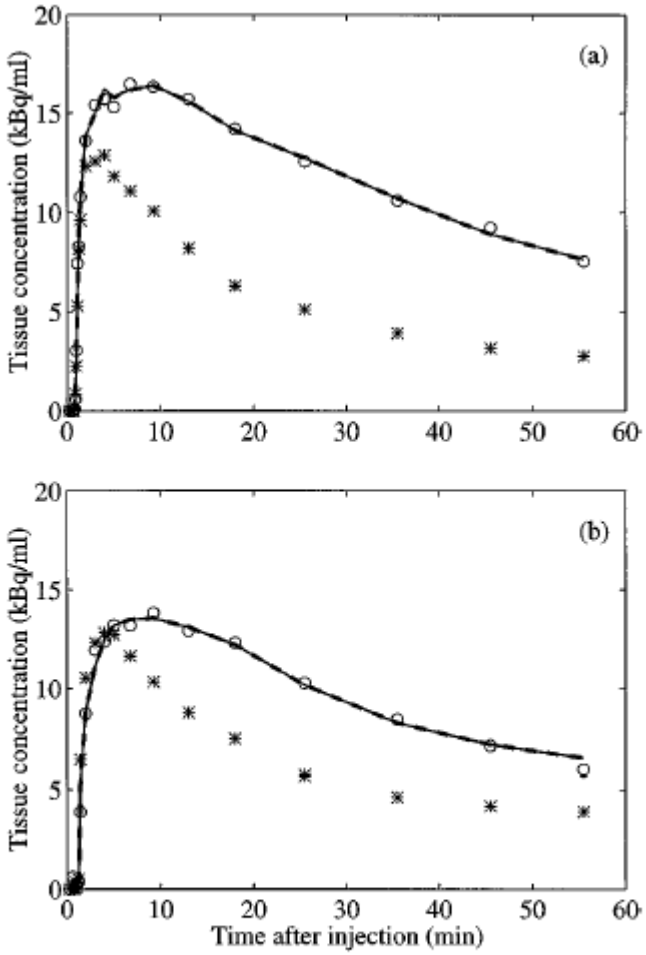
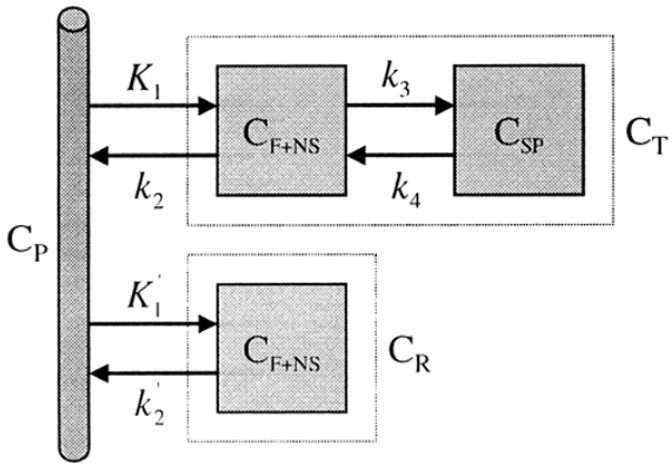


FIG. 1. Examples of fits to human [11C]SCH 23390 data for (a) high and (b) low BP values (1.32 and 0.60, respectively). The three-parameter (solid line) and four-parameter (dashed line) fits to the striatum data (o) are indistinguishable from each other. The cerebellum data (*) are also given.

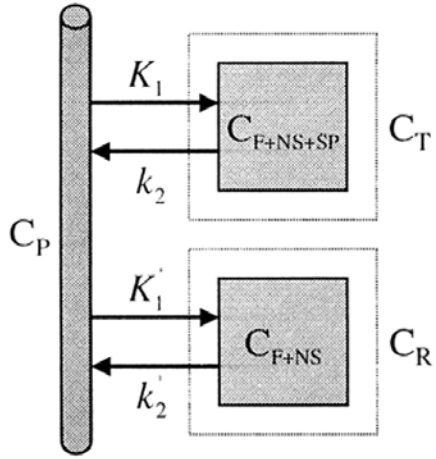
Reference Tissue Models



Four parameters:

$R_I = \frac{K_1}{K_1^*}$, k_2, k_3, k_4

Lammertsma, A.A. et al. *J. Cereb. Blood Flow Metab.* 16 (1996), 42 - 52.



Three parameters:

$R_I = \frac{K_1}{K_1^*}$, k_2, $f_2 \cdot BP$

Lammertsma, A.A. and Hume, S.P. *NeuroImage* 4 (1996), 153 - 158.

- PET ligands with fast kinetics
- A basis function implementation of the SRTM is widely used for the generation of parametric images.

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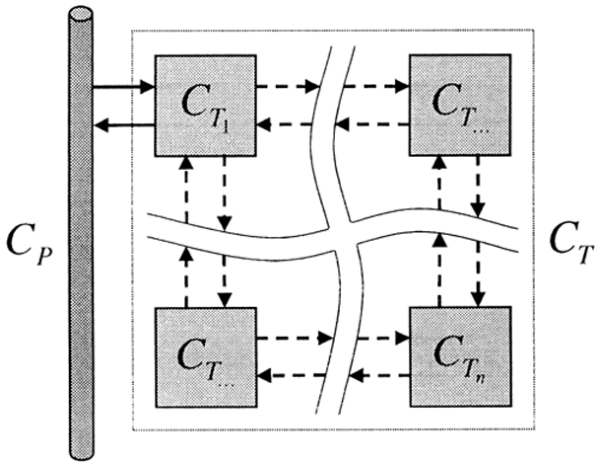
3. Simplified analysis of receptor studies with PET

Graphical Analysis (Gjedde-Patlak plot, Logan plot, Ichise's methods)

and Spectral Analysis

Do not require a particular (compartmental) model configuration.

Describe irreversible (e.g. Gjedde-Patlak plot) or reversible (e.g. Logan plot) systems.



Provide estimates of macroparameters such as VD_{tot} (with plasma input function) or a ratio of *VD*s (when used with a reference tissue input function).

In Graphical Analysis, a threshold for the inclusion of the data has to be defined. Dependent on the implementation of the noise model, answers may be biased.

These methods have become particularly popular for the generation of parametric images.

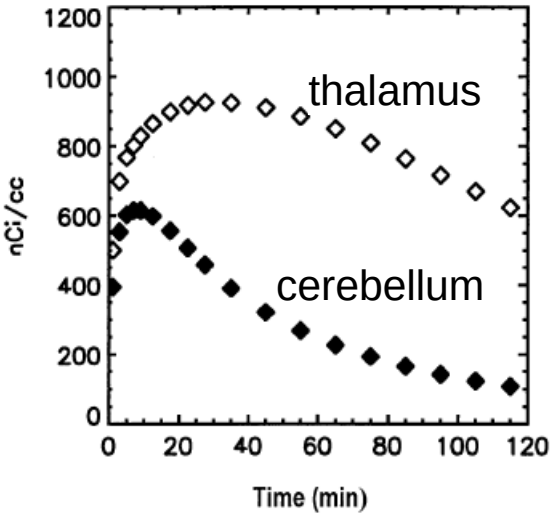
Logan, J.: Graphical Analysis of PET Data Applied to Reversible and Irreversible Tracers. *Nucl. Med. Biol.* 27 (2000), 661 - 670.

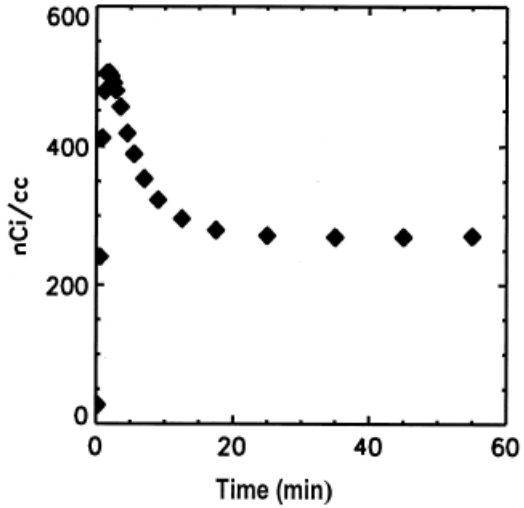
3. Simplified analysis of receptor studies with PET

Logan plot

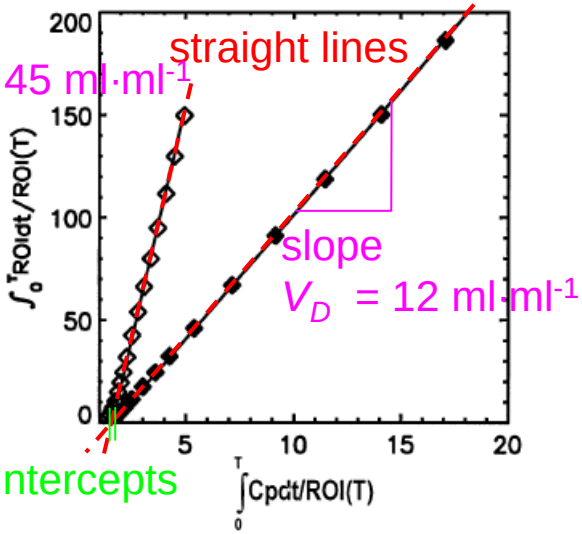
Gjedde-Patlak plot

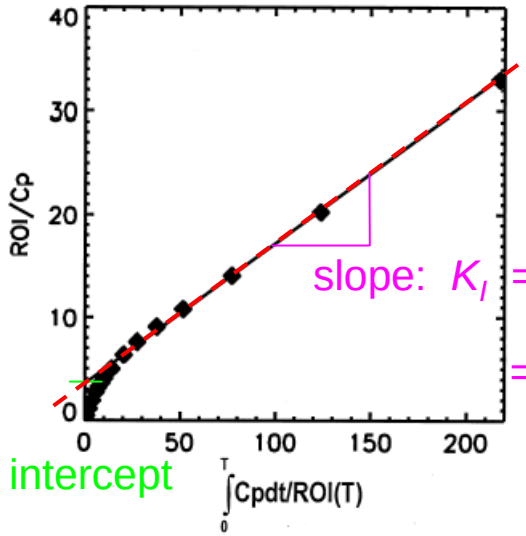
Simulated data of a reversibly binding ligand





Tissue time-activity curve from a [^{11}C]L-deprenyl-D2 study (monamine oxidase B inhibitor)





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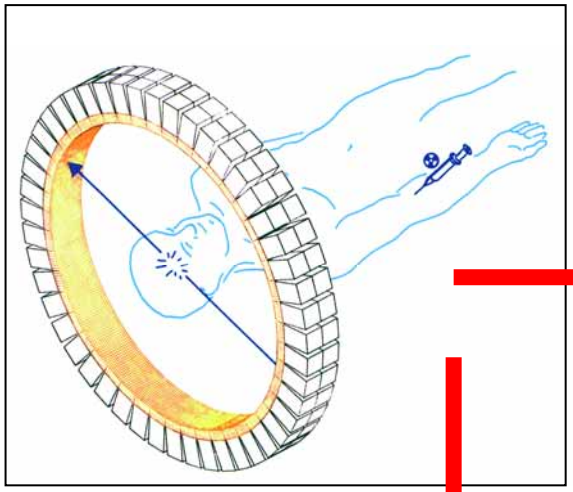
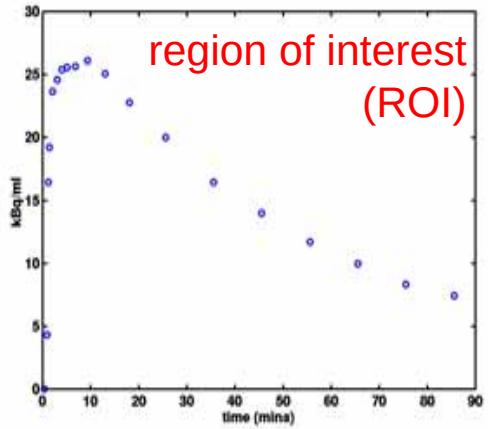
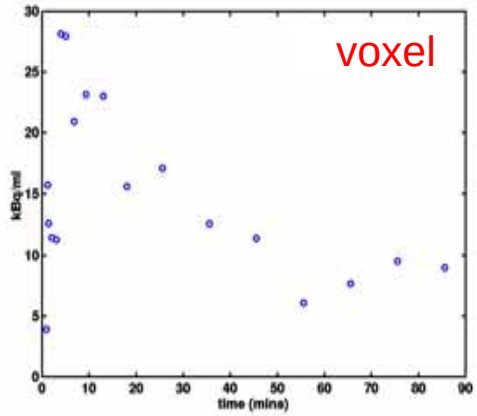
4. Design & implementation of receptor studies with PET



Measurement of the tissue response:

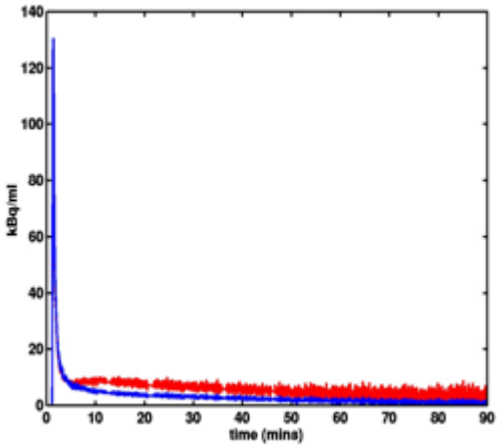




time-activity curves: regional or per voxel
→ signal-to-noise ratio

Measurement of the arterial input function:

- partition between plasma and erythrocytes,
- metabolites,
- free fraction in plasma,
- ...



Model: parameter estimates
binding parameters: *BP*, *VD*, K_1, ...

- bolus injection: single, double, multiple, …
- bolus + infusion protocol: Are temporal changes of parameters during the scan detectable?
- displacement studies with selective blocker

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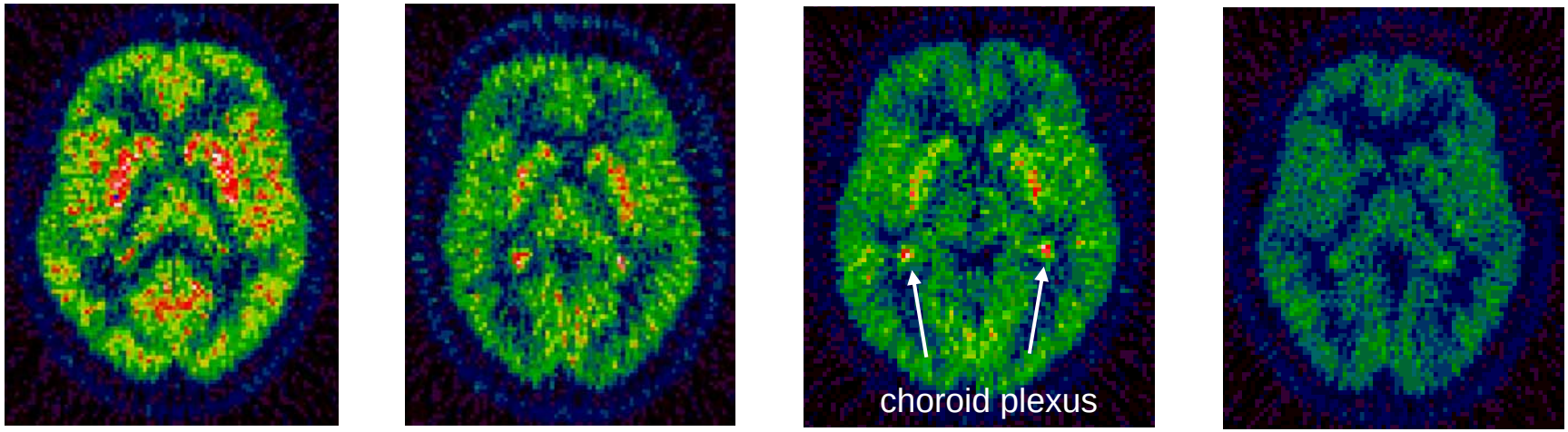
4. Example of a receptor study with PET

Dose-occupancy study with [^{11}C]GR205171

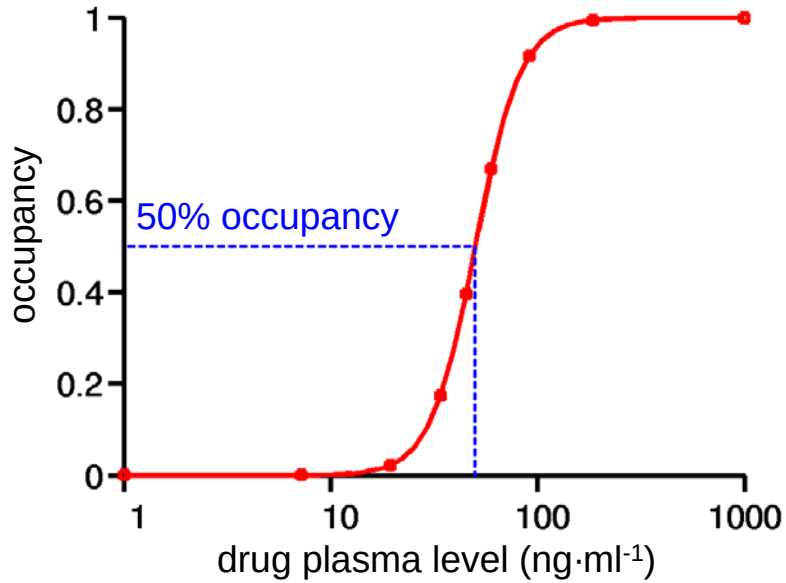
Baseline scan | 80 mg NK_1 inhibitor | 160 mg NK_1 inhibitor | 400 mg NK_1 inhibitor



Two PET scans:

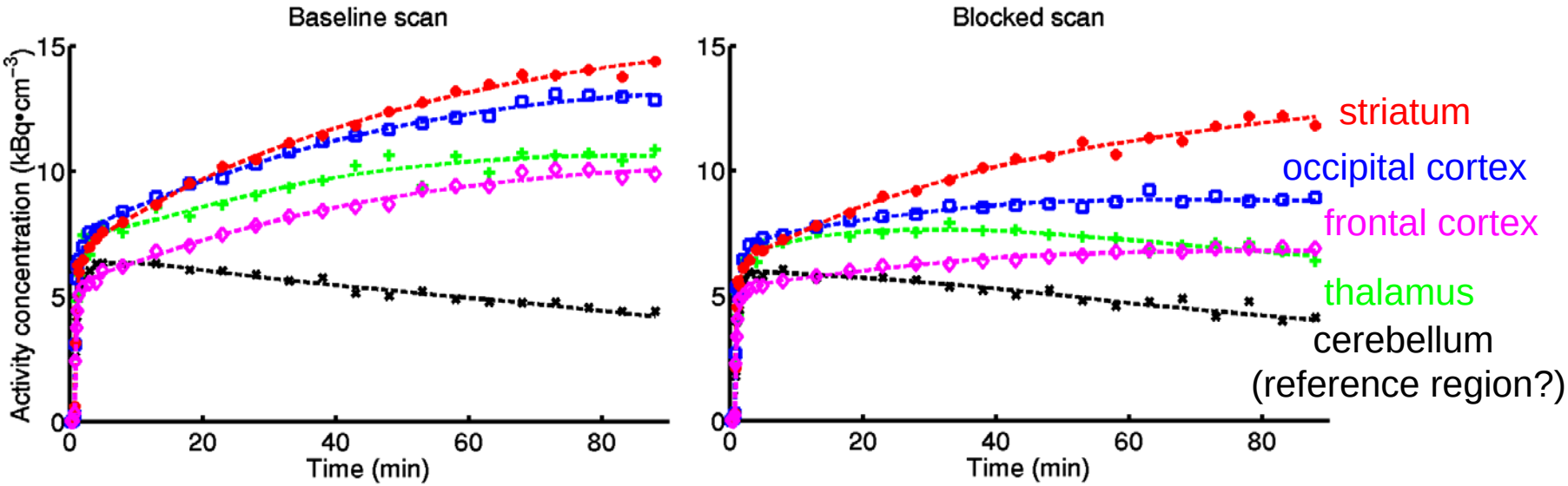
1. A tracer alone scan (baseline scan).
2. A blocked scan after administration of an NK_1 inhibitor.

Estimation of receptor occupancy: $Occ = 1 - \frac{BP_{blocked}}{BP_{baseline}}$



Study objective: establishment of a dose-occupancy relationship.

4. Example of a receptor study with PET



	Baseline scan		Blocked scan		Estimated occupancy
	VD_{tot}	$f_2 \cdot BP$	VD_{tot}	$f_2 \cdot BP$	
striatum	179 ± 47.6	15.1 ± 4.64	52.1 ± 3.7	5.25 ± 0.49	**0.65**
occipital cortex	87.1 ± 12.1	6.81 ± 1.40	22.3 ± 1.2	1.68 ± 0.18	**0.75**
frontal cortex	71.5 ± 11.7	5.42 ± 1.28	18.1 ± 0.9	1.17 ± 0.13	**0.78**
thalamus	46.3 ± 11.2	3.16 ± 1.11	13.9 ± 0.6	0.67 ± 0.09	**0.79**
cerebellum	11.1 ± 1.3		8.3 ± 0.3		

- VD_{tot} estimated with a reversible two-tissue, four rate constants plasma input function model.
- Equilibrium reached (only in some or in all regions)?
- Displaceable binding in the reference region (cerebellum)?

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4. Example of a receptor study with PET

Regionally varying occupancy estimates are a typical symptom of the use of inappropriate models. The following analyses of the example data set from the slowly equilibrating PET ligand [^{11}C]GR205171 result in an underestimation of the occupancy in all regions except thalamus:

	Graphical analysis of irreversible binding (Patlak method) with reference tissue input function			**Simplified reference tissue model**		
	Baseline K_I^* (min^{-1})	**Blocked** K_I^* (min^{-1})	Estim. occupancy	**Baseline** $f_2 \cdot BP$	**Blocked** $f_2 \cdot BP$	Estim. occupancy
striatum	0.0181	0.0156	**0.14**	4.75	3.24	**0.32**
occipital cortex	0.0150	0.0082	**0.45**	4.61	1.62	**0.65**
frontal cortex	0.0119	0.0073	**0.38**	3.50	1.78	**0.49**
thalamus	0.0106	0.0024	**0.77**	4.16	0.54	**0.87**

→ For dose-occupancy (or: control versus disease) studies, care has to be applied when designing the protocol and choosing the model for quantification. If a simplified method has been validated only under baseline (normal) condition, one cannot automatically assume that this method is equally applicable under blocked (disease) condition. **In case of doubt, revert to the standard model!**

5. Summary

In vivo assessment of ligand binding to receptor sites is based on the principles of receptor pharmacology. In most cases, a classical single binding site model is assumed. The key factor for the usefulness of neuroreceptor PET ligands is almost always the amount of specific versus nonspecific binding.

Tracer kinetic modelling reduces two time-activity curves (i.e. the input function and the tissue response curve) into a few parameters (like *VD*, *BP* or k_3) which are related to receptor binding. Goal is to minimise the influence of other *in vivo* processes as peripheral metabolism and cerebral blood flow on the binding outcome measures.

The success of *in vivo* receptor measurements is predetermined by the understanding of the underlying biological system and the validation of the assumptions on which the PET studies are based. *Then* mathematical methods can be very valuable tools for the analysis of the gathered data.

When done properly, neuroreceptor PET studies can provide useful contributions to drug development. The genuine strength of PET is its very high sensitivity (*picomolar concentrations*) and the possibility of <u>quantitative</u> imaging of *in vivo* binding to receptors.

6. List of references

The standard model for the analysis of neuroreceptor PET studies:

• Mintun, M.A.; Raichle, M.E.; Kilbourn, M.R.; Wooten, G.F.; Welch, M.J.: A quantitative model for the in vivo assessment of drug binding sites with positron emission tomography. *Ann. Neurol.* 15 (1984), 217 - 227.

Simplifications of the model structure:

• Koeppe, R.A.; Holthoff, V.A.; Frey, K.A.; Kilbourn, M.R.; Kuhl, D.E.: Compartmental analysis of [^{11}C]flumazenil kinetics for the estimation of ligand transport rate and receptor distribution using positron emission tomography. *J. Cereb. Blood Flow Metab.* 11 (1991), 735 - 744.

Comprehensive review article with specific examples ([^{11}C]diprenorphine, [^{11}C]flumazenil)

• Cunningham, V.J.; Lammertsma, A.A.: Radioligand studies in brain: Kinetic analysis of PET data. *Med. Chem. Res.* 5 (1994), 79 - 96.

Review articles on graphical analysis methods ("Patlak" and "Logan" plots):

• Logan, J.: Graphical Analysis of PET Data Applied to Reversible and Irreversible Tracers. *Nucl. Med. Biol.* 27 (2000), 661 - 670.

• Slifstein, M.; Laruelle, M.: Effects of statistical noise on graphic analysis of PET neuroreceptor studies. *J. Nucl. Med.* 41 (2000), 2083 - 2088.

Introduction of spectral analysis with examples ([^{18}F]FDG and [^{11}C]diprenorphine):

• Cunningham, V.J.; Jones, T.: Spectral Analysis of Dynamic PET Studies. *J. Cereb. Blood Flow Metab.* 13 (1993), 15 - 23.

6. List of references

Introduction of reference tissue models:

• Lammertsma, A.A.; Bench, C.J.; Hume, S.P.; Osman, S.; Gunn, K.; Brooks, D.J.; Frackowiak, R.S.J.: Comparison of Methods for Analysis of Clinical [^{11}C]Raclopride Studies. *J. Cereb. Blood Flow Metab.* 16 (1996), 42 - 52.

• Lammertsma, A.A.; Hume, S.P.: Simplified Reference Tissue Model for PET Receptor Studies. *NeuroImage* 4 (1996), 153 - 158.

Design of bolus or infusion protocols in order to maximise detectability of changes in ligand binding:

• Endres, C.J.; Carson, R.E.: Assessment of dynamic neurotransmitter changes with bolus or infusion delivery of neuroreceptor ligands. *J. Cereb. Blood Flow Metab.* 18 (1998), 1196 - 1210.

Compartmental modelling review using notation of linear algebra:

• Gunn. R.N.; Gunn, S.R.; Cunningham, V.J.: Positron emission tomography compartmental models. *J. Cereb. Blood Flow Metab.* 21 (2001), 635 - 652.

Recent brief review on the quantitative analysis of PET data to support drug development:

• Cunningham, V.J.; Gunn, R.N.; Matthews, J.C:. Quantification in positron emission tomography for research in pharmacology and drug development. *Nucl. Med. Commun.* 25 (2004), 643 - 646.