PET Tracer Kinetic Modelling

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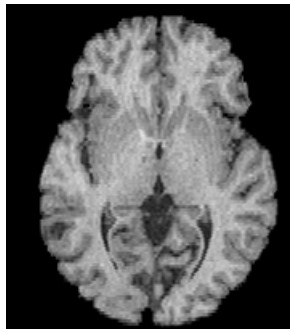
Radiopharmaceuticals	**Radioligand receptor target/type of radiotracer**
Carbon-11	
[11C]Flumazenil	Central Benzodiazepine
[11C]Ro 15-4513	Central Benzodiazepine
[11C]SCH 23390	Dopamine D1
[11C]Raclopride	Dopamine D2
[11C]FLB 457	Dopamine D2
[11C]RTI-32	Dopamine transporter site
[11C]Diprenorphine	Opiate
R-[11C]PK 11195	PK binding site
[*carbonyl*-11C]WAY-100635	Serotonergic 5-HT1A
[11C]MDL 100907	Serotonergic 5-HT2A
m-[11C]Hydroxyephedrine	Noradrenaline uptake site
S-[11C]CGP 12177	b-Adrenergic
[11C]GB 67	a1-Adrenoceptors
2-[11C]Thymidine	Cell proliferation

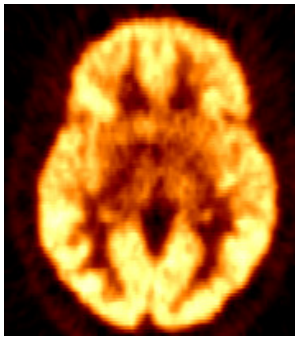
Occupancy

- Occupancy studies measure occupancy of the target by the candidate drug.
- Require the existence or development of a PET ligand (usually different from the candidate drug).
- Occupancy studies best performed just after or during FTIH

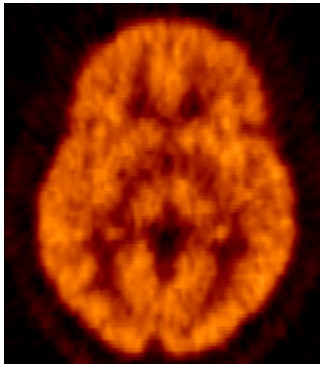
Occupancy of 5HT2A receptors by risperidone using [11C]MDL100907



MRI

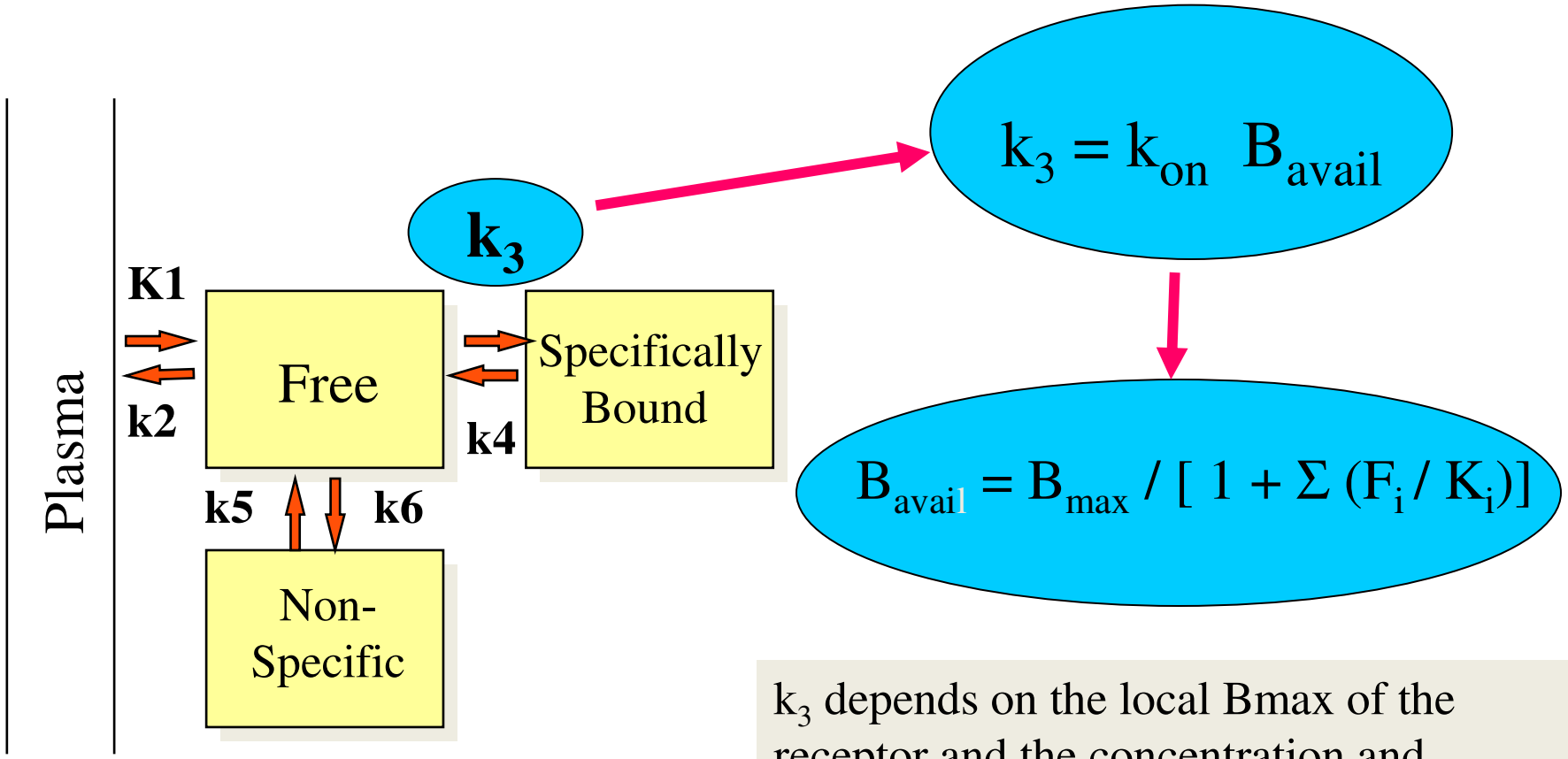


Binding Potential Maps (mL/g)
Baseline Scan



After 4 mg risperidone

The standard neuroreceptor ligand model



k_3 depends on the local Bmax of the receptor and the concentration and affinity of competing exogenous and endogenous ligands

Mintun, M.A. et al., A quantitative model for the in vivo assessment of drug binding sites with positron emission tomography, Ann. Neurol. 15 (1984) 217–227.

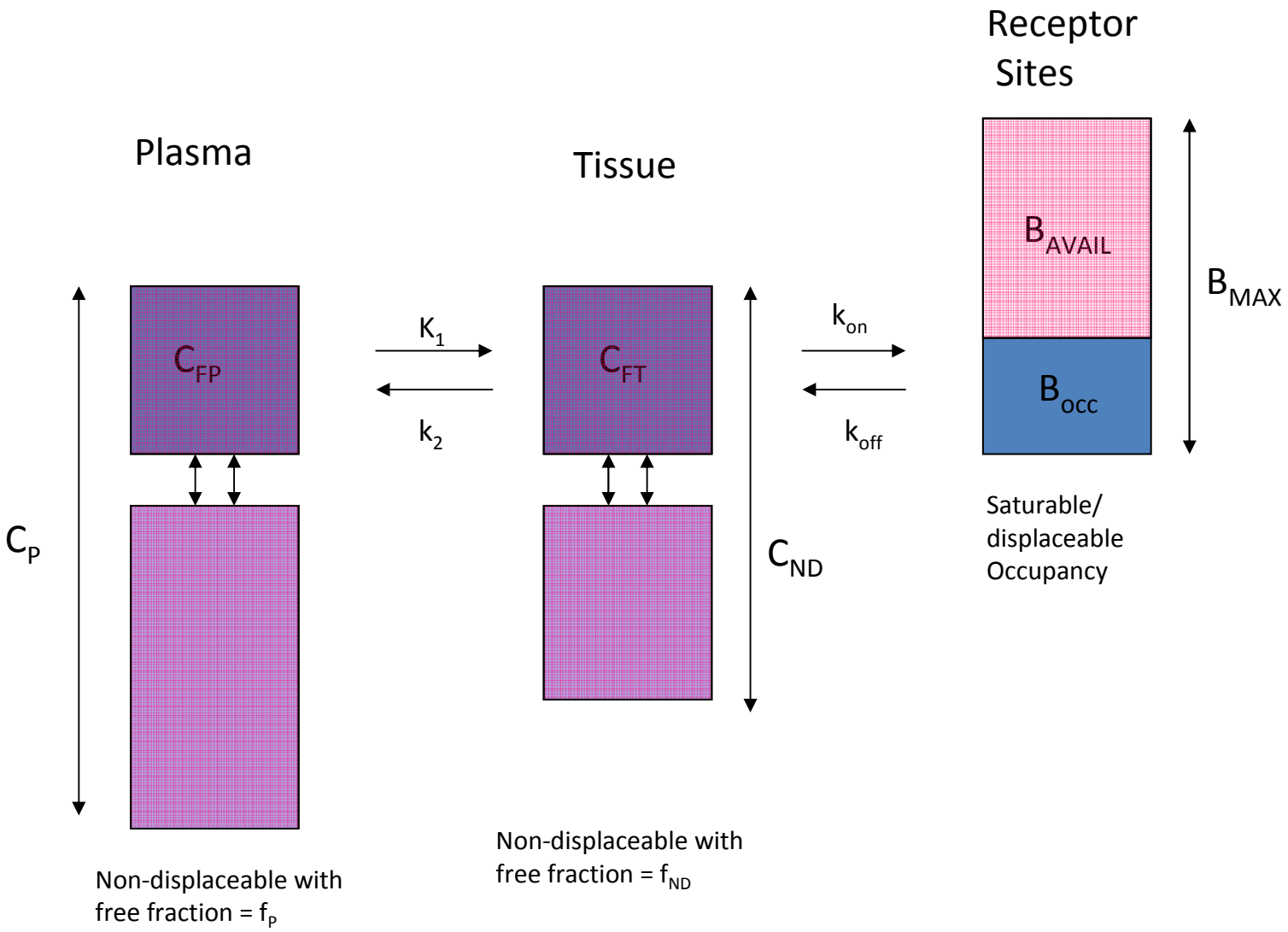
The situation in vivo is more complex

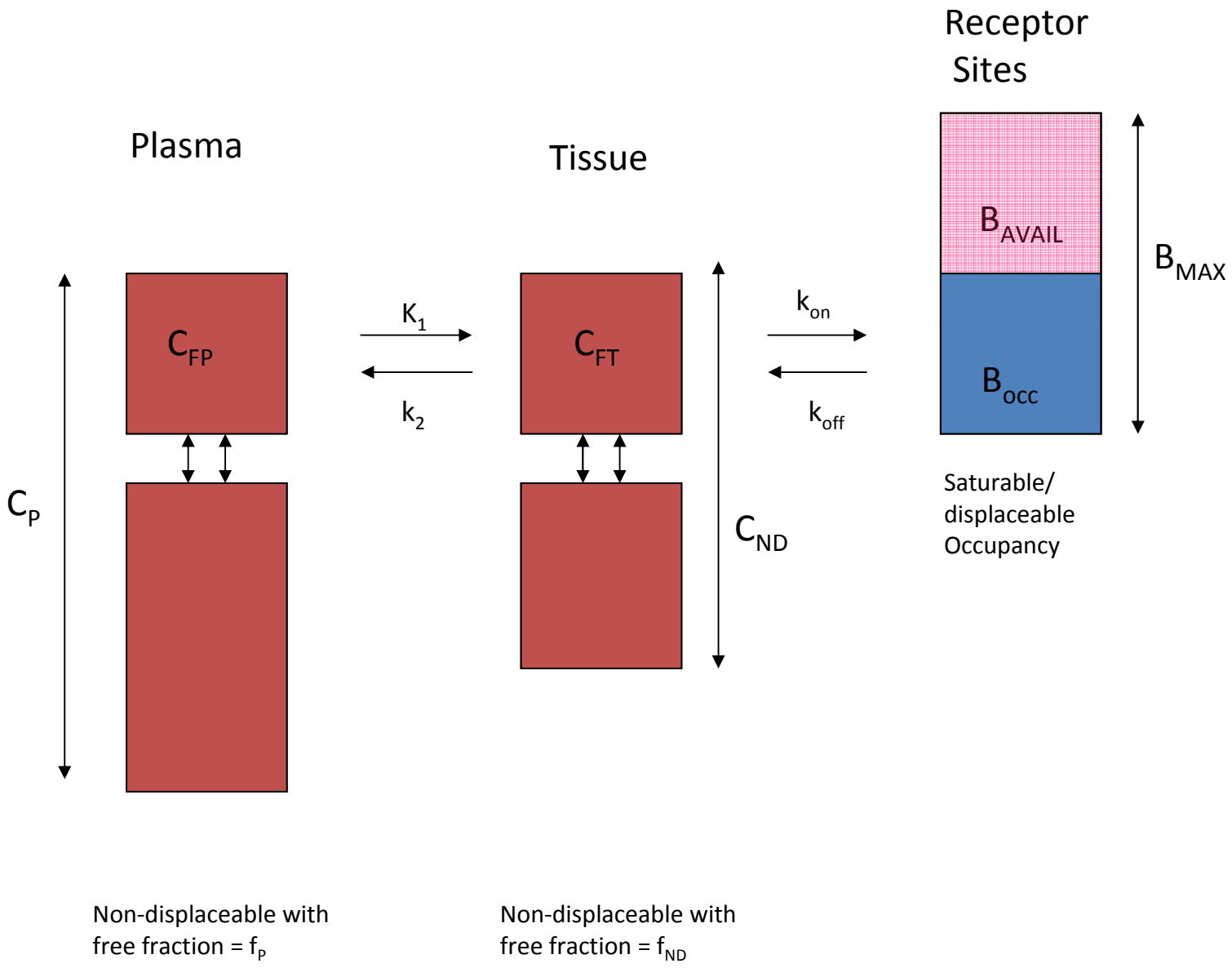
Usually only one or two compartments are identifiable and these do not necessarily correspond to the neat partitions suggested by the model

The Individual microparameters are often not numerically identifiable.

Even when they are, their apparent values do not ‘behave’ as would be expected from the Classic model. Eg PGP effects and ‘k4 = koff’

Does this matter ?


Plasma
Tissue
Receptor Sites
C_{FP}
C_{FT}
K_1
k_2
k_{on}
k_{off}
B_{AVAIL}
B_{occ}
B_{MAX}
C_P
C_{ND}
Saturable/ displaceable Occupancy
Non-displaceable with free fraction = f_P
Non-displaceable with free fraction = f_{ND}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C_{ND}
Saturable/ displaceable Occupancy
Non-displaceable with free fraction = f_P
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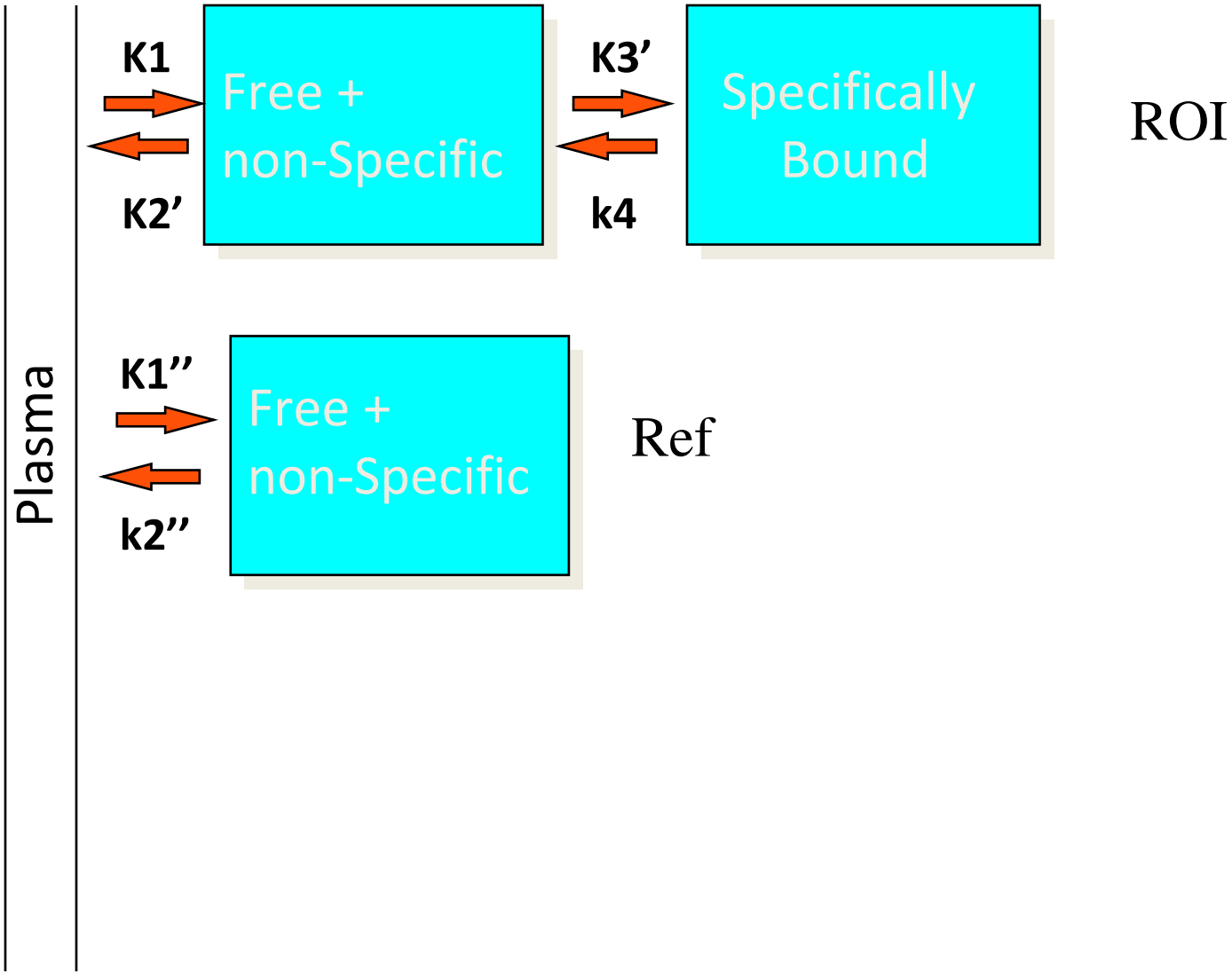
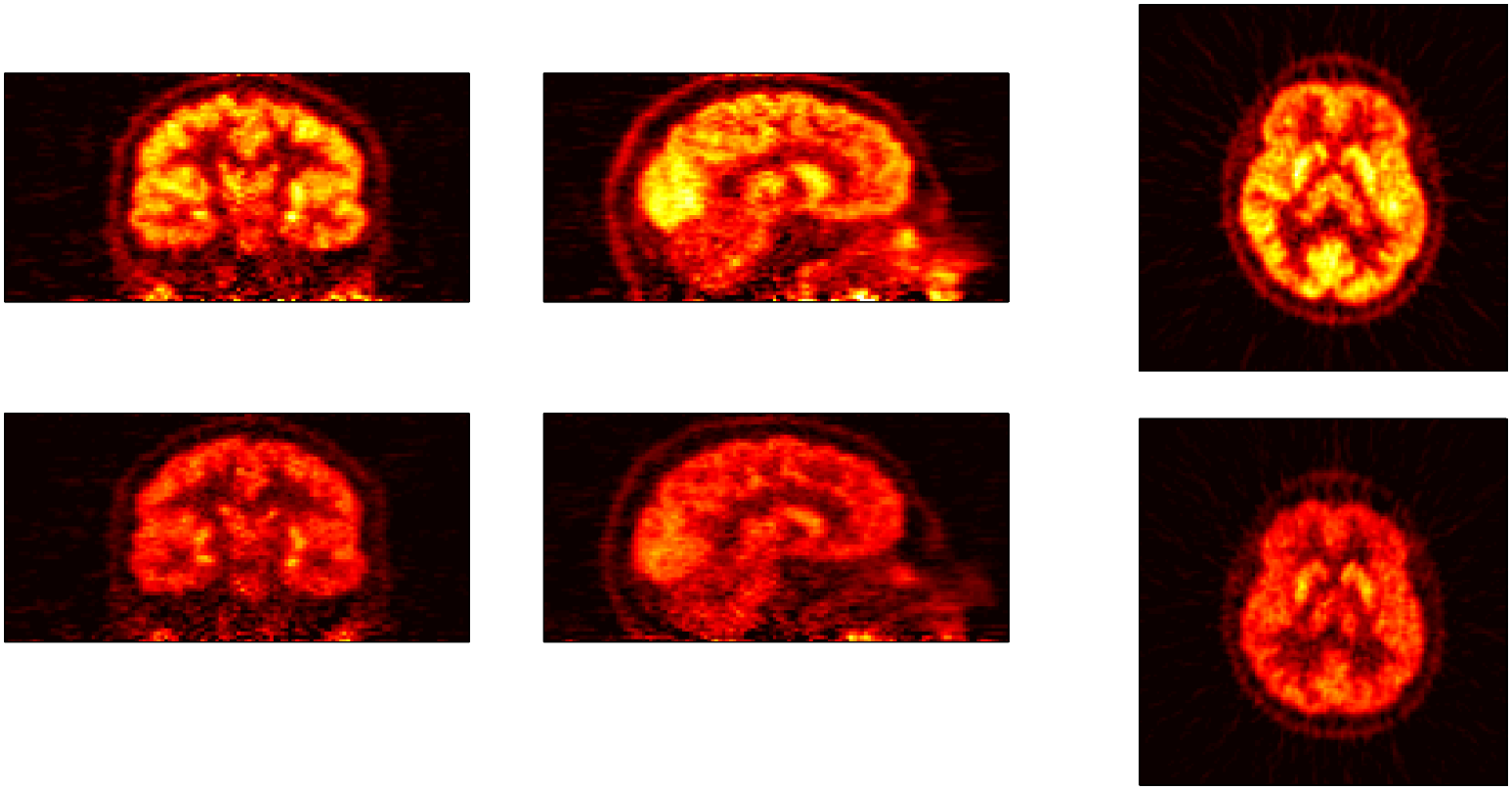
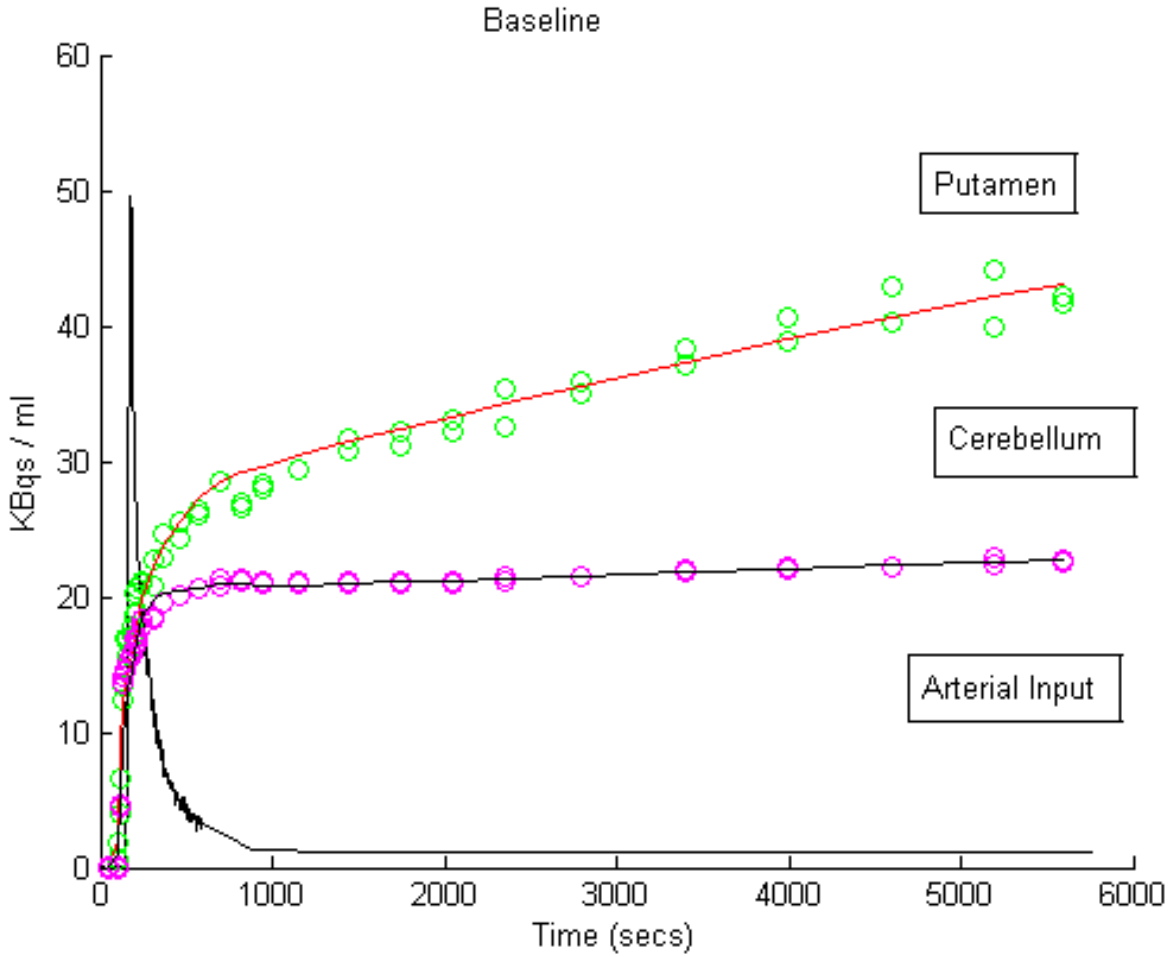
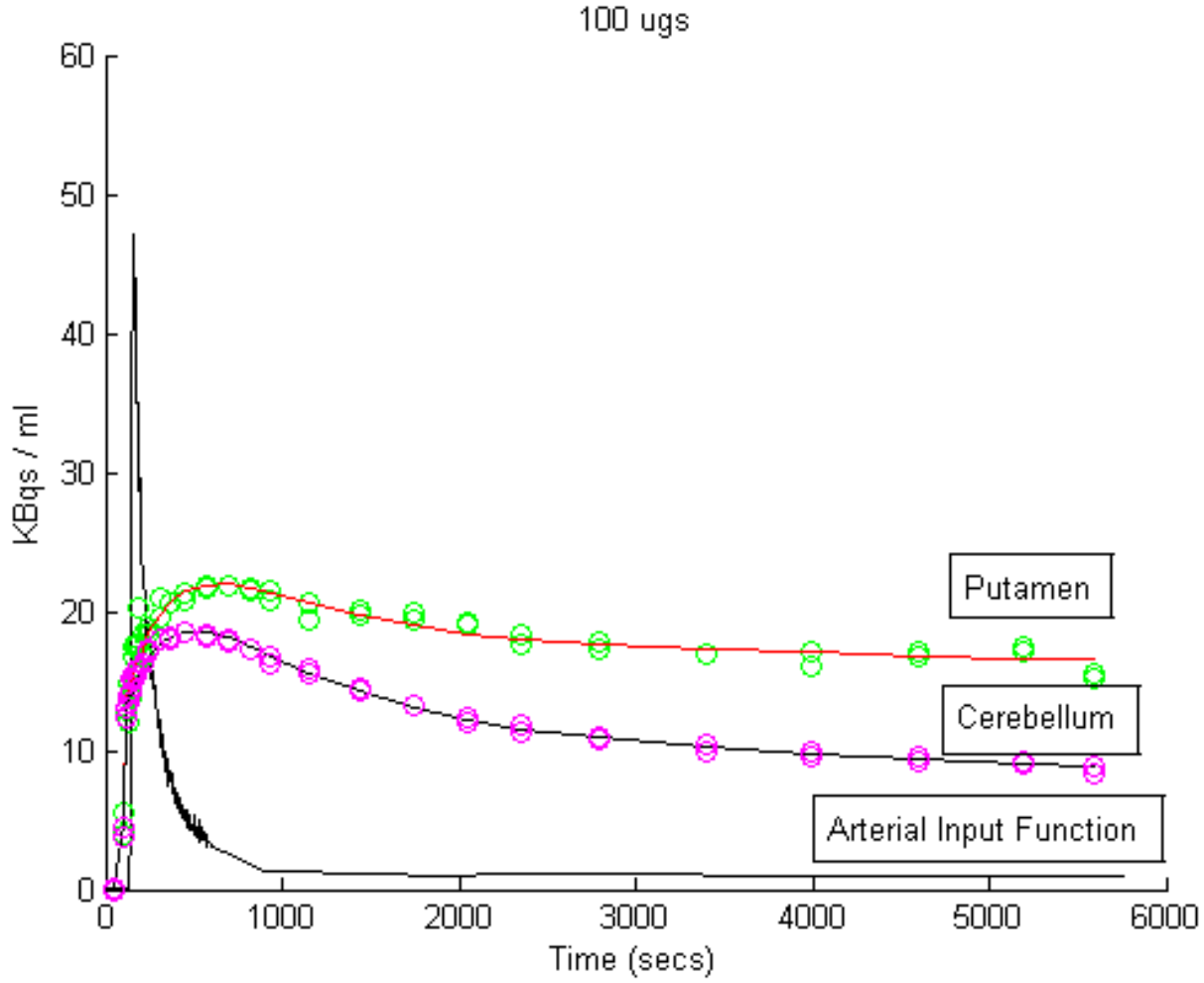
Reference Regions

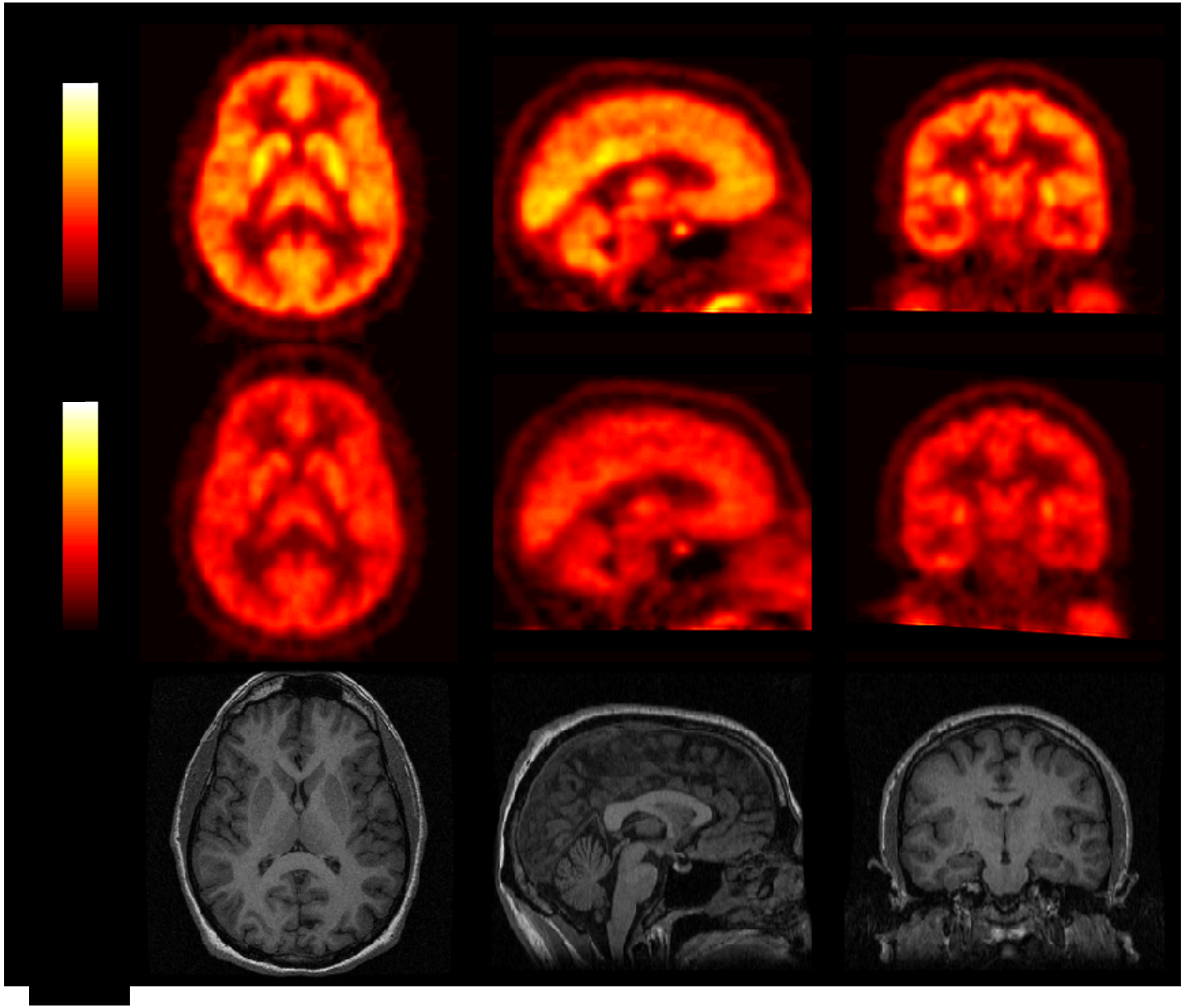


Occupancy of NK1 receptor sites by an exogenously administered antagonist.




Baseline
Putamen
Cerebellum
Arterial Input
KBqs / ml
Time (secs)
0
10
20
30
40
50
60
0
1000
2000
3000
4000
5000
6000


100 ugs
KBqs / ml
Time (secs)
Putamen
Cerebellum
Arterial Input Function
0
10
20
30
40
50
60
0
1000
2000
3000
4000
5000
6000



Baseline
H3 PET
(0-90mins)

4hr post
50 ug
GSK189254A
(0-90mins)

Structural
MRI

Plasma Input Models

Reversible Kinetics

$$IRF(t) = \sum_{i=1}^{n} \phi_i e^{-\theta_i t}$$

$$V_D = \int_0^{\infty} IRF(t)\ dt = \sum_{i=1}^{n} \frac{\phi_i}{\theta_i}$$

Irreversible Kinetics

$$IRF(t) = \sum_{i=1}^{n-1} \phi_i e^{-\theta_i t} + \phi_n$$

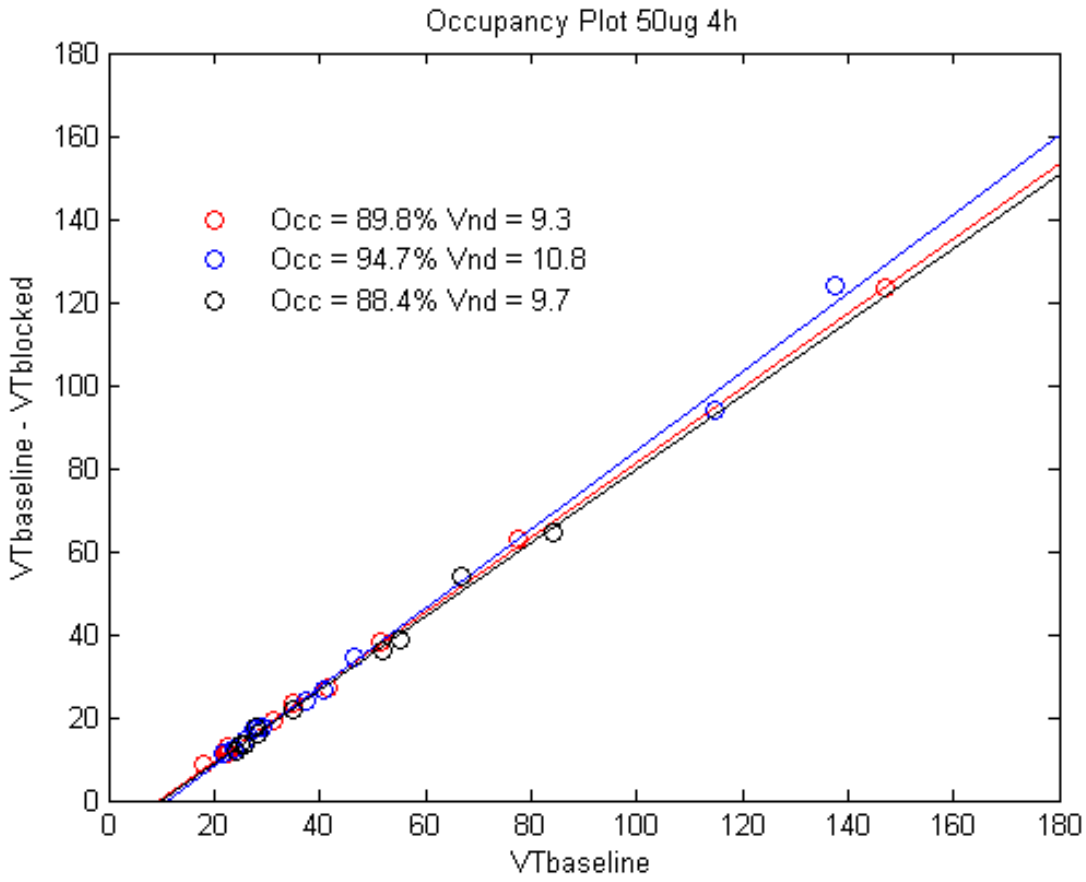
$$K_I = \lim_{t \to \infty} IRF(t) = \phi_n$$

n = Number of Tissue Compartments
(Nearly all these models have positive coefficients)

$$\theta_i > 0, \quad K_1 = \sum_{i=1}^{n} \phi_i$$

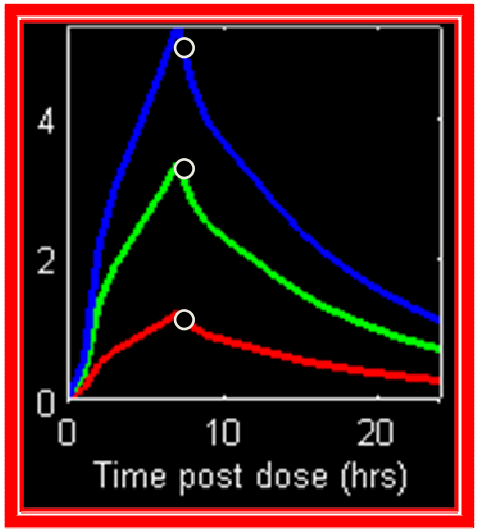
Occupancy Plot in absence of true reference region

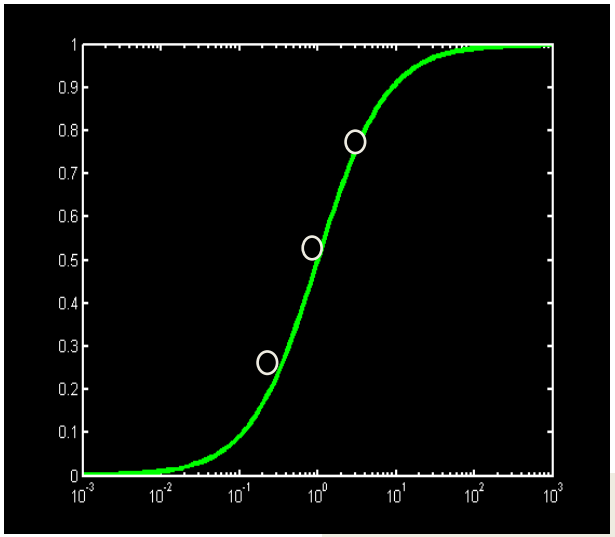
$$(V_{T\ baseline} - V_{T\ blocked}) = Occ.V_{T\ baseline} - Occ.V_{ND}$$

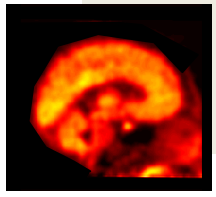


Occupancy = 91.0 ± 3.3%

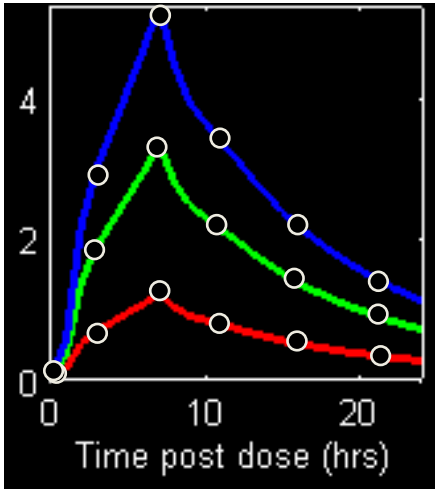
Measurement of Occupancy - Previously



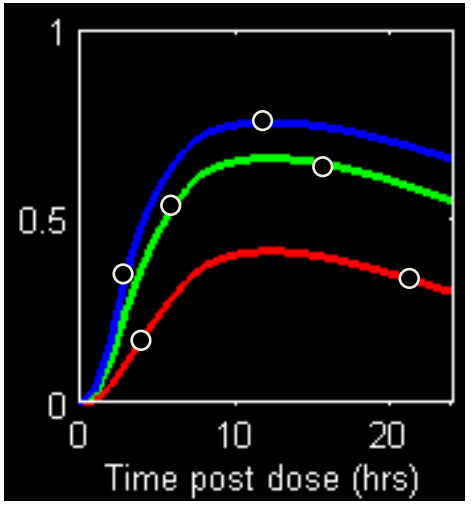


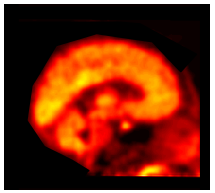


Measurement of Occupancy - Current



PK – PD Model





PK/PD Models

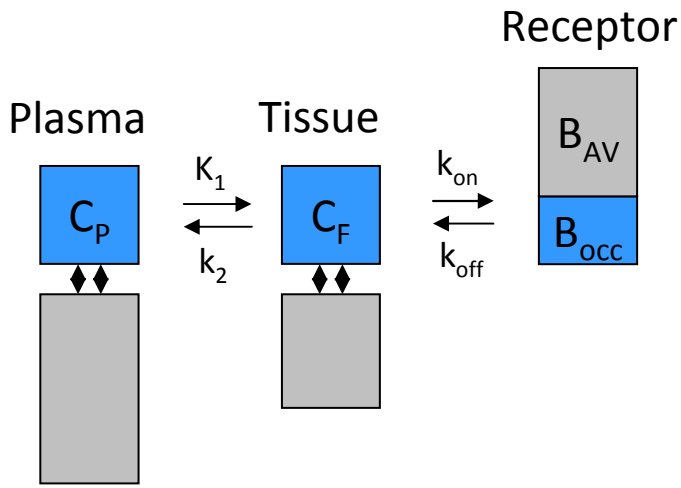
- Model I: C_p-K_d Model
  - Assumes the free brain concentration is equal to the plasma concentration and that the occupancy is instantaneously related in a E-Max way to the brain concentration

$$TOC(t) = \frac{C_P(t)}{C_P(t) + K_d}$$

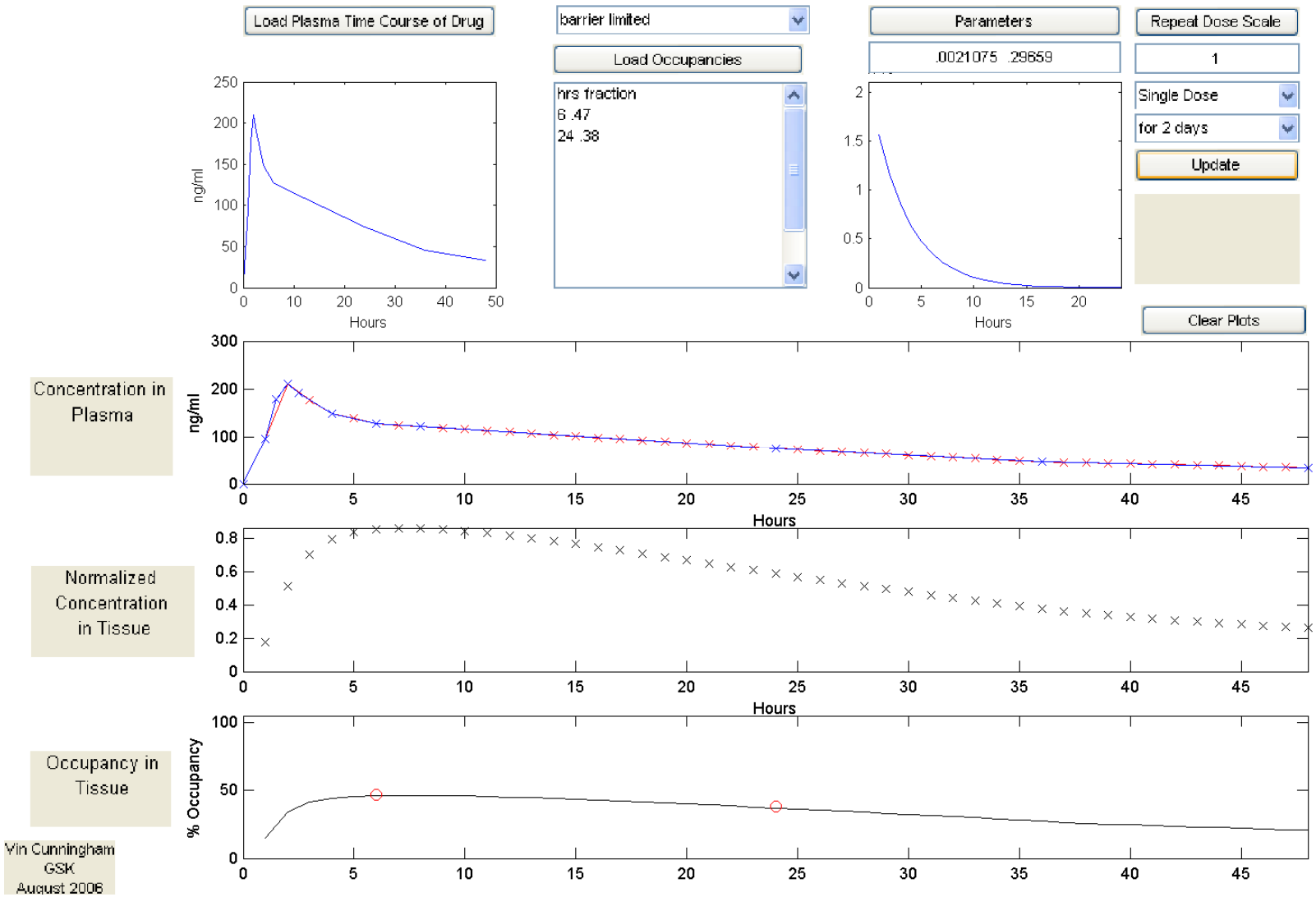
- Model II: BBB Limited Model
  - Assumes brain concentration is described as a single exponential convolved with the plasma concentration and that the occupancy is instantaneously related in a EMax fashion to the brain concentration.

$$TOC(t) = \frac{C_P(t) \otimes e^{-\beta t}}{C_P(t) \otimes e^{-\beta t} + \gamma}$$

- Model III: k_{on}-k_{off} Limited Model
  - Assumes receptor association and dissociation are finite.



GSK206136
5-HTT
11C-DASB
Subject 204



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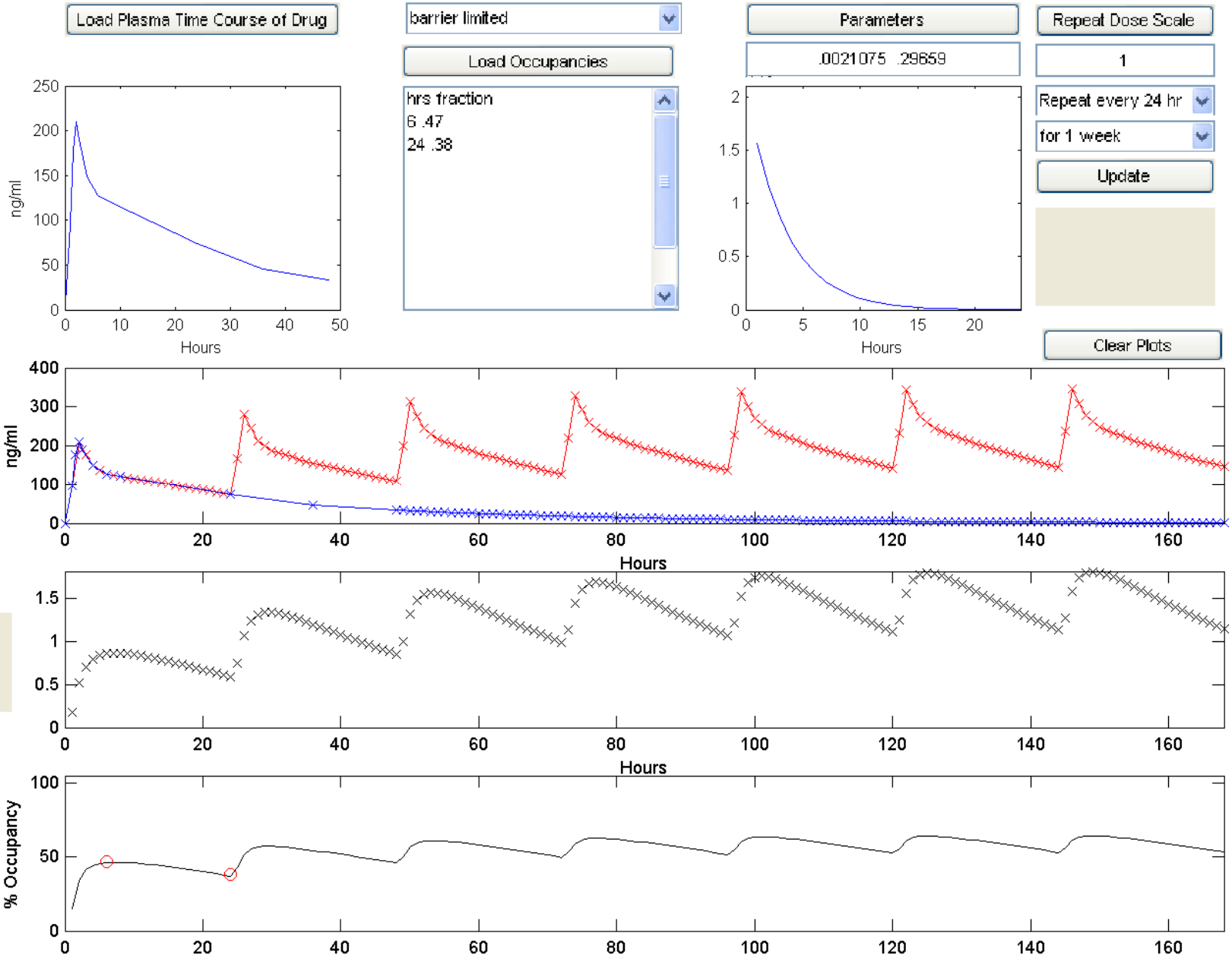

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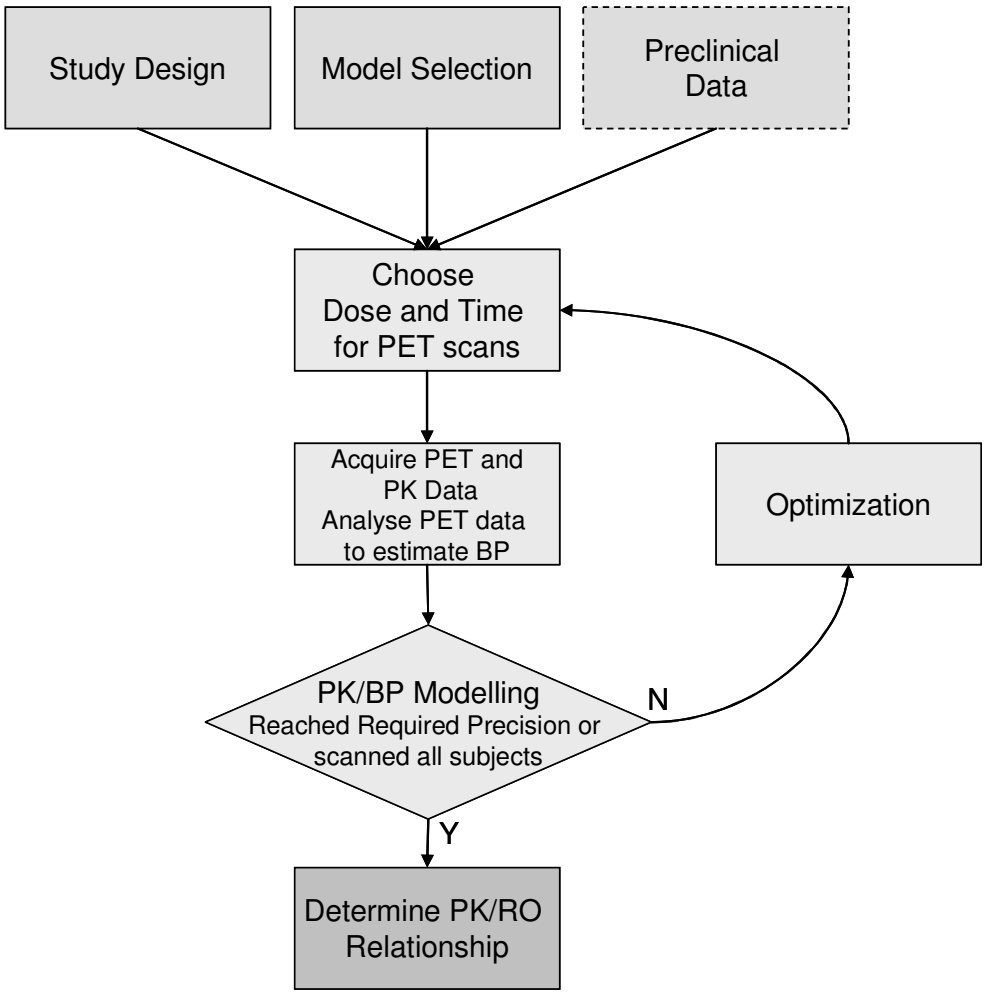
Study Design
Model Selection
Preclinical Data
Choose Dose and Time for PET scans
Acquire PET and PK Data
Analyse PET data to estimate BP
Optimization
PK/BP Modelling
Reached Required Precision or scanned all subjects
N
Y
Determine PK/RO Relationship