FP7 Neurophysics WORKSHOP 23-24 Jan 2012: Pharmacological fMRI

Warwick Conference Centre, University of Warwick, Coventry UK

Model Based Analyses

Direct and Indirect PK-PD modelling

Roger Gunn

Imanova Ltd. and Imperial College, London

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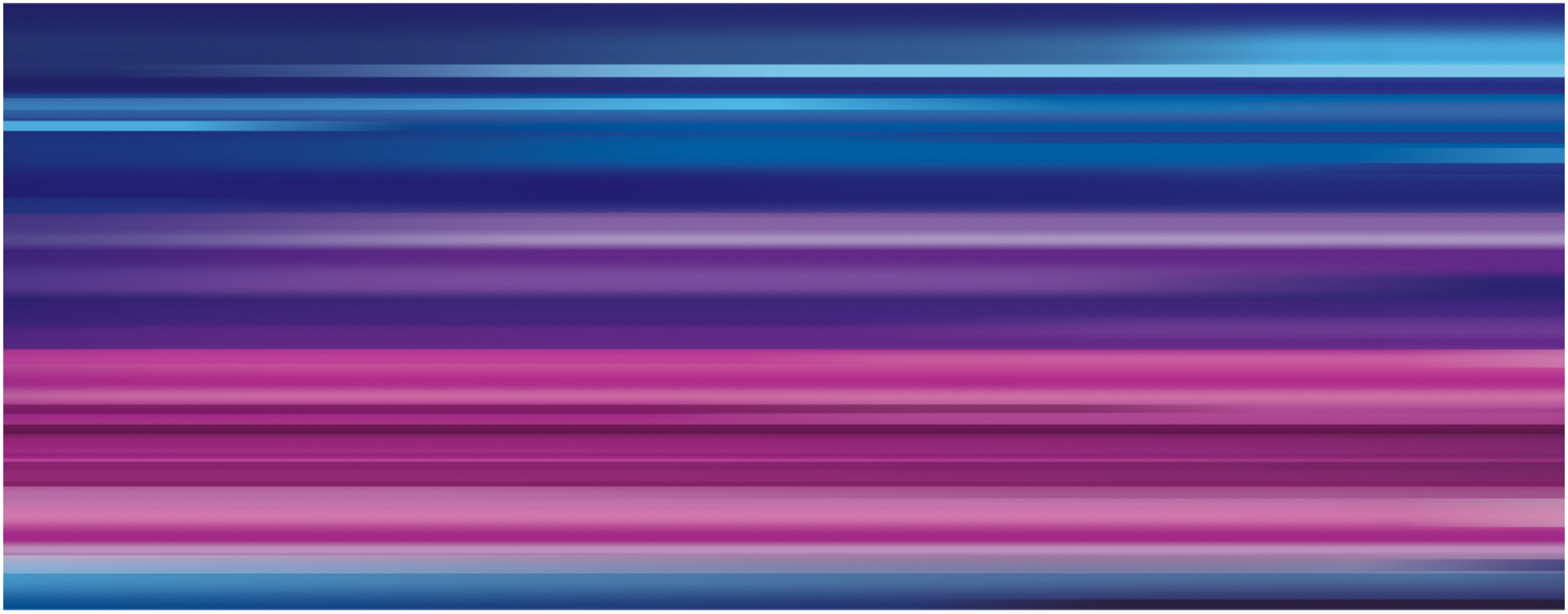
Centre for Imaging Sciences

Imperial College London



Overview

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- Introduction
- Direct PK/PD Modelling
- Indirect PK/PD Modelling
- Predicting Repeat Dose Response from Single Dose data

PK-PD Modelling

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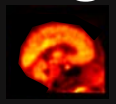
- Relating the blood concentration of the drug (PK) to the Pharmacodynamic Response (PD)



  - Characterize efficacy in terms of dose/pk conc
  - Safety/therapeutic index

- Examples of Imaging PD Measures
  - PET Occupancy at a particular Target
    - Occupancy can often be related to efficacy
  - fMRI measures of activation

PK-PD Modelling

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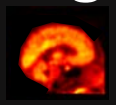
- Relating the blood concentration of the drug (PK) to the Pharmacodynamic Response (PD)



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- Examples of Imaging PD Measures
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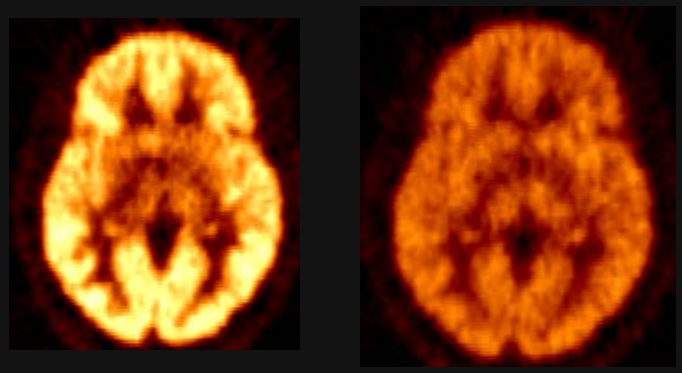
PET Occupancy

- 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



Binding Potential Map (mL/g)
Baseline Scan After 4 mg risperidone

Applying Imaging Endpoints at the right Time

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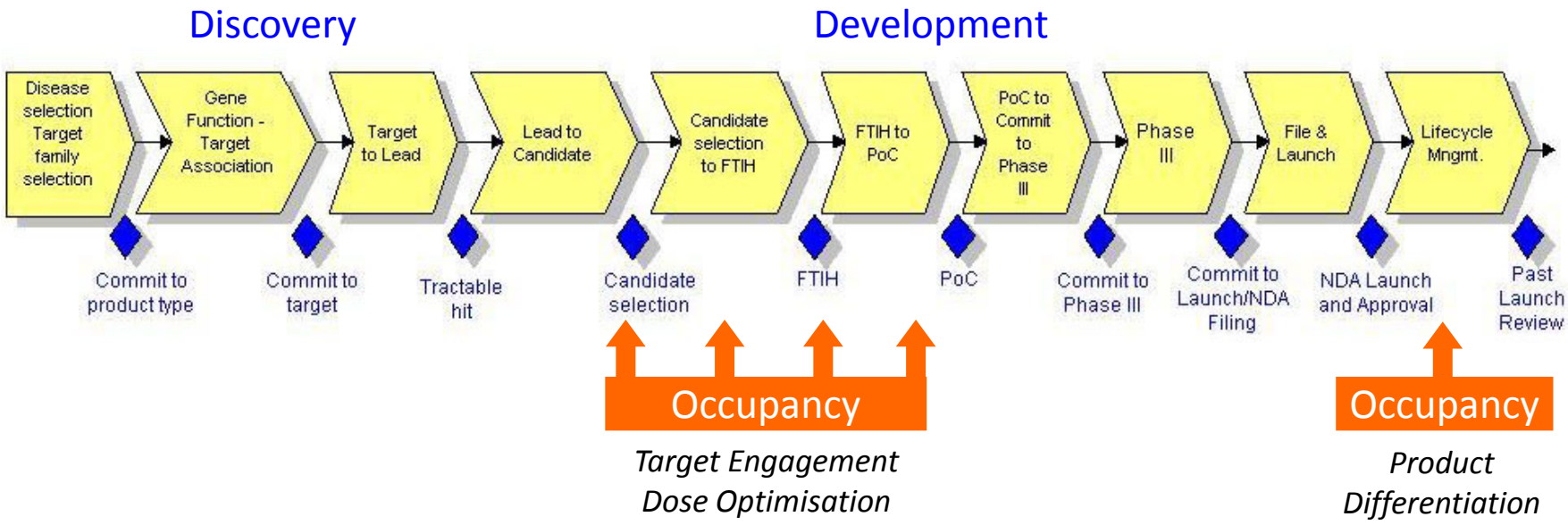
- Does the molecule reach the CNS in potentially pharmacologically active concentrations?
- Does the molecule interact with the target of interest ?
- Can imaging help to differentiate drugs ?



Characterizing the PK-RO Relationship

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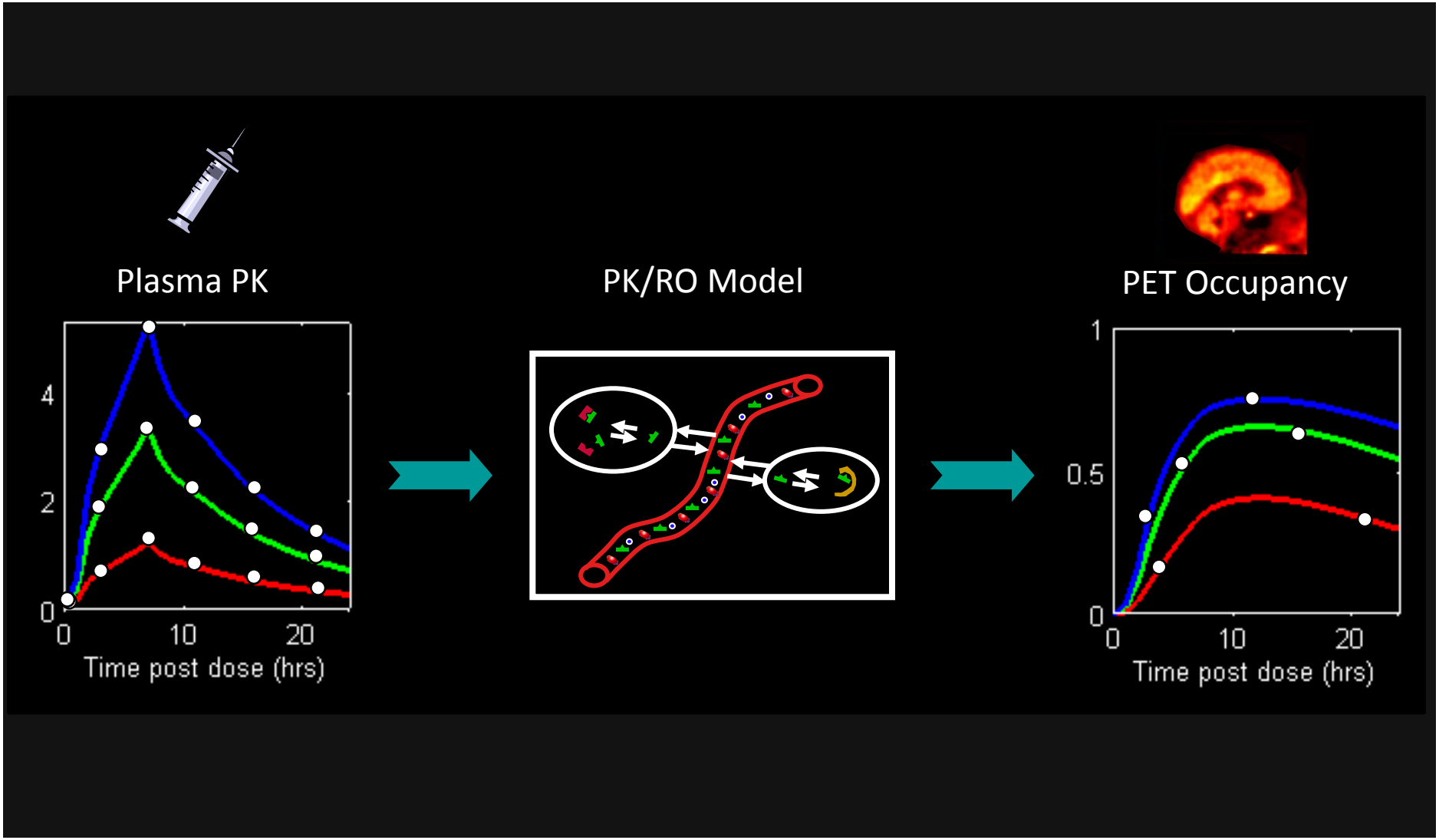
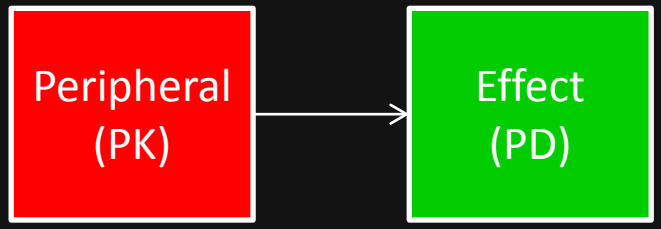
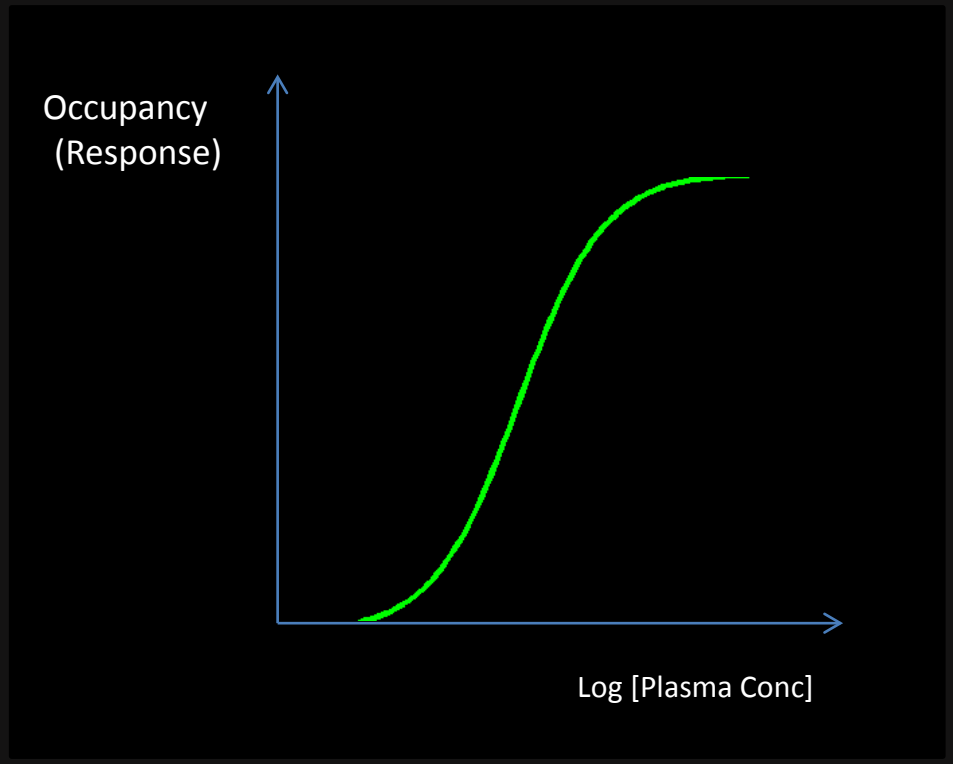


Direct Model



$$Occ = \frac{C_P}{C_P + EC_{50}}$$



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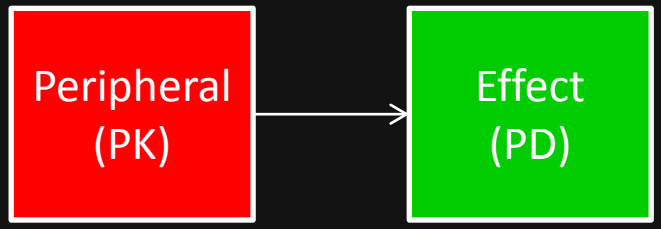

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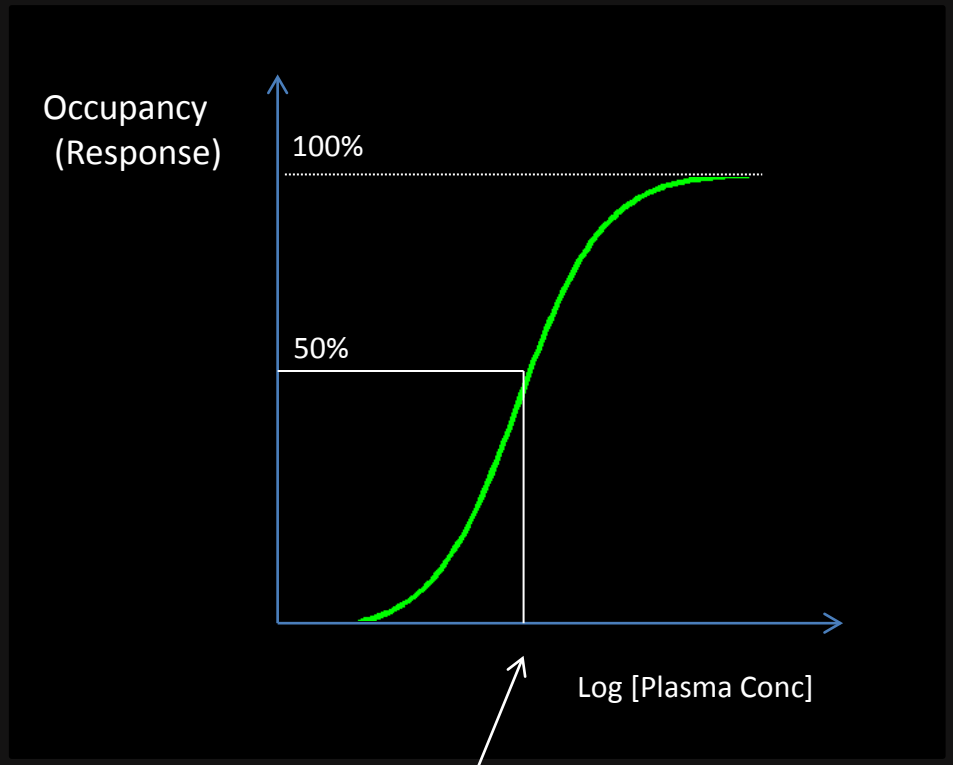

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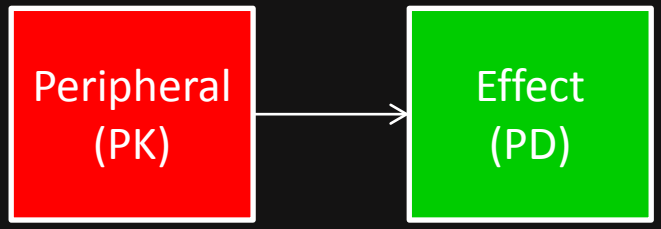
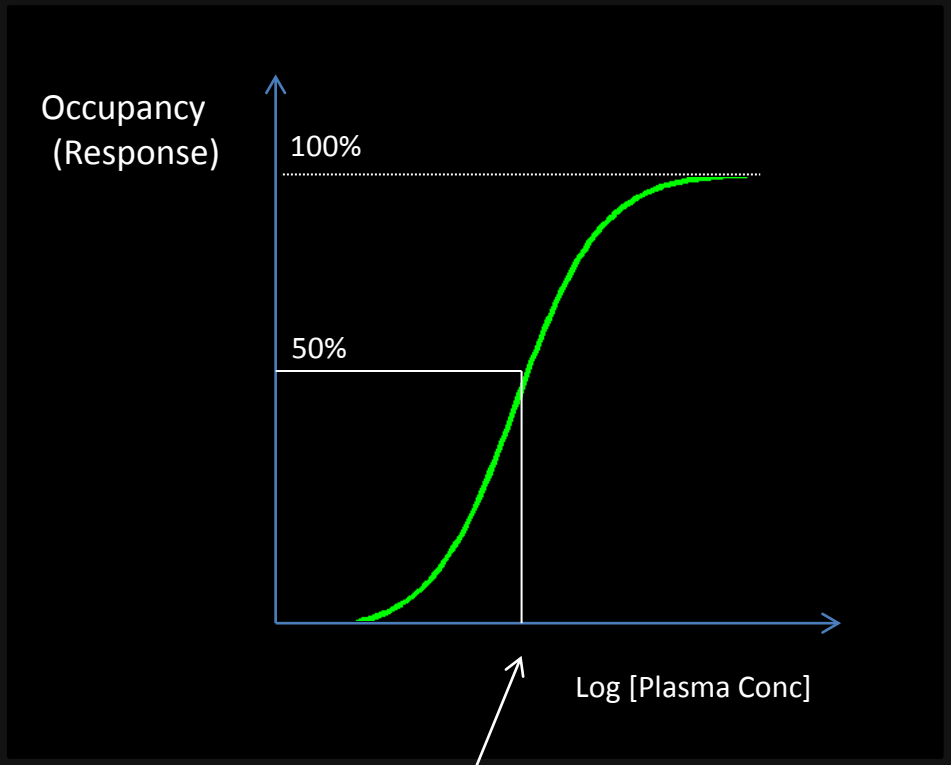


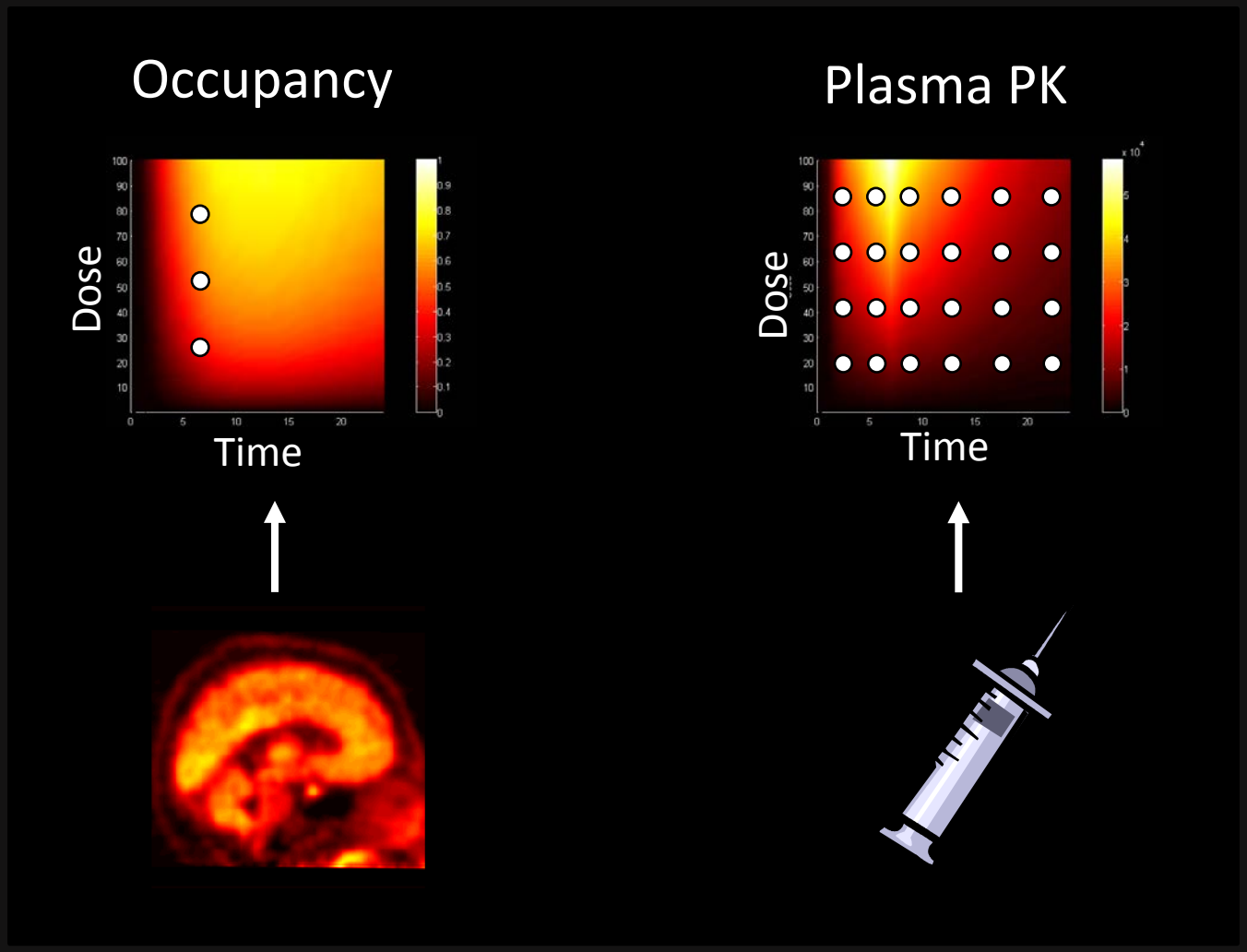
$$Occ = \frac{C_P}{C_P + EC_{50}}$$

More General "Hill" Equation

$$Occ = \frac{Occ_{max} {C_P}^N}{{C_P}^N + EC_{50}^N}$$



Simple Single Dose Example



Occupancy of GlyT1 antagonist

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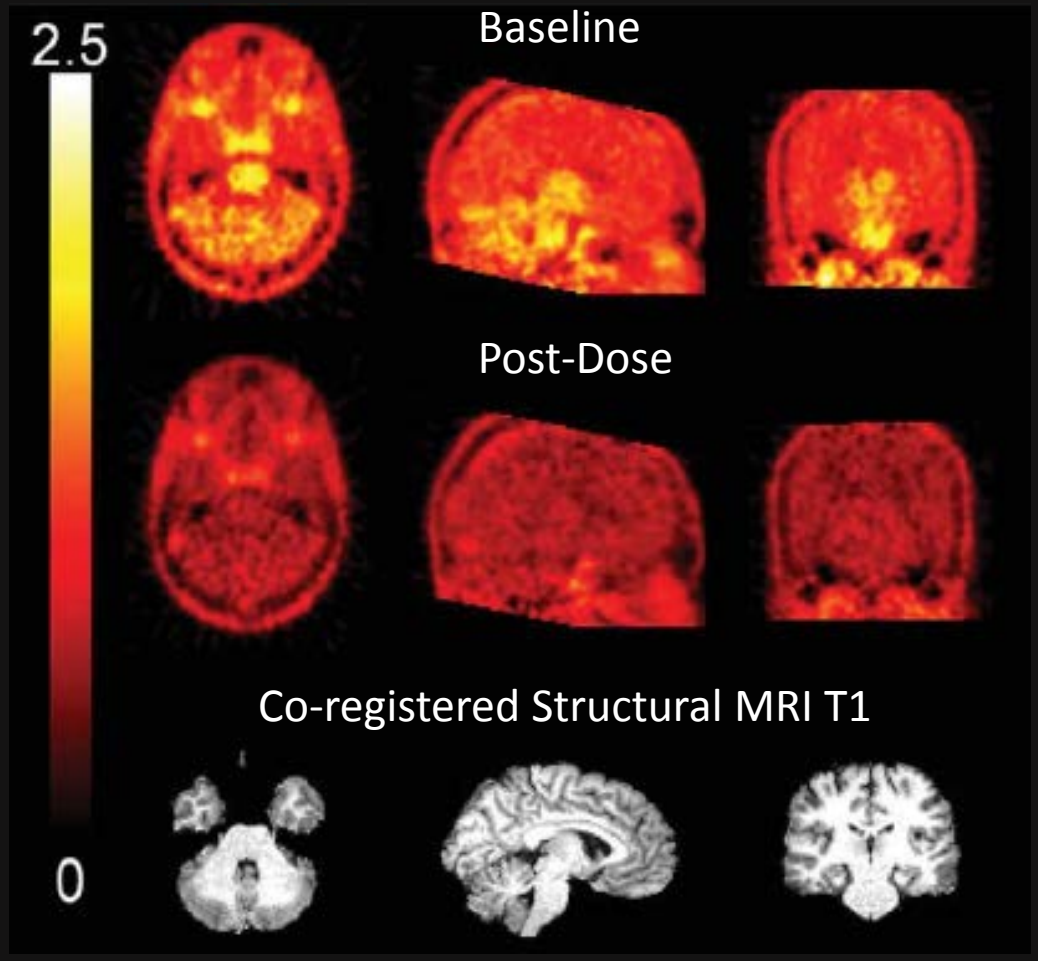
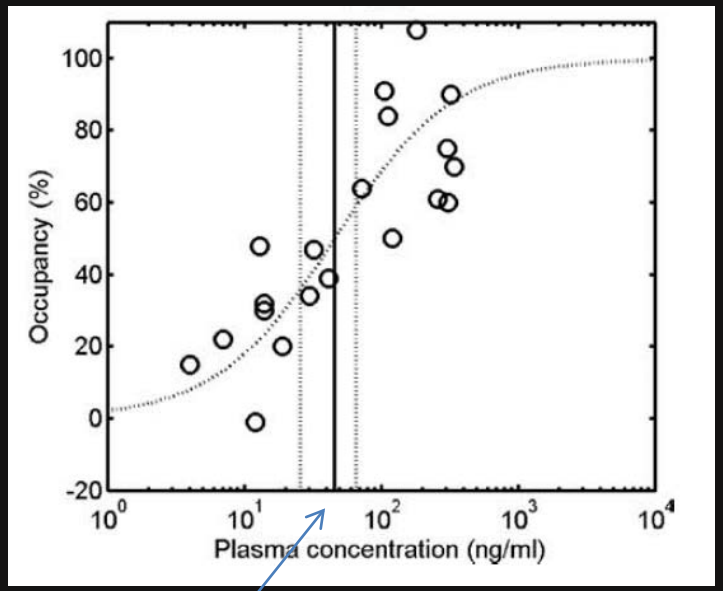


Direct Model Fit to Occupancy (PD) and Plasma Concentration (PK)

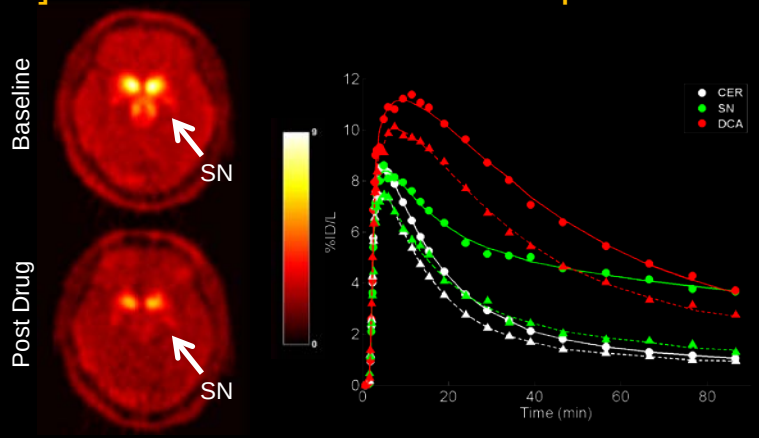


EC_{50}

Gunn, Synapse, 2011

Differentiation based on predicted therapeutic index

[11C]PHNO measurement of Dopamine D3 Receptor Occupancy



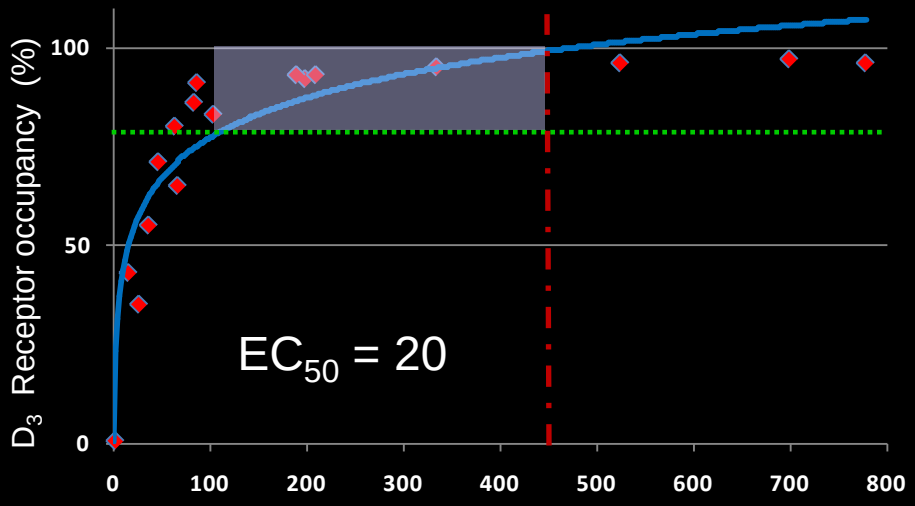
Predicted receptor occupancy values

Target receptor occupancy for therapeutic effect

Concentration associated with ΔQT = 10ms

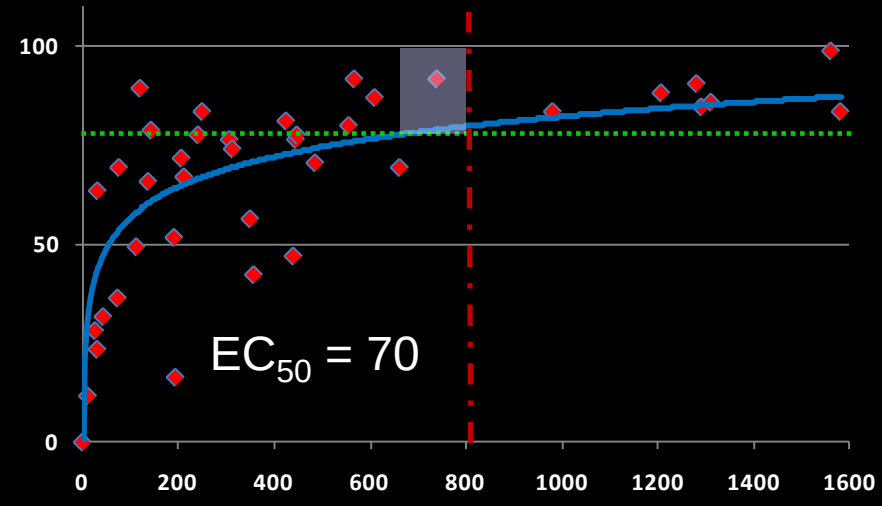
Drug A

Predicted therapeutic index = 4.5



Drug B

Predicted therapeutic index = 1.3



Plasma concentration (ng/mL)

Roger Gunn, 23/01/2012

Optimal Design of these experiments

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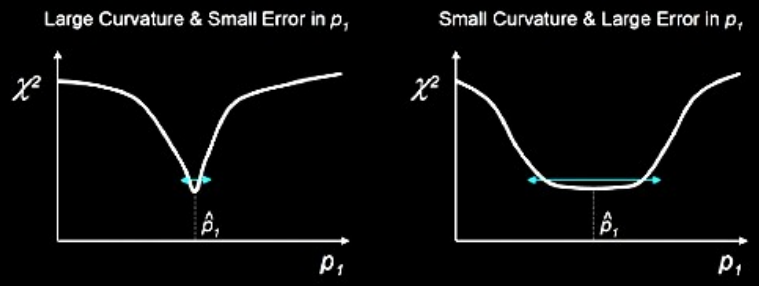
- Given a Model and Set of Parameters
  - OD Determines an optimum set of sampling points

$$\chi^2(\mathbf{p}) = \sum_{i=1}^{N} \left[\frac{y_i - f(t_i;\mathbf{p})}{\sigma_i} \right]^2$$

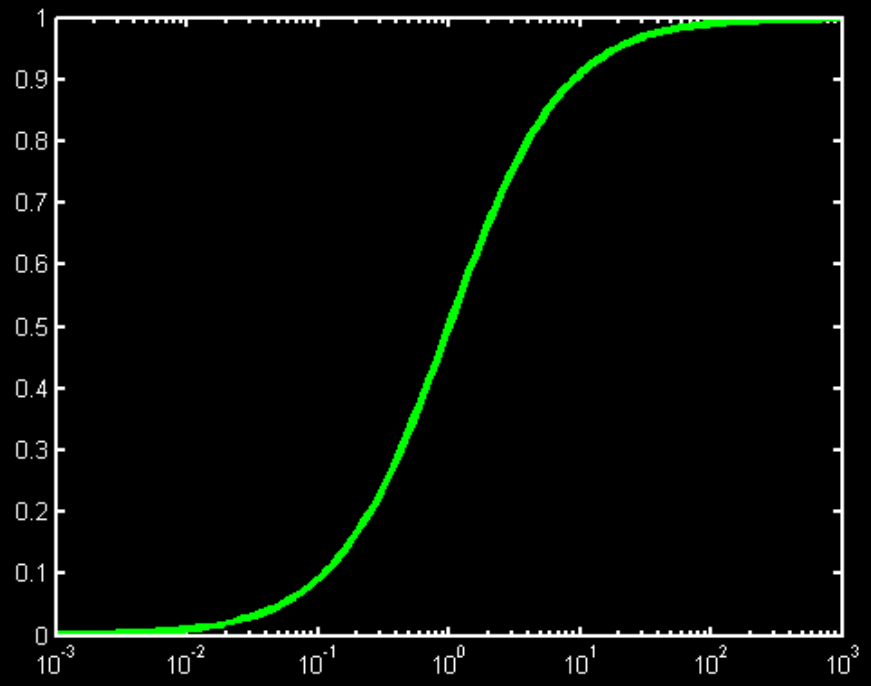
$$\frac{\partial^2 \chi^2}{\partial p_j \partial p_k} = 2 \sum_{i=1}^{N} \frac{1}{\sigma_i^2} \left[\frac{\partial y(t_i;\mathbf{p})}{\partial p_j} \frac{\partial y(t_i;\mathbf{p})}{\partial p_k} - [y_i - f(t_i;\mathbf{p})] \frac{\partial^2 y(t_i;\mathbf{p})}{\partial p_j \partial p_k} \right]$$

$$H_{jk} = \sum_{i=1}^{N} \frac{1}{\sigma_i^2} \left[\frac{\partial y(t_i;\mathbf{p})}{\partial p_j} \frac{\partial y(t_i;\mathbf{p})}{\partial p_k} \right]$$



Optimal Design: A Simple Example

- Emax Model: Dose-Occupancy Model
  - 1 parameter (ED_{50})
  - 1 data point: What dose should we sample at ?



$$Occ\left(D; ED_{50}\right) = \frac{D}{D + ED_{50}}$$

Optimal Design: A Simple Example

- Calculate Information Matrix from partial derivatives

$$\frac{\partial Occ\left(D;ED_{50}\right)}{\partial ED_{50}} = \frac{-D}{\left(D+ED_{50}\right)^{2}}$$

$$H = \frac{\partial Occ\left(D;ED_{50}\right)}{\partial ED_{50}} \frac{\partial Occ\left(D;ED_{50}\right)}{\partial ED_{50}} = \frac{D^{2}}{\left(D+ED_{50}\right)^{4}}$$

Optimal Design: A Simple Example

- Maximize determinant (D-Optimal) over D

$$\max_{\{D\}}\left(Det(H)\right)=\max_{\{D\}}\left(\frac{D^2}{\left(D+ED_{50}\right)^4}\right)$$

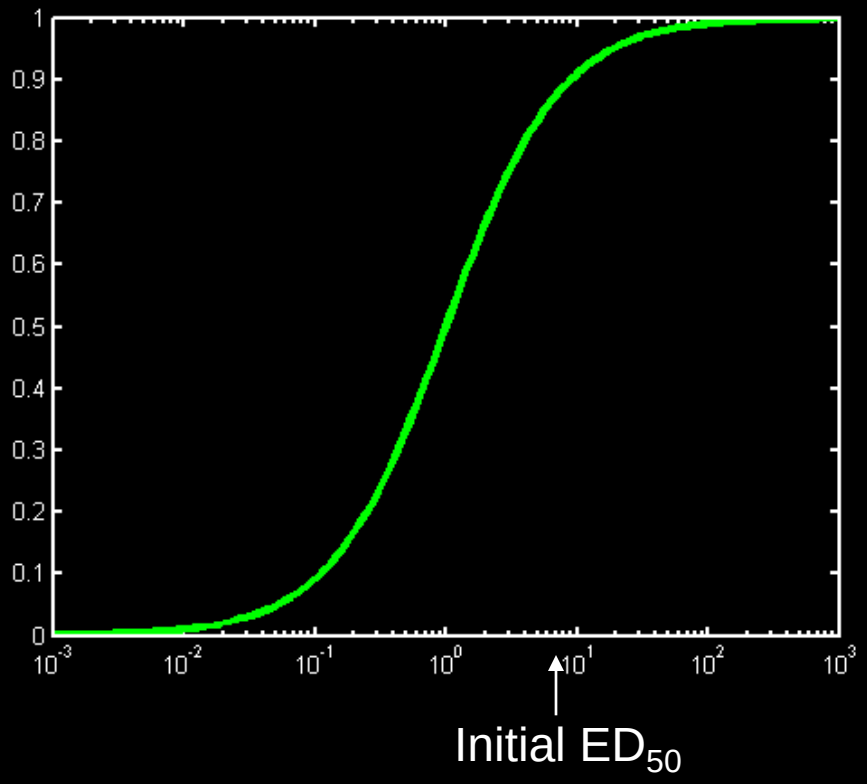
- In this simple case can differentiate and set=0 to find max,

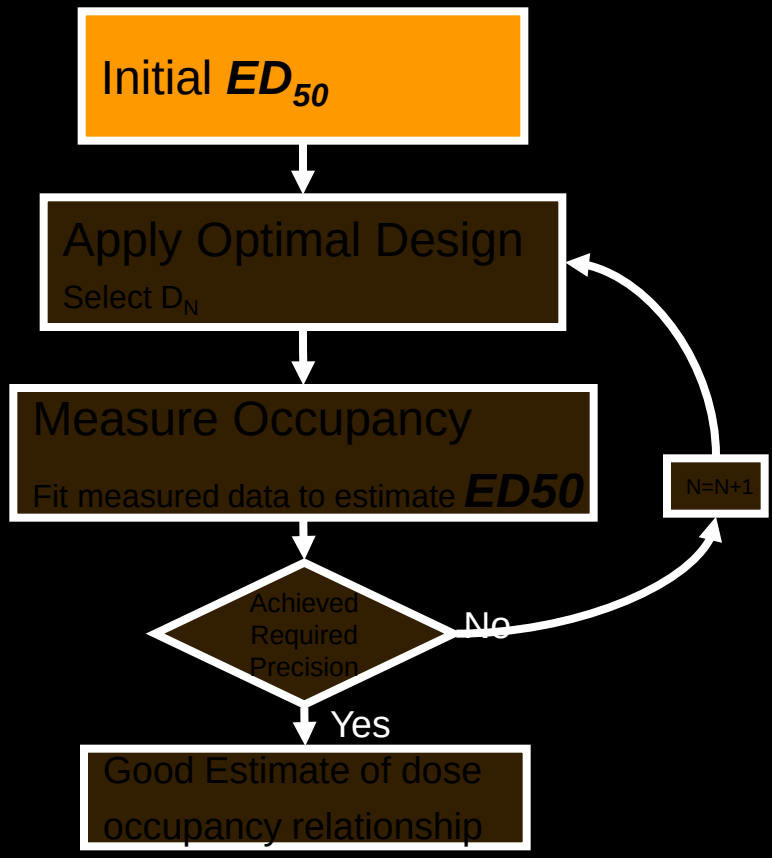
$$\frac{\partial Det(H)}{\partial D}=\frac{2D\left(ED_{50}-D\right)}{\left(D+ED_{50}\right)^5}$$

$$\Rightarrow \quad D=ED_{50}$$

Adaptive Optimal Design: Simple Example

- Emax Model: Dose-Occupancy Model
  - 1 parameter (ED_{50})
  - N data points





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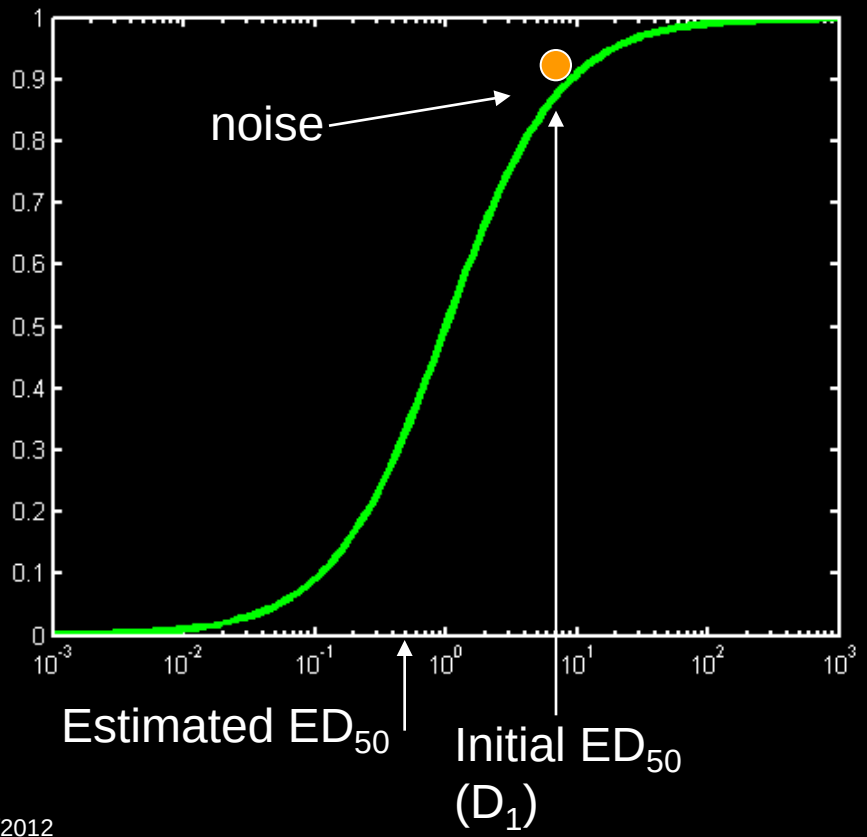

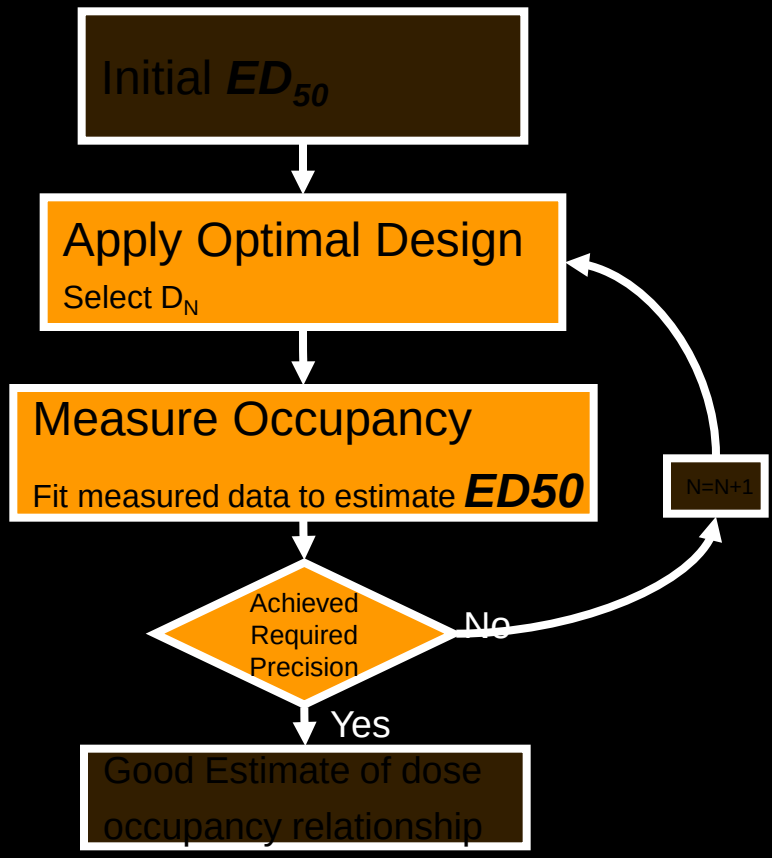

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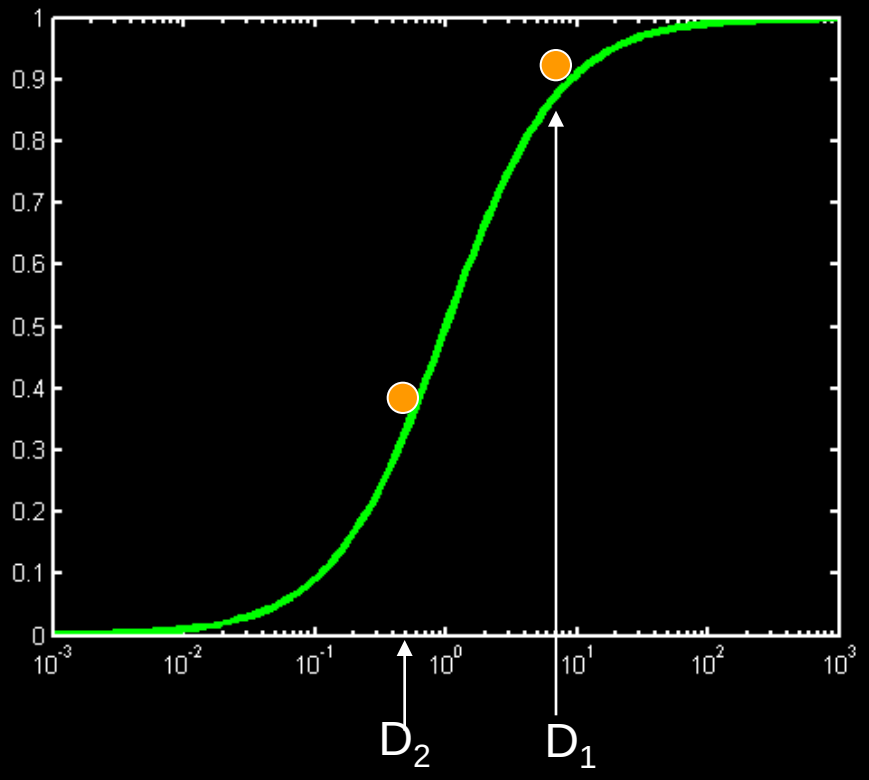

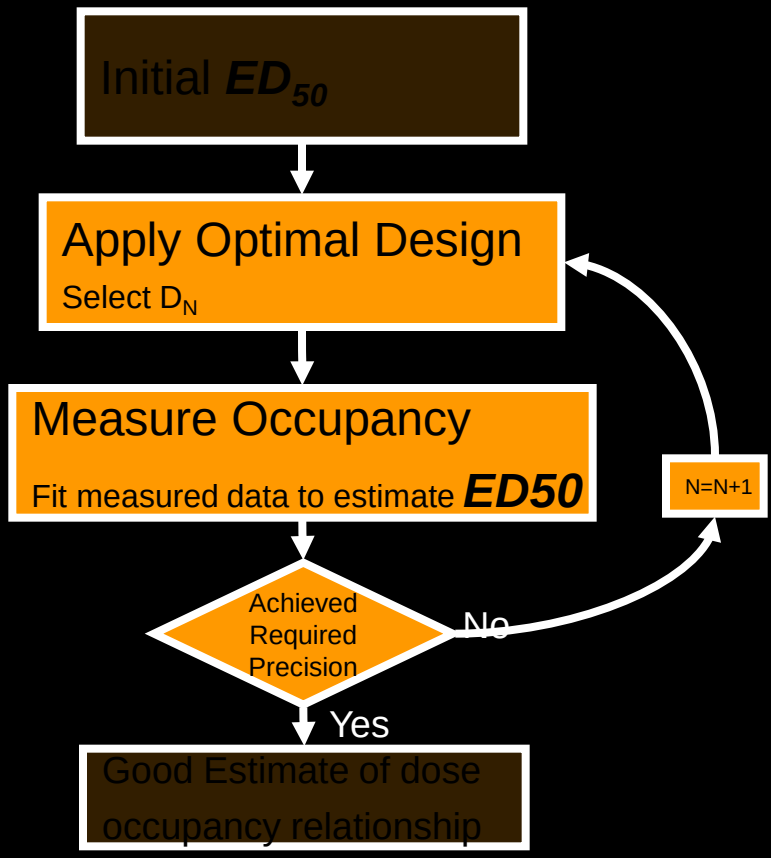

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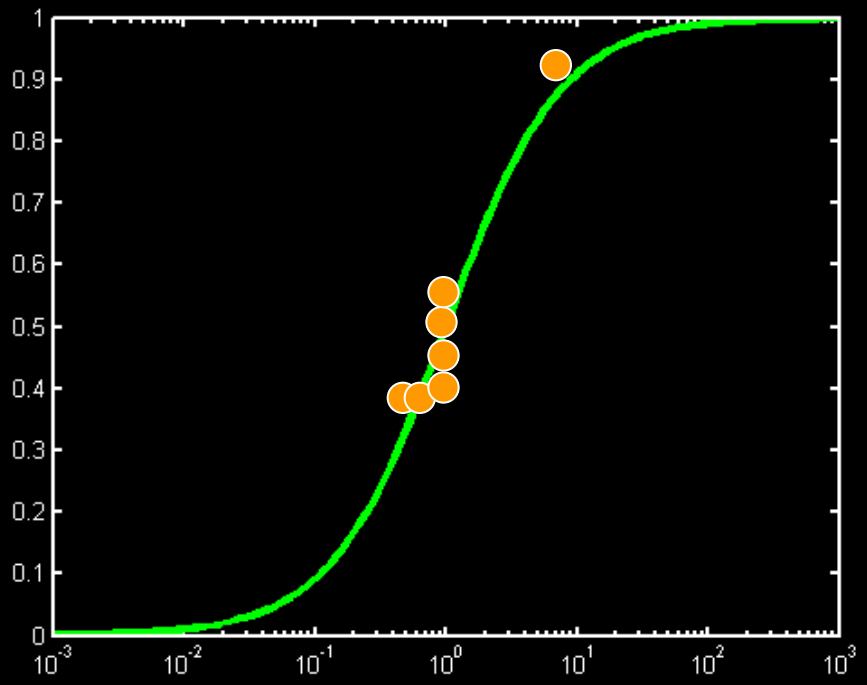
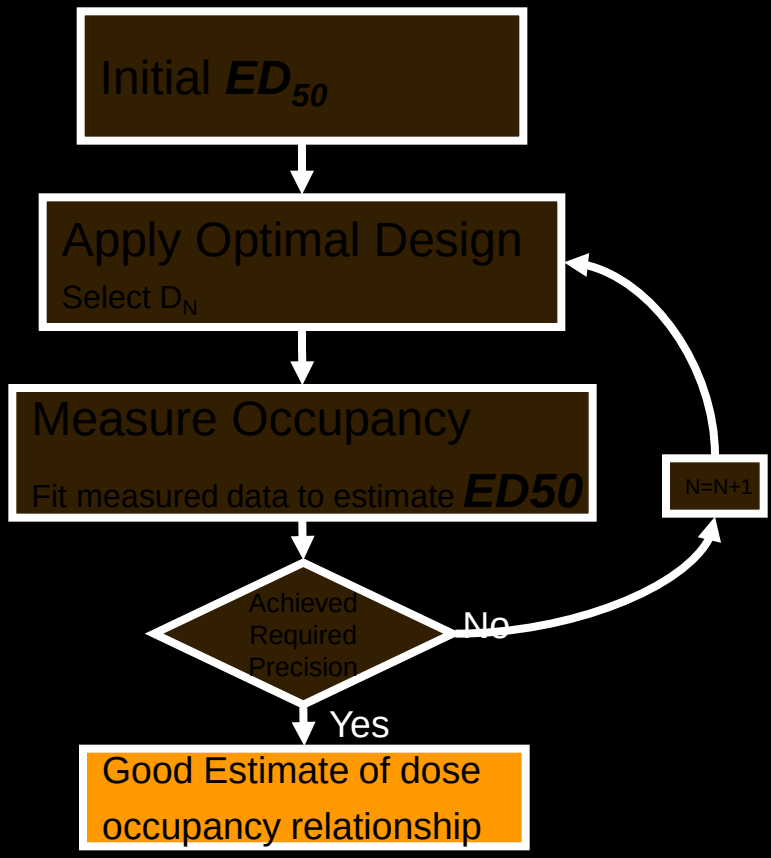
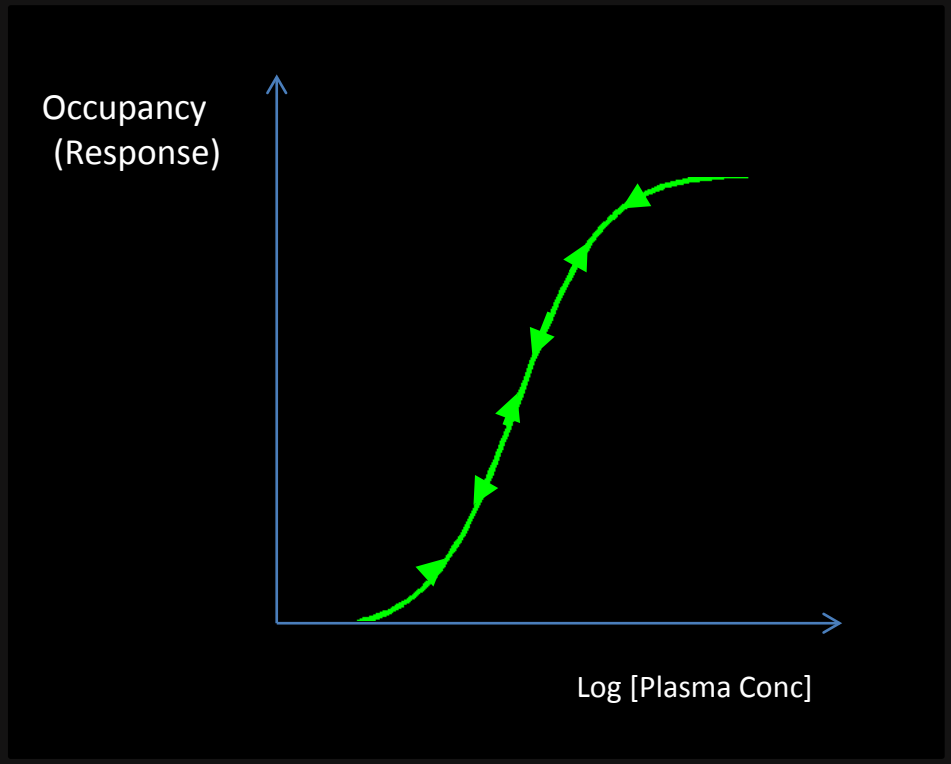




Direct Model - Summary



Occupancy (or response) is determined by the instantaneous plasma concentration and the direct model parameters (EC_{50}).

Can be sampled using Adaptive Optimal Experimental Design

Extended Single Dose Example

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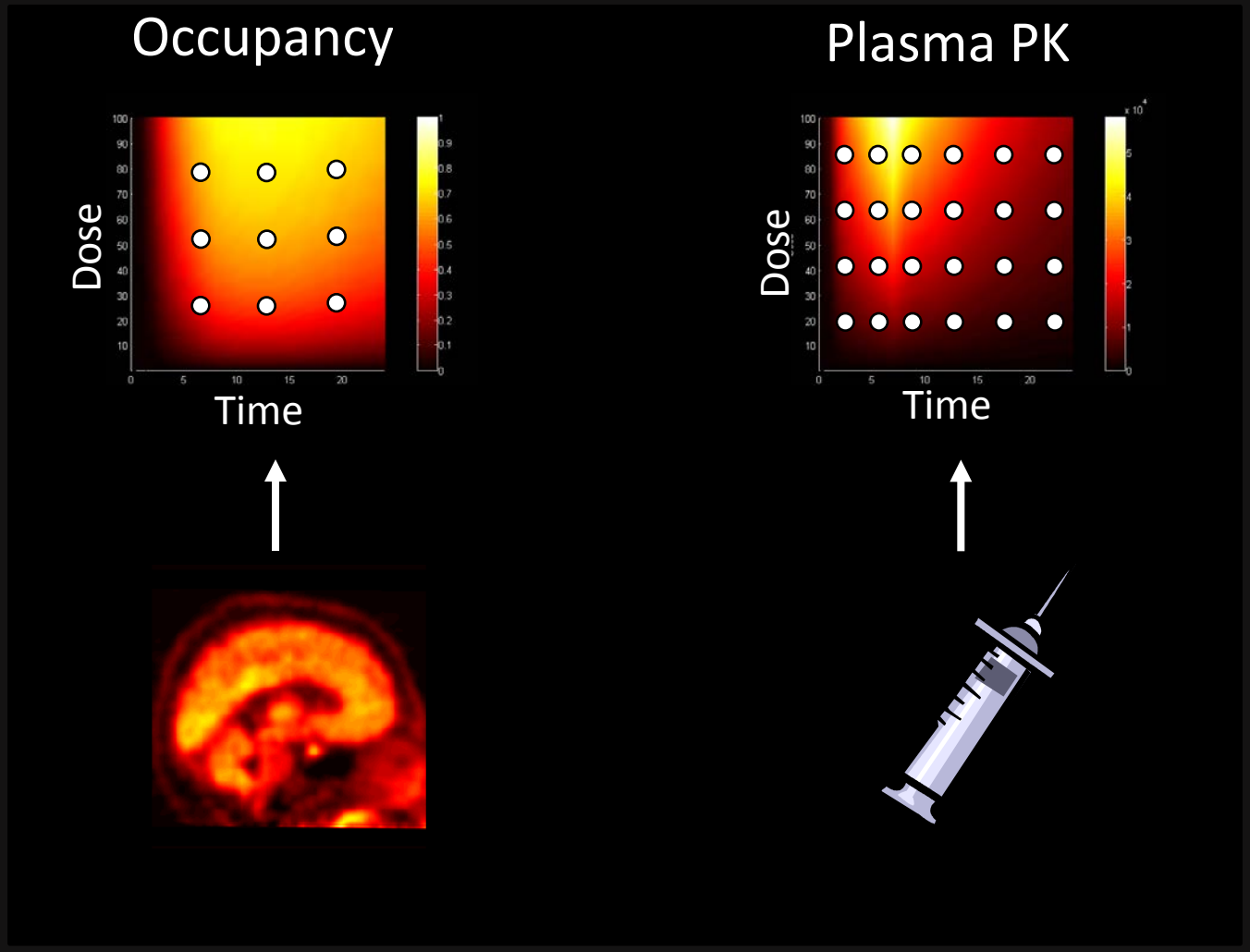
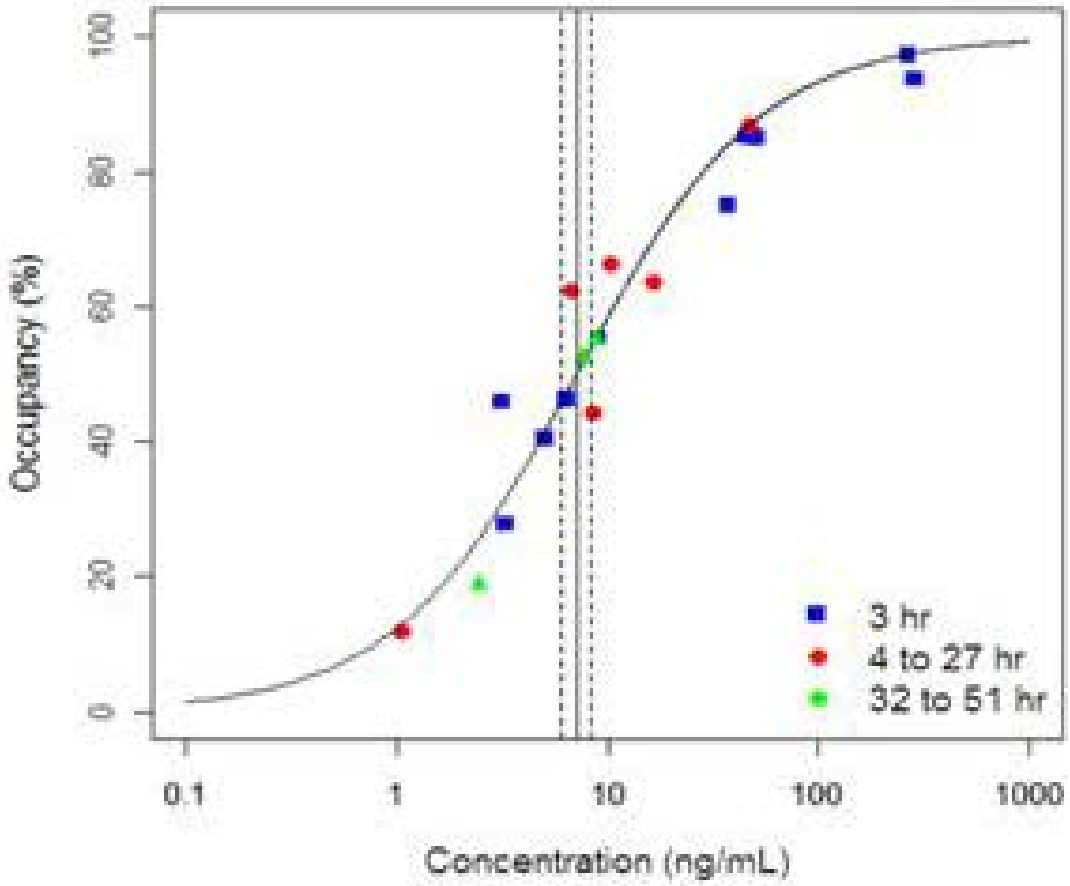


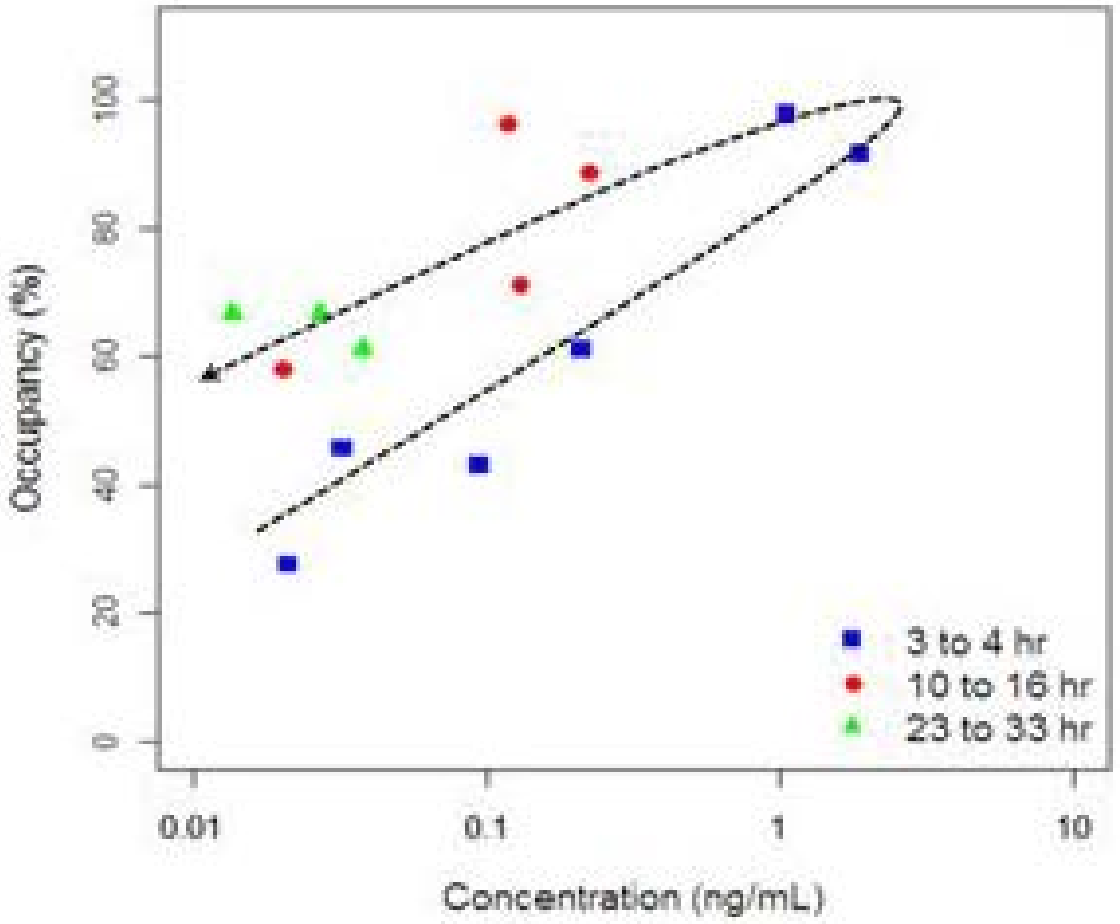
GSK1521498 μ-opioid PET receptor occupancy



Direct Model Fit

Rabiner, Mol Psych, 2011

Naltrexone μ-opioid PET receptor occupancy



Polynomial Interpolation

Rabiner, Mol Psych, 2011

GSK1521498 vs. Naltrexone:

Differentiation based on RO (PET) / PD (fMRI) relationships

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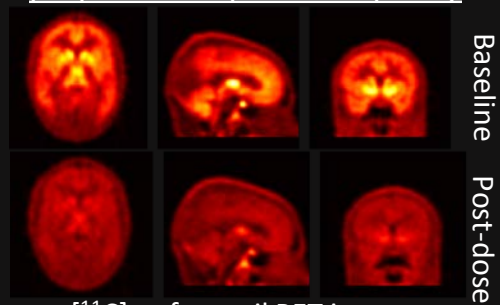
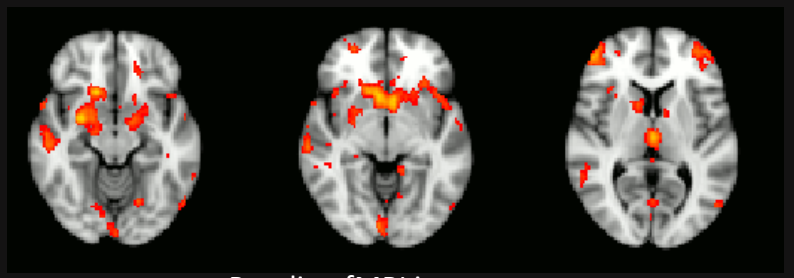
μ opioid receptor occupancy



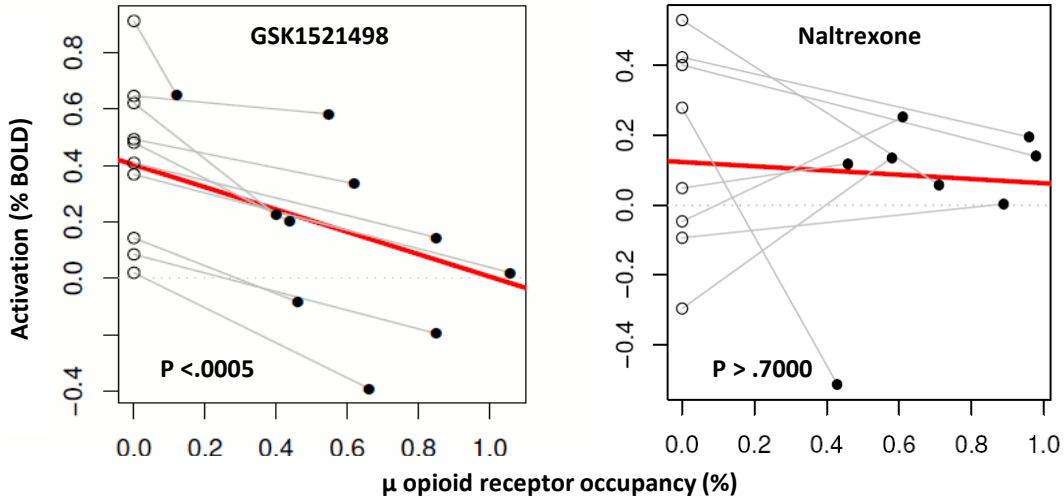
[^{11}C]carfentanil PET images

Brain activation to sweet tastes



Baseline fMRI images

μ opioid RO & amygdala response to sweet taste

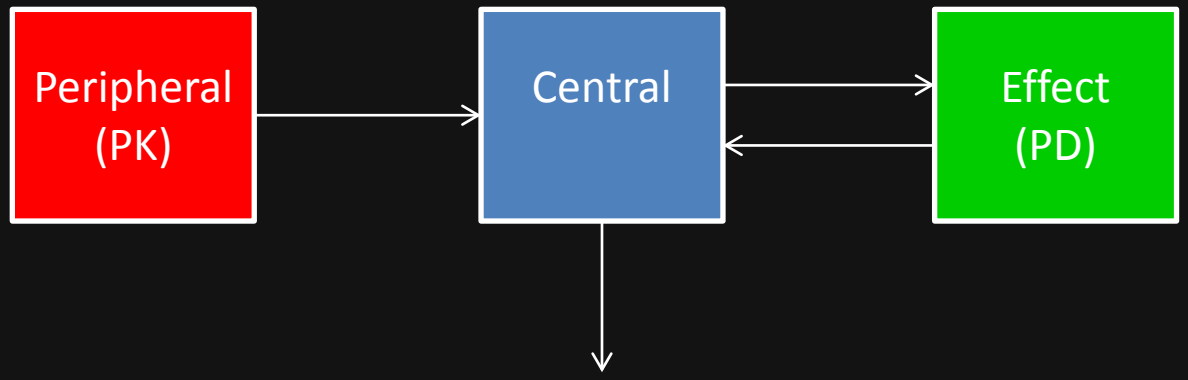


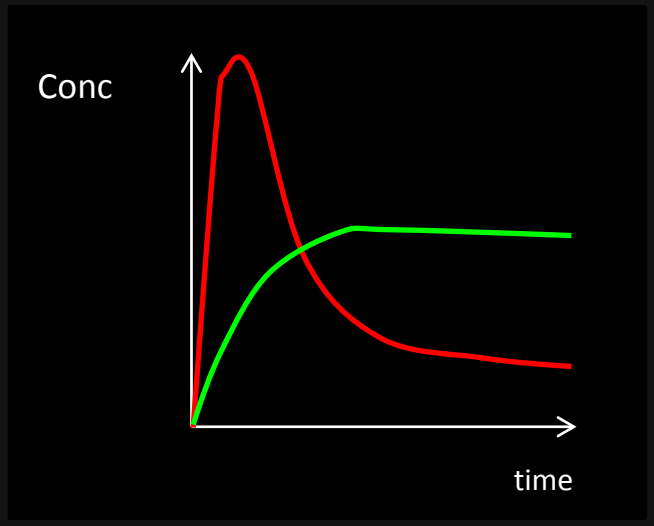
GSK1521498 attenuated the preferential response to smoothie (over H_20) in amygdala and hippocampus as a function of μ opioid RO

Naltrexone did **NOT** affect the preferential response to smoothie in any brain region

Rabiner, Mol Psych, 2011

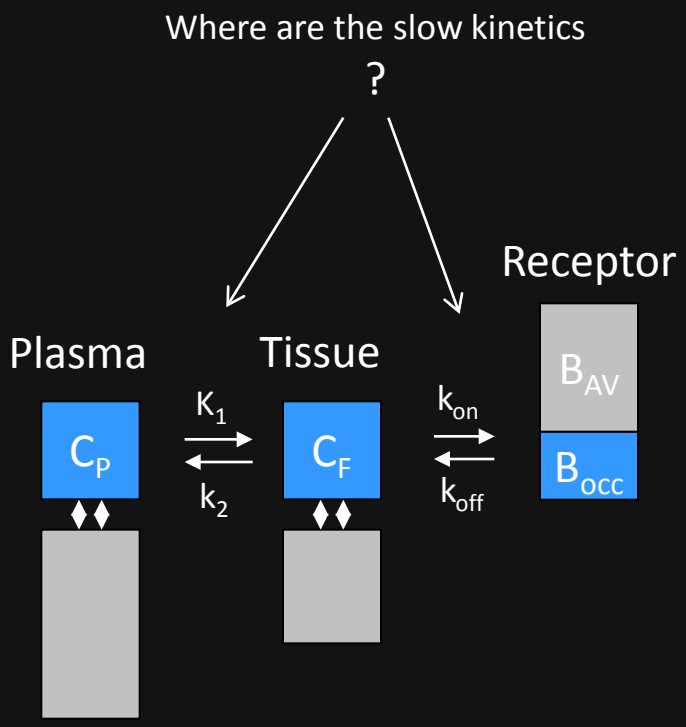
Indirect Models





Hysteresis effect
or
Indirect effect
or
delay effect
or
…

Indirect PK RO Models

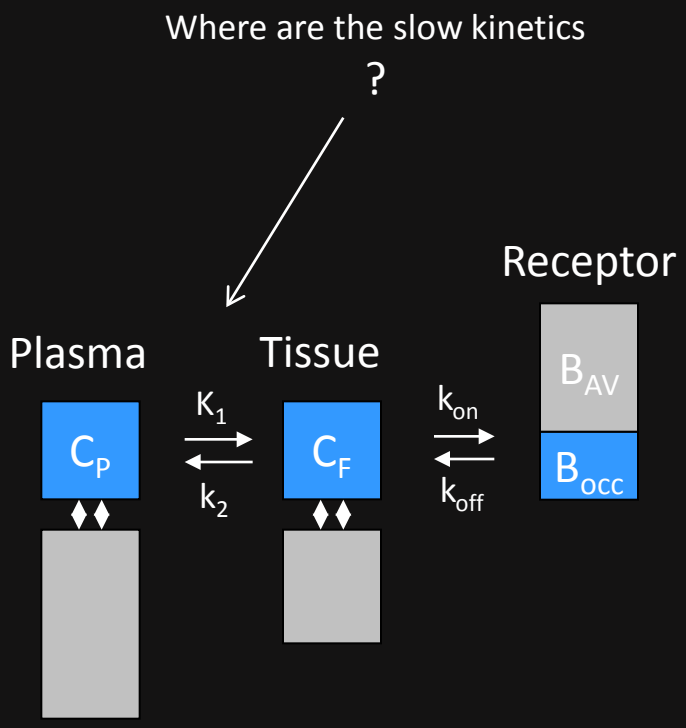


Indirect PK RO Models

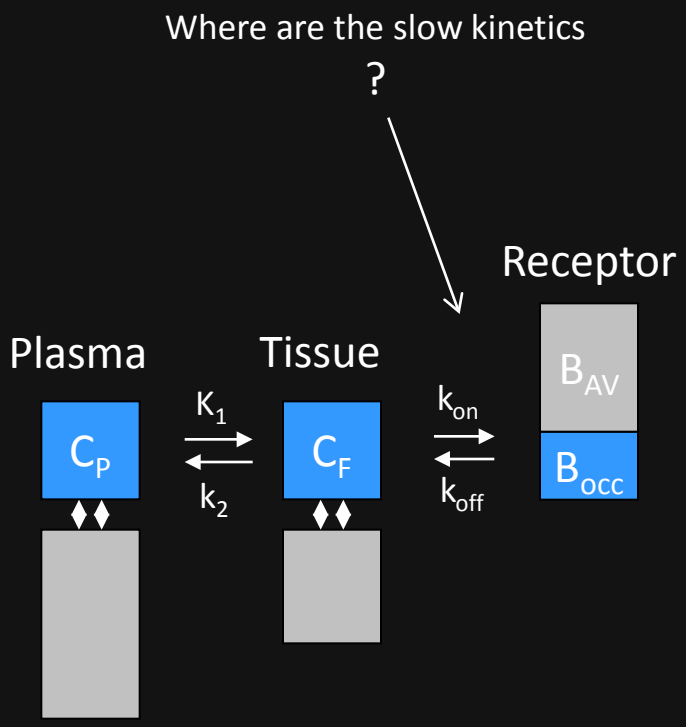
Model I: BBB Limited Model

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.

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



Indirect PK RO Models



Model II: k_{on}-k_{off} Limited Model

Assumes receptor association and dissociation are finite.

$$\frac{dRO}{dt} = k_{on} \cdot C_P \cdot (R_T - RO) - k_{off} \cdot RO$$

Indirect PK RO Models

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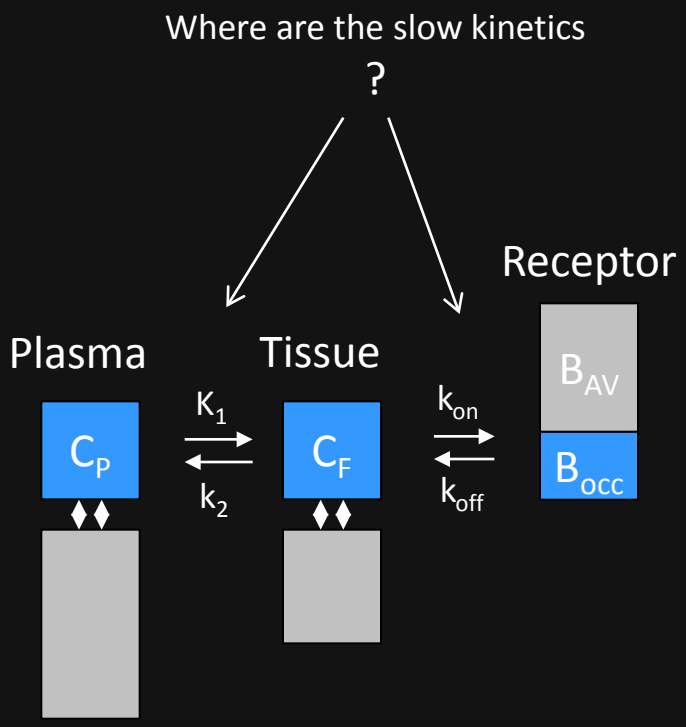
Assumes receptor association and dissociation are finite.

$$\frac{dRO}{dt} = k_{on} \cdot C_P \cdot (R_T - RO) - k_{off} \cdot RO$$



Mathematically can have more complex systems with both effects

Direct & Indirect Models

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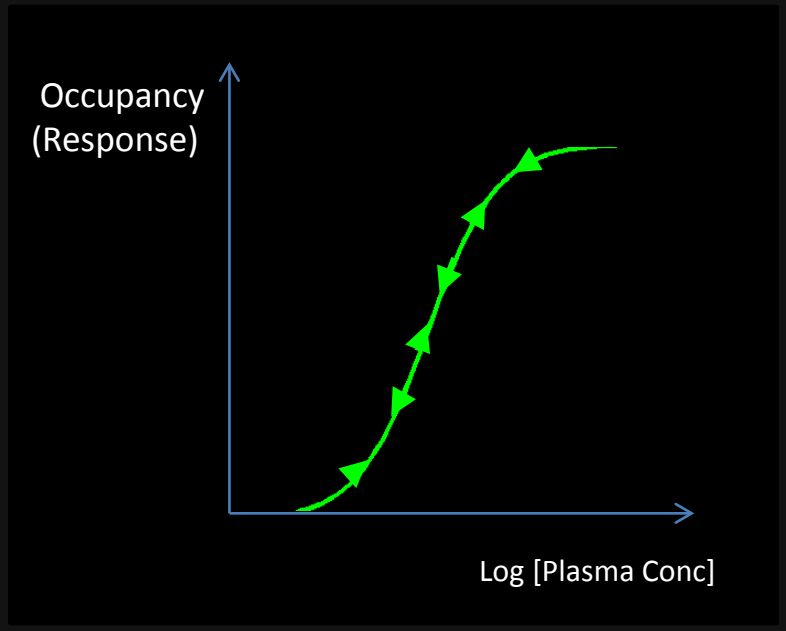
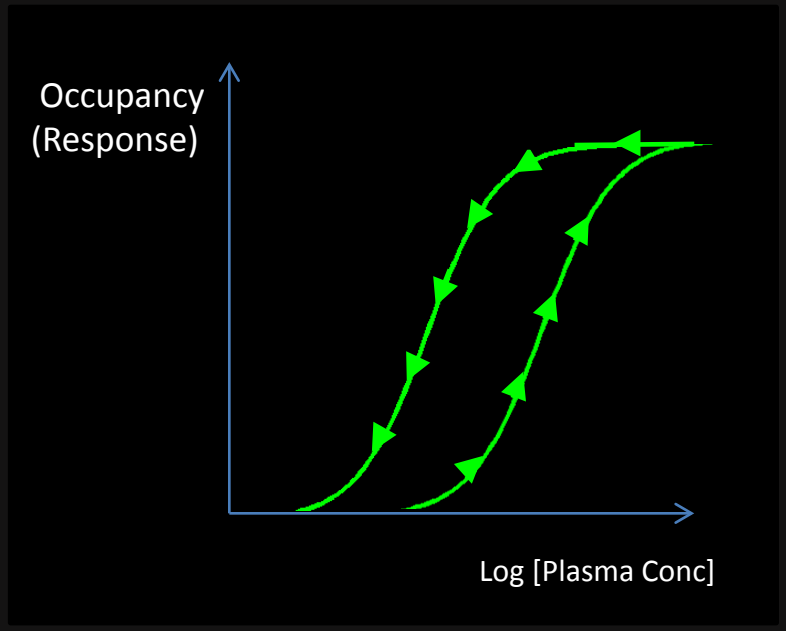
Direct Model



Occupancy (or response) is determined by the instantaneous plasma concentration and the direct model parameters (e.g. EC_{50}).

Indirect Model



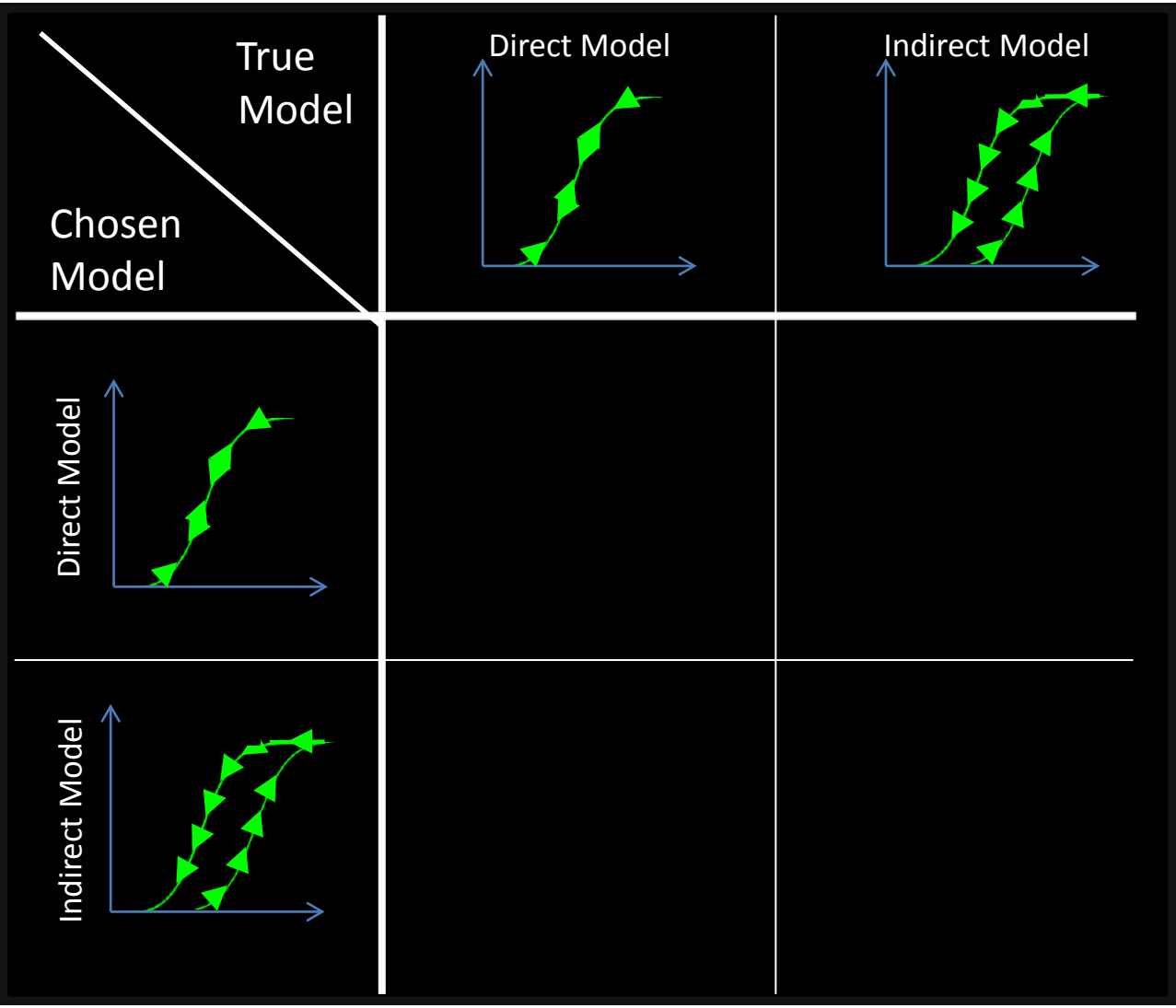
Occupancy (or response) is determined by the historical plasma concentration and the indirect model parameters (e.g. $EC_{50,}$ k_{off}).

"Hysteresis, Indirect, delay effect "

Model Selection and Implications

Model Parsimony Criteria used to Determine Best Model

Balance of Goodness of Fit and Model Complexity



Model Selection and Implications

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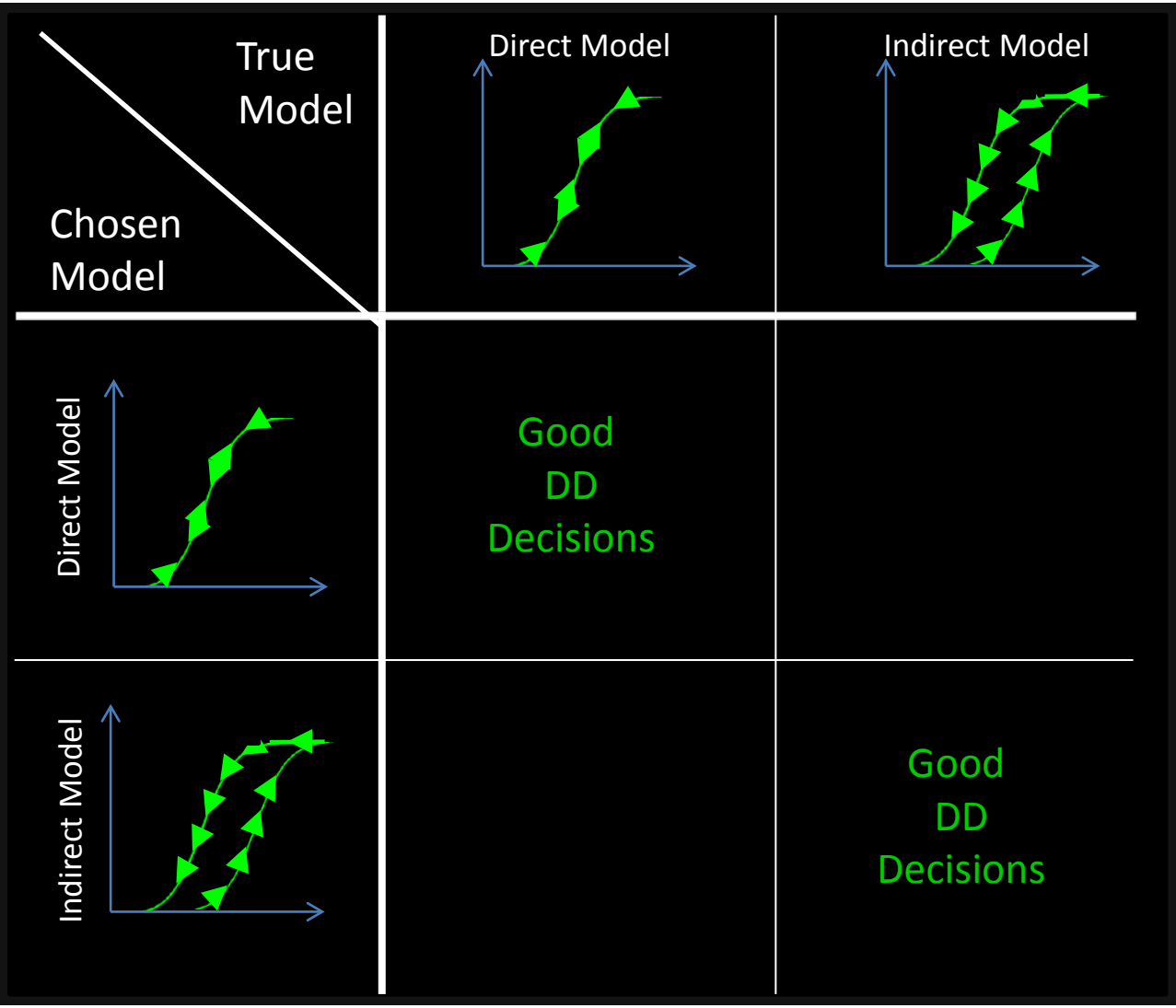
Model Parsimony Criteria used to Determine Best Model

Balance of Goodness of Fit and Model Complexity



Model Selection and Implications

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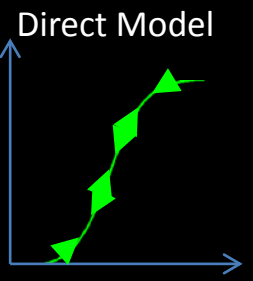
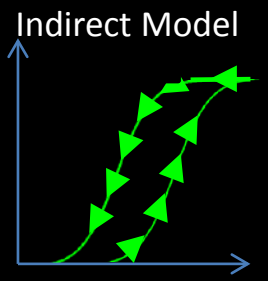
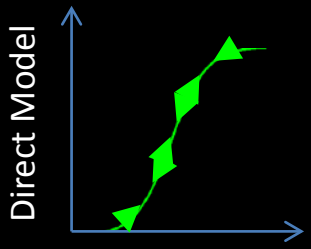
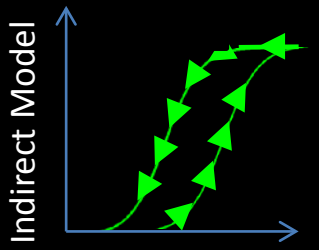
Model Parsimony Criteria used to Determine Best Model

Balance of Goodness of Fit and Model Complexity

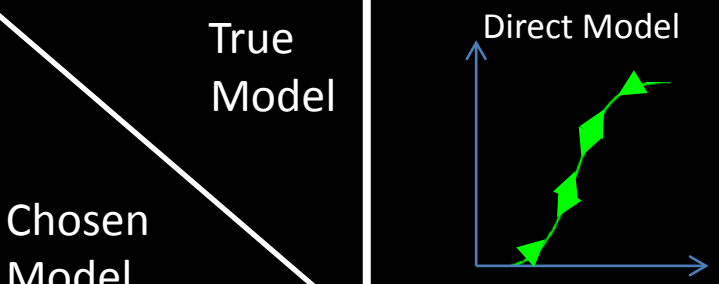
Chosen Model \ True Model	 Direct Model	 Indirect Model
 Direct Model	Good DD Decisions	Poor DD Decisions "Dose to Low"
 Indirect Model		Good DD Decisions

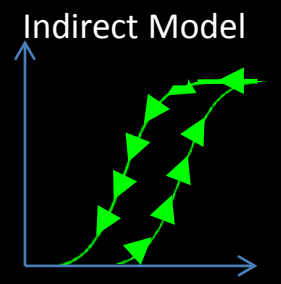
Model Selection and Implications

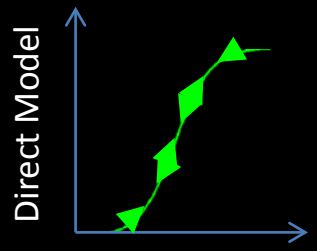
Model Parsimony Criteria used to Determine Best Model

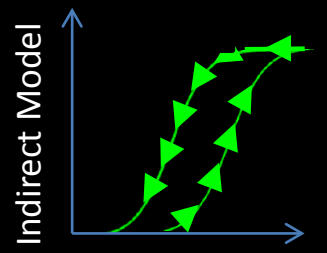
Balance of Goodness of Fit and Model Complexity

Chosen Model \ True Model	Direct Model	Indirect Model
Direct Model	Good DD Decisions	Poor DD Decisions "Dose to Low"
Indirect Model	Poor DD Decisions "Increased variance"	Good DD Decisions

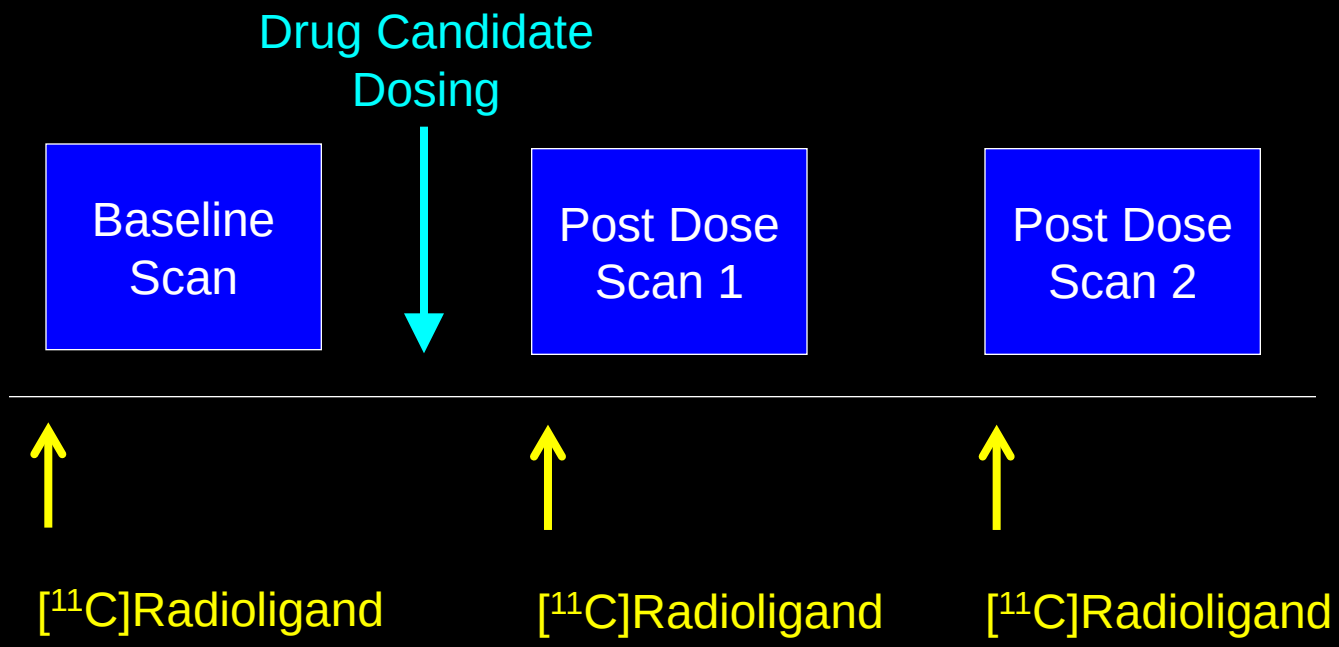








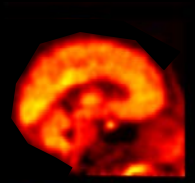
Receptor Occupancy in Drug Development



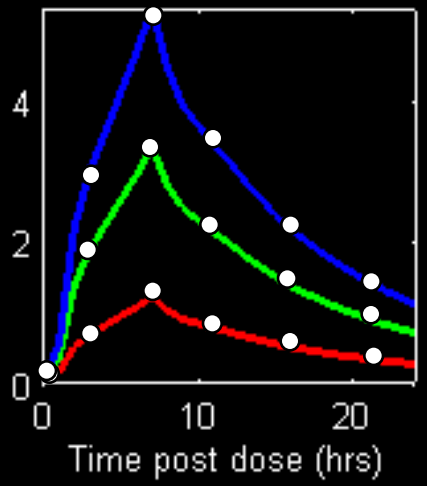
- Dosimetry considerations typically limits the number of scans to 3
- Occupancy will vary as a function of time and dose
- Example: 4 volunteers, scanned at 4 h and 7 d post MTD

  Mean Occupancy at 4 h post MTD : 44%
  Mean Occupancy at 7 d post MTD: 52%
  Target Occupancy: >75%
  Go or No Go?

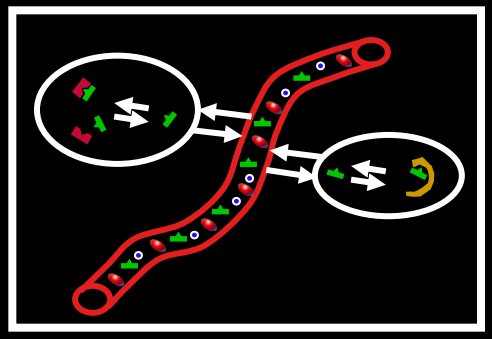
Characterizing the PK-RO Relationship



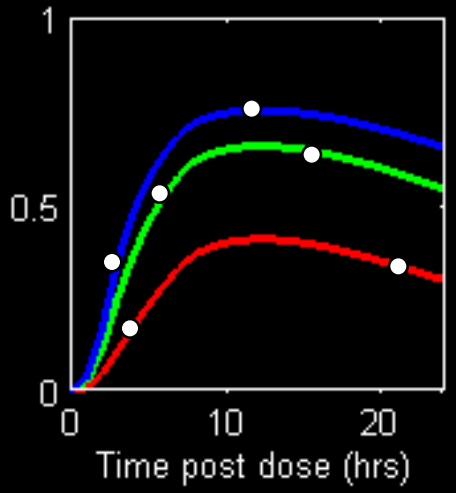
Plasma PK

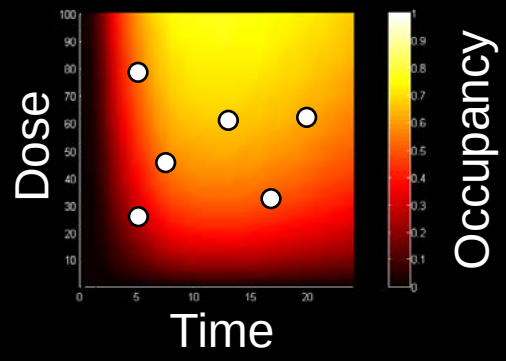


PK/RO Model



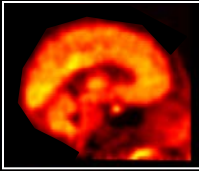
PET Occupancy





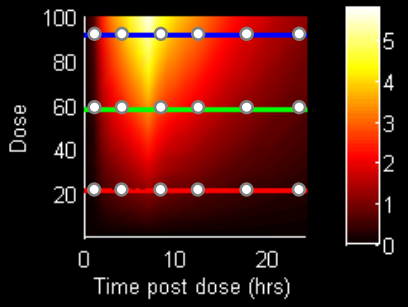
Predicting RD occupancy from SD studies

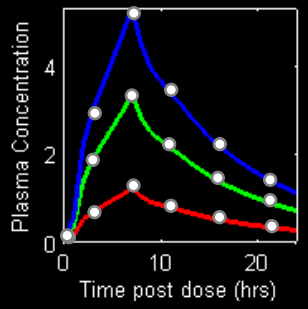
Plasma PK



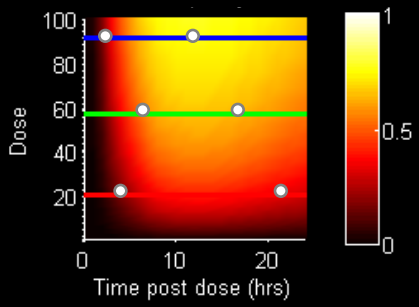
Occupancy (PET)

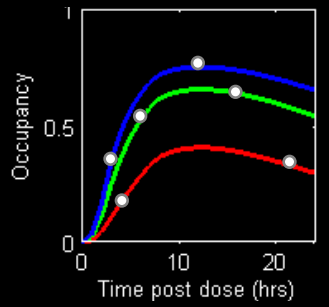
Single Dose (SD)





PK/RO Model

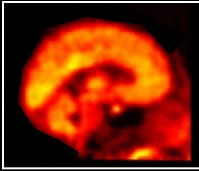




Roger Gunn, 23/01/2012

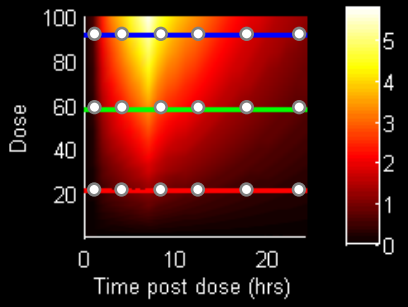
Predicting RD occupancy from SD studies

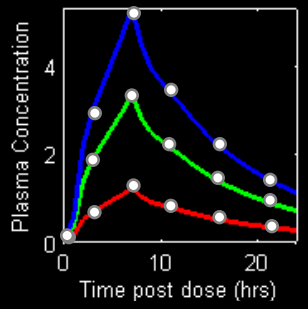
Plasma PK



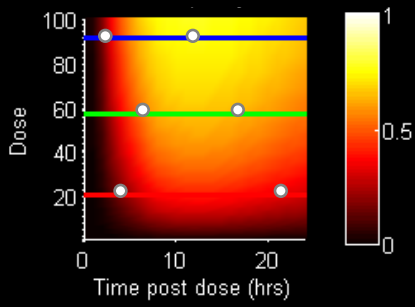
Occupancy (PET)

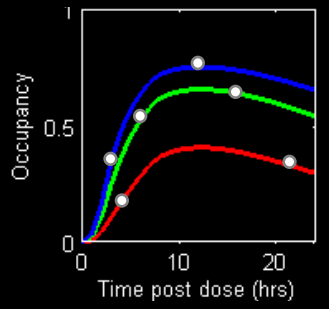
Single Dose (SD)





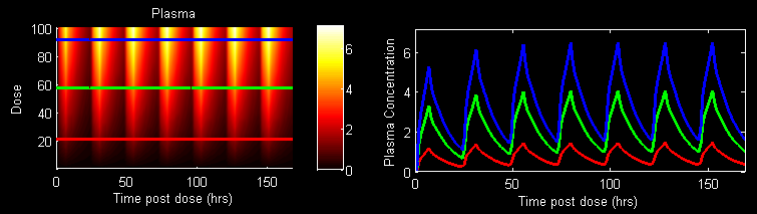
PK/RO Model





SD → RD PK Model

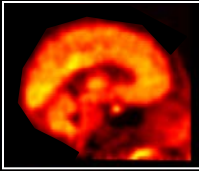
Repeat Dose (RD)



Roger Gunn, 23/01/2012

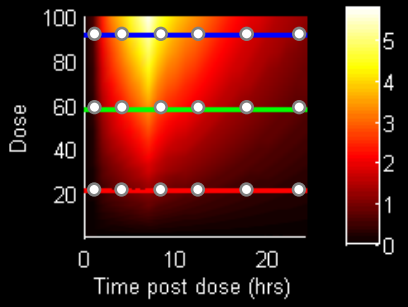
Predicting RD occupancy from SD studies

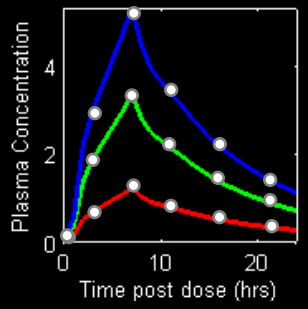
Plasma PK



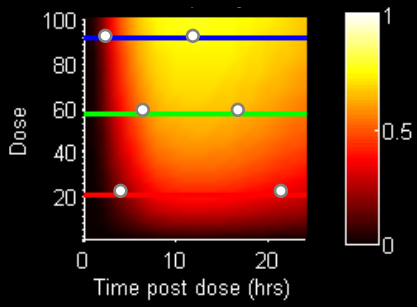
Occupancy (PET)

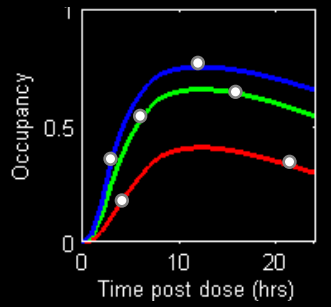
Single Dose (SD)





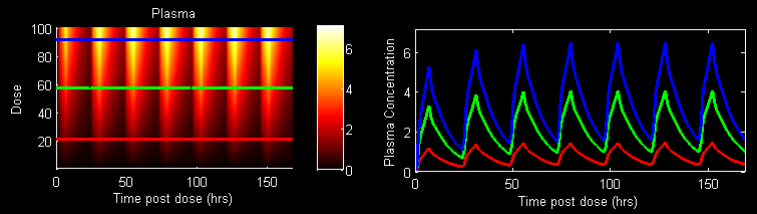
PK/RO Model

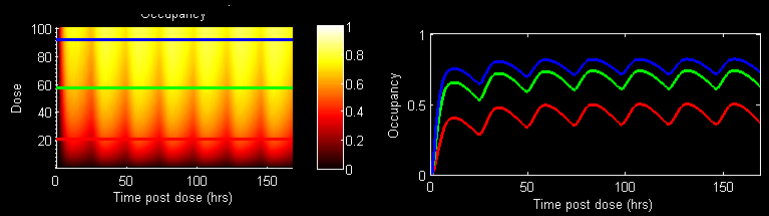




SD → RD PK Model

Repeat Dose (RD)

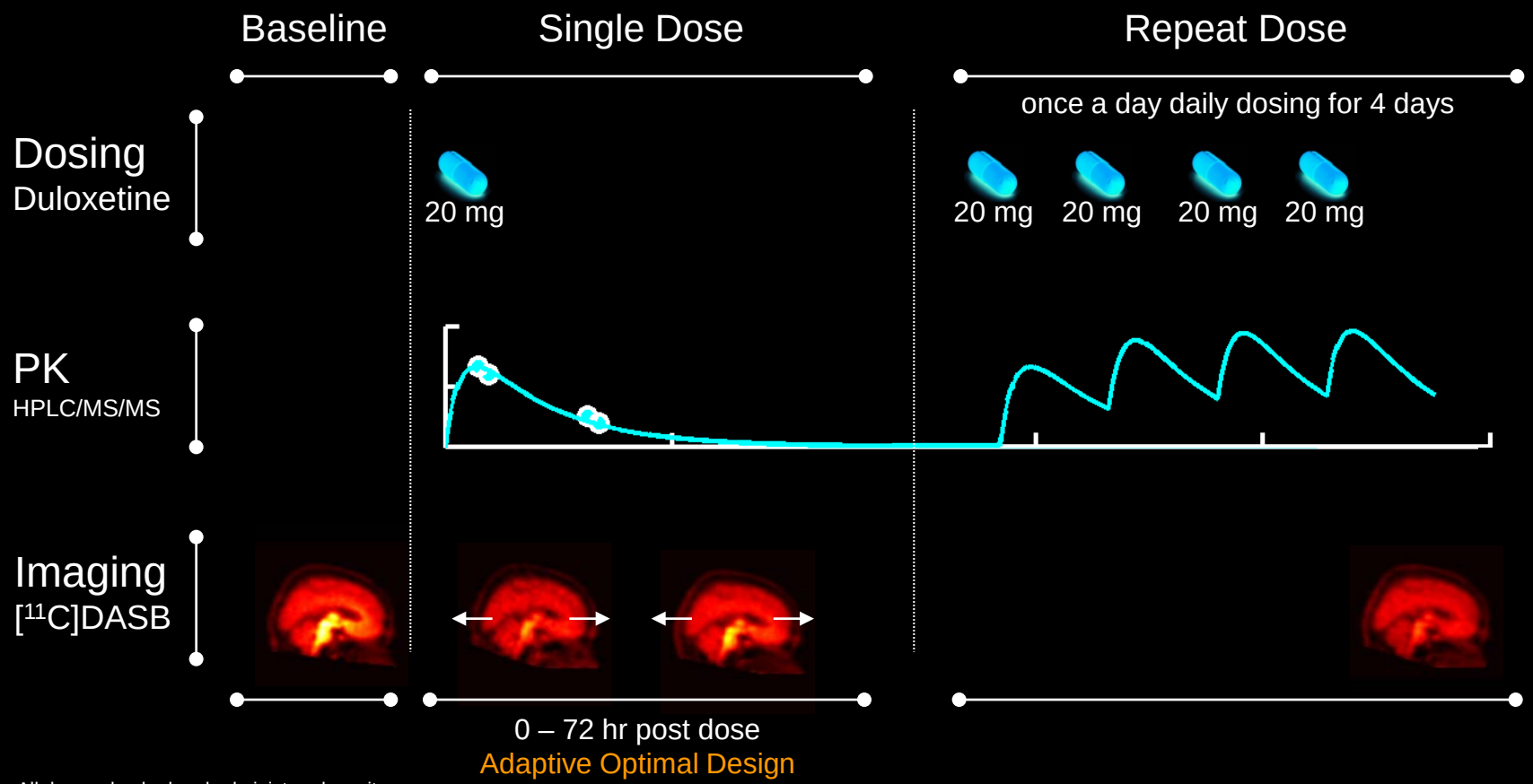




Roger Gunn, 23/01/2012

SERT occupancy by Duloxetine

Experimental Design

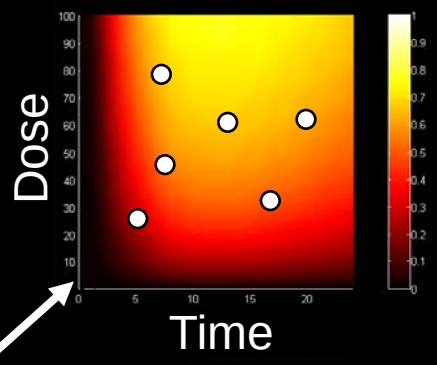


All doses checked and administered on site

Abanades et al, JCBFM, 2011

Single Dose: PK/Occupancy Model

Occupancy



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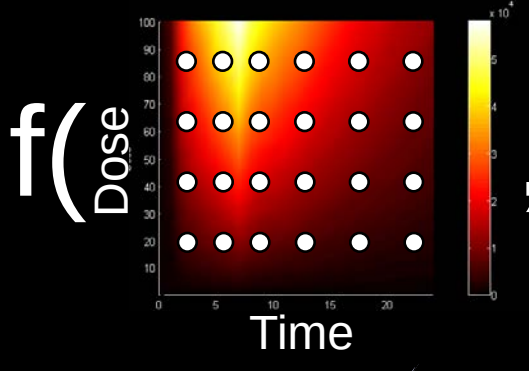
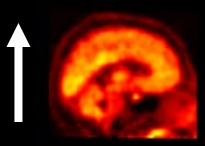
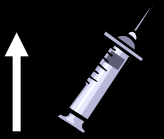
Plasma PK



f(,***p***)

Optimize Sampling





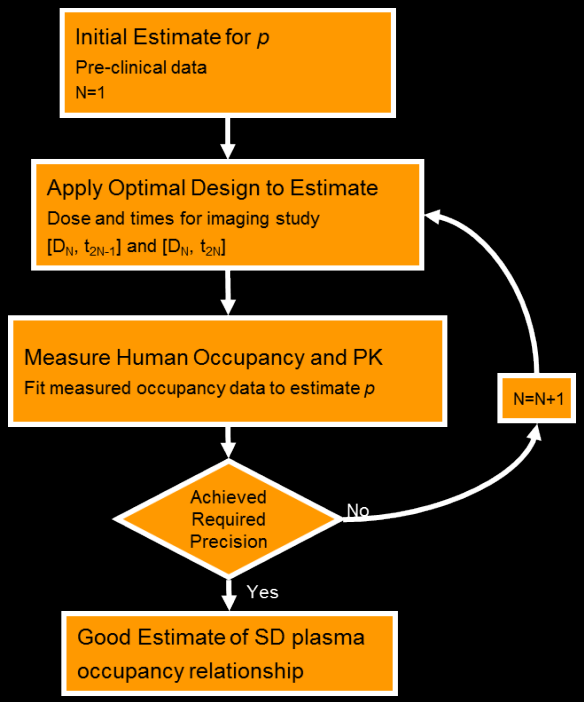
Adaptive-Optimal Design

- Measures
  - Expensive
  - Technically sophisticated
- Optimal sampling critical to define Dose-Time Occupancy Surface

Established Methods

- Measures
  - Cheaper
  - Technically simpler

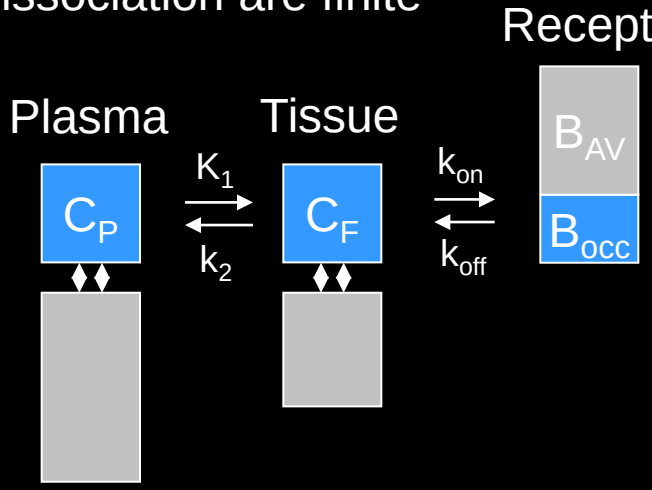
Application of Adaptive Optimal Designs to estimate PK-RO Model Parameters



Indirect Model

k_{on} - k_{off} Limited Model

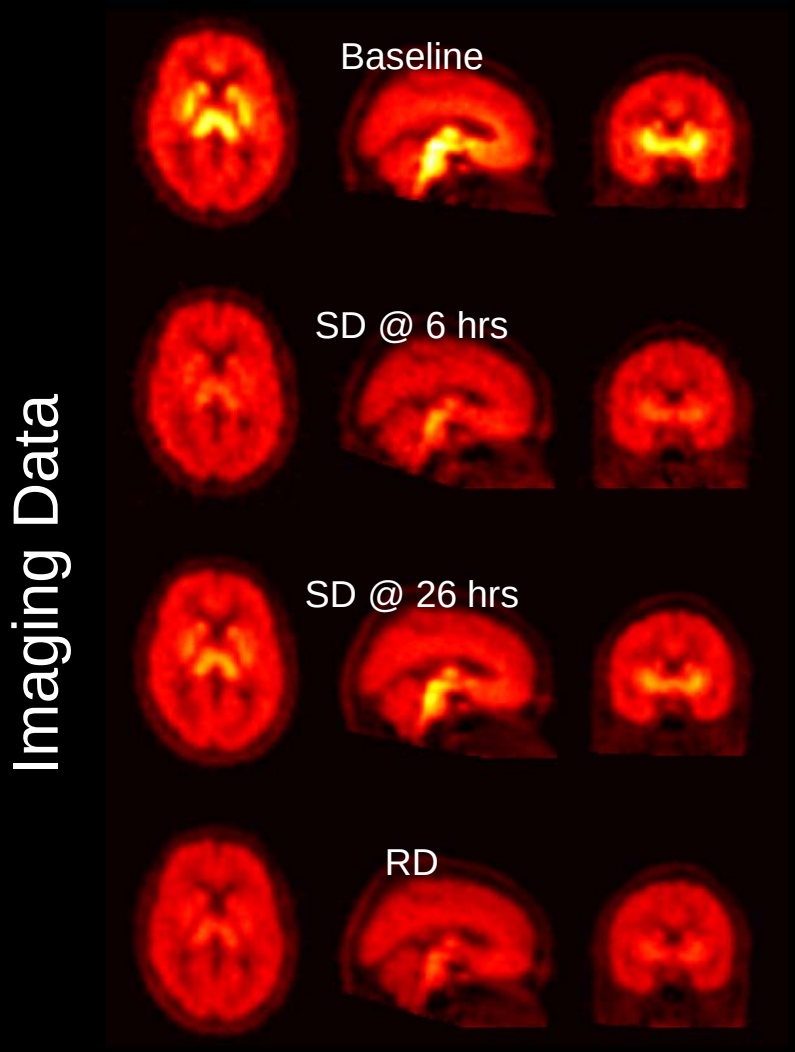
Assumes receptor association and dissociation are finite

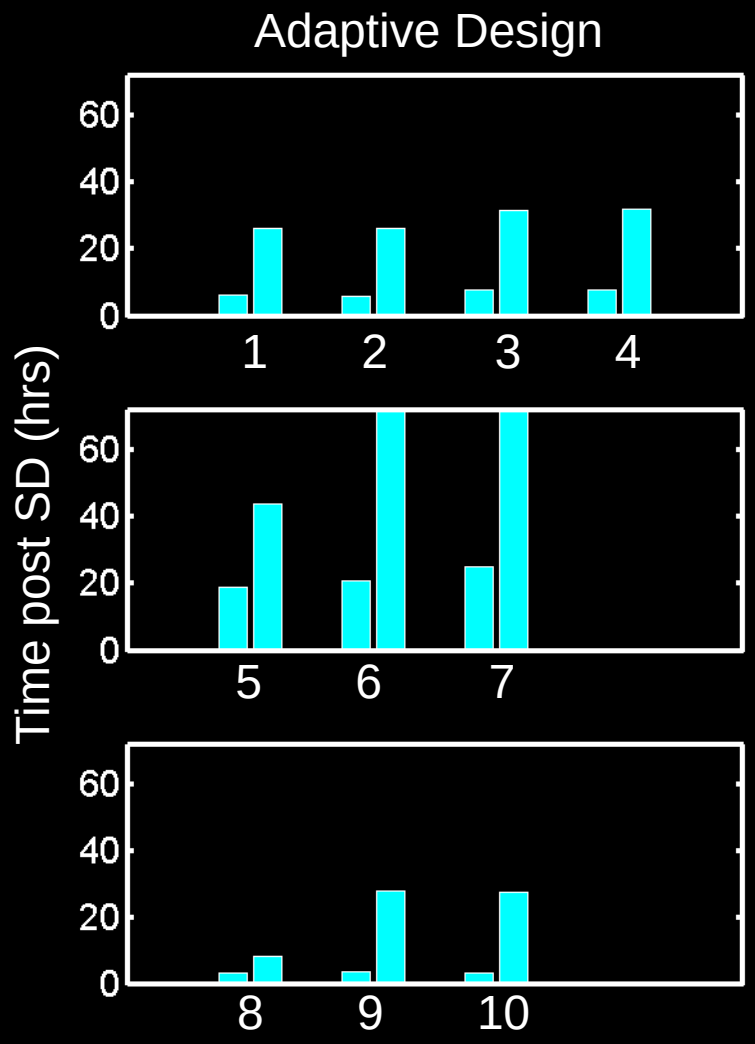


$$\frac{dRO}{dt} = k_{on} \cdot C_P \cdot (R_T - RO) - k_{off} \cdot RO$$

2 Parameters

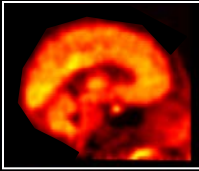
SERT occupancy by Duloxetine





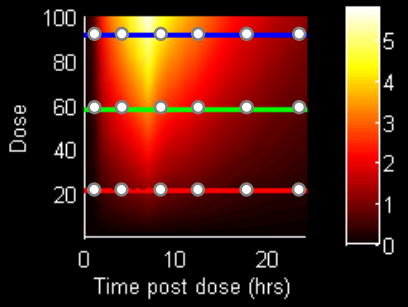
Predicting RD occupancy from SD studies

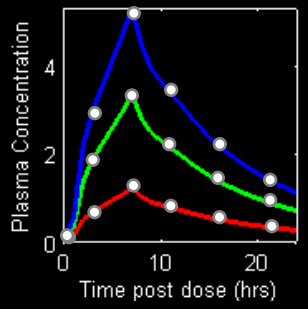
Plasma PK



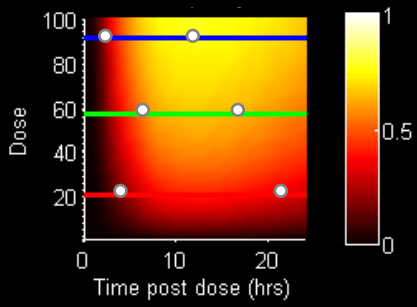
Occupancy (PET)

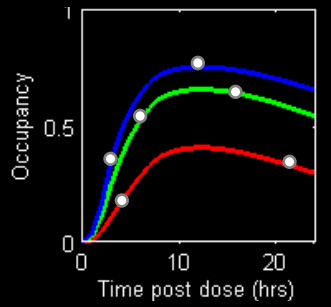
Single Dose (SD)





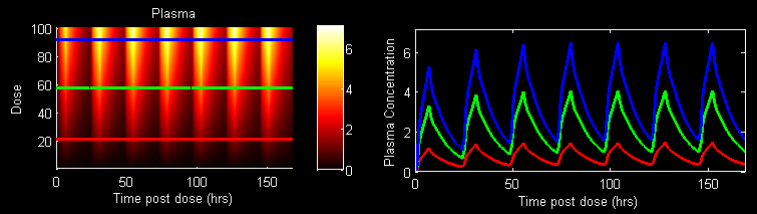
PK/RO Model

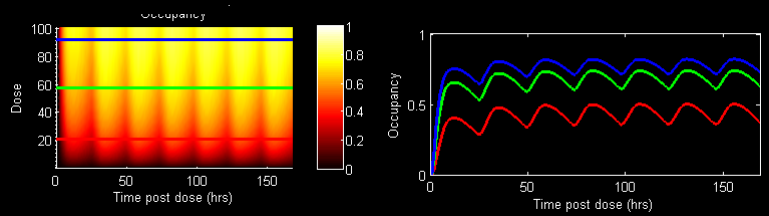




SD → RD PK Model

Repeat Dose (RD)

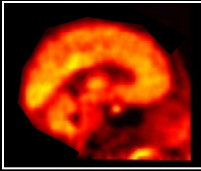




Roger Gunn, 23/01/2012

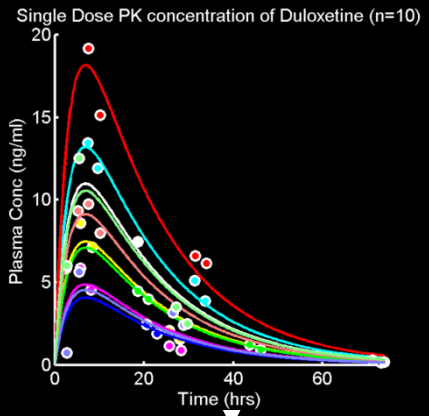
Predicting RD occupancy from SD studies

Plasma PK



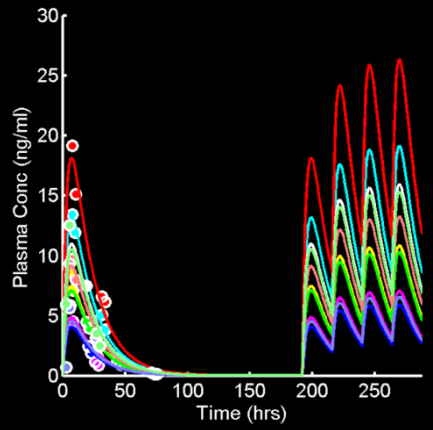
Occupancy (PET)

Single Dose (SD)



SD → RD PK Model

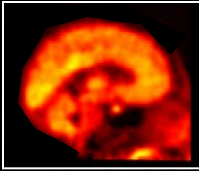
Repeat Dose (RD)



Roger Gunn, 23/01/2012

Predicting RD occupancy from SD studies

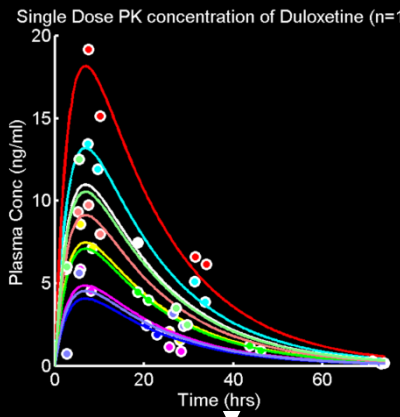
Plasma PK



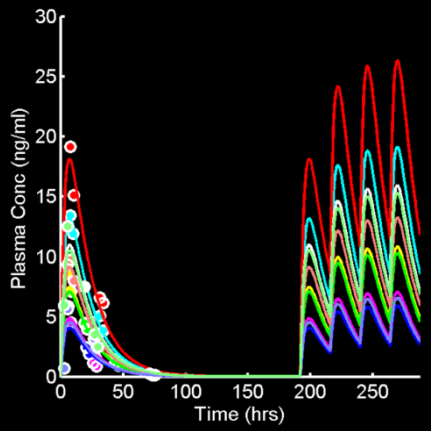
Occupancy (PET)

Single Dose (SD)

Repeat Dose (RD)

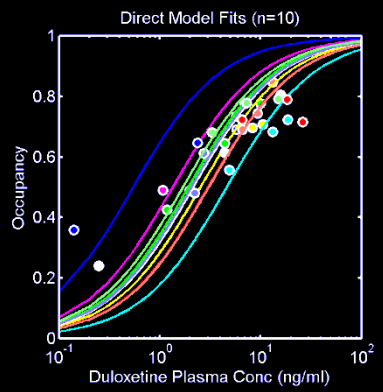


SD → RD PK Model

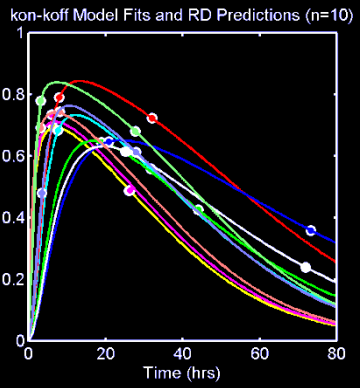


PK/RO Model

Direct Model



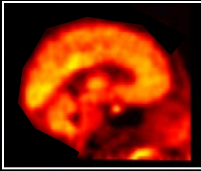
Indirect Model



Roger Gunn, 23/01/2012

Predicting RD occupancy from SD studies

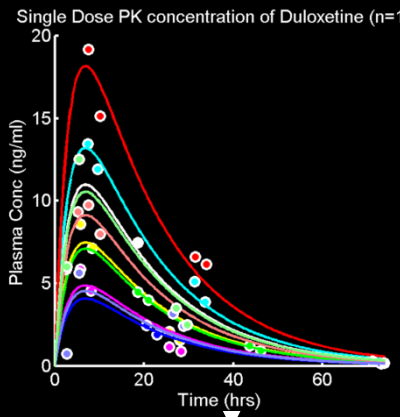
Plasma PK



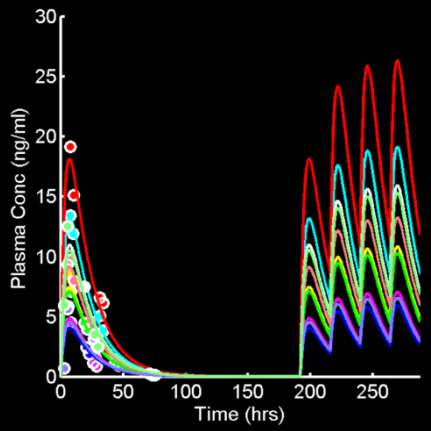
Occupancy (PET)

Single Dose (SD)

Repeat Dose (RD)

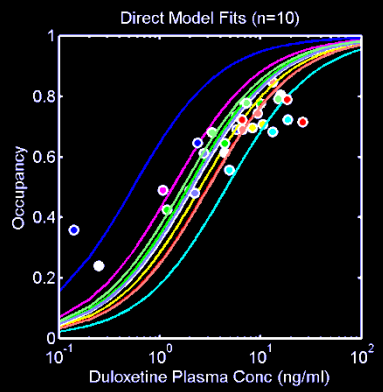


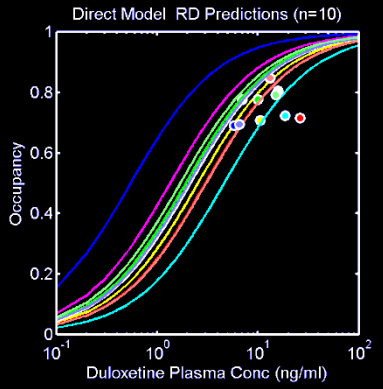
SD → RD PK Model



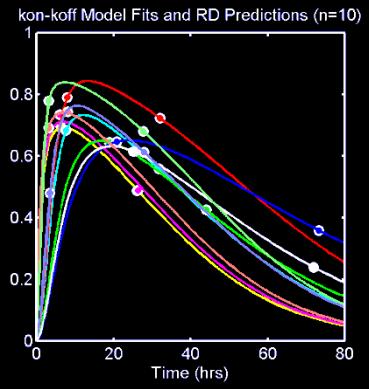
PK/RO Model

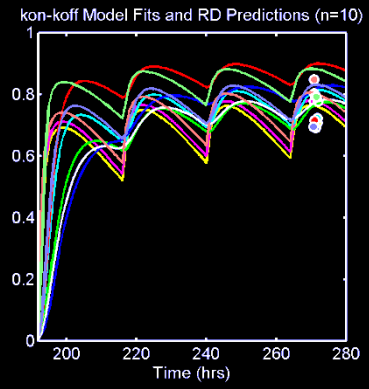
Direct Model





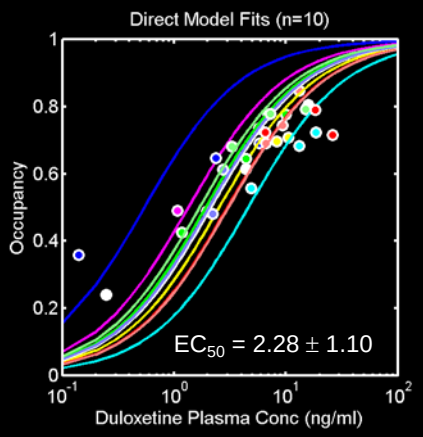
Indirect Model



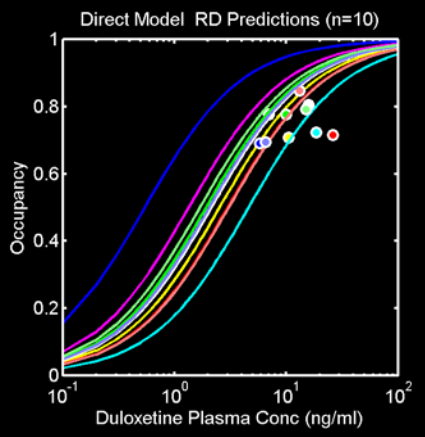


Roger Gunn, 23/01/2012

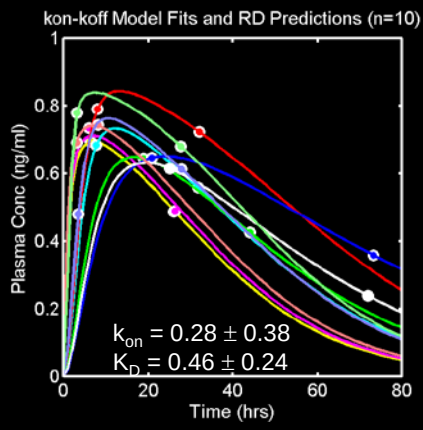
Direct & Indirect Model Fits and RD Prediction



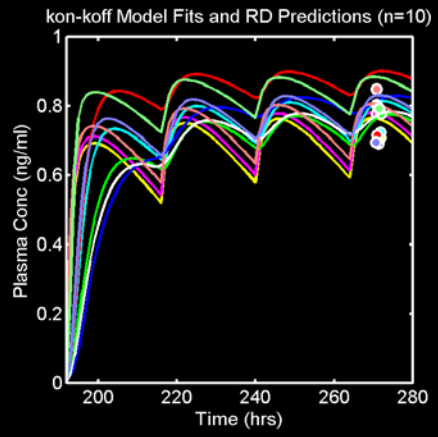
SD Model Fits



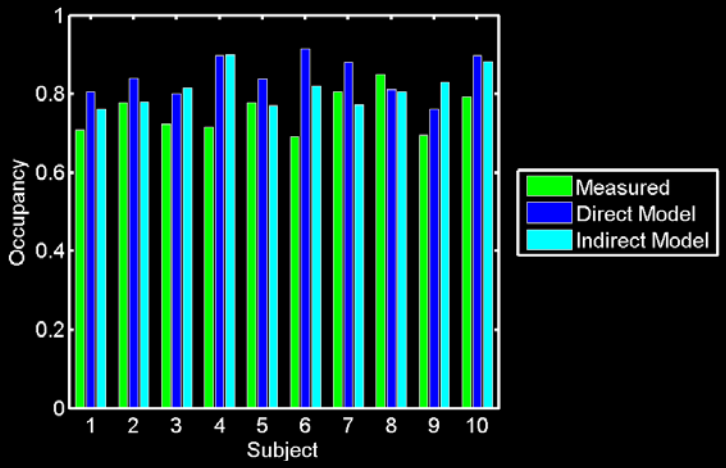
RD Model Predictions



SD Model Fits



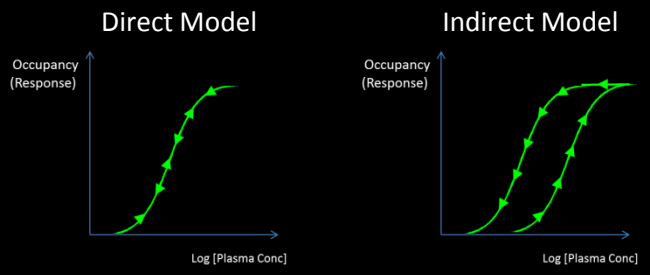
RD Model Predictions

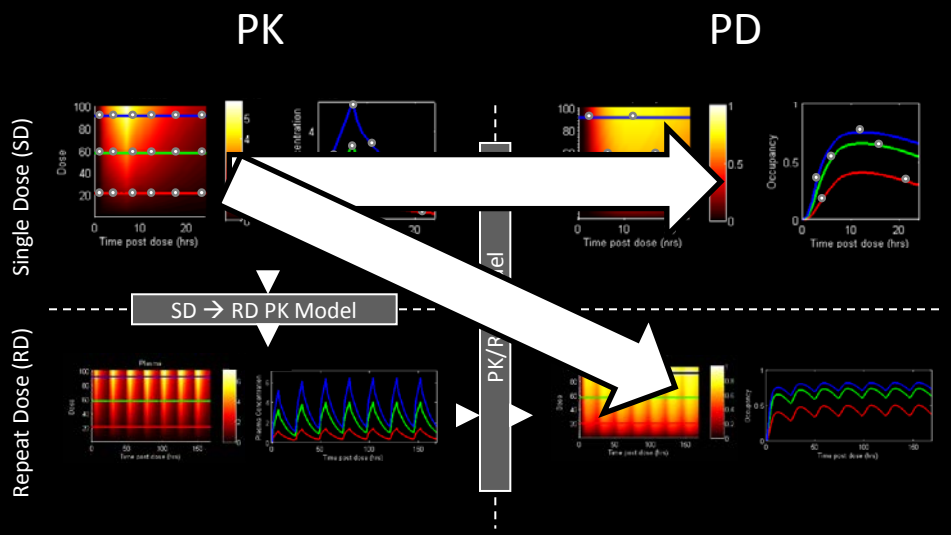


Indirect Model is the better predictor of RD occupancy

Abanades et al, JCBFM, 2010

Summary





- PK/RO Modelling
  - Direct/Indirect Model
- Multiple Time Point Assays
- Adaptive Designs
- Predict RD Response

If we can accurately characterise the relationship between

PK (dose/conc)
and
PD (efficacy)

this puts us in a strong Drug Development position