Bayesian Hierarchical Modeling of Receptor Occupancy in PET Trials

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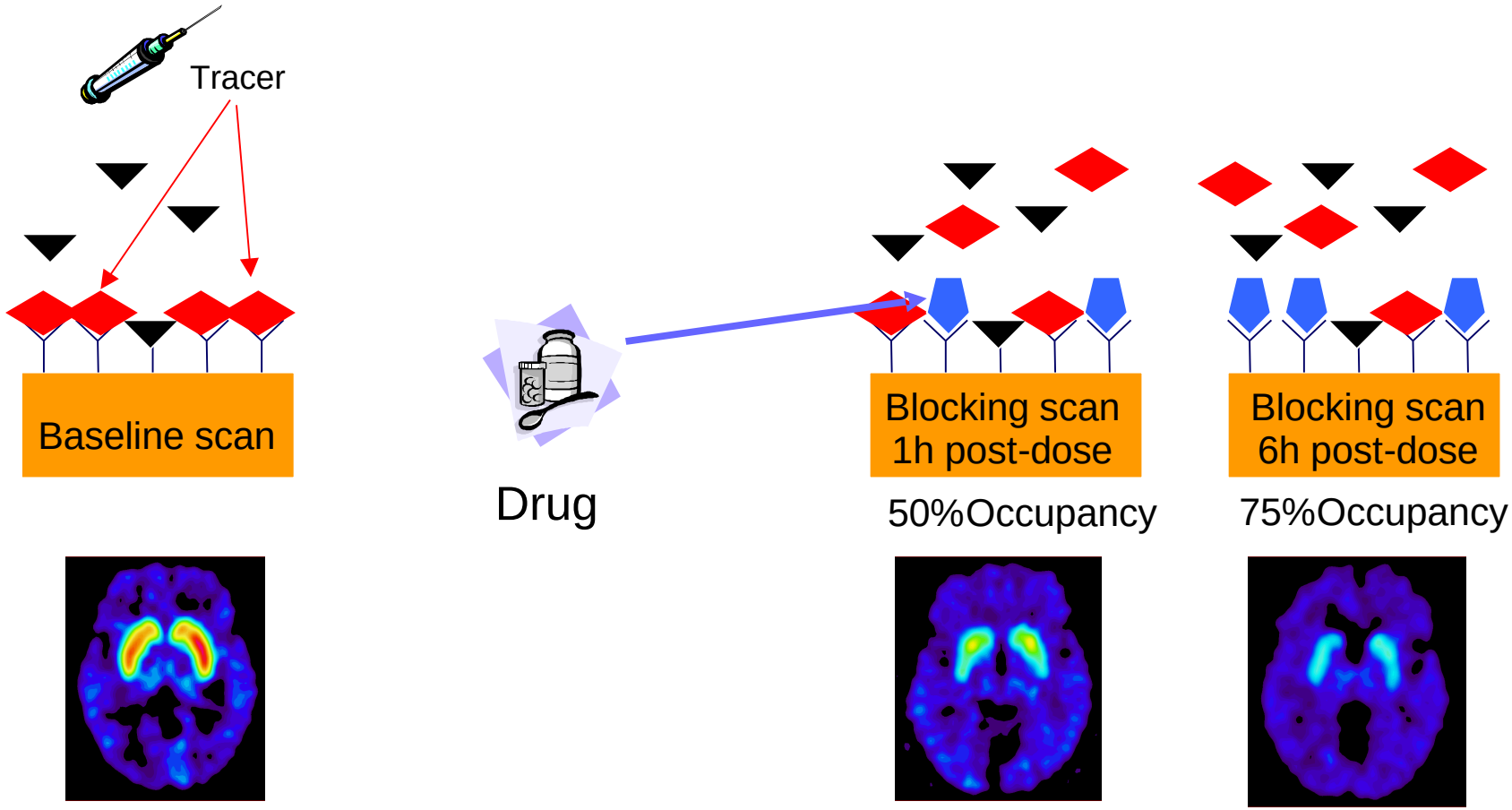
Lilly
Answers That Matter.

Thanks!

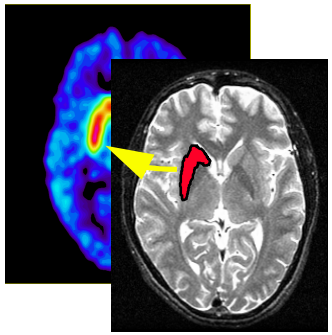
- François Vandenhende
- Jennifer Witcher
- Yan Nie

Typical Receptor Blockade Trial Design

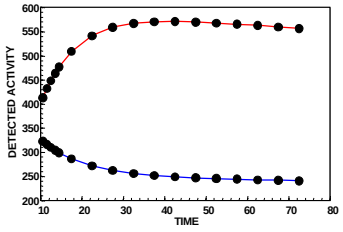


Complex Task

Region of Interest



Dynamic Time Activity Curves



Modeling of the TACs

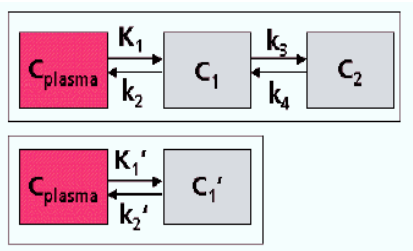
$$\frac{Striatum}{Cerebellum}$$

Ratio method

Analytic models

$$\int_0^{90} \sum alotofmath$$

Binding Potential



Percent Change from baseline

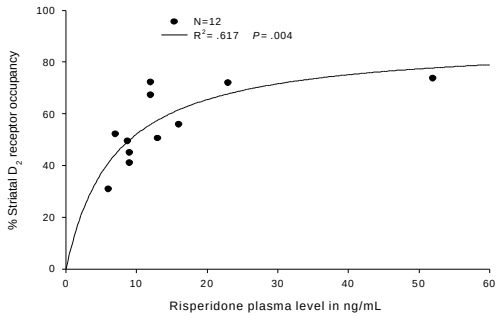
$$RO = \frac{\text{image} - \text{image}}{\text{image}}$$

Measures of interest

50% Occupancy

Modeling

***Figure 2*: Non-linear relationship: plasma levels and occupancy**



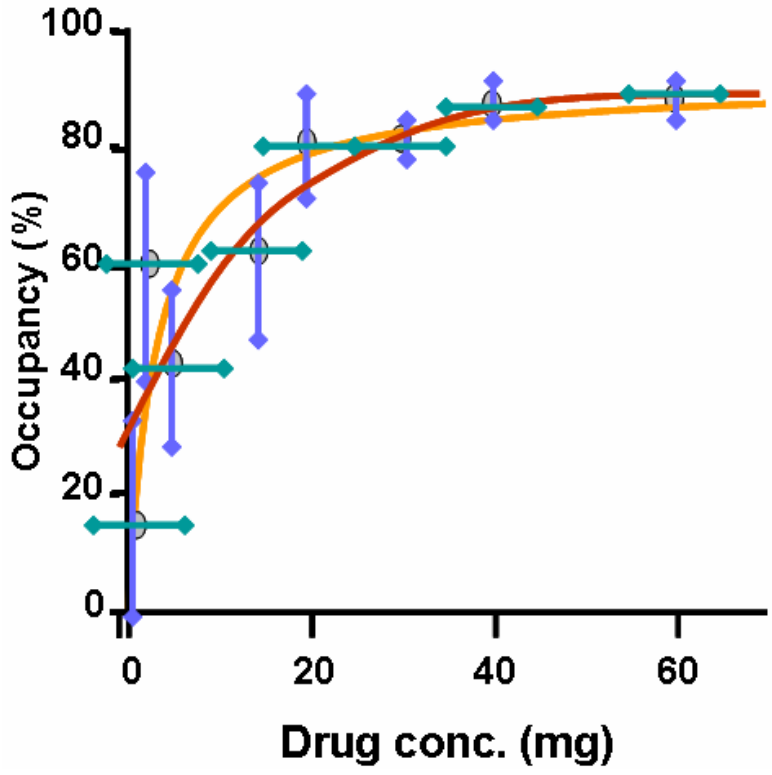
Dose /Time/PK

Modeling Approaches

- Stepwise process
  1. RO model
  2. PK model
  3. PK/RO model

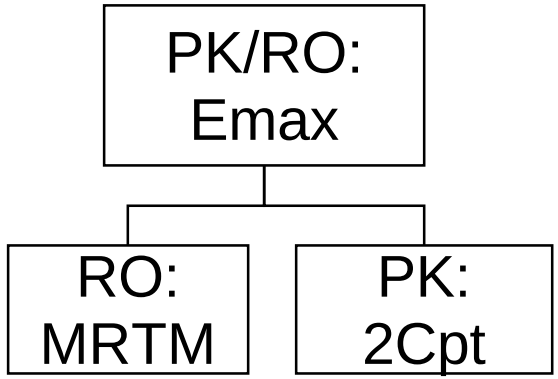
  Standard approach
- Each step carries some assumptions and uncertainty
- How can we deal with uncertainty ?
  - combine all steps
  - hierarchical modeling
  - Bayesian analysis

  Proposed approach

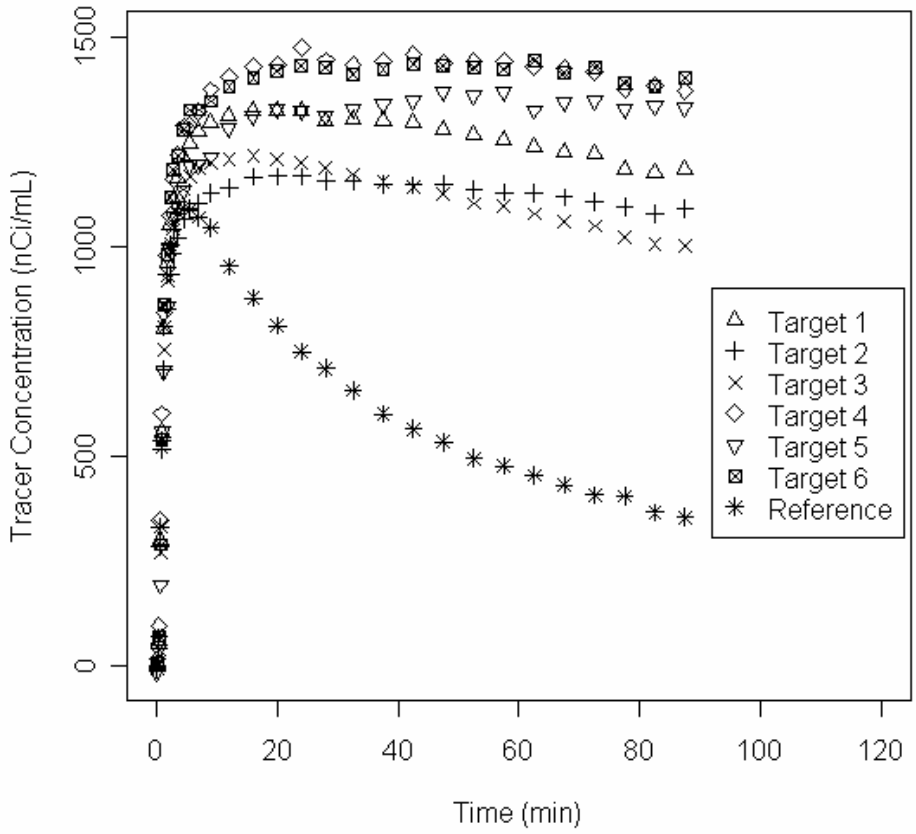


Case Study

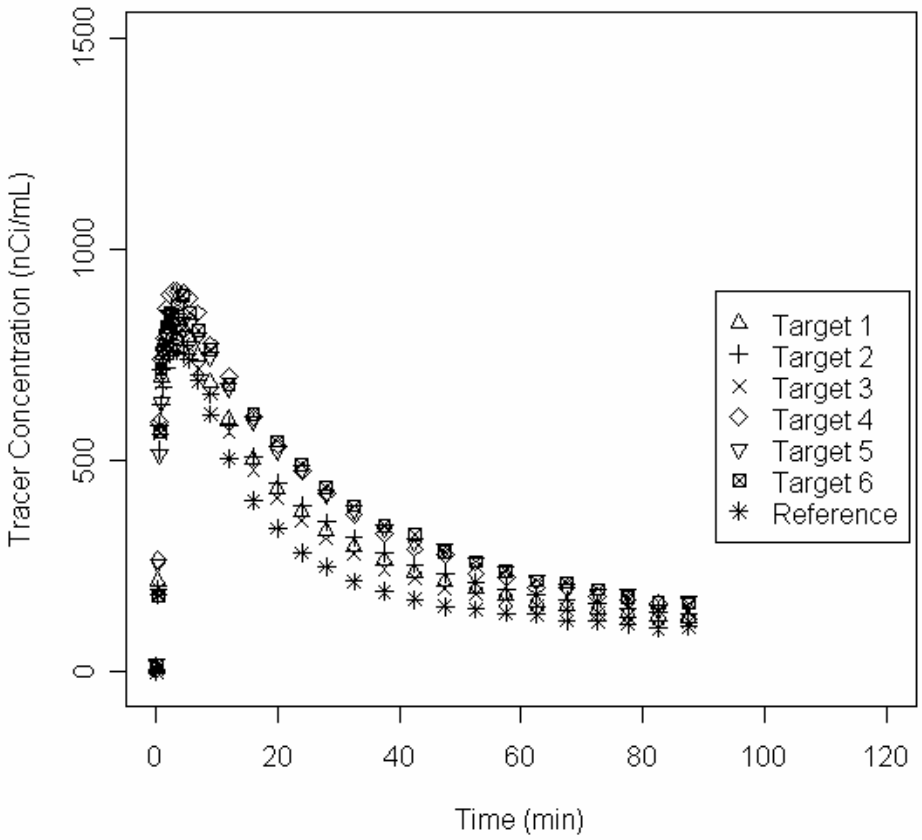
- Trial Design:
  - 12 subjects
  - 4 doses: 30, 80, 120 and 160mg
  - 4 scans/subject (with C11 tracer).
    - Baseline
    - 2, 7 and 24 h after single oral dose of CNS product.
    - 3 PK samplings during each scan
- Objectives:
  - Show evidence of central activity.
  - Study dose-occupancy relationship
  - Measure time-on-target.



Time Activity Curves



Baseline Scan



Blocking Scan

Receptor Occupancy Estimation

Multilinear Reference Tissue Model (Ichise et al, 2003).

$$TAC_{subj,scan,ROI} \sim N(\mu_{subj,scan,ROI}, \sigma^2_{TAC}),$$

$$\mu = \begin{cases} \alpha[\overline{TAC} - (BP_{base,ROI} + 1)(\overline{TAC}_{ref} + TAC_{ref}\beta)] & \text{Baseline scan} \\ \alpha[\overline{TAC} - \{BP_{base,ROI}(1 - RO_{block,ROI}) + 1\}(\overline{TAC}_{ref} + TAC_{ref}\beta)] & \text{Blocking scans} \end{cases}$$

4 parameters

- $BP_{base,ROI}$: Regional binding potential at baseline
- $RO_{block,ROI:}$ Regional receptor occupancy for each blocking scan
- Nuisance parameters: α and β.

Handling of Multiple Target Regions

Random effect for occupancy in various brain regions

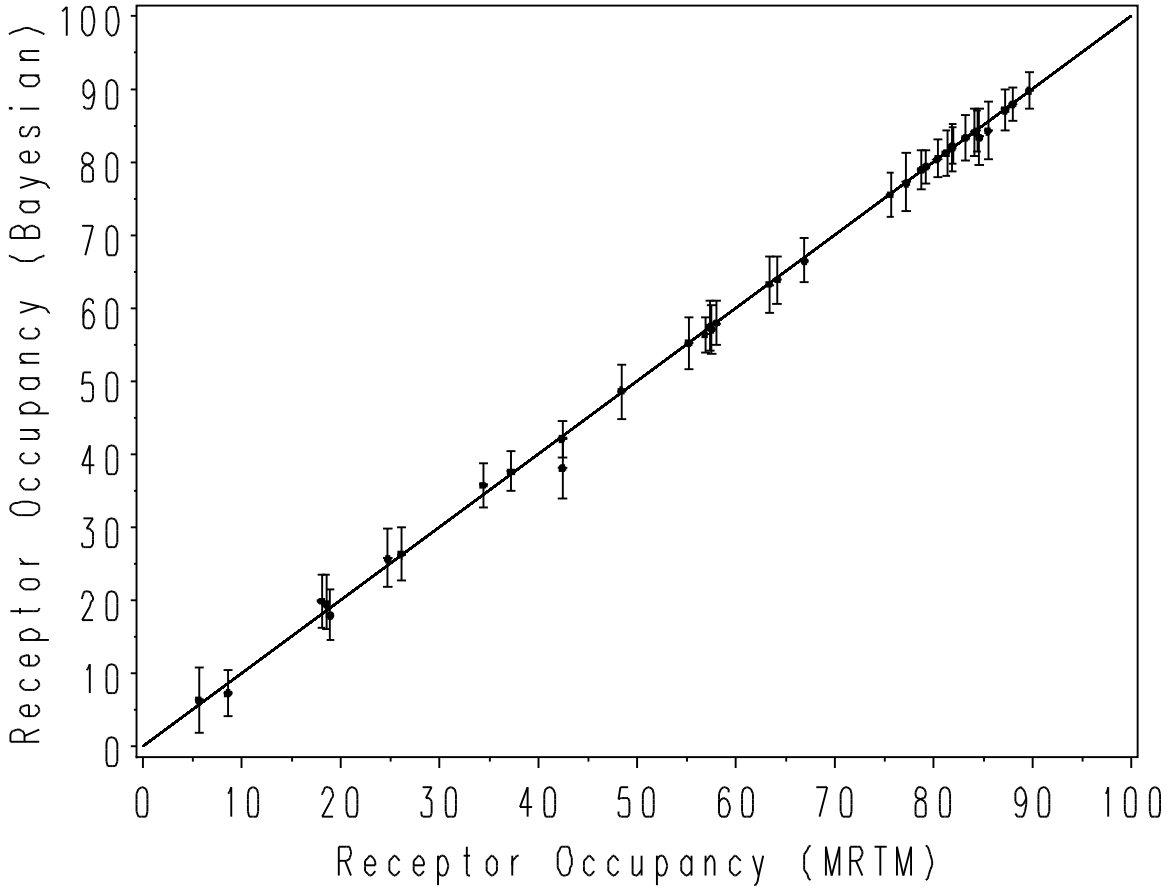
$$RO_{scan,ROI} \sim N(\rho_{scan}, \sigma_{\rho}^{2}).$$

ρ_{scan} is the mean occupancy across regions.

σ_{ρ}^{2} is the inter-regional variability.

Non informative priors were used for all parameters of the RO model.

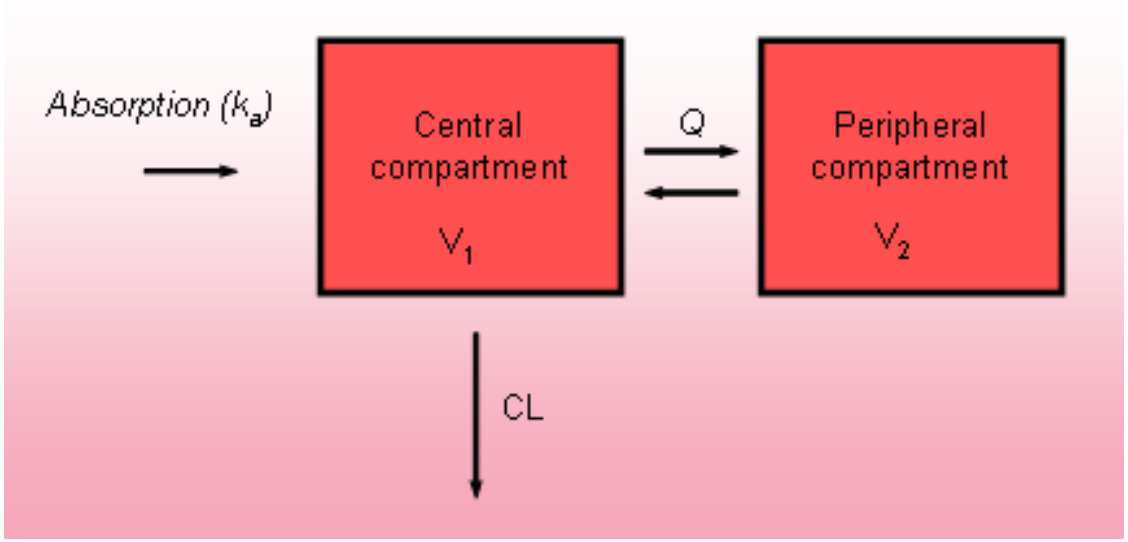
Individual Occupancy Estimates



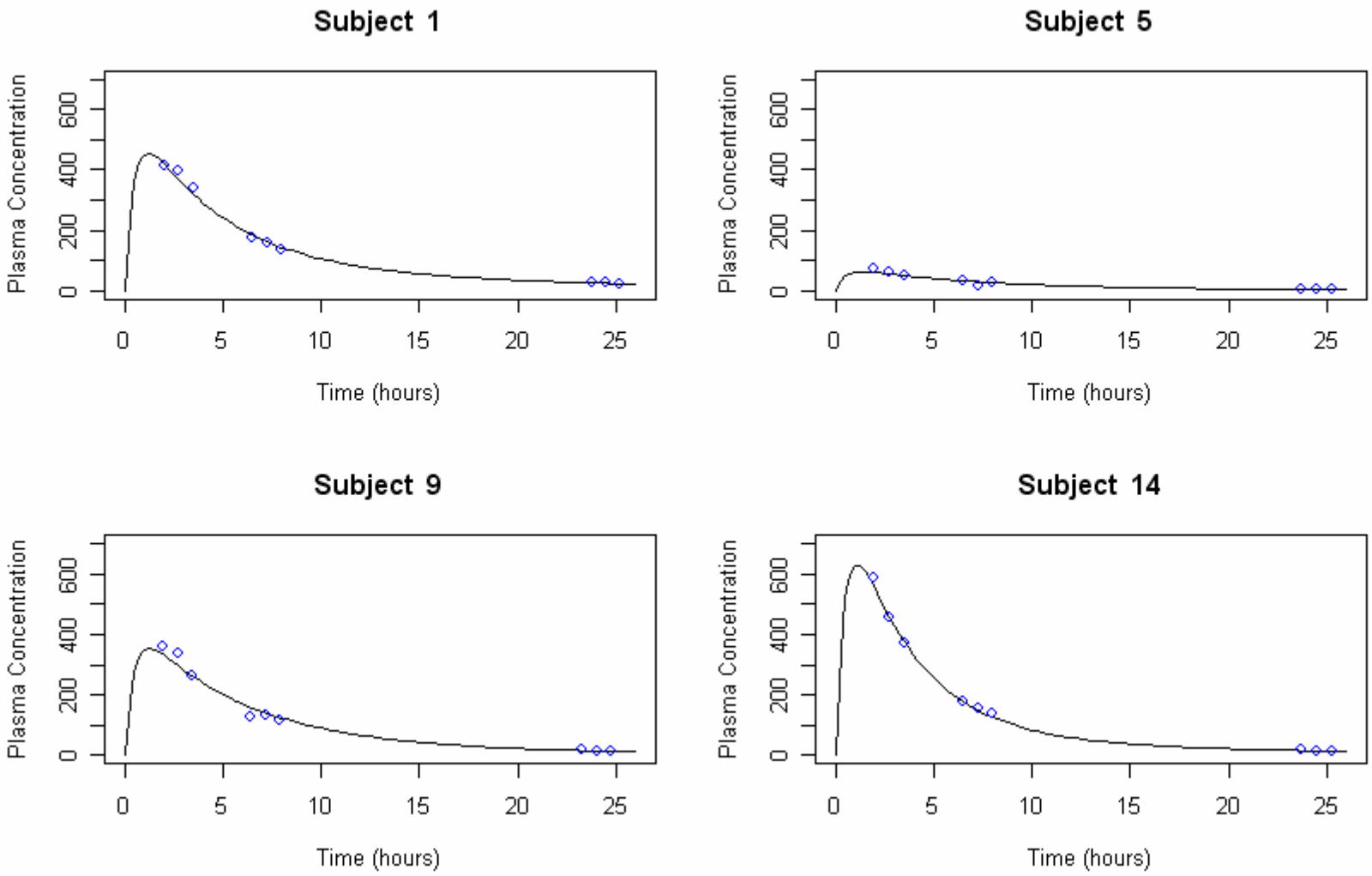
- Bayesian (TAC only) and MRTM estimates are similar
- Uncertainty is explicitly taken into account with Bayesian modeling

Pharmacokinetic Model

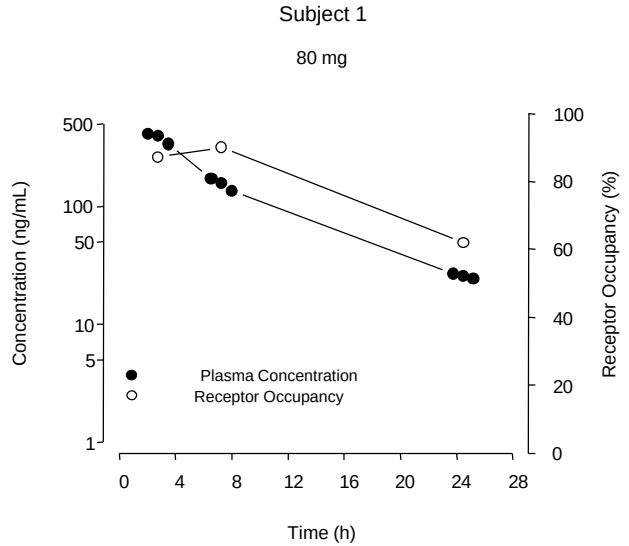
- Two-compartment model for oral dosing
- Parameterization in terms of k_a, V_1, V_2, Q, CL
- Subject-specific parameters for V_1 and CL
- Informative priors based on historical data

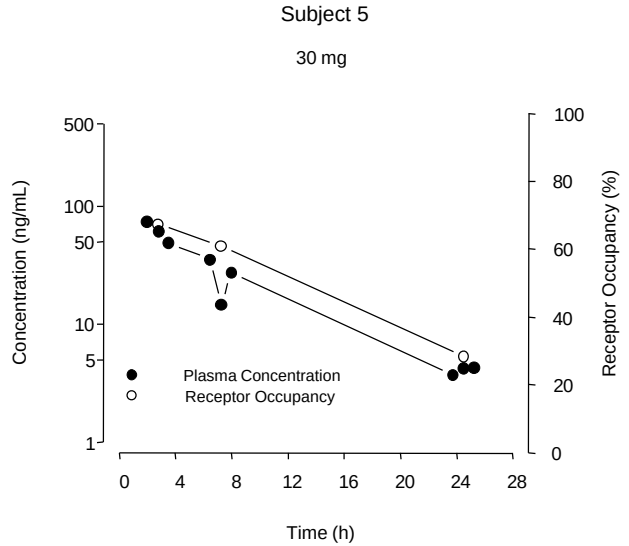


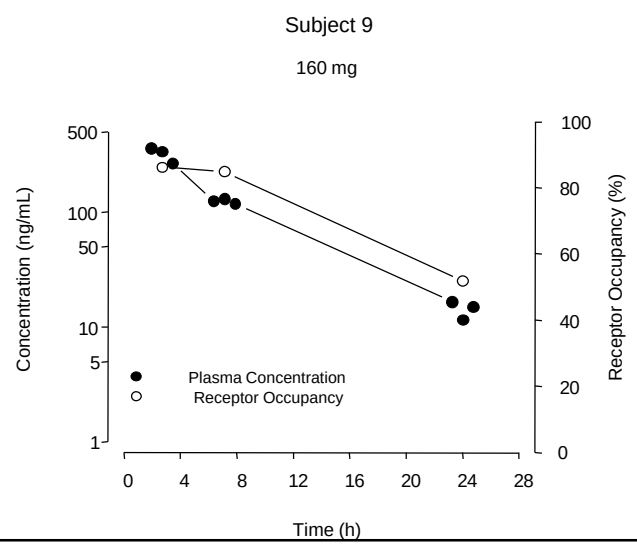
Pharmacokinetic Model

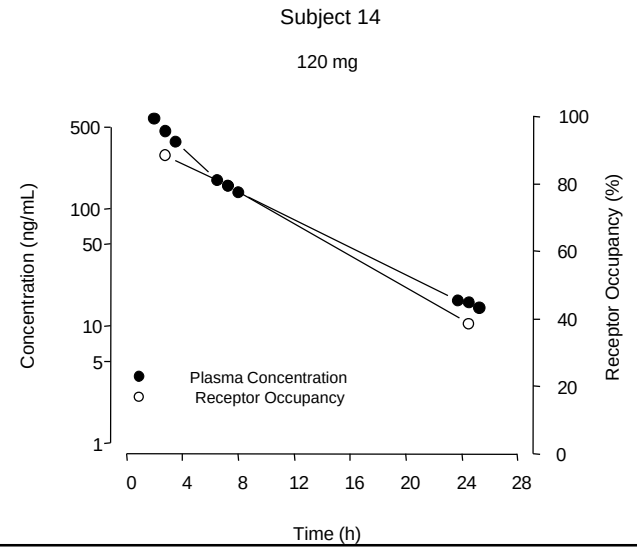


Observed Plasma Concentrations and Receptor Occupancy









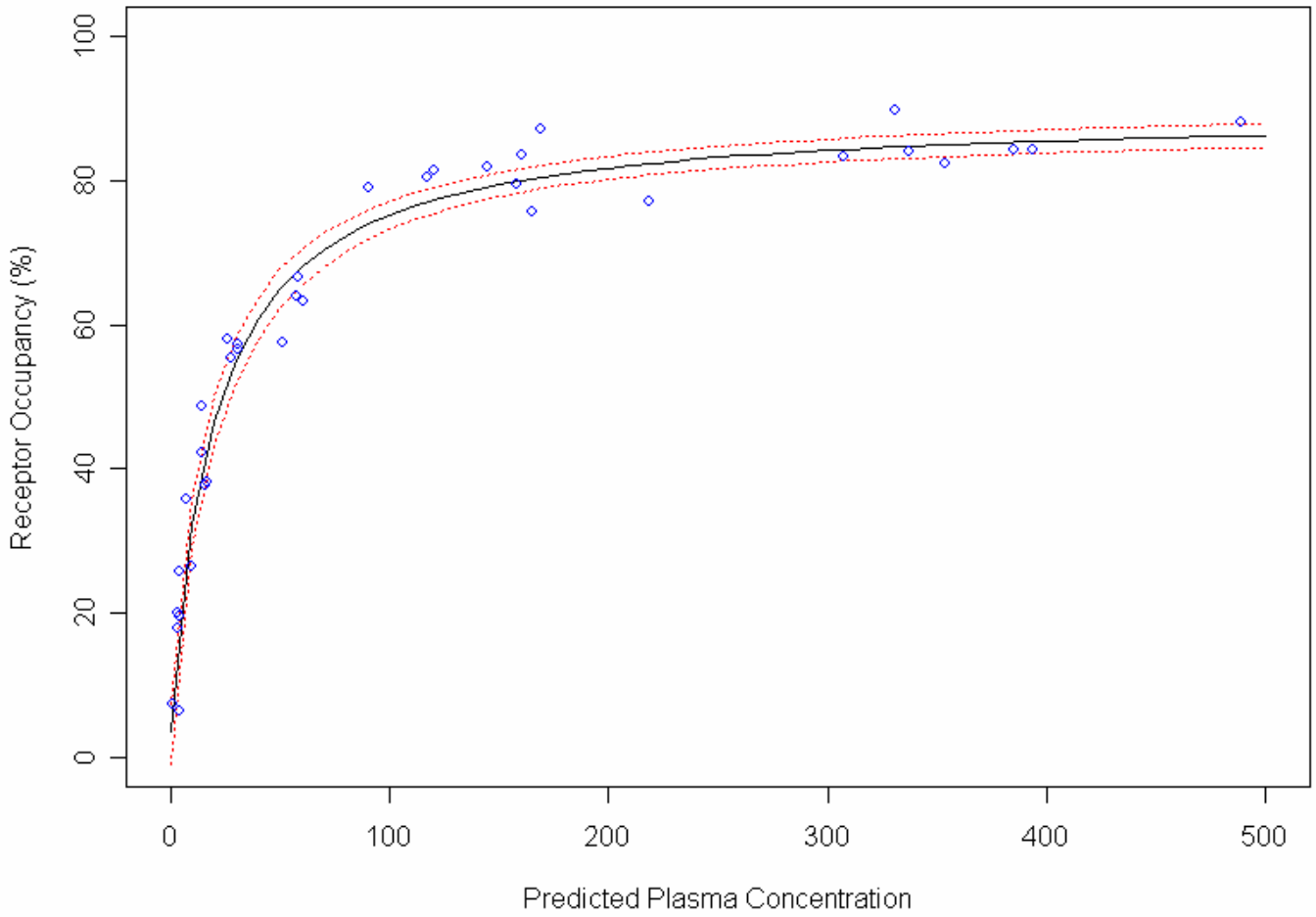
PK/RO Model

- Assumption of a direct relationship appears reasonable

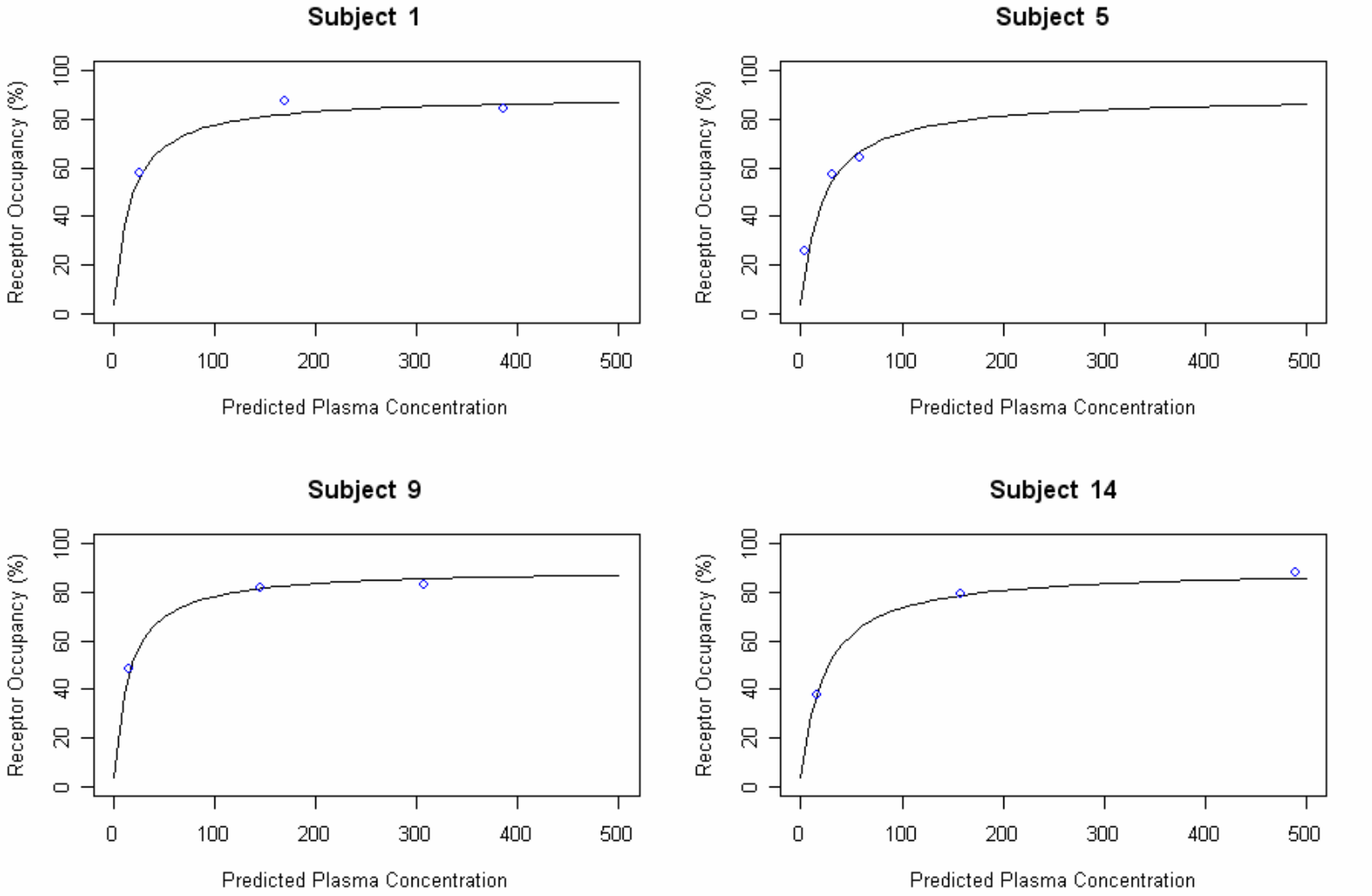
$$\rho_{scan} = E0 + \frac{E\max \cdot C(dose,t)}{EC50_i + C(dose,t)}$$

- Parameters:
  - E0: occupancy in drug-free condition
  - Emax: maximum occupancy
  - EC50 (subject-specific): concentration producing 50% of maximum occupancy
  - Non informative priors for all parameters

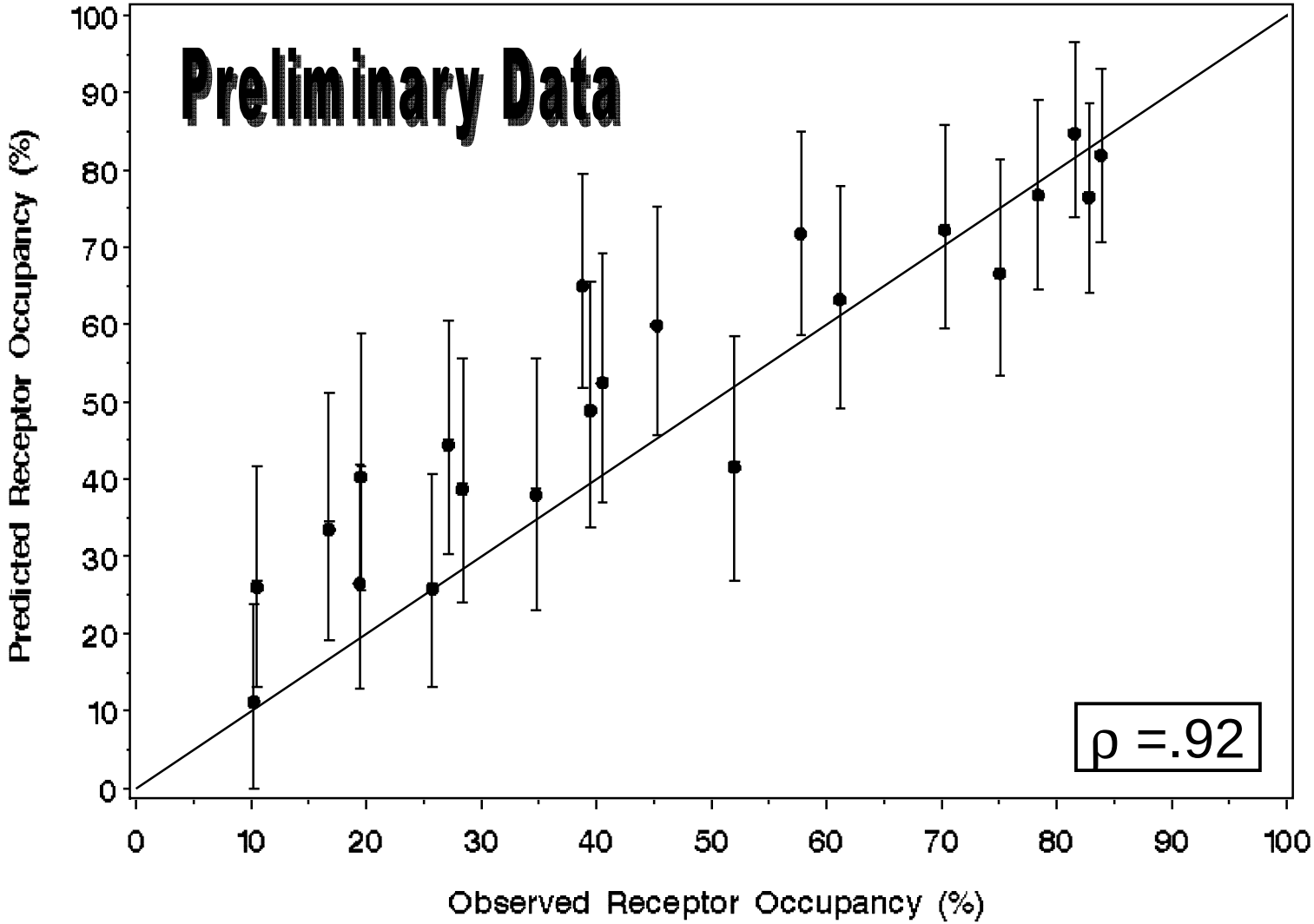
PK/RO Model



PK/RO Model



Model Predictions for Multiple Dose Trial



Discussion

- Hierarchical PK/RO modeling adds value
  - Reliable decision making in the face of uncertainty
  - In-silico predictions are cost-effective
  - Bayesian approach integrates the PET trial within drug development history
- Winbugs implementation
  - Inference is made straightforward even for such complex models
  - Implementation phase may be slightly frustrating
  - Call from SAS or R
- Work out extensions on a case by case basis
  - Other brain kinetic models (eg, SRTM)
  - Other pharmacokinetic models
  - Other PK/RO models (eg, to accomodate a delayed response)