Pharmacokinetic/Pharmacodynamic Modelling of the Analgesic Effects of Tramadol in the Pediatric Population

María J. Garrido and Iñaki F. Trocóniz

Dpt. of Pharmacy (University of Navarra)

Ferdinand Rombout

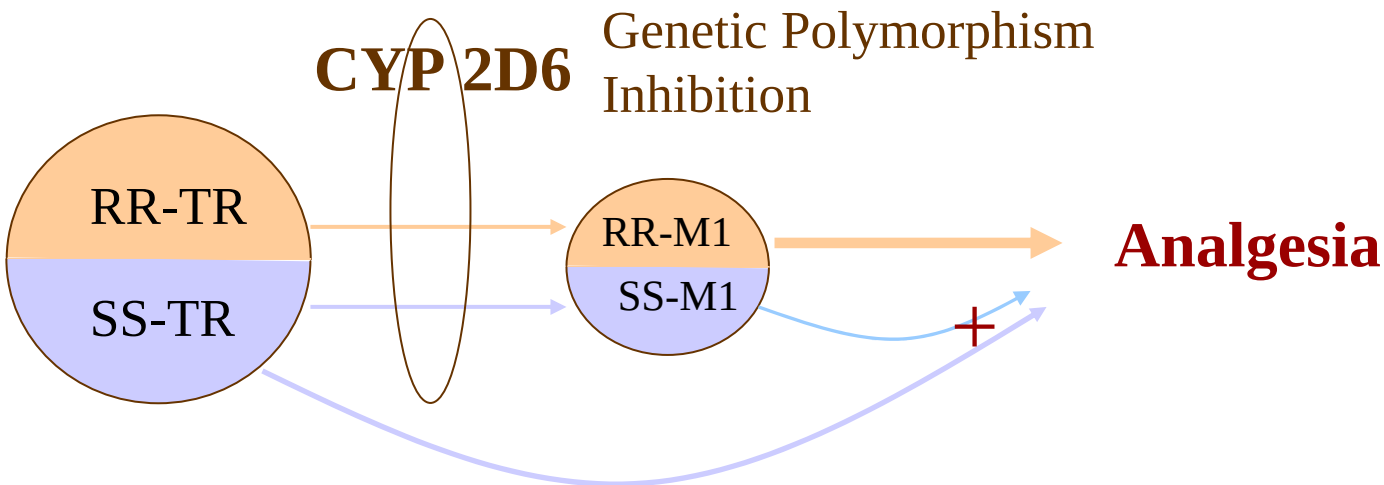
Modelling and Simulation (Grünenthal GmbH)

Summary

- **Background of the Molecule**
- **Relevance**
- **Study Design and Description of the Data**
- **Methodology**
- **Modelling Results**
- **Applications of the Model**

Background of the Molecule

- **Proposed mechanism of action***



*** Based on "in vitro" pharmacology and pre-clinical pk/pd studies [Valle et al., JPET (2000); Garrido et al., JPET (2000, 2003)]**

No inter-conversion between

parent compounds and metabolites

enantiomers

Relevance

- **The population PK/PD characteristics of T in adults or children have not been properly explored**
- **There are no population analysis with T**
- **The ability of children to produce M1 is not known**

Study Design

- **Randomised, double-blind multi-centre study**
- **Main inclusion criteria**
  - **Age: 2 to 8 years**
  - **Postoperative pain**
  - **Anesthesia according to study protocol**
    - **Intraoperative administration of opiods had to be finished at least 30 min before the end of surgery**

Study Design (II)

- **Drug administration**
  - **1 mg/kg dose of T was infused in 2.5 min at the end of surgery (time of skin closure)**
  - **One third of the initial dose of T was infused in 2.5 min at 15, 30 and/or 45 min after the end of surgery if pain relief was not adequate**
  - **Rescue medication with other analgesics was allowed 60 min after the end of surgery**

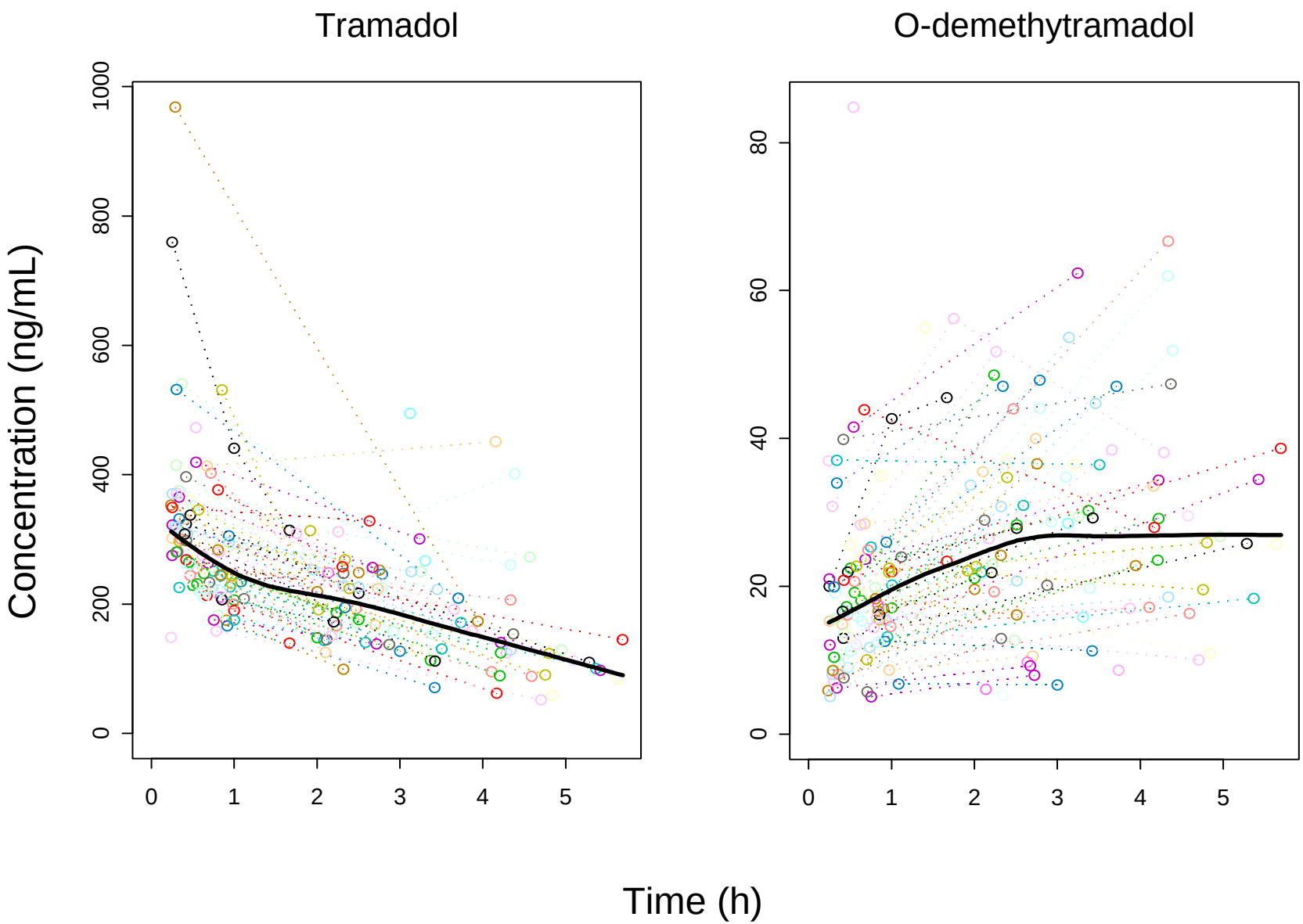
Description of the Data

- **Patient population**
  - **104 Caucasian children**
  - **Eleven covariates**
    - **Demographics (height, weight, age, sex)**
    - **Surgery related (type, duration)**
    - **Co-medications**
    - **Patients were not geno-, phenotyped**

Description of the Data

- **Pharmacokinetic collection**
  - **93 children with PK information**
  - **1 to 3 samples per patient**
  - **Racemic concentrations**
  - **BLQ were not used**
  - **There were not patients with available T samples but not M1**

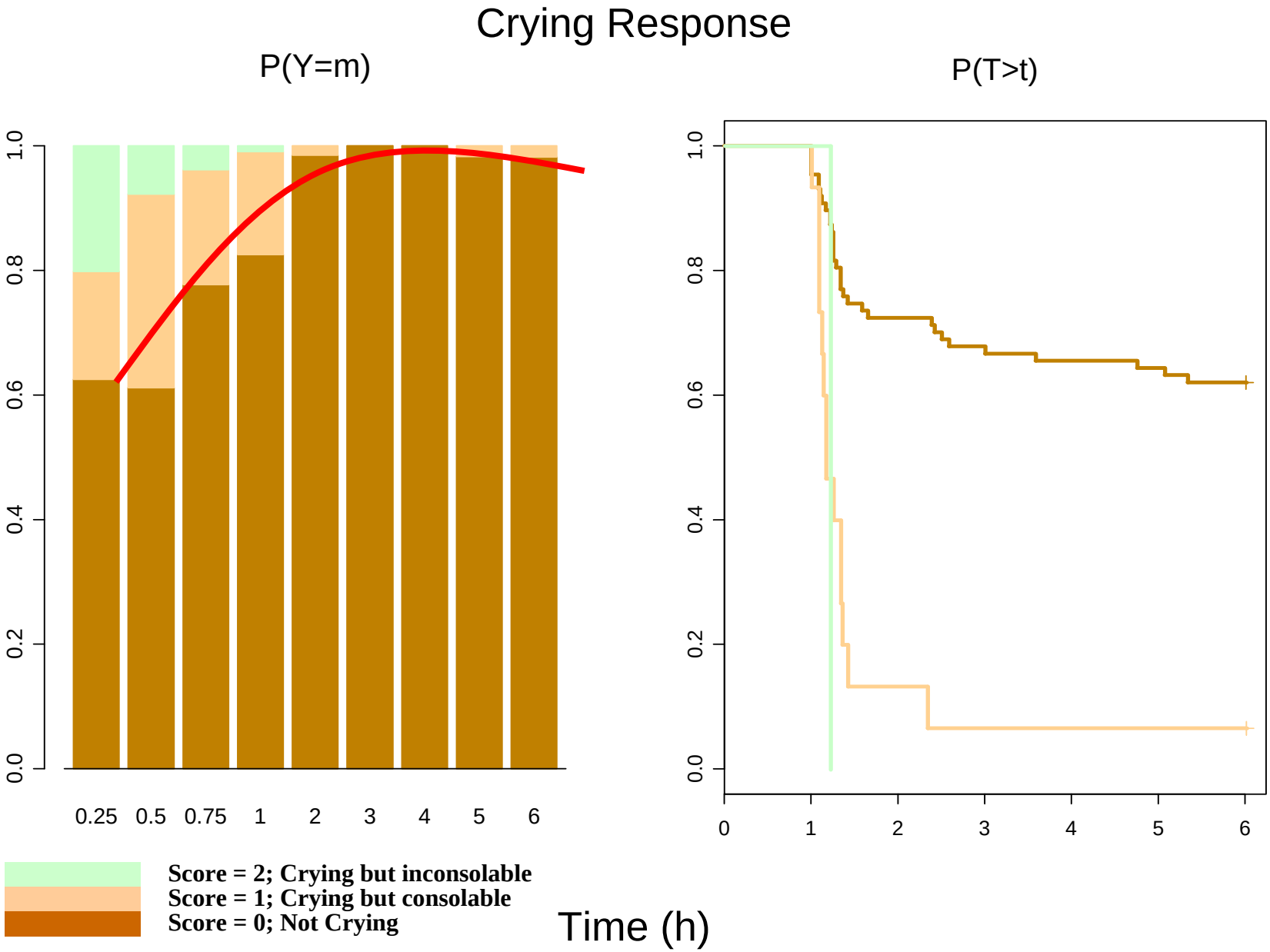
Description of the Data



Description of the Data

- **Pharmacodynamic collection**
  - **Objective Pain scale variables and Sedation**
    - **Crying, Movement, Agitation, Verbal evaluation and Increase in blood pressure**
    - **15, 30, 45 min, and 1, 2, 3, 4, 5 and 6 h**
      - **15 - 60 min: 104 observations/time**
      - **120 - 360 min: 65 to 55 observations/time**

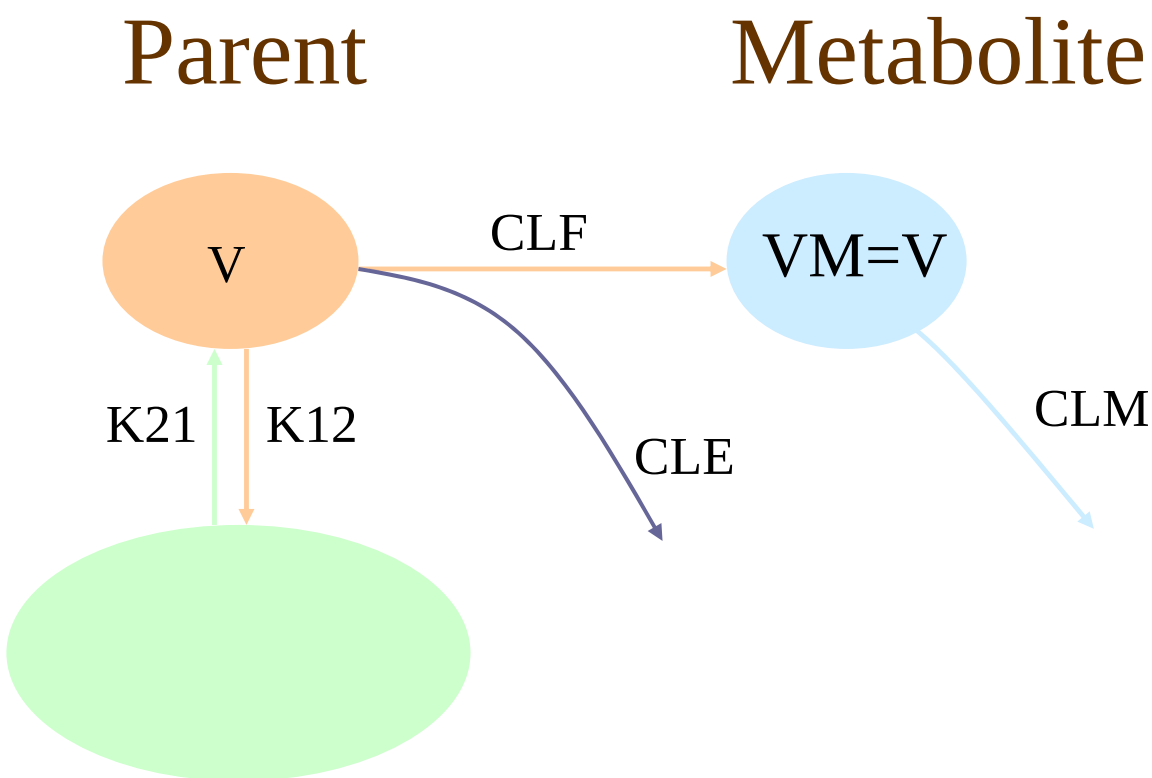
Description of the Data

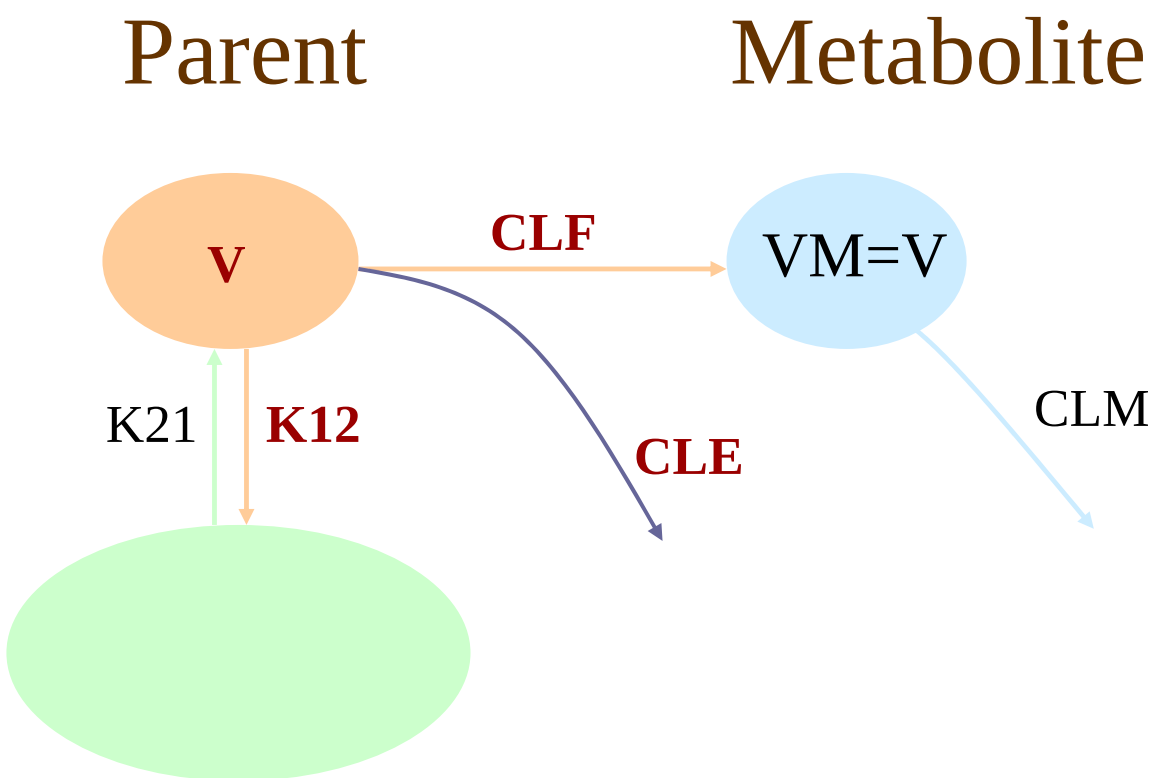


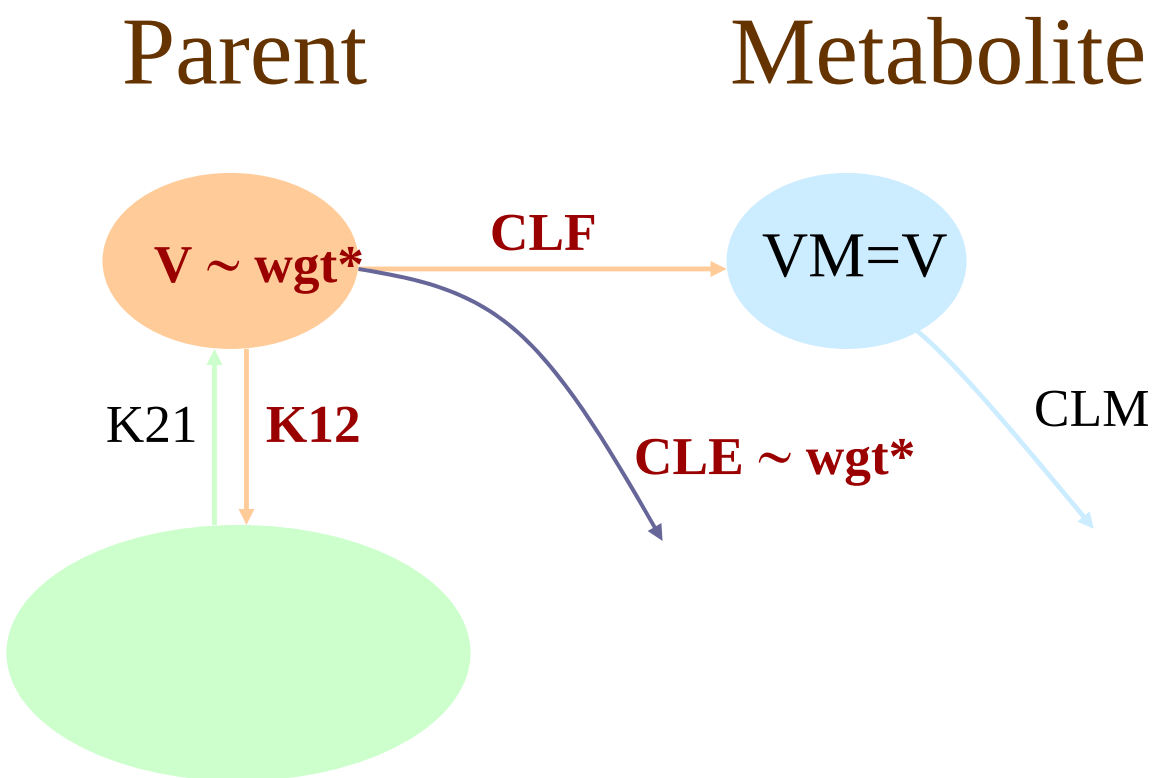
Methodology of Analysis

- **Population PK/PD done sequentially**
- **NONMEM V**
- **FO (PK) and LAPLACIAN LIKE (PD)**
- **PD data after remedication were not included**
- **Validation**
  - **Simulation/estimation (MPE, MAPE of θ, Ω, Σ)**
  - **Posterior predictive check**

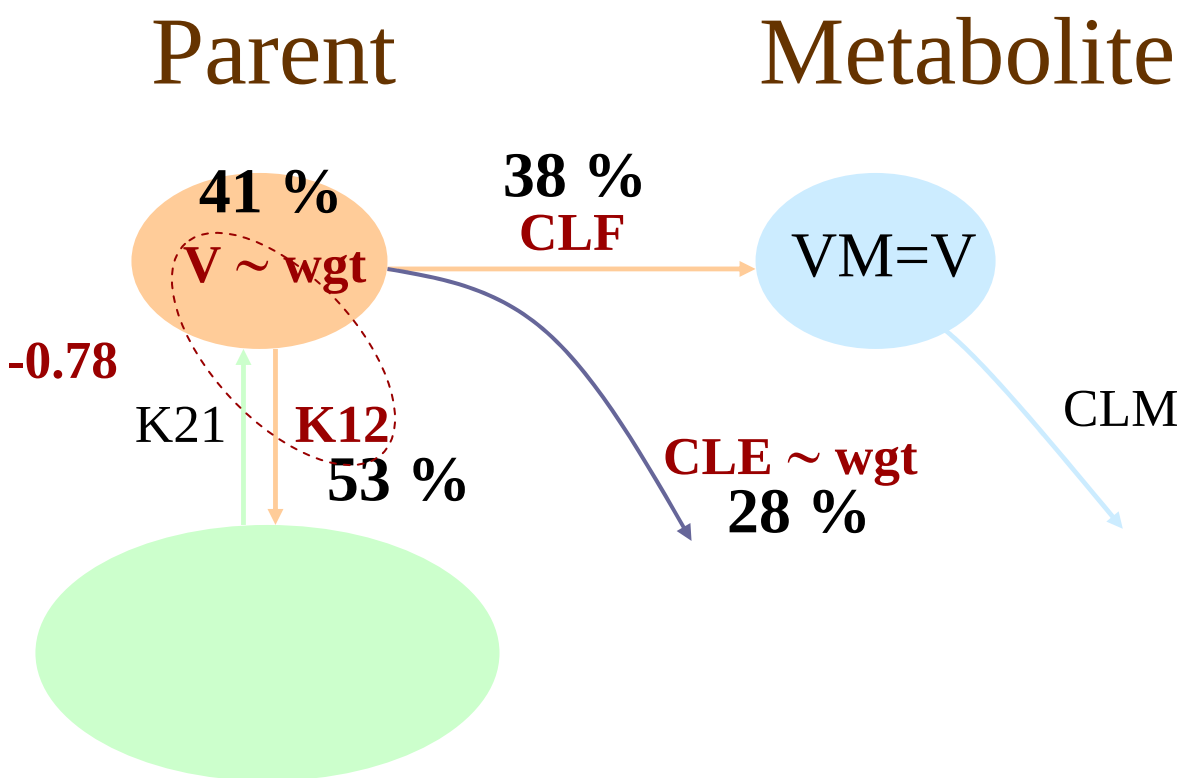
Results (pharmacokinetics)




Parent
Metabolite
V
CLF
VM=V
K21
K12
CLE
CLM



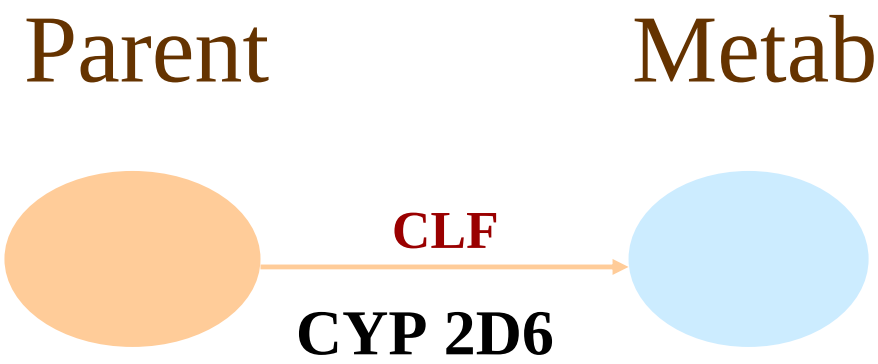
*** > 30 points decrease in MOF**



Residual Additive

Parent = 24 %

Metabolite = 18 %



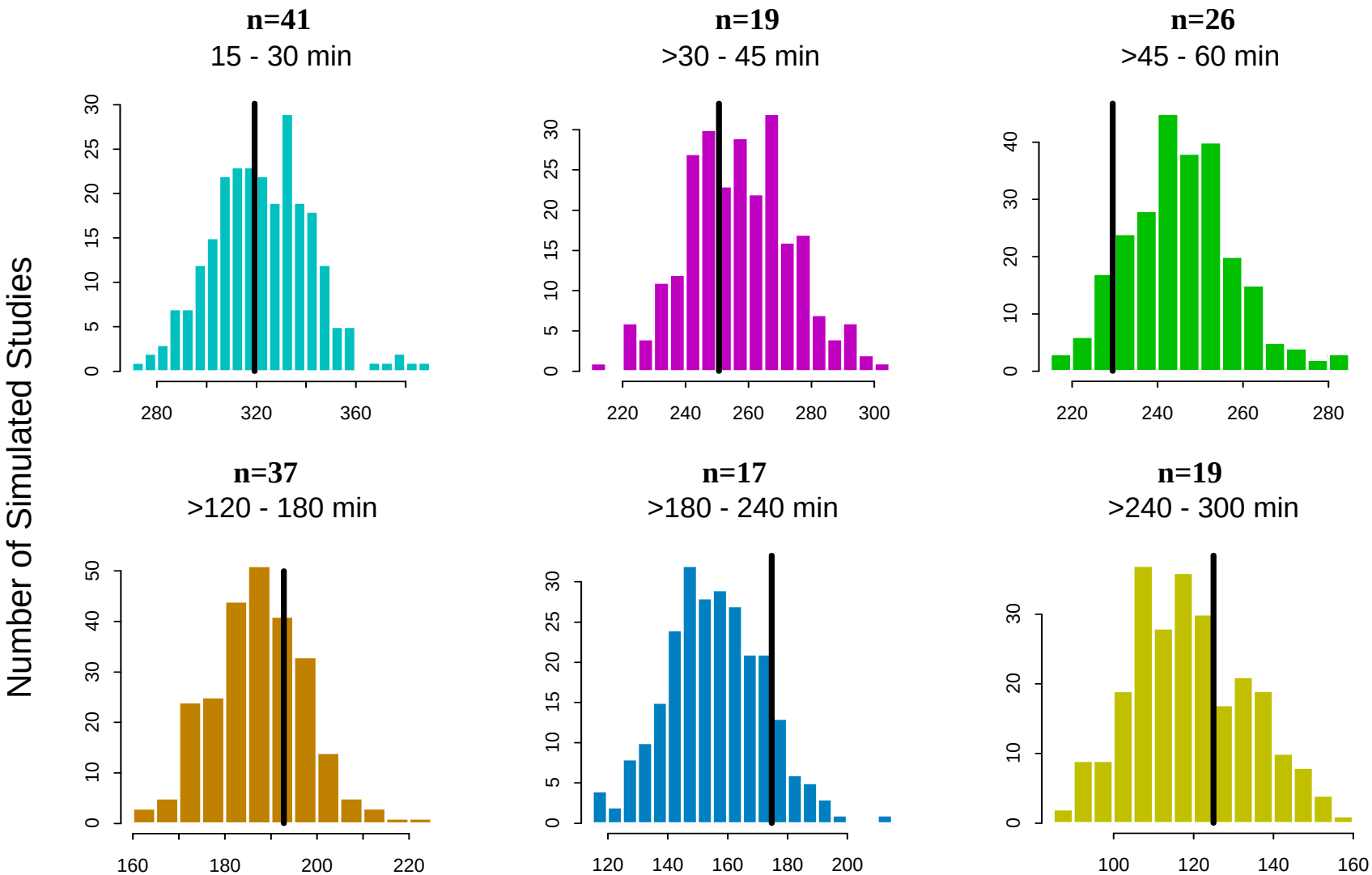
- **Mixture model**
  - **NSPOP = 2**
  - **MOF = 18 points decrease in MOF**
  - **ω^2_{CLF} resulted negligible**

but

  - **Estimated fraction of slow metabolizers = 30 %**
  - **Differences in CLF between fast and slow was 50%**
  - **Validation: MPE for CLF_{fast} and CLF_{slow} > 25 %**

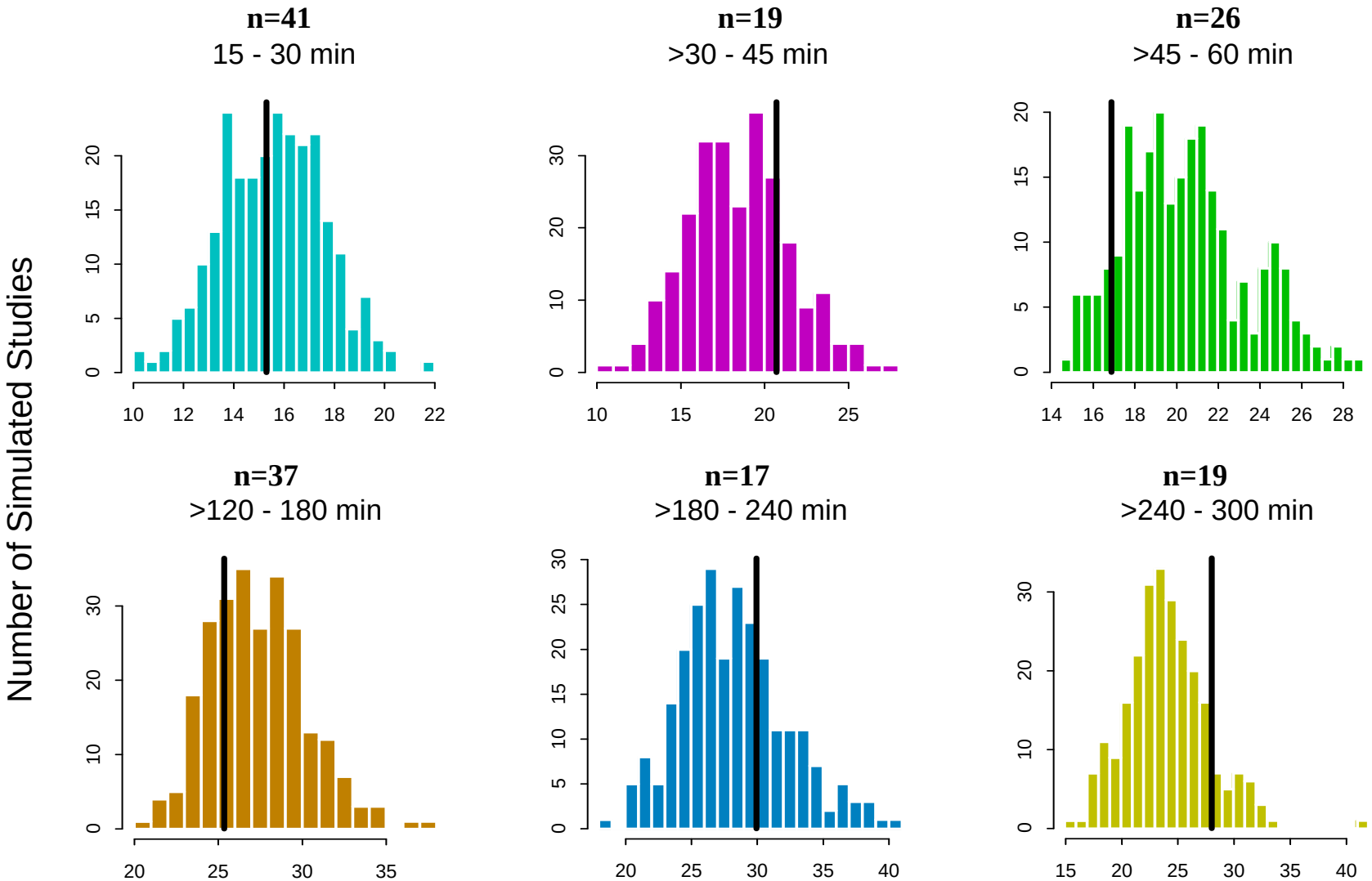
Validation

Tramadol

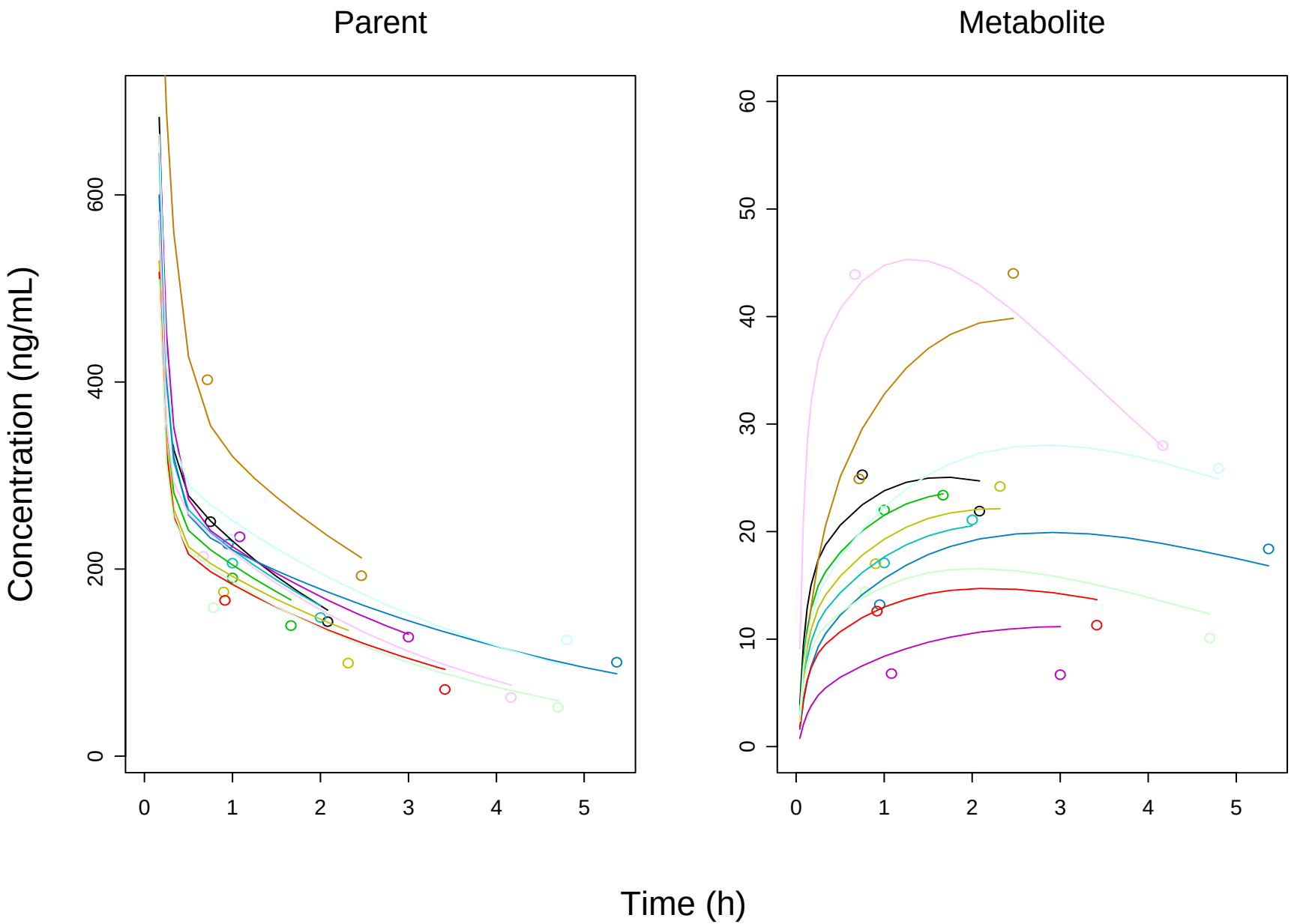


Validation

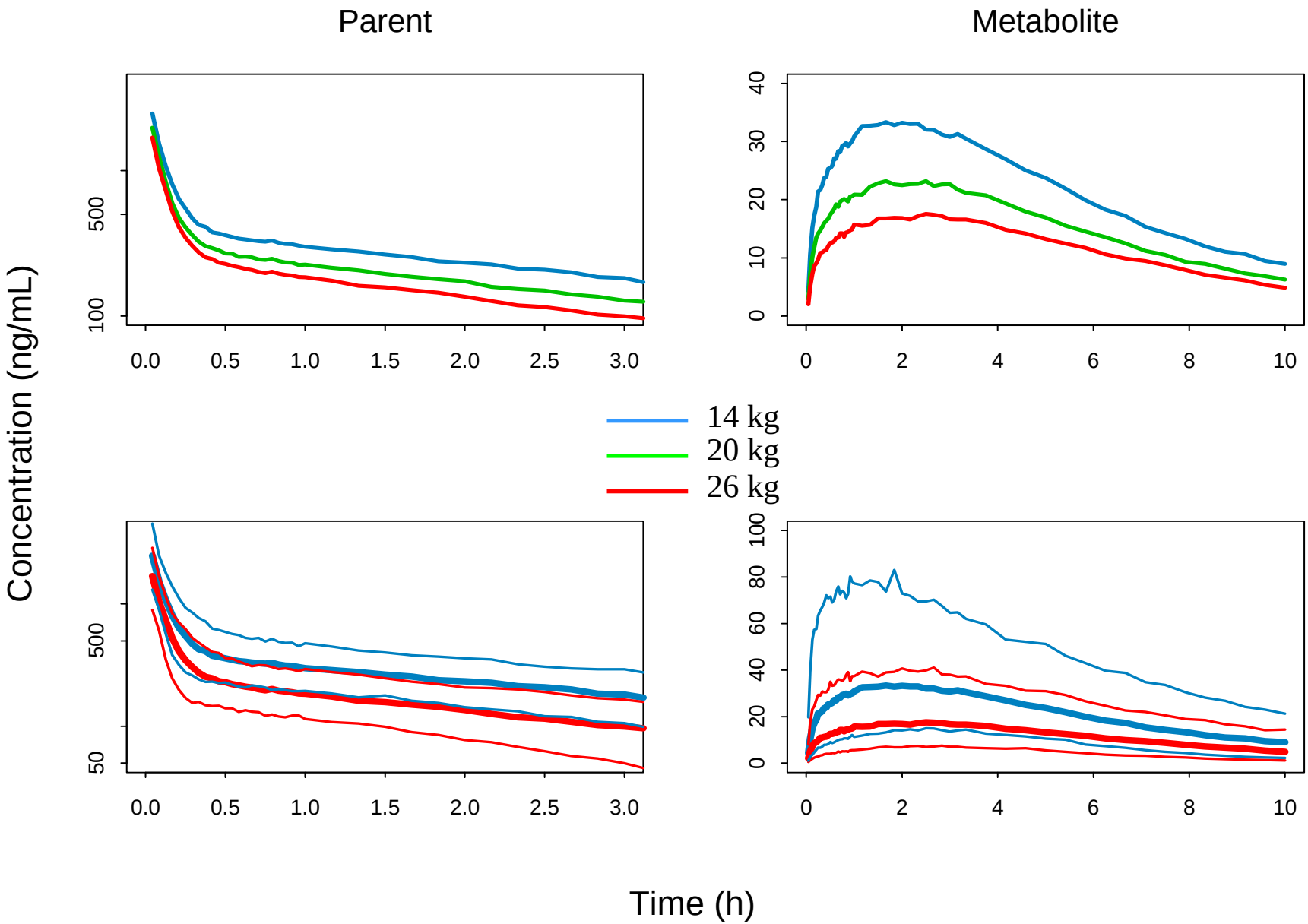
Metabolite



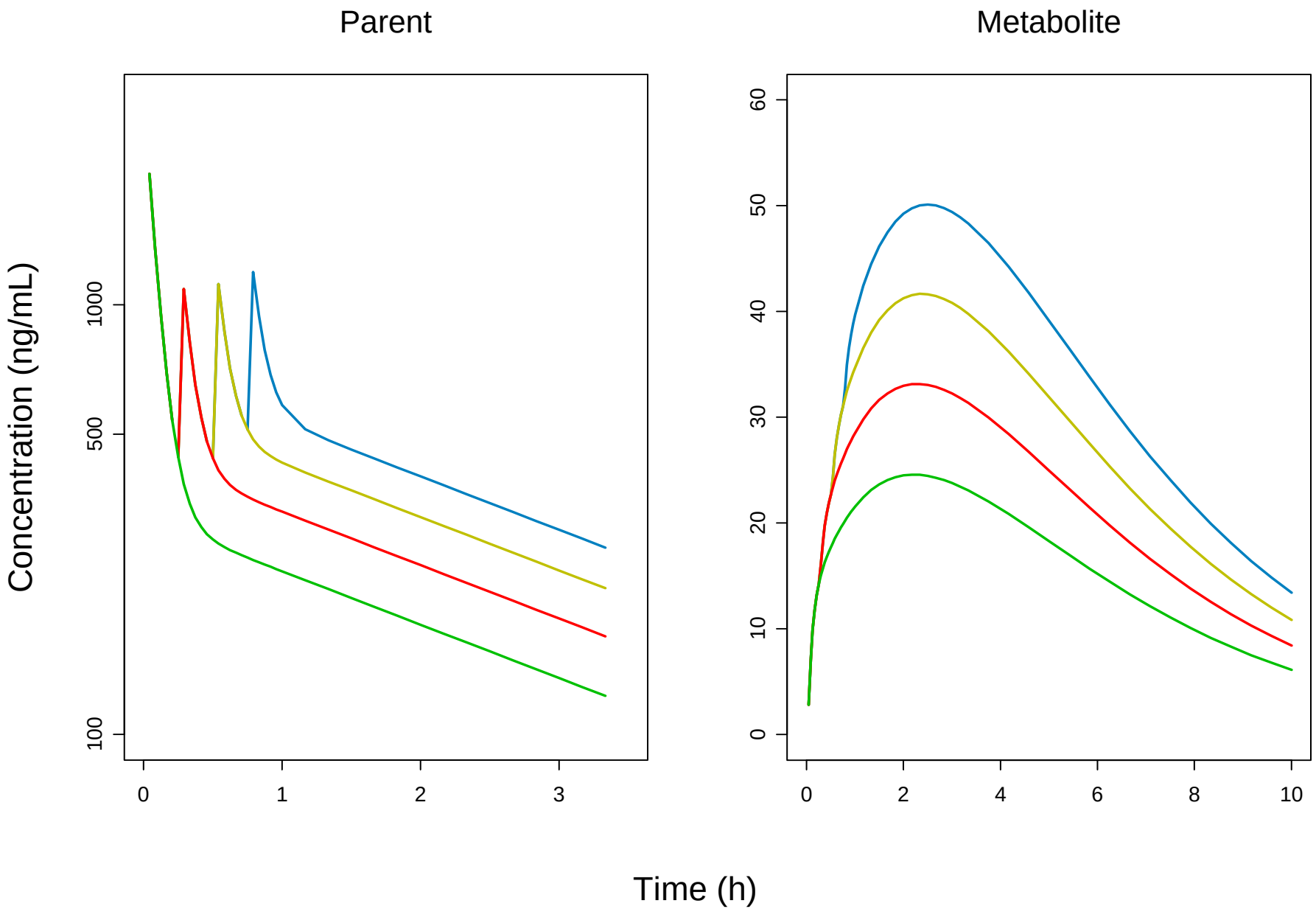
Model Predictions



Model Exploration



Model Exploration



Pharmacodynamic Modelling

- **Ordered categorical data**
- **Presence of censored information**
- **No baseline information**
- **Progression of pain**
- **Residual anesthetic effect**
- **Drug effects**

- **Ordered categorical data**
  - **Logistic regression**
    - **Logit = f( ) + η**
    - **$P(Y_{ij}=m|\eta_i) = P(Y_{ij} \leq m|\eta_i) - P(Y_{ij} \leq (m-1)|\eta_i)$**

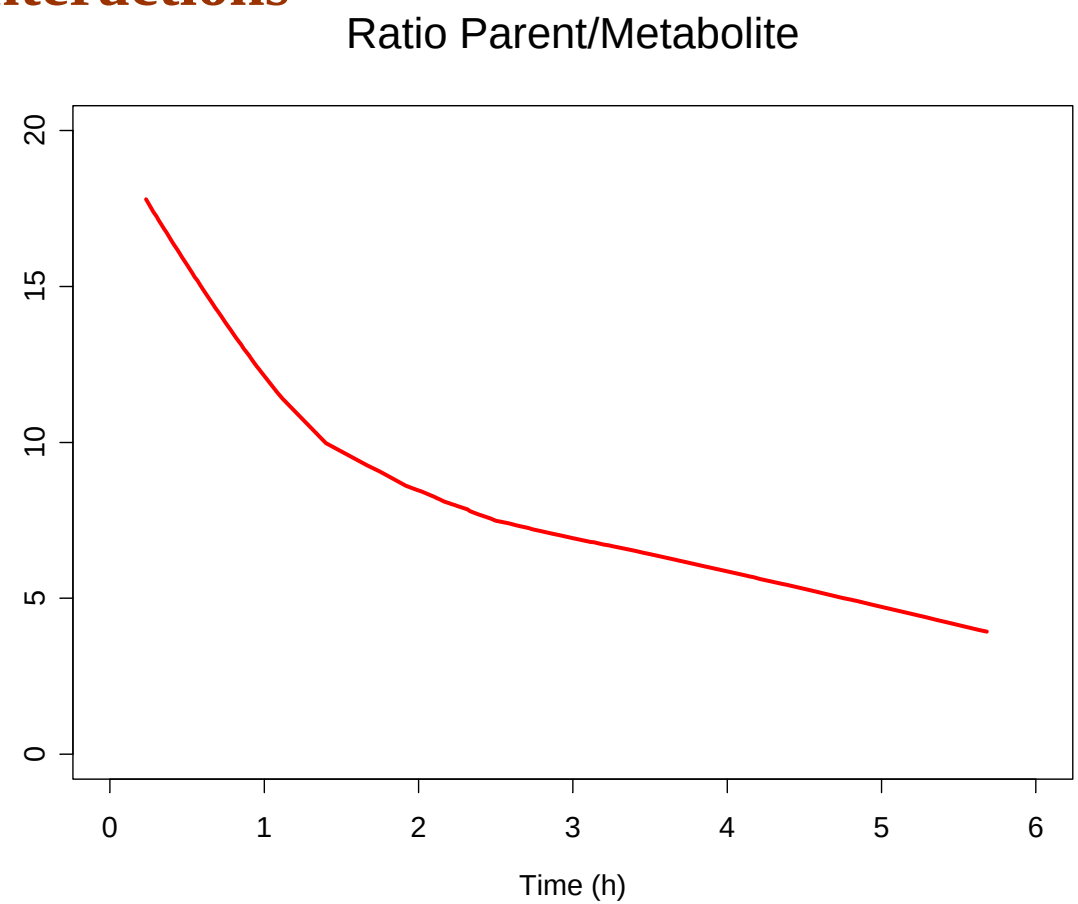
- **Censored information**
  - **Crying scores and Time to event data were simultaneously fitted**
    - **Hazard = g(drug effects, time)**

- **Progression of postoperative pain**
  - **Probably small**
  - **Modelled as a monotonic increasing function**

- **Baseline data are not available**
  - **It was assumed that $P(Y=0) > 0.95$**
  - **Just at the end of the surgery most children should be still anesthetized**

- **Residual anesthetic effect**
  - **Rapid decline**
  - **Modelled as exponential decrease with time**

- **Drug effects**
  - **Plasma or effect site**
  - **Linear or Non-linear models**
  - **One active compound**
  - **Drug interactions**



Results

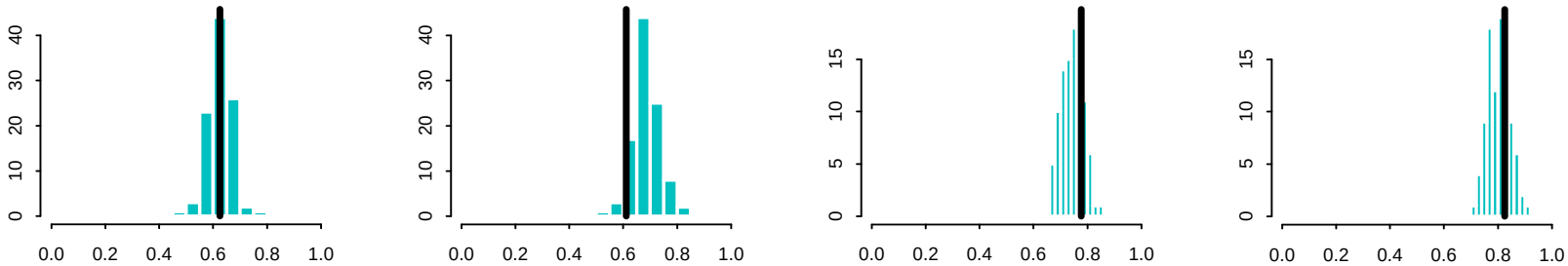
- **Pain progression: (P>0.05)**
- **Residual anesthetic effect: (P>0.05)**
- **Censored information**
  - **Model estimates very similar to those obtained from the fit of crying data alone**
- **Drug effects**
  - **T was effective (P<0.001)**
  - **Effect site (P<0.01)**
  - **Metabolite the best predictor**
  - **Interaction model (P>0.05)**

Results

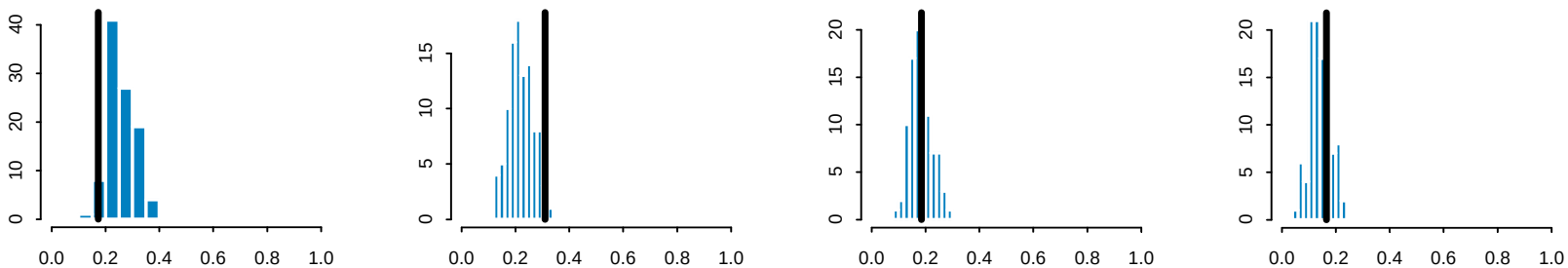
- **Model for crying**
  - $L = \theta_{Baseline} + \theta_{Slope} \times C_{eM1} + \theta_{wgt} \times Weight + \eta$
- **Model for remediation**
  - **If time ≤ 1 h: Hazard = 0**
  - **If time > 1h: Hazard = $\theta_0 - \theta_{EMAX} \times C_{eM1}/(C_{eM1}+C_{50})$**

Validation

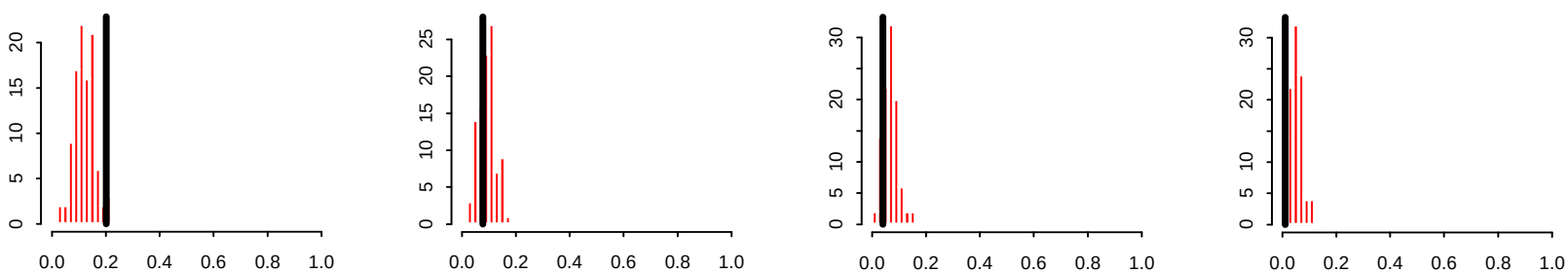
P(Y=0)



P(Y=1)

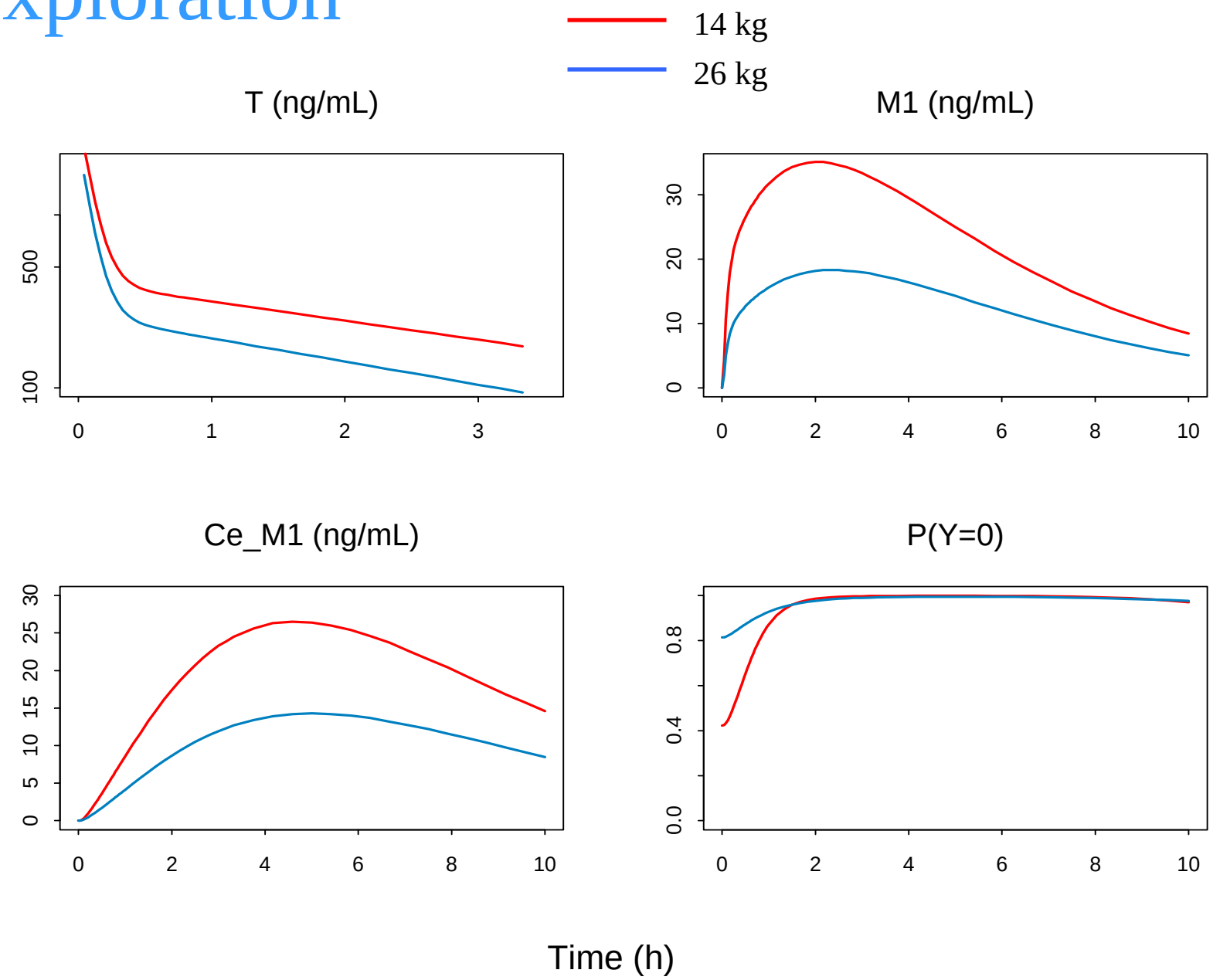


P(Y=2)



15 min **30 min** **45 min** **60 min**

Exploration

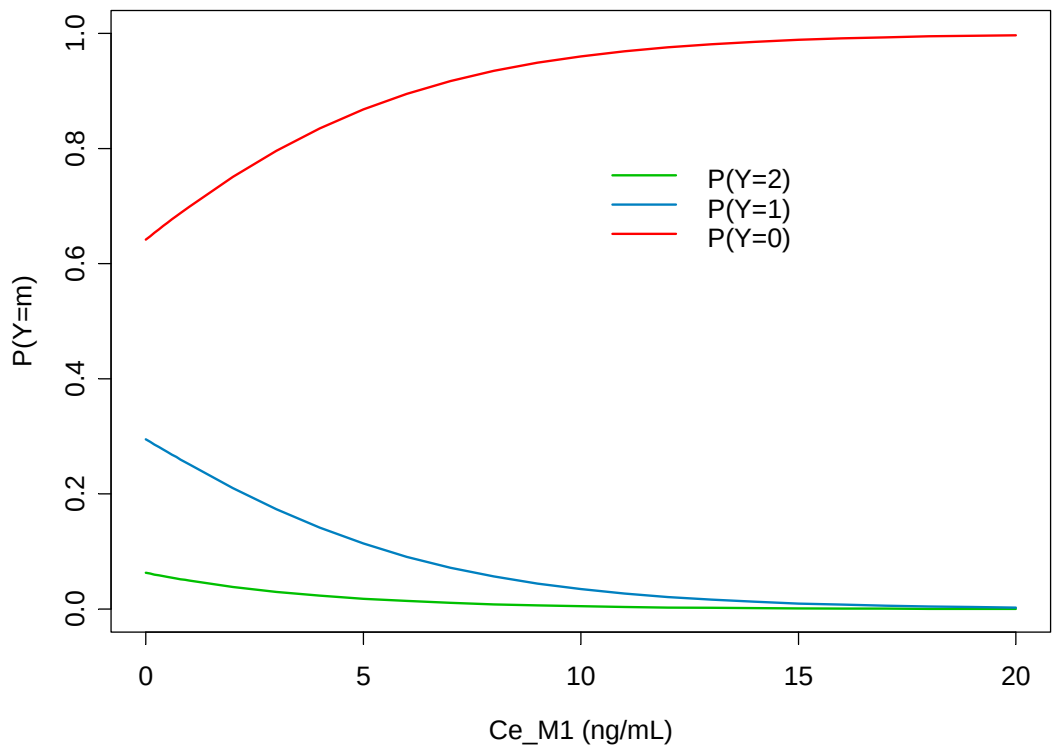


- **Indication of a residual anaesthetic effect?**

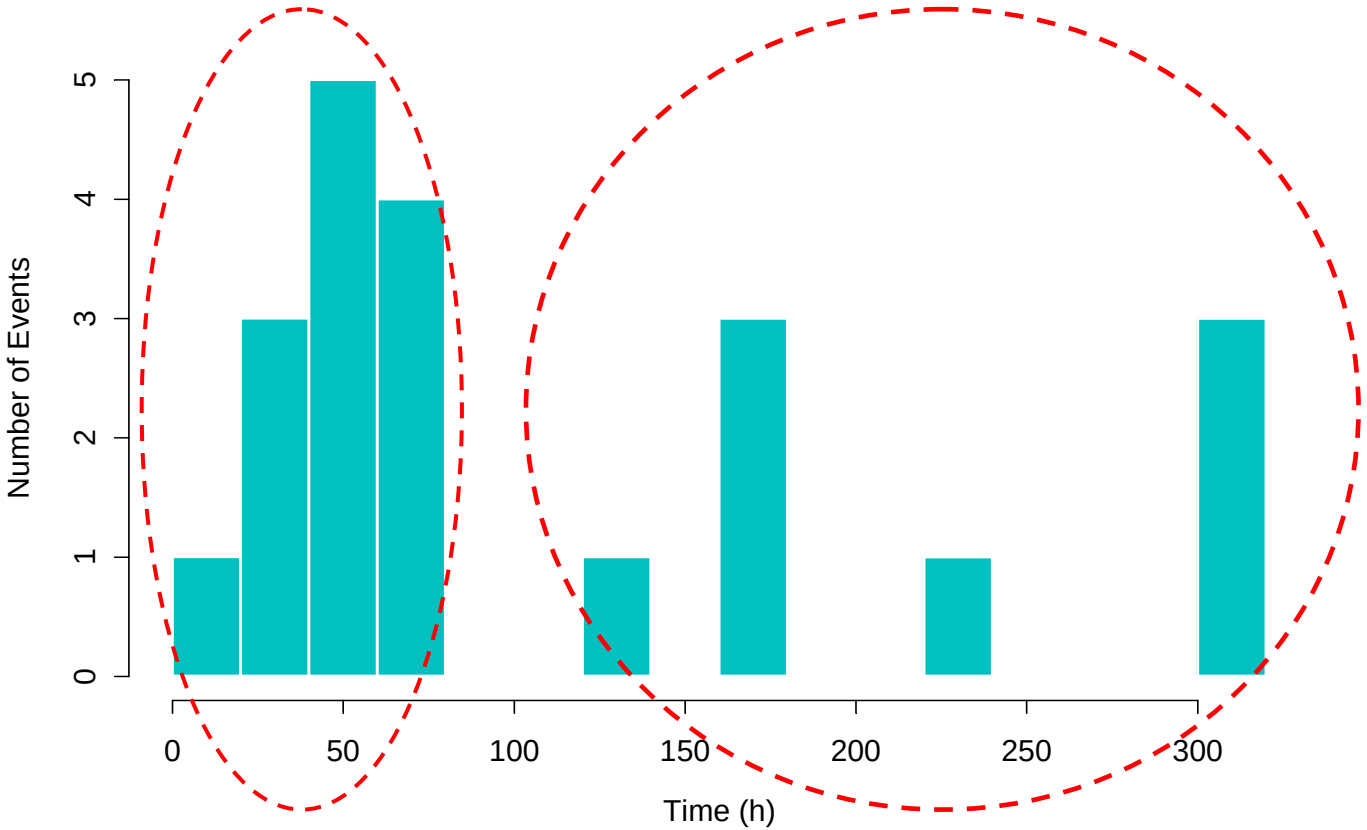
  $L = \theta_{Baseline} + \theta_{Slope} \times (1 + \theta_{wgt} \times Weight) \times C_{eM1} + \eta$ (worse fit)

  Stanski et al., (1993): $t_{1/2\ opiod} \sim f(weight)$

- **1 mg/kg dose for bigger children seems to be OK**
- **For smaller children an improvement in response could be achieve by obtaining at early times effect site concentrations ~ 10-15 ng/mL**



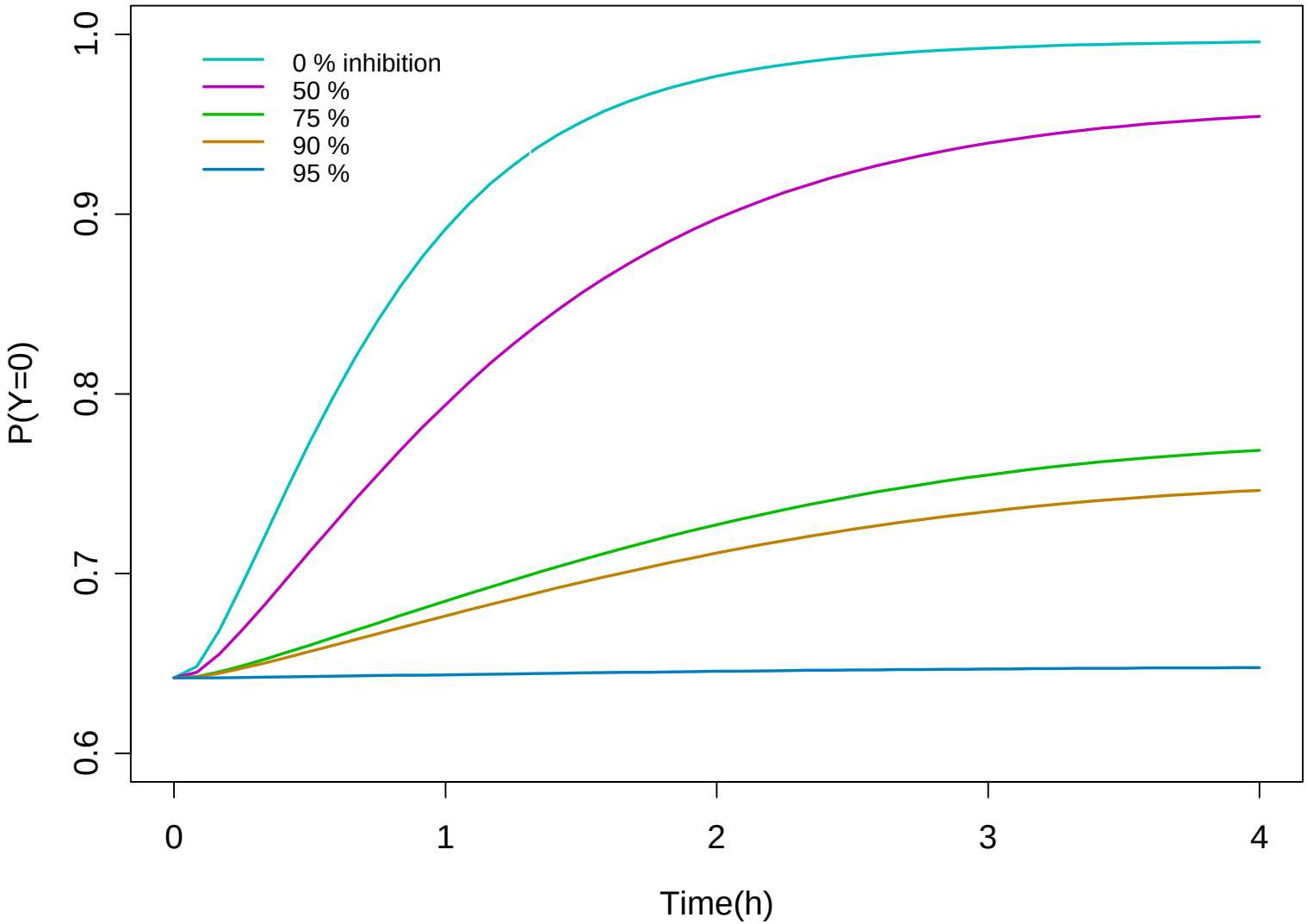
- **Twenty mild adverse events (vomits)**



[M1] 14 - 56 ng/mL

Exploration

- **CYP 2D6 activity ~ Response**



Summary

- **Population PK/PD characteristics of T have been described under this clinical scenario**
- **Difficult to compare with adults due to the lack of information**
- **M1 seems to be the major responsible of T effects**
- **Body weight has an impact on both PK and PD**
- **In principle results from modelling are suitable to optimice dosing in children**