Incorporating PGx into Population PK Modeling

Session #2: Working with a PK modeler to incorporate PGx into a model

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Background

- Doctor of Pharmacy, University of Missouri-Kansas City
- UNC-Duke Collaborative Clinical Pharmacology Training Program
- Pharmacokinetics/Pharmacodynamics Research Scientist, Metrum Research Group
- Adjunct Assistant Professor, Pharmacotherapy and Experimental Therapeutics, Eshelman School of Pharmacy, University of North Carolina at Chapel Hill

Disclosures

> The views and opinions expressed in this presentation are my own and do not necessarily reflect those of my employer or affiliated institutions.

Why am I here?

- To promote synergy between pharmacogenomic (PGx) experts and pharmacometric (PMx) scientists

Objectives

- Introduce fundamental concepts in population pharmacokinetic (PK) modeling
- Demonstrate how modeling and simulation can support clinical PGx evidence generation
- Stimulate discussion around ideas, challenges, and opportunities for integrating modeling and simulation into PGx research

Metrumazole

UpToDate

- Theoretical antifungal agent dosed twice daily
- Primarily metabolized by Cytochrome P450 (CYP) enzyme system
- METRO study (**M**etrumazol**E** **T**rial for **R**esponse **O**utcomes)
  - Poor metabolizer (PM) phenotype associated with increased efficacy
  - Rapid metabolizer (RM) phenotype associated with decreased efficacy

Clinical Question 1

> How does metrumazole PK differ between patients with poor, normal, and rapid metabolizer phenotypes?

Clinical Question 2

> How did steady state exposure metrics (e.g., Cmax, Cmin, Cavg) compare between patients with poor, normal, and rapid metabolizer phenotypes in the METRO study?

Clinical Question 3

> What fraction of the rapid metabolizer patient population would experience subtherapeutic trough concentrations under a dosing strategy that does not adjust for PGx phenotype?

METRO PK Data

Rich PK sampling for Cohort 1; sparse PK sampling for Cohort 2

	Number			Group percent		Overall percent	
Dose (mg)	SUBJ	OBS	BLQ	OBS	BLQ	OBS	BLQ
Cohort-1							
50	50	795	0	100.0	0.0	50.6	0.0
Cohort-2							
10	46	179	0	23.1	0.0	11.4	0.0
25	52	203	0	26.2	0.0	12.9	0.0
50	51	197	0	25.4	0.0	12.5	0.0
100	51	197	0	25.4	0.0	12.5	0.0
All data	250	1571	0	—	—	100.0	0.0

SUBJ: subjects
BLQ: below limit of quantification
OBS: observations
Source code: pk-eda-tables.R
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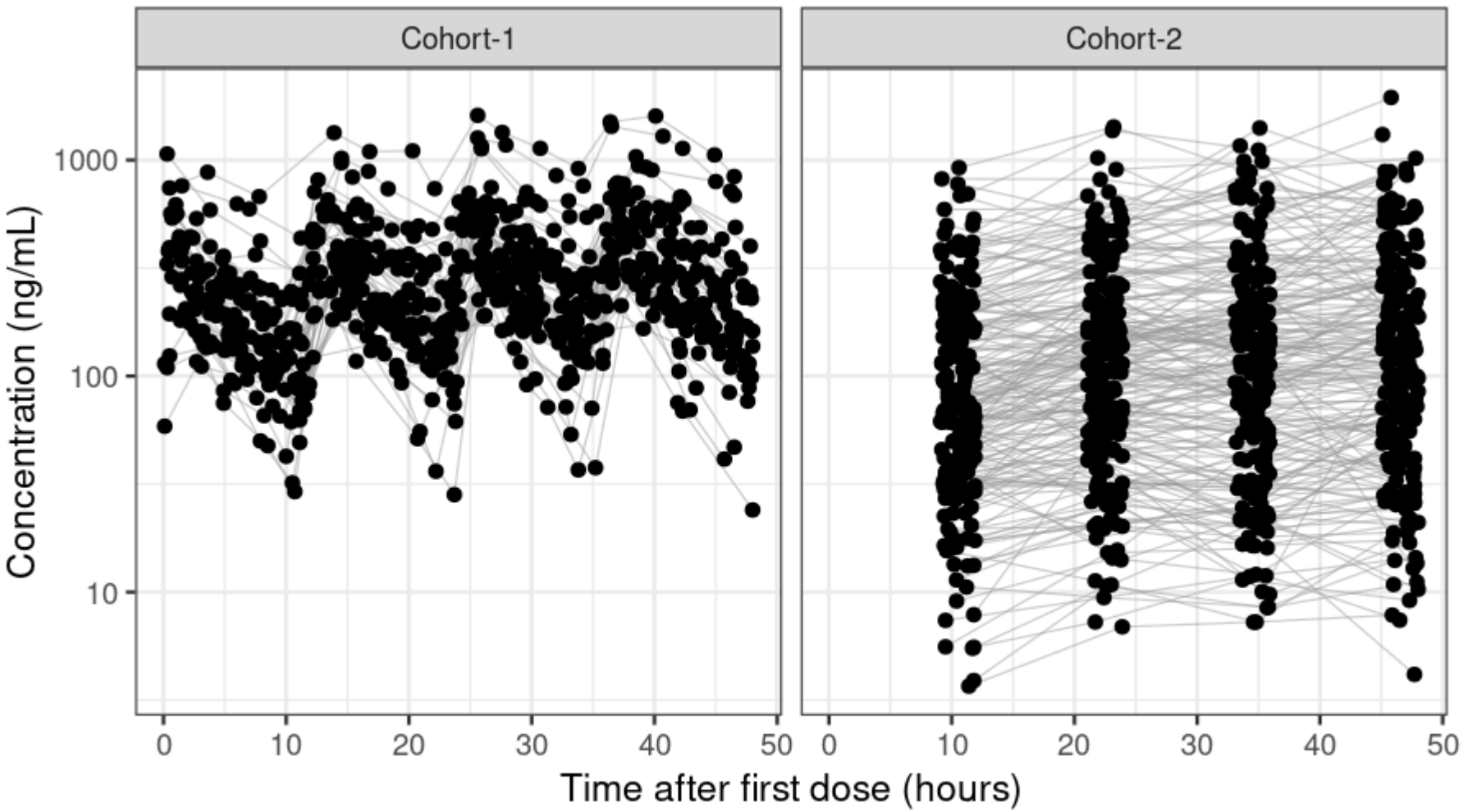
PK by METRO Cohort



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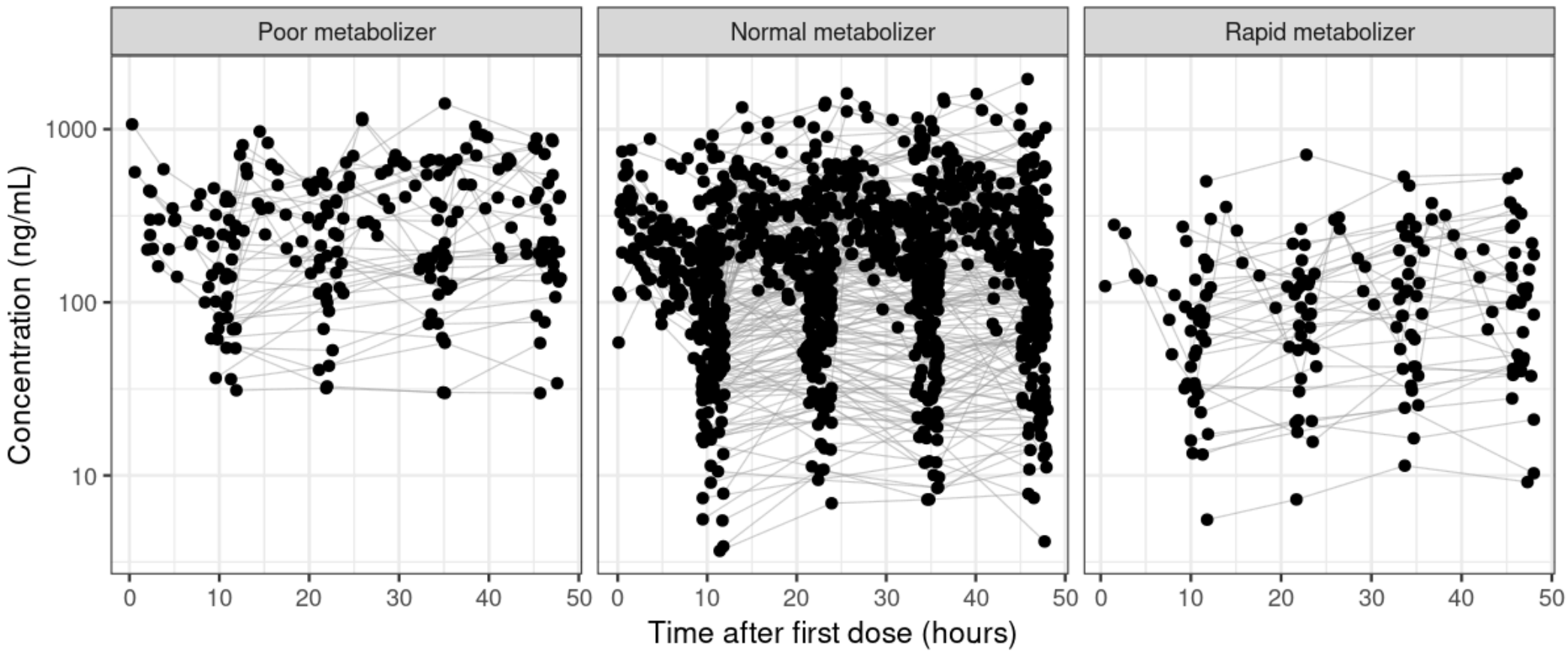
PK-PGx Relationship



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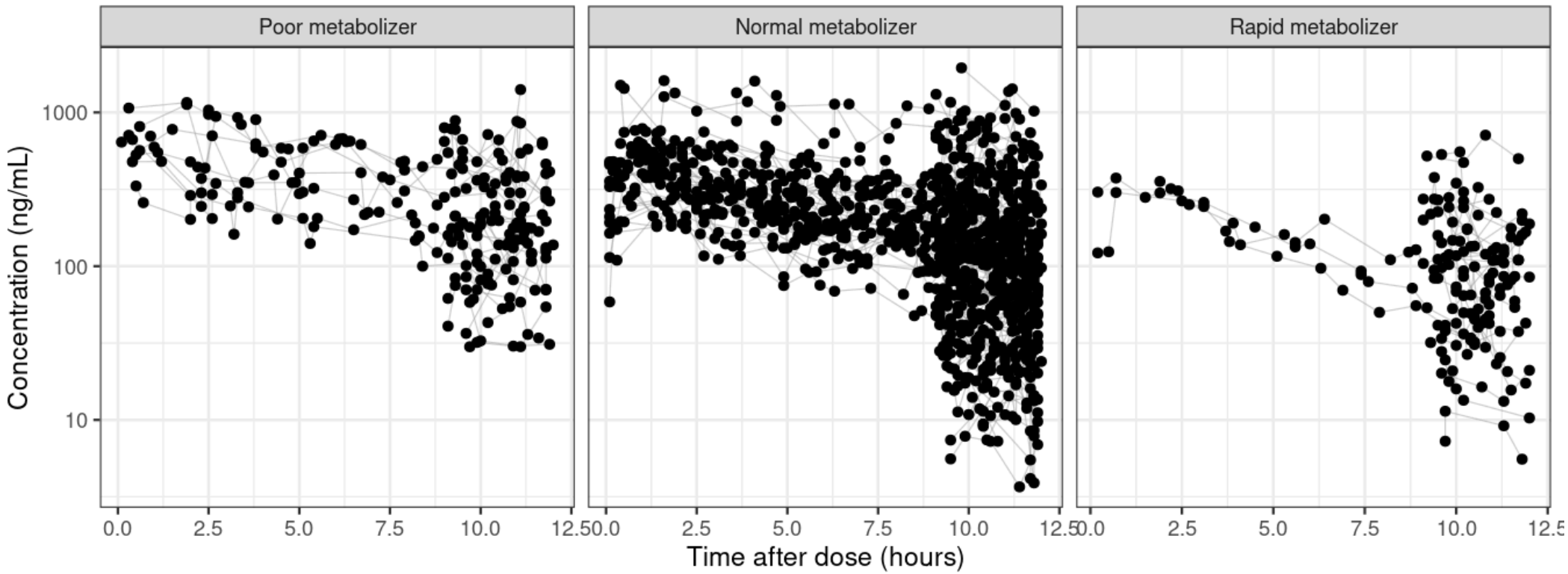
PK-PGx Relationship



Source code: pk-eda-figures.R
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Stop and Think

> Which (if any) of the three clinical questions can be answered with this PK-PGx data?

Why include PGx in a Population PK model?

To model, or not to model?

- Handle rich, sparse, and unbalanced PK data
- Account for differences in dosing history, PK sampling times, and/or PK sampling strategies between individuals
- Improve power to detect covariate effects (e.g., PGx metabolizer phenotypes on clearance)
- Adjust for confounding factors (e.g., body weight on volume of distribution)
- To simulate!

Mixed Effects Models

- **Fixed Effects**: Parameters that quantify population-level average effects or expected behavior across the population
  - Commonly referred to as θs (THETAs)
  - Example: “The typical clearance for individuals with a normal metabolizer phenotype is 10 L/hr”
- **Random Effects**: Describe variability across individuals and observations
  - Interindividual variability (IIV)
  - Residual unexplained variability (RUV)

Two Levels of Random Effects

- **Interindividual variability (IIV)**: The magnitude of variability in PK parameters between individuals within a population
  - Example: “Between-patient variability in metrumazole clearance, after accounting for body weight and CYP metabolizer phenotype, is approximately 30%”
- **Residual unexplained variability (RUV)**: Within-patient variability that is not explained by fixed effects (structural parameters and covariate effects) or IIV random effects
  - Commonly thought of as assay or observation error, but can be much more

Mixed Effects Models

Individual PK parameters are a function of fixed effects and a random sample from the random effects distribution

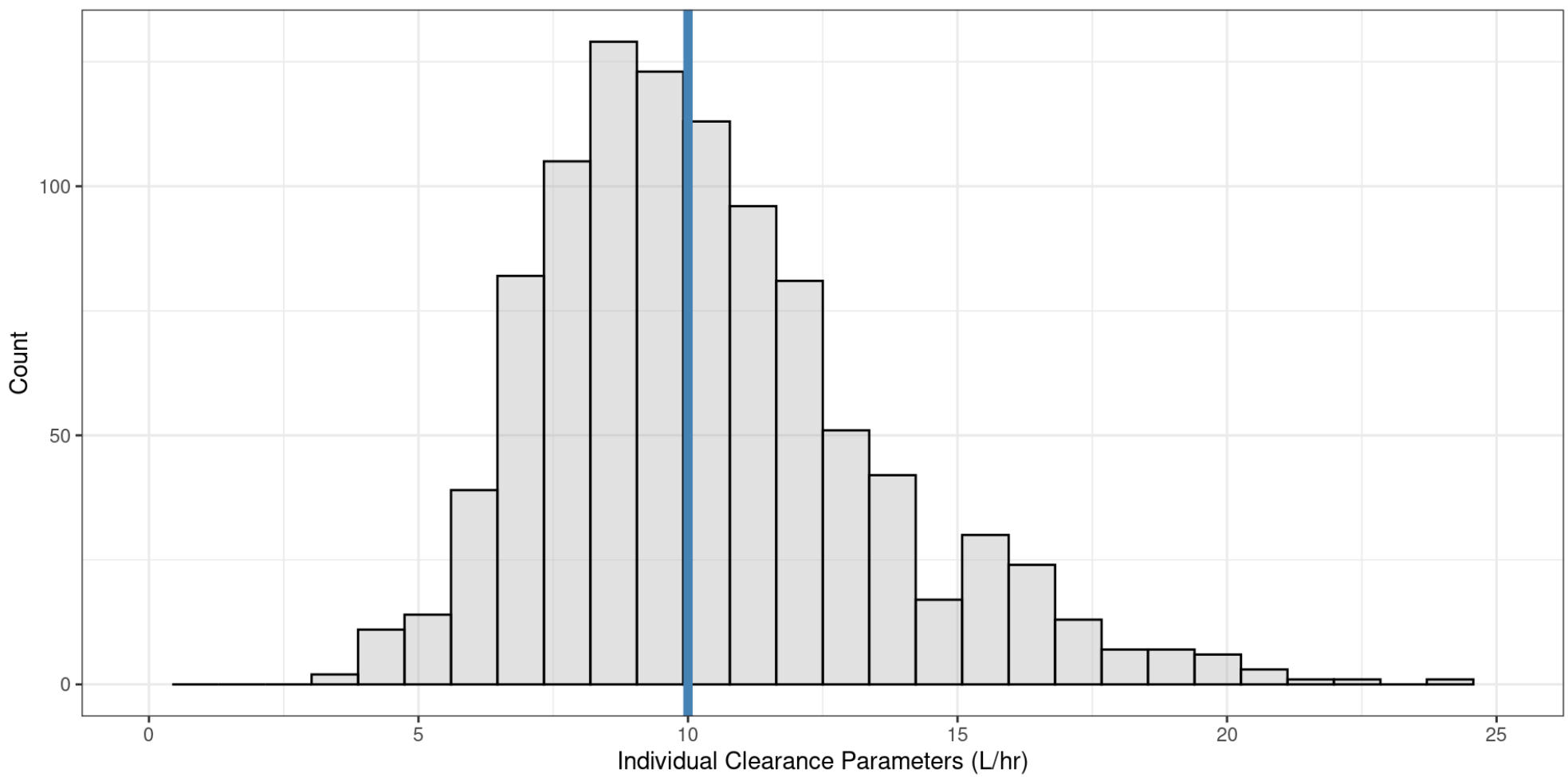
$$TVCL = \theta_1 \cdot \frac{TBW^{\theta_2}}{70} \cdot \theta_3^{CYP_{PM}}$$

$$CL_i = TVCL \cdot \exp(\eta_{CL})$$

$$\eta_{CL} \sim N(0, \omega^2)$$

IIV Example

TVCL = 10 L/hr; ω^2 = 0.09; CV% ~ 30%



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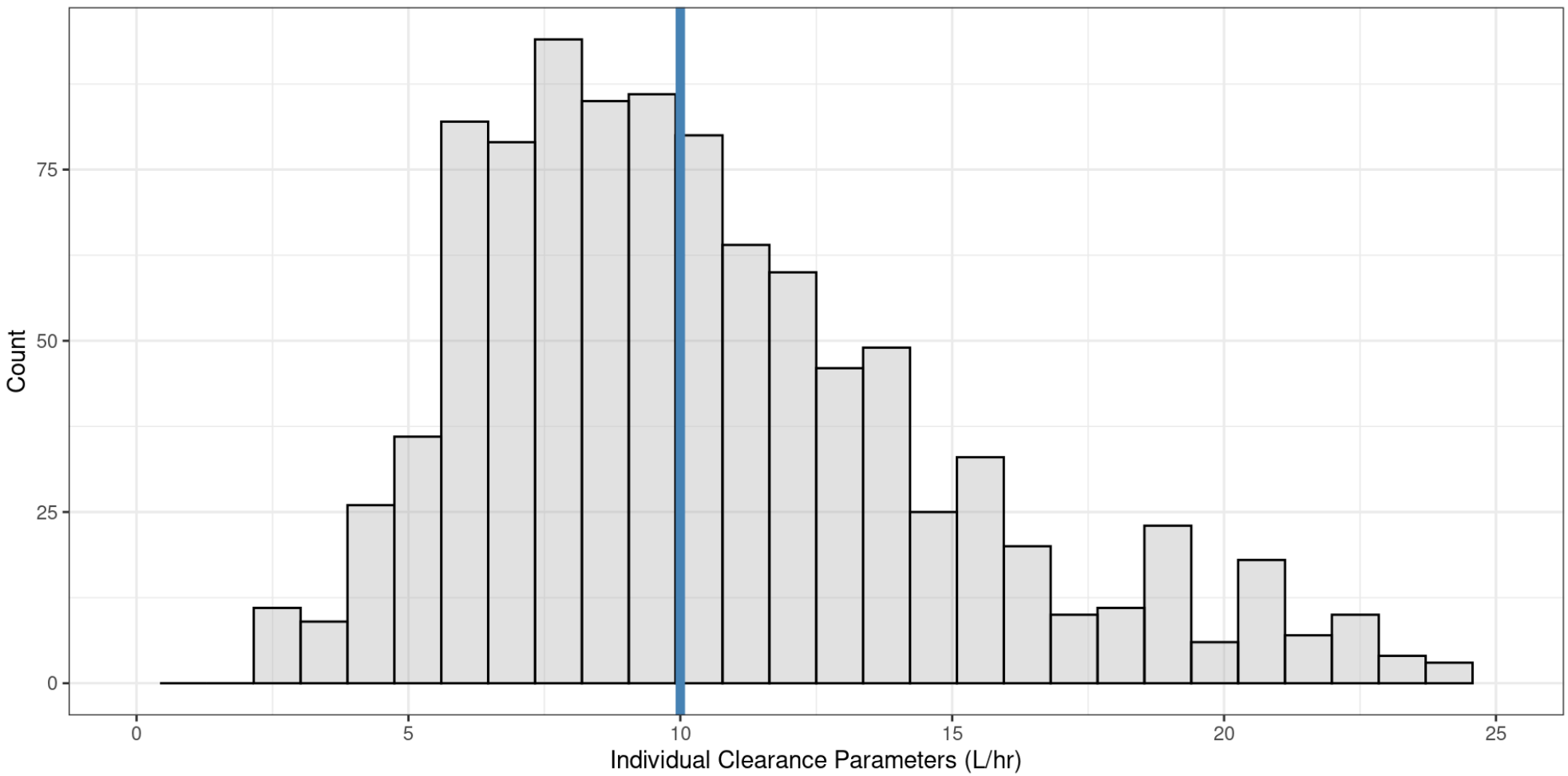
IIV Example

TVCL = 10 L/hr; ω^2 = 0.2; CV% ~ 50%



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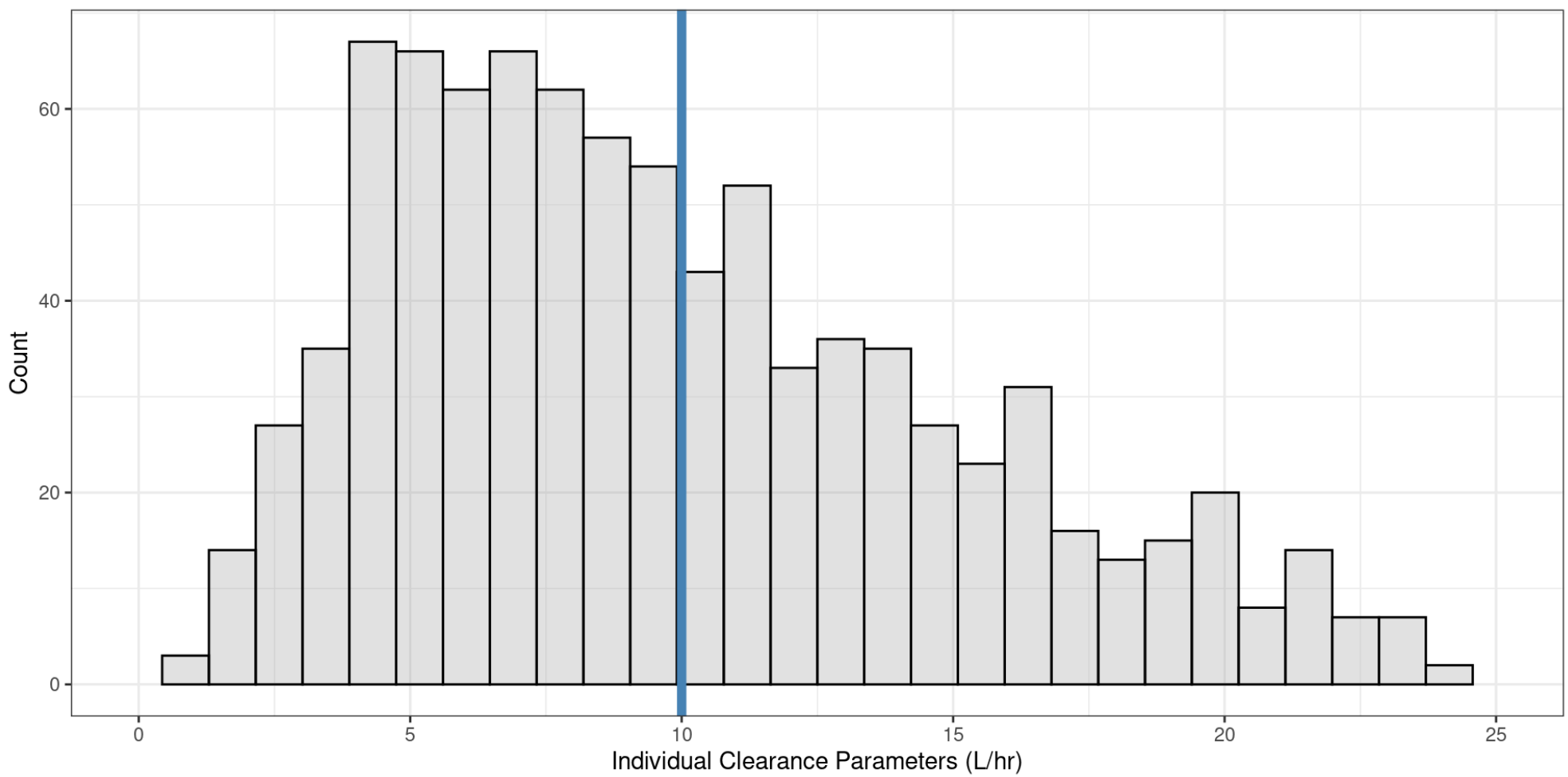
IIV Example

TVCL = 10 L/hr; ω^2 = 0.50; CV% ~ 80%



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PK Model Predictions

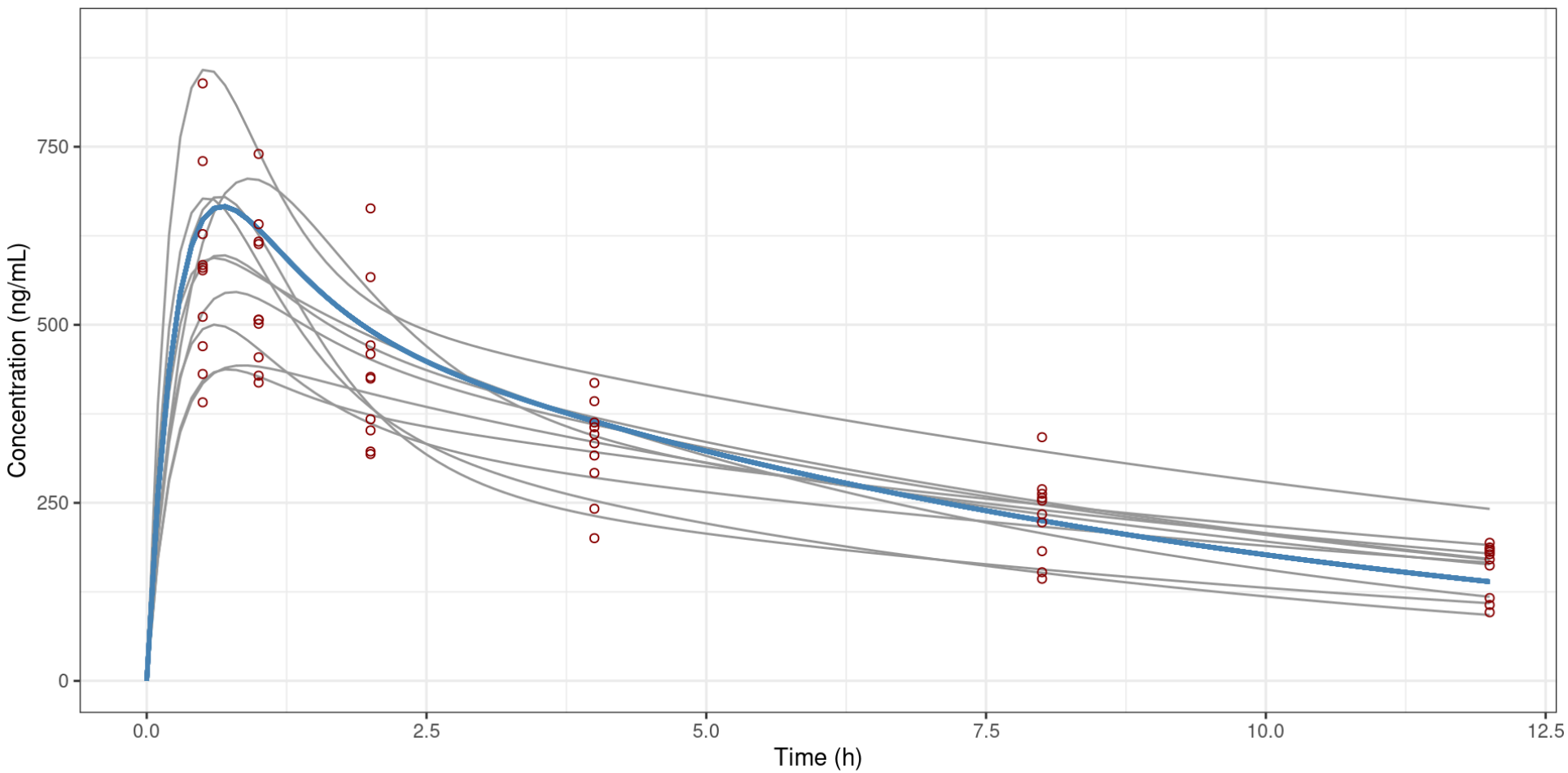
Population predicted concentrations for 10 individuals with a CYP normal metabolizer phenotype receiving metrumazole 100 mg PO

PK Model Predictions

Individual predicted concentrations for 10 individuals with a CYP normal metabolizer phenotype receiving metrumazole 100 mg PO

PK Model Predictions

Plausible concentration measurements (PK samples) from these individuals



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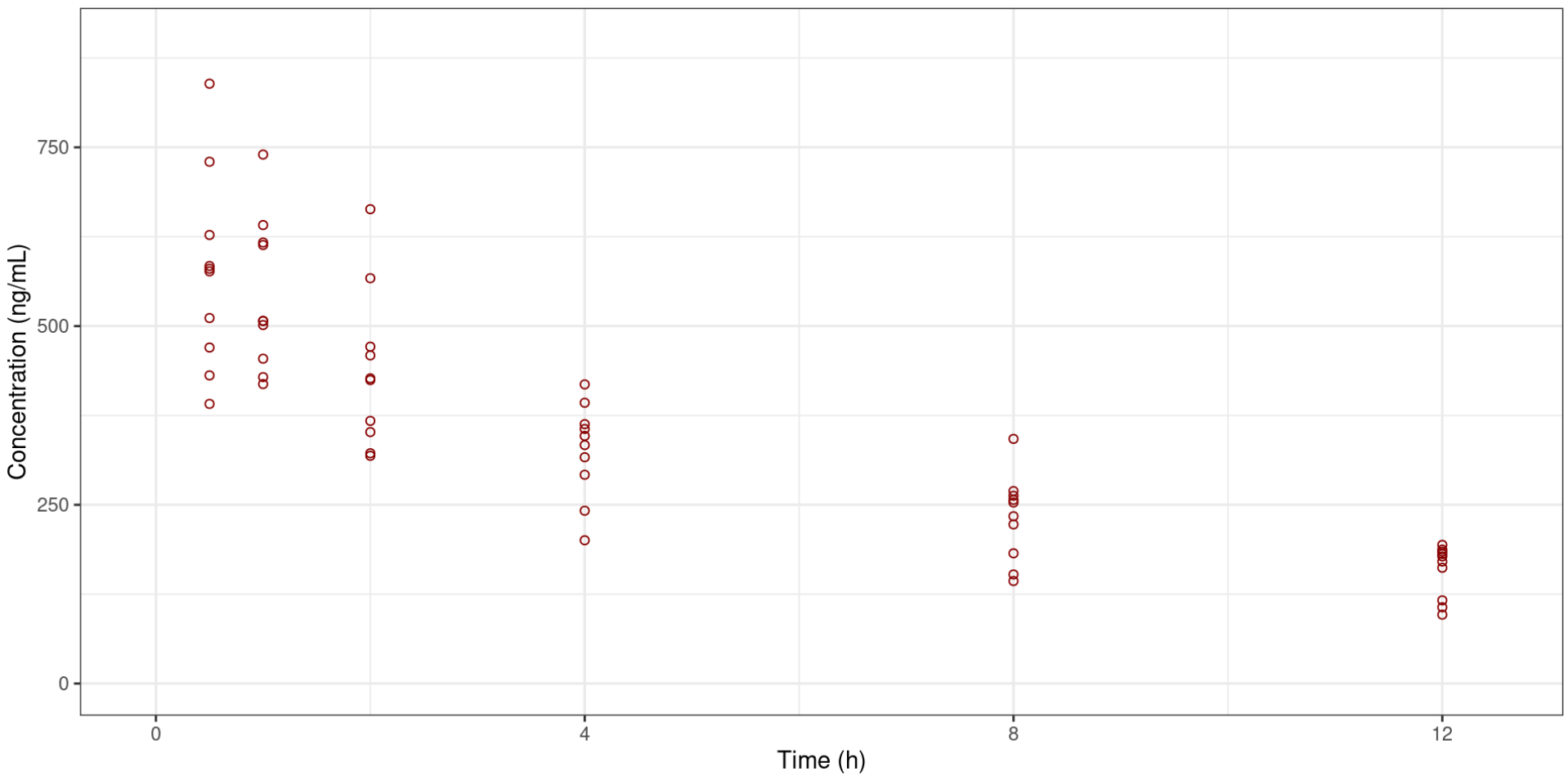
PK Model Predictions

Plausible concentration measurements (PK samples) from these individuals



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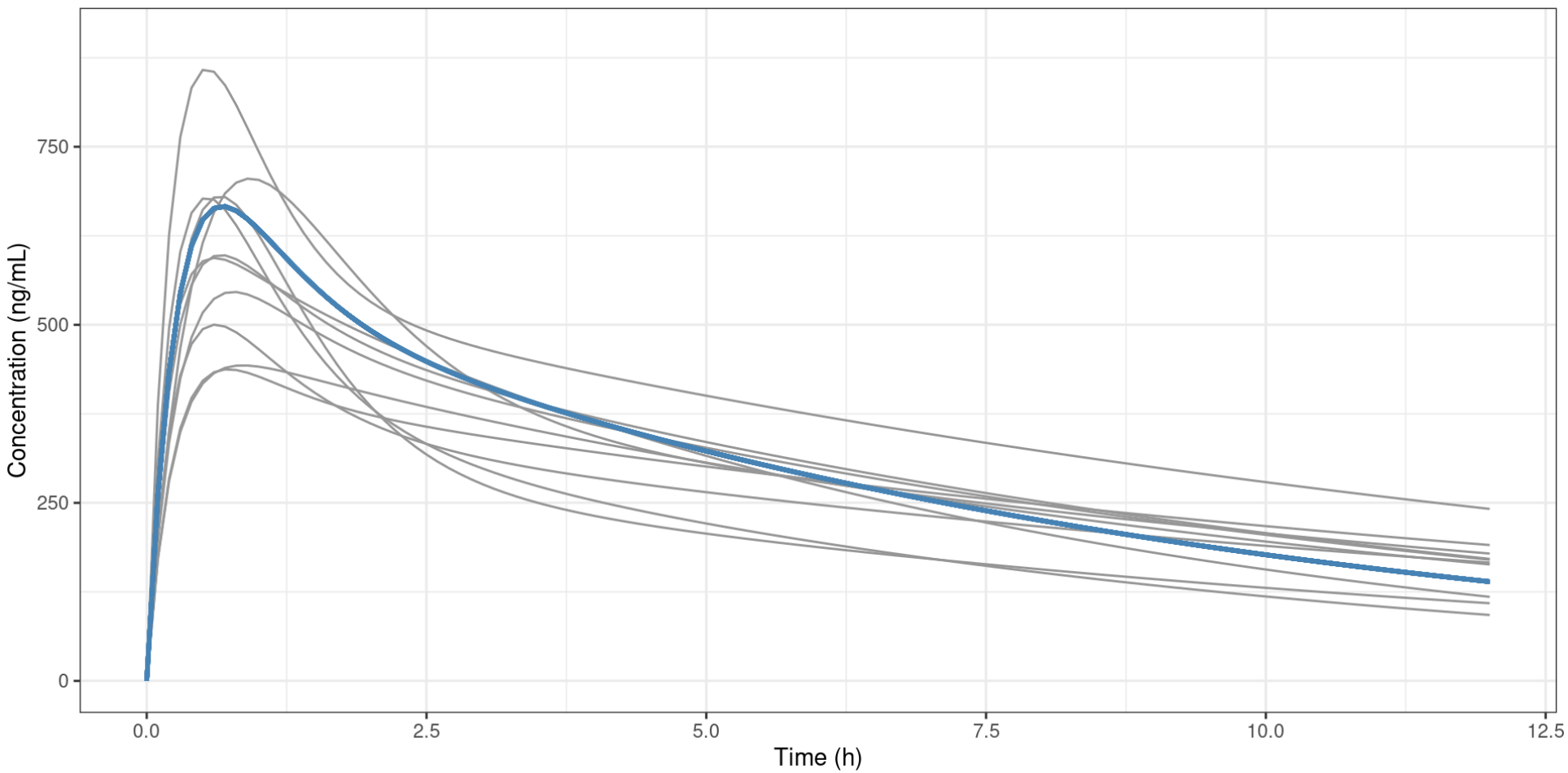
PK Model Predictions

Population PK model helps us go from observations to population and individual predictions



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Parameterizing PGx Effects

Parameterizing PGx Effects

Additive Effects

$$TVCL = \theta_1 + \theta_2 \cdot CYP_{RM}$$

Proportional Effects

$$TVCL = \theta_1 \cdot (1 + \theta_2 \cdot CYP_{RM})$$

$$TVCL = \theta_1 \cdot \theta_2^{CYP_{RM}}$$

$$\log(TVCL) = \theta_1 + \theta_2 \cdot CYP_{RM}$$

Parameterizing PGx Effects

Nonlinear Elimination

$$TVCL/V = \frac{Vmax \cdot C}{Km + C}$$

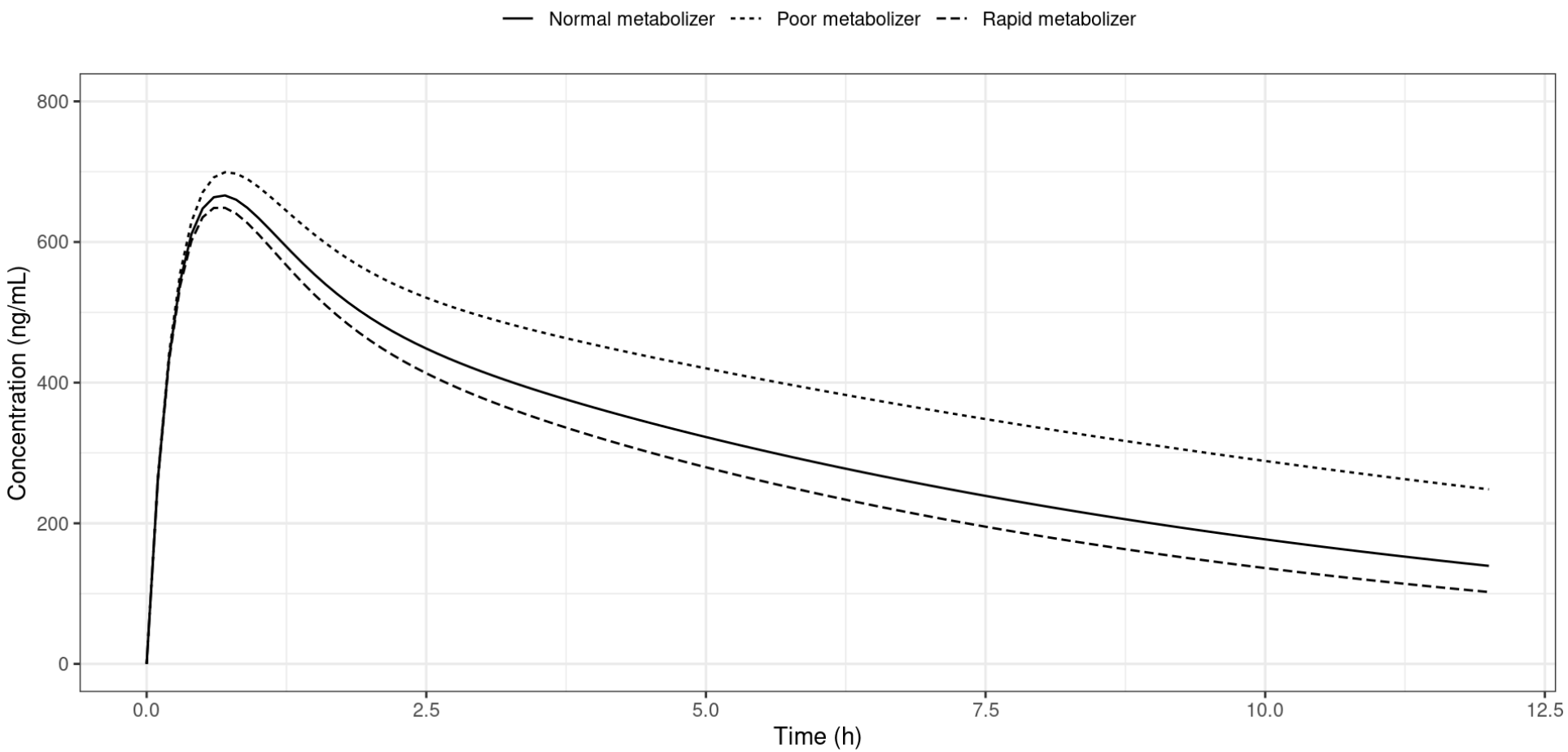
$$Vmax = \theta_1 + \theta_2 \cdot CYP_{RM}$$

Activity Score (AS)

$$TVCL = \theta_1 + \frac{AS^{\theta_3}}{AS^{\theta_3} + \theta_2^{\theta_3}}$$

Parameterizing PGx Effects

Covariate effects describe the differences in typical values of PK parameters (e.g., TVCL for PM, NM, RM)



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Parameterizing PGx Effects

- The PK modeler should rely on the PGx expert for appropriate integration of the PGx data into the PK model
- The most appropriate implementation will likely be guided by the available data, weight of existing evidence, and questions intended to be answered with the model

Metrumazole Population PK Model

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Fixed Effects Estimates

			Estimate	95% CI
Structural model parameters				
CL/F (L/hr)	$\exp(\theta_1)$	Apparent clearance	18.7	17.3, 20.2
V2/F (L)	$\exp(\theta_2)$	Apparent central volume of distribution	29.5	17.7, 49.2
Q/F (L/hr)	$\exp(\theta_3)$	Apparent intercompartmental clearance	84.7	67.5, 106
V3/F (L)	$\exp(\theta_4)$	Apparent peripheral volume of distribution	110	93.6, 129
KA (hr^{-1})	$\exp(\theta_5)$	First-order absorption rate	1.30	0.827, 2.04
D1 (hr)	$\exp(\theta_6)$	Duration of zero-order absorption	0.0234	0.0119, 0.0462

Parameters estimated in the log-domain were back-transformed for clarity.
Parameter estimates are presented relative to a reference subject.
CI = estimate $\pm$ 1.96 * SE
Abbreviations: CI: confidence interval; SE: standard error
Source code: pk-param-table.R
Source file: pk-param-struct.tex

Covariate Effect Estimates

			Estimate	95% CI
Covariate effect parameters				
CL/F∼eGFR	θ_9	eGFR effect on apparent clearance	0.269	0.209, 0.329
CL/F∼Sex	$\exp(\theta_{10})$	Male sex effect on apparent clearance	0.973	0.894, 1.06
CL/F∼Age	θ_{11}	Age effect on apparent clearance	0.257	0.132, 0.383
CL/F∼PM	$\exp(\theta_{12})$	Poor metabolizer phenotype effect on apparent clearance	0.687	0.610, 0.774
CL/F∼RM	$\exp(\theta_{13})$	Rapid metabolizer phenotype effect on apparent clearance	1.31	1.16, 1.47
V2/F∼Sex	$\exp(\theta_{14})$	Male sex effect on apparent volume of distribution	1.80	1.34, 2.42

Parameters estimated in the log-domain were back-transformed for clarity.
Parameter estimates are presented relative to a reference subject.
CI = estimate $\pm$ 1.96 * SE
Abbreviations: CI: confidence interval; SE: standard error
Source code: pk-param-table.R
Source file: pk-param-cov-effect.tex

Random Effect Estimates

		Estimate	95% CI	Shrinkage (%)
Interindividual variance parameters				
IIV-CL/F	$\Omega_{(1,1)}$	0.0897 [CV%=30.6]	0.0691, 0.110	7.59
IIV-V2/F	$\Omega_{(2,2)}$	0.0816 [CV%=29.2]	-0.0169, 0.180	70.2
IIV-Q/F	$\Omega_{(3,3)}$	0.175 [CV%=43.7]	0.00772, 0.342	65.1
IIV-V3/F	$\Omega_{(4,4)}$	0.0682 [CV%=26.6]	0.0339, 0.102	53.6
IIV-KA	$\Omega_{(5,5)}$	0.0282 [CV%=16.9]	-0.0554, 0.112	79.6
IIV-D1	$\Omega_{(6,6)}$	0.180 [CV%=44.5]	-0.161, 0.522	94.9
Interindividual covariance parameters				
CL/F-V2/F	$\Omega_{(2,1)}$	0.00893 [Corr=0.104]	-0.0414, 0.0593	-
Residual variance				
Proportional	$\Sigma_{(1,1)}$	0.0102 [CV%=10.1]	0.00901, 0.0113	9.84
Proportional	$\Sigma_{(2,2)}$	0.0944 [CV%=30.7]	0.0828, 0.106	13.8

Abbreviations: CI: confidence interval; SE: standard error
CI = estimate $\pm$ 1.96 * SE
CV% of log-normal omegas = sqrt(exp(estimate) - 1) * 100
CV% of sigma = sqrt(estimate) * 100
Source code: pk-param-table.R
Source file: pk-param-random.tex

CYP Estimates

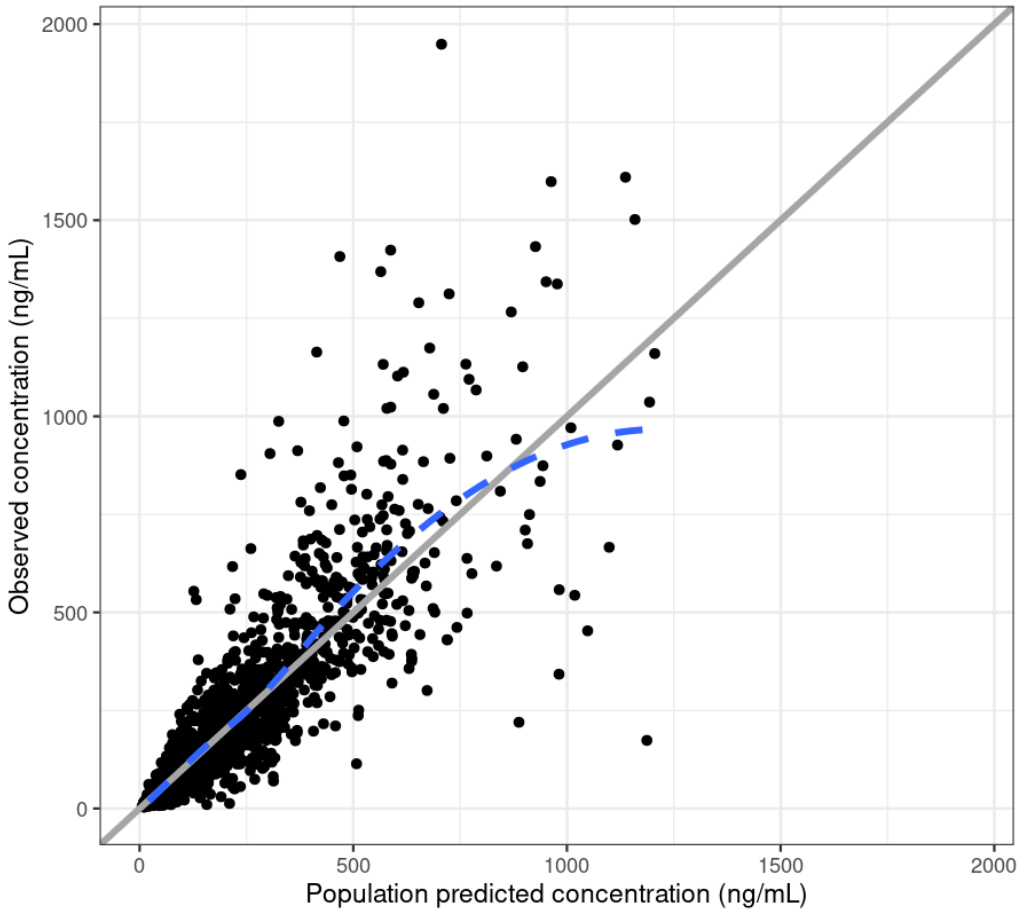
			Estimate	95% CI
Structural model parameters				
CL/F (L/hr)	$\exp(\theta_1)$	Apparent clearance	18.7	17.3, 20.2
Covariate effect parameters				
CL/F∼PM	$\exp(\theta_{12})$	Poor metabolizer phenotype effect on apparent clearance	0.687	0.610, 0.774
CL/F∼RM	$\exp(\theta_{13})$	Rapid metabolizer phenotype effect on apparent clearance	1.31	1.16, 1.47
Interindividual variance parameters				
IIV-CL/F	$\Omega_{(1,1)}$	Variance of CL/F	0.0897 [CV%=30.6]	0.0691, 0.110
Residual variance				
Proportional	$\Sigma_{(1,1)}$	Variance	0.0102 [CV%=10.1]	0.00901, 0.0113

Parameters estimated in the log-domain were back-transformed for clarity.
Parameter estimates are presented relative to a reference subject.
CI = estimate $\pm$ 1.96 * SE
Source code: pk-param-table.R
Source file: pk-param-cyp.tex

Model Evaluation

DV vs PRED and IPRED

Observations (DV) versus population (PRED) and individual predicted (IPRED) concentrations



Source code: diagnostics-poppk.Rmd
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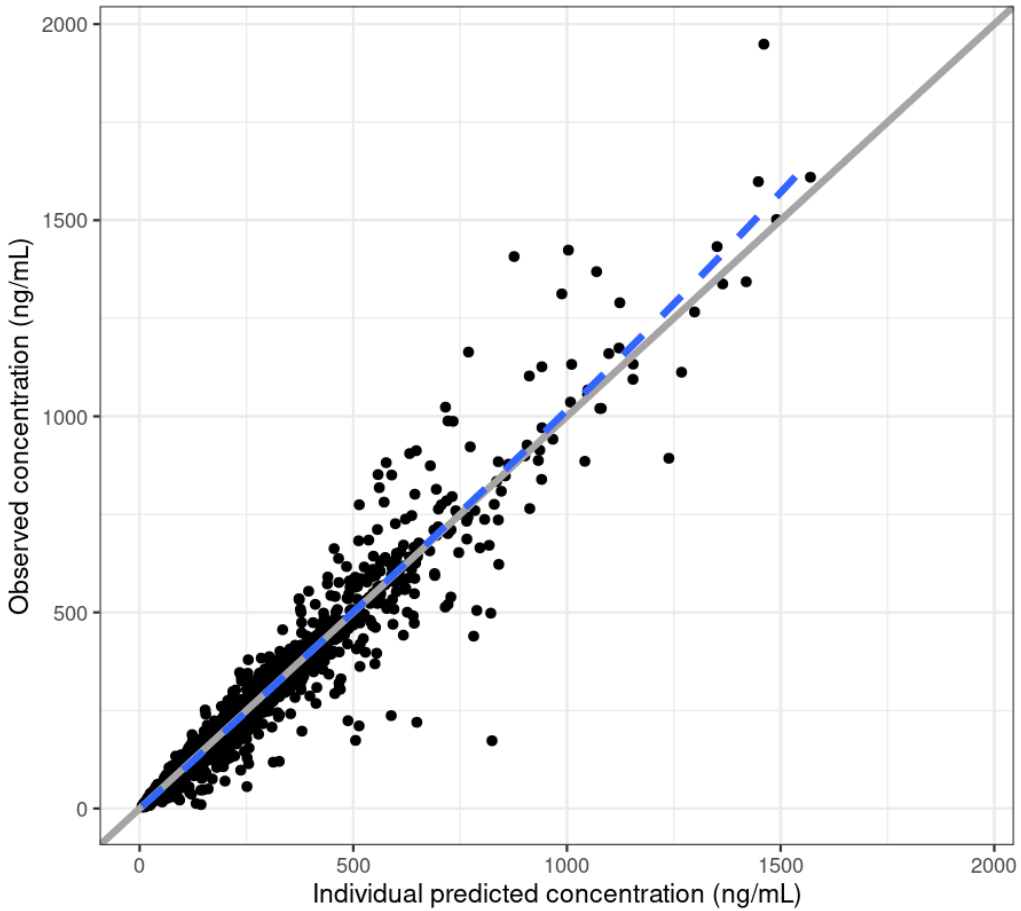
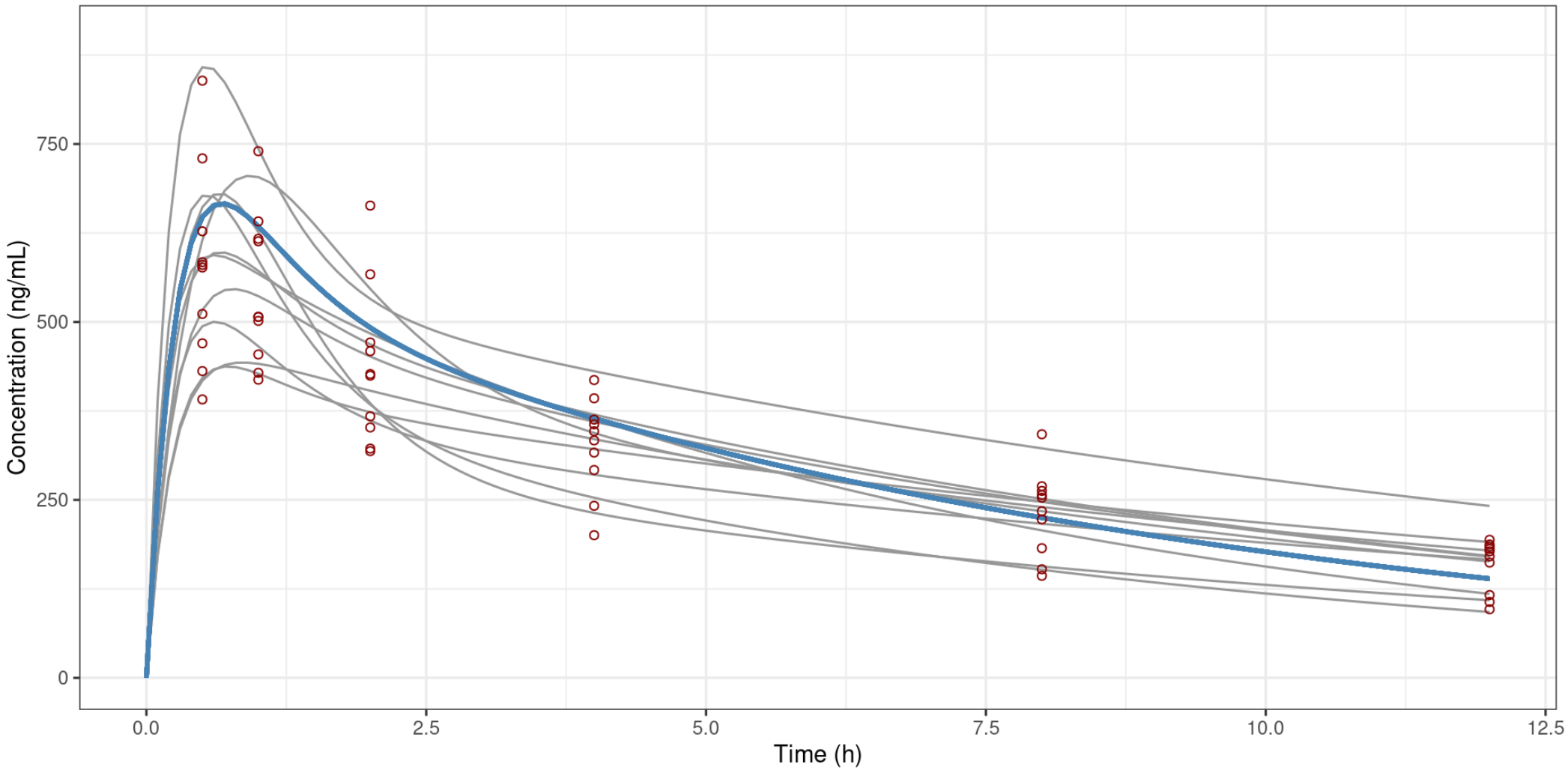


Source code: diagnostics-poppk.Rmd
Source graphic: deliv/figure/poppk/diagnostics/100/100-dv-ipred.png

DV versus PRED and IPRED



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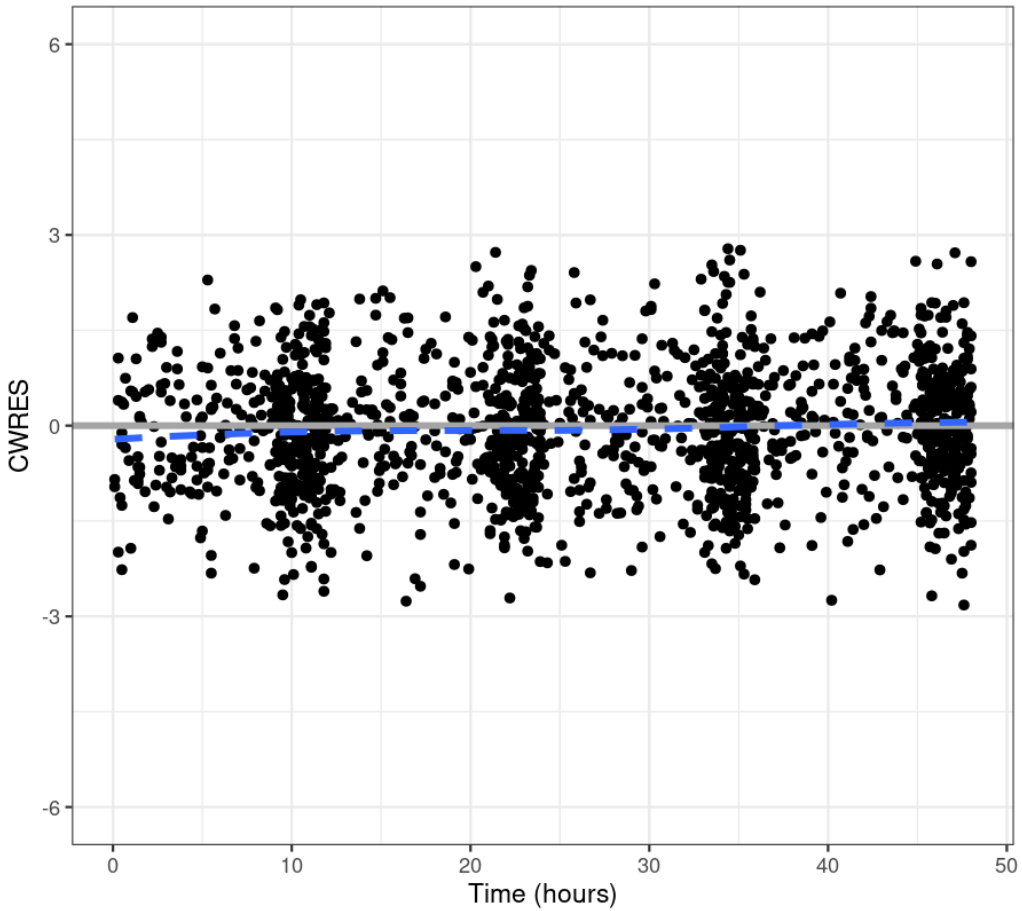
CWRES vs TIME and PRED

Conditional weighted residuals (CWRES) versus time and population predicted concentration (PRED)



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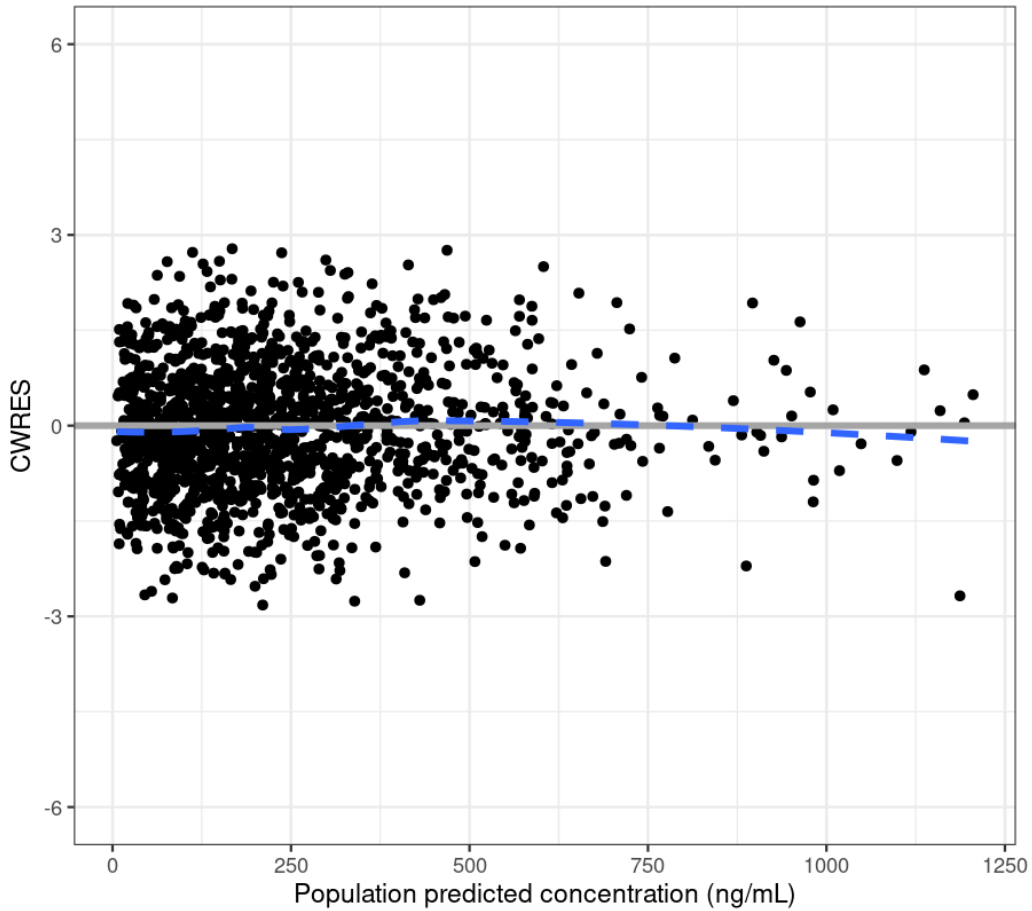


Source code: diagnostics-poppk.Rmd
Source graphic: deliv/figure/poppk/diagnostics/100/100-cwres-pred-time-tad-i001.png

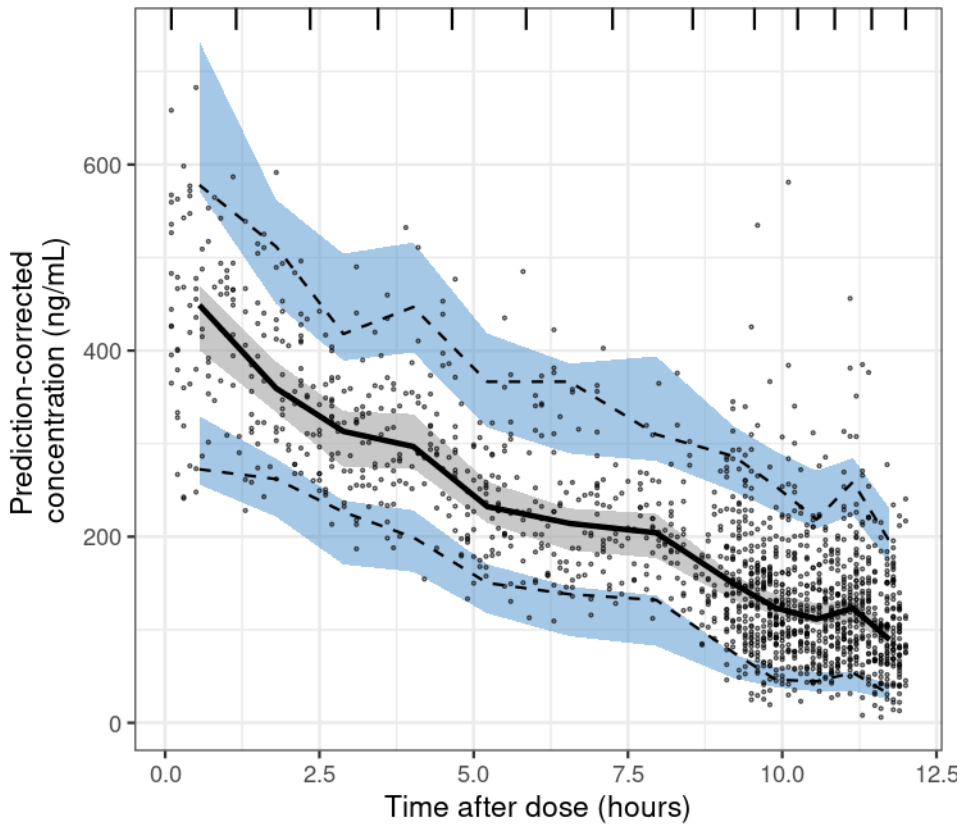
Simulation Diagnostics

Simulation Diagnostics

- “How well does the model describe the data-generating process?”
- Based on the premise that a well-fitting model should be able to generate data with similar features to the data that it was fit to
- Assess concordance between summary statistics (e.g., percentiles) of observed and simulated data

Visual Predictive Check

- N = 1000 simulation replicates
- Comparison of the 5th, 50th, and 95th percentiles of observed and simulated concentration observations



Source code: pk-vpc.R
Source graphic: deliv/figure/poppk/diagnostics/100/100-pcvpc-tad.png

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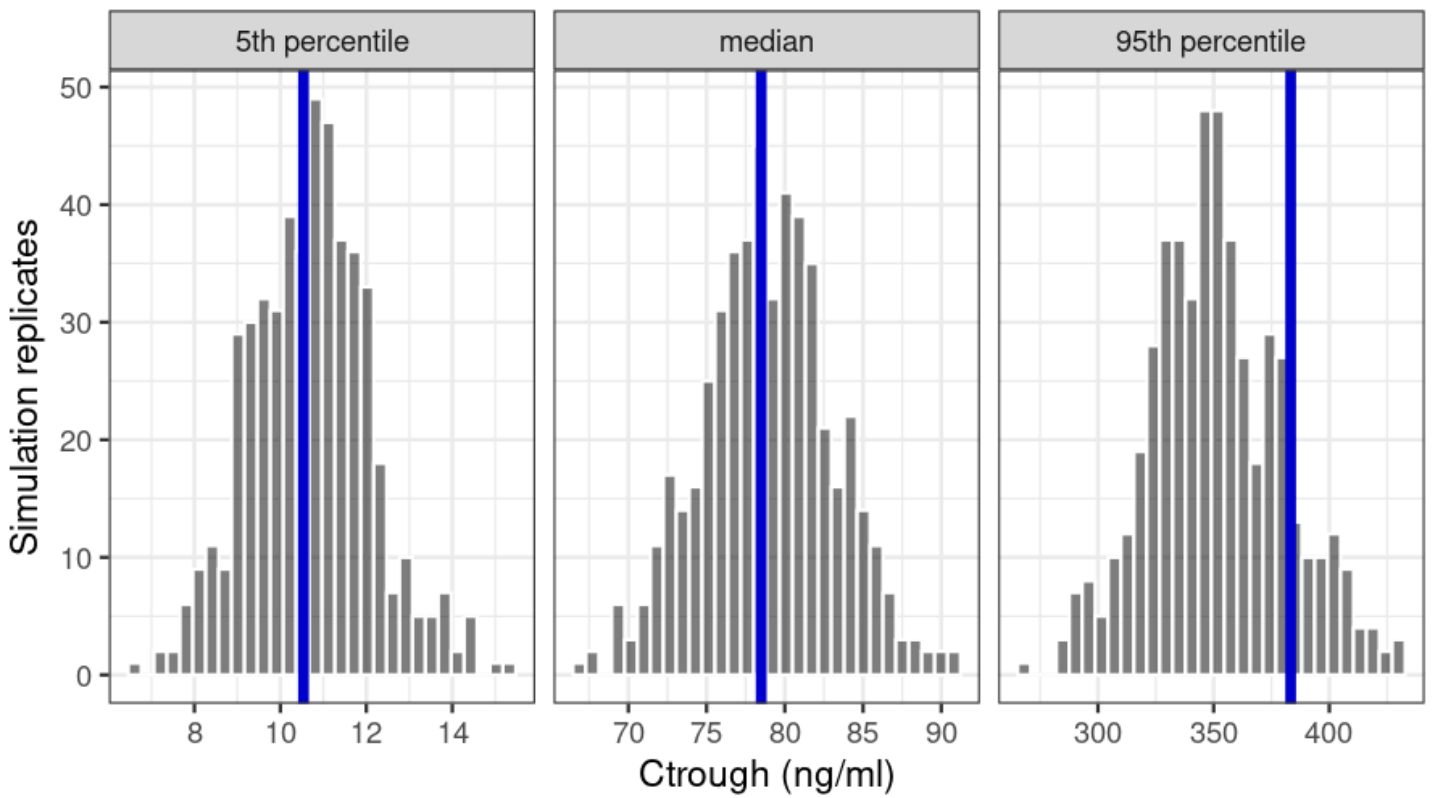
Predictive Check

Comparison of the 5th, 50th, and 95th percentiles of observed and simulated exposure metrics



Source code: pk-pcheck.R
Source graphic: deliv/figure/poppk/diagnostics/100/100-cmin-pcheck.png

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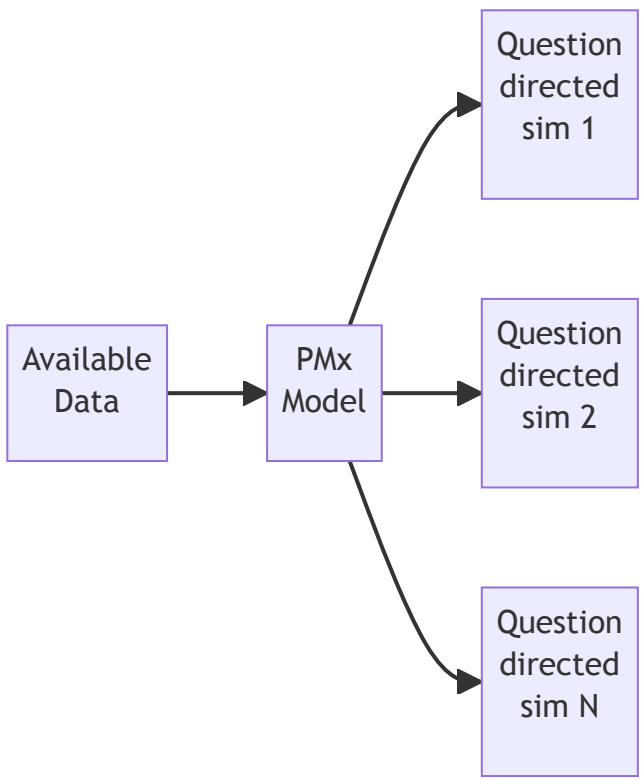
Simulation

Motivation

- The model itself is rarely the full answer
- Typically, we have some PK and PGx data…
- But real-world data collection and/or study designs rarely anticipate all of our clinical questions
- Or the science is just too complex to generate data that directly answers our question

Simulation

Simulation allows us to leverage currently available data to address questions for which we lack direct information



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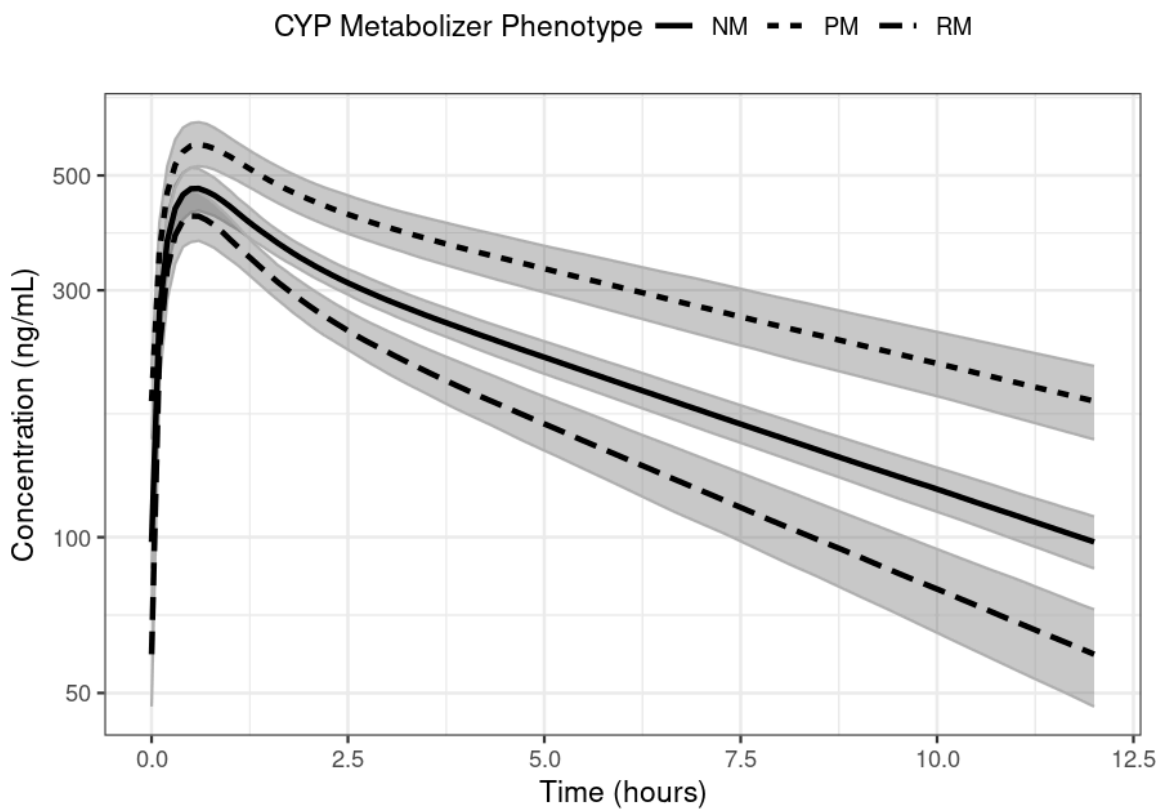
Clinical Question 1

> How does metrumazole PK differ between patients with poor, normal, and rapid metabolizer phenotypes?

Uncertainty Simulations

Simulate PK profiles for each CYP phenotype with uncertainty from fixed effects parameter estimates



Source code: pk-sim.R
Source graphic: deliv/figure/poppk/sim/100/100-sim-pk-profile.png

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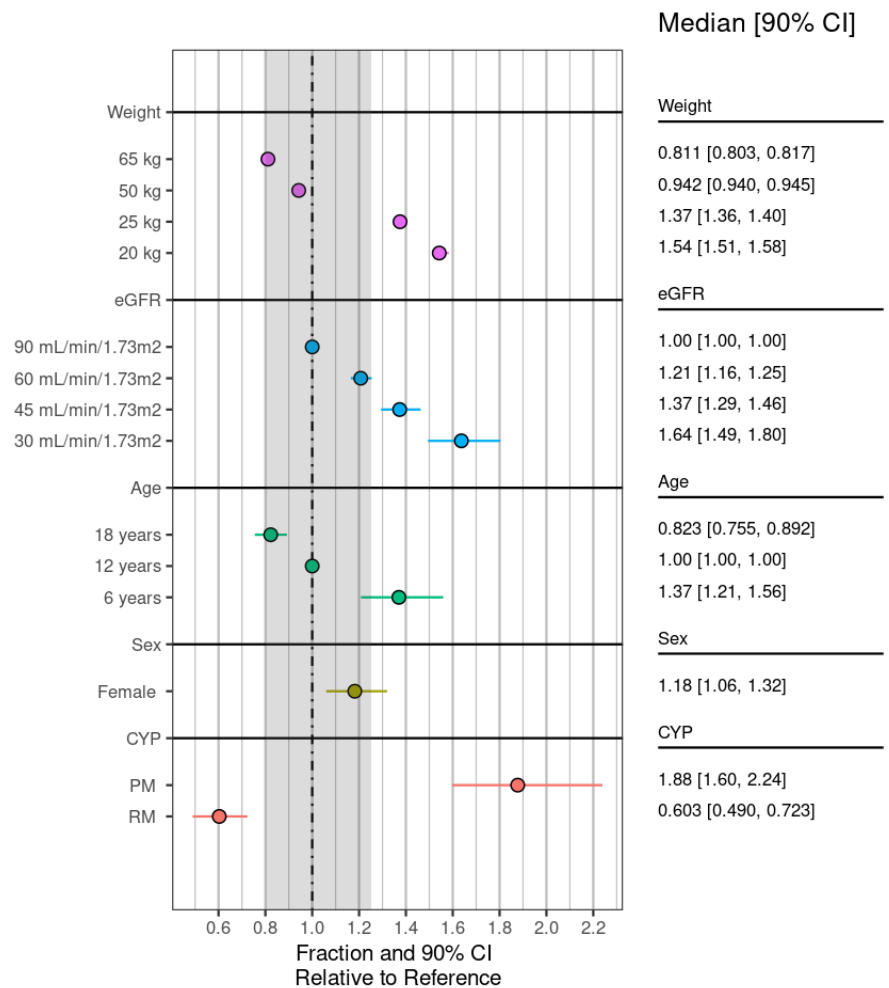
Implications for Exposure Metrics

- Assess the impact of each covariate effect on steady state Ctrough concentration
- Interpret relative to a reference range (e.g., 0.8 to 1.25 bioequivalence criteria)



Source code: pk-forest.R
Source graphic: deliv/figure/poppk/forest/100/100-forest-cmin.png

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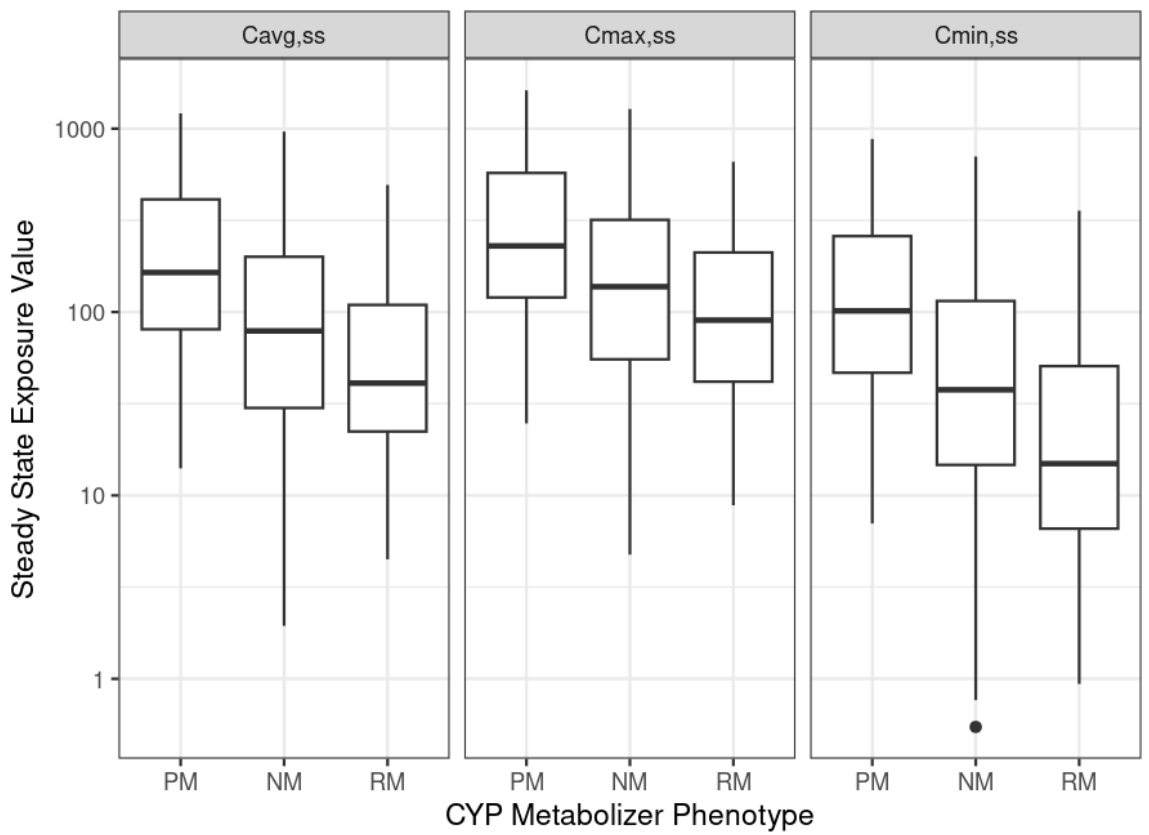
Clinical Question 2

> How did steady state exposure metrics (e.g., Cmax, Cmin, Cavg) compare between patients with poor, normal, and rapid metabolizer phenotypes in the METRO study?

Individual PK Simulations

Use individual estimates of PK parameters to simulate steady state exposure metrics for all METRO subjects



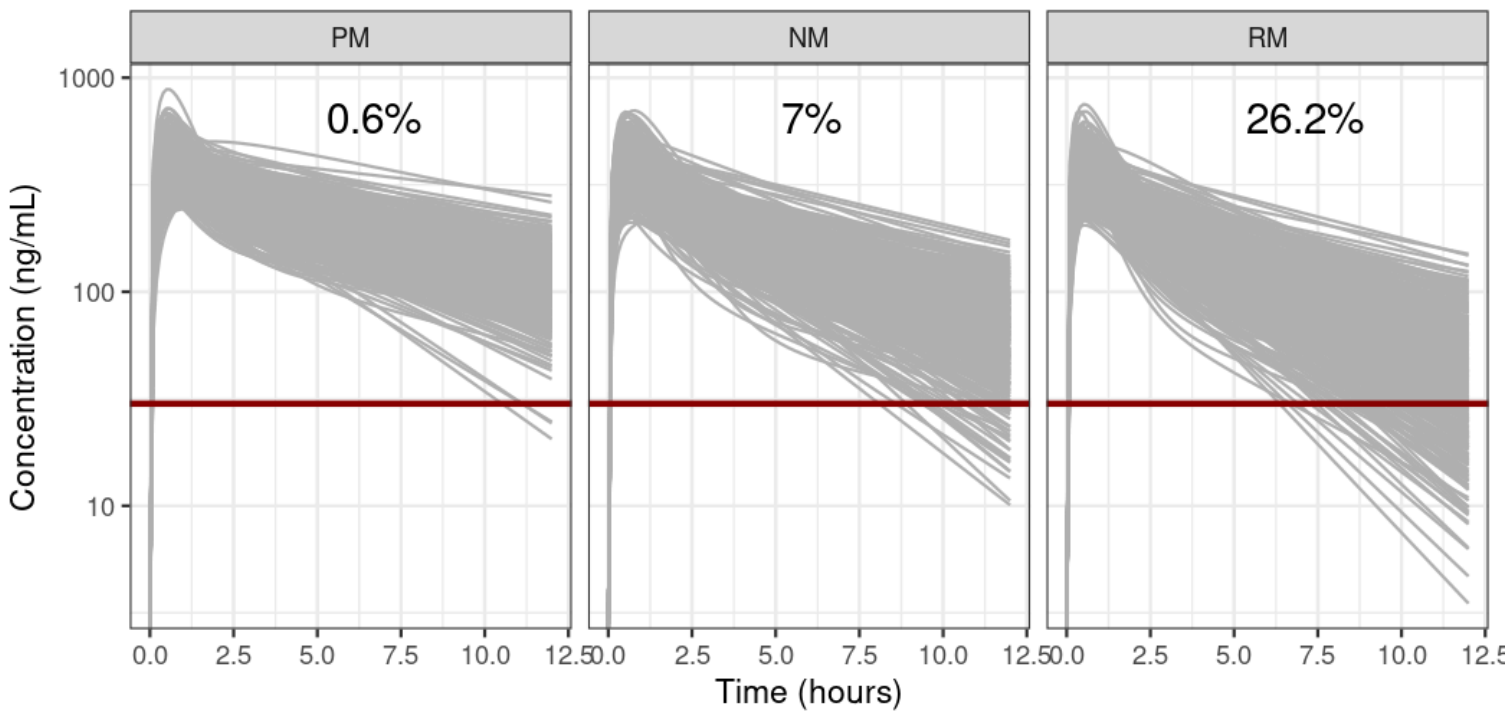
Source code: pk-sim.R
Source graphic: deliv/figure/poppk/sim/100/100-sim-pk-ebe-exposure.png

Clinical Question 3

> What fraction of the rapid metabolizer patient population would experience subtherapeutic trough concentrations under a dosing strategy that does not adjust for PGx phenotype?

Population PK Simulations

Simulate with fixed effects and IIV random effects to quantify proportion of each patient population expected to experience subtherapeutic Ctrough concentrations



Source code: pk-sim.R
Source graphic: deliv/figure/poppk/sim/100/100-sim-pk-pop-ref.png

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Simulation Recap

The developed population PK model was used to:

- Assess the impact of CYP metabolizer phenotype on metrumazole PK and exposure metrics (Clinical Question 1)
- Compare steady state exposure metrics for all individuals in the METRO study (Clinical Question 2)
- Quantify the proportion of patients in each CYP metabolizer phenotype population expected to experience subtherapeutic concentrations with a dosing strategy that does not adjust for PGx phenotype (Clinical Question 3)

Take Home

- Population PK modeling and simulation can dramatically increase the insight obtained from PGx data
- Model-based simulations can be used to generate evidence for a broad range of clinical questions that can’t be answered with the raw data
- There is great potential for synergy between PGx experts and PMx scientists to support PGx evidence generation!

The End

- Visit my poster on how to **power pharmacogenomic studies** with a population PK model
- Visit Metrum Research Group to explore many open-source learning materials
- Learn how to use mrgsolve, a free and open-source software for simulating from PK/PD and quantitative systems pharmacology models, in your own work