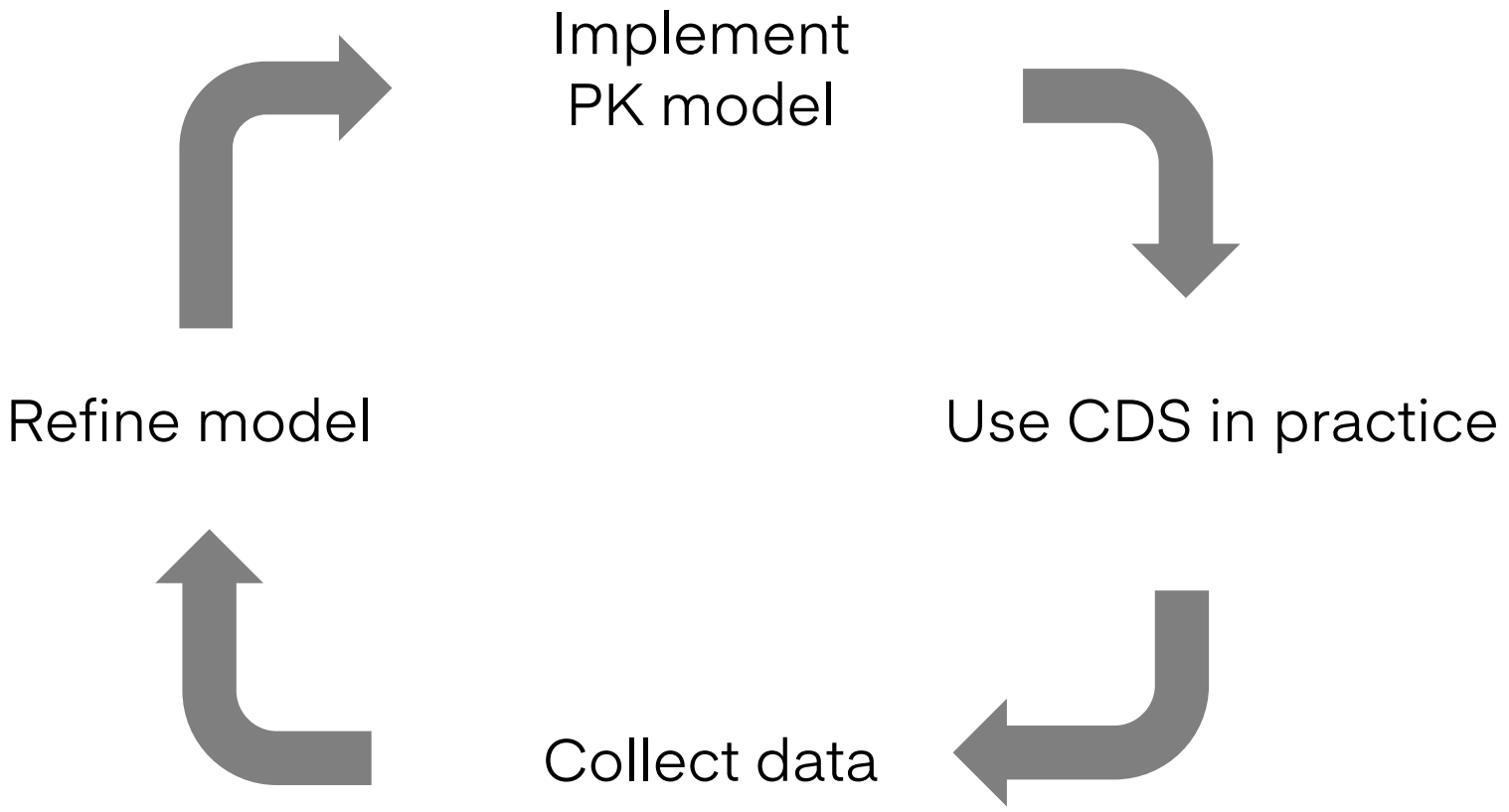
Insight RX

Composite Importance Sampling (CIS) for continuous learning in precision dosing

Ron Keizer

Continuous learning (PAGE 2018)



Keizer et al. PAGE 2018

Why continuous learning?

- Improved drug efficacy / reduced toxicity
- Increase trust in software
- Reduce TDM sampling

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Data stream

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Data stream

Numbers

~ 500 patients/day TDM

~ 15 drugs

... and increasing

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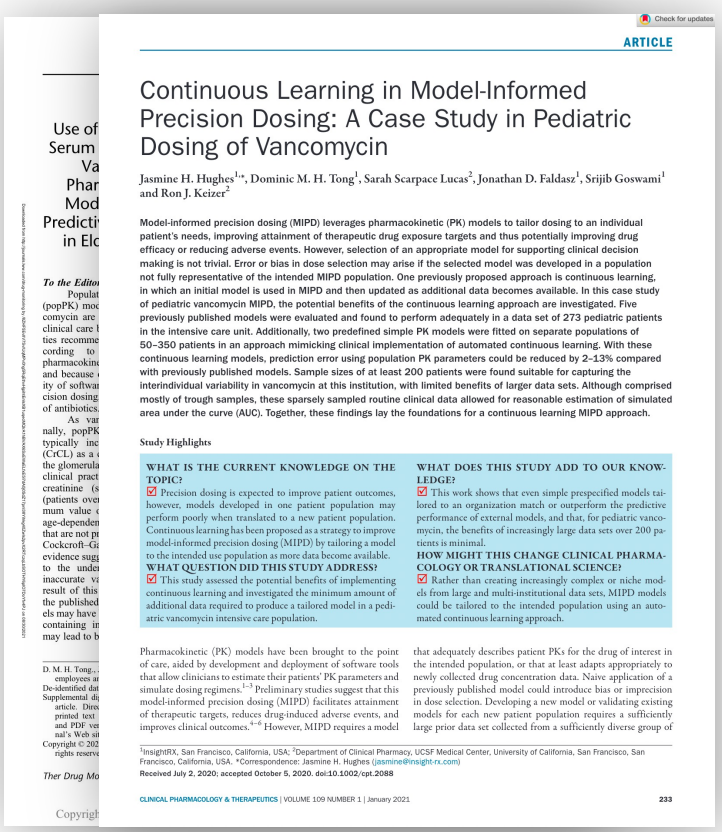
Model updates (manual)



Check for updates

ARTICLE

Continuous Learning in Model-Informed Precision Dosing: A Case Study in Pediatric Dosing of Vancomycin

Jasmine H. Hughes[1,*], Dominic M. H. Tong[1], Sarah Scarpace Lucas[2], Jonathan D. Faldasz[1], Srijib Goswami[1] and Ron J. Keizer[2]

Model-informed precision dosing (MIPD) leverages pharmacokinetic (PK) models to tailor dosing to an individual patient's needs, improving attainment of therapeutic drug exposure targets and thus potentially improving drug efficacy or reducing adverse events. However, selection of an appropriate model for supporting clinical decision making is not trivial. Error or bias in dose selection may arise if the selected model was developed in a population not fully representative of the intended MIPD population. One previously proposed approach is continuous learning, in which an initial model is used in MIPD and then updated as additional data becomes available. In this case study of pediatric vancomycin MIPD, the potential benefits of the continuous learning approach are investigated. Five previously published models were evaluated and found to perform adequately in a data set of 273 pediatric patients in the intensive care unit. Additionally, two predefined simple PK models were fitted on separate populations of 50–350 patients in an approach mimicking clinical implementation of automated continuous learning. With these continuous learning models, prediction error using population PK parameters could be reduced by 2–13% compared with previously published models. Sample sizes of at least 200 patients were found suitable for capturing the interindividual variability in vancomycin at this institution, with limited benefits of larger data sets. Although comprised mostly of trough samples, these sparsely sampled routine clinical data allowed for reasonable estimation of simulated area under the curve (AUC). Together, these findings lay the foundations for a continuous learning MIPD approach.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
☑ Precision dosing is expected to improve patient outcomes, however, models developed in one patient population may perform poorly when translated to a new patient population. Continuous learning has been proposed as a strategy to improve model-informed precision dosing (MIPD) by tailoring a model to the intended use population as more data become available.

WHAT QUESTION DID THIS STUDY ADDRESS?
☑ This study assessed the potential benefits of implementing continuous learning and investigated the minimum amount of additional data required to produce a tailored model in a pediatric vancomycin intensive care population.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
☑ This work shows that even simple prespecified models tailored to an organization match or outperform the predictive performance of external models, and that, for pediatric vancomycin, the benefits of increasingly large data sets over 200 patients is minimal.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?
☑ Rather than creating increasingly complex or niche models from large and multi-institutional data sets, MIPD models could be tailored to the intended population using an automated continuous learning approach.

Pharmacokinetic (PK) models have been brought to the point of care, aided by development and deployment of software tools that allow clinicians to estimate their patients' PK parameters and simulate dosing regimens.[1–3] Preliminary studies suggest that this model-informed precision dosing (MIPD) facilitates attainment of therapeutic targets, reduces drug-induced adverse events, and improves clinical outcomes.[4–6] However, MIPD requires a model that adequately describes patient PKs for the drug of interest in the intended population, or that at least adapts appropriately to newly collected drug concentration data. Naive application of a previously published model could introduce bias or imprecision in dose selection. Developing a new model or validating existing models for each new patient population requires a sufficiently large prior data set collected from a sufficiently diverse group of

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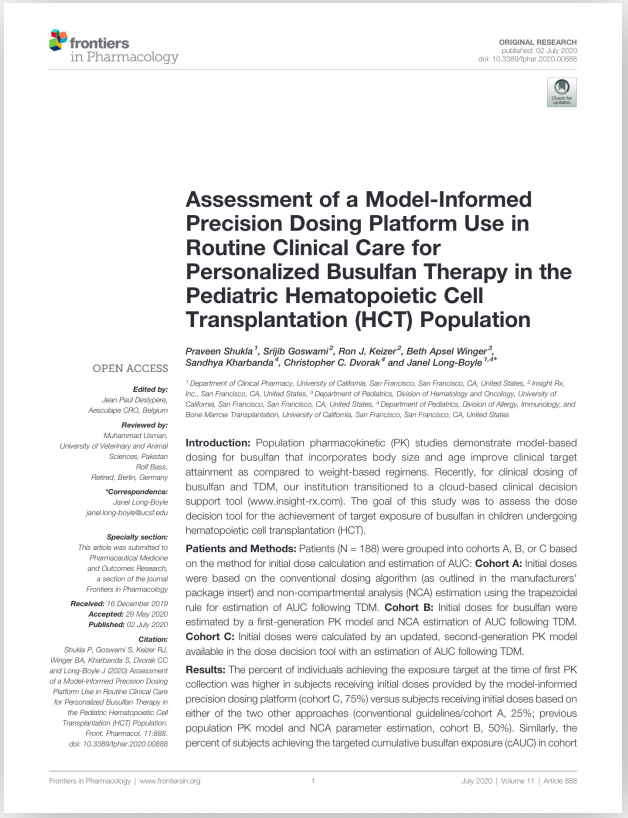
Vancomycin

Tong DMH et al. TDM 2021
Hughes JH et al. CPT 2021



frontiers in Pharmacology

ORIGINAL RESEARCH
published: 02 July 2020
doi: 10.3389/fphar.2020.00888

Assessment of a Model-Informed Precision Dosing Platform Use in Routine Clinical Care for Personalized Busulfan Therapy in the Pediatric Hematopoietic Cell Transplantation (HCT) Population

Praveen Shukla[1], Srijib Goswami[2], Ron J. Keizer[2], Beth Apsel Winger[3], Sandhya Kharbanda[4], Christopher C. Dvorak[4] and Janel Long-Boyle[1,4]

[1] Department of Clinical Pharmacy, University of California, San Francisco, San Francisco, CA, United States, [2] Insight Rx, Inc., San Francisco, CA, United States, [3] Department of Pediatrics, Division of Hematology and Oncology, University of California, San Francisco, San Francisco, CA, United States, [4] Department of Pediatrics, Division of Allergy, Immunology, and Bone Marrow Transplantation, University of California, San Francisco, San Francisco, CA, United States

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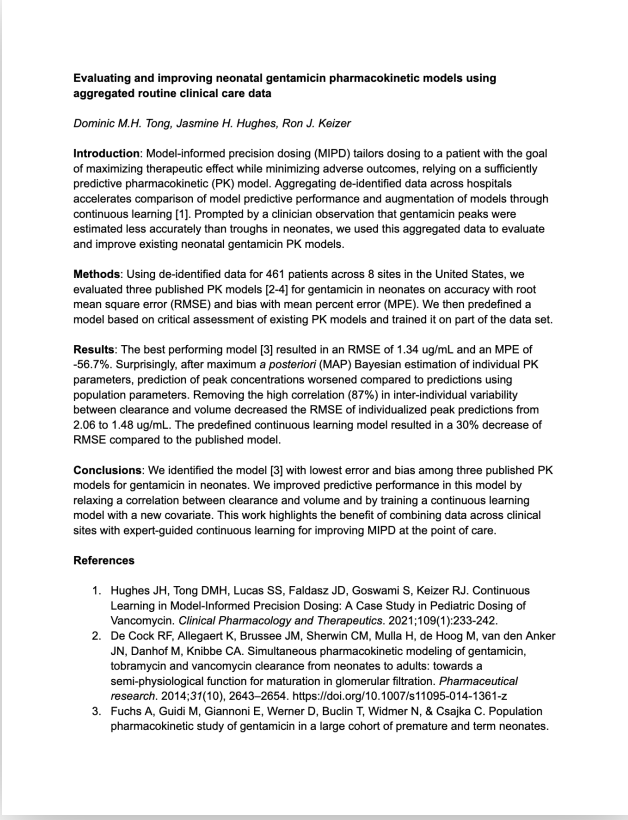
Introduction: Population pharmacokinetic (PK) studies demonstrate model-based dosing for busulfan that incorporates body size and age improve clinical target attainment as compared to weight-based regimens. Recently, for clinical dosing of busulfan and TDM, our institution transitioned to a cloud-based clinical decision support tool (www.insight-rx.com). The goal of this study was to assess the dose decision tool for the achievement of target exposure of busulfan in children undergoing hematopoietic cell transplantation (HCT).

Patients and Methods: Patients (N = 188) were grouped into cohorts A, B, or C based on the method for initial dose calculation and estimation of AUC: **Cohort A:** Initial doses were based on the conventional dosing algorithm (as outlined in the manufacturers' package insert) and non-compartmental analysis (NCA) estimation using the trapezoidal rule for estimation of AUC following TDM. **Cohort B:** Initial doses for busulfan were estimated by a first-generation PK model and NCA estimation of AUC following TDM. **Cohort C:** Initial doses were calculated by an updated, second-generation PK model available in the dose decision tool with an estimation of AUC following TDM.

Results: The percent of individuals achieving the exposure target at the time of first PK collection was higher in subjects receiving initial doses provided by the model-informed precision dosing platform (cohort C, 75%) versus subjects receiving initial doses based on either of the two other approaches (conventional guidelines/cohort A, 25%; previous population PK model and NCA parameter estimation, cohort B, 50%). Similarly, the percent of subjects achieving the targeted cumulative busulfan exposure (cAUC) in cohort

Busulfan

Shukla P et al. Frontiers Pharmacol 2020



Evaluating and improving neonatal gentamicin pharmacokinetic models using aggregated routine clinical care data

Dominic M.H. Tong, Jasmine H. Hughes, Ron J. Keizer

Introduction: Model-informed precision dosing (MIPD) tailors dosing to a patient with the goal of maximizing therapeutic effect while minimizing adverse outcomes, relying on a sufficiently predictive pharmacokinetic (PK) model. Aggregating de-identified data across hospitals accelerates comparison of model predictive performance and augmentation of models through continuous learning [1]. Prompted by a clinician observation that gentamicin peaks were estimated less accurately than troughs in neonates, we used this aggregated data to evaluate and improve existing neonatal gentamicin PK models.

Methods: Using de-identified data for 461 patients across 8 sites in the United States, we evaluated three published PK models [2-4] for gentamicin in neonates on accuracy with root mean square error (RMSE) and bias with mean percent error (MPE). We then predefined a model based on critical assessment of existing PK models and trained it on part of the data set.

Results: The best performing model [3] resulted in an RMSE of 1.34 ug/mL and an MPE of -56.7%. Surprisingly, after maximum *a posteriori* (MAP) Bayesian estimation of individual PK parameters, prediction of peak concentrations worsened compared to predictions using population parameters. Removing the high correlation (87%) in inter-individual variability between clearance and volume decreased the RMSE of individualized peak predictions from 2.06 to 1.48 ug/mL. The predefined continuous learning model resulted in a 30% decrease of RMSE compared to the published model.

Conclusions: We identified the model [3] with lowest error and bias among three published PK models for gentamicin in neonates. We improved predictive performance in this model by relaxing a correlation between clearance and volume and by training a continuous learning model with a new covariate. This work highlights the benefit of combining data across clinical sites with expert-guided continuous learning for improving MIPD at the point of care.

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3. Fuchs A, Guidi M, Giannoni E, Werner D, Buclin T, Widmer N, & Csajka C. Population pharmacokinetic study of gentamicin in a large cohort of premature and term neonates.

Gentamicin

Tong DMH et al. IATDMCT 2022

How can we update models automatically?

Insight RX

NLME vs *ideal* continuous learning algorithm

Aspect	NLME [1,2] / MCMC [3] approaches	Ideal
Computational load	Intensive at scale	Incremental estimation
Stability	Dirty data → estimation instabilities	Resilient to dirty data
Covariate effects	Static	Ad hoc
Dataset	Combine data for estimation	Federated

[1] Chen et al. PAGE 2022
[2] Lavielle et al. PAGE 2022
[3] Maier et al. CPT 2021

Insight RX

Define proposal distribution

Sample from proposal distribution

Calculate likelihood for each parameter set

Calculate posterior distribution, mean

Importance sampling?

Define proposal distribution

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Insight RX

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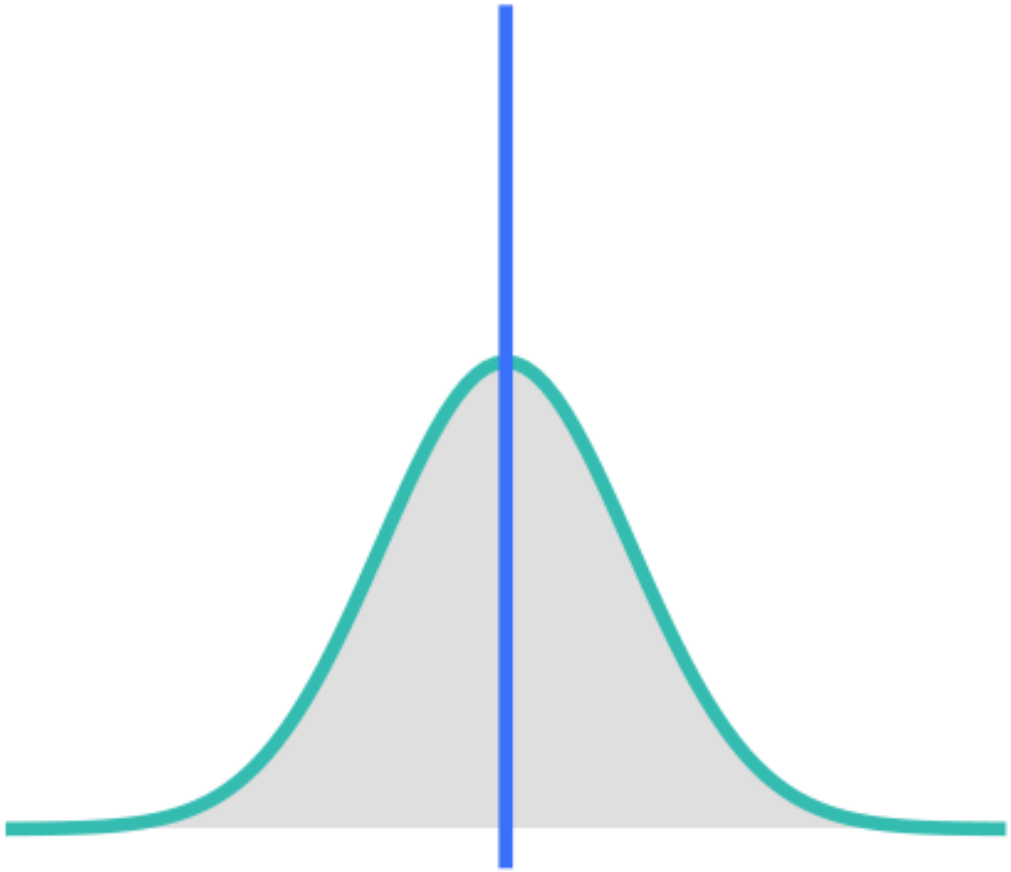

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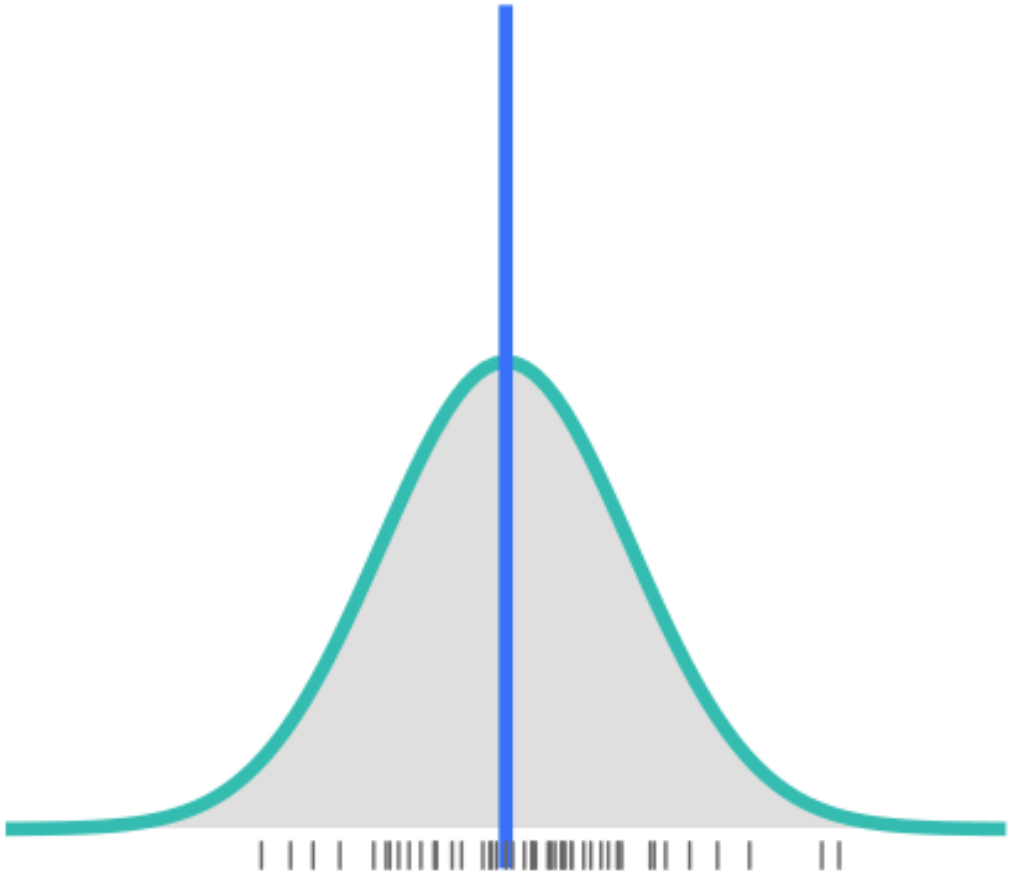

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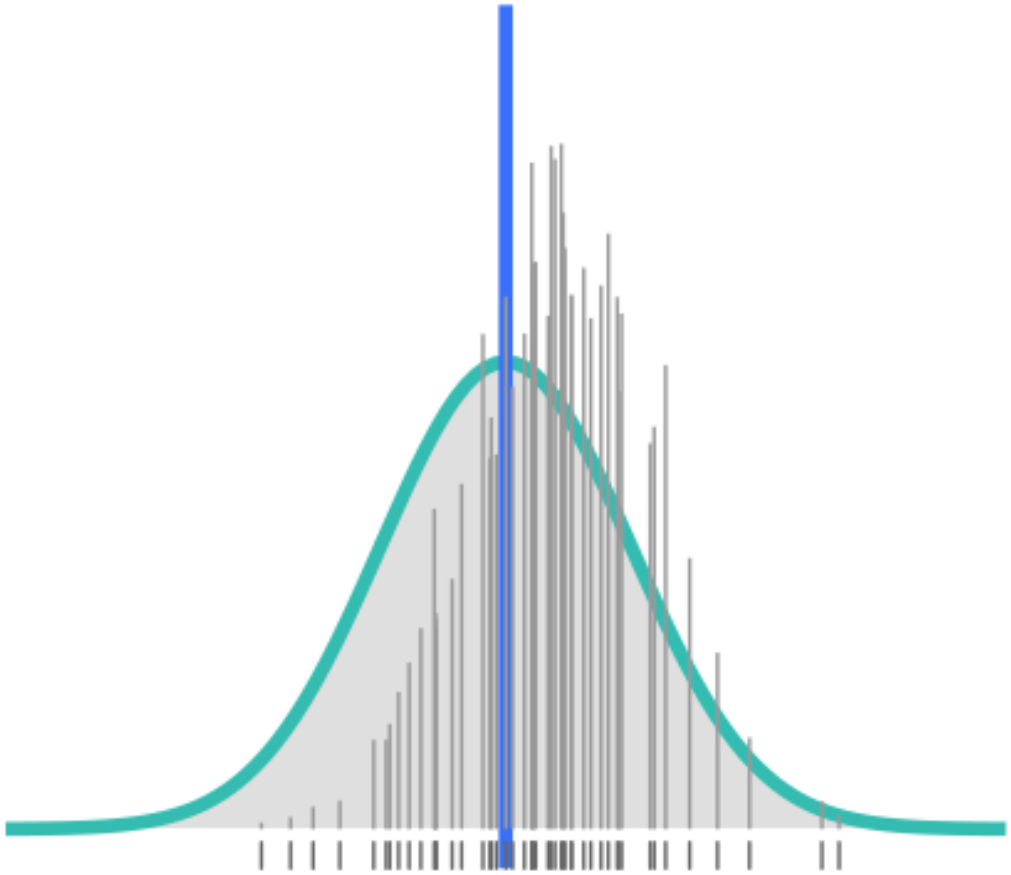

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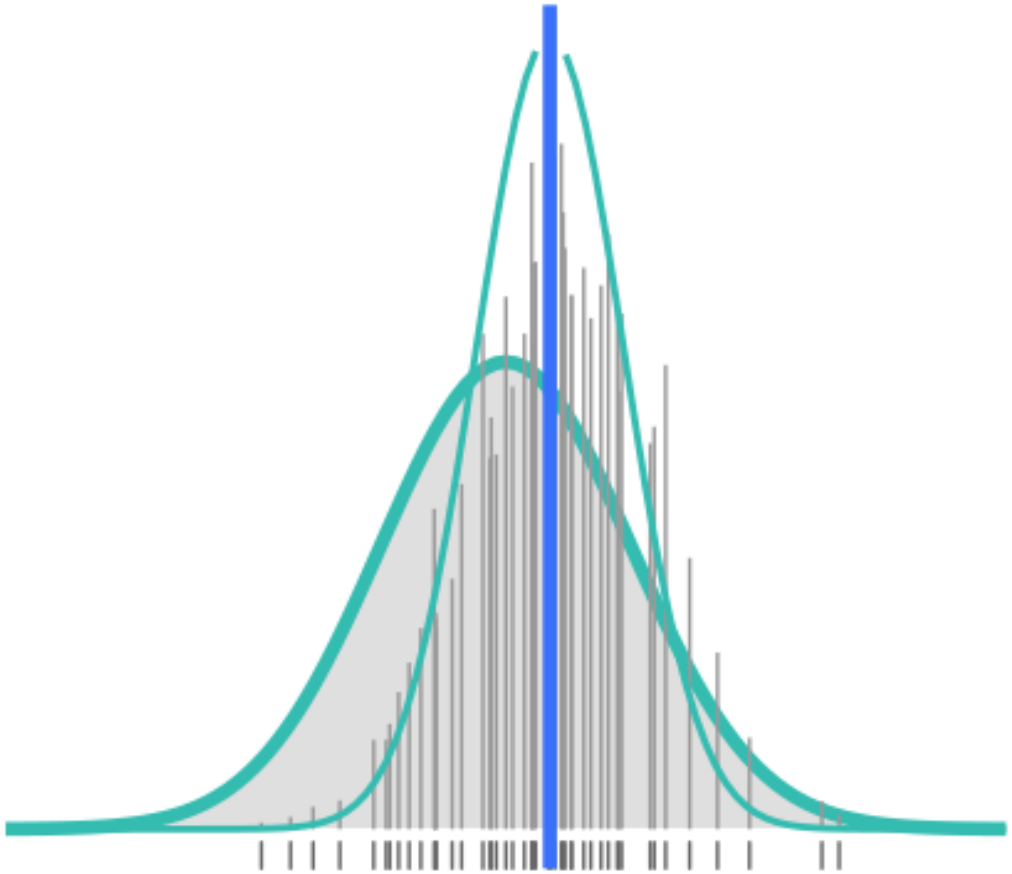

Define proposal distribution

Sample from proposal distribution

Calculate likelihood for each parameter set

Calculate posterior distribution, mode

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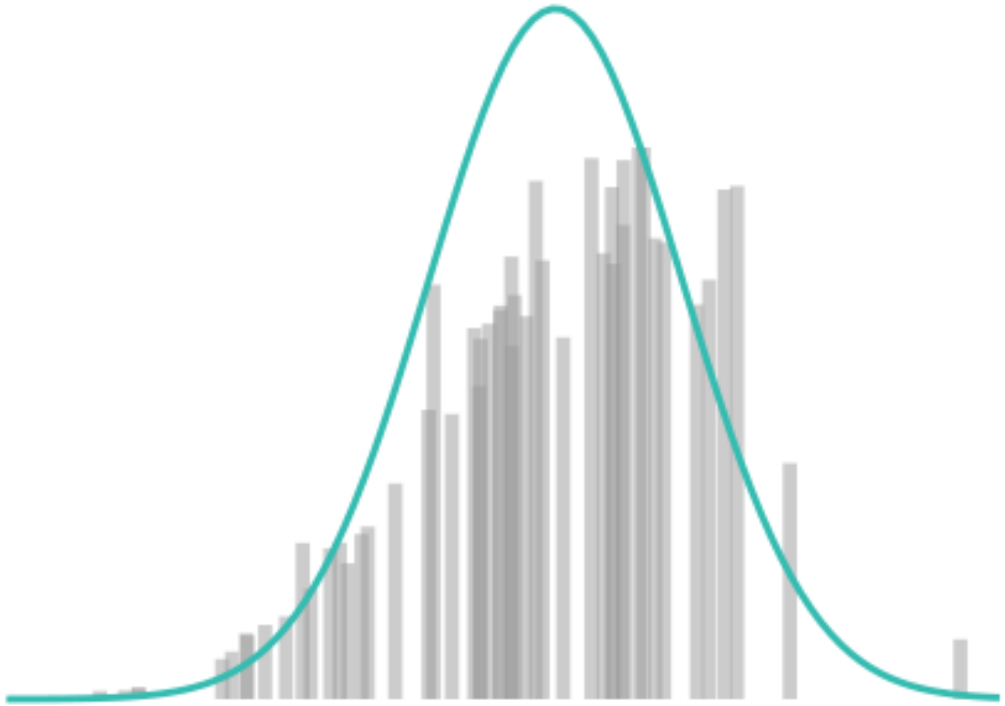

Posterior distribution

Composite of individual likelihoods

Calculate likelihood for new individual & add to cumulative

Recalculate posterior density

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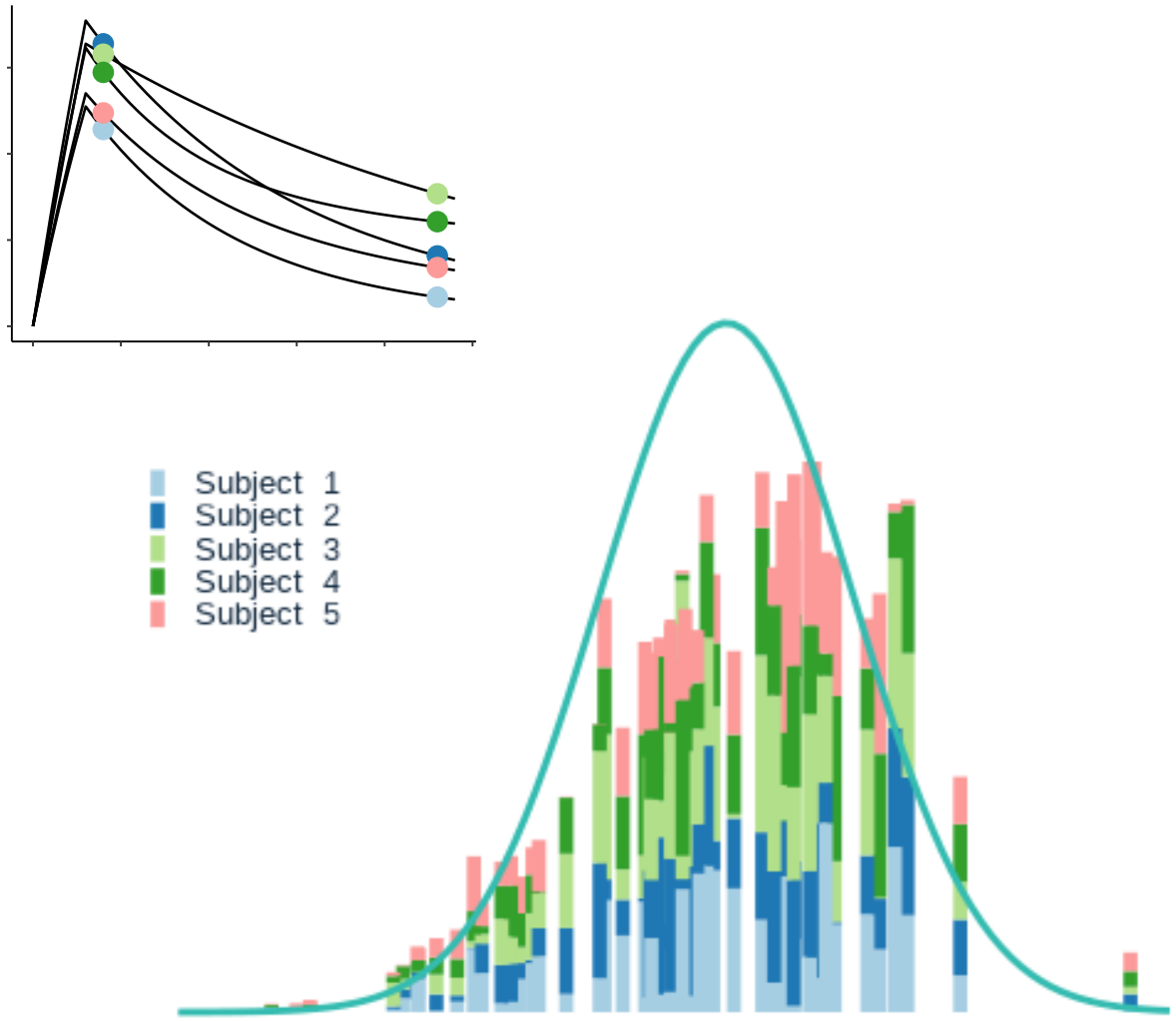

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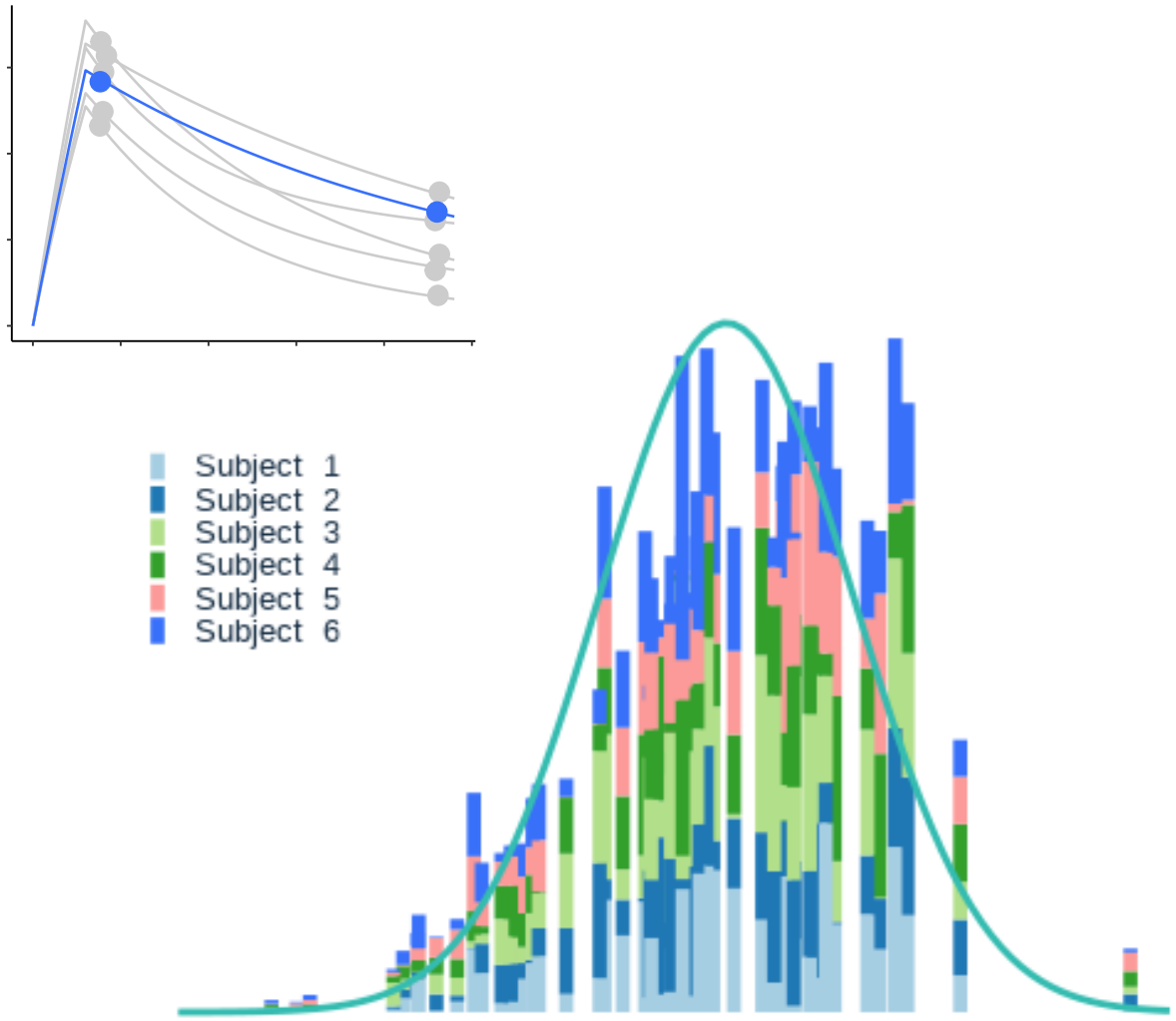

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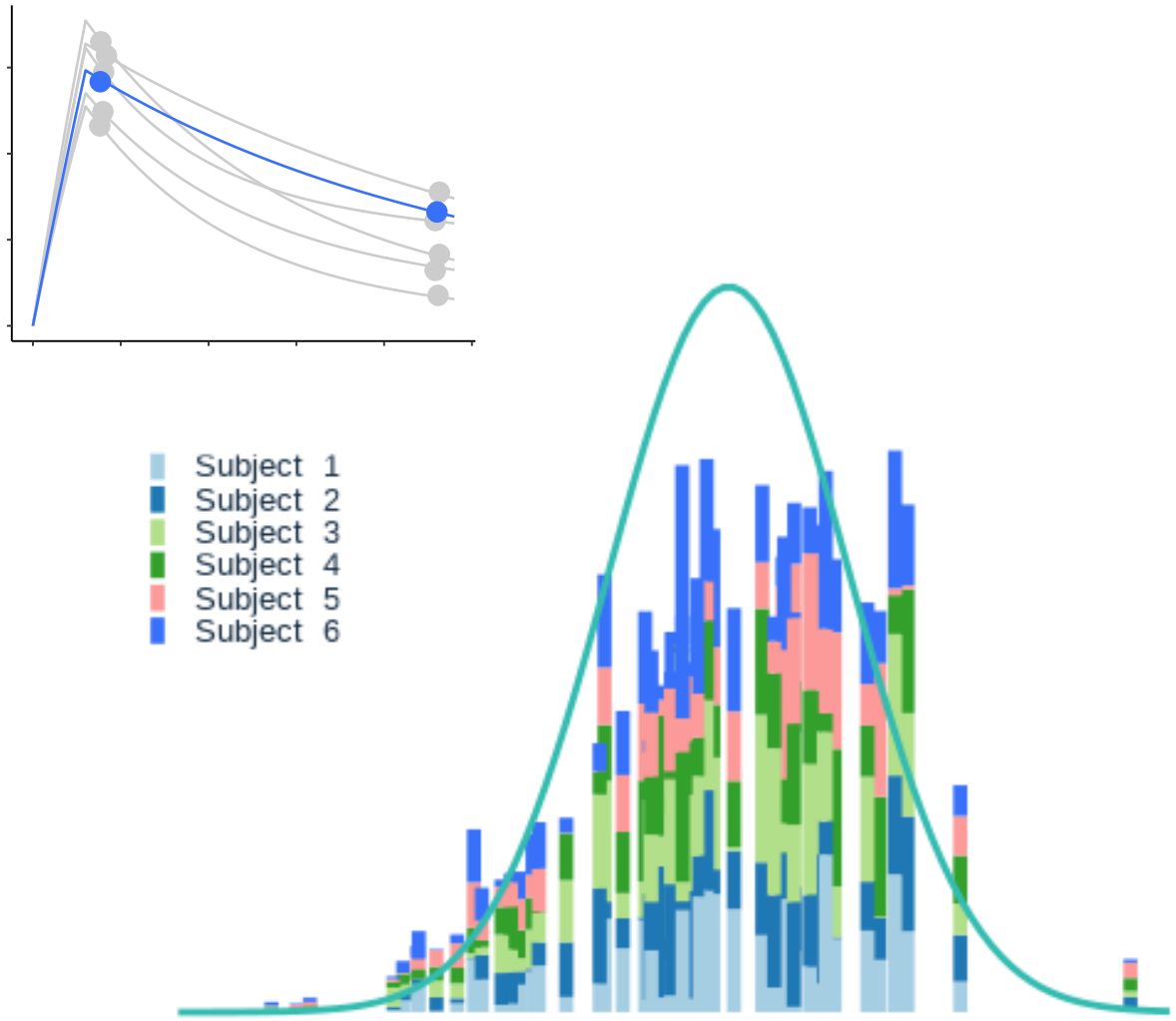

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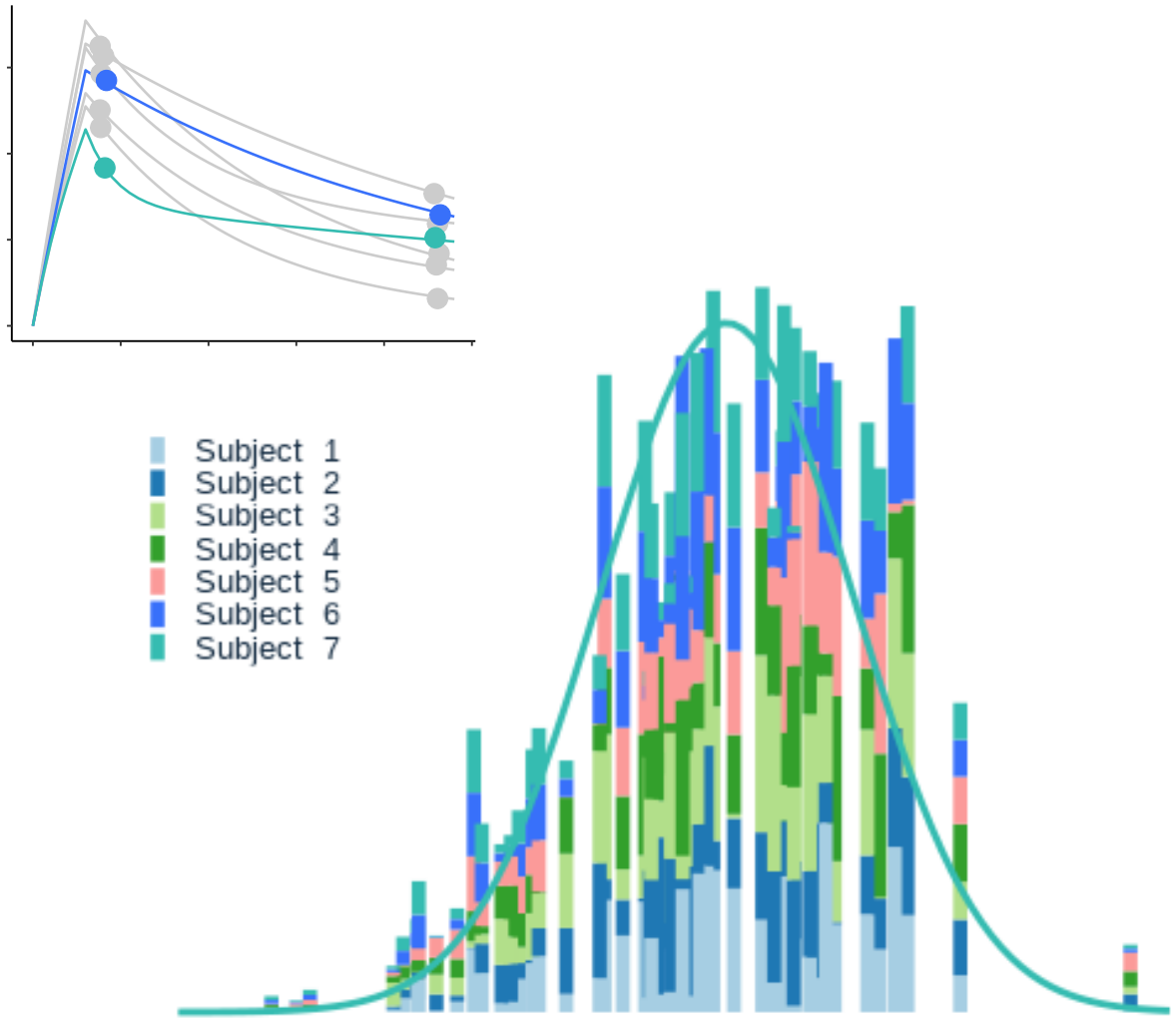

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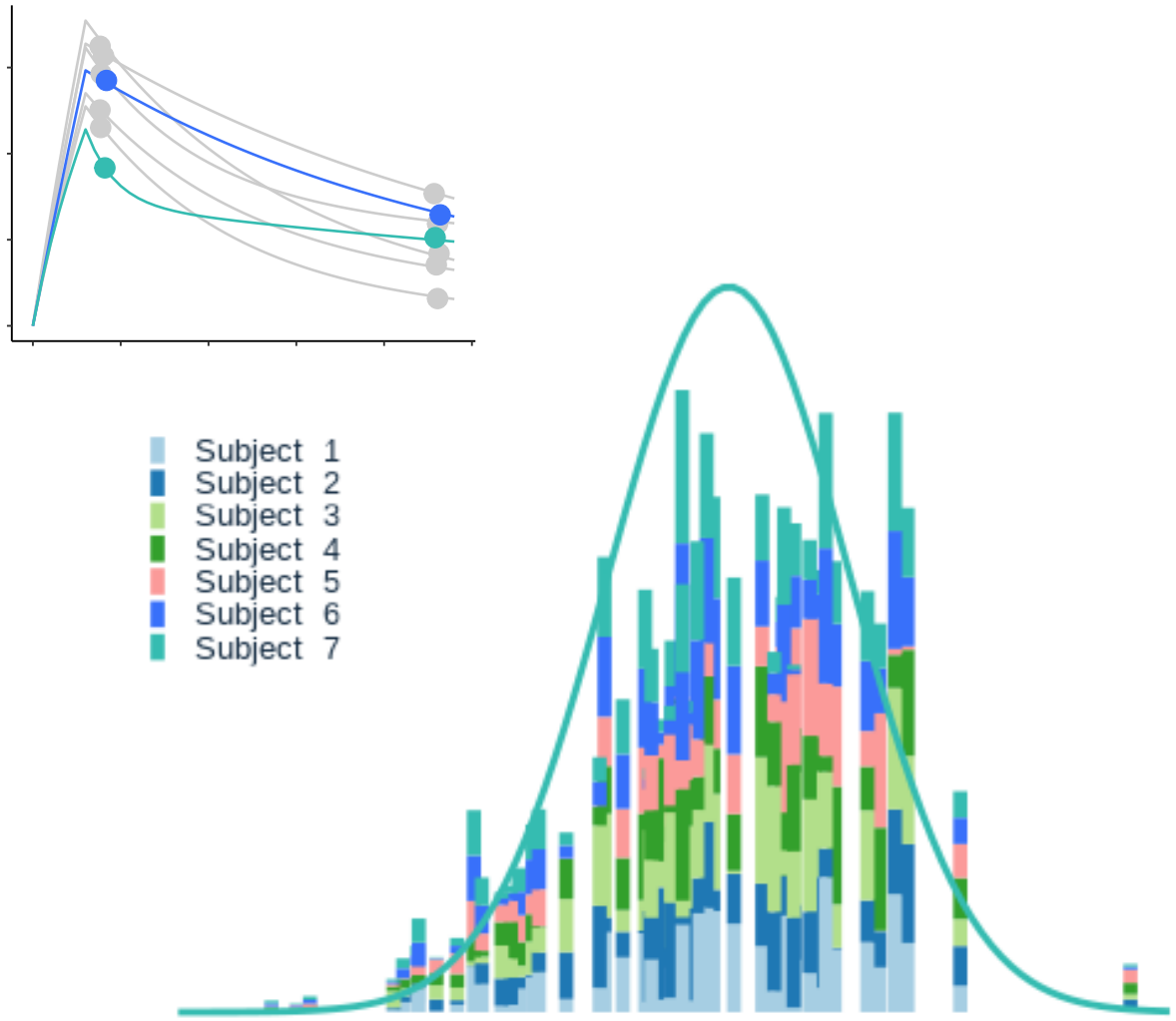

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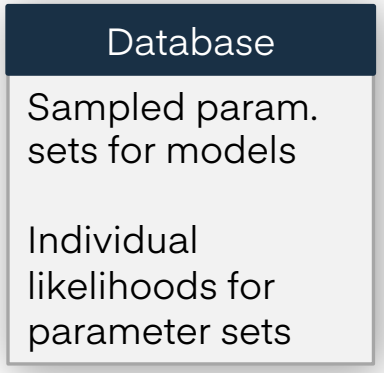
Insight RX

Technical implementation



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Technical implementation

New patient data

Dosing data
TDM data
Covariates

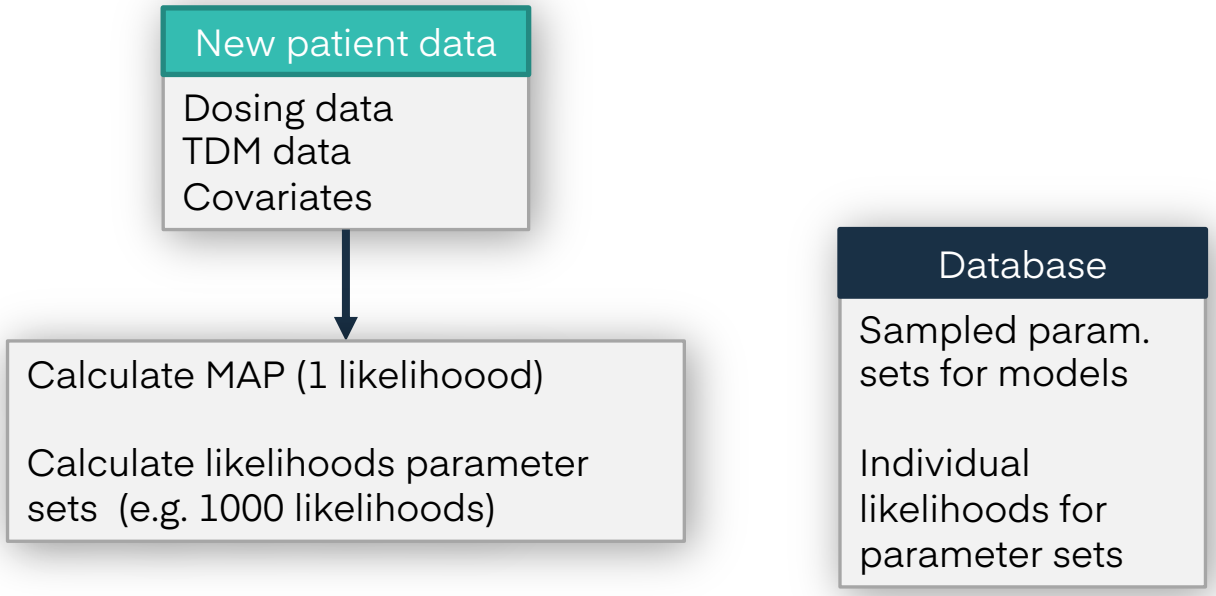
Database

Sampled param. sets for models

Individual likelihoods for parameter sets

Insight RX

Technical implementation



1. Dosne et al. JPKPD 2016

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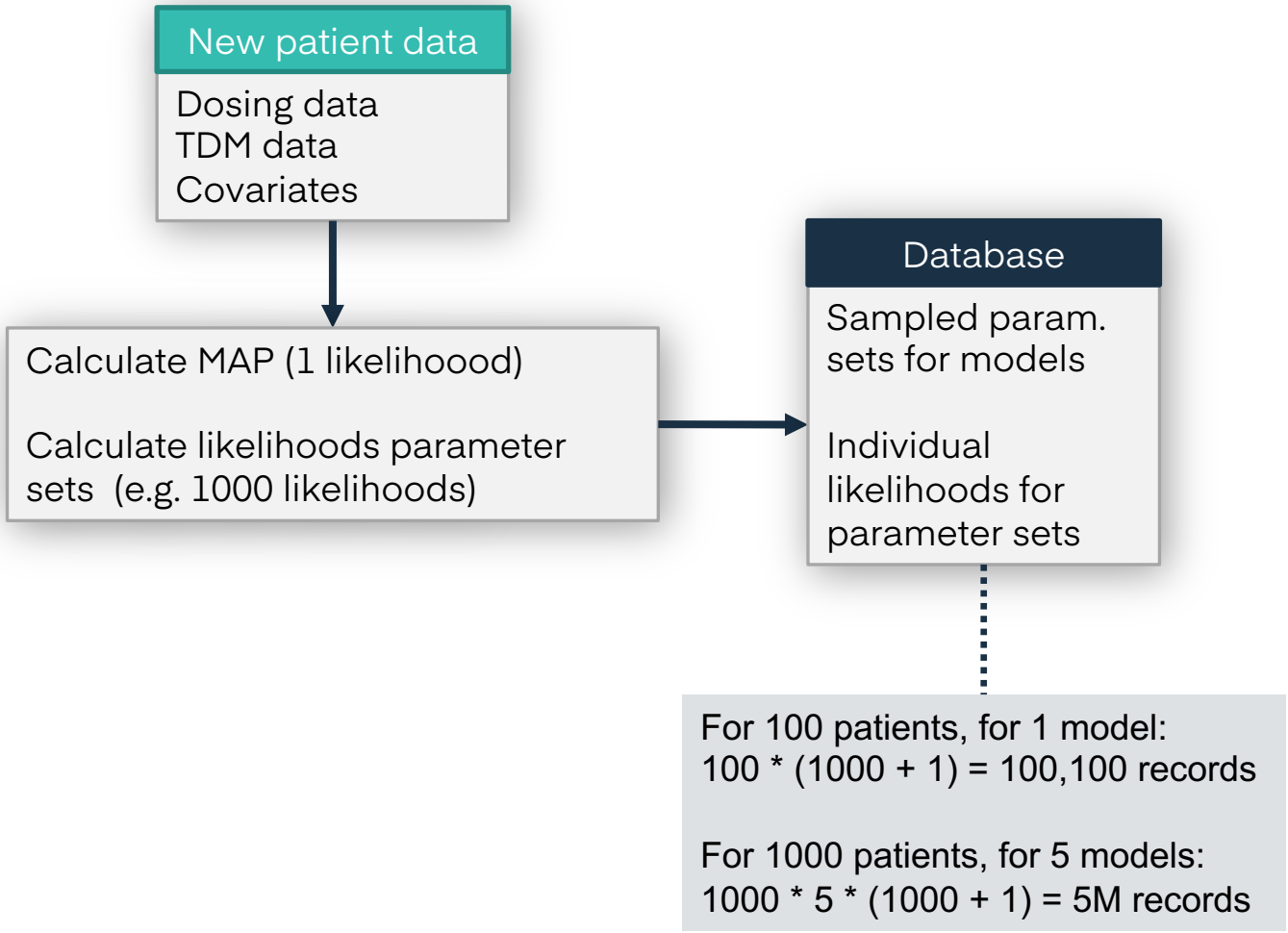

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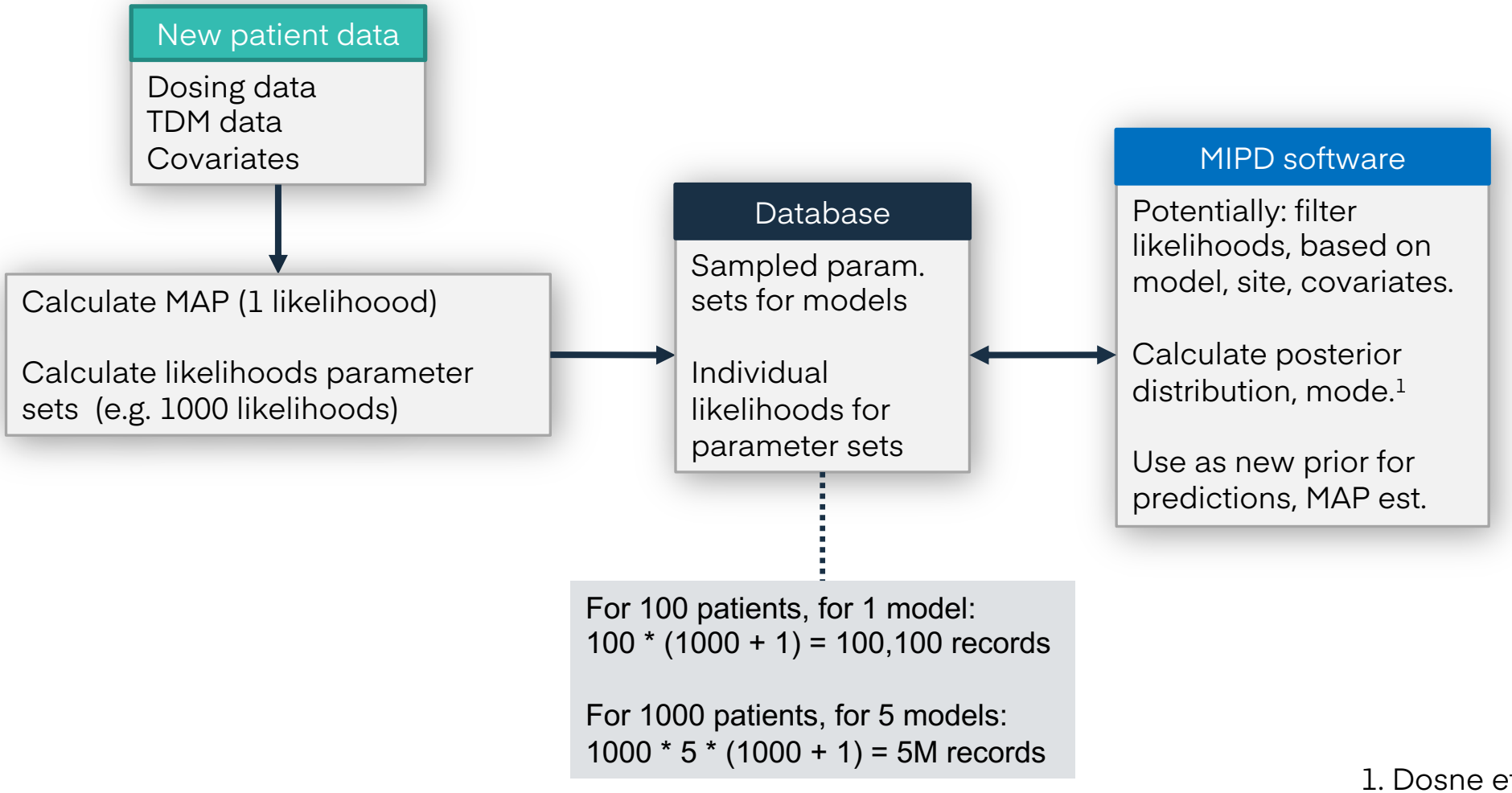

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Composite importance sampling

- An approach to incrementally calculate the posterior by adding individual likelihoods

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- **Prerequisite**: sampled parameter sets are **static** and sampled at start of analysis!

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    - no need to re-estimate / resample whole dataset
    - ad hoc covariate analysis
    - federated

Composite importance sampling

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  - Advantages:
    - no need to re-estimate / resample whole dataset
    - ad hoc covariate analysis
    - federated

  - Disadvantage:
    - cannot adaptively explore the parameter space

Caveats: curse of dimensionality

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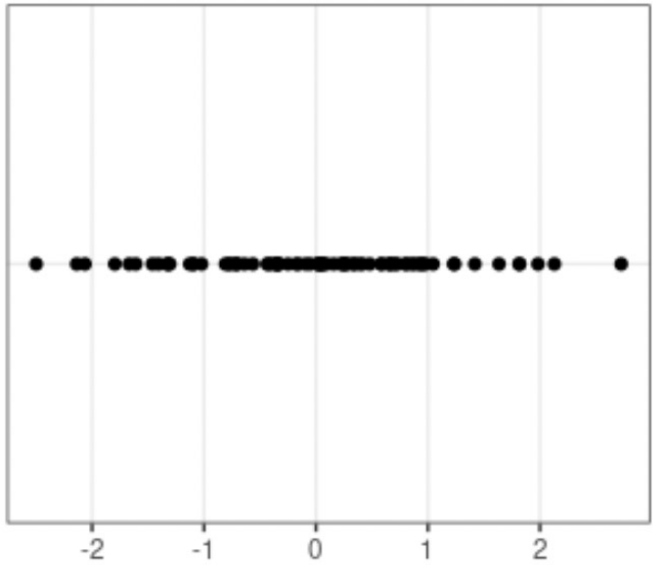
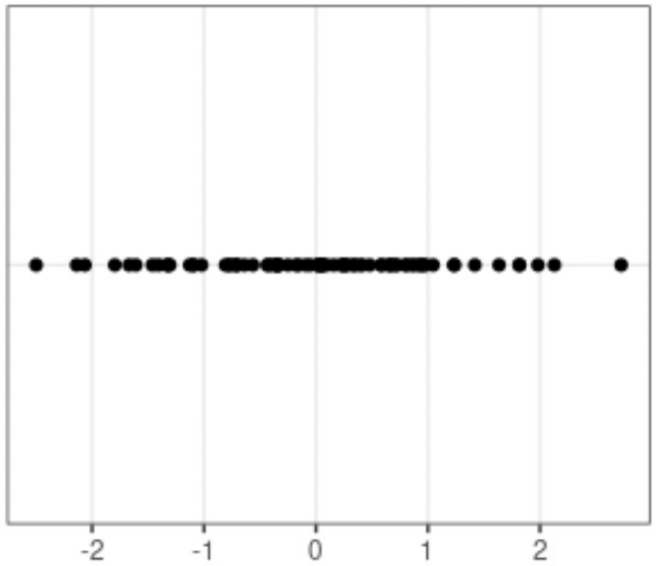


1 parameter
6 regions

Caveats: curse of dimensionality



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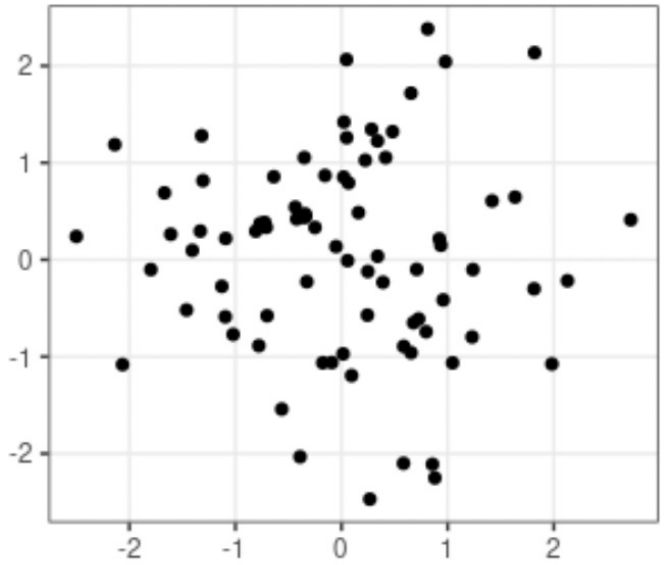
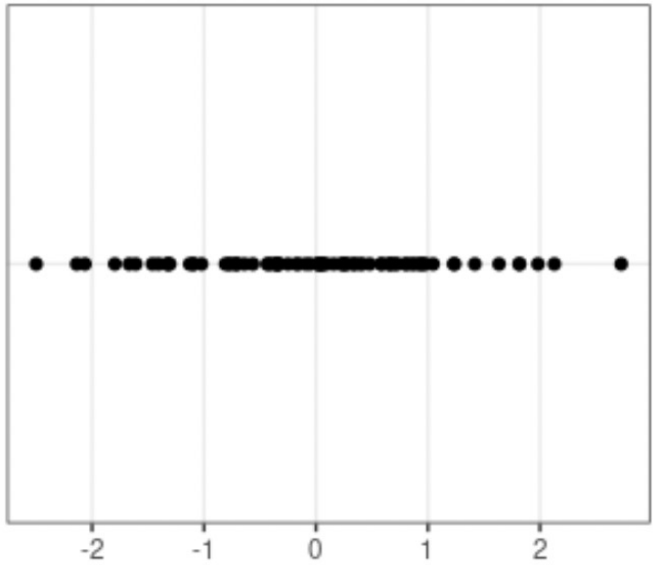


2 parameters
6 x 6 regions

Caveats: curse of dimensionality



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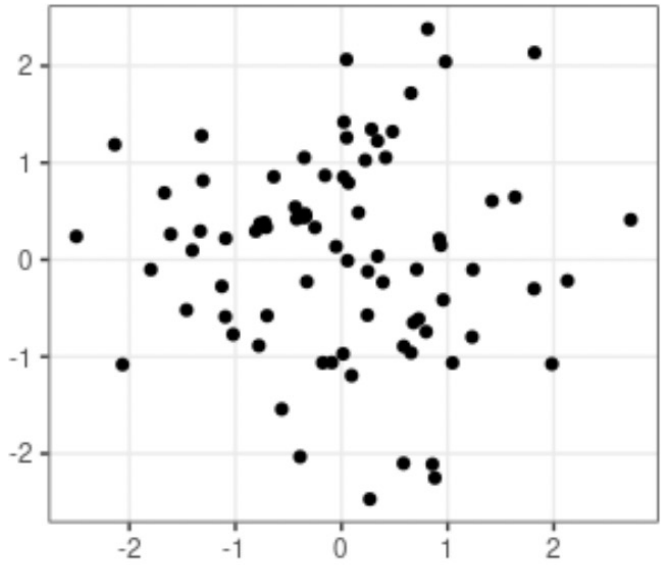

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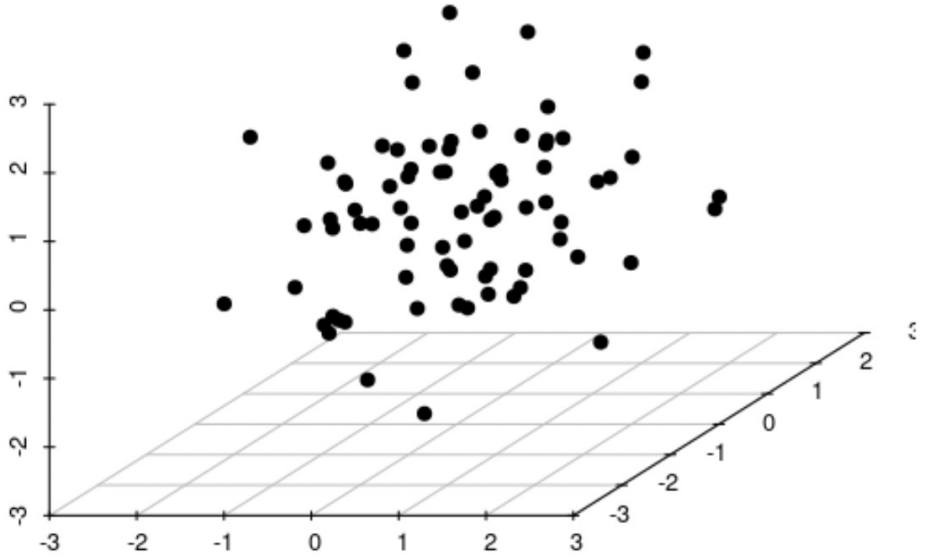

3 parameters
6 x 6 x 6 regions

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Is CIS able to update model parameters in MIPD, to improve predictive performance?

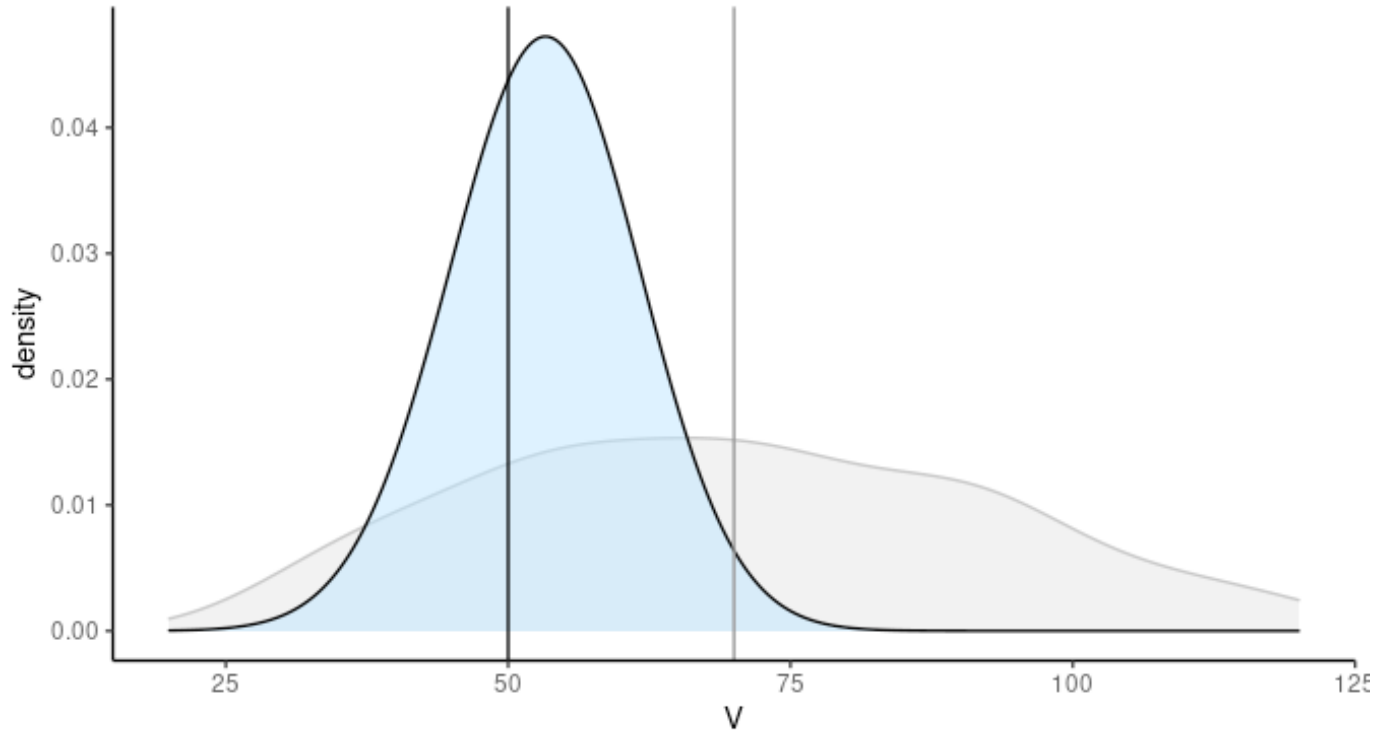
Simulated example 1: one-compartment PK

Biased estimate for Volume

Prior: 70 L

True: 50 L

Simulated example 1: one-compartment PK



Biased estimate for Volume

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Simulated example 1: one-compartment PK

Allometric scaling

Prior: not implemented

True:

$CL \times (WT/70)^{0.75}$

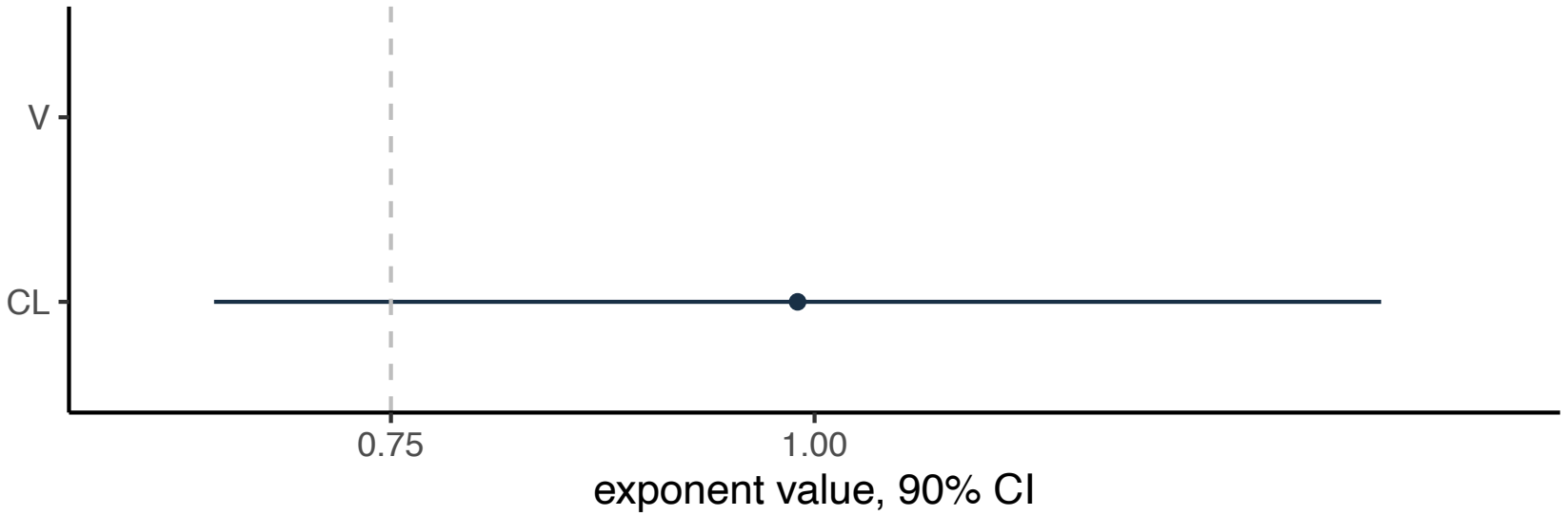
$V \times (WT/70)$

“Importance-weighted regression”

or

“Covariate Shift Adaptation” [1]

Simulated example 1: one-compartment PK



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Sugiyama, JMLR 2007

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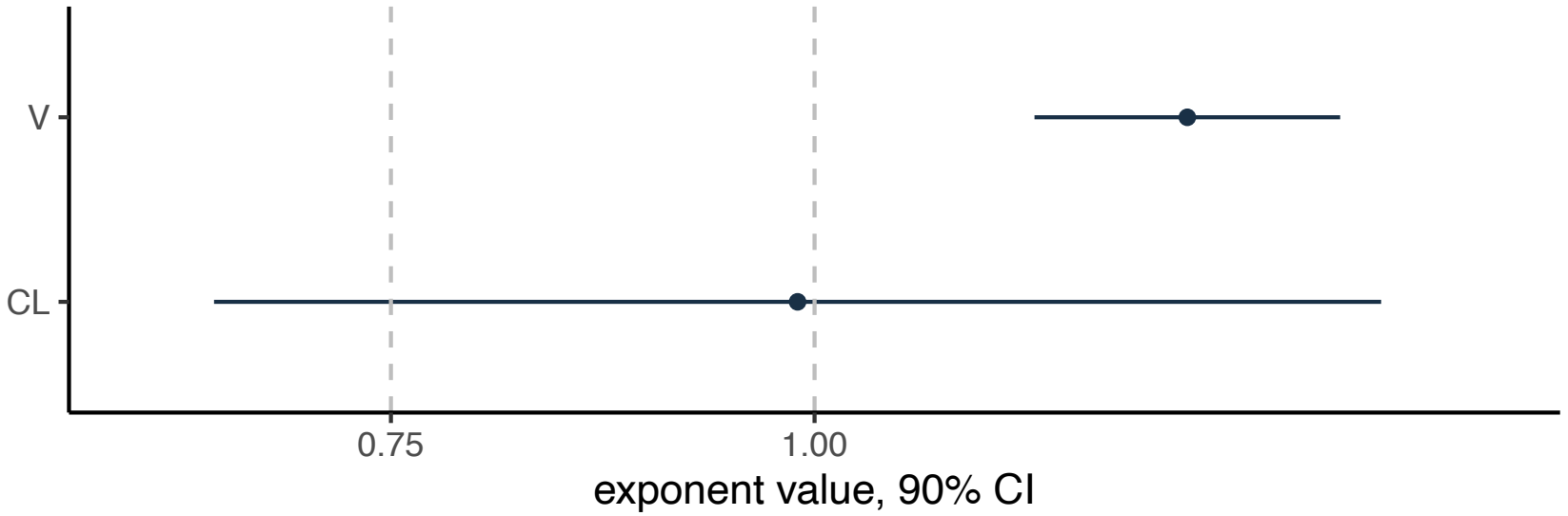

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Simulated example 1: one-compartment PK

Genotype effect CL

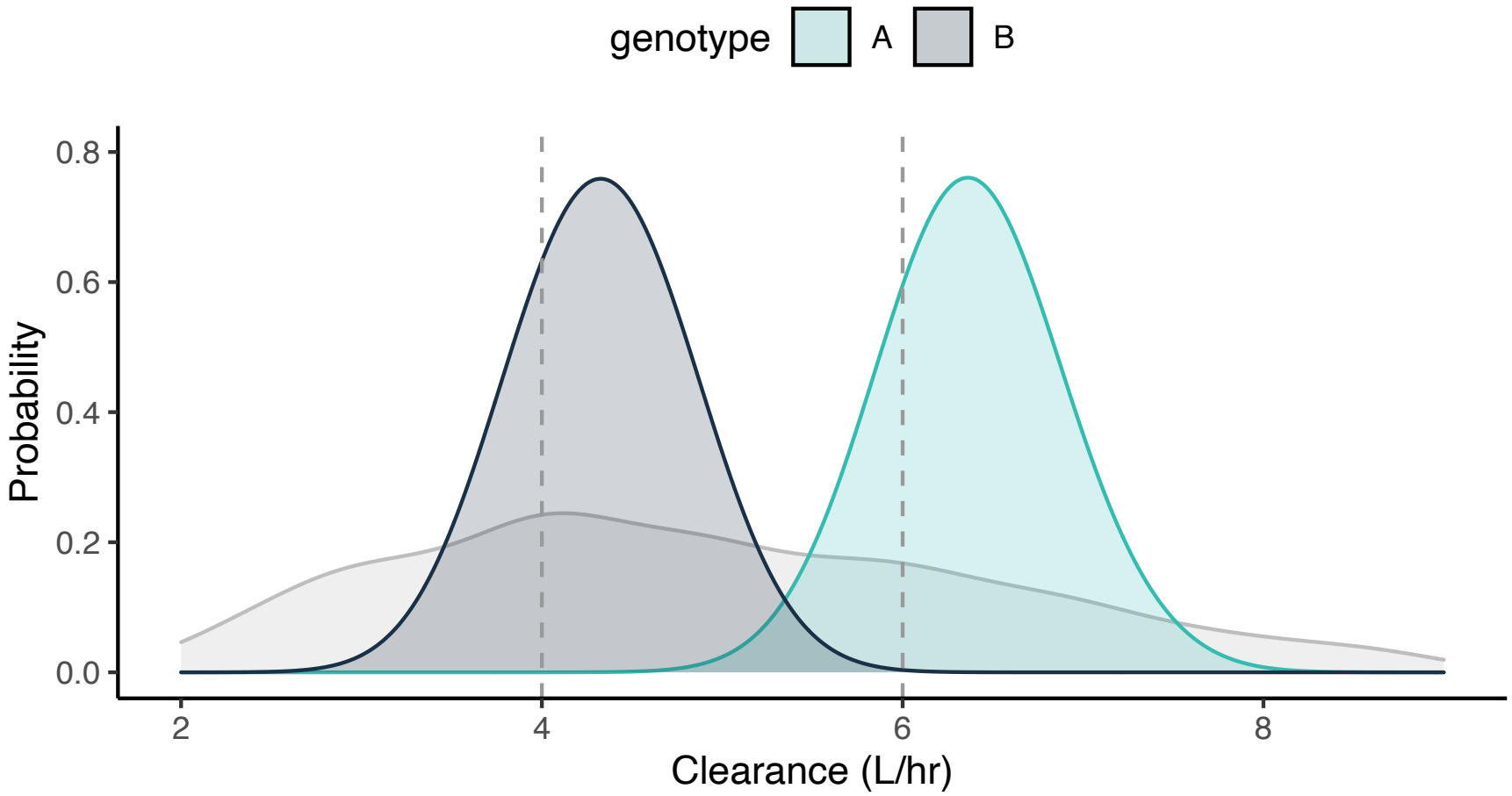
Prior: 5 L

True:

genotype A = 4 L

genotype B = 6 L

Simulated example 1: one-compartment PK



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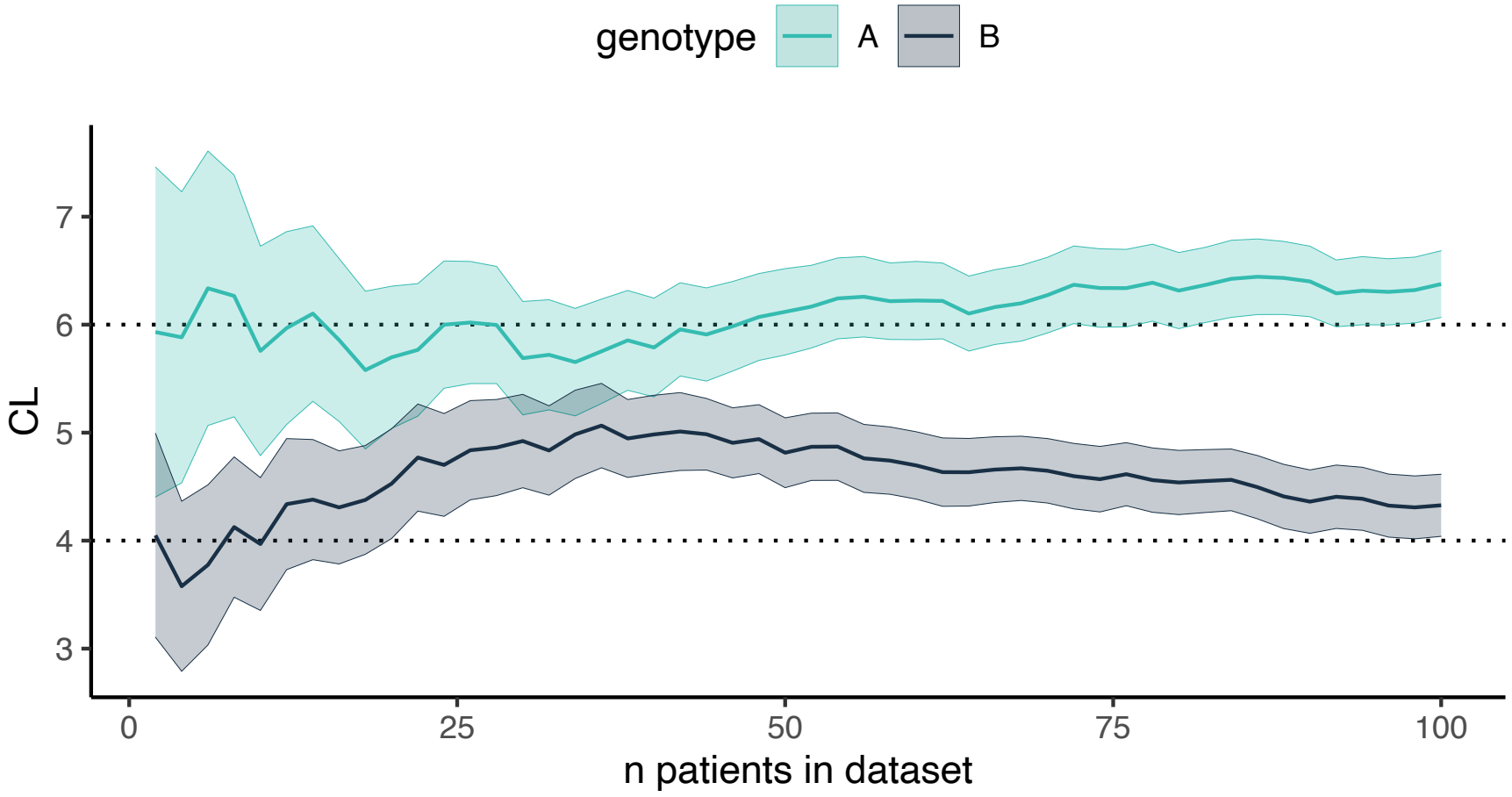


Genotype effect CL

Prior: 5 L

True:

genotype A = 4 L

genotype B = 6 L

Simulated example 2: neutropenia PK-PD

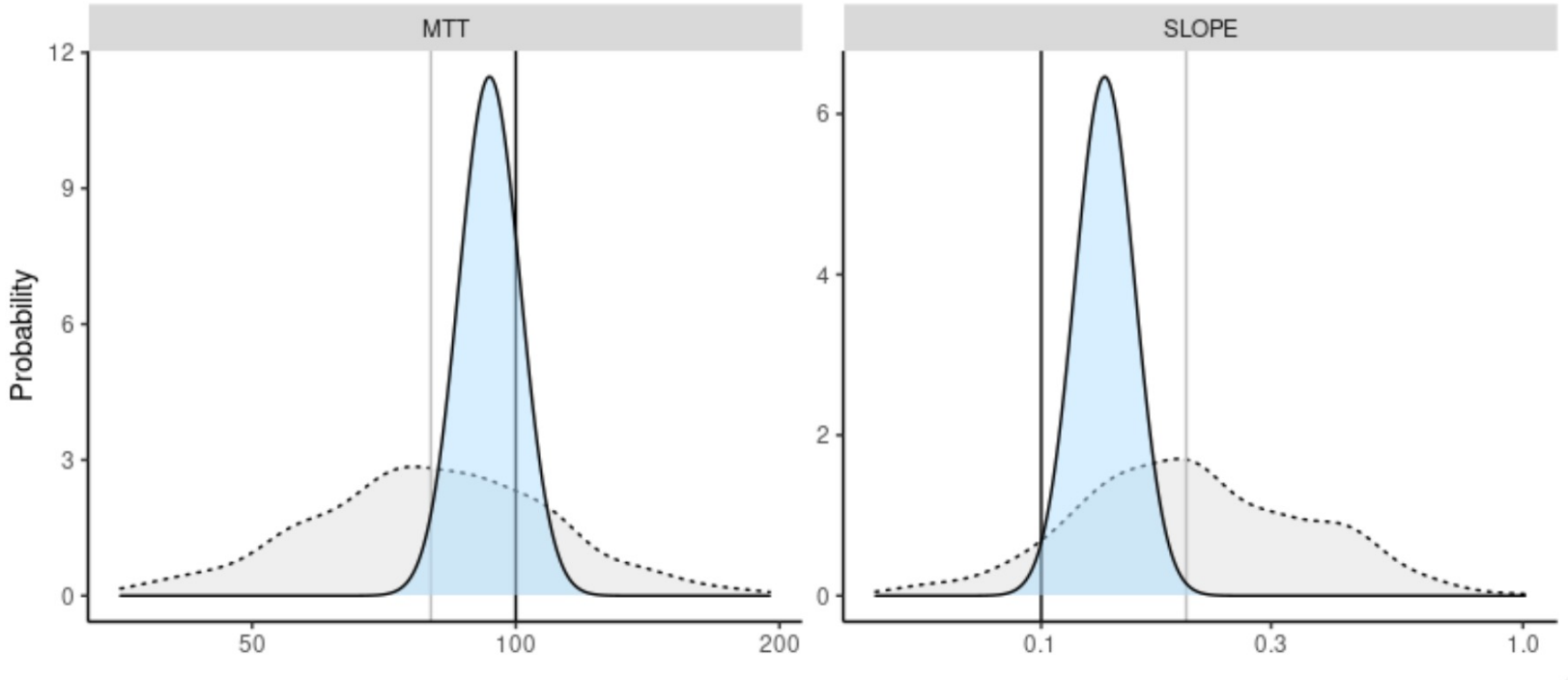
Estimation of MTT & slope

mean transit time (MTT): **+20%**

drug effect (slope): **+50%**

Insight RX

Simulated example 2: neutropenia PK-PD



Estimation of MTT & slope

mean transit time (MTT): **+20%**

drug effect (slope): **+50%**

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Real-world data: gentamicin in neonates

Improve biased model?

RMSE &

Comparison to NLME

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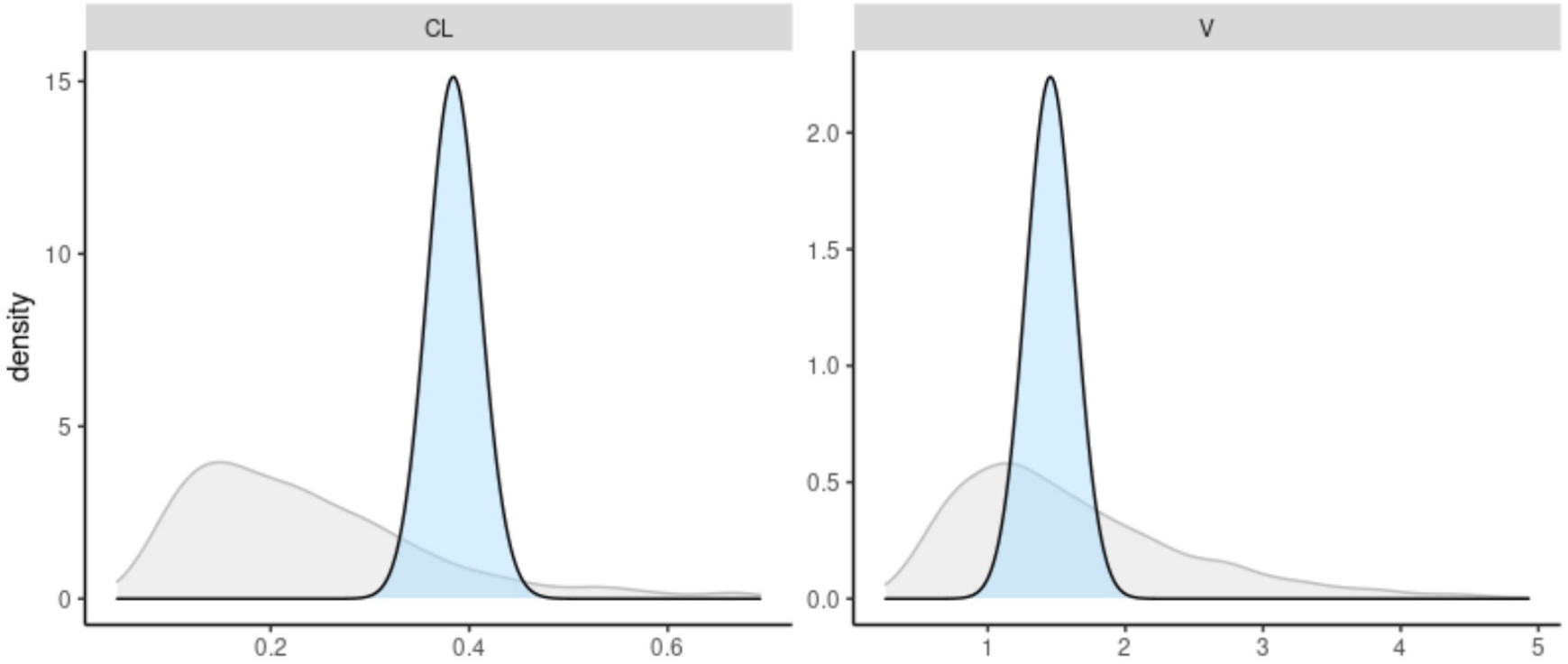
Real-world data: gentamicin in neonates



Improve biased model?

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Real-world data: gentamicin in neonates

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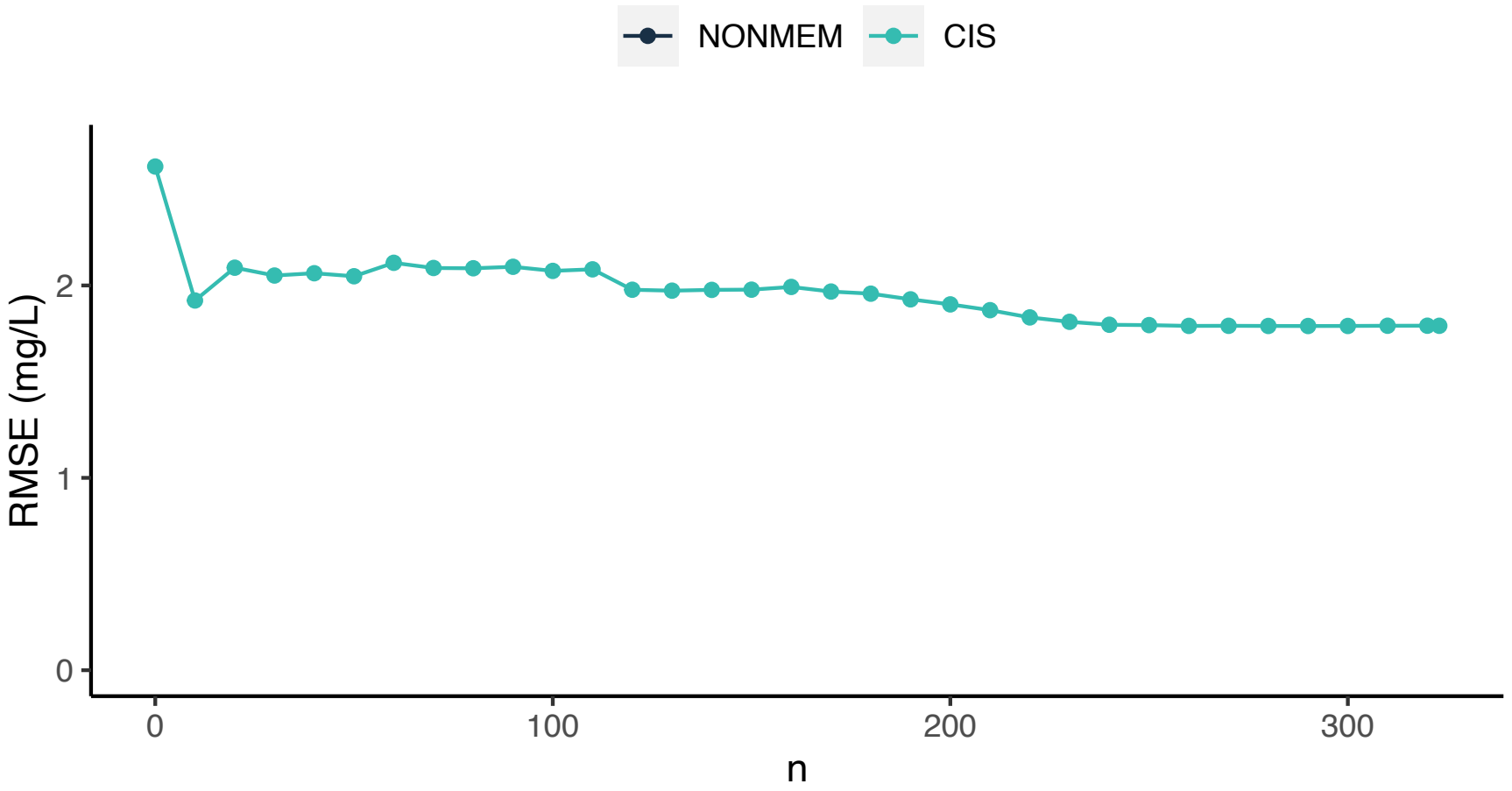
Real-world data: gentamicin in neonates



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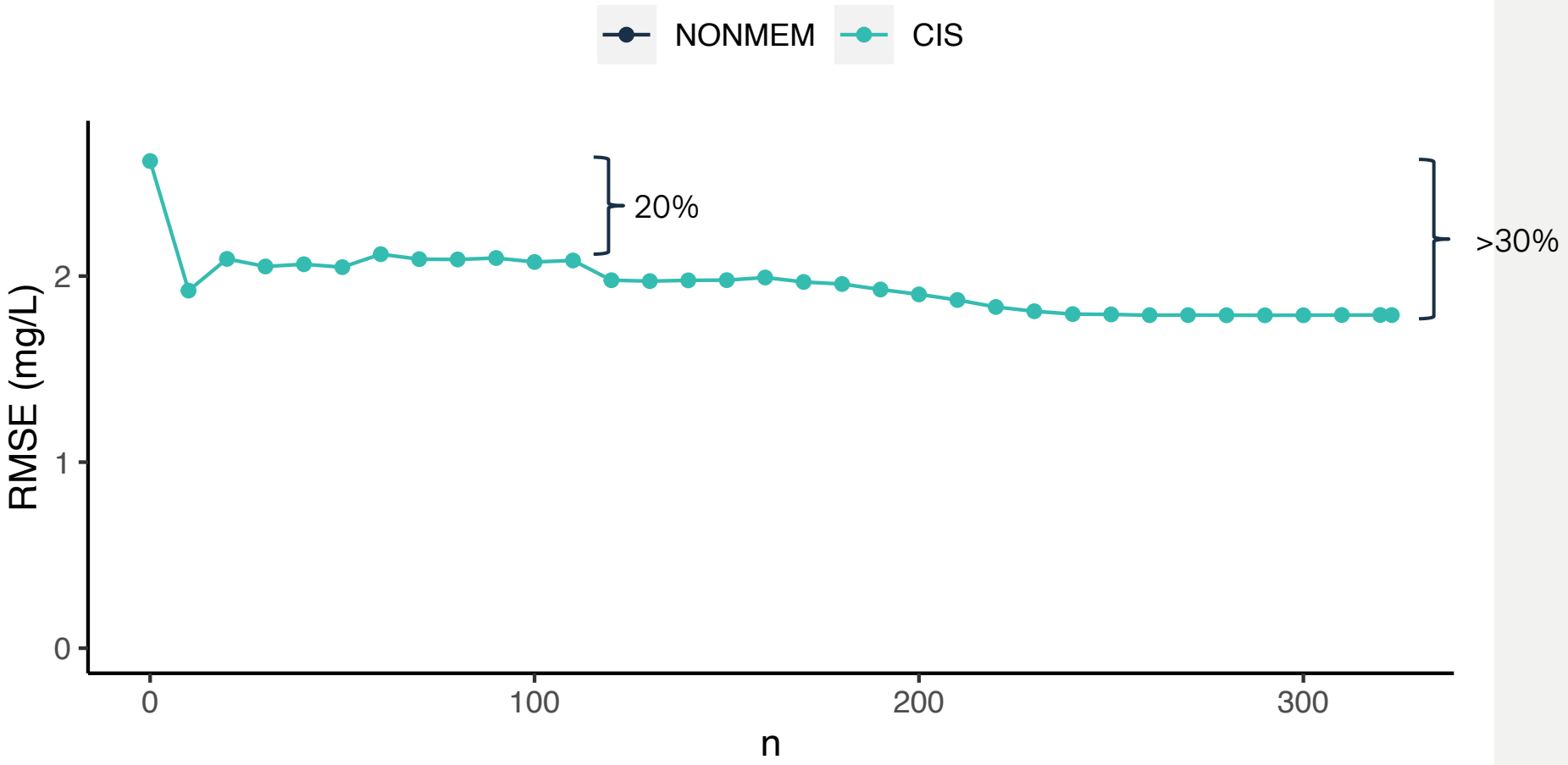
Real-world data: gentamicin in neonates



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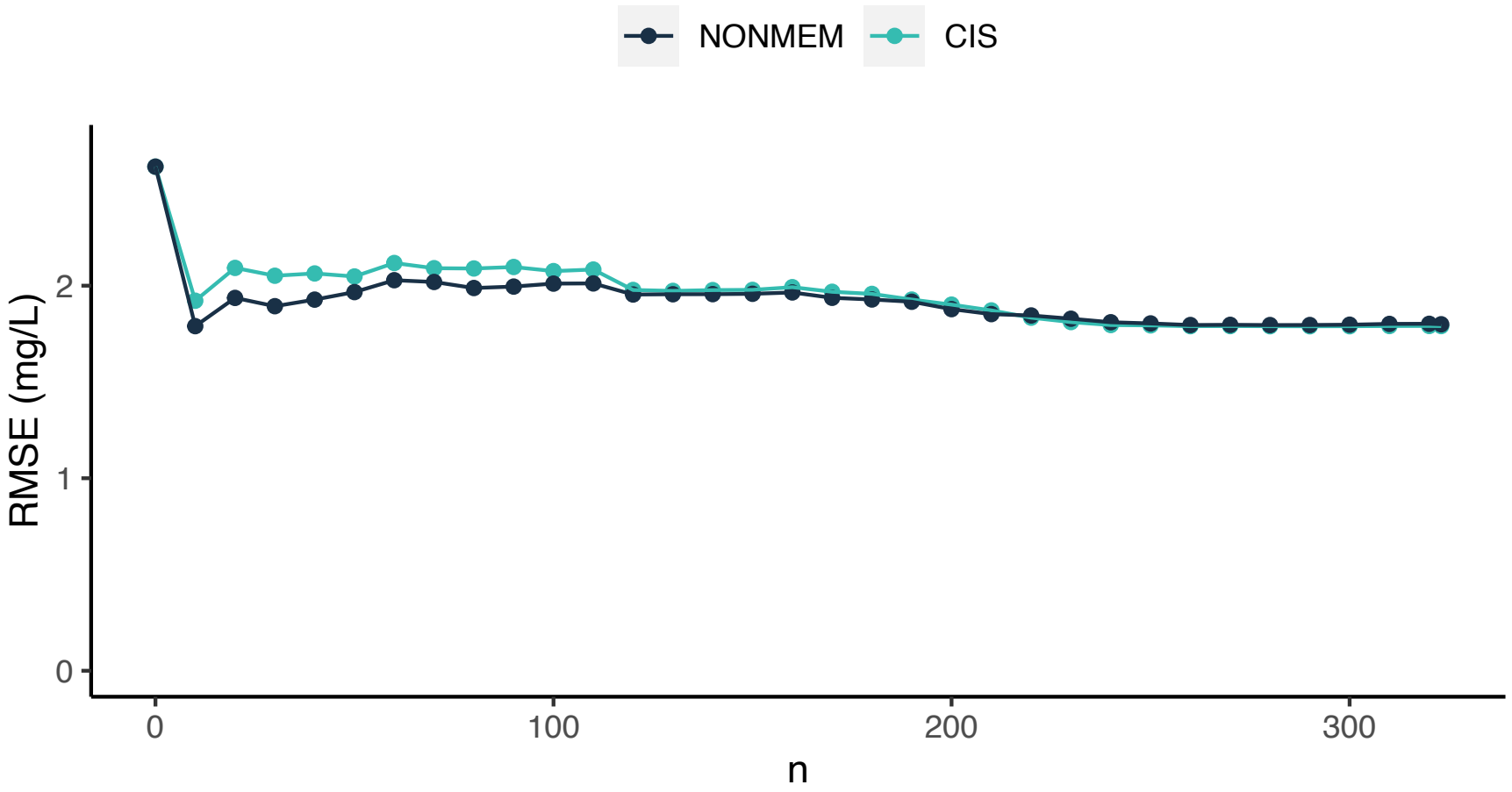
Real-world data: gentamicin in neonates



Improve biased model?

RMSE &

Comparison to NLME

Summary

- A simple continuous learning method for data streams

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- Advantages:
  - incremental estimation
  - ad hoc covariate analysis: train model per site

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- A simple continuous learning method for data streams
- Advantages:
  - incremental estimation
  - ad hoc covariate analysis: train model per site
- Drawbacks:
  - only lower-dimensional estimation, simpler models

Future work

- How many parameters can be estimated reliably?

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- How to apply safely in MIPD

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- How many parameters can be estimated reliably?
- How to apply safely in MIPD
- What are appropriate diagnostics?

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Thank you for listening

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