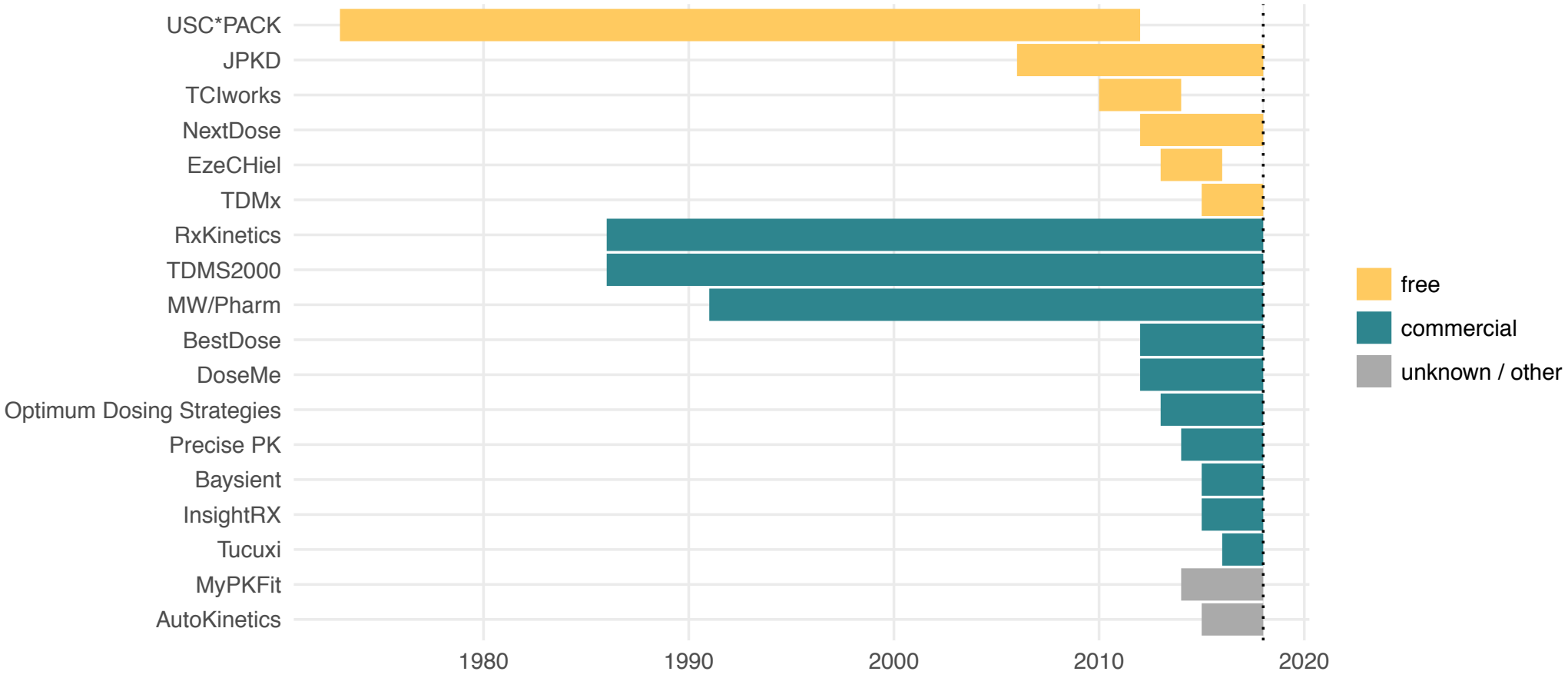
Insight RX

Experiences in applied clinical pharmacometrics:

challenges, recommendations, and research opportunities

Ron Keizer



Sources:
Fuchs et al. Clin Pharmacokinet 2013
http://campus.usal.es/~galenica/clinpkin/software.htm

* start/end dates are approximate

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Introduction

EMR integration

Clinical analytics

Continuous learning

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challenges to successful adoption

1. user interface (UI/UX)
2. education / support
3. integration with hospital systems (EHR)
4. funding
5. prove cost/benefit
6. regulatory
7. **science**

https://www.youtube.com/watch?v=CClMA7FCpX0
ACoP preconference 2018

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themes of this talk

1. model selection
2. individual fit
3. between-occasion variability
4. beyond exposure

1
model selection

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model selection

"How do I know this model works for my patients?"

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model selection

- even when right age class, **assumptions:**
  - trial population == new population
    - parameter distribution
    - covariate effects
    - error magnitude
  - no bias data collection / analysis
    - drug administration
    - drug assay
    - creatinine assay
    - etc…

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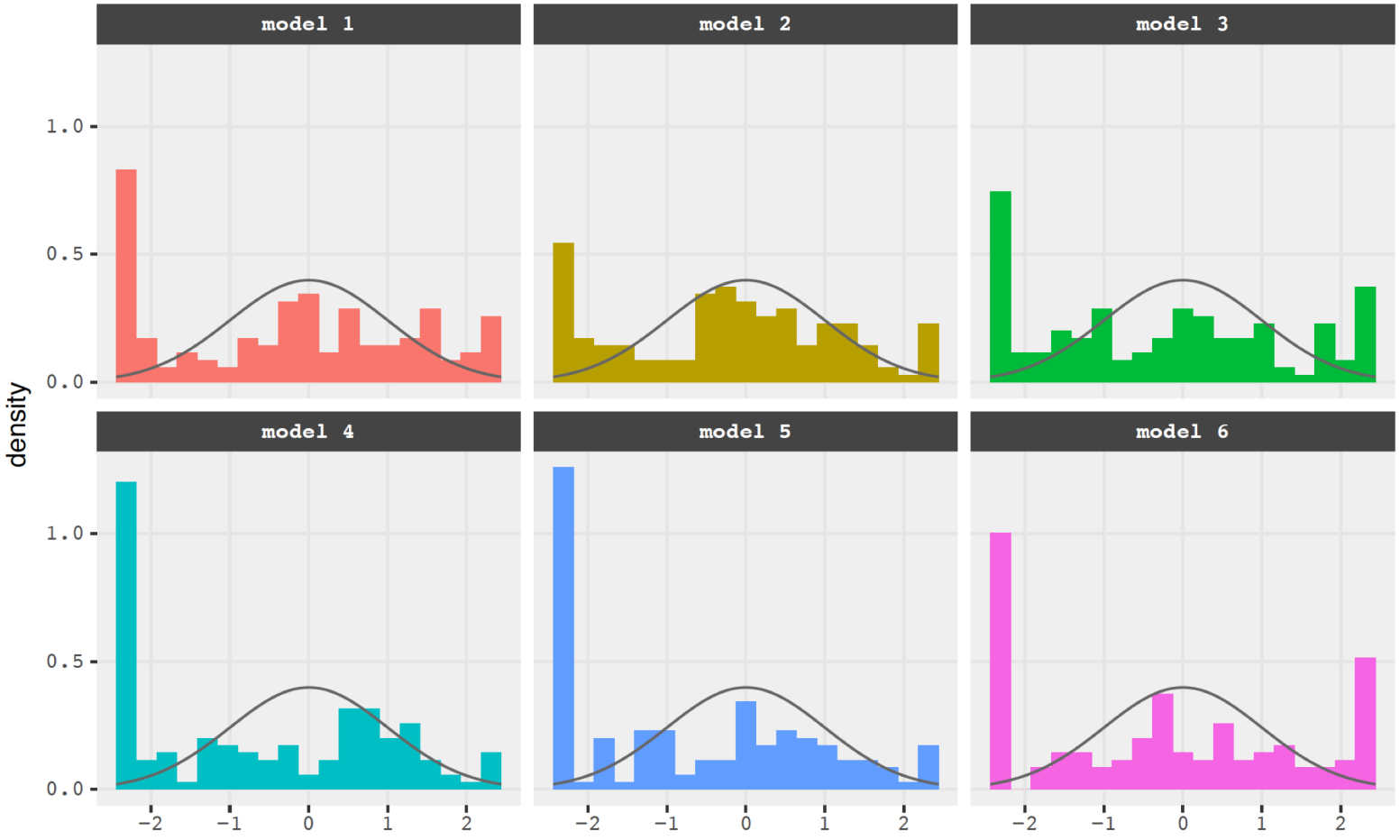
model selection: **retrospective evaluation**

- Pull data from EMR
  demographics + dosing + TDM
- Implement candidate models
- Perform predictive checks
  population-level / individual level
  a priori / a posteriori

model selection: a priori evaluation



Manuscript in preparation.
Collaboration with Radboud Applied Pharmacometrics Group
(R ter Heine, E Svensson, R Aarnoutse, R Bruggeman)

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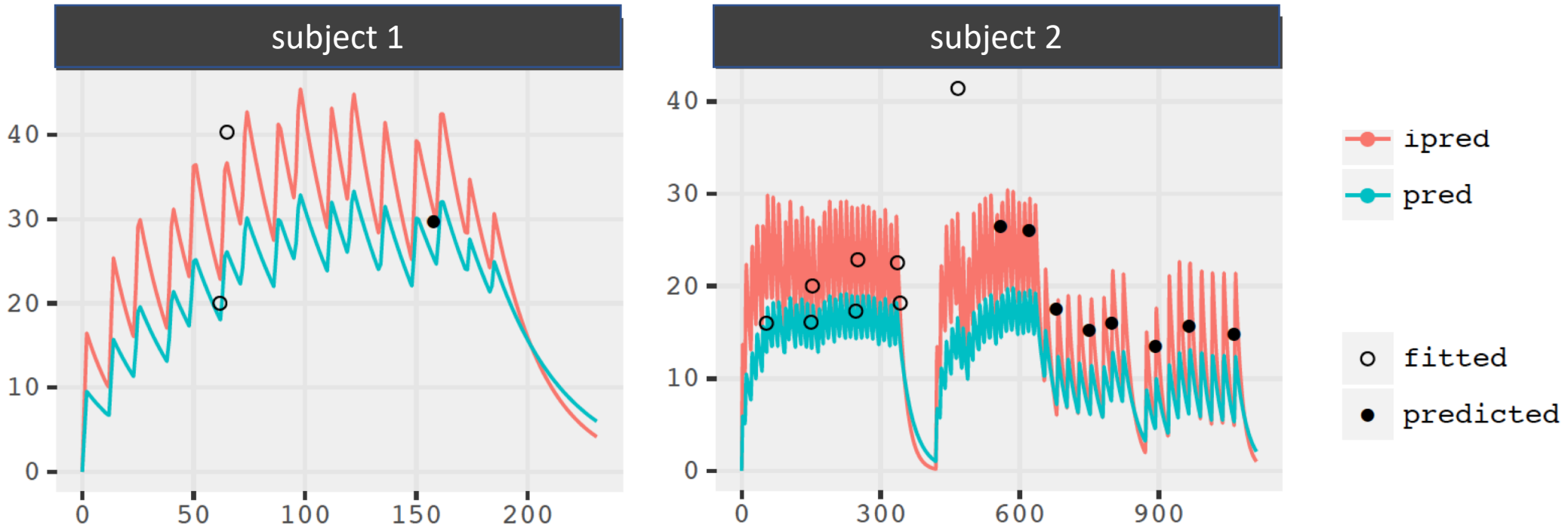
model selection: a posteriori evaluation



Similar functionality available in **`proseval`** (PsN)

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model selection: **retrospective evaluation**

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model selection: **retrospective evaluation**

goal = fit for purpose

2
individual fit

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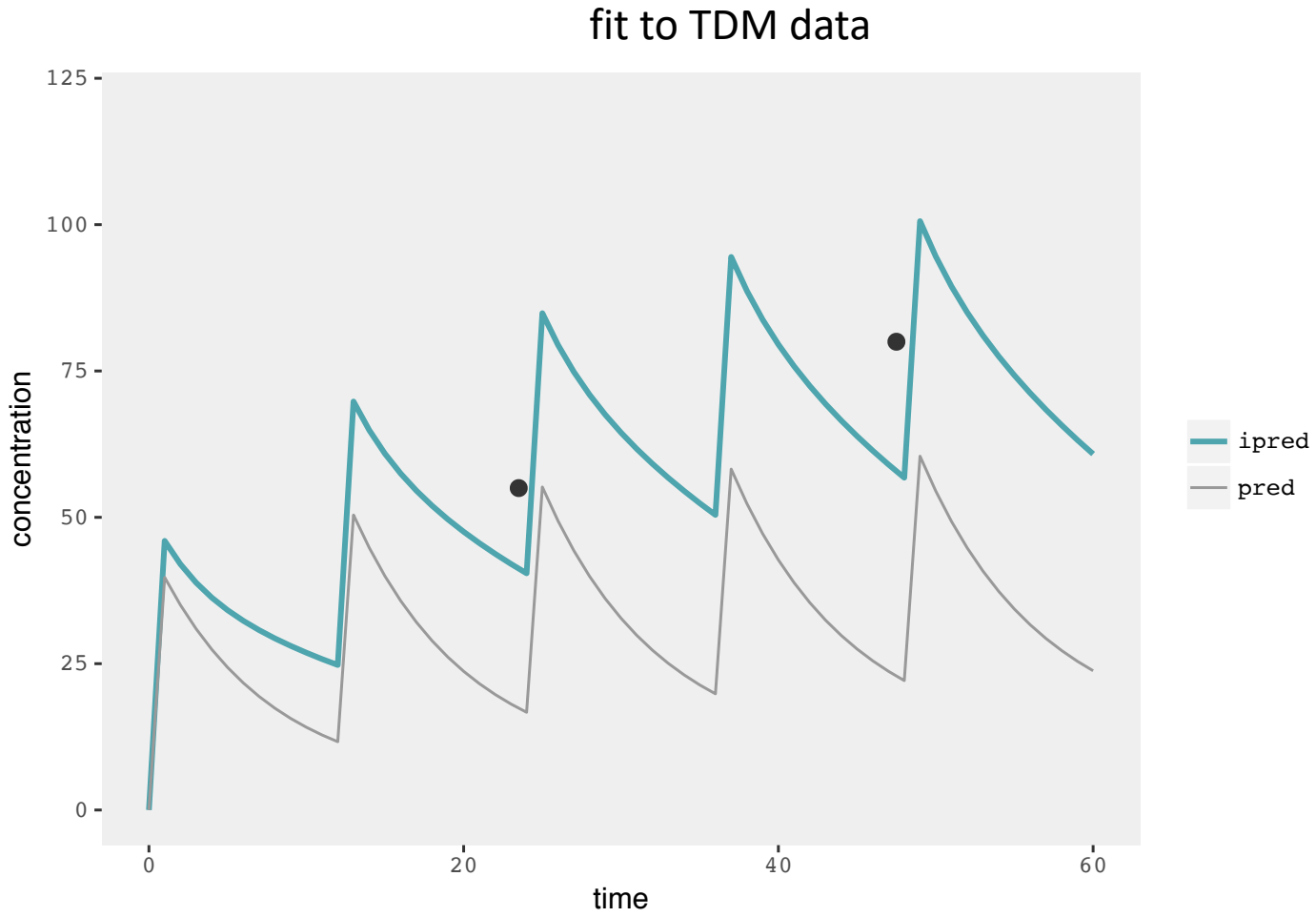
individual fit

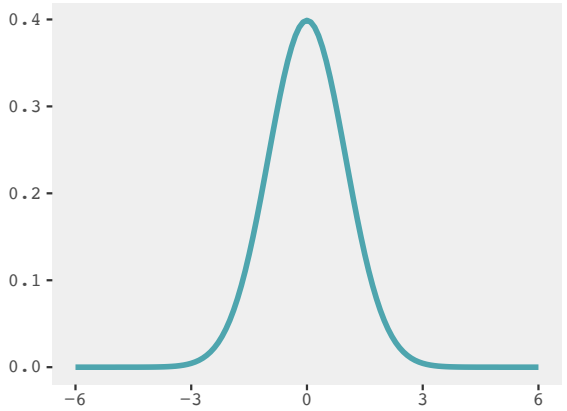
"Why is the fit for this patient off?"

individual fit: outlier subject

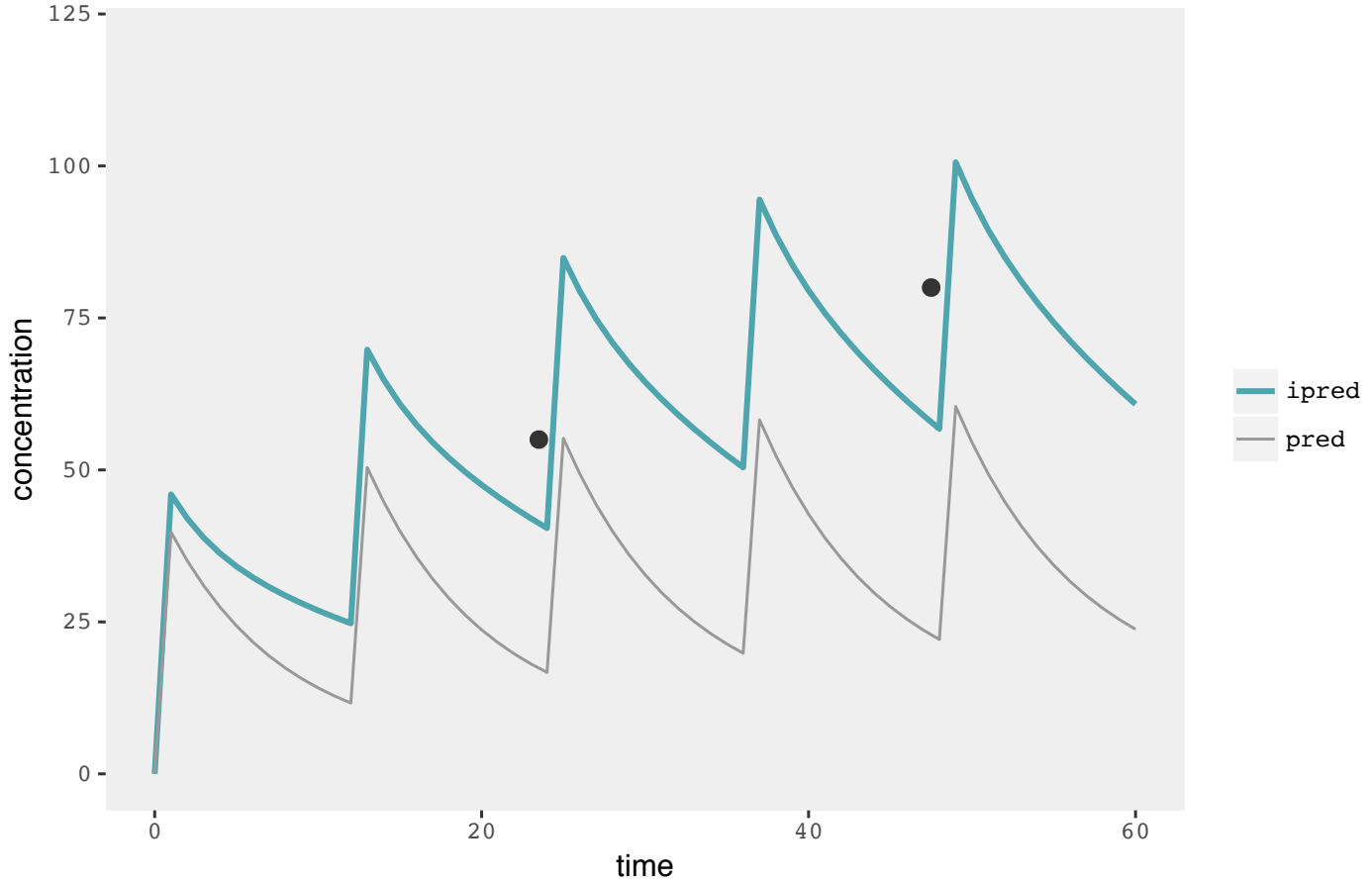


individual fit: outlier subject

distribution of η



fit to TDM data



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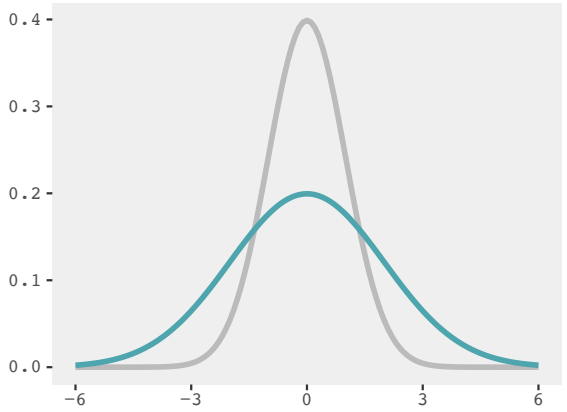
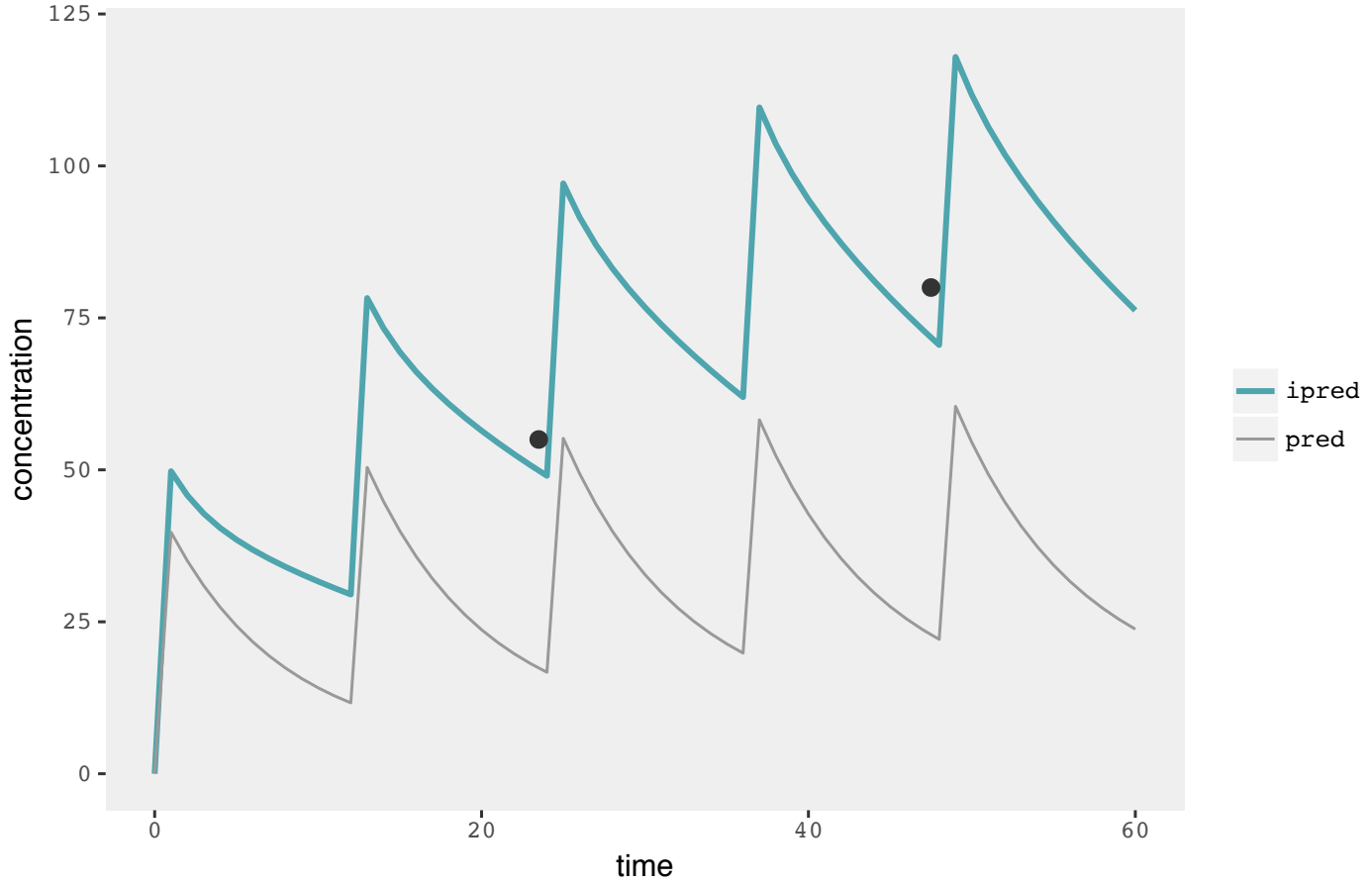
individual fit: **parametric** prior-adjustment

distribution of η



fit to TDM data



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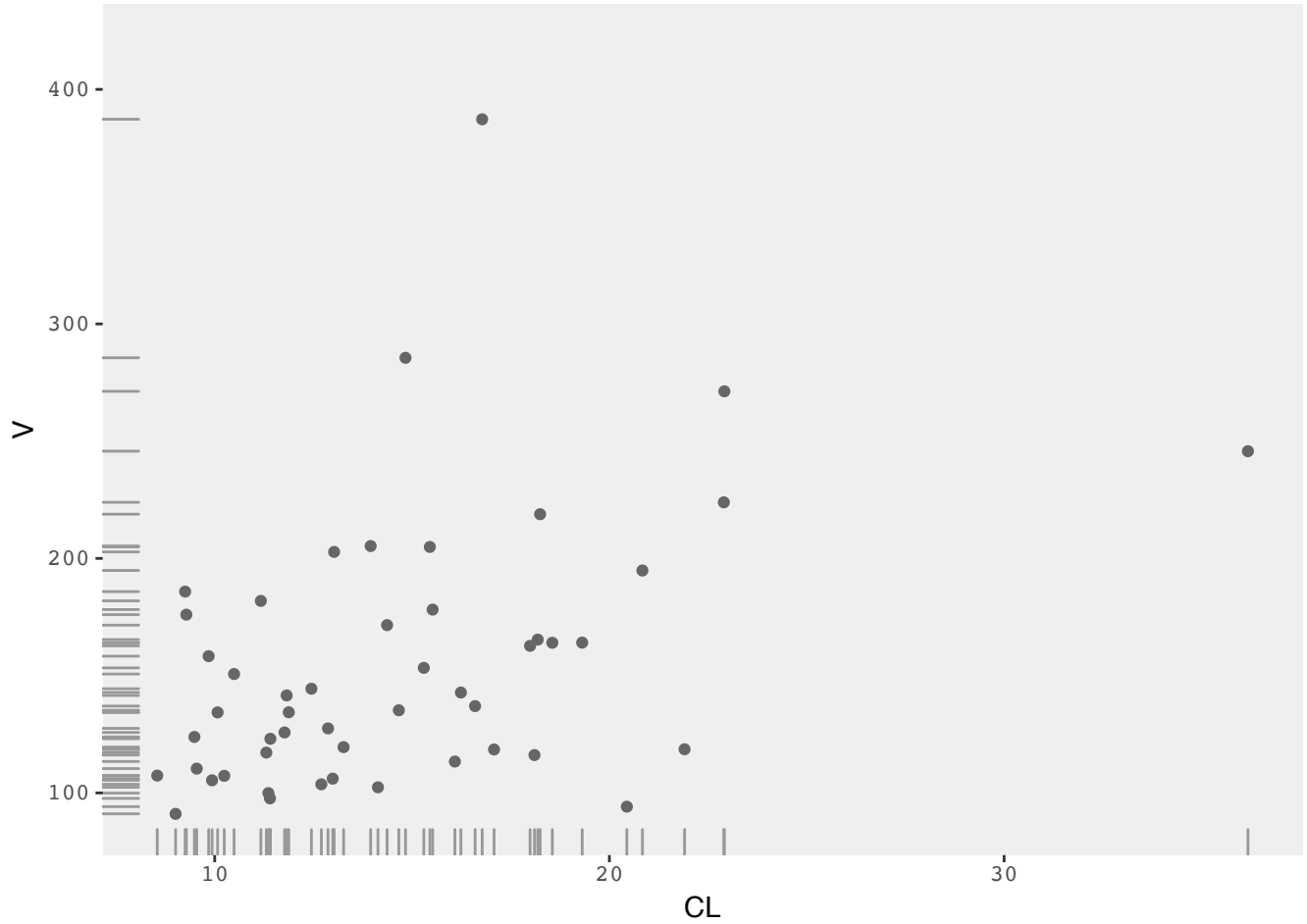
individual fit

Apply with care!

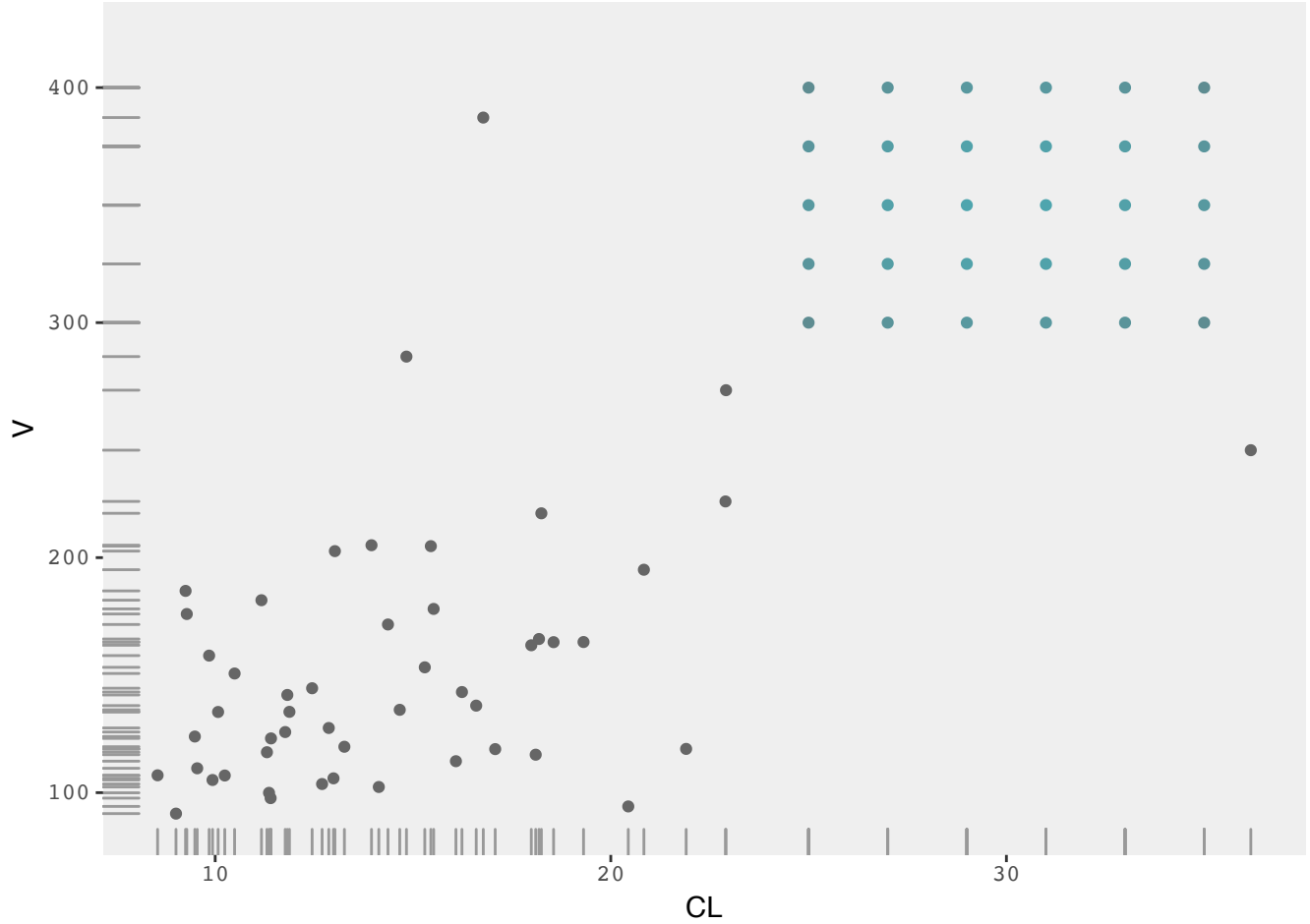
overfitting
inter-occasion variability
regression to the mean

individual fit: **non-parametric** prior-adjustment



Jelliffe and Neely. Individualized Drug Therapy for Patients

individual fit: **non-parametric** prior-adjustment



Jelliffe and Neely. Individualized Drug Therapy for Patients

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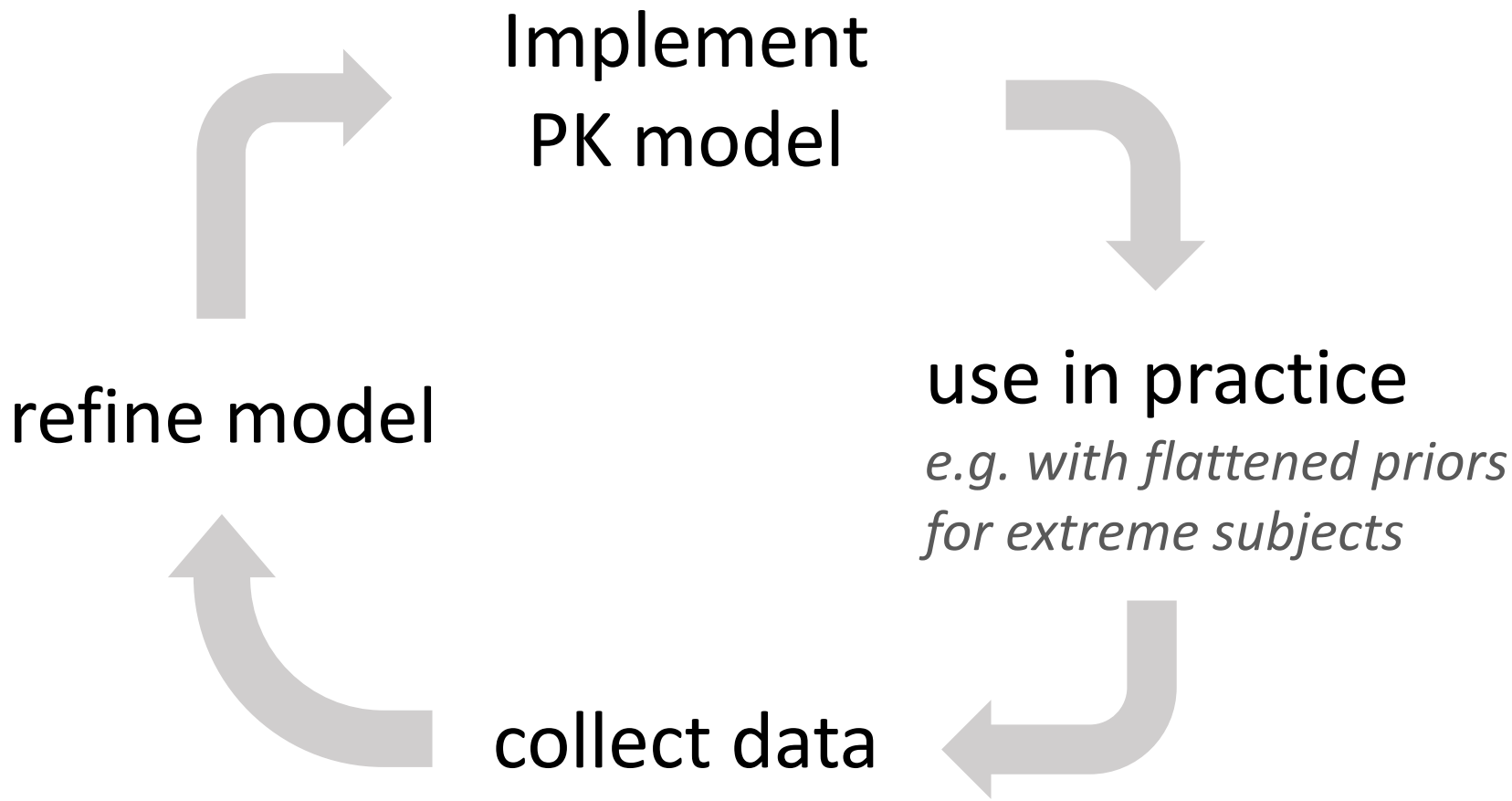
Individual fit: model updating



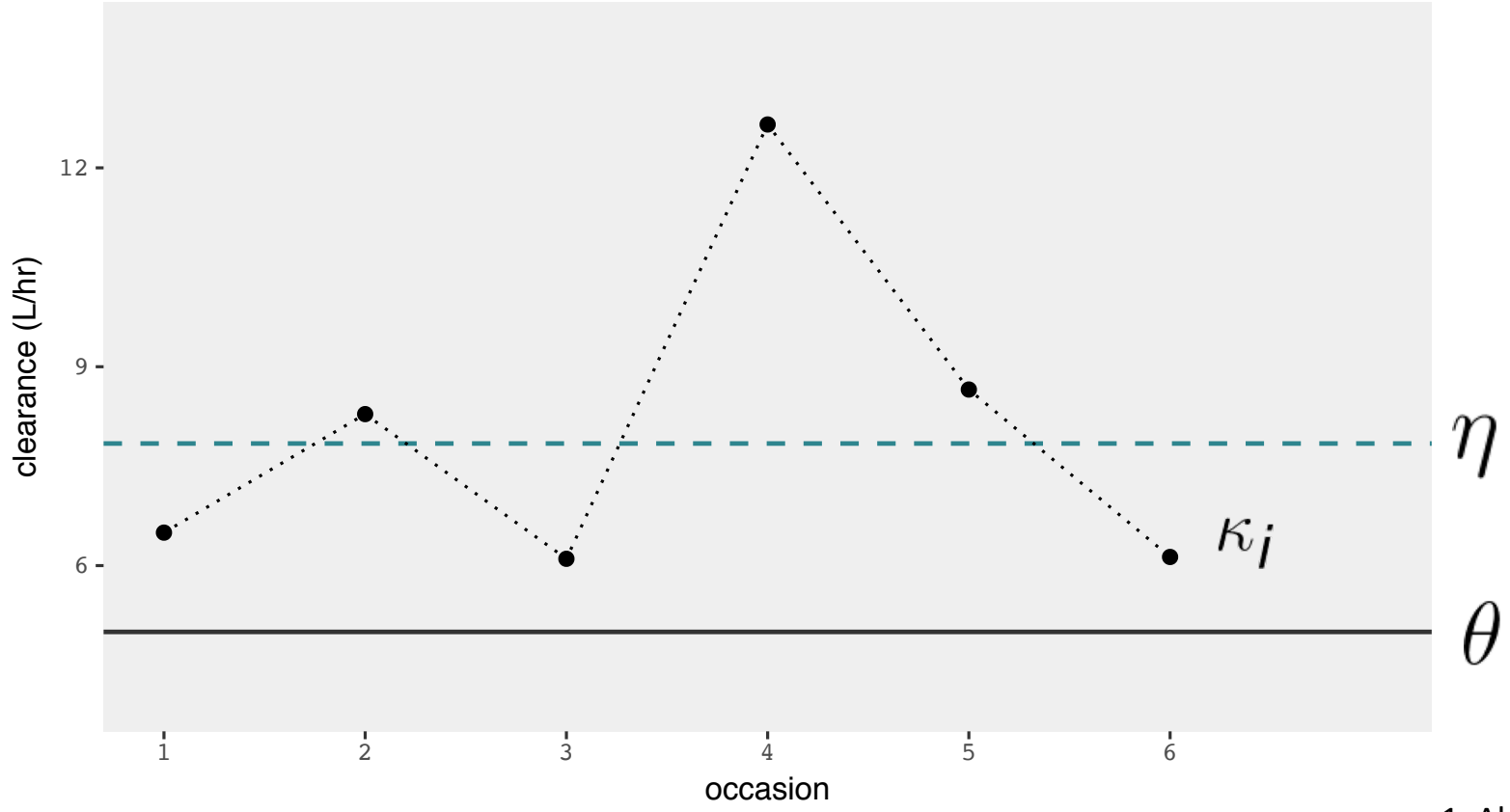
3
inter-occassion variability

Inter-occasion variability

"I saw this patient last month, can we use the knowledge learned from his previous visit?"

inter-occasion variability

"Use of individual estimates specific to a previous occasion lead to reduced predictive power in forecasting future exposure" [1]



1. Abrantes J et al. PAGE 2017

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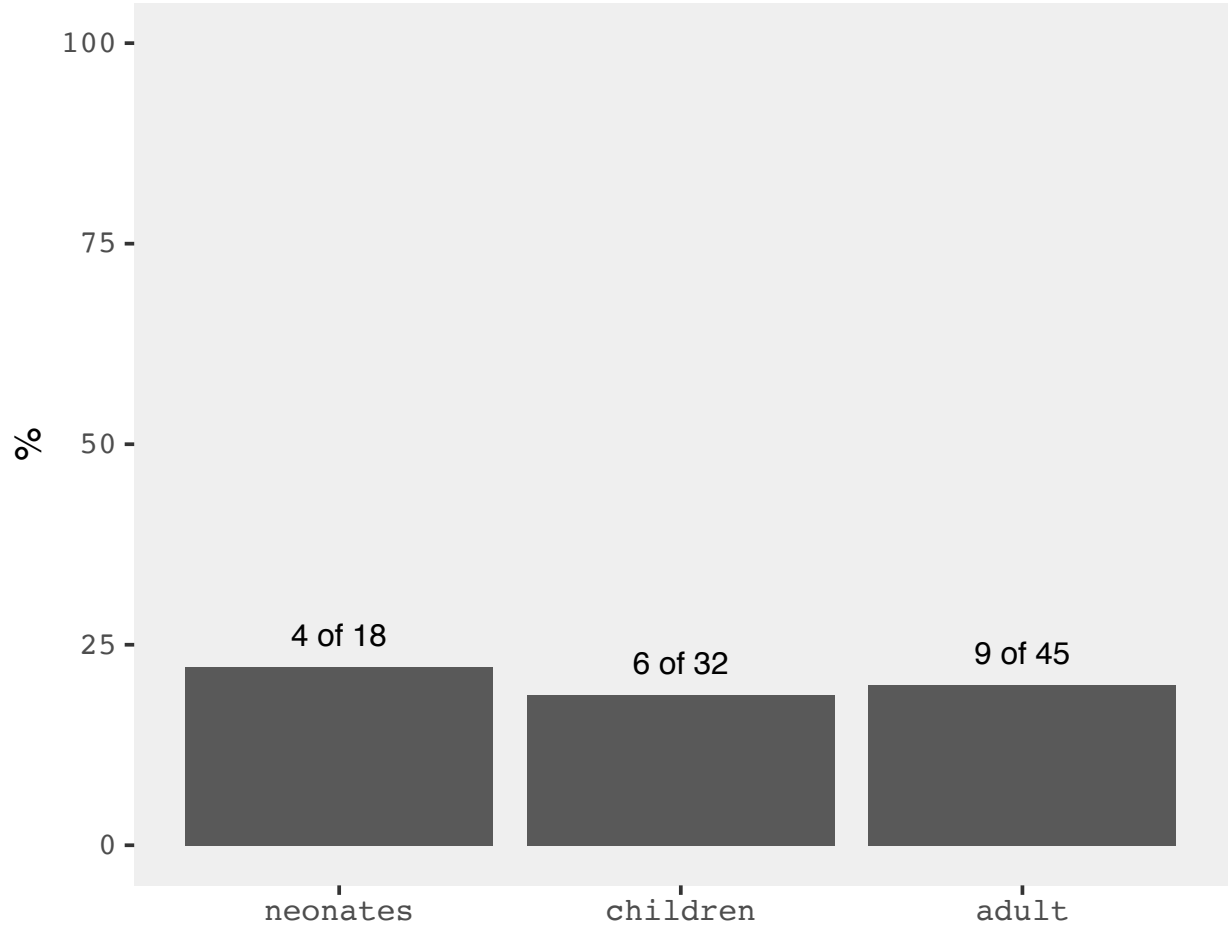
inter-occasion variability

first issue

- what is occasion?
  - “visit”
  - “treatment cycle”
  - “1 day”
  - “arbitrary n days”
- often not defined specifically in original paper
- not always matching clinical practice

inter-occasion variability: **models including IOV**



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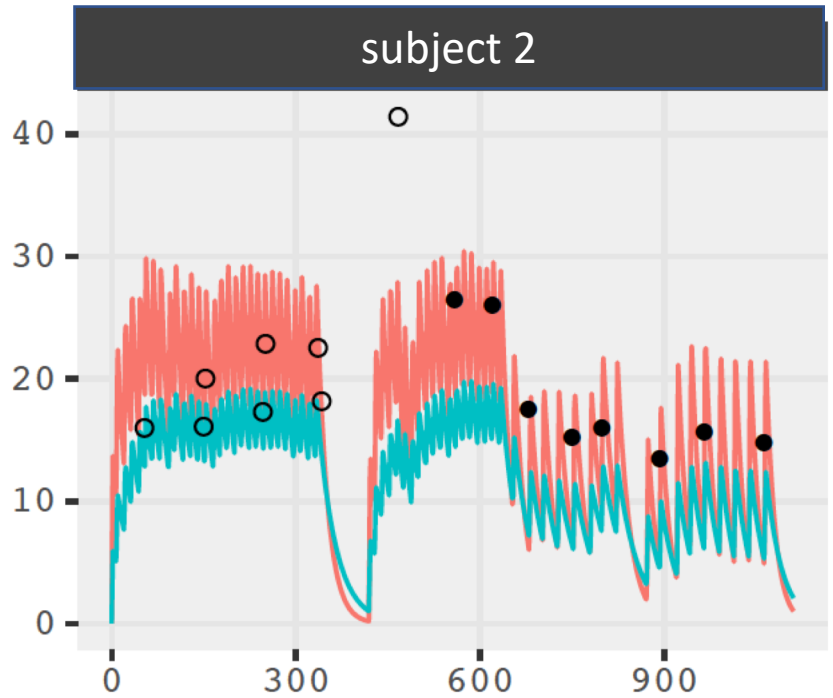
inter-occasion variability

long-term data is common



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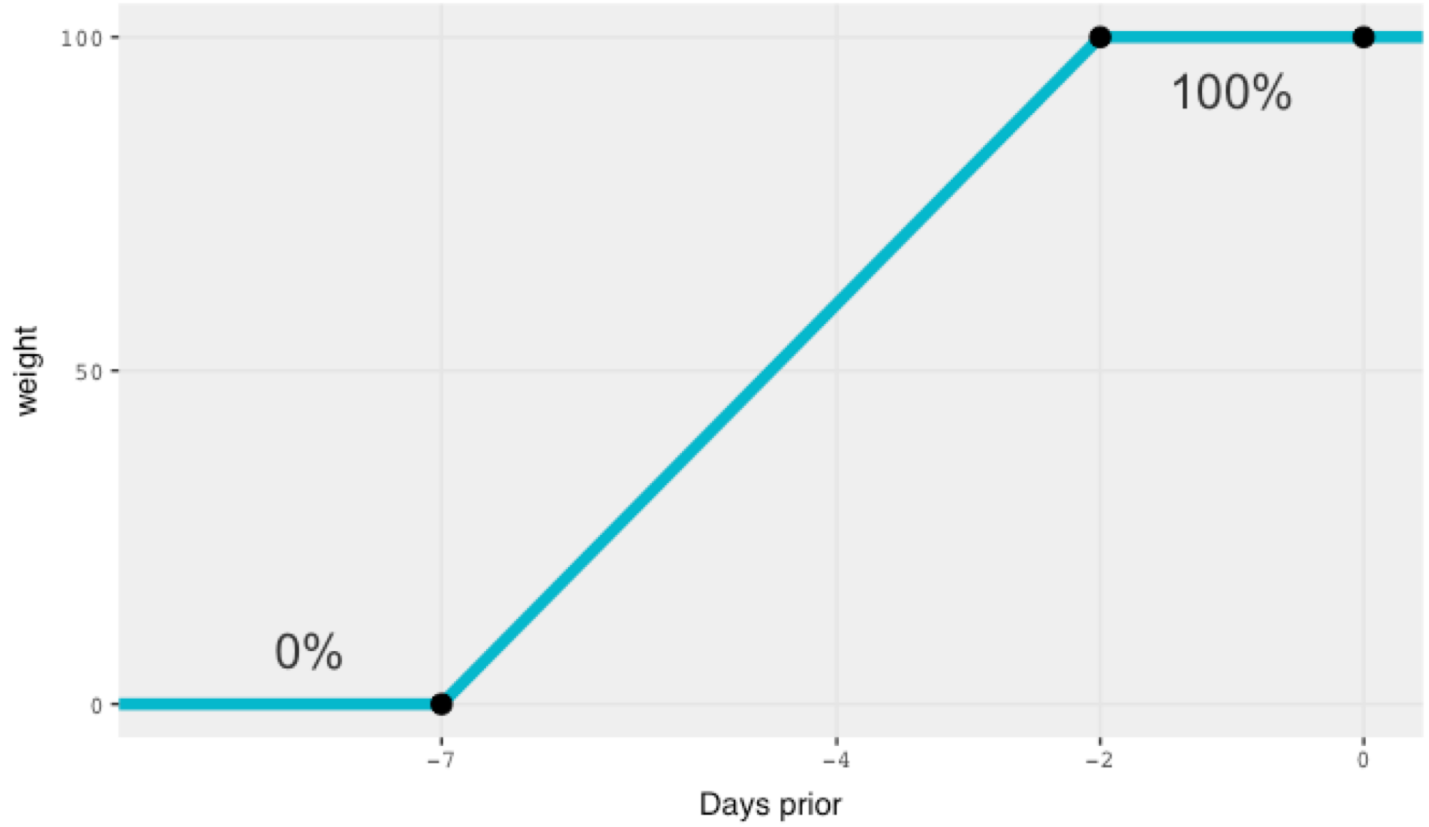
inter-occasion variability

when no IOV reported: ignore IOV, but weigh data with time



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inter-occasion variability

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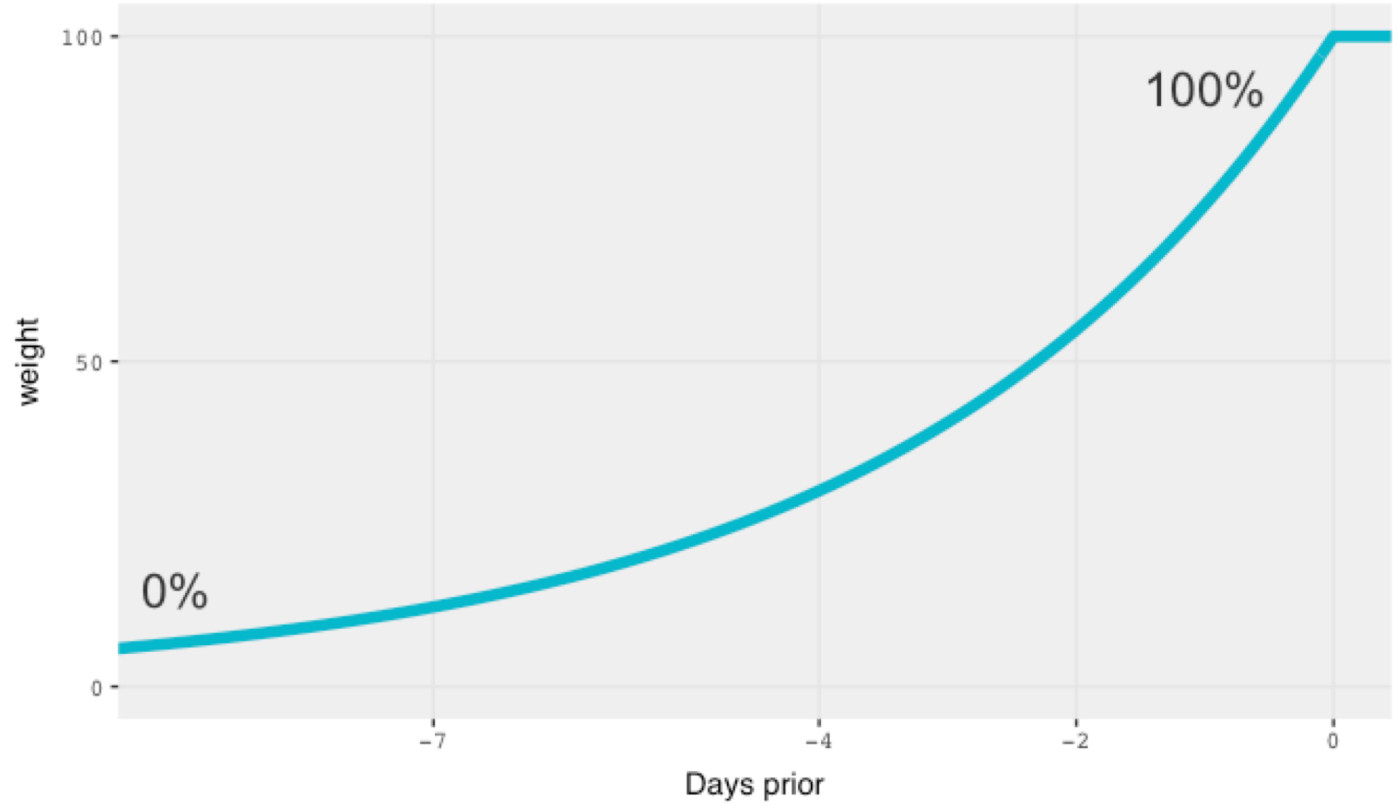


Inter-occasion variability

"I saw this patient last month, can we use the knowledge learned from his previous visit?"

4

beyond exposure

Exposure-outcome relationships

"C_{min} should be 15-20 mg/L to be effective"

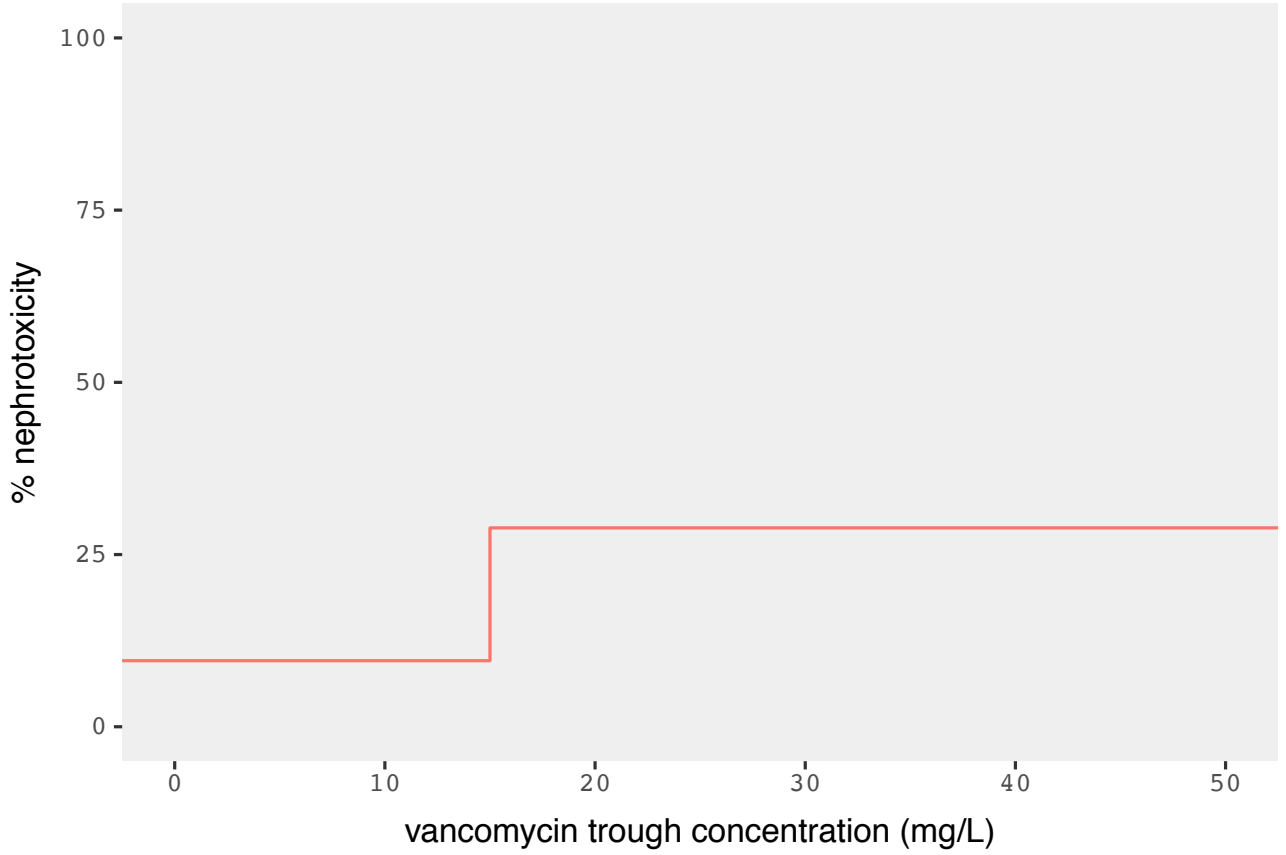
"If C_{min} >20 then 5x higher nephrotoxicity"

- subjective, qualitative, usually ROC-based[1]
- population-dependent

1) A-K Hamberg and RJ Keizer. Ther Drug Monit. 2017 Jun;39(3):303

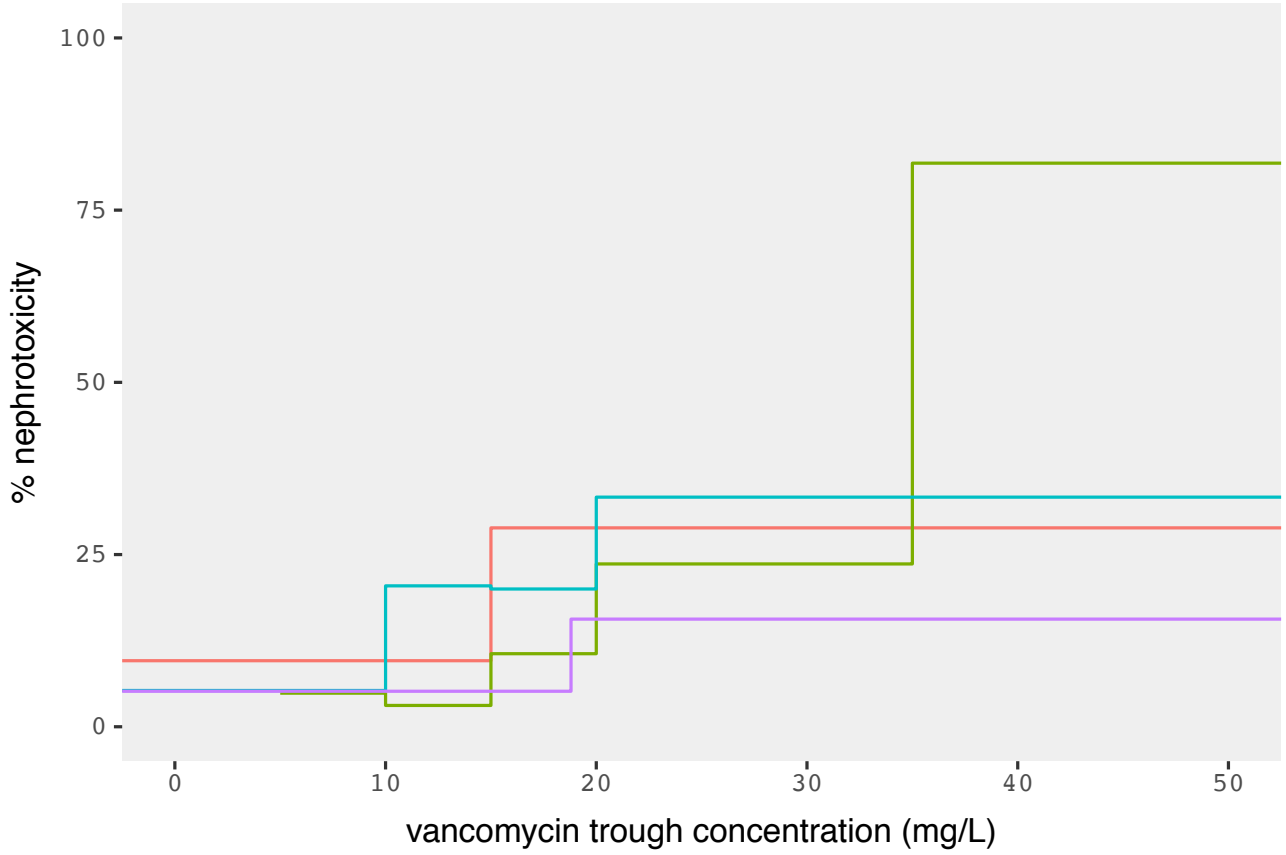
Exposure-outcome relationships

binary decision rules



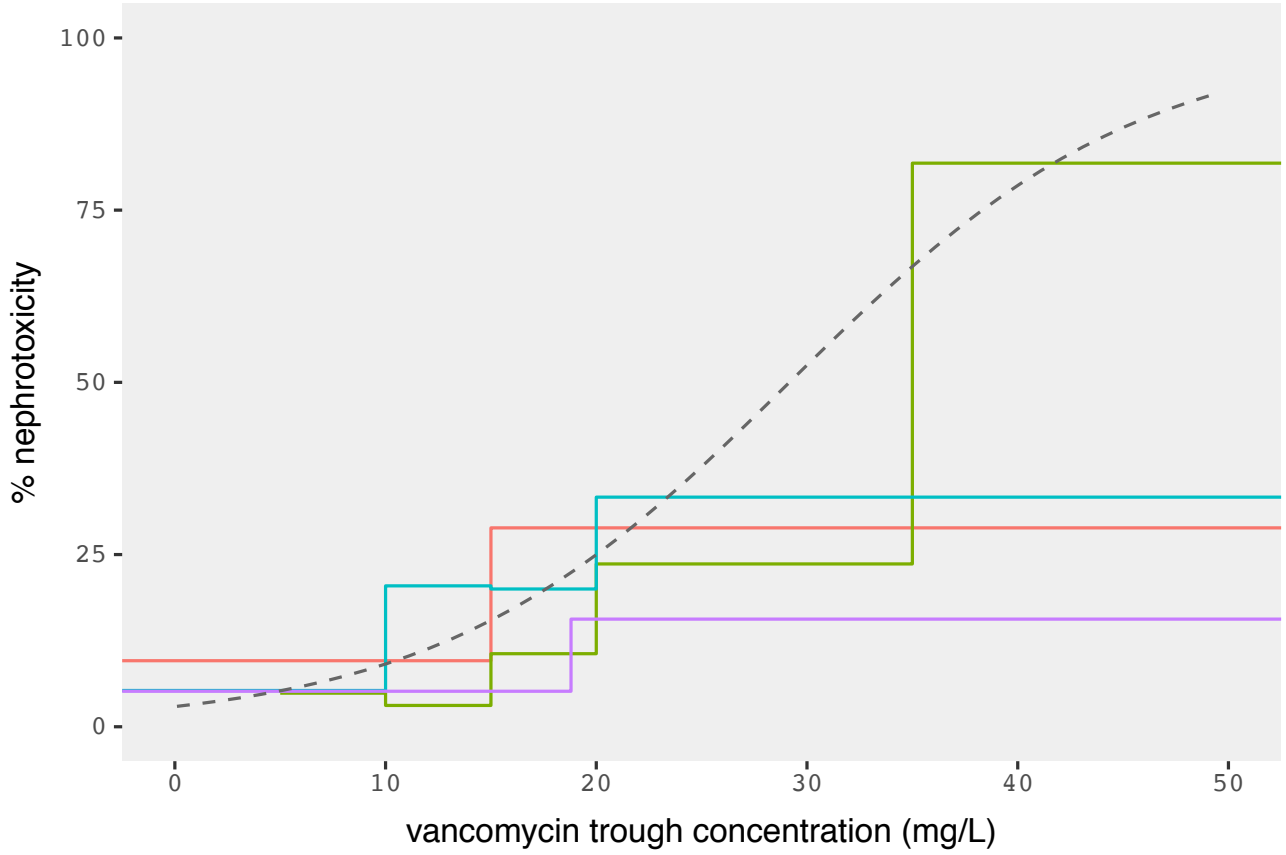
Exposure-outcome relationships

binary decision rules



Exposure-outcome relationships

continuous link with outcome / toxicity



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Exposure-outcome relationships

Instead of binary exposure rules:

Example table

regimen	AUC_{24}	C_{trough}
1000 mg q12	400	10
1500 mg q12	600	15
2000 mg q12	800	20
1000 mg q8	600	18

- allows individualization on PD, toxicity, outcome, as well as on PK

Exposure-outcome relationships

Exposure target attainment → **Pharmacological** aim

Improved outcome / Reduced toxicity → **Medical** aim

Reduced costs → **Financial** aim

Acknowledgements

for our collaborations and discussions along the presented topics

Sirj Goswami
Ranvir Mangat

Adam Frymoyer
Shabnam Gaskari

Jonathan Faldasz
Janel Long-Boyle
Rada Savic

Rob ter Heine
Roger Bruggeman
Elin Svensson
Krista van Steeg

Anna-Karin Hamberg
Joao Abrantes
Elisabet Nielsen
Mats Karlsson