Introduction to model-informed precision dosing

Using warfarin treatment as a use case

Outline

Why model-informed precision dosing (MIPD)?

What is MIPD?

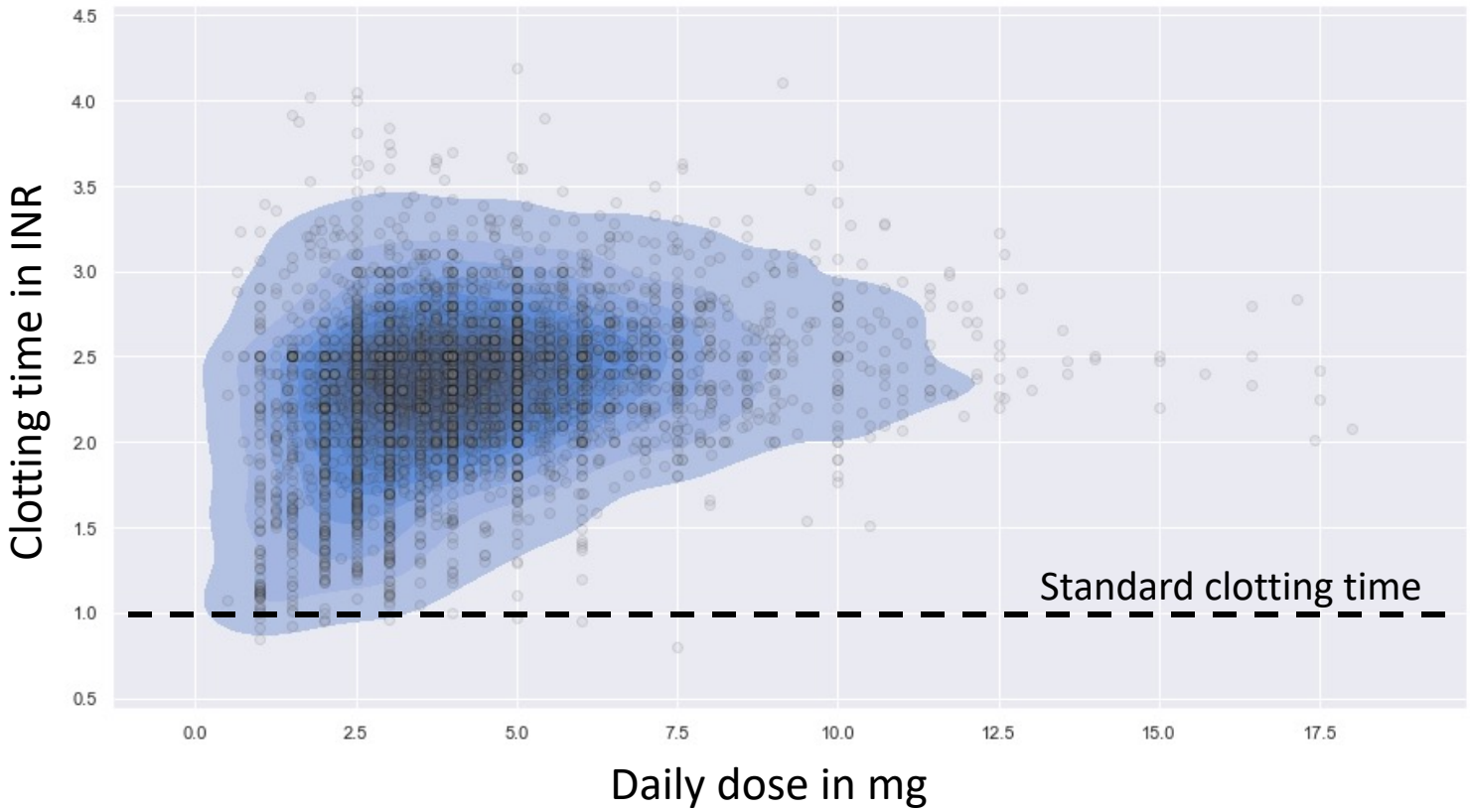
How do we test MIPD?

How well does MIPD work?

Why MIPD?

Clinical records of warfarin treatment

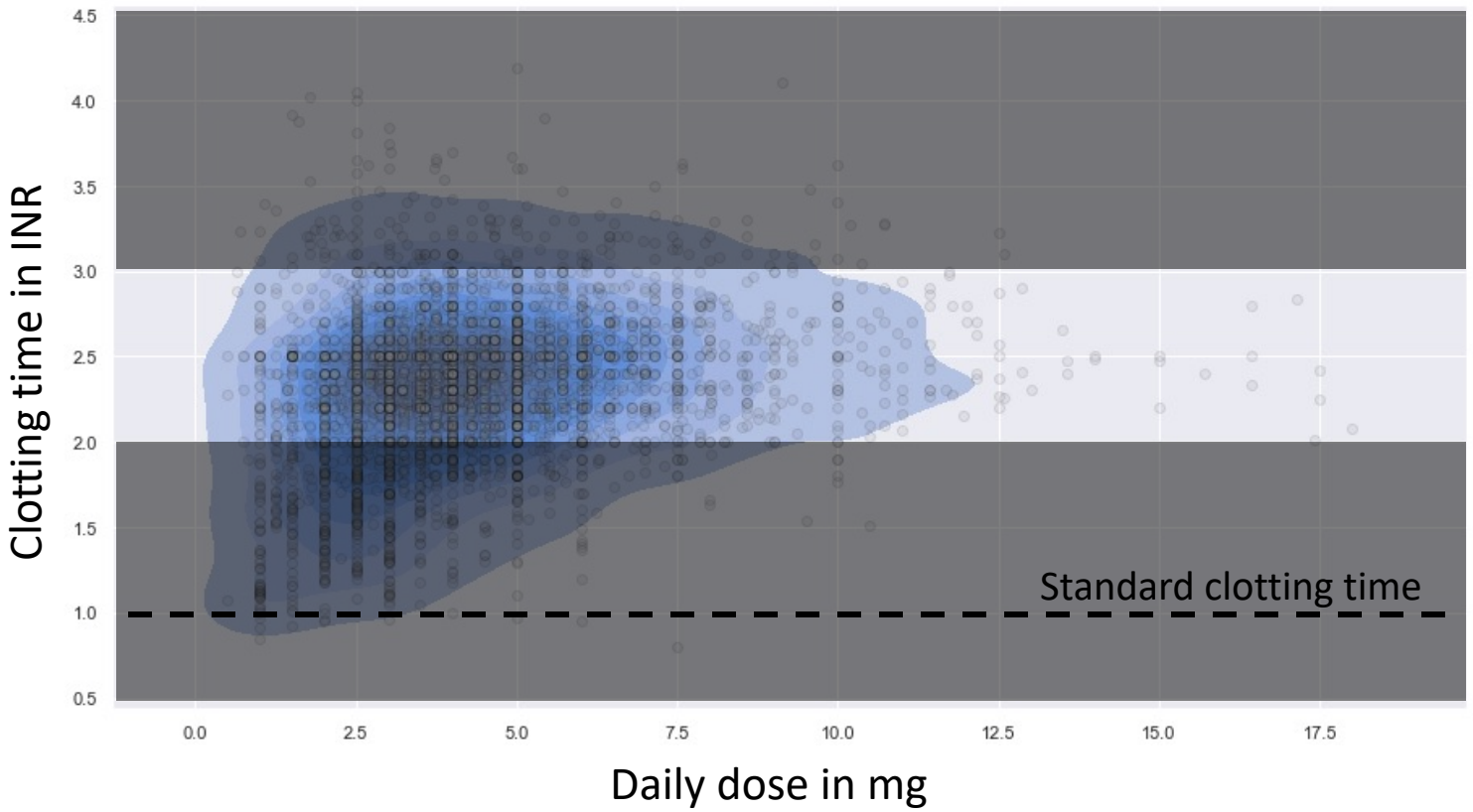
Inter-individual variability



International Warfarin Pharmacogenetics Consortium. New England Journal of Medicine. 2009 Feb 19;360(8):753-64.

Clinical records of warfarin treatment

Inter-individual variability



International Warfarin Pharmacogenetics Consortium. New England Journal of Medicine. 2009 Feb 19;360(8):753-64.

What is MIPD?

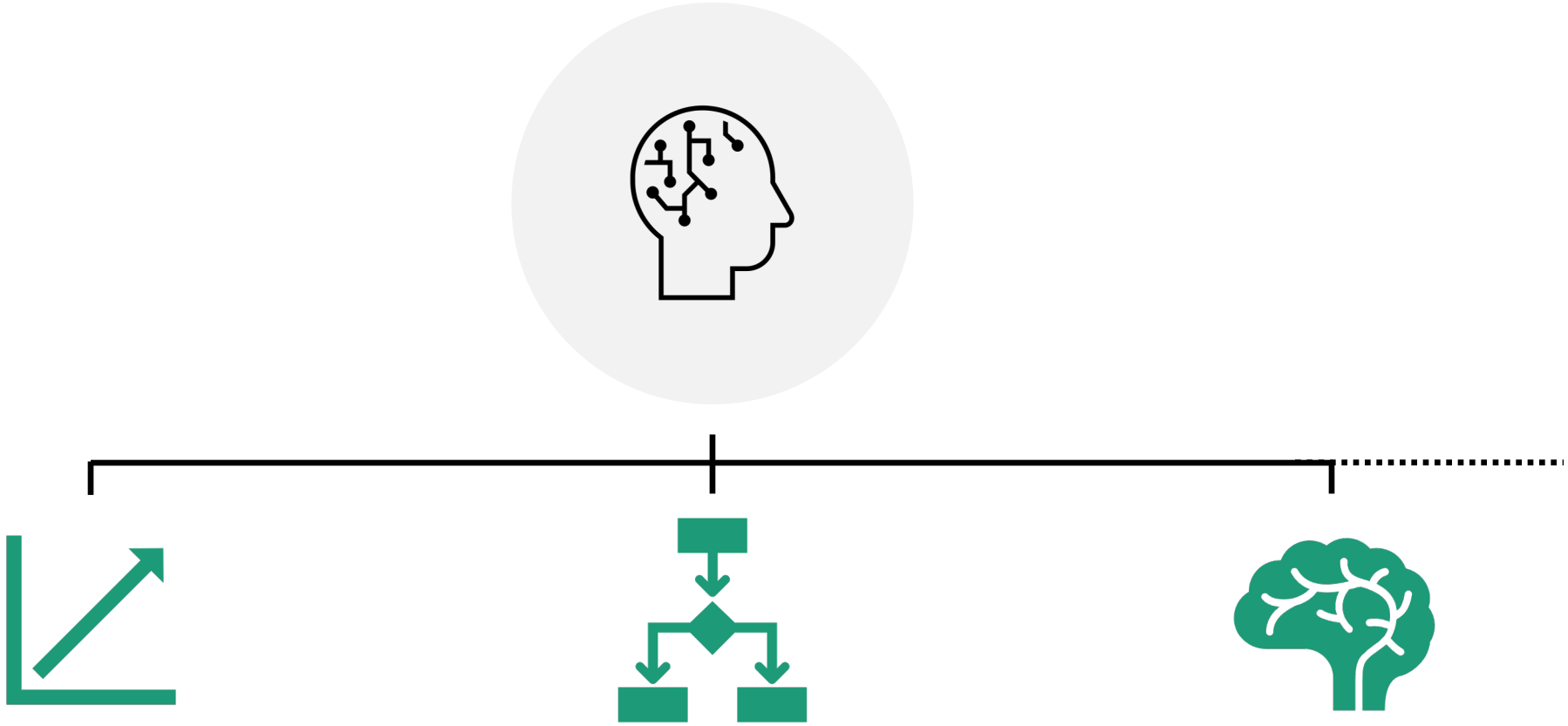
Two main approaches

MACHINE LEARNING

PKPD MODELLING

PKPD: Pharmacokinetic and pharmacodynamic

MIPD using machine learning



Linear regression

Decision trees

Neural networks

Linear regression

REGRESSOR

MAINTENANCE DOSE

$$Y = \sum_{k=1}^{K} X_k \beta_k + \varepsilon$$

PREDICTORS

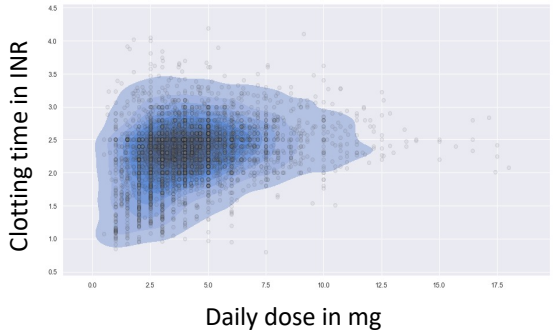
VKORC1

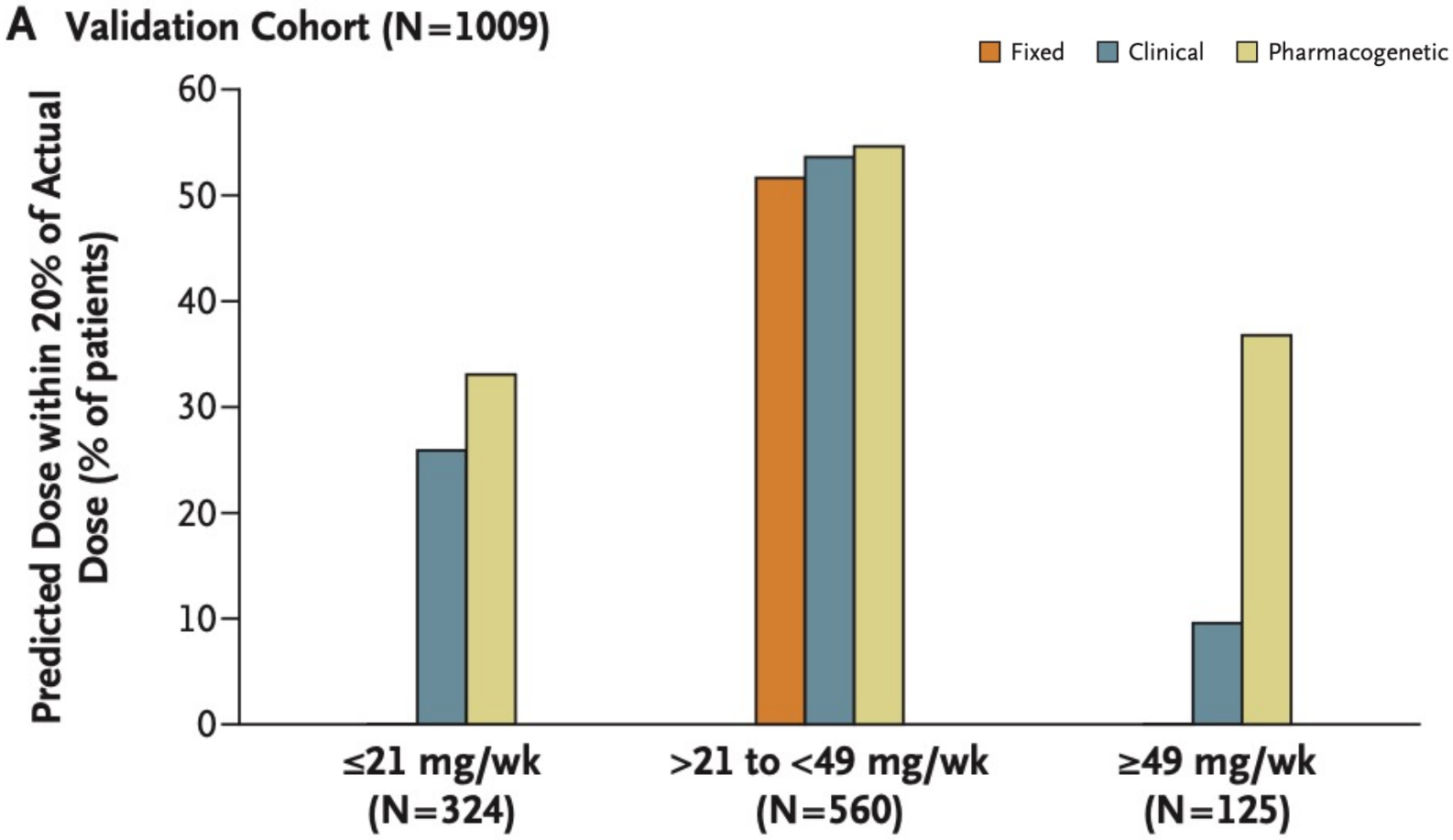
CYP2C9

Age

Target INR

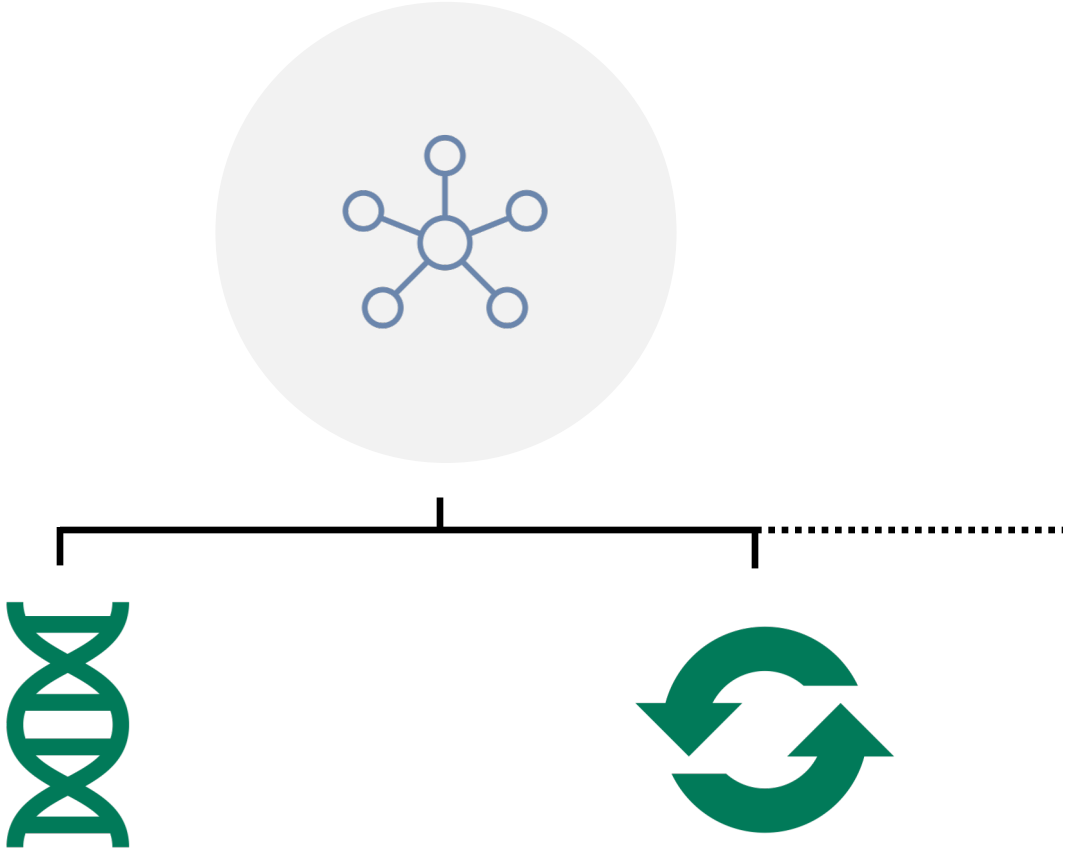
Linear regression: performance





International Warfarin Pharmacogenetics Consortium. New England Journal of Medicine. 2009 Feb 19;360(8):753-64.

MIPD using PKPD modelling

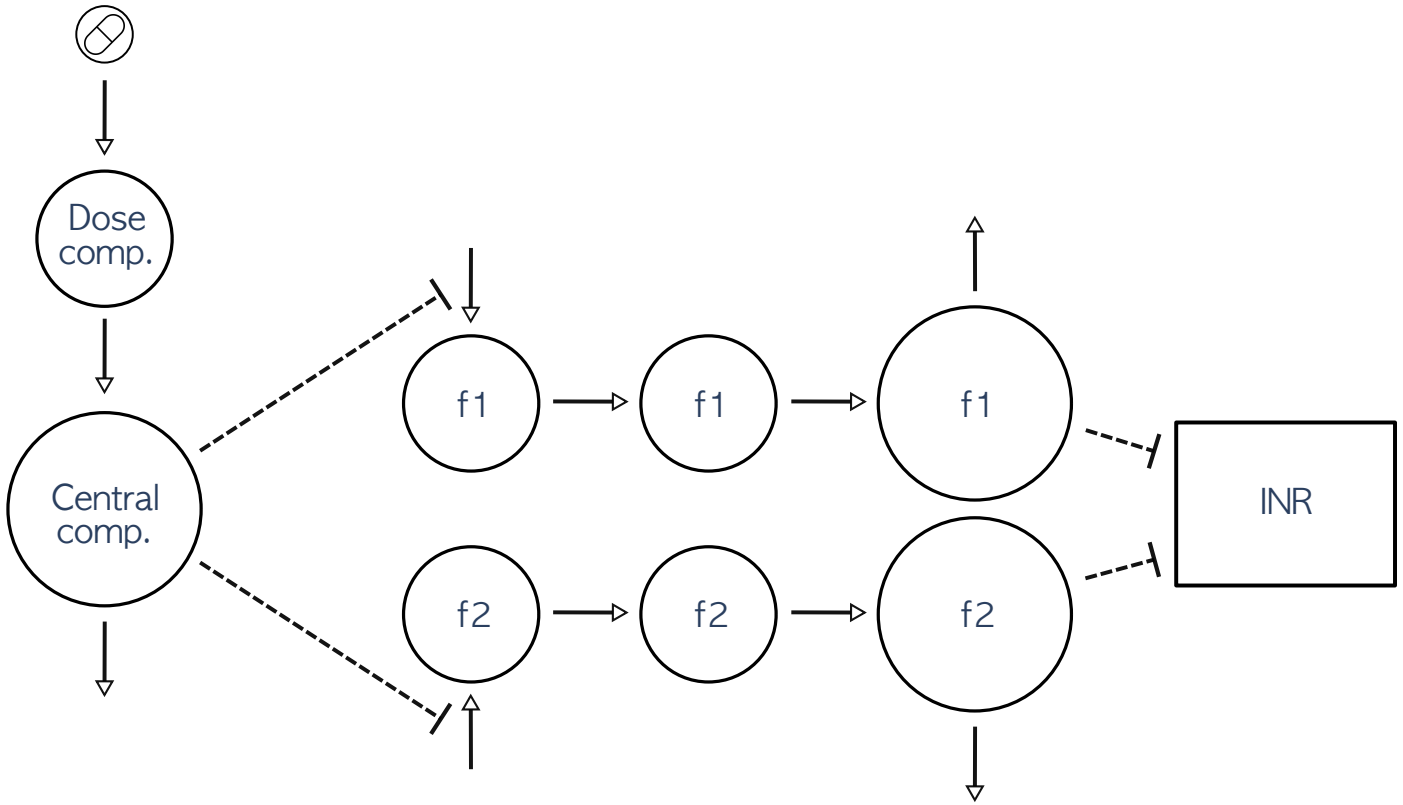


Covariate-based dosing regimen optimisation

Bayesian dosing regimen optimisation

PKPD modelling

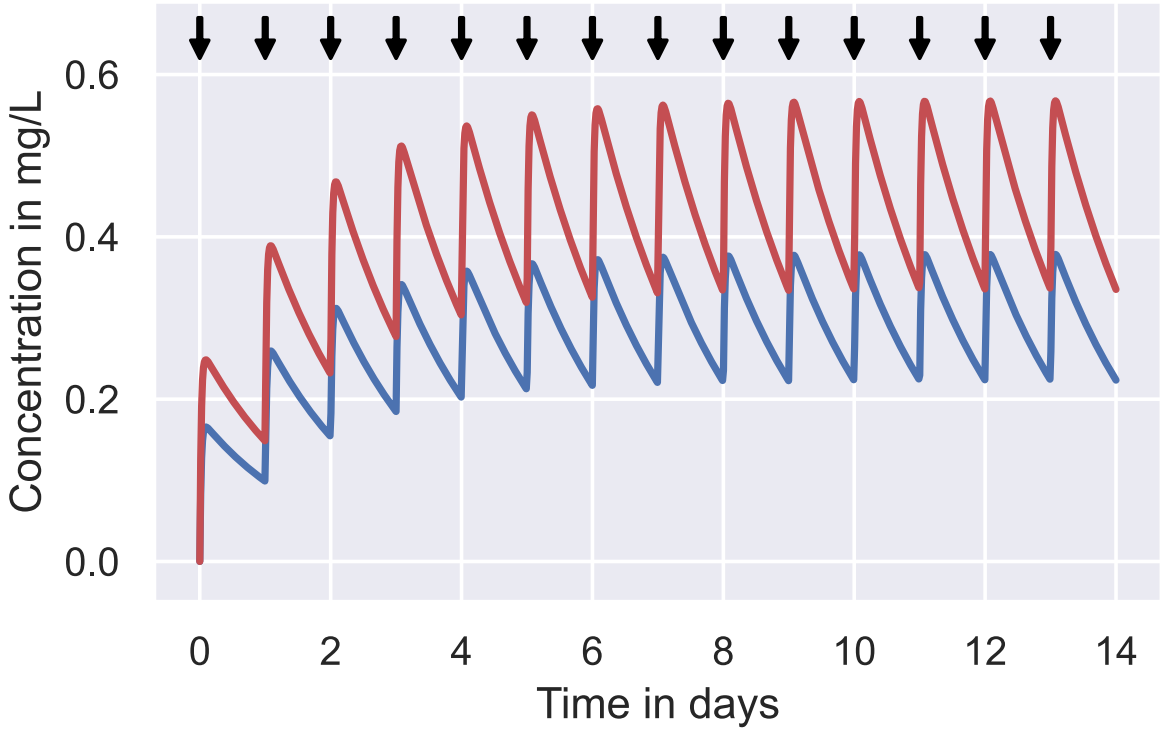
Semi-mechanistic models of treatment response

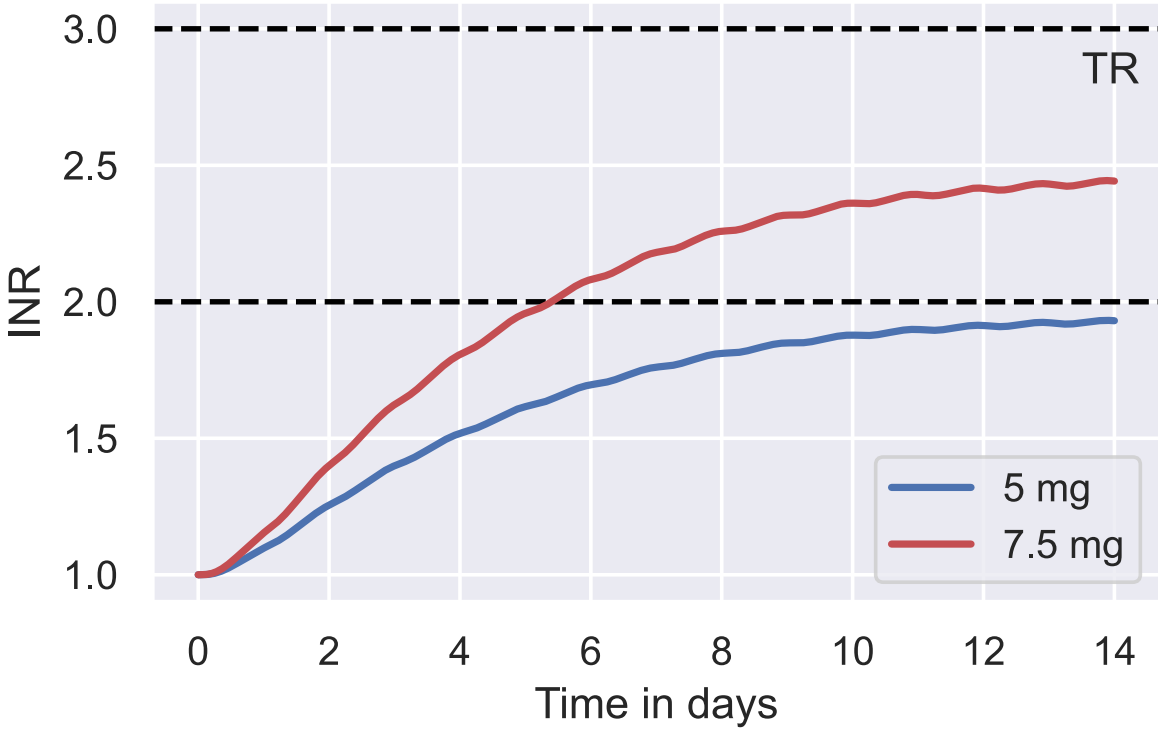


$\bar{y}(t, r, \psi)$

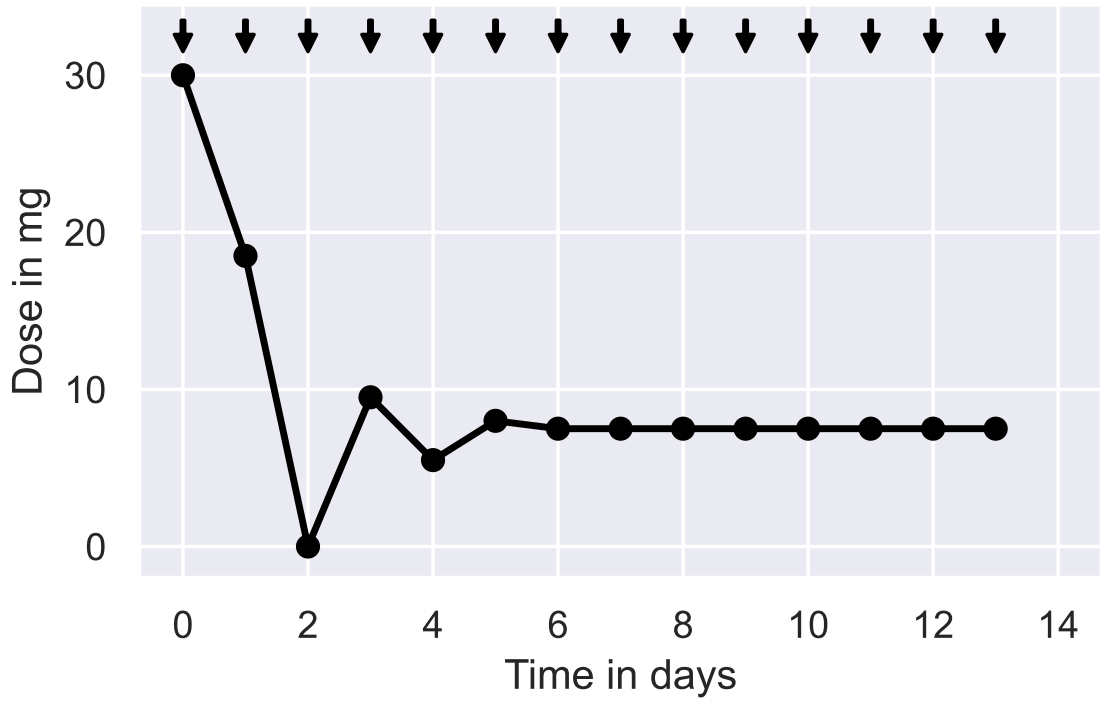
Hamberg et al. Clinical Pharmacology & Therapeutics. 2010 Jun;87(6):727-34.

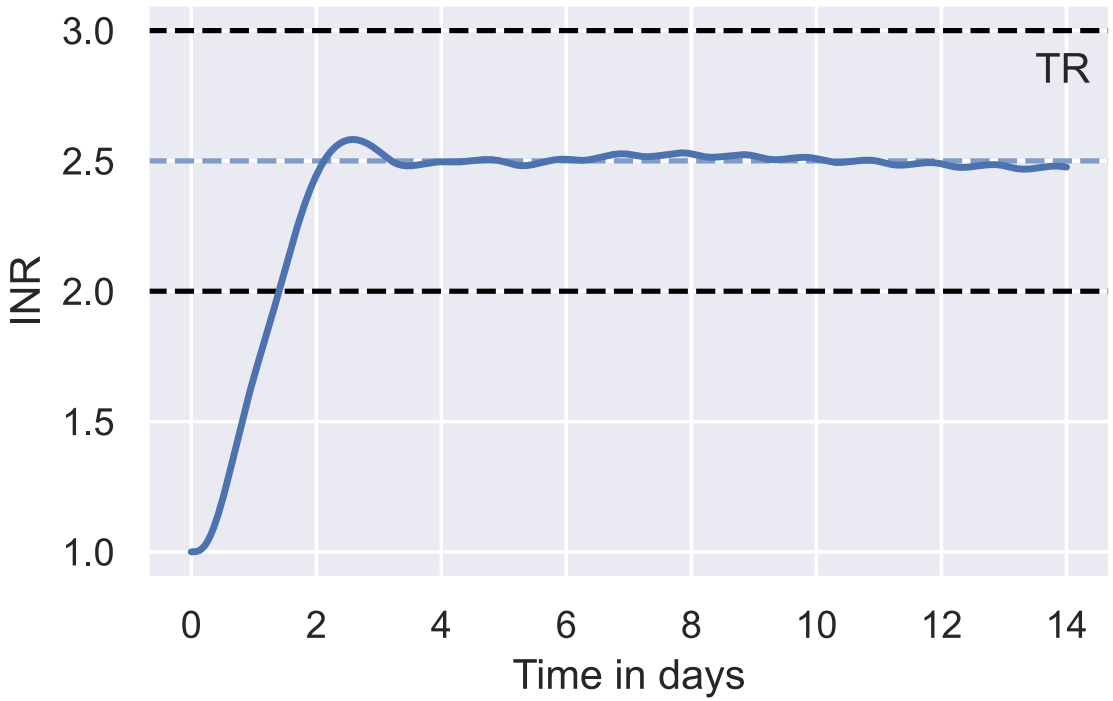
Predictions of PKPD models





$\bar{y}(t, r, \psi)$



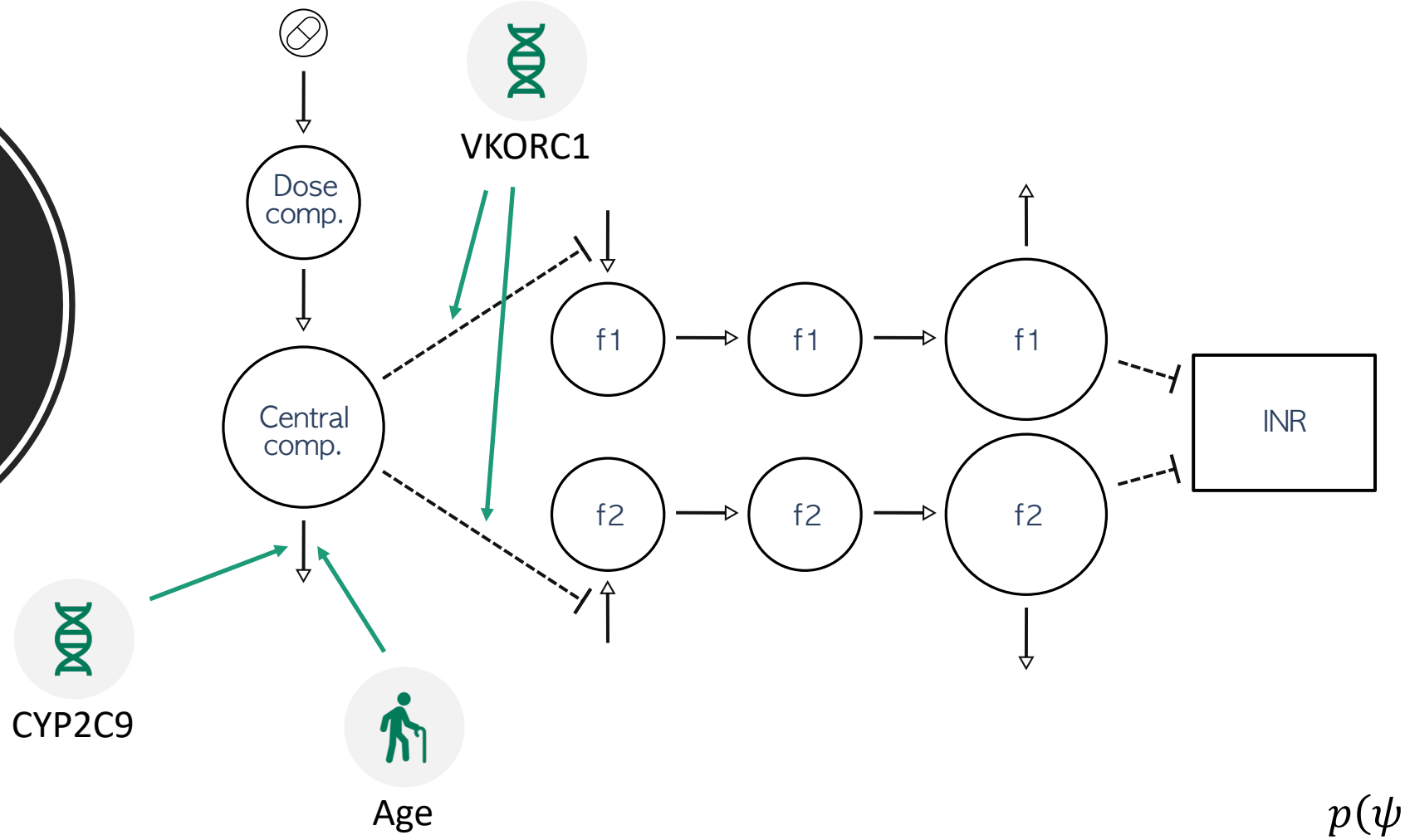


Optimise dosing regimen to target desired treatment response

$$MSE = \sum_{j=1}^{n} \left(\bar{y}(t_j, r, \psi) - y_j^*\right)^2$$

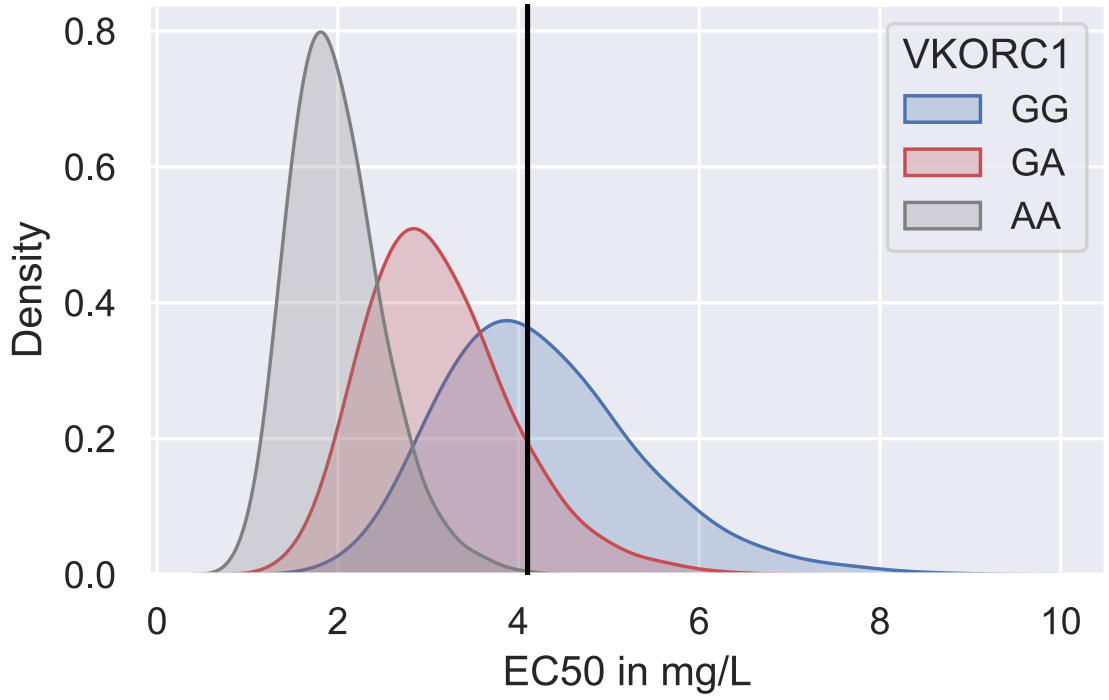
Explained and unexplained variability

Nonlinear mixed effects model



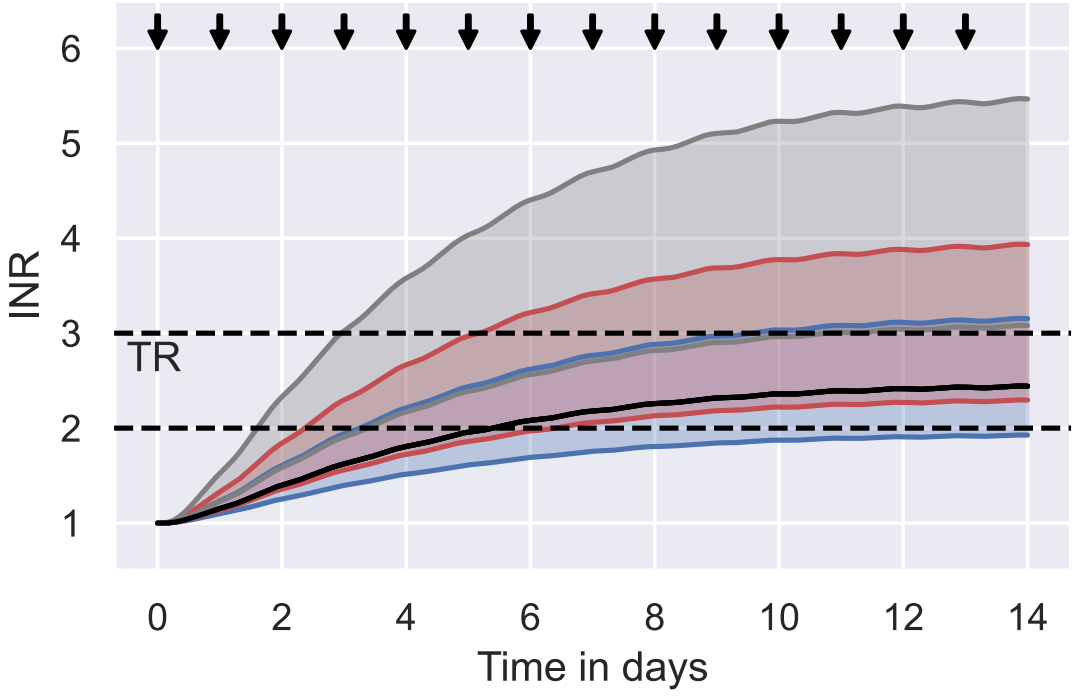
$p(\psi \mid \theta, \chi)$

POPULATION DISTRIBUTION OF EC50



$p(\psi \mid \theta, \chi)$

PREDICTIONS FOR DIFFERENT EC50 VALUES

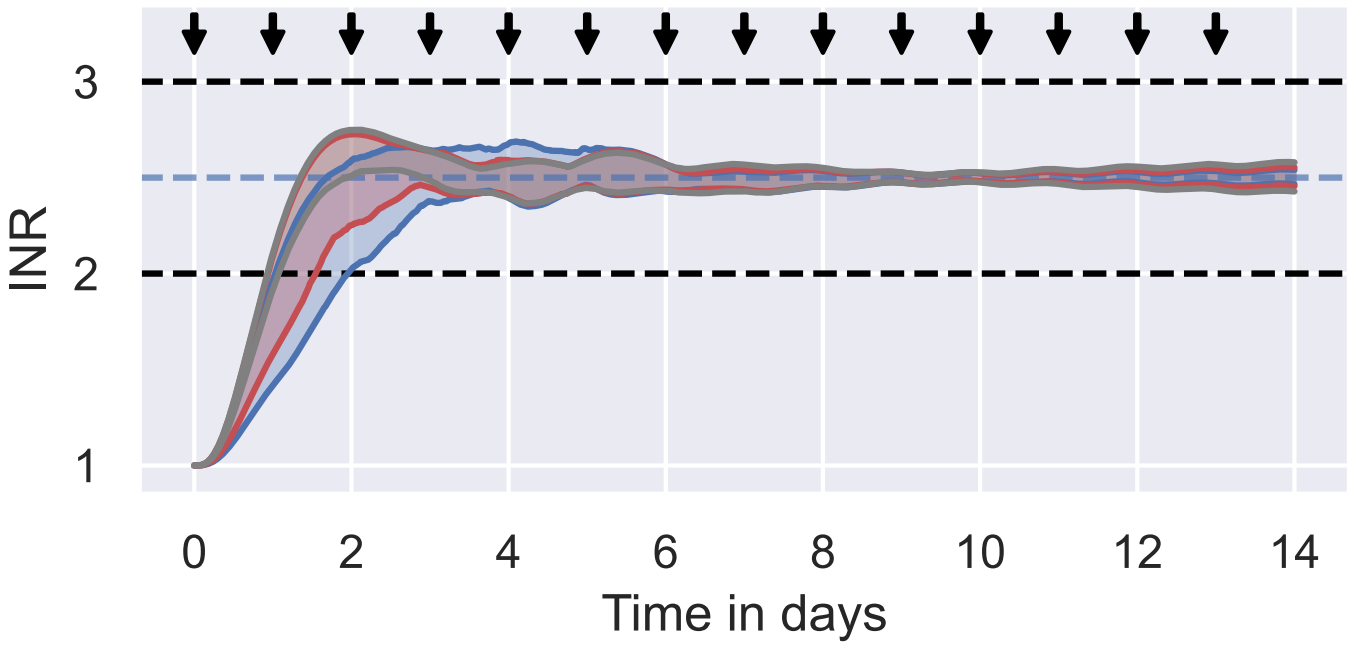


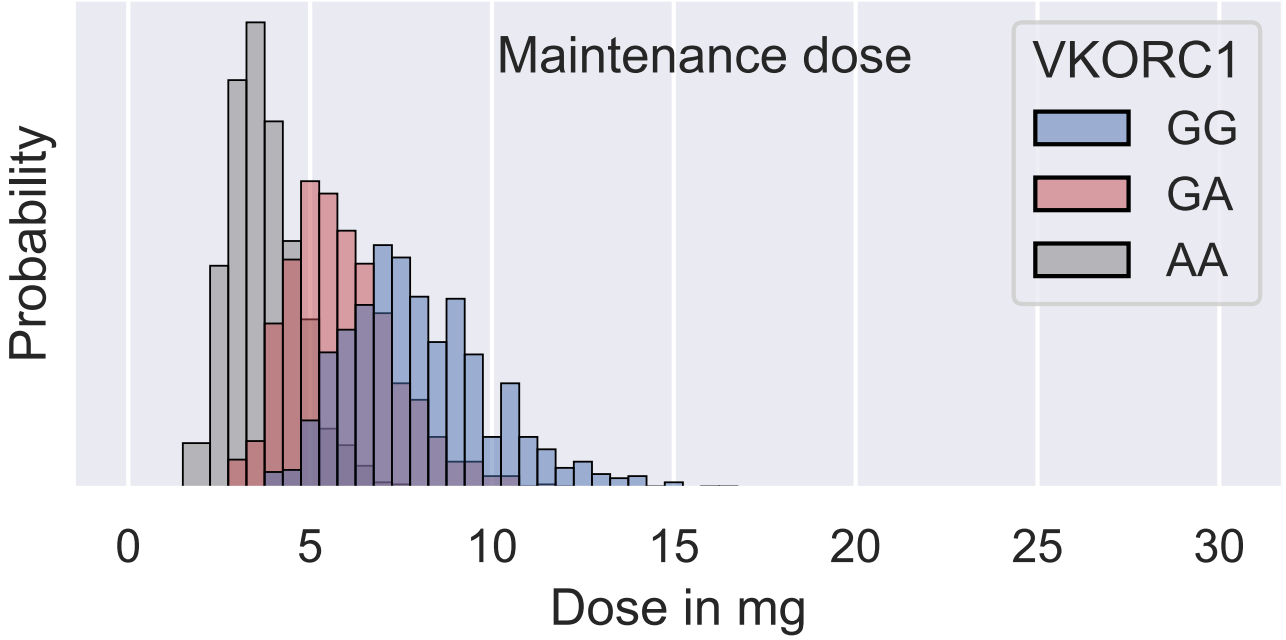
$\bar{y}(t, r, \psi)$

Inter-individual variability in PKPD models

VKORC1

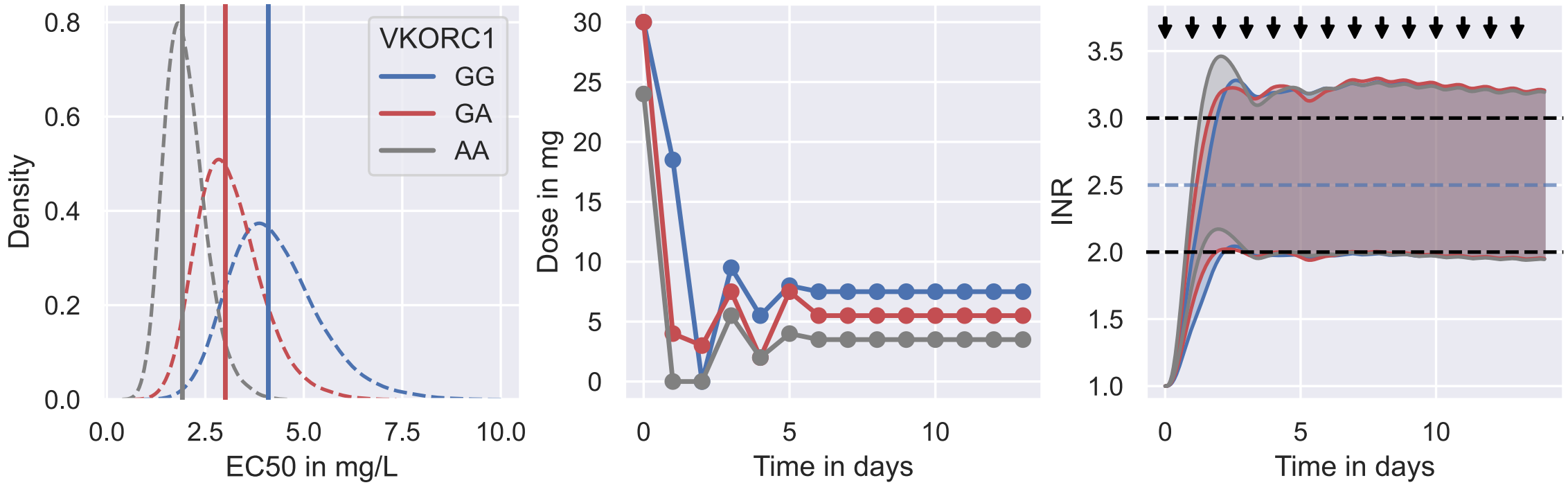
Variability of optimal treatment strategy





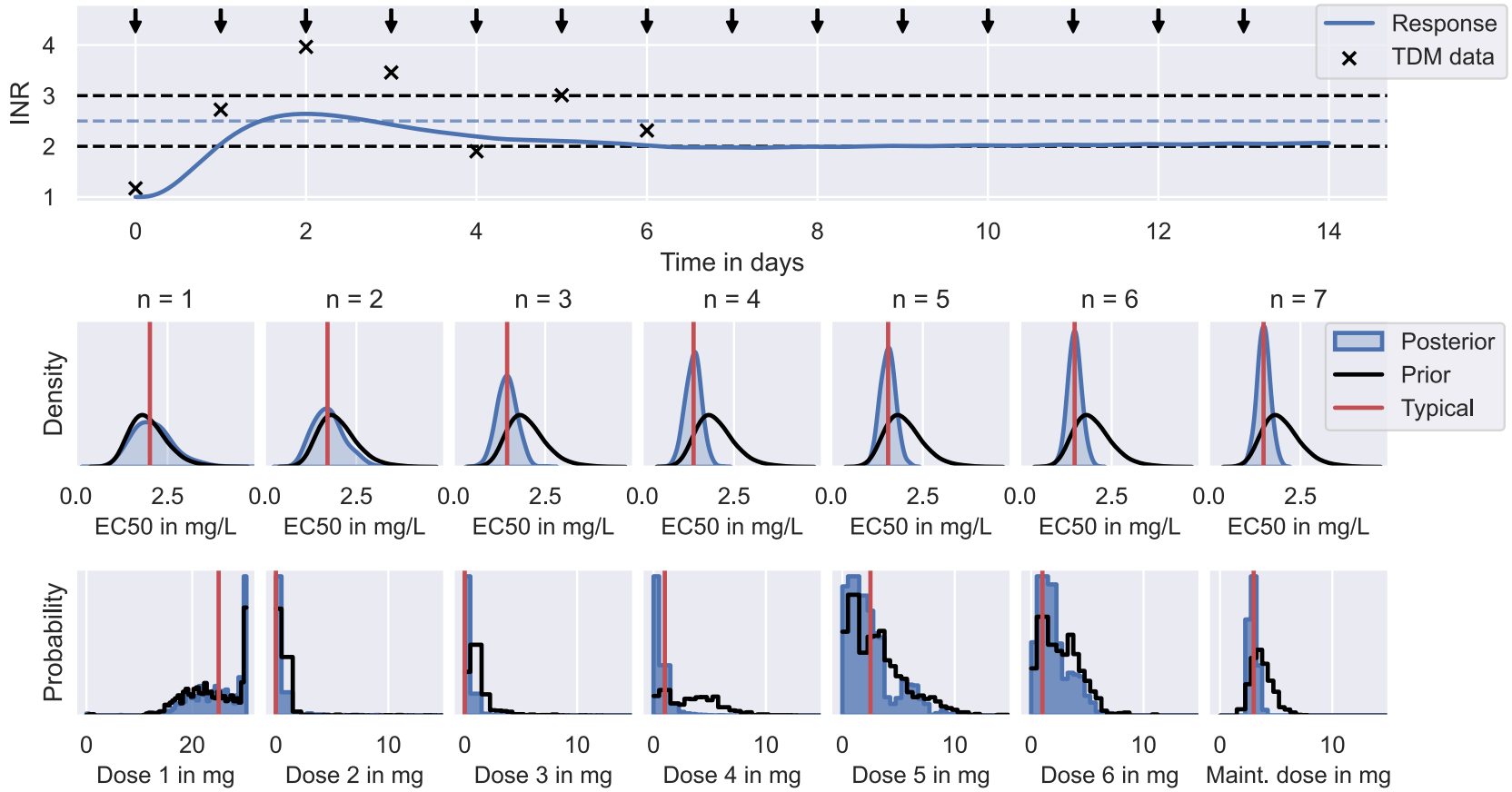
PKPD models can predict individualised dosing regimens

How do we know which model parameters to use?



Covariate-based dosing regimen optimisation

$$\hat{\psi} = \mathbb{E}[\psi \mid \theta, \chi]$$



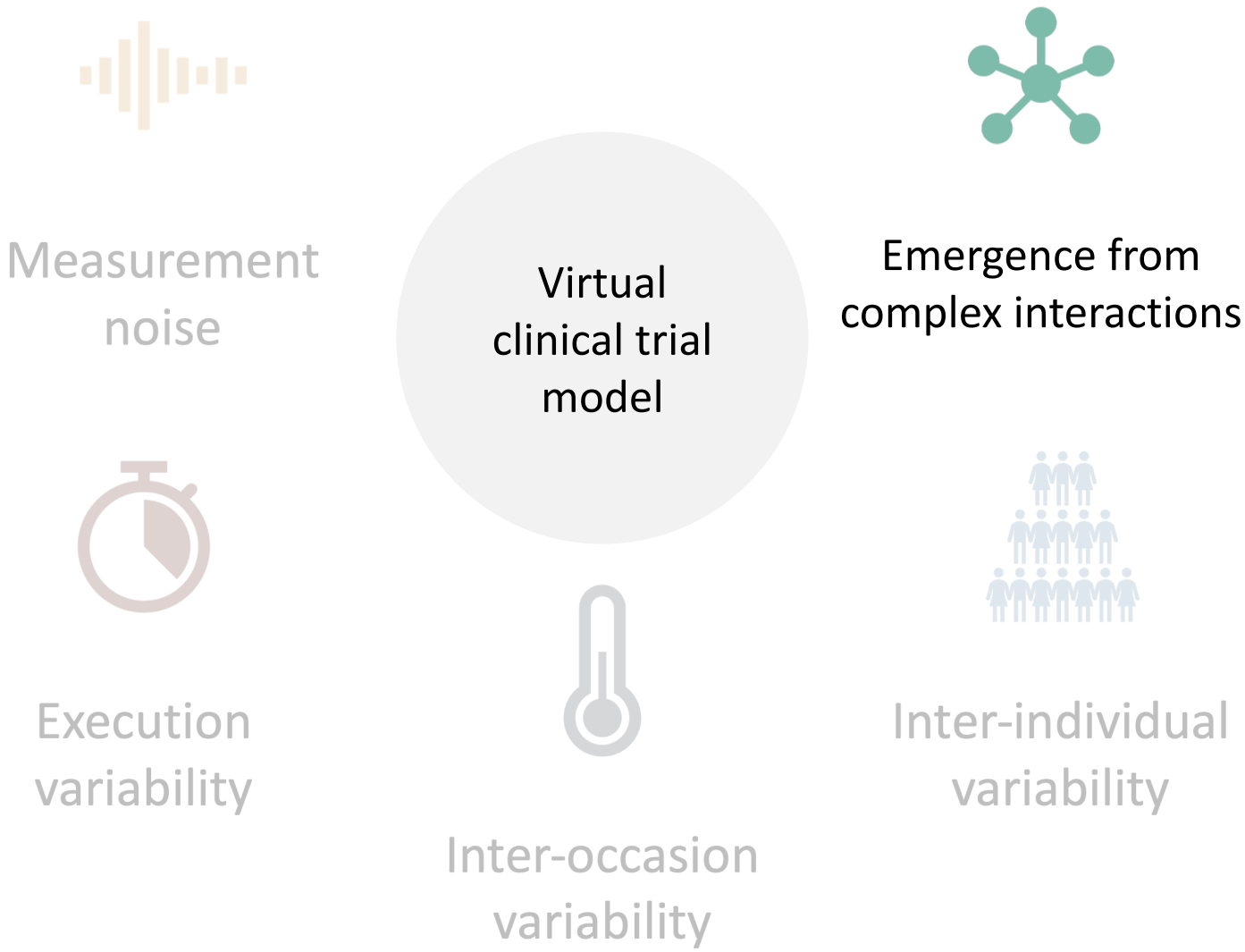
Bayesian dosing regimen optimisation

$$p(\psi|\theta,\chi) \longrightarrow p(\psi|\mathcal{D},\chi)$$

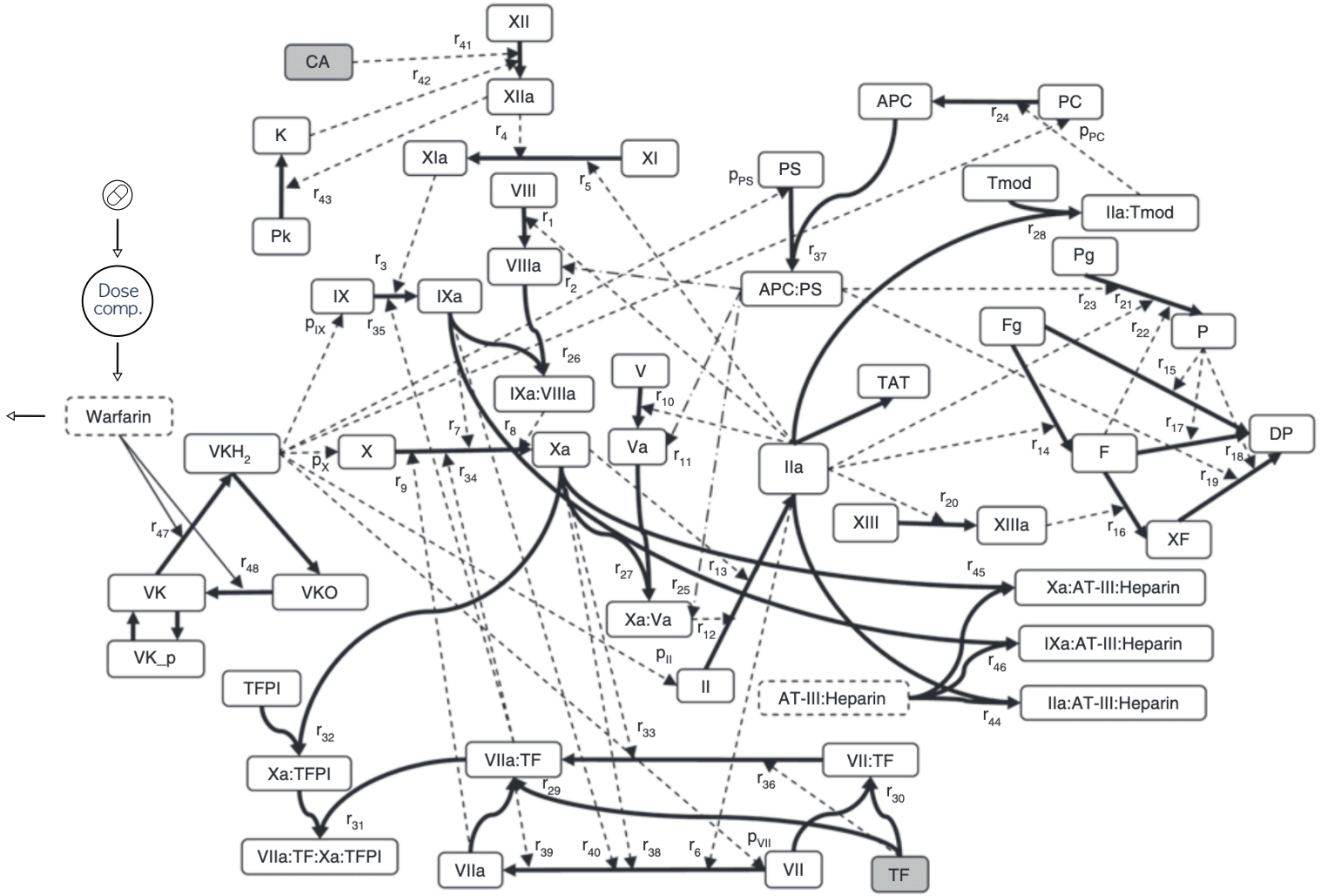
$$\hat{\psi} = \mathbb{E}[\psi \mid \mathcal{D},\chi]$$

How do we test MIPD?

Perform virtual clinical trials



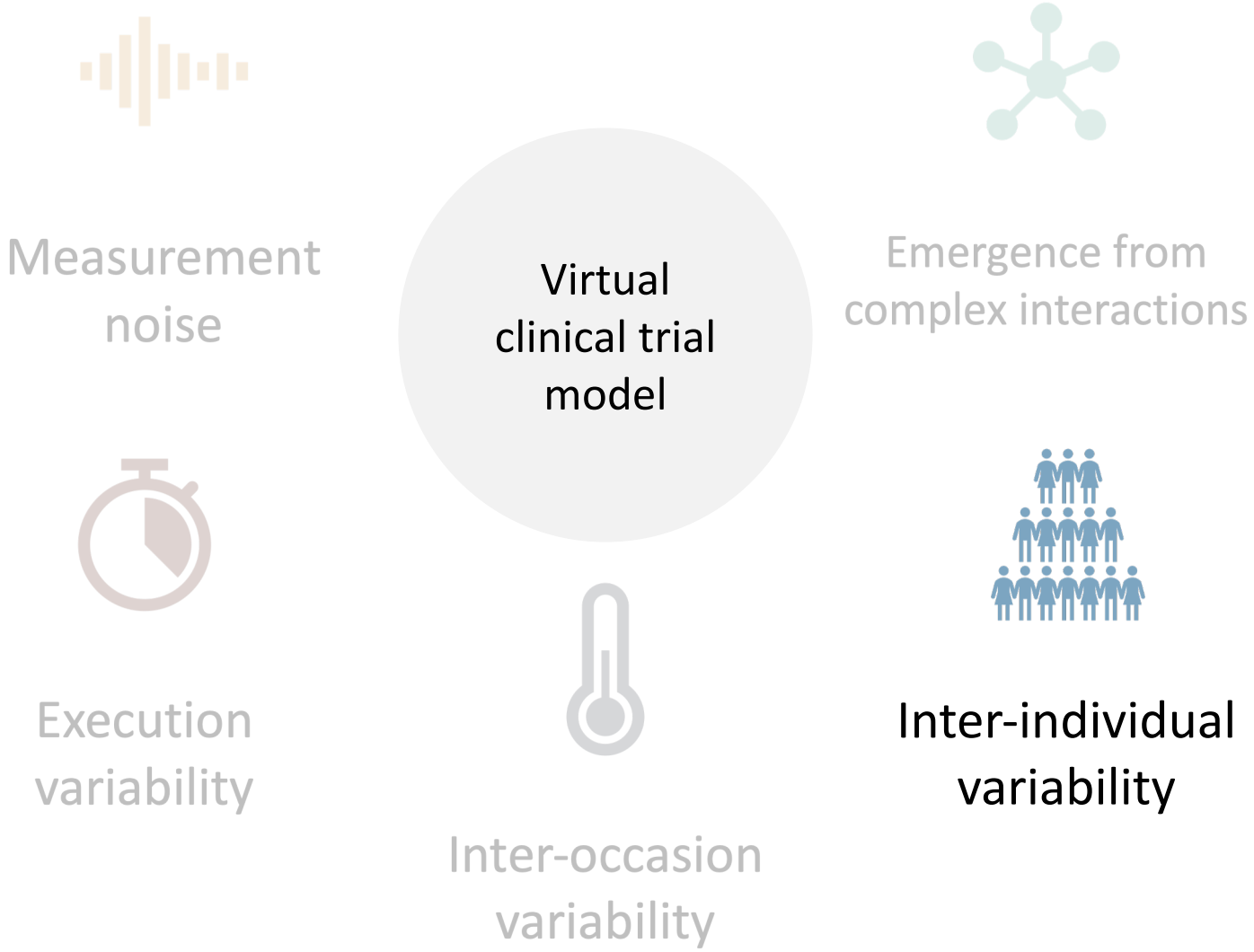
Emergence from complex interactions



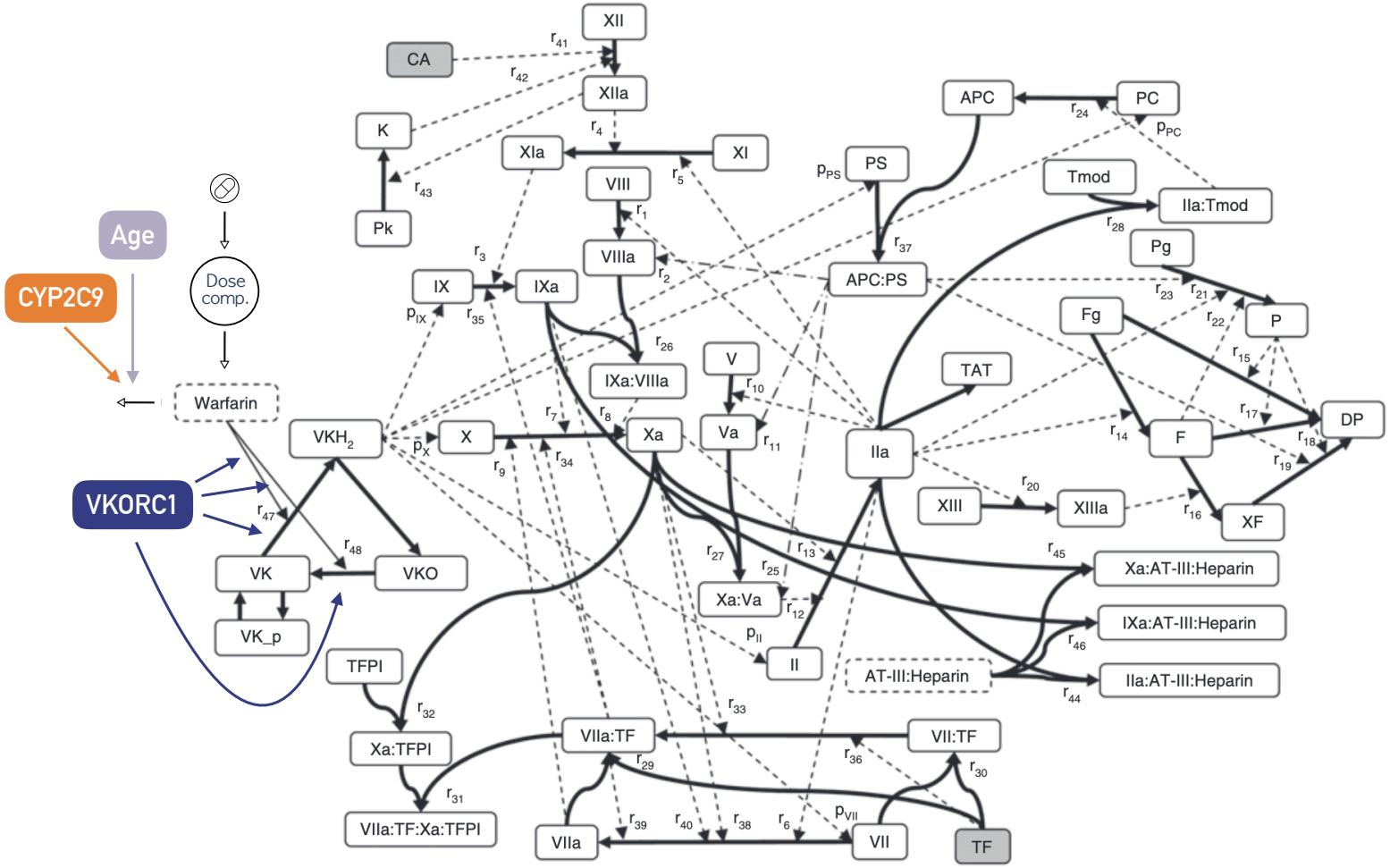
Wajima T, Isbister GK, Duffull SB. Clinical Pharmacology & Therapeutics. 2009 Sep;86(3):290-8.

$\bar{y}(t, r, \psi)$

Perform virtual clinical trials



Inter-individual variability

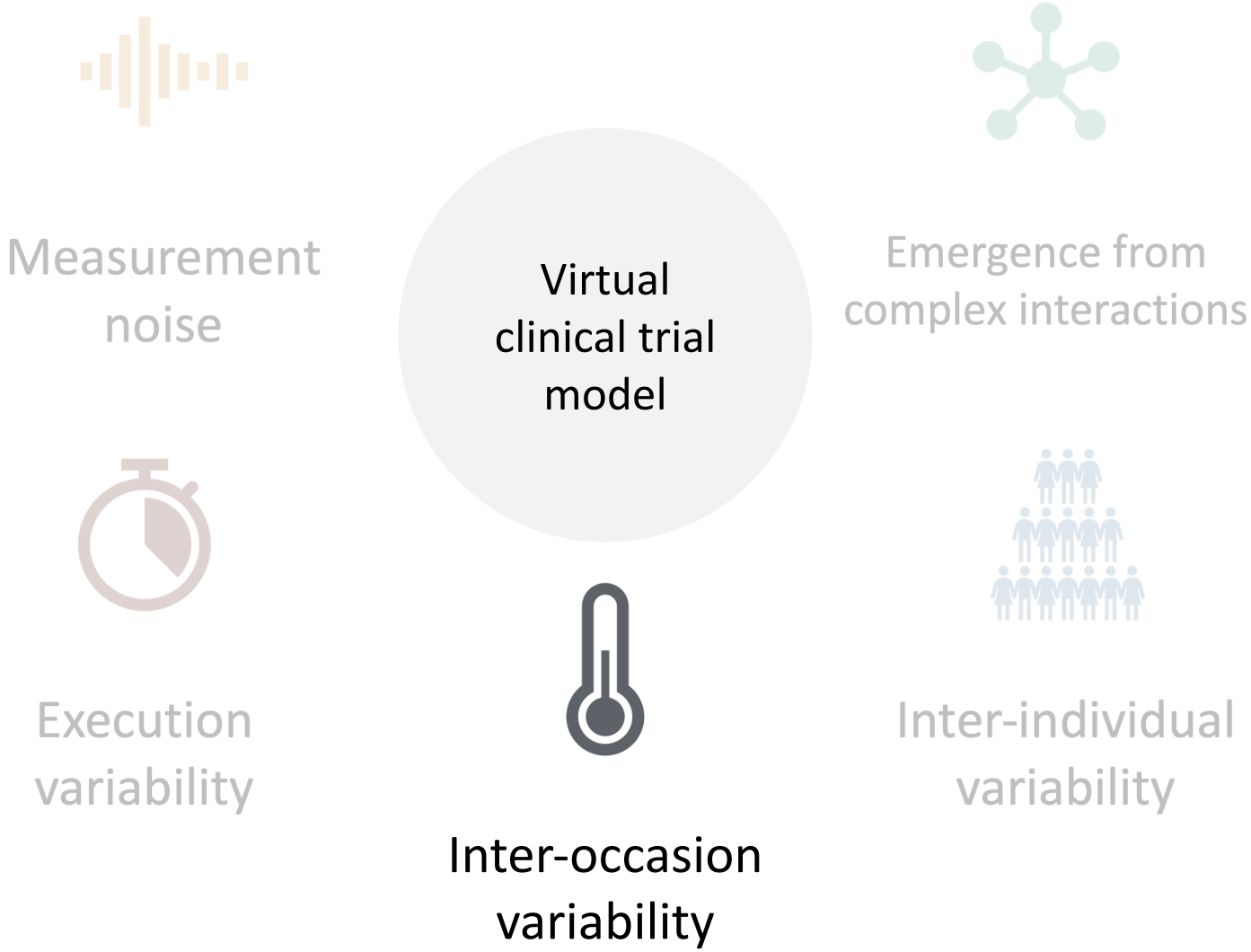


Explained & unexplained variability

$p(\psi \mid \theta, \chi)$

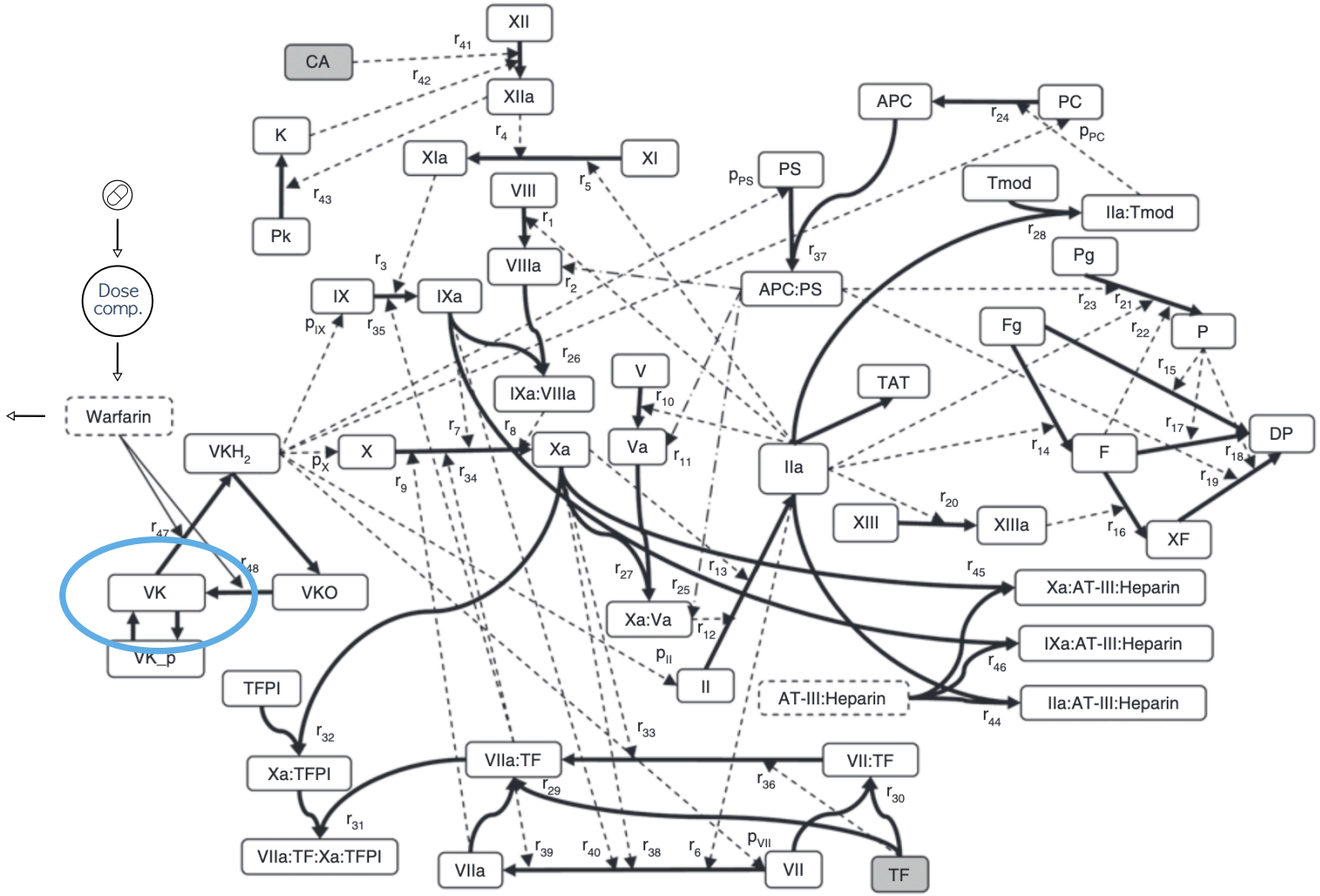
Hartmann S, Biliouris K, Lesko LJ, Nowak-Göttl U, Trame MN. Frontiers in Pharmacology. 2020 Jul 14;11:1041.

Perform virtual clinical trials

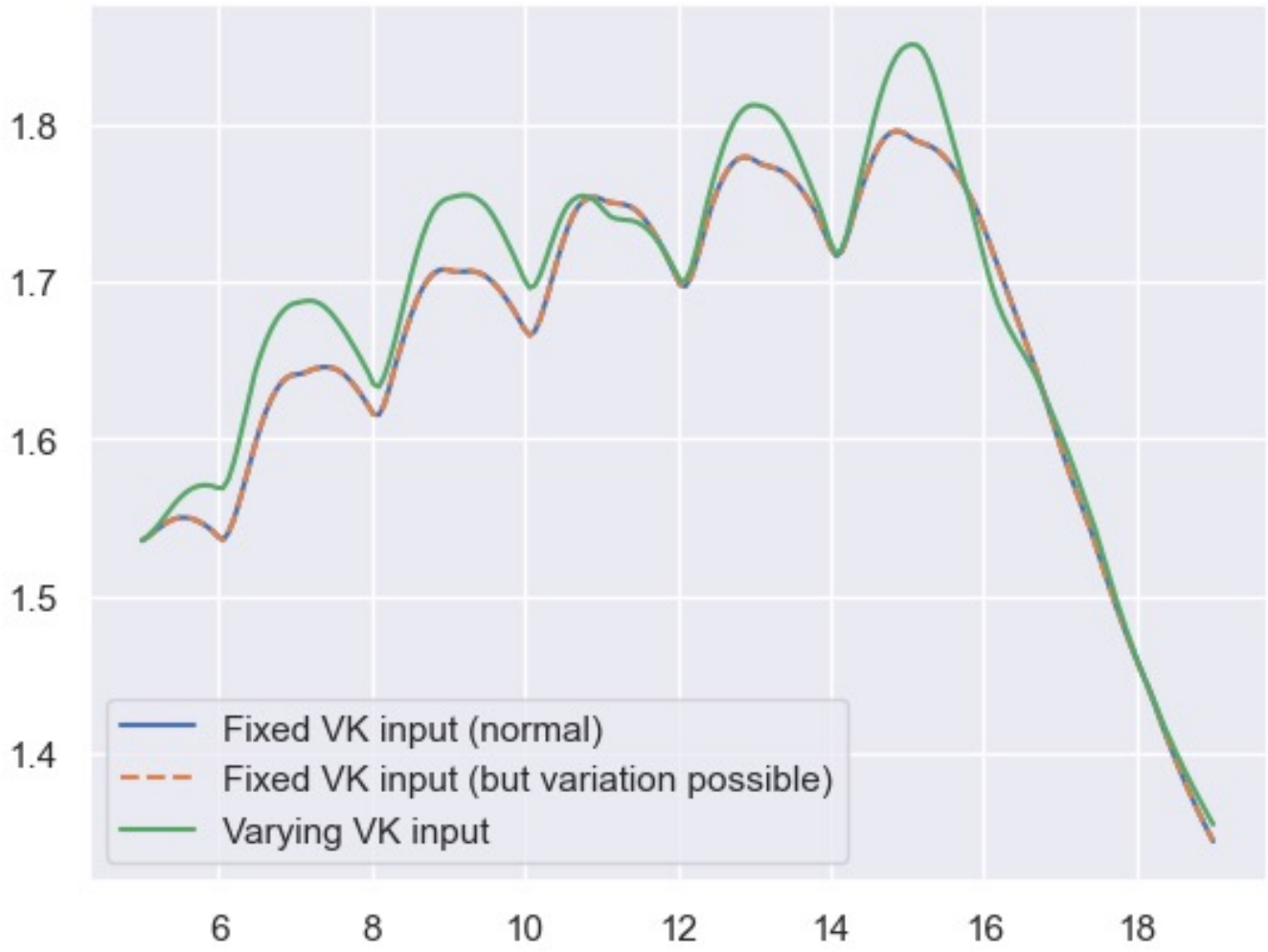


Inter-occasion variability

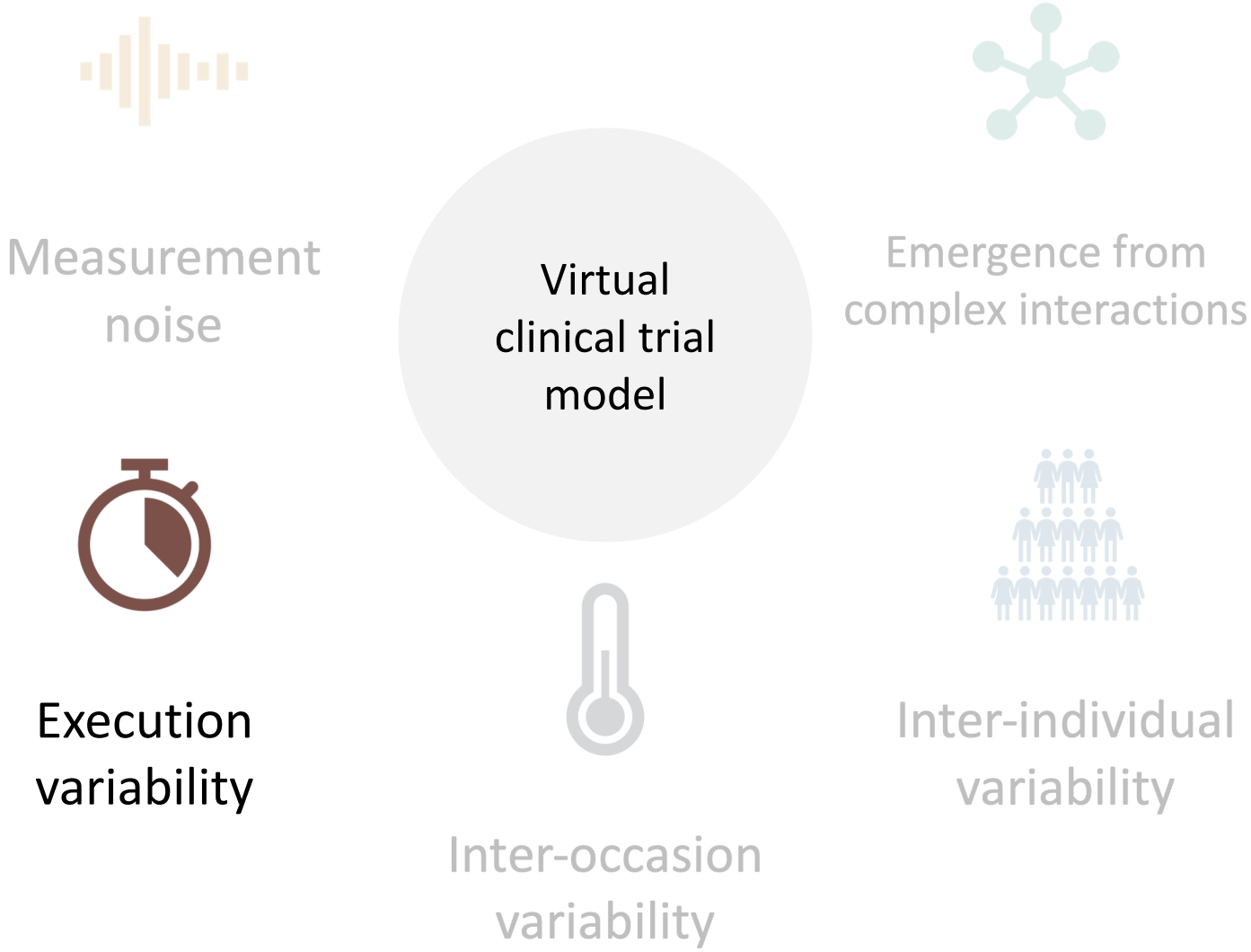
Time-varying vitamin K consumption



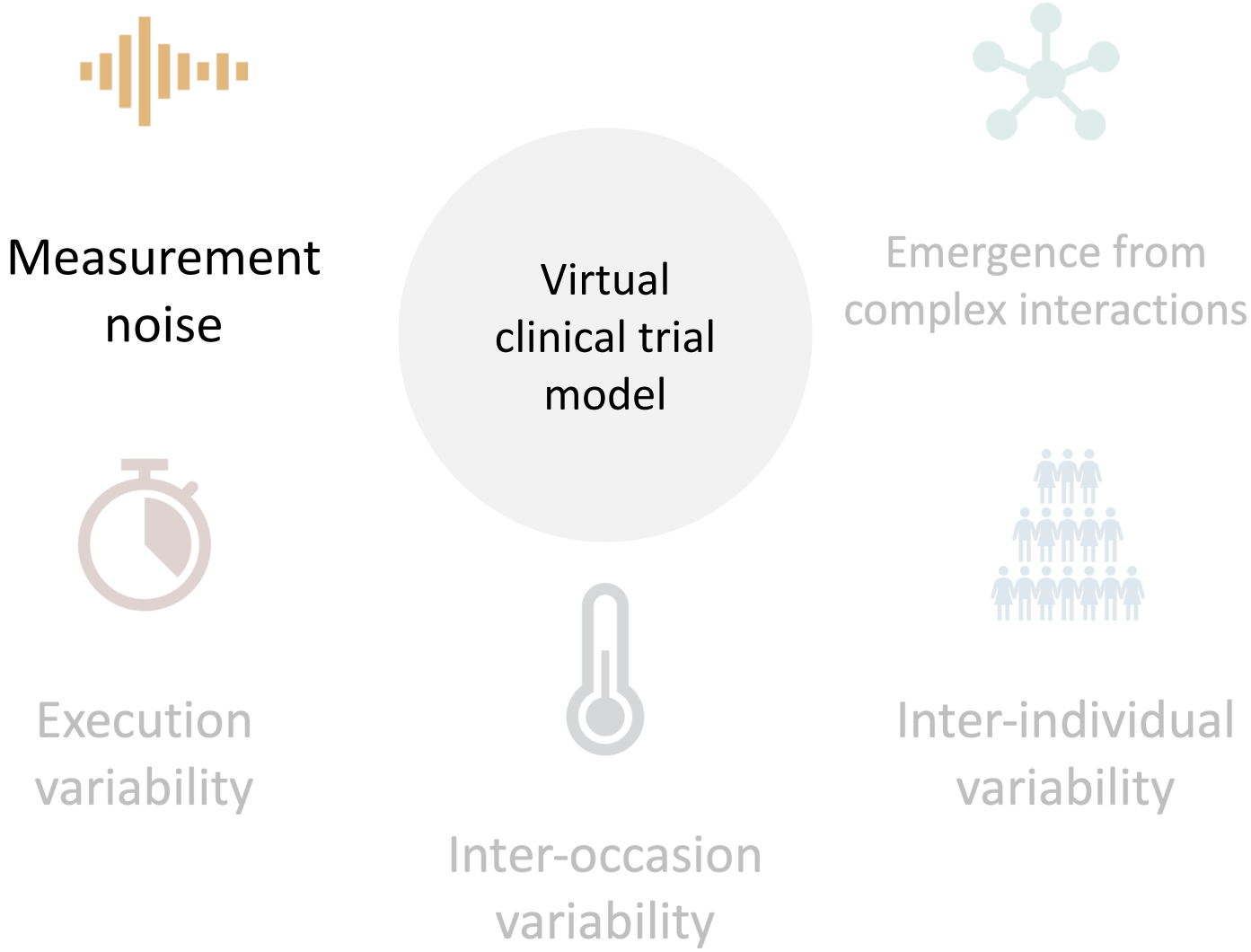
Inter-occasion variability



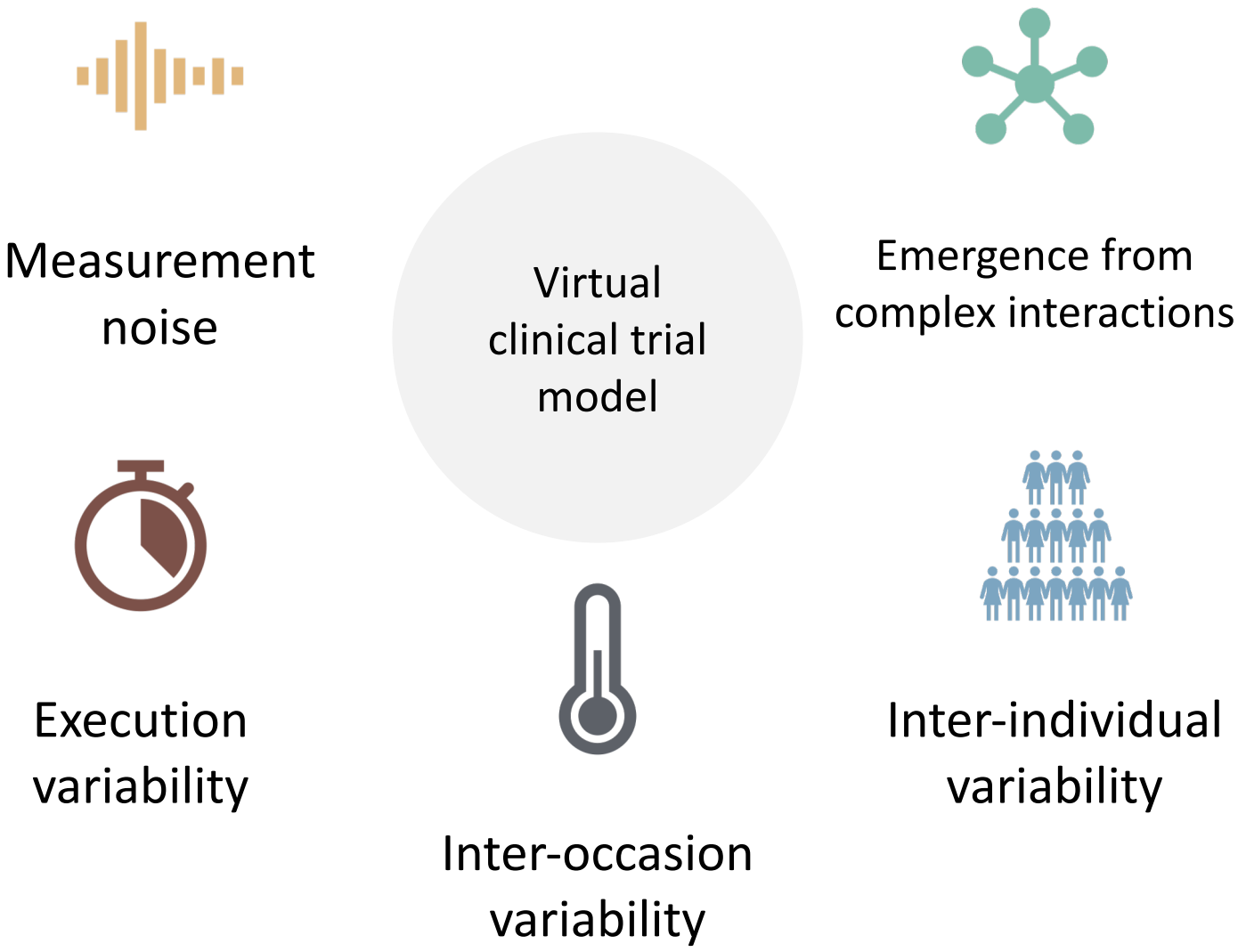
Perform virtual clinical trials



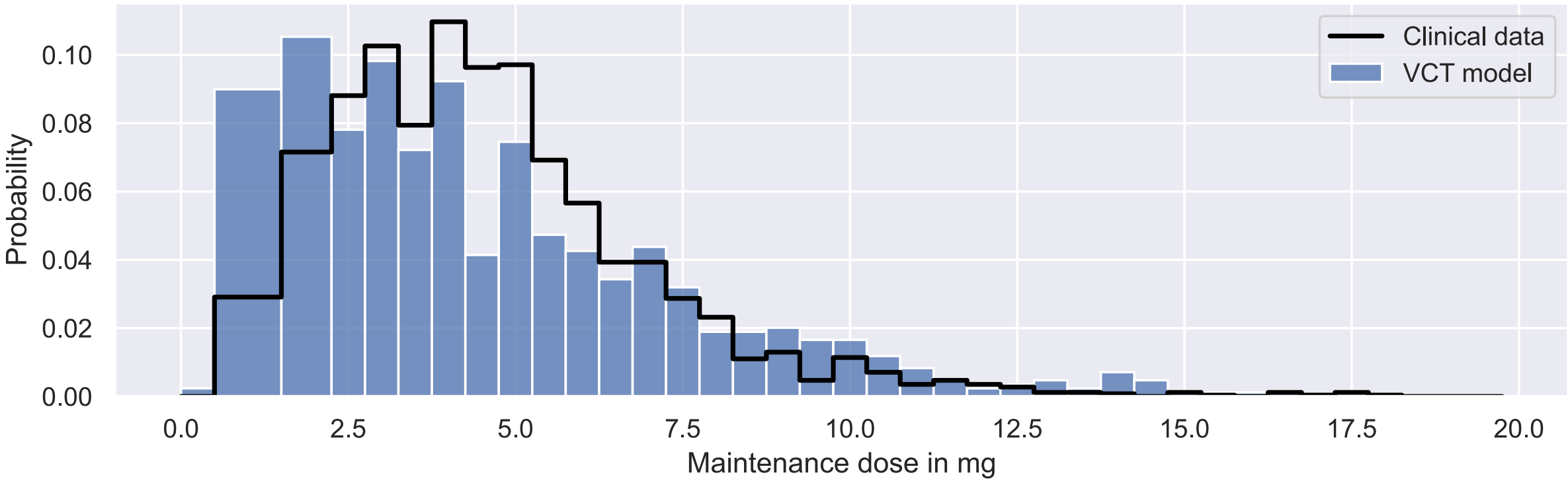
Perform virtual clinical trials



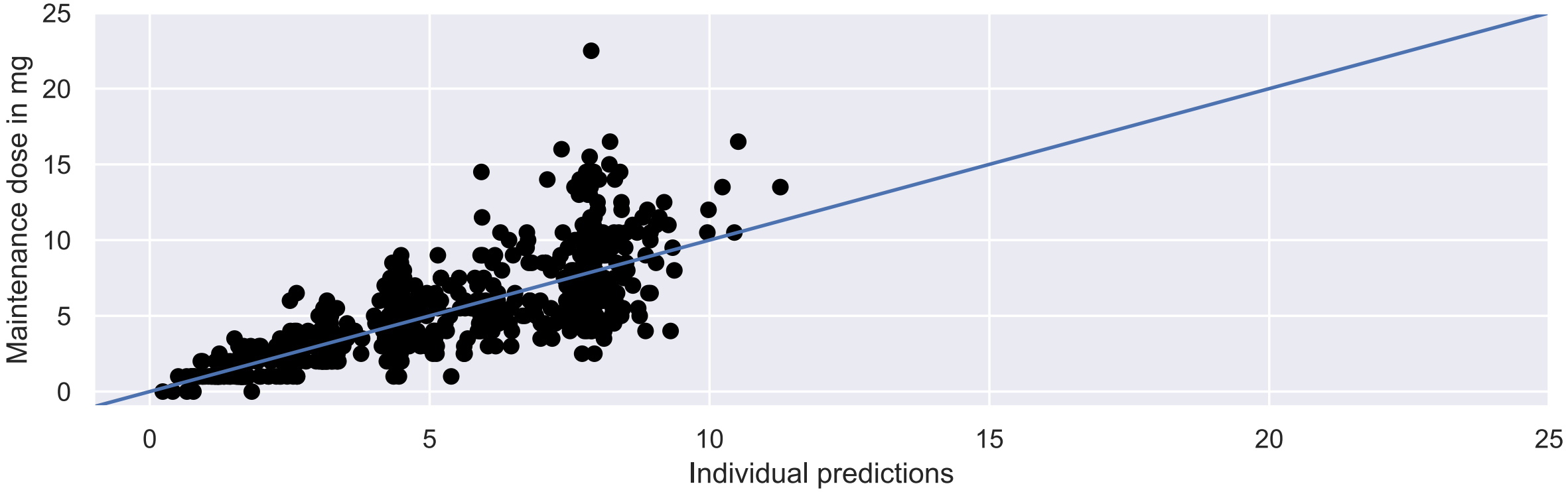
Perform virtual clinical trials



Model versus reality



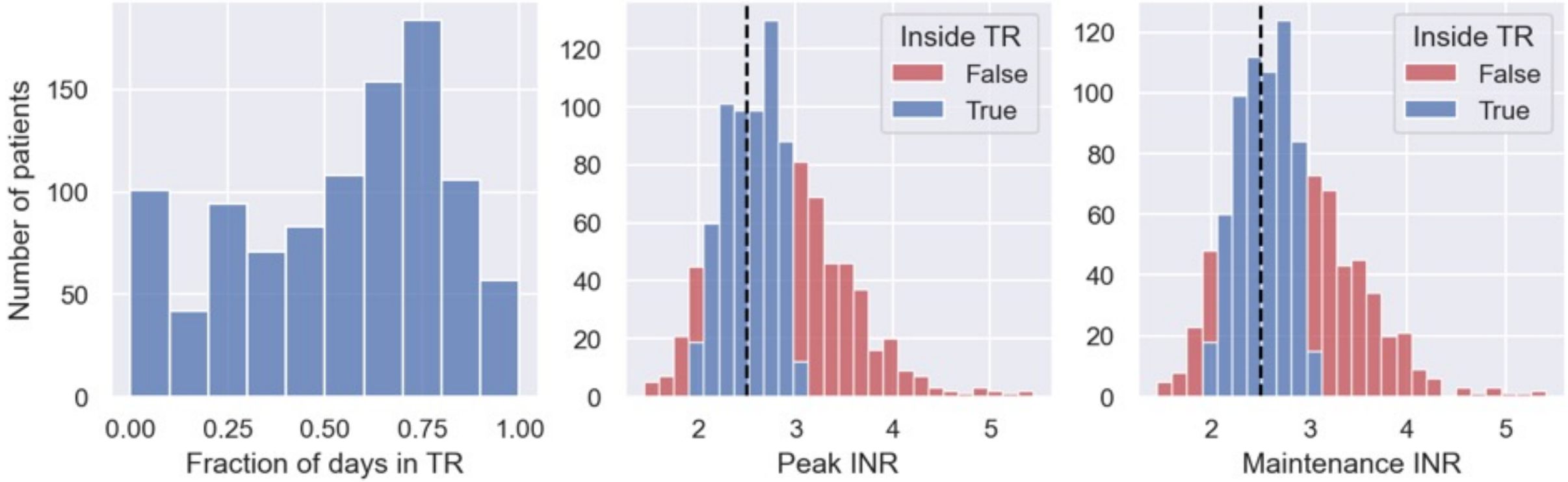
How well does MIPD work?



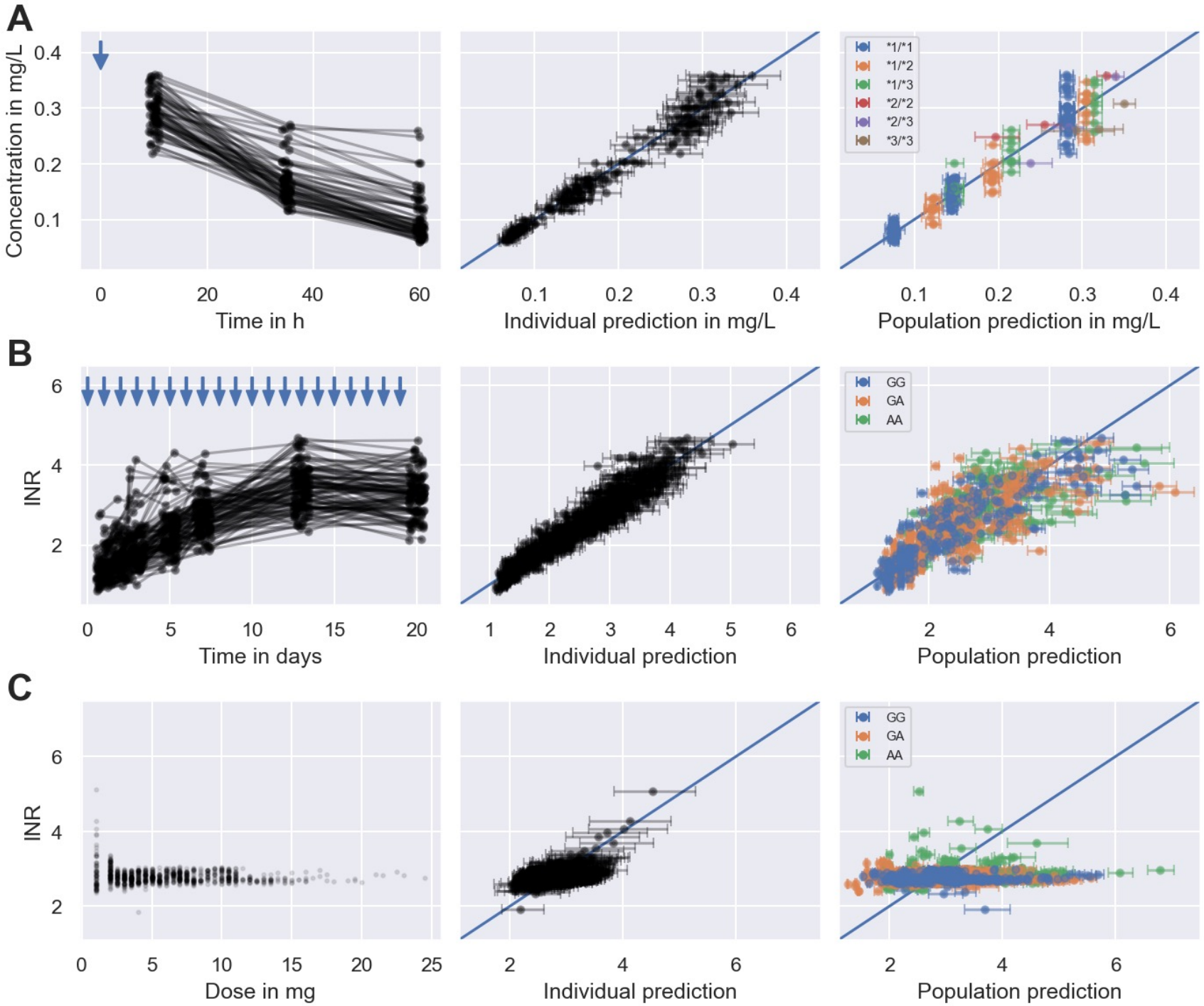
Calibration of linear regression model

$$\text{Obj. func.} = \sum_{i=1}^{N}\left(\sum_{k=1}^{K} X_{ik}\beta_k - y_i\right)^2 + \lambda \sum_{k=1}^{K} |\beta_k|$$

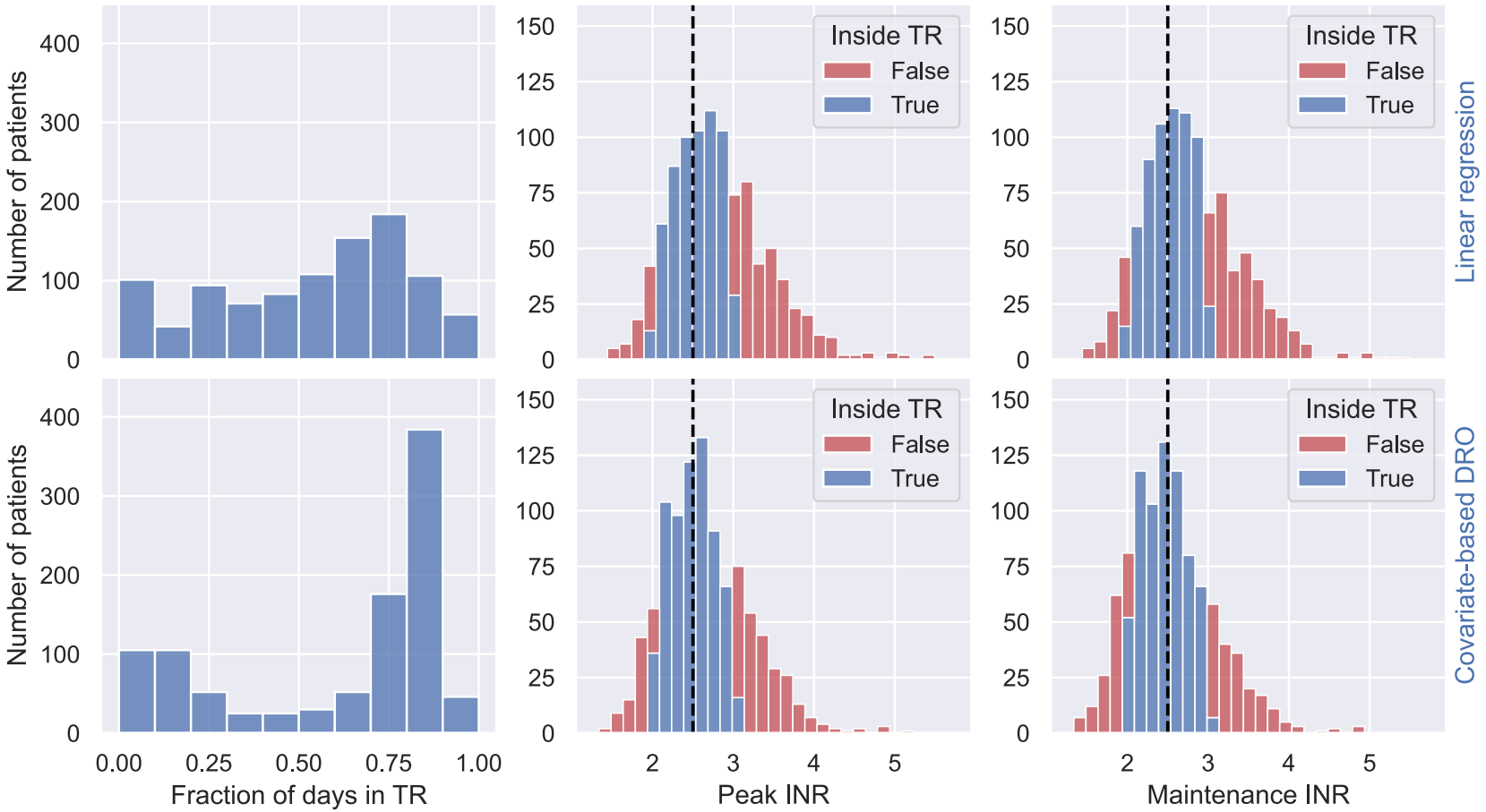
Virtual MIPD trial: linear regression



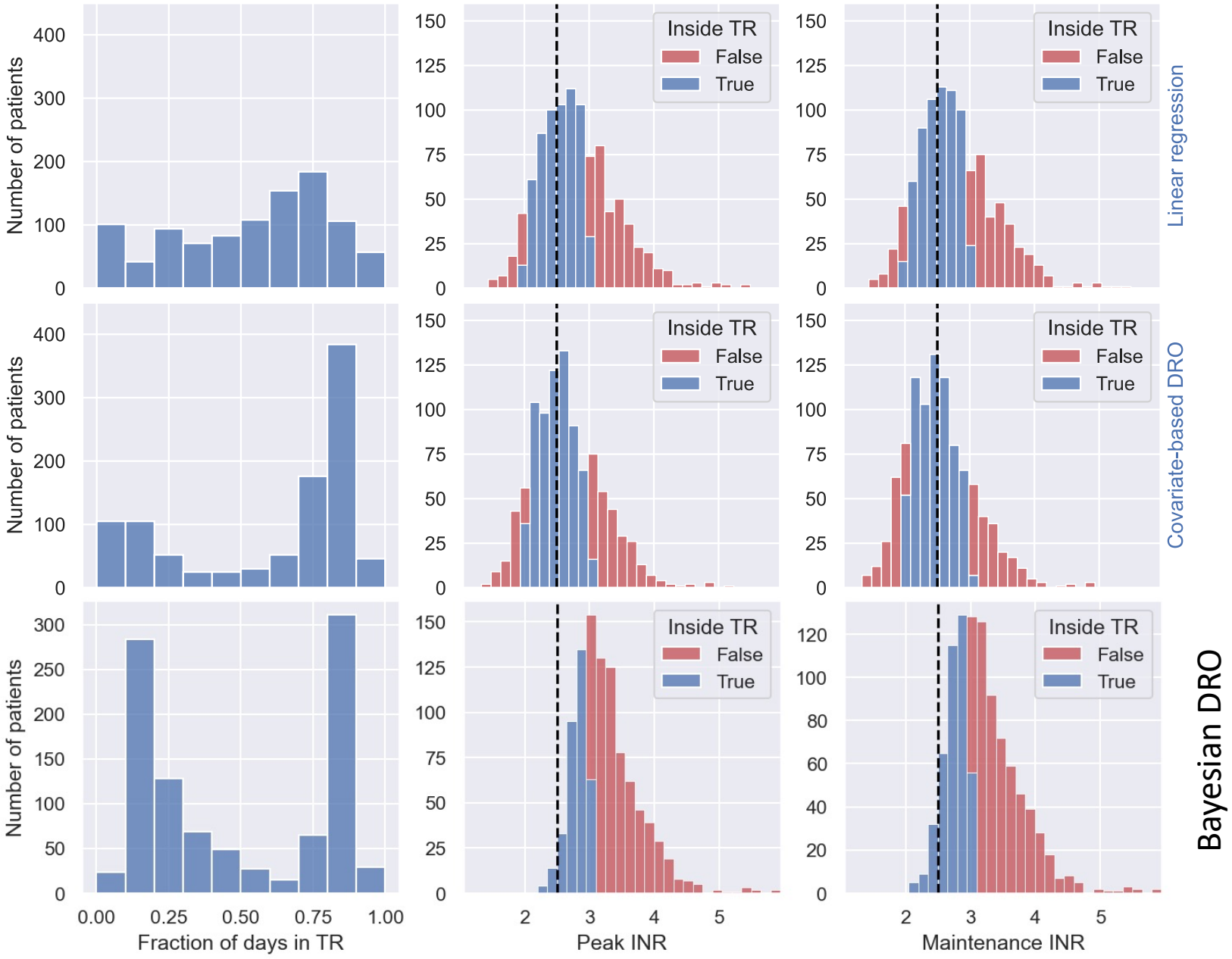
Calibration of PKPD model

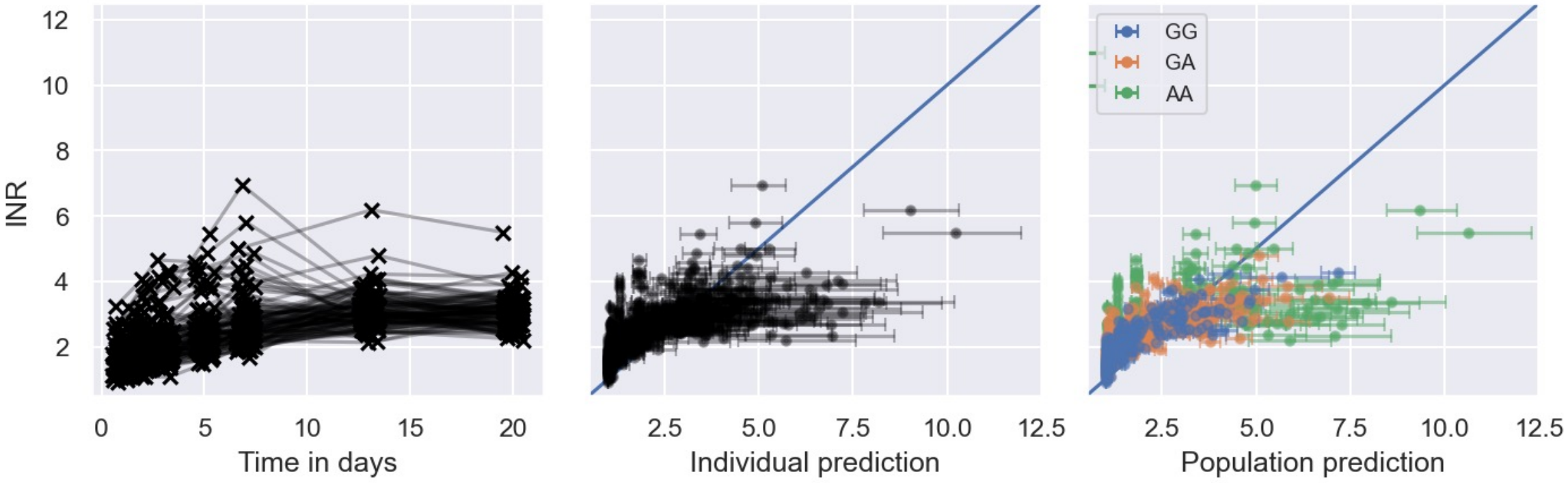


Virtual MIPD trial: PKPD model (I)



Virtual MIPD trial: PKPD model (II)





Model is misspecified

Better model currently in progress…

Thank you for listening!