UNIVERSIDAD DE LA REPÚBLICA URUGUAY

GIDP
GRUPO INTERDISCIPLINARIO EN DOSIFICACIÓN DE PRECISIÓN

Towards a flexible model-informed precision dosing software solution using MonolixSuite™

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About us

UNIVERSIDAD DE LA REPÚBLICA URUGUAY

HOSPITAL DE CLINICAS
Dr. Manuel Quintela

Precision Dosing: tailoring treatments to patients' needs

Individualization of drug treatment regimens based on patient characteristics known to alter drug absorption, disposition and/or response, with the aim of maximizing the probability of attaining both goals: efficacy and safety.

Opposed to the flat dose or *one-size-fits-all* approach

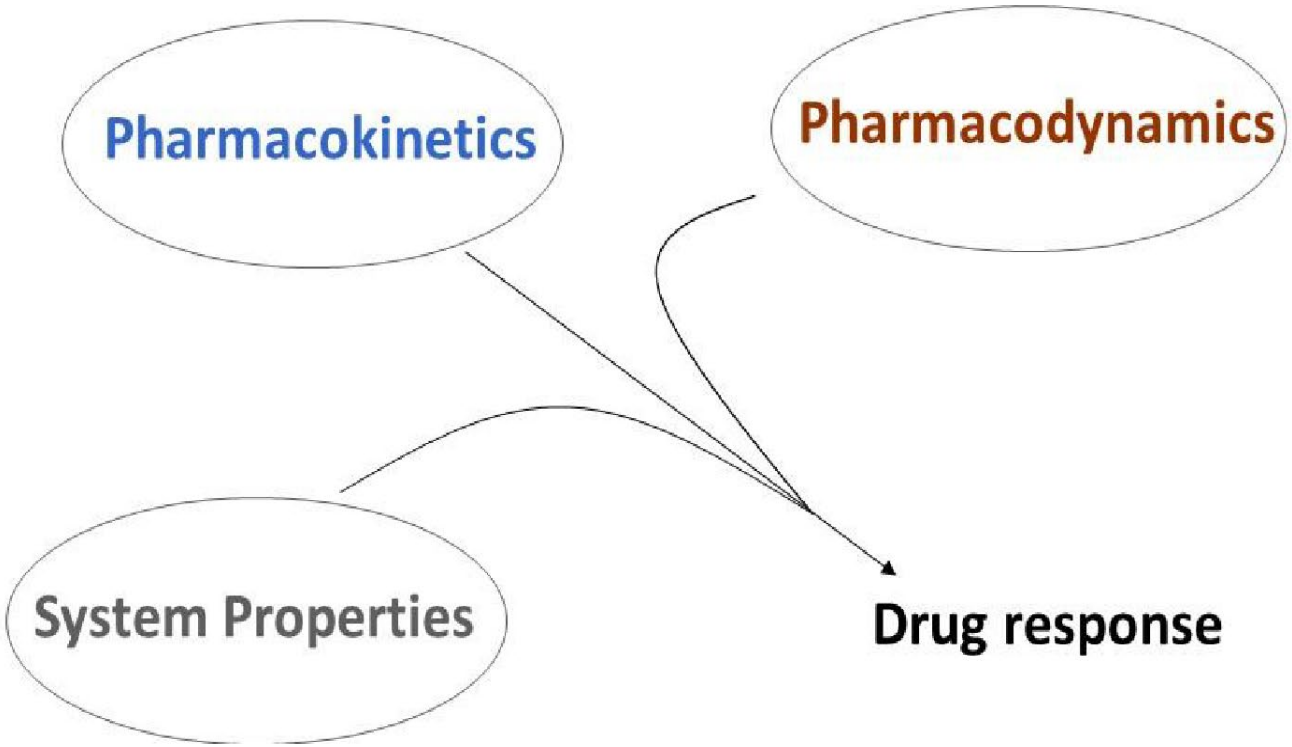
Few drugs work in all patients under the same dosage regimen

Precision Dosing: tailoring treatments to patients' needs

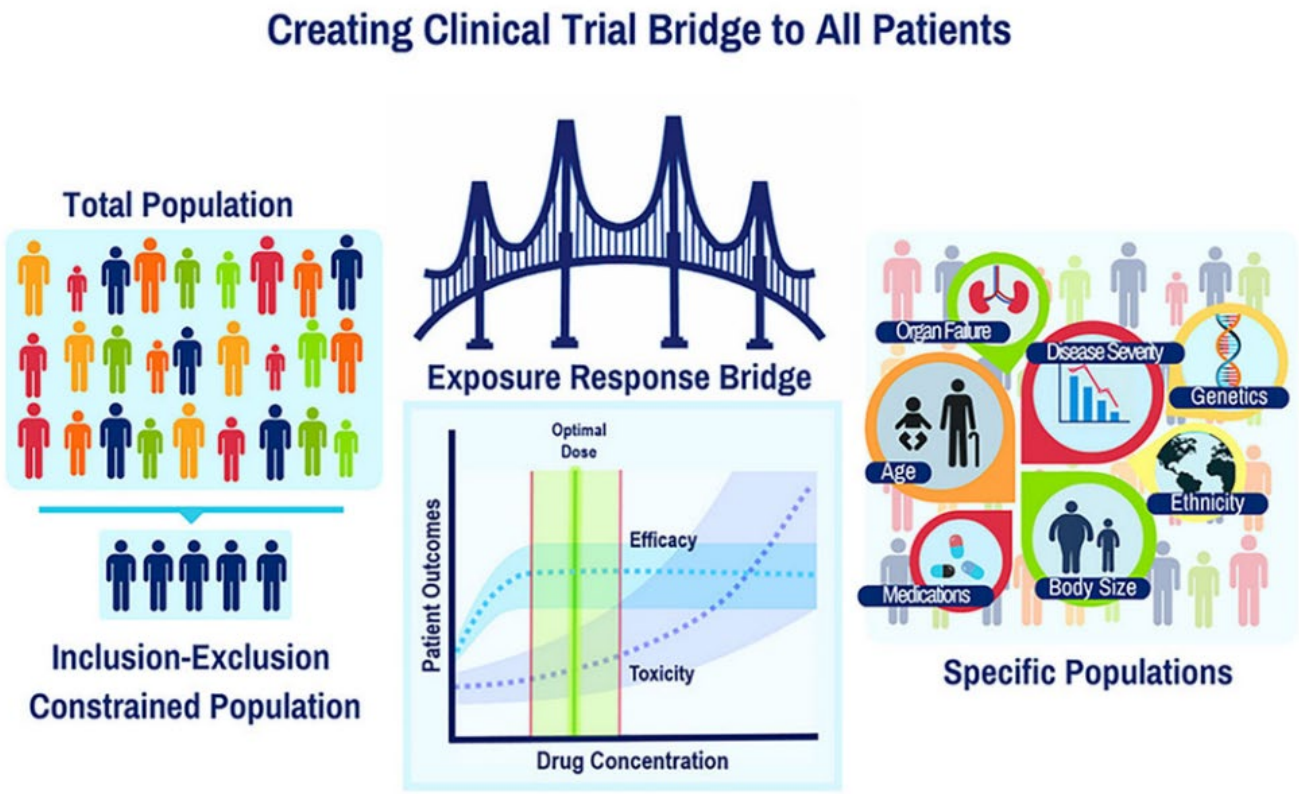
Individualization of drug treatment regimens based on patient characteristics known to alter drug absorption, disposition and/or response, with the aim of maximizing the probability of attaining both goals: efficacy and safety.

Delivering the right drug, in the right dose, to the right patient, at the right time.
A cornerstone of precision medicine

Quantitative pharmacology: Pharmacometrics



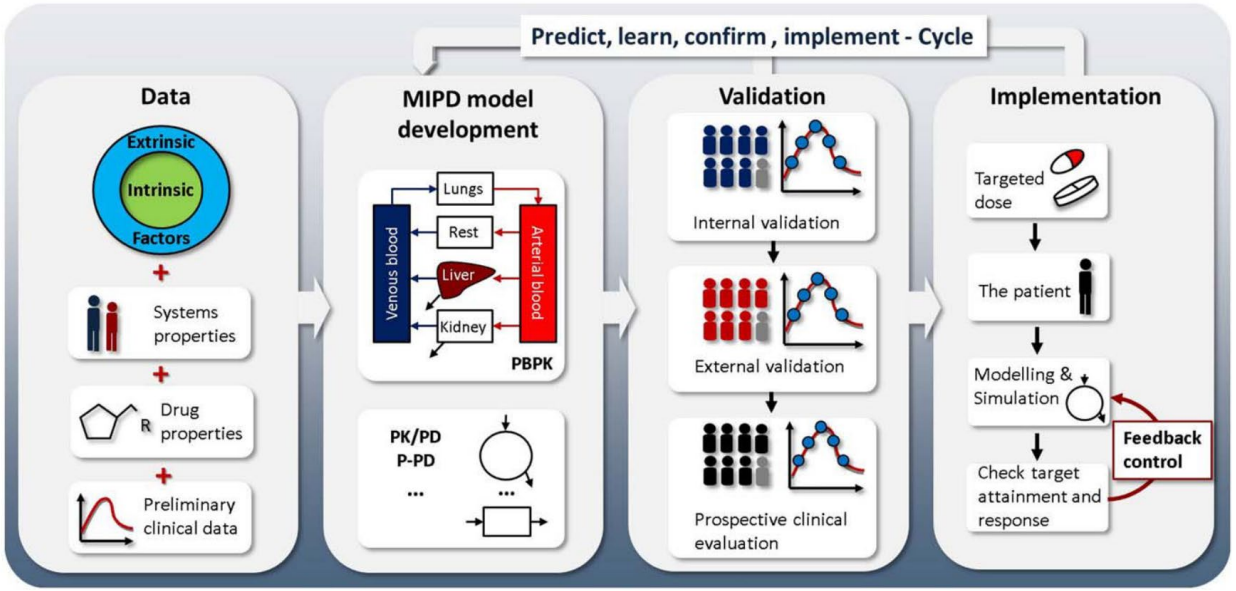
MIPD – key to bridge knowledge and improve the accuracy of dosing recommendations



Gonzalez D et al (2017) Clin Transl Sci

Precision dosing + Quantitative pharmacology = Model-Informed Precision Dosing (MIPD)

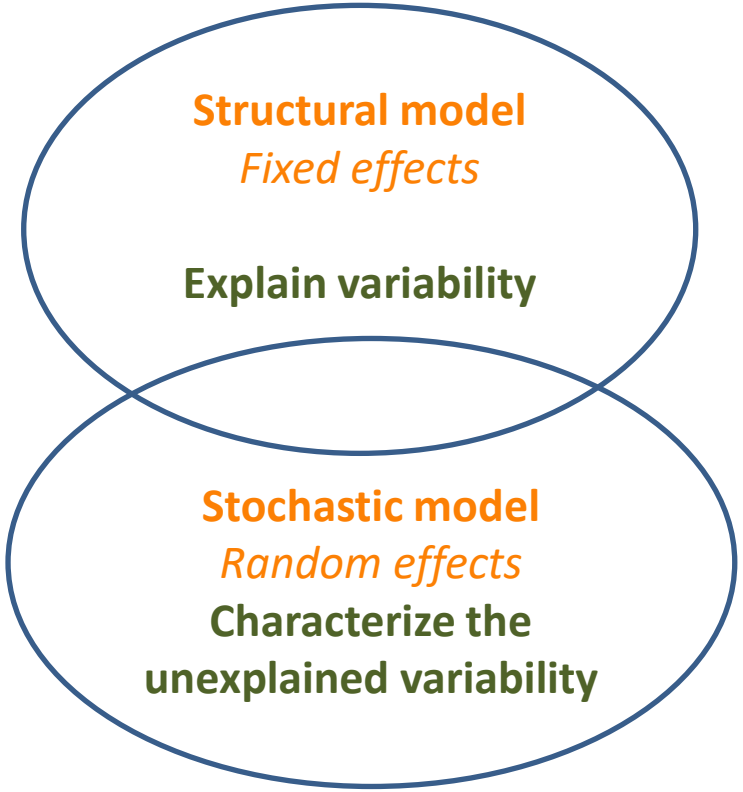
Use of modeling & simulation approaches (e.g. pharmacometrics: population PK/PD models, PBPK, regression models, decision trees, etc.) in combination with individually measured patient and disease characteristics to inform clinical decisions within the context of precision dosing.

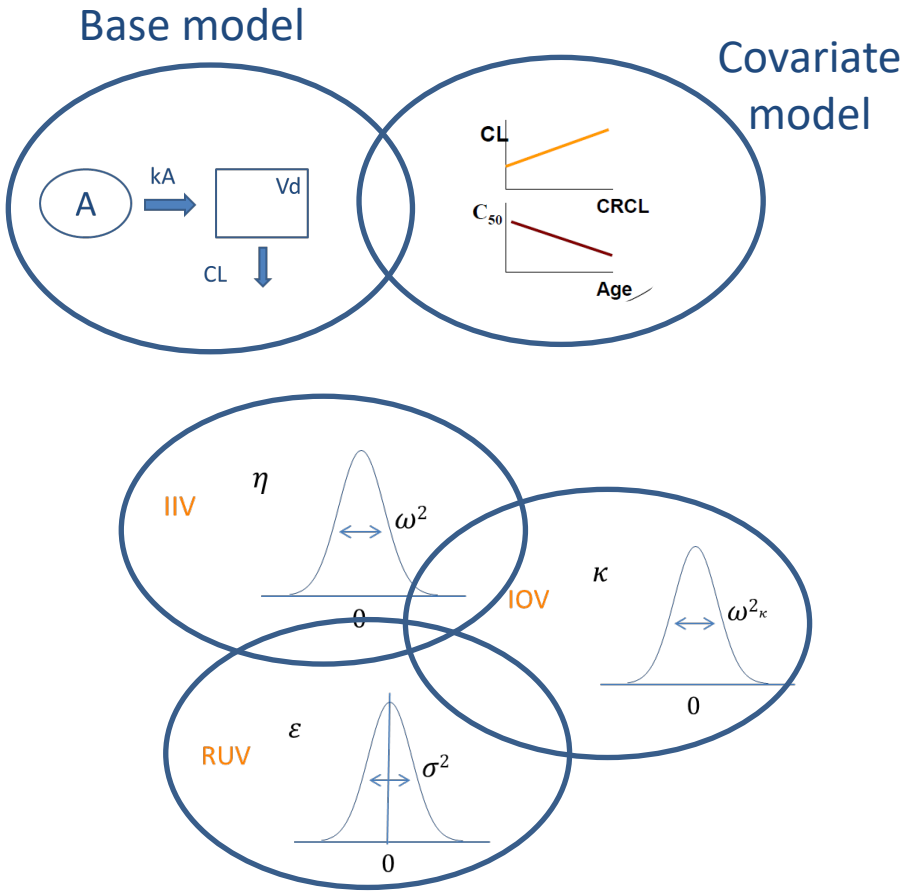


Darwich AS et al (2017) Why has model-informed precision dosing not yet become common clinical reality? lessons from the past and a roadmap for the future. *Clin Pharmacol Ther* **101**:646–656.

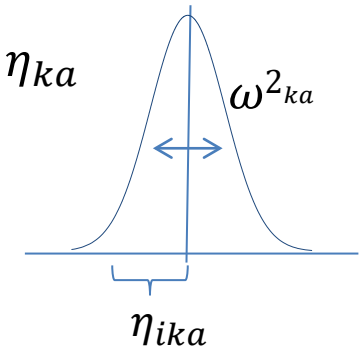
Model-Informed Precision Dosing (MIPD)

- Nonlinear mixed effects models

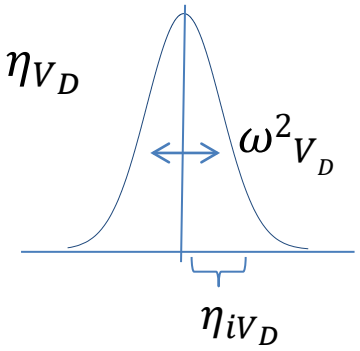




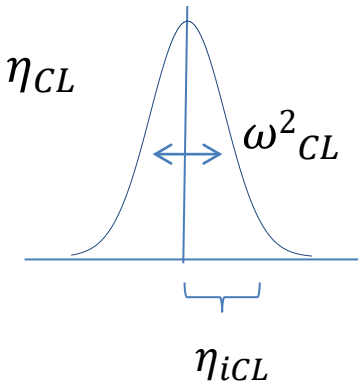
Model-Informed Precision Dosing (MIPD)



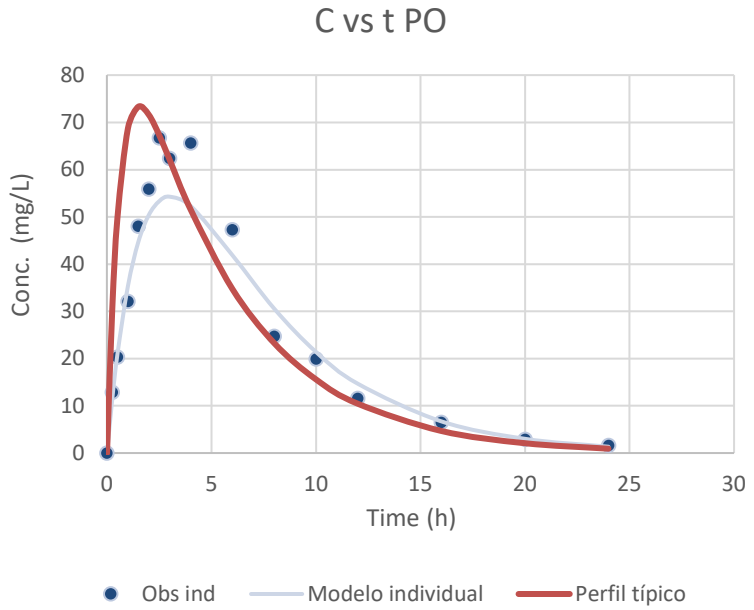
$$ka_i = ka_{pop} + \eta_{ika}$$
$$\eta_{ka} \sim N(0, \omega^2_{ka})$$



$$Vd_i = Vd_{pop} + \eta_{iVd}$$
$$\eta_{Vd} \sim N(0, \omega^2_{Vd})$$



$$CL_i = CL_{pop} + \eta_{iCL}$$
$$\eta_{CL} \sim N(0, \omega^2_{CL})$$



A NLME model provides the *a priori* prediction based on typical distributions and can be combined with patient's data to obtain *a posteriori* distributions and predictions for a given subject

Individualizing pharmacometrics models

Empirical Maximum A-posteriori Estimation

Balance between **prior knowledge** (parameter distribution in a given population) and **individual data**

$$MAP(OFV) \cong \sum_{j=1}^{p} \frac{(\theta_j - \hat{\theta}_j)^2}{\omega_j^2} + \sum_{i=1}^{n} \frac{(y_i - f(\theta_j, x))^2}{\sigma^2}$$

A balance between prior knowledge and collected data

Empirical Maximum A-posteriori Estimation

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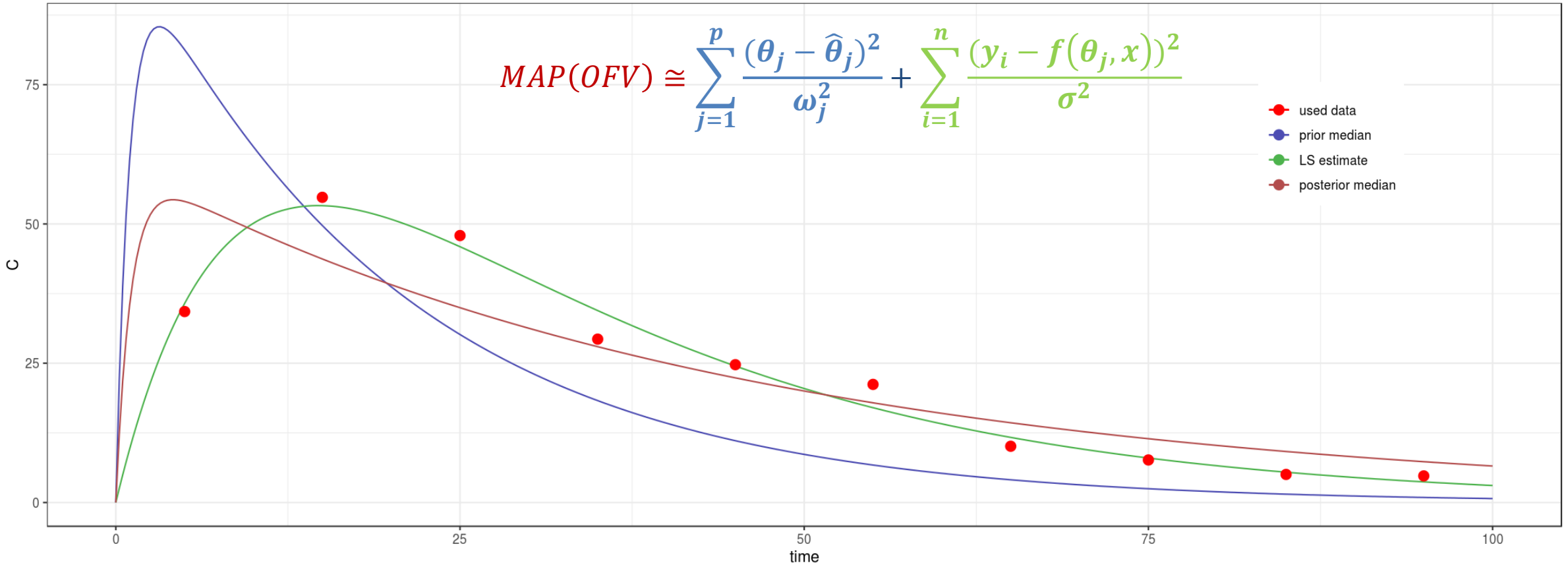

A balance between prior knowledge and collected data

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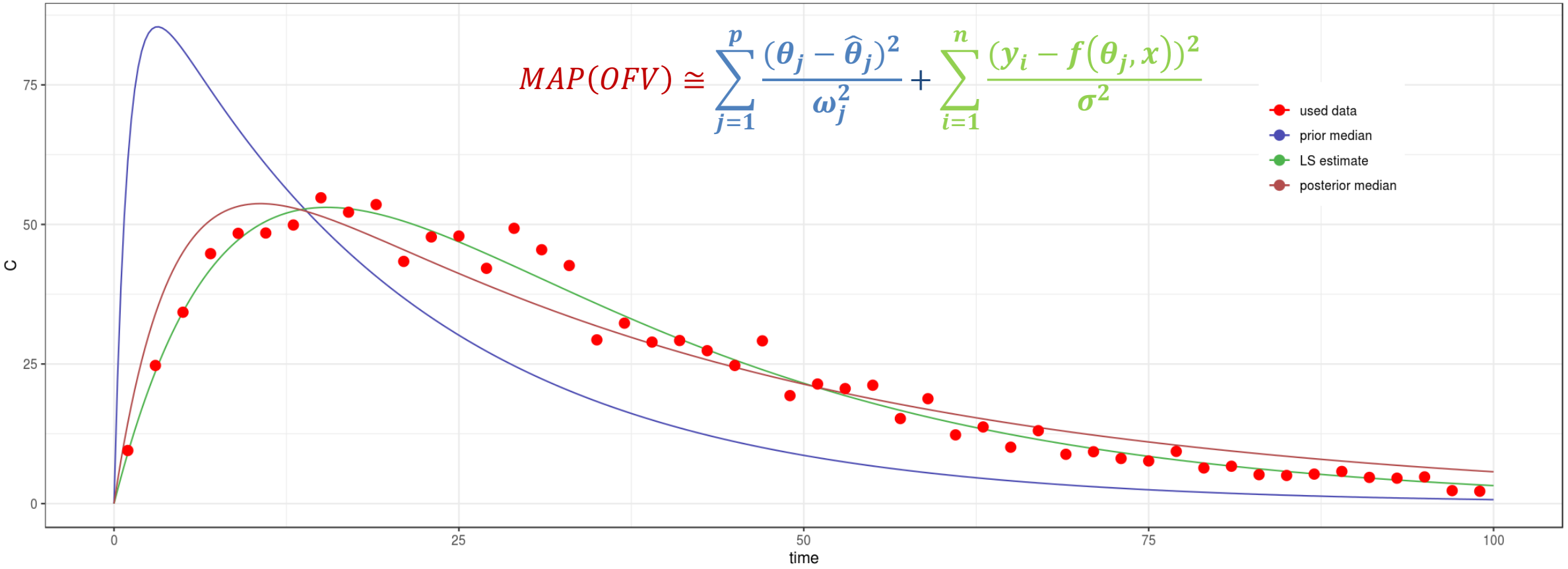
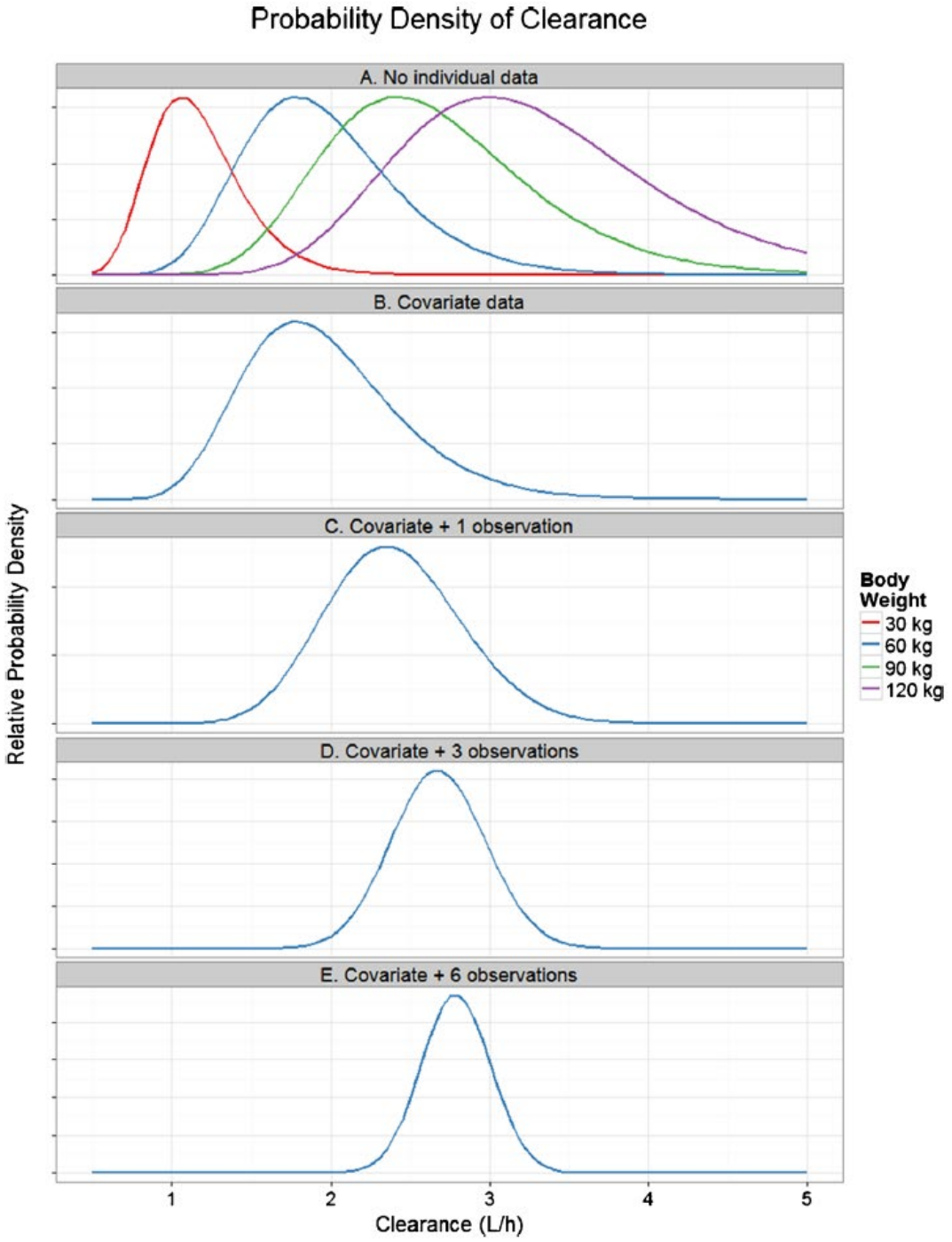


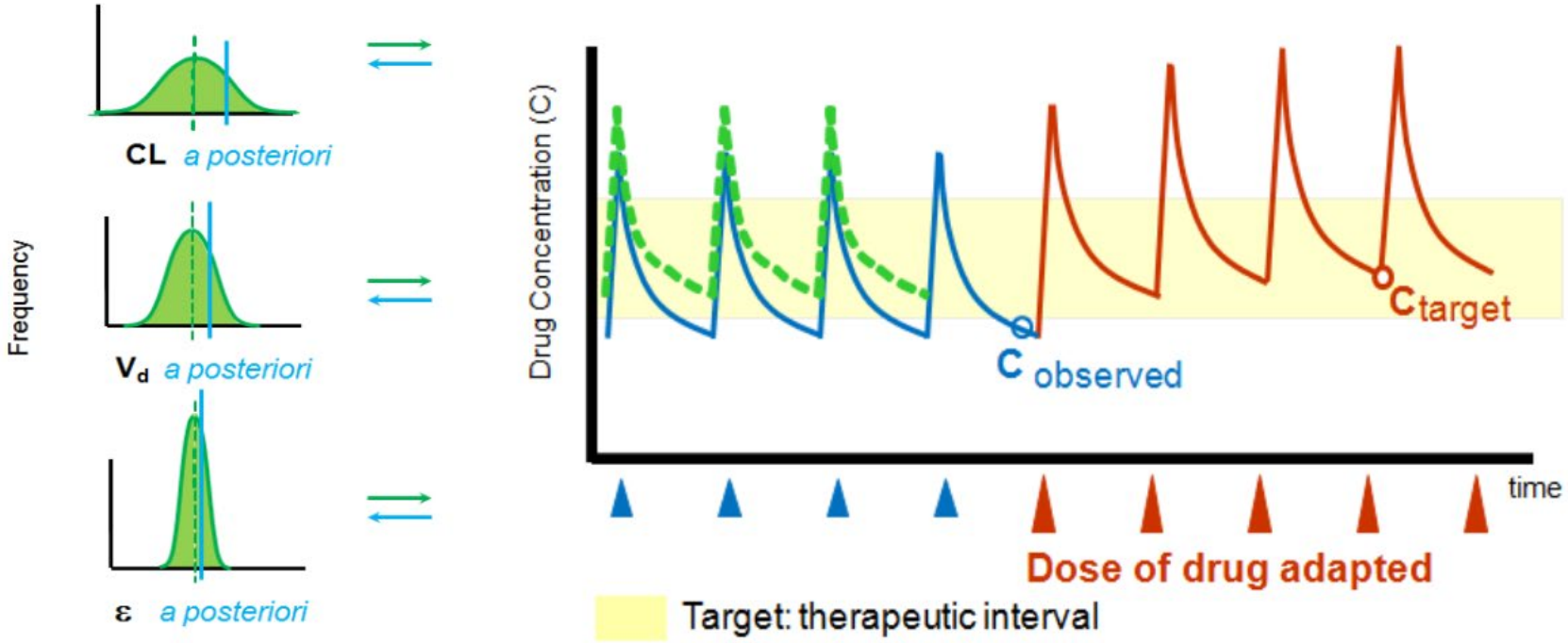
M Lavielle – http://shiny.webpopix.org/mcmc/bayes1/

Bayesian updating



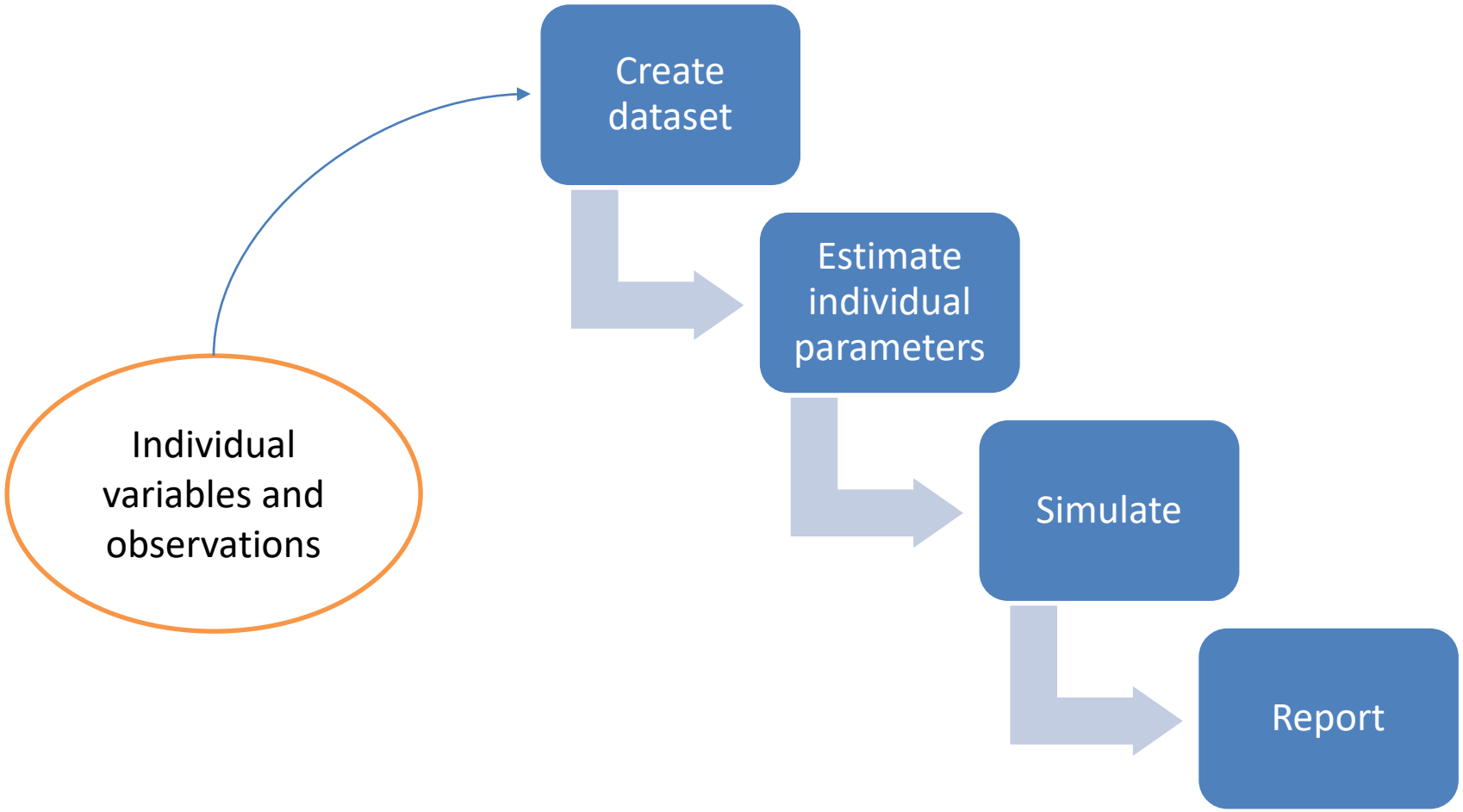
Upton D. et al. 2014. AAPSJ Dashboard systems: implementing pharmacometrics from bench to bedside.

Bayesian forecasting



A. Fuchs. Implementation of Bayesian Therapeutic Drug Monitoring in Modern Patient Care

A complicated and time-consuming task



MIPD works!

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

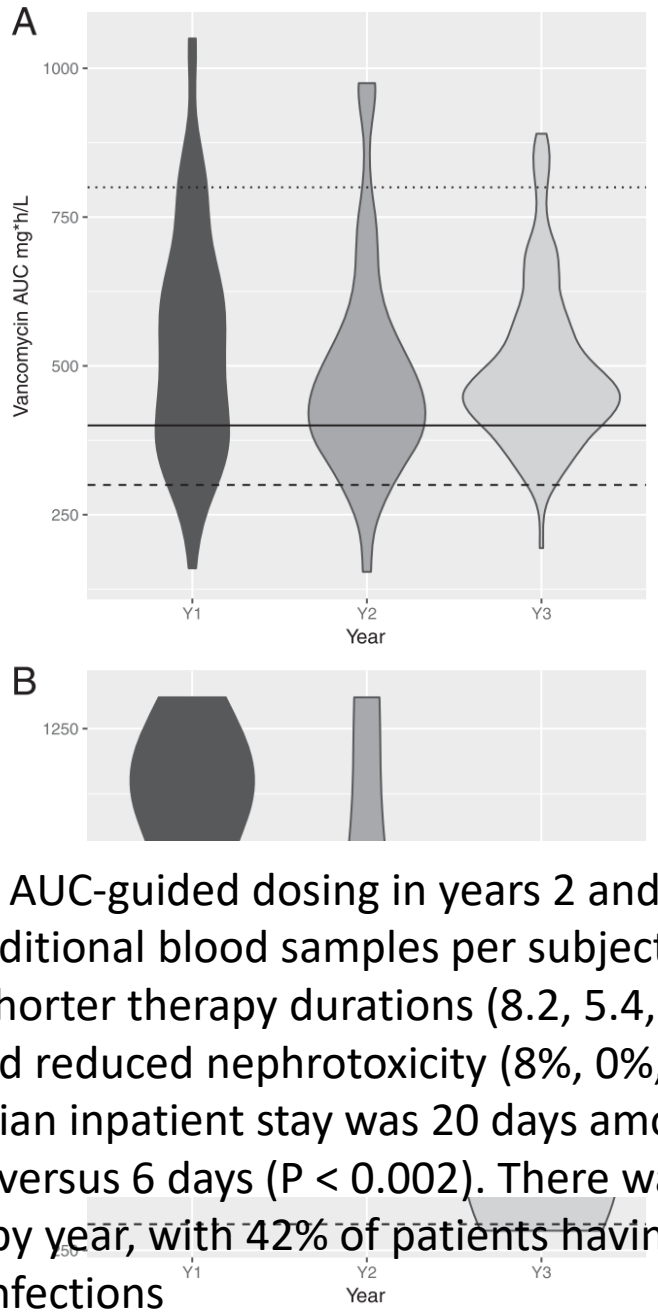
CLINICAL THERAPEUTICS

Prospective Trial on the Use of Trough Concentration versus Area under the Curve To Determine Therapeutic Vancomycin Dosing

Michael N. Neely,[a,b] Lauren Kato,[c] Gilmer Youn,[a] Lironn Kraler,[a] David Bayard,[b] Michael van Guilder,[b] Alan Schumitzky,[b] Walter Yamada,[b] Brenda Jones,[a] Emi Minejima[c]

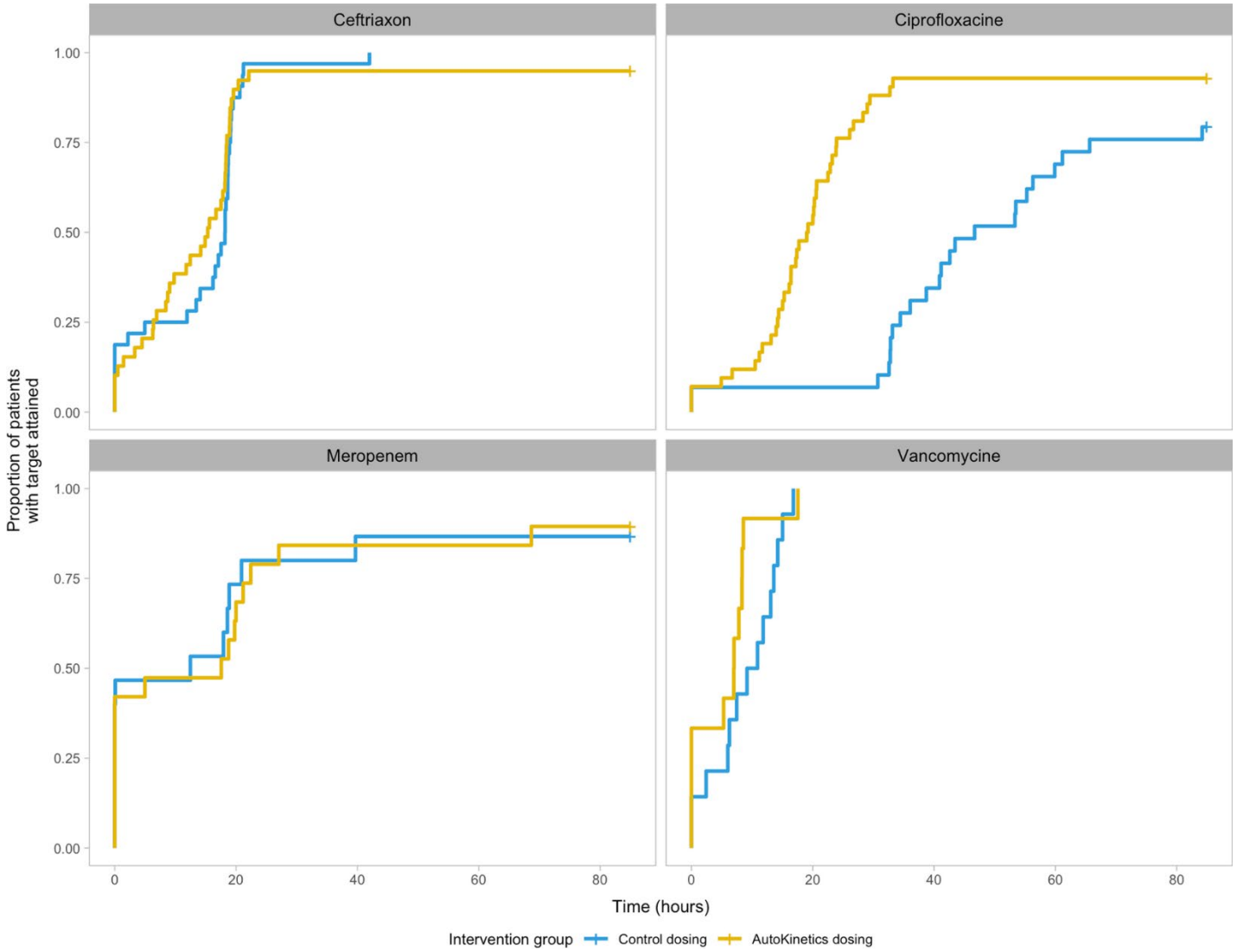
TABLE 1 Characteristics of all enrolled subjects

Subject parameter	Value(s)			
	Yr 1 control (n = 75)	Yr 2 BestDose—MM (n = 88)	Yr 3 BestDose—MMopt (n = 89)	P
Mean (range) age, yrs	47.7 (19.0–71.0)	48.0 (18.0–93.0)	50.3 (22.0–81.0)	0.42
No. (%) of male sex	61 (81)	67 (76)	67 (75)	
Mean (range) wt, kg	82.4 (47.7–150.9)	81.0 (46.4–193.6)	78.8 (30.3–180.0)	
Mean (range) ht, cm	171.9 (149.9–198.1)	169.1 (149.9–193.0)	168.6 (127.4–188.0)	
No. (%) of indicated race				
Native American	0	0	1 (1)	
Asian	0	4 (5)	4 (4)	
African American	9 (12)	13 (15)	17 (19)	
Caucasian	66 (88)	70 (80)	66 (74)	
Not reported	0	1 (1)	1 (1)	
No. (%) Hispanic				
Yes	54 (72)	61 (69)	49 (55)	
No	21 (28)	19 (22)	39 (44)	
Not reported	0	8 (9)	1 (1)	
Baseline serum creatinine, mg/dl	0.82 (0.36–1.63)	0.84 (0.33–2.71)	0.83 (0.39–2.21)	0.9
Baseline creatinine clearance, ml/min (Cockroft-Gault)	146.9 (36.0–665.5)	131.1 (31.7–281.0)	126.8 (27.8–286.8)	0.14



Bayesian AUC-guided dosing in years 2 and 3 was associated with fewer additional blood samples per subject (3.6, 2.0, and 2.4; $P < 0.003$), shorter therapy durations (8.2, 5.4, and 4.7 days; $P < 0.03$), and reduced nephrotoxicity (8%, 0%, and 2%; $P < 0.01$). The median inpatient stay was 20 days among nephrotoxic patients versus 6 days ($P < 0.002$). There was no difference in efficacy by year, with 42% of patients having microbiologically proven infections

MIPD works!

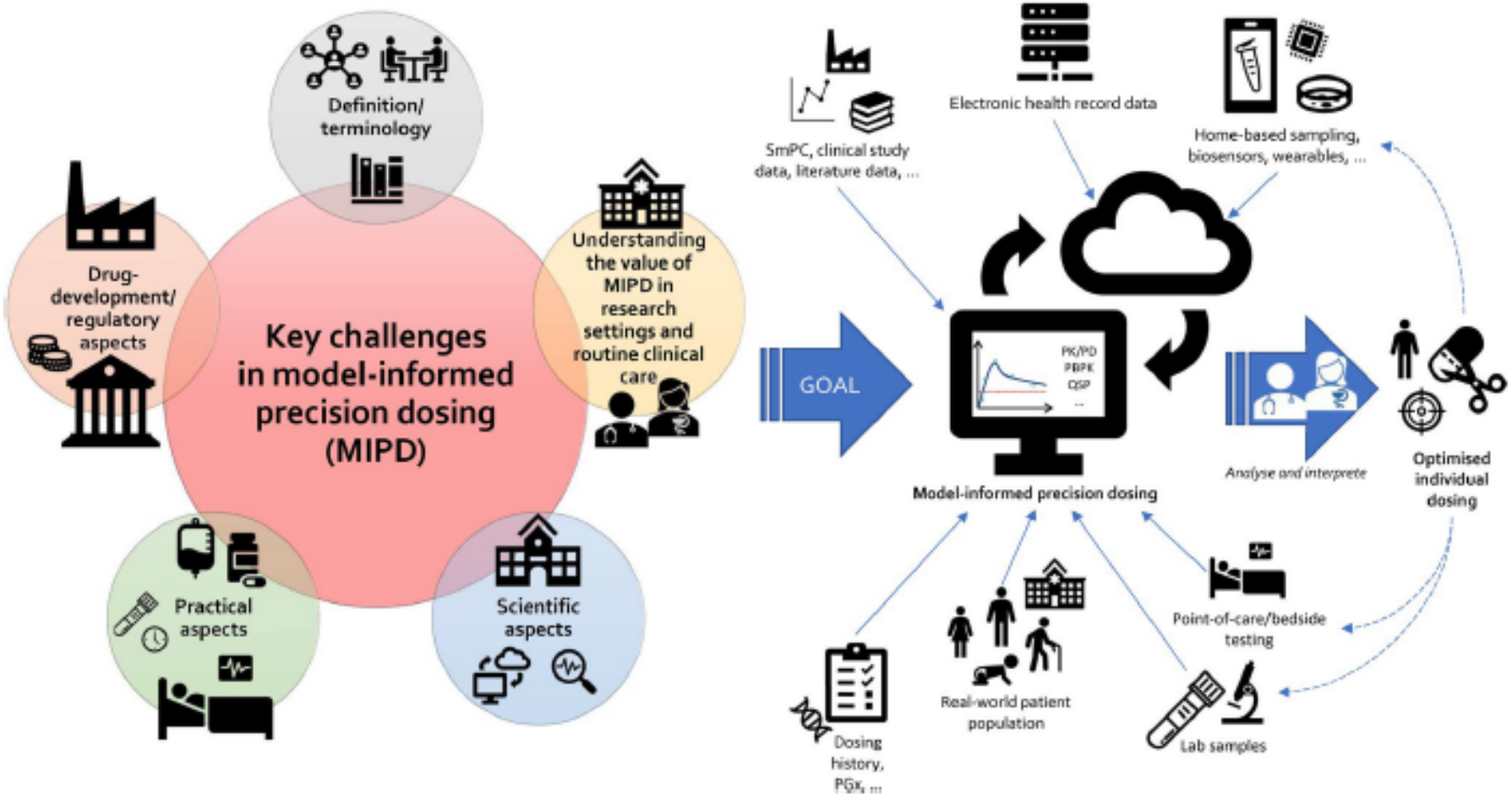


Roggeveen, L.F., Guo, T., Fleuren, L.M. et al. Crit Care 26, 265 (2022). https://doi.org/10.1186/s13054-022-04098-7

MIPD works!

- Clinical benefits
- Financial impact
  - Reduce the incidence of preventable ADRs
  - Improve adherence
  - Reduce hospitalization days

MIPD has not been widely integrated into clinical practice



Kluwe, F .et al. (2021), Perspectives on Model-Informed Precision Dosing in the Digital Health Era: Challenges, Opportunities, and Recommendations. Clin. Pharmacol. Ther., 109: 29-36. doi: 10.1002/cpt.2049

MIPD Software is quickly evolving

	AutoKinetics	BestDose	DoseMeRx	ID-ODS	InsightRX Nova	MwPharm++	NextDose	PrecisePK	TDMx	Tucuxi
Founder	Paul Elbers Rob Bosman	Roger Jelliffe	Robert McLeay	Andras Farkas Gergely Daroczi	Sirj Goswami Ron Keizer Ranvir Mangat	Johannes H. Proost Cees Neef Jiří Potáček Nieko Punt	Sam Holford Nick Holford	Philip Anderson Anjum Gupta	Sebastian Wicha	Yann Thoma
CEO	NA	NA	Charles Cornish	NA	Sirj Goswami	Jiří Potáček	NA	Anjum Gupta	NA	NA
Company/ institution	Departments of Intensive Care Medicine of Amsterdam UMC, location VUmc and OLVG Oost Hospital	Laboratory of Applied Pharmacokinetics and Bioinformatics, Children's Hospital Los Angeles	DoseMe (Tabula Rasa HealthCare Company)	Optimum Dosing Strategies	Insight Rx Inc.	Mediware a.s.	University of Auckland	Healthware Inc.	Institute of Pharmacy, University of Hamburg	School of Engineering and Management Vaud (HEIG-VD)
Location of company/ institution	Amsterdam, The Netherlands	Los Angeles, California, USA	Moorestown, New Jersey, USA	Bloomingdale, New Jersey, USA	San Francisco, California, USA	Groningen, The Netherlands/ Prague, Czech Republic	Auckland, New Zealand	San Diego, California, USA	Hamburg, Germany	Yverdon-les-Bains, Switzerland
Computer language of source code	Asp.net and vb.net	Fortran, R	Perl, R, python	Ionic, R	R, JavaScript	C#	Javascript, PHP, MySQL, NM-TRAN	C++, PHP Web App: JSX, C++	R/C++	C++
Software version (compatible platform or mobile application name or website)	Desktop (Windows), Web-based	Desktop (Windows), Web-based (bestdoserx.com/)	Web-based (app.doseme-rx.com), Android and iOS (DoseMe)	Web-based (app.id-ods.org), Android (ID-ODS Adult), iOS (app.id-ods.org)	Web-based (pk.insight-rx.com)	Desktop (Windows), Web-based, Android, iOS (mwpharm.online)	Web-based (nextdose.org)	Desktop (Windows, Mac), Web-based (app.precisepk.com/login)	Web-based (tdmx.eu/Launch-TDMx/)	Desktop (Windows, Mac, Linux)
Website	autokinetics.eu	lapk.org/bestdose.php	doseme-rx.com	optimum-dosing-strategies.org/id-ods/	insight-rx.com	mediware.cz	nextdose.org	precisepk.com	tdmx.eu/	tucuxi.ch
Purpose of use	research and clinical	research	research and clinical	clinical	research and clinical	research and clinical	research and clinical	research and clinical	research and clinical	clinical

Kantasiripitak W. et al. Front. Pharmacol., 07 May 2020 Volume 11 - 2020 | https://doi.org/10.3389/fphar.2020.00620

Our own difficulties and needs

- Software accessibility ($)
- Engage medical staff and hospital authorities
- Ability to apply the models that best fit our needs and perspectives
- Start off on the right foot in terms of model performance

Inter-model variability

Vancomycin

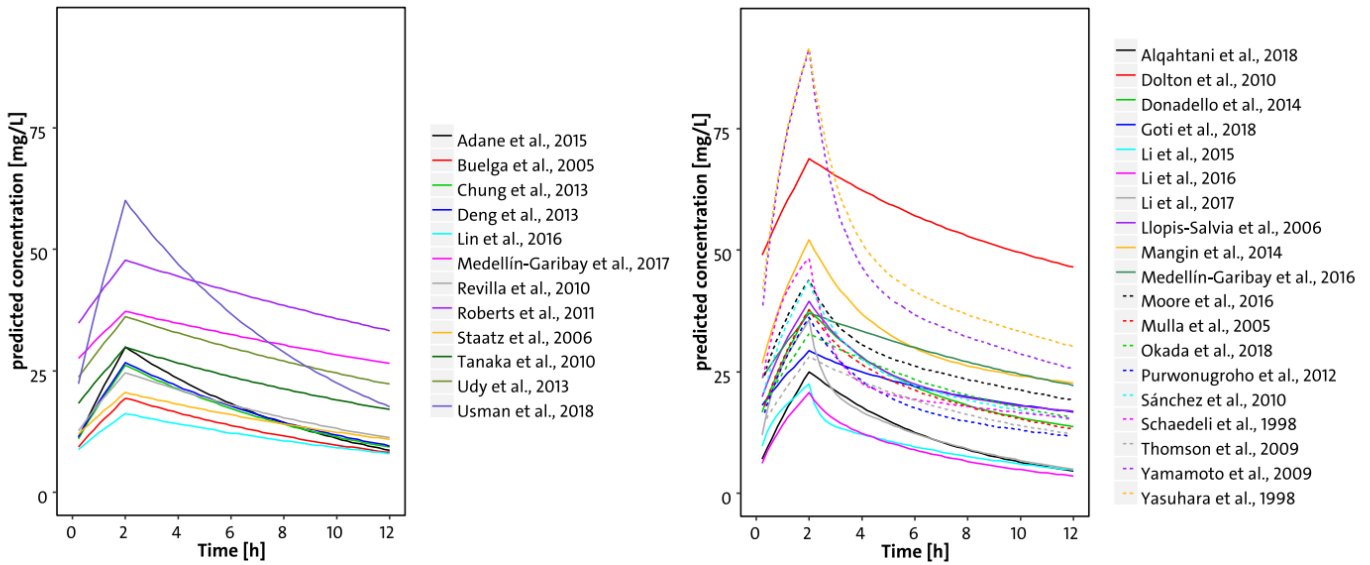
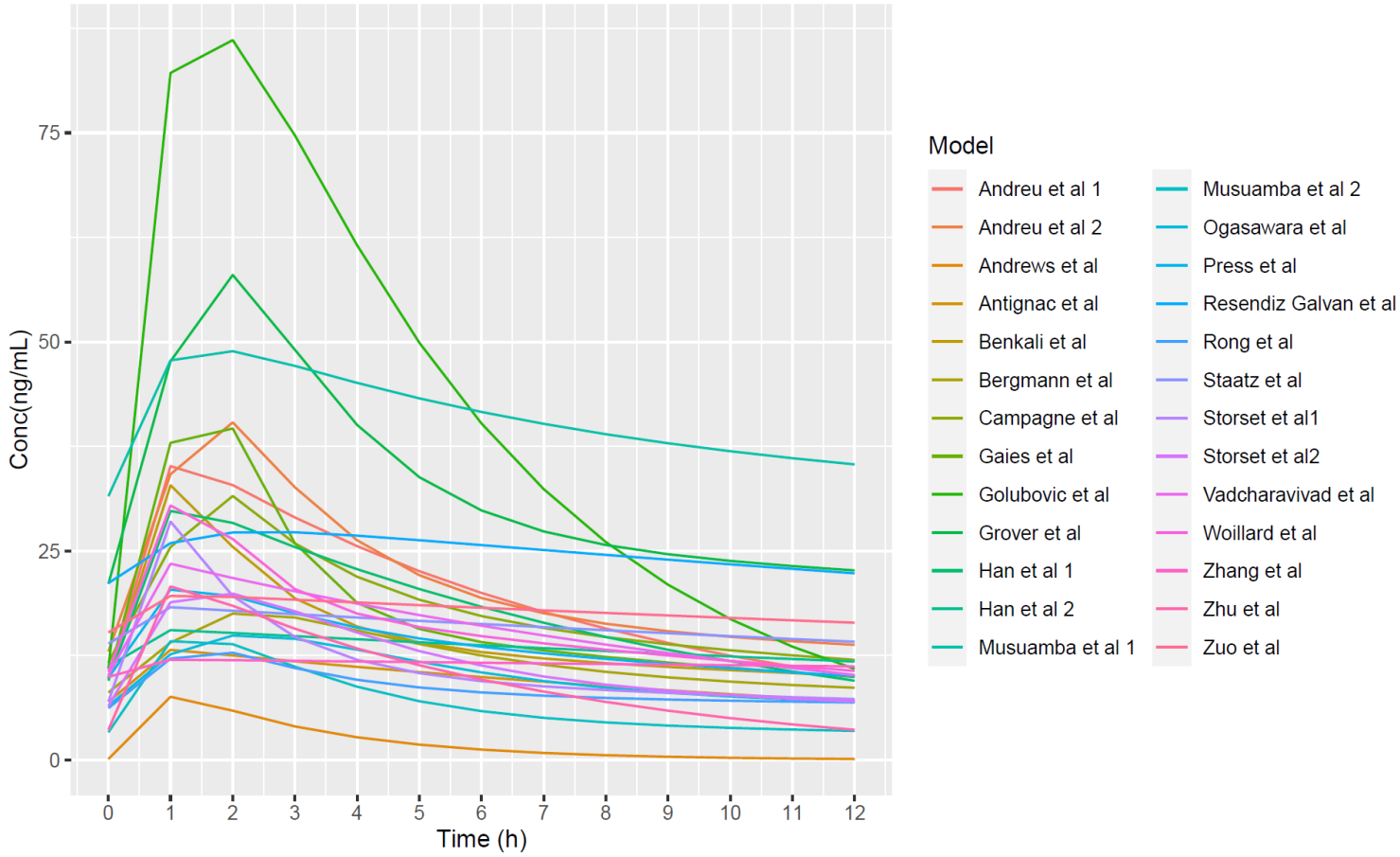


Fig. 1. Simulated steady-state vancomycin pharmacokinetic profiles of a standard patient (male, 50 years old, body weight 75kg, body height 1.7m, serum creatinine 85 μmol/L, twice daily vancomycin dosing of 1000 mg with an infusion length of 2 h) for each of the one-compartment models (left, $n = 12$) and two-compartment models (right, $n = 19$) examined. No inter-/intra-patient variability was simulated.

Broeker A. et al. 2019. Clinical Microbiology and Infection 25 (2019) 1286.e1e1286.e7

Inter-model variability

Tacrolimus



Model validation

Vancomycin

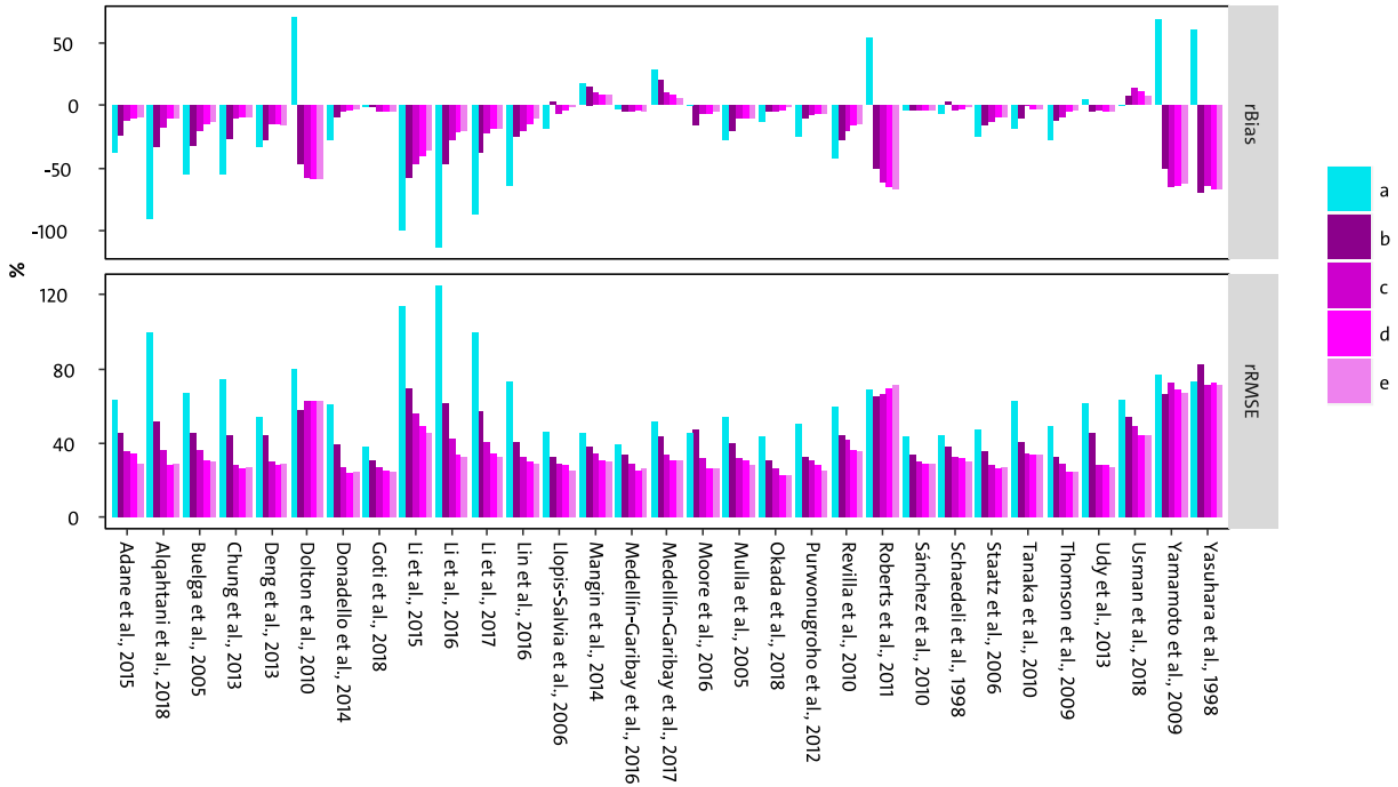
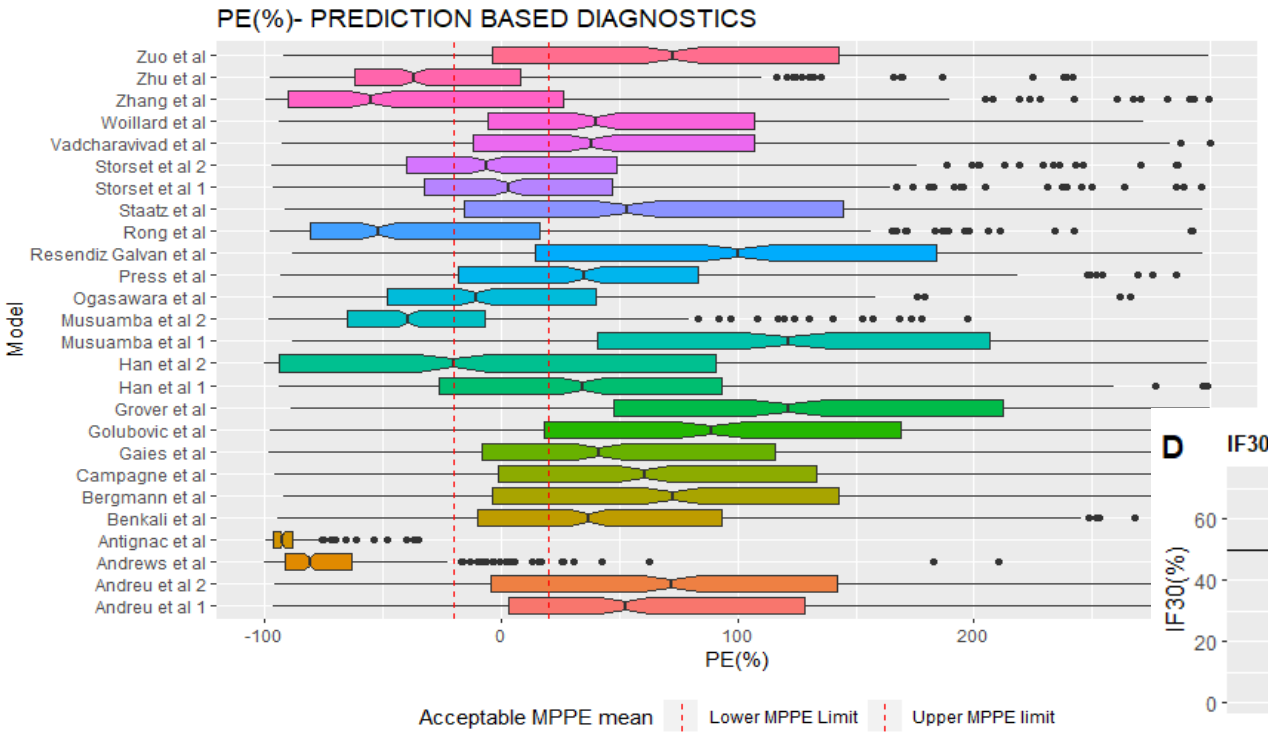


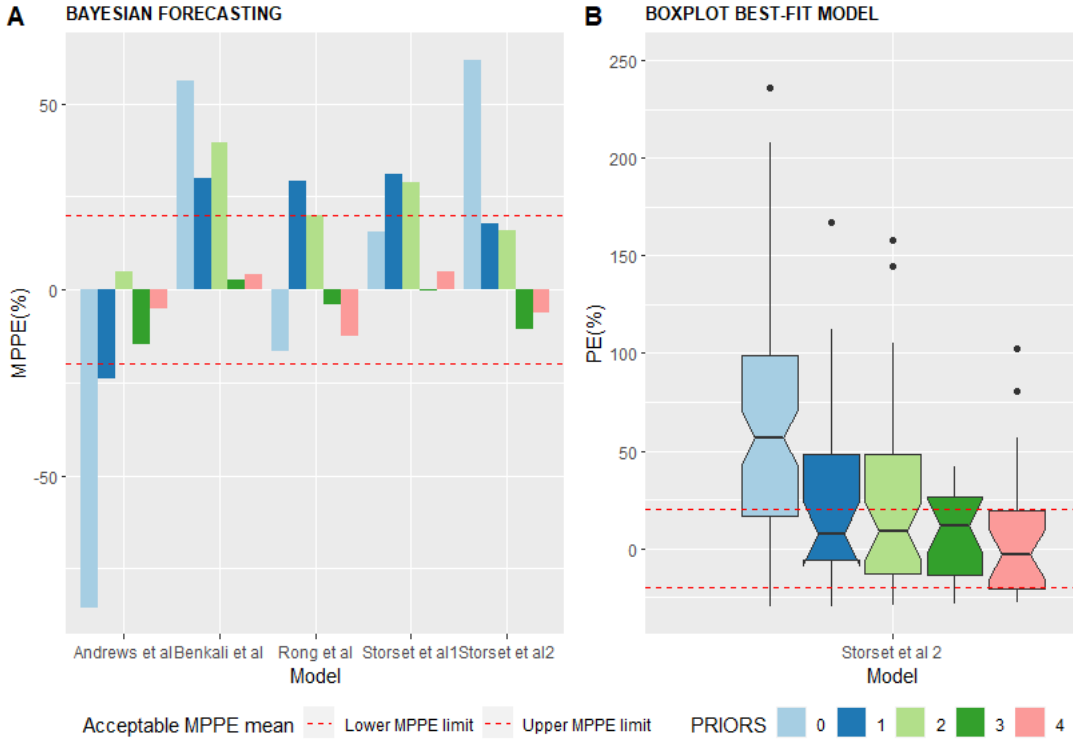
Fig. 2. The relative bias (rBias) and relative root mean squared error (rRMSE) of the predicted versus the observed vancomycin concentrations following the fourth dosing occasion (87 patients). (a) *A priori* prediction using the patient covariates only; (b) Bayesian forecasting employing measurements from the first dosing occasion; (c) the third (i.e. most recent) dosing occasion; (d) the second and third dosing occasions; (e) the first, second and third dosing occasions.

Broeker A. et al. 2019. Clinical Microbiology and Infection 25 (2019) 1286.e1e1286.e7

Model validation

Tacrolimus (n=40)

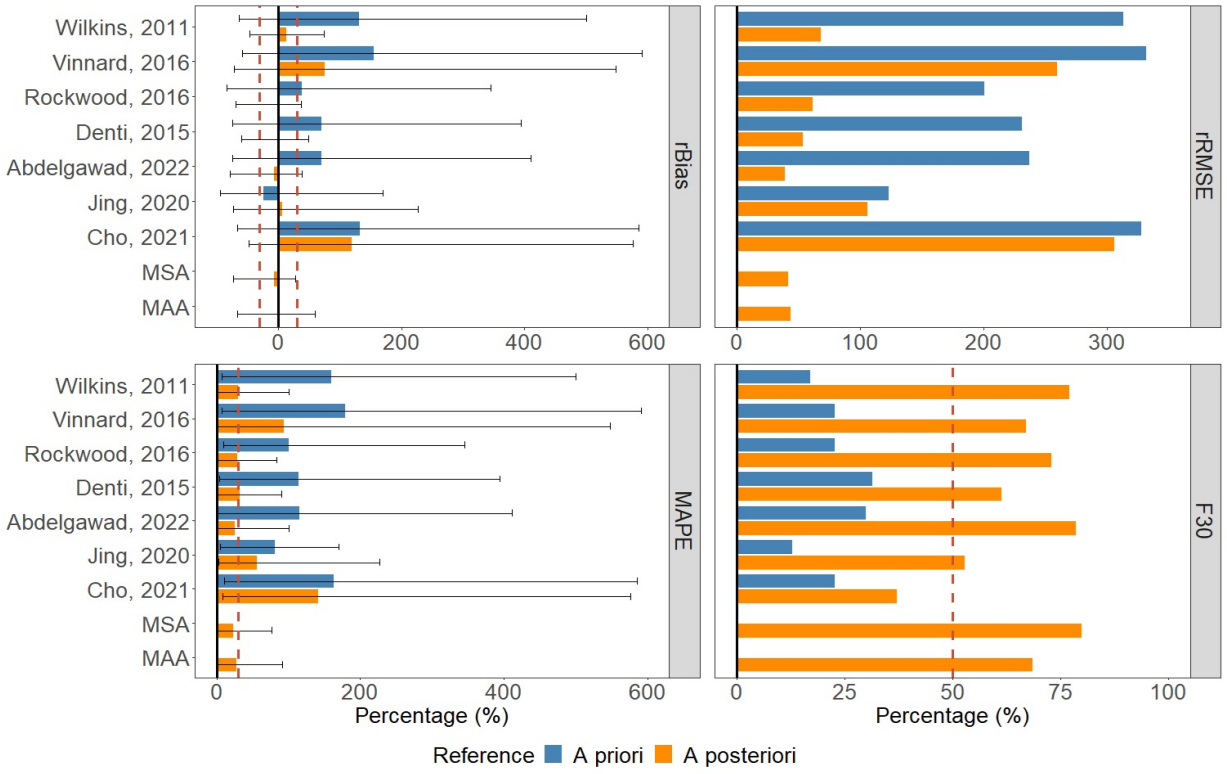




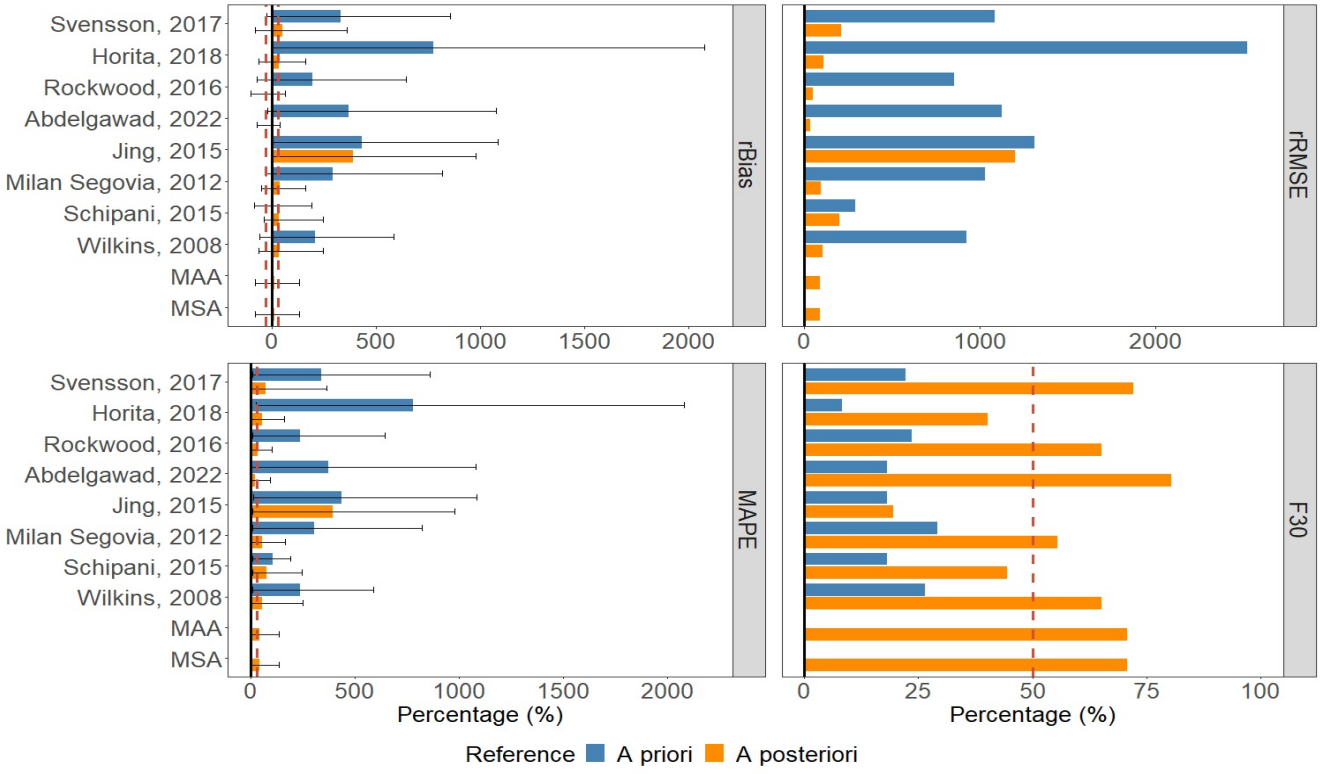
Model validation

Isoniazid/Rifampicin (n=38)

Isoniazid



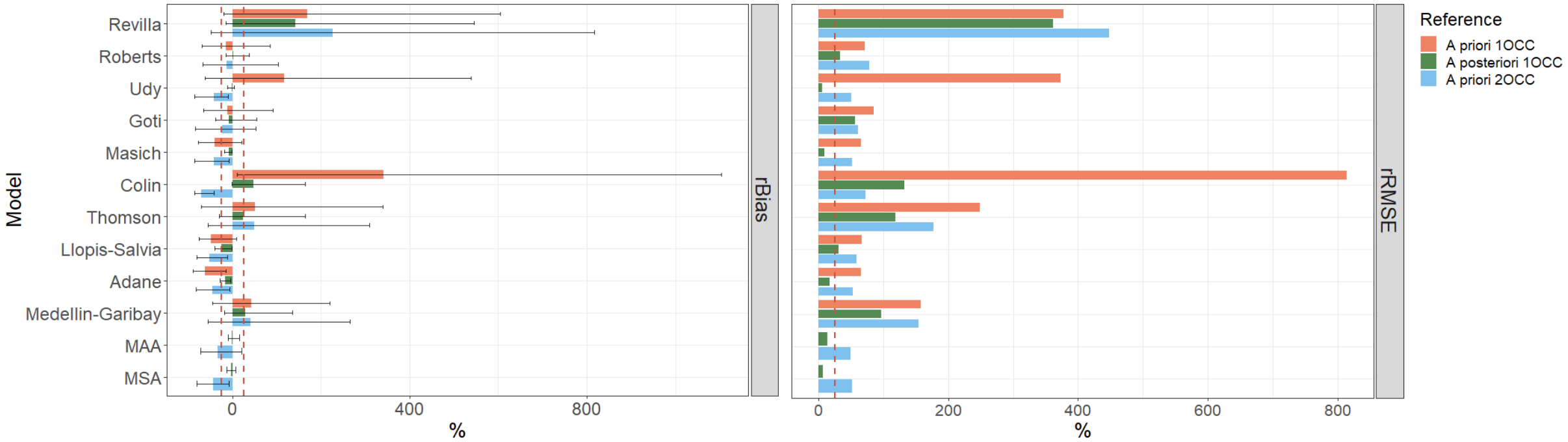
Rifampicin



MIPD in Uruguay

Vancomycin

31 critically ill patients



Software perspective

As MIPD is advancing to the clinical setting, there is a need for flexible software solutions that support its application by pharmacometric groups, contributing to demonstrate the advantages of the approach in clinical practice and clinical research.

Grupo Interdisciplinario en Dosificación de Presición
Interdisciplinary model-informed precision dosing group

- Pharmaceutics
- Medical doctors
  - Nephrology
  - Neonates
  - Infectious diseases
  - Intensivists
- Veterinary doctors
- Statisticians
- Computer engineers

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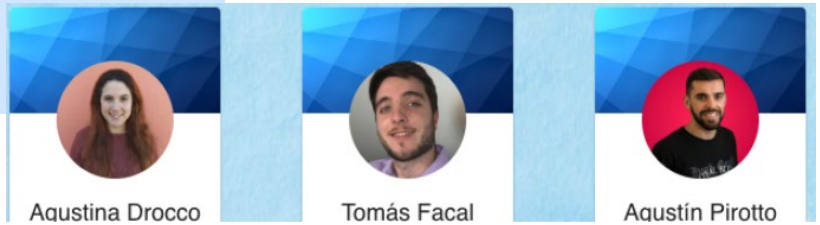
EN DOSIFICACIÓN DE PRECISIÓN

Developing a software solution

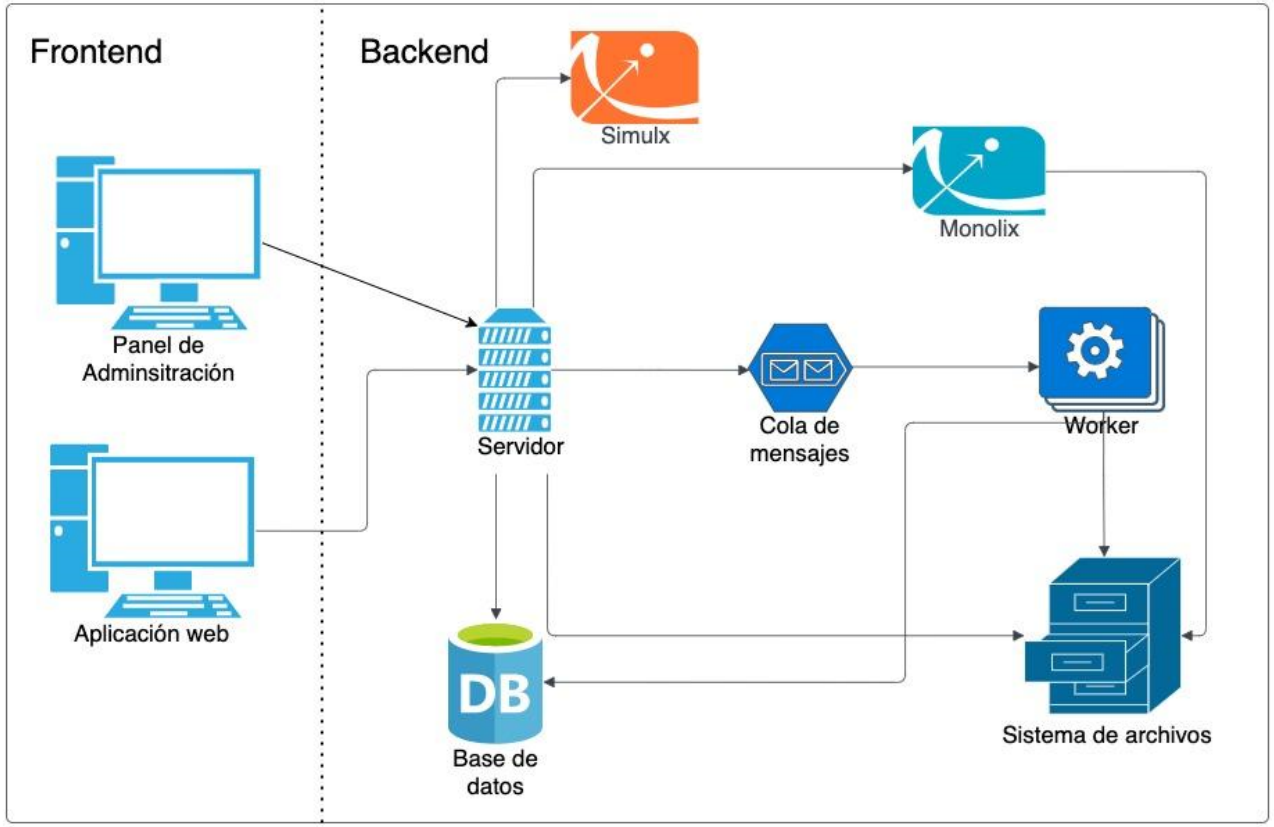
- Key characteristics
  - Accessibility (cloud-based, server-client architecture)
  - User friendly with 3 modules:
    - Physician (able to simulate from the population parameters)
    - Pharmacist at the TDM unit (able to perform the bayesian forecasting)
    - Admin (able to change models and structure)
  - Store individual data (dosing history, patient covariates, drug measurements)
  - Able to integrate new NLME models
  - Provide PK metrics of interest
  - Generate reports

Finglix

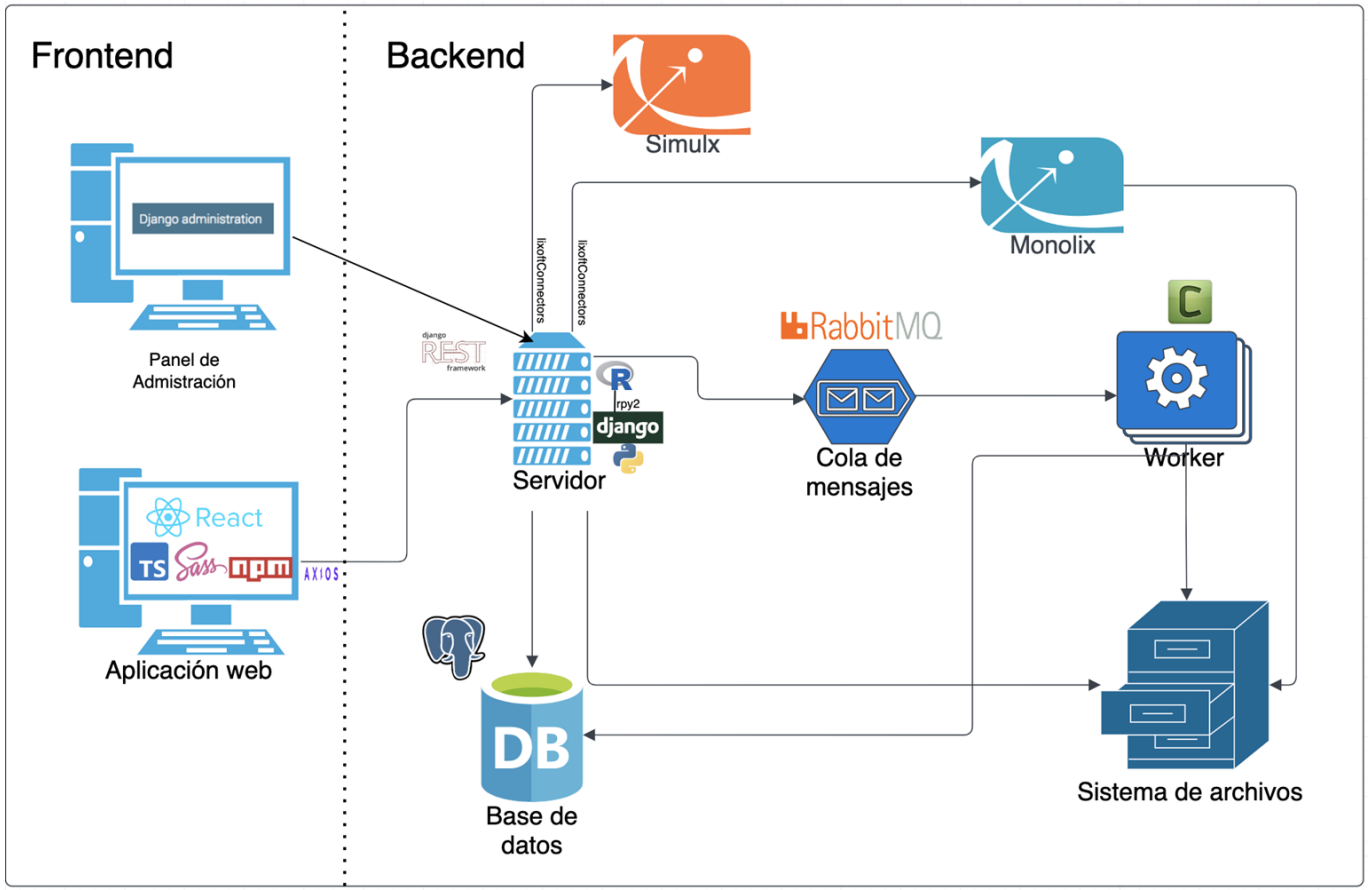
- A prototype to implement MIPD at the University Hospital (Udelar), Montevideo - Uruguay



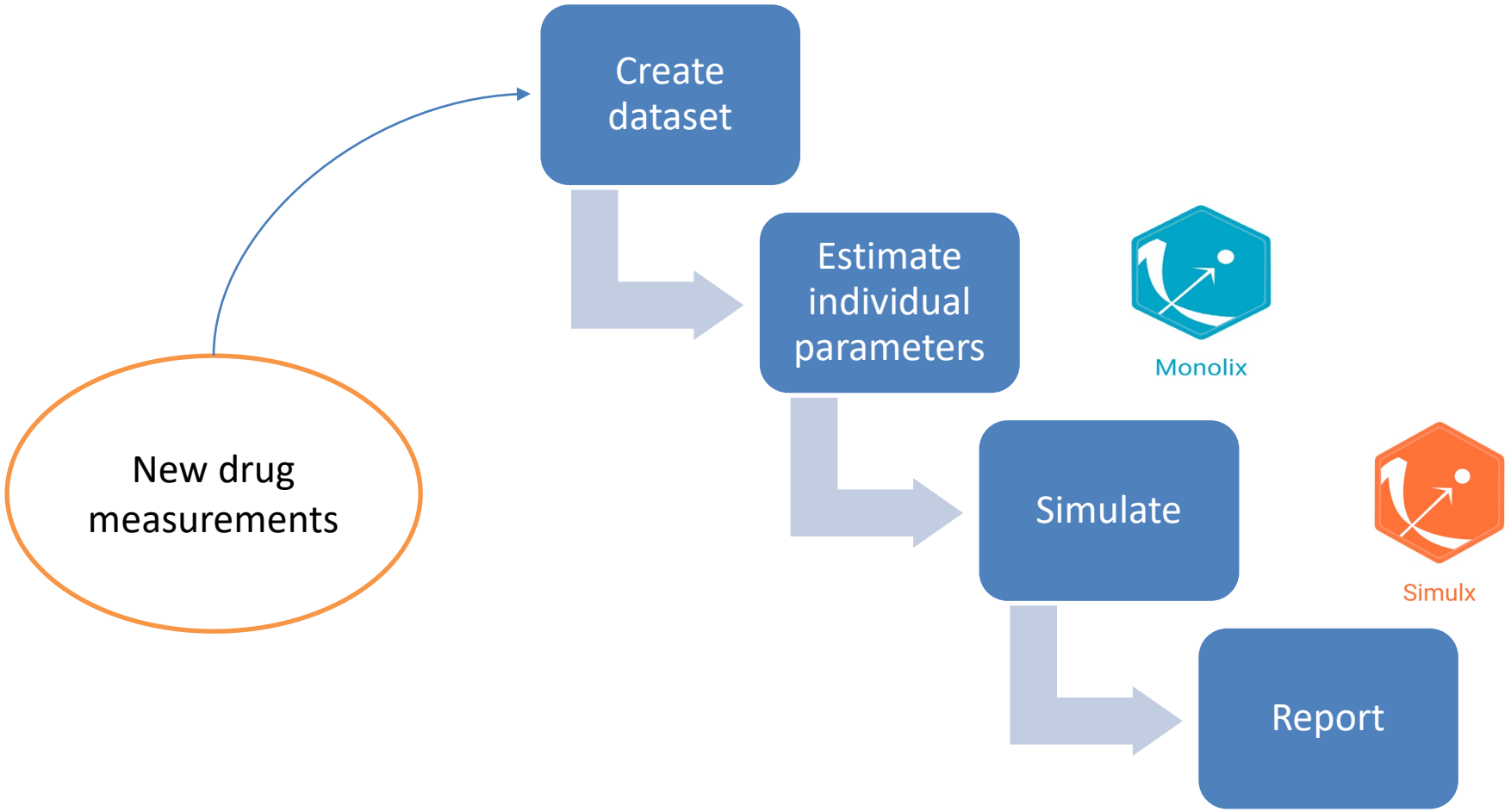
Finglix: Arquitecture



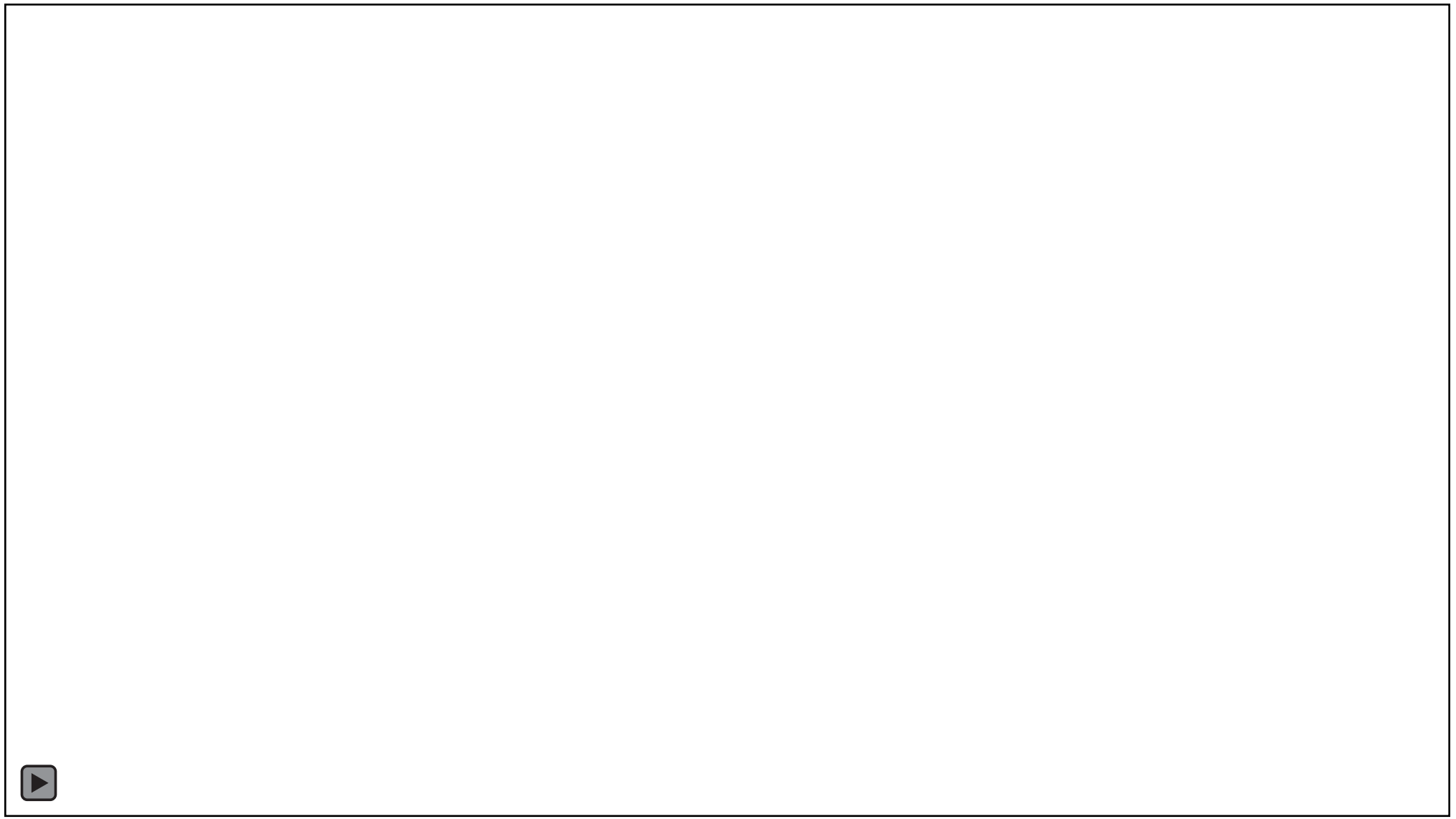
Finglix: tools



Finglix: tools



Finglix



Finglix: Next steps

- Provide dose recommendation based on exposure/response targets
- Covariate visualization
- Compartmentalize information by medical service
- Methods:
  - Model averaging
  - Weights for available observations
  - IOV handling

Take home message

- Interdisciplinarity is essential for MIPD success
- Several key challenges to be solved on site
- Need to prove to the medical staff and health care center authorities the benefits of MIPD
- Great software available for MIPD
  - Pharmacometricians might want to use their own validated models (Finglix).

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Thank you