Stellenbosch UNIVERSITY IYUNIVESITHI UNIVERSITEIT

forward together
sonke siya phambili
saam vorentoe

Introduction to Pharmacometrics

Modeling in the context of African Health

Ahmed A Abulfathi

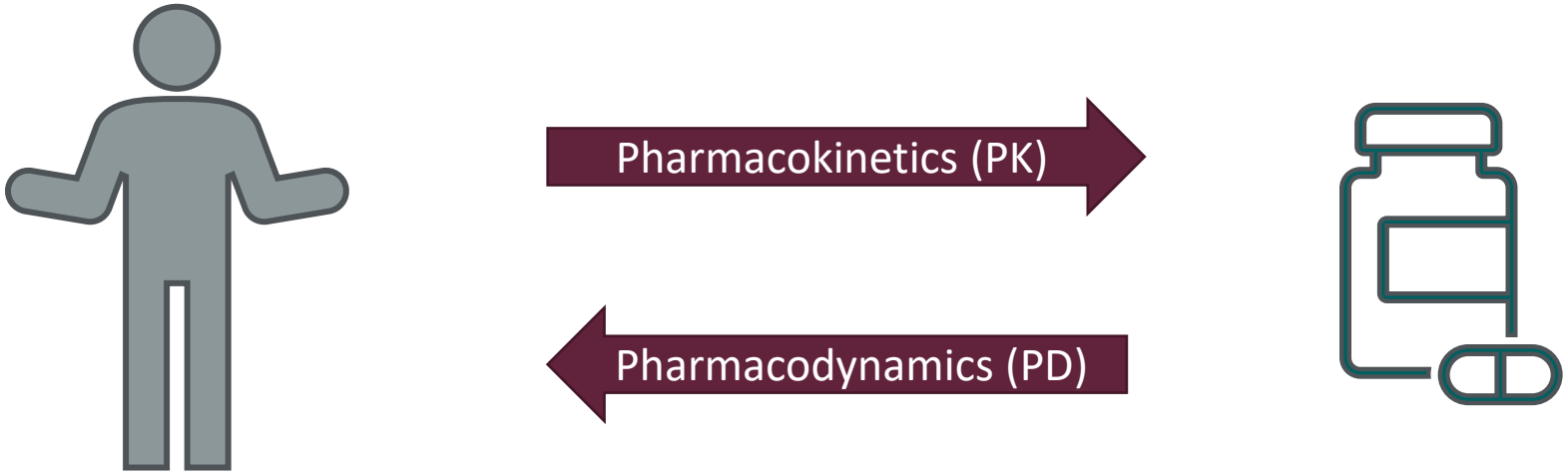
10 July 2023

Presentation to 7th International Conference of PSSN

cp+ | pharmacometrics africa

Terminology

Pharmacokinetics versus pharmacodynamics



It's all about Dose-Response…

Getting the right dose to the right patient

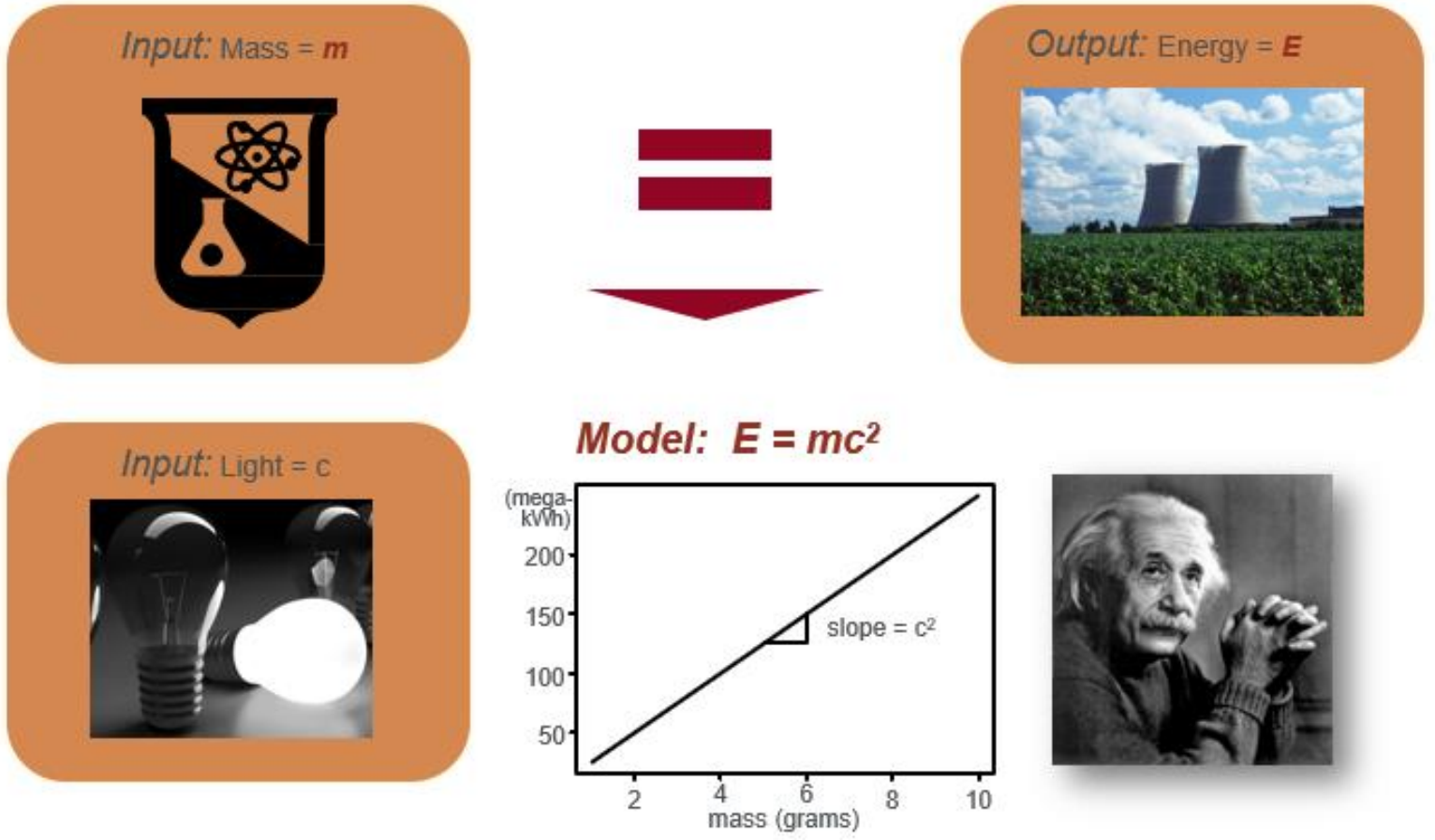
"All things are poison, and nothing is without poison;
only the dose permits something not to be poisonous."
Paracelsus (1493-1541)

Image from http://www.swisstox.ch/

Stellenbosch UNIVERSITY IYUNIVESITHI UNIVERSITEIT
forward together
sonke siya phambili
saam vorentoe

What is a model?

A way to predict outputs from inputs



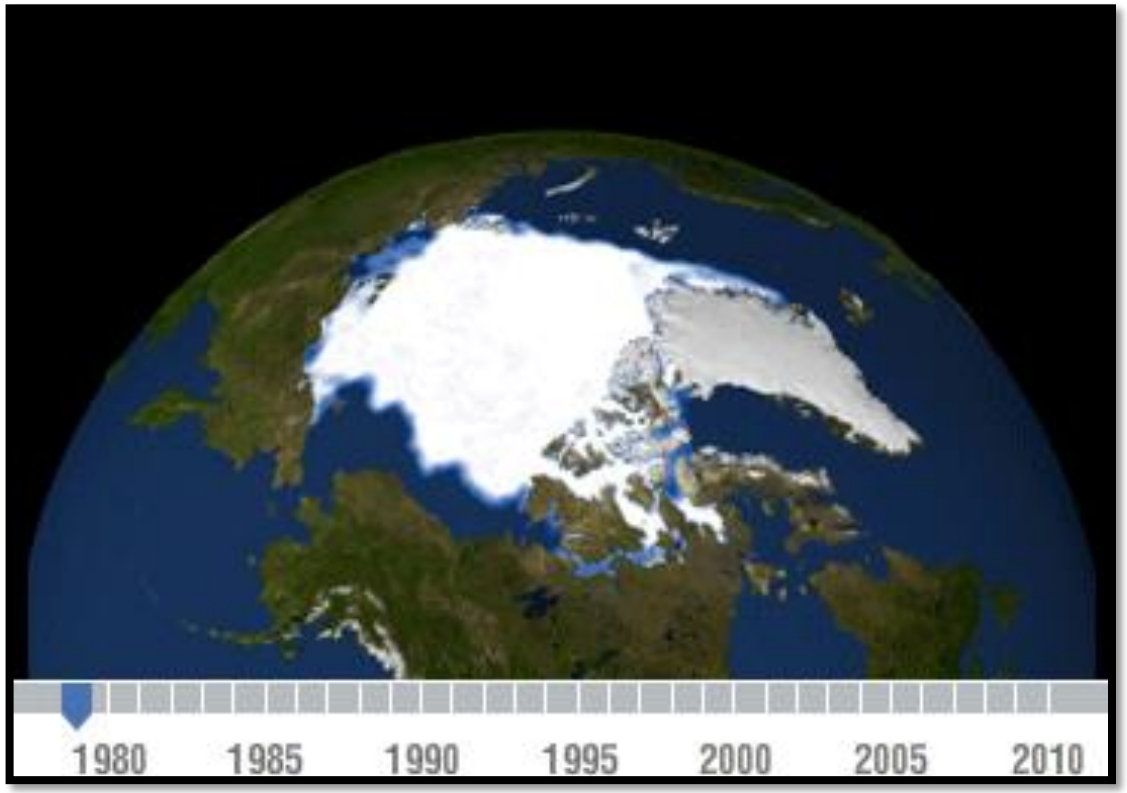
pharmacometrics africa

Stellenbosch UNIVERSITY IYUNIVESITHI UNIVERSITEIT
forward together
sonke siya phambili
saam vorentoe

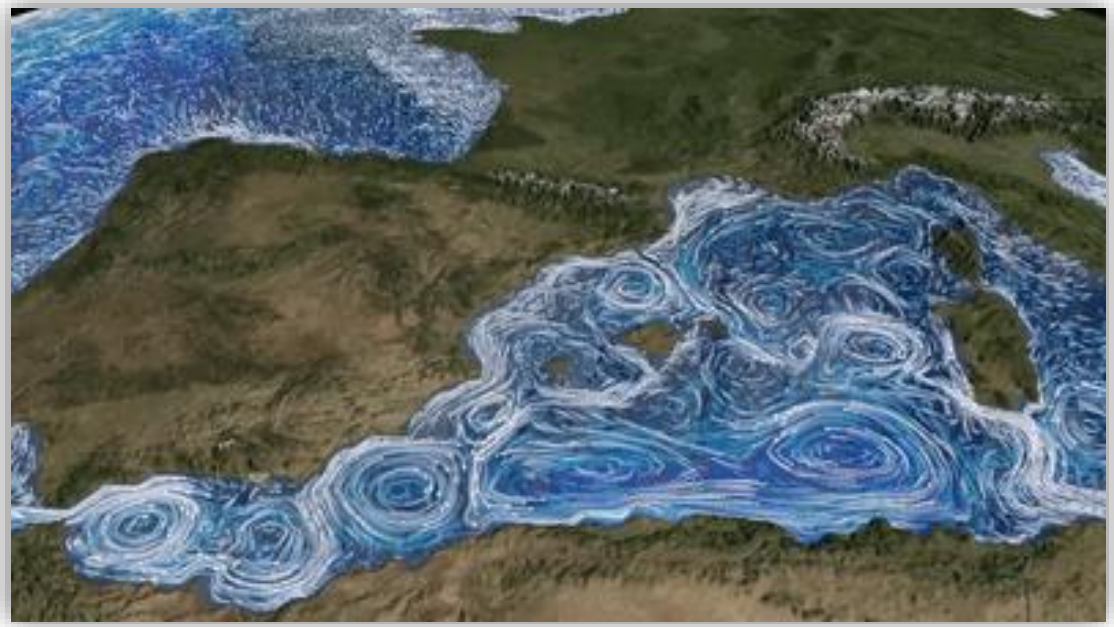
What is a model?

Best examples – Climate change models

Model is a physical, and/or mathematical and/or conceptual representation of a system of ideas, events or process



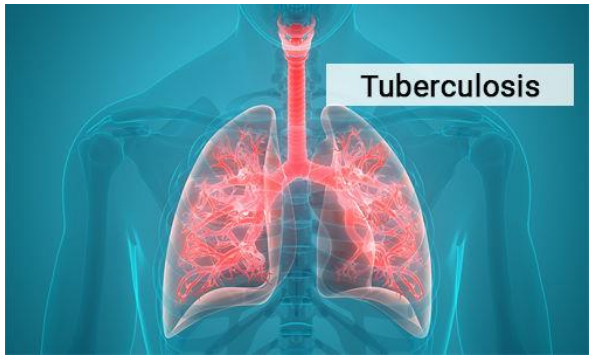
https://commons.wikimedia.org/wiki/File:Arctic_sea_ice_loss_animation.gif



https://pin.it/4GLWEwA

cp+ | pharmacometrics africa

Why do we perform mathematical modelling?

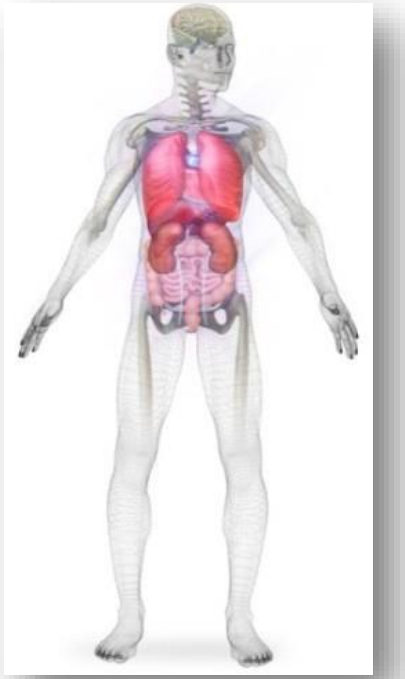


Describe
complex physiological, pharmacological, disease systems

Integrate information across
- time
- dose-levels
- studies
- drugs
- diseases

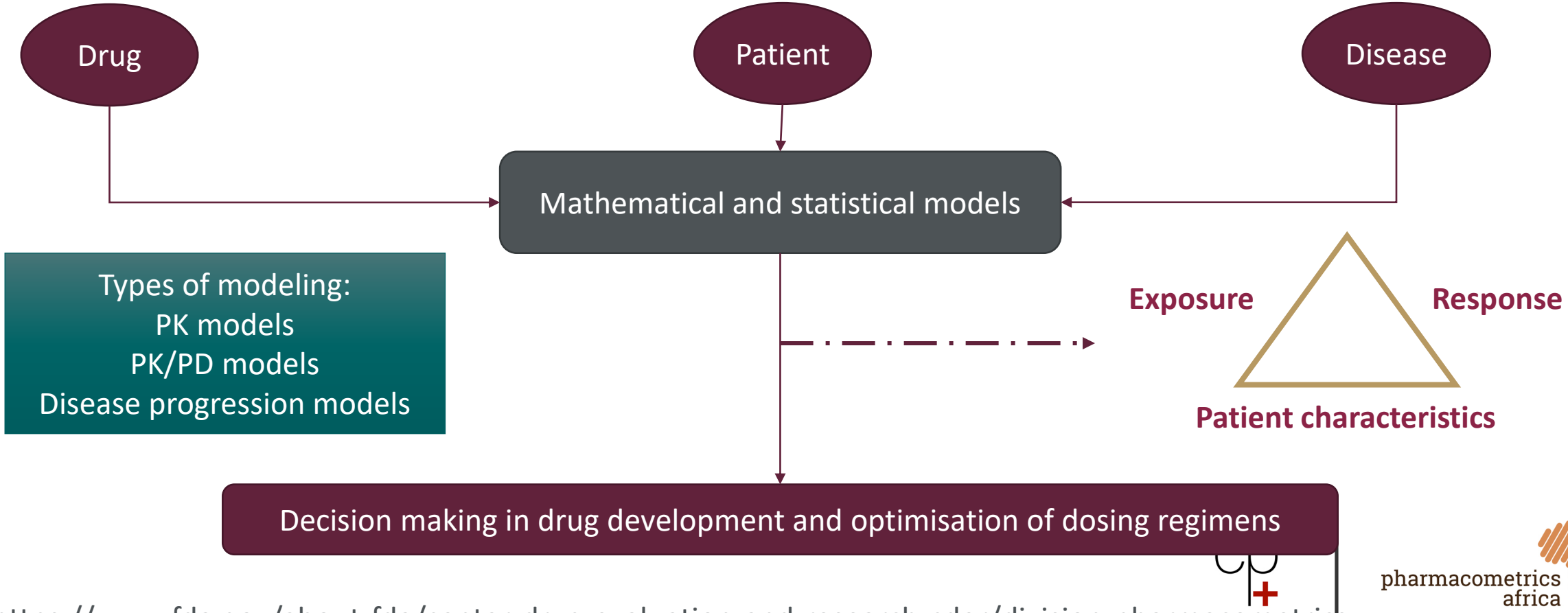
Knowledge repository

Predict
and extrapolate



What is Pharmacometrics?

An integrative and quantitative science



https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/division-pharmacometrics

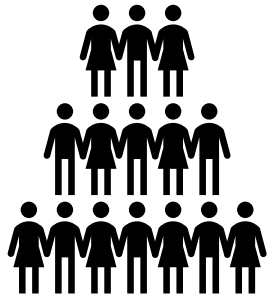
pharmacometrics africa

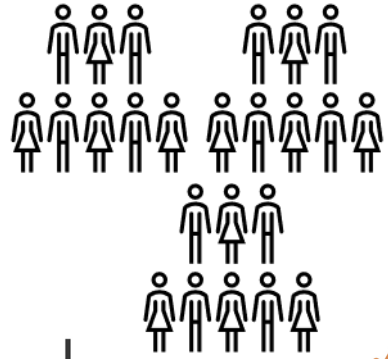
Stellenbosch UNIVERSITY IYUNIVESITHI UNIVERSITEIT

forward together
sonke siya phambili
saam vorentoe

Drug discovery and development

Target discovery → Lead Optimization → Preclinical → Clinical (Phase 1-3) → Post-marketing (real world data)



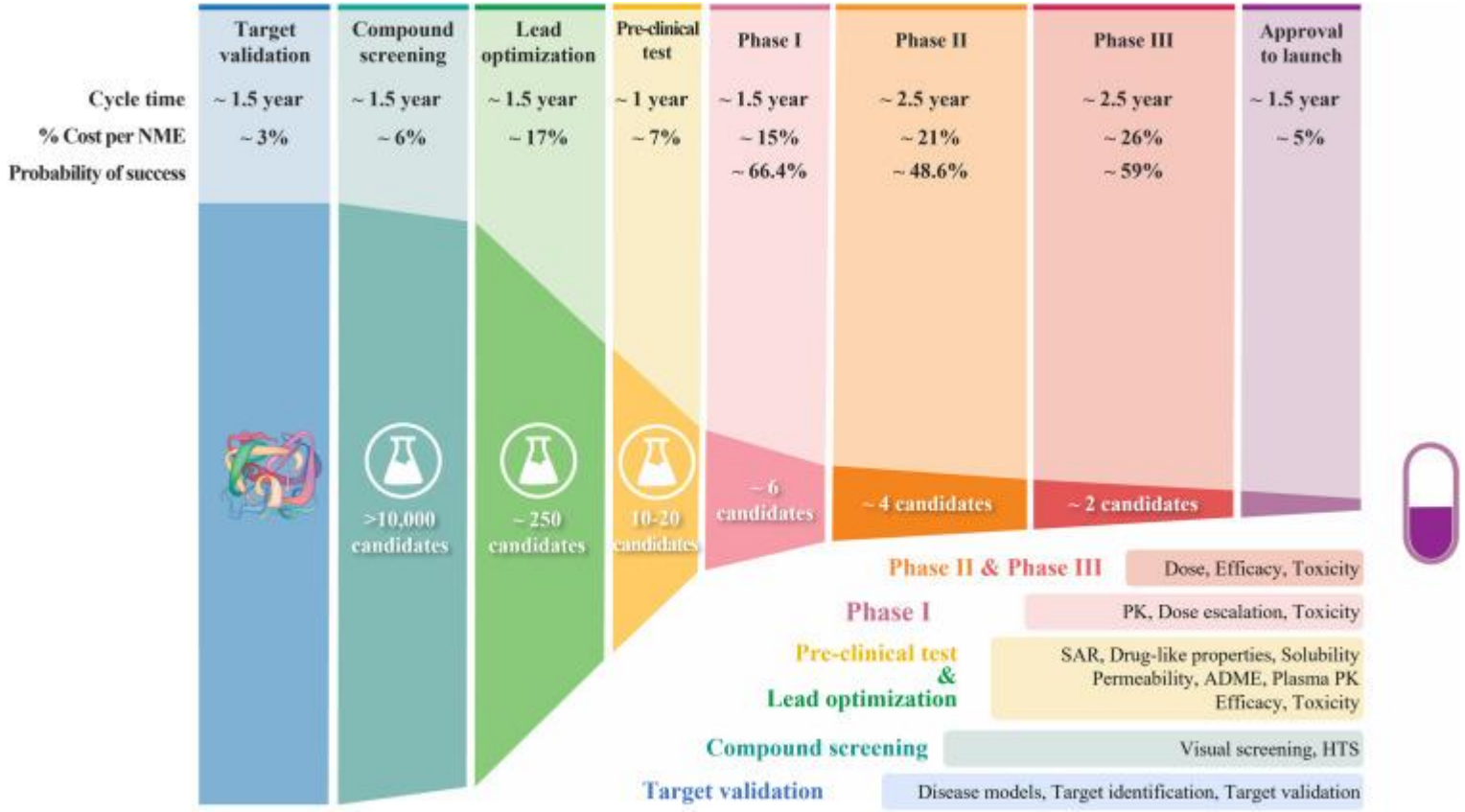


cp+

pharmacometrics africa

High attrition rates

The process of drug discovery and development, and the failure rate at each step

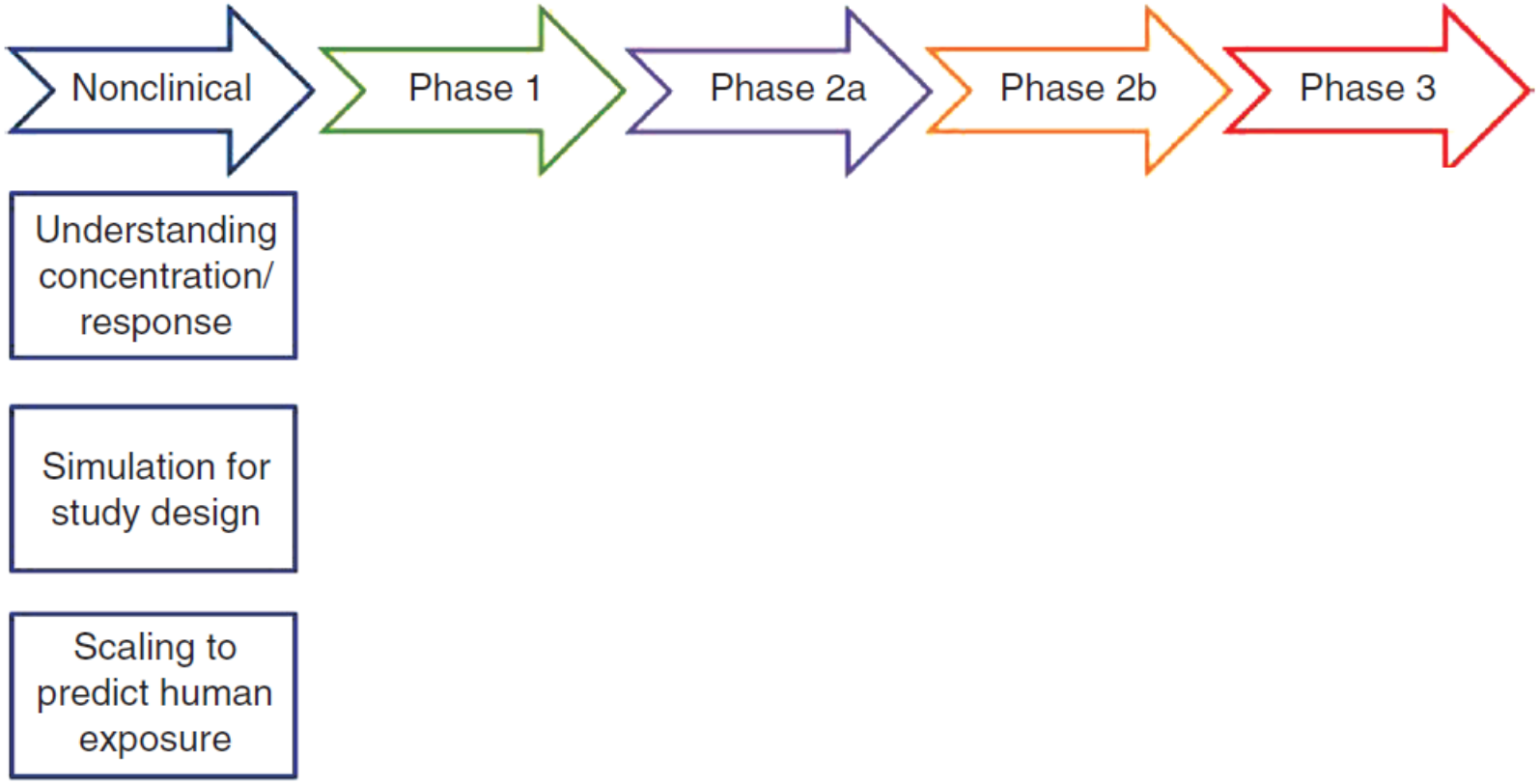


Analyses of clinical trial data from 2010 to 2017 show four possible reasons attributed to the 90% clinical failures of drug development:

- lack of clinical efficacy (40%–50%)
- unmanageable toxicity (30%)
- poor drug-like properties (10%–15%)
- lack of commercial needs and poor strategic planning (10%)

https://doi.org/10.1016/j.apsb.2022.02.002

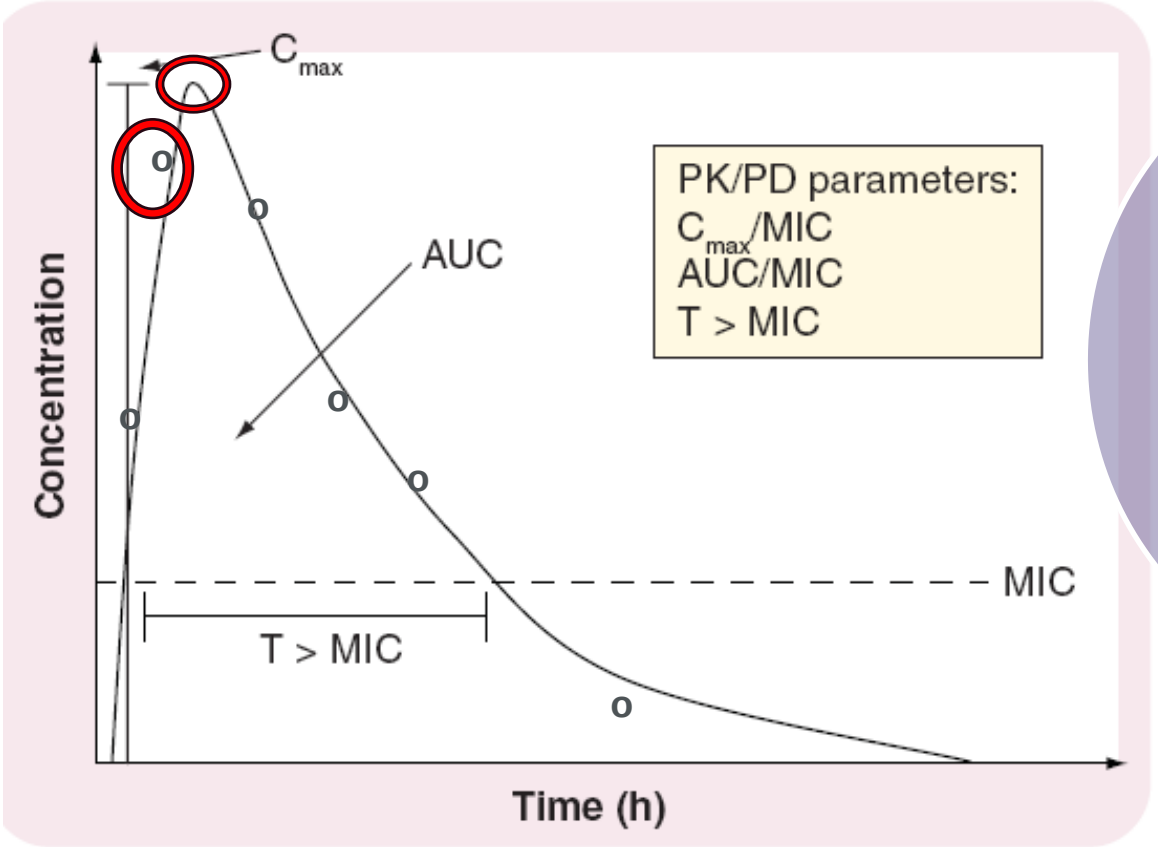
Modelling and simulation during drug development



https://doi:10.1038/psp.2012.4

Non-Compartmental Analysis in Pharmacokinetics

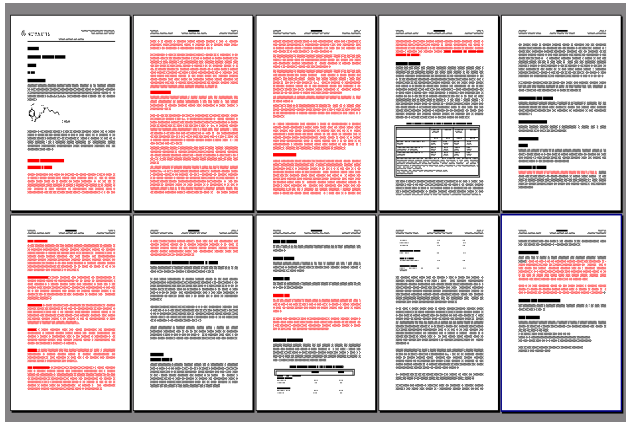
Slope **H**eight **A**rea **M**oments



Metrics of PK and PD Response (anti-infectives example)

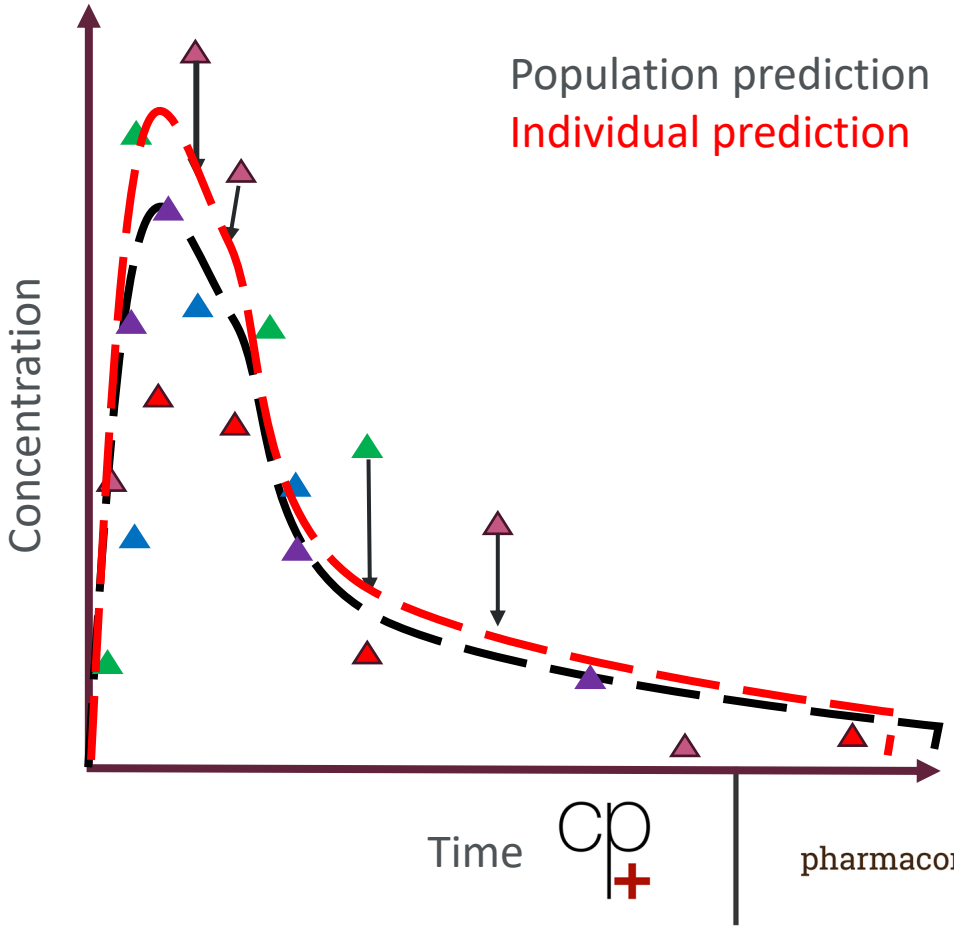
- MIC: minimum inhibitory concentration
- C_{max}: maximum plasma concentration
- AUC: area under the curve
- T > MIC: duration of concentrations above MIC

Clinical pharmacology contributions to a product label

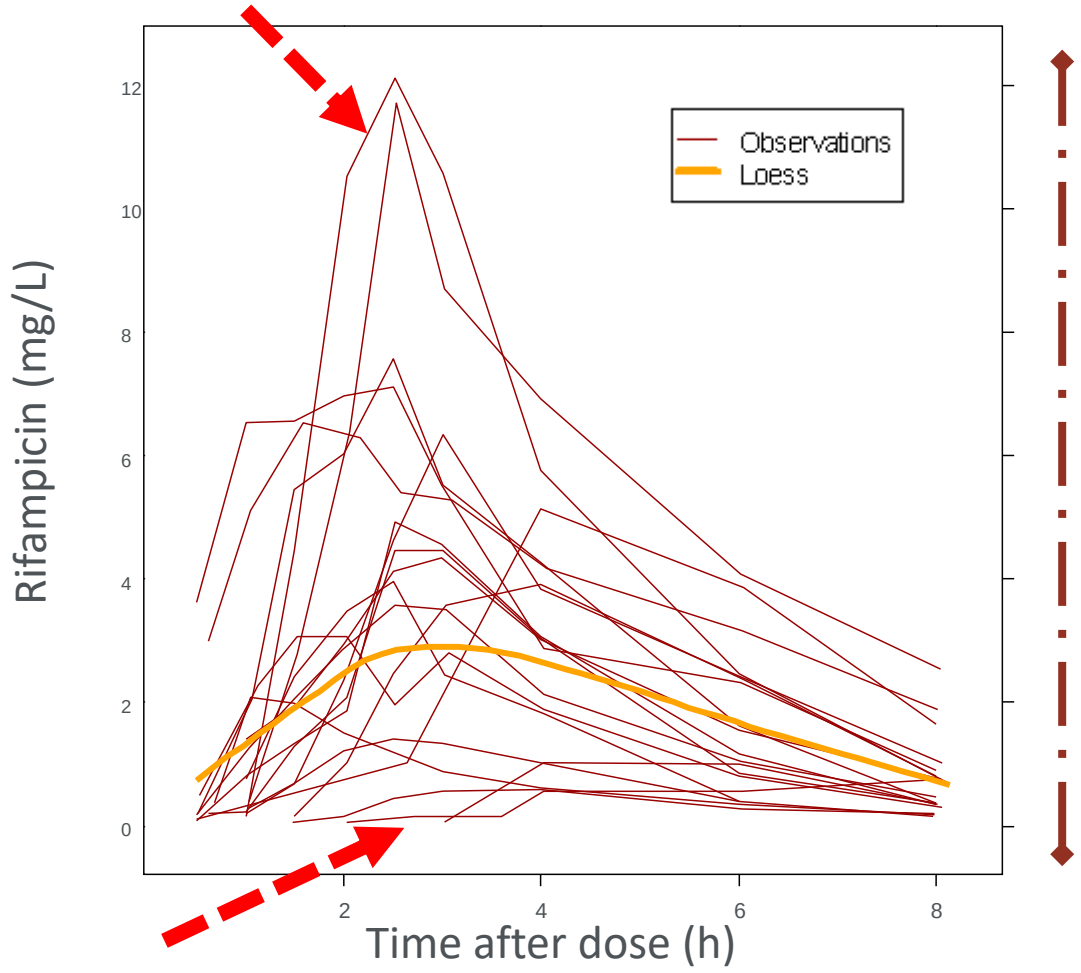


How is the model-based analysis approach different from non-compartmental analysis?

Models will tell us about the interindividual and residual **variability**



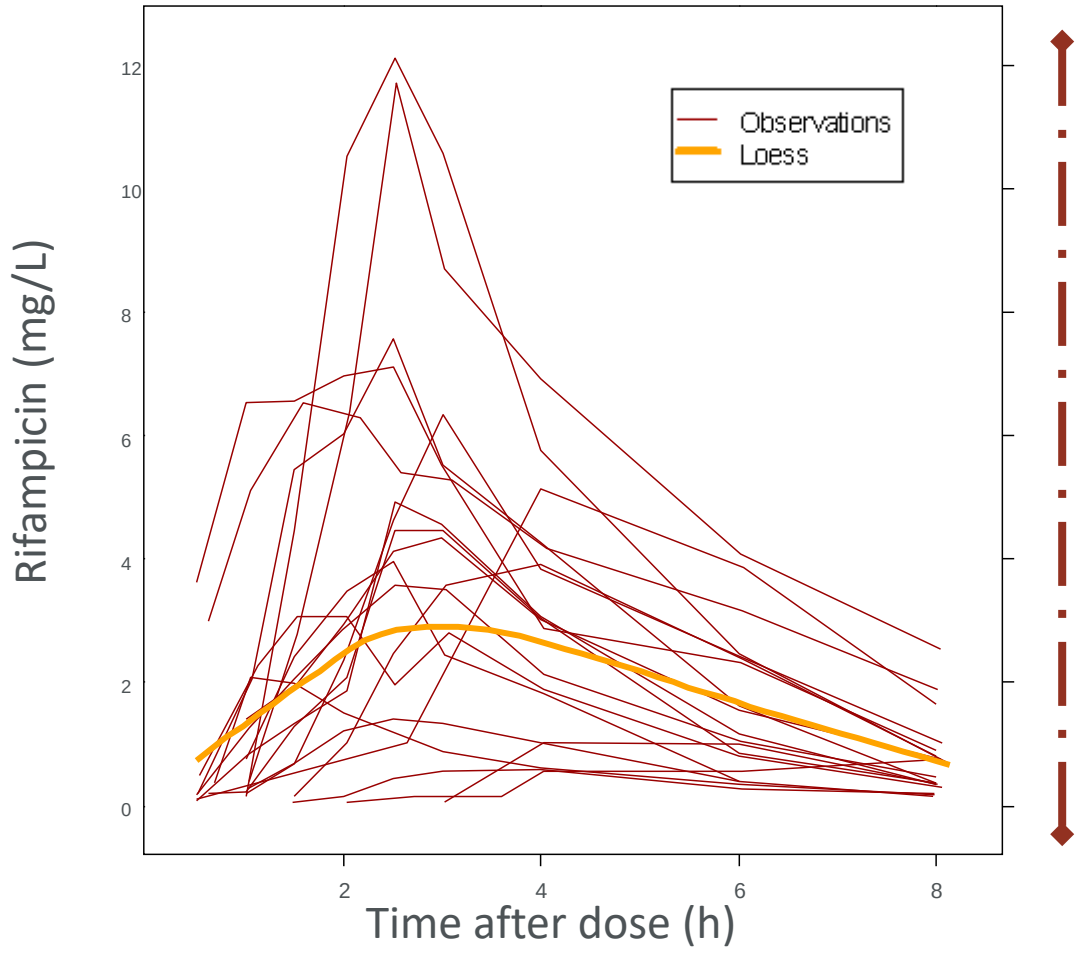
Rifampicin – Anti TB drug



- Rifampicin: large number of apparently **delayed or incomplete absorption**
- Similar experience of **variable pharmacokinetics** with other first-line anti-TB drugs
- A mathematical model can describe the typical patient; and
- Quantify and identify **sources of variability**

Source: Justin Wilkins et al, PhD, UCT. Several publications and PAGE presentations

Naïve pooled analysis



Lines spread around the mean curve – presents variability

We can analyse the data together

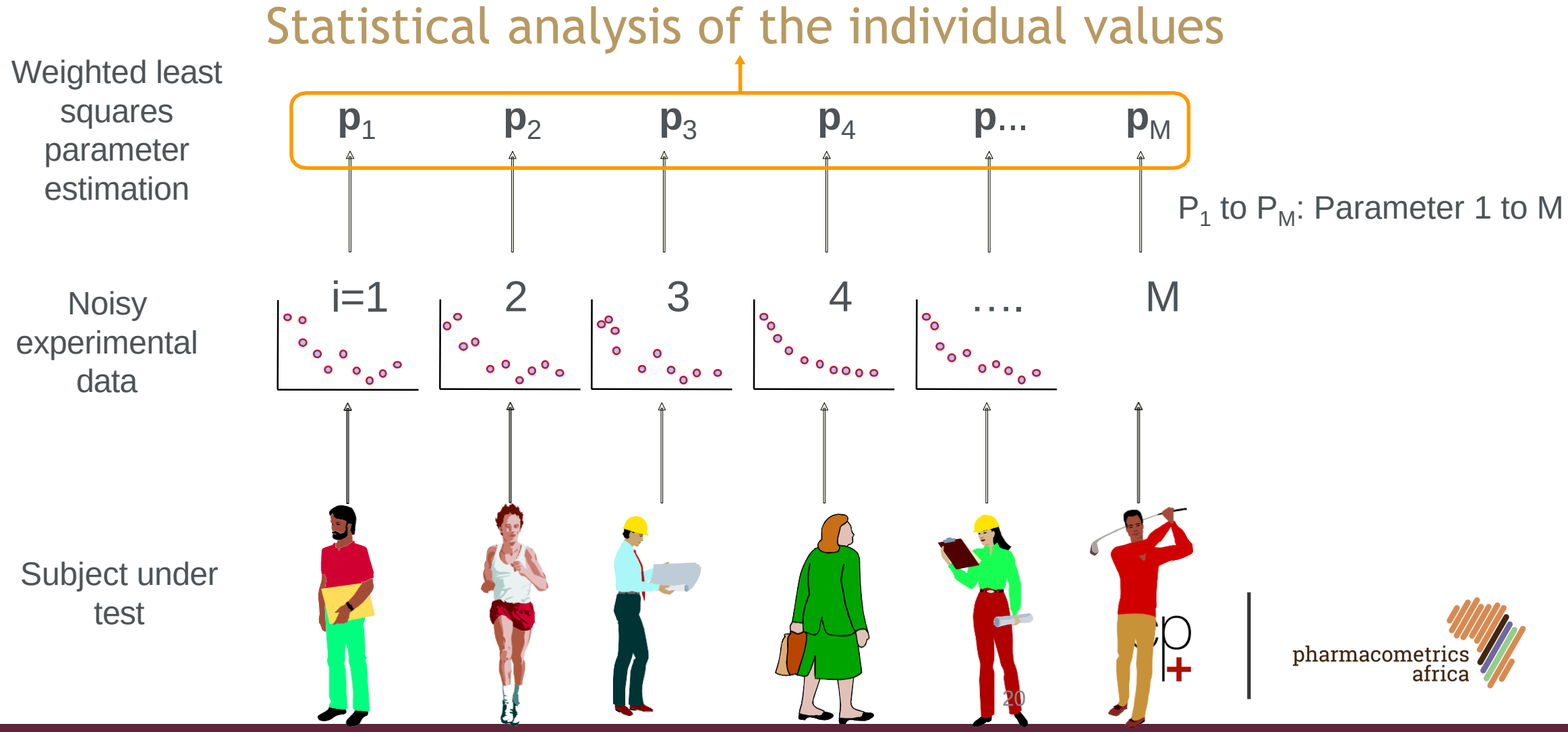
Bundles all the sources of variability

Can give bias or imprecise results

Does not provide any information about variability between individuals

Source: Justin Wilkins et al, PhD, UCT. Several publications and PAGE presentations

Describing patient variability – Standard two stage



Non-linear mixed effects modeling

Better in describing patient variability

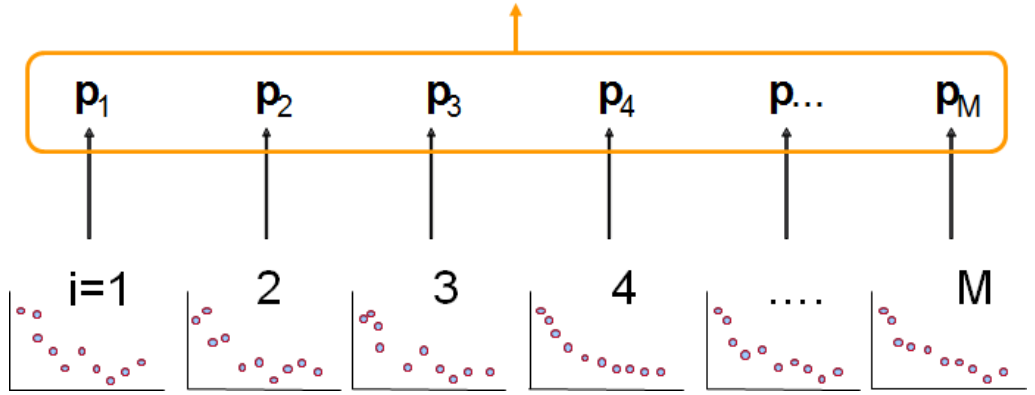
θ Population Typical Values

Ω Between-Subject or -Occasion Variability

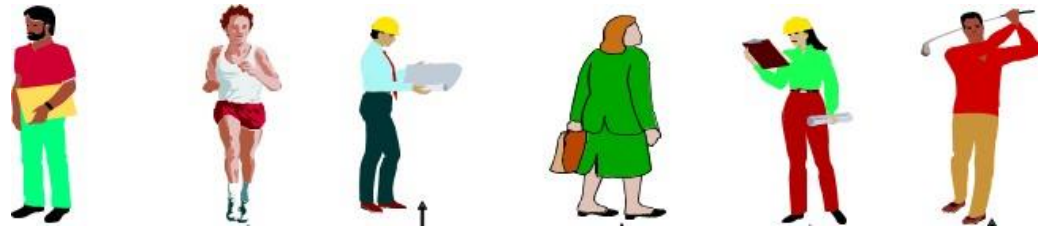
Σ Residual Unexplained Variability

Estimation of the population parameters

Noisy experimental data



Subject under test



cp

pharmacometrics africa

Fitting the model

Linear regression

$Y = a \times x + b$

Minimisation of sum of squared residuals (SS)

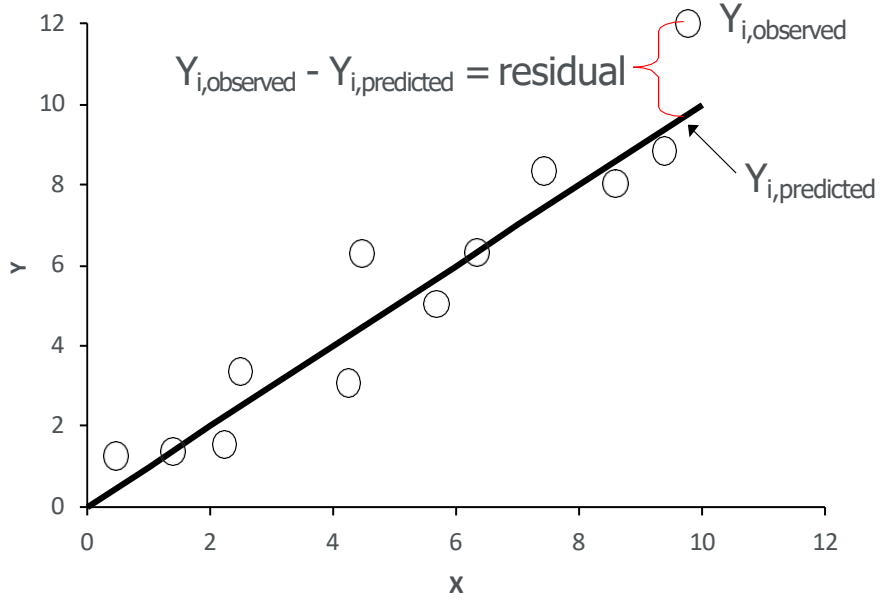
$\Sigma [Y_{i,observed} - Y_{i,predicted}]^2$

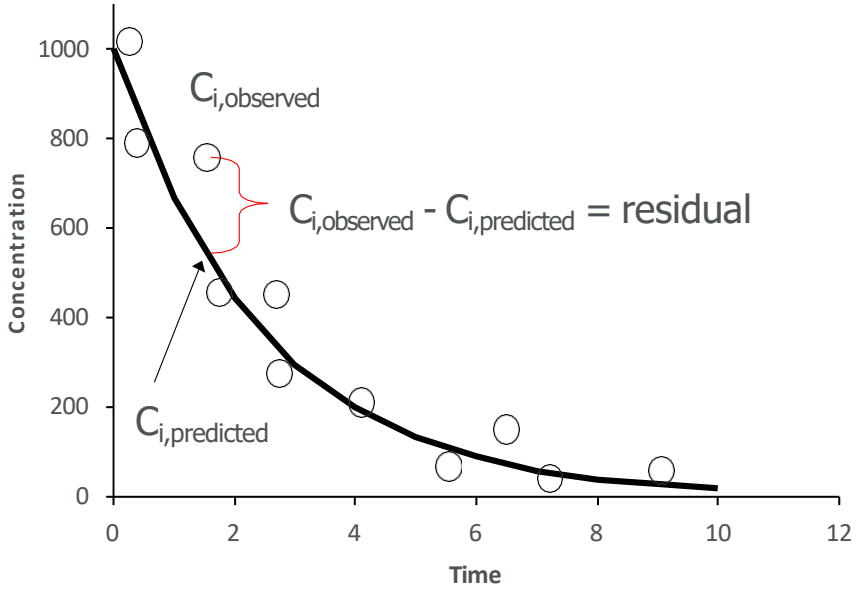
$C = C_0 \times e^{-k \times t}$

$C_0 = Dose_{IV}/V$ $k = CL/V$

Reparametrisation:

$C = [Dose_{IV}/V] \times e^{-(CL/V) \times t}$

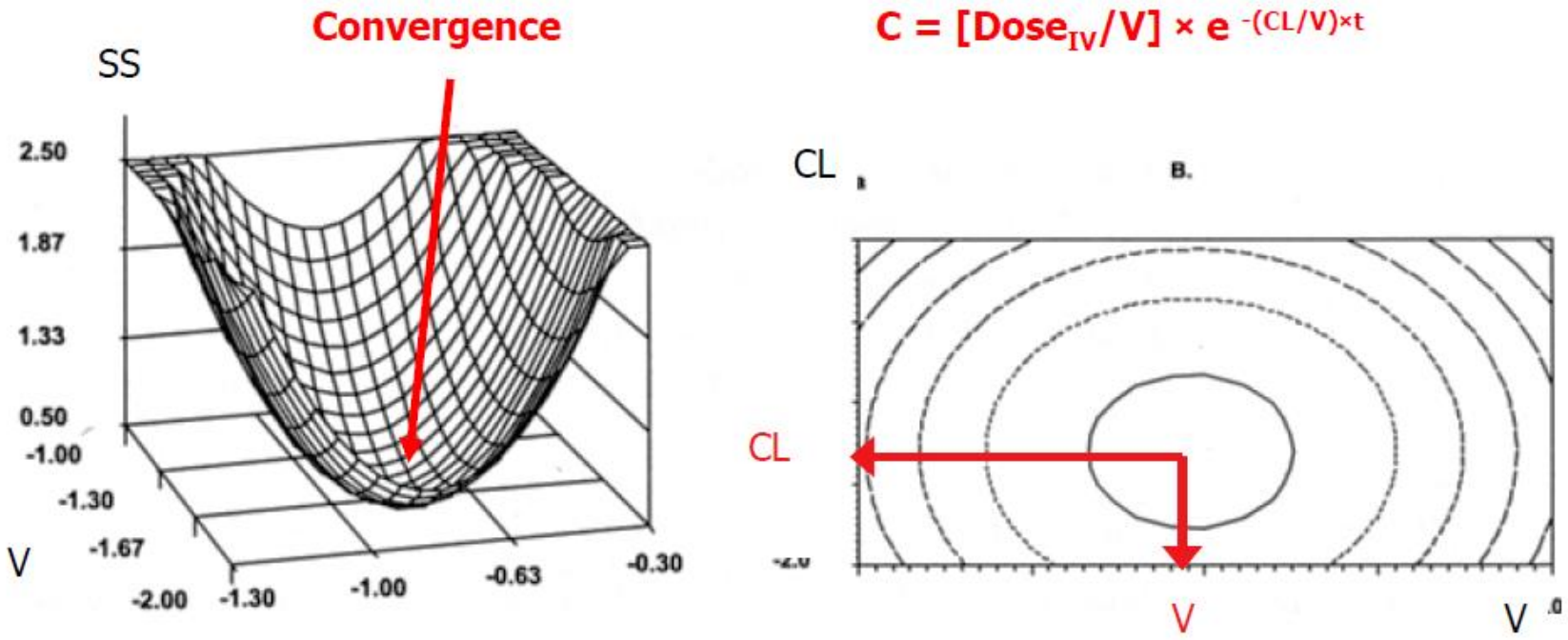




nacometrics africa

Fitting the model

Sum of squared residuals (SS) surface



New combinations of parameter values are tested iteratively until convergence is reached.

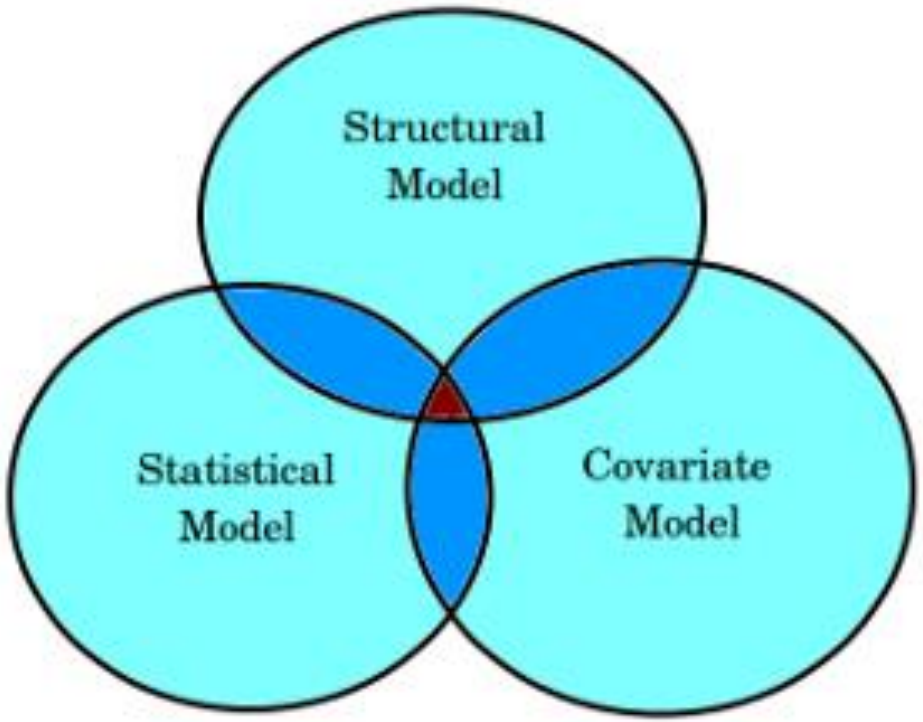
The best model parameters are those that correspond to the lowest SS

cp+

pharmacometrics africa

Nonlinear mixed effects model summary

Components of a population model



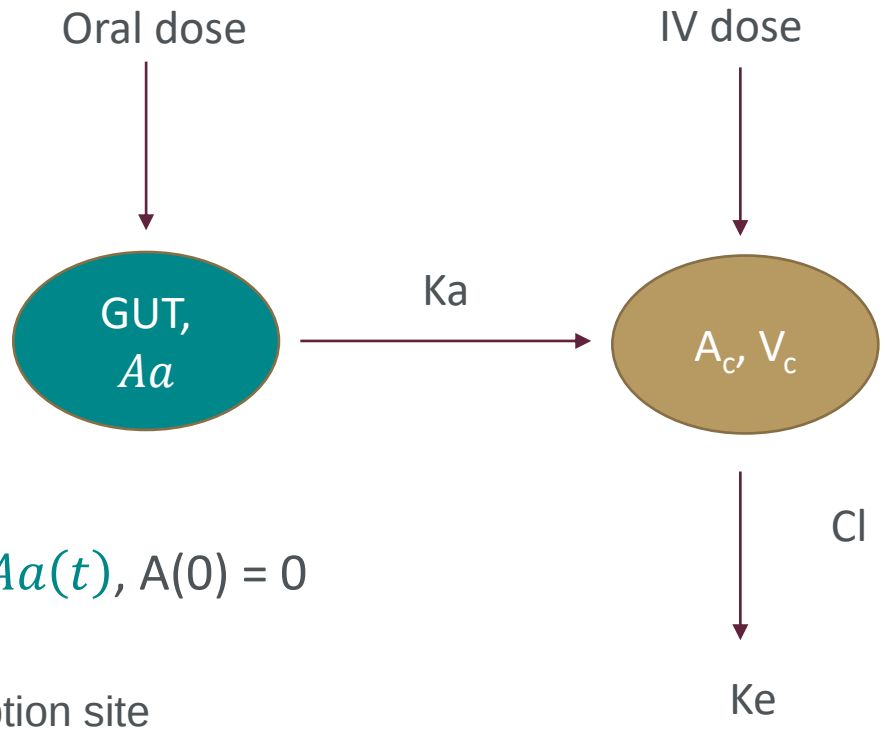
Summary

- STRUCTURAL
  - The deterministic part, the equation defining average trend e.g. $\frac{dA_c}{dt} = k_a A_a - keA_c$
- STATISTICAL
  - Inter-individual (parameter level)
  - Inter-occasion (parameter level)
  - Residual (observation level)
- COVARIATE
  - Demographic variable explaining variability e.g., weight, genotype, renal function

Specialist and general statistical software e.g., NONMEM, Monolix, Phoenix NLME, **R, nlmixr2**, etc.

Example of a possible mathematical relationship after drug administration - Structural model

One compartment model – oral or intravenous administration



Structural models are functions that describe the time course of a measured response, and can be represented as algebraic or differential equations.

$$\frac{dA_a(t)}{dt} = -kaAa(t), \text{ A(0) = 0}$$

$$\frac{dA_c(t)}{dt} = k_aA_a(t) - keA_c(t), A(0) = 0$$

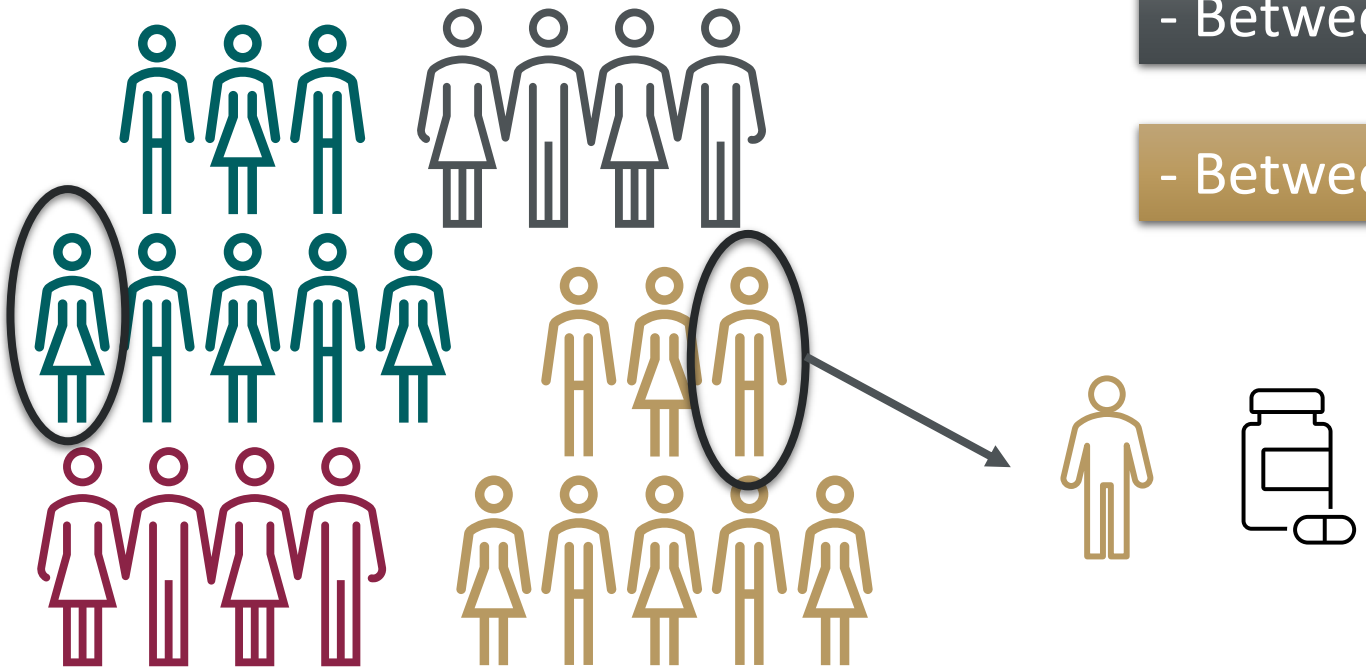
$Aa(t)$ = amount at absorption site

$Ke = Cl/V$, V=Volume of compartment, Cl =Clearance

MouldDR, Upton RN. Basic concepts in population modeling, simulation, and model-based drug development.*CPT Pharmacometrics Syst Pharmacol*. 2012;1(9):e6. Published 2012 Sep 26. doi:10.1038/psp.2012.4

Quantifying variability becomes even more important with narrow therapeutic index

Statistical Model

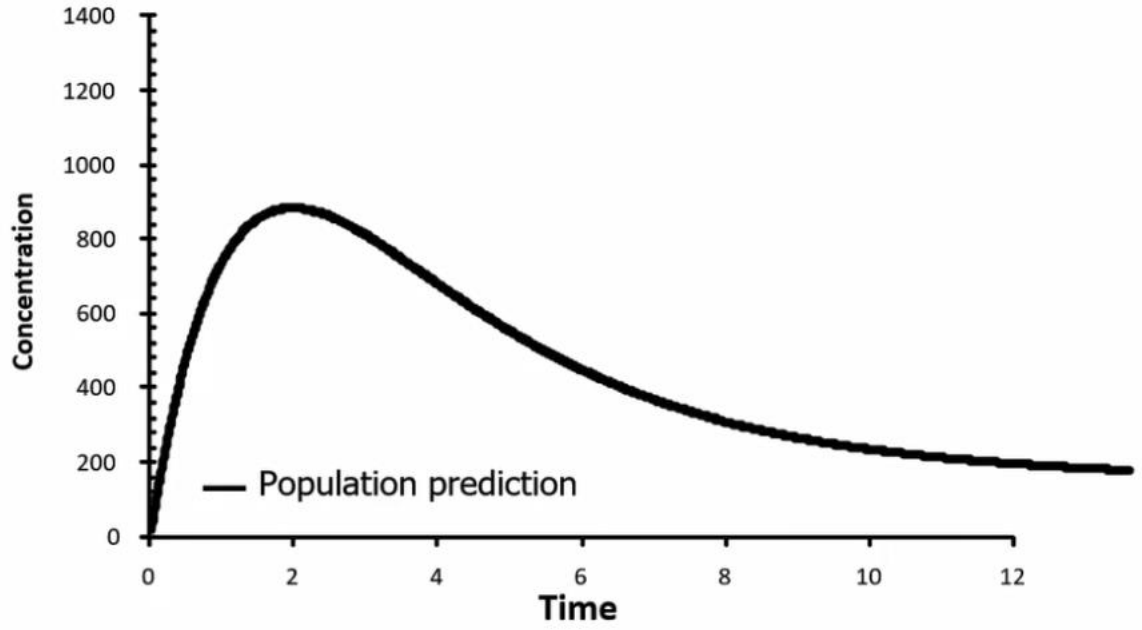


- Between subject variability

- Between occasion variability

Hierarchical variability in a non-linear mixed effects model

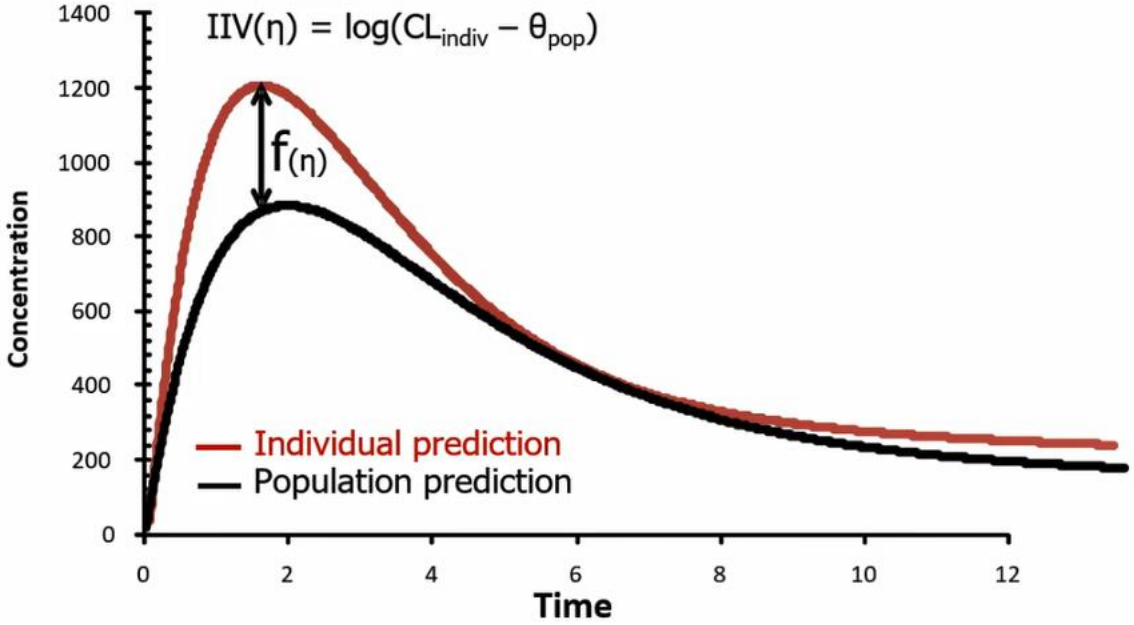
Hierarchical variability in a non-linear mixed effects model

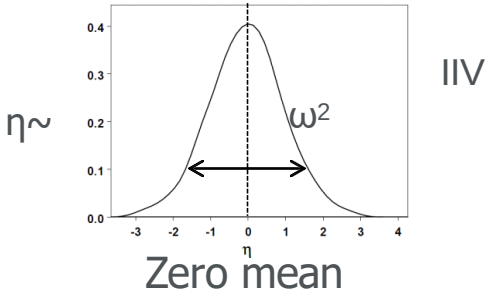


Typical value

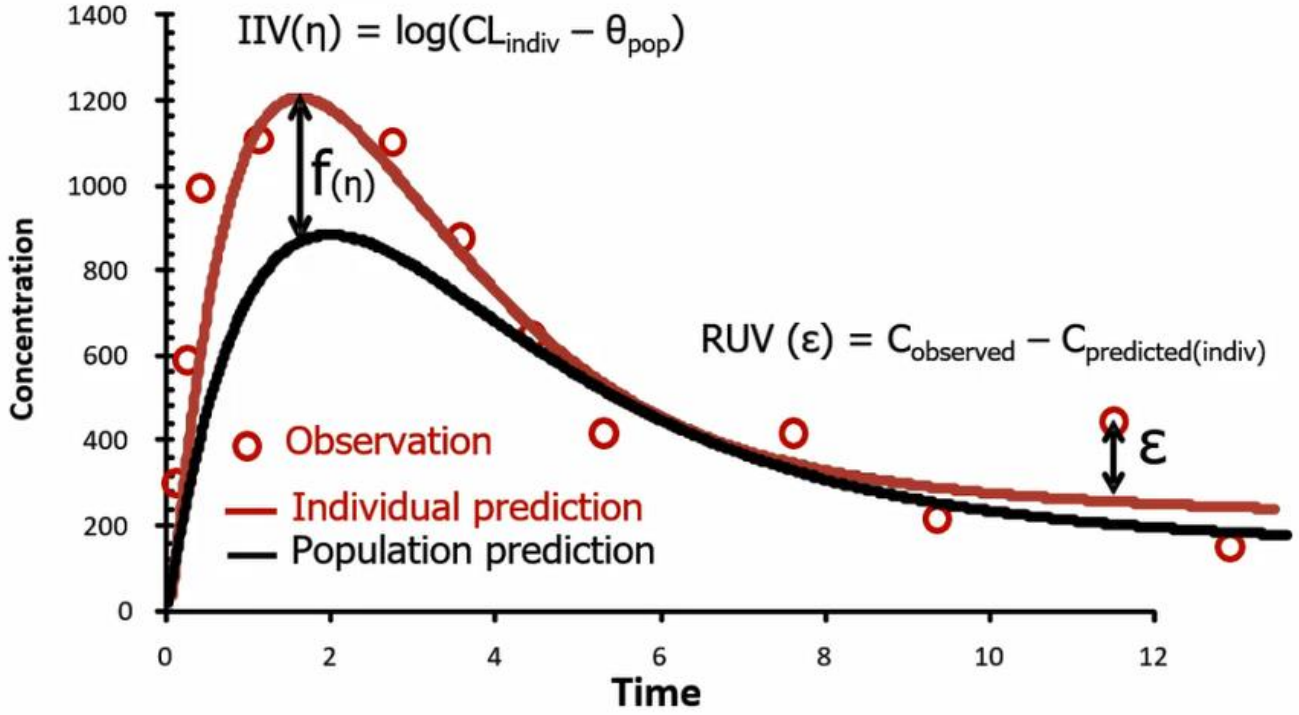
$y = f(\theta)$

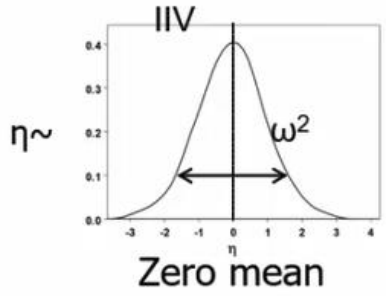
Hierarchical variability in a non-linear mixed effects model

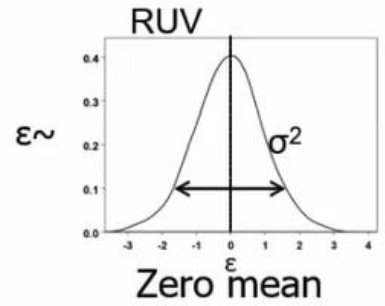


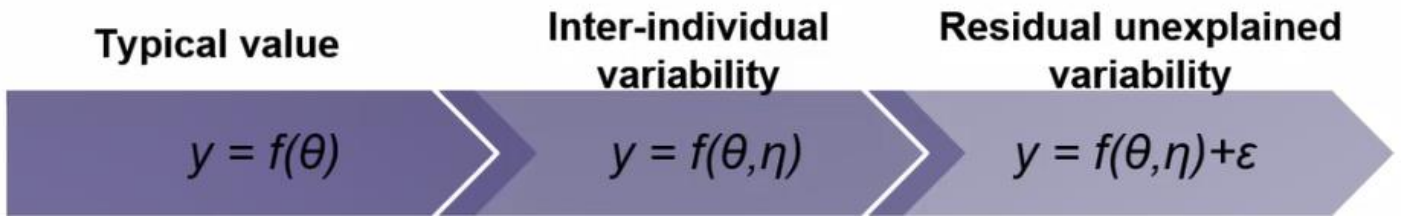


Hierarchical variability in a non-linear mixed effects model



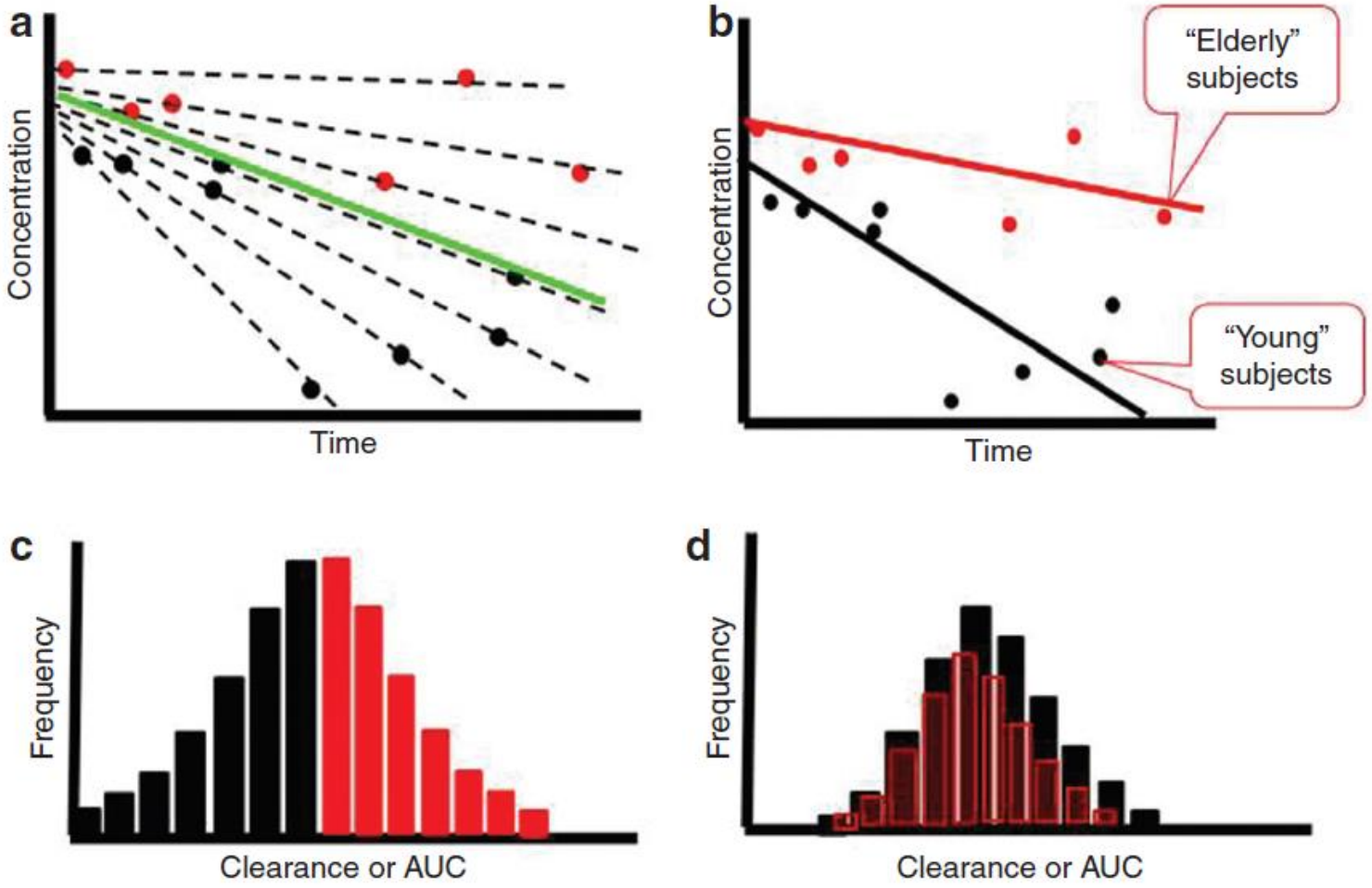






pharmacometrics africa

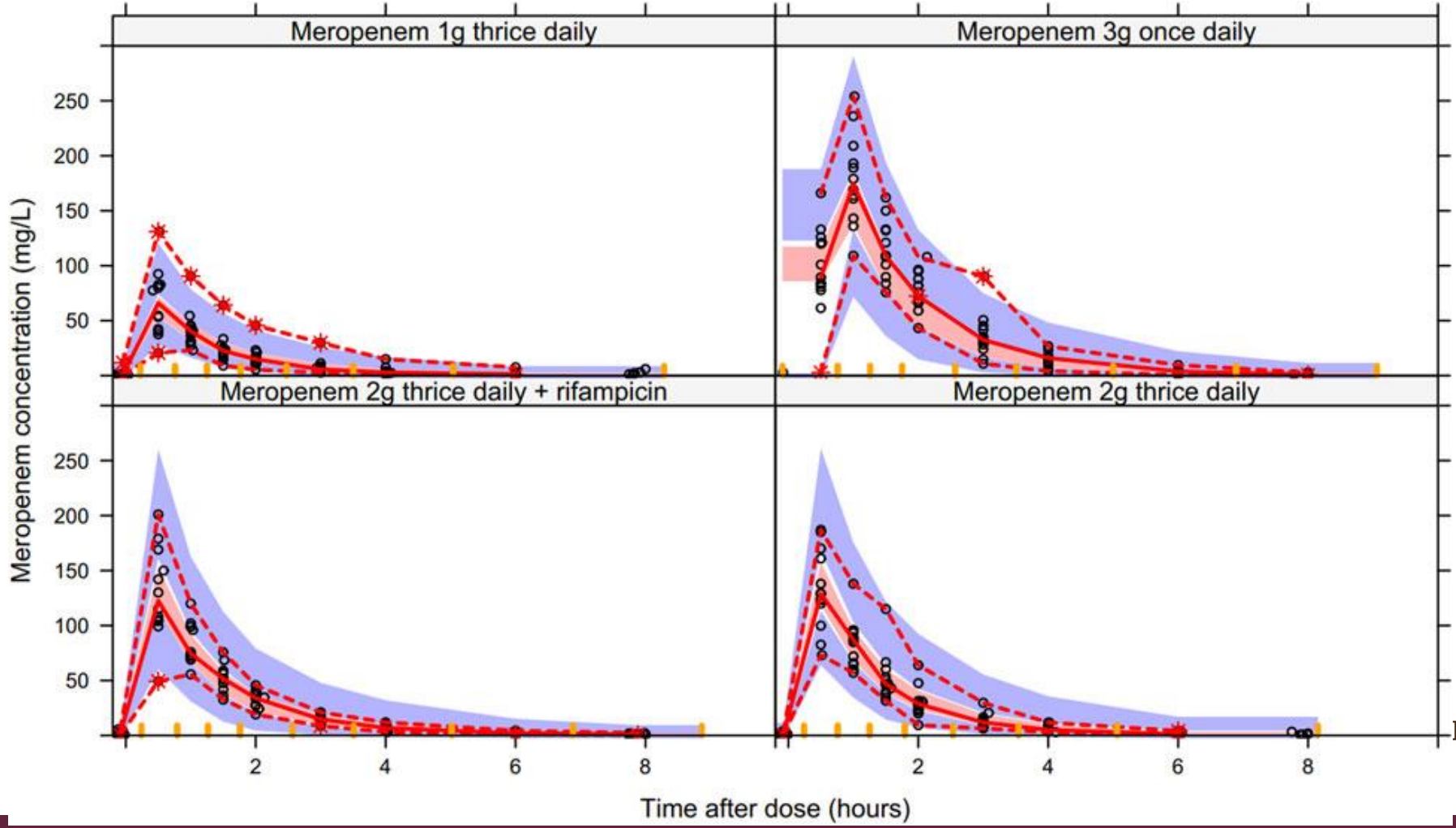
Covariate model allows us to account for the source of variability



MouldDR, Upton RN. Basic concepts in population modeling, simulation, and model-based drug development.*CPT Pharmacometrics Syst Pharmacol*. 2012;1(9):e6. Published 2012 Sep 26. doi:10.1038/psp.2012.4

Models are checked to confirm they reflect the original data,…

Visual predictive checks



harmacometrics africa

Stellenbosch UNIVERSITY IYUNIVESITHI UNIVERSITEIT
forward together
sonke siya phambili
saam vorentoe

Drugs don't have doses - people have doses

Therapeutics

ACCP

The Journal of Clinical Pharmacology
2018, 58(9) 1134–1139

DOI: 10.1002/jcph.1254

Evaluation of the Effectiveness of Dose Individualization to Achieve Therapeutic Vancomycin Concentrations

Ahmed A. Abulfathi, MMed[1*], Maxwell Chirehwa, MSc[2†], Bernd Rosenkranz, PhD[1†], and Eric H. Decloedt, MMed[1*]

Abstract

The glycopeptide antibiotic vancomycin is used for treatment of methicillin-resistant Gram-positive cocci. Adequate vancomycin plasma concentrations are related to bacterial cure. However, inter- and intrapatient variability make it difficult to achieve therapeutic vancomycin concentrations. The primary objective of this study was to determine the effectiveness of using computerized therapeutic drug monitoring (TDM) to assist in achieving therapeutic vancomycin concentrations at a tertiary hospital in South Africa. This was a 2-period study consisting of a retrospective 1-month observational period followed by a prospective 1-month period in which computerized TDM was implemented as an intervention to assist with vancomycin dose individualization. During the prospective period, all vancomycin TDM results were followed by dosage individualization using computerized TDM. The retrospective period included 77 patients with 292 vancomycin concentrations: 69% (53/77) adult and 31% (24/77) pediatric patients. The prospective period included 80 patients with 217 vancomycin concentrations measured: 69% (55/80) adult and 31% (25/80) pediatric patients. Fewer vancomycin TDM data were requested during the prospective period with a median (interquartile range) of 2 (1–3) samples per patient compared with 3 (1–5) samples per patient during the retrospective period. The odds ratio of achieving therapeutic trough concentrations was 3.63 (95%CI 1.81–7.3) in the prospective period when TDM-adjusted vancomycin dosing and appropriate TDM procedures were applied. The use of computerized TDM resulted in a higher frequency of therapeutic vancomycin concentrations in a middle-income setting. Trough vancomycin concentrations alone correlate poorly with the area under plasma concentration-time curve from 0 to 24 hours.

Keywords

Vancomycin, Population Pharmacokinetics, Individualized, Dosing, Computerized TDM, Therapeutic

cp+

pharmacometrics africa

Stellenbosch UNIVERSITY IYUNIVESITHI UNIVERSITEIT
forward together sonke siya phambili saam vorentoe

Pharmacometrics at the patient bedside

Dose optimization (Dose to targeted AUC 400 mg.h/L)

- Mrs Y, 54-year-old female was admitted in ICU. During the ICU stay she was diagnosed with MRSA requiring vancomycin. She was given a loading dose of 2mg followed by 2g over a 24-hour infusion. Creatinine 41 mmol/L.

1st vancomycin concentration: 11,92 mg/L

In response the doctor administers 2.5 g over 24 hours.

2nd vancomycin concentration: 17,92 mg/L

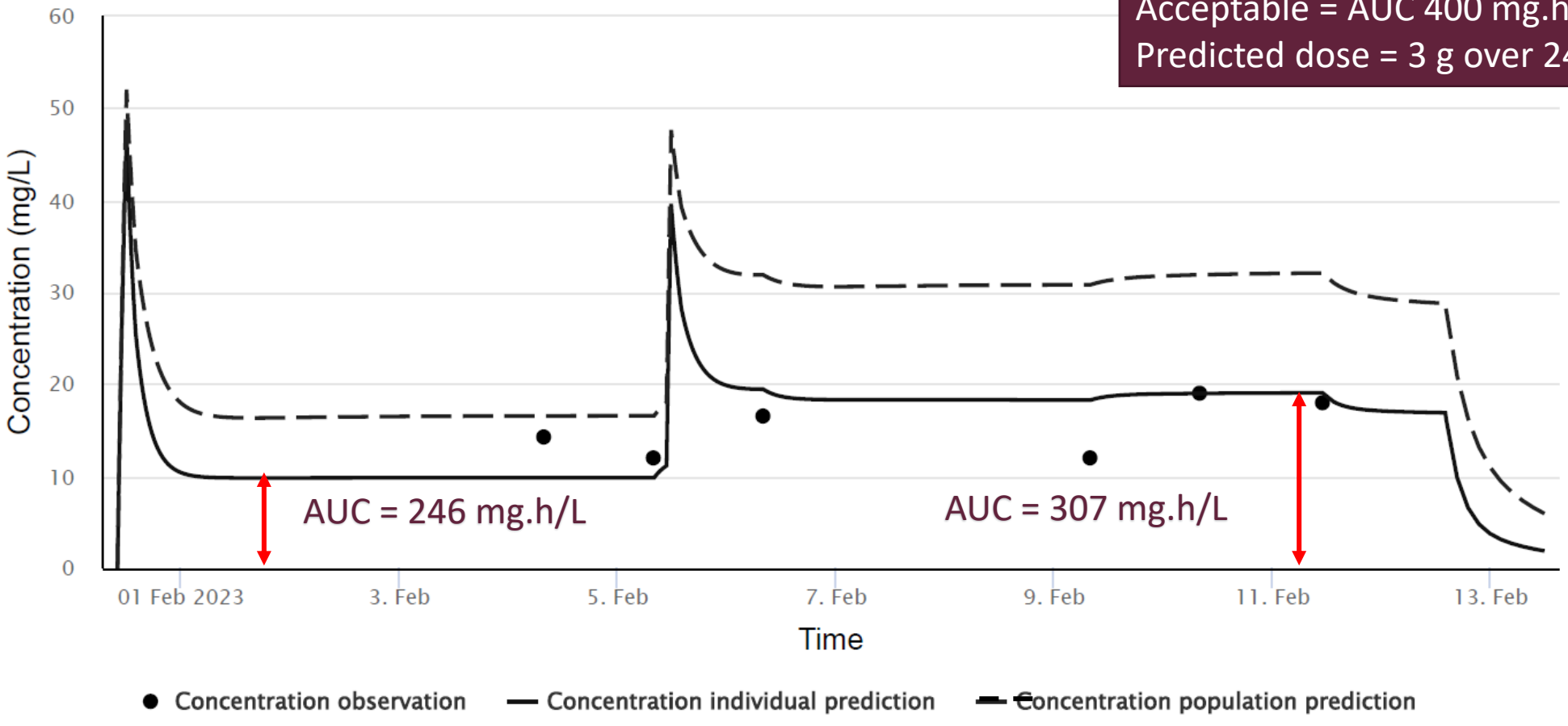
Are we dosing appropriately – given this is a critically ill patient with augmented renal function?

cp+ | pharmacometrics africa

Pharmacometrics at the patient bedside

Model informed dosing prediction - vancomycin

Acceptable = AUC 400 mg.h/L
Predicted dose = 3 g over 24 hours



It's all about Dose-Response…

Getting the right dose to the right patient

"All things are poison, and nothing is without poison;
only the dose permits something not to be poisonous."
Paracelsus (1493-1541)

Image from http://www.swisstox.ch/

Stellenbosch UNIVERSITY IYUNIVESITHI UNIVERSITEIT
forward together sonke siya phambili saam vorentoe

A skill to be developed in Africa…

Citation: CPT: Pharmacometrics & Systems Pharmacology (2013) 2, e1; doi:10.1038/psp.2013.45

www.nature.com/psp

PERSPECTIVE

Pharmacometrics: Opportunity for Reducing Disease Burden in the Developing World: the Case of Africa

G Pillai[1], G Davies[2], P Denti[3], J-L Steimer[4], H McIlleron[3], S Zvada[3], E Chigutsa[3], E Ngaimisi[5], F Mirza[1], B Tadmor[6] and NHG Holford[7]

Pharmacometricians are virtually nonexistent in Africa and the developing world. The unrelenting burden of infectious diseases, which are often treated using medicines with narrow effectiveness, safety dose ranges, and the growing prevalence and recognition of noncommunicable diseases represents a significant threat for the patients although affording an opportunity for advancing science. This article outlines the case for pharmacometricians to redirect their expertise to focus on the disease burden affecting the developing world.

CPT: Pharmacometrics & Systems Pharmacology (2013) **2**, e1; doi:10.1038/psp.2013.45; published online 00 Month 2013

cp+ | pharmacometrics africa

Stellenbosch UNIVERSITY IYUNIVESITHI UNIVERSITEIT

forward together
sonke siya phambili
saam vorentoe

Pharmacometrics Africa

A non-profit company - goal to develop quantitative clinical pharmacology among African scientists

pharmacometrics africa

What is Pharmacometrics?

Pharmacometrics is an emerging discipline that uses mathematical and statistical tools to quantify drug, disease, and trial information to aid efficient drug development and/or regulatory decisions. It designs and applies mathematical models to describe the relationship between drug exposure (pharmacokinetics) and response (pharmacodynamics) for both desired and undesired effects, and aims to include in such models the effects of individual patient characteristics.

Welcome to Pharmacometrics Africa

Pharmacometrics Africa is a platform for interested groups to establish and run open access quantitative clinical pharmacology educational programs in partnership with local research organisations and academic groups.

Learn more about what we're up to, who we are and what you can do to help.

https://pmxafrica.org/

cp+ | pharmacometrics africa

Stellenbosch UNIVERSITY IYUNIVESITHI UNIVERSITEIT

forward together
sonke siya phambili
saam vorentoe

WCoP 2022 – free recordings available

Dear Colleagues,

Welcome to the website of the 3rd World Conference on Pharmacometrics (WCoP) that was held in 2022 on the continent of Africa in Cape Town, South Africa.

WCoP 2022 was a hybrid conference, with both live attendance from the delegates that joined in person in Cape Town, and virtual attendance via an online platform. This followed our decision to postpone our originally scheduled 2020 meeting due to COVID-19. The flexibility afforded by the HYBRID conference format allowed us to host 462 delegates of which 110 joined the meeting in-person at the Century City Convention Centre in Cape Town.

Welcome Letter

In our welcome letter to delegates, we highlighted how the success previous meetings in Seoul, South Korea in 2012 and Brisbane, Australia in 2016 has been a source of motivation for the Executive Committee to expand the global reach of our science beyond Europe and the US. We quoted the familiar statistics of how Africa accounts for 15% of the global population and 25% of the global disease burden: yet only produces about 2% of the world's research output and holds only 0.1% of the world's patents. Research and development pipelines for the diseases that disproportionately affect African countries are grossly inadequate. Furthermore, clinical pharmacology studies that underpin drug label claims for efficacy and safety are rarely studied in Africa. Such assessments are important to understand dosing requirements in communities that might have different intrinsic (e.g. genetics, physiology, comorbidity) and extrinsic (local medical practice, diet) factors compared to patients in the more developed economies where these studies are usually conducted.

Your hosts:

pharmacometrics africa

Continue the Momentum

cp+ | pharmacometrics africa

Stellenbosch UNIVERSITY IYUNIVESITHI UNIVERSITEIT
forward together
sonke siya phambili
saam vorentoe

WCoP 2022 - free recordings available

- https://wcop2022.org/
- https://www.youtube.com/watch?v=phhsh8R_sYQ&t=22s
- https://www.youtube.com/watch?v=VqzVdV0NcR0
- https://www.youtube.com/watch?v=SgIc6bkGQCY
- https://www.youtube.com/watch?v=_hxdonlgps8
- https://www.youtube.com/watch?v=2k8fJfUw6oo&t=2s

cp+ | pharmacometrics africa

Stellenbosch UNIVERSITY IYUNIVESITHI UNIVERSITEIT
forward together sonke siya phambili saam vorentoe

Acknowledgements

- Slide compilation done with:
  - Colin Pillai – CP and associates, Pharmacometrics Africa
  - Paolo Denti – University of Cape Town
  - Veshni Pillay-Fuentes Lorente – Stellenbosch University
  - Joe Standing – University College London

cp+ | pharmacometrics africa

thank you | enkosi | dankie