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pharmacometrics africa

PK/PD (quantitative pharmacology) intro lecture

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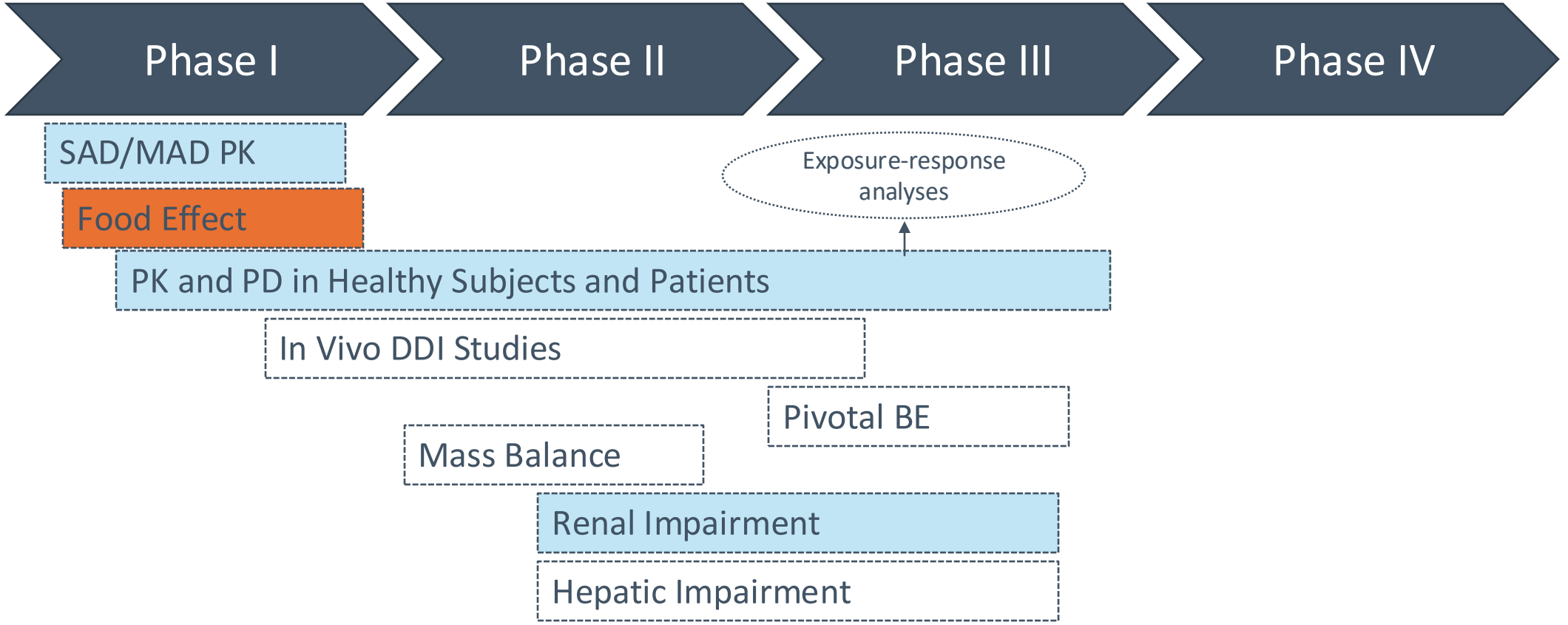
Clinical pharmacology and drug development



Additional considerations:
Pharmacogenomics, Population PK, PBPK, Paediatrics, Geriatrics, Pregnancy/Lactation, bridging studies, bioanalytical methods and for biologics immunogenicity

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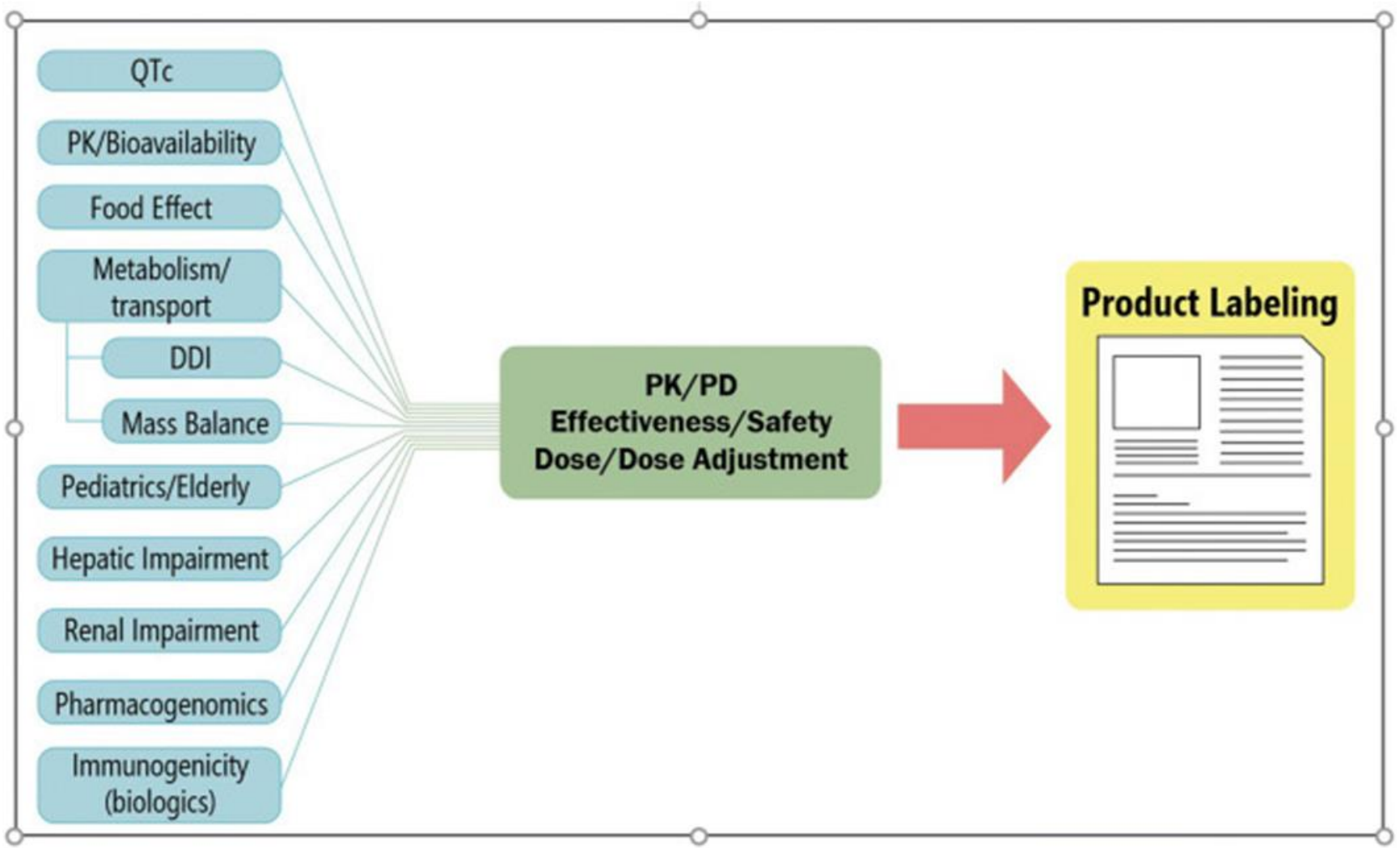
Drug labeling



https://doi.org/10.1208/s12248-021-00563-3

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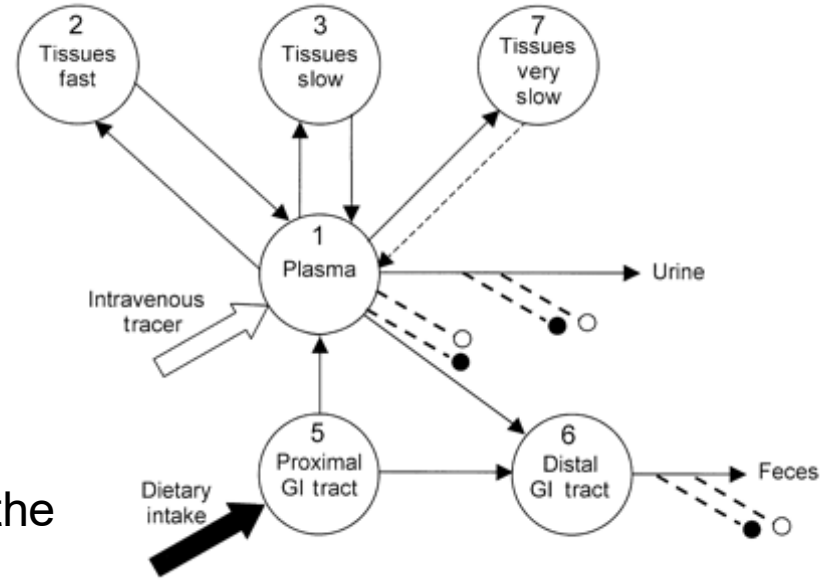
What is pharmacometrics

Definition of pharmacometrics from the website of the US Food and Drug Administration:

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.**



Pharmacometrics designs and applies mathematical models to describe the relationship between

- **drug exposure (or pharmacokinetics),**
- **response (or pharmacodynamics) for**
- **both desired and undesired effects, and**
- **aims to include in such models the effects of individual patient characteristics**.

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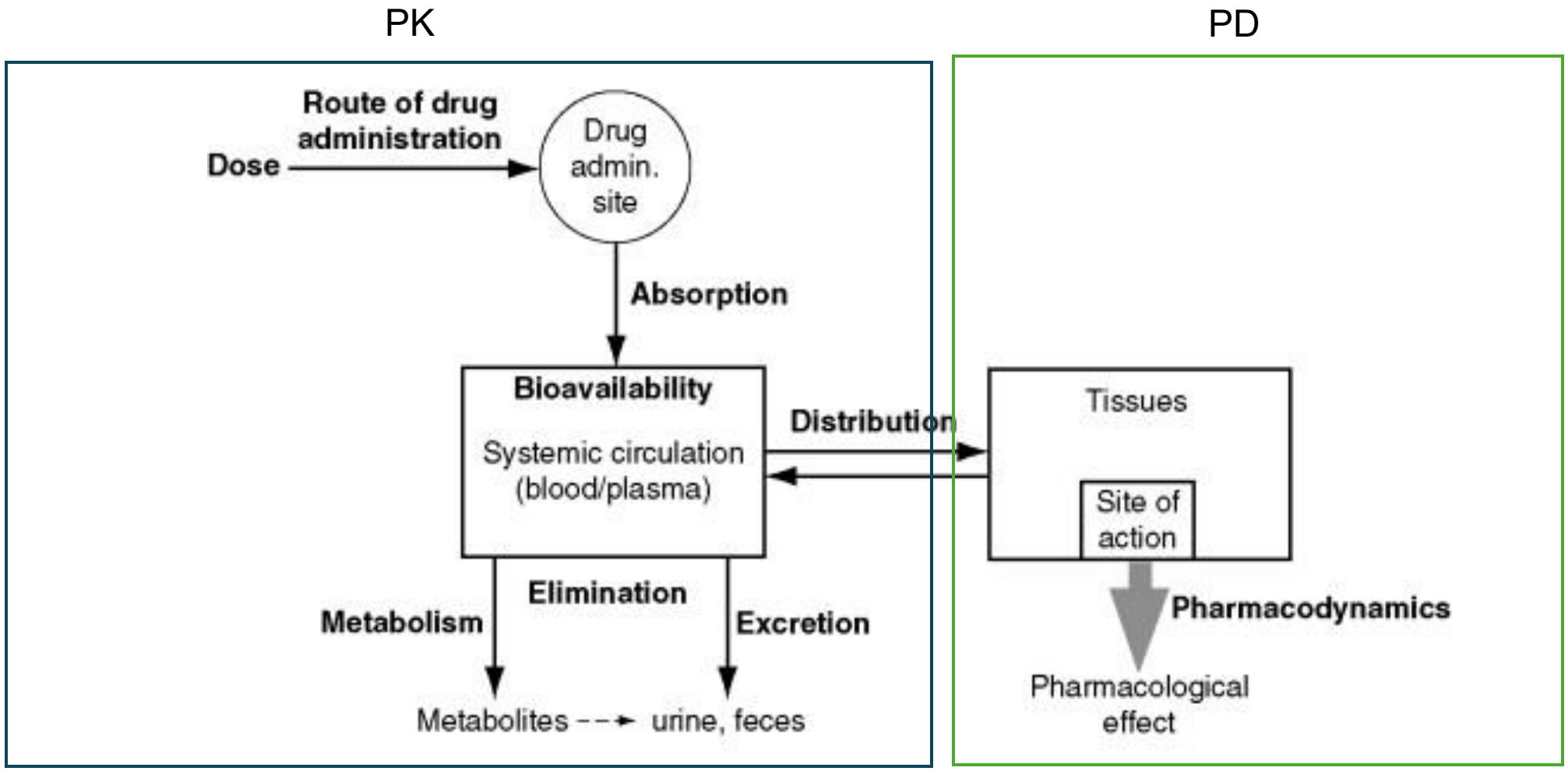
Dose and response



Disposition = Absorption + Distribution + Metabolism + Excretion

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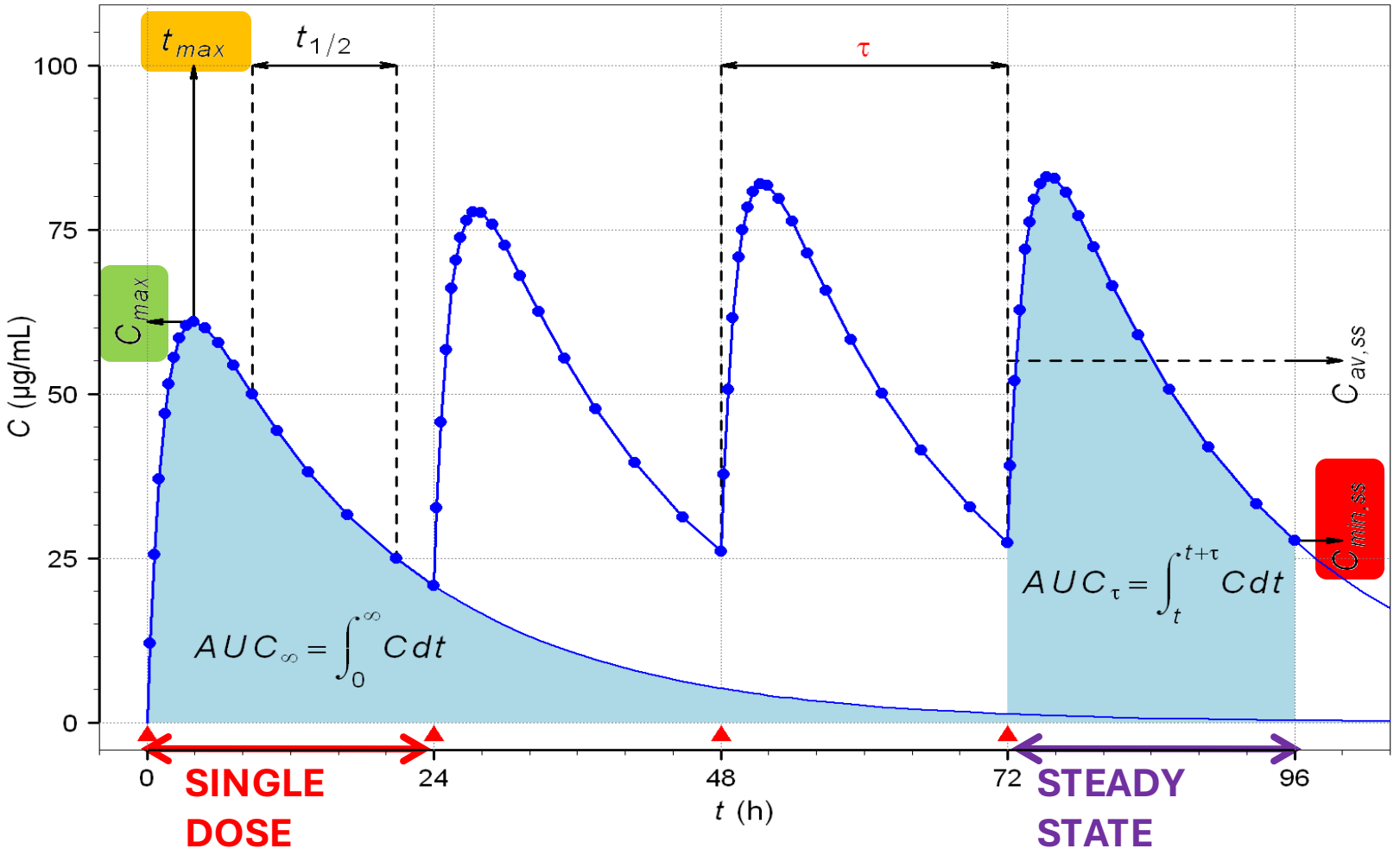
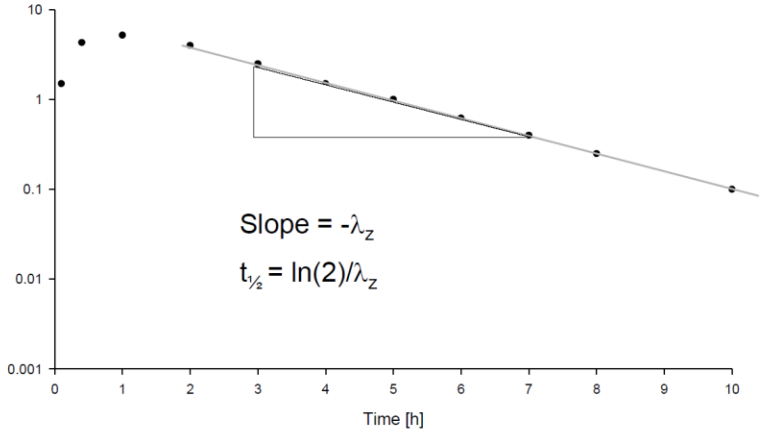
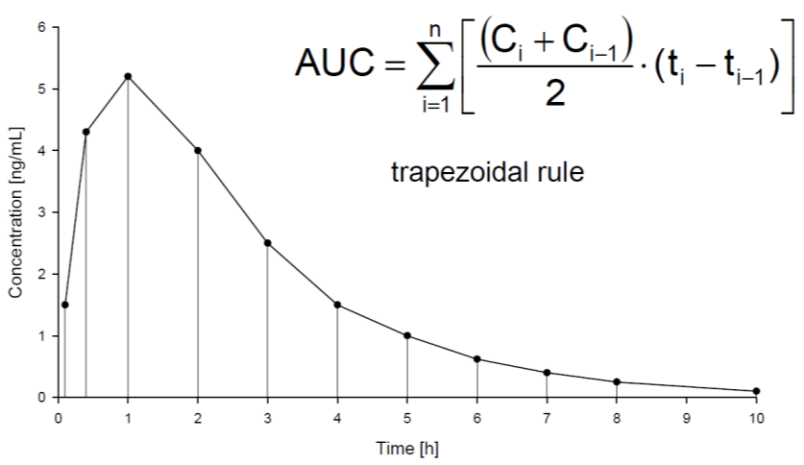
Drug and NCA (conc. Analysis)







Saturable kinetics and Michaelis-Menten

Saturable kinetics can be approximated

- as 1st order for lower concentrations,
- and 0 order for higher concentrations, as the system saturates (phenytoin and alcohol).

$$\frac{dC}{dt} = V_{max} \cdot \frac{C}{K_m + C}$$

Maximum rate

Michaelis constant

Concentration at which $V_{max}/2$ is reached

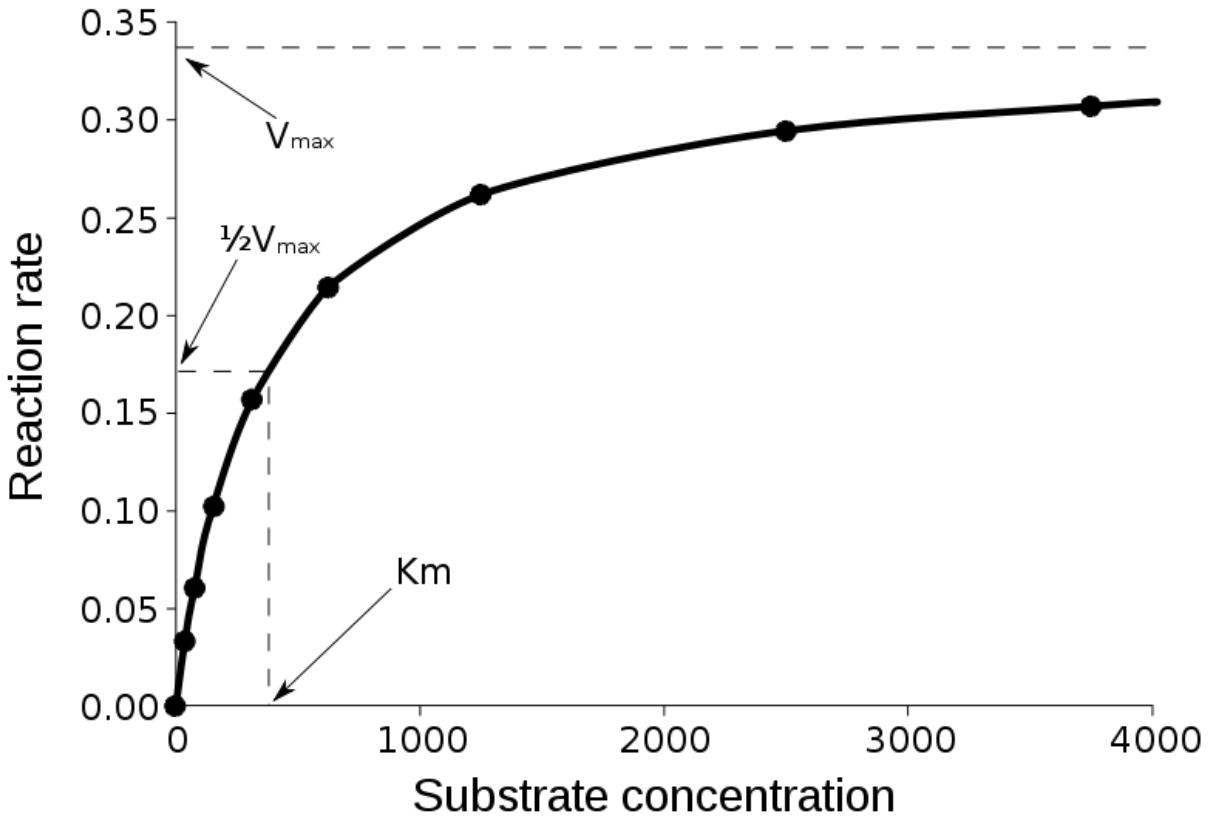
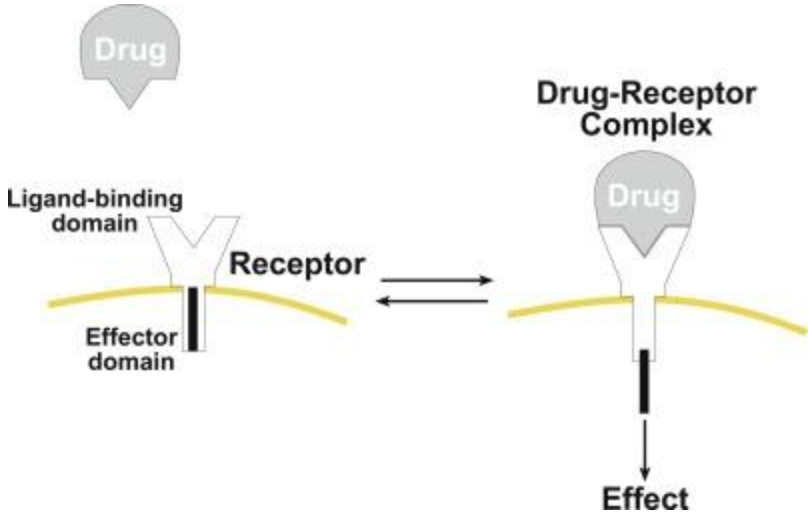
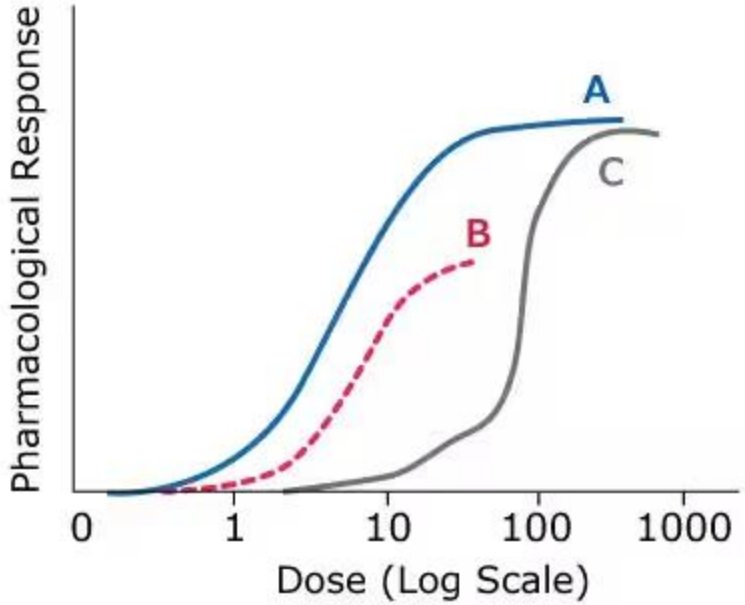


Image from http://en.wikipedia.com

Response and clinical outcomes



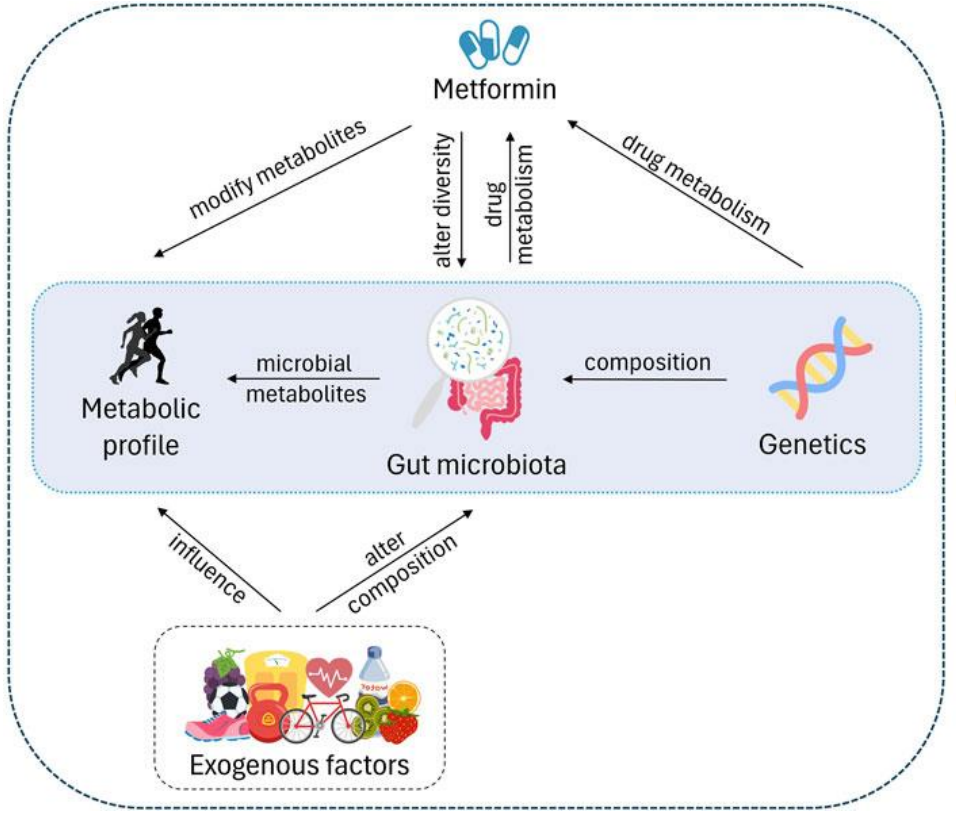


Dose-response relationships may be **graded or quantal.**

- **Graded dose-response relationships:**
  - a **Graded** dose-response relationship describes a drug effect which increases in proportion to increasing drug dose.
- **Quantal dose-response relationships:**
  - a **Quantal** dose-response relationship describes a drug effect which is binary (either present or absent).

$$E = \frac{E_{max} \times C}{C + EC_{50}}$$

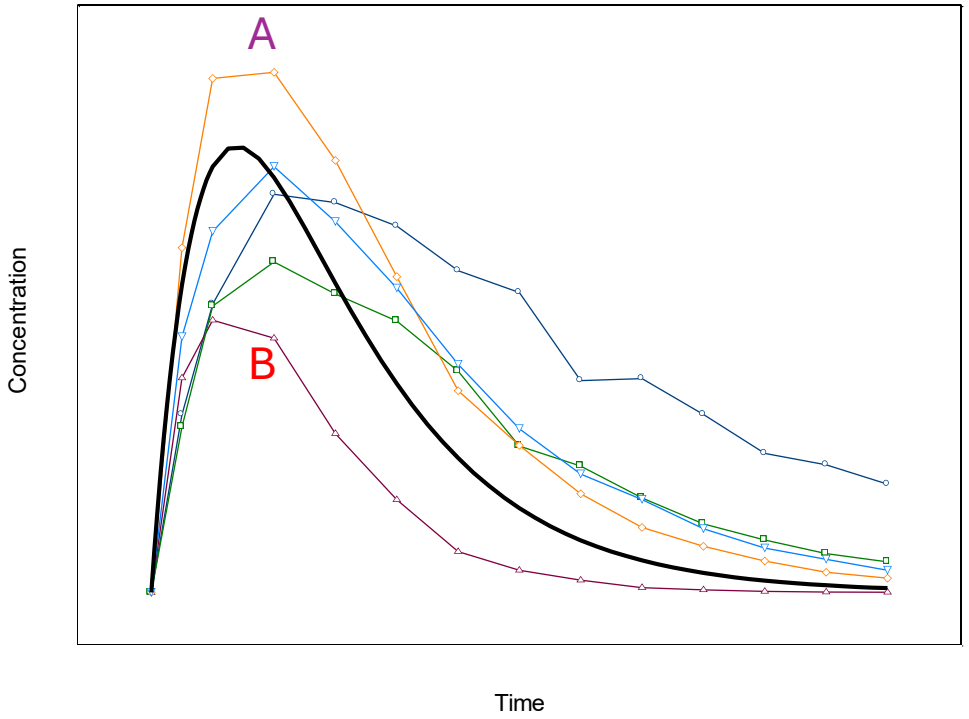
Variability amongst patients

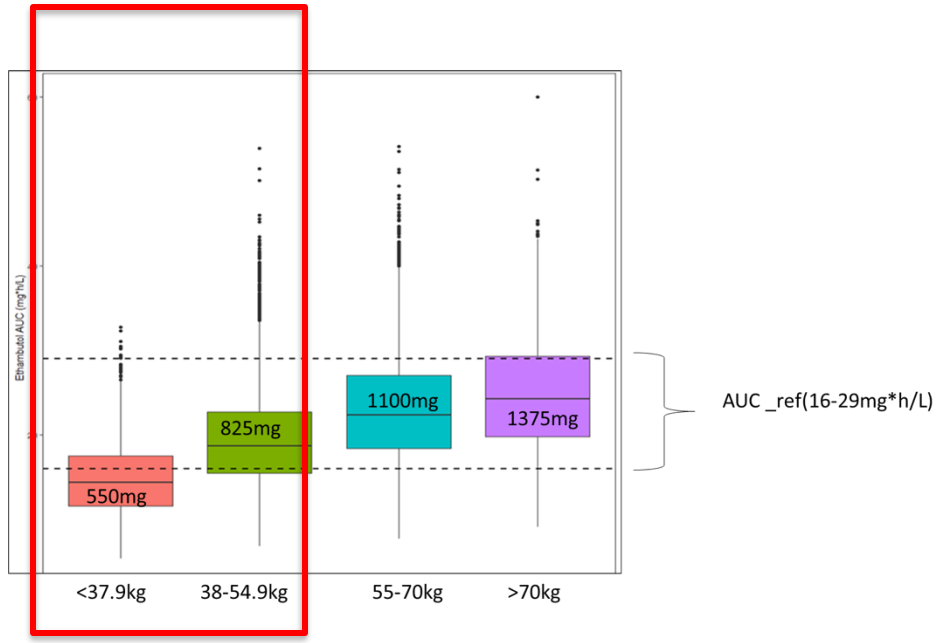


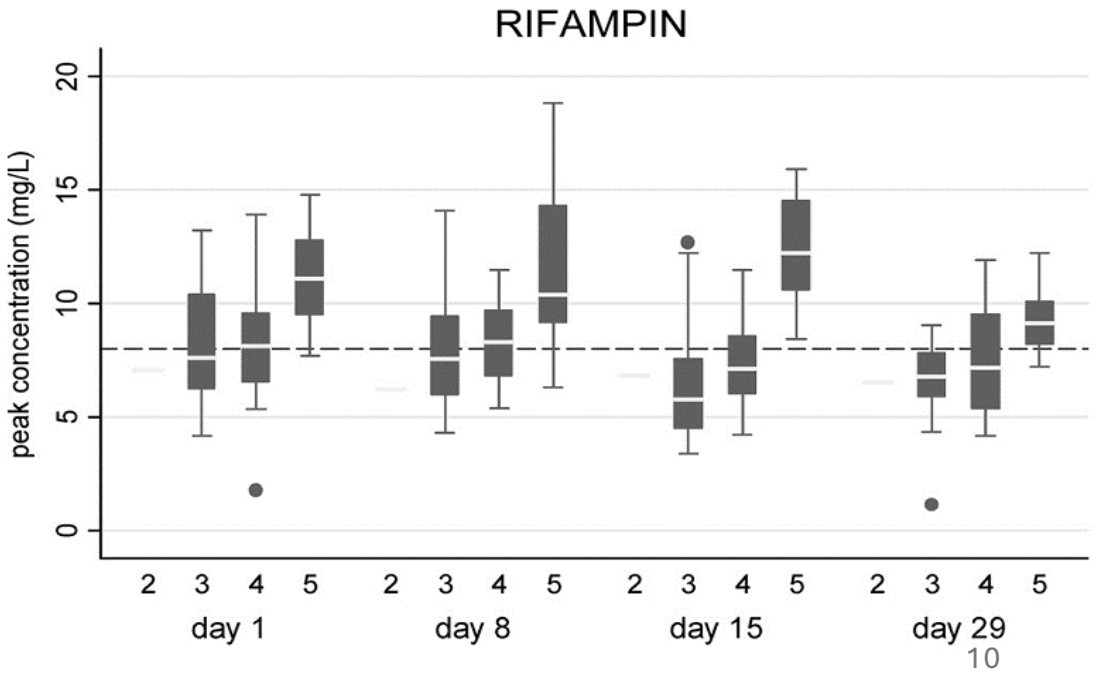
Inter-individual variability in response to metformin

Variability and exposure

$$C = \frac{k_a \cdot D}{V(k_a - k_e)}\left(e^{-k_e \cdot time} - e^{-k_a \cdot time}\right)$$







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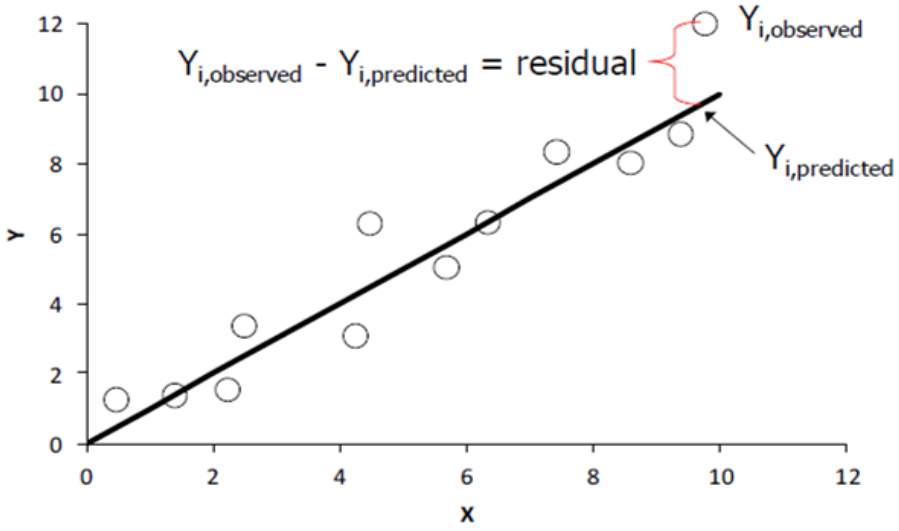
Models to explain PK/PD for drugs

- Linear regression
- Y = **a**x + **b**
- Minimization of squared residuals (SS)
- Linear models can be solved analytically for intercept and slope estimates.

$\Sigma(Y_{i,observed} - Y_{i,predicted})^2$

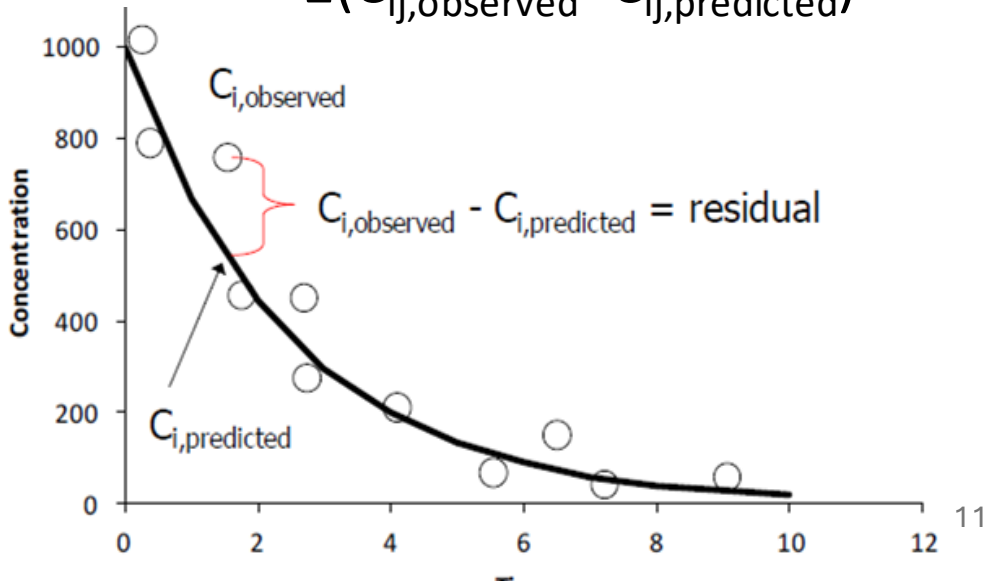


- Non-linear regression

$$\hat{Cp}_{ij} = \frac{Dose_i}{V_i} \cdot e^{-\frac{CL_i}{V_i} \cdot t_{ij}}$$

- Minimization of squared residuals (SS)

$\Sigma(C_{ij,observed} - C_{ij,predicted})^2$



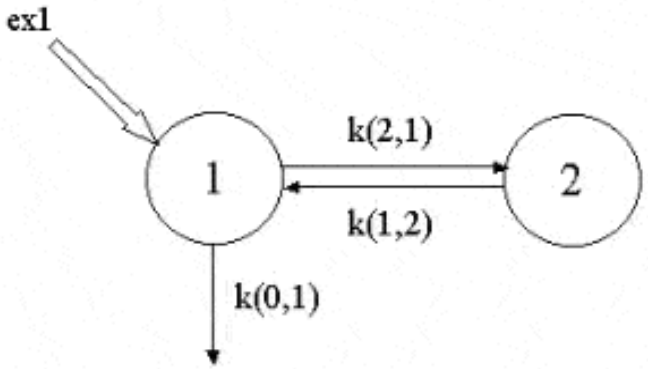
Empirical and mechanistic models

- Empirical Models
  - Generally little prior knowledge on model structure
  - Parameters are not assumed to reflect biological processes
  - Parsimonious and powerful interpolations
  - Easy to apply for automated model building

- “Mechanism-based Models” or “Mechanistic Models”
  - Model structure is informed by prior knowledge on the biological system
  - Parameters are intended to reflect biological processes
  - Generally better for making extrapolations

Compartmental analysis

- Drug in the body moves between compartments, obeying laws described by a set of differential equations.
- The compartments are mathematical concepts.
- They may not correspond to physical parts of the body and the flows between them may be actual flows of substance, or metabolic processes.
- The equations contain parameters such as transfer rates, volumes, delays.

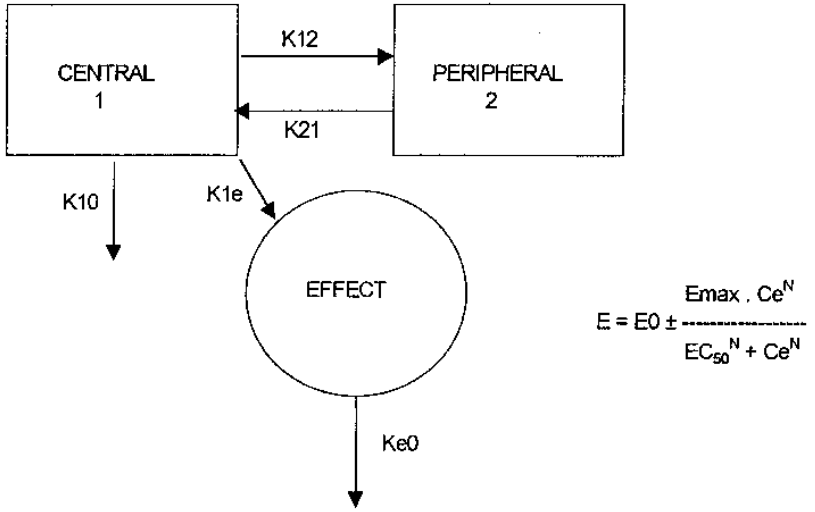


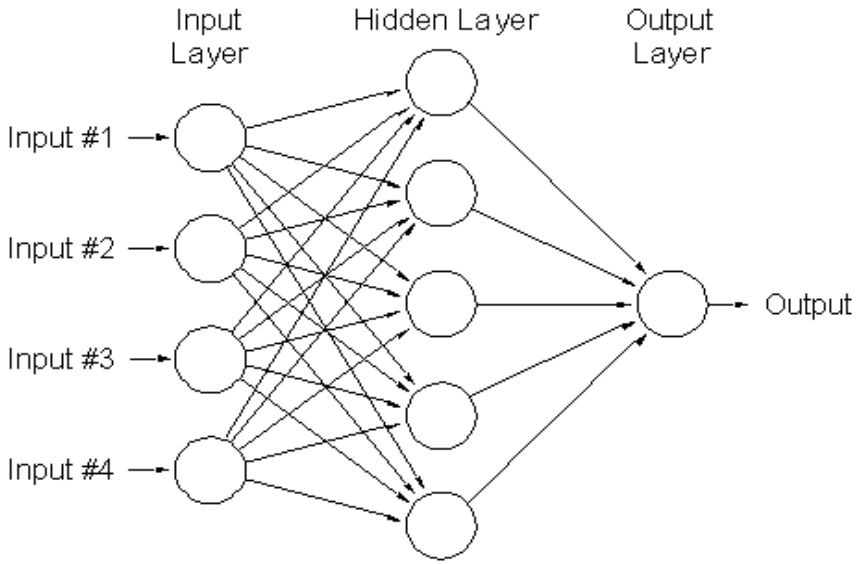
$$\frac{dq_1}{dt} = -(k(0,1)+k(2,1))q_1(t) + k(1,2)q_2(t) + ex1$$

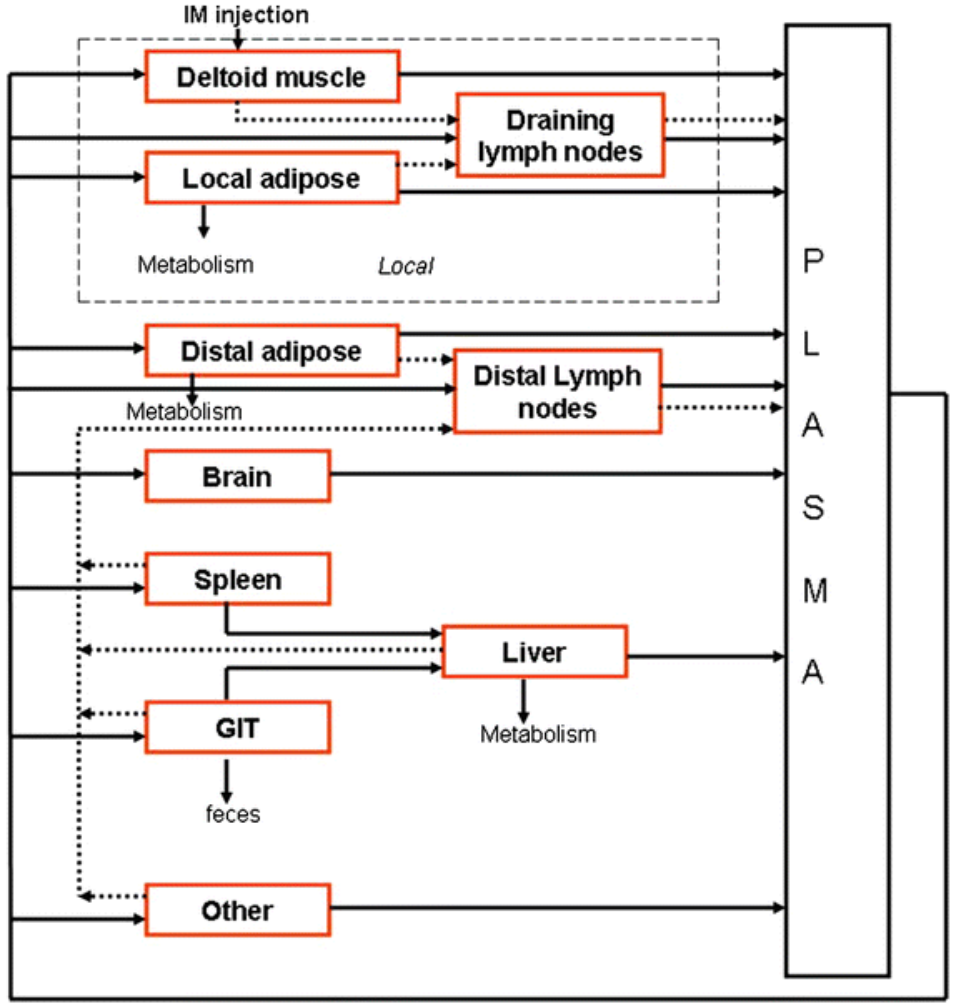
$$\frac{dq_2}{dt} = k(2,1)q_1(t) - k(1,2)q_2(t)$$

Image from http://depts.washington.edu/rfpk/

More on models







Methods for population analysis

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Naïve pooled

- Individual observations from each subject are 'pooled' to obtain average PK parameters.
- Estimation does not take into account whether the number of observations at each time point are equal or not; also subjects' characteristics (weight, height etc.) are not considered → **naïve**

Native two stage

- Individual observations from each subject are modelled separately to obtain average PK parameters for each subject.
- **Uncertainty in individual parameter estimates is ignored.**
- Each subject's covariates and PK parameters are correlated to explain BSV
- Population mean (or typical value) and variance are calculated

Other: Naïve average, MAP Bayesian methods

Nonlinear Mixed-Effects Modelling

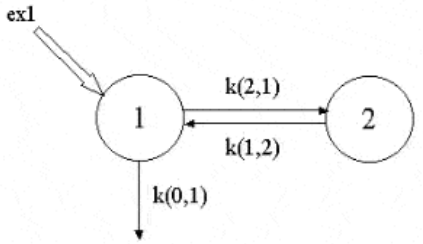
Populatio n Typical Values θ

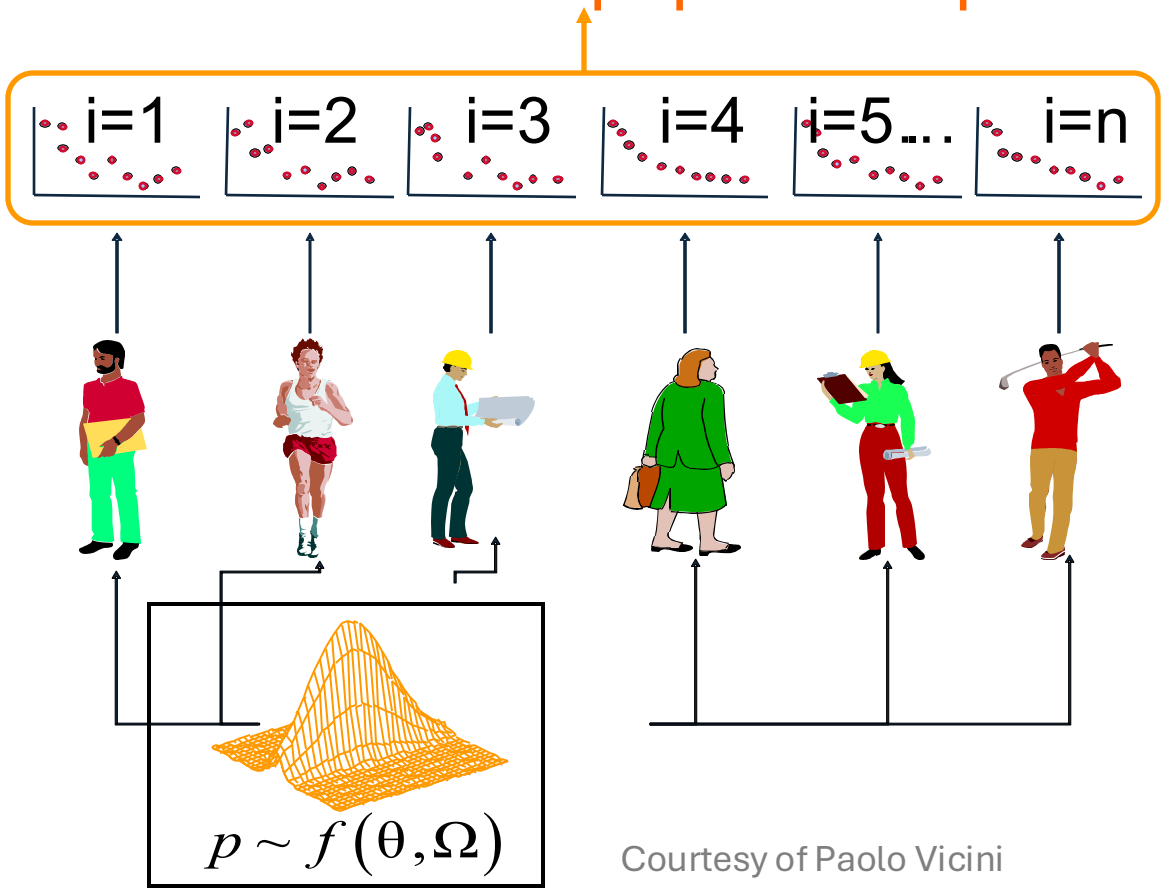
Between-Subject or -Occasion Variability Ω

Residual Unexplained Variability Σ

Estimation of the population parameters

Structural model

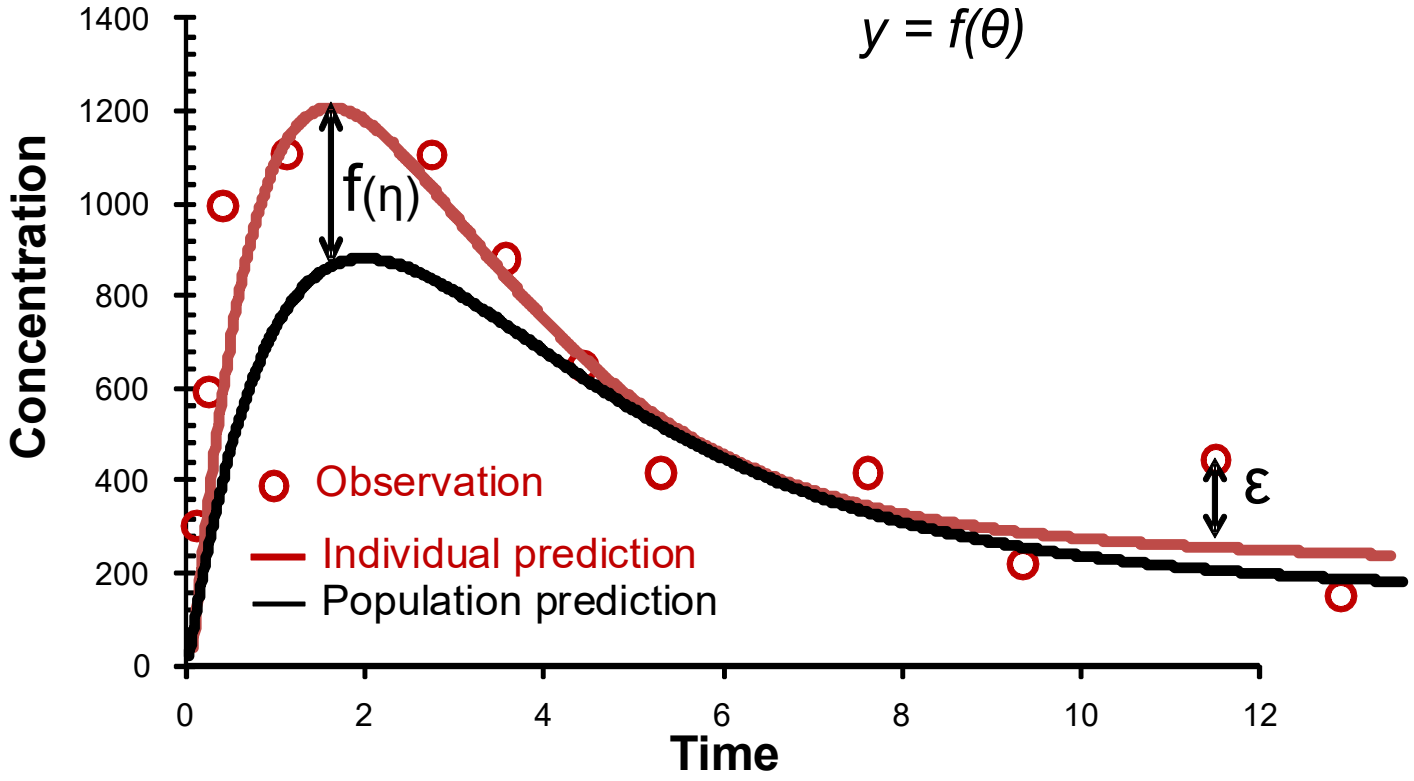




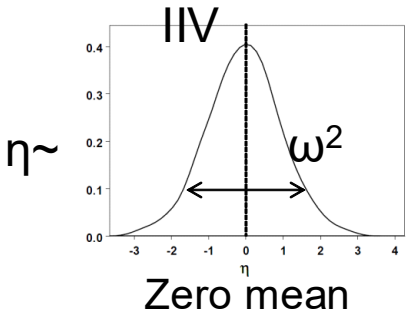
Courtesy of Paolo Vicini

Nested hierarchical random error

$y = f(\theta)$

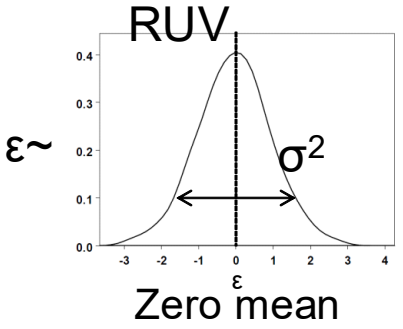


Typical value



Parameter level: IIV and IOV

$y = f(\theta,\eta)$



Concentration/Model prediction Level: Residual unexplained variability

$y = f(\theta,\eta)+\varepsilon$

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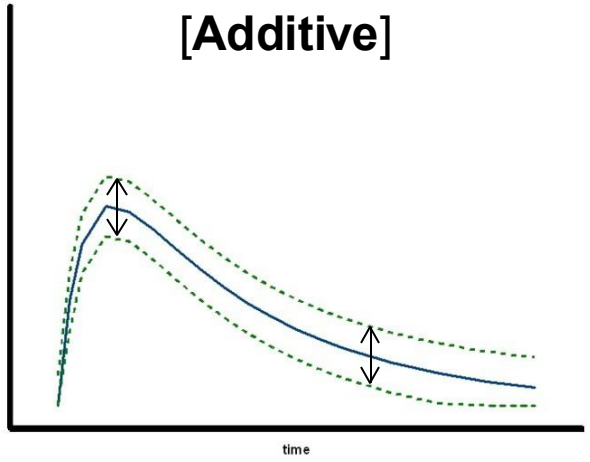
RUV model patterns

y_{ij} = prediction + ε_{ij}

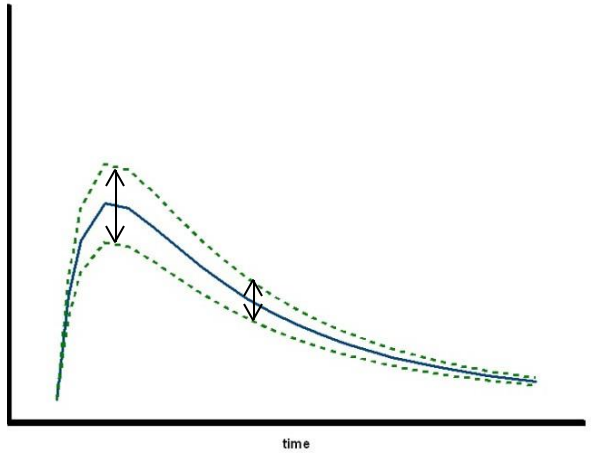
[**Additive**]



Homoscedastic error

- the residual variability is constant

y_{ij} = prediction × (1+ ε_{ij}) [**Proproportional**]

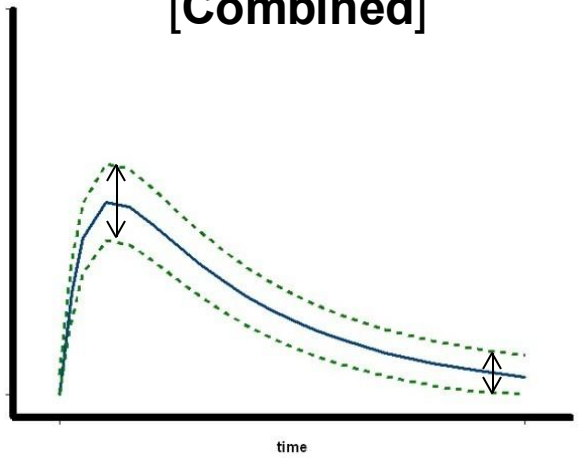


Heteroscedastic error

- the residual variability is proportional to the size of the prediction (~ concentration)

y_{ij} = prediction × (1+ ε_{1ij}) + ε_{2ij}

[**Combined**]



Slope-intercept error

- the residual variability is *approximately* proportional at high predictions and constant at low

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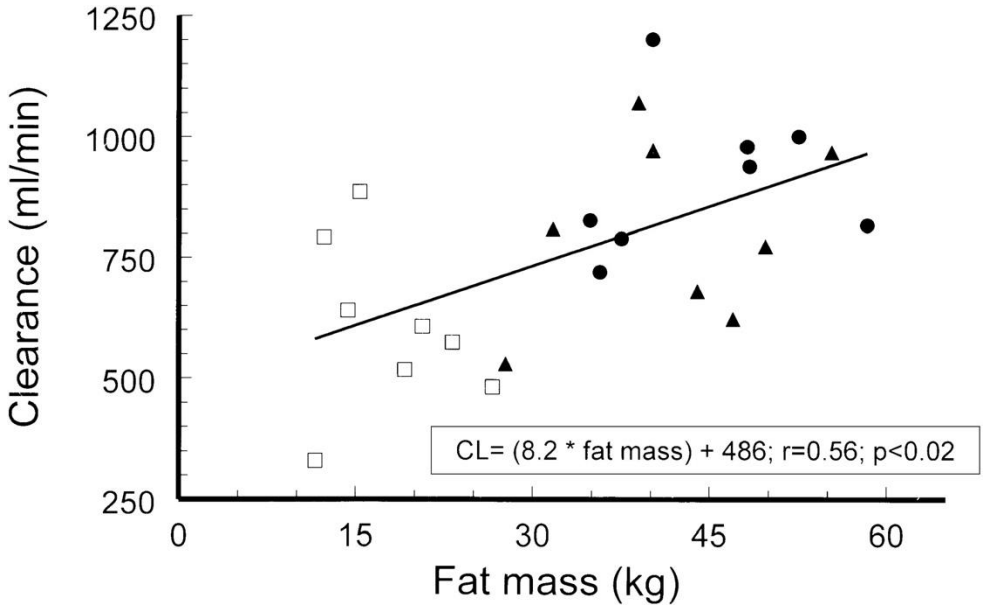
Identifying source of variability

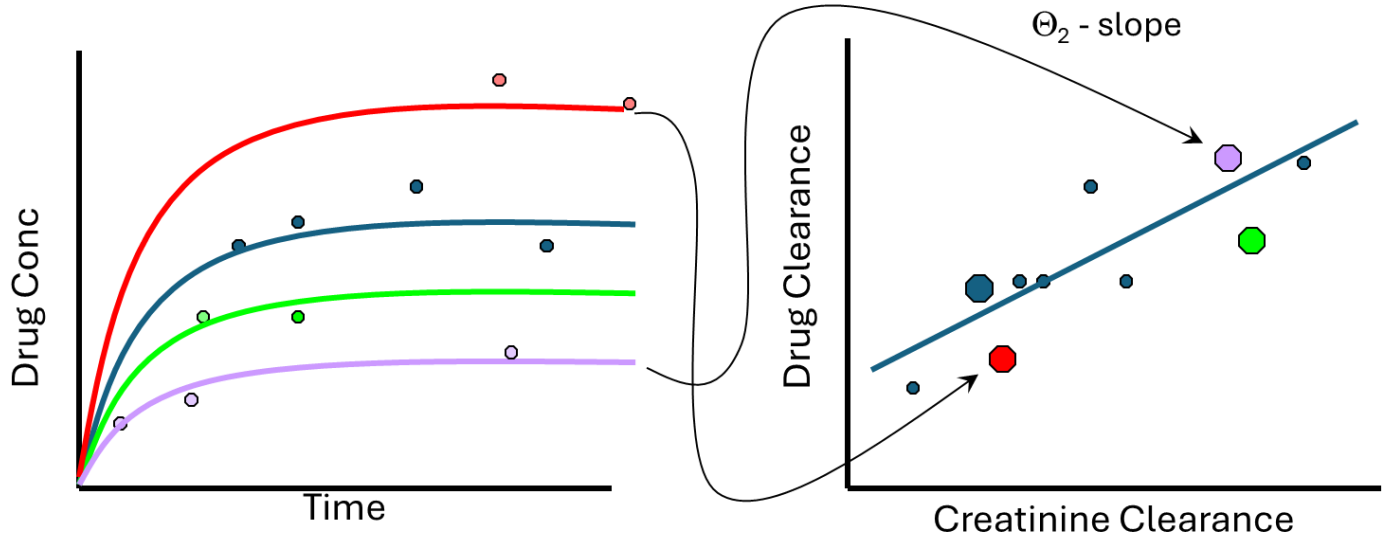


$CL = CL(liver) + CL(renal) + CL(other)$

$CL = \Theta_1 + \Theta_2 \bullet CCr \pm \eta$

Θ_1 – intercept

Θ_2 - slope



From: R Miller, Pfizer Global R&D

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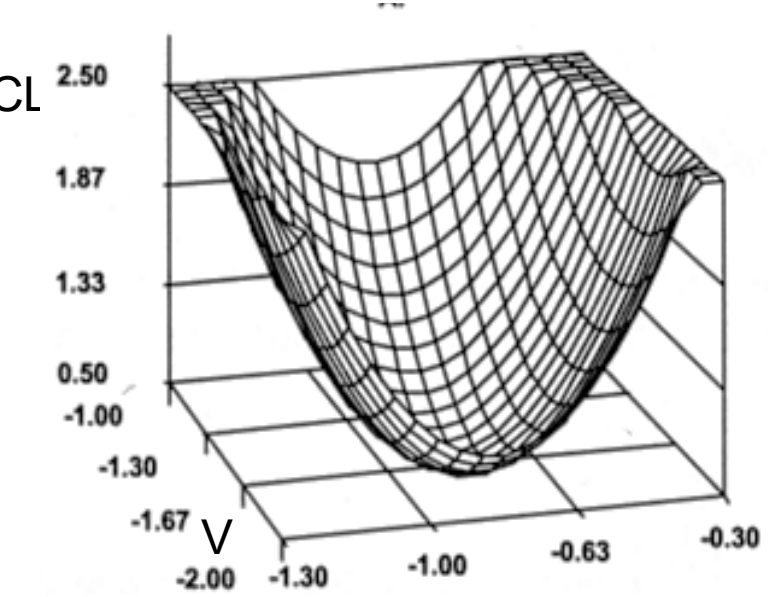
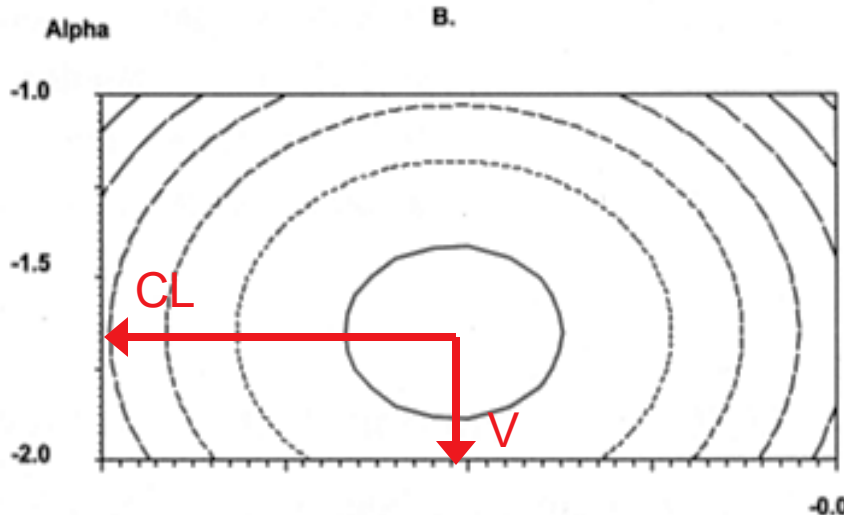
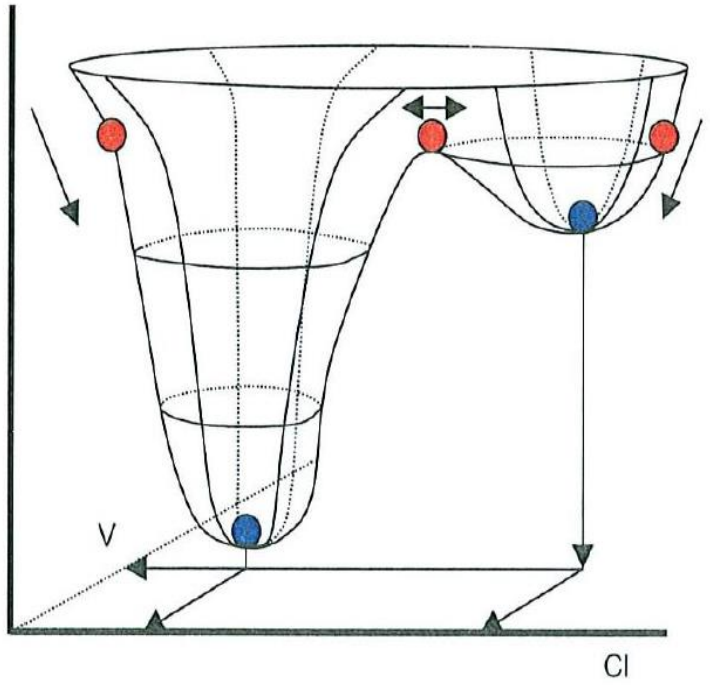
Parameter estimates





Local vs Global minima



Source: Pharmacokinetic and Pharmacodynamic Data Analysis: Concepts & Applications. J Gabrielsson & D Weiner

- Initial estimates or combinations are tested iteratively (convergence)
- The best model parameters are those that correspond to the lowest Sum of Squares

$$L(\beta_0, \beta_1, \sigma^2; X) = \sum_{i=1}^{n} \log p(y_i | X = x_i; \beta_0, \beta_1, \sigma^2)$$

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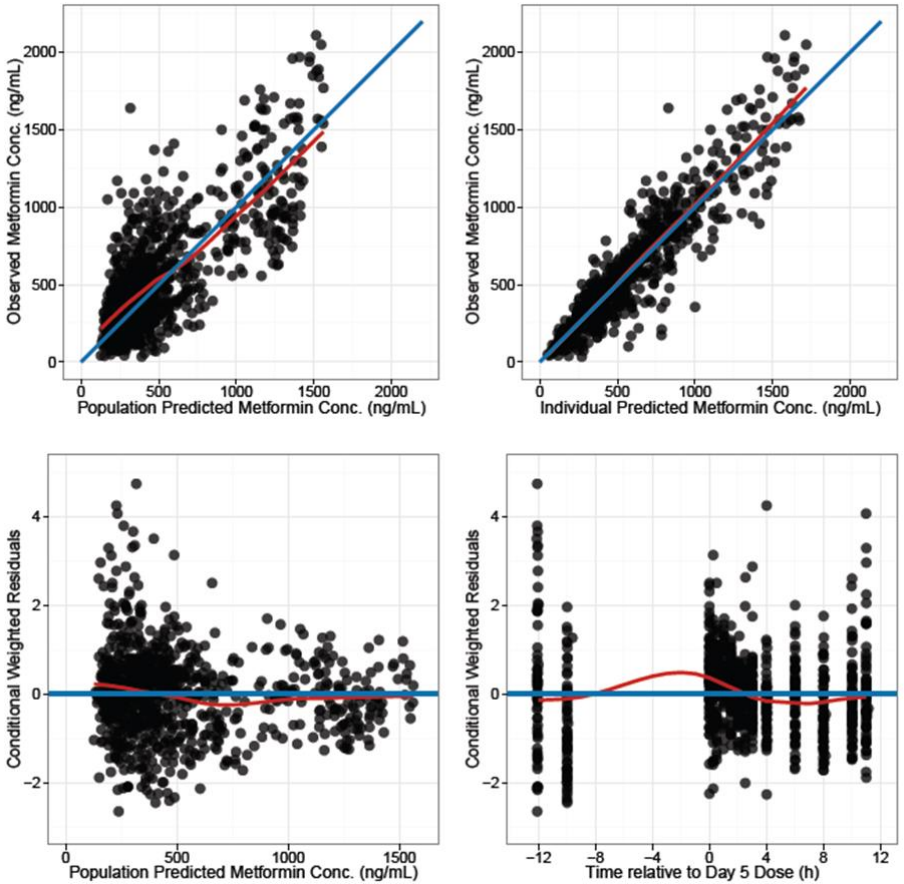
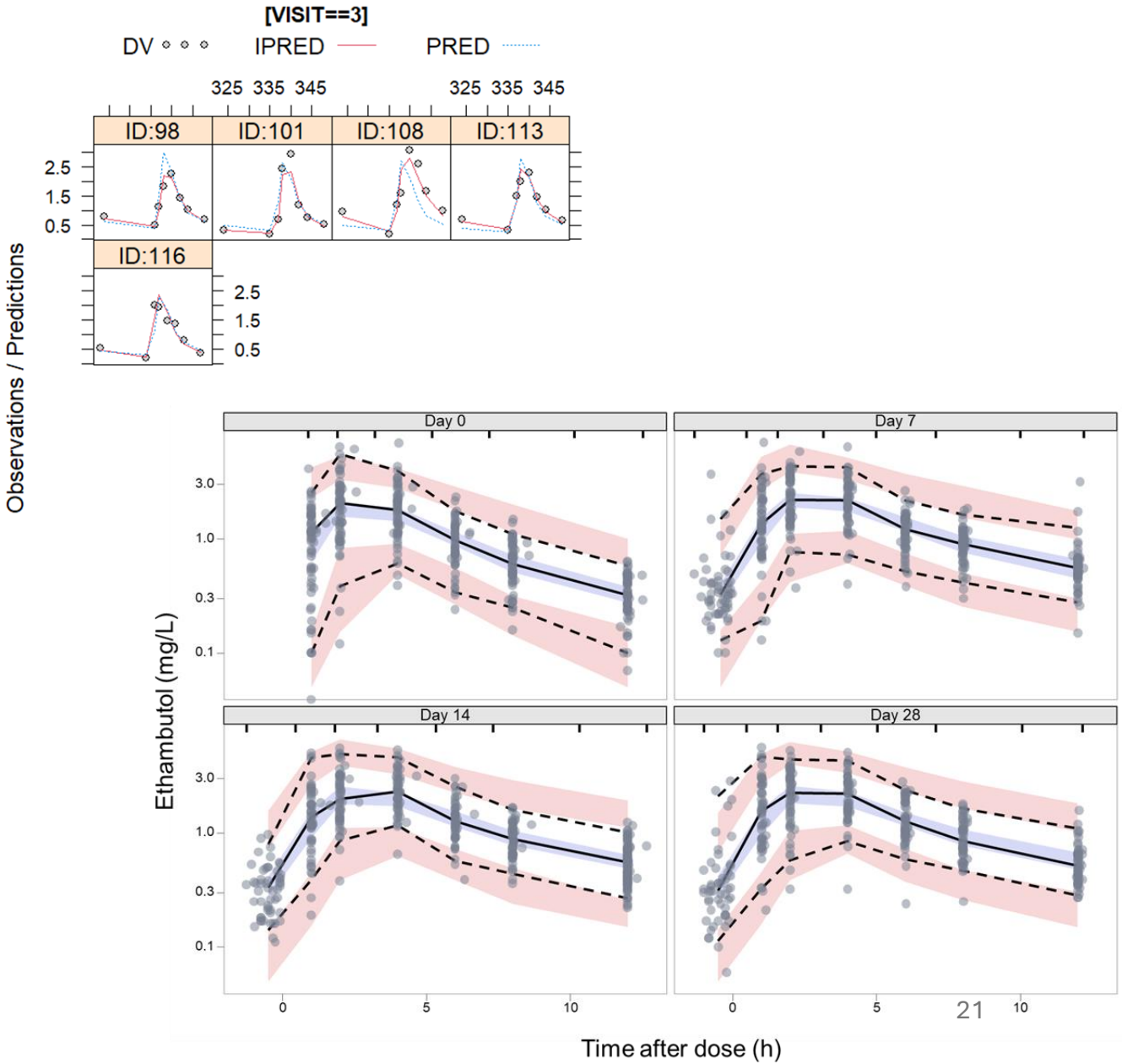
Model evaluation





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Model application

- Dose individualization
- Clinical trial design
- Many more

Thank you

Further reading

- Mould DR, Upton RN. Basic concepts in population modeling, simulation, and model-based drug development-part 2: introduction to pharmacokinetic modeling methods. CPT Pharmacometrics Syst Pharmacol. 2013 Apr 17;2(4):e38. doi: 10.1038/psp.2013.14. PMID: 23887688; PMCID: PMC3636497.
- Upton, R., & Mould, D. (2013). Basic Concepts in Population Modeling, Simulation, and Model-Based Drug Development: Part 3—Introduction to Pharmacodynamic Modeling Methods. CPT: Pharmacometrics & Systems Pharmacology, 3(1), 1-16. https://doi.org/10.1038/psp.2013.71
- Liu Q et al (2021): Clinical Pharmacology Regulatory Sciences in Drug Development and Precision Medicine: Current Status and Emerging Trends. The AAPS Journal 23:54 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8041391/pdf/12248_2021_Article_563.pdf