Pharmacokinetic Issues

A Basic Refresher

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Pharmacokinetics

φαρμακός (drug) + κινητικός (putting in motion)

- Term introduced in 1953.
  - Friedrich H Dost, *Der Blutspiegel: Kinetik der Konzentrationsabläufe in der Kreislaufflüssigkeit* (1953)
- *Pharmacokinetics* may be simply defined as what the body does to the drug, as opposed to *pharmacodynamics* which may be defined as what the drug does to the body.
  - Leslie Z Benet, *Pharmacokinetics: Basic Principles and Its Use as a Tool in Drug Metabolism* (1984)

Pharmacokinetic process

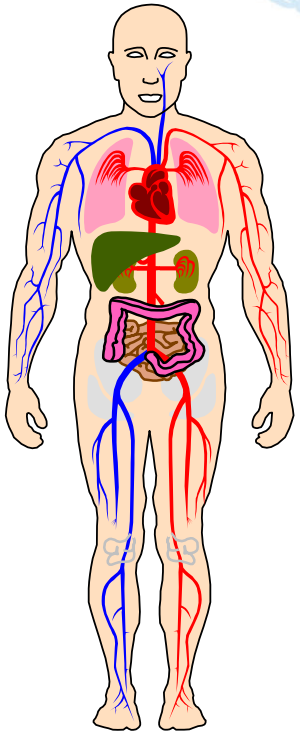
(L)ADME

- **L**iberation
  - Release & dissolution
- **A**bsorption
  - Permeation (diffusion & transport)

Absorption

- **D**istribution
  - Peripheral compartment(s)
- **M**etabolisation
  - Gut wall & first pass
- **E**xcretion
  - Urine, feces, sweat, air,…

Elimination



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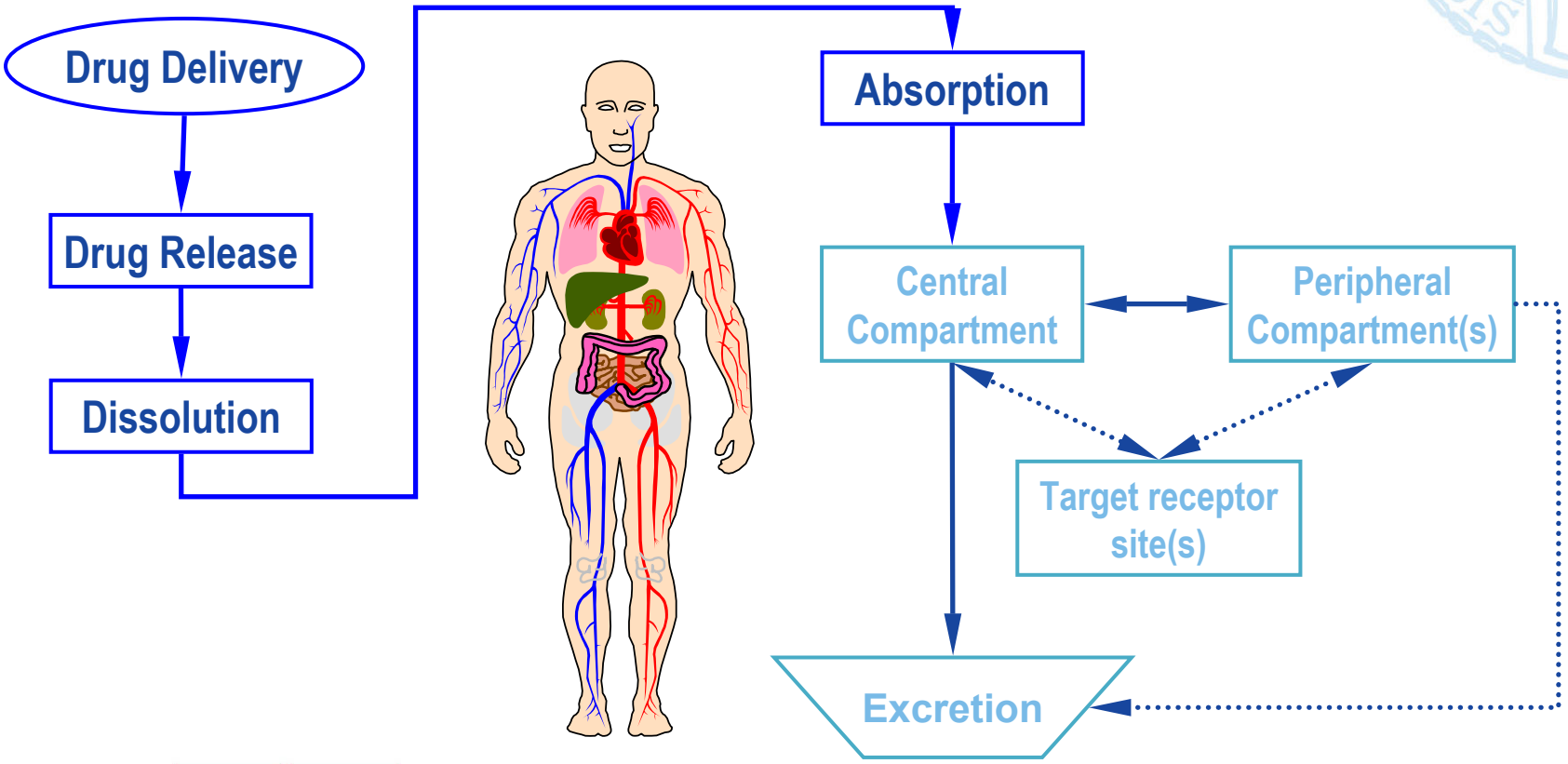
Pharmacokinetic process



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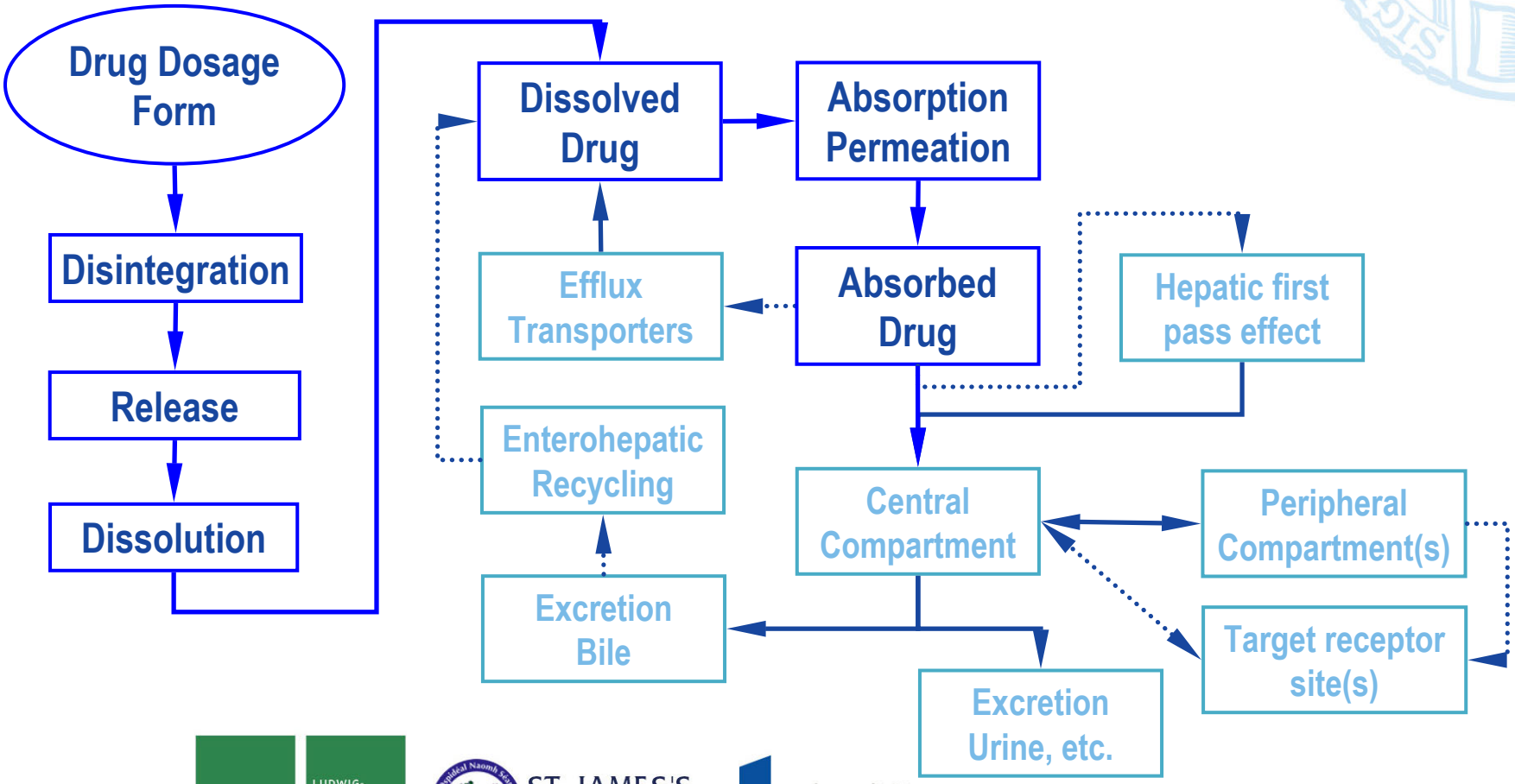
Pharmacokinetic process



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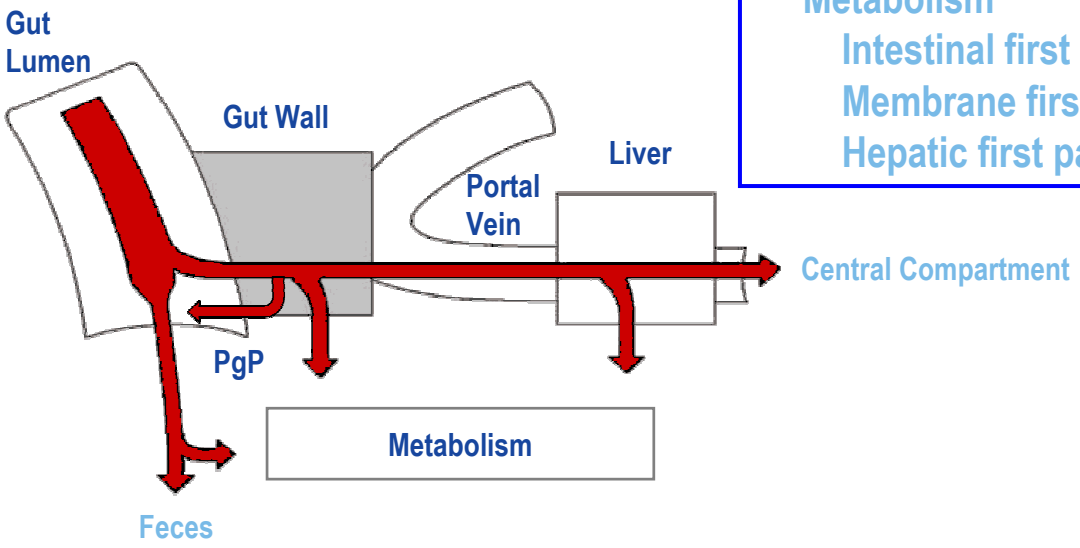
Pharmacokinetic process

Biopharmaceutical phase
- Disingration
- Release
- Dissolution

Pharmacokinetic phase
- Absorption
  - Passive diffusion
  - Active transport
- Metabolism
  - Intestinal first pass
  - Membrane first pass
  - Hepatic first pass



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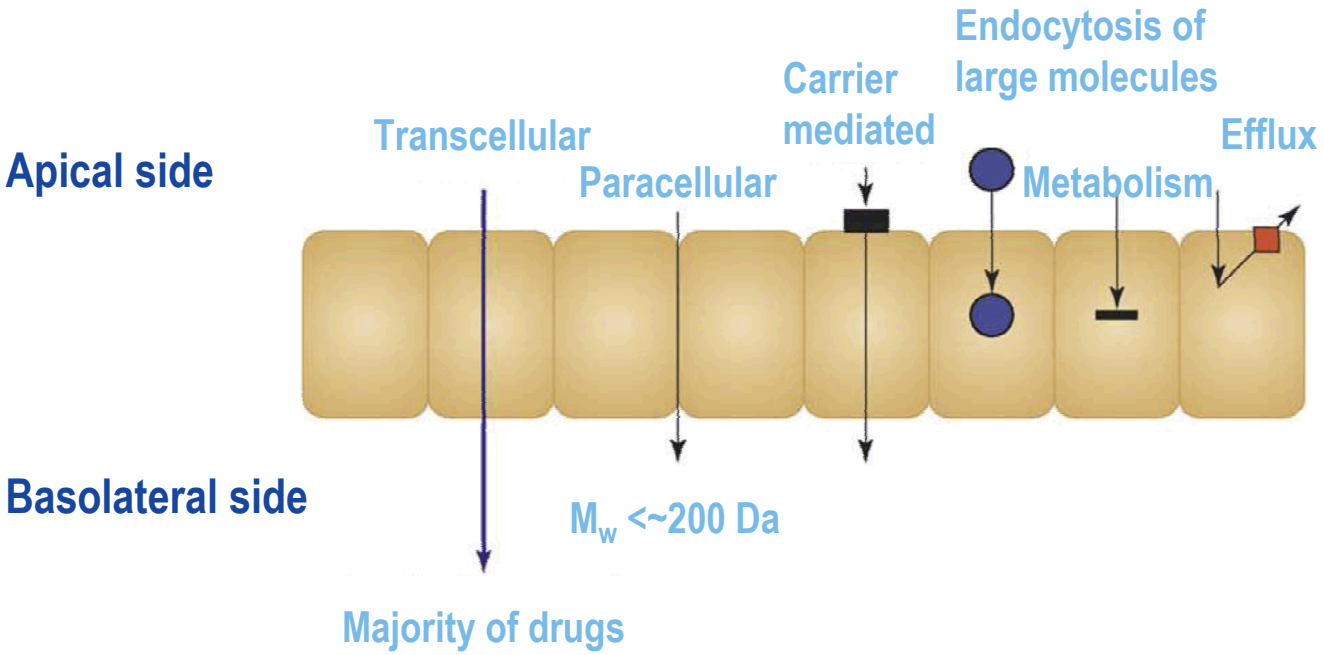
Pharmacokinetic process

Absorption revisited



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Pharmacokinetic models

The body is simplified to one – or more – 'Compartments' where the drug is distributed

- One compartment model
  - Drug is distributed homogeneously within the entire body.
- Two compartment model
  - The first (central) compartment is *loosely* related to the blood and heavily perfused organs: Liver, kidneys, lung, muscles, (brain).
  - The second (peripheral) compartment describes less perfused tissues (fat, bones, …).

Pharmacokinetic models

Compartment models

- Compartments are
  - described by a volume and
  - pathways which link them.
- These links may be
  - unidirectional (absorption, excretion) or
  - bidirectional (central ↔ peripheral)
- Most common models are ‘mammillary’, *i.e.*,
  - absorption to the central compartment,
  - distribution to peripherial and back to the central compartment, and
  - elimination from the central compartment.

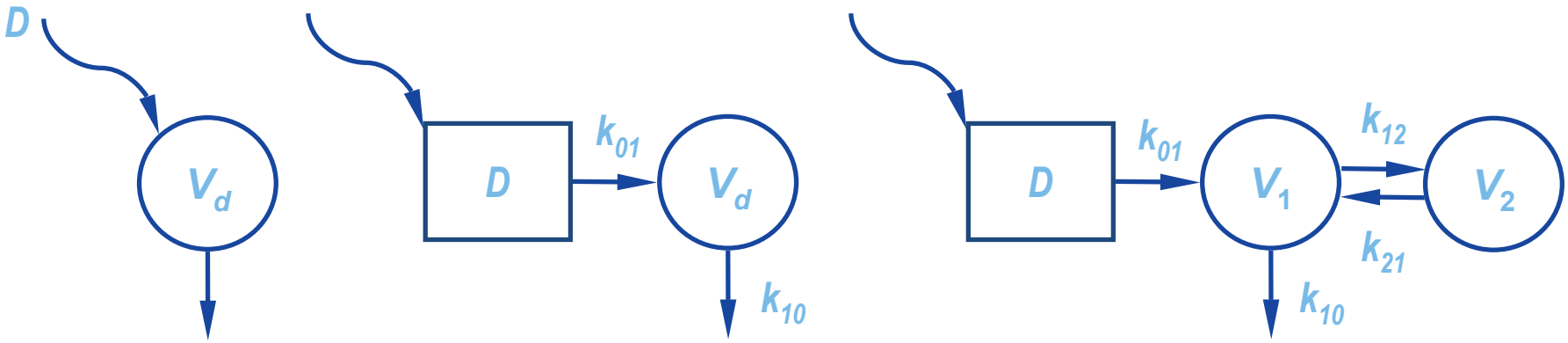
Pharmacokinetic models

Examples

One comp. IV

One comp. EV

Two comp's EV



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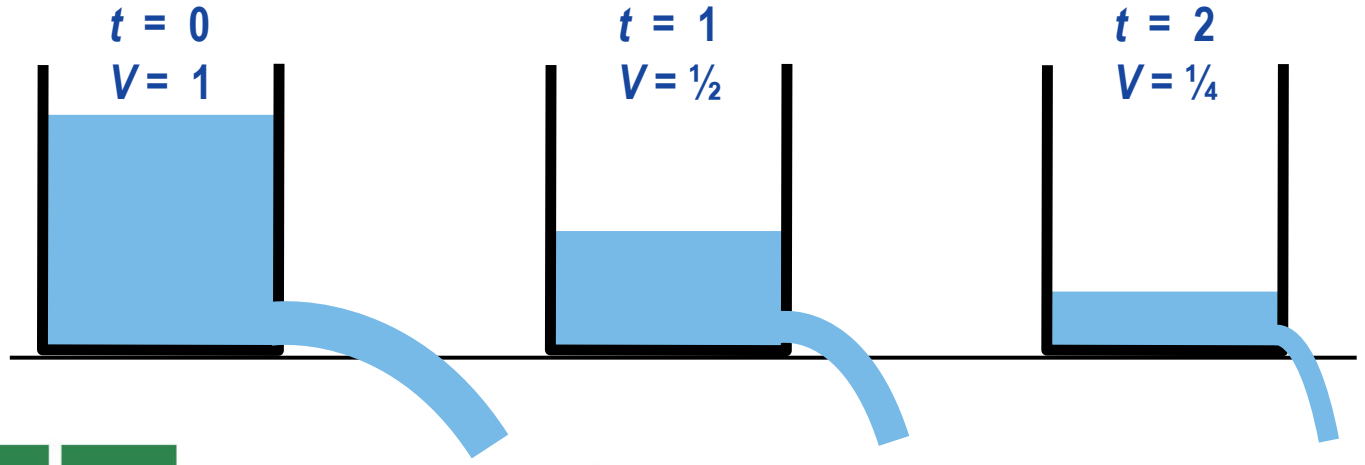
One compartment model, IV dose

Excursion into Hydrodynamics

- Driving force for draining an *open* tank:
  Hydrostatic pressure (height of liquid column & gravity).
- Emptied volume decreases with time.
- Same *proportion* is emptied in the same time interval.



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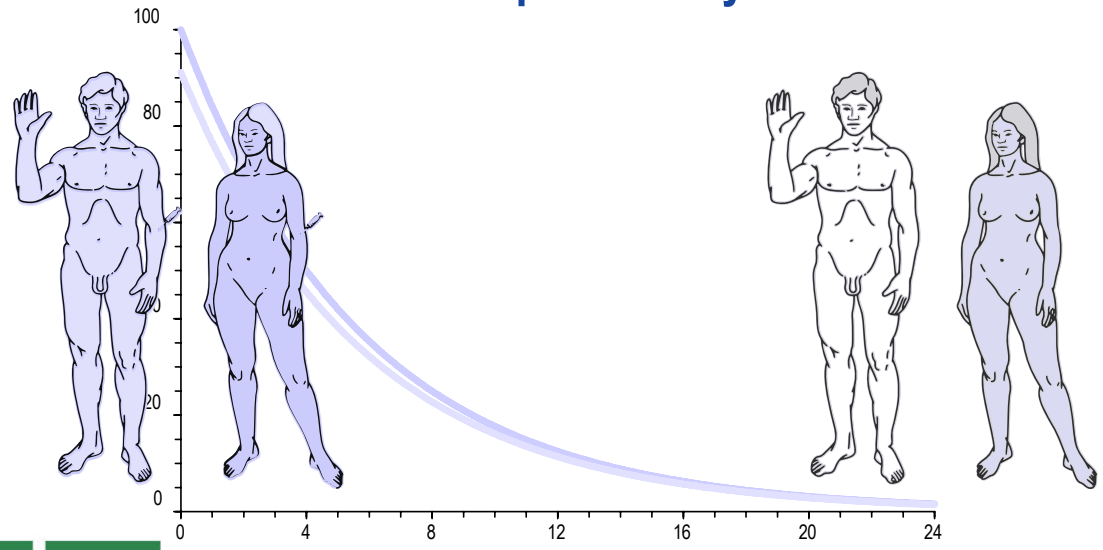
One compartment model, IV dose

The whole body is simplified to one ‘compartment’

- Practically instantaneous distribution.
- Homogenous within all tissues.
- Concentrations decline exponentially.



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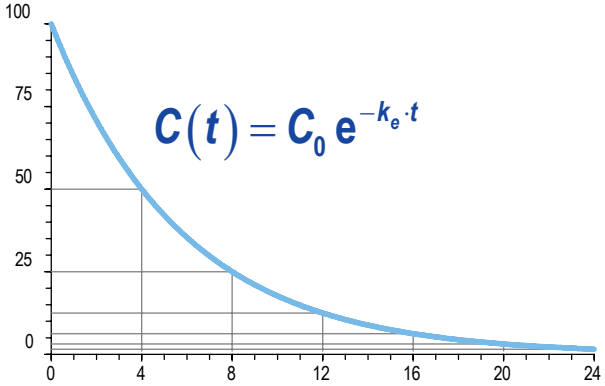
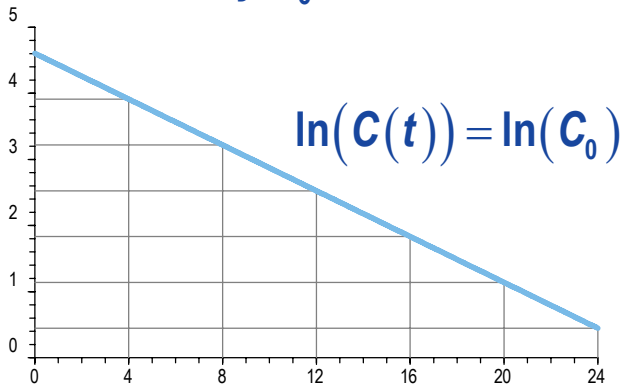
One compartment model, IV dose

Half life

- Troughout the profile concentration drops to ½ of its previous value within one 'half life' ($t_{½}$).
- In a semilogarithmic plot the profile shows a straight line with
  - a slope of $-\ln(2)/t_{½}$, which is the elimination rate constant k_e and
  - the intercept is related to the initial concentration by $C_0 = e^{intercept}$.





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One compartment model, IV dose

Volume of distribution

- At administration the entire dose (D) is assumed to homogenously dissolve in the 'Volume of distribution' (V_d).
- We can only measure concentrations.
  - At $t = 0$ we get $V_d = \frac{C_0}{D}$.
  - Cave: V_d describes a *hypothetical* compartment, whereas in reality the distribution might not be homogenous. Some lipophilic drugs have a V_d of hundreds of liters…
  - Classical PK is *not* directly related to physiology.
  - Essentially, all models are wrong, but some are useful. *George Box*

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One compartment model, IV dose

Clearance

- Instead of describing elimination by the rate constant k_e (unit: 1/time) we can also ask for the *fraction* of V_d which is completelly 'cleared' of the drug per unit of time.
- This parameter is called 'Clearance' *CL* (unit: volume/time), which leads to basic equations of pharmacokinetics:

$$CL = V_d \cdot k_e \text{ or } \frac{D}{AUC}, \text{ where } AUC = \int_{t=0}^{t=\infty} C(t)\,dt$$

$$[\text{volume} / \text{time}] = \frac{[\text{mass}]}{[\text{time} \times \text{mass} / \text{volume}]}$$

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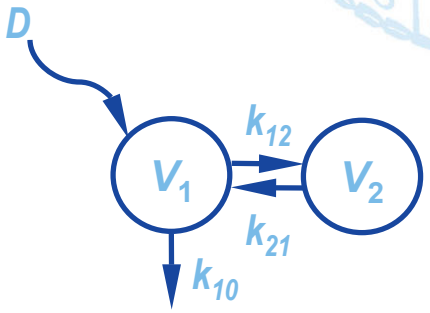
PK Modeling

Model building process



- Define the model.
- This leads to a set of differential equations.
- The integrated form of the equations is used to fit the observed concentrations to the model.
- Once the model's parameters are obtained, we can make predictions.
- We can introduce covariates which may influence concentrations (*e.g.*, body weight, age, sex, HCT, …).
- We can try to link PK with pharmacodynamics – which regimen leads to an optimum effect?

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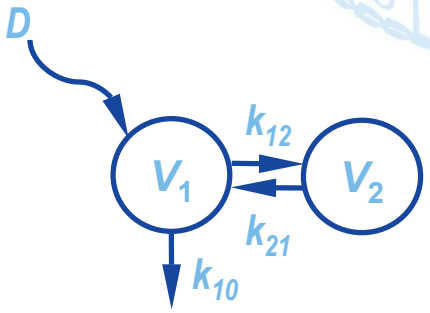
PK Modeling

Model building process

- Define the model
  - Compartments
  - Links between them
- This leads to a set of differential equations:



$$x_1'(t) = -k_{10}x_1(t) - k_{12}x_1(t) + k_{21}x_2(t), \quad x_1(0) = D$$
$$x_2'(t) = +k_{12}x_1(t) - k_{21}x_2(t), \quad x_2(0) = 0$$

  - Simple ones can be solved mathematically.
  - More complicated ones by means of ‘Laplace Transformations’.
  - Some can be only numerically integrated (software required).

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PK Modeling

Model building process

- The integrated form of the equations comes in two ‘flavors’
  - Micro-constants (volumes of distribution, rate constants or clearances)
    - One compartment IV bolus, parameterized in rate constant or clearance

$$\hat{C}(t) = \frac{D}{V} e^{-k_{10} \cdot t} \quad \text{or} \quad \hat{C}(t) = \frac{D}{V} e^{-\frac{CL \cdot t}{V}}$$

  - Macro- or hybrid-constants (sum of exponentials)
    - Two compartments IV bolus

$$\hat{C}(t) = A \cdot e^{-\alpha \cdot t} + B \cdot e^{-\beta \cdot t}$$

PK Modeling

Model building process

- Micro *vs.* macro…
  - The two parameterizations are equivalent, *i.e.*, they have a strict mathematical relationship – though the formulas relating them might be nasty (*e.g.*, two-comp. IV micro →macro)

$$\alpha = \frac{1}{2}\left(k_{10} + k_{12} + k_{21} + \sqrt{\left(k_{10} + k_{12} + k_{21}\right)^2 - 4k_{10}k_{21}}\right)$$

$$\beta = \frac{1}{2}\left(k_{10} + k_{12} + k_{21} - \sqrt{\left(k_{10} + k_{12} + k_{21}\right)^2 - 4k_{10}k_{21}}\right)$$

$$A = \frac{D\left(\alpha - k_{21}\right)}{V_1\left(\alpha - \beta\right)}$$

$$B = \frac{D\left(k_{21} - \beta\right)}{V_1\left(\alpha - \beta\right)}$$

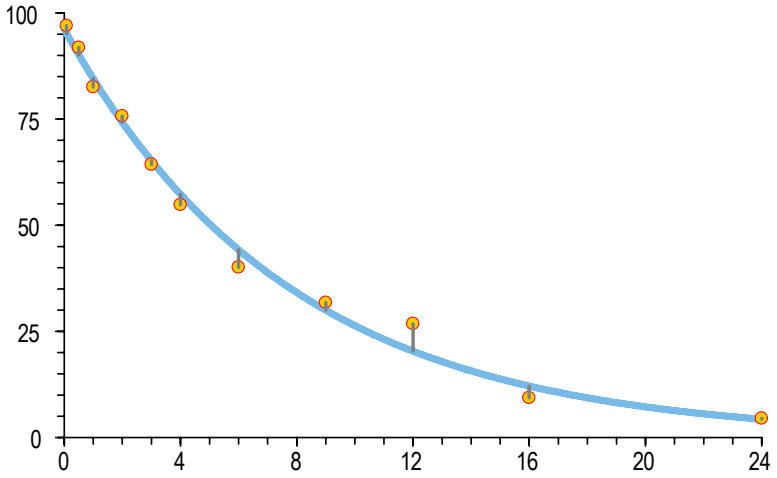
PK Modeling

Model building process

- The integrated form of equations is used to fit the observed concentrations to the model
  - Different methods exist.
  - Most simple one:
    Minimize the sum of least squares

$$\sum_{i=1}^{i=n}\left(C_i - \hat{C}_i\right)^2 \rightarrow \text{Min!}$$

where C_i are the *observed* and $\hat{C}_i$ the *predicted* concentrations.



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PK Modeling

Model building process

- Once the model's parameters are obtained, we can make predictions:
  - We can not only describe the time course of concentrations in plasma, but also in 'deeper' compartments and urine.
  - Derive suitable dosage regimens, *e.g.*,
    - Deal with accumulation,
    - Minimize fluctuations of concentrations in steady state,
    - Keep minimum concentrations above a threshold, …
- We can assess whether patients' metrics influence concentrations. Examples:
  - Volume of distribution generall increases with body weight: $C \downarrow$
  - Clearance may decrease with age: $C \uparrow$

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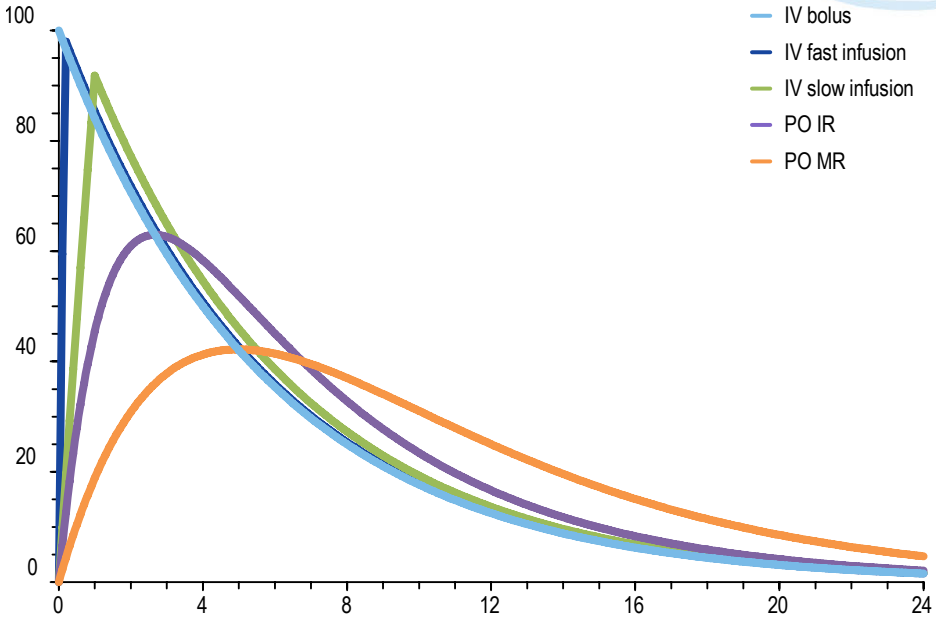
Interludes

Rate of drug input

- Average concentrations and the *AUC* are *independent* from the input-rate. Only maximum concentrations – and therefore, fluctuations in steady state – are affected.



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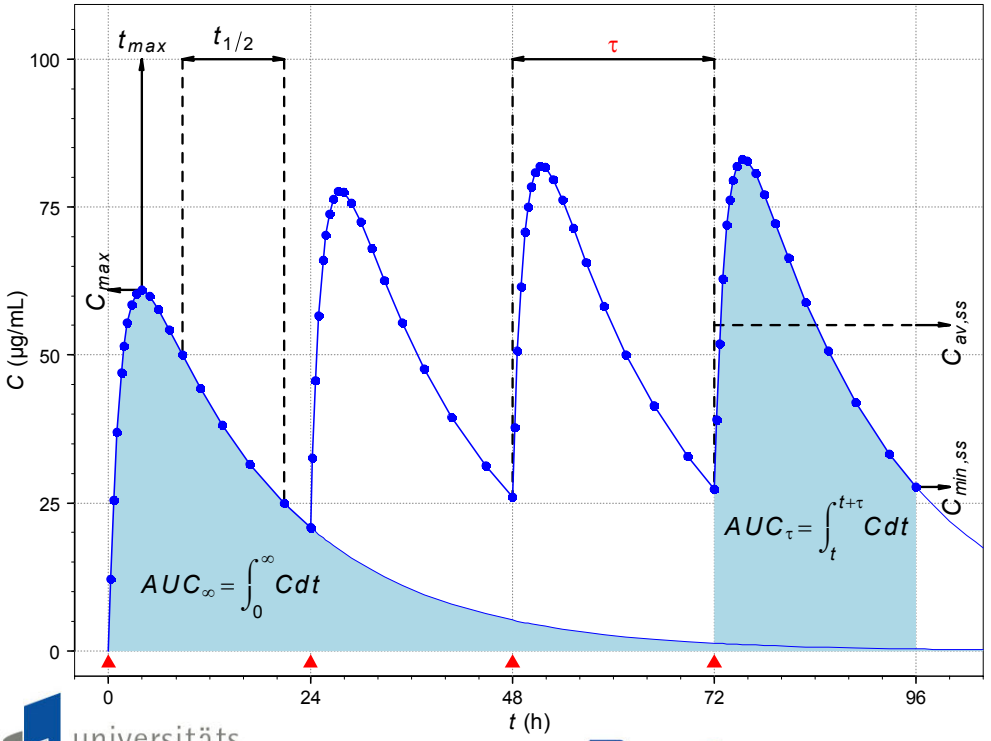
Interludes

Dost's *'Law of Corresponding Areas'* aka *'Superposition Principle'*

- In a linear PK system the Area Under the Curve in steady state within one dosing interval ($AUC_{0-\tau}$) equals $AUC_{0-\infty}$ after a single dose.



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Interludes

Relevance of phases

- Generally the slowest phase is responsible for accumulation. Commonly ‘terminal half life’ is used synonymously with ‘biological half life’. However, sometimes the slow phase is not relevant.
- In any multi-compartment model (parameterized in macro-constants) the *AUC* is given as

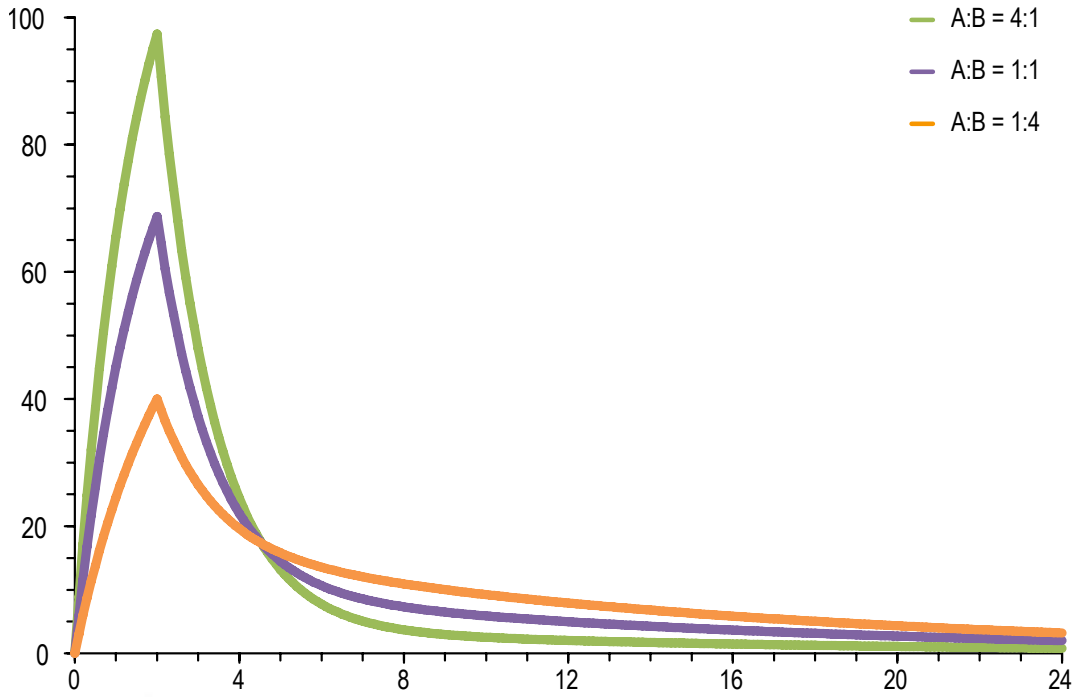
$$AUC_{0-\infty} = \sum_{i=1}^{i=n} \frac{X_i}{\lambda_i}$$

where X_i are the coefficients and λ_i the exponents.

Interludes

Relevance of phases

- In the example all parameters are identical, except *A* and *B* (*A* + *B* is kept constant).
- $AUC_{0-\infty}$ are identical.
- However, the slow phases account for 71%, 91%, and 98% of $AUC_{0-\infty}$.



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Interludes

Mean of Residence Times

- Distribution and elimination are stochastic processes.
  - Some molecules leave the circulation very quickly, whereas others stay for a long time.
  - Example
    - We dose 2000 IU (activity 4.5 MIU/mg) of FVIII (265 kDa) which will be eliminated with a half life of twelve hours. 1.67 nmol are $\approx 10^{15}$ (one quadrillion = 1 000 000 000 000 000!) molecules. If we could 'tag' individual molecules, we would see the first ones already leaving the central circulation within ~2 minutes. However, most stay longer…
  - If we register how long each molecule stays in the body (*i.e.*, their 'residence times') we could draw a histogram – like for any other distribution.

Interludes

Mean of Residence Times

- This histogram is actually the concentration-time curve.
- Distributions can be described by their so-called ‘statistical moments’.
  - The ‘zero’ moment is given as

    $$S_0 = \int f(x)\,\mathrm{d}x$$
  - The first as

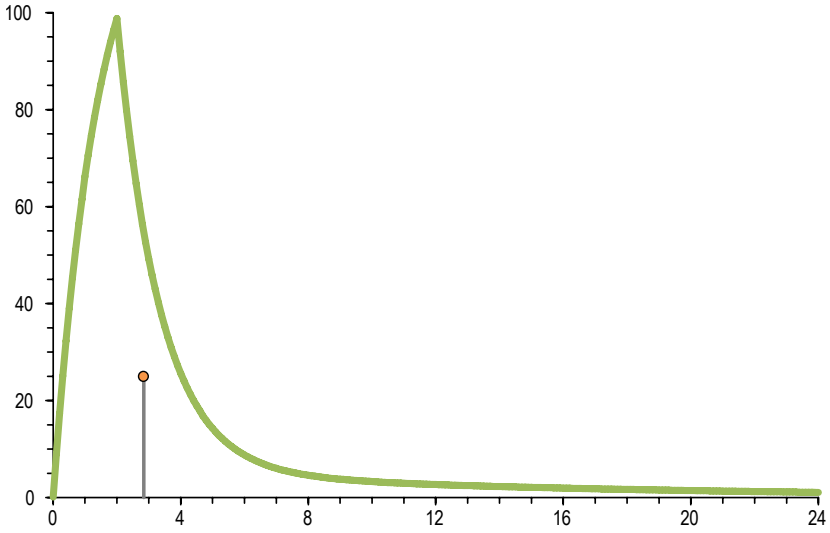
    $$S_1 = \int x \cdot f(x)\,\mathrm{d}x$$
  - The second as

    $$S_2 = \int x^2 \cdot f(x)\,\mathrm{d}x$$

Interludes

Mean of Residence Times

- In pharmacokinetics $S_0 = AUC$ and $S_1 = AUMC$, the 'Area Under the Moment Curve'.
- The 'Mean of Residence Times' is calculated as
  - $MRT = AUMC / AUC$ (IV and EV administration)
  - $MRT = AUMC / AUC - \frac{1}{2}t^*$ (infusion, where t^* = length of infusion)
- Rule of thumb: after MRT ~⅔ of the drug have been eliminated.
- S_2 is rarely used (leads to VRT, the 'Variance of Residence Times').



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Two-Stage Procedure

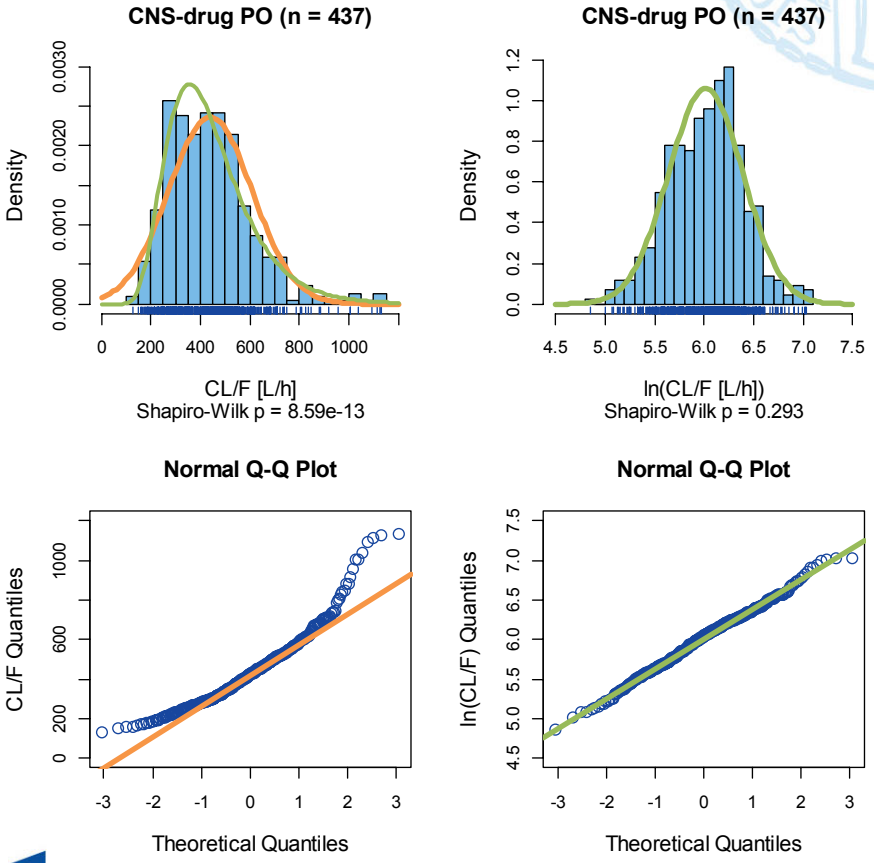
In general we are not interested in describing the PK of *one particular* patient, but at least the *group* of patients in a study.

- **Stage 1**
  - **Fit individual patients to a model.**
  - **Derive a set of PK parameters.**
- **Stage 2**
  - **From this set of PK parameters calculate means and standard deviations.**
  - **Optionally calculate a confidence interval which we can use in predicting what to expect in the *population* of patients.**

Two-Stage Procedure

Problems

- *Which* mean?
  - Many biologic variables *do not* follow a normal distribution.
  - *Geometric* mean: Clearances, volumes.
  - *Harmonic* mean: Rate constants.
  - *Arithmetic* mean: Excreted amounts.



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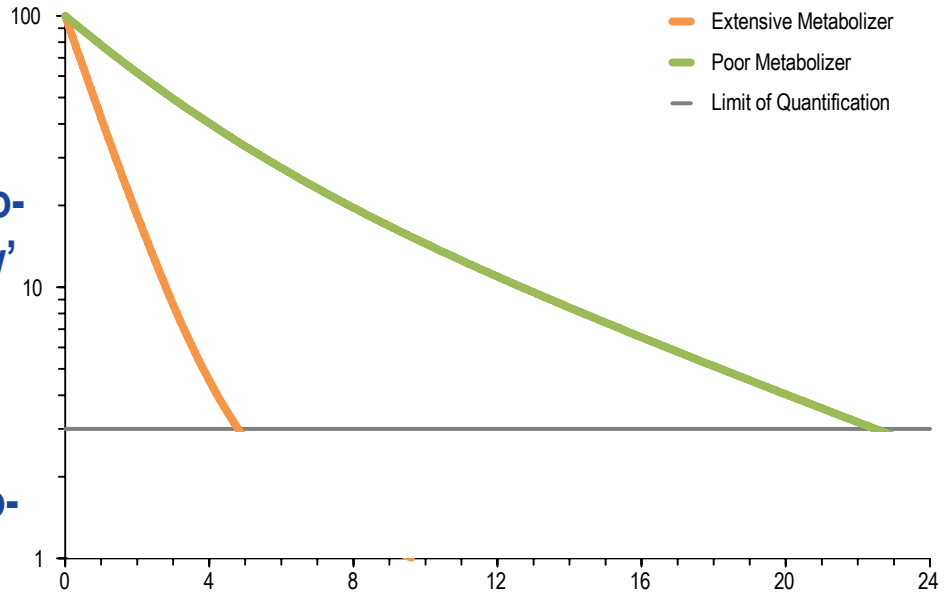
Two-Stage Procedure

Problems

- What if patients are best fit to *different* models?
  - Patients may belong to different genotypes (*e.g.*, extensive and poor metabolizers).
  - Due to limitations of the bioanalytical method the 'slow' phase is not observed in EMs.
  - Best fits are a one-comp. model for the EM and a two-comp. model for the PM.



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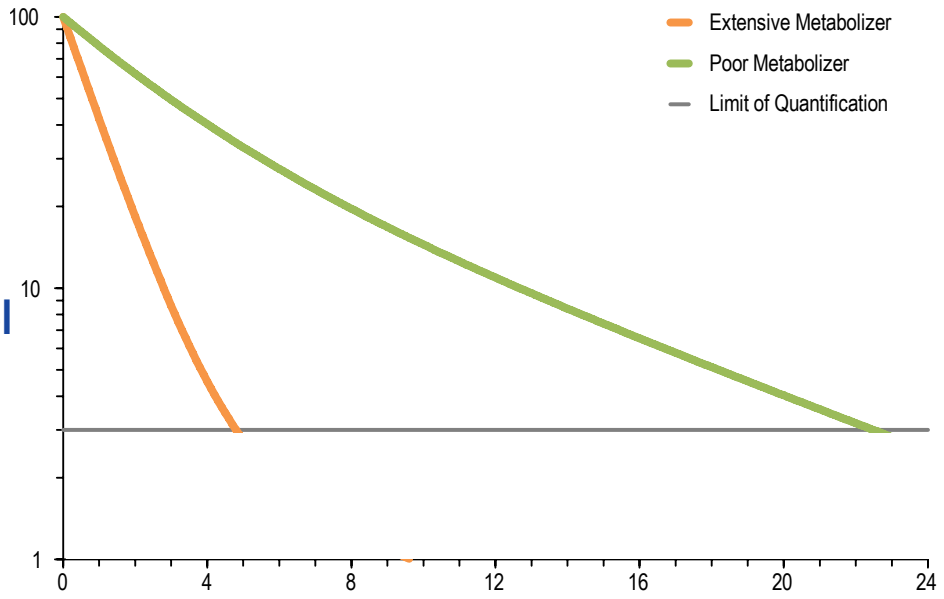
Two-Stage Procedure

Problems

- What if patients are best fit to *different* models?
  - Although eliminations are identical (parallel lines in the last phase) – we don't see it in the EM.
  - The model of the PM has five parameters (V_1, V_2, k_{10}, k_{12}, k_{21}), but the EM's model only two (V_1, k_{10}).
  - It does not make sense to calculate means – 'apples and oranges'…



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Population PK Modeling

Problems in the Two-Stage Procedure lead in the early 1970s to 'Population PK Modeling'

- Simultaneous fit of all patients' data
  - Separation of residual error into intra- and inter-individual components.
  - Direct assessment of covariates (body weight, age, sex, HCT, …).
- PK of an 'average patient' is derived
  - Taking variabilities into account we can predict the PK of the entire *population* of patients.
  - Since covariates are already part of the model, we can predict the PK of a *particular patient* based upon them.

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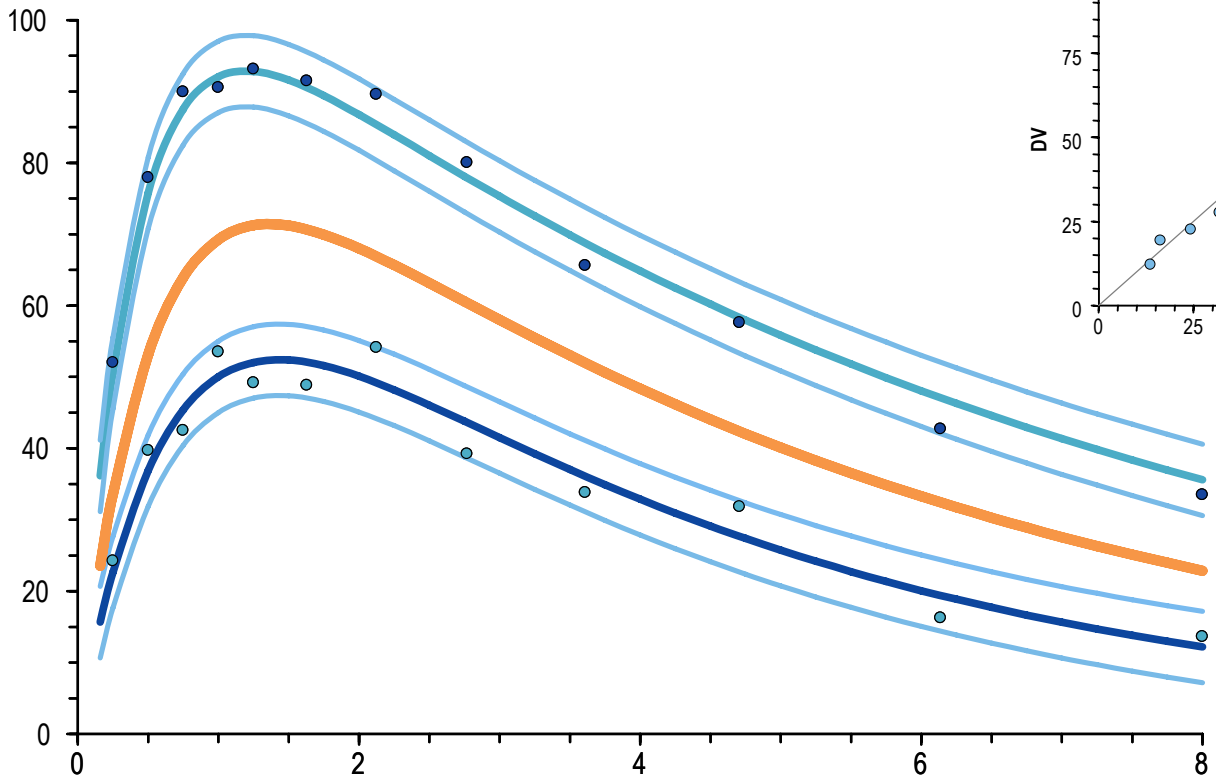
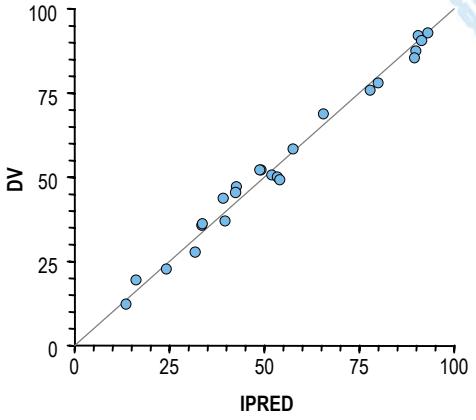
Population PK Modeling





intraindividual variability
interindividual variability

residual error

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Population PK Modeling

Basics

- Nonlinear Mixed Effects Model
  - *Mixed* Effects Model: *Fixed* and *Random* Effects
- Estimates Population PK parameters (*V*, *CL*, …)
  - Fixed Effects (thetas θ)
- Estimates Variability
  - Random Effects (etas η)
    - Intersubject Variability
    - Interoccasion Variability (day to day)
    - It is expected that etas are distributed $N(0, \omega^2)$.

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Population PK Modeling

Basics

- Estimates Variability (cont'd)
  - Residual Error (epsilons ε)
    - Intrasubject: Measurement error, model misspecification, …
    - It is expected that epsilons are distributed N(0, σ^2).
- Identify factors determining intersubject Variability: Covariates
  - Demographics: Body weight / surface area, age, sex, …
  - Genotypes: CYP450, …
  - Physiology: Renal (creatinine clearance) or hepatic impairment, HCT, disease state, …
  - Influence of concomitantly administered drugs (DDI)
  - Others: Food, circadian variation, formulation, …

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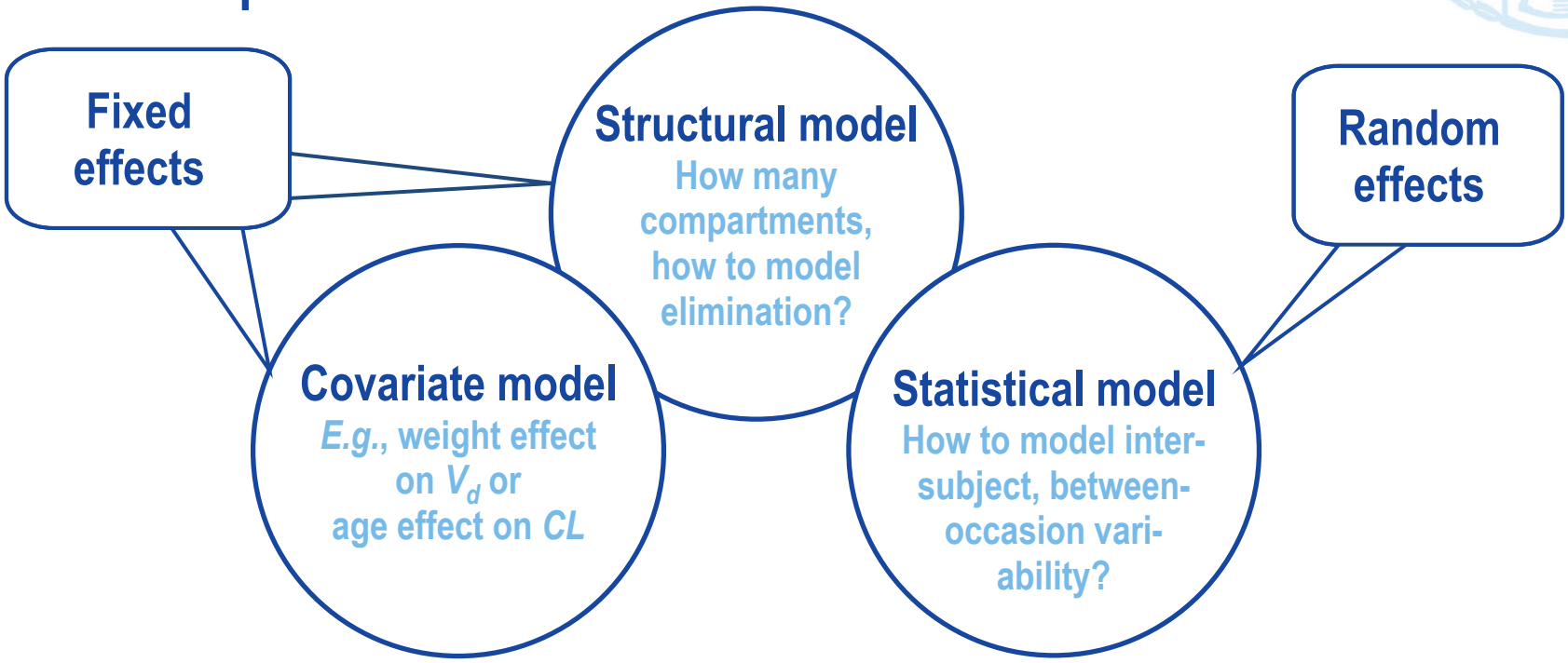
Population PK Modeling

Model

- $y_{ij} = f(\Theta_i) + \varepsilon_{ij}$, where
  - y_{ij} is the j^{th} observation of the i^{th} subject,
  - f is a model that describes all observations,
  - Θ_i is a vector of subject i's parameter values (θ), and
  - ε_{ij} is the residual error of subject i's j^{th} observation.
- The elements of Θ_i are usually $\theta_i = \theta \cdot e^{\eta}$, where
  - θ is the typical value for a parameter and
  - ω^2 is the variance of η values.

Population PK Modeling

Components



Population PK Modeling

Advantages

- Studies in the target population
- Sparse sampling (only 2 – 3 samples / subject) possible
  - Routine sampling in Phase II/III.
  - Special populations (Pediatrics, cancer/AIDS, hemophilia, critical care patients, eldery, …).
- Unlike in 'rich data sets' missing data not problematic
  - Imbalanced designs common
    - Different doses / subject.
    - Different number of samples / subject.
    - Different sampling times / subject.

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Population PK Modeling

Advantages

- Covariates part of the model
  - Fewer restrictions on in-/exclusion criteria.
  - 'What if' scenarios in planing further studies.
  - Full model allows prediction of 'real world PK' – leads to more reliable dose regimen / posology.
  - An established and fully validated PopPK model allows precise dosing of individual patients – leading to *personalized medicine*.

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Population PK Modeling

Disadvantages

- Complex methodology
  - Might require simulations (optimal sampling times for sparse sampling); stepwise refinement of model during study.
  - Statistical models not trivial.
  - Expensive software with steep learning curve.
  - Carl Metzler: *"PK Modeling – Art or Science?"*
- Time consuming
  - Easily ~10times longer than classical Two-Stage PK – even for an experienced modeler.

Population PK Modeling

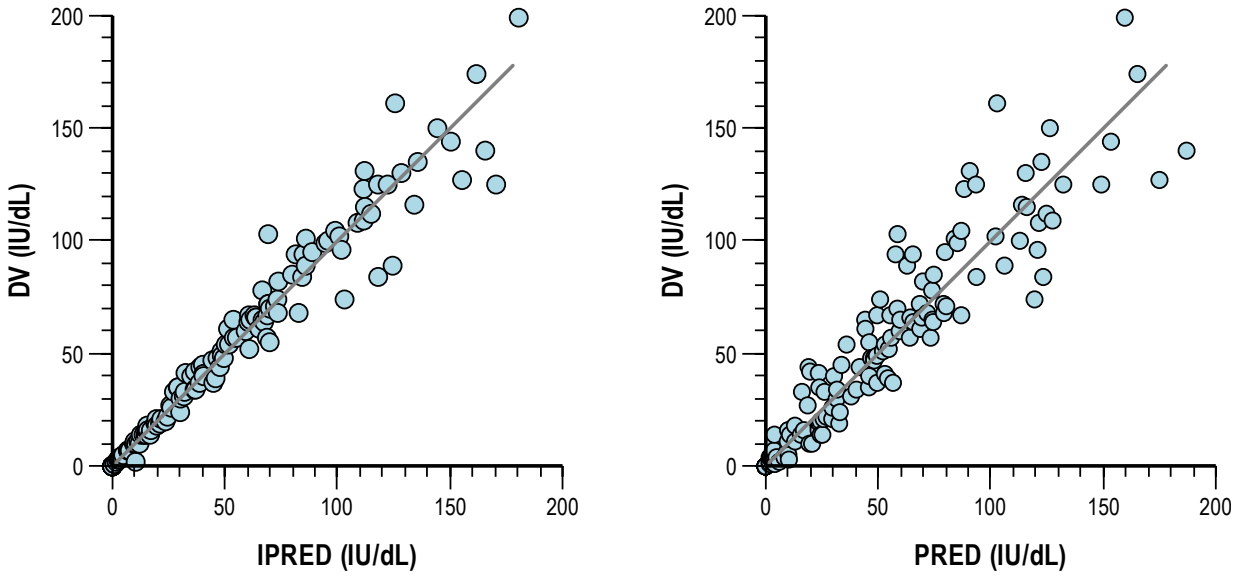
Disadvantages

- Validation might require multiple studies
  - Internal validation:
    Use only a part of the study's data to set up a model and compare predictions with the other part.
  - External validation:
    Predictions *vs.* another study
- Cost/Benefit ratio
  - Unclear beforehand whether the model will give more than a trivial result (like: concentrations depend on body weight).

Population PK Modeling

Example

- ADVATE, 19 patients, short infusion, rich data set, 2-comp model, covariates: age on V_1, CL and body weight on V_1, V_2, CL; FOCE ELS



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Pharmacokinetic Issues

Thank You!
Open Questions?

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