

# Pharmacokinetics Modelling Course: 3. PK Parameters, Variability, SBML

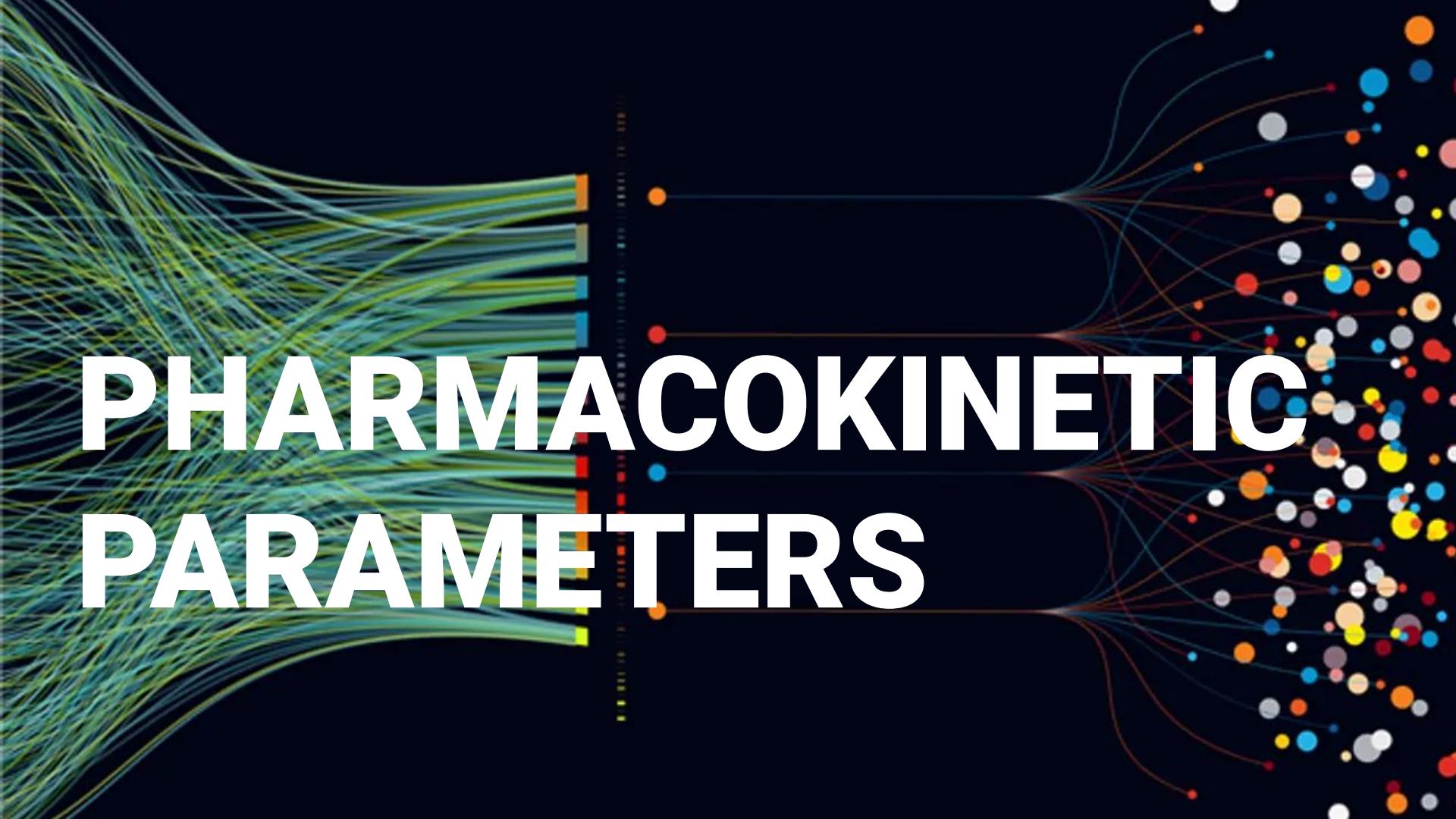
Matthias König, MB19, SS2023

Humboldt-University Berlin, Systems Medicine of the Liver Lab

<https://livermetabolism.com>

konigmatt



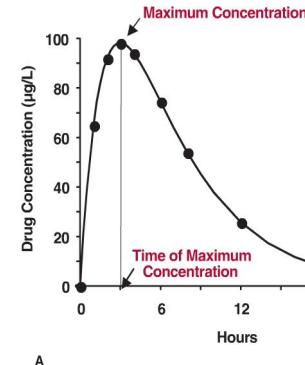
The background features a dark blue gradient with a complex network of thin, glowing lines in shades of green, yellow, and orange flowing from left to right. On the right side, there is a cluster of numerous small, semi-transparent colored circles in various sizes and colors, including red, orange, yellow, green, and blue.

# PHARMACOKINETIC PARAMETERS

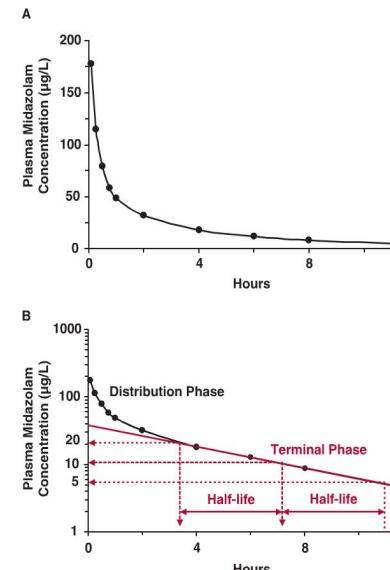
# Pharmacokinetic parameter

Pharmacokinetic parameters are numerical values that describe how a drug behaves in the body. They play a vital role in determining the dosage and frequency of drug administration.

1. **Absorption:** This parameter involves how the drug is absorbed into the bloodstream from the site of administration. The rate and extent of absorption can influence the onset, intensity, and duration of a drug's effect.
2. **Distribution:** This refers to how the drug spreads throughout the body. The volume of distribution ( $V_d$ ) is a key parameter that quantifies the extent to which a drug is distributed in the body's tissues compared to its concentration in the blood.
3. **Metabolism (Biotransformation):** Metabolism is how the drug is chemically modified or broken down in the body, primarily by liver enzymes. This can change the drug's activity and affects how quickly it's cleared from the body.
4. **Elimination (Excretion):** This parameter refers to the removal of the drug from the body, primarily through the kidneys (urine) or liver (bile). The rate of elimination is usually expressed as the drug's half-life ( $t_{1/2}$ ), which is the time it takes for the concentration of the drug in the body to be reduced by half.
5. **Clearance (Cl):** This is a measure of the body's efficiency in eliminating the drug, expressed as volume/time (like mL/min). It's a crucial parameter that determines the steady-state concentration of the drug for a given dosage regimen.
6. **Bioavailability (F):** This is the fraction of the administered dose of a drug that reaches the systemic circulation in an unchanged form. It's a crucial parameter, especially for oral medications.
7. **Area Under the Curve (AUC):** This is a measure of the total exposure of the body to the drug. It's calculated as the integral of the concentration-time curve, from administration to elimination.
8. **Peak Concentration ( $C_{max}$ ) and Time to Reach Peak Concentration ( $t_{max}$ ):**  $C_{max}$  is the highest concentration a drug achieves in the body after administration, and  $t_{max}$  is the time it takes to reach this peak concentration.



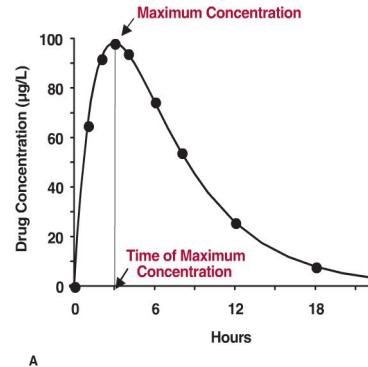
**FIGURE 2-1.** Drug concentration–time curve following a single oral dose showing the maximum systemic exposure ( $C_{max}$ ) and the time of its occurrence ( $t_{max}$ ). The concentration could represent drug in whole blood, plasma, or serum.



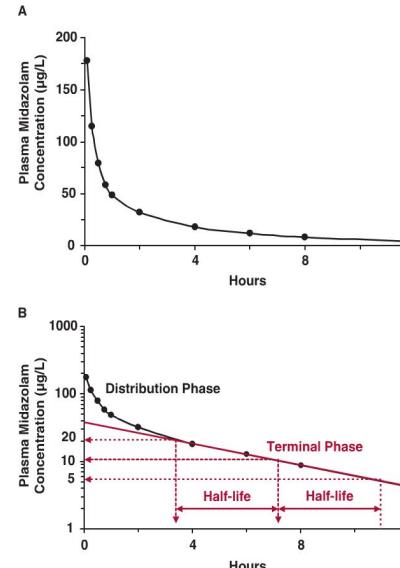
**FIGURE 3-4.** A. Plasma concentration of midazolam with time in an individual after an 8.35-mg i.v. bolus dose of midazolam hydrochloride (7.5 mg of the base) in a healthy adult. B. The data in A are redisplayed as a semilogarithmic plot. Note the short distribution phase. (From: Penttiläinen PJ, Väistöalmi L, Himberg JJ, Crevoisier C. Pharmacokinetics of midazolam following i.v. and oral administration in patients with chronic liver disease and in healthy subjects. *J Clin Pharmacol* 1989;29: 272–277.)

# Pharmacokinetic parameter

- $C_{max}$  : Maximal concentration
- $T_{max}$  : time of maximal concentration
- AUC : area under the curve
- $k_{el}$ : elimination rate fitting linear part of terminal phase (log)
- $t_{1/2}$  : half-life ( $= \ln 2/k_{el}$ ) time for concentration to fall to half
- $Vd$ : volume of distribution ( $= CL/k$ ), dilution space
- $CL$ : clearance ( $= \text{Dose}/\text{AUC}$ ,  $= \text{Dose}/C(0)_{\text{extrapolated}}$ )



**FIGURE 2-1.** Drug concentration–time curve following a single oral dose showing the maximum systemic exposure ( $C_{max}$ ) and the time of its occurrence ( $t_{max}$ ). The concentration could represent drug in whole blood, plasma, or serum.



**FIGURE 3-4.** A. Plasma concentration of midazolam with time in an individual after an 8.35-mg i.v. bolus dose of midazolam hydrochloride (7.5 mg of the base) in a healthy adult. B. The data in A are redisplayed as a semilogarithmic plot. Note the short distribution phase. (From: Pentikäinen PJ, Väistönen L, Himberg JJ, Crevoisier C. Pharmacokinetics of midazolam following i.v. and oral administration in patients with chronic liver disease and in healthy subjects. *J Clin Pharmacol* 1989;29: 272–277.)

# Area under the curve (AUC)

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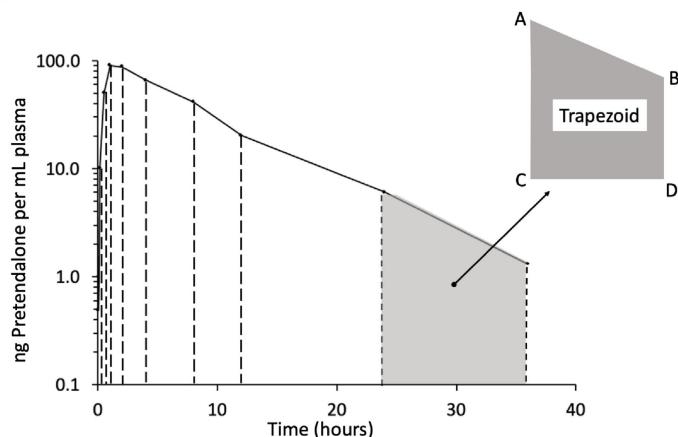


Figure 22: illustration of calculation of area of each trapezoid across the drug-concentration time plot using the linear trapezoidal rule.

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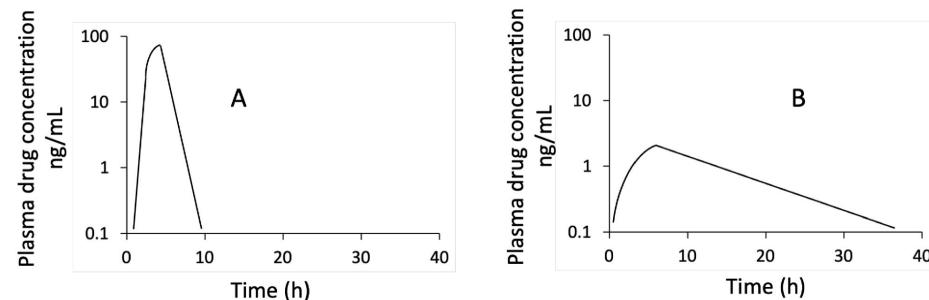


Figure 20: two pharmacokinetic curves of different shape but with the same AUC.

# AUC extrapolation

## Area Under the Curve (AUC):

- It's a pharmacokinetic parameter that represents the total exposure of the body to a drug.
- AUC is calculated as the integral of the drug concentration-time curve, from the time of administration until the drug is eliminated from the body.
- The AUC provides valuable information about the drug's bioavailability and clearance rate.
- It's widely used in therapeutic drug monitoring, dose adjustment, and comparison of generic drugs with original brands (bioequivalence studies).

## AUC Interpolated to Infinity ( $AUC_{0-\infty}$ ):

- This is an extension of the AUC that accounts for the drug amount that remains in the body and has not yet been eliminated at the last measured time point.
- It's calculated by adding the AUC from time zero to the last measurable concentration ( $AUC_{0-t}$ ) and the extrapolated AUC from the last measurable concentration to infinity (Clast/elimination rate constant).
- $AUC_{0-\infty}$  provides a more complete picture of the body's exposure to the drug over an infinite period.
- It is particularly useful when determining the bioavailability of a drug, as it accounts for the total drug exposure from the time of administration onwards.

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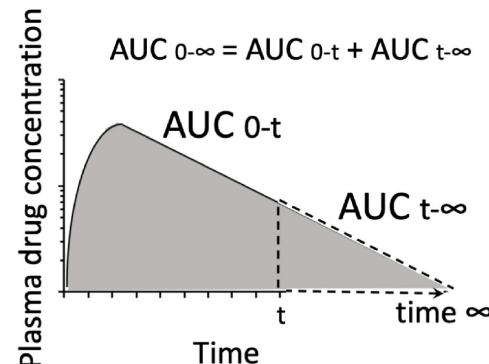
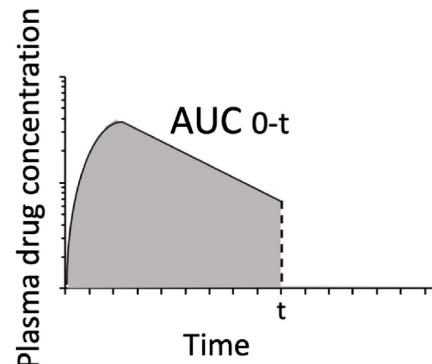


Figure 19: grey areas underneath the drug-concentration versus time curve are diagrammatic representations of areas under the curve with  $AUC_{0-t}$  (on the left) and  $AUC_{0-\infty}$  (on the right) for a typical oral administration. Dotted lines on the right-hand plot represent extrapolation of  $AUC_{0-t}$  to  $AUC_{0-\infty}$ .

# Pharmacokinetic parameters (pretendalone)

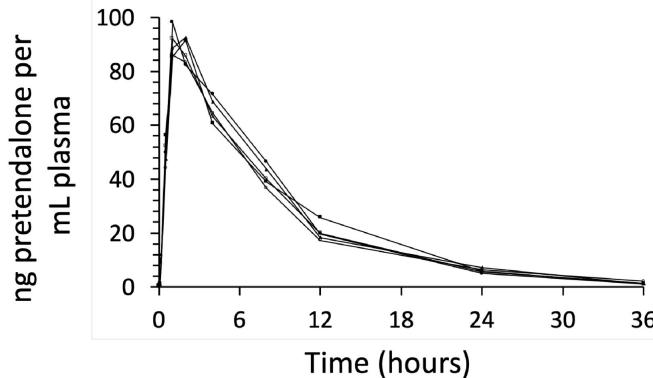


figure 2: plot of time versus concentration (ng Pretendalone per mL plasma) for five subjects following a 50 mg single oral dose.

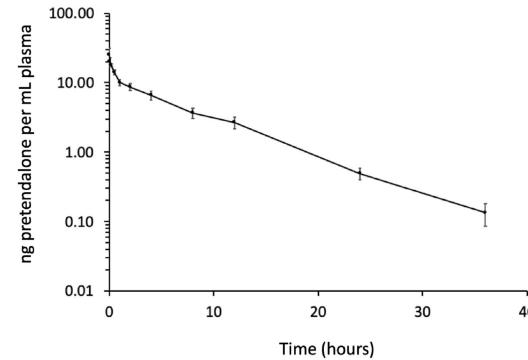


Figure 4: semi-log plot of time versus mean concentration (ng Pretendalone per mL plasma) following a 2 mg single bolus intravenous dose. Error bars are  $\pm$  one standard deviation (n=5).

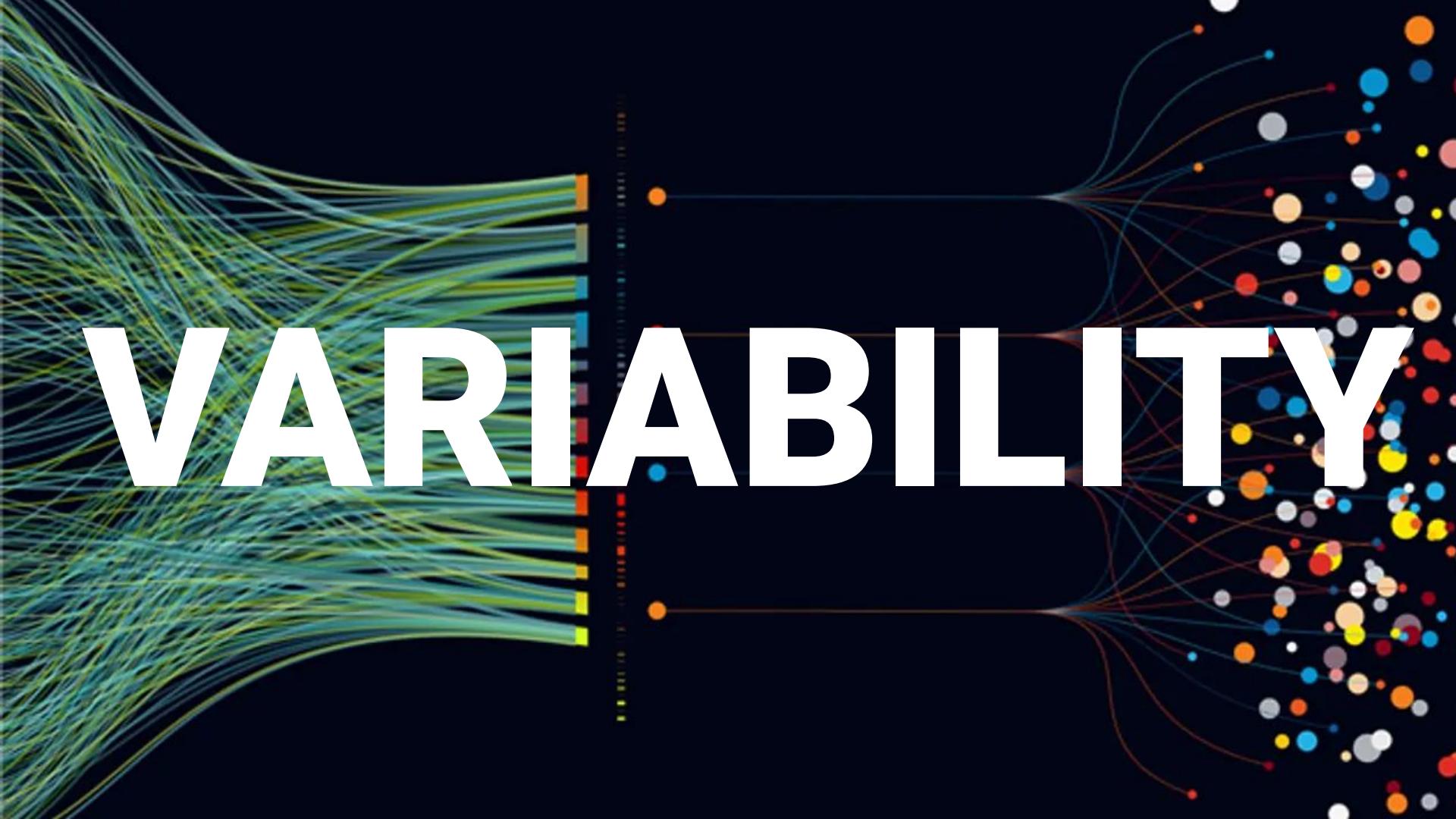
Pharmacokinetic parameter	Symbol	Unit	Mean	Standard Deviation
Maximum plasma drug concentration	$C_{\max}$	ng/mL	92.08	4.31
Time to $C_{\max}$	$t_{\max}$	h	1.4	0.55
Elimination rate constant	$k$	$h^{-1}$	0.123	0.009
Elimination half-life oral	$t_{1/2}$	h	5.64	0.46
Area under the plasma drug concentration time curve between zero and 36 hours	$AUC_{0-36}$	ng/mL.h	789.76	26.66
Area under the plasma drug concentration time curve between zero and infinite time	$AUC_{0-\infty}$	ng/mL.h	800.67	22.59
Absolute oral bioavailability	$F$	Ratio, no unit	0.35	0.02

Appendix 1: summary of pharmacokinetic parameters for the imaginary drug Pretendalone following a 50 mg single oral dose.

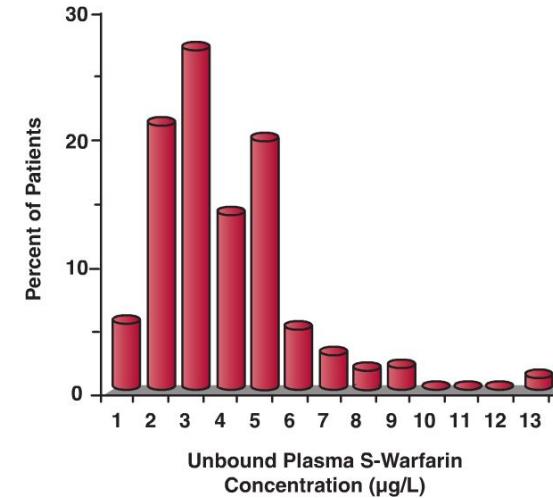
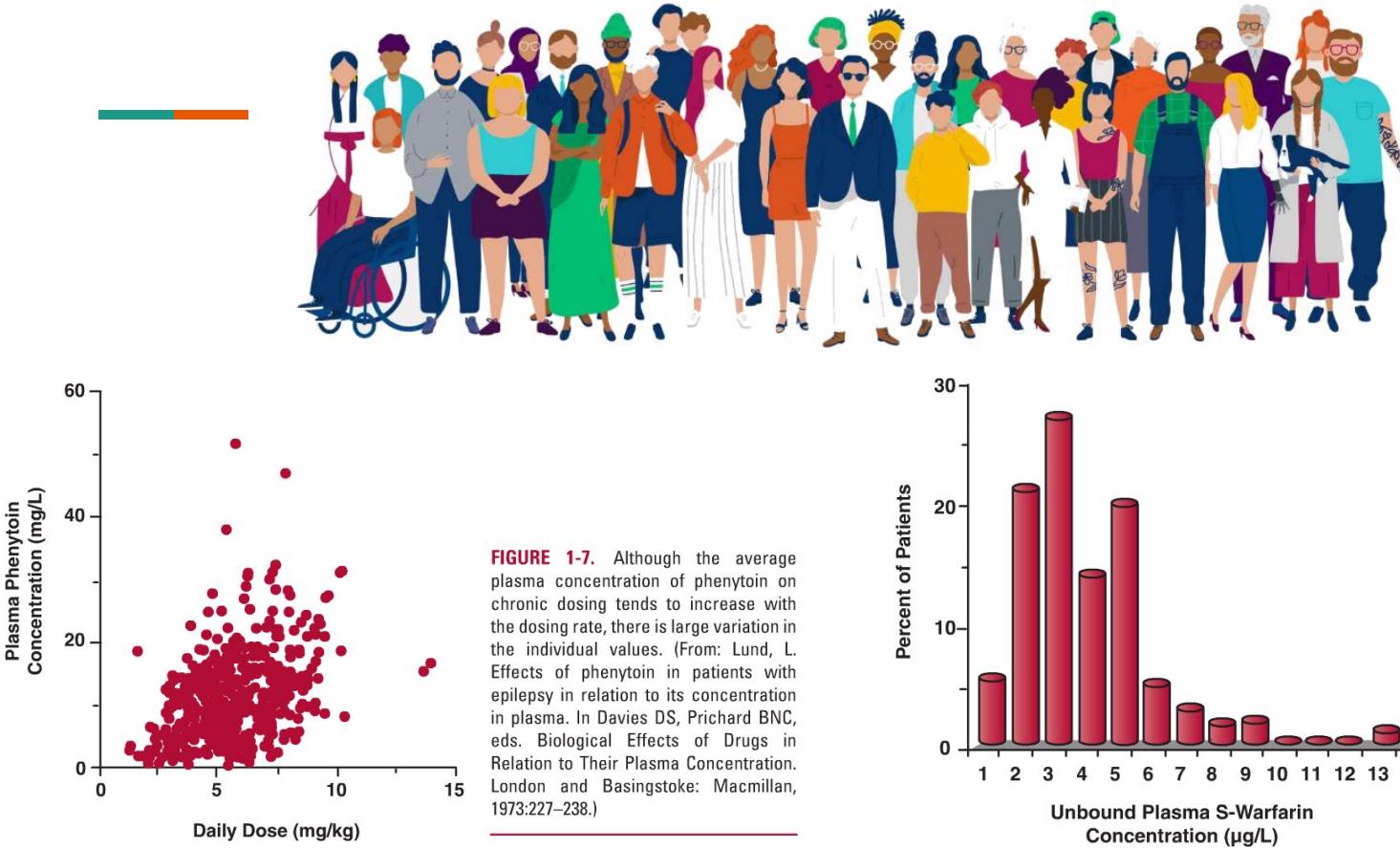
Pharmacokinetic parameter	Symbol	Unit	Mean	Standard Deviation
Elimination rate constant	$k$	$h^{-1}$	0.123	0.008
Elimination half-life	$t_{1/2}$	h	5.65	0.38
Area under the plasma drug concentration time curve between zero and 36 hours	$AUC_{0-36}$	ng/mL.h	90.00	4.76
Area under the plasma drug concentration time curve between zero and infinite time	$AUC_{0-\infty}$	ng/mL.h	91.15	5.05
Volume of distribution	$V$	L	179.11	10.10
Clearance	$CL$	L/h	22.00	1.23

Appendix 1: summary of pharmacokinetic parameters for the imaginary drug Pretendalone following a 2 mg single intravenous dose.

# VARIABILITY

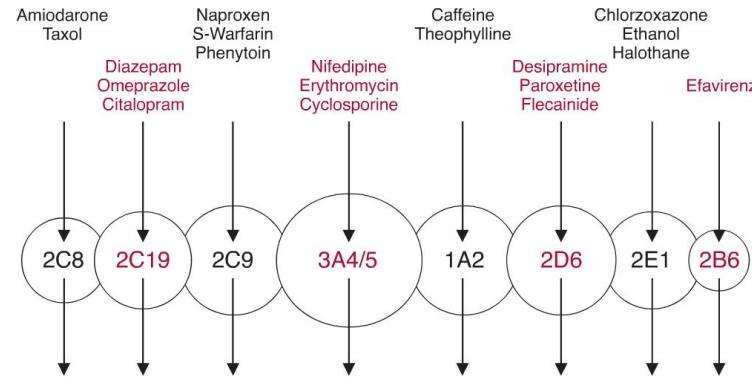
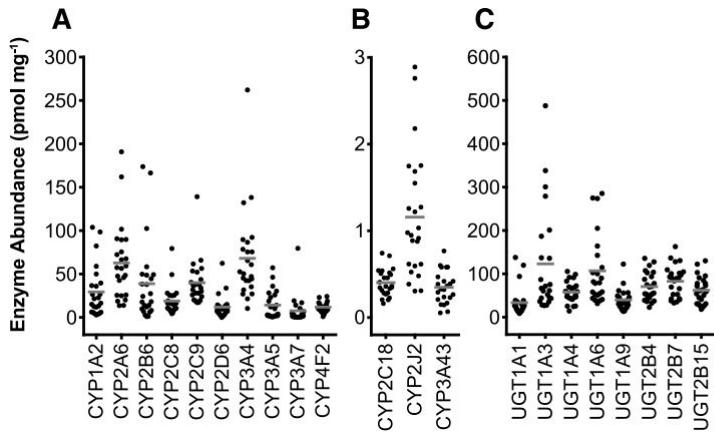
The background of the image features a dark blue gradient. On the left side, there is a dense bundle of thin, curved lines in shades of green, yellow, and blue, resembling a bundle of optical fibers or a neural network. On the right side, there is a cluster of numerous small, semi-transparent colored circles in various sizes and colors (orange, red, yellow, blue, grey) connected by thin lines, creating a network-like structure. The word "VARIABILITY" is centered in large, bold, white capital letters.

# Large interindividual variability



# Variability in enzymes

- differences in individual protein amounts
- often dynamic (induction/repression)



**FIGURE 5-3.** Graphic representation of the different forms of human cytochrome-P450 enzyme (circles) with different but often overlapping substrate specificities. The arrows indicate the single metabolic pathways. Representative substrates are listed above each enzyme.

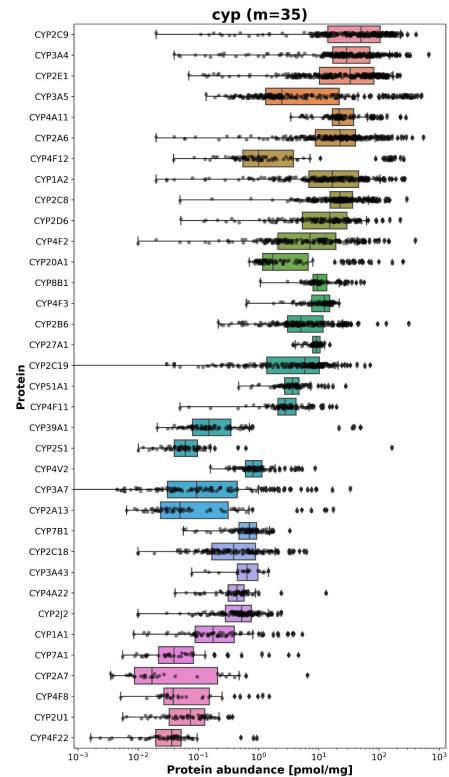
**Fig. 2.** A scatter plot of the measured abundance values of P450 (A and B) and UGT (C) enzymes. The number of samples is 24 for each enzyme except CYP2C9, CYP3A5, CYP3A7, CYP3A43, UGT1A3, UGT1A4, and UGT1A6 ( $n = 23$ ). Lines indicate population means of the sets of data.

Tozer TN, Rowland M. **Essentials of pharmacokinetics and pharmacodynamics.** Third edition.

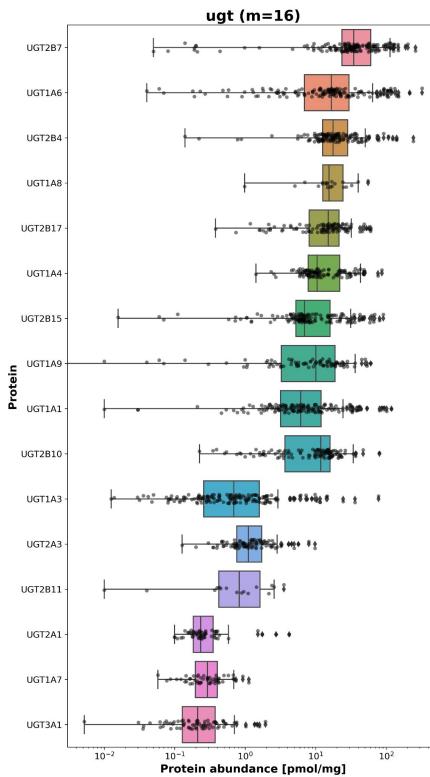
Achour B, Barber J, Rostami-Hodjegan A. **Expression of hepatic drug-metabolizing cytochrome p450 enzymes and their intercorrelations: a meta-analysis.** Drug Metab Dispos. 2014 Aug;42(8):1349-56. doi: 10.1124/dmd.114.058834. Epub 2014 May 30. PMID: 24879845.

# Large variability & multitude of isoforms (Human Liver)

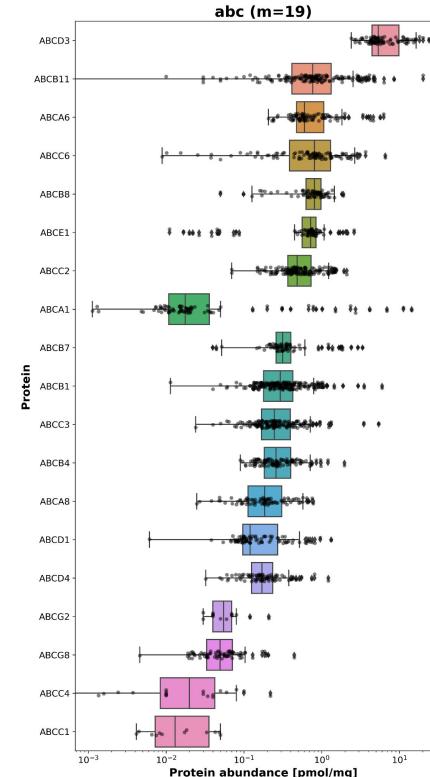
## Cytochrome P450 (CYP)



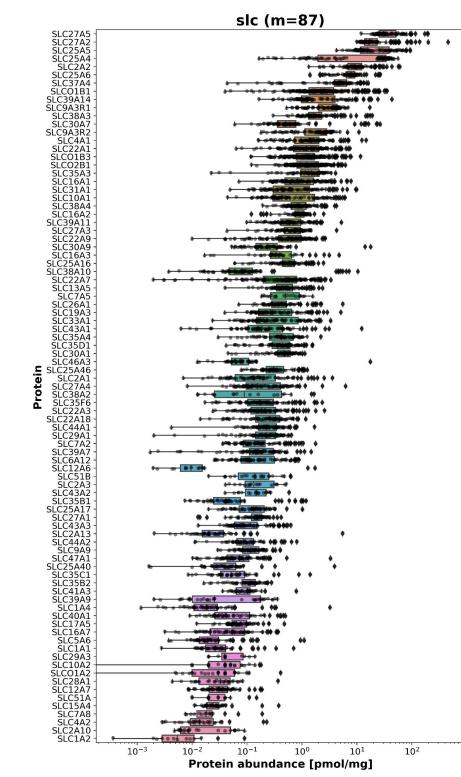
# UDP-glucuronosyltransferases (UGT)



# ATP-binding cassette (ABC)

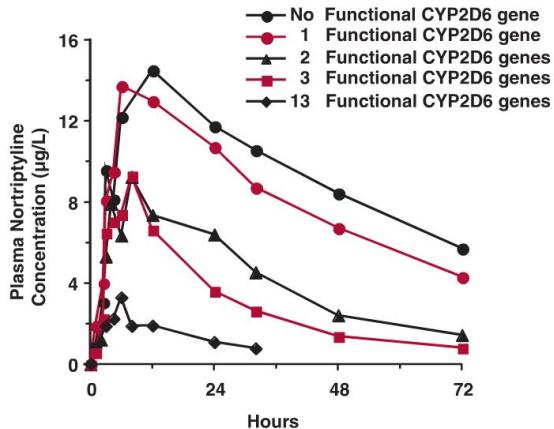


## Solute Carrier (SLC)

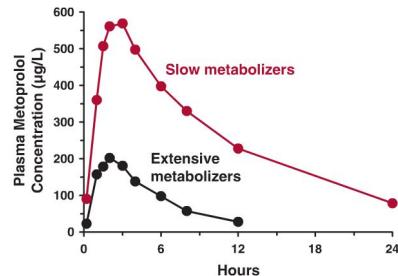


Afruja Hossain, Sophie Silberhorn, Matthias König. **Protein distributions of drug metabolizing and transporting enzymes in the Human Liver.** In preparation.

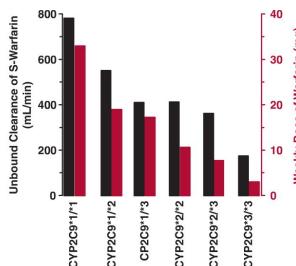
# Pharmacogenomics



**FIGURE 13-2.** Strong genetic influence in the pharmacokinetics of nortriptyline is clearly demonstrated by the high correlation between the plasma concentration–time profile and the number of functional CYP2D6 genes possessed by an individual; the larger the number of functional genes, the higher is the clearance and the lower is the exposure profile following a single 25-mg dose of nortriptyline. (From: Dalén P, Dahl ML, Bernal Ruiz ML, et al. 10-Hydroxylation of nortriptyline in white persons with 0, 1, 2, 3, and 13 functional CYP2D6 genes. Clin Pharmacol Ther 1998;63:444–452.)



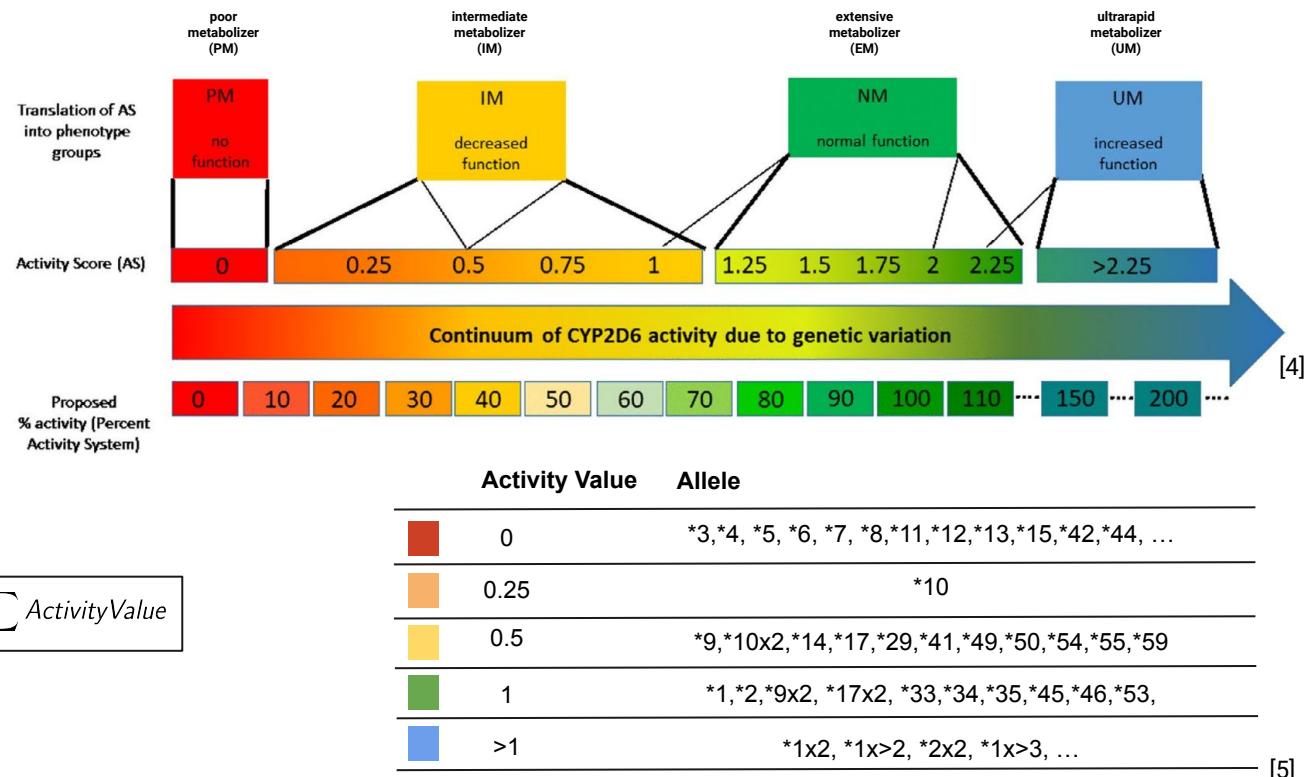
**FIGURE 13-3.** Plasma metoprolol concentrations after a single oral dose of 200-mg metoprolol tartrate were much higher in poor (colored line) than in extensive (black line) CYP2D6 metabolizers. Because metoprolol is a drug of high hepatic clearance, the difference between poor and extensive metabolizers is expressed in the large difference in oral bioavailability, because of differences in first-pass hepatic loss. (From: Lennard MS, Silas JH, Freestone S, et al. Oxidative phenotype—a major determinant of metoprolol metabolism and response. Reprinted by permission of New Eng J Med 1982;307:1558–1560.)



**FIGURE 13-4.** Genetics plays a significant role in the maintenance dose requirement of warfarin used in the treatment of various cardiovascular diseases. Shown are the unbound clearance of S-warfarin (black) in groups of patients with different CYP2C9 genotypes, all titrated and stabilized to a narrow target INR (International Normalization Ratio) range, a measure of anticoagulation, of between 2 and 3, and the mean weekly maintenance dose (obtained by summing the daily dose over 1 week, in color). Warfarin is administered as the racemate, with most of the therapeutic effect associated with the more active S-isomer, which is primarily eliminated by CYP2C9-catalyzed metabolism. Homozygous patients with two wild-type alleles (denoted by CYP2C9\*1/\*1) have the highest S-warfarin clearance and require the highest maintenance dose, and those with two of the most deficient alleles (CYP2C9\*3/\*3) have the lowest clearance and need the smallest maintenance dose. Heterozygous patients have intermediate clearance. However, as noted in Fig. 12-4 (Chapter 12, *Variability*), in addition to pharmacokinetic variability, there is also considerable interindividual variability in pharmacodynamics of this compound. (From: Scordo MG, Pengo V, Spina E, et al. Influence of CYP2C9 and CYP2C19 genetic polymorphisms of warfarin maintenance dose and metabolic clearance. Clin Pharmacol Ther 2002;72:702–710.)

# CYP2D6 Polymorphism

- genetic variants have different activity values
- subjects carry combinations of these variants
- sum of individual activity values is the activity score (AS)



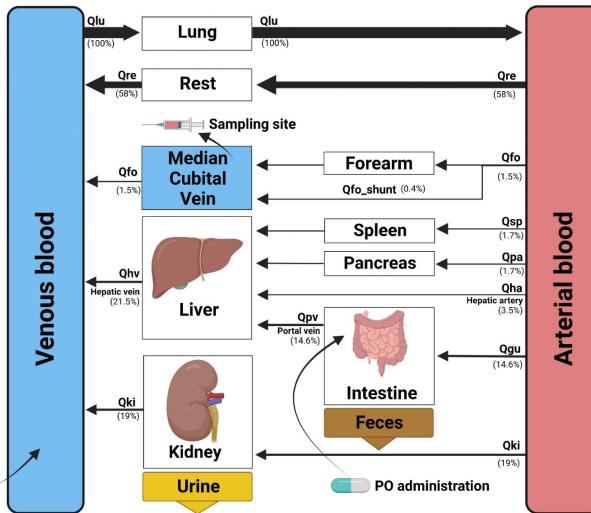
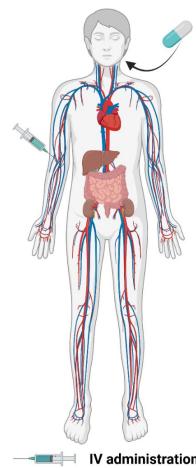
$$\text{Activity Score (AS)}: AS = \sum \text{ActivityValue}$$

[4] K. E. Caudle et al., "Standardizing CYP 2D6 Genotype to Phenotype Translation: Consensus Recommendations from the Clinical Pharmacogenetics Implementation Consortium and Dutch Pharmacogenetics Working Group," *Clin Transl Sci*, vol. 13, no. 1, pp. 116–124, Jan. 2020, doi: 10.1111/cts.12692.

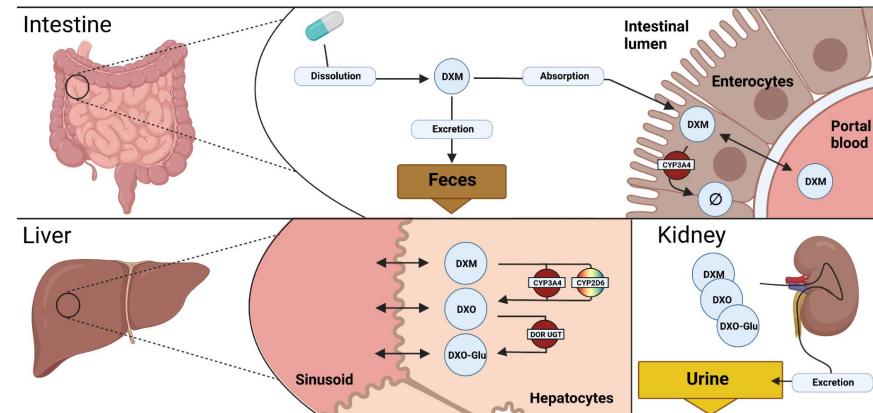
[5] M. Whirl-Carrillo<sup>1</sup>, R. Huddart<sup>1</sup>, L. Gong, K. Sangkuhl, C.F. Thorn, R. Whaley and T.E. Klein. ["An evidence-based framework for evaluating pharmacogenomics knowledge for personalized medicine"](#) *Clinical Pharmacology & Therapeutics* (2021) online ahead of print.

# Dextromethorphan - Genetic polymorphisms CYP2D6

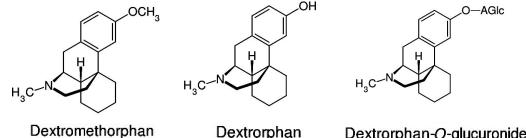
## Whole-body model



## Tissue models



## Substance/Metabolites



J.Grzegorzewski,  
*Physiologically based pharmacokinetic (PBPK) modeling of the role of CYP2D6 polymorphism for metabolic phenotyping with dextromethorphan*  
<https://doi.org/10.1101/2022.08.23.504981> [in print, Frontiers in Pharmacology]

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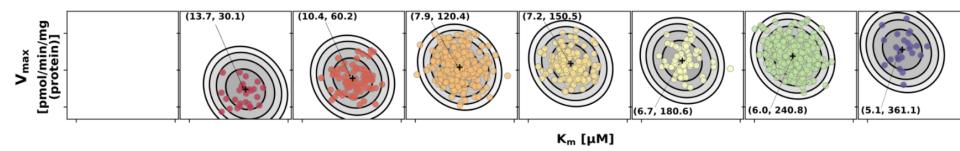
M.König

# Model of CYP2D6 polymorphism and variability

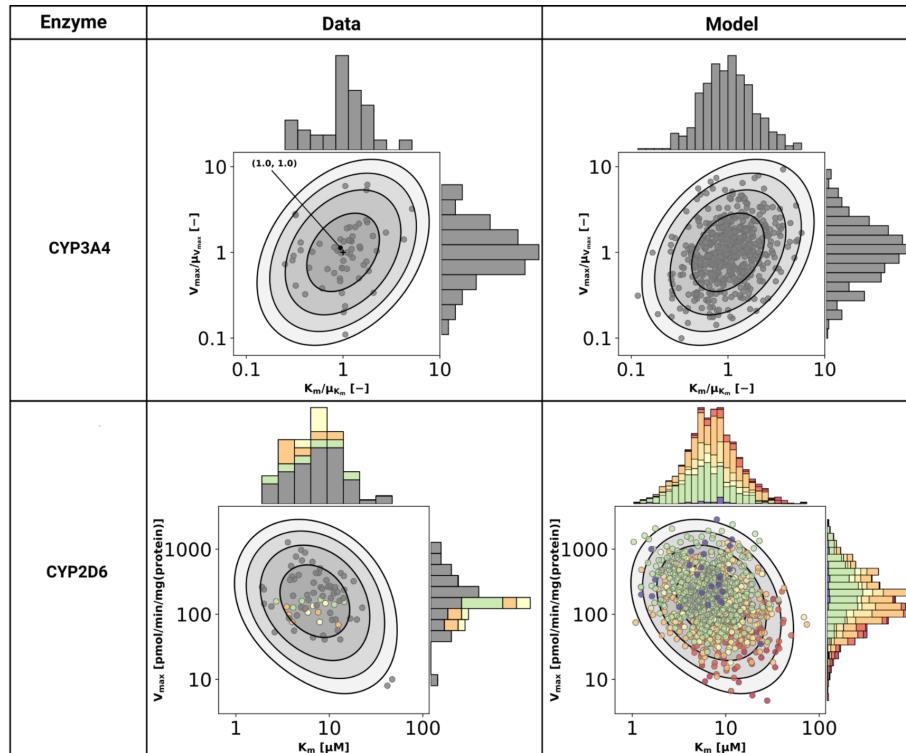
Activity Value	Allele
0	*3, *4, *5, *6, *7, *8, *11, *12, *13, *15, *42, *44, ...
0.25	*10
0.5	*9, *10x2, *14, *17, *29, *41, *49, *50, *54, *55, *59
1	*1, *2, *9x2, *17x2, *33, *34, *35, *45, *46, *53,
>1	*1x2, *1x>2, *2x2, *1x>3, ...

Michaelis-Menten:  $v = \frac{V_{max} [S]}{K_m + [S]}$

Activity Score (AS):  $AS = \sum ActivityValue$

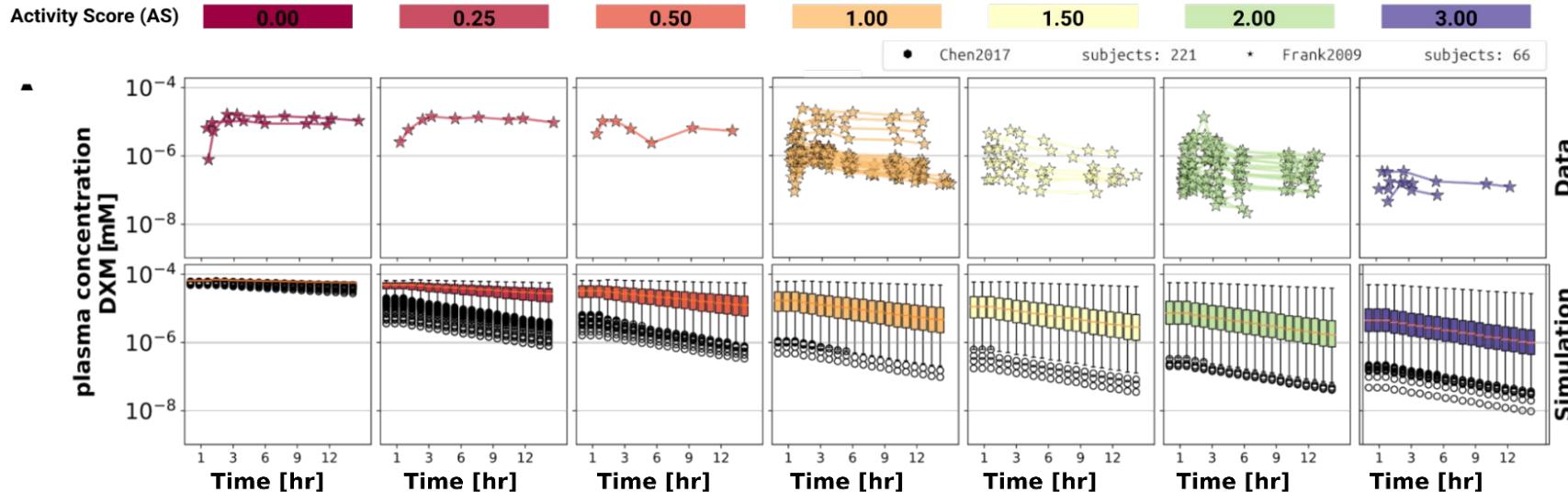
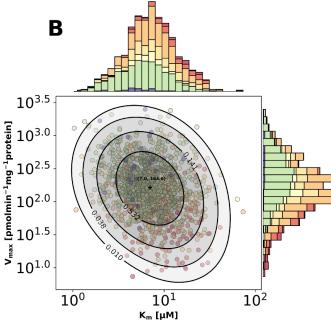


AS	0.00	0.25	0.50	1.00	1.25	1.50	2.00	3.00
gPT	gPM	gIM	gIM	gIM	gEM	gEM	gEM	gUM
$\mu_{Vmax}$	0.00	30.1	60.2	120.4	150.5	180.6	240.8	361.1
$\mu_{Km}$	0.00	13.7	10.4	7.9	7.2	6.7	6.0	5.1
P(AS)	0.06	0.02	0.07	0.29	0.13	0.06	0.33	0.02



# Effect of polymorphism on pharmacokinetics

- Prediction of effect of genetic variants
- Time course of dextromethorphan (DXM) and metabolites

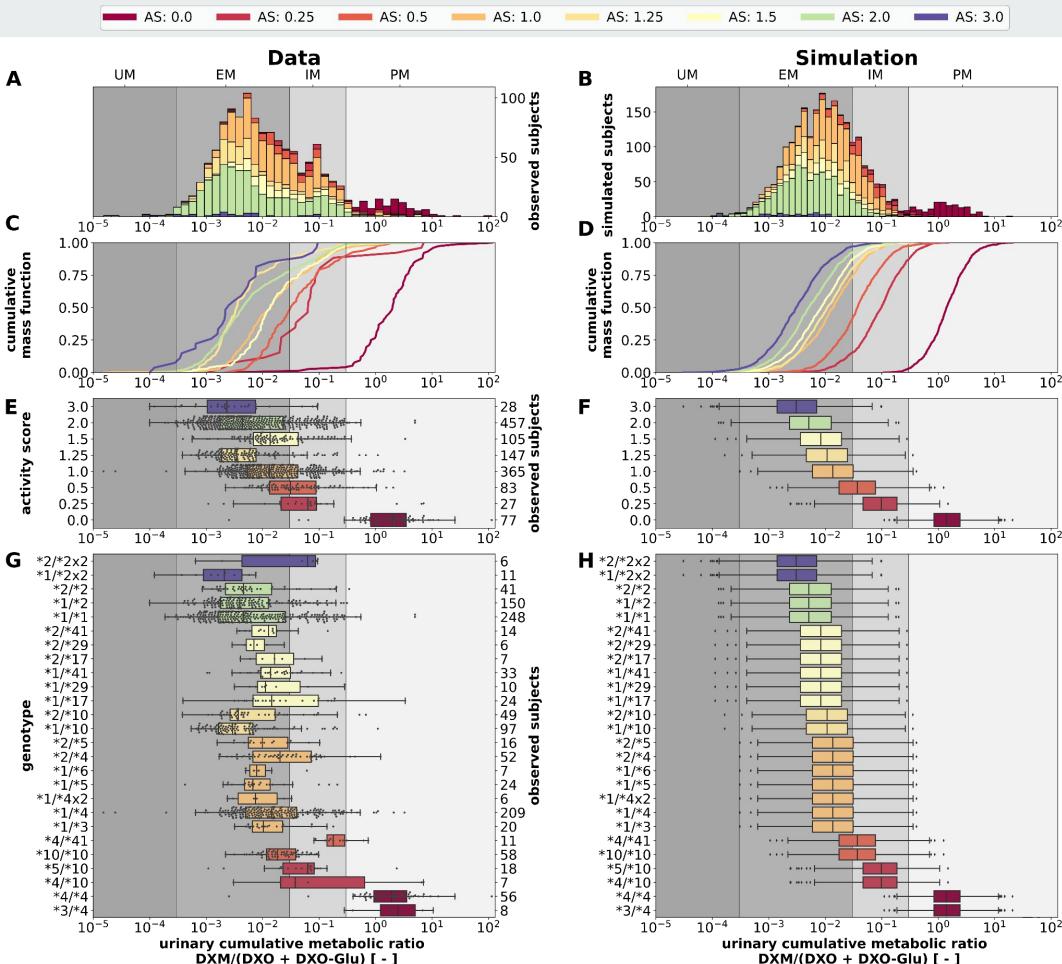


# Metabolic phenotyping

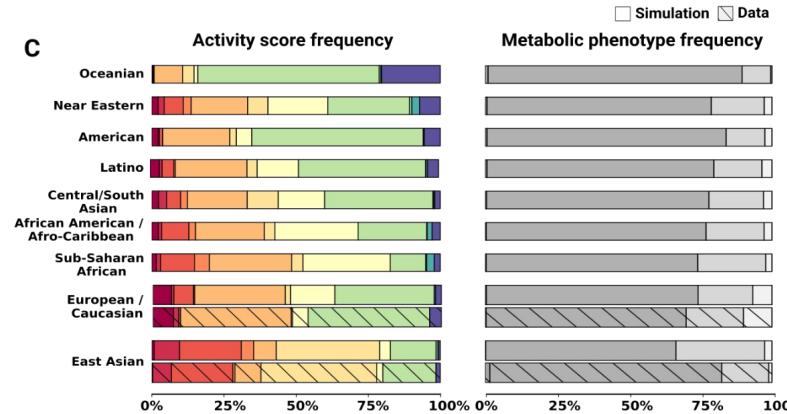
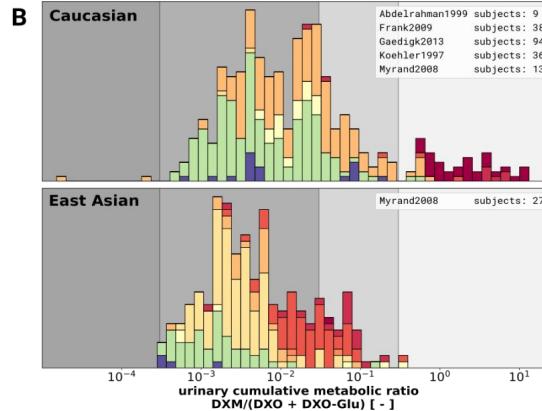
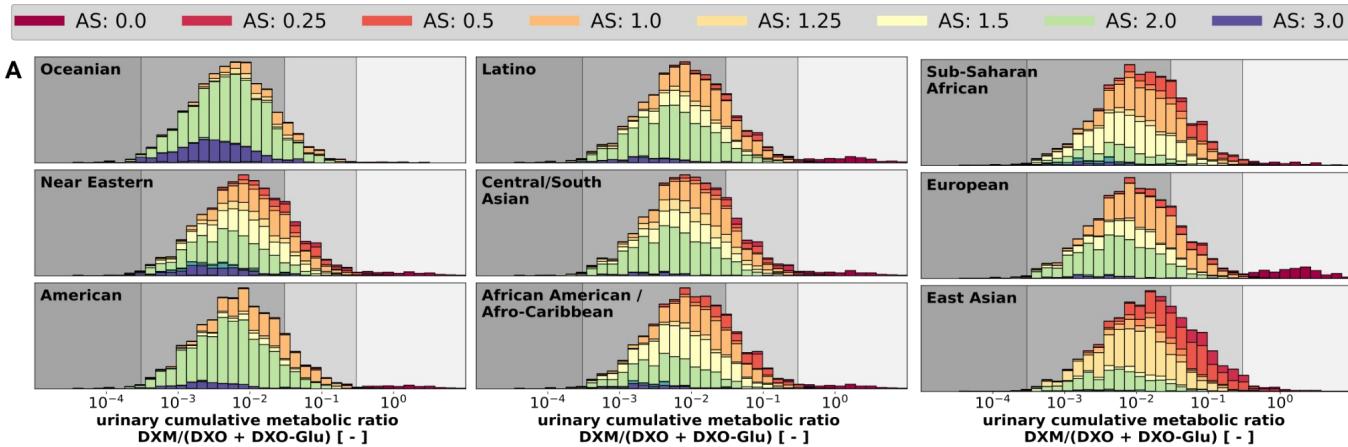
- Model predicts effect of CYP2D6 activity and genetic polymorphisms
- Urinary cumulative metabolic ratio (UCMR) for metabolic phenotyping

J.Grzegorzewski, J.Brandhorst, M.König  
*Physiologically based pharmacokinetic (PBPK) modeling of the role of CYP2D6 polymorphism for metabolic phenotyping with dextromethorphan*  
<https://doi.org/10.1101/2022.08.23.504981>

In print, Frontiers in Pharmacology



# Dextromethorphan - CYP2D6 populations



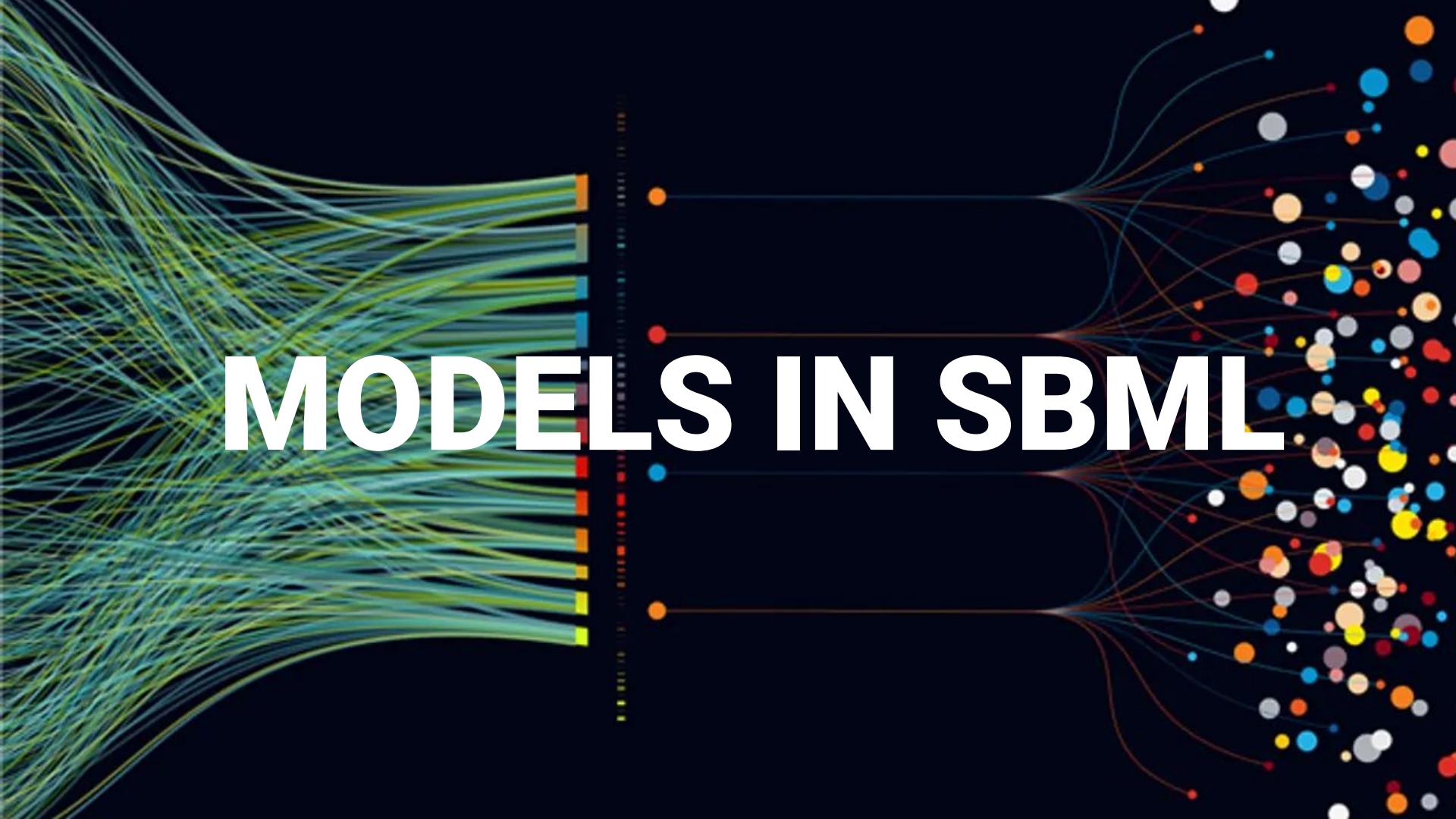
J.Grzegorzewski,  
J.Brandhorst,

**M.König  
based  
(PBPK)  
modeling of the role of  
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metabolic phenotyping with  
dextromethorphan**

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In print, Frontiers in  
Pharmacology

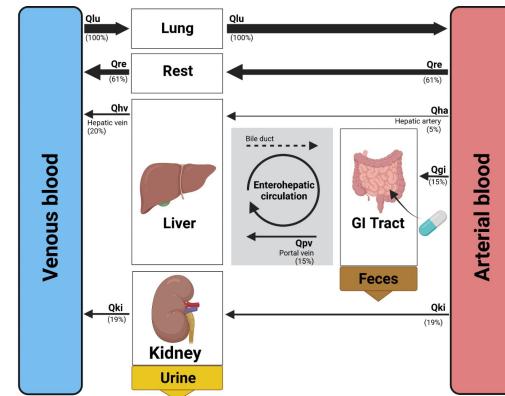
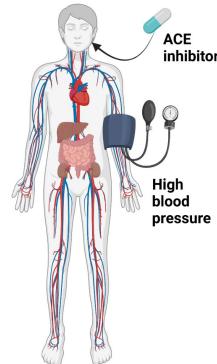
# MODELS IN SBML

The background of the slide features a complex, abstract network visualization. On the left, several vertical columns of nodes are connected by numerous thin, colored lines (predominantly green and blue) that fan out towards the right. On the far right, there is a dense cluster of many small, semi-transparent circular nodes in various colors (orange, yellow, red, blue, grey). A single horizontal line of nodes connects the two main clusters. In the center, the title "MODELS IN SBML" is written in large, bold, white capital letters.

# Systems Biology Markup Language

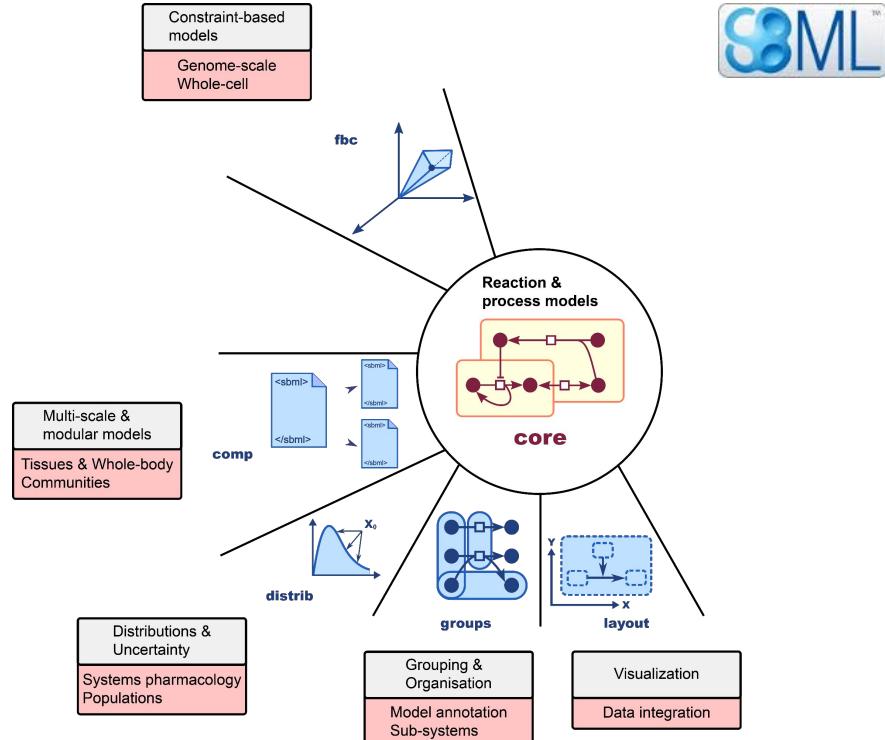


- SBML is a software data format for describing models in biology (<https://sbml.org>)
- It's a little like HTML but for model instead of web pages
- independent of any particular tool
- free and open
- De facto standard

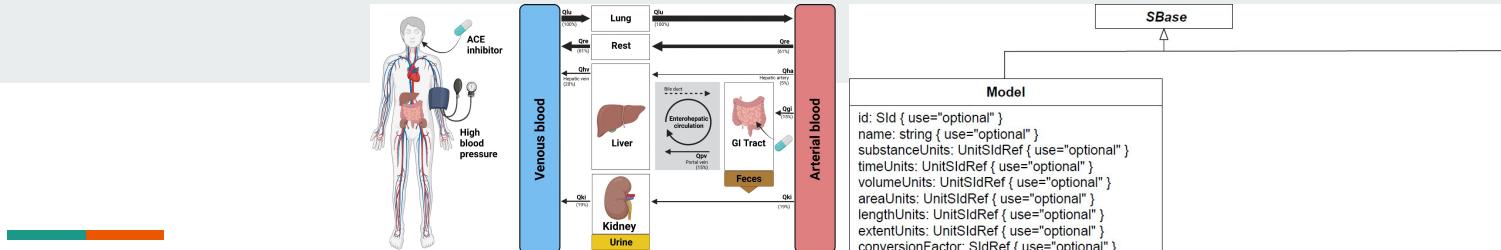


# SBML

- Process-based ODE models
- Reproducible & exchangeable model encoding (**SBML**)
- Annotations to modelling, biological and medical ontologies (**SBML core**)
- Hierarchical models/multi-scale models
- (**SBML comp**)
- Unit validation, unit checking, unit conversion
- Distributions in models & uncertainty in data and parameters (**SBML distrib**)
- Mass- & charge balance (**SBML fbc**)
- Use wide range of tools (visualization, parameter fitting, simulation, ...)
- <http://sbml.org>



Keating SM, Waltemath D, König M, ... , Hucka M; SBML Level 3 Community members.  
SBML Level 3: an extensible format for the exchange and reuse of biological models. Mol Syst Biol. 2020 Aug;16(8):e9110. doi: 10.1525/msb.20199110.



# SBML core

- Compartments
  - containers/volumes (e.g. liver volume)
- Species
  - molecules in compartments (e.g. glucose in plasma)
- Parameters
  - parameters with values (e.g. cardiac output)
- AssignmentRules
  - mathematical relationships between other parameters, species, compartments (e.g. BMI = bodyweight/height<sup>2</sup>)
- Reactions
  - processes converting species in other species (e.g. enzymatic conversion; e.g. transport via blood flow)

# sbmlutils

Python utilities for working with SBML models  
<https://github.com/matthiaskoenig/sbmlutils>

## Packages

- core, fbc, comp, distrib, layout

## Features

- model creation, manipulation & merging
- unit support
- model annotation
- interpolations
- file converters (XPP)

## New

- Simplified unit support (unit code completion)
- Markdown annotations
- OMEX support
- Resolving/rendering/validating OMEX metadata
- Interactive model reports (<https://sbml4humans.de>)

```
Parameter(  
    "ICGIM_ki_bil",  
    0.02,  
    unit=U.mM,  
    name="Ki bilirubin of icg import",  
    sboTerm=SBO.INHIBITORY_CONSTANT,  
    notes=""  
    bilirubin reference range:  
    ...  
    ~ 0.1 - 5 [g/dL]  
    (10 [mg/l] /584.6623 [g/mole]) ~ 0.0171 mmole/l  
    ...  
  
    setting Ki in reference range  
    """,  
,
```

## Parameter

**ICGIM\_ki\_bil** Ki bilirubin of icg import

**id** ICGIM\_ki\_bil  
**metaID** meta\_ICGIM\_ki\_bil  
**name** Ki bilirubin of icg import  
**sbo** SBO:0000261

**value** 0.02



**constant**



**units** mmol/l

**derivedUnits** mmol/l

**cvtterms**

BQB\_IS sbo SBO:0000261

**inhibitory constant**

Synonym: Ki

## notes

bilirubin reference range:

~ 0.1 - 5 [g/dL]  
(10 [mg/l] /584.6623 [g/mole]) ~ 0.0171 mmole/l

setting Ki in reference range



# SBML4Humans

<https://sbml4humans.de>

- **interactive SBML report** with navigation between SBML objects
- **web application** (no setup)
- **search and filter functionality**
- **resolve/render metadata**
- **hierarchical models** (SBML comp)
- **distributions and uncertainties** (SBML distrib)
- **flux balance** (SBML fbc)
- **COMBINE archives** (multiple models)
- **URL endpoint** for integration in tools/ workflows/ webpages/ presentations

[https://sbml4humans.de/model\\_url?url=https://www.ebi.ac.uk/biomodels/model/download/BIOMD000000000001.2?filename=BIOMD000000000001\\_url.xml](https://sbml4humans.de/model_url?url=https://www.ebi.ac.uk/biomodels/model/download/BIOMD000000000001.2?filename=BIOMD000000000001_url.xml)

## Parameter

### HCT hematocrit

<b>id</b>	<b>HCT</b>
<b>metaID</b>	meta_HCT
<b>name</b>	hematocrit
<b>sbo</b>	SBO:00000002
<b>value</b>	0.51
<b>constant</b>	✓
<b>units</b>	—
<b>derivedUnits</b>	—
<b>cvtterms</b>	

BQB\_IS sbo SBO:00000002

#### quantitative systems description parameter

A numerical value that defines certain characteristics of systems or system functions. It may be part of a calculation, but its value is not determined by the form of the equation itself, and may be arbitrarily assigned.

BQB\_IS ncit C64796

#### Hematocrit Measurement

A measure of the volume of red blood cells expressed as a percentage of the total blood volume. Normal in males is 43-49%, in females 37-43%.

#### Synonyms

- HCT
- Packed Cell Volume
- Hematocrit
- Erythrocyte Volume Fraction
- PCV
- Hematocrit Measurement
- EVF

BQB\_IS omit 0007571

#### Hematocrit

BQB\_IS efo 0004348

#### hematocrit

#### Parameter (1)

id	name	constant	value	units	derivedUnits	assignment
HCT	hematocrit	✓	0.51	—	—	—

#### AssignmentRule (8)

id	name	variable	math	derivedUnits
Vve	Vve		$(1 - HCT) \cdot (BW \cdot FVee - FVar \cdot FVee \cdot FVpo + FVve \cdot BW \cdot Fblood - (FVar + FVee + FVpo + FVhv))$	t
Var	Var		$(1 - HCT) \cdot (BW \cdot FVar - FVar \cdot FVee \cdot FVpo + FVve \cdot BW \cdot Fblood - (FVar + FVee + FVpo + FVhv))$	t
Vpo	Vpo		$(1 - HCT) \cdot (BW \cdot FVpo - FVpo \cdot FVee \cdot FVpo + FVve \cdot BW \cdot Fblood - (FVar + FVee + FVpo + FVhv))$	t
Vhv	Vhv		$(1 - HCT) \cdot (BW \cdot FVhv - FVhv \cdot FVee \cdot FVpo + FVve \cdot BW \cdot Fblood - (FVar + FVee + FVpo + FVhv))$	t
Vre_plasma	Vre_plasma		$Vre \cdot Fblood \cdot (1 - HCT)$	t
Vgi_plasma	Vgi_plasma		$Vgi \cdot Fblood \cdot (1 - HCT)$	t
Vli_plasma	Vli_plasma		$Vli \cdot Fblood \cdot (1 - HCT)$	t
Vlu_plasma	Vlu_plasma		$Vlu \cdot Fblood \cdot (1 - HCT)$	t

# cy3sbml

Cytoscape app for visualizing SBML models  
<https://github.com/matthiaskoenig/cy3sbml>

## Features

- kinetic & reaction-species view
- subgraphs & filtering
- annotation support
- works for large scale networks (genome-scale)
- sbmlutils integration (py2cytoscape)

