

# Pharmacokinetics Modeling Course:

## 1. Introduction, structural model, ODE, simple systems

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<https://livermetabolism.com>

konigmatt



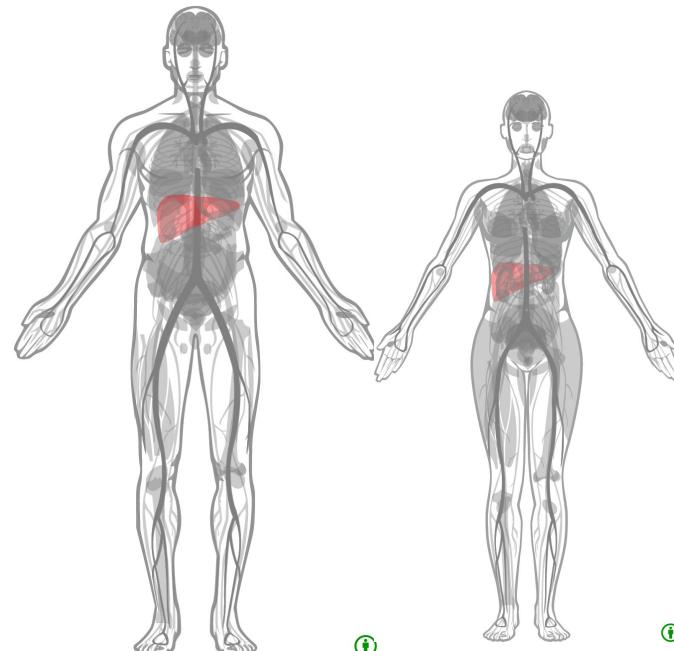
# Course summary

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**Pharmacokinetic modelling is the study of how drugs are absorbed, distributed, metabolized, and excreted in the body.**

The course on pharmacokinetic modelling will cover topics such as pharmacokinetic principles, drug distribution, clearance, and elimination, and the factors that affect these processes. Students will learn about different models used to describe pharmacokinetics, such as compartmental models and physiologically-based pharmacokinetic models, and how to use these models to predict drug concentrations and optimize dosing regimens. Other topics that might be covered include pharmacodynamics, drug-drug interactions, and the use of pharmacokinetic modelling in drug development and clinical practice. Overall, a course on pharmacokinetic modelling will provide students with a comprehensive understanding of the principles and techniques used to describe the movement of drugs through the body, and how this knowledge can be applied to improve drug therapy.

For more information see: <https://livermetabolism.com>.



# **Requirements for passing**

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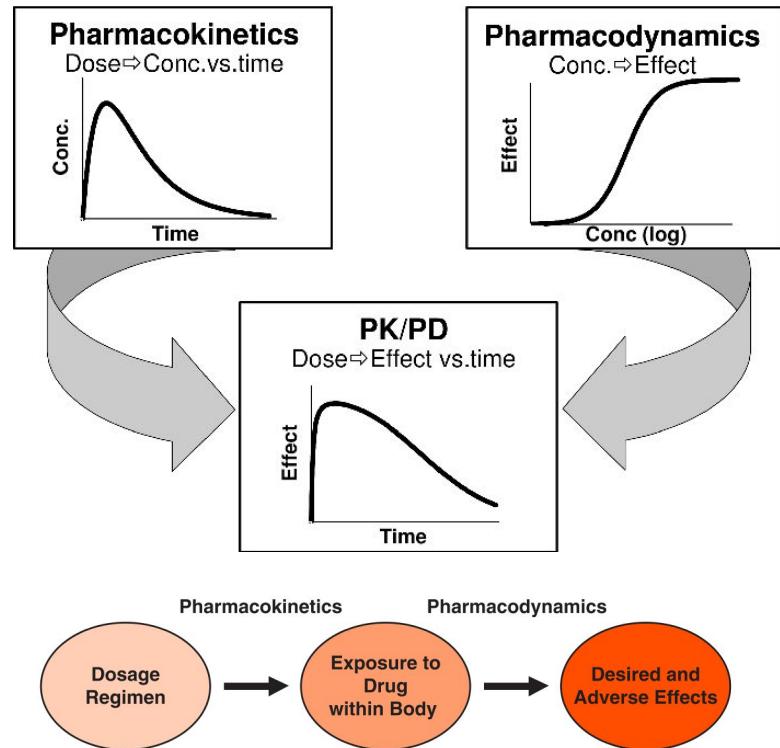
- participate in the course over the four days
- complete daily tasks





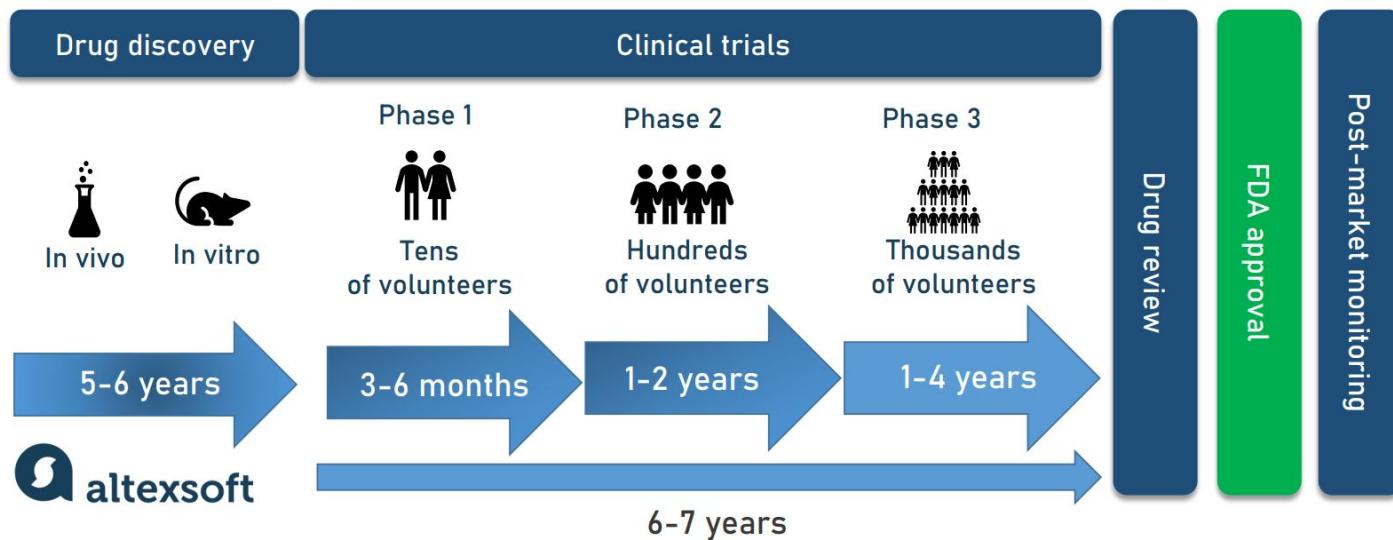
# Pharmacokinetics (PK) & pharmacodynamics (PD)

- **Pharmacokinetics is what the body does to the drug**
  - study of the time course of drug absorption, distribution, metabolism, and excretion
  - **drug disposition**
- **Pharmacodynamics is what the drug does to the body**
  - **desired (and adverse) effects**



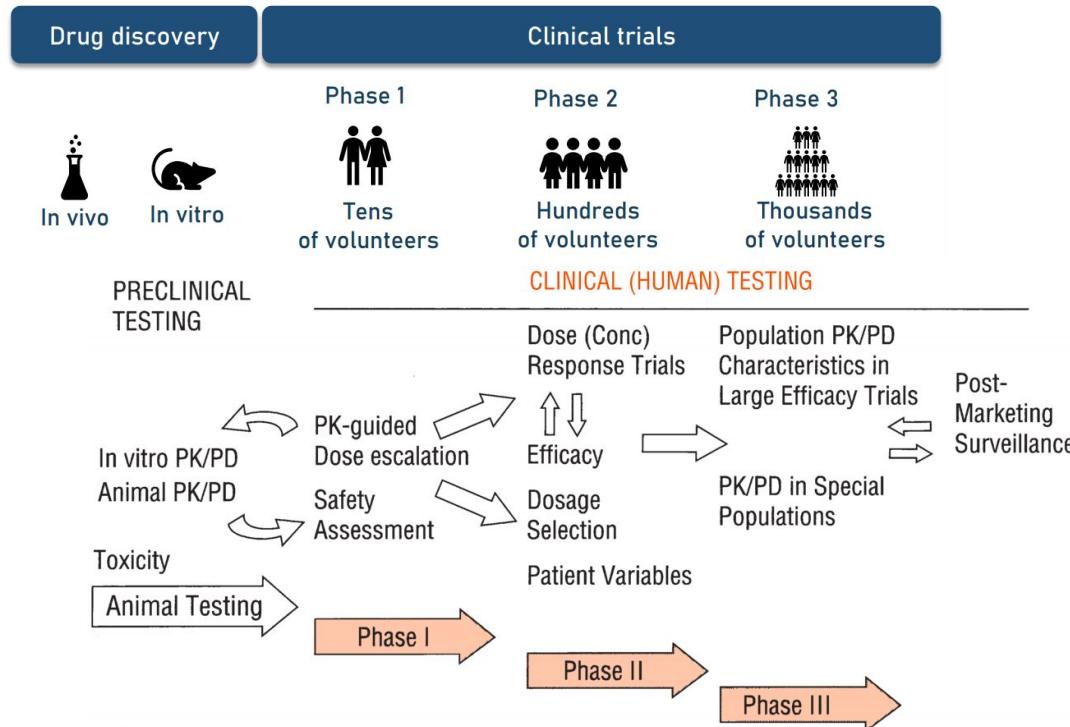
# Drug development phases

## DRUG DEVELOPMENT STAGES AND TIMELINE



# PK/PD in drug development

- pharmacokinetics of a drug/substance key property in drug development
- pharmacokinetic modelling provides important insights

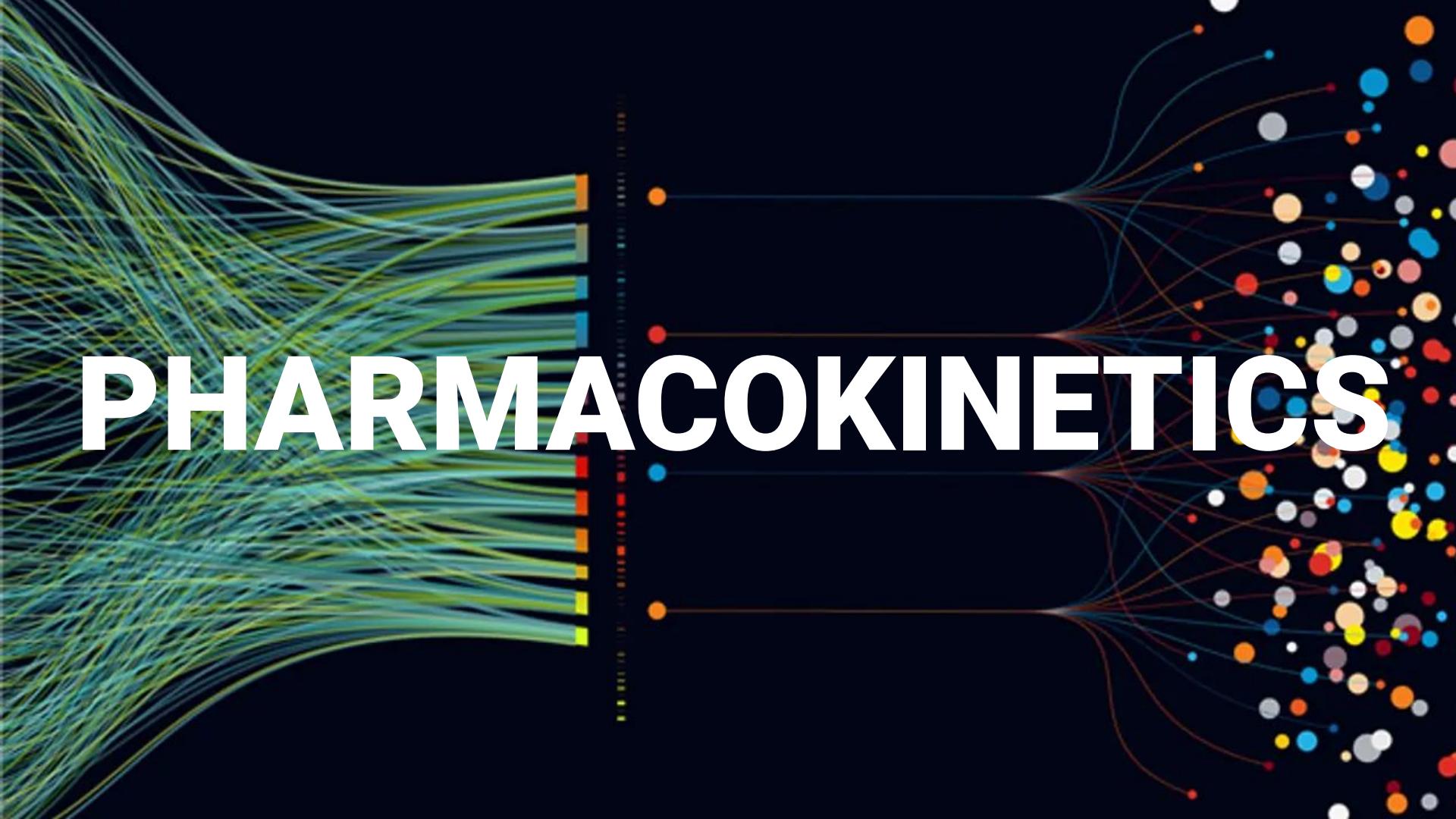


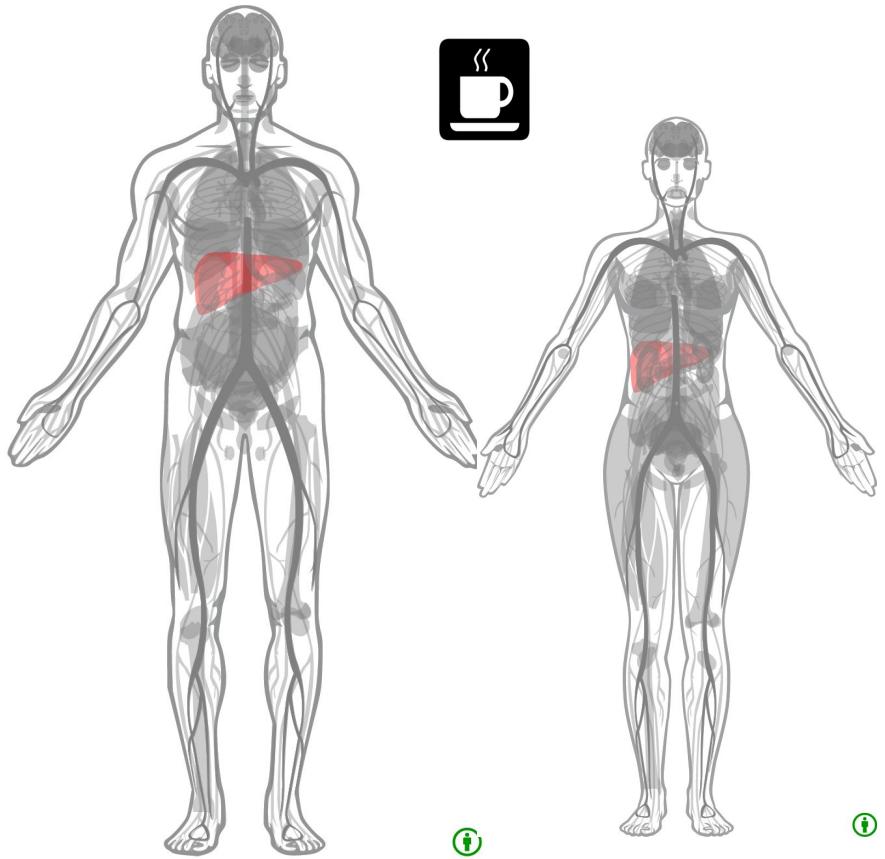
**FIGURE 1-11** The development and subsequent marketing of a drug. The preclinical data help to identify promising compounds and to suggest useful doses for testing in humans. Phases I, II, and III of human assessment generally correspond to the first administration to humans, early evaluation in selected patients, and the larger trials, respectively. PK and PD data gathered during all phases of drug development help to efficiently define appropriate dosage regimens. Postmarketing surveillance, particularly for safety, helps to refine the PK/PD information. PK, pharmacokinetic; PD, pharmacodynamic.

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

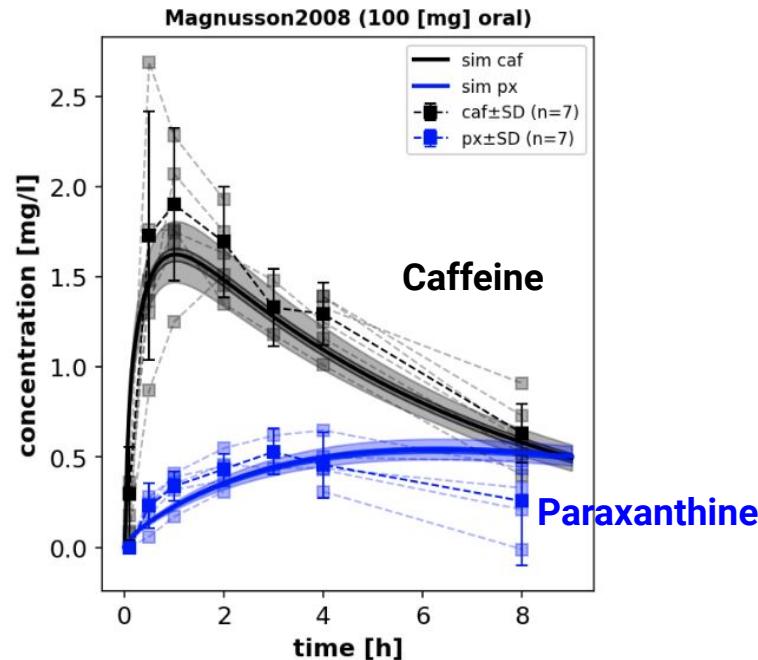
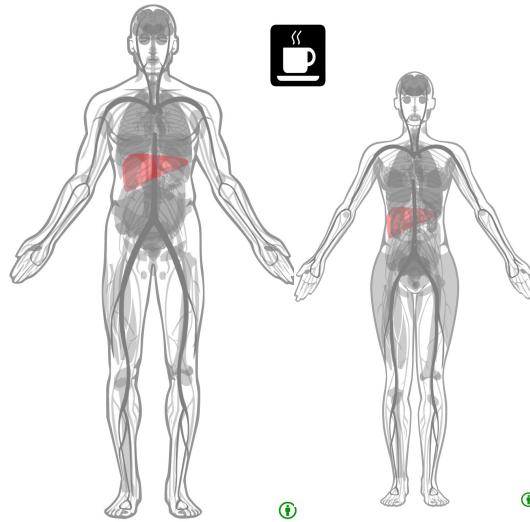
AI in Drug Discovery and Repurposing: Benefits, Approaches, and Use Cases  
<https://www.altextsoft.com/blog/ai-drug-discovery-repurposing/>

# PHARMACOKINETICS

The background features a dark blue gradient with a complex network of thin, glowing lines in shades of green, yellow, and orange. These lines converge towards the center of the frame, where they meet a vertical column of small, colorful dots. From this central point, the lines diverge again, creating a radial pattern of colored dots on the right side of the image.

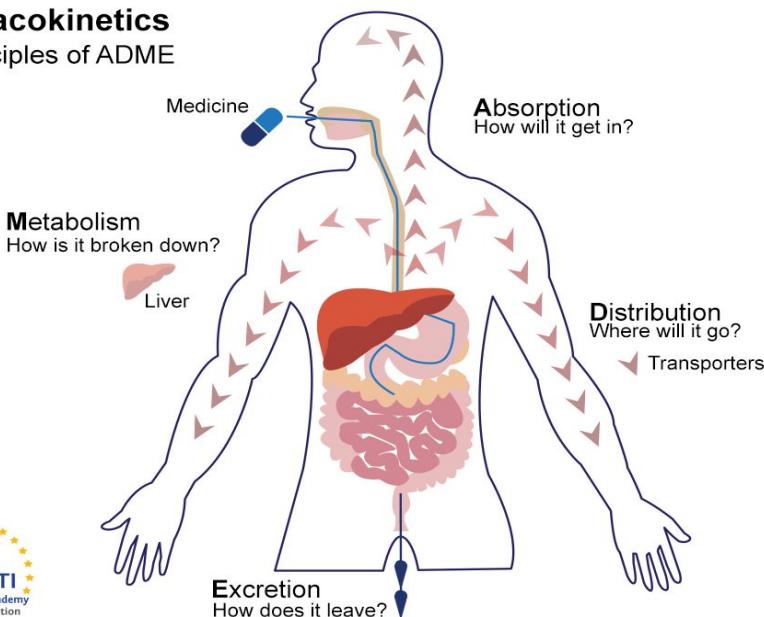


## 100 mg oral caffeine



# ADME

## Pharmacokinetics The principles of ADME



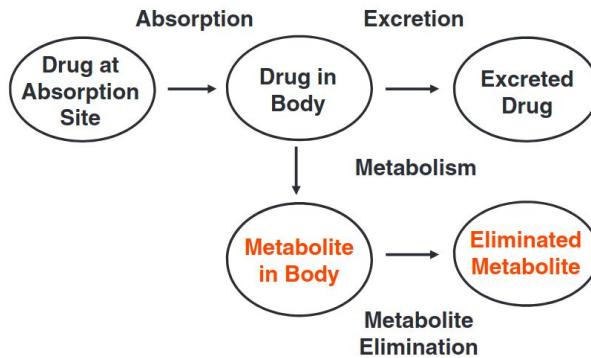
ADME processes determine pharmacokinetics

- **Absorption**
- **Distribution**
- **Metabolization**
- **Elimination**

# ADME

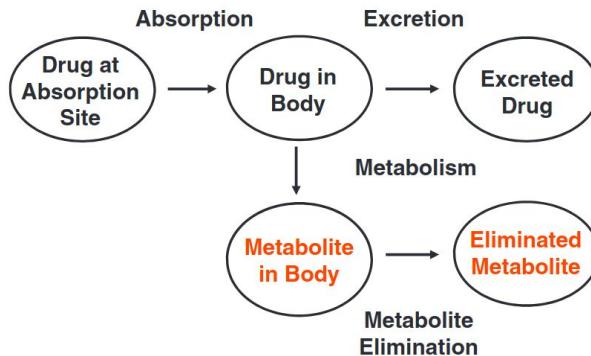
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**FIGURE 2-5** A drug is simultaneously absorbed into the body and eliminated from it by excretion and metabolism. The processes of absorption, excretion, and metabolism are indicated with arrows, and the compartments with ovals. The compartments represent different locations and different chemical species (color = metabolite). Metabolite elimination may occur by further metabolism (not shown) or excretion.

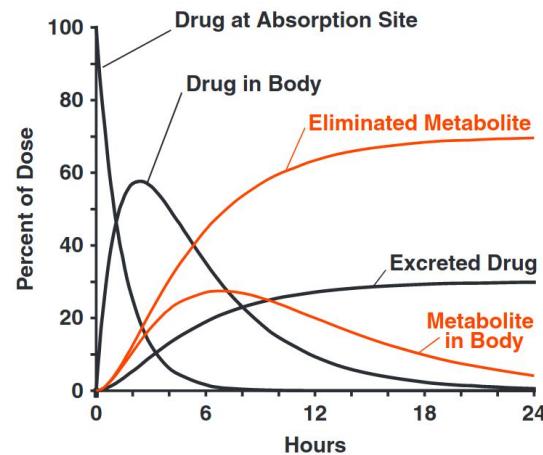


# ADME

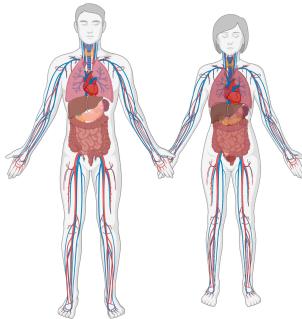
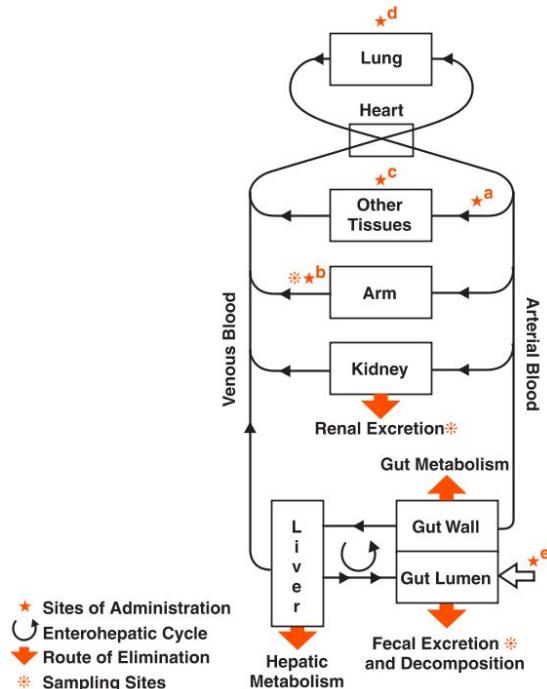
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**FIGURE 2-6** Time course of drug and metabolite in each of the compartments shown in Fig. 2-5. The amount in each compartment is expressed as a percentage of the dose administered. In this example, the dose is completely absorbed. At all times, the sum of the molar amounts in the five compartments equals the dose.



# ADME

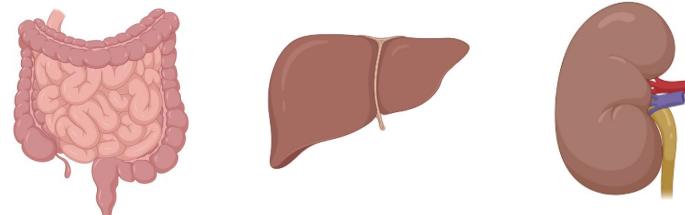
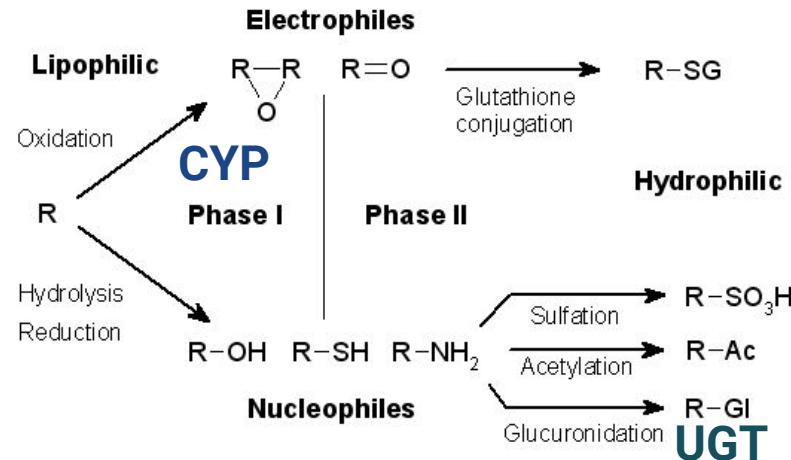


**FIGURE 2-2** Once absorbed from any of the many sites of administration, drug is conveyed by blood to all sites within the body, including the eliminating organs. Sites of administration include: **a**, artery; **b**, peripheral vein; **c**, muscle and subcutaneous tissue; **d**, lung; and **e**, gastrointestinal tract, the most common route (denoted by open arrow). When given intravenously into an arm vein, the opposite arm should then be used for blood sampling. The movement of virtually any drug can be followed from site of administration to site of elimination.

- many sites of administration
  - a) artery
  - b) peripheral vein (iv)
  - c) muscle and subcutaneous tissue
  - d) lung
  - e) gastrointestinal tract (oral)
- sampling sites
  - venous blood, urine, feces
- elimination
  - hepatic metabolism
  - renal excretion/metabolism
  - gut metabolism
  - fecal excretion
- distribution via blood flow and systemic circulation

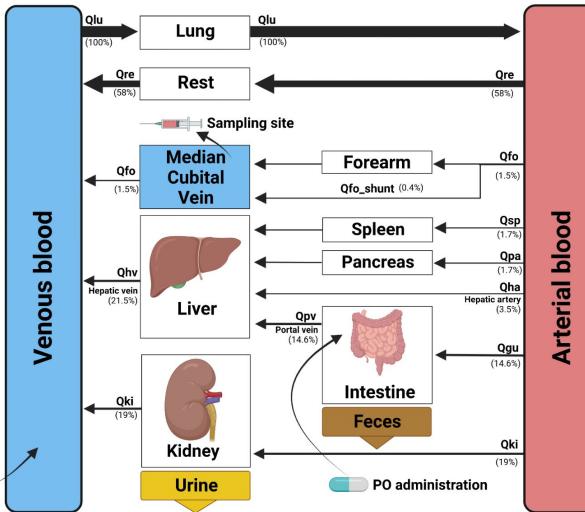
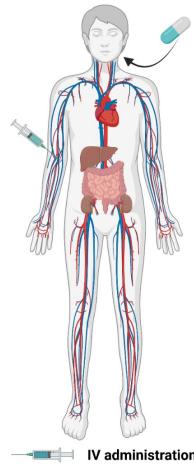
# Drug metabolism in a nutshell

- metabolism of xenobiotics is often divided into 3 phases: **modification, conjugation, and excretion**.
- Cytochrome P450 (CYP)** main players in phase I (modification)
- UDP-glucuronosyltransferases (UGT)** main players phase II (conjugation)
- ATP-binding cassette (ABC)** and **Solute Carrier (SLC)** transporters are main drug transporters
- Multiple isoforms** of CYP, UGT, ABC and SLC with different substrate specificity
- Multiple organs**
  - Intestine:** often metabolism during absorption
  - Liver:** main organ of **drug metabolism**
  - Kidneys:** minor metabolism & **excretion** of (modified) compounds in the urine

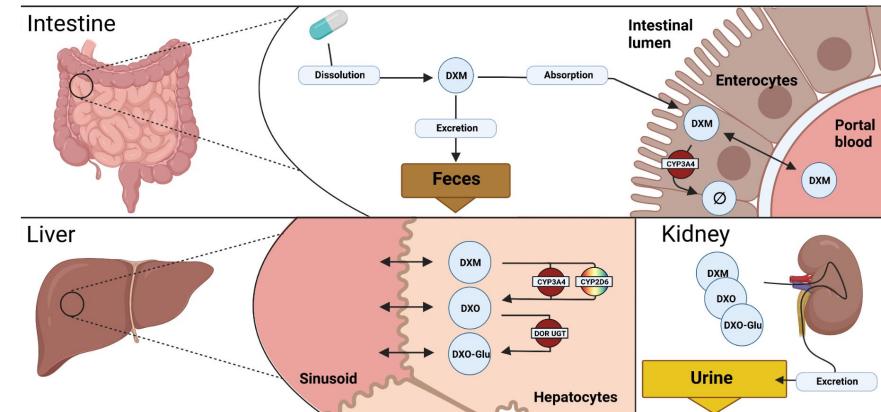


# Example: Dextromethorphan model (ADME)

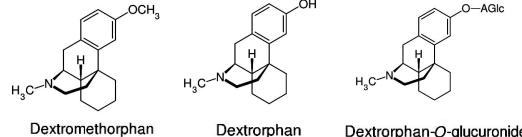
## Whole-body model



## Tissue models

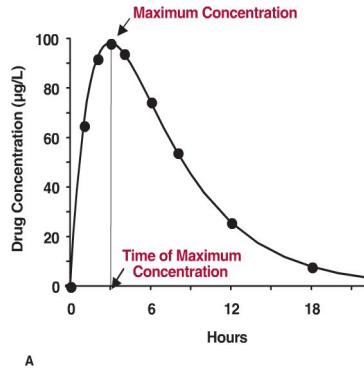


## Substance/Metabolites

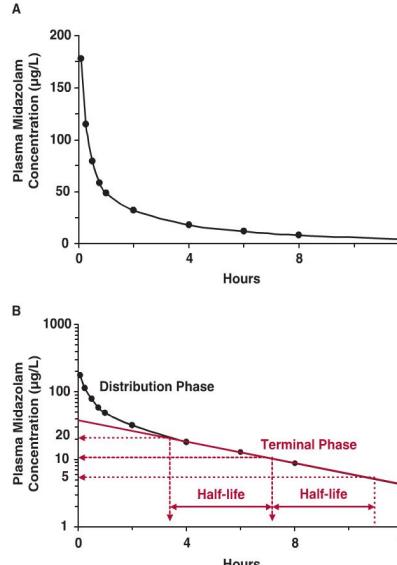


# Pharmacokinetic parameter

- $C_{max}$  : 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 ( $= \text{Dose}/\text{AUC}$ ,  $= \text{Dose}/C(0)_{\text{extrapolated}}$ )



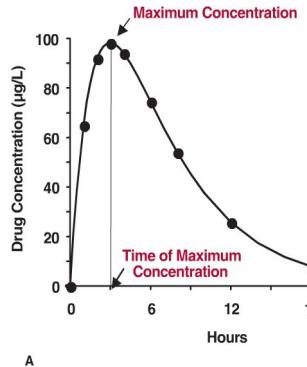
**FIGURE 2-1.** Drug concentration–time curve following a single oral dose showing the maximum systemic exposure ( $C_{max}$ ) and the time of its occurrence ( $t_{max}$ ). The concentration could represent drug in whole blood, plasma, or serum.



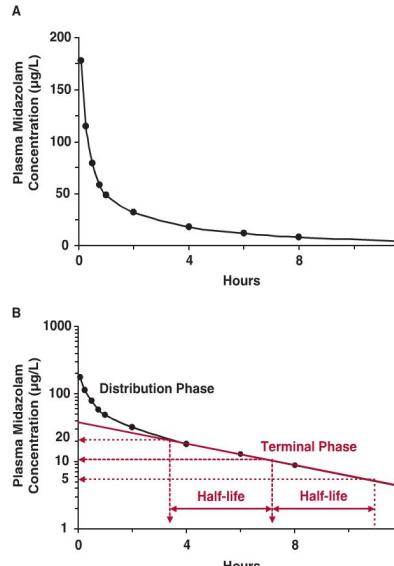
**FIGURE 3-4.** A. Plasma concentration of midazolam with time in an individual after an 8.35-mg i.v. bolus dose of midazolam hydrochloride (7.5 mg of the base) in a healthy adult. B. The data in A are redisplayed as a semilogarithmic plot. Note the short distribution phase. (From: Pentikäinen PJ, Väistönen 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.)

# Pharmacokinetic parameter

- Pharmacokinetic properties
  - determine route of administration
  - dose and frequency of dosing
  - onset of action
  - peak action time
  - duration of action



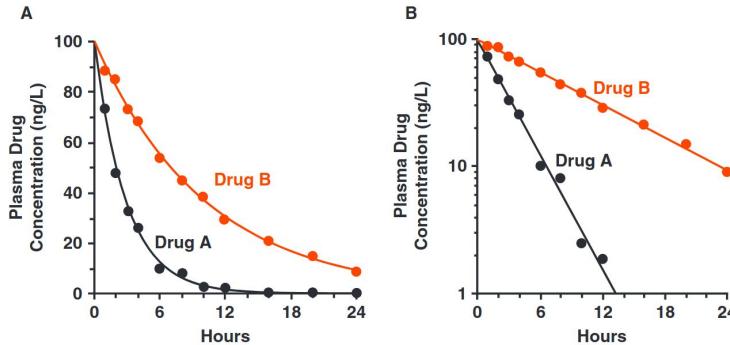
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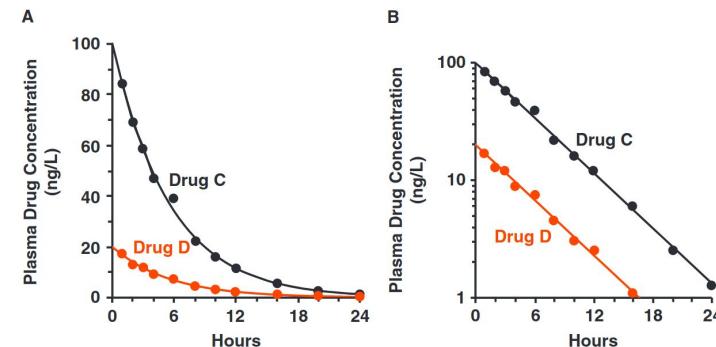
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# Variability between drugs

- large differences in physico-chemical properties between compounds
- large differences in pharmacokinetic parameters



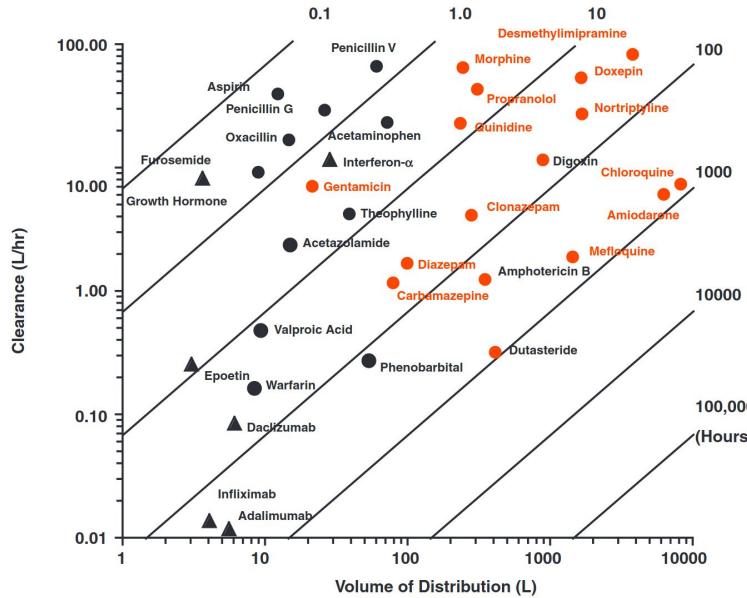
**FIGURE 5-1** Drugs A (black circle) and B (colored circle) show the same initial (peak) exposure, but have different half-lives and total exposure-time profiles (AUC). Regular (cartesian) plot (left). Semilogarithmic plot (right). Doses of both drugs are the same.



**FIGURE 5-2** Drugs C (black circle) and D (colored circle) have the same half-life but different initial and total exposure-time (AUC) profiles. Regular (cartesian) plot (left). Semilogarithmic plot (right). Doses of both drugs are the same.

# Variability between drugs

- large variability in pharmacokinetic parameters between drugs

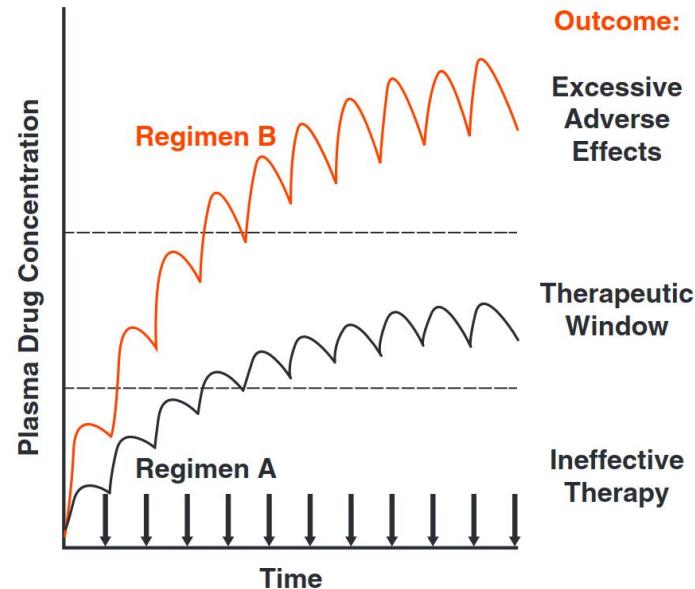


**FIGURE 5-8** Clearance (ordinate) and volume of distribution (abscissa) of selected acidic (black circle) and basic (colored names), as well as protein (black triangle), drugs vary widely. Diagonal lines on the fully logarithmic plot show the combinations of clearance and volume values with the same half-lives (hours). Note that drugs with very low clearance and very large volumes (*lower right-hand quadrant*) are uncommon; their half-lives are often too long for these drugs to be used practically in drug therapy. Note also that large protein drugs have volumes of distribution close to plasma volume (3 L) and that basic compounds tend to have larger volumes of distribution than acids. Digoxin and dutasteride are neutral compounds, while amphotericin B is both a weak acid and a weak base.

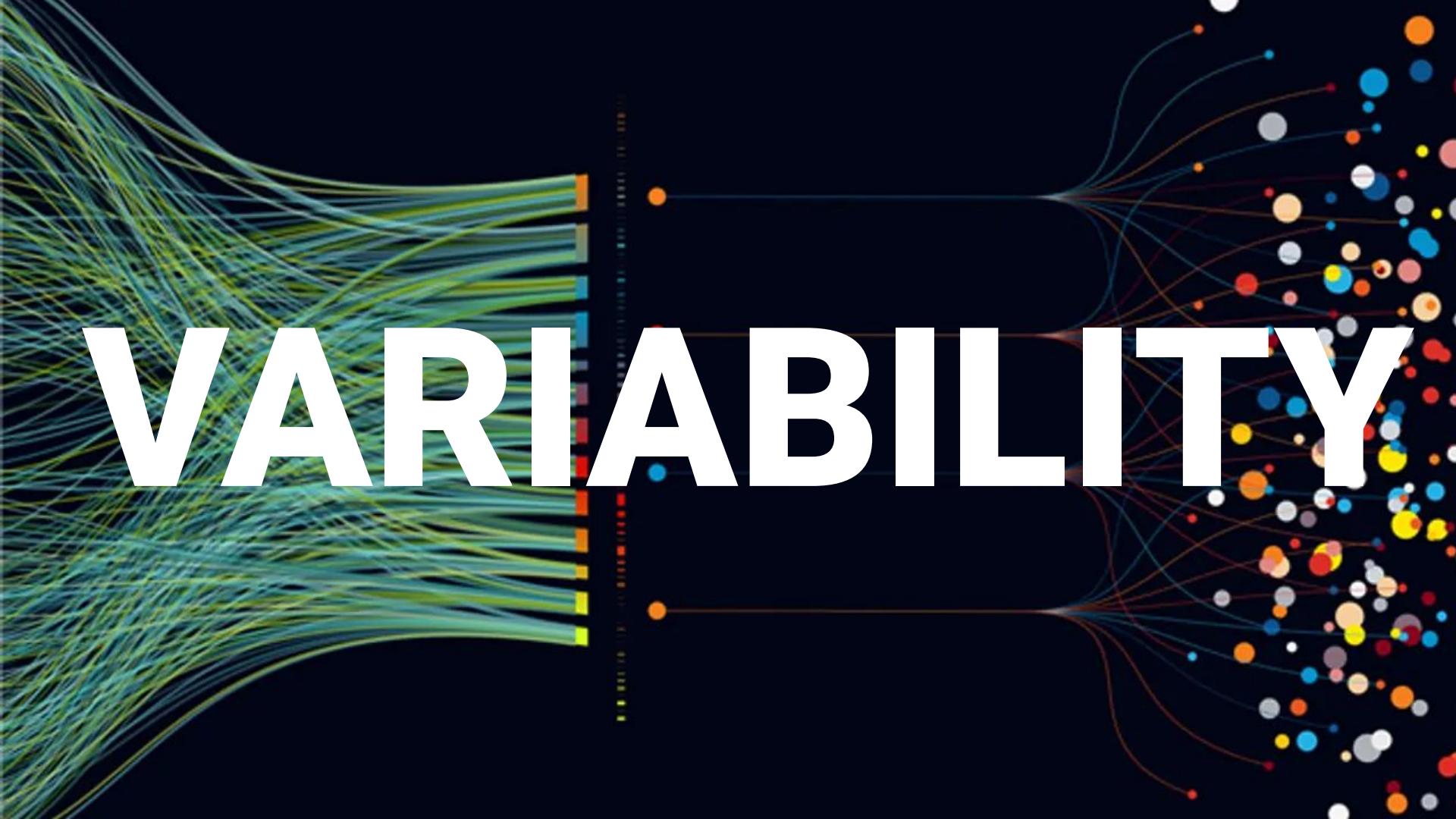
# Optimal dosing regime & Therapeutic window

- avoid adverse effects
- avoid ineffective therapy (**efficacy**)

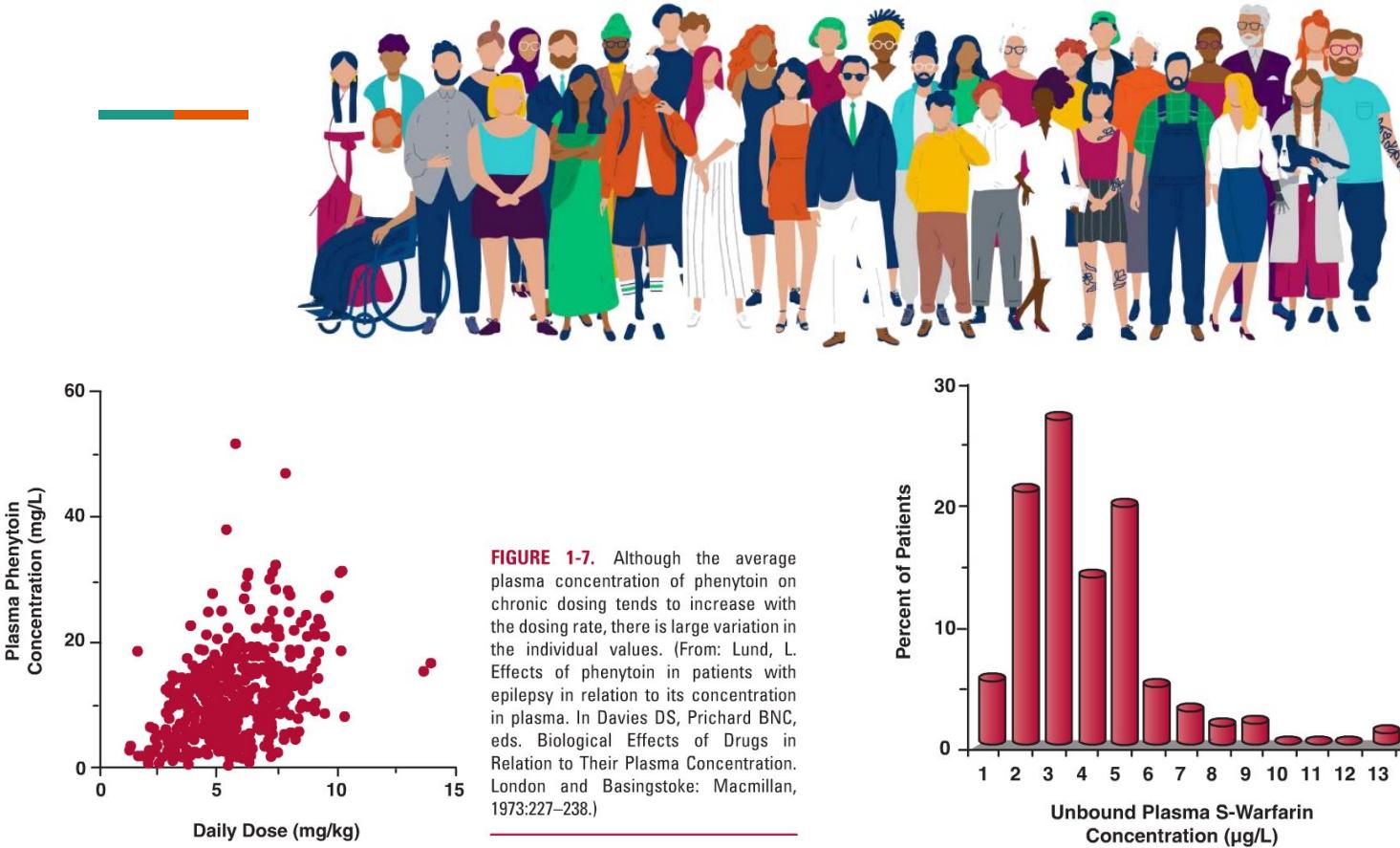
**FIGURE 1-4** When a drug is given repetitively in a fixed dose and at a fixed time interval (arrows), it accumulates within the body until a plateau is reached. With regimen A, therapeutic success is achieved, although not initially. With regimen B, the therapeutic objective is achieved more quickly, but the drug concentration is ultimately too high, resulting in excessive adverse effects.



# VARIABILITY

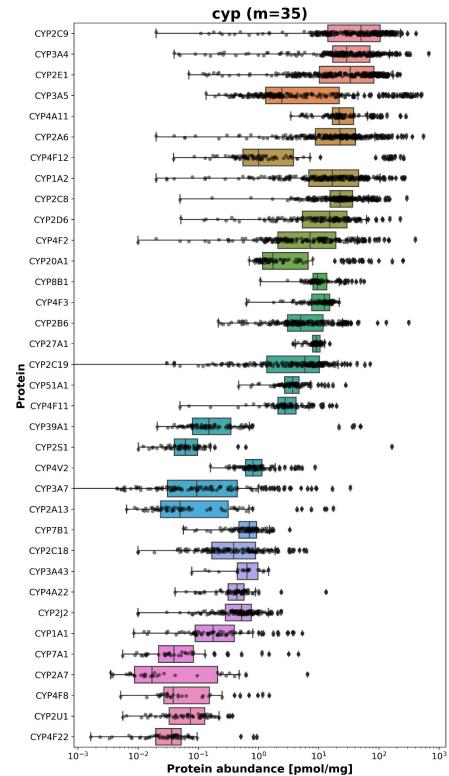
The background of the image features a complex network of thin, colored lines (ranging from blue and green to orange and yellow) that flow from left to right, creating a sense of motion and connectivity. Interspersed among these lines are numerous small, semi-transparent circular dots in various colors (blue, orange, yellow, red, grey). A vertical column of small, colored dots is positioned in the center-left area, aligned vertically with the word 'VARIABILITY'. The overall aesthetic is modern and scientific, suggesting concepts like data flow, information transfer, or genetic variation.

# Large interindividual variability

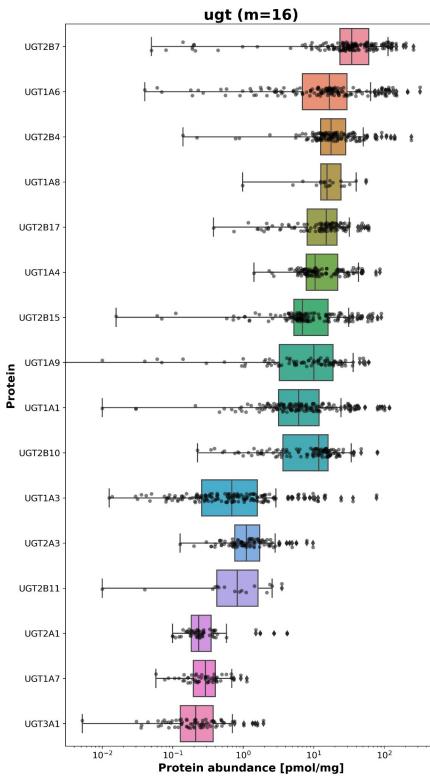


# Large variability & multitude of isoforms (Human Liver)

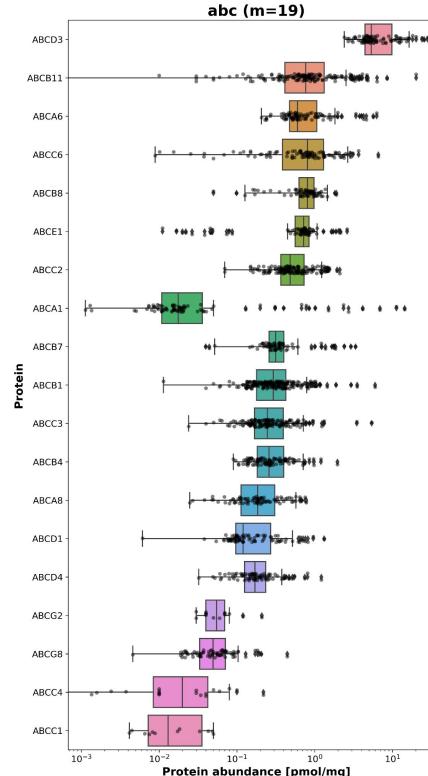
## Cytochrome P450 (CYP)



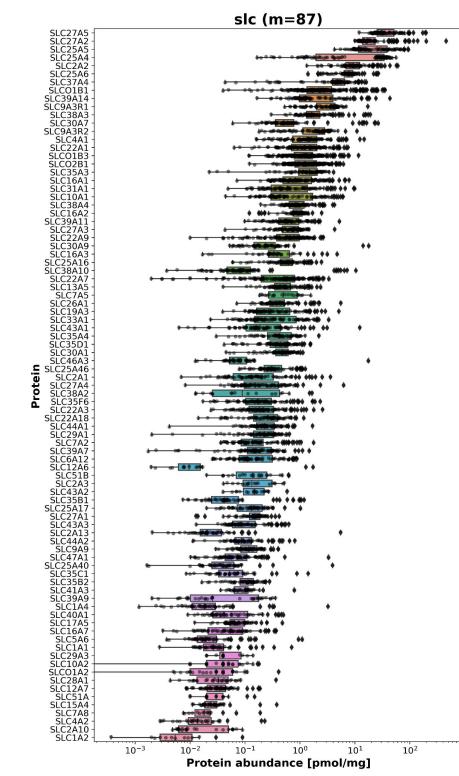
## UDP-glucuronosyltransferases (UGT)



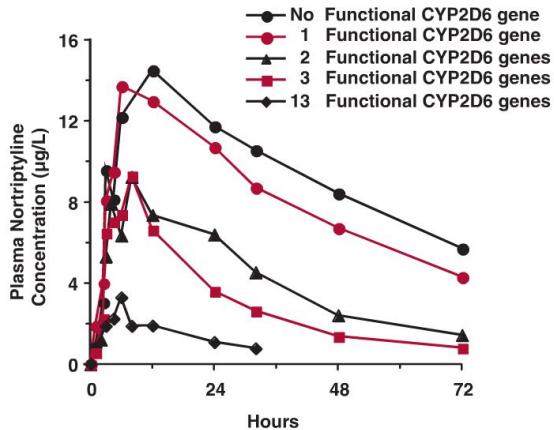
## ATP-binding cassette (ABC)



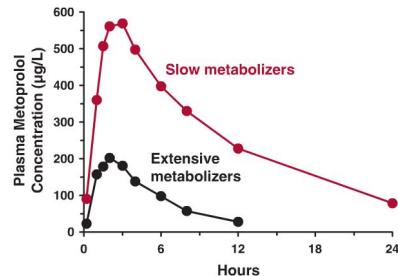
## Solute Carrier (SLC)



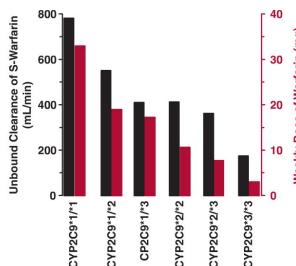
# Pharmacogenomics



**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.)

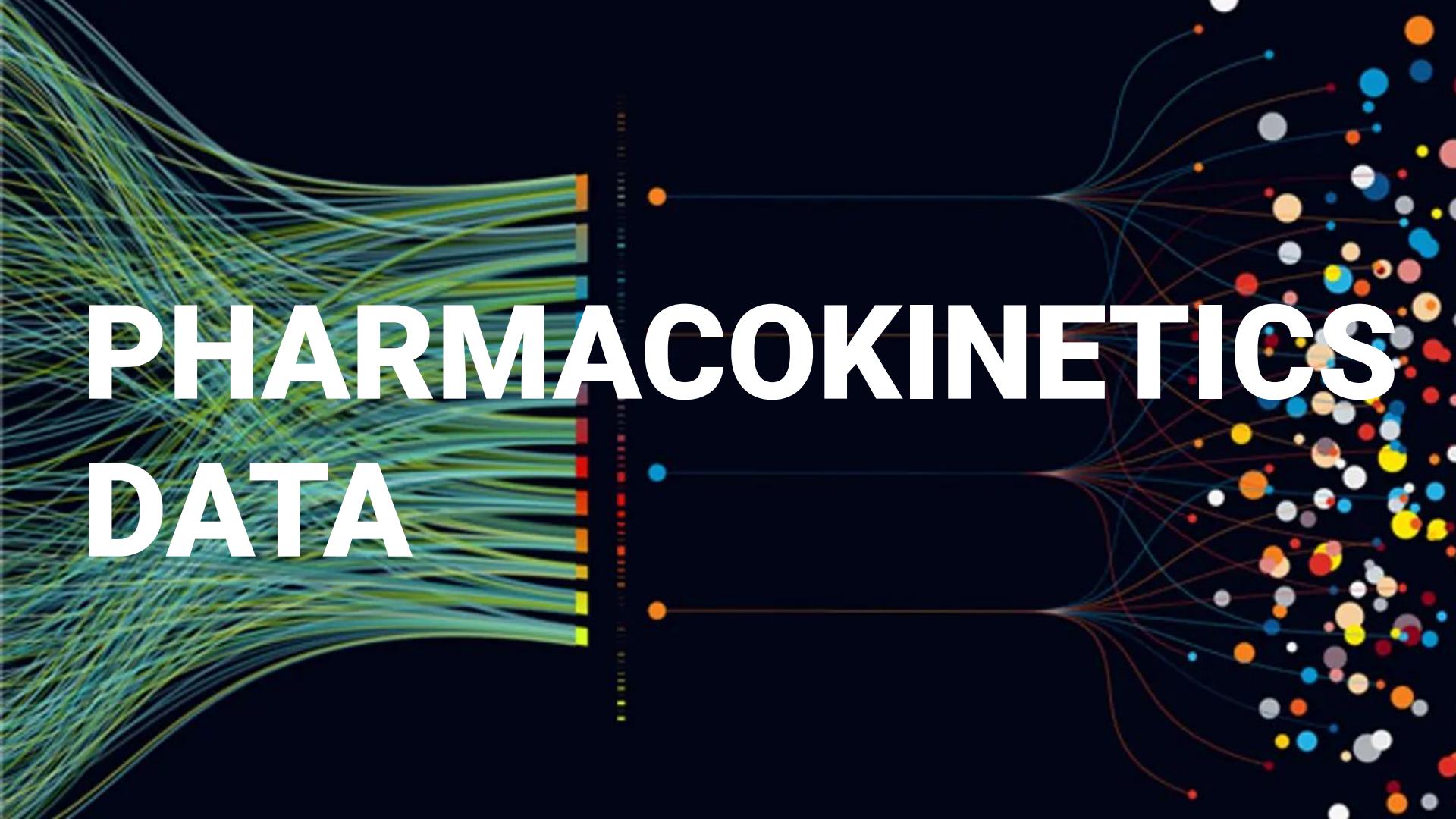


**FIGURE 13-3.** Plasma metoprolol concentrations after a single oral dose of 200-mg metoprolol tartrate were much higher in poor (colored line) than in extensive (black line) CYP2D6 metabolizers. Because metoprolol is a drug of high hepatic clearance, the difference between poor and extensive metabolizers 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.)

# PHARMACOKINETICS DATA

The background of the slide features a dark blue gradient. On the left side, there is a dense bundle of thin, wavy lines in various colors, including green, yellow, and blue. These lines converge towards a vertical dotted line in the center. To the right of this central line, there is a more scattered cluster of larger, semi-transparent colored circles in shades of orange, yellow, red, and grey. The overall effect is one of data flow or connectivity.

Our subjects were 13 normal males (age range 18 to 71 years; mean weight  $\pm$  S.D.  $80.0 \pm 12.18$  kg), nine normal females not taking OCS (age range 22 to 33 years; mean weight  $\pm$  S.D.  $58.0 \pm 5.9$  kg), and nine healthy females (age range 22 to 33 years; mean weight  $\pm$  S.D.  $58.4 \pm 9.6$  kg) who had been on OCS for more than 6 months. Five of the 9 normal women not taking OCS were studied during the second half of their menstrual cycle and 4 during the first half. All subjects studied had a normal clinical history, physical examination, and sequential multiple analyzer of 12 vital determinations (SMA<sub>12</sub>) profiles and, apart from oral contraceptives as indicated above, had taken no drugs or alcohol for at least 2 weeks prior to the study. Smokers were not included in this study.

After an overnight fast the subjects received 250 mg of caffeine (approximately equivalent to 3 cups of coffee) in a capsule with 150 ml of water.

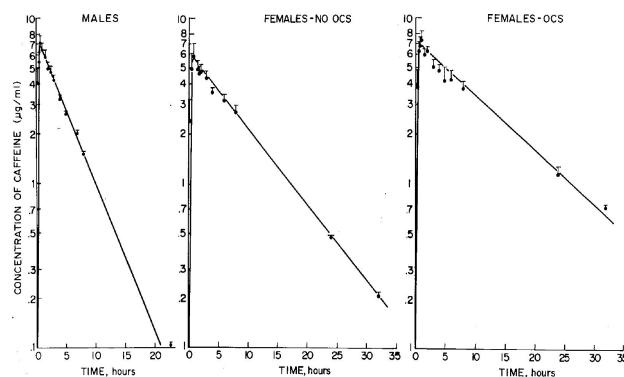


Fig. 1. Comparison of caffeine plasma concentration/time profiles in 13 healthy male subjects (left panel), nine healthy females taking no OCS (center panel), and nine healthy females on OCS (right panel) (mean  $\pm$  S.E.).

Table I. Pharmacokinetic parameters of caffeine (250 mg) in males, females, and females on OCS

	Normal males (n = 13)	Normal females taking no OCS (n = 9)	Normal females on OCS (n = 9)
t <sub>1/2(β)</sub> (hr)	$5.5 \pm 2.6$	$6.2 \pm 1.6$	$10.7 \pm 3.0^\dagger$
V <sub>d(β)</sub> (L/kg)	$0.54 \pm 0.18$	$0.69 \pm 0.16^*$	$0.72 \pm 0.24$
V <sub>d(extrap)</sub> (L/kg)	$0.54 \pm 0.13$	$0.70 \pm 0.14^*$	$0.75 \pm 0.28$
Plasma clearance (ml/min/kg)	$1.3 \pm 0.42$	$1.3 \pm 0.35$	$0.79 \pm 0.21^\dagger$
Plasma binding (%)	$31.4 \pm 1.9$	$31.5 \pm 4.5$	$29.35 \pm 2.17$
Plasma clearance of unbound drug (ml/min/kg)	$1.8 \pm 0.6$	$1.97 \pm 0.57$	$1.12 \pm 0.28^\dagger$

Values are mean  $\pm$  S.D.

\*p < 0.05 for normal males vs females taking no OCS.

†p < 0.001 for females taking no OCS vs. females on OCS.

## Groups



## Individuals



## Intervention



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## Time courses

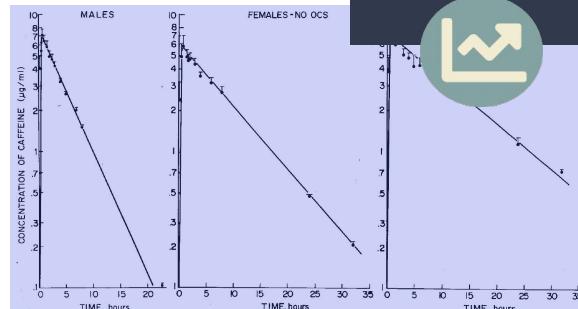


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Plasma clearance (ml/min/kg)	$1.3 \pm 0.42$	$1.3 \pm 0.35$	$0.79 \pm 0.21^\dagger$
Plasma binding (%)	$31.4 \pm 1.9$	$31.5 \pm 4.5$	$29.35 \pm 2.17$
Plasma clearance of unbound drug (ml/min/kg)	$1.8 \pm 0.6$	$1.97 \pm 0.57$	$1.12 \pm 0.28^\dagger$

Values are mean  $\pm$  S.D.

\* $p < 0.05$  for normal males vs females taking no OCS.

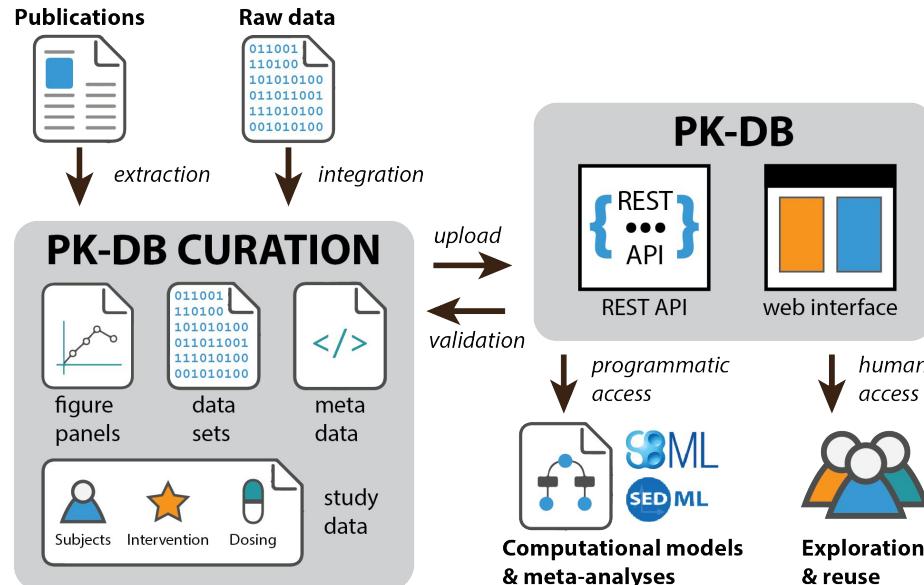
† $p < 0.001$  for females taking no OCS vs. females on OCS.

## Outputs



## Live Demonstration

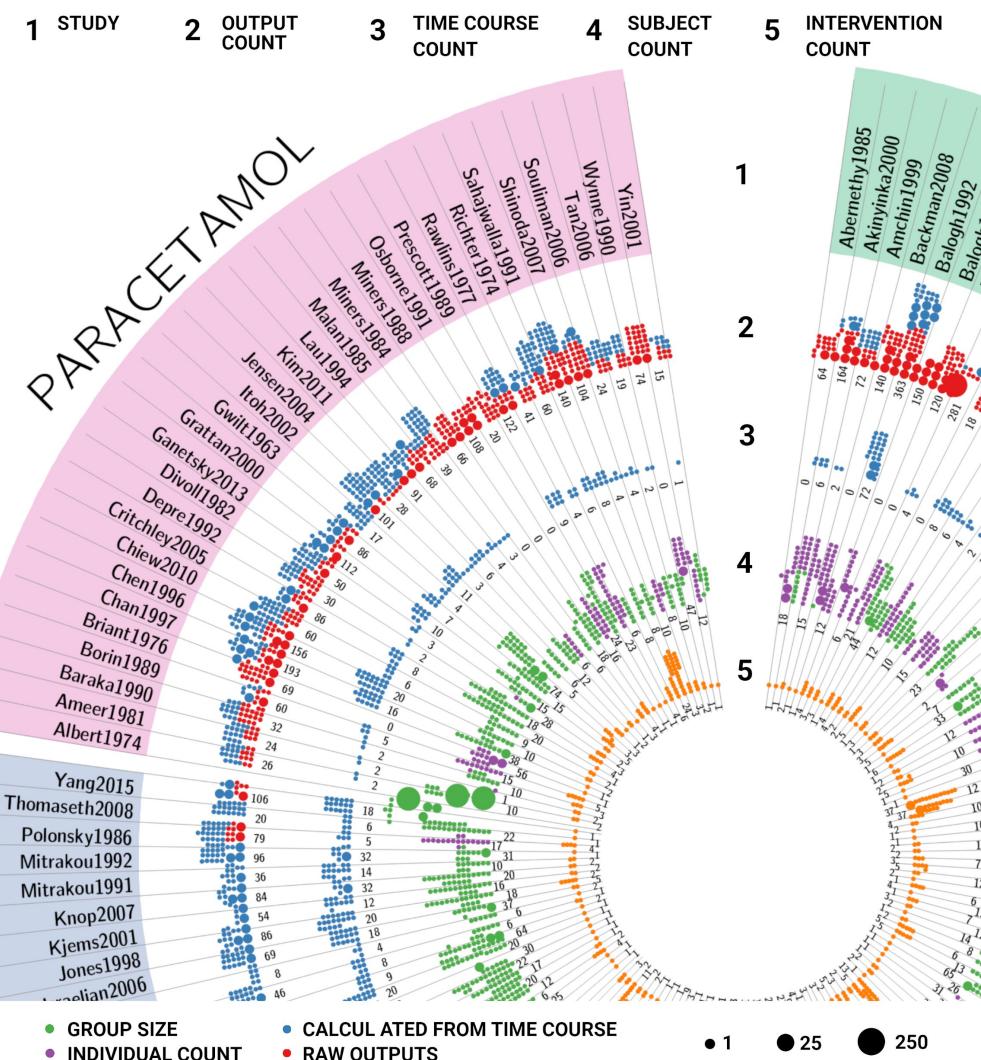
# Database for pharmacokinetics data (PK-DB)



Grzegorzecki J, Brandhorst J, Green K, Eleftheriadou D, Duport Y, Barthorsch F, Köller A, Ke DYJ, De Angelis S, König M. **PK-DB: pharmacokinetics database for individualized and stratified computational modeling**. Nucleic Acids Res. 2021 Jan 8;49(D1):D1358-D1364. doi: [10.1093/nar/gkaa990](https://doi.org/10.1093/nar/gkaa990). PMID: 33151297; PMCID: PMC7779054.  
<https://pk-db.com/>

# PK-DB content

		DATA
758	Studies	Clinical or experimental study measuring data in groups and/or individuals.
2439	Groups	Group of individuals for which data was reported, e.g., the control group and the group which received an intervention. A group is described by certain characteristica, e.g., bodyweight, health status, smoking status or medication.
17050	Individuals	A single subject in the study. A subject is characterized by the group it belongs to as well as individual characteristica like age, body weight or sex. Individuals are only created if outputs or timecourses have been reported on the subject level (not group level).
2163	Interventions	Intervention which was performed in the study. Often interventions consist of application of a substance, e.g. caffeine or codeine. Other examples are changes in lifestyle like smoking cessation.
136330	Outputs	Clinical or experimental output. These can be single parameters or variables, e.g. pharmacokinetic parameters like AUC, clearance or half-life of the applied substances. An output is always linked to the respective intervention and group or individual.
6662	Timecourses	Clinical or experimental time course measurements. Often timecourses are concentration measurements. A timecourse is always linked to the respective intervention and group or individual.
150	Scatters	Correlations between outputs are often provided as scatter plots (e.g. age ~ clearance).



● GROUP SIZE

● INDIVIDUAL COUNT

● CALCULATED FROM TIME COURSE

● RAW OUTPUTS

• 1

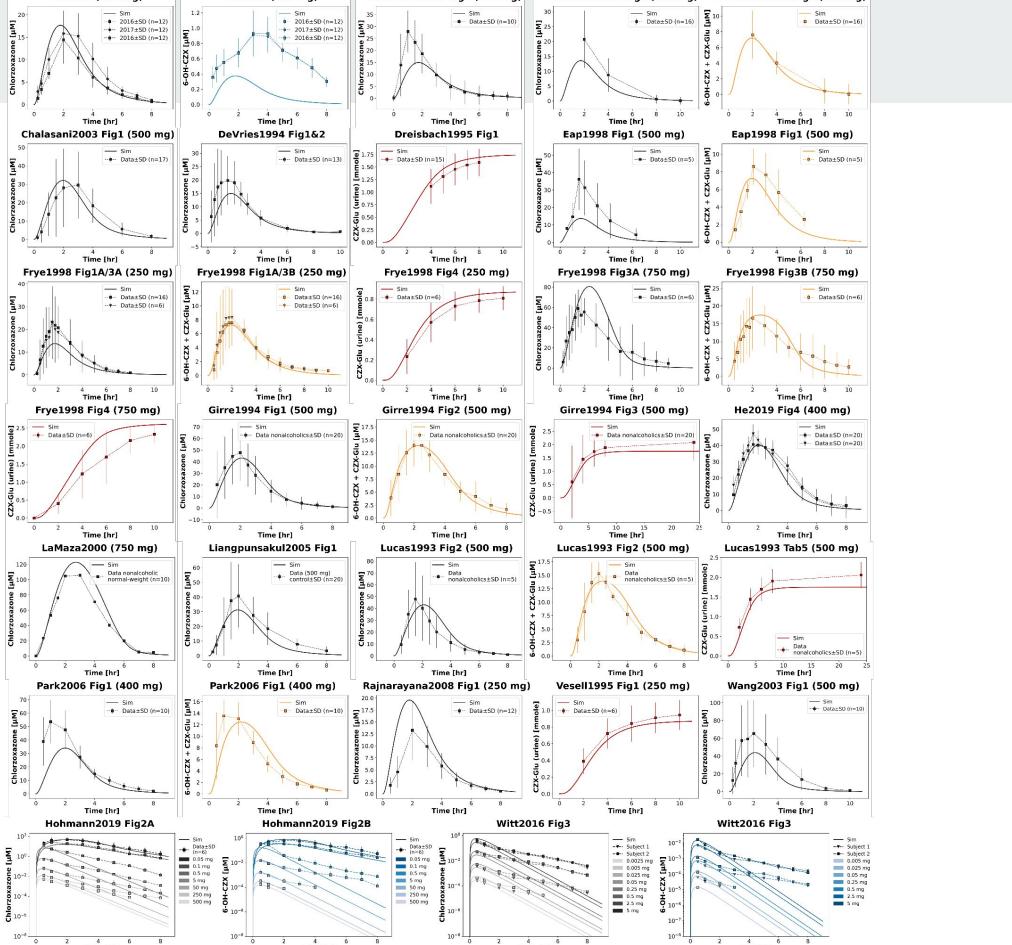
• 25

• 250

Table 1: Overview of curated clinical studies.

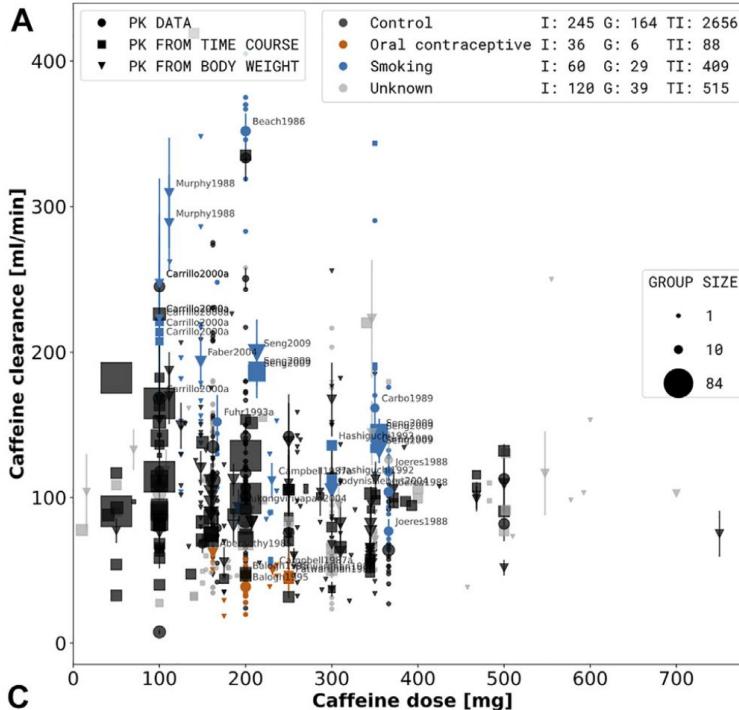
References	PK-DB	PMID	Dosing protocol	Health status	Data	Fit	Validation
Bedada and Neerat (2016)	PKDB00621	26680654	250 mg, oral, single dose, tablet	healthy	plasma time-course (CZX, 6-OH-CZX*)	✓ *	
Bedada and Boga (2017)	PKDB00622	27670974	250 mg, oral, single dose, tablet	healthy	plasma time-course (CZX, 6-OH-CZX*)	✓ *	
Bedada and Neerat (2018)	PKDB00623	28983678	250 mg, oral, single dose, tablet	healthy	plasma time-course (CZX, 6-OH-CZX*)	✓ *	
Benowitz et al. (2003)	PKDB00623	14586387	250 mg, oral, single dose, tablet	healthy	plasma time-course (CZX), urinary recovery	✓	
Chalasani et al. (2003)	PKDB00623	12600151	500 mg, oral, single dose, tablet	healthy	plasma time-course (CZX), urinary recovery	✓	
Burkart et al. (1998)	PKDB00624	9542473	250 mg, oral, single dose, tablet	healthy	plasma time-course (CZX, 6-OH-CZX), urinary recovery	✓	
de Vries et al. (1994)	PKDB00626	7849234	250 mg, oral, single dose, tablet	healthy	plasma time-course (CZX), urinary recovery	✓	
Dreisbach et al. (1995)	PKDB00627	12534643	500 mg, oral, single dose, tablet	healthy	plasma time-course (CZX, 6-OH-CZX), urine course (6-OH-CZX) metabolic ratios, urinary recovery	✓	
Ernstgard et al. (2004)	PKDB00699	15255802	250, 500, 750 mg, oral, multiple dose, tablet	healthy	plasma time-course (CZX, 6-OH-CZX), urine time course (6-OH-CZX)	✓	
Frye et al. (1998)	PKDB00629	9597564	250, 750 mg, oral, multiple dose, tablet	healthy	plasma time-course (CZX, 6-OH-CZX), urine time course (6-OH-CZX)	✓	
Girre et al. (1994)	PKDB00631	7910460	500 mg, oral, single dose, tablet	healthy, alcoholics	plasma time-course (CZX, 6-OH-CZX), urine time-course (6-OH-CZX)	✓ ✓	
He et al. (2019)	PKDB00632	31363741	400 mg, oral, single dose, tablet	0.005, 0.01, 0.05, 0.5, 5 mg as solution, 250, 500 mg as tablet, oral, multiple dose	plasma time-course (CZX)	✓	
Hohmann et al. (2019)	PKDB00633	31222796	400 mg, oral, single dose, tablet	healthy	plasma time-course (CZX, 6-OH-CZX*)	✓	
Hukkanen et al. (2010)	PKDB00698	20233178	250 mg, oral, single dose, tablet	healthy	urinary recovery	✓	
Kharasch et al. (1993)	PKDB00623	8513656	750 mg, oral, single dose, tablet	healthy	plasma time-course (CZX), urinary recovery	✓	
de la Maza et al. (2000)	PKDB00634	10832901	750 mg, oral, single dose, tablet	healthy	plasma time-course (CZX)	✓	
Liangpunsakul et al. (2005)	PKDB00636	15841467	500 mg, single dose, tablet	healthy	plasma time-course (CZX)	✓	
Lucas et al. (1993)	PKDB00637	8120116	500 mg oral, single dose, tablet	healthy, alcoholics	plasma time-course (CZX, 6-OH-CZX), urine time course (6-OH-CZX)	✓ ✓	
Lucas et al. (1995)	PKDB00688	7625570	500 mg oral, single dose, tablet	alcoholics	metabolic ratios	✓	
Mishin et al. (1998)	PKDB00638	9820389	750 mg, oral, single dose, tablet	alcoholics	plasma time-course (CZX, 6-OH-CZX)	✓	
Oneta et al. (2002)	PKDB00689	7955797	500 mg, 250 mg, oral, multiple dose, tablet	alcoholics	metabolic ratios	✓	
Orellana et al. (2006)		16321567	500 mg, oral, single dose, tablet	healthy, steatosis, steatohepatitis	metabolic ratios	✓	
O'Shea et al. (1994)	PKDB00697	11804663	250 mg, oral, single dose, tablet	healthy	plasma time-course (CZX, 6-OH-CZX), urinary recovery	✓	
Park et al. (2006)	PKDB00641	16397290	400 mg, oral, single dose, tablet	healthy	plasma time-course (CZX, 6-OH-CZX)	✓	
Rajmurrayana et al. (2008)	PKDB00643	19326774	250 mg, oral, single dose, tablet	healthy	plasma time-course (CZX)	✓	
Vesell et al. (1995)	PKDB00644	7773304	250 mg, oral, single dose, tablet	healthy	plasma time-course (CZX), urine time-course (6-OH-CZX)	✓	
Wang et al. (2003)	PKDB00639	12534643	500 mg, oral, single dose, tablet	healthy	plasma time-course (CZX), urinary recovery	✓	
Witt et al. (2016)	PKDB00640	27300008	5, 2.5, 0.5, 0.05, 0.005, 0.0025mg, oral, single dose, solution	healthy	plasma time-course (CZX, 6-OH-CZX*)	✓	
Wilkinson et al. (1997)	PKDB00700	881642	ethanol: 11.2, 22.5, 33.7, 45.0 g, oral, single dose, solution	healthy	plasma time-course (ethanol)	✓	

\* 6-OH-CZX was measured without the chlorzoxazone-O-glucuronide.

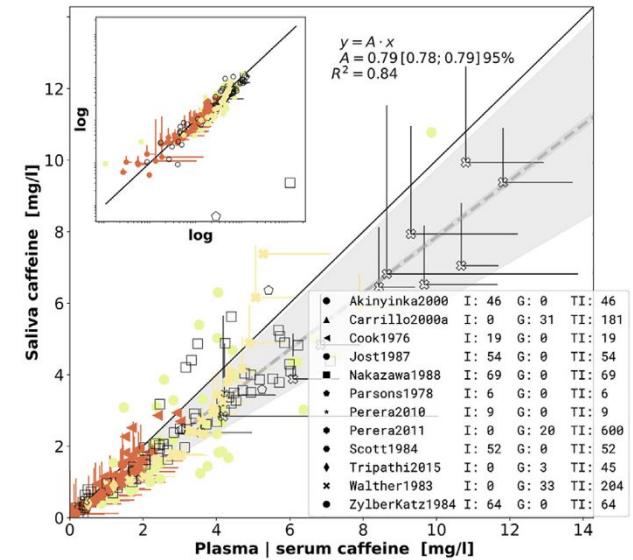
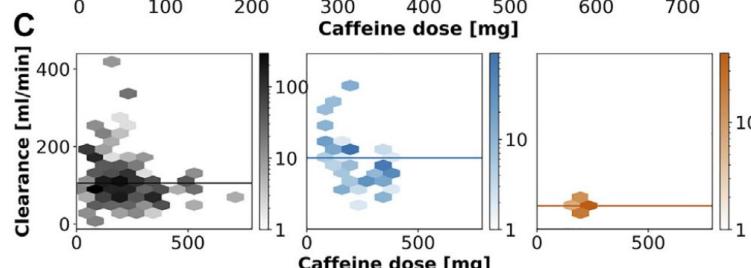


A physiologically based pharmacokinetic model for HM. J. Küttner, J. Grzegorzewski, bioRxiv 2023.04.12.536571 (preprint). doi:10.1101/2023.04.12.536571

# Caffeine meta-analysis



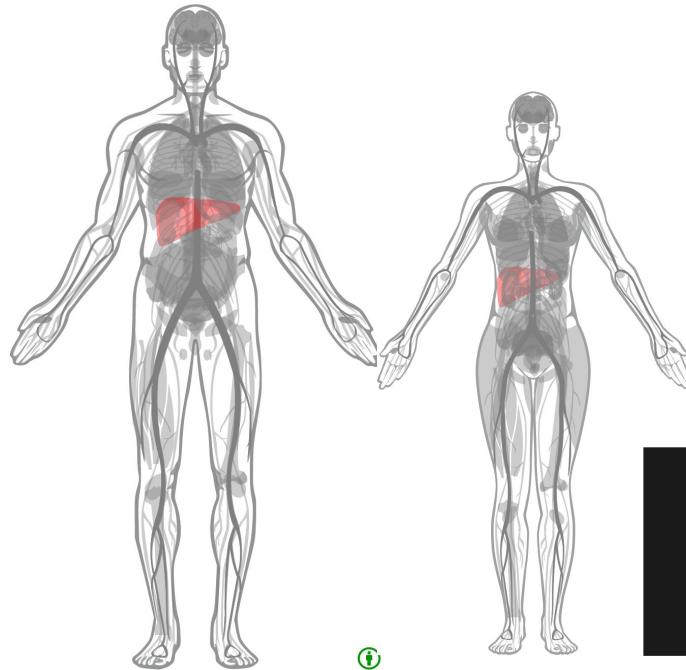
control  
smoking  
oral  
contraceptives



J.Grzegorzewski, F.Bartsch, A.Köller, and M.König  
*Pharmacokinetics of caffeine: A systematic analysis of reported data for application in metabolic phenotyping and liver function testing*

Frontiers in Pharmacology 2022, Vol12; doi: [10.3389/fphar.2021.752826](https://doi.org/10.3389/fphar.2021.752826)

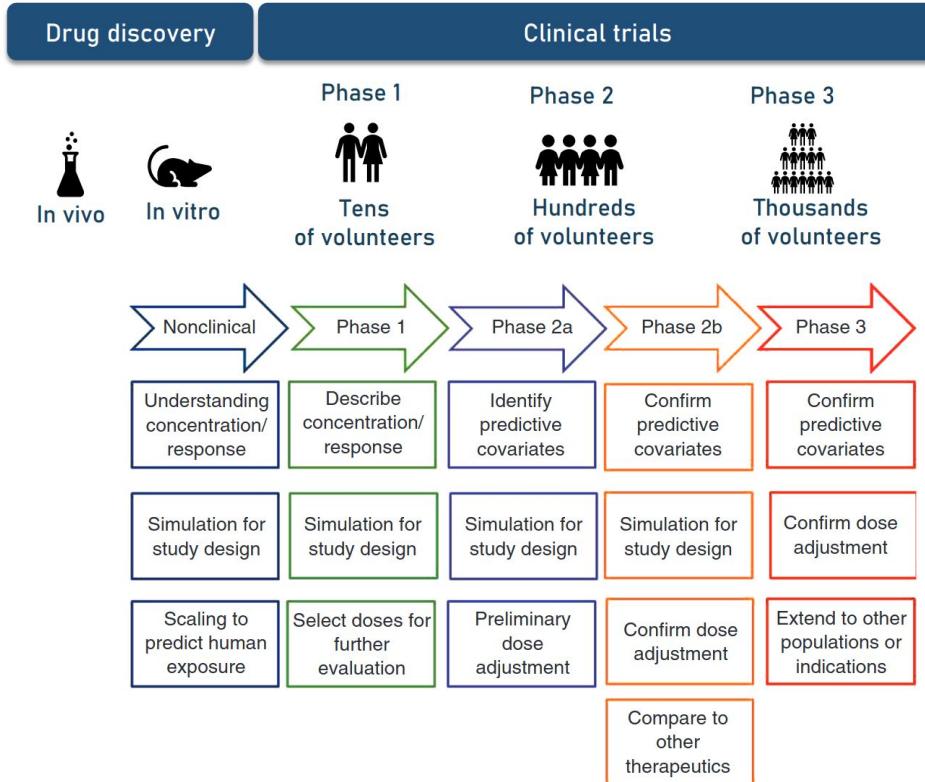
Grzegorzewski J, Brandhorst J, Green K, Eleftheriadou D, Duport Y, Barthoerscht F, Köller A, Ke DYJ, De Angelis S, König M. *PK-DB: pharmacokinetics database for individualized and stratified computational modeling* Nucleic Acids Res. 2020 Nov 5:gkaa990. doi: [10.1093/nar/gkaa990](https://doi.org/10.1093/nar/gkaa990).



# MODELS

# Modeling

- simulation of study design
- understanding concentration response
- dose selection and dose-regimen design
- extension to special populations



Mould DR, Upton RN. **Basic concepts in population modeling, simulation, and model-based drug development.** CPT Pharmacometrics Syst Pharmacol. 2012 Sep; 26(1)(e6). doi: 10.1038/psp.2012.4. PMID: 23835886; PMCID: PMC3606044.

Figure 1 Modeling and simulation during drug development.

# Structural models as algebraic equations

---

- simplest representation is an **algebraic equation** representing a **one-compartment model**
- drug being administered as single intravenous dose
- relationship between
  - independent variable time (t)
  - dependent variable concentration (C)
  - C depends on Dose, clearance (CL), and distribution volume (V)

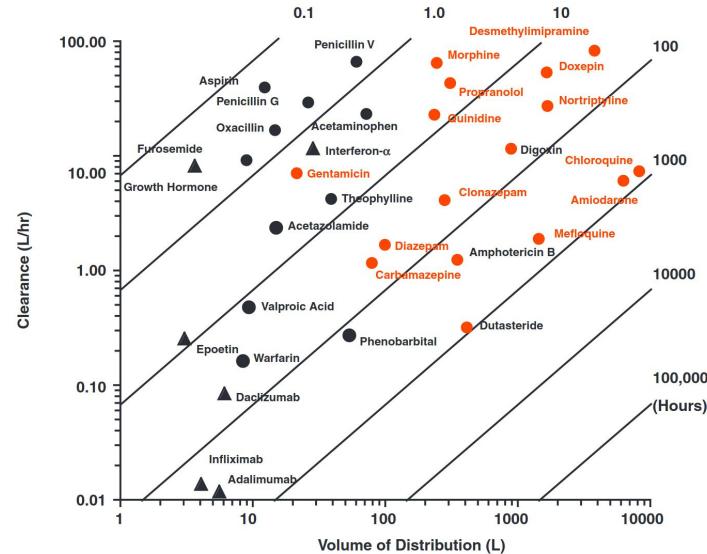
$$C_{(t)} = \frac{\text{Dose}}{V} e^{-\frac{CL}{V} \cdot t}$$

# Structural models as algebraic equations

- Parametrization with clearance (CL) and volume of distribution (Vd)
- Simulation of concentration time course after given iv Dose

$$C_{(t)} = \frac{\text{Dose}}{V} e^{-\frac{CL}{V} \cdot t} \quad (1)$$

Mould DR, Upton RN. **Basic concepts in population modeling, simulation, and model-based drug development.** CPT Pharmacometrics Syst Pharmacol. 2012 Sep 26;1(9):e6. doi: 10.1038/psp.2012.4. PMID: 23835886; PMCID: PMC3606044.



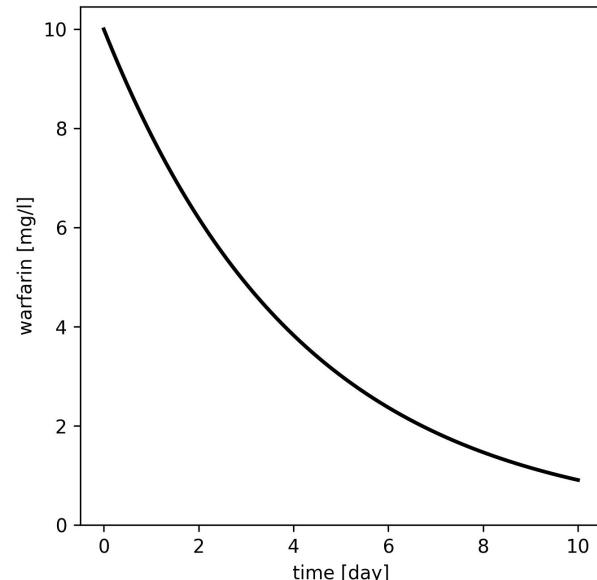
**FIGURE 5-8** Clearance (ordinate) and volume of distribution (abscissa) of selected acidic (black circle) and basic (colored names), as well as protein (black triangle), drugs vary widely. Diagonal lines on the fully logarithmic plot show the combinations of clearance and volume values with the same half-lives (hours). Note that drugs with very low clearance and very large volumes (lower right-hand quadrant) are uncommon; their half-lives are often too long for these drugs to be used practically in drug therapy. Note also that large protein drugs have volumes of distribution close to plasma volume (3 L) and that basic compounds tend to have larger volumes of distribution than acids. Digoxin and dutasteride are neutral compounds, while amphotericin B is both a weak acid and a weak base.

# Structural models as algebraic equations

```
1 from matplotlib import pyplot as plt
2 import numpy as np
3
4 # Warfarin
5 V = 10 # [l]
6 CL = 0.1 # [L/hr]
7 Dose = 100 # [mg]
8 t = np.linspace(start=0, stop=10*24, num=200) # [hr]
9 C = Dose/V * np.exp(-CL/V * t) # [mg/l]
10
11 # plot
12 f, ax = plt.subplots(nrows=1, ncols=1, figsize=(5, 5), dpi=300)
13 ax.plot(t/24.0, C, label="warfarin", color="black", linewidth=2.0)
14 ax.set_xlabel("time [day]")
15 ax.set_ylabel("warfarin [mg/l]")
16 ax.set_ylim(bottom=0)
17 plt.show()
```

Mould DR, Upton RN. **Basic concepts in population modeling, simulation, and model-based drug development.** CPT Pharmacometrics Syst Pharmacol. 2012 Sep 26;1(9):e6. doi: 10.1038/psp.2012.4. PMID: 23835886; PMCID: PMC3606044.

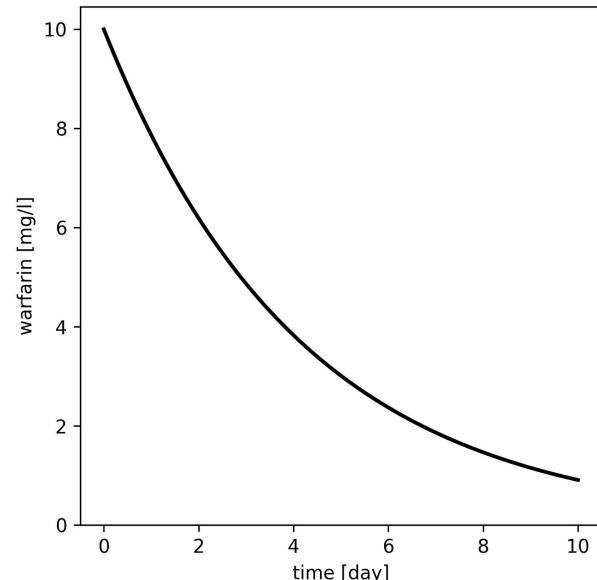
$$C_{(t)} = \frac{\text{Dose}}{V} e^{-\frac{CL}{V} \cdot t} \quad (1)$$



# Structural models as algebraic equations

```
1  from matplotlib import pyplot as plt
2  import numpy as np
3
4  # Warfarin
5  V = 10 # [l]
6  CL = 0.1 # [L/hr]
7  Dose = 100 # [mg]
8  t = np.linspace(start=0, stop=10*24, num=200) # [hr]
9  C = Dose/V * np.exp(-CL/V * t) # [mg/l]
10
11 # plot
12 f, ax = plt.subplots(nrows=1, ncols=1, figsize=(5, 5), dpi=300)
13 ax.plot(t/24.0, C, label="warfarin", color="black", linewidth=2.0)
14 ax.set_xlabel("time [day]")
15 ax.set_ylabel("warfarin [mg/l]")
16 ax.set_ylim(bottom=0)
17 plt.show()
```

$$C_{(t)} = \frac{\text{Dose}}{V} e^{-\frac{CL}{V} \cdot t} \quad (1)$$

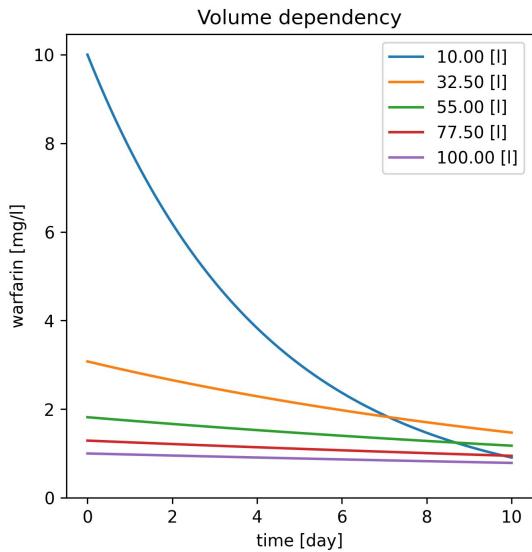
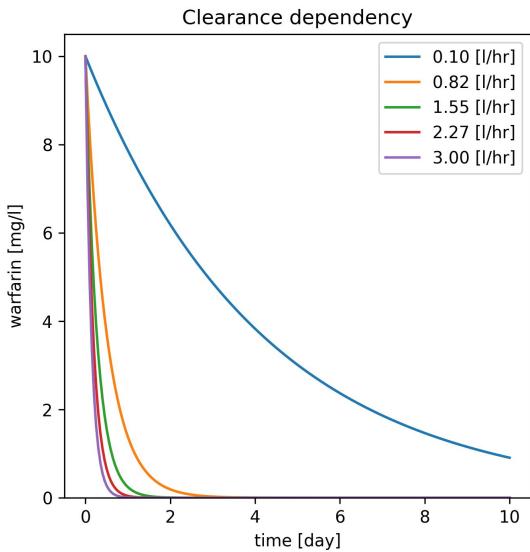
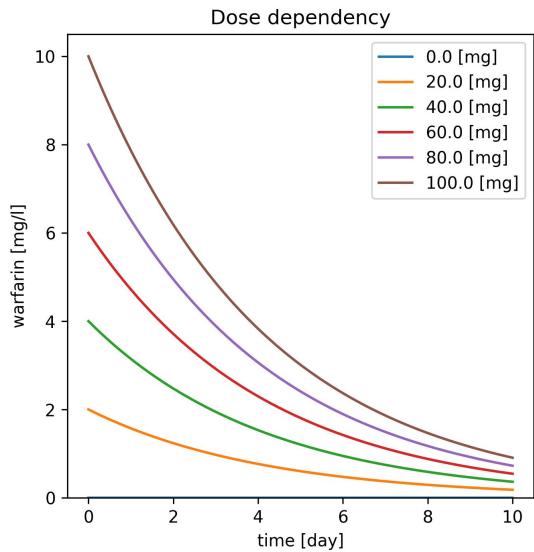


Mould DR, Upton RN. **Basic concepts in population modeling, simulation, and model-based drug development.** CPT Pharmacometrics Syst Pharmacol. 2012 Sep 26;1(9):e6. doi: 10.1038/psp.2012.4. PMID: 23835886; PMCID: PMC3606044.

# Parameter scans



$$C_{(t)} = \frac{\text{Dose}}{V} e^{-\frac{CL}{V} \cdot t} \quad (1)$$



# Ordinary differential equations (ODE)

- a differential equation describes the rate of change of a variable
- $dC/dt$  denotes the rate of change of the concentration over time
- differential equations require specification of the initial value ( $C_0$ )

$$C_{(t)} = \frac{\text{Dose}}{V} e^{-\frac{CL}{V} \cdot t} \quad (1)$$

$$\frac{dC}{dt} = -\frac{CL}{V} * C \quad (2)$$

$$C_0 = \frac{\text{Dose}}{V}$$

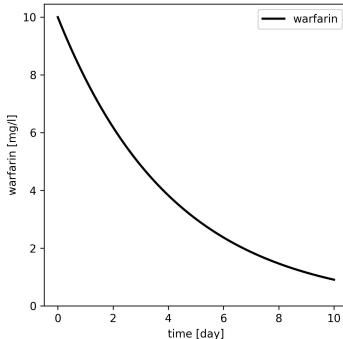
Mould DR, Upton RN. Basic concepts in population modeling, simulation, and model-based drug development. CPT Pharmacometrics Syst Pharmacol. 2012 Sep 26;1(9):e6. doi: 10.1038/psp.2012.4. PMID: 23835886; PMCID: PMC3606044.

# Numerical integration

- ODEs can be solved via numerical integration
- e.g. Euler method as simplest case
- solving a system of equations is computationally intensive

$$\frac{dC}{dt} = -\frac{CL}{V} * C$$

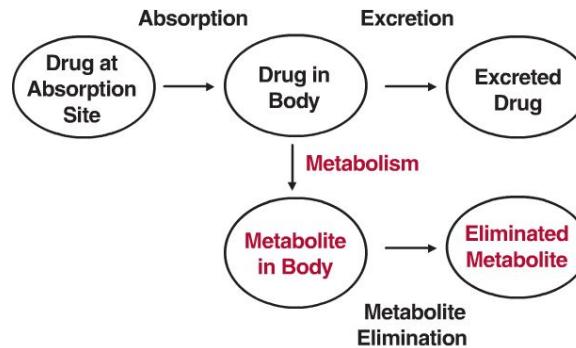
$$C_0 = \frac{\text{Dose}}{V}$$



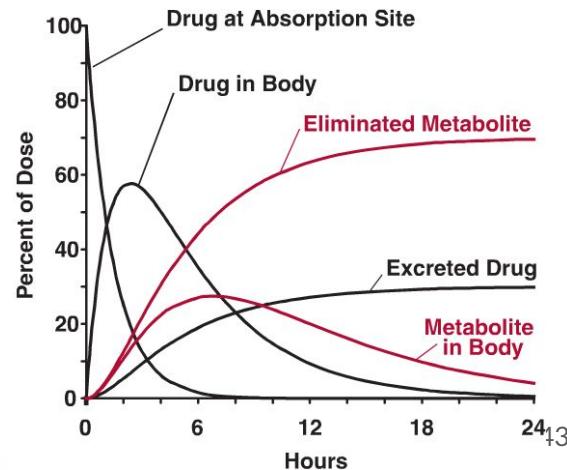
```
1  from scipy.integrate import odeint
2  from matplotlib import pyplot as plt
3  import numpy as np
4
5  # Parameter
6  V = 10  # [l]
7  CL = 0.1  # [L/hr]
8  Dose = 100  # [mg]
9
10
11 def ydot(y, t):
12     """ODE system: dx/dt"""
13     C = y[0]
14     return np.array([-CL/V * C])
15
16
17 # initial condition
18 y0 = np.array([Dose/V, ])  # [mg/l]
19
20 # Numerical integration
21 t = np.linspace(start=0, stop=10*24, num=200)  # [hr]
22 C = odeint(ydot, y0, t)
23
24 f, ax = plt.subplots(nrows=1, ncols=1, figsize=(5, 5), dpi=300)
25 ax.plot(t/24.0, C[:, 0], label="warfarin", color="black", linewidth=2.0)
26 ax.set_xlabel("time [day]")
27 ax.set_ylabel("warfarin [mg/l]")
28 ax.set_xlim(bottom=0)
29 ax.legend()
30 plt.show()
```

# Compartment models

- Pharmacokinetics can be modeled via compartment models
- Simple pharmacokinetic models have proven useful in many applications
- Main processes (**ADME**)
  - **Absorption**
  - **Distribution**
  - **Metabolization**
  - **Excretion**



**FIGURE 2-5.** A drug is simultaneously absorbed into the body and eliminated from it, by excretion and metabolism. The processes of absorption, excretion, and metabolism are indicated with arrows and the compartments with ovals. The compartments represent different locations and different chemical species (color = metabolite). Metabolite elimination may occur by further metabolism or excretion.



**FIGURE 2-6.** Time course of drug and metabolite in each of the compartments shown in Fig. 2-5. The amount in each compartment is expressed as a percentage of the dose administered. In this example, all the dose is absorbed. At any time, the sum of the molar amounts in the five compartments equals the dose.

# Example of compartment model

- system of ODEs
- solved numerically
- A(D)ME
  - Absorption ( $v_a$ )
  - Metabolism ( $v_m$ )
  - Elimination ( $v_{u,A}$ ,  $v_{u,B}$ )
- Mass action equations with rate constants  $k_a$ ,  $k_m$ ,  $k_e$

Physiologically based pharmacokinetic (PBPK) modeling for dynamical liver function tests and CYP phenotyping. Jan Grzegorzewski (supervisor: Matthias König). PhD Thesis, Jan 2023

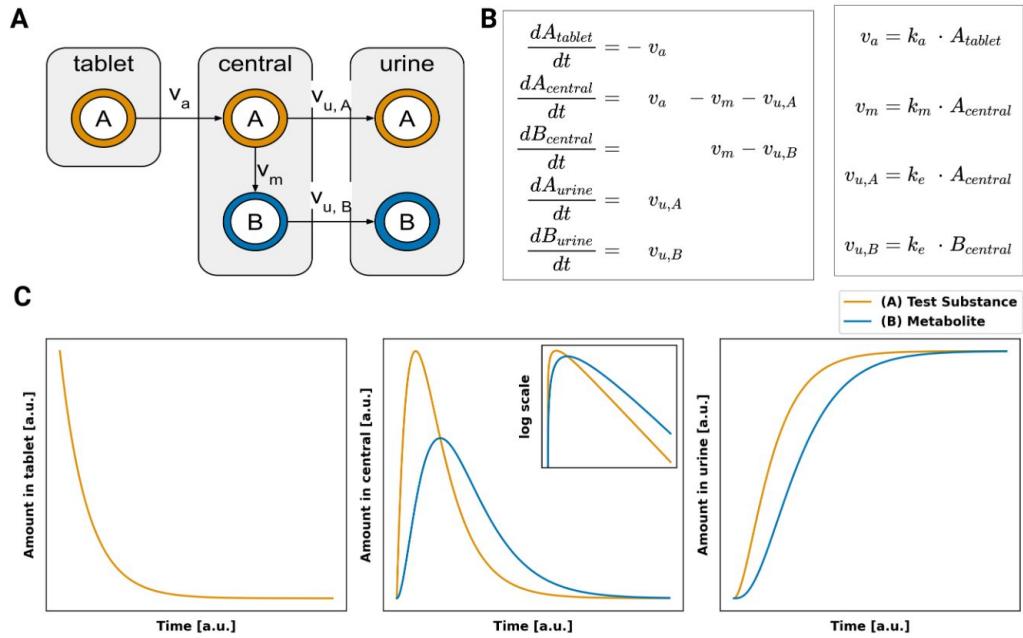
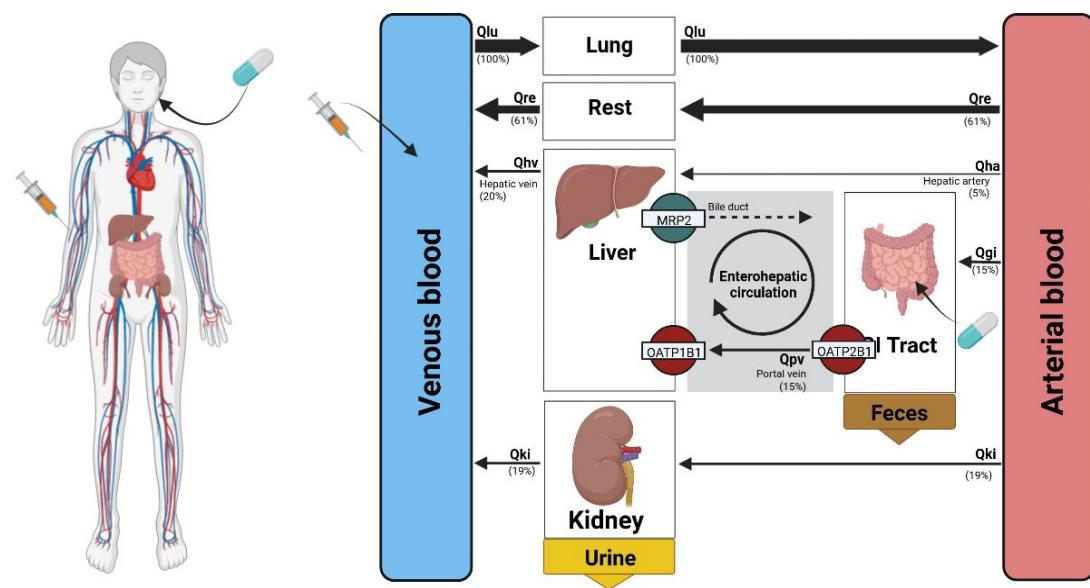


FIGURE 2.3: Simple ODE-based pharmacokinetics model. **A)** The system consists of three compartments (tablet, central, urine) that are connected via transport reactions. The model contains two substances the test substance A (orange); and the metabolite B (blue). The test substance A is metabolized to metabolite B in the central compartment. **B)** The resulting system of ordinary differential equations (ODEs). The rate of absorption, metabolism, and excretion ( $v_a$ ,  $v_m$ ,  $v_{u,A}$ ,  $v_{u,B}$ ) are modeled via irreversible mass-action kinetics. **C)** With an initial amount of  $A_{\text{tablet}} = 10$  and rates  $k_a = 1$ ,  $k_m = 1$ , and  $k_e = 1$ , all in [a.u.], the resulting amounts over time of the substances in the tablet, central, urine compartments are depicted.

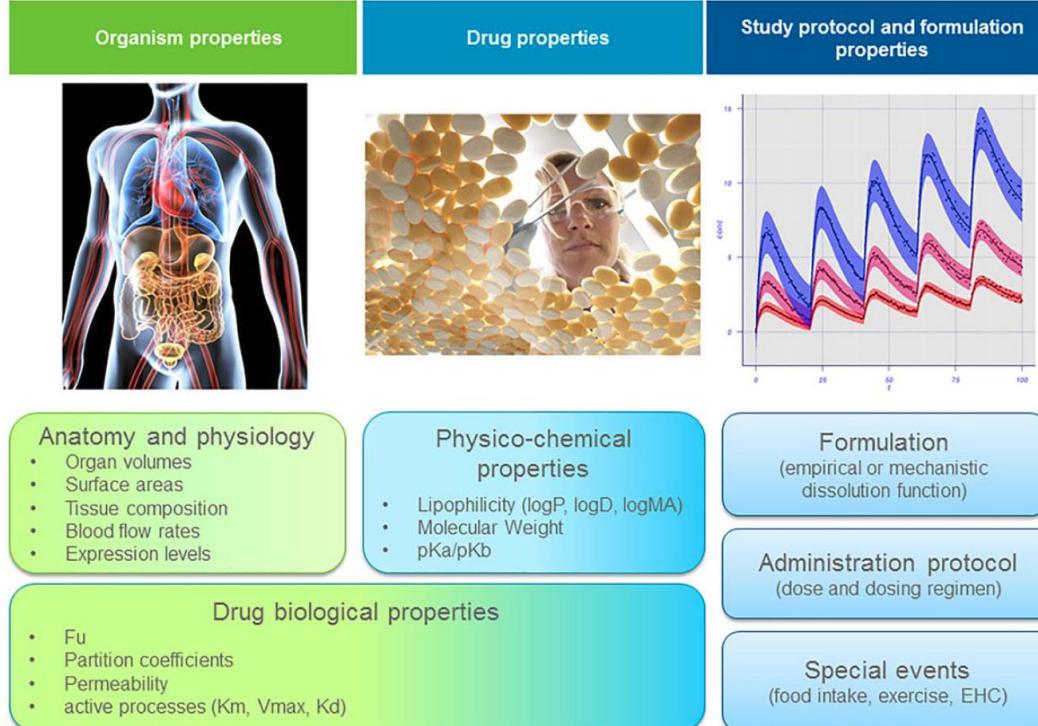
# Physiologically based pharmacokinetics (PBPK) models

- **Human physiology *in silico***  
Combine test substance information with physiology
- **Multi-scale Body-Organ**
- **High pharmacological & clinical relevance**  
Individualization



# PBPK Models

## Building blocks of a PBPK model



### Compartments

- organs

### State variables

- drug & metabolite amounts

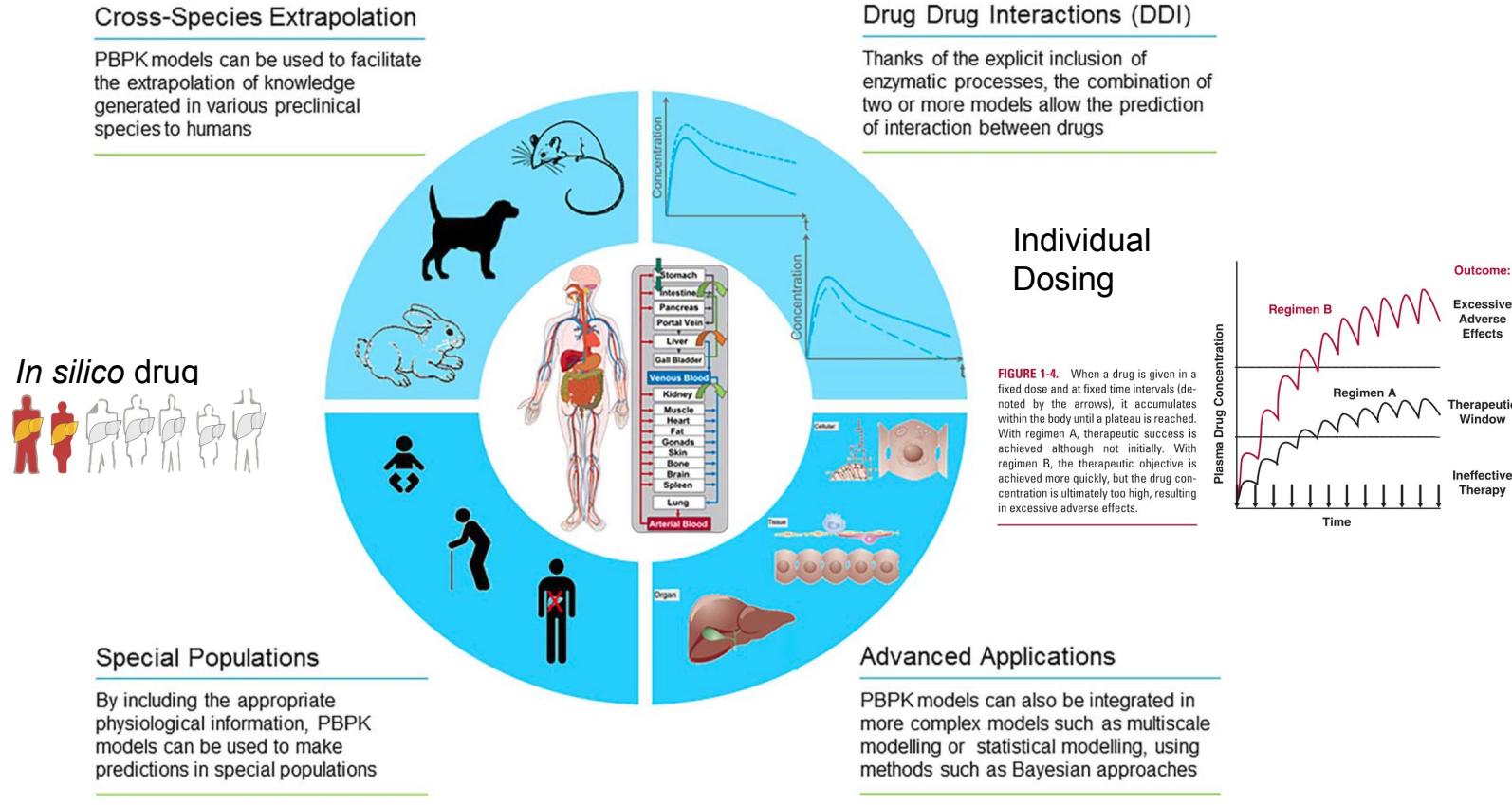
### Ordinary Differential equations (ODE) & rules

- Blood flows, Transport, Disposition
- Metabolism, Elimination
- Absorption

### Parameters

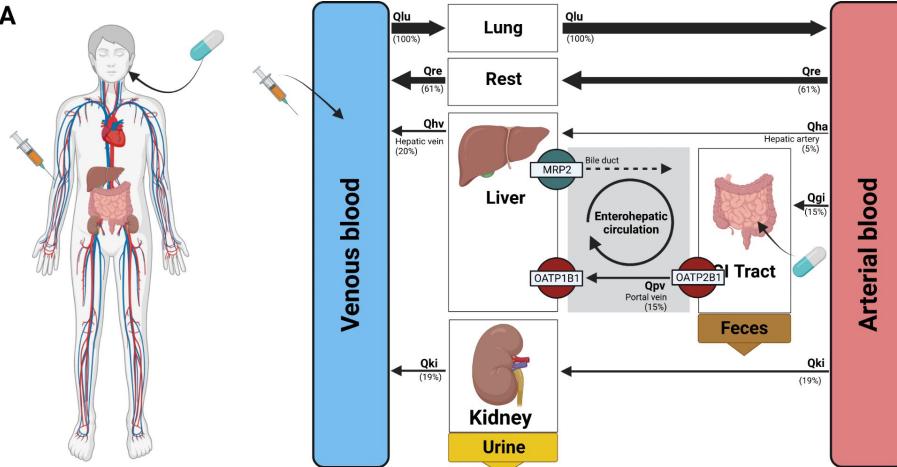
- Tissue partition coefficients
- Protein binding
- Kinetic parameter (transport & elimination)
- Blood flows, organ volumes, ...

# PBPK Applications

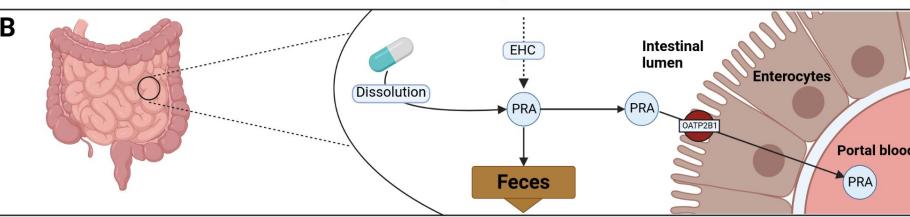


# Pravastatin - Hepatorenal impairment

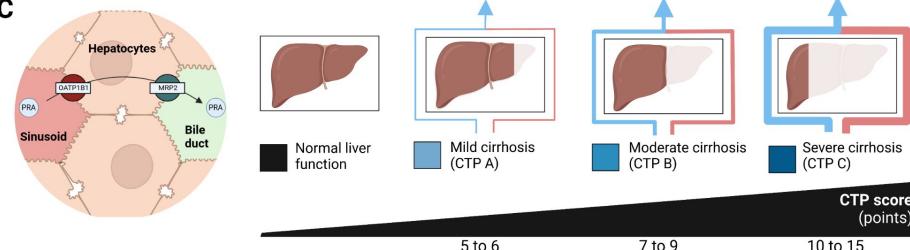
A



B



C

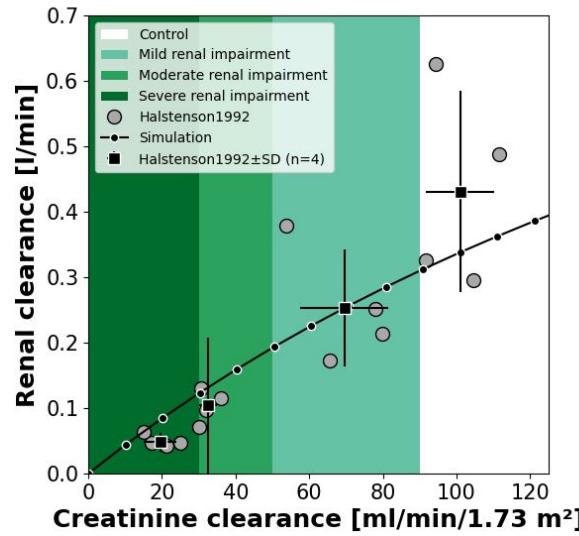
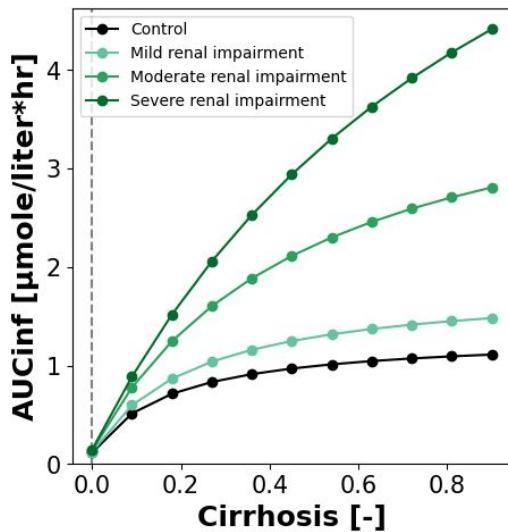
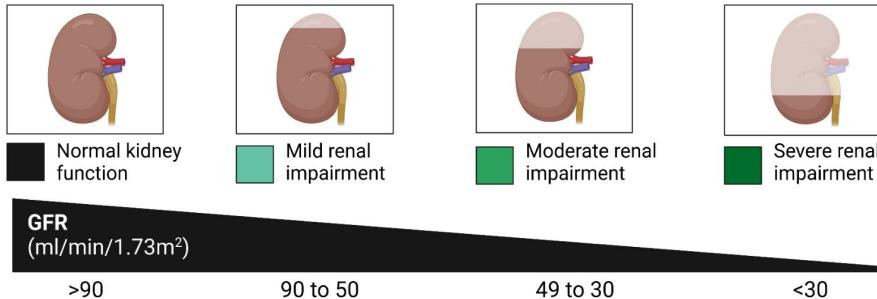
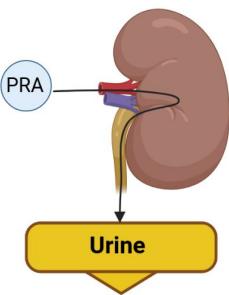


HL Pujol, J Grzegorzewski, F Bartsch, HM Tautenhahn,  
M.König

**A physiologically based pharmacokinetic (PBPK) model of pravastatin: Impact of hepatorenal impairment and genetic polymorphisms of OATP1B1, OATP2B1 and MRP2**

<https://www.youtube.com/watch?v=ddQYx4fGgRE>

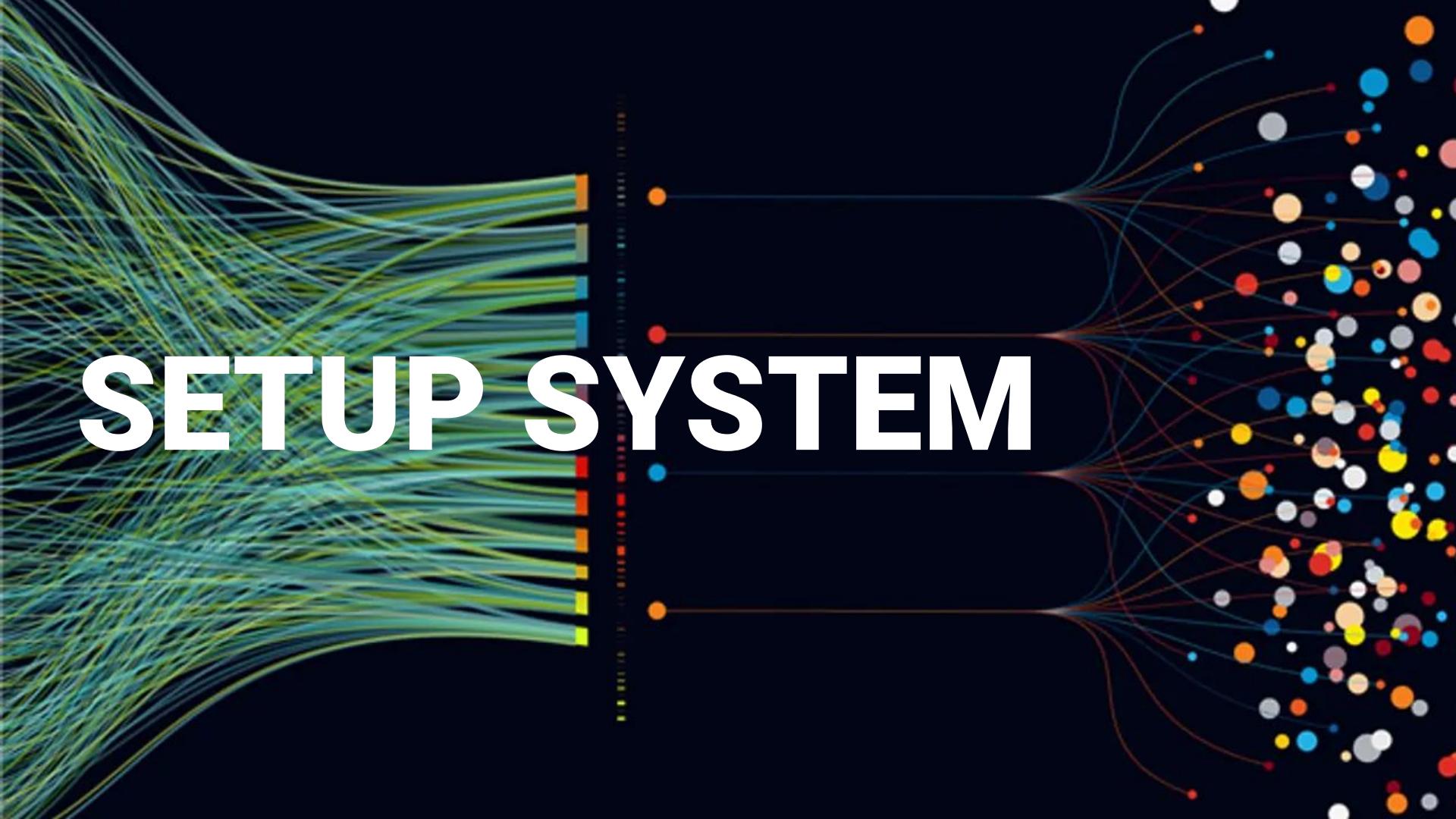
# Pravastatin - Renal impairment



HL Pujol, J Grzegorzewski, F Bartsch, HM Tautenhahn,  
M.König  
**A physiologically based pharmacokinetic (PBPK) model of pravastatin: Impact of hepatorenal impairment and genetic polymorphisms of OATP1B1, OATP2B1 and MRP2**

<https://www.youtube.com/watch?v=ddQYx4fGgRE>

# SETUP SYSTEM

The background features a dark blue gradient with a complex network of thin, glowing lines in shades of green, yellow, and orange. These lines converge towards the center of the frame, where they connect to small, semi-transparent circular dots. From these dots, thicker lines branch out to the right side of the image, leading to a dense cluster of larger, colorful circles in various sizes and hues (orange, yellow, red, blue, white). The overall effect is one of data flow, connectivity, and digital complexity.

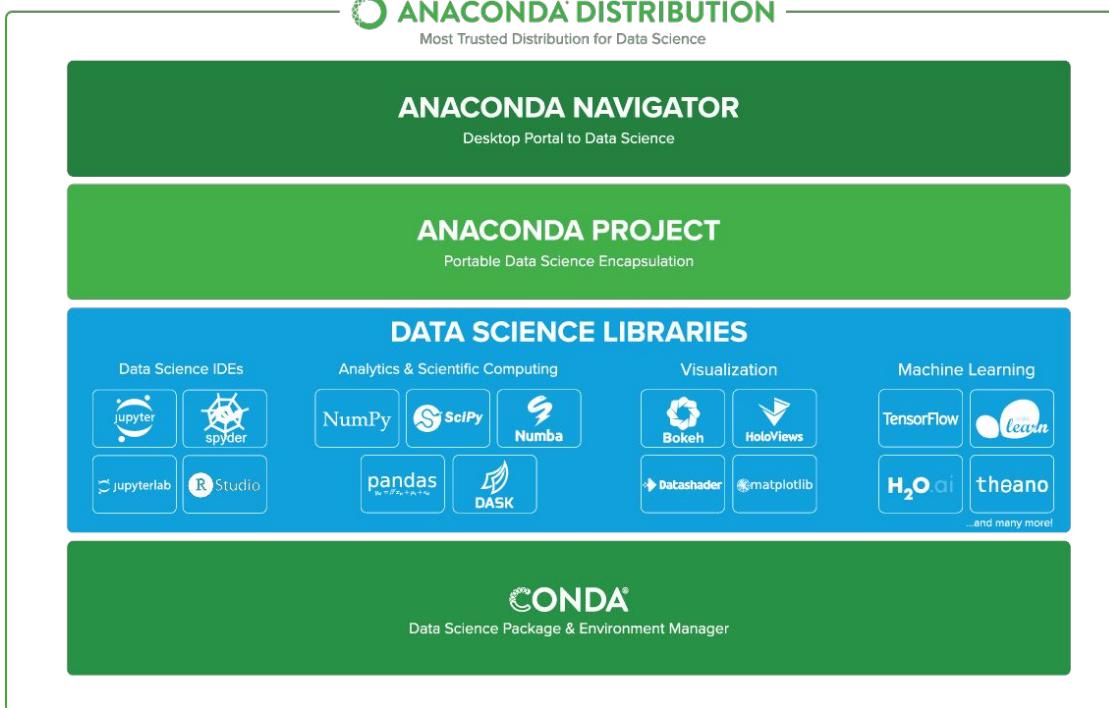
# Install Anaconda

Install Anaconda Distribution

<https://docs.anaconda.com/free/anaconda/#installation>

**Anaconda® Distribution is a free Python/R data science distribution that contains:**

- [conda](#) - a package and environment manager for your command line interface
- [Anaconda Navigator](#) - a desktop application built on conda, with options to launch other development applications from your managed environments
- [250 automatically-installed packages](#) that work well together out of the box
- access to the [Anaconda Public Repository](#), with 8000 open-source data science and machine learning packages



The image shows the official Anaconda Distribution landing page. At the top, there's a green header with the text "ANA CONDA DISTRIBUTION" and "Most Trusted Distribution for Data Science". Below the header are two main sections: "ANA CONDA NAVIGATOR" (a desktop portal) and "ANA CONDA PROJECT" (portable data science encapsulation). The central part of the page is titled "DATA SCIENCE LIBRARIES" and features four categories: Data Science IDEs (Jupyter, JupyterLab, Spyder, R Studio), Analytics & Scientific Computing (NumPy, SciPy, Numba, pandas, DASK), Visualization (Bokeh, Holoviews, DataShader, matplotlib), and Machine Learning (TensorFlow, scikit-learn, H2O.ai, Theano). At the bottom, there's a green footer with the text "CONDA" and "Data Science Package & Environment Manager".

# Setup conda environment

---

- create conda environment mb19
  - open terminal
  - create environment

```
conda create -n mb19
```

- install packages

```
pip install numpy scipy  
matplotlib pandas
```

## Activating/Deactivating environments

- To see a list of environments: **conda env list**

```
vperezg@login1:/home/vperezg>conda env list  
# conda environments:  
#  
base          * /prod/apps/conda/3  
bio-computation /prod/apps/conda/3/envs/bio-computation  
machine-learning /prod/apps/conda/3/envs/machine-learning  
machine-learning-gpu /prod/apps/conda/3/envs/machine-learning-gpu  
prosado        /prod/apps/conda/3/envs/prosado  
qiime2-2019.7   /prod/apps/conda/3/envs/qiime2-2019.7  
quantum-chem    /prod/apps/conda/3/envs/quantum-chem
```

- To load an env: **conda activate <env\_name>**

```
vperezg@login1:/home/vperezg>conda activate bio-computation  
(bio-computation) vperezg@login1:/home/vperezg>
```

- To unload: **conda deactivate**

```
(bio-computation) vperezg@login1:/home/vperezg>conda deactivate  
vperezg@login1:/home/vperezg>
```

# Install Spyder

- available via the anaconda navigator
- alternative use Jupyterlab
- alternative use Jupyter notebooks



The Scientific Python Development Environment

A screenshot of the Spyder IDE interface. The left side shows a code editor with several files open, including `plugin.py`, `plot_example.py`, and `ipythonconsole.py`. The code in `plugin.py` is as follows:

```
# -*- coding: utf-8 -*-
# Copyright © Spyder Project Contributors
# Licensed under the terms of the MIT License
# (see spyder/__init__.py for details)

"""
Plots Plugin.

Third party imports
from spyder.occure import Signal

Local imports
from spyder.api.plugins import Plugins, SpyderDockablePlugin
from spyder.api.translations import get_translation
from spyder.plugins.plots.widgets.main_widget import PlotsWidget

# Localization
_ = get_translation('spyder')

class Plots(SpyderDockablePlugin):
    """
    Plots plugin.
    NAME = 'plots'
    REQUIRES = [Plugins.IPythonConsole]
    TABIFY = [Plugins.VariableExplorer, Plugins.Help]
    WIDGET_CLASS = PlotsWidget
    CONF_SECTION = NAME
    CONF_FILE = False
    DISABLE_ACTIONS_WHEN_HIDDEN = False

    # --- SpyderDockablePlugin API
    def get_name(self):
        return _("Plots")

    def get_description(self):
        return _("Display, explore and save console generated plots.")

    def get_icon(self):
        return self.create_icon('hist')

    def register(self):
        # Plugins
        ipyconsole = self.get_plugin(Plugins.IPythonConsole)

        # Signals
        ipyconsole.sig_shellwidget_changed.connect(self.set_shellwidget)
        ipyconsole.sig_shellwidget_created.connect(
            self.set_shellwidget)
        ipyconsole.sig_shellwidget_deleted.connect(
            self.remove_shellwidget)
```

The right side of the interface includes a Variable Explorer showing variables like `a`, `filename`, `i`, `my_set`, `r`, `t`, `thisdict`, `tinylist`, `x`, and `y`. Below the Variable Explorer is a 3D surface plot and a polar plot.

