

Pharmacokinetic Modelling

Matthias König, MB19, SS2023 Lecture 6, 2023-06-05
 Humboldt-University Berlin, Systems Medicine of the Liver Lab
<https://livermetabolism.com>
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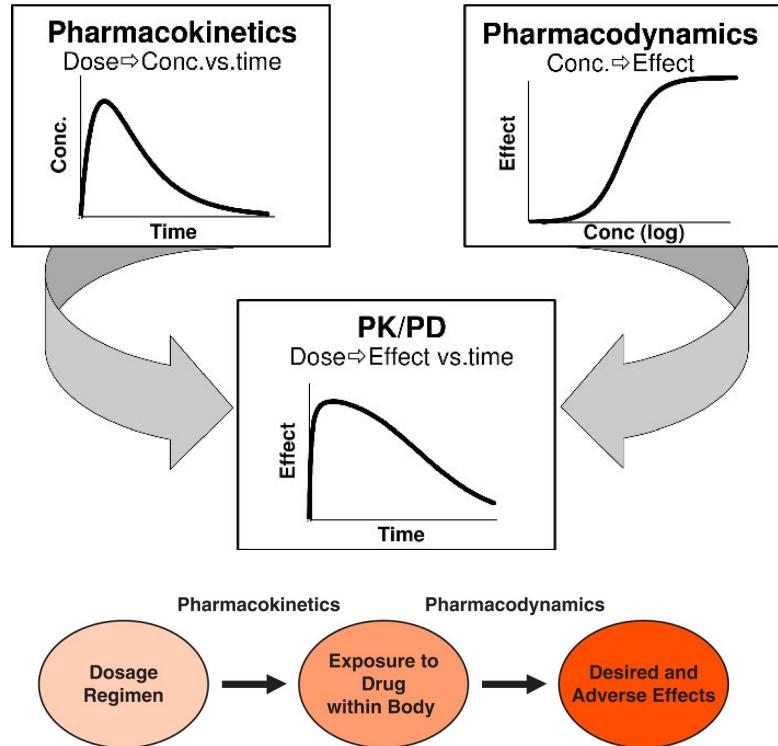






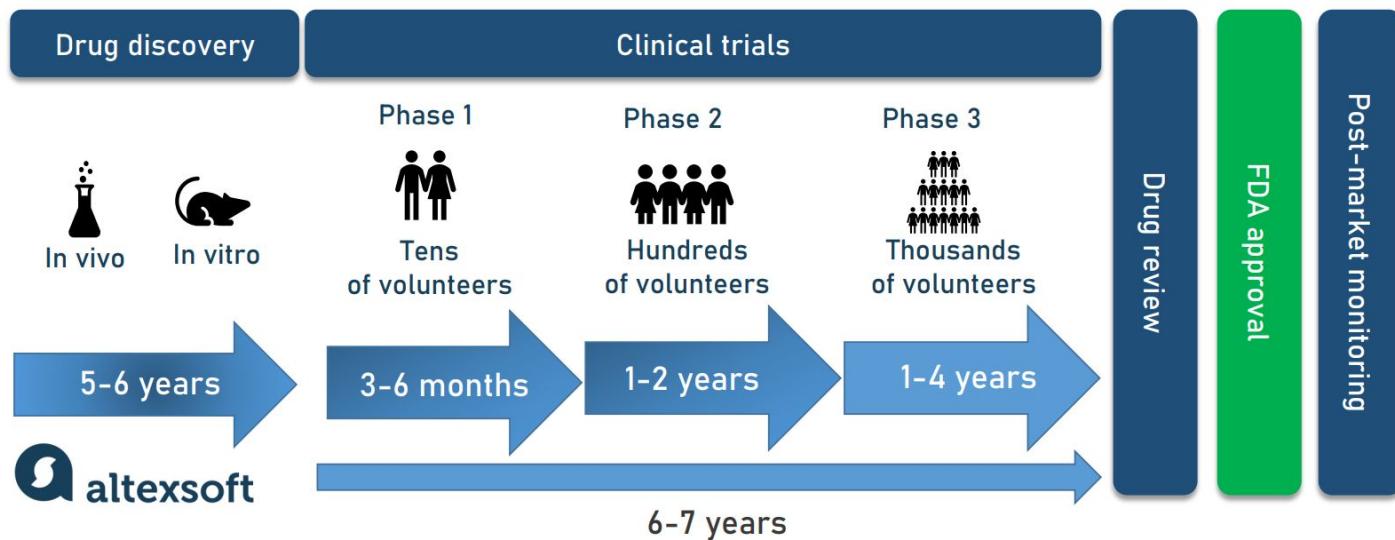
Pharmacokinetics (PK) & pharmacodynamics (PD)

- **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/PK in drug development

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

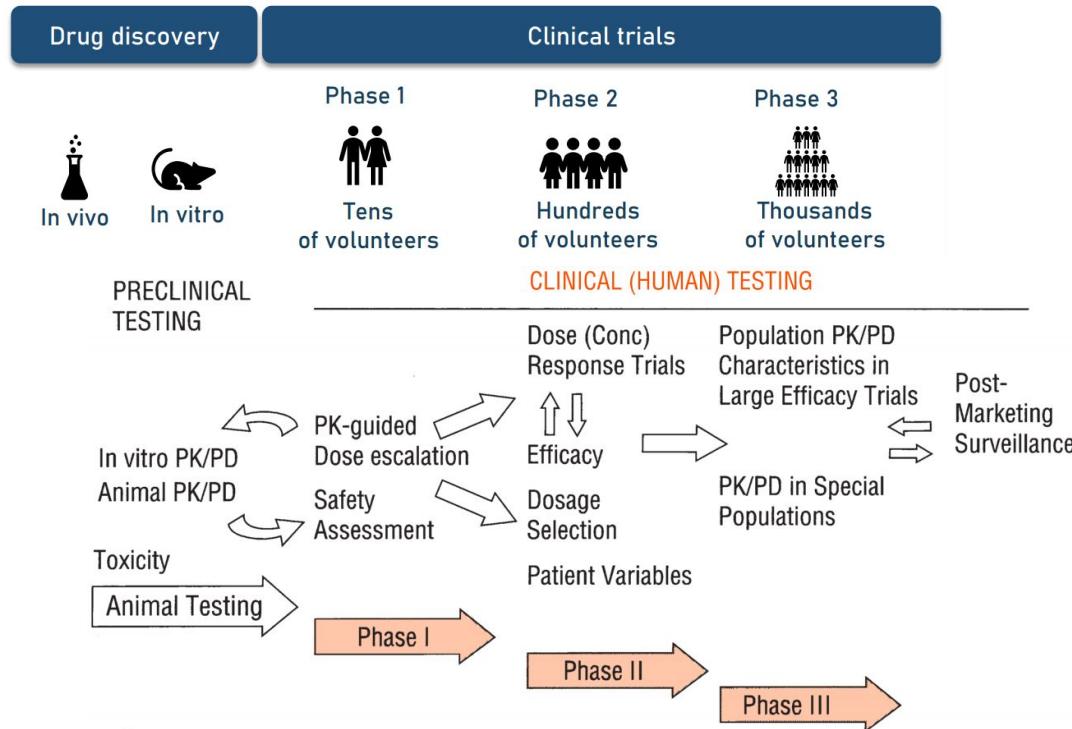
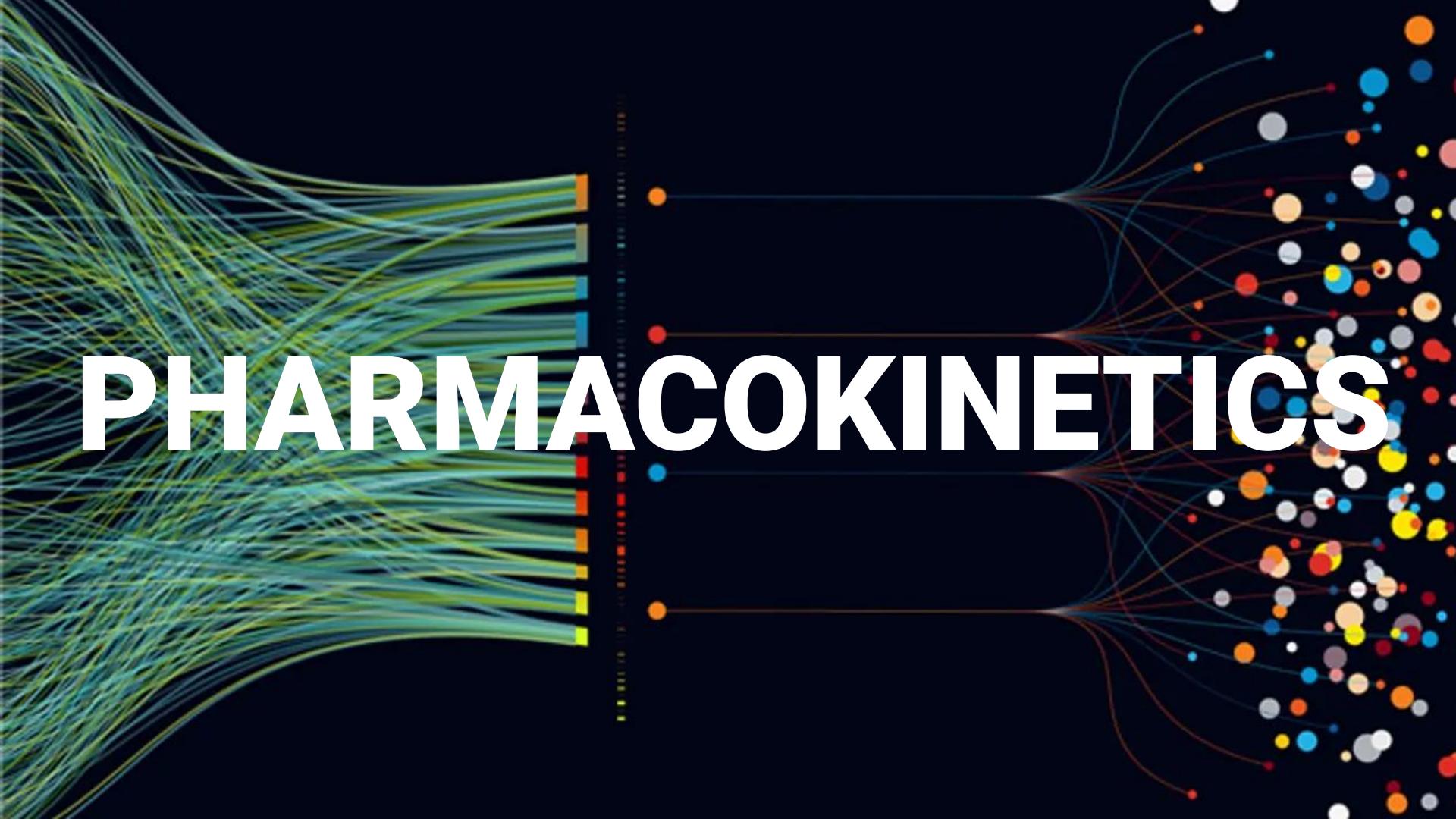


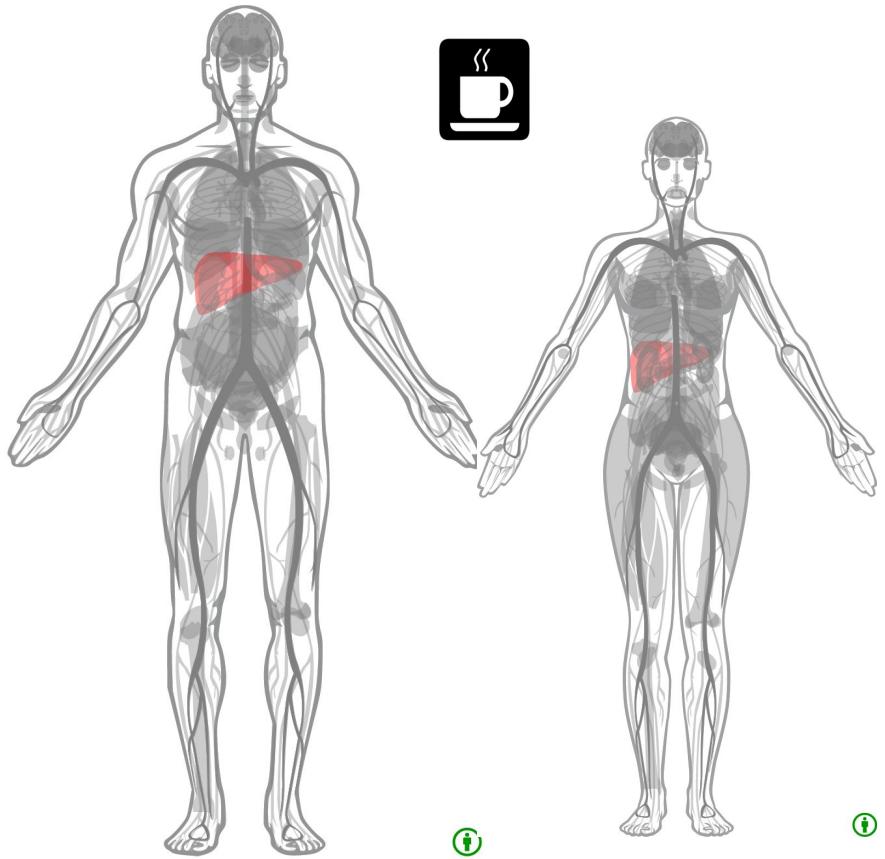
FIGURE 1-11 The development and subsequent marketing of a drug. The preclinical data help to identify promising compounds and to suggest useful doses for testing in humans. Phases I, II, and III of human assessment generally correspond to the first administration to humans, early evaluation in selected 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

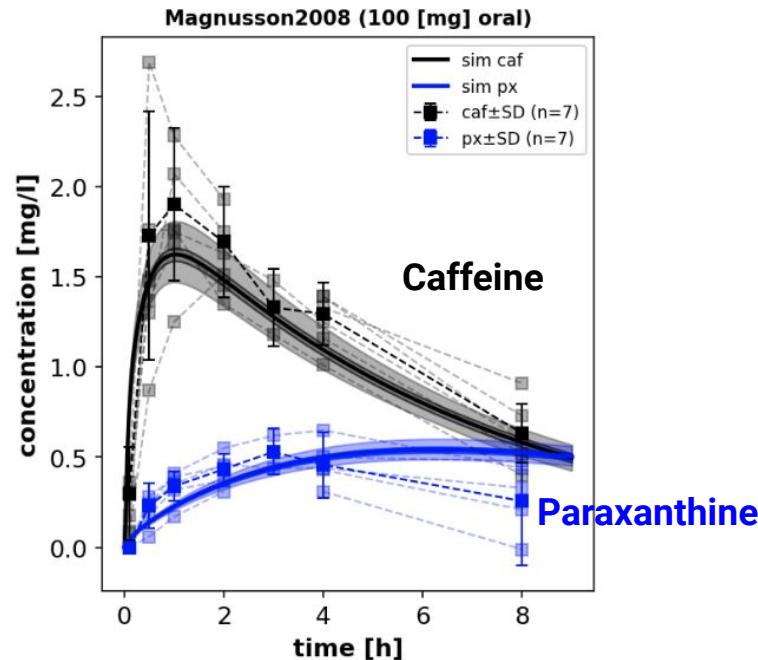
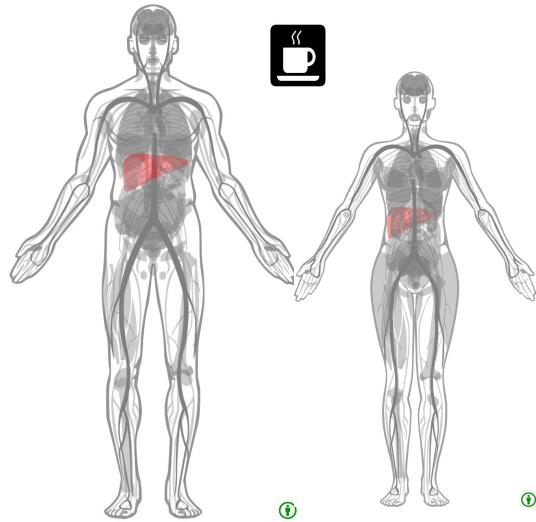
AI in Drug Discovery and Repurposing: Benefits, Approaches, and Use Cases
<https://www.altextsoft.com/blog/ai-drug-discovery-repurposing/>

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.

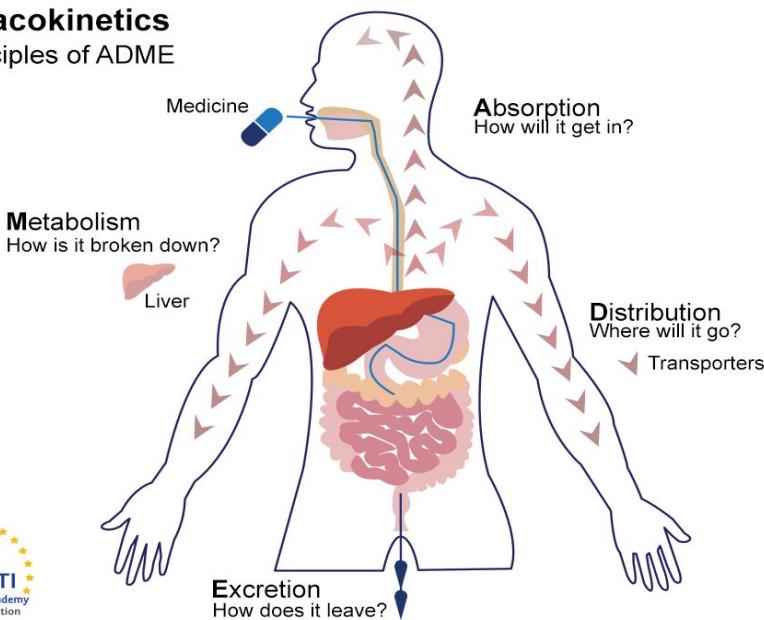


100 mg oral caffeine



ADME

Pharmacokinetics The principles of ADME

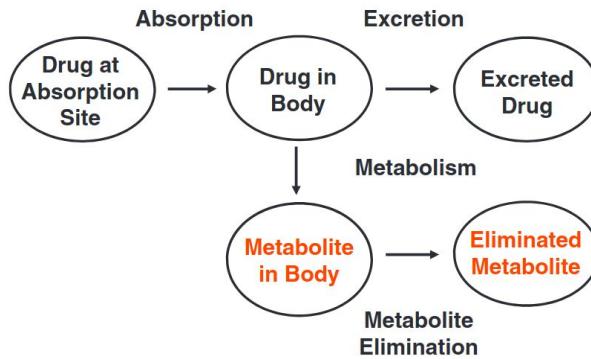


ADME processes determine pharmacokinetics

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

ADME

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

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.

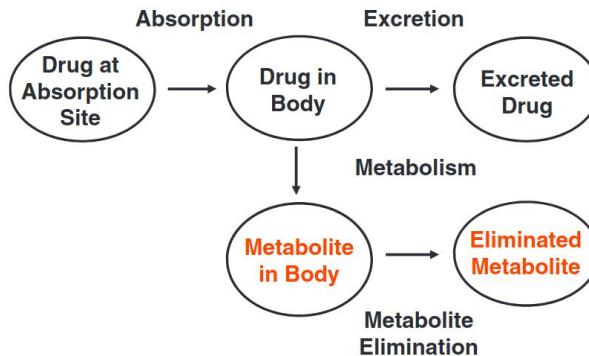
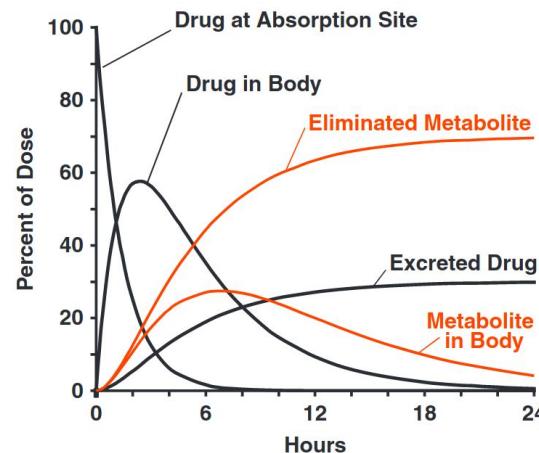


FIGURE 2-6 Time course of drug and metabolite in each of the compartments shown in Fig. 2-5. The amount in each compartment is expressed as a percentage of the dose administered. In this example, the dose is completely absorbed. At all times, the sum of the molar amounts in the five compartments equals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



ADME

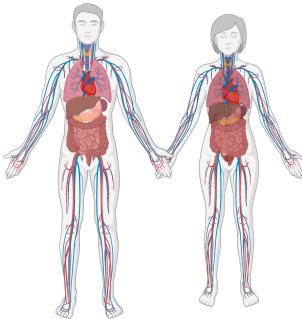
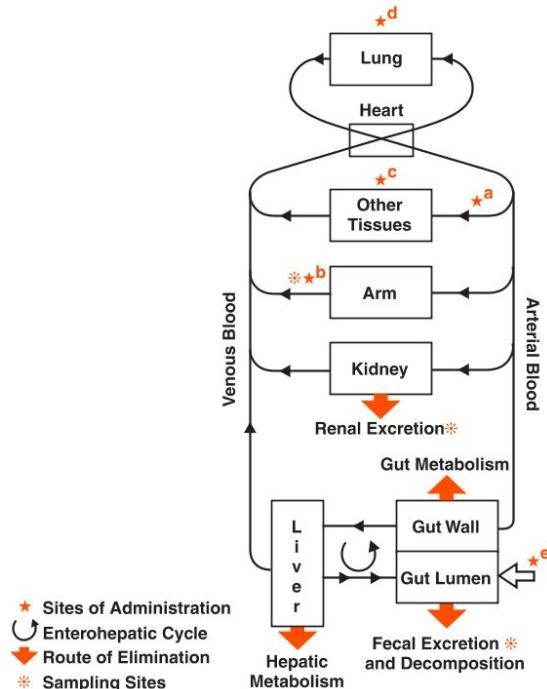


FIGURE 2-2 Once absorbed from any of the many sites of administration, drug is conveyed by blood to all sites within the body, including the eliminating organs. Sites of administration include: a, artery; b, peripheral vein; c, muscle and subcutaneous tissue; d, lung; and e, gastrointestinal tract, the 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

Bioavailability

- **bioavailability:** due to losses during absorption, intestinal metabolism, efflux and hepatic extraction only a fraction of the drug appears in the systemic circulation

Clinical implications

- **Delays or loss of drug during absorption** can introduce a large variability in drug response.
- **Disease conditions and co-medications** may profoundly affect the absorption of certain drugs.

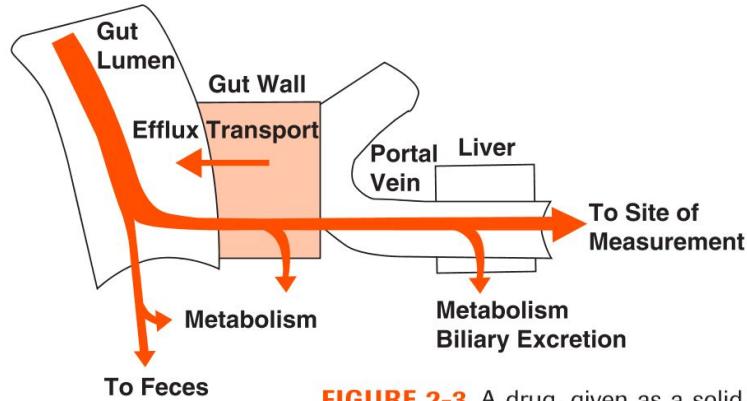
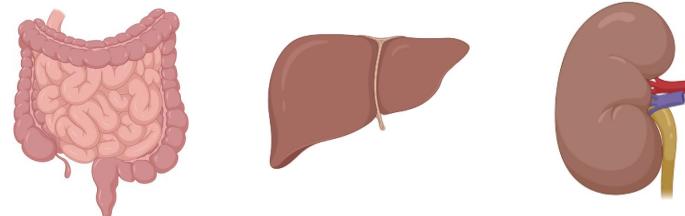
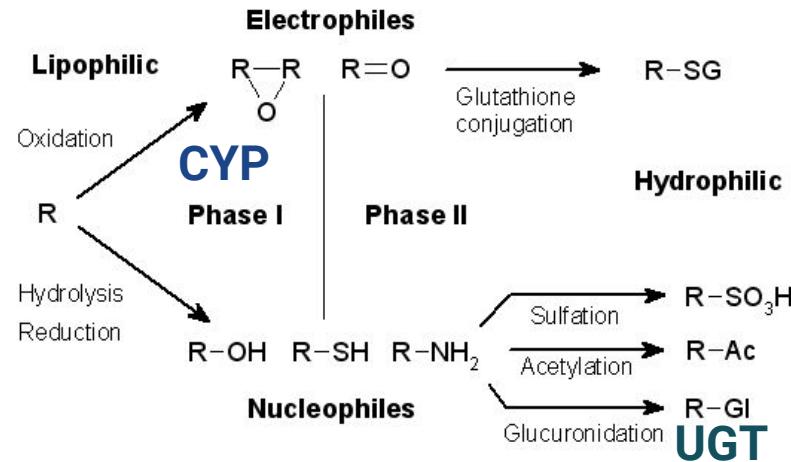


FIGURE 2-3 A drug, given as a solid, encounters several barriers and sites of loss in its sequential movement (colored arrows) through the gastrointestinal tissues and the liver. Incomplete dissolution, degradation in the gut lumen, metabolism by enzymes, and efflux by transporters, in the gut wall are causes of incomplete input into the systemic circulation. Removal of drug as it first passes through the liver may further reduce systemic input.

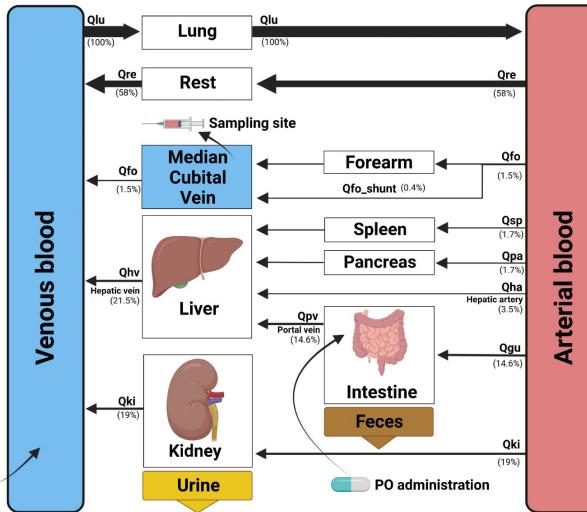
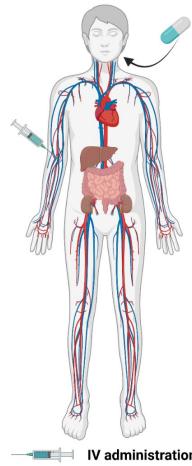
Drug metabolism in a nutshell

- 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

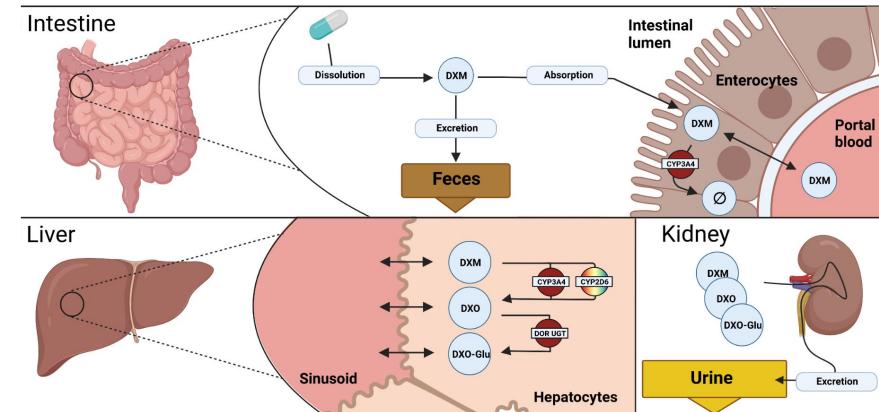


Example: Dextromethorphan model (ADME)

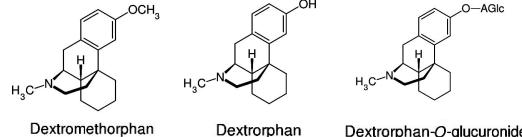
Whole-body model



Tissue models



Substance/Metabolites



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]

J.Brandhorst,
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]

M.König

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

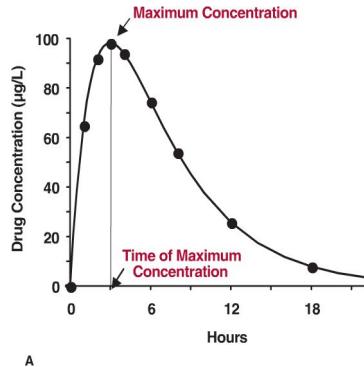


FIGURE 2-1. Drug concentration–time curve following a single oral dose showing the maximum systemic exposure (C_{max}) and the time of its occurrence (t_{max}). The concentration could represent drug in whole blood, plasma, or serum.

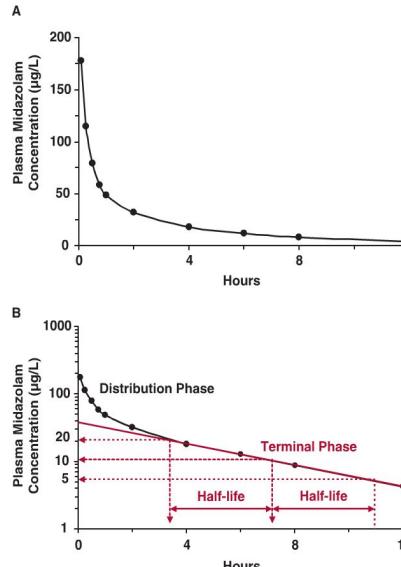


FIGURE 3-4. A. Plasma concentration of midazolam with time in an individual after an 8.35-mg i.v. bolus dose of midazolam hydrochloride (7.5 mg of the base) in a healthy adult. B. The data in A are redisplayed as a semilogarithmic plot. Note the short distribution phase. (From: Pentikäinen PJ, Väistönen 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: 272–279.)

Pharmacokinetic parameter

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

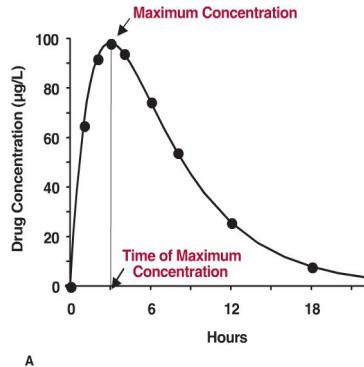


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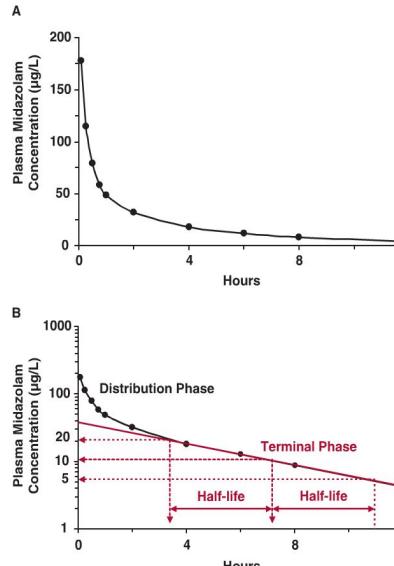


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Variability between drugs

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

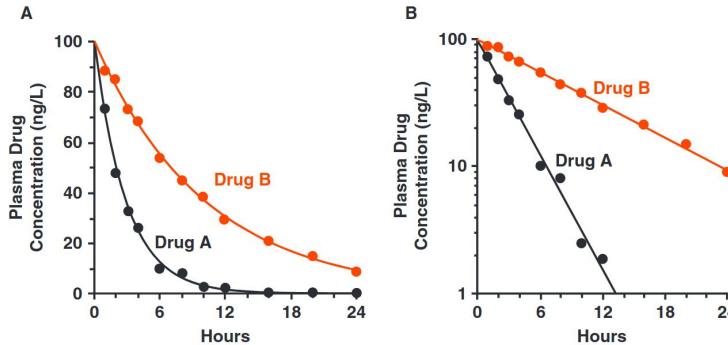


FIGURE 5-1 Drugs A (black circle) and B (colored circle) show the same initial (peak) exposure, but have different half-lives and total exposure-time profiles (AUC). Regular (cartesian) plot (*left*). Semilogarithmic plot (*right*). Doses of both drugs are the same.

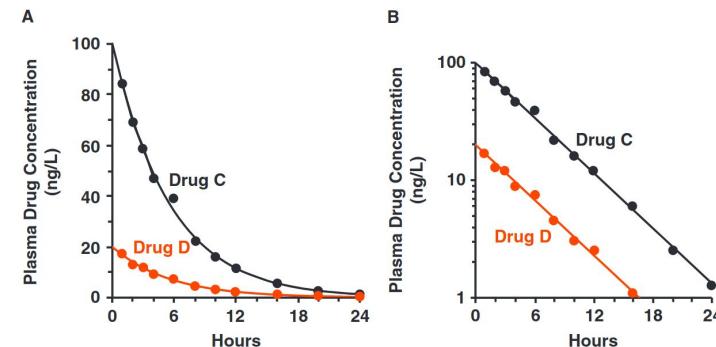


FIGURE 5-2 Drugs C (black circle) and D (colored circle) have the same half-life but different initial and total exposure-time (AUC) profiles. Regular (cartesian) plot (*left*). Semilogarithmic plot (*right*). Doses of both drugs are the same.

Variability between drugs

- large variability in pharmacokinetic parameters between drugs

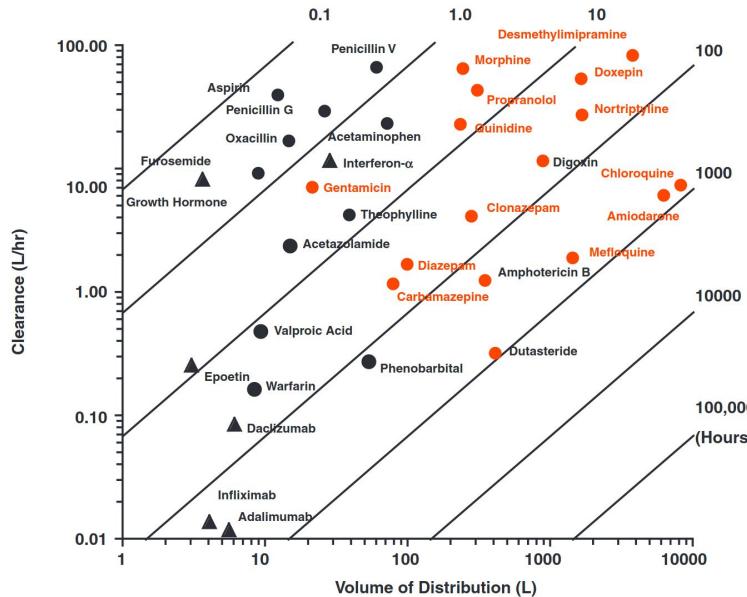
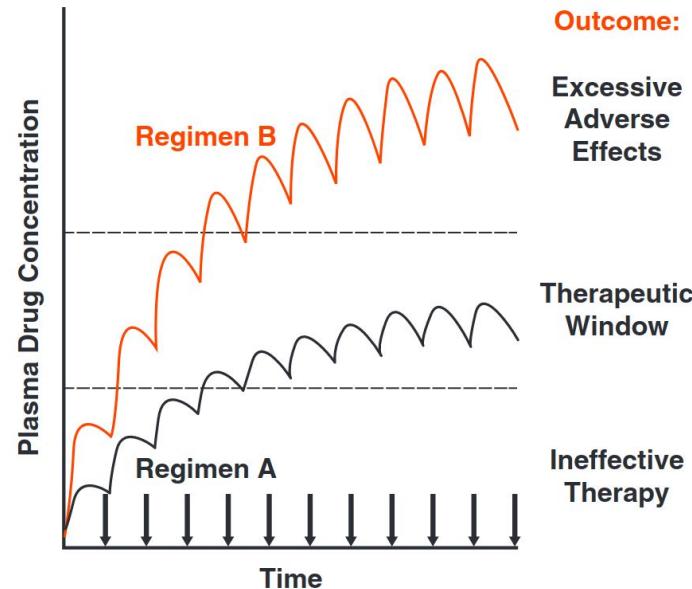


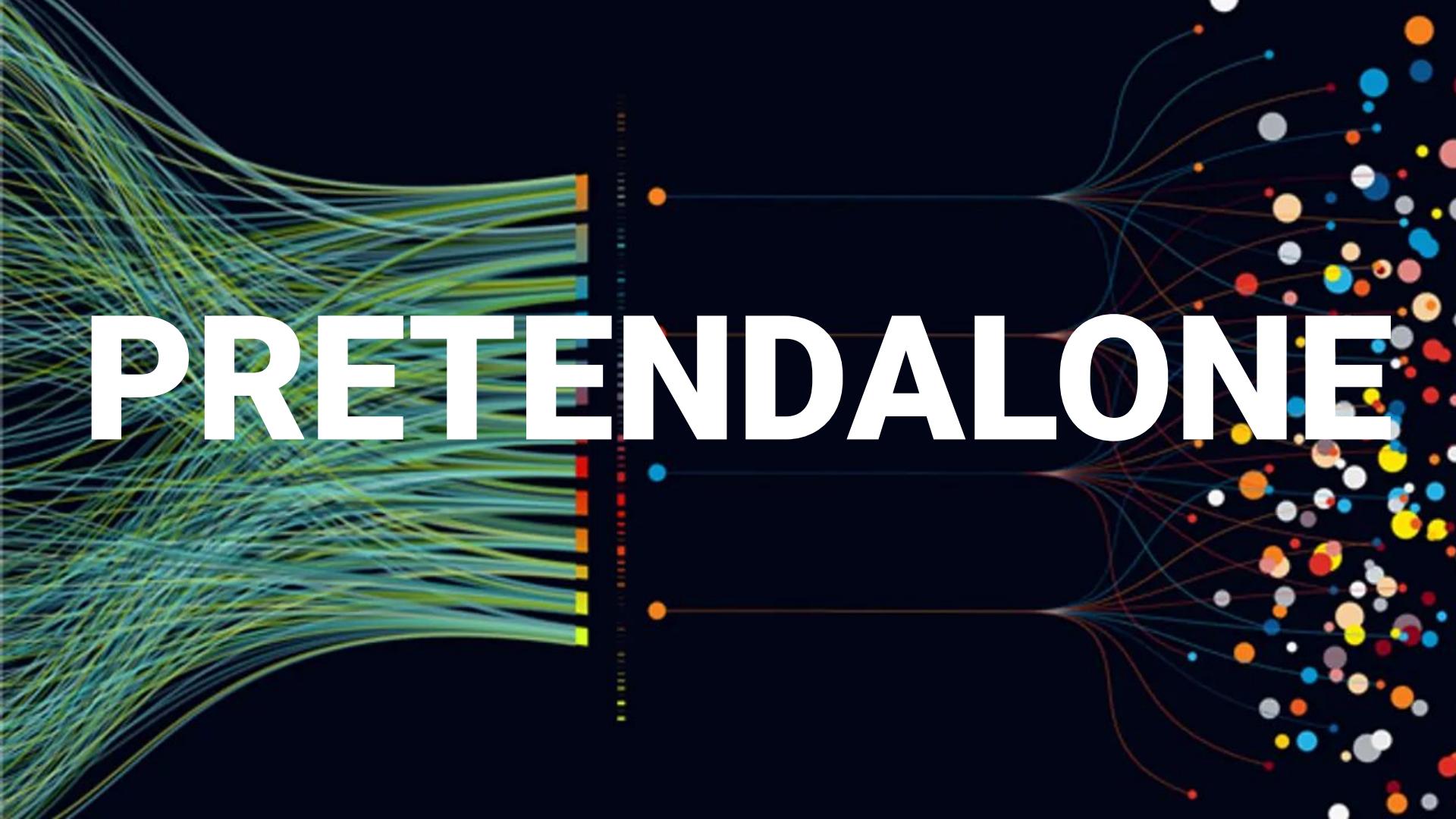
FIGURE 5-8 Clearance (ordinate) and volume of distribution (abscissa) of selected acidic (black circle) and basic (colored names), as well as protein (black triangle), drugs vary widely. Diagonal lines on the fully logarithmic plot show the combinations of clearance and volume values with the same half-lives (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.



The background features a dark blue gradient with a complex network of thin, glowing lines in shades of green, yellow, and blue. 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 symmetrical, branching pattern that resembles a tree or a neural network. The overall effect is one of motion and connectivity.

PRETEND ALONE

Pretendalone trial

- 5 subjects receive
 - 50 mg oral pretendalone
 - 2 mg bolus injection



Oral pretendalone application



- example drug
- application in 5 subjects
- measurement in plasma

Subject / statistic → Time ↓	1	2	3	4	5	Arithmetic Mean	Std Dev	%CV	Geomean
1 min	0.51	0.43	0.39	0.51	0.60	0.49	0.08	16.88	0.48
5 min	1.10	1.01	1.27	0.88	0.70	0.99	0.22	21.80	0.97
10 min	11.30	12.00	9.88	8.95	8.45	10.12	1.51	14.94	10.03
30 min	52.40	47.40	56.28	49.88	44.10	50.01	4.66	9.31	49.84
1 h	92.10	88.70	85.44	98.21	86.07	90.10	5.24	5.81	89.98
2 h	85.80	92.50	91.53	82.38	83.30	87.10	4.67	5.36	87.00
4 h	63.20	68.70	60.66	71.44	64.55	65.71	4.33	6.59	65.60
8 h	39.99	43.57	39.00	46.38	36.60	41.11	3.87	9.41	40.96
12 h	20.00	18.30	25.77	19.73	17.32	20.22	3.29	16.25	20.03
24 h	5.50	7.20	5.84	5.01	6.47	6.00	0.85	14.22	5.96
36 h	1.30	1.11	0.99	1.11	2.05	1.31	0.43	32.56	1.27

Table 1: concentration (ng Pretendalone per mL plasma) in five subjects following a 50 mg single oral dose.

Oral pretendalone application

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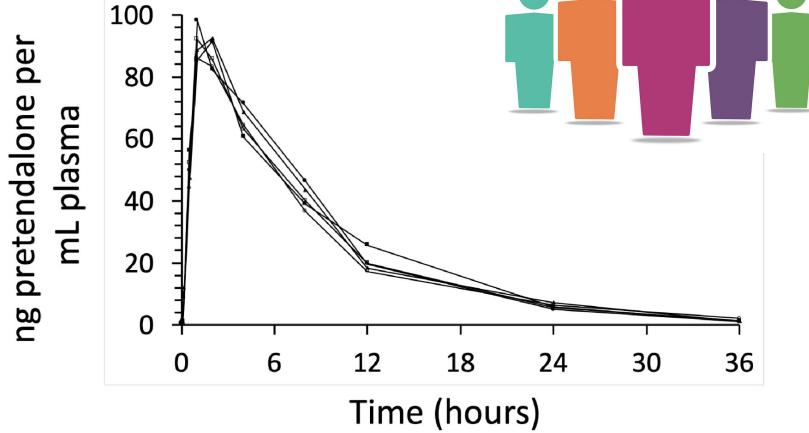


Figure 2: plot of time versus concentration (ng Pretendalone per mL plasma) for five subjects following a 50 mg single oral dose.

Subject / statistic → Time ↓	1	2	3	4	5	Arithmetic Mean	Std Dev	%CV	Geomean
1 min	0.51	0.43	0.39	0.51	0.60	0.49	0.08	16.88	0.48
5 min	1.10	1.01	1.27	0.88	0.70	0.99	0.22	21.80	0.97
10 min	11.30	12.00	9.88	8.95	8.45	10.12	1.51	14.94	10.03
30 min	52.40	47.40	56.28	49.88	44.10	50.01	4.66	9.31	49.84
1 h	92.10	88.70	85.44	98.21	86.07	90.10	5.24	5.81	89.98
2 h	85.80	92.50	91.53	82.38	83.30	87.10	4.67	5.36	87.00
4 h	63.20	68.70	60.66	71.44	64.55	65.71	4.33	6.59	65.60
8 h	39.99	43.57	39.00	46.38	36.60	41.11	3.87	9.41	40.96
12 h	20.00	18.30	25.77	19.73	17.32	20.22	3.29	16.25	20.03
24 h	5.50	7.20	5.84	5.01	6.47	6.00	0.85	14.22	5.96
36 h	1.30	1.11	0.99	1.11	2.05	1.31	0.43	32.56	1.27

Table 1: concentration (ng Pretendalone per mL plasma) in five subjects following a 50 mg single oral dose.

Oral pretendalone application

- semilogarithmic plots
- mean \pm SD

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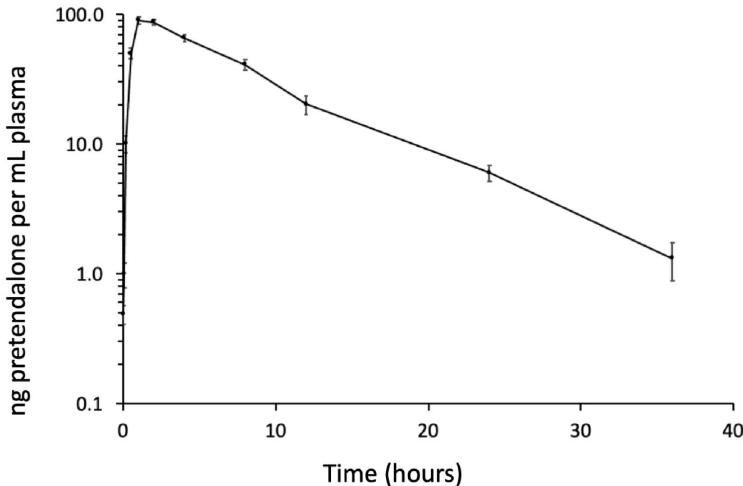


Figure 3: semi-log plot of time versus mean concentration (ng Pretendalone per mL plasma, n=5) following a 50 mg single oral dose. Error bars are \pm one standard deviation.

Absorption & elimination phase

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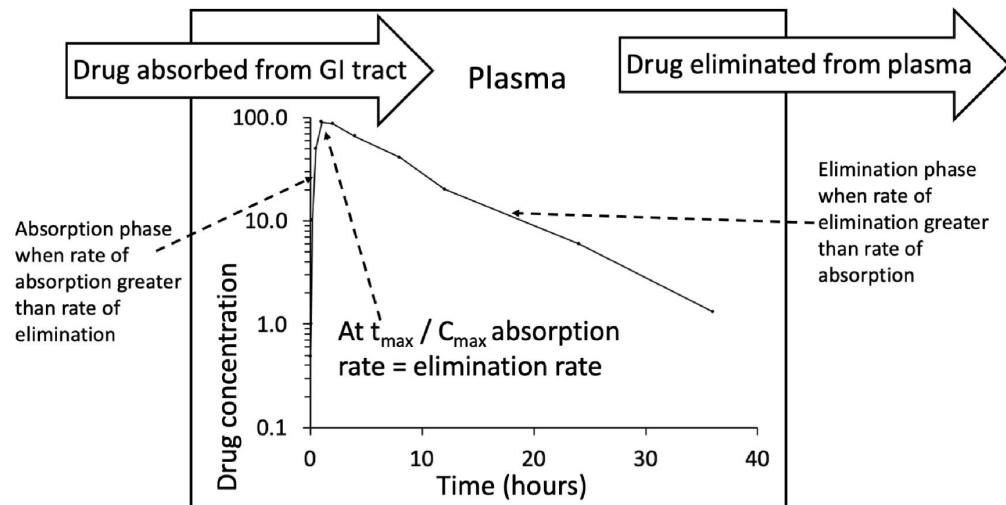


Figure 6: diagrammatic representation showing how the shape of the absorption and elimination phases are due to an equilibrium between the two processes.

Example parameters

- maximum time and concentration

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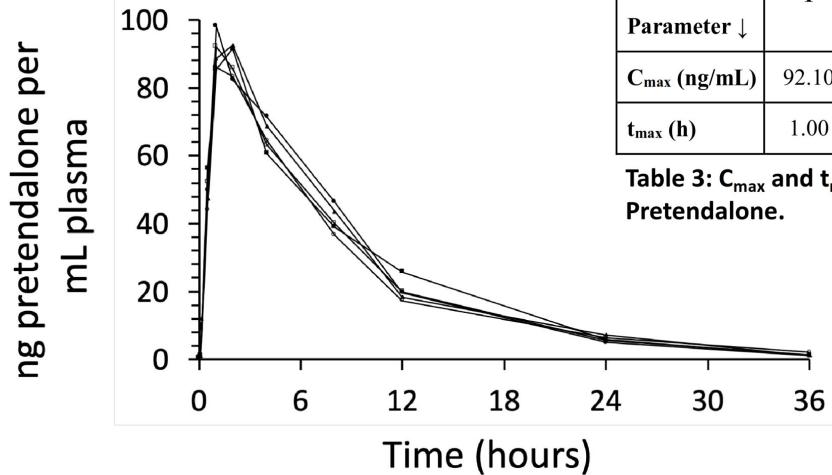


Table 3: C_{\max} and t_{\max} for five subjects receiving a single oral dose of 50 mg Pretendalone.



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

Elimination rate

- interpolation of concentration time-course

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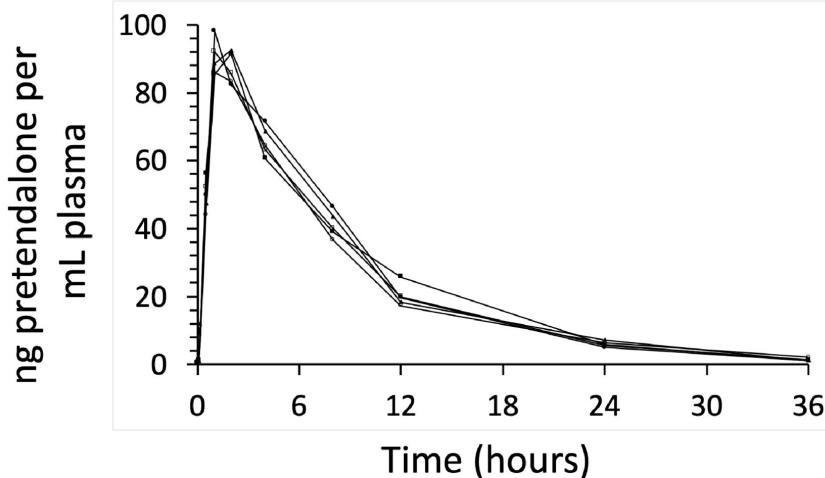


Figure 2: plot of time versus concentration (ng Pretendalone per mL plasma) for five subjects following a 50 mg single oral dose.

Subject	t_1 (h)	C_1 (ng/ml)	t_2 (h)	C_2 (ng/mL)	$k (h^{-1})$ from Equation 2
1	4	63.20	36	1.30	0.121
2	4	68.70	36	1.11	0.129
3	4	60.66	36	0.99	0.129
4	4	71.44	36	1.11	0.130
5	4	64.55	36	2.05	0.108
Mean					0.123
Std Dev					0.009
%CV					7.59

Table 4: calculation of the elimination rate constant for five subjects receiving a single oral dose of 50 mg Pretendalone.

Drug formulation

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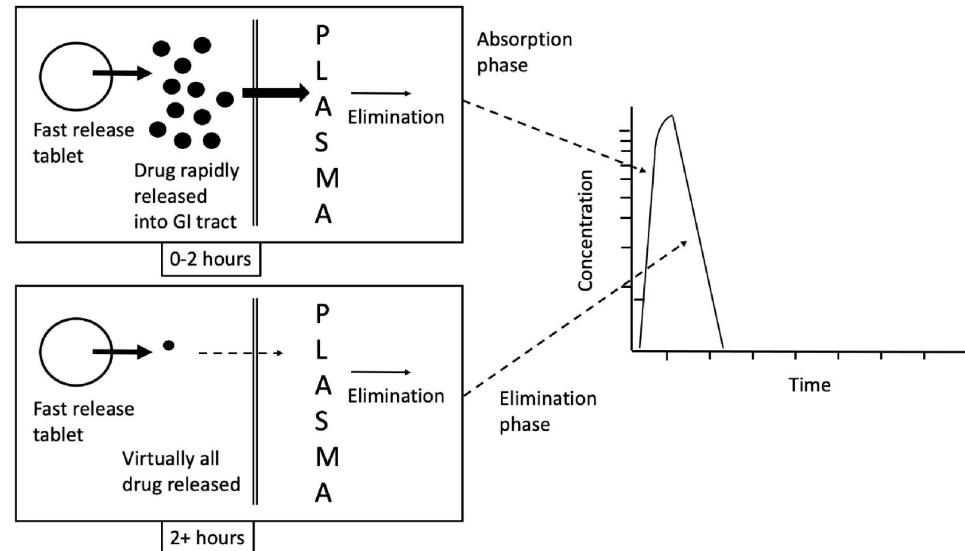


Figure 8: illustration of how the absorption and elimination phases are affected by rapid release of drug into the gastrointestinal tract (GI Tract).

Drug formulation

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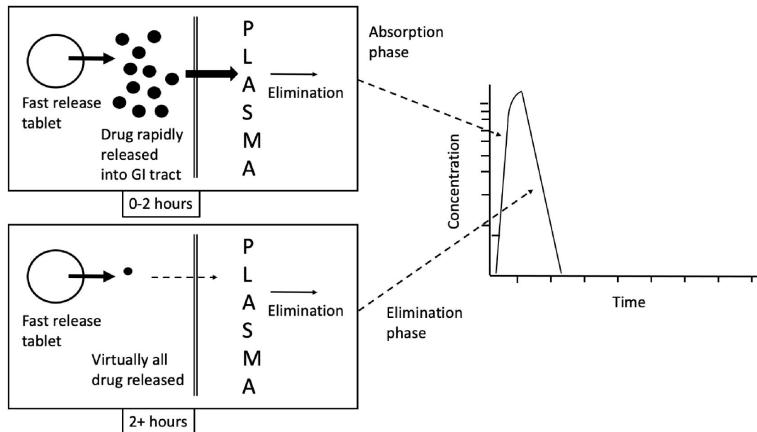


Figure 8: illustration of how the absorption and elimination phases are affected by rapid release of drug into the gastrointestinal tract (GI Tract).

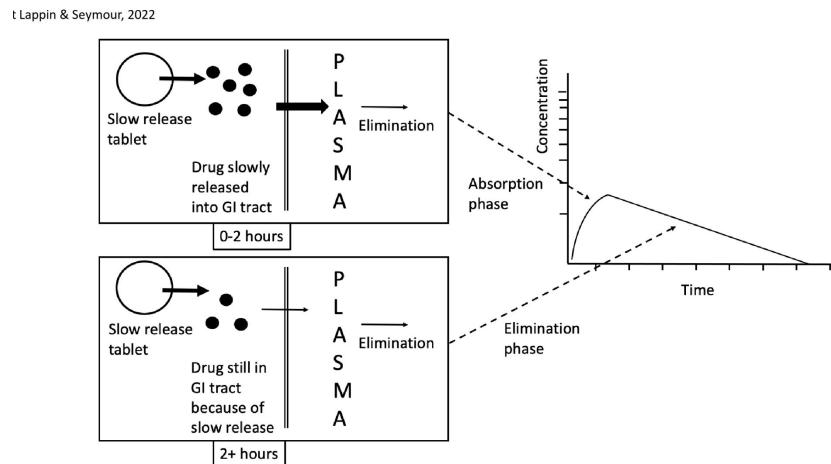


Figure 9: illustration of flip-flop kinetics caused by slow release of drug into the gastrointestinal tract (GI Tract).

Area under the curve (AUC)

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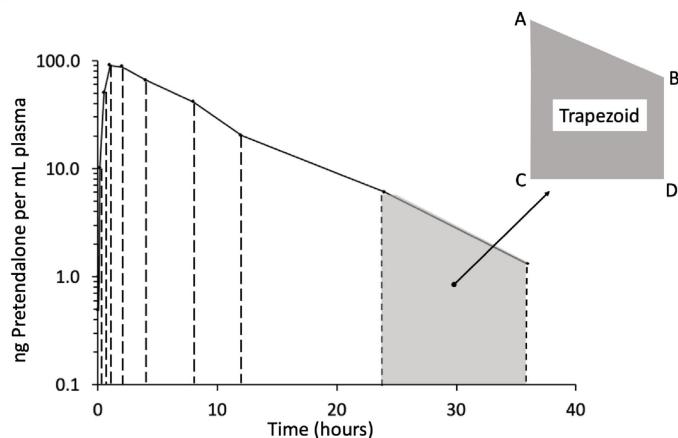


Figure 22: illustration of calculation of area of each trapezoid across the drug-concentration time plot using the linear trapezoidal rule.

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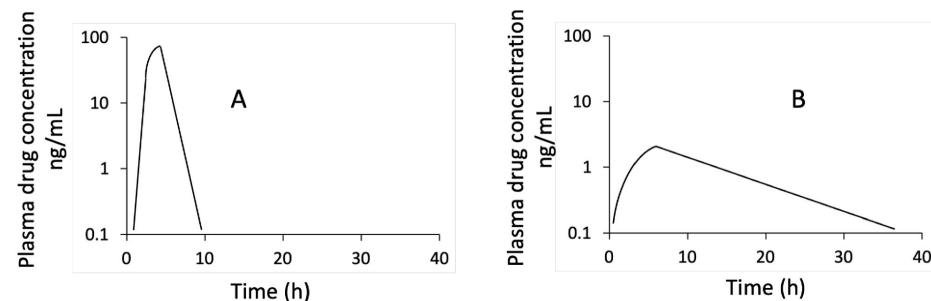


Figure 20: two pharmacokinetic curves of different shape but with the same AUC.

AUC extrapolation

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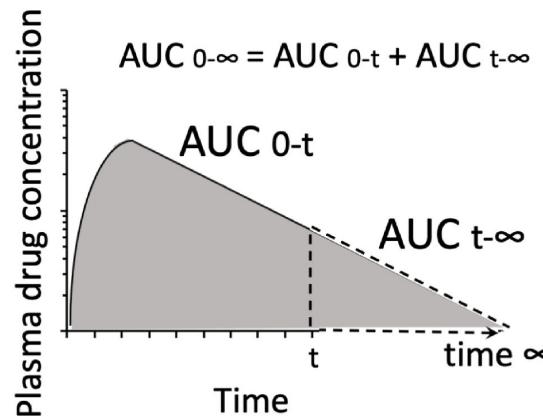
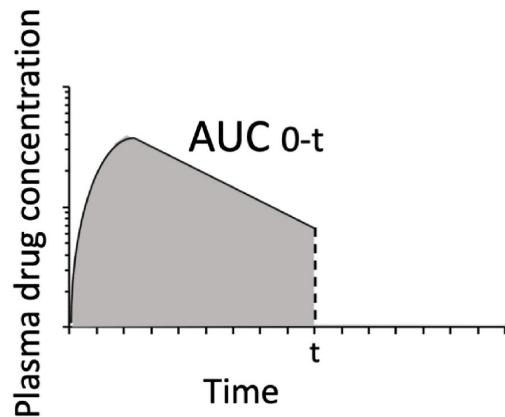


Figure 19: grey areas underneath the drug-concentration versus time curve are diagrammatic representations of areas under the curve with AUC_{0-t} (on the left) and $AUC_{0-\infty}$ (on the right) for a typical oral administration. Dotted lines on the right-hand plot represent extrapolation of AUC_{0-t}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

Volume of distribution (Vd)

- virtual volume based on dose and concentration

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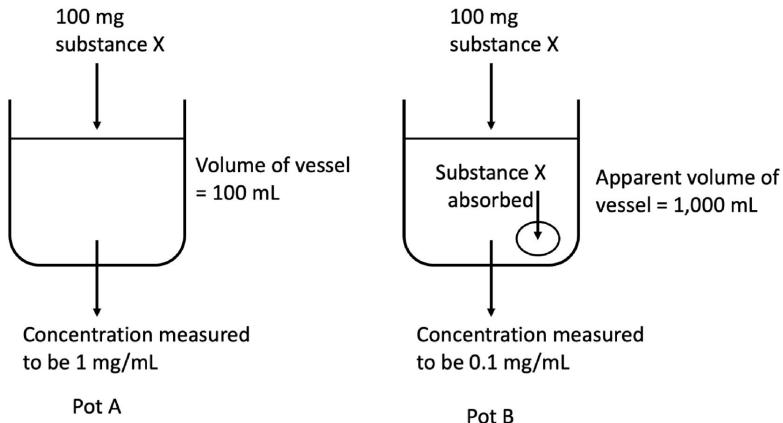


Figure 24: a model illustrating the concept of volume of distribution.

Drug	V (L)
Warfarin	9.8 ± 8.4
Paracetamol (acetaminophen)	70 ± 8.5
Morphine	230 ± 63
Verapamil	350 ± 147
Chloroquine	Approx 14,000
Cannabidiol	Approx 2,500

Table 15: volume of distribution for some selected drugs in humans.

Pharmacokinetic parameters (pretendalone)

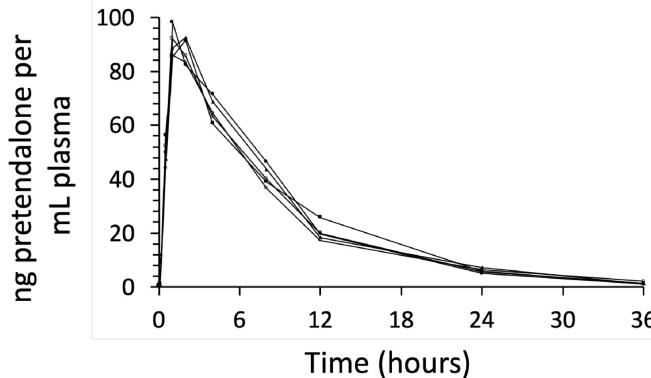


figure 2: plot of time versus concentration (ng Pretendalone per mL plasma) for five subjects following a 50 mg single oral dose.

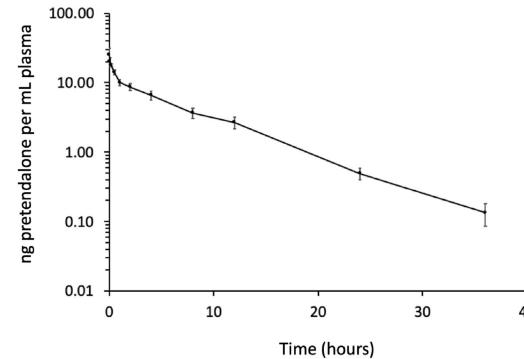


Figure 4: semi-log plot of time versus mean concentration (ng Pretendalone per mL plasma) following a 2 mg single bolus intravenous dose. Error bars are \pm one standard deviation (n=5).

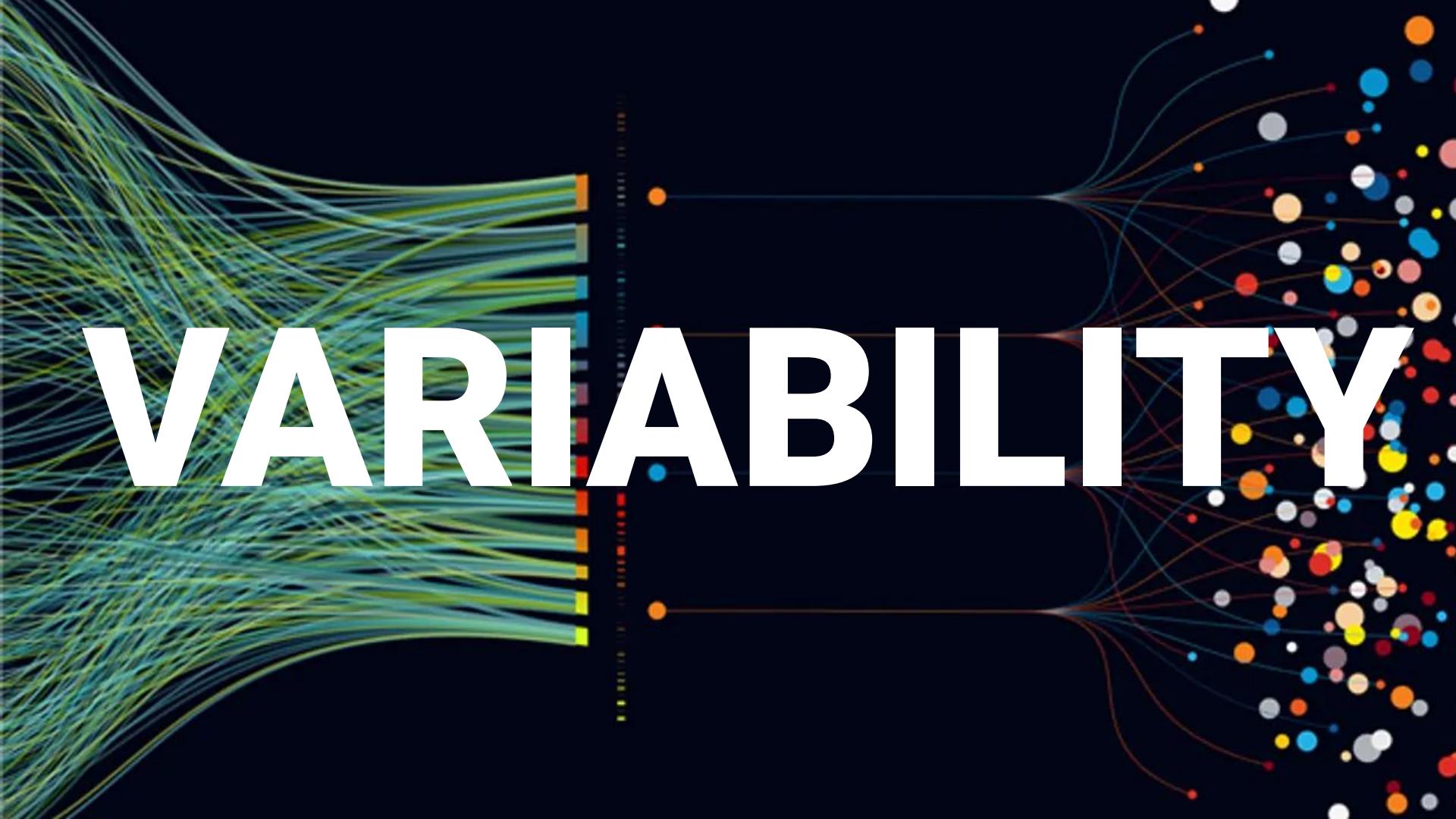
Pharmacokinetic parameter	Symbol	Unit	Mean	Standard Deviation
Maximum plasma drug concentration	C_{\max}	ng/mL	92.08	4.31
Time to C_{\max}	t_{\max}	h	1.4	0.55
Elimination rate constant	k	h^{-1}	0.123	0.009
Elimination half-life oral	$t_{1/2}$	h	5.64	0.46
Area under the plasma drug concentration time 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.

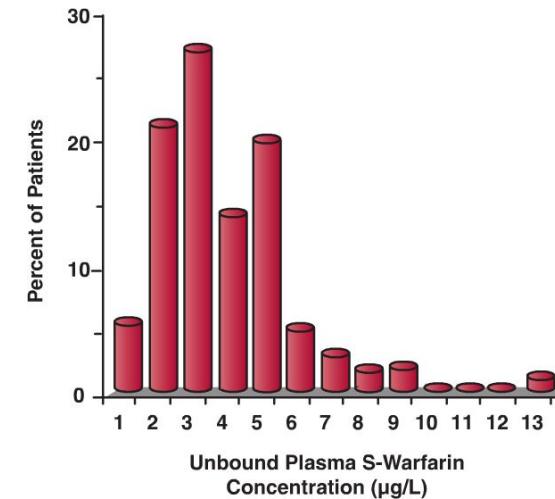
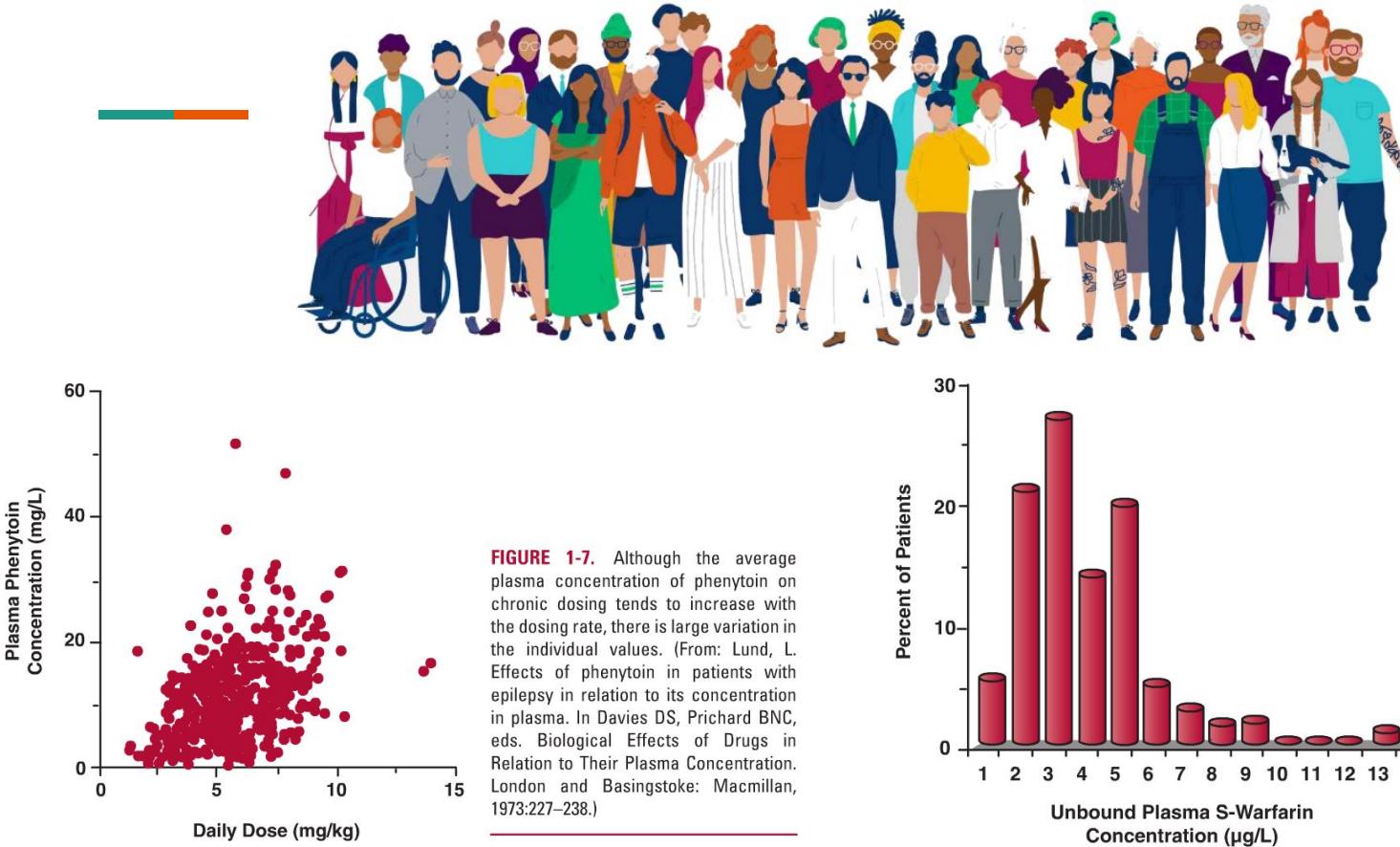
Pharmacokinetic parameter	Symbol	Unit	Mean	Standard Deviation
Elimination rate constant	k	h^{-1}	0.123	0.008
Elimination half-life	$t_{1/2}$	h	5.65	0.38
Area under the plasma drug concentration time curve between zero and 36 hours	AUC_{0-36}	ng/mL.h	90.00	4.76
Area under the plasma drug concentration 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)

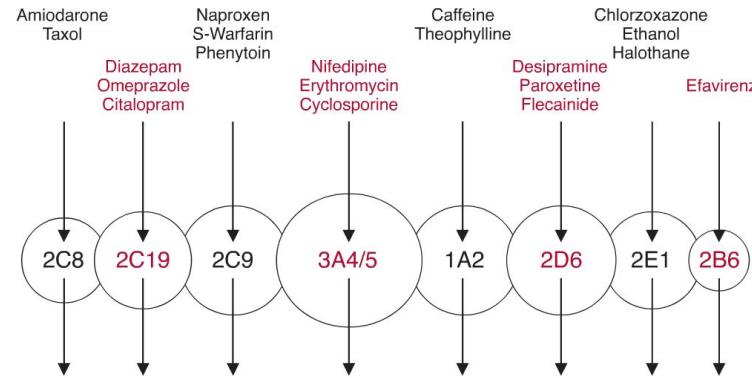
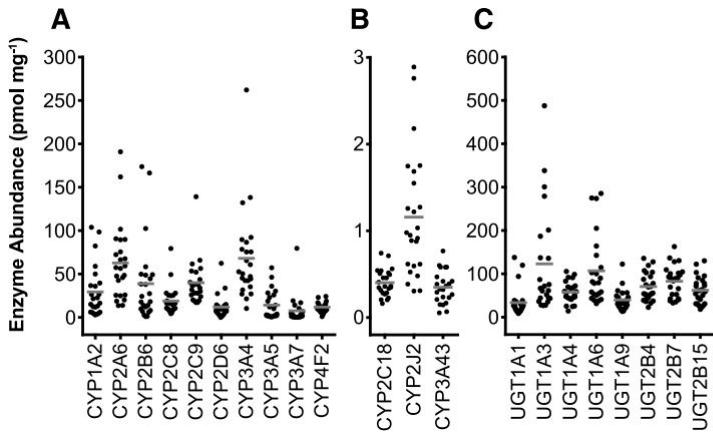


FIGURE 5-3. Graphic representation of the different forms of human cytochrome-P450 enzyme (circles) with different but often overlapping substrate specificities. The arrows indicate the single metabolic pathways. Representative substrates are listed above each enzyme.

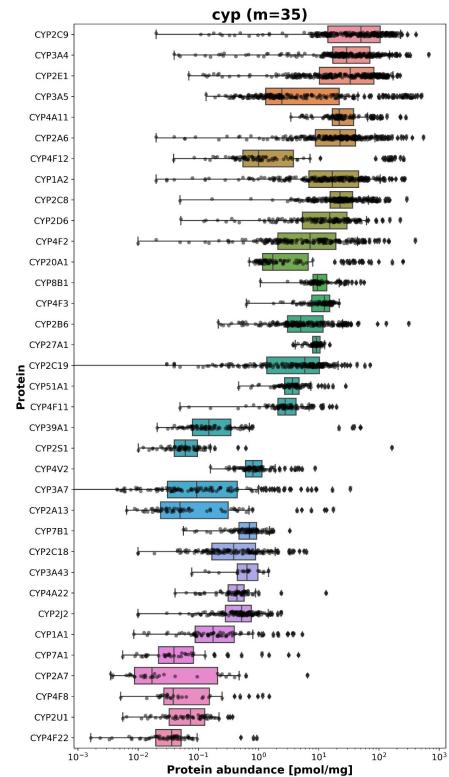
Fig. 2. A scatter plot of the measured abundance values of P450 (A and B) and UGT (C) enzymes. The number of samples is 24 for each enzyme except CYP2C9, CYP3A5, CYP3A7, CYP3A43, UGT1A3, UGT1A4, and UGT1A6 ($n = 23$). Lines indicate population means of the sets of data.

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

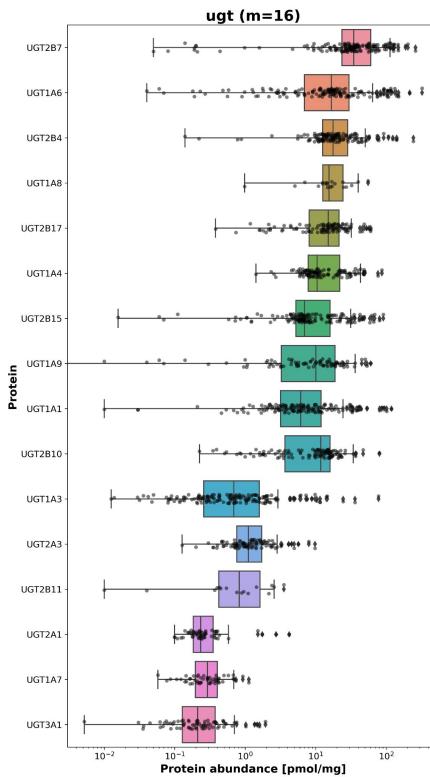
Achour B, Barber J, Rostami-Hodjegan A. **Expression of hepatic drug-metabolizing cytochrome p450 enzymes and their intercorrelations: a meta-analysis.** Drug Metab Dispos. 2014 Aug;42(8):1349-56. doi: 10.1124/dmd.114.058834. Epub 2014 May 30. PMID: 24879845.

Large variability & multitude of isoforms (Human Liver)

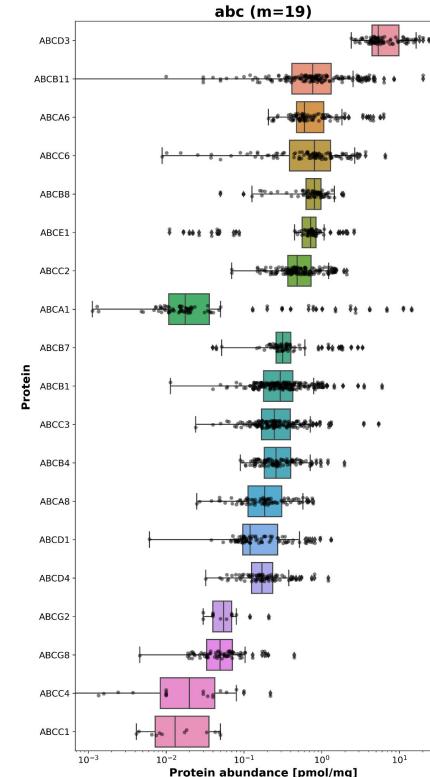
Cytochrome P450 (CYP)



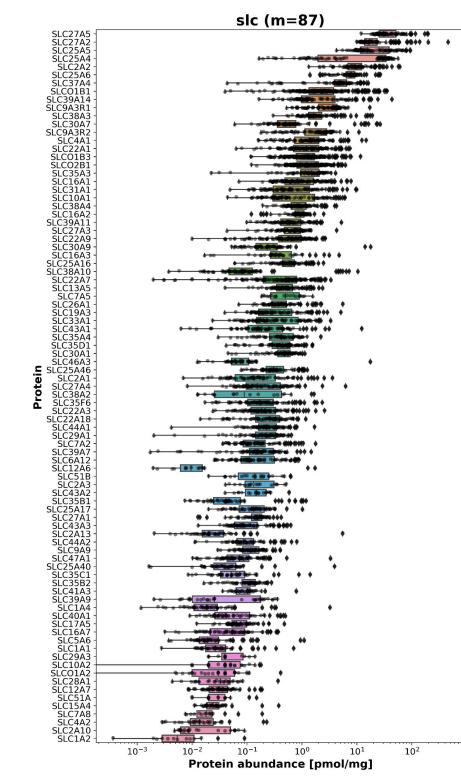
UDP-glucuronosyltransferases (UGT)



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

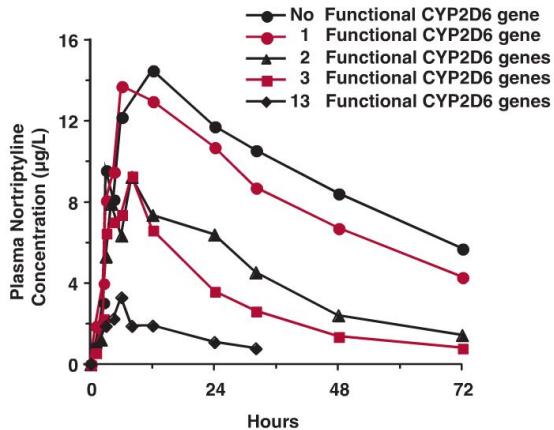


FIGURE 13-2. Strong genetic influence in the pharmacokinetics of nortriptyline is clearly demonstrated by the high correlation between the plasma concentration–time profile and the number of functional CYP2D6 genes possessed by an individual; the larger the number of functional genes, the higher is the 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.)

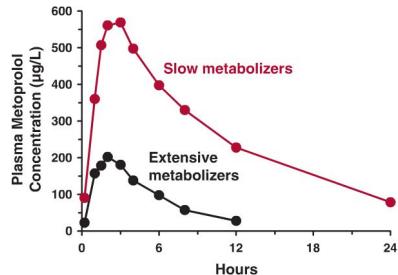


FIGURE 13-3. Plasma metoprolol concentrations after a single oral dose of 200-mg metoprolol tartrate were much higher in poor (colored line) than in extensive (black line) CYP2D6 metabolizers. Because metoprolol is a drug of high hepatic clearance, the difference between poor and extensive metabolizers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

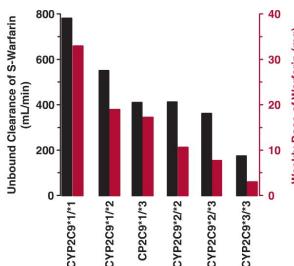
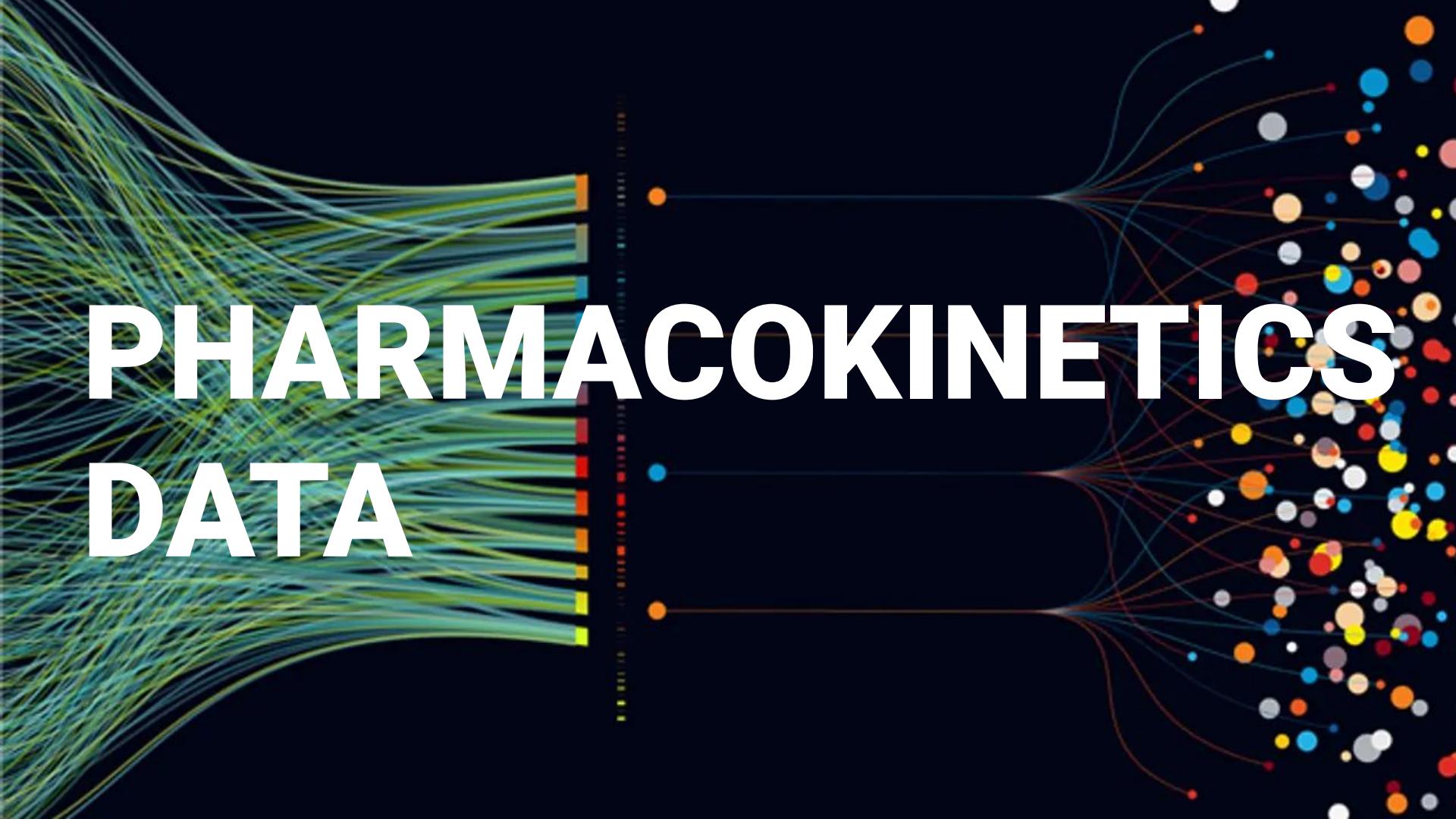
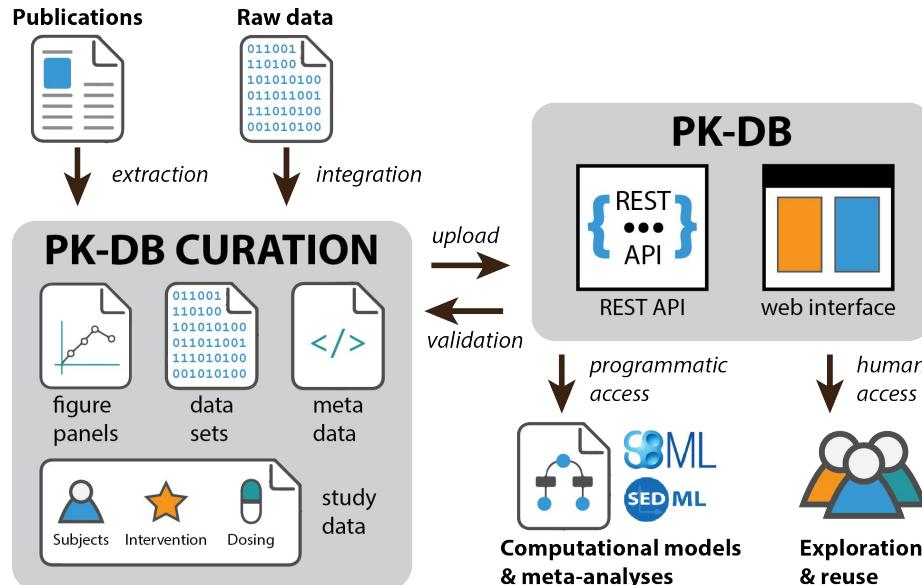


FIGURE 13-4. Genetics plays a significant role in the maintenance dose requirement of warfarin used in the treatment of various cardiovascular diseases. Shown are the unbound clearance of S-warfarin (black) in groups of patients with different CYP2C9 genotypes, all titrated and stabilized to a narrow 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.)

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.

Database for pharmacokinetics data (PK-DB)



Grzegorzevski 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/>

Our subjects were 13 normal males (age range 18 to 71 years; mean weight \pm S.D. 80.0 ± 12.18 kg), nine normal females not taking OCS (age range 22 to 33 years; mean weight \pm S.D. 58.0 ± 5.9 kg), and nine healthy females (age range 22 to 33 years; mean weight \pm S.D. 58.4 ± 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 (SMA₁₂) 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.

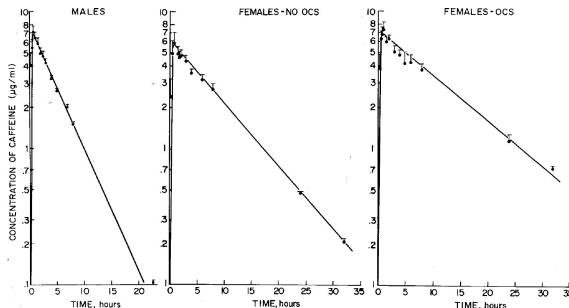


Fig. 1. Comparison of caffeine plasma concentration/time profiles in 13 healthy male subjects (left panel), nine healthy females taking no OCS (center panel), and nine healthy females on OCS (right panel) (mean \pm S.E.).

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)
$t_{1/2}(\beta)$ (hr)	5.5 ± 2.6	6.2 ± 1.6	$10.7 \pm 3.0^\dagger$
$V_d(\beta)$ (L/kg)	0.54 ± 0.18	$0.69 \pm 0.16^*$	0.72 ± 0.24
$V_d(\text{extrap})$ (L/kg)	0.54 ± 0.13	$0.70 \pm 0.14^*$	0.75 ± 0.28
Plasma clearance (ml/min/kg)	1.3 ± 0.42	1.3 ± 0.35	$0.79 \pm 0.21^\dagger$
Plasma binding (%)	31.4 ± 1.9	31.5 ± 4.5	29.35 ± 2.17
Plasma clearance of unbound drug (ml/min/kg)	1.8 ± 0.6	1.97 ± 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



Our subjects were 13 normal males (age range 18 to 71 years; mean weight \pm S.D. 80.0 ± 12.18 kg), nine normal females not taking OCS (age range 22 to 33 years; mean weight \pm S.D. 58.0 ± 5.9 kg), and nine healthy females (age range 22 to 33 years; mean weight \pm S.D. 58.4 ± 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 (SMA₁₂) 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.

Time courses

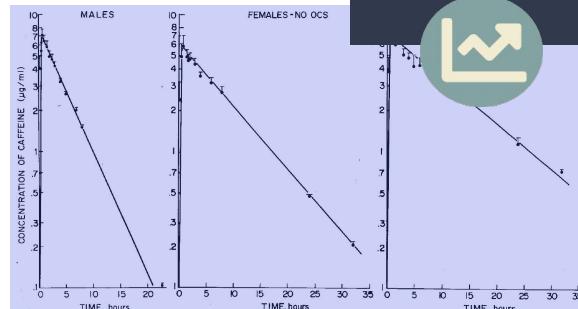


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Values are mean \pm S.D.

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

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

Outputs



Live Demonstration

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).

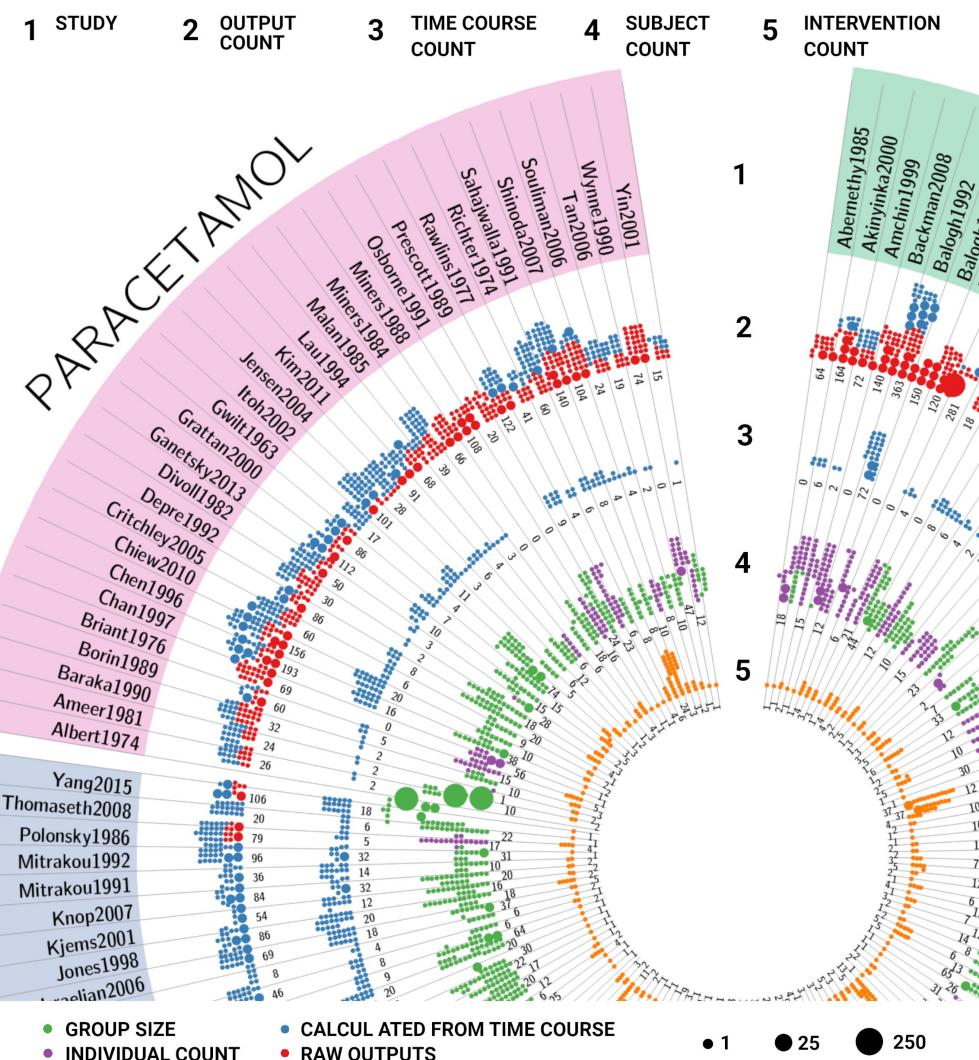
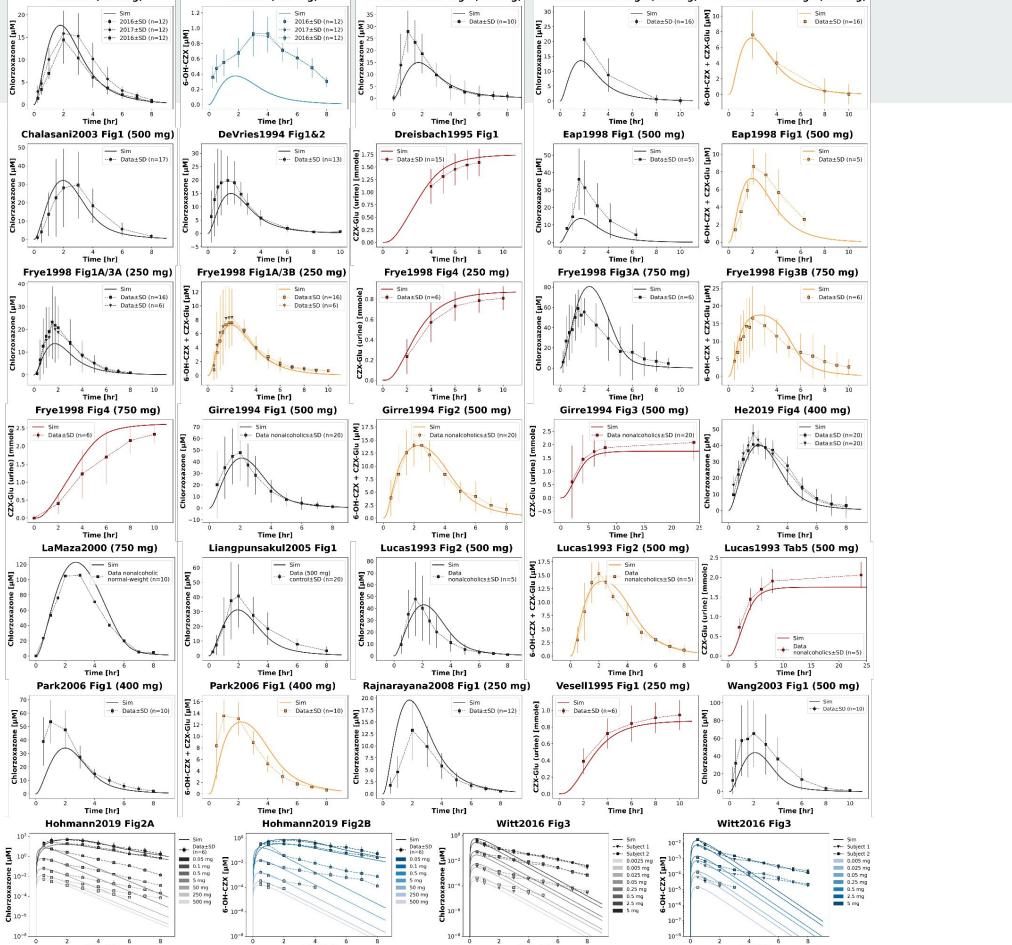


Table 1: Overview of curated clinical studies.

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	✓	
Ernstrand 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	750 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)	✓	

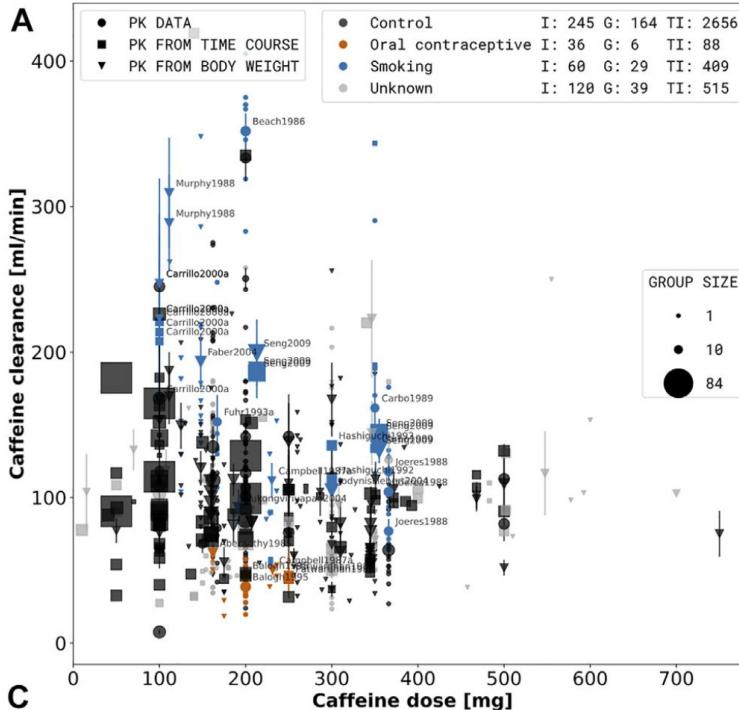
* 6-OH-CZX was measured without the chlorzoxazone-O-glucuronide.



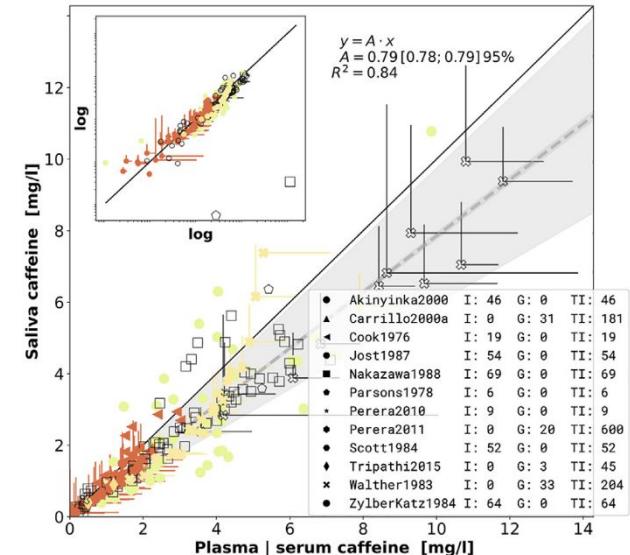
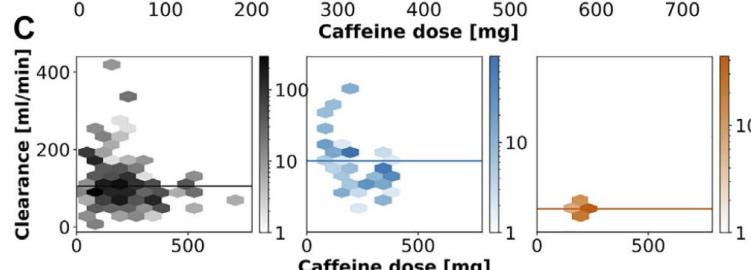
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pharmacokinetic
model
for
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Küttner,
Grzegorzewski,
bioRxiv 2023.04.12.536571 (preprint). doi:10.1101/2023.04.12.536571

Caffeine meta-analysis



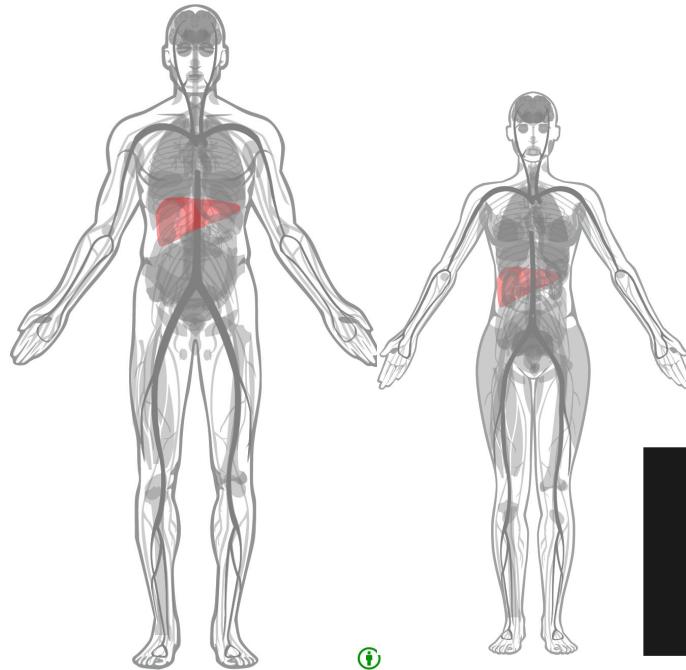
control
smoking
oral
contraceptives



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)

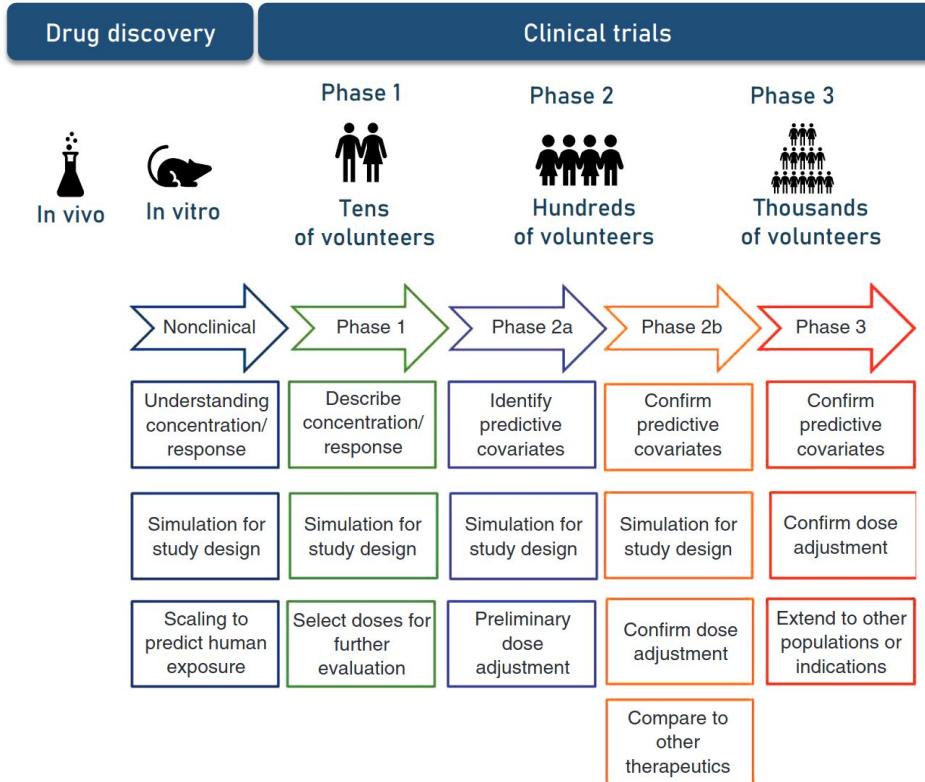
Grzegorzewski J, Brandhorst J, Green K, Eleftheriadou D, Duport Y, Barthoerscht F, Köller A, Ke DYJ, De Angelis S, König M. *PK-DB: pharmacokinetics database for individualized and stratified computational modeling* Nucleic Acids Res. 2020 Nov 5:gkaa990. doi: [10.1093/nar/gkaa990](https://doi.org/10.1093/nar/gkaa990).



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)(9):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.

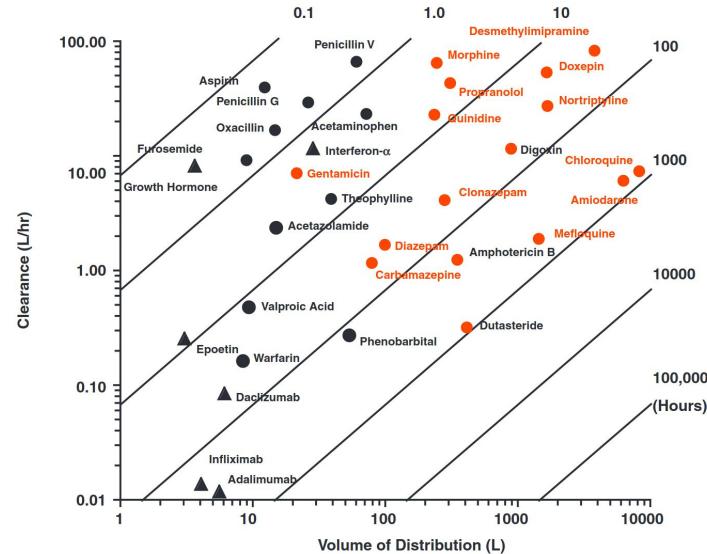


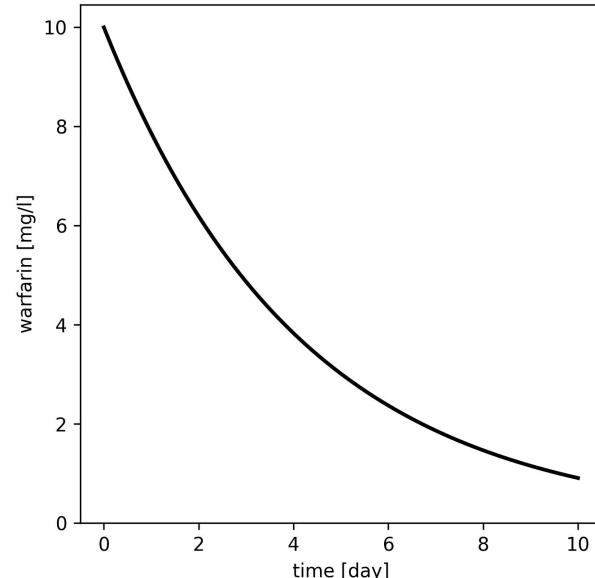
FIGURE 5-8 Clearance (ordinate) and volume of distribution (abscissa) of selected acidic (black circle) and basic (colored names), as well as protein (black triangle), drugs vary widely. Diagonal lines on the fully logarithmic plot show the combinations of clearance and volume values with the same half-lives (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.

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

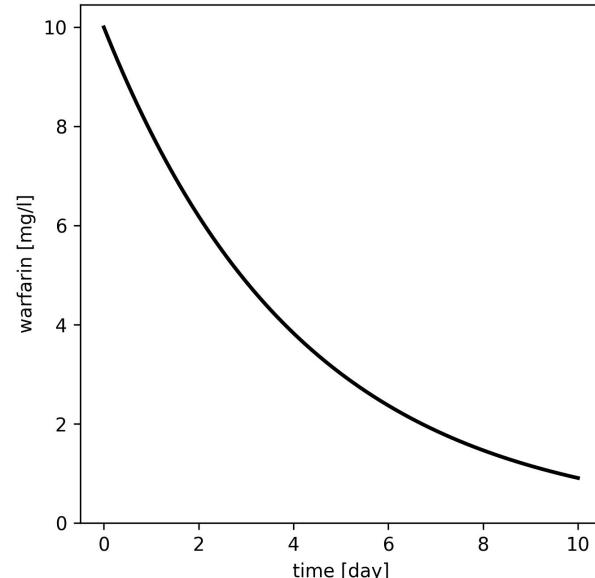


Structural models as algebraic equations

```
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]
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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.

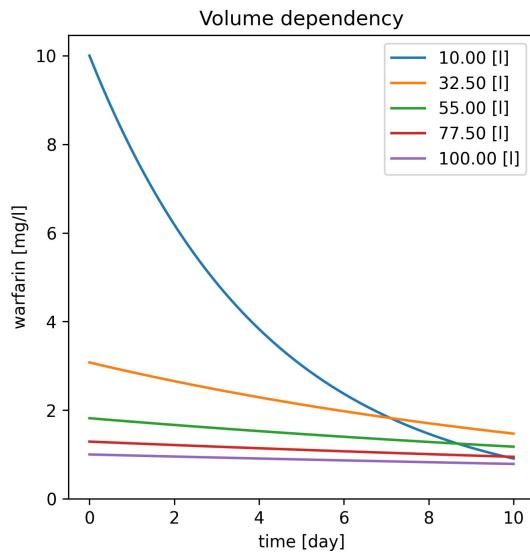
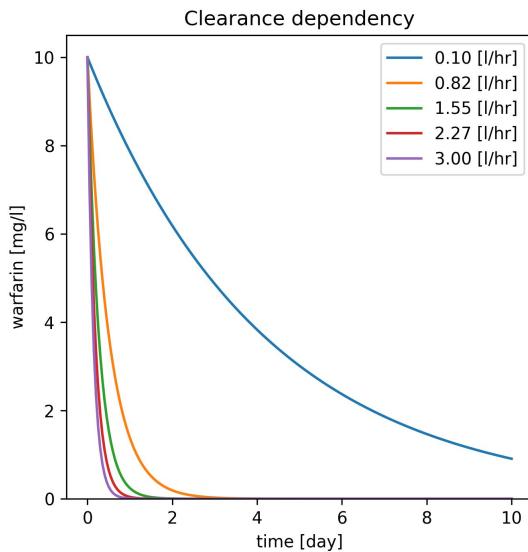
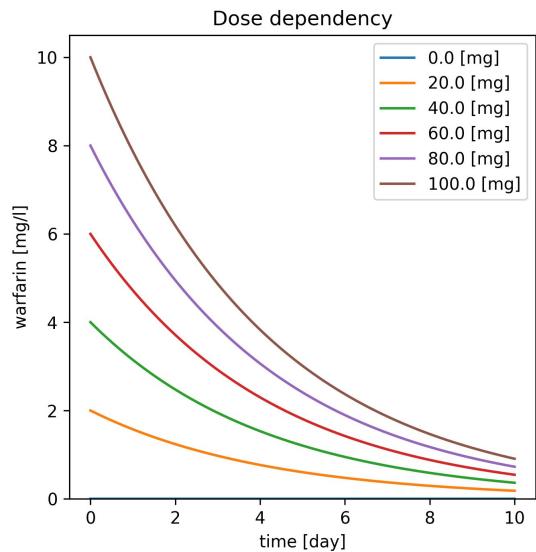
$$C_{(t)} = \frac{\text{Dose}}{V} e^{-\frac{CL}{V} \cdot t} \quad (1)$$



Parameter scans

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

(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)

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

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

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

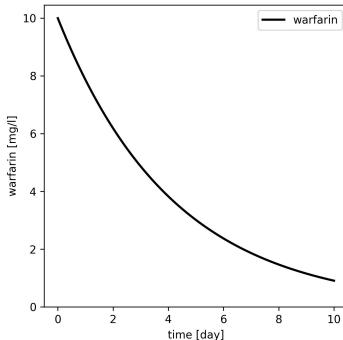
Mould DR, Upton RN. Basic concepts in population modeling, simulation, and model-based drug development. CPT Pharmacometrics Syst Pharmacol. 2012 Sep 26;1(9):e6. doi: 10.1038/psp.2012.4. PMID: 23835886; PMCID: PMC3606044.

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**

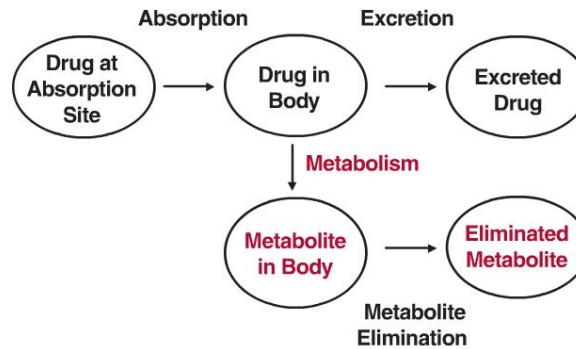


FIGURE 2-5. A drug is simultaneously absorbed into the body and eliminated from it, by excretion and metabolism. The processes of absorption, excretion, and metabolism are indicated with arrows and the compartments with ovals. The compartments represent different locations and different chemical species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

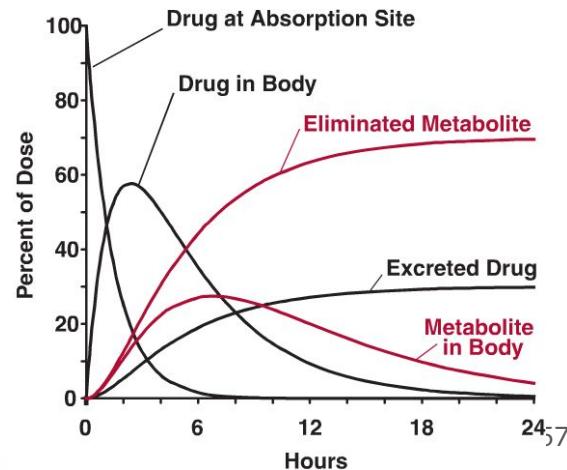


FIGURE 2-6. Time course of drug and metabolite in each of the compartments shown in Fig. 2-5. The amount in each compartment is expressed as a percentage of the dose administered. In this example, all the dose is absorbed. At any time, the sum of the molar amounts in the five compartments equals the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

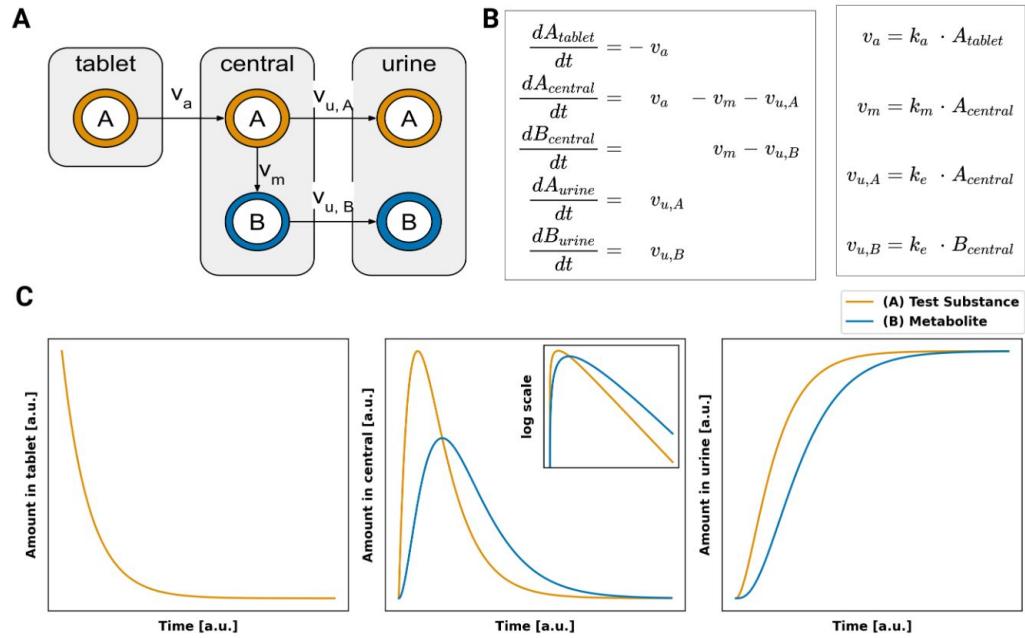


FIGURE 2.3: Simple ODE-based pharmacokinetics model. **A)** The system consists of three compartments (tablet, central, urine) that are connected via transport reactions. The model contains two substances the test substance A (orange); and the metabolite B (blue). The test substance A is metabolized 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.

Example absorption models

- A. first-order absorption with different rate of absorption
- B. first-order absorption with different lag-times
- C. Transit chain ($n=3$, different rates)
- D. Transit chain (different n)

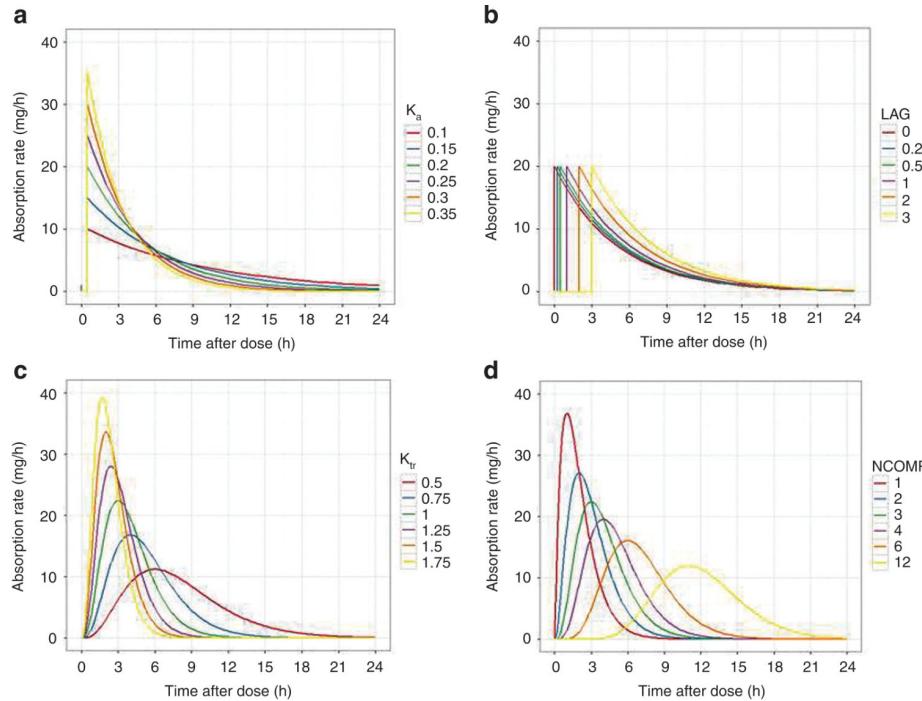
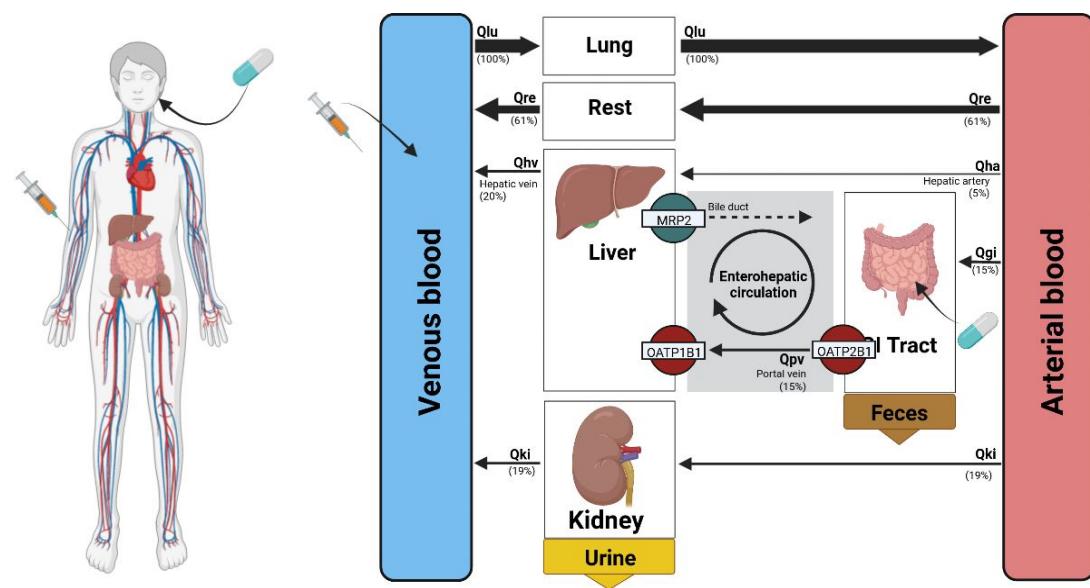


Figure 1 Models of extravascular absorption. The time profile of absorption rate for selected absorption models. (a) A first-order absorption model with different values of the absorption rate constant (K_a). Absorption lag was 0.5 h in all cases. (b) A first-order absorption model with different values of the absorption lag (LAG). Absorption rate constant was 0.5/h in all cases. (c) A three-compartment transit chain model with different values of the transit chain rate constant (K_{tr}). Note that decreasing the rate constant lowers the overall absorption rate and delays the time of its maximum value. (d) Transit chain models with different numbers of transit chain compartments (NCOMP). The transit chain rate constant was 1/h in all cases. Note that increasing the number of compartments introduces a delay before absorption, and functionally acts as a lag. The dose was 100 mg in all cases (hence the area under the curve should be 100 mg for all models).

Mould DR, Upton RN. Basic concepts in population modeling, simulation, and model-based drug development-part 2: introduction to pharmacokinetic modeling methods. CPT Pharmacometrics Syst Pharmacol. 2013 Apr;17(2):e38. doi: 10.1038/psp.2013.14. PMID: 23887688; PMCID: PMC3636497.

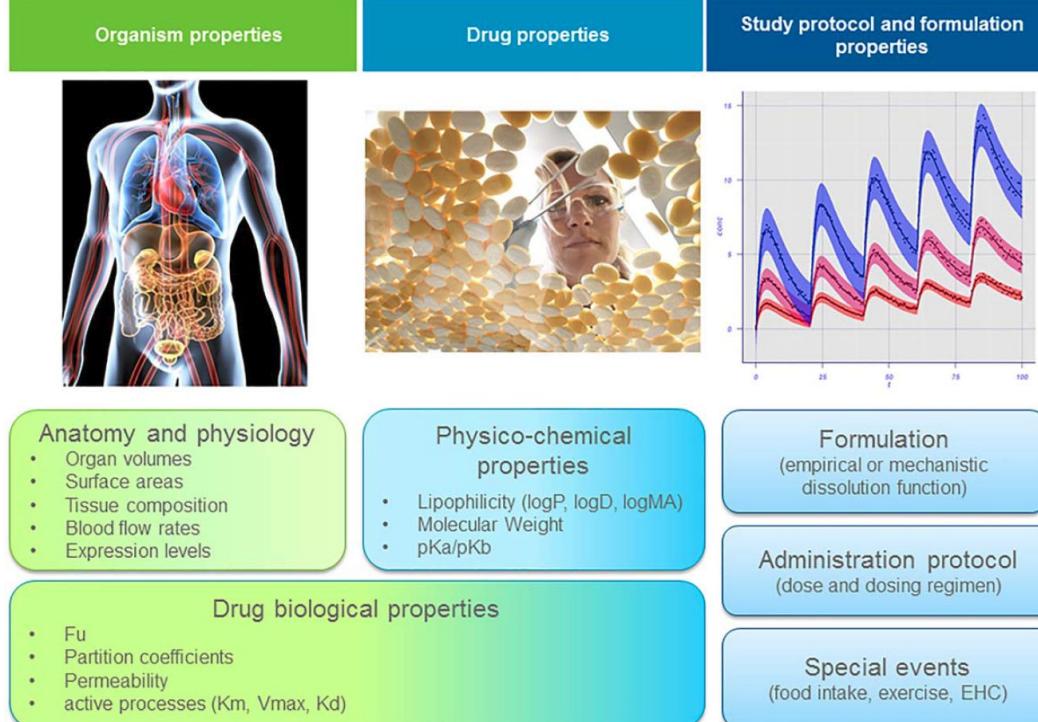
Physiologically based pharmacokinetics (PBPK) models

- **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

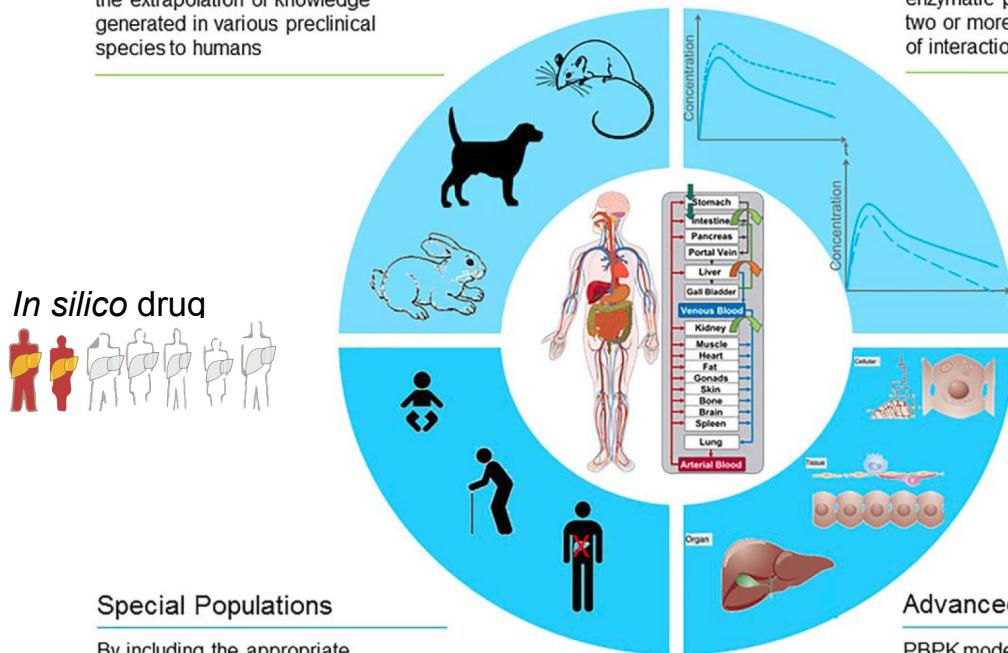
Parameters

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

PBPK Applications

Cross-Species Extrapolation

PBPK models can be used to facilitate the extrapolation of knowledge generated in various preclinical species to humans



Drug Drug Interactions (DDI)

Thanks of the explicit inclusion of enzymatic processes, the combination of two or more models allow the prediction of interaction between drugs

Individual Dosing

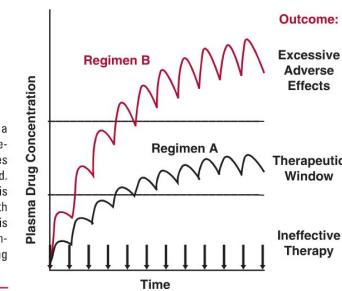


FIGURE 1-4. When a drug is given in fixed dose and at fixed time intervals (denoted by the arrows), it accumulates within the body until a plateau is reached. With regimen A, therapeutic success is achieved although not initially. With regimen B, the therapeutic objective is achieved more quickly, but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

Special Populations

By including the appropriate physiological information, PBPK models can be used to make predictions in special populations

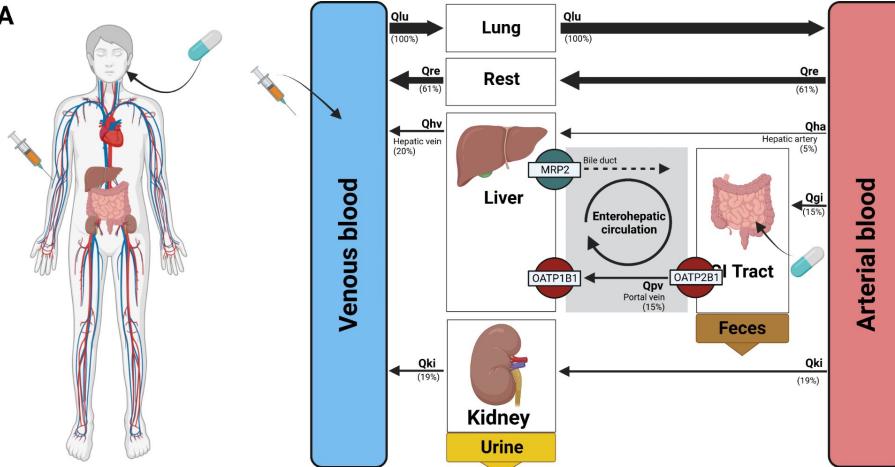
Advanced Applications

PBPK models can also be integrated in more complex models such as multiscale modelling or statistical modelling, using methods such as Bayesian approaches

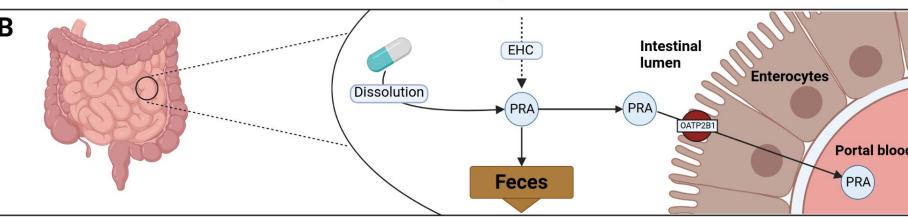
Figure 3 Schematic representation of the most common applications of PBPK modeling.

Pravastatin - Hepatorenal impairment

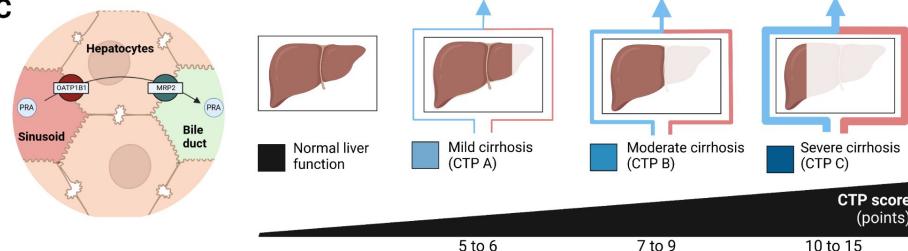
A



B



C

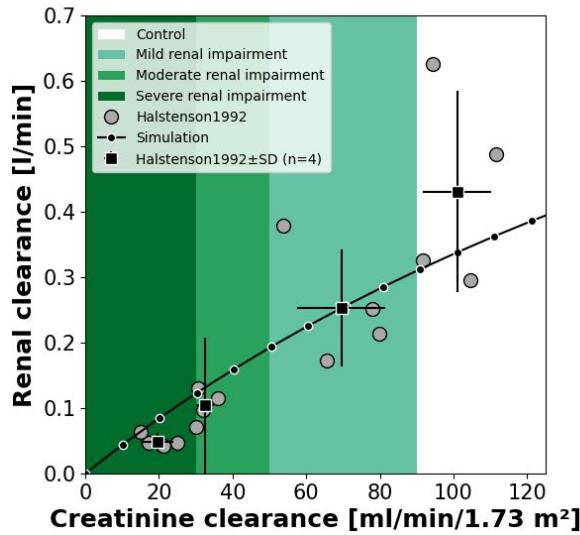
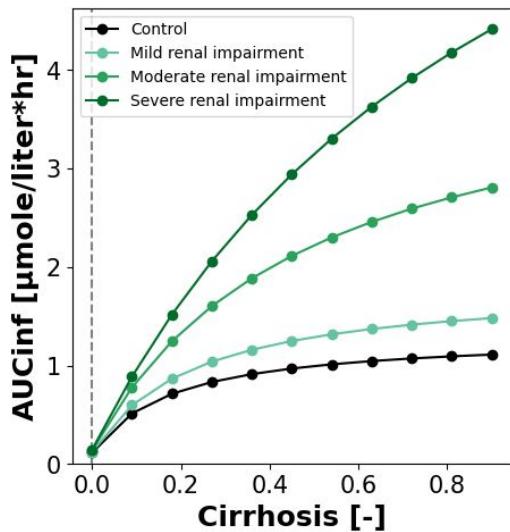
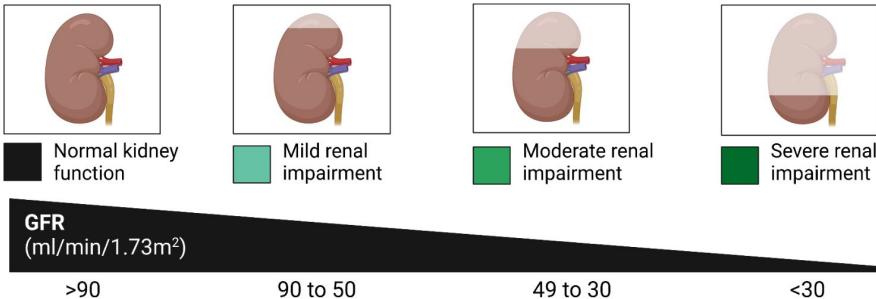
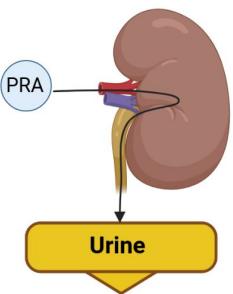


HL Pujol, J Grzegorzewski, F Bartsch, HM Tautenhahn,
M.König

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

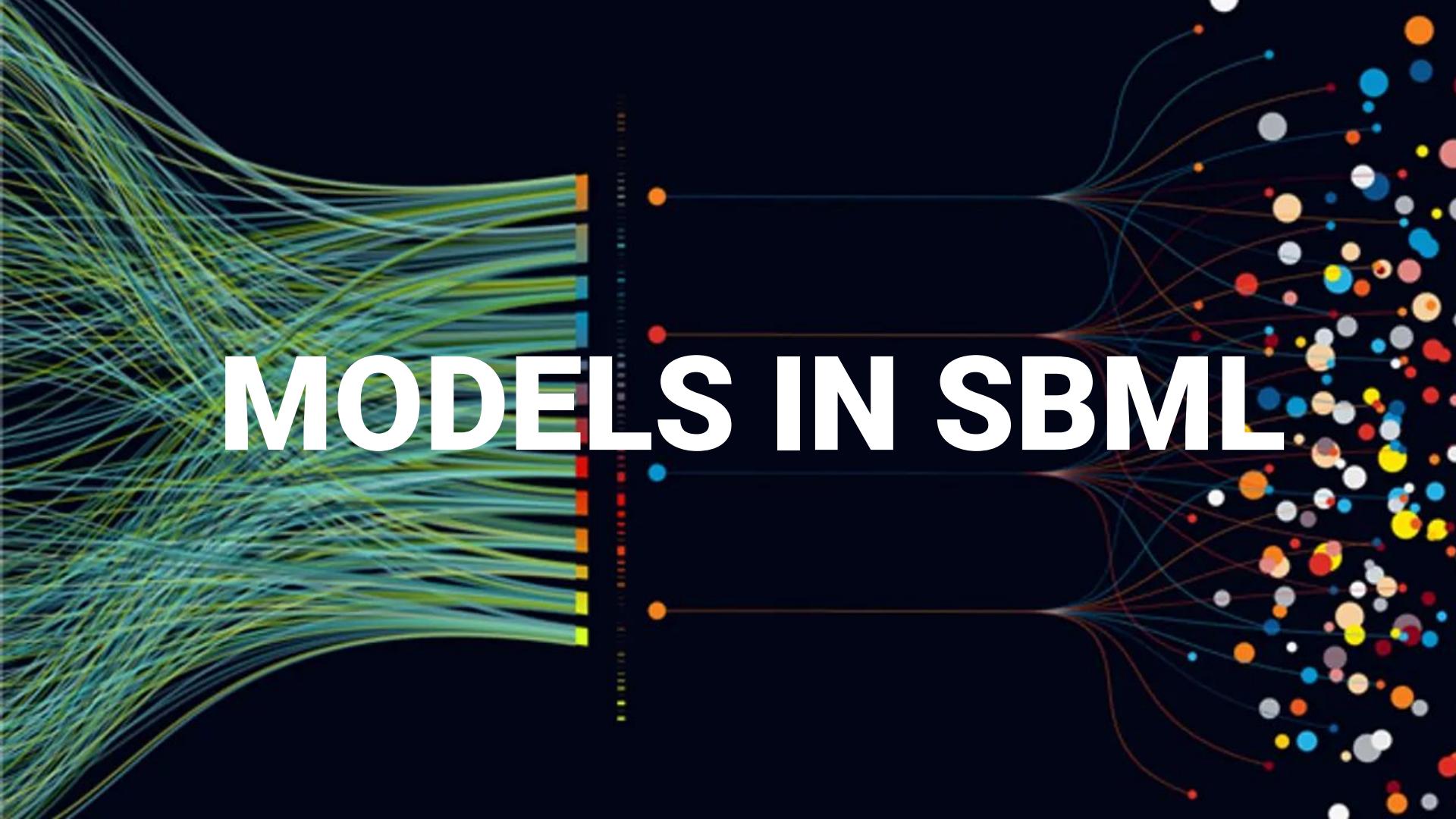
<https://www.youtube.com/watch?v=ddQYx4fGgRE>

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>

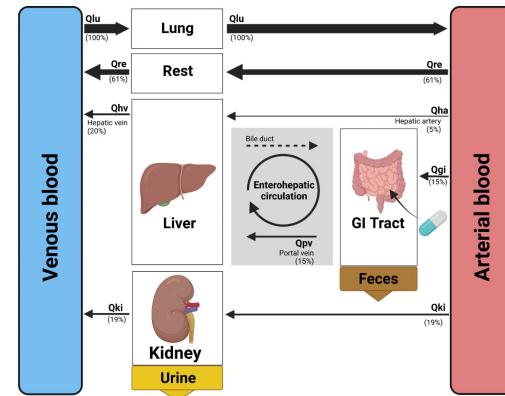
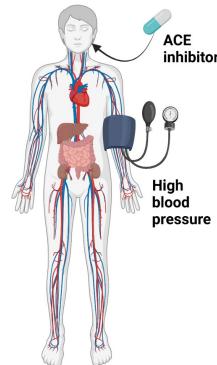
MODELS IN SBML

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

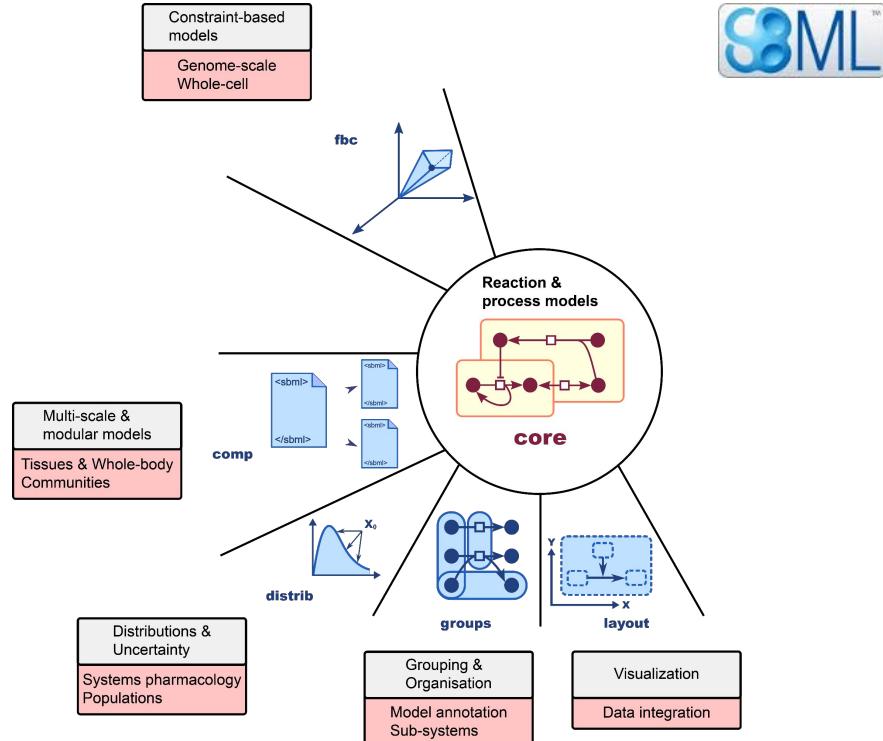


- SBML is a software data format for describing models in biology (<https://sbml.org>)
- It's a little like HTML but for model instead of web pages
- independent of any particular tool
- free and open
- De facto standard

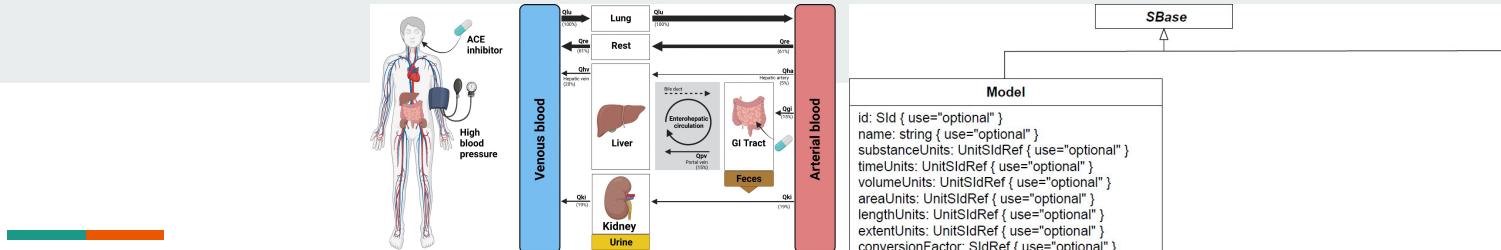


SBML

- 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/height²)
- Reactions
 - processes converting species in other species (e.g. enzymatic conversion; e.g. transport via blood flow)



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

Parameter

HCT hematocrit

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

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)

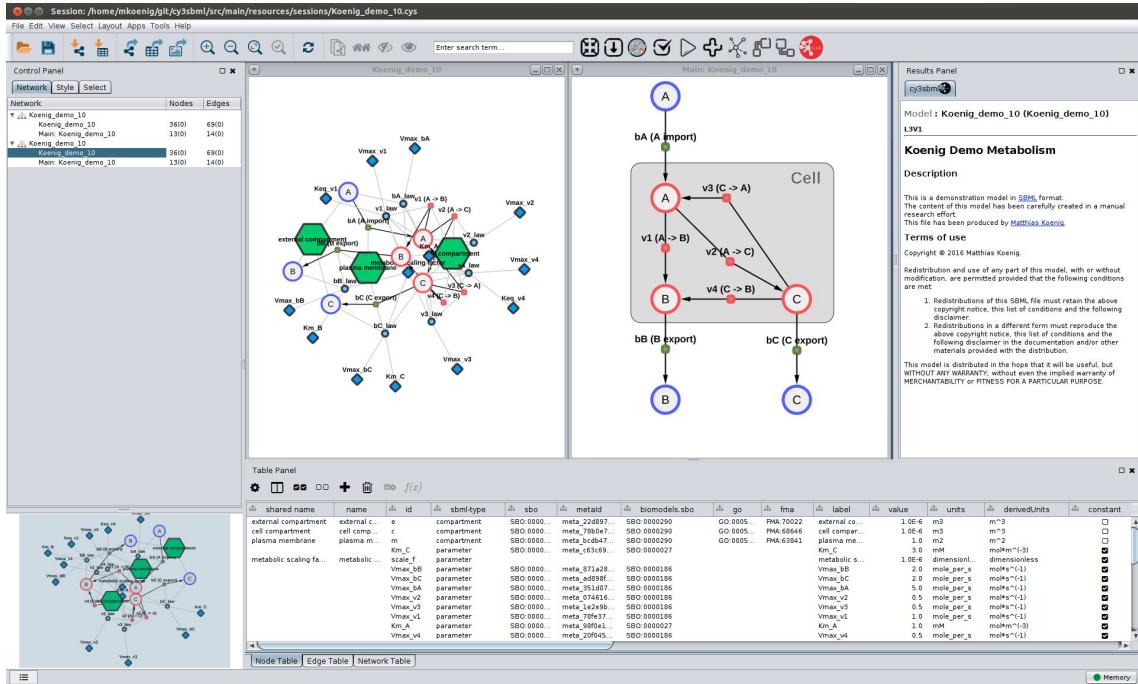
id	name	variable	math	derivedUnits
Vve	Vve		$(1 - HCT) \cdot (BW \cdot FVee - FVar \cdot FVee \cdot FVpo + FVve \cdot BW \cdot Fblood - (FVar + FVee + FVpo + FVhv))$	t
Var	Var		$(1 - HCT) \cdot (BW \cdot FVar - FVar \cdot FVee \cdot FVpo + FVve \cdot BW \cdot Fblood - (FVar + FVee + FVpo + FVhv))$	t
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

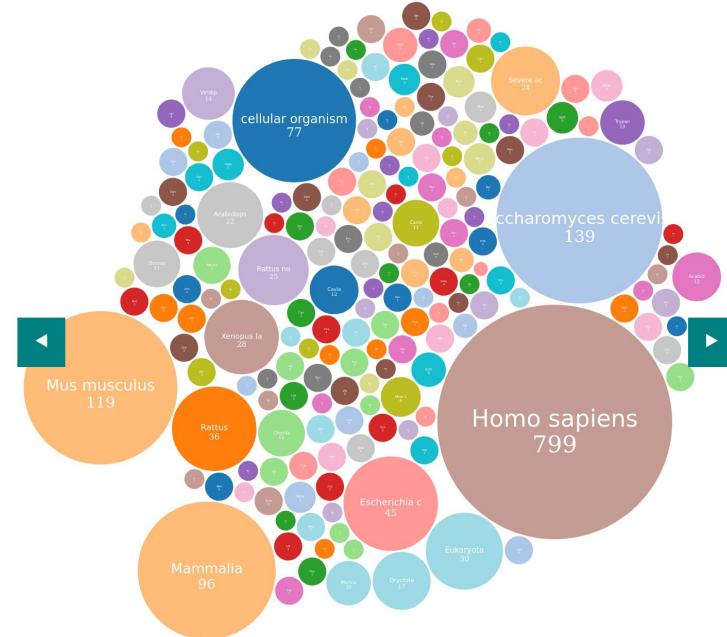
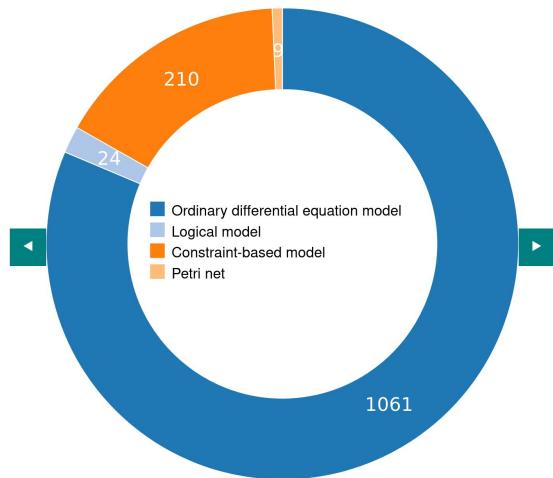
- kinetic & reaction-species view
- subgraphs & filtering
- annotation support
- works for large scale networks (genome-scale)
- sbmlutils integration (py2cytoscape)



Biomodels

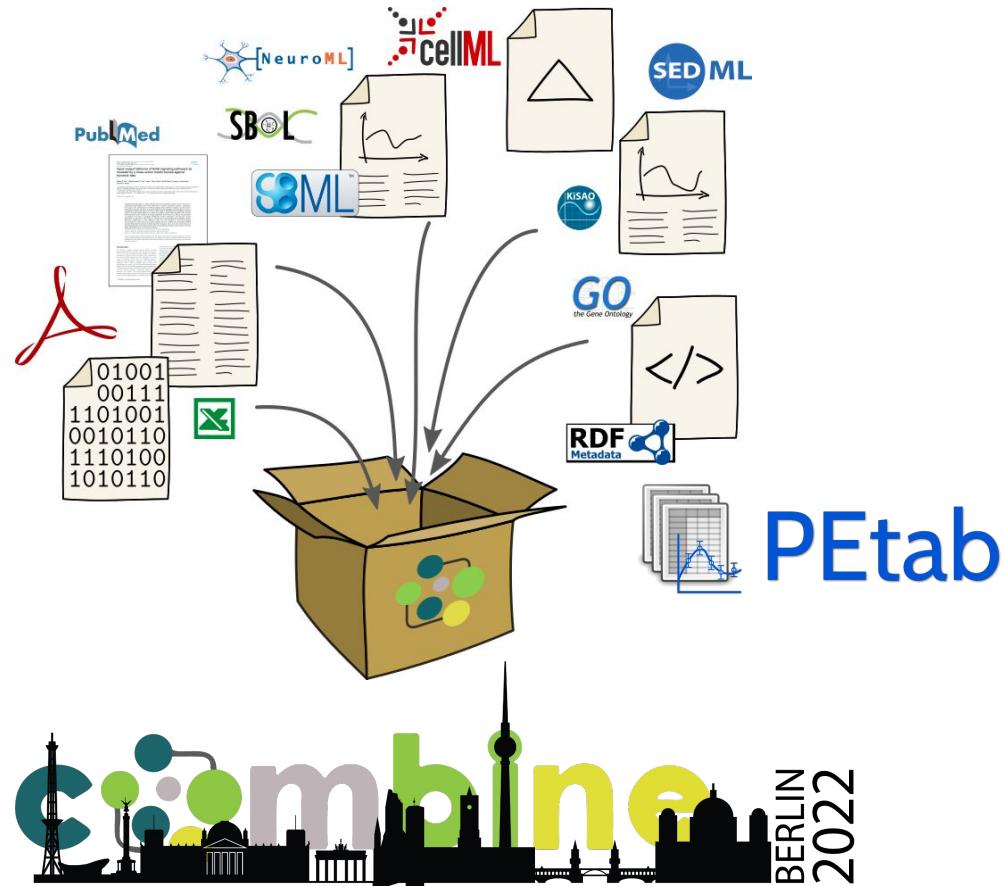


- collection of available models
<https://www.ebi.ac.uk/biomodels/>
 - curated and non-curated models



COMBINE Standards

- **SBML**
 - reproducible models
- **COMBINE archive**
 - packaging & distribution
- **SED-ML**
 - simulation experiments
- **OMEX metadata**
 - annotation
- **PETab**
 - parameter fitting



FAIR Models & Data (CC-BY)

<https://github.com/dextromethorphan-model>

SBML4Humans

OMEX
manifest.xml
model.xml

SEARCH
Search

COMPONENTS
SBMLDocument (1)
Model (1)
Compartment (38)
Species (77)
Parameter (325)
AssignmentRule (200)
RateRule (3)
Reaction (98)
UnitDefinition (74)

Parameter (325)

id	name	constant	value	units	derivedUnits	assignment
BW	body weight [kg]	✓	75	kg	kg	
HEIGHT	height [cm]	✓	170	cm	cm	
HR	heart rate [1/min]	✓	70	1/min	1/min	
HRrest	heart rate (resting) [1/min]	✓	70	1/min	1/min	
BSA	body surface area [m ²]	✓	0	m ²	m ²	$BSA = \frac{0.024265 \cdot (BW^{\frac{0.5375}{1}} \cdot (HEIGHT^{\frac{0.9941}{1}}))}{0.024265 \cdot (BW^{\frac{0.5375}{1}} \cdot (HEIGHT^{\frac{0.9941}{1}}))}$
COB	cardiac output per bodyweight [ml/s/kg]	✓	1.548	ml/s/kg	ml/s/kg	
CO	cardiac output [ml/s]	✓	108.33	ml/s	ml/s	$CO = BW \cdot COB + \frac{(HR - HR_{rest}) \cdot COB}{60}$
QC	cardiac output [L/hr]	✓	6499800	1/min	1/min	$QC = \frac{CO}{60} \cdot 60$
COHRI	increase of cardiac output per heartbeat [ml/min*min]	✓	150	ml	ml	
Fblood	blood fraction of organ volume	✓	0.02	—	—	

AssignmentRule (200)

id	name	variable	math	derivedUnits
dmx_dxo_plasma	dmx_dxo_plasma	C_{dxo}	C_{dxo}	—
dxo_total_plasma	dxo_total_plasma	$C_{dxo} + C_{fov_dxo_glu}$	$\frac{mmol}{l}$	—
dxa_dxo_total_plasma	dxa_dxo_total_plasma	$C_{dxo} + C_{fov_dxo_glu}$	$\frac{mmol}{l}$	—
dxo_total_rev	dxo_total_rev	$C_{rxv_dxo} + C_{fov_dxo_glu}$	$\frac{mmol}{l}$	—
dxa_dxo_rev	dxa_dxo_rev	C_{rxv}	$\frac{mmol}{l}$	—
dxa_dxo_total_rev	dxa_dxo_total_rev	$C_{rxv} + C_{fov_dxo_glu}$	$\frac{mmol}{l}$	—
dxa_dxo_total_fov	dxa_dxo_total_fov	C_{fov}	$\frac{mmol}{l}$	—
dxa_dxo_fov	dxa_dxo_fov	$C_{fov} + C_{fov_dxo_glu}$	$\frac{mmol}{l}$	—
dxa_dxo_urine	dxa_dxo_urine	A_{urine}	$\frac{mmol}{l}$	—

RateRule (2)

<https://matthiaskoenig.github.io/dextromethorphan-model/>

Code Issues Pull requests Actions Projects Security Insights

main 1 branch 2 tags

Code

matthiaskoenig updated

Parameter
QC cardiac output [L/hr]

id	metaID	name	sbo	value	constant	units	derivedUnits	assignment
QC	meta_QC	cardiac output [L/hr]	SBO_00000000	6499800	✓	1/min	1/min	$QC = \frac{CO}{60} \cdot 60$

cvtterms
BQB_IS sbo SBO_00000002 quantitative systems description parameter A quantitative 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.

README.md

RELEASE.md

DOI 10.5281/zenodo.6976102

Dextromethorphan Physiologically Based Pharmacokinetic (PBPK) Model

This repository provides the dextromethorphan physiologically based pharmacokinetics (PBPK) model.

The model is distributed as SBML available from [dextromethorphan_body_flat.xml](#) with corresponding SBML4humans model report at https://sbml4humans.de/model_url?url=https://raw.githubusercontent.com/matthiaskoenig/dextromethorphan-model/main/models/dextromethorphan_body_flat.xml

König* M, Grzegorzewski J, Golebiewski M., Hermjakob H, Hucka M, Olivier B, Keating SM, Nickerson D, Schreiber F, Sheriff R, Waltemath D
Ten Simple Rules for FAIR Sharing of Experimental and Clinical Data with the Modeling Community
Preprints 2021, 2021080303, doi: 10.20944/preprints202108.0303.v2

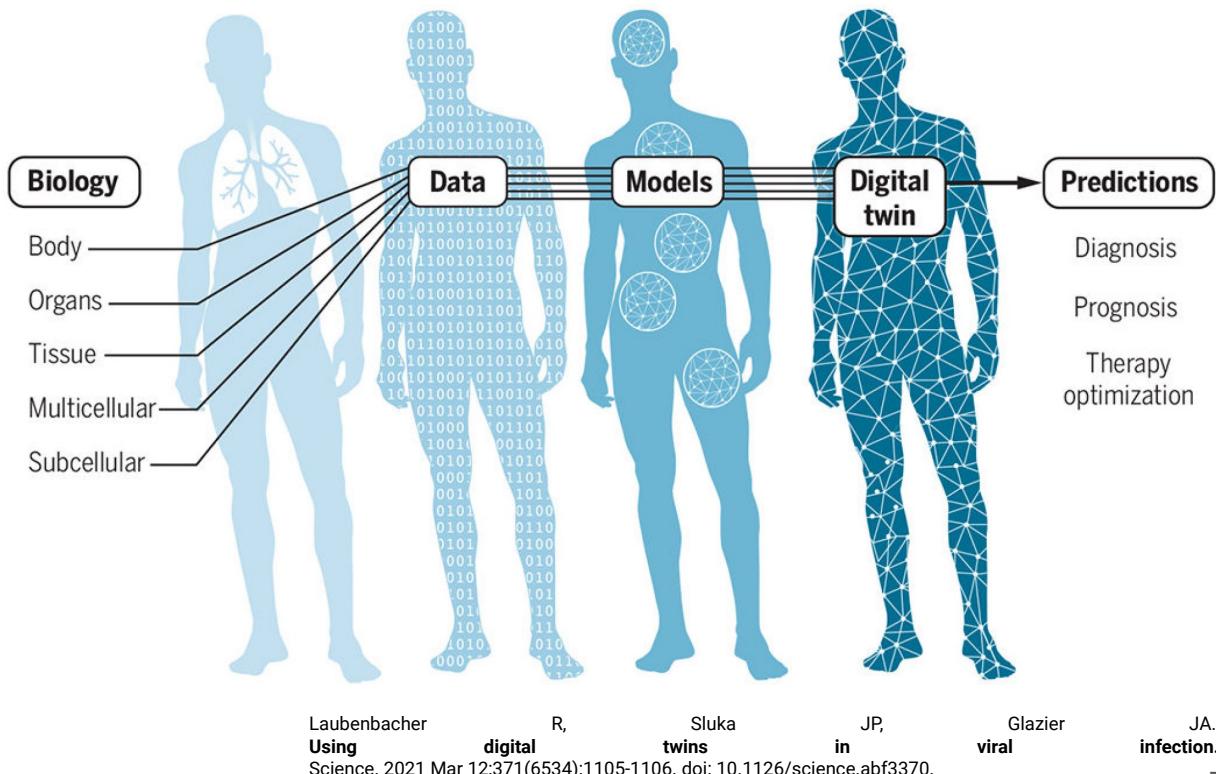
Ramachandran, K.*; König, M.*; Scharf, M.; Nguyen, T.V.N.; Hermjakob, H.; Waltemath, D.; Malik Sheriff, R.S. (* equal contribution)
FAIR Sharing of Reproducible Models of Epidemic and Pandemic Forecast
Preprints 2022, 2022060137 (doi: 10.20944/preprints202206.0137.v1).

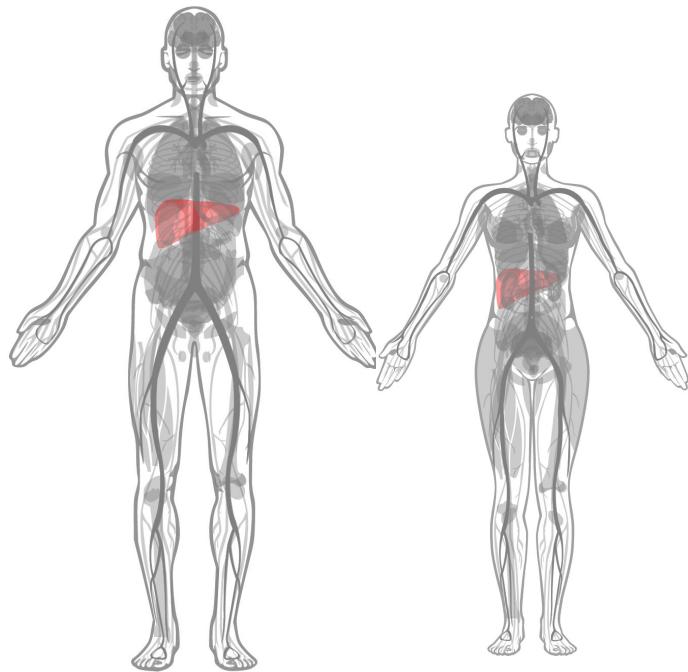
FUTURE



Digital twins

- A digital twin is a virtual model designed to accurately reflect a physical object.
- Combination of reproducible models on different scales
- Individualization of models





Questions?