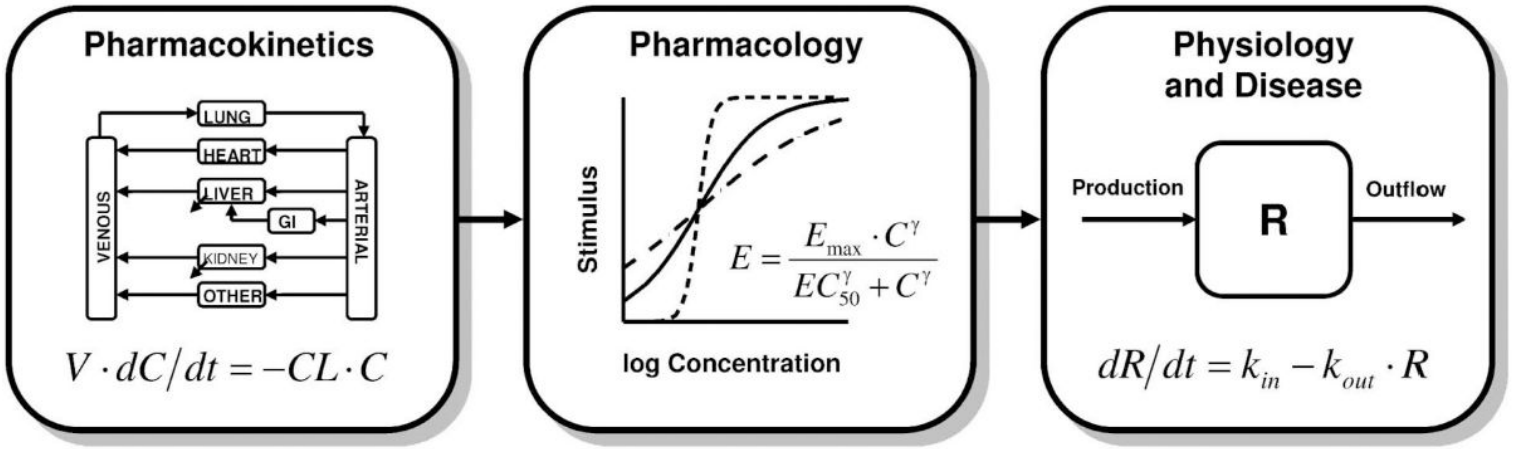
AMIDD Lecture 9: Pharmacokinetic and Pharmacodynamic Modelling



Mager, Donald E., Sukyung Woo, and William J. Jusko. 2009. “Scaling Pharmacodynamics from In Vitro and Preclinical Animal Studies to Humans.” Drug Metabolism and Pharmacokinetics 24 (1): 16–24.

Dr. Jitao David Zhang, Computational Biologist

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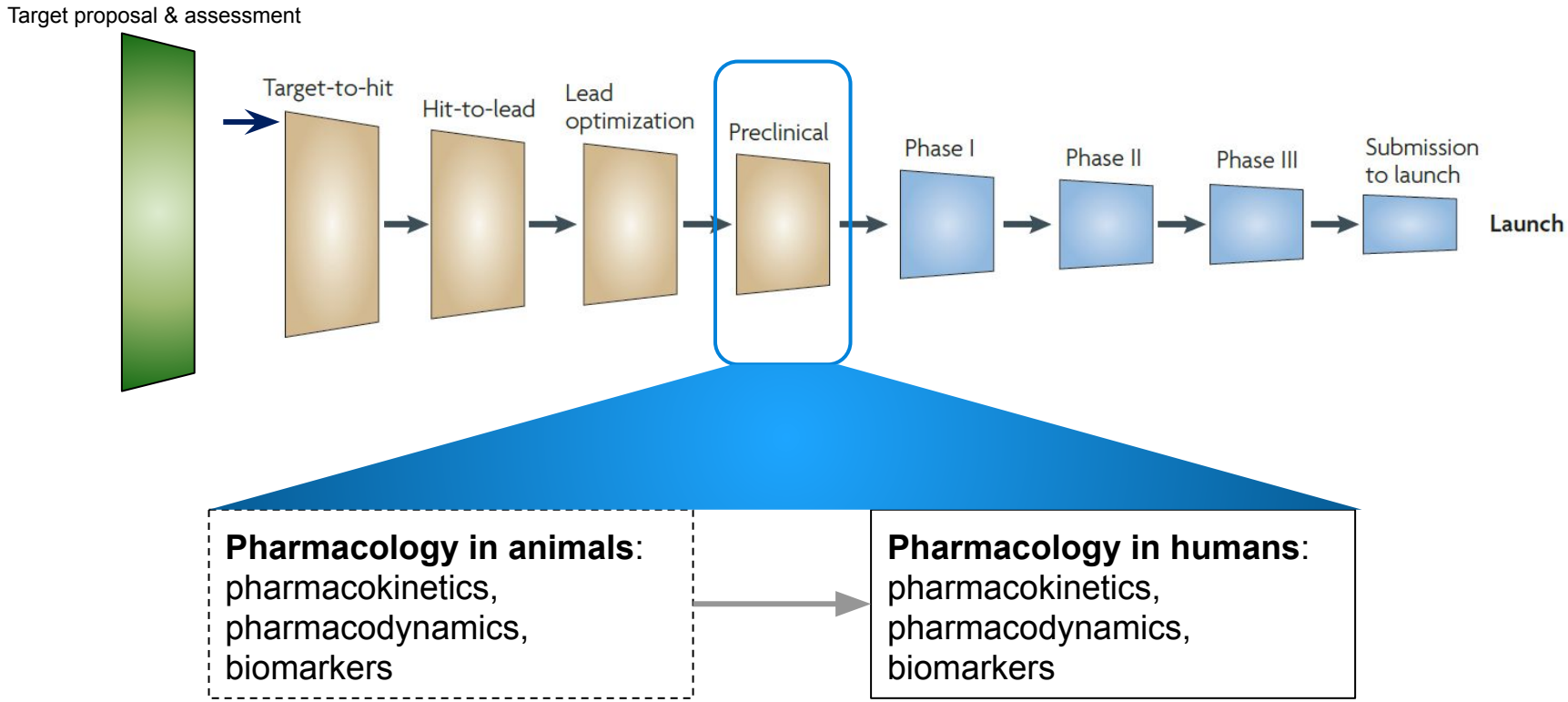
Topics

- **Pharmacokinetic (PK) modelling**
- **Joint pharmacokinetic-pharmacodynamic (PK-PD) modelling**
- **PBPK modelling**

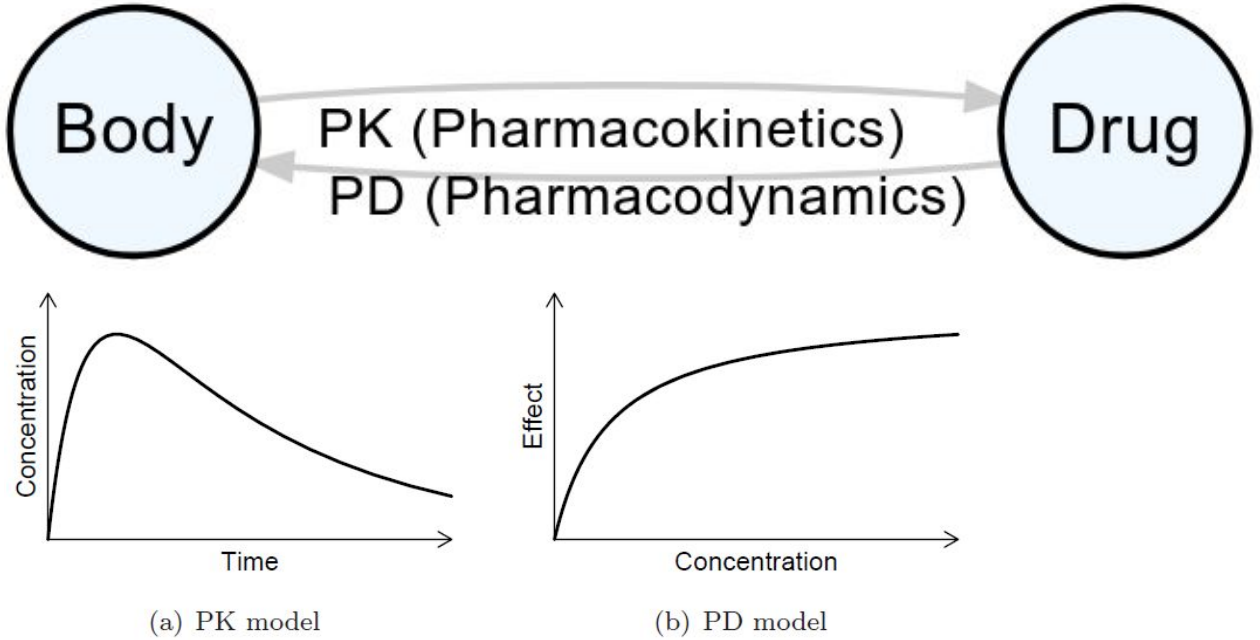
Questions in preclinical development: what to give, how to give, how much, and how often?



Adapted from Paul *et al.* "How to Improve R&D Productivity: The Pharmaceutical Industry's Grand Challenge." Nature Reviews Drug Discovery, 2010

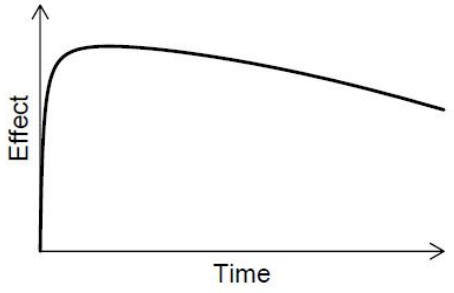
Pharmacokinetic and pharmacodynamic modelling

- Pharmacokinetics (PK) describes how the drug is absorbed, distributed, metabolised, and excreted by the body. The ADME properties are affected by physicochemical properties of the drug, and other properties such as human behavior (*e.g.* food and drug intake) and genetics.
- Pharmacodynamics (PD) describes the effect of the drug to the body, mediated by drug-target interactions. PD is affected by PK, as well as other properties such as behaviour and genetics.



(a) PK model (b) PD model

- A basic mathematical model of PK is a compartment model that can be transcribed as a set of differential equations that describe the relationship between drug concentration and time.
- PD models can have versatile forms, for instance a linear model, or a non-linear model (e.g. Hill's function), a compartment model, or other forms.

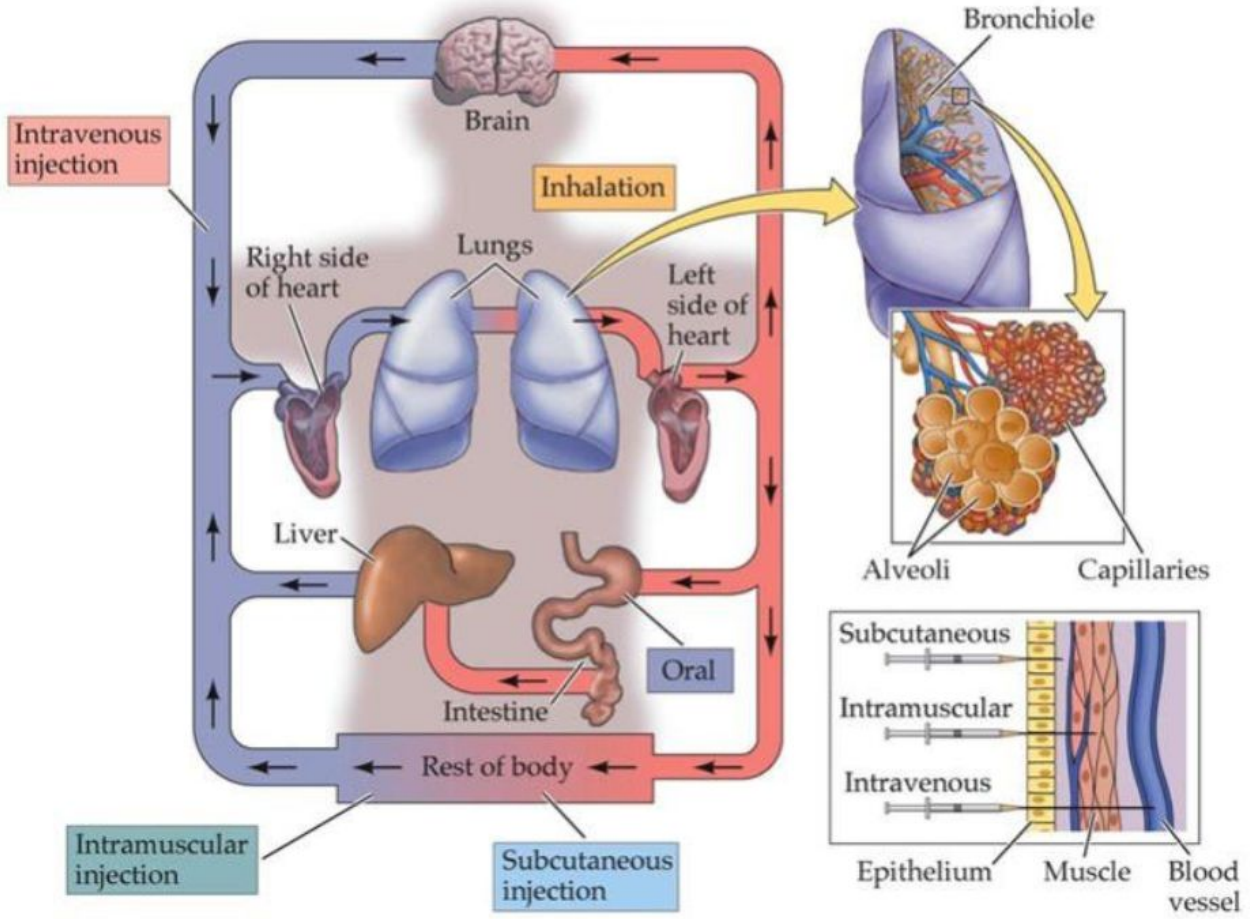


(c) Combined PK/PD model

Mortensen, Stig Bousgaard, Anna Helga Jónsdóttir, Søren Klim, and Henrik Madsen. 2008. "Introduction to PK/PD Modelling - with Focus on PK and Stochastic Differential Equations." Technical University of Denmark, DTU Informatics.

Principles of absorption

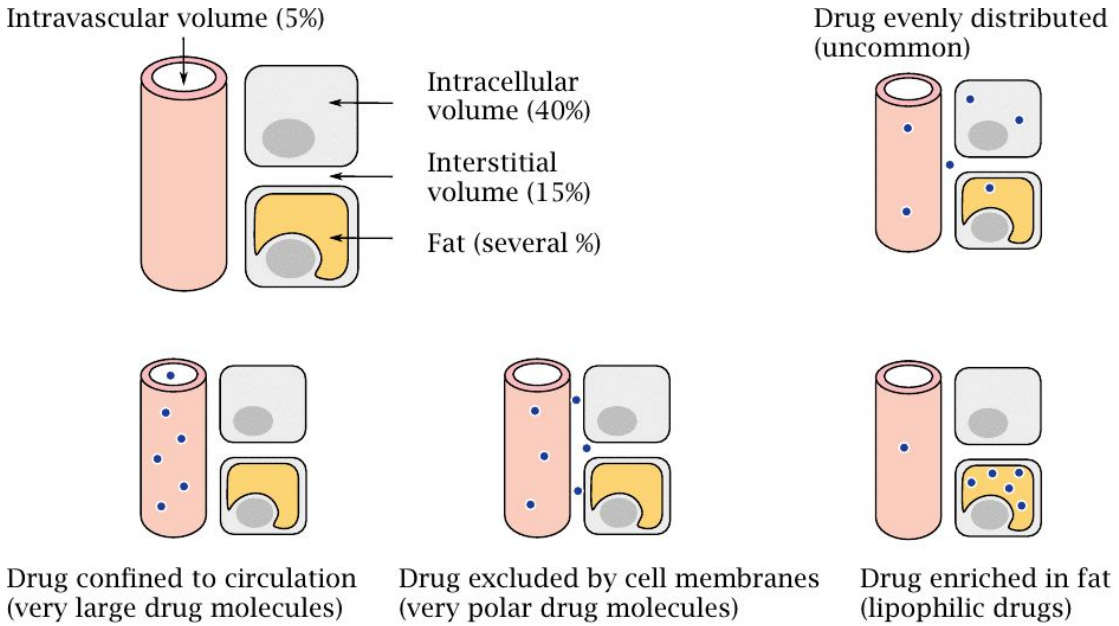
- Sometimes preceded by the process of *liberation*, the release of the active component from the formulation
- Process by which a drug compound transfers from an extravascular site of dosing (*e.g.* gut, lung, muscle, and skin) into systemic circulation, known as the **central compartment**.
- Intravenous administration in a *bolus* dose (single dose, short time) can be modelled as instant absorption. Infusion using a constant rate over time can be modelled as instant absorption by time.
- Extravascular dosing, for instance (a) oral or (b) injection into muscle or fat tissue, needs to be absorbed. During this process the drug concentration may reduce due to metabolism and trapping. The ratio between active drug concentration reaching the central compartment and the in-take concentration is known as the **bioavailability**.



Psychopharmacology, Figure 1.2

Principles of distribution

- Following absorption, drug molecules are distributed into organs and tissues.
- Different organs and tissues receive different doses of the drug, and the concentration-time relationship also varies.
- Distribution of a drug in a tissue depends on both **physiological factors**, including the vascular permeability, blood flow, the perfusion rate of the tissue, and **physicochemical properties of the drug**, including plasma protein binding, and lipophilicity.
    - Example 1: Liver and kidney are better perfused than muscle and fat, and the brain is usually inaccessible due to the blood-brain barrier.
    - Example 2: Only free compounds that are not bound to plasma proteins can exert pharmacological functions. Compounds with excessive protein binding have a delayed distribution.



Major components of drug distribution, U Waterloo

We use the Volume of distribution, V_D, to describe the extent of a drug distribution. The larger the value is, the better the distribution to tissues. A value larger than human circulation volume (0.08 l/kg) is possible, which indicates good distribution in the tissues.

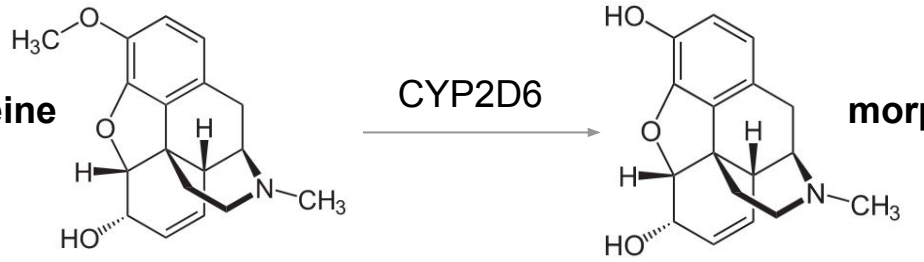
$$V_D = \frac{\text{total amount of drug in the body}}{\text{drug blood plasma concentration}}$$

Principles of metabolism and excretion, which together contribute to *clearance*

Metabolism

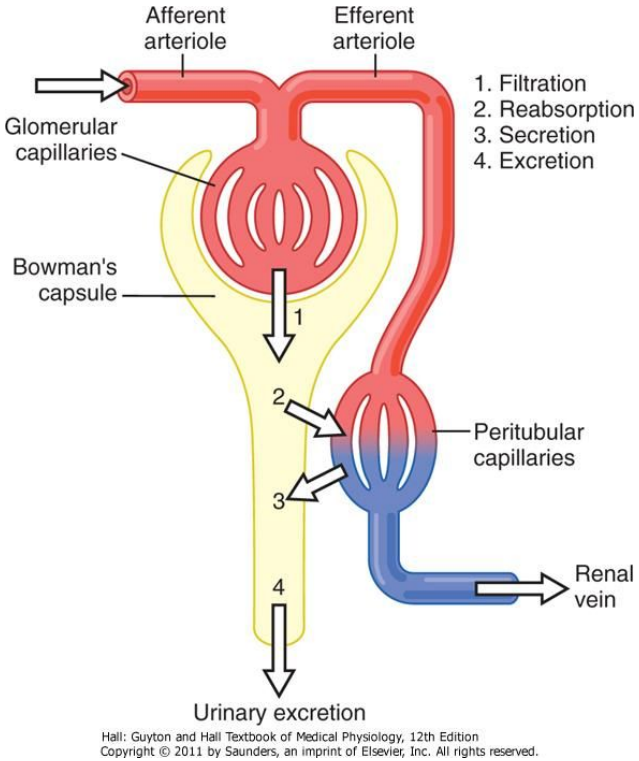
- Drug metabolism serves defense against xenobiotics. It facilitates the excretion of the drug by making it hydrophilic.It happens mainly in liver and, for oral drugs, in intestine.
- Drug metabolism can deactivate a compound (very often the case) or activate a compound, turning a **pro-drug** into its active form, *e.g.* codeine to morphine, below).
- Drug metabolism varies between individuals, between ages in the same individual, and can be affected by drugs as well. Drugs that induce or repress drug-metabolism genes (e.g. cytochrome P450, CYPs) can cause drug-drug interaction.

codeine CYP2D6 **morphine**



Excretion

- Excretion follows metabolism and removes drugs and their metabolites from the body.
- The main excretion route is the **urinary** and **biliary** (thereby with feces) **excretion**.
- Urinary excretion include three components: glomerular filtration, secretion, and reabsorption.
- Patients with kidney diseases may have reduced excretion, calling for adjusted dosing.



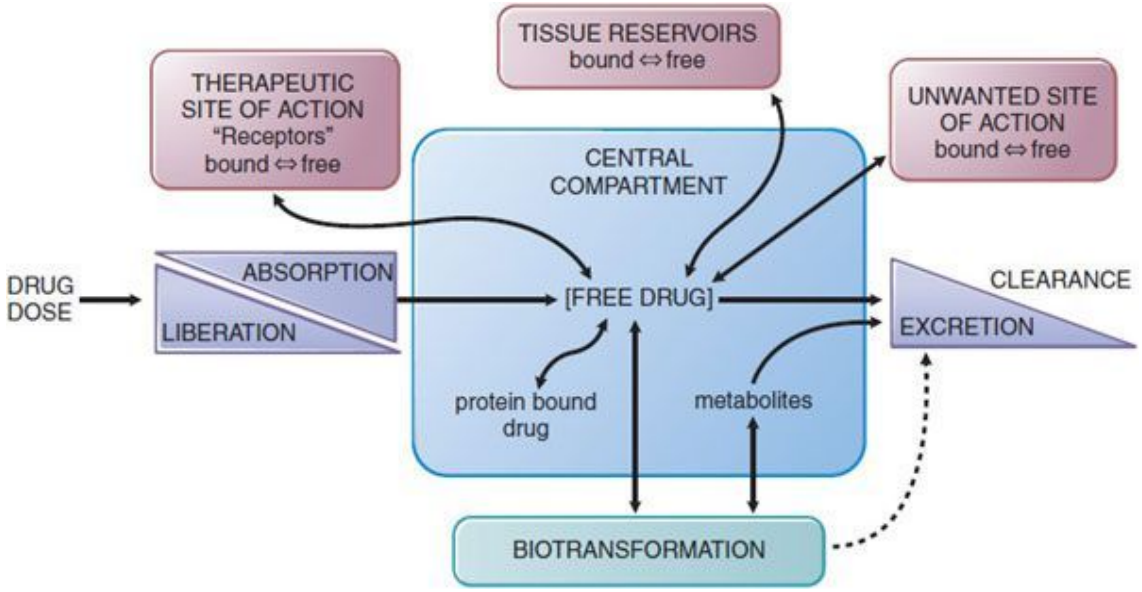
Modelling pharmacokinetics with ADME properties

Why ADME properties matter?

- They determine how much drug is found where at which time point. The ADME properties, given the pharmacodynamics and off-target effects of the drug, determine the efficacy and safety profiles of a drug.
- Animal ADME parameters can contribute to estimation and inference of human parameters, which contribute to dosing regimen selection with the help of modelling and simulation (how much? how often? *etc.*)

How are ADME properties determined and predicted?

- QSAR/machine-learning models trained with molecular descriptors and *in-vitro* assay results, for instance for V_d, which is well predictable.
- *In-vitro* assays, for instance permeability (the PAMPA assay), and hepatic clearance (hepatocyte or microsomal assay).
- *In-vivo* measurements



Pharmacokinetics: The Dynamics of Drug Absorption, Distribution, Metabolism, and Elimination

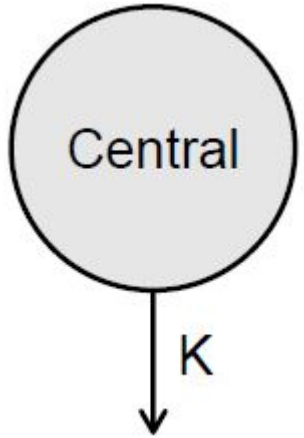
Mathematical modelling of PK: one-compartment model, bolus

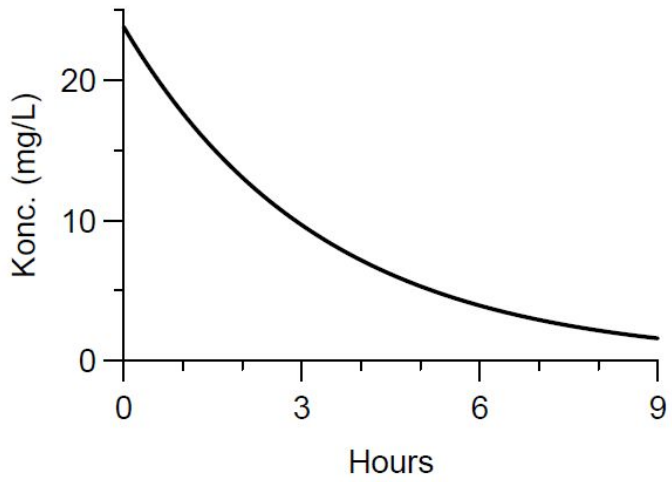
We denote the concentration of the drug as *A*, and the rate of clearance (metabolism and excretion) as *K*. Assuming a bolus dose, according to the law of mass action and first-order kinetics, we can write

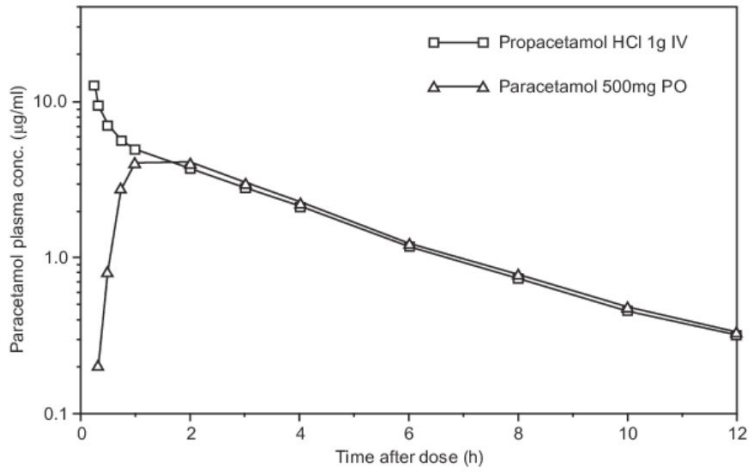
$$\frac{dA}{dt} = -K \cdot A$$

When we denote the initial dose as A_0, we can express the general solution of the model as

$$A_{bolus}(t) = A_0 \exp(-K \cdot t)$$







(Left) simulation from *Introduction to PK/PD Modelling - with Focus on PK and Stochastic Differential Equations* (Right) empirical data of propacetamol HCl (IV, intravenous) and paracetamol (PO, *per os*, oral).

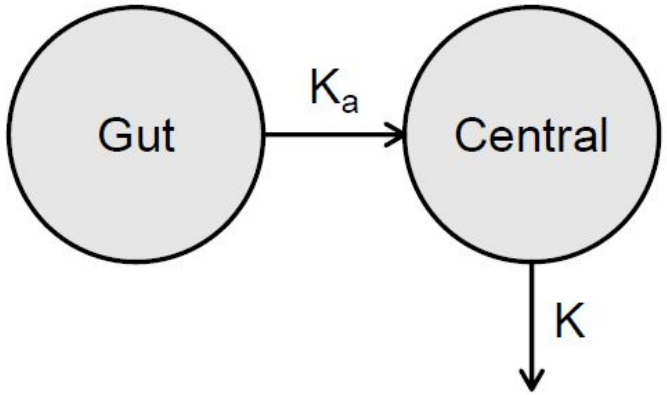
Propacetamol is a pro-drug of paracetamol. The chemical modification (esterification) makes it more water soluble, allowing it delivered via IV.

Question: what is the half-life of the drug, $t_{1/2}$, the time it takes for reducing the amount of drug left in the body by 50%?

One-compartment model, oral dosing

For oral dosing, an extra gut compartment (right) is often sufficient to model the absorption phase

$$\frac{dA_{gut}}{dt} = -K_a \cdot A_{gut}$$

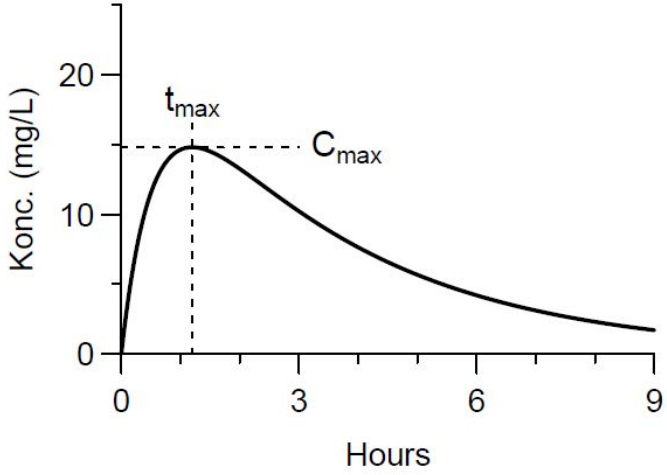


Suppose rate the absorption of the drug is faster than the elimination process (K*a*>*K*), we can model the concentration in the central compartment as

$$\frac{dA}{dt} = \overbrace{F \cdot K_a \cdot A_{gut}}^{\text{from gut}} - \overbrace{K \cdot A}^{\text{elimination}}$$

In reality, we cannot easily assess the concentration of drug in the gut. Is it possible to derive the relationship between central-compartment concentration *A* and time *t* given the initial condition?

Yes: we can find the expression of *A*(t) analytically in a closed form using *Laplace transform*, which translates a function of a continuous variable (*e.g.* time) to a function of a complex variable (frequency) (see backup).



One-compartment model, oral (or extravascular) dosing

$$A_{oral}(t) = \frac{K_a F A_0}{K_a - K}\left(\exp(-K \cdot t) - \exp(-K_a \cdot t)\right)$$

replacing amount with concentration

$$C_{oral}(t) = \frac{A_{oral}(t)}{V} = \frac{K_a F A_0}{V(K_a - K)}\left(\exp(-K \cdot t) - \exp(-K_a \cdot t)\right)$$

solving by differentiation

$$t_{max} = \frac{1}{K_a - K} \ln\left(\frac{K_a}{K}\right)$$

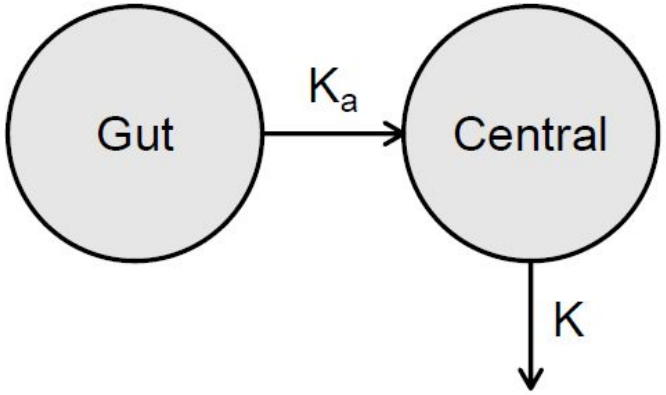
replacing t with t_{max}

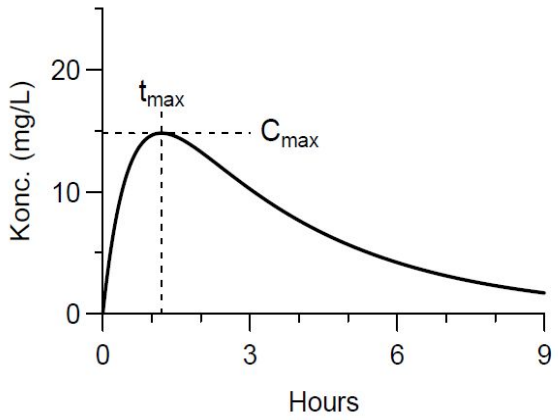
$$C_{max,oral} = \frac{K_a F A_0}{V(K_a - K)}\left(\exp(-K \cdot t_{max}) - \exp(-K_a \cdot t_{max})\right)$$

simplification

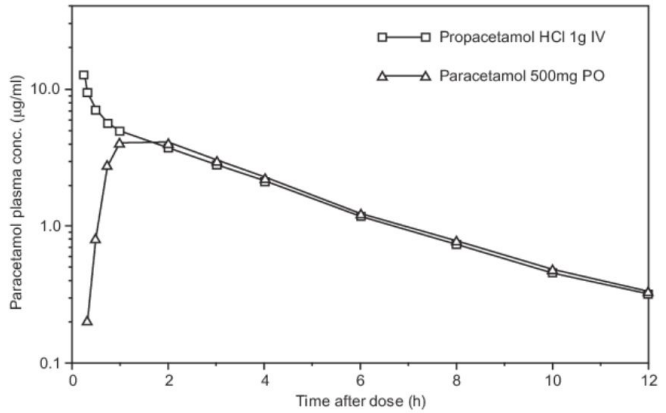
$$C_{max,oral} = \frac{F A_0}{V} \exp(-K \cdot t_{max})$$

- The parameter t_{max} describes the time to reach the maximum plasma concentration of the drug since dosing.
- The parameter C_{max} describes the maximum plasma concentration of the drug.





Simulated PK profile of 1000mg paracetamol (PO)



Empirical PK profile of 1000mg paracetamol (PO)

Constant-rate infusion and multiple dosing

We can administer the drug with infusion over time. If we assume a constant infusion amount R_{in} and a constant clearance constant *CL*, we can derive the analytical solution of drug contraration with regard to time.

- **Question:** what form does it have?

If a pill releases its active ingredient gradually, its plasma concentration can be effectively equivalent to that of a constant-rate infusion. If multiple pills are taken with time intervals, the constant R_{in} can be expressed as a product of bioavailability *F* and initial dose A_0, divided by the time interval of taking pills τ. The concentration of **multiple dosing (MD)** can be expressed as the sum of individual dosing profiles (*N* indicates the number of doses)

The system reaches equilibrium when the infusion rate equals the clearance rate (*dC/dt=0)*. Therefore we can deduce the concentration at stead ystate C_{SS} by the ratio of infusion rate and clearance. Due to the exponential distribution, 90% of the the steady-state concentration is reached after 3-4 half-lives.

$$\frac{dC}{dt} = \frac{R_{in}}{V} - \frac{CL}{V} \cdot C$$

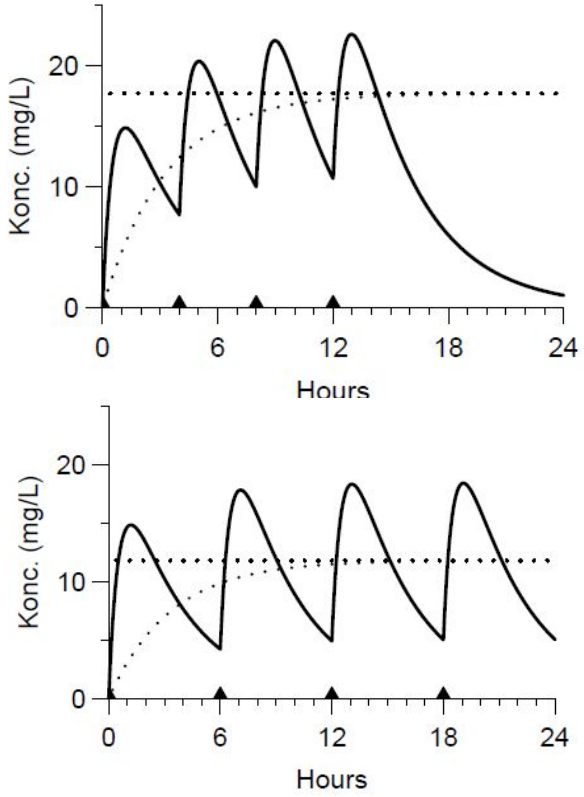
$$C(t) = \frac{R_{in}}{CL}\left[1 - \exp\left(-\frac{CL}{V}t\right)\right]$$

$$R_{in} = \frac{F \cdot A_0}{\tau}$$

$$C_{MD}(t) = \sum_{n=0}^{N-1} C_{oral}(t - n\tau)$$

$$\frac{R_{in}}{V} = \frac{CL}{V} C_{SS}$$

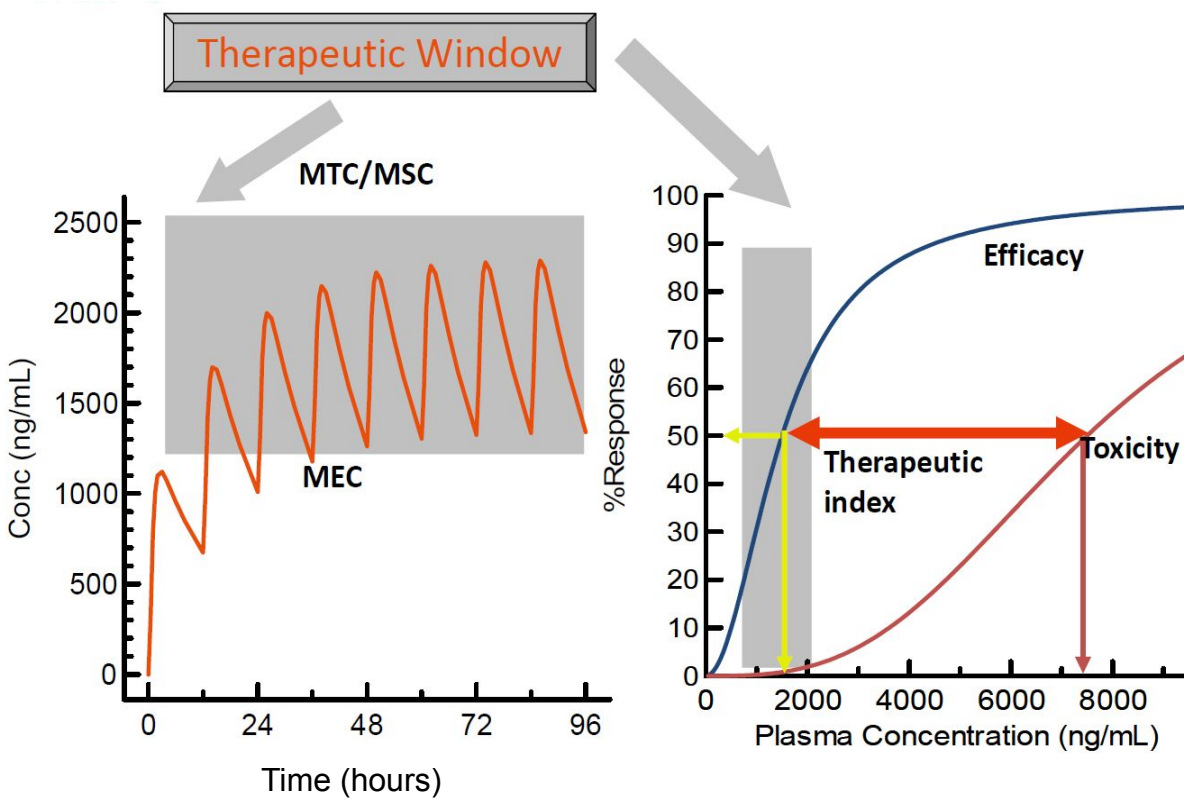
$$C_{SS} = \frac{R_{in}}{CL}$$



Multiple dosing of paracetamol, with 4 oral doses of 1g per dose given at two different intervals (top: 4h, bottom: 6h). Thick line: total concentration. Dotted line: the rate of constant infusion.

Why do we care about multi-dosing PK?

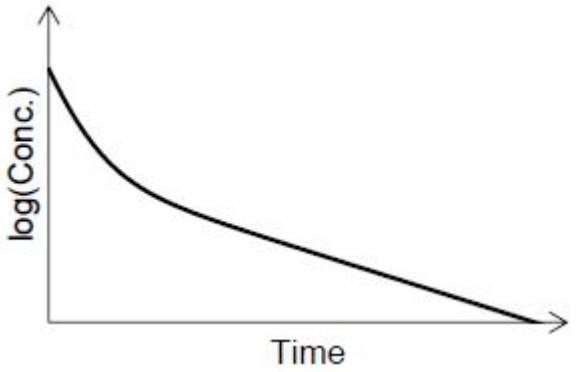
- The PK profile determines
  - dose (how much)
  - dosing regimen (how much, how often, how long)
  - dosage form (which formulation)
  - dosage route (systemic? local?)
- The **therapeutic window** (from the view of PK) or the **therapeutic index** (from the view of PD) determines how much and often a drug is dosed.
- A narrow therapeutic index may lead to additional requests from the regulatory authority in preclinical development or additional labelling in drug product, if not stop of the development project.



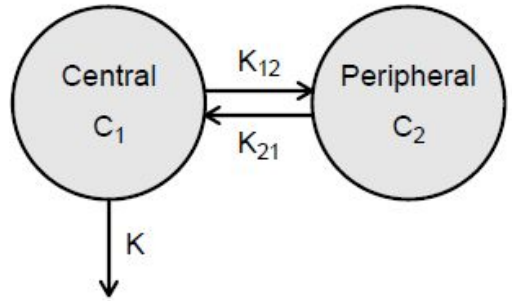
Courtesy of Jun Shi. MEC: minimal effect concentration; MTC/MSC: minimum toxic concentration/maximum safe concentration

Two-compartment model

A piecewise linear relationship between logarithm-transformed concentration and time often indicates that one-compartment model is not sufficient. Multi-compartment models can be used in these cases.



suggests



Similar to one-compartment model, we can set up two differential equations describing the compartment model. The solution has the general form of a weighted sum of two exponentially distributed variables.

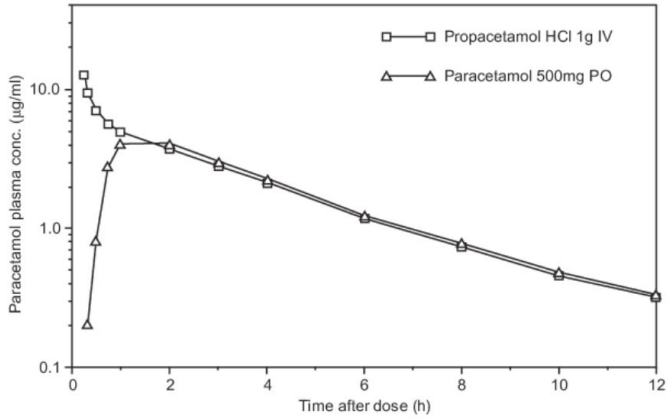
$$\frac{dC_1}{dt} = K_{21} \cdot C_2 - K_{12} \cdot C_1 - K \cdot C_1$$
$$\frac{dC_2}{dt} = K_{12} \cdot C_1 - K_{21} \cdot C_2$$

solution

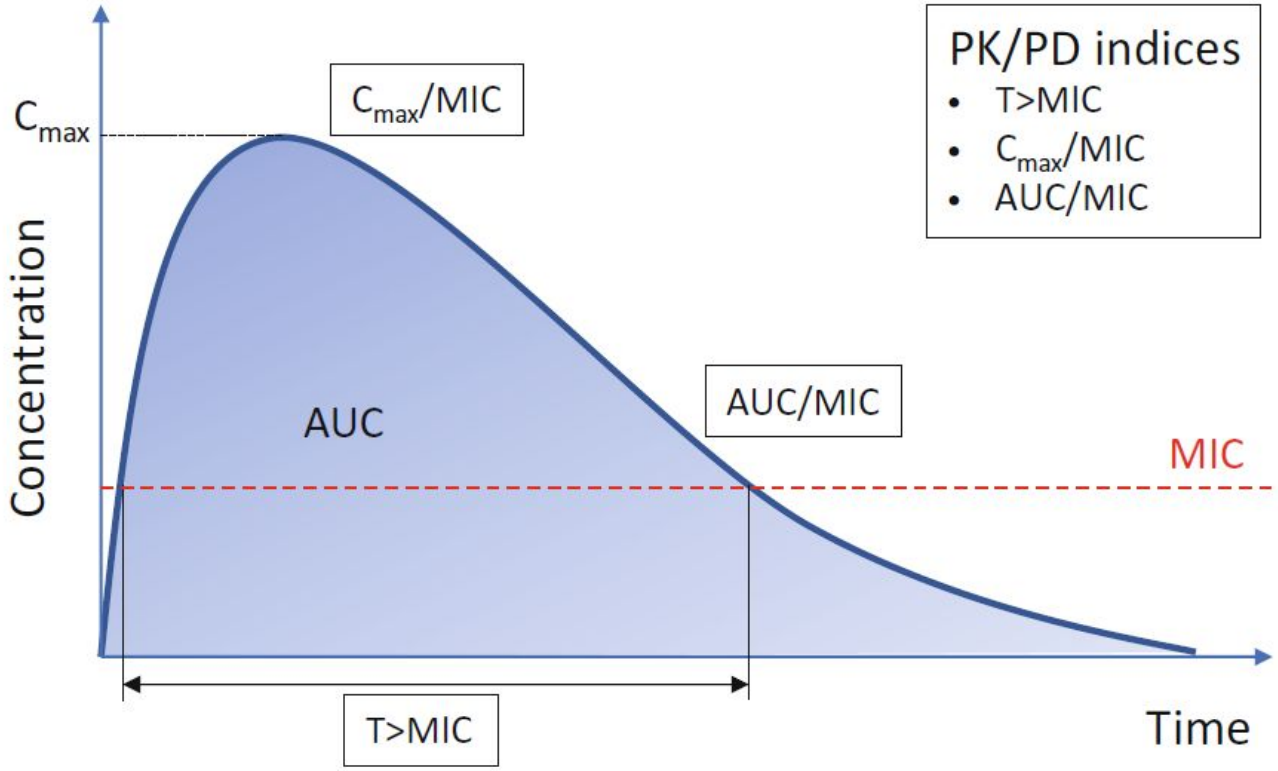
$$C = A \cdot \exp(-\alpha t) + B \cdot \exp(-\beta t)$$

$$t_{1/2,\alpha} = \frac{\log(2)}{\alpha} \qquad t_{1/2,\beta} = \frac{\log(2)}{\beta}$$

The propacetamol data that we seen before may be modelled by a two-compartment model.



The simplest joint PK/PD model: a binary PD model with a step function

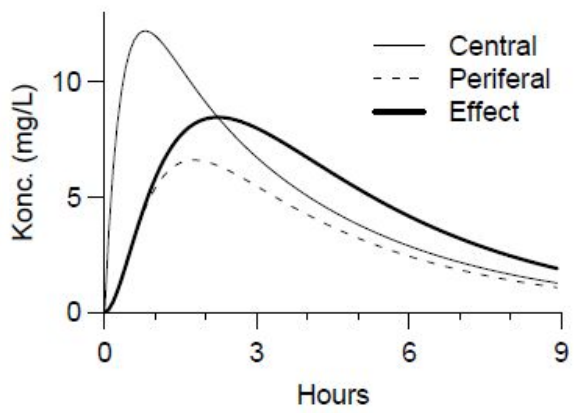


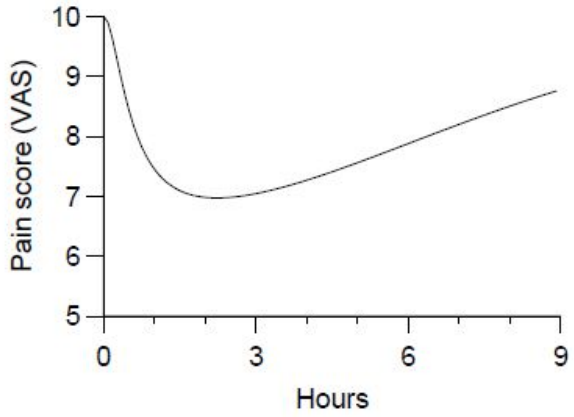
Pharmacokinetic-pharmacodynamic indices of a theoretical drug molecule. MIC: Minimum inhibitory concentration (MIC).

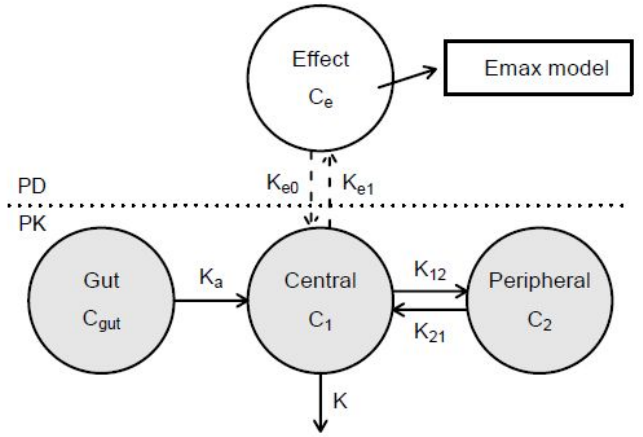
Yu, Yichao, Diether Rüppel, Willi Weber, and Hartmut Derendorf. 2018. "PK/PD Approaches." In Drug Discovery and Evaluation: Methods in Clinical Pharmacology.

An example of joint PK/PD model of an oral dose of 1000mg paracetamol

- PD models have many forms. The example is taken from Mortensen *et al.* and Gibb and Anderson (2008). It uses a hypothetical effect compartment with an E_{max} model (the Hill function that we introduced before) to model the effect. It does not influence of the PK model.
  - Question: what good the effect compartment do?
- The effect is measured on a visual analogue scale (VAS) from 0-10 where a reduction indicates pain relief.







PK model

$$\begin{aligned} dC_{gut}/dt &= -K_a C_{gut} \\ dC_1/dt &= -k_{12}C_1 + k_{21}C_2 - k_{10}C_1 + FK_aC_{gut} \\ dC_2/dt &= k_{12}C_1 - k_{21}C_2 \end{aligned}$$

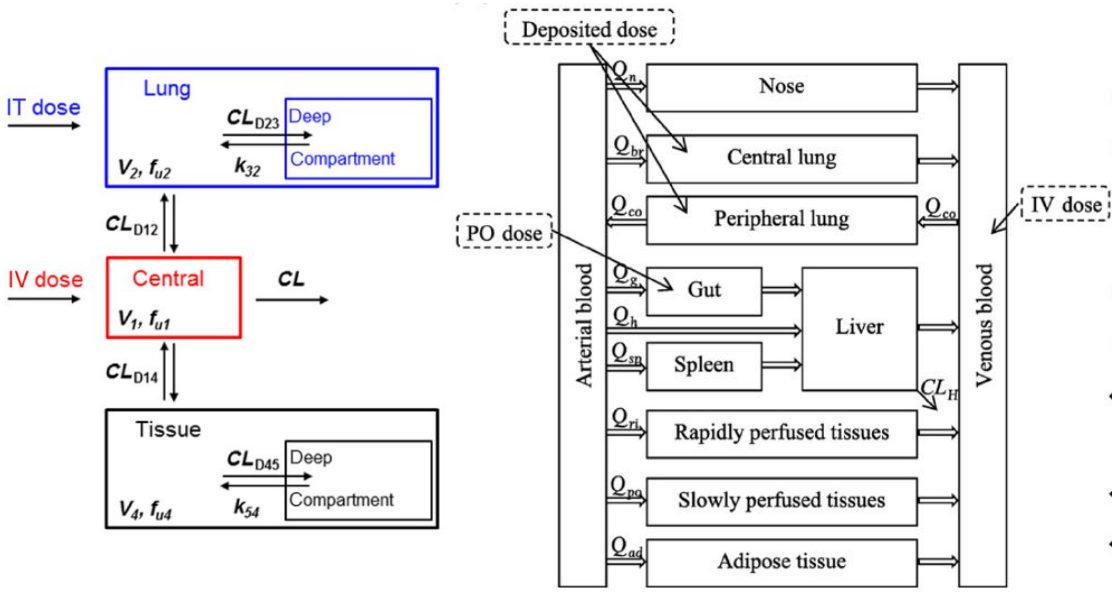
Effect compartment

$$dC_e/dt = k_{e1}C_1 - k_{e0}C_e$$

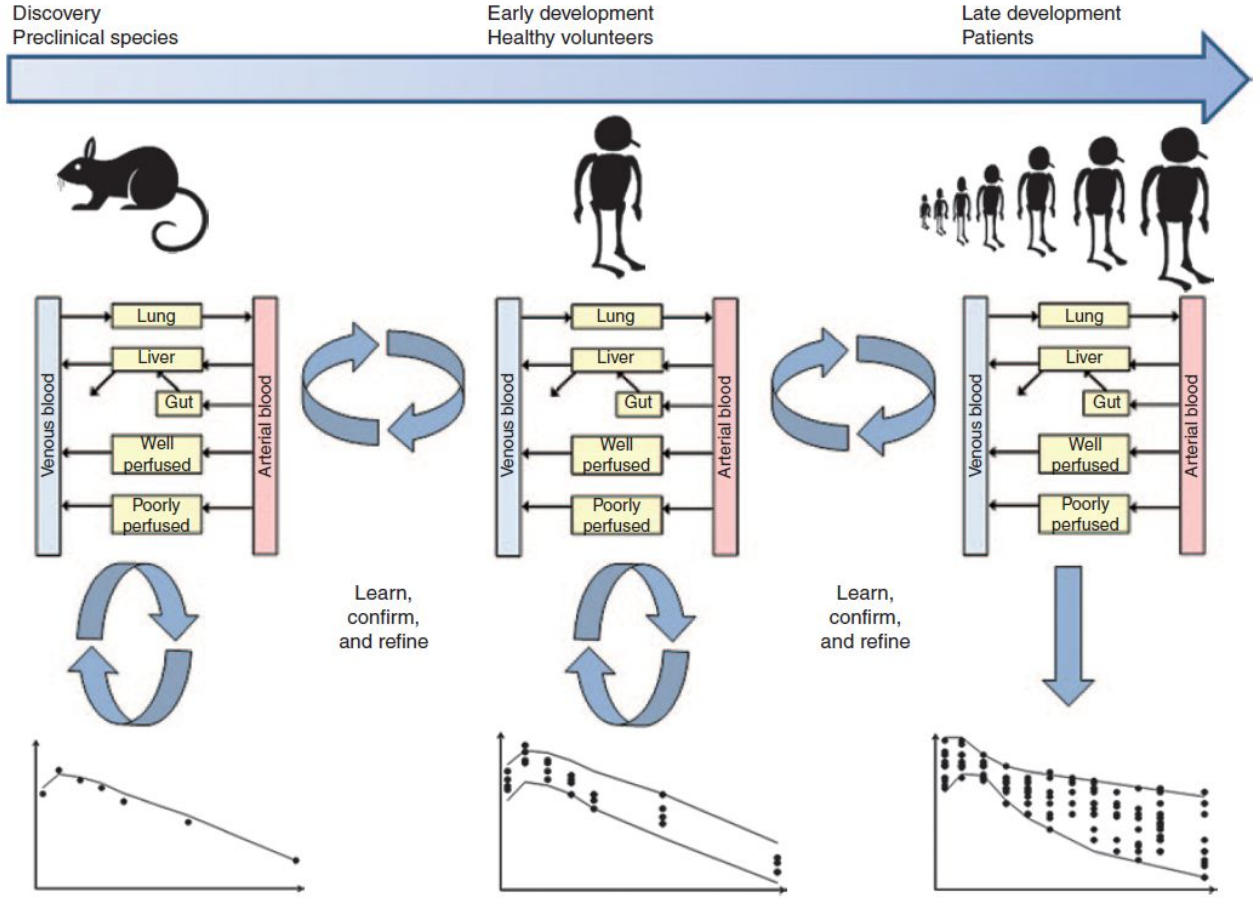
PD model

$$\text{Effect} = 10 - \frac{E_{max}C_e}{\text{EC}_{50} + C_e}$$

Physiologically based pharmacokinetic (PBPK) models



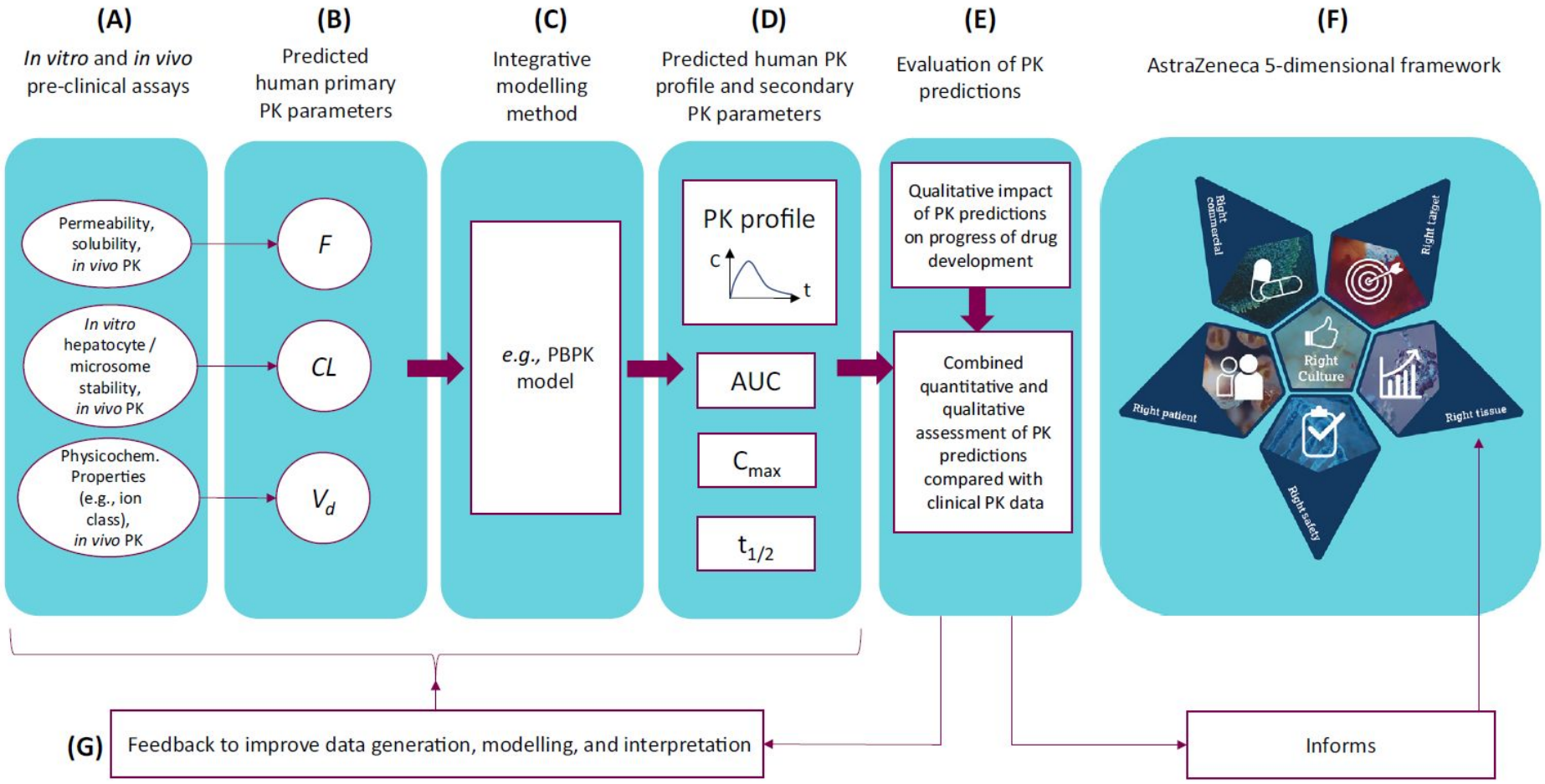
(Left) A semi-physiological model (Right) A fully physiology-based PK model



PBPK is usually performed in an iterative “learn, confirm, and refine” approach. Initially, the PBPK simulation is performed in animals using animal PBPK models, animal *in vitro* data, and compound physicochemical data. The animal simulation is compared with the in vivo data, if this simulation in animals is reasonable, then the healthy volunteer simulation is performed using a human PBPK model. These simulations can then be extended to various patient populations using relevant physiology. If the simulation at any stage is inaccurate, further experiments may be performed to understand the mismatch and to improve the PBPK model.

Right figure: Jones, H. M., and K. Rowland-Yeo. 2013. “Basic Concepts in Physiologically Based Pharmacokinetic Modeling in Drug Discovery and Development.” CPT: Pharmacometrics & Systems Pharmacology 2 (8): 63.

An industrial PK modelling workflow: example of AstraZeneca

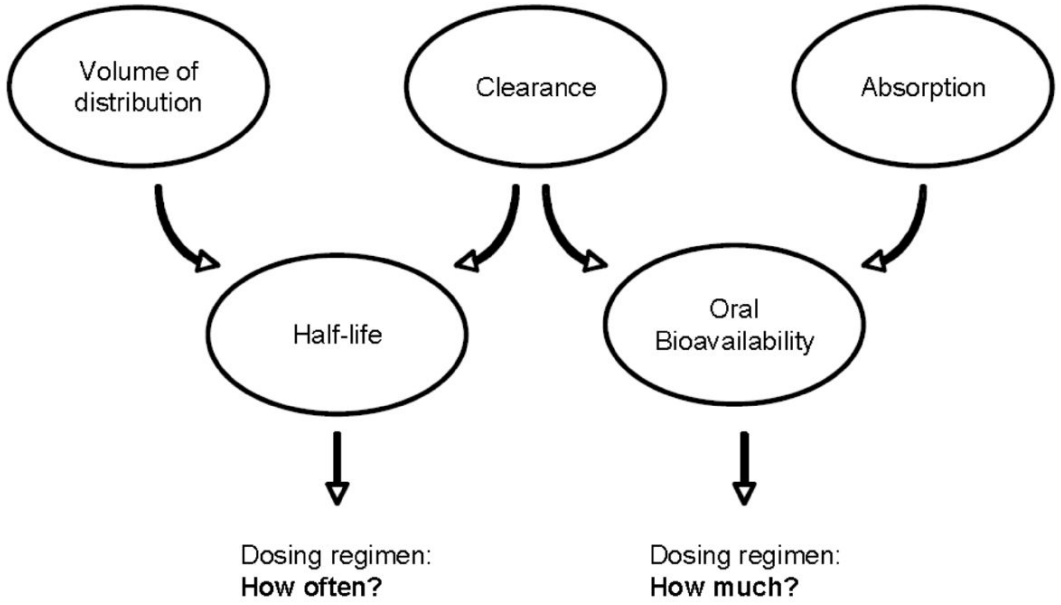


Davies, Michael, *et al.*. 2020. "Improving the Accuracy of Predicted Human Pharmacokinetics: Lessons Learned from the AstraZeneca Drug Pipeline Over Two Decades." Trends in Pharmacological Sciences 41 (6): 390–408.

Summary

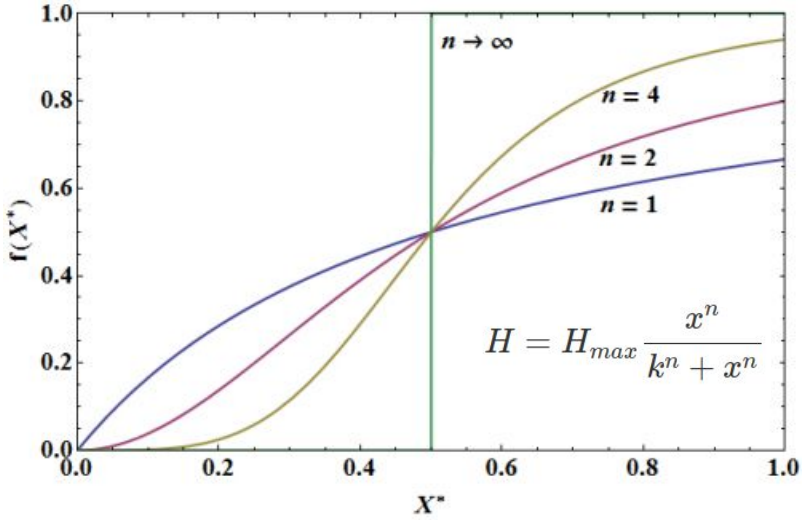
Pharmacokinetics: what the body does to the drug

- Determined by ADME properties
- Determines dose, dosing regimen, dosage form, and dosage route
- Important parameters:
  - Bioavailability (*F*): absorption - metabolism - efflux - degradation
  - Clearance (*CL*)
  - Volume of distribution (V_D)



Pharmacodynamics: what the drug does to the body

- Determined by interaction with targets and off-targets
- Determines efficacy and safety profiles
- Can be modelled in many different ways. Common choices include:
  - Step function
  - Linear function
  - Non-linear function (*e.g.* the Hill function)



From the biophysics wiki article by Andreas Piehler

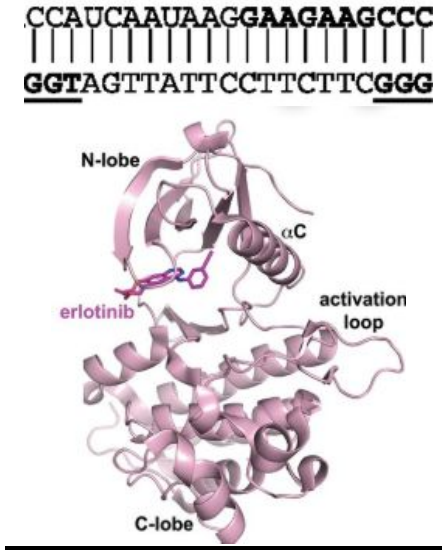
Offline activities

1. Anonymous feedback form: https://forms.gle/havddpXNmkKZ8LJc6
2. Required reading:
    a. The backup slides of Lecture 9 to learn about the principles of population modelling, especially non-linear mixed-effect models (NLMEs) and clinical trials.
3. Optional reading:
    a. Davies, Michael, *et al.*. 2020. "Improving the Accuracy of Predicted Human Pharmacokinetics: Lessons Learned from the AstraZeneca Drug Pipeline Over Two Decades." Trends in Pharmacological Sciences 41 (6): 390–408. *A good introduction to prediction of PK profiles in industry.*
    b. Jones, H. M., and K. Rowland-Yeo. 2013. "Basic Concepts in Physiologically Based Pharmacokinetic Modeling in Drug Discovery and Development." CPT: Pharmacometrics & Systems Pharmacology 2 (8): 63. https://doi.org/10.1038/psp.2013.41. *A good introduction to PBPK modelling*

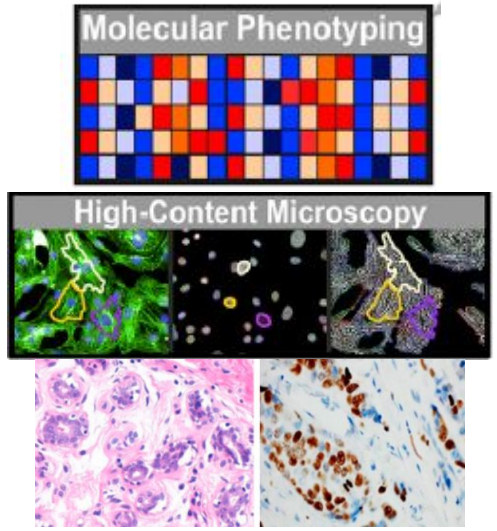
Conclusion of the course

Multiscale Modelling of Drug Mechanism and Safety

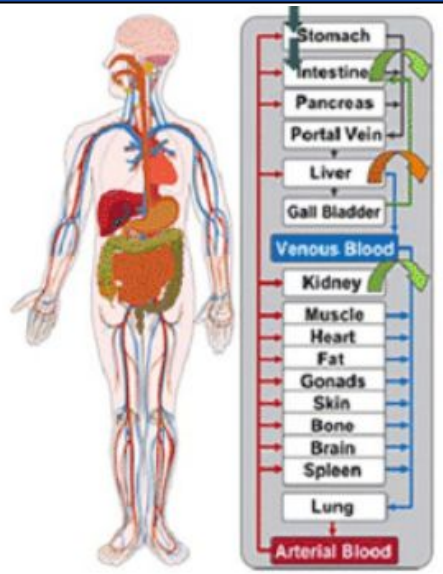
Forward translation



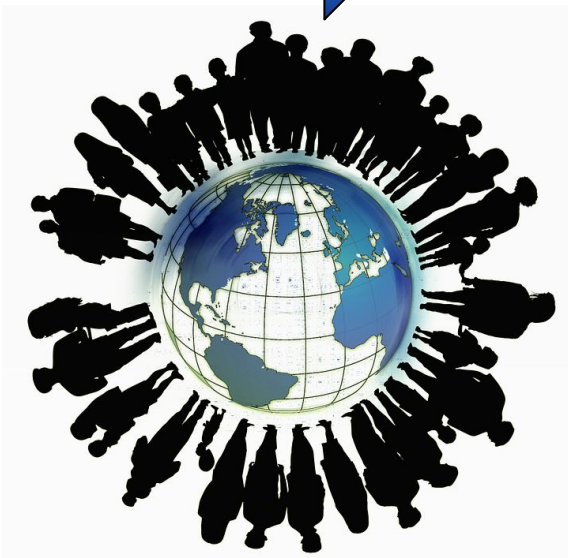
Molecular modelling



Omics & cellular modelling



Organ & system modelling



Populational modelling

Reverse translation

Principles that we covered: molecular biology (the central dogma), bioinformatics (DP and MC/HMM), chemoinformatics and CADD (molecular descriptors, QSAR, docking), omics (RNA sequencing), pharmacology (PK, PD, PBPK), population modelling (NLME), ...

Thank you for...

- Attending the course virtually;
- Giving me and the course feedback;
- Hopping between disciplines together with me;
- Reading (maybe too) much material;
- Taking time for offline activities;
- Asking and answering questions;
- Googling strange terms that you have never heard of;
- Bearing with my accent, speaking speed, and poor drawing;
- Being interested in applied mathematics and informatics in drug discovery.

Hopefully see some of you in MCBDD 2022!

Mathematical and Computational Biology in Drug Discovery

http://mcbdd.ch

- Syllabus
  - Module Zero: Introduction
  - Module I: What are drug targets and where to find them?
  - Module II: What can we do if there are no good targets?
  - Module III: What kind of drug should we develop?
  - Module IV: What efficacy and safety profiles can we expect?
  - Module V: For which patients will the drug work and how does it work, *really*?

Backup material

Solving the two-equation system with the Laplace transform

System: Letting $A_a(t)$ be the amount of drug at the absorption site at time t

$$\begin{aligned} \dot{A}(t) &= k_a A_a(t) - k_e A(t) \\ \dot{A}_a(t) &= -k_a A_a(t) \end{aligned}$$

with initial conditions $A_a(0) = A_{a0} = FD$, $A(0) = A_0 = 0$, where F is the fraction available (take $F \equiv 1$ for simplicity)

Marie Davidian, MA/ST 810, *Mathematical-Statistical Modeling and Analysis of Complex Systems*, NC State University.
A table of Laplace transforms can be found on intmath.com

Laplace transform of $A(t)$: $\mathcal{L}\,A = \int_0^\infty e^{-st} A(t)\,dt$

$$\begin{aligned} s\mathcal{L}\,A - A_0 &= k_a \mathcal{L}\,A_a - k_e \mathcal{L}\,A \quad (1) \\ s\mathcal{L}\,A_a - A_{a0} &= -k_a \mathcal{L}\,A_a \quad (2) \end{aligned}$$

- Solve (2) for $\mathcal{L}\,X_a$ and substitute in (1) to obtain

$$\mathcal{L}\,A = \frac{k_a F D}{(s + k_e)(s + k_a)}$$

- From a table of Laplace transforms, we find immediately that

$$A(t) = \frac{k_a F D}{k_a - k_e}\{e^{-k_e t} - e^{-k_a t}\}$$

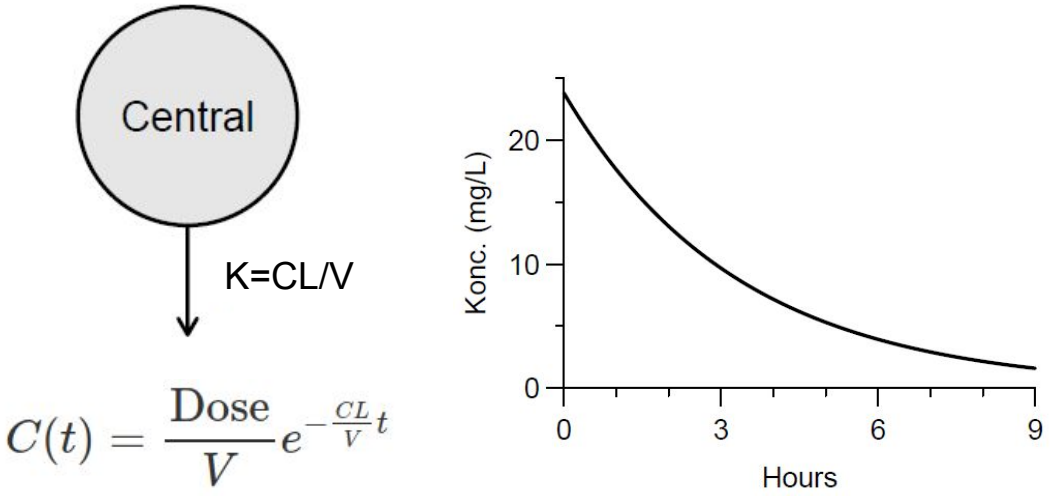
so that (divide by V)

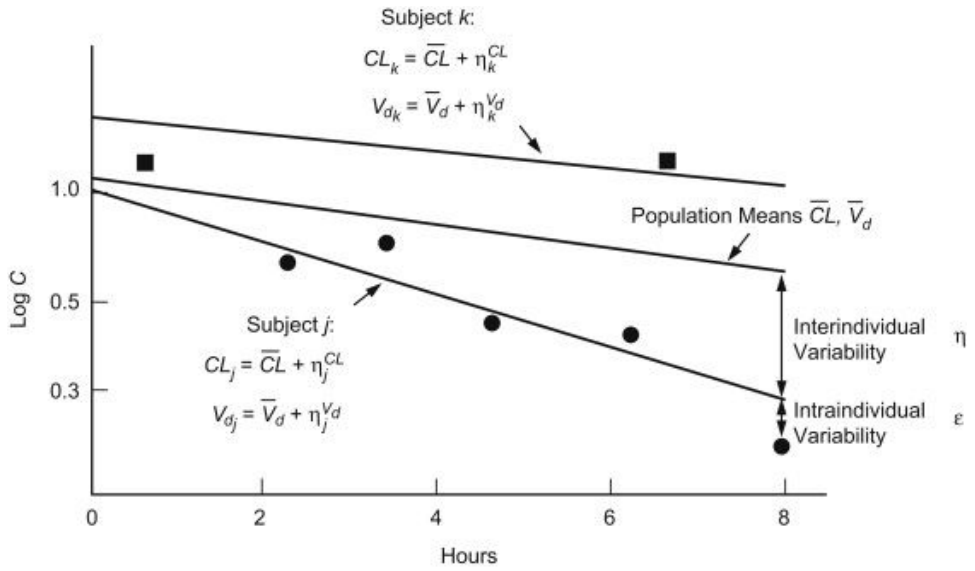
$$C(t) = \frac{k_a F D}{V(k_a - k_e)}\{e^{-k_e t} - e^{-k_a t}\}$$

See more about the Laplace transform and other numeric transforms in Bracewell, R. N. 1990. "Numerical Transforms." Science 248 (4956): 697–704.

Population modelling deals with two levels of variability, which calls for mixed-effect models

- Consider a simple one-compartment model, with an intravenous bolus dose (right).
- **Two types of variability**
  - **Between-subject variability**, *e.g.* the differences in clearance rate among patients
  - **Between-occasion variability**, *e.g.* the differences from one time point to the other within each patient.
- A **mixed-effect model** (mixed=fixed+random effect model, a type of hierarchical model or *multilevel model*) is needed to model such data.
- If we assume that V_D is a constant value that is the same for all subjects, but clearance varies between subjects (for instance due to ethnicity), then V_D is a fixed-effect parameter and *CL* is a random-effect parameter.
- If we assume that both V_D and *CL* vary between subjects, then both are random-effect parameters.





Bottom figure: Raymond Miller, in Principles of Clinical Pharmacology (Third Edition), 2012

A general form of nonlinear mixed-effect models

The Bayesian language

$$y_{ij} \sim \mathcal{N}(\mu_{ij}, \Sigma_i)$$
$$\mu_{ij} = f(t_{ij}, \beta_i, d_i)$$
$$\beta_i \sim \mathcal{N}(\beta, D)$$

- y_{ij} is the j^{th} response for the i^{th} subject
- f is a scalar function nonlinear with regard to β
- β is a $k \times 1$ parameter vector, giving PK parameters such as absorption, V_D, and CL.
- t_{ij} is the j^{th} time of measurement for the i^{th} subject
- d_i is the dose of the i^{th} subject
- j ranges from 1 to n_i
- D is a $k \times k$ covariance matrix
- Σ_i is an $n_i \times n_i$ covariance matrix

The Frequentist language

$$y_{ij} = f(t_{ij}, \underline{\beta}_i, d_i) + \varepsilon_{ij}$$
$$\underline{\beta}_i \sim N(\underline{\beta}, D)$$
$$\underline{\varepsilon}_i \sim N(\underline{0}, R_i)$$

y_{ij} is the j^{th} response for the i^{th} subject

f is a scalar function nonlinear in $\underline{\beta}$

$\underline{\beta}$ is a $k \times 1$ parameter vector

t_{ij} is the j^{th} time for the i^{th} subject

d_i is the i^{th} subject's dose

j ranges from 1 to n_i

ε_{ij} is residual error

D is a $k \times k$ covariance matrix

R_i is an $n_i \times n_i$ covariance matrix

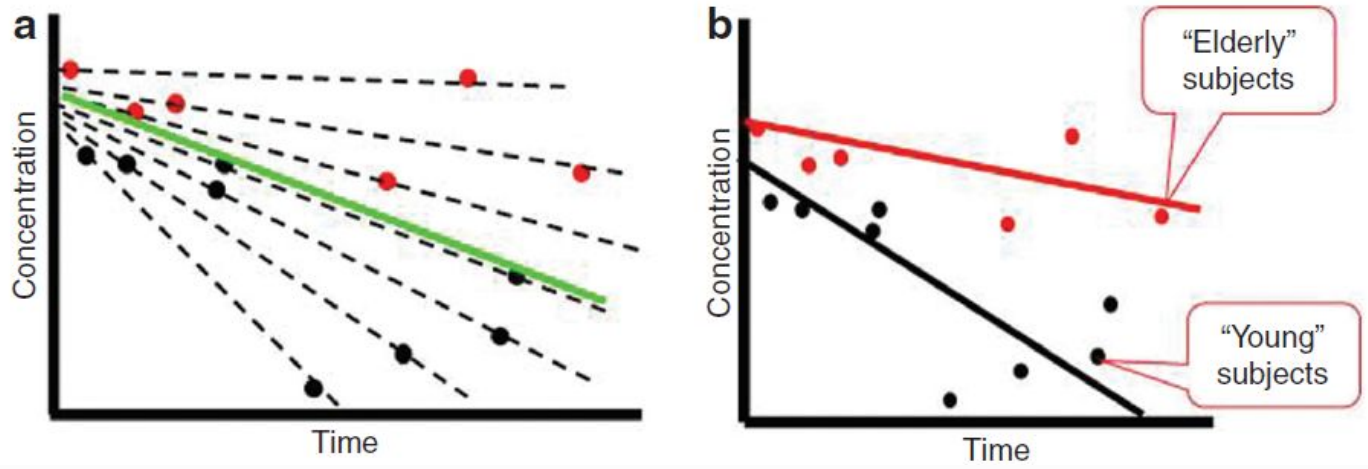
In practice, maximum-likelihood estimation (MLE) based modelling fitting is performed by numerical methods including *Laplace approximation* and *Gaussian quadrature*.

One of the mostly used software is **NONMEM** (non-linear mixed effects modeling), a commercial software. Other platforms are being actively developed, for instance GTS and ITS.

Further reading: Introduction to PK/PD Modeling for Statisticians by Alan Hartford (AbbVie), ASA Biopharm FDA-Industry Statistics Workshop. The Frequentist language was adapted from it.

NLME modelling helps understanding clinical PK-PD parameters

- Non-linear mixed-effect (NLME) models can model both drug response and disease progression.
- By incorporating covariants (biomarkers, *etc.*), NLME models can model and reveal group-specific PK/PD responses.



	Vemurafenib			
	240 mg bid	**480 mg bid**	**720 mg bid**	**960 mg bid**
Day 1	*n* = 12	*n* = 12	*n* = 12	*n* = 16
AUC_8 (μg·h/mL)	8.3 ± 6.13 (73.9)	13.8 ± 7.72 (55.8)	21.9 ± 12.97 (59.3)	27.0 ± 18.87 (69.9)
AUC_{24} (μg·h/mL)	40.9 ± 23.43 (57.3)	62.4 ± 35.71 (57.2)	111.6 ± 34.22 (30.7)	130.6 ± 71.78 (55.0)
C_{max} 0–8 h (μg/mL)	1.9 ± 1.66 (85.3)	2.6 ± 1.56 (60.5)	4.4 ±1.98 (44.6)	4.8 ± 3.34 (69.8)
t_{max} 0–8 h (h)	4.0 (1.92–8.00)	4.0 (1.95–5.00)	5.0 (2.00–8.08)	5.0 (2.00–8.00)
Day 15	*n* = 10	*n* = 10	*n* = 9	*n* = 11
AUC_8 (μg·h/mL)	117.8 ± 50.52 (42.9)	233.8 ± 106.93 (45.7)	343.3 ± 151.23 (44.1)	392.2 ± 126.37 (32.2)
AUC_{168} (μg·h/mL)	920.3 ± 538.35 (58.5)	2243.5 ± 1336.15 (59.6)	3127.1 ± 1789.97 (57.2)	3530.3 ± 1811.43 (51.3)
C_{max} 0–168 h (μg/mL)	17.2 ± 7.43 (43.1)	35.4 ± 17.44 (49.2)	52.7 ± 22.40 (42.5)	61.4 ± 22.76 (37.1)
$t_{½}$ (h)	31.5 ± 19.05 (60.4)	38.4 ± 24.18 (63.0)	34.9 ± 19.48 (55.9)	34.1 ± 19.66 (57.7)
Accumulation ratio (AUC_8 on day 15/day 1)	24.9 ± 29.4 (118)	23.3 ± 16.0 (68.7)	18.8 ± 12.4 (66.0)	23.2 ± 16.5 (71.1)

Top: Mould, D R, and R N Upton. 2012. "Basic Concepts in Population Modeling, Simulation, and Model-Based Drug Development." CPT: Pharmacometrics & Systems Pharmacology 1 (9): 1–14.

Right: Zhang, Weijiang, Dominik Heinzmann, and Joseph F. Grippo. 2017. "Clinical Pharmacokinetics of Vemurafenib." Clinical Pharmacokinetics 56 (9): 1033–43. AUC_8 and AUC_{168}: AUC from time zero to 8h or 168 h.

Clinical studies and clinical trials

- A **clinical study** is research using human volunteers (*i.e.* participants), with the intention to add to medical knowledge.
- Two main types of clinical studies: **clinical trials** (also called interventional studies) and **observational studies**. In clinical trials, participants are assigned to specific **interventions** by the investigator, which is not the case in observational studies.
- **Most drug and vaccine candidates fail**.
- Only drugs undergoing successful clinical studies are approved by regulatory agencies. For instance, FDA usually requires that a drug must show statistical significance in two 'adequate and well-controlled' pivotal Phase III studies as a precondition of its approval.

Probability of Success[2] by Clinical Trial Phase and Therapeutic Area

	P1 to P2	*P2 to P3*	*P3 to Approval*	*Overall*
Oncology	57.6	32.7	35.5	3.4
Metabolic/Endocrinology	76.2	59.7	51.6	19.6
Cardiovascular	73.3	65.7	62.2	25.5
Central Nervous System	73.2	51.9	51.1	15.0
Autoimmune/Inflammation	69.8	45.7	63.7	15.1
Genitourinary	68.7	57.1	66.5	21.6
Infectious Disease	70.1	58.3	75.3	25.2
Ophthalmology	87.1	60.7	74.9	32.6
Vaccines (Infectious Disease)	76.8	58.2	85.4	33.4
Overall	66.4	48.6	59.0	13.8
Overall (Excluding Oncology)	73.0	55.7	63.6	20.9

Source: Chi Heem Wong, Kien Wei Siah, Andrew W Lo. "Estimation of clinical trial success rates and related parameters." *Biostatistics* 20(2): April 2019, Pages 273-286. Published online: 31 January 2018. DOI: 10.1093/biostatistics/kxx069

Data between 2000 and 2015 of 406,038 trials (of which 185,994 were unique) and well over 21,000 compounds were collected. The table was formatted by ACSH.

Phases of clinical trials prior to approval

- **Aim:** To get PK data and to verify the drug behaves as expected.
- **Dose:** *Microdosing e.g. <= 1/100 NOAEL (no observed adverse effect level) or pharmacologically active dose.*
- **Subjects:** Usually <15 healthy subjects
- **Time:** A few weeks

- To find a safe dose range and optimal dosing region and identify safety profile. Further PK and PD data are collected.
- Subtherapeutic single and multiple ascending doses
- Usually 20-100 healthy volunteers, in certain indications (e.g. cancer) patients can participate.
- Usually a few months

- To assess efficacy and side effects of the drug, and determine dosing regimen
- Therapeutic dose
- Usually 100-300 patients with a specific disease
- At least a year and longer

- To test efficacy, effectiveness, and safety profiles in a large number of patients, compared with standard-of-care treatment option
- Therapeutic dose
- Usually 300-3000 patients
- Usually several years

* Since early 2000. See an update-to-date review by Burt, Tal, Graeme Young, Wooin Lee, Hiroyuki Kusuhara, Oliver Langer, Malcolm Rowland, and Yuichi Sugiyama. 2020. "Phase 0/Microdosing Approaches: Time for Mainstream Application in Drug Development?" Nature Reviews Drug Discovery 19 (11): 801–18.

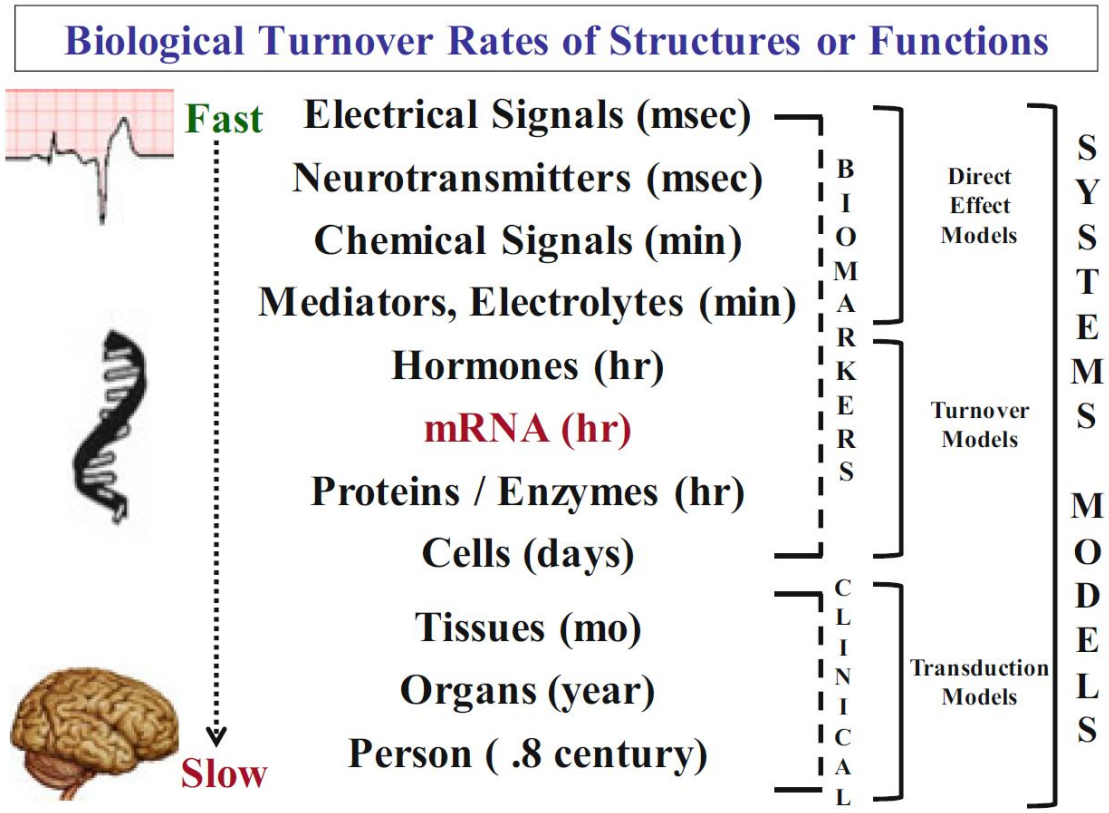
We use clinical endpoints, biomarkers, and surrogate endpoints to judge whether a drug works or not

• **Clinical endpoints:** direct evidence of clinical outcome, reflecting how a patient feels (*e.g.* relieve of anxiety and depression), functions (*e.g.* hospitalization), responds to pathogens (*e.g.* infection rate), or how long a patient survives (*e.g.* progression-free survival, overall survival). It can be expensive and take long to measure them.

• **Biomarkers:** objectively measured and evaluated as an indicator of normal biological, pathogenic processes or pharmacological response to a drug, which can take many forms

- **Biochemical**, *e.g.* alanine aminotransferease (ALT), CD4+, cholesterol
- **Anatomical/morphological**, *e.g.* tumor Size, artery diameter, and imaging results of PET, CT-Scan, MRI, *etc.*
- **Histological**, *e.g.* biopsy pathology, whole blood count (WBC)
- **Other measurements**, *e.g.* Blood pressure, pain relief, QT interval in electrocardiogram, *etc.*

• **Surrogate endpoints:** biomarkers supported by strong evidence so that they may substitute a clinical end point when obtaining registration, *e.g.* neutralising antibodies against spike proteins of the coronavirus in the plasma as a surrogate of reduced rate of infection.



Jusko, William J. 2016. "Foundations of Pharmacodynamic Systems Analysis." In Systems Pharmacology and Pharmacodynamics, edited by Donald E. Mager and Holly H.C. Kimko, 161–75. AAPS Advances in the Pharmaceutical Sciences Series. Cham: Springer International Publishing.