Offline activities of Lecture 7

Q1. What is positron emission tomography (PET)? Why is it often used in drug discovery and clinical development? An sensitive imaging method to monitor drug distribution and pharmacokinetics/-dynamics.
Q2: What does convolution filtering mean in image analysis? Please use your own language to describe it. A linear model to represent pixel by neighbouring pixels.
Q3: What type of filter is used normally to smooth images? Why? The Gaussian filter, parameterized, fast, and flexible.
Q4: What is a closing, and what is an opening in morphological filtering? I like this most by Dominique Ostermayer: '*Closing and opening are best explained in terms of the underlying binary morphological operations dilation and erosion. The image is divided into the set of the pixels belonging to the object of interest (X) and the other pixels. A structuring element S (comparable to a neighborhood of a pixel) is centered at a pixel of the image.* Dilation: all pixels for which the intersection of S and X is nonempty are included; Erosion: all pixels for which S is fully contained in X are included; Closing: first dilation is applied and then erosion is applied to the resulting set E(D(X)); Opening: first erosion is applied and dilation is then applied to the resulting set'.
Q5: What are common measures of co-localization? Pearson's correlation coefficient, overlap coefficient, Manders Colocalization coefficient
Q6: Why we need to calculate the Hessian matrix in image analysis? To reduce background intensity gradients (shading effects) or discontinuities. It helps to resolve the different plane levels, i.e. making a 3D image out of 2D planes.
Q7: What types of geometric image transformations are mostly used? Rigid transformation (translations, rotations), affine transformations (rigid transformation, scalings and skewings), and curved transformation (affine trans., certain nonlinear or elastic deformations)
Q8: In the Google AI blog post: how is the FROC score defined? Why it is necessary? A measure of the sensitivity (percentage of tumors detected) at a set number of allowed false positives. The sensitivity of the algorithm improves if more false positives are allowed.
Q9: in what areas of drug discovery is image analysis used for what purposes? Screening, toxicity studies (pathology), PK/PD studies, and diagnostics

Questions:

- Where does the background signal come from in the case of fluorescent imaging? (Molecular Imaging, p. 128, right column) (1) (imaging technique) instrument setup and imaging parameters—for example, light from the excitation source, camera noise, and ambient light, (3) (sample dependent) autofluorescence of samples, vessels, and imaging media, or the fluorescence resulting from fluorophores not bound to specific targets
- Can the convolution filtering process be seen as something similar as a kernel function in support vector machines (we just had a lecture about that and I found it somewhat similar, that's why I'm asking...but it's perhaps a bit of a stretch) Yes! Convolution is the process of adding each element of the image to its local neighbors, weighted by the kernel.

AMIDD Lecture 8: Pharmacokinetic and Pharmacodynamic Modelling

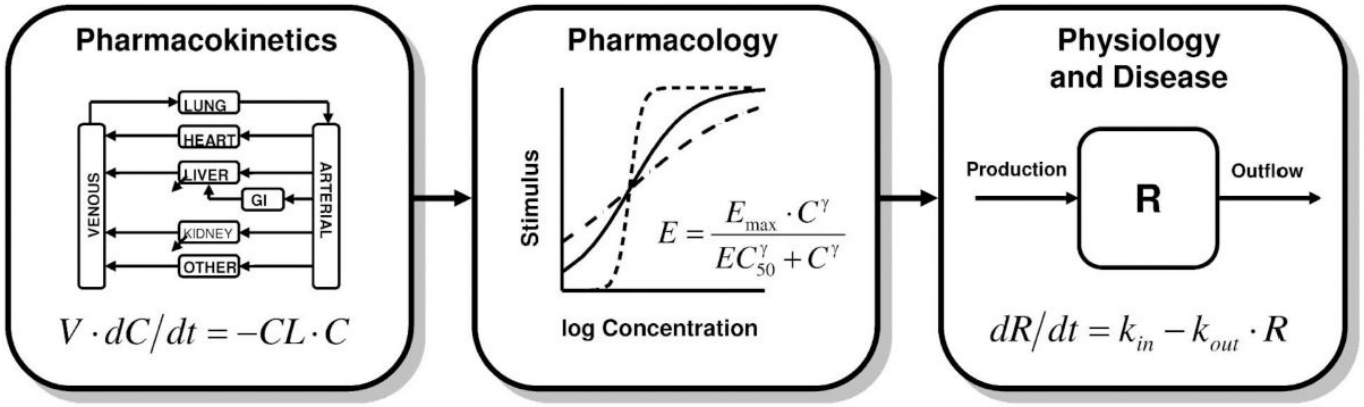

Fig. 1.
Major components of mechanism-based PK/PD models.

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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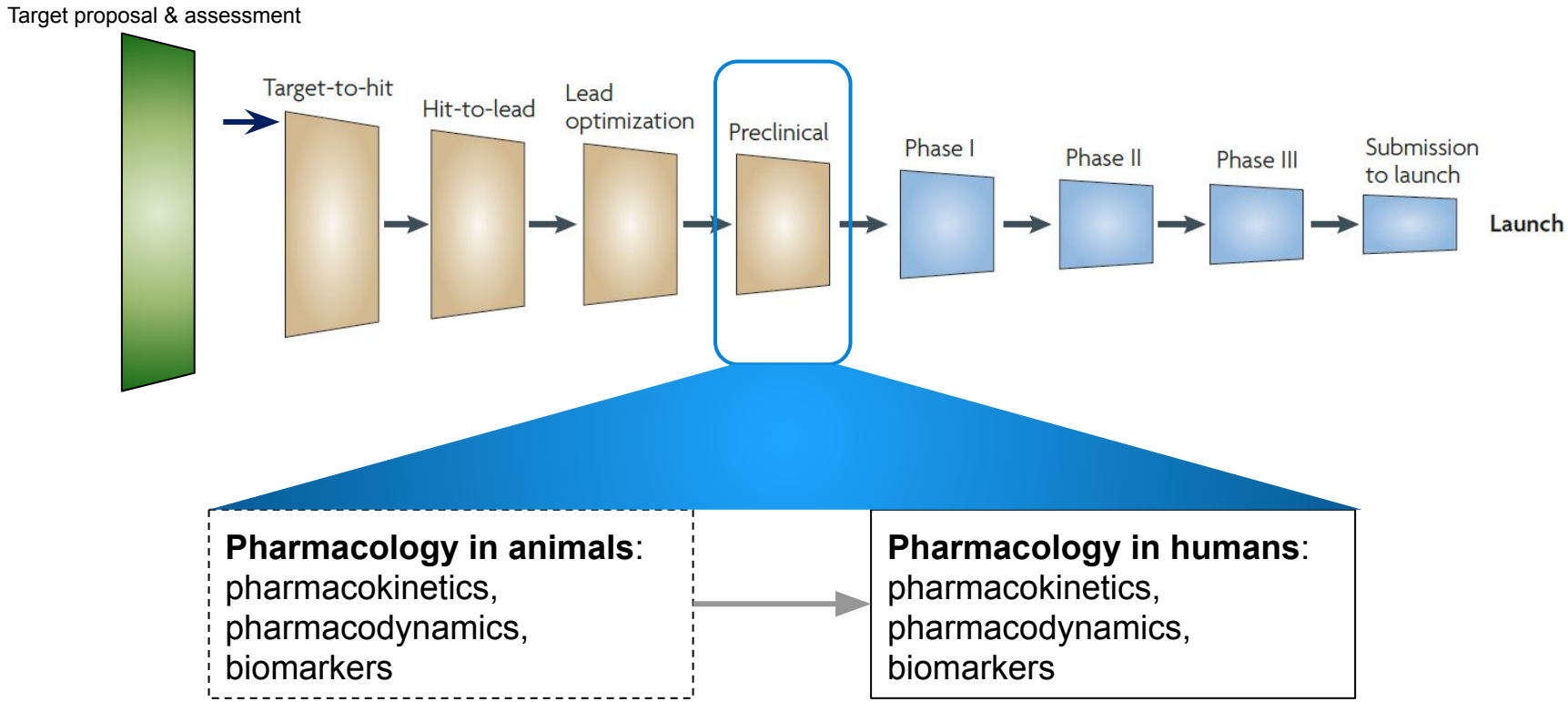
Topics

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

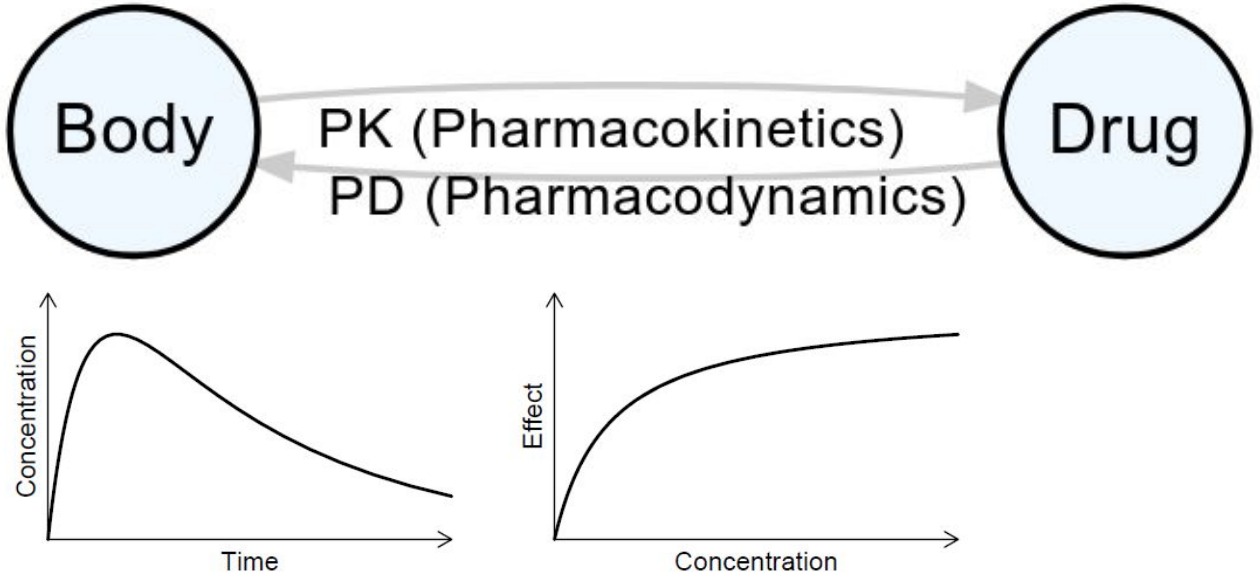
Questions in preclinical development: what to give, how to give, how much, and how often?



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

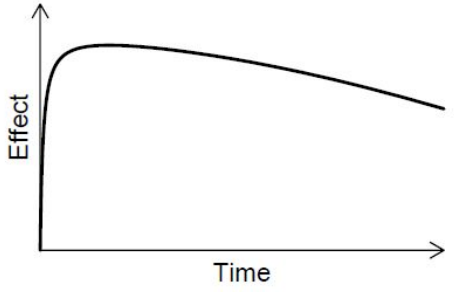
Pharmacokinetic and pharmacodynamic modelling

- 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.



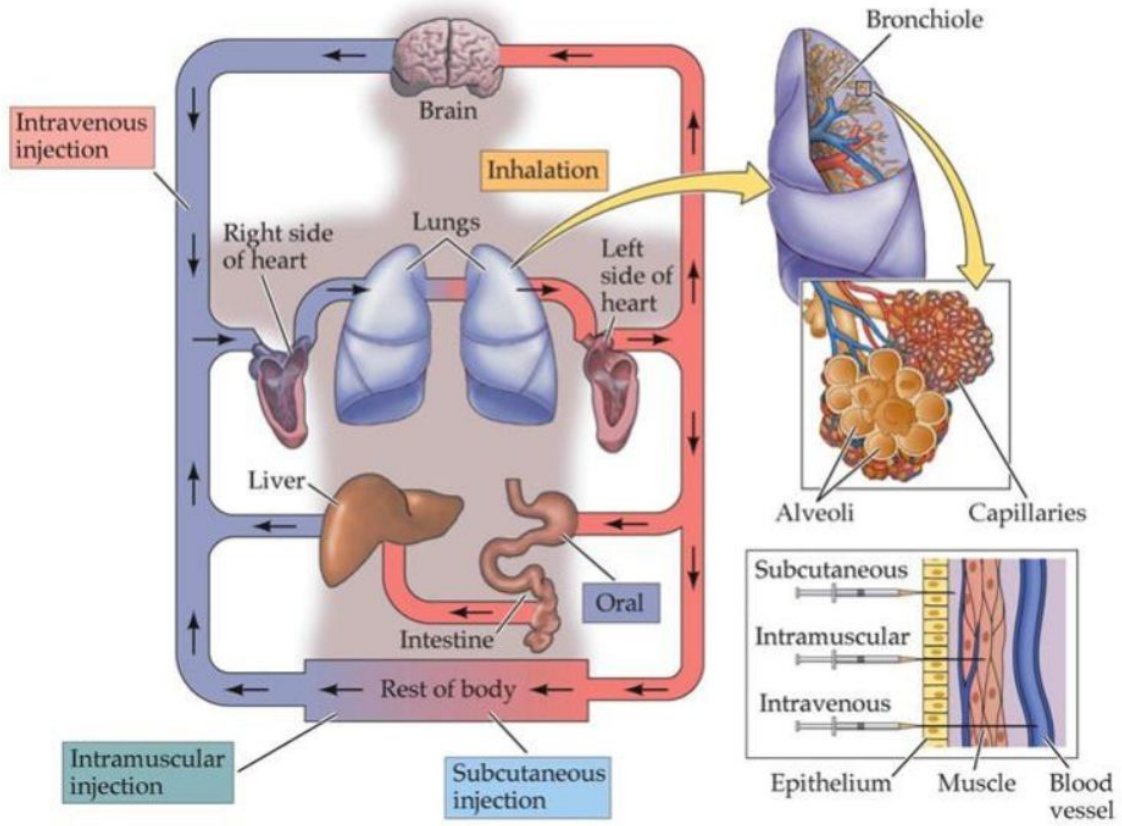
(c) Combined PK/PD model

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

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 (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**.



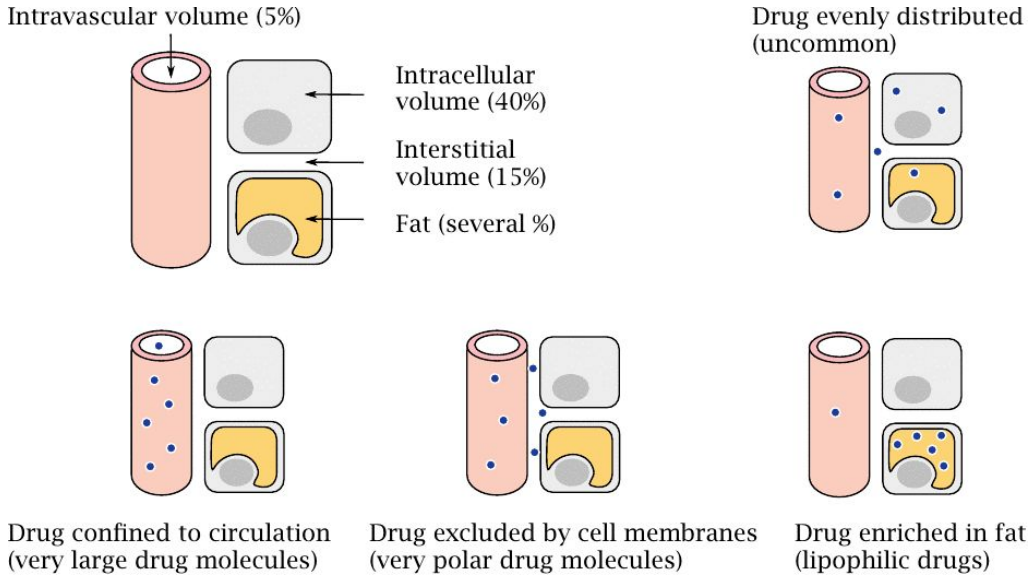
Psychopharmacology, Figure 1.2

Principles of distribution

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.

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.



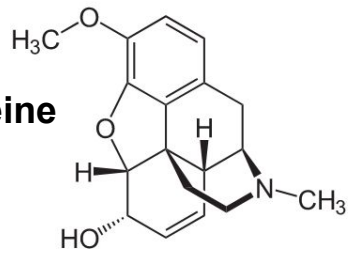
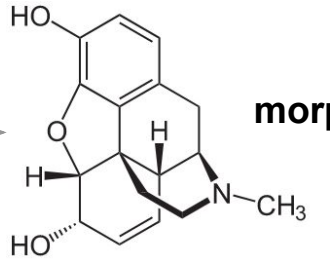
Major components of drug distribution, U Waterloo

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

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

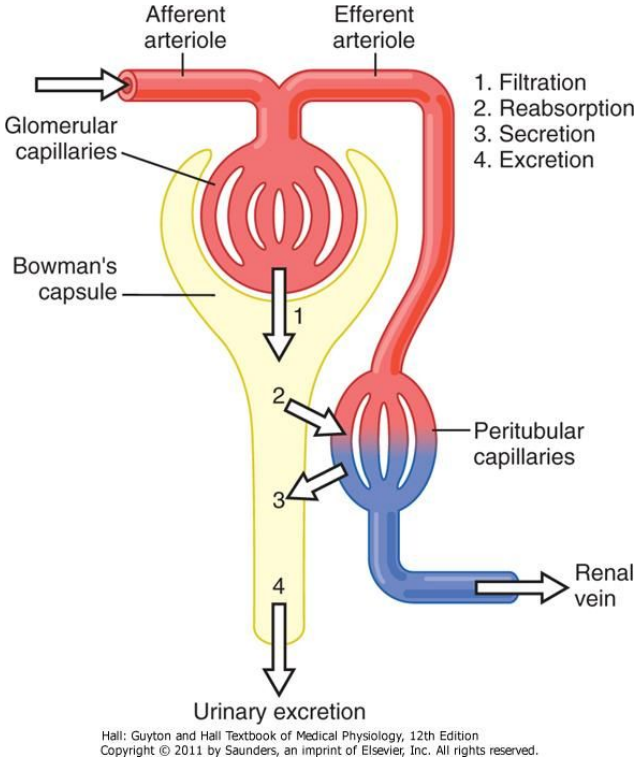
Metabolism

- 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.



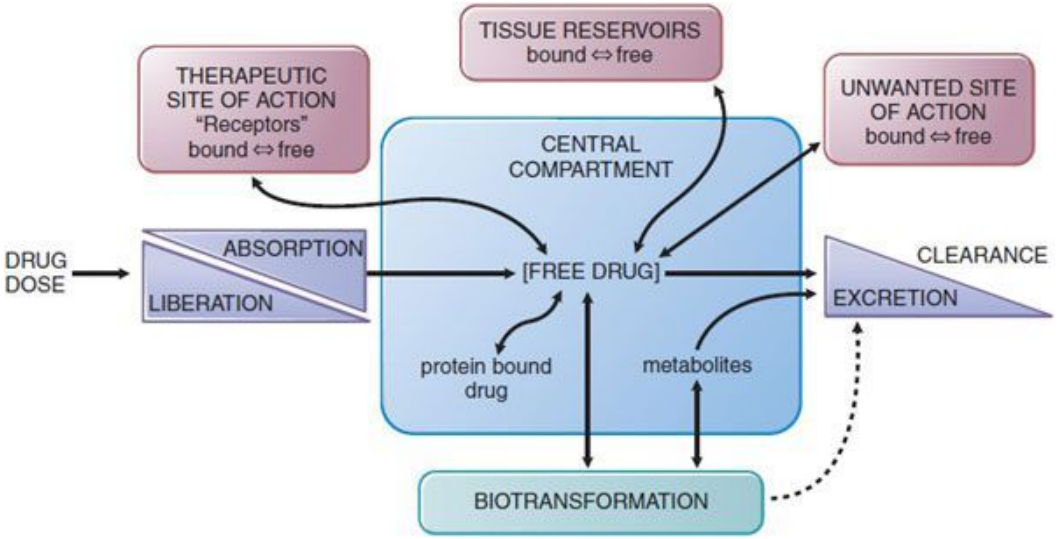
Modelling pharmacokinetics with ADME properties

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?

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



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

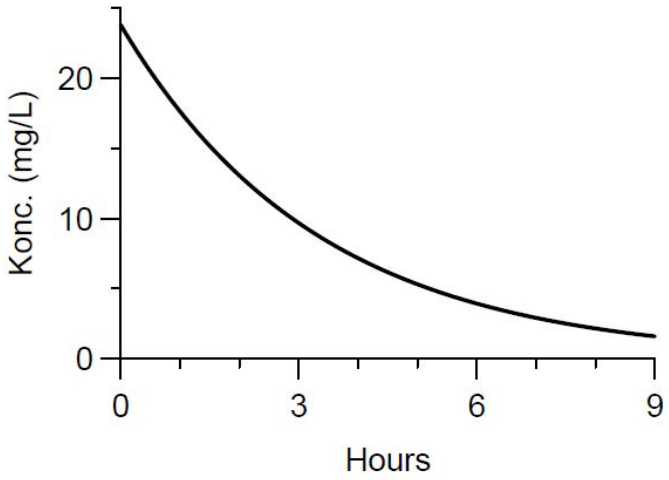
Mathematical modelling of PK: one-compartment model, bolus

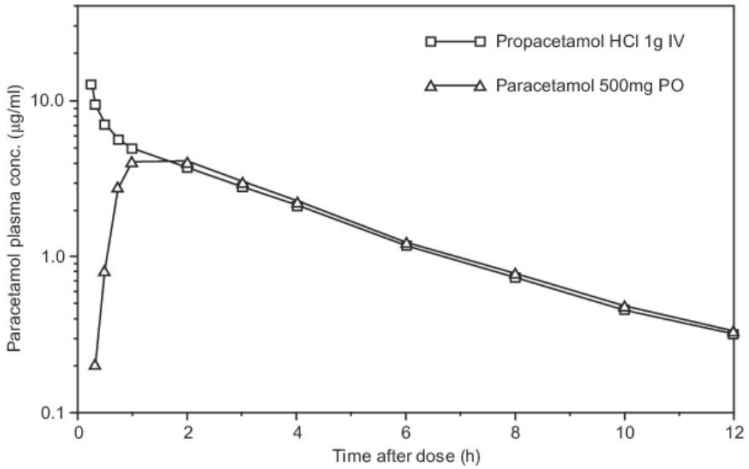
We denote the concentration of the drug as *A*, and the rate of clearance (metabolism and excretion) as *K*. Assuming a bolus dose, according to the law of mass action and first-order kinetics, we can write

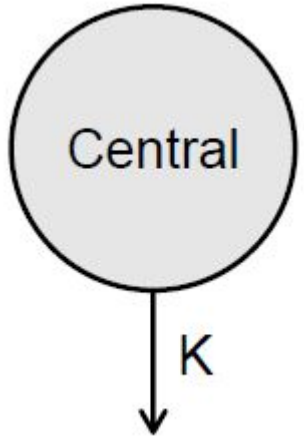
$$\frac{dA}{dt} = -K \cdot A$$

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).

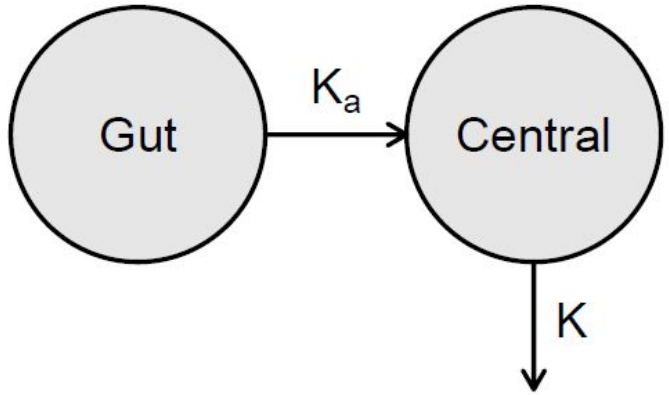
Propacetamol is a pro-drug of paracetamol. The chemical modification (esterification) makes it more water soluble, allowing it delivered via IV.

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

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

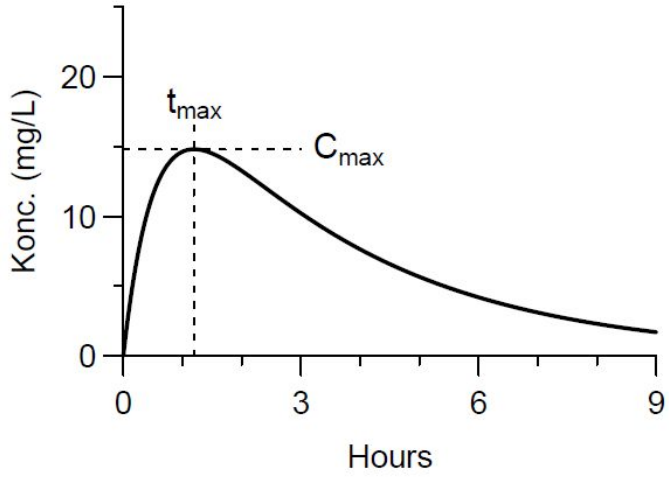


Suppose rate the absorption of the drug is faster than the elimination process (K*a*>*K*), we can model the concentration in the central compartment as

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

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

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

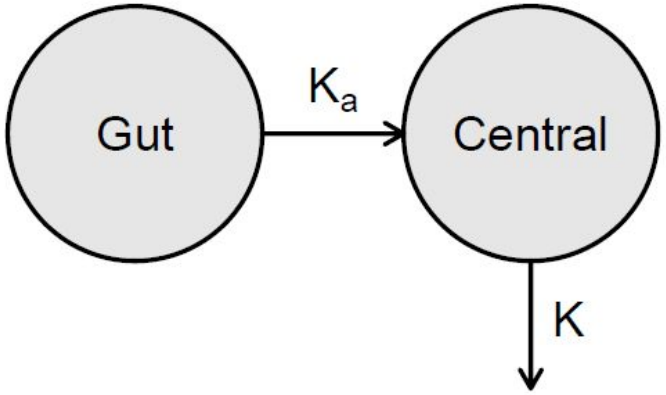
replacing t with t_{max}

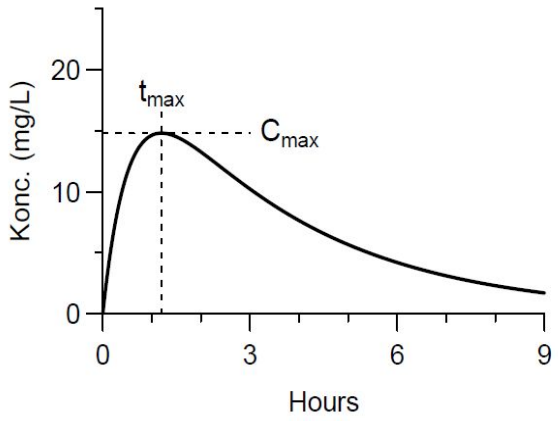
$$C_{max,oral} = \frac{K_a F A_0}{V(K_a - K)}\left(\exp(-K \cdot t_{max}) - \exp(-K_a \cdot t_{max})\right)$$

simplification

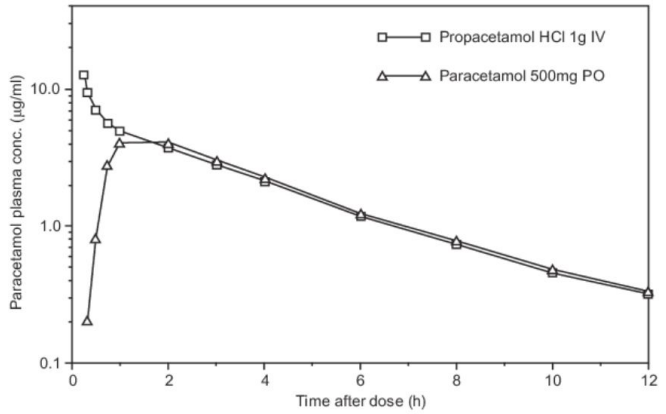
$$C_{max,oral} = \frac{F A_0}{V} \exp(-K \cdot t_{max})$$

- 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?

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

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

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)

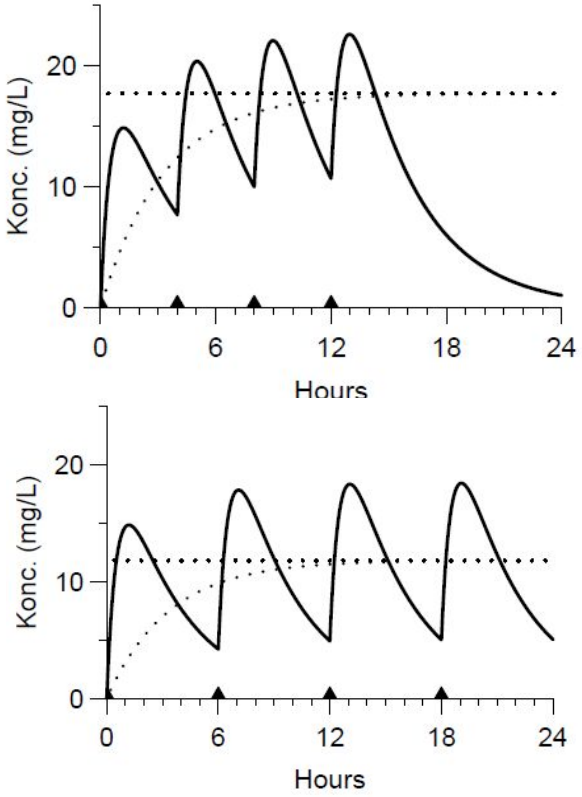
$$R_{in} = \frac{F \cdot A_0}{\tau}$$

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

The system reaches equilibrium when the infusion rate equals the clearance rate (*dC/dt=0)*. Therefore we can deduce the concentration at stead state 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.

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

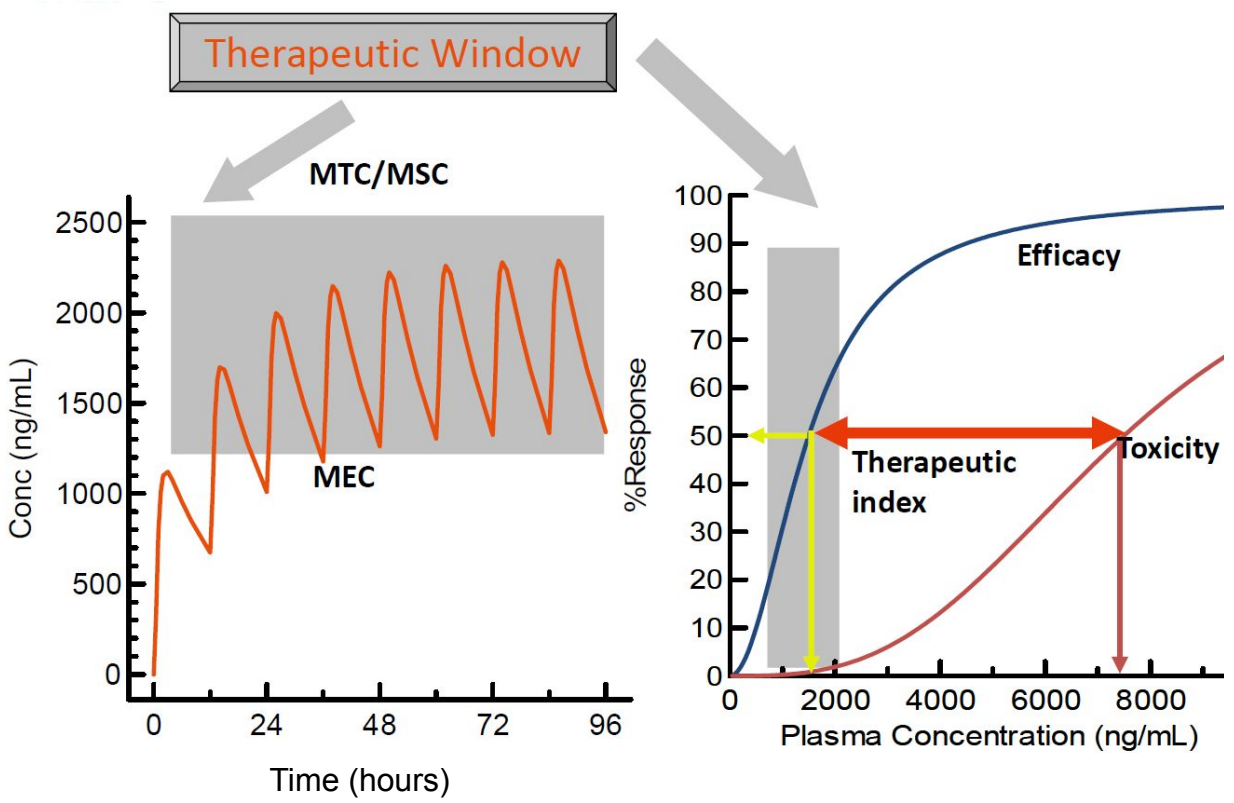
$$C_{SS} = \frac{R_{in}}{CL}$$



Multiple dosing of paracetamol, with 4 oral doses of 1g per dose, shown as a thick line. The dotted line is the constant rate infusion at a corresponding rate.

Why do we care about multi-dosing PK?

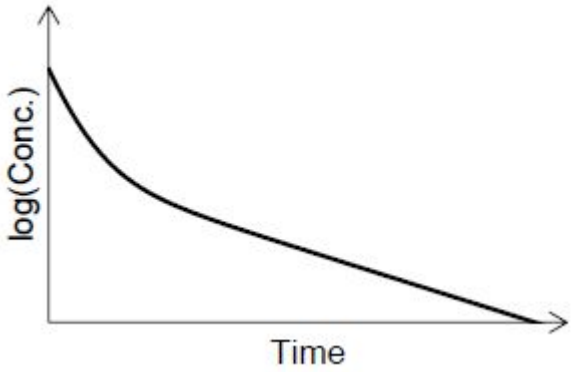
- The PK profile determines
  - dose (how much)
  - dosing regimen (how much, how often, how long)
  - dosage form (which formulation)
  - dosage route (systemic? local?)
- The **therapeutic window** (from the view of PK) or the **therapeutic index** (from the view of PD) determines how much and often 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.



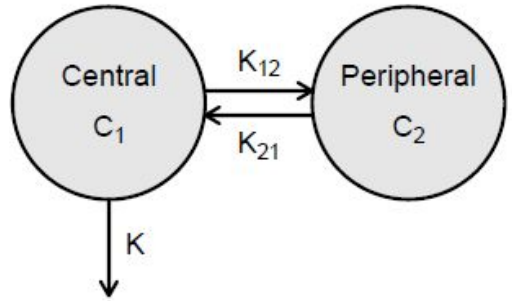
Courtesy of Jun Shi. MEC: minimal effect concentration; MTC/MSC: minimum toxic concentration/maximum safe concentration

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.

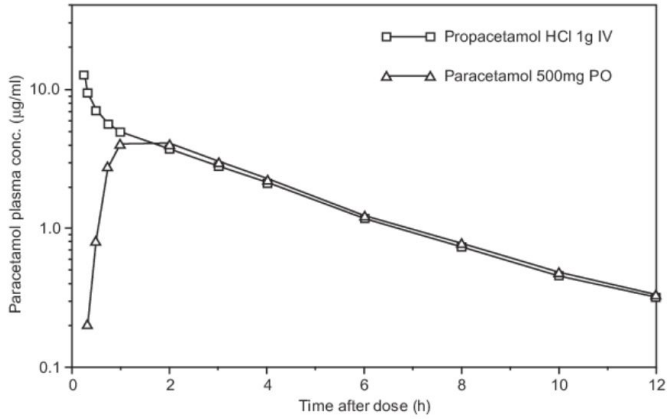
$$\frac{dC_1}{dt} = K_{21} \cdot C_2 - K_{12} \cdot C_1 - K \cdot C_1$$
$$\frac{dC_2}{dt} = K_{12} \cdot C_1 - K_{21} \cdot C_2$$

solution

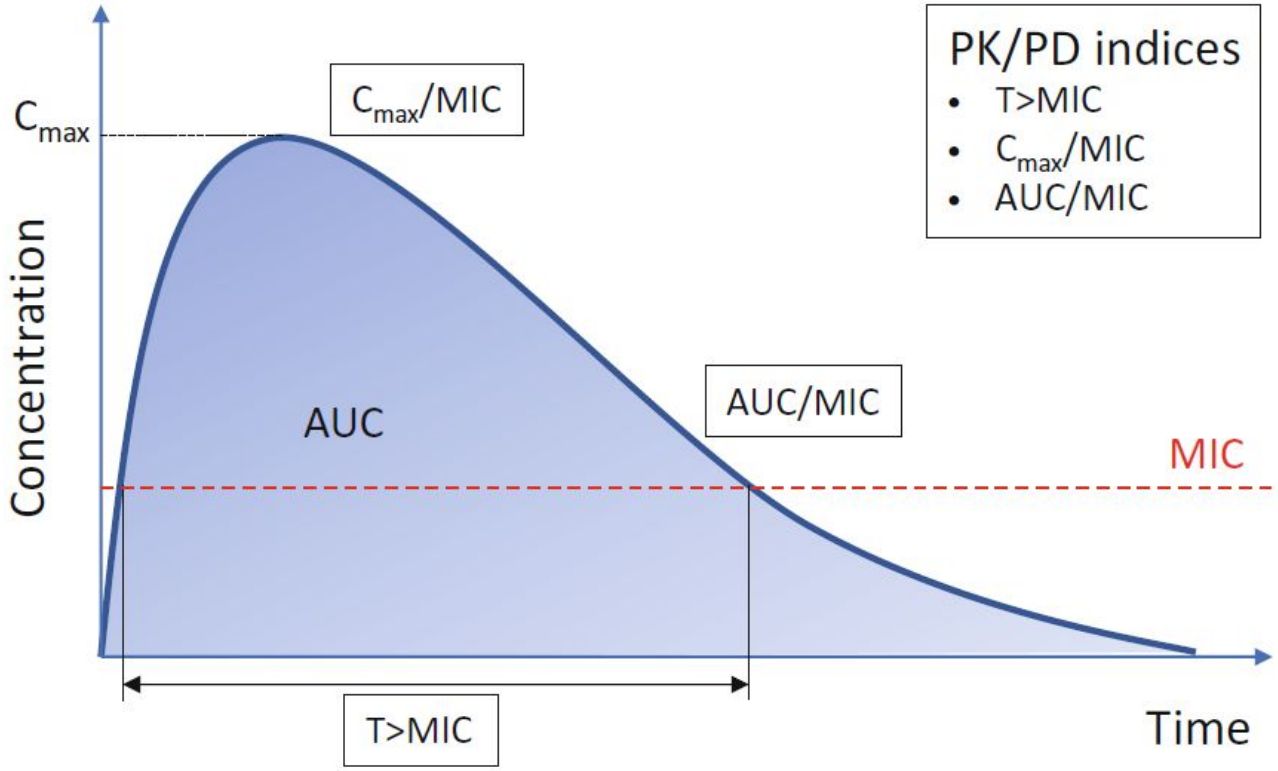
$$C = A \cdot \exp(-\alpha t) + B \cdot \exp(-\beta t)$$

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

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

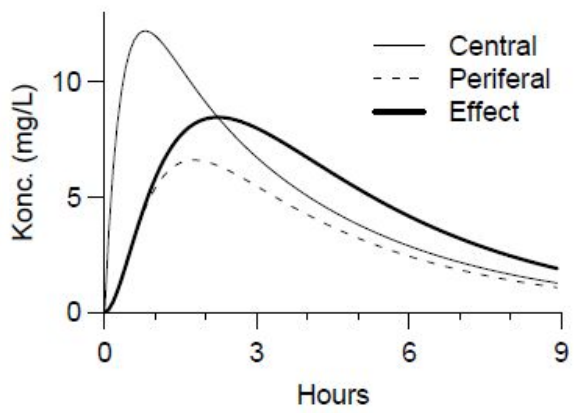


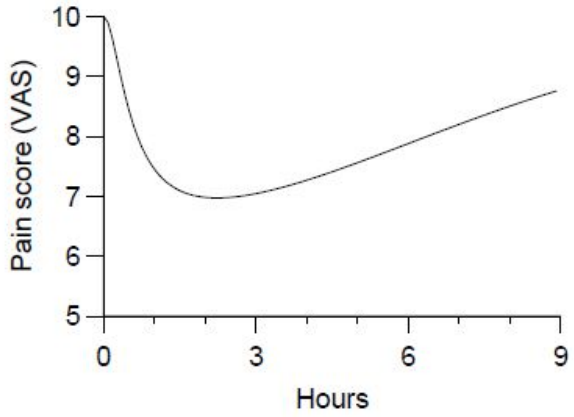
Pharmacokinetic-pharmacodynamic indices of a theoretical drug molecule. MIC: Minimum inhibitory concentration (MIC).

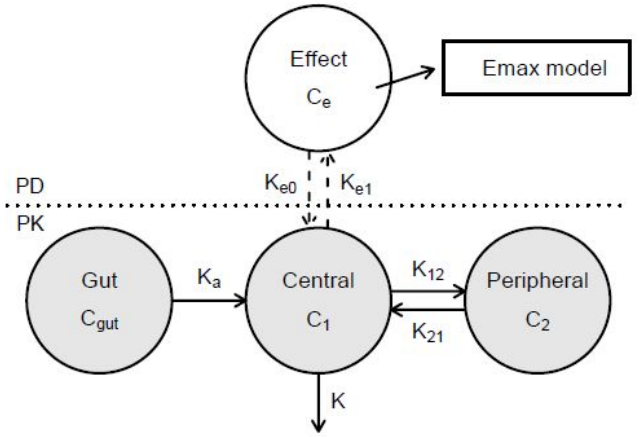
Yu, Yichao, Diether Rüppel, Willi Weber, and Hartmut Derendorf. 2018. "PK/PD Approaches." In Drug Discovery and Evaluation: Methods in Clinical Pharmacology.

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

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

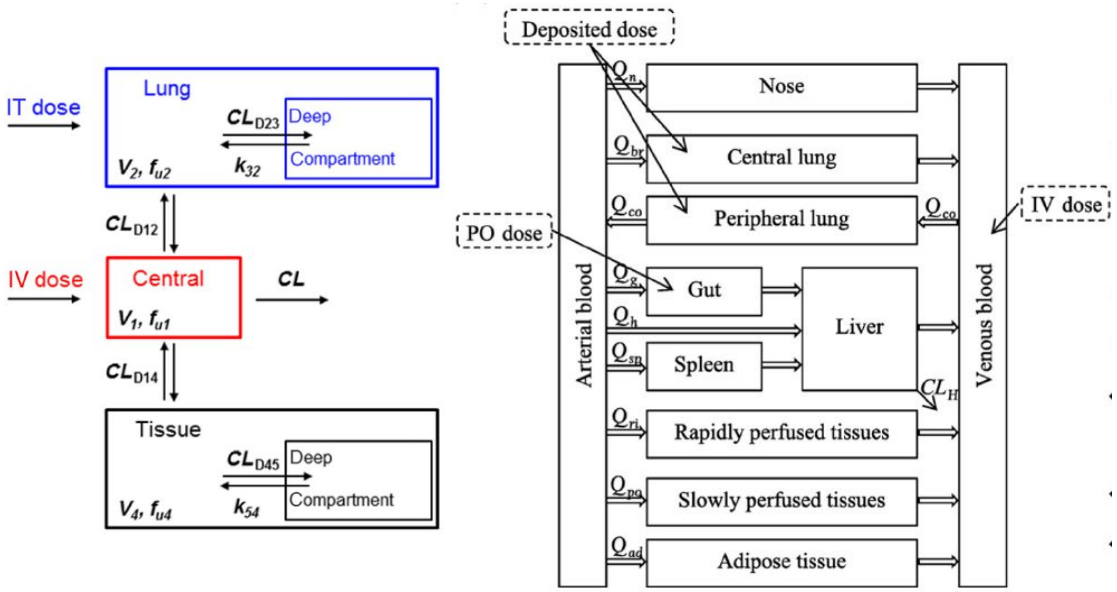
Effect compartment

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

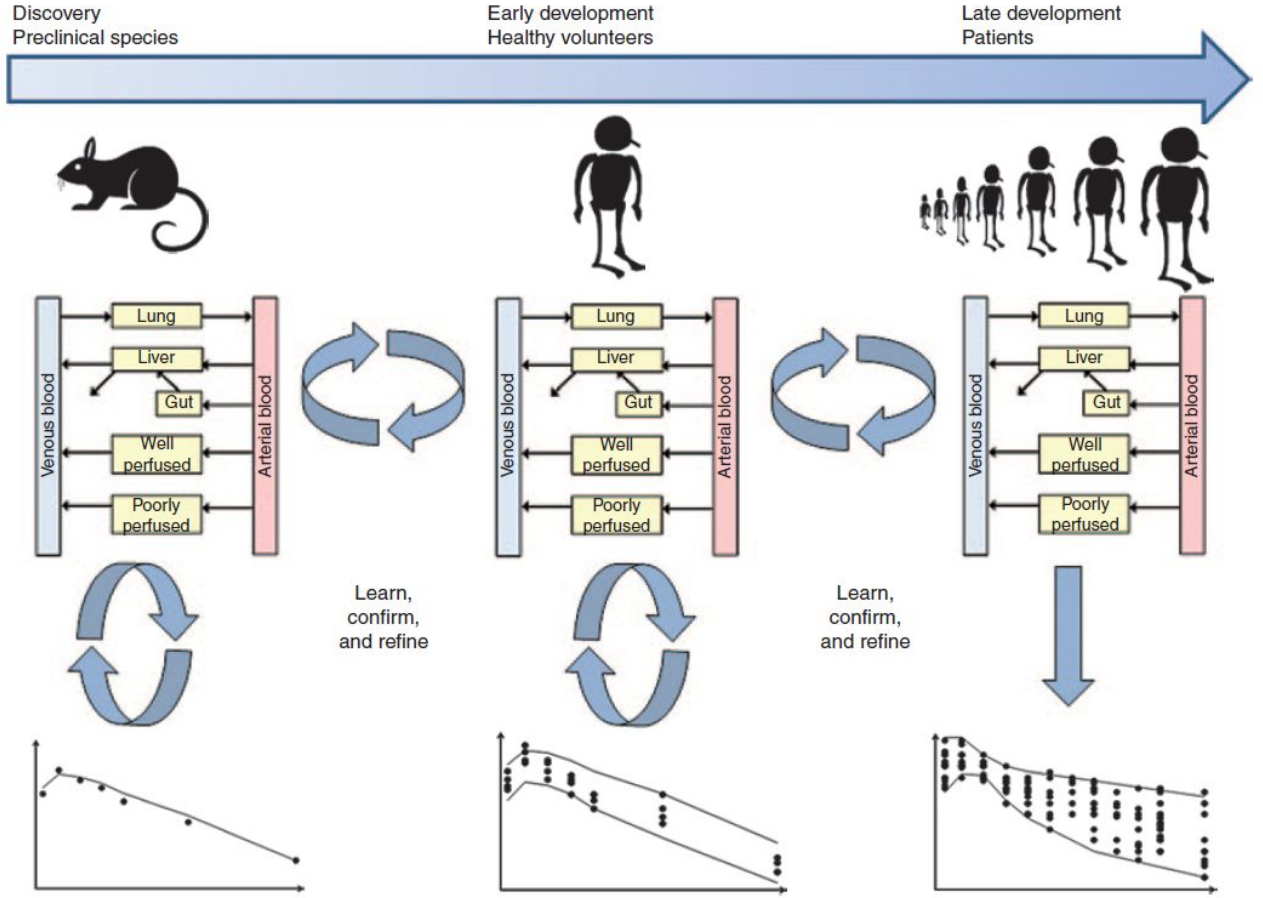
PD model

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

Physiologically based pharmacokinetic (PBPK) models



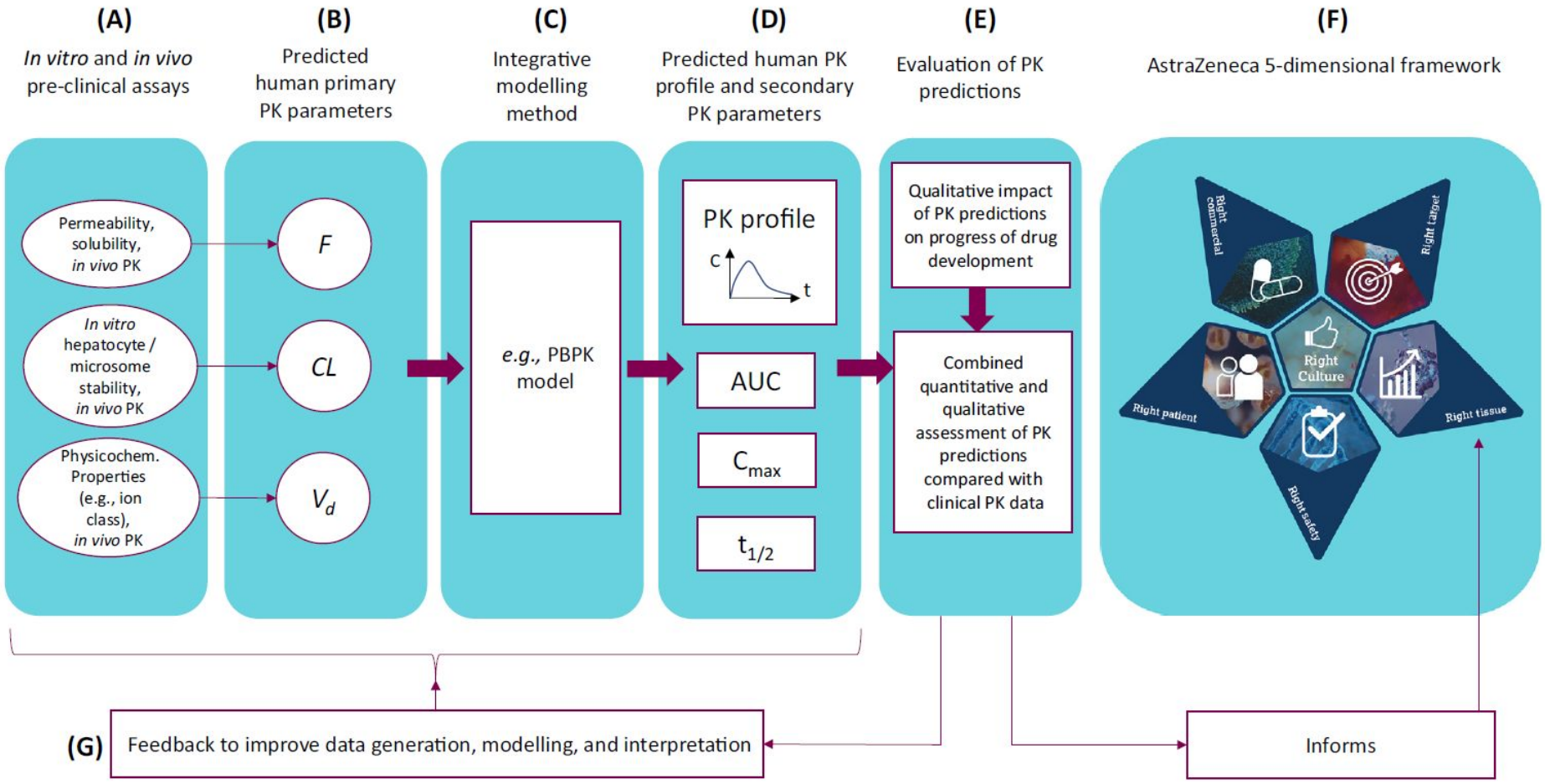
(Left) A semi-physiological model (Right) A fully physiology-based PK model



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

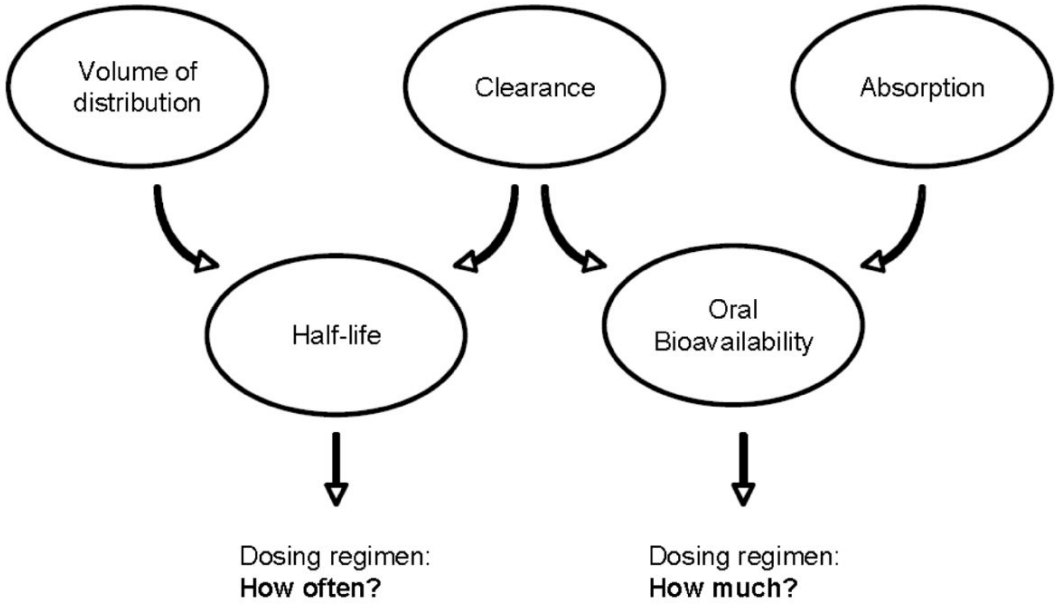


Davies, Michael, *et al.*. 2020. "Improving the Accuracy of Predicted Human Pharmacokinetics: Lessons Learned from the AstraZeneca Drug Pipeline Over Two Decades." Trends in Pharmacological Sciences 41 (6): 390–408.

Summary

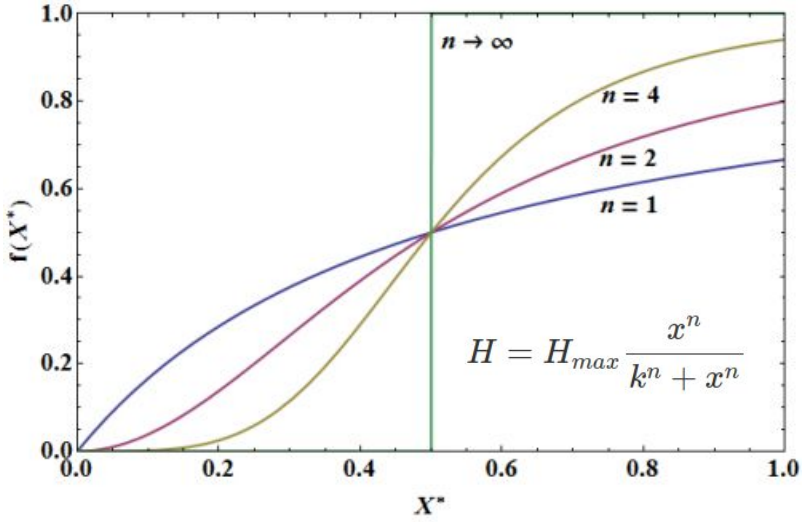
Pharmacokinetics: what the body does to the drug

- 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/3e9f7xmYngehsv8M6
2. 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*

Backup material

Presentation topics and references

1. **Phenotypic screening:**
   - **a.** Kleinstreuer, Nicole C., Jian Yang, Ellen L. Berg, Thomas B. Knudsen, Ann M. Richard, Matthew T. Martin, David M. Reif, et al. 2014. "**Phenotypic Screening of the ToxCast Chemical Library to Classify Toxic and Therapeutic Mechanisms.**" Nature Biotechnology 32 (6): 583–91. https://doi.org/10.1038/nbt.2914.
   - **b.** Moffat, John G., Fabien Vincent, Jonathan A. Lee, Jörg Eder, and Marco Prunotto. 2017. "**Opportunities and Challenges in Phenotypic Drug Discovery: An Industry Perspective.**" Nature Reviews Drug Discovery 16 (8): 531–43. https://doi.org/10.1038/nrd.2017.111.
   - c. Swinney, David C., and Jason Anthony. 2011. "**How Were New Medicines Discovered?**" Nature Reviews Drug Discovery 10 (7): 507–19. https://doi.org/10.1038/nrd3480.

2. **Machine learning**
   - a. Vamathevan, Jessica, Dominic Clark, Paul Czodrowski, Ian Dunham, Edgardo Ferran, George Lee, Bin Li, et al. 2019. "" Nature Reviews Drug Discovery 18 (6): 463. https://doi.org/10.1038/s41573-019-0024-5.**Applications of Machine Learning in Drug Discovery and Development**.
   - b. Yang, Kevin K., Zachary Wu, and Frances H. Arnold. 2019. "**Machine-Learning-Guided Directed Evolution for Protein Engineering.**" Nature Methods 16 (8): 687. https://doi.org/10.1038/s41592-019-0496-6.
   - c. McCloskey, Kevin, Eric A. Sigel, Steven Kearnes, Ling Xue, Xia Tian, Dennis Moccia, Diana Gikunju, et al. 2020. "**Machine Learning on DNA-Encoded Libraries: A New Paradigm for Hit Finding.**" Journal of Medicinal Chemistry, June. https://doi.org/10.1021/acs.jmedchem.0c00452.

3. **Productivity and cost of drug discovery and development**
   - a. Dickson, Michael, and Jean Paul Gagnon. 2004. "**Key Factors in the Rising Cost of New Drug Discovery and Development.**" Nature Reviews Drug Discovery 3 (5): 417. https://doi.org/10.1038/nrd1382.
   - b. Paul, Steven M., Daniel S. Mytelka, Christopher T. Dunwiddie, Charles C. Persinger, Bernard H. Munos, Stacy R. Lindborg, and Aaron L. Schacht. 2010. "**How to Improve R&D Productivity: The Pharmaceutical Industry's Grand Challenge.**" Nature Reviews Drug Discovery 9 (3): 203–14. https://doi.org/10.1038/nrd3078.
   - c. Waring, Michael J., John Arrowsmith, Andrew R. Leach, Paul D. Leeson, Sam Mandrell, Robert M. Owen, Garry Pairaudeau, et al. 2015. "**An Analysis of the Attrition of Drug Candidates from Four Major Pharmaceutical Companies.**" Nature Reviews Drug Discovery 14 (7): 475–86. https://doi.org/10.1038/nrd4609.

4. **Mathematical biology**
   - a. Allen, Richard, and Helen Moore. 2019. "**Perspectives on the Role of Mathematics in Drug Discovery and Development.**" Bulletin of Mathematical Biology, January, 1–11. https://doi.org/10.1007/s11538-018-00556-y.
   - b. Turing, Alan Mathison. 1952. "**The Chemical Basis of Morphogenesis.**" Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences 237 (641): 37--72.
   - c. Tuszynski, Jack A, Philip Winter, Diana White, Chih-Yuan Tseng, Kamlesh K Sahu, Francesco Gentile, Ivana Spasevska, et al. 2014. "**Mathematical and Computational Modeling in Biology at Multiple Scales.**" Theoretical Biology & Medical Modelling 11 (December). https://doi.org/10.1186/1742-4682-11-52.

Presentation and project explained

Deadline: Slides and name(s) of the presenters need to submitted to me one day before the presentation.

Grading: Partly determined by the median scores your peers give you (70%), whether or not you present, and partly given by me as a group score (30%).

Project:

- You will write a short assay (1000-2500 words) introducing a mathematical/computational concept for non-experts, with examples and ideally application in drug discovery.
- The concepts are selected from the reference papers of the presentation topics by me, and you can select which one you want to work on.
- Your work will be published on the website unless you explicitly do not wish that. Details will be distributed next week.

Any questions?

Internship announcement

Machine Learning for Automated image processing and feature selection in the context of Vascular Tube Formation Assays

- Angiogenesis is involved in many diseases. Simple and scalable assays like Endothelial Tube Formation have been around for many years but have started to give quantitative results only recently.
- Thanks to semi-automated image segmentation and quantification, it is possible to extract basic network topology metrics, such as the total network length, the connectivity of the network, the number of nodes, etc. Nevertheless, it remains a challenge to relate these metrics to physiopathological phenotypes, which has not been addressed either in the literature or in practice.
- We propose to take advantage of the complex (but low throughput) assays that we are developing in-house, like microfluidic-based 3D vascularization (organs-on-chip) or microfluidic-based sprouting assays, in addition to molecular phenotyping, to help understand endothelial network formation in the context of the tube formation assay.
- Using thousands of images that are generated with known public and internal compounds related to vascular biology, the student will **build machine learning models to identify combinations of meaningful metrics that can correlate with the pathophysiological conditions**. He or she will develop the analysis pipeline, identify the best-performing models, and explore these models for explanatory and predictive purposes.

Solving the two-equation system with 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

$$\mathcal{L}A = \frac{k_a FD}{(s+k_e)(s+k_a)}$$

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

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

so that (divide by V)

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

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