Pharmacometrics

Introduction to Pharmacokinetics

Novartis-Academia Hackathon

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Overview

- Target Audience: people with a quantitative background that are new to pharmacometrics.
  - Simple, linear differential equations will be used
- Topics covered
  - Absorption, Distribution, Metabolism and Elimination (in reverse order)
  - Clearance (the most important PK parameter)
  - Volume of distribution
  - 1 and 2 compartment models
  - Allometric scaling
- Key take-aways
  - The "fundamental law" of PK: $C_{avg,ss} = \frac{F \cdot Dose}{CL \cdot \tau}$ (true for linear PK)
  - PK models are motivated by known pharmacology, but parameters are empirical and may not directly relate to physiological parameters

Acknowledgements
(Based on material from)

- Rowland, M., Tozer, T. N. *Clinical pharmacokinetics and pharmacodynamics: concepts and applications*
- Peter Bonate, Astellas
- Richard Brundage, U Minnesota
- Leon Aarons, U Manchester
- Jean-Louis Steimer, Novartis
- Martin Fink, Novartis
- Nick Holford, U Auckland http://holford.fmhs.auckland.ac.nz/Teaching/pharmacometrics/advanced.php

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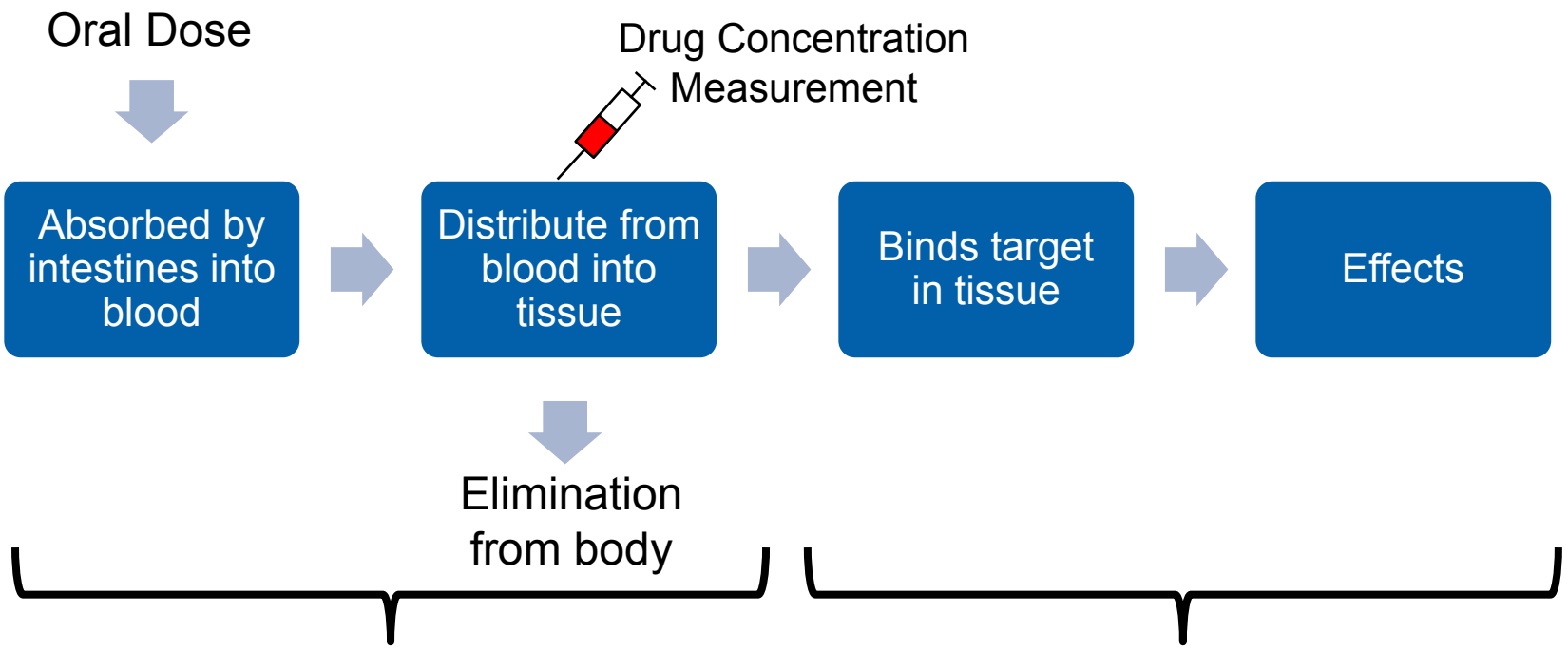
Motivation – the importance of finding the right dose of a drug

- Tylenol helps to reduce pain and fever and is safe at daily doses ≤3,000 mg/day
- >5,000 mg/day can cause liver damage
- >10,000 mg/day can be lethal.
- You can learn about safety and efficacy from clinical trials
- Making best use of this data requires models to integrate the data

(paracetamol)

Johnson & Johnson

The “PKPD” pathway of drug effect



Pharmacokinetics (PK):
How body affects drug

Should children and adults receive the same dose?

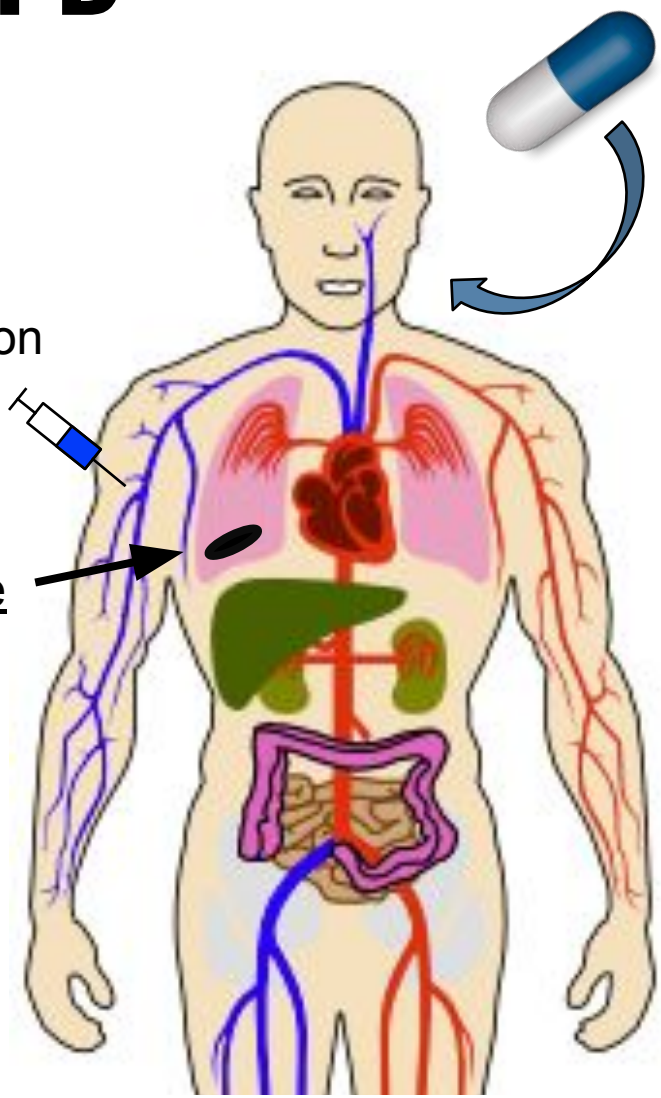
Pharmacodynamics (PD):
How drug affects body

What dose is needed to shrink a tumor without causing severe neutropenia

Measuring PKPD

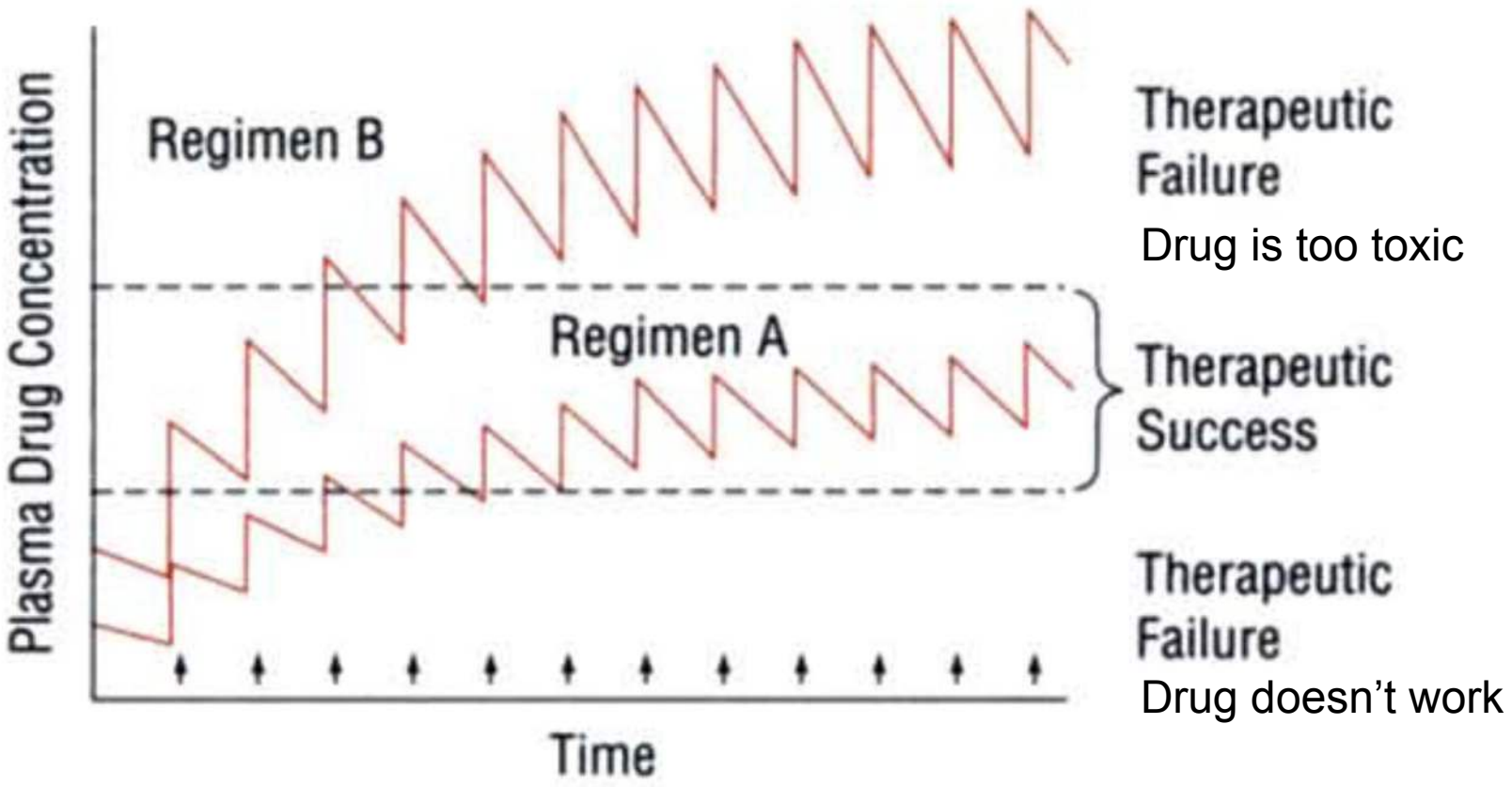
PK (Pharmacokinetics) example
Measurement of drug concentration from circulation

PD (Pharmacodynamics) example
Change in tumor size, as measured by X-Ray



Dose Regimen
- amount given
- frequency
- method (oral, patch, etc.)

Understanding PKPD can help in picking the optimal dose regimen



From Rowland and Tozer

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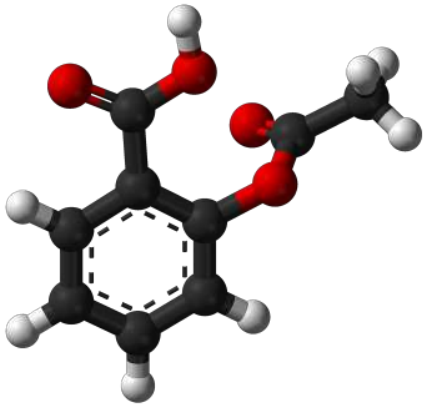
Types of Drugs

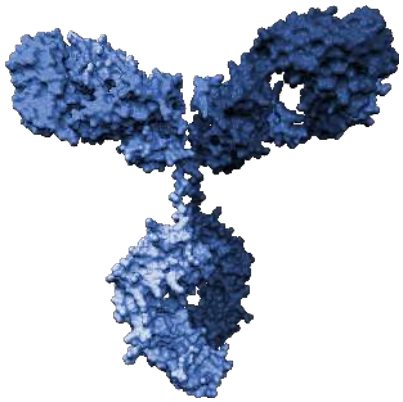
Small Molecule



~1 nm
500 Da

Aspirin
Tylenol

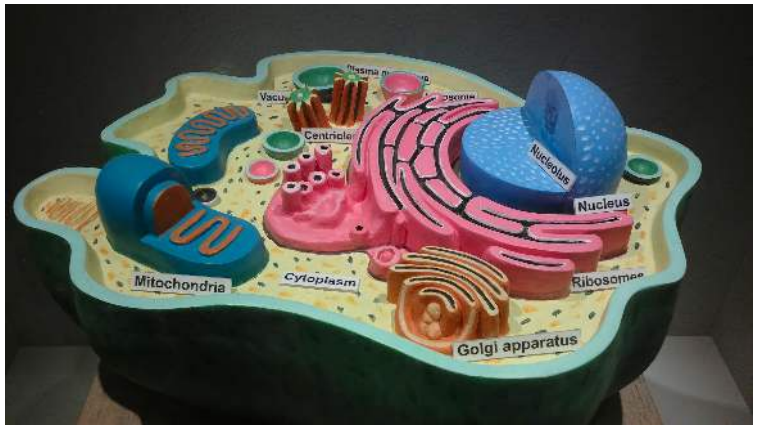
Antibody



~10 nm
150,000 Da

Humira
Keytruda

Cell Based Therapies



100,000 nm
~10^{14} Da

Kymriah
Stem Cell Transplant

Introduction to Pharmacokinetics

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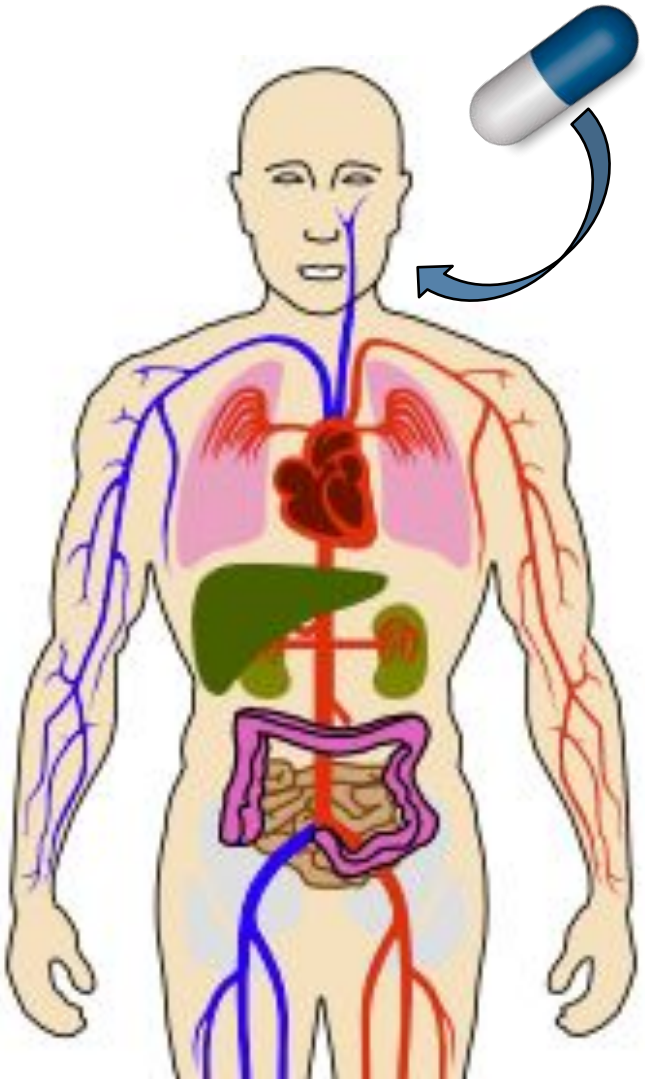
Why Do We Measure Blood or Plasma Concentrations When the Site of Action is Someplace Else?

Key process of pharmacokinetics (ADME)

- Absorption
- Distribution
- Metabolism
- Excretion



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Volume of Distribution

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Key Lessons

- For intravenous dose
  - Initial Concentration = Dose/Volume
  - Volume is a “theoretical concept” and does not necessarily reflect blood or body volume

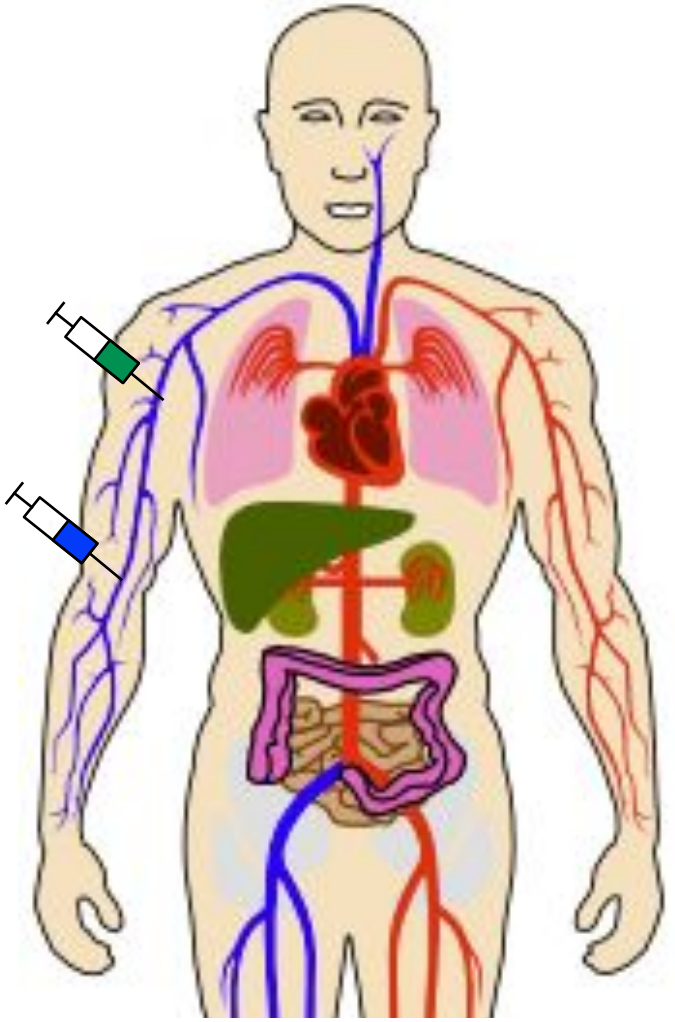
Definition of dose and concentration

Dose
Measurement: Mass
Units: mg

Concentration (C)
Measurement: Mass/Volume
Units: mg/ml

Volume (V)
"Theoretical Volume" needed to contain administered drug at the measured concentration

Key Formula
Right after IV dosing (time = 0)
$C(0) = Dose/V \rightarrow V = Dose/C_0$



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Volume of distribution example

C_0 = Dose/V or Dose=C_0 V

Drug Concentration in Beaker

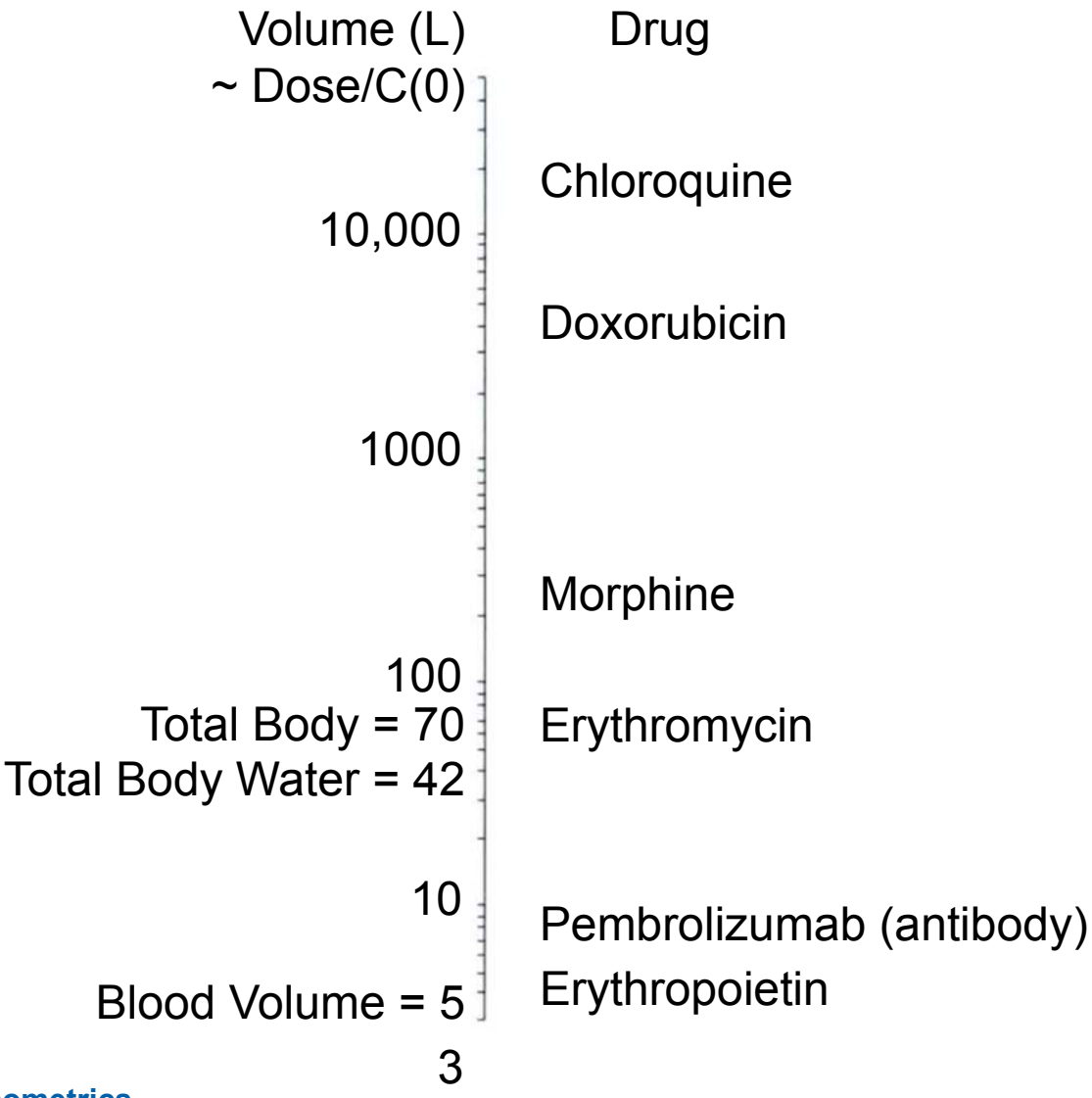
Dose = 1000 mg
C_0 = 20 mg/mL
V = 50 mL

Drug Concentration with Activated Charcoal (absorbs drug)

Dose = 1000 mg
C_0 = 0.2 mg/mL
V = 5000 mL

From Pete Bonate

Volumes for different drugs



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How can chloroquine have a volume of 10,000L, the size of an X?

- A drug may appear to have a larger volume if
  - It is lipophilic (sticks to fat, instead of water) and distributes to body and is not observed in blood.
  - Accumulates in red blood cells and not present in the plasma sample
- Key lesson: Volume (and all PK parameters) are “apparent” and cannot always be easily related to physiological properties

10,000 L

https://www.watertankfactory.com.au/water-tanks/r10000-litre-rainwater-tank/

Key Lessons

- Volume relates amount in body to concentration measured in circulation.
- Volumes are not necessarily physiologically meaningful and can be as large as 10,000 L.

Pharmacokinetics after single intravenous bolus dose

Part 1 – focus on elimination (ignore distribution)

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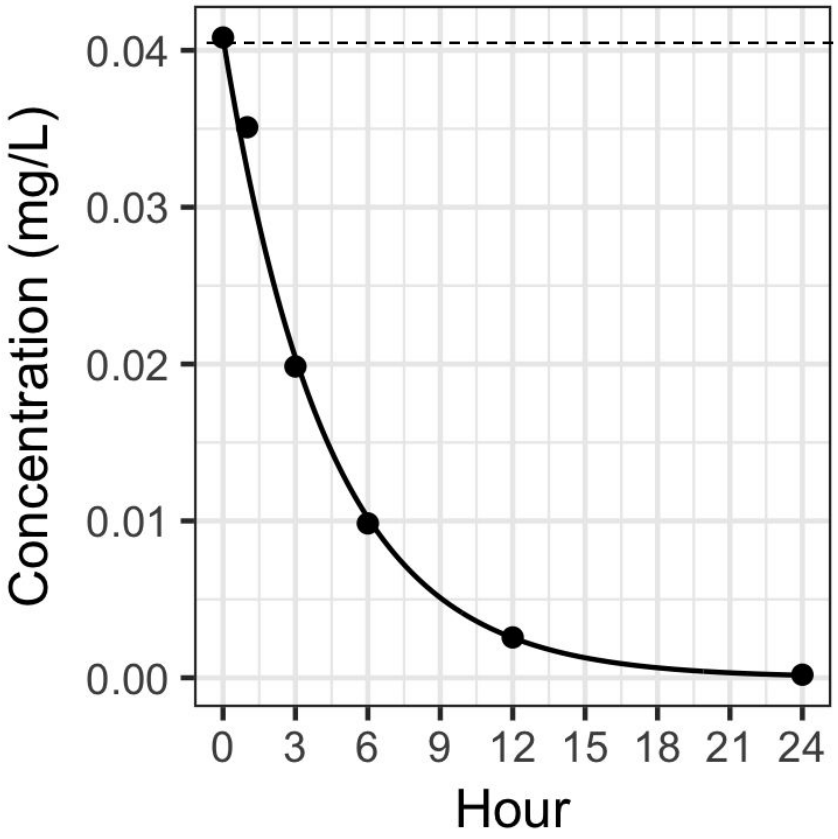
Examples of intravenous drugs

- Chemotherapies (doxorubicin)
- Pain medications (morphine)
- Increase blood pressure (epinepherine)

Drug concentration over time



Dose = 10 mg

C_0 = 0.04 mg/L

V = Dose/C_0
= 250 L

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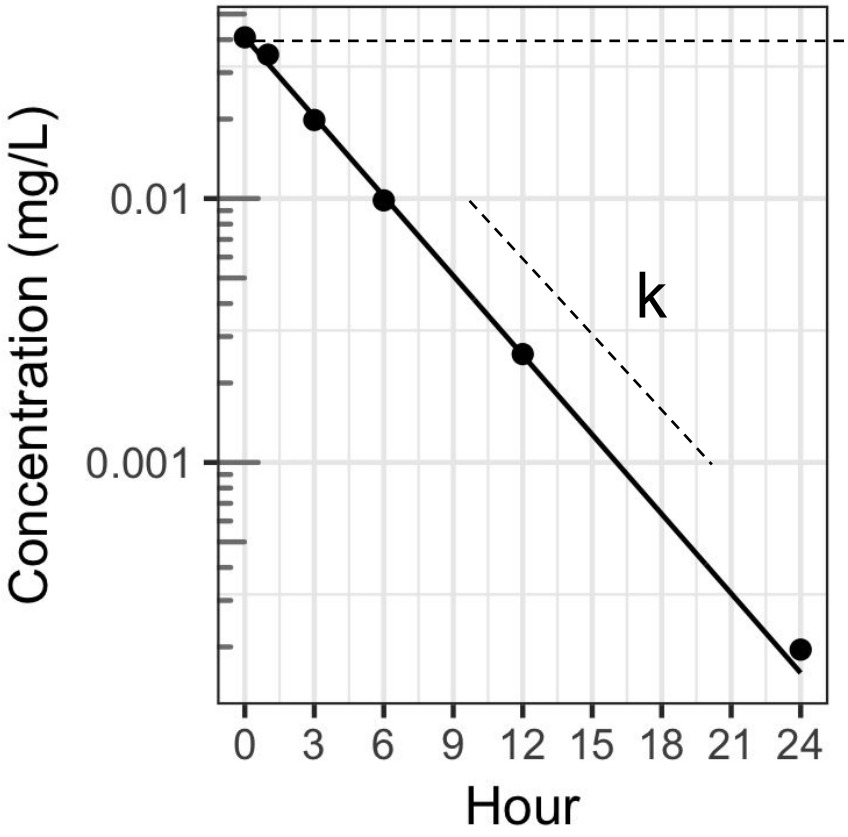
Drug concentration over time
Log scale



Dose = 10 mg

C_0 = 0.04 mg/L

V = 250 L

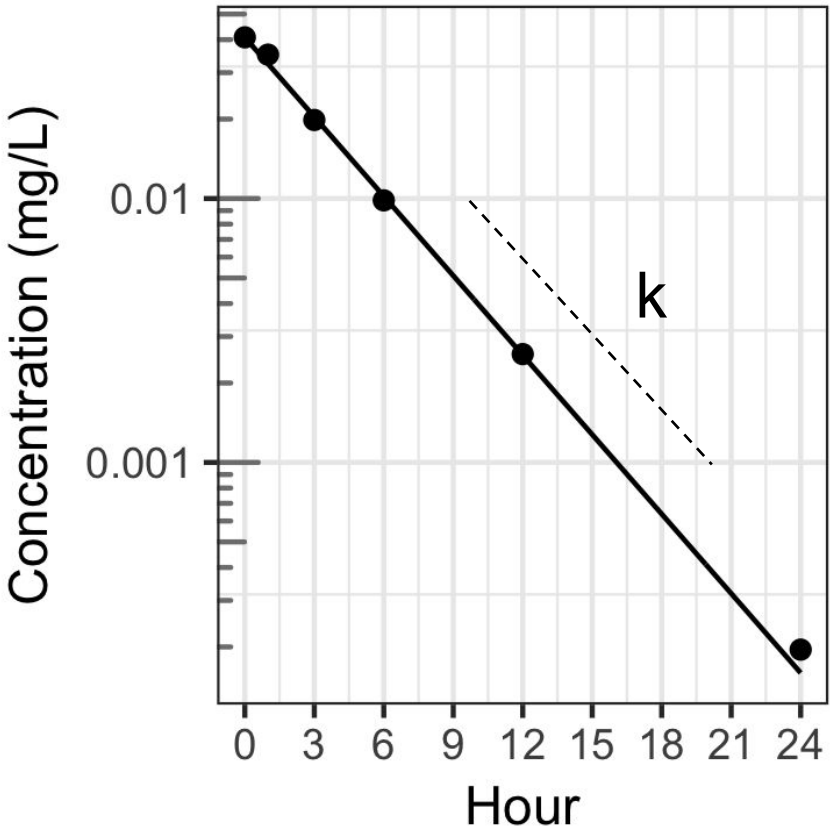
k = 0.23/h
= elimination rate
units = 1/time

$$C(t) = C_0 e^{-kt}$$

$$\begin{aligned} Amt(t) &= V \cdot C(t) \\ &= V \cdot C_0 e^{-kt} \\ &= Dose \cdot e^{-kt} \end{aligned}$$

Half-life definition – how long for half of drug to be eliminated

$$C(t) = C_0 e^{-kt}$$



How long does it take for half the drug to be eliminated?

At what time does:

$$½ \cdot C_0 = C_0 e^{-kt_{1/2}}$$

$$½ = e^{-kt_{1/2}}$$

$$\ln(½) = -kt_{1/2}$$

$$\boxed{\frac{0.693}{k} = t_{1/2}}$$

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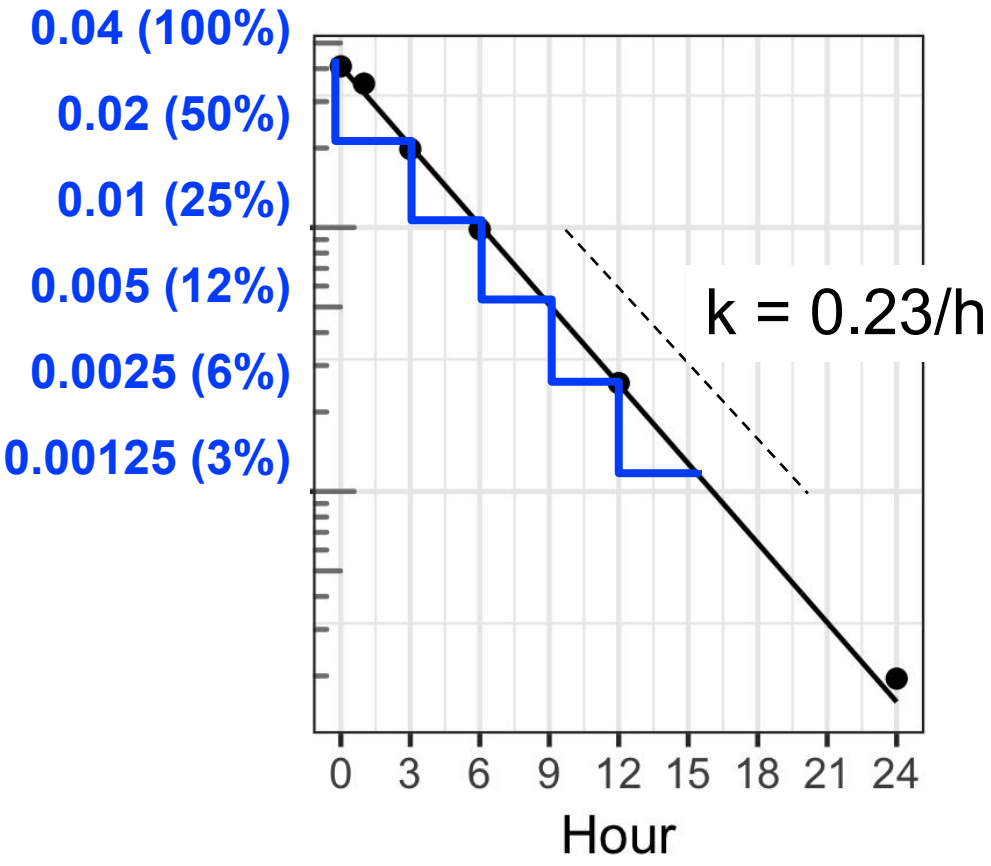
Half-life example

$$C(t) = C_0 e^{-kt}$$



$$t_{1/2} = \frac{0.693}{k} = \frac{0.693}{0.23/h} = 3\ h$$

Every 3 hours,
concentration declines by half

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The shorter the terminal half-life, the more frequently the drug is dosed

Name	Half-life	Dose Frequency
Tylenol	3 hours	4 per day
Aleve	14 hours	2 per day
Keytruda	25 days	1 per 3 weeks

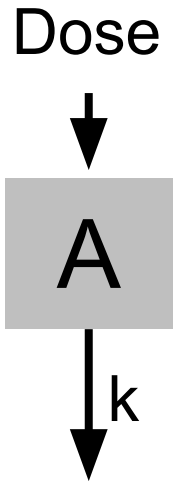
Dosing interval also depends on duration of effect

SEE QUIZ QUESTIONS

Compartmental Model

Concentration (mg/L): $C(t) = C_0 \cdot e^{-kt}$

Amount (mg): $A(t) = Dose \cdot e^{-kt}$



Rate of change of amount in body

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

Mathematical introduction to Clearance [L/h]

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

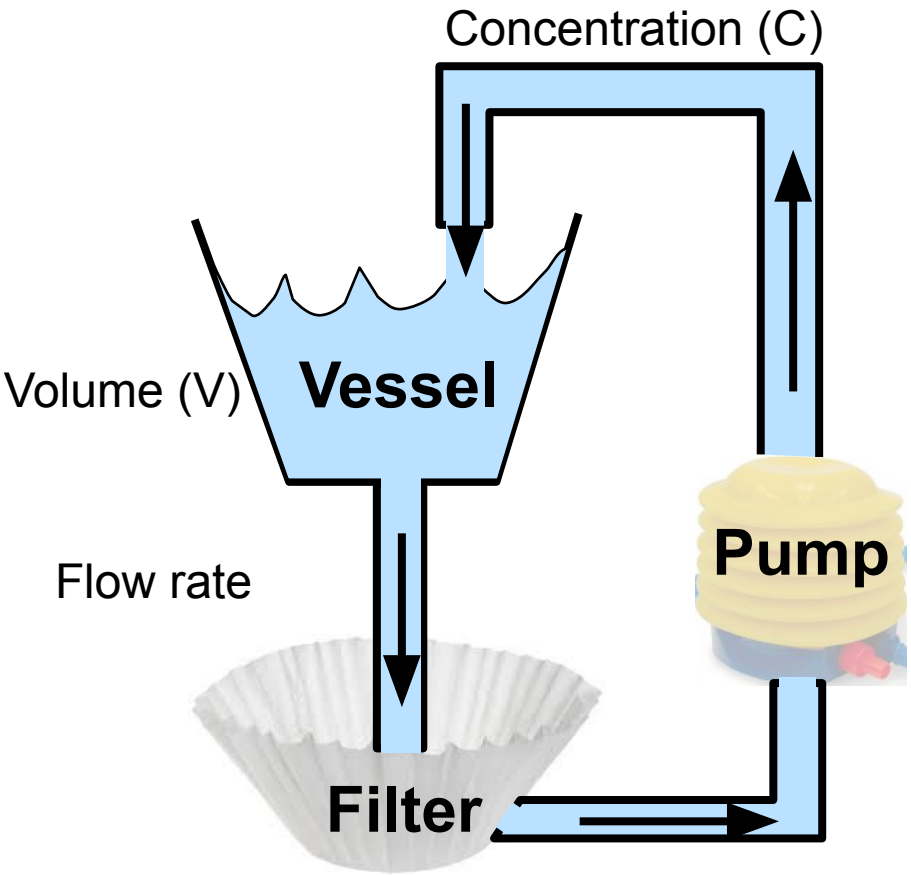
$$\frac{dA}{dt} = -(k \cdot V) \cdot \left(\frac{A}{V}\right)$$

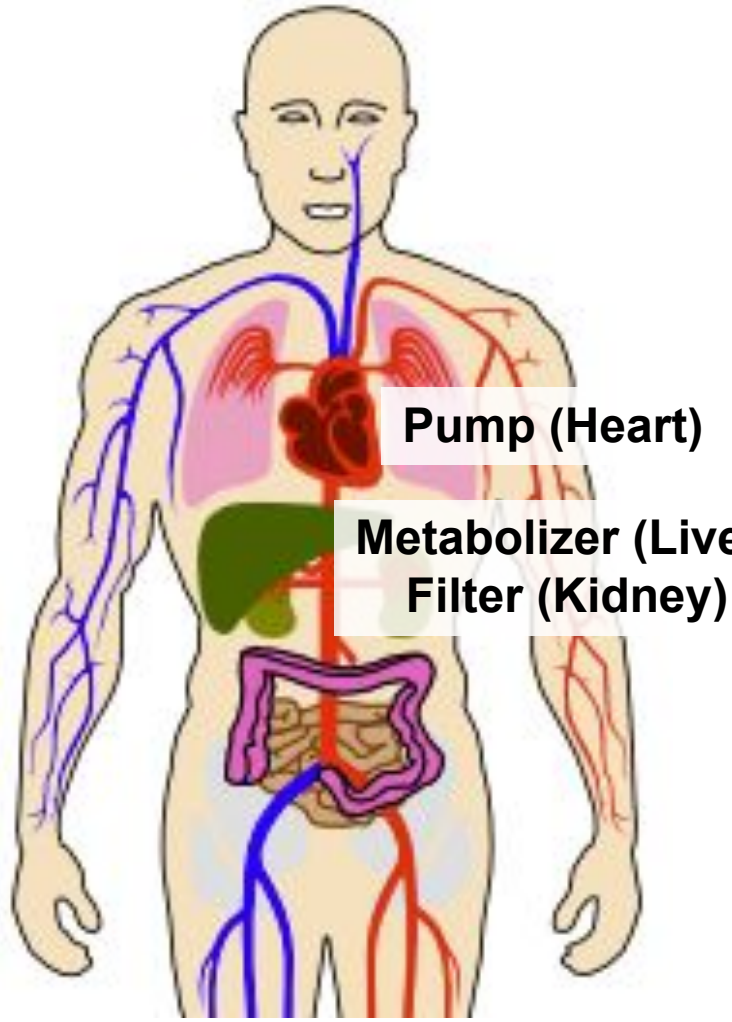
$$\frac{dA}{dt} = -CL \cdot C$$

$$\frac{mg}{L} = \frac{L}{h} \cdot \frac{mg}{L}$$

Clearance is a flow rate of plasma that is completely eliminated of drug

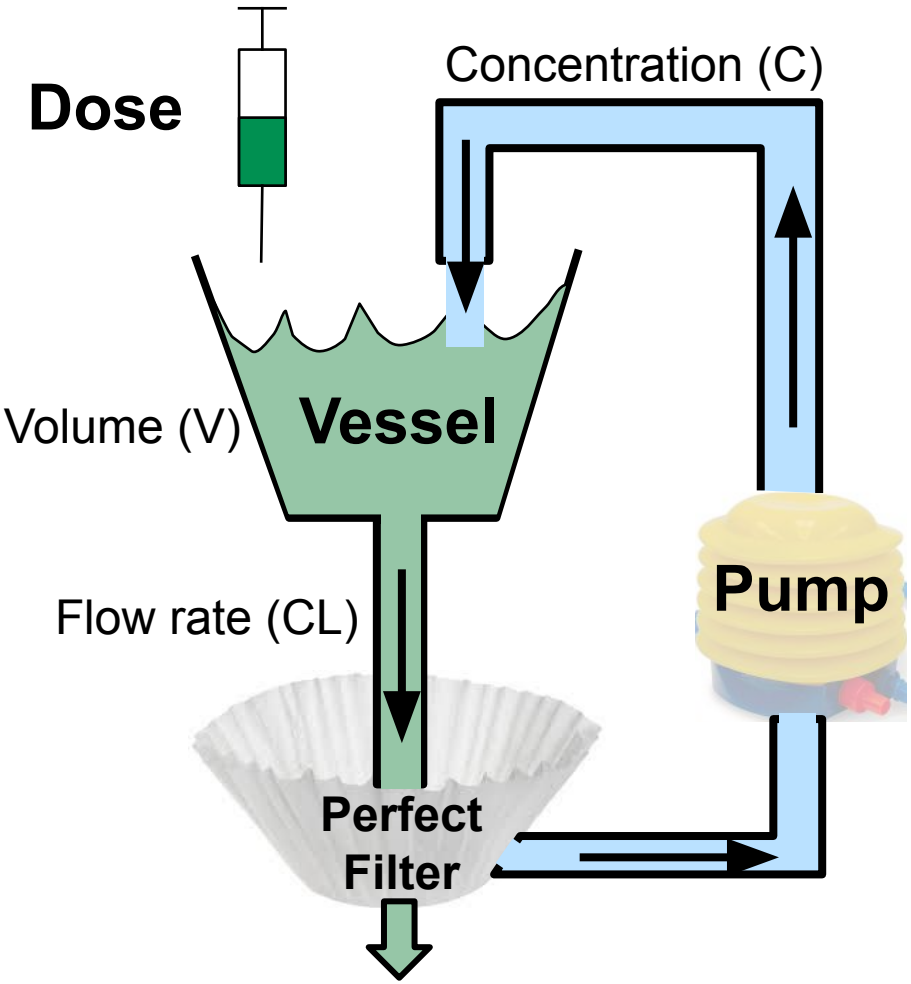
Mechanical Analogy

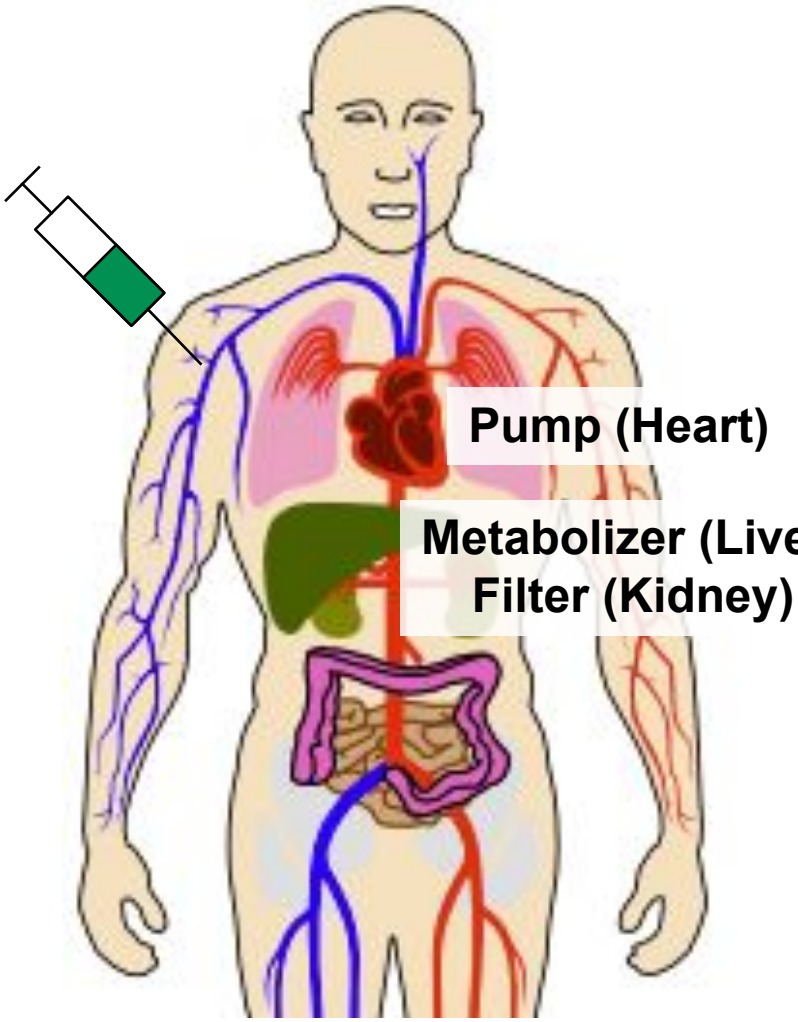




From Leon Aarons

Mechanical Analogy





If filter eliminates all drug that passes through, then CL is the flow rate

$$\frac{dAmt}{dt} = -CL \cdot C$$

From Leon Aarons

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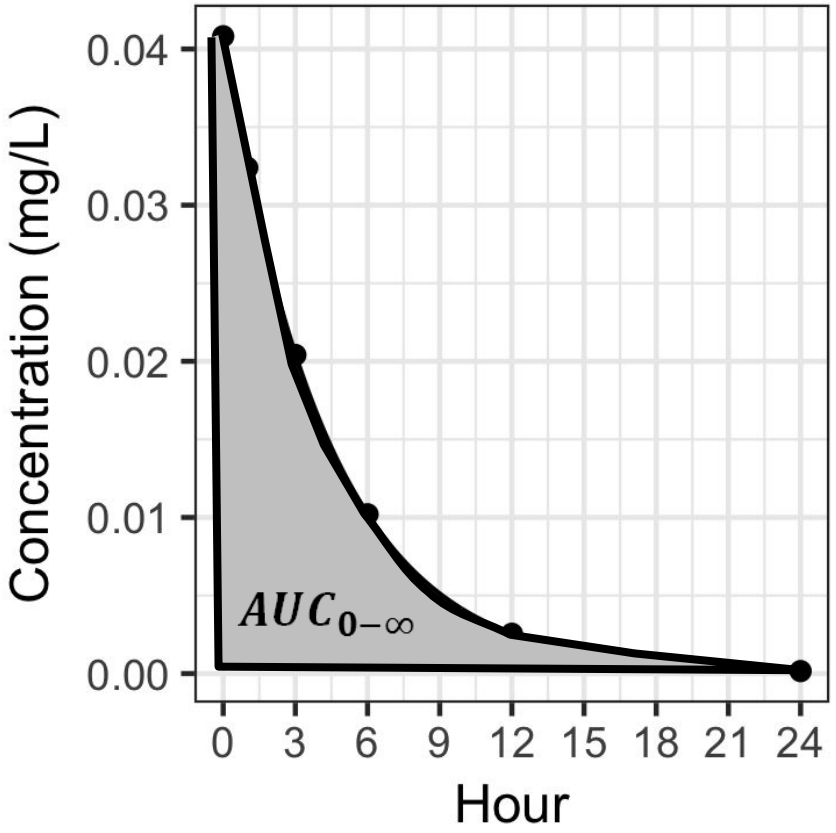
Clearance is the most important PK parameter

Clearance is helpful in understanding the average concentration at steady state

- After sufficient time under the same dosing regimen, one reaches “steady state”, where
  - Rate In = Rate Out = CL·C
- Let’s say:
  - You want to maintain concentration ~ 10 mg/L
  - You know that CL = 3 L/h
- Then:
  - Rate Out = (3 L/h)·(10 mg/L) = 30 mg/h
- The maintenance dose (Rate In) is 30 mg/h.

Clearance relates to the Area Under the conc. Curve ($AUC_{0-\infty}$)



Total drug in = Total drug out

Dose $= \int_0^\infty CL \cdot C(t)dt$

If clearance does not depend on concentration (linear)

Dose $= CL \cdot \int_0^\infty C(t)dt$

Dose $= CL \cdot AUC_{0-\infty}$

$$AUC_{0-\infty} = \frac{\text{Dose}}{\text{CL}}$$

Formula doesn't depend on specific model for C(t), Volume or half-life. It only requires linear clearance

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Major Sites of Elimination

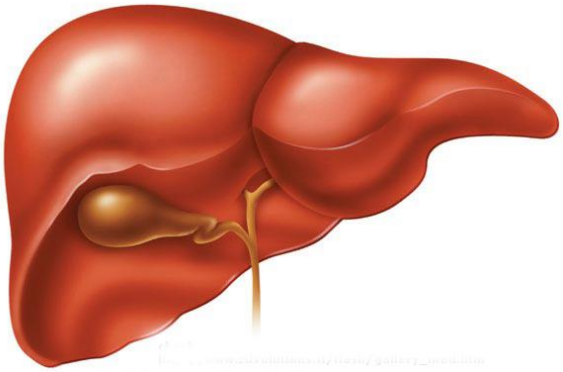
Small Molecules

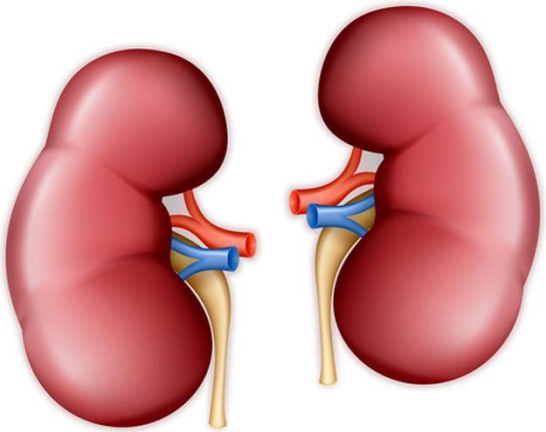
Biologics

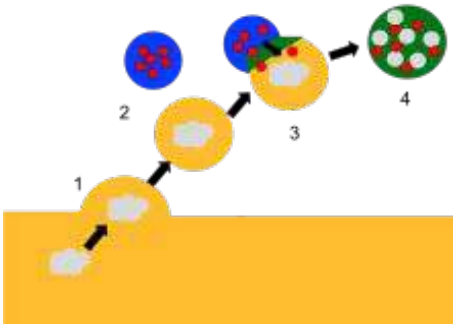
Liver

Kidneys

Lysosome







All cells

Mainly metabolism

Mainly excretion (urine)

Proteolysis (in cells)

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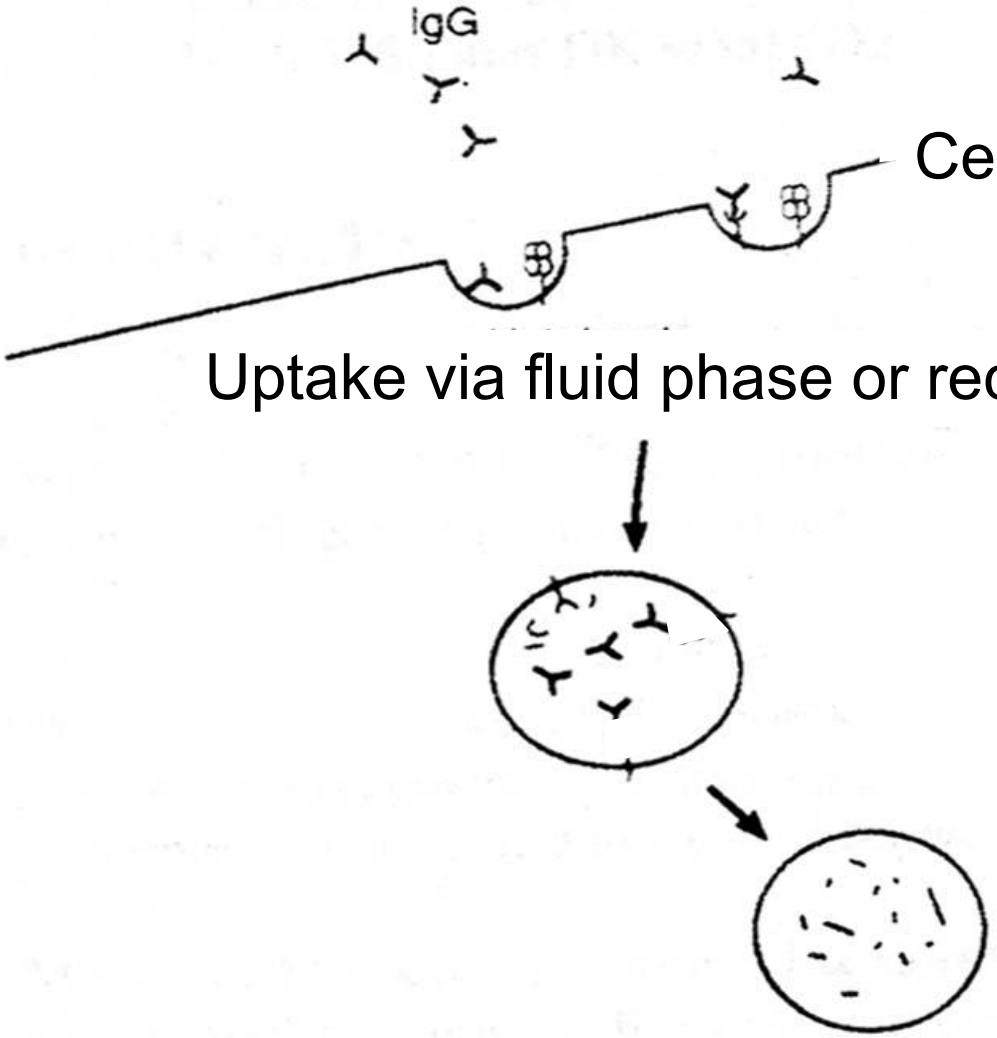
Proteins in general are eliminated through lysosomal degradation

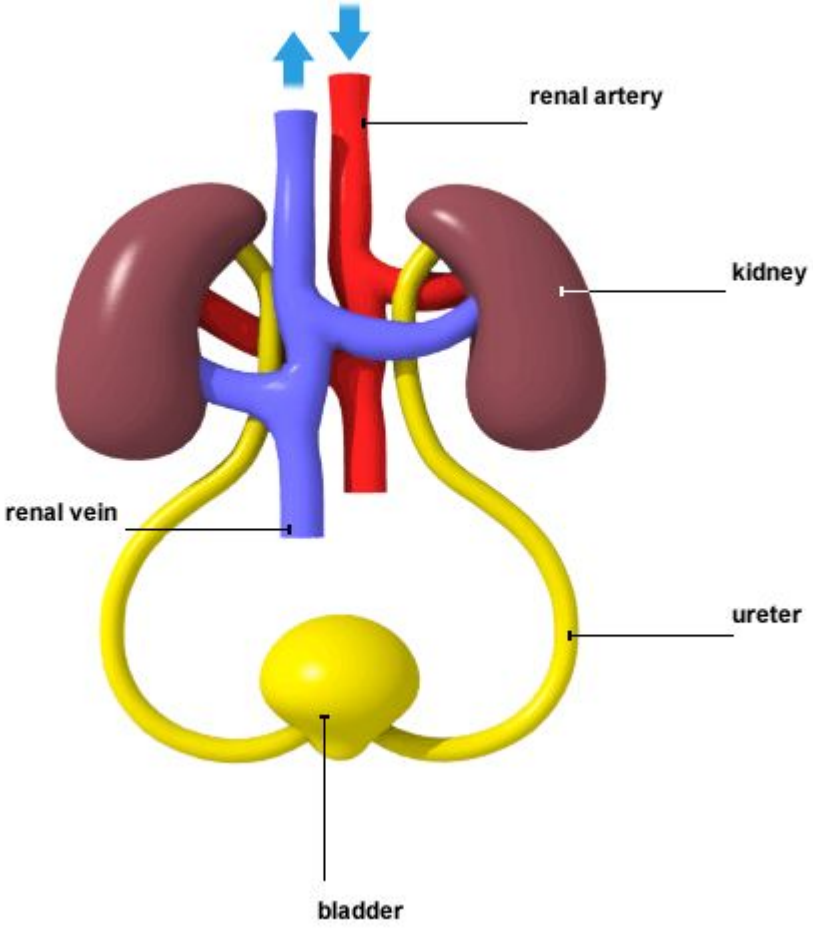


This process can occur in many tissues. Endothelial cells is one major location

AS

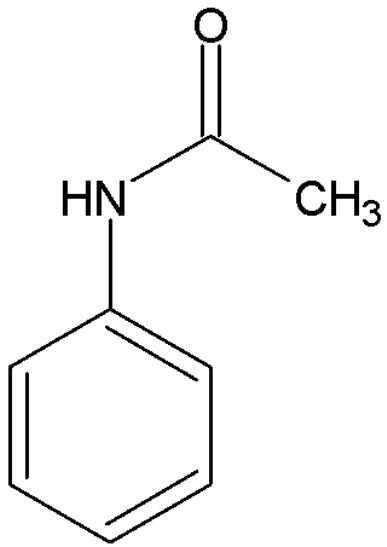
Function of Kidneys

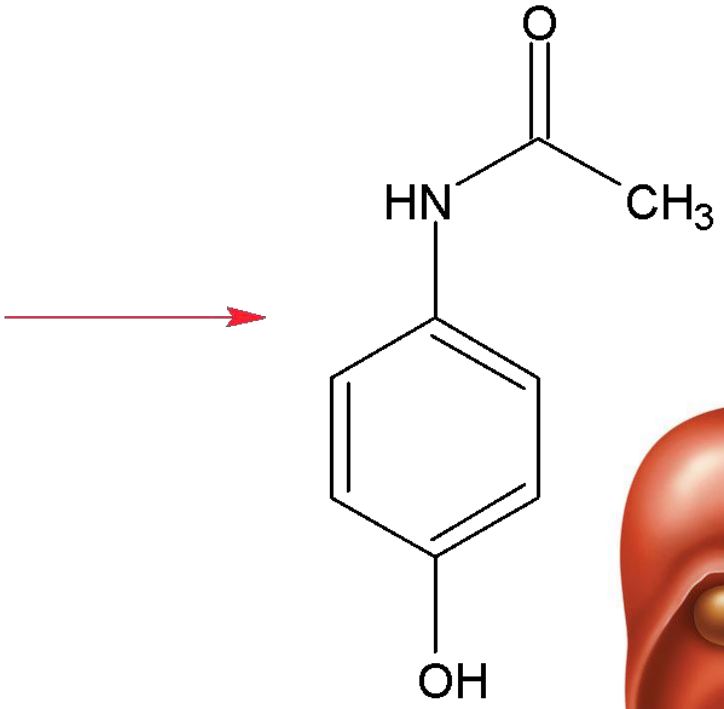
- "Cleans the blood"
  - Filter the blood and remove endogenous metabolic waste, such as urea, uric acid, and creatinine
  - Remove foreign substances
- Regulate body water content, hormones, mineral composition, and acidity
- Can also metabolize drugs (glucuronidation)

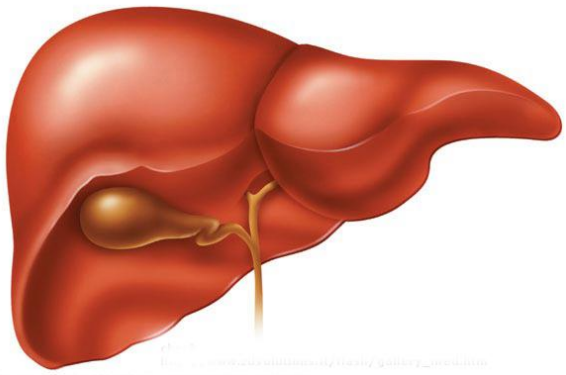


From Pete Bonate

Phase 1 Metabolism: add small polar groups. Hydroxylation







Acetanilid

p-hydroxyacetanalid

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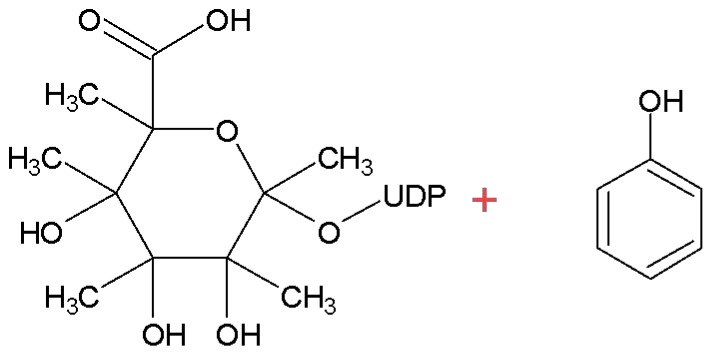
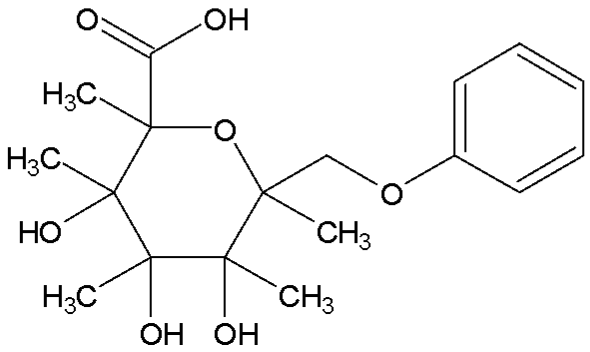
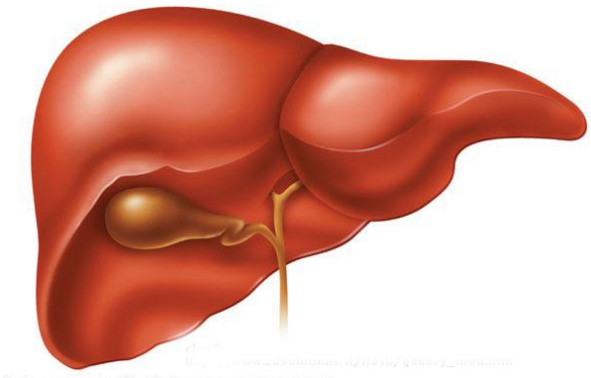
Phase 2 Metabolism: add larger polar molecules



UDPGA

Phenol





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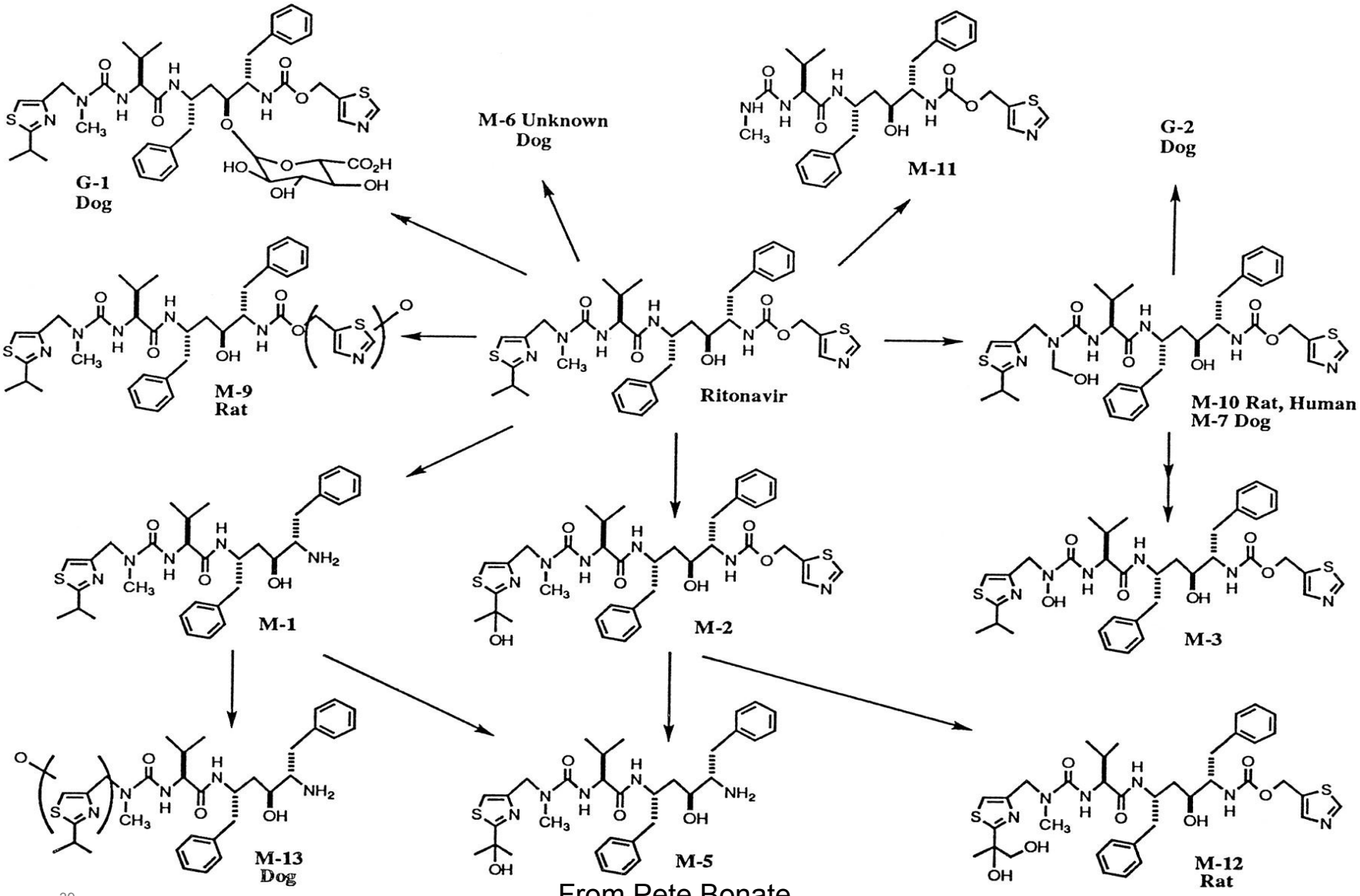
Metabolic Pathways Can Be Complex and Consist of Both Phase 1 and Phase 2



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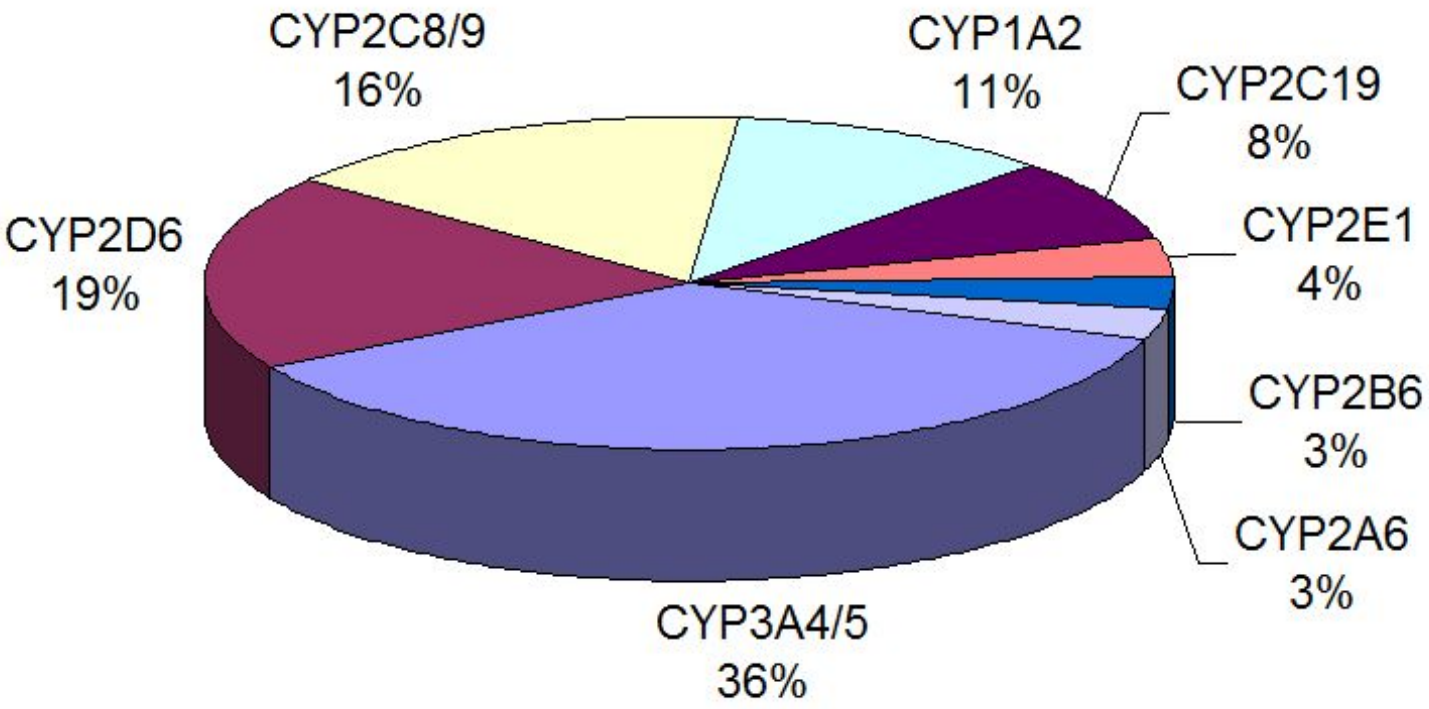
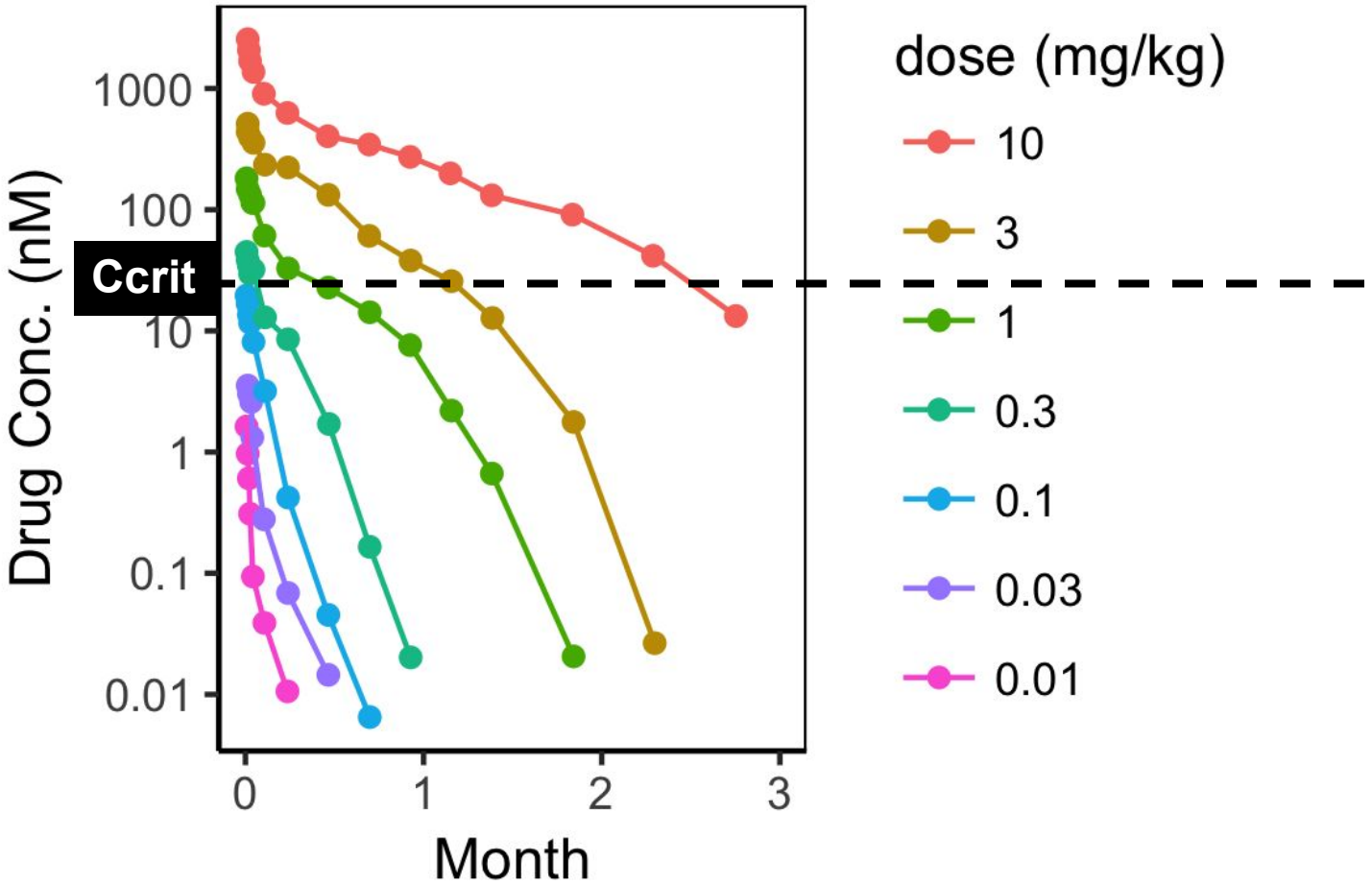
Cytochrome P450 (CYP) metabolizes drug

- Catalyze most Phase I biotransformations
- Found in every species and every tissue
  - In particular in the liver, kidney, GI tract, and brain



From Pete Bonate

Nonlinear pharmacokinetics occurs at "critical concentration" = C_{crit}



Burmester, G. R. et al. Mavrilimumab, a human monoclonal antibody targeting gm-csf receptor-α, in subjects with rheumatoid arthritis: a randomised, double-blind, placebo- controlled, phase I first-in-human study. Annals of the rheumatic diseases 70, 1542–1549 (2011).

If route of elimination saturates, elimination is reduced

$$\frac{dA}{dt} = -CL \cdot C - \underbrace{\frac{V_{max} \cdot C}{K_m + C}}$$

At small concentrations,

$$\frac{dA}{dt} = -CL \cdot C - \underbrace{\frac{V_{max} \cdot C}{K_m}}$$

$$= \left(-CL - \frac{V_{max}}{K_m}\right) C$$

At large concentrations,

$$\frac{dA}{dt} = -CL \cdot C - \underbrace{V_{max}}$$

$$\approx -CL \cdot C$$

Faster elimination at lower concentrations

“Derivation” for C_{crit}

$$\frac{dA}{dt} = -CL \cdot C - \frac{V_{max} C}{C + K_m};$$

For large doses (and concentrations), $C \gg K_m$

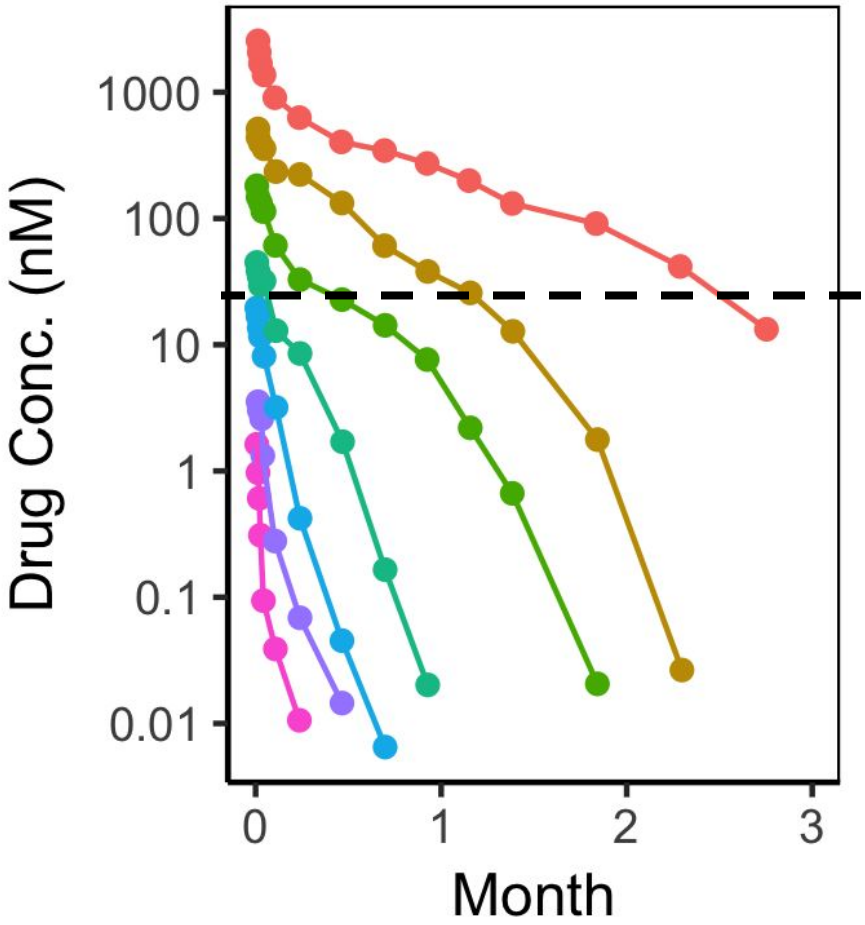
$$\frac{dA}{dt} \approx -CL \cdot C - \mathrm{V_{max}}$$

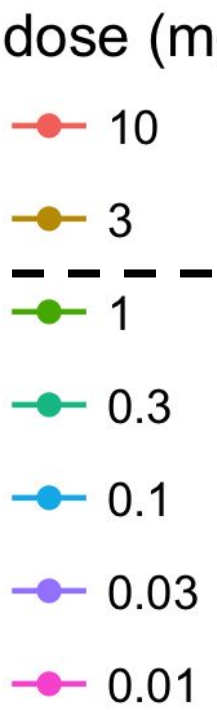
Define C_{crit} to be where the linear (CL·C) and nonlinear (V_m) components contribute equally to total elimination

$$CL \cdot C_{\mathrm{crit}} = \mathrm{V_{max}} \rightarrow \boxed{\mathrm{C_{crit}} = \frac{V_{\mathrm{max}}}{CL}}$$

Stein, Andrew M., and Lambertus A. Peletier. "Predicting the Onset of Nonlinear Pharmacokinetics." CPT: pharmacometrics & systems pharmacology 7.10 (2018): 670-677.

Nonlinear pharmacokinetics occurs at "critical concentration" = C_{crit}





$$C_{crit} = \frac{V_{max}}{CL}$$

Pharmacometrics is a relatively young field.

There are opportunities to analyze simple models and contribute to understanding

AM Stein and L Peletier, to appear in CPT:PSP (2018)
Presented at ACoP in 2017

SEE QUIZ QUESTIONS

Key Lessons

- Clearance tells you the average concentration at steady state (given an input dosing rate)
  - Rate In = Rate Out = CL · C
- Small molecules are eliminated mainly by the liver and the kidneys.
- Large molecules (proteins) are eliminated mainly by endocytosis and proteolysis.

Continuous Dosing: Infusion

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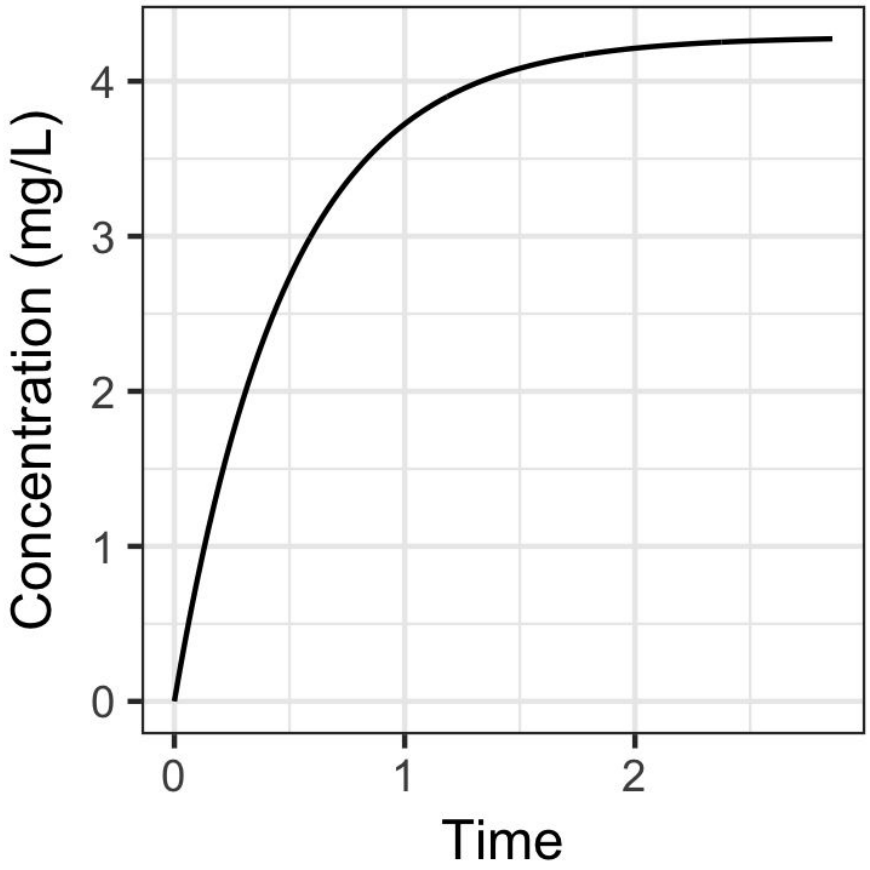
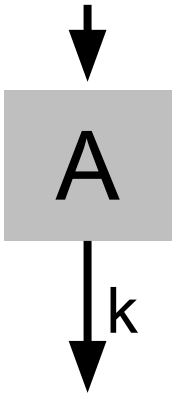
Continuous infusion



Dose Rate (R_0, mg/h)



$$\frac{dA}{dt} = R_0 - k \cdot A$$

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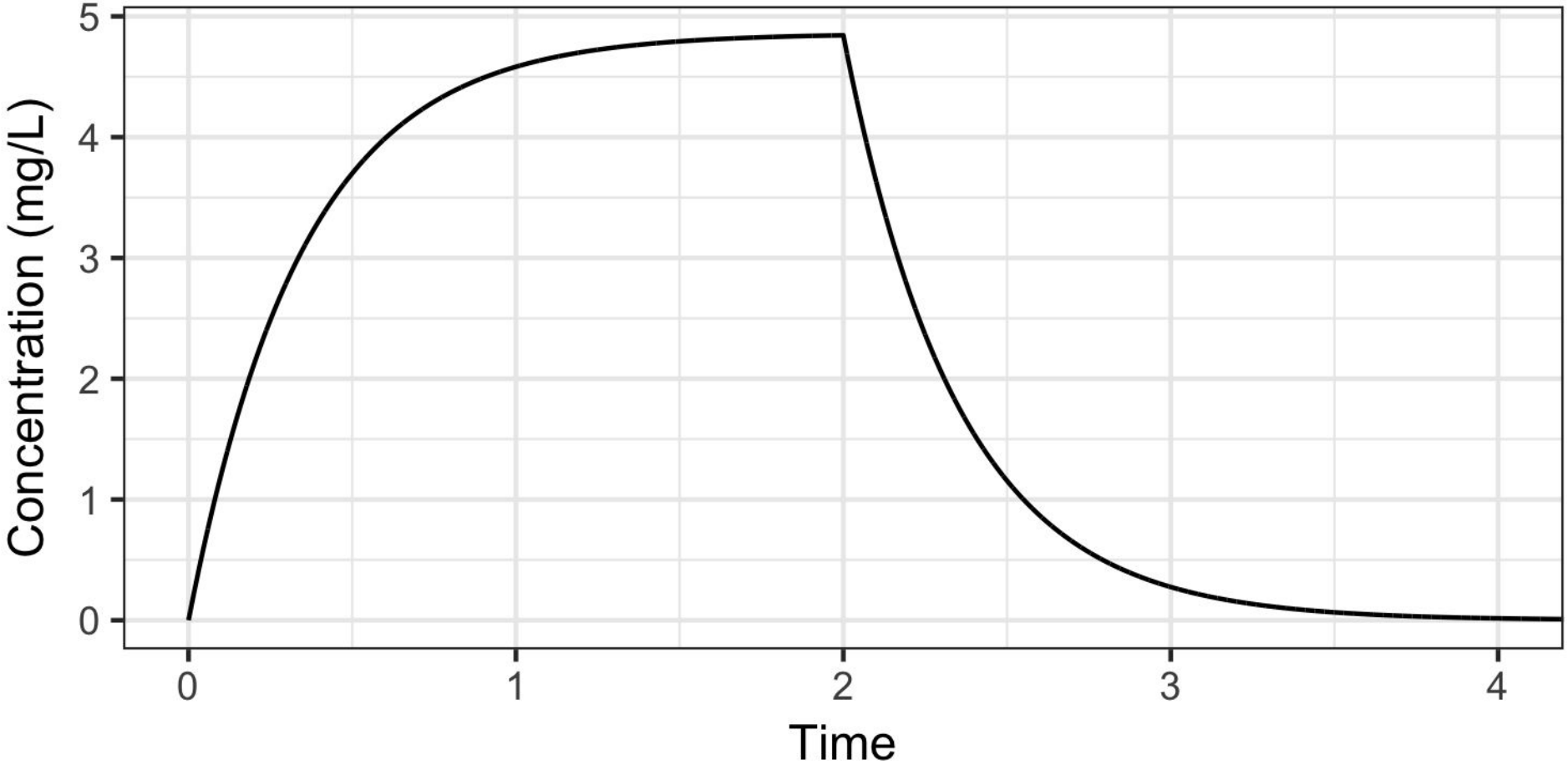
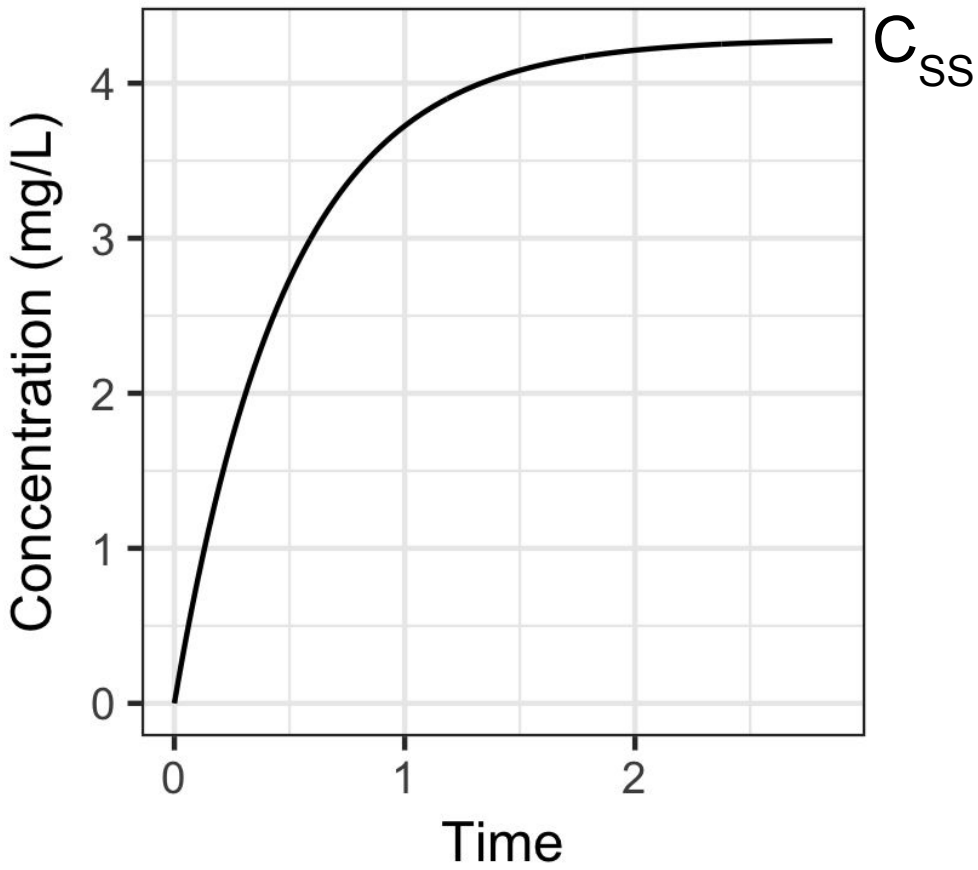
Continuous infusion



NOVARTIS

Continuous infusion



$$\frac{dA}{dt} = R_0 - k \cdot A$$

At steady state, $\frac{dA}{dt} = 0$

$$0 = R_0 - k \cdot A_{ss}$$

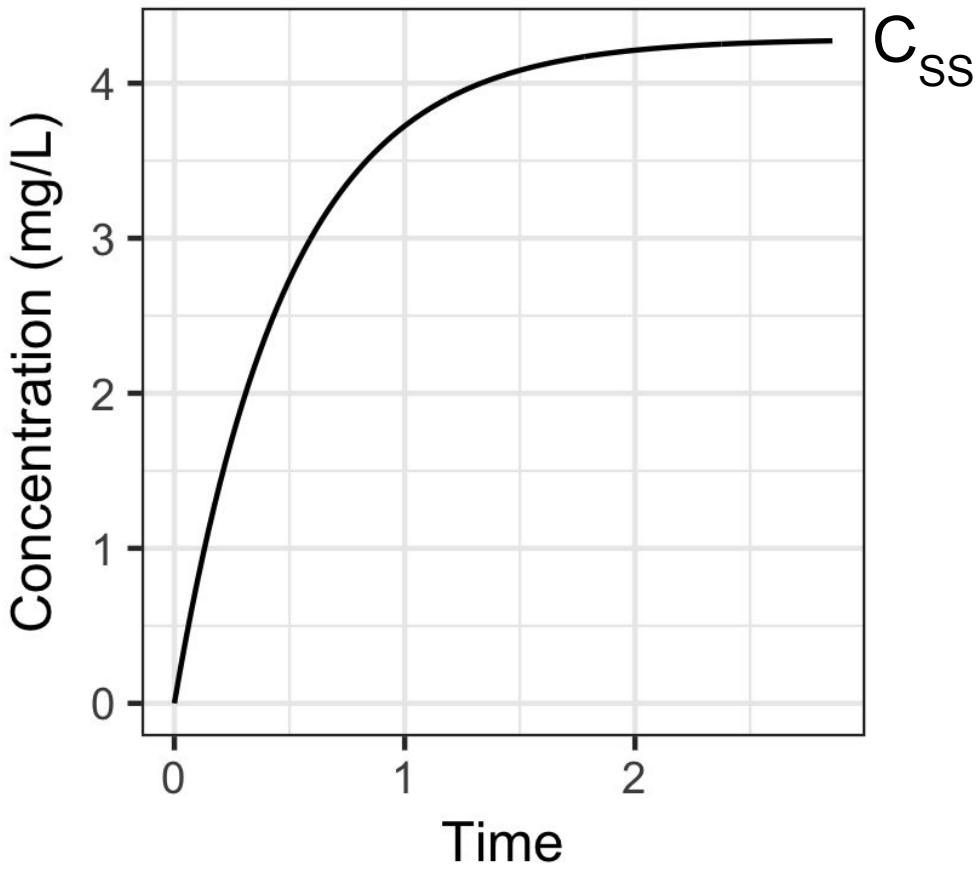
$$A_{ss} = \frac{R_0}{k}$$

$$C_{ss} = \frac{A_{ss}}{V}$$

$$= \frac{R_0}{k \cdot V} = \frac{R_0}{CL}$$

NOVARTIS

Continuous infusion



$$\frac{dA}{dt} = R_0 - k \cdot A$$

$$A_{ss} = \frac{R_0}{k}, \qquad C_{ss} = \frac{R_0}{CL}$$

$$A(t) = A_{ss}\left(1 - e^{-kt}\right)$$

$$C(t) = C_{ss}\left(1 - e^{-kt}\right)$$

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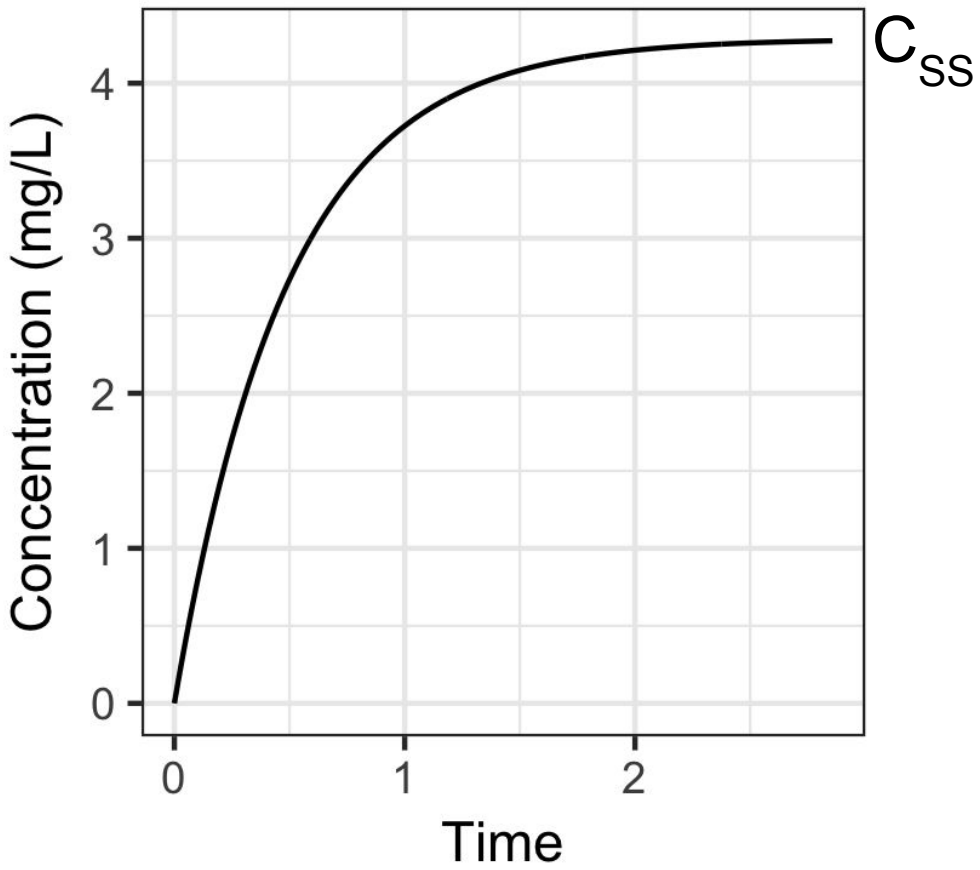
At what time do you reach steady state?



$$C(t) = C_{ss}\left(1 - e^{-kt}\right)$$

Key Lesson: Sensitivity

- If you double the infusion rate, you double the steady state drug concentration
- If a patient has reduced clearance (e.g. due to liver impairment for a drug metabolized in liver) that reduces CL, then the steady state drug concentration is reduced.

$$C_{ss} = \frac{R_0}{CL}$$

Repeated Dosing - Bolus

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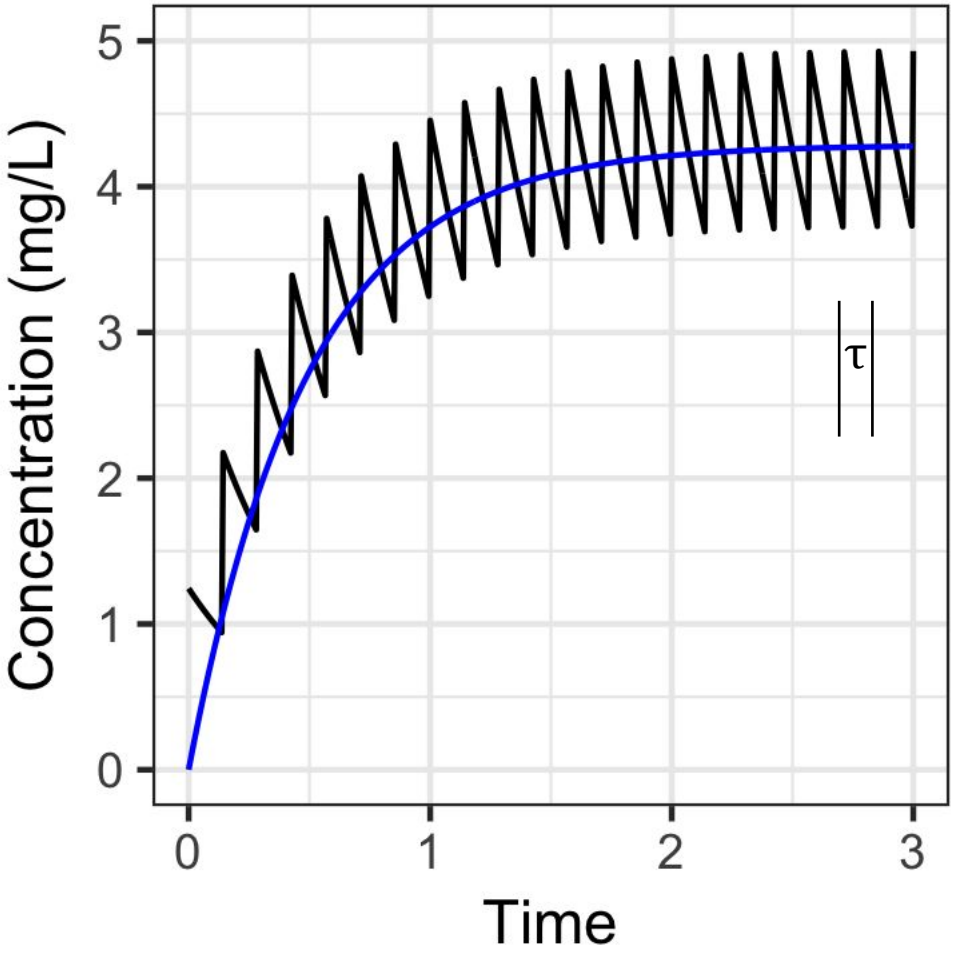
Repeated dosing



Similar to infusion dose

Define τ to be the dosing interval

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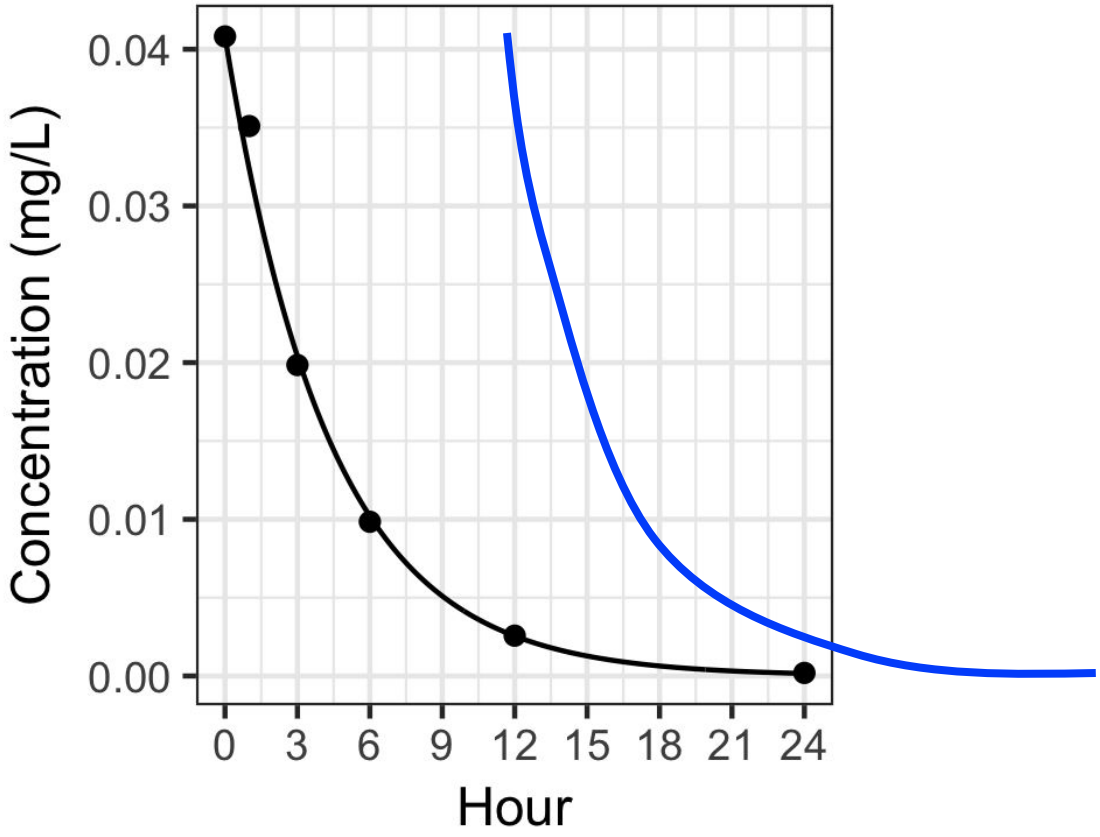
Recall formula for single bolus dose and amend for dose at another time

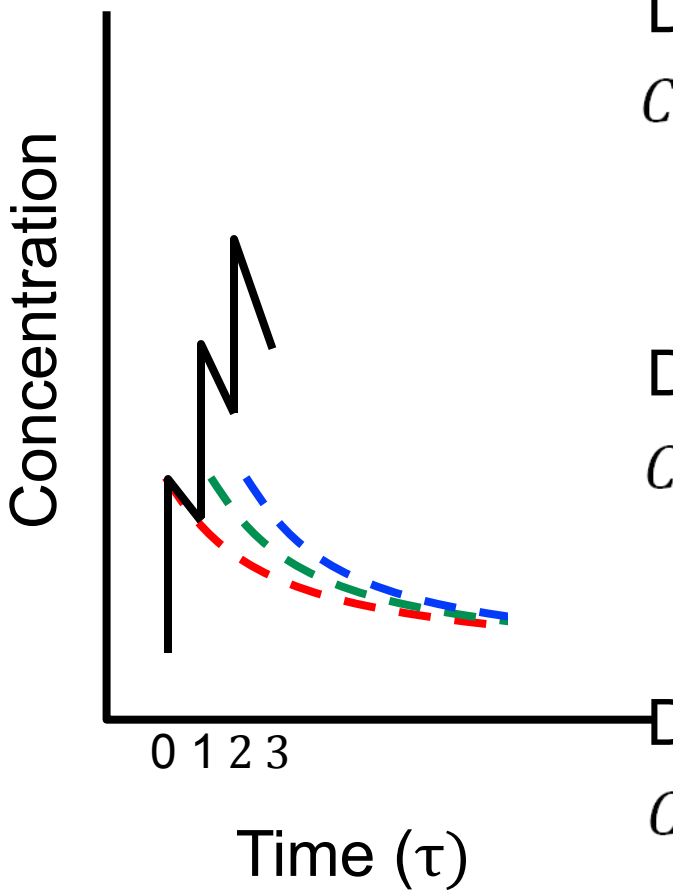
C_1 is the response of a single dose at time 0

$$C_1(t) = C_0 e^{-kt}$$

$$C_1(t-12) = C_0 e^{-k(t-12)}$$



Each dose contributes one “bolus dose” term



During third dose (2τ-3τ)

$$C(t) = C_1(t) + C_1(t-\tau) + C_1(t-2\tau)$$
$$= C_0 e^{-kt} + C_0 e^{-k(t-\tau)} + C_0 e^{-k(t-2\tau)}$$

During second dose (τ-2τ)

$$C(t) = C_1(t) + C_1(t-\tau)$$
$$= C_0 e^{-kt} + C_0 e^{-k(t-\tau)}$$

During first dose (time 0-τ)

$$C(t) = C_1(t)$$
$$= C_0 e^{-kt}$$

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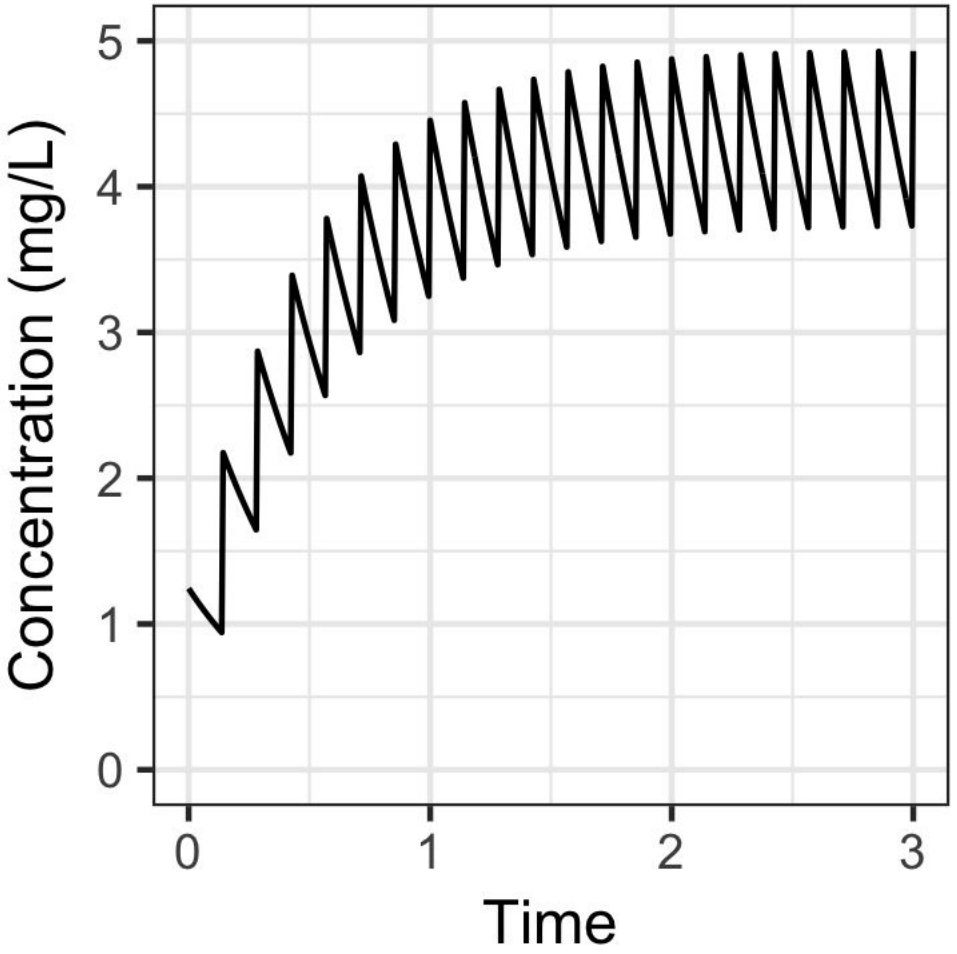
The general formula for N doses



$$C_1(t) = C_0 e^{-kt}$$

$$C(t) = \sum_{n=0}^{N-1} C_1(t - n\tau)$$

$$C(t) = \sum_{n=0}^{N-1} C_0 e^{-k(t-n\tau)}$$

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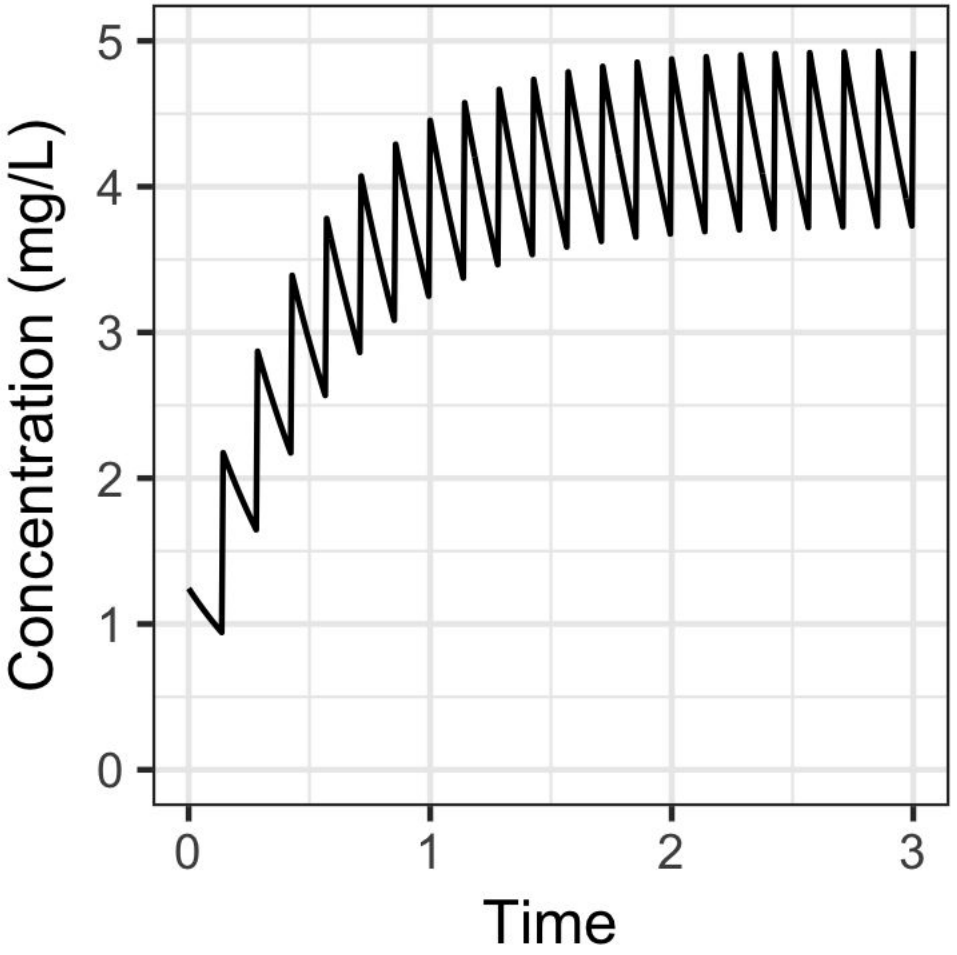
This formula is a geometric series



$$C(t) = \sum_{n=0}^{N-1} C_0 e^{-k(t-n\tau)}$$

$$= \sum_{n=0}^{N-1} C_0 e^{-kt} e^{kn\tau}$$

$$= C_0 e^{-kt} \sum_{n=0}^{N-1} \left(e^{k\tau}\right)^n$$

As N □ ∞

$$C(t) = \frac{C_0 e^{-kt}}{1 - e^{-k\tau}}$$

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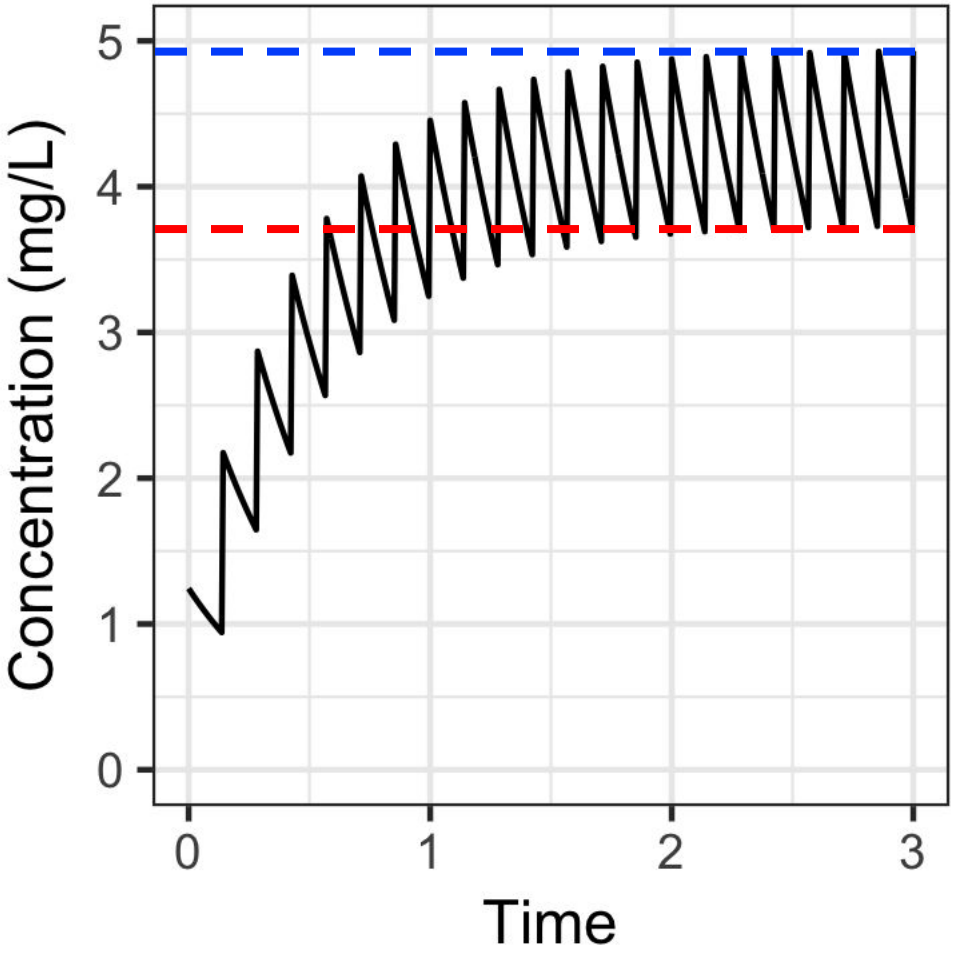
Formulas for Cmax,ss and Cmin,ss



$$C_{max,ss} = \frac{C_0}{1 - e^{-k\tau}}$$

$$C_{min,ss} = \frac{C_0 e^{-k\tau}}{1 - e^{-k\tau}}$$

Recall that k and C_0 depends on both V and CL

What about average concentration $C_{avg,ss}$?

$$C(t) \xrightarrow{N \to \infty} \frac{C_0 e^{-kt}}{1 - e^{-k\tau}}$$

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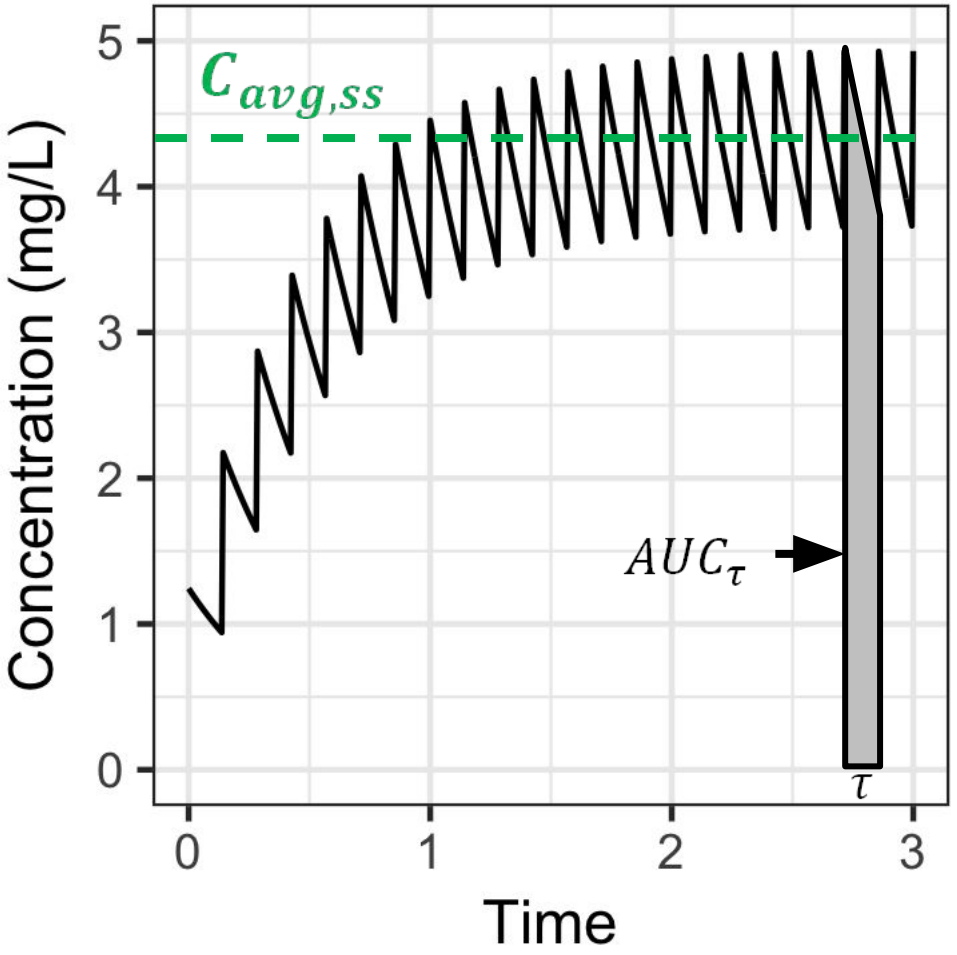
Formula for Cavg,ss (for linear PK)



Total drug in = Total drug out

Dose $= \int_{n\tau}^{(n+1)\tau} CL \cdot C(t)dt$

If clearance doesn't depend on concentration (linear)

Dose $= CL \cdot \int_{n\tau}^{(n+1)\tau} C(t)dt$

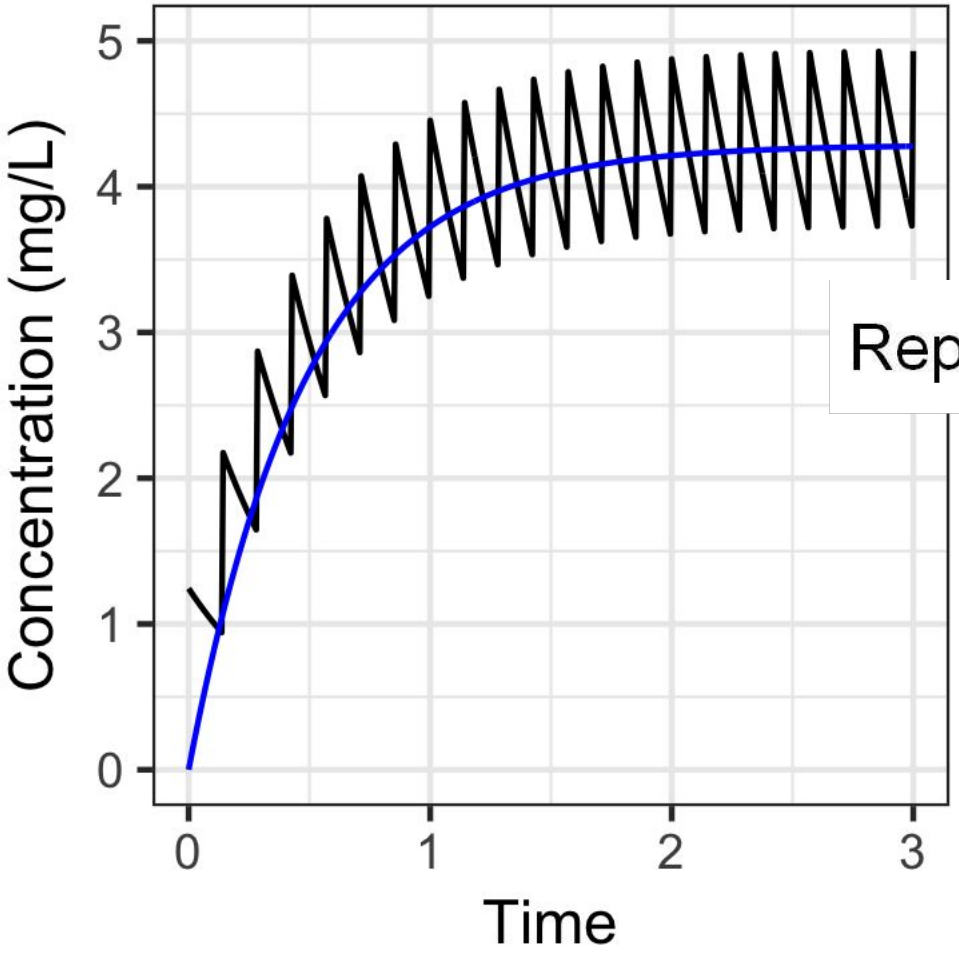
Dose $= CL \cdot AUC_\tau$

$$AUC_\tau = \frac{\text{Dose}}{\text{CL}}$$

$$C_{avg,ss} = \frac{AUC_\tau}{\tau} = \frac{\text{Dose}}{\text{CL}\cdot\tau}$$

Formula doesn't depend on specific model for C(t)
It only requires linear clearance

Repeated dosing similar to infusion



Infusion: $C_{ss} = \frac{\text{Infusion Rate}}{CL}$

Repeat dose $C_{avg,ss} = \frac{Dose/\tau}{CL}$

Infusion Rate ~ Dose Rate

Infusion Rate ~ Dose/τ

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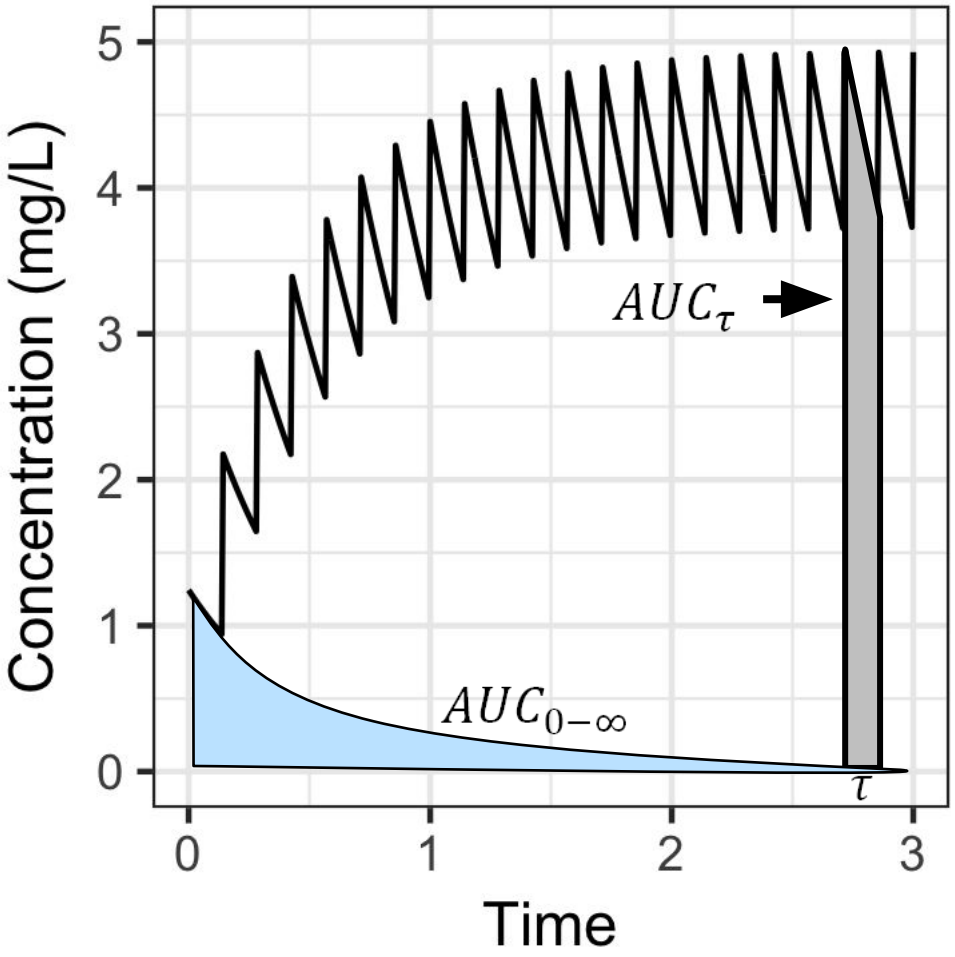
Cool and useful result: $AUC_{0-\infty} = AUC\tau$



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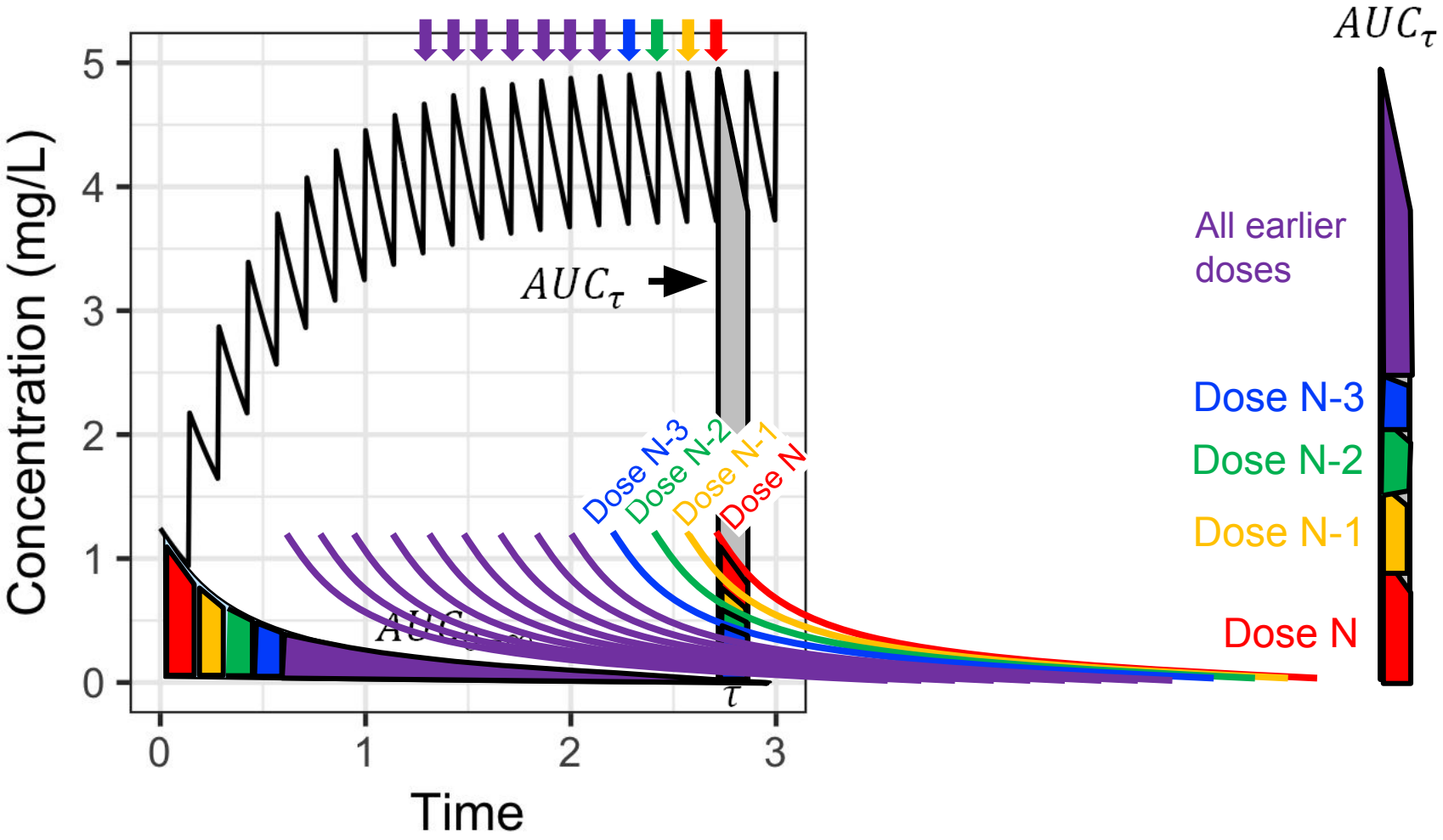
$AUC_{0-\infty}$ = AUC_{τ} Graphical Demonstration



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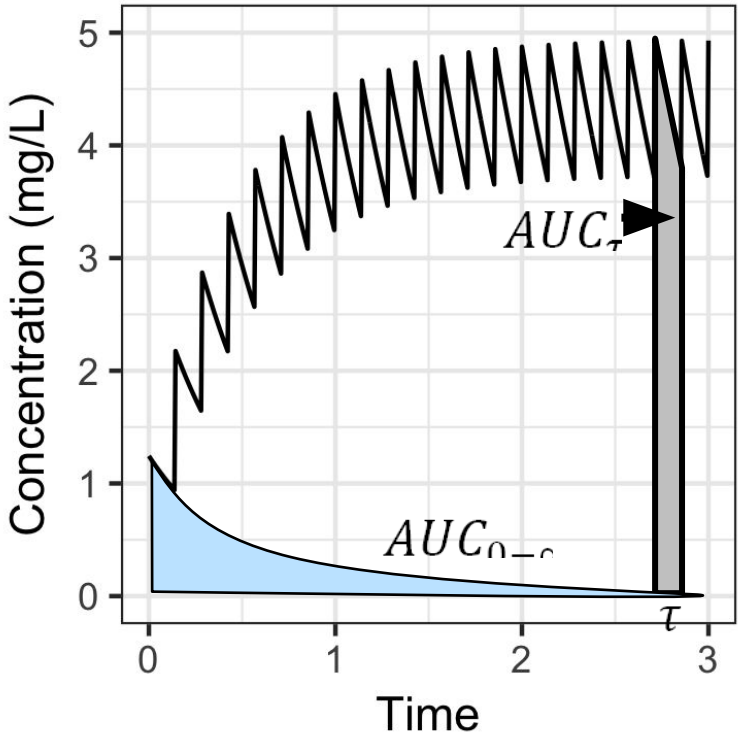
$AUC_{0-\infty}$ = AUC_{τ} Mathematical Demonstration

$$
\begin{aligned}
AUC_\tau &= \int_{n\tau}^{(n+1)\tau} C(t)dt \\
&= \int_{n\tau}^{(n+1)\tau} \left[C_1(t) + C_1(t-\tau) + C_1(t-2\tau) + \ldots + C_1(t-n\tau)\right] dt \\
&= \int_{n\tau}^{(n+1)\tau} C_1(t)dt + \int_{n\tau}^{(n+1)\tau} C_1(t-\tau)dt + \int_{n\tau}^{(n+1)\tau} C_1(t-2\tau)dt + \ldots + \int_{n\tau}^{(n+1)\tau} C_1(t-n\tau)dt \\
&= \int_{n\tau}^{(n+1)\tau} C_1(t)dt + \int_{(n-1)\tau}^{n\tau} C_1(t)dt + \int_{(n-2)\tau}^{(n-1)\tau} C_1(t)dt + \ldots + \int_{0}^{\tau} C_1(t)dt \\
&= \int_{0}^{(n+1)\tau} C_1(t)dt \\
&\rightarrow \int_{0}^{\infty} C_1(t)dt \text{ as } n \rightarrow \infty \\
AUC_\tau &= AUC_{0-\infty}
\end{aligned}
$$

Key Insights

- For IV drugs, $C_{avg,ss}$ depends only on dose, dosing interval and clearance
  - Cavg = Dose/(CL·τ)
  - CL can be estimated from either $AUC_{0-\infty}$ or AUC_{τ}
- The time to steady state depends on volume and half-life.



$$C_{avg,ss} = \frac{AUC_{\tau}}{\tau} = \frac{AUC_{0-\infty}}{\tau} = \frac{\text{Dose}}{\text{CL} \cdot \tau}$$

SEE QUIZ QUESTIONS

Distribution

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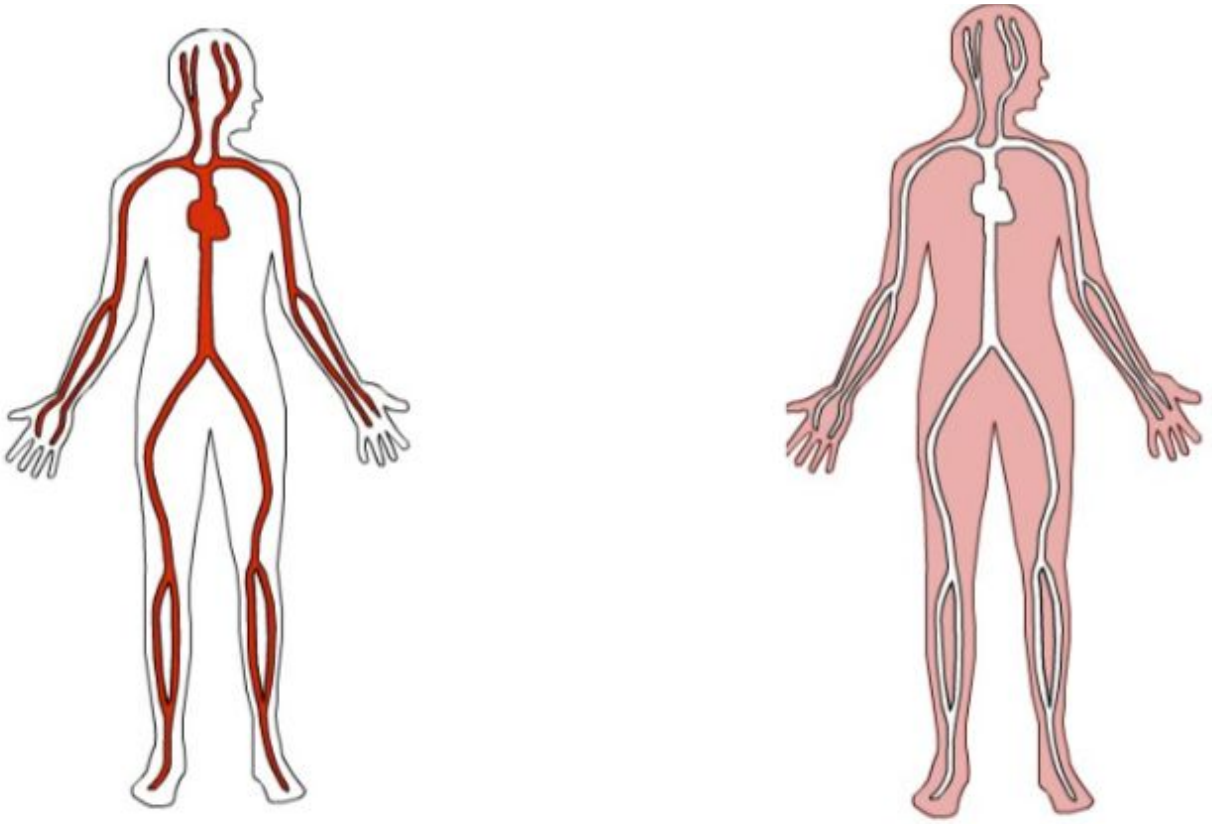
Distribution

Systemic Circulation

Distribution

Other Tissues



From Leon Aarons

Factors that can effect distribution

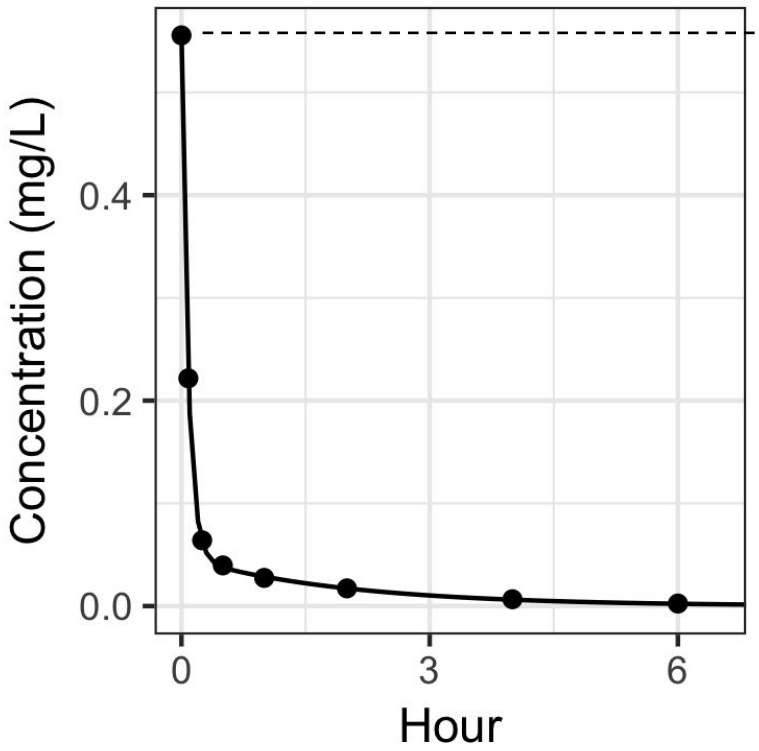
- Lipophilicity (able to dissolve and move through fats)
- Transport proteins can move drugs around
- Blood proteins (e.g. albumin) will bind to low molecular weight drugs and prevent them from moving into tissue

From Leon Aarons

Profile of a single dose (Linear Space)

Dose = 10 mg

C_0 = 0.055 mg/L



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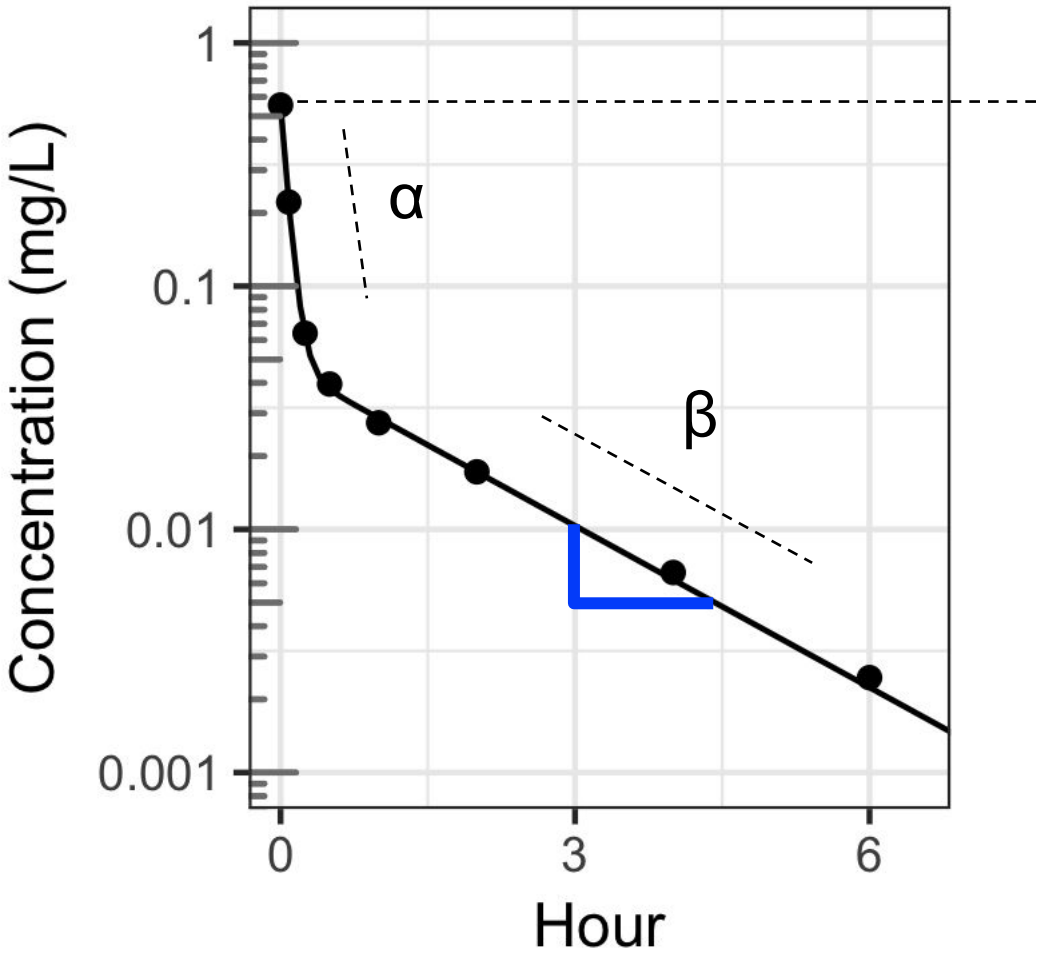
Profile of a single dose (Log Space)

$$C(t) = Ae^{-\alpha t} + Be^{-\beta t}$$



Dose = 10 mg

C_0 = 0.55 mg/L

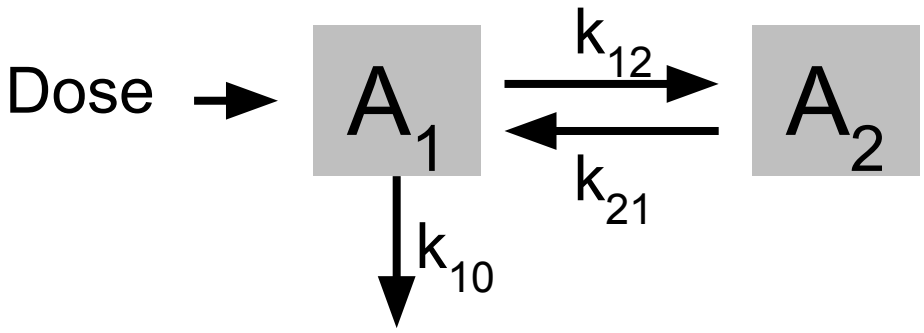
V_1 = Dose/C_0
= 18 L

α = initial decline
= 12/h

β = terminal slope
= 0.5/h

$t_{1/2\beta}$ = 1.4 h

Compartmental Model formulation



Rate of change of amount in each compartment

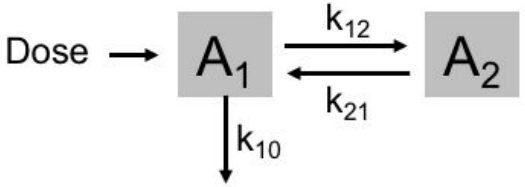
$$\frac{dA_1}{dt} = -k_{10} \cdot A_1 - k_{12} \cdot A_1 + k_{21} \cdot A_2$$

$$\frac{dA_2}{dt} = k_{12} \cdot A_1 - k_{21} \cdot A_2$$

Finding the analytical solution

$$\frac{dA_1}{dt} = -k_{10} \cdot A_1 - k_{12} \cdot A_1 + k_{21} \cdot A_2$$

$$\frac{dA_2}{dt} = k_{12} \cdot A_1 - k_{21} \cdot A_2$$



$$\frac{d}{dt}\begin{pmatrix} A_1 \\ A_2 \end{pmatrix} = \underbrace{\begin{pmatrix} -(k_{10}+k_{12}) & k_{21} \\ k_{12} & -k_{21} \end{pmatrix}}_{M} \begin{pmatrix} A_1 \\ A_2 \end{pmatrix}$$

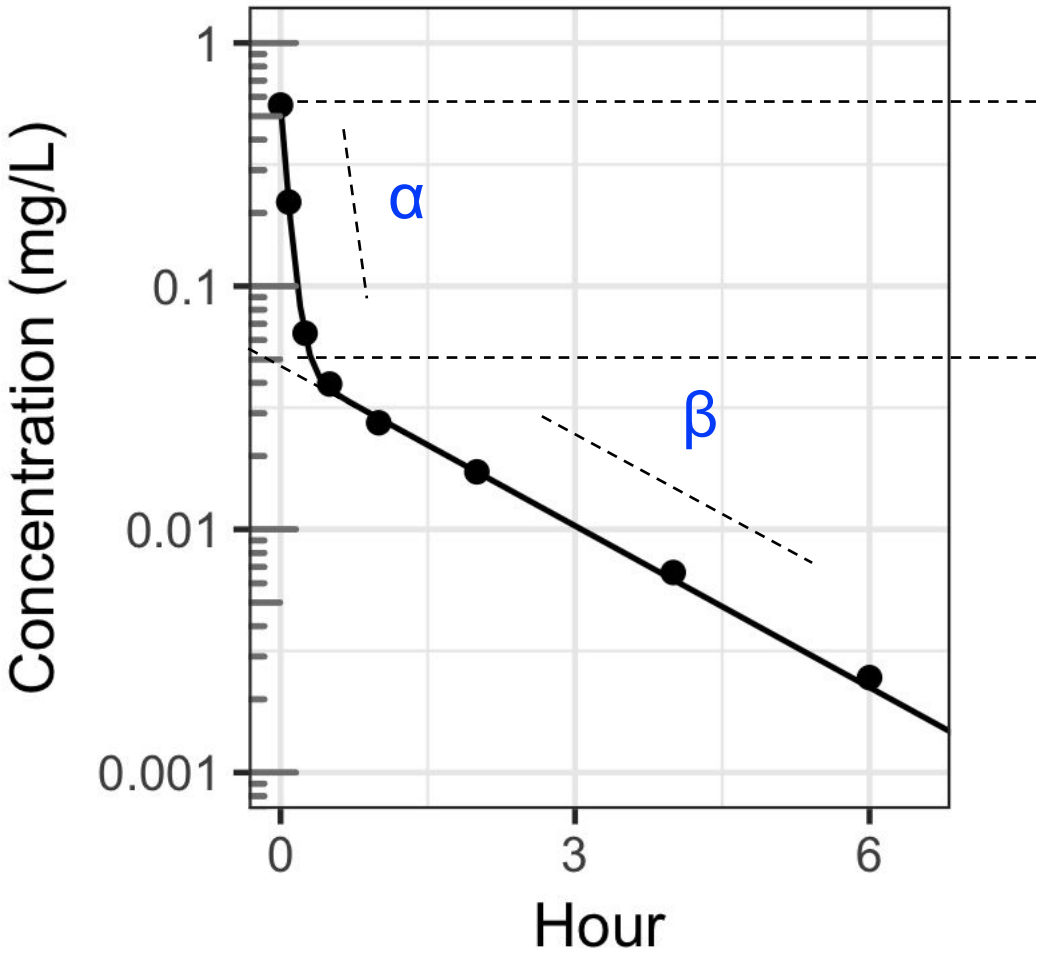
α and β are the eigenvalues of M

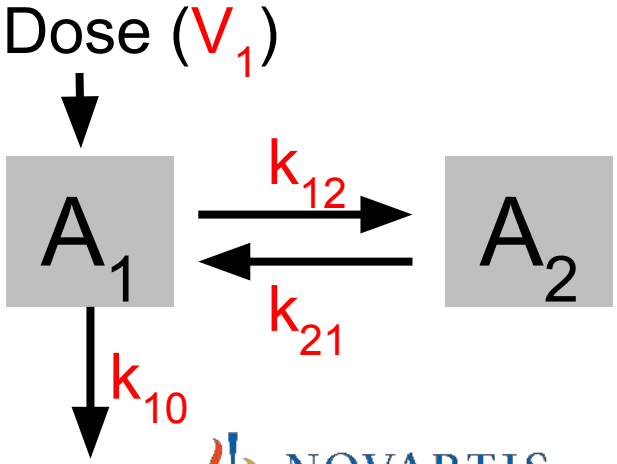
A and B come from the eigenvectors of M and the initial dose

Details in www.pfim.biostat.fr/PFIM_PKPD_library.pdf

Compartment model and prolife each have 4 parameters

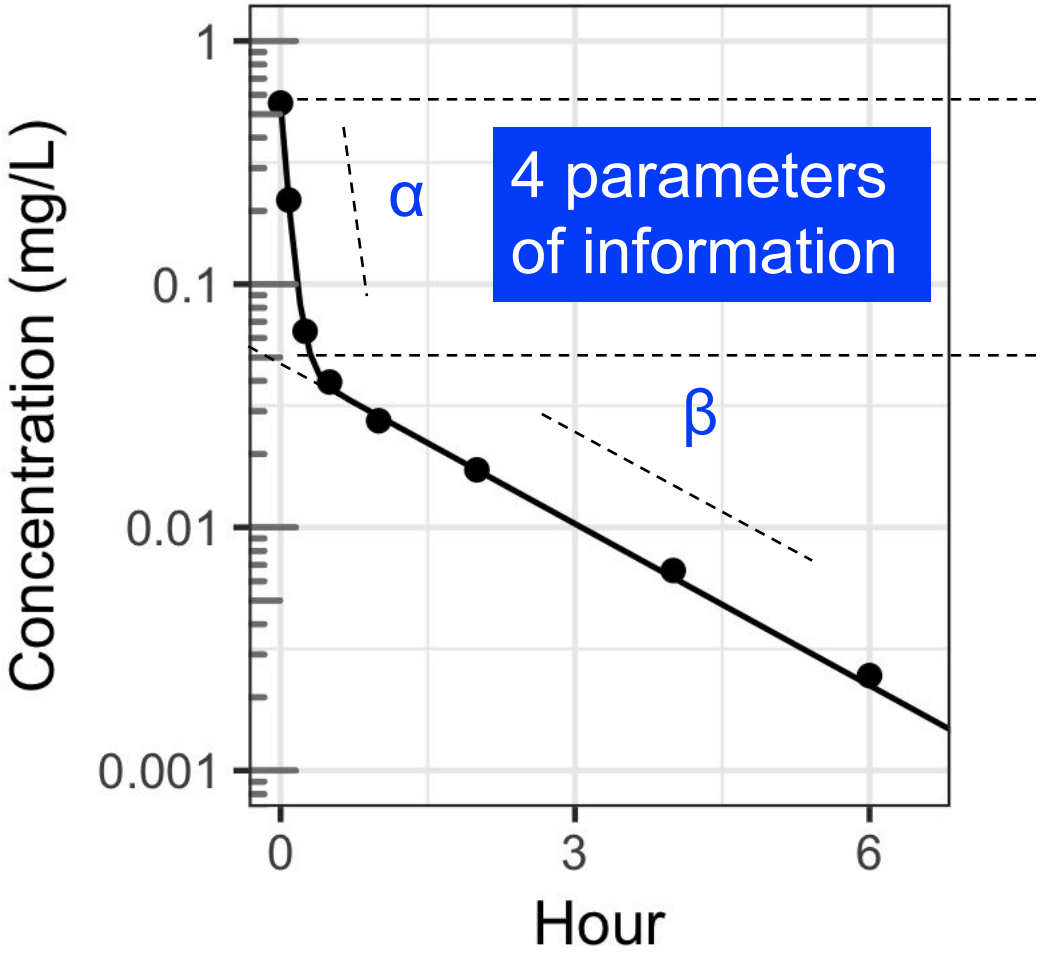
$$C(t) = Ae^{-\alpha t} + Be^{-\beta t}$$





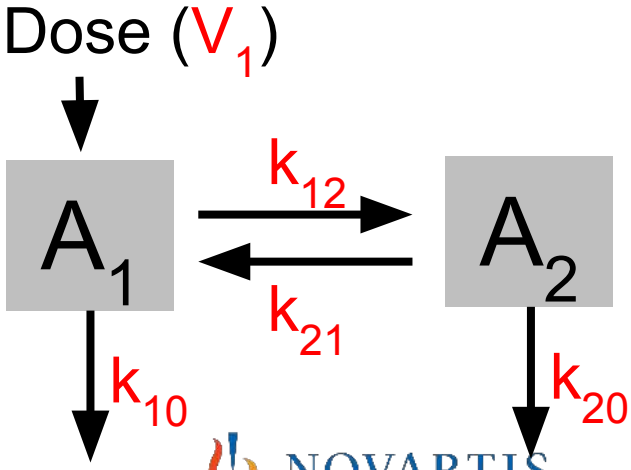
Elimination from the peripheral compartment not identifiable.

$$C(t) = Ae^{-\alpha t} + Be^{-\beta t}$$



4 parameters of information

5 parameters In model is too many



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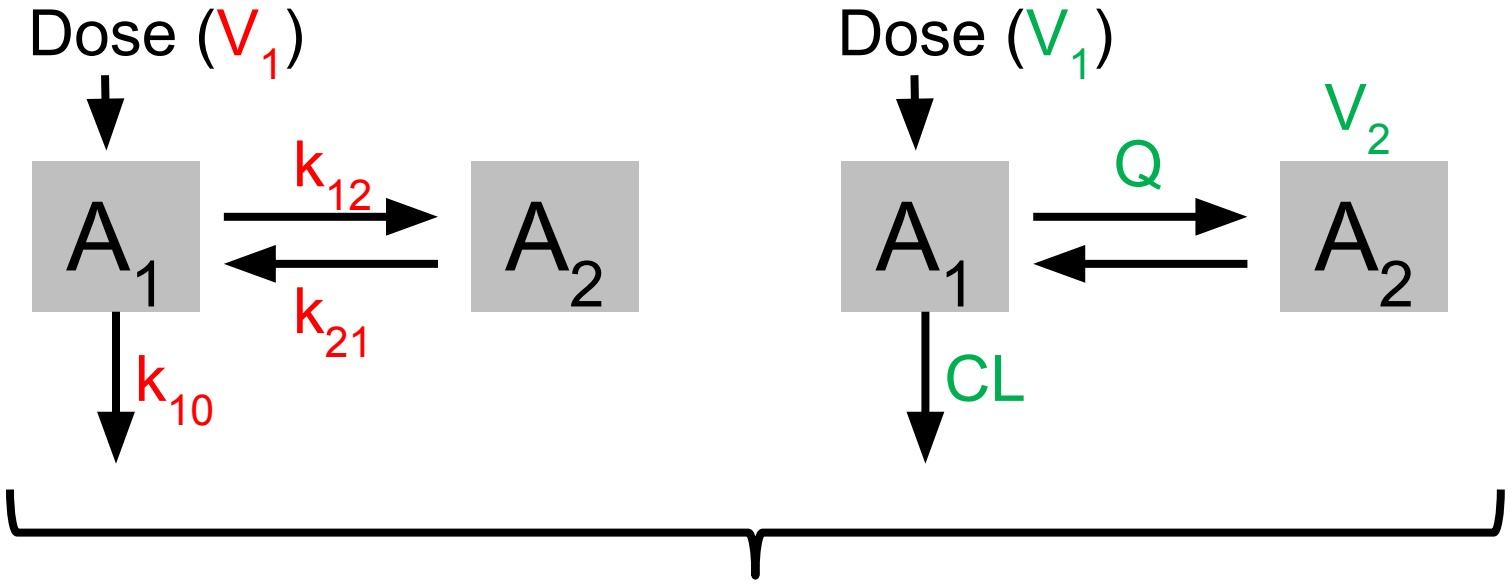
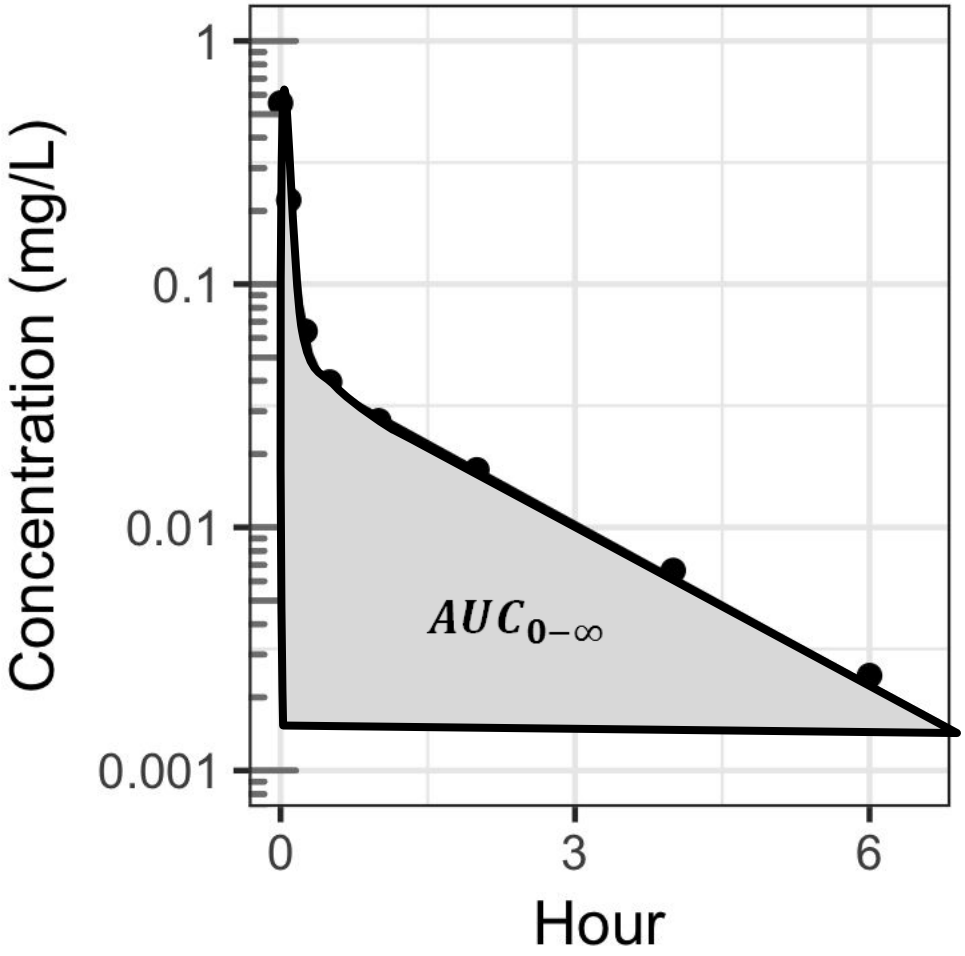
Alternative parameterization for 2 compartment model

$\{V_1, k_{10}, k_{12}, k_{21}\}$ $\{V_1, CL, Q, V_2\}$



$$CL = k_{10} \cdot V_1$$
$$Q = k_{12} \cdot V_1$$
$$V_2 = V_1 \cdot (k_{12}/k_{21})$$

Clearance still relates to the Area Under the conc. Curve ($AUC_{0-\infty}$)



Total drug in = Total drug out

Dose $= \int_0^\infty CL \cdot C(t)dt$

If clearance doesn't depend on concentration (linear)

Dose $= CL \cdot \int_0^\infty C(t)dt$

Dose $= CL \cdot AUC_{0-\infty}$

$$AUC_{0-\infty} = \frac{\text{Dose}}{\text{CL}}$$

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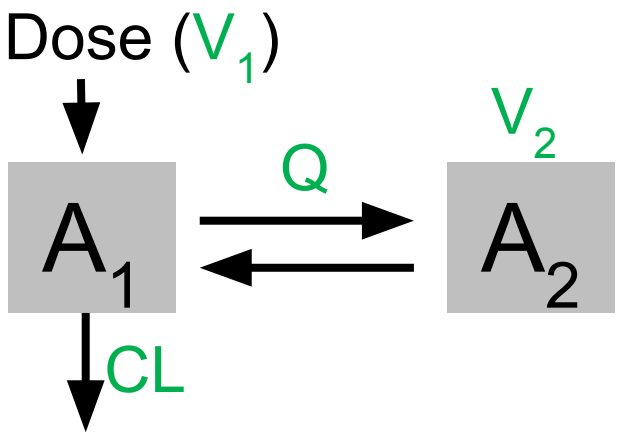
Be careful in interpreting parameters from the model



Directly observable params:

- V_1 = Dose/C_0
- CL = $AUC_{0-\infty}$ = AUC_{τ}

"Apparent" parameters

- V_2 is not a physiological volume and harder to "identify" from data
- C_2 = A_2/V_2 is not a meaningful concentration and should never be used

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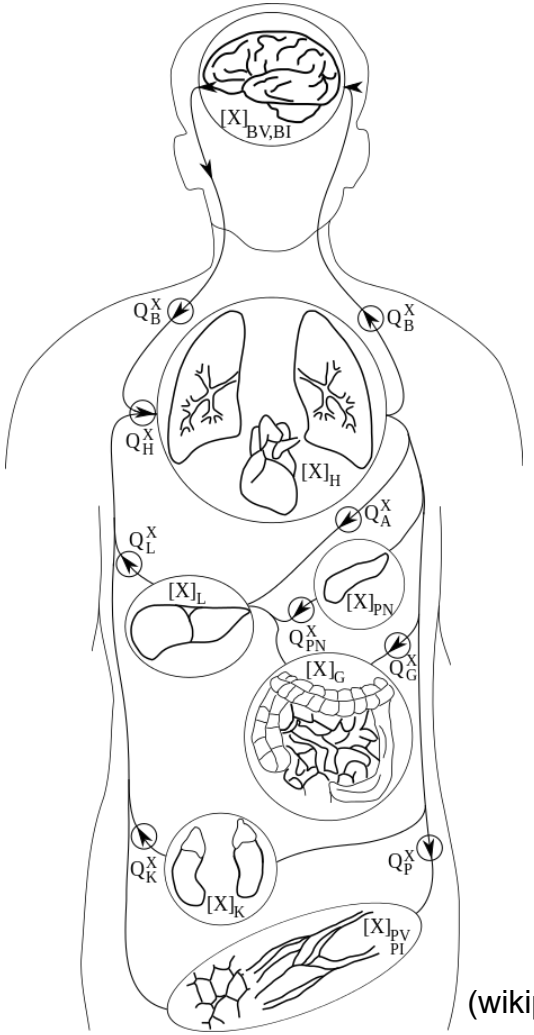
Really, there are many more peripheral compartments, but the 2 compartment approximation often works



(wikipedia for PBPK)

Key Lessons

- Distribution leads to two (or more) compartment kinetics
- Multiple “half-lives” are observable in the data.
- Even for two models, $AUC_{0-\infty}$, AUC_{τ} and $C_{avg,ss}$ are still driven by CL, when CL is independent of concentration
  - This result holds for any number of compartments
- The volume becomes a function of time and the behavior of this function at time zero (V_1) or as time goes to infinity (V_z, V_{ss}) are often what is reported

Absorption and bioavailability

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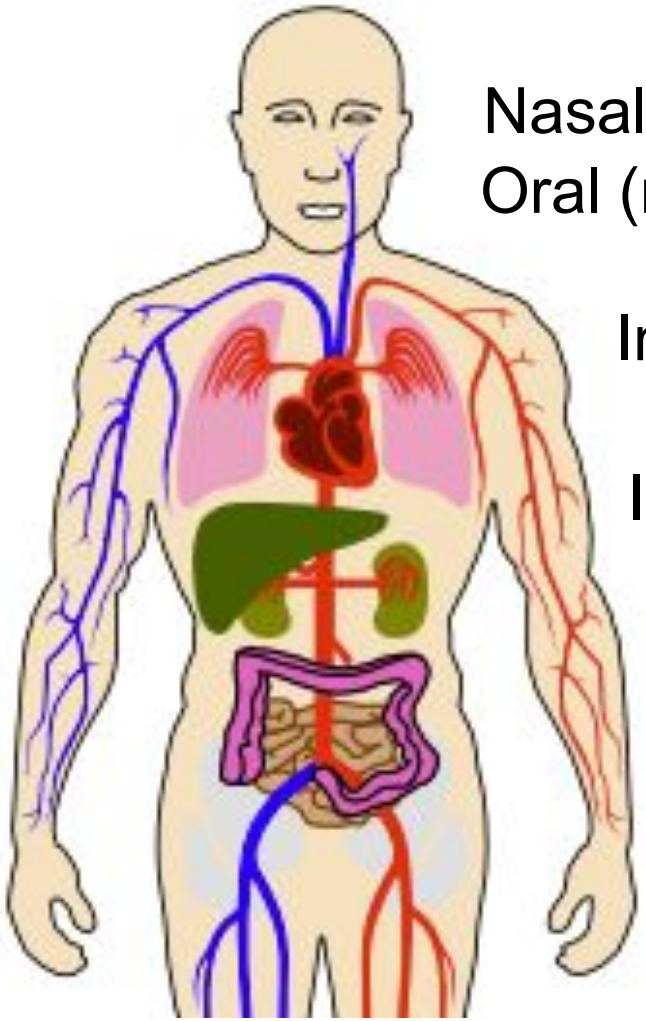
Routes of Administration (examples)



Nasal (nose)
Oral (mouth)

Inhalation (lung)

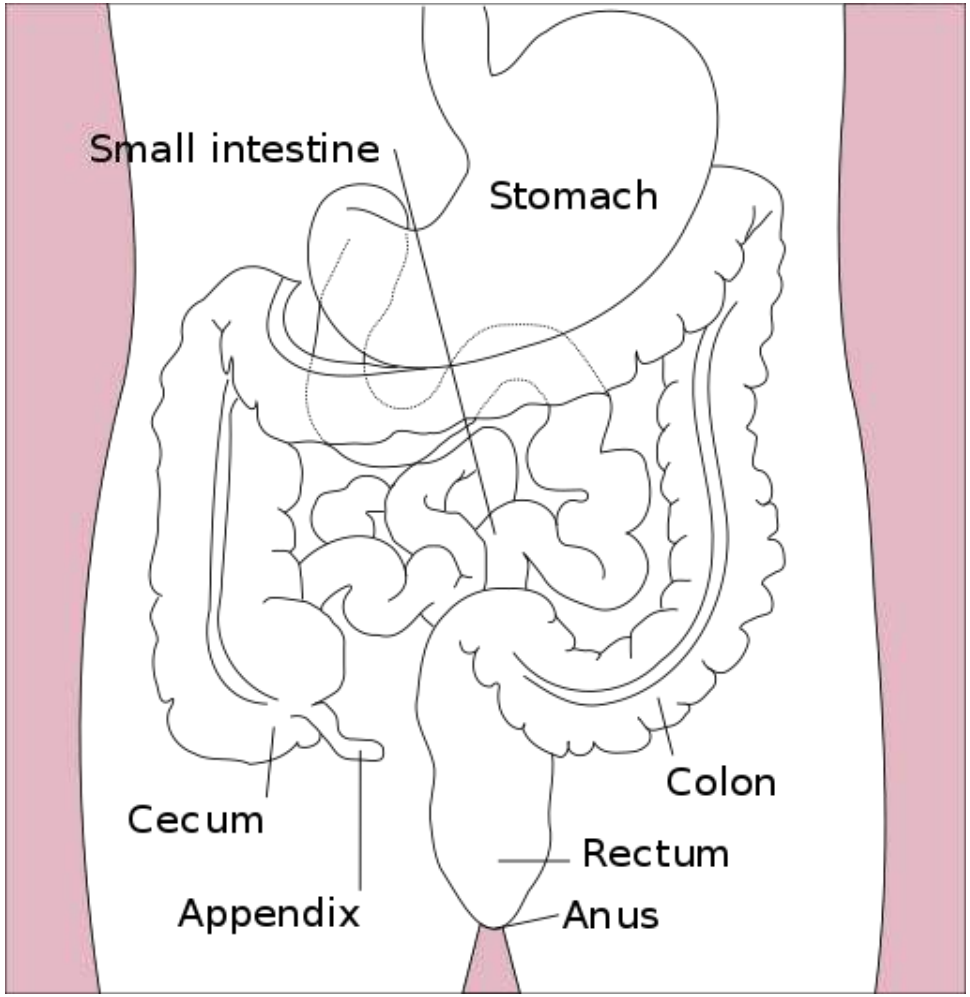
Intravenous (vein)

Intramuscular (muscle)

Subcutaneous (under skin)

Transdermal (skin patch)

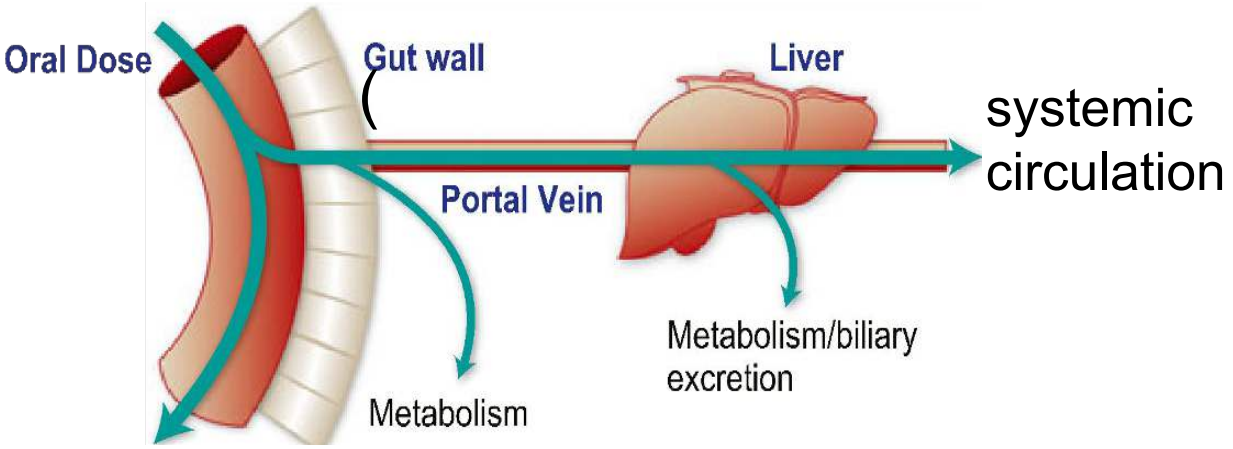
Oral dose of drug is absorbed through the gastrointestinal tract



Wikipedia

Bioavailability (some drug is lost)

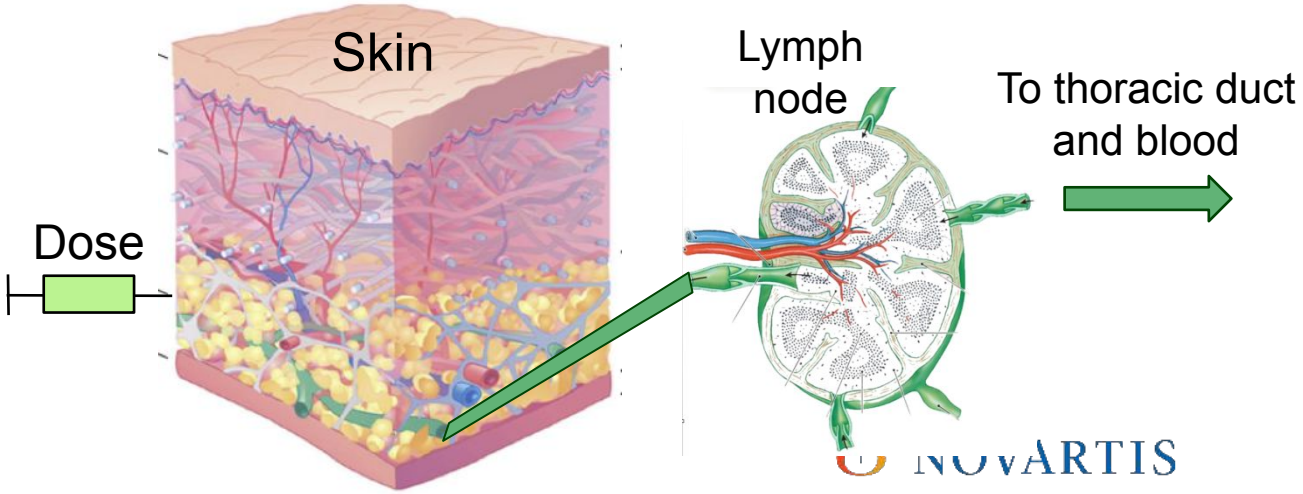
Oral dose small molecule



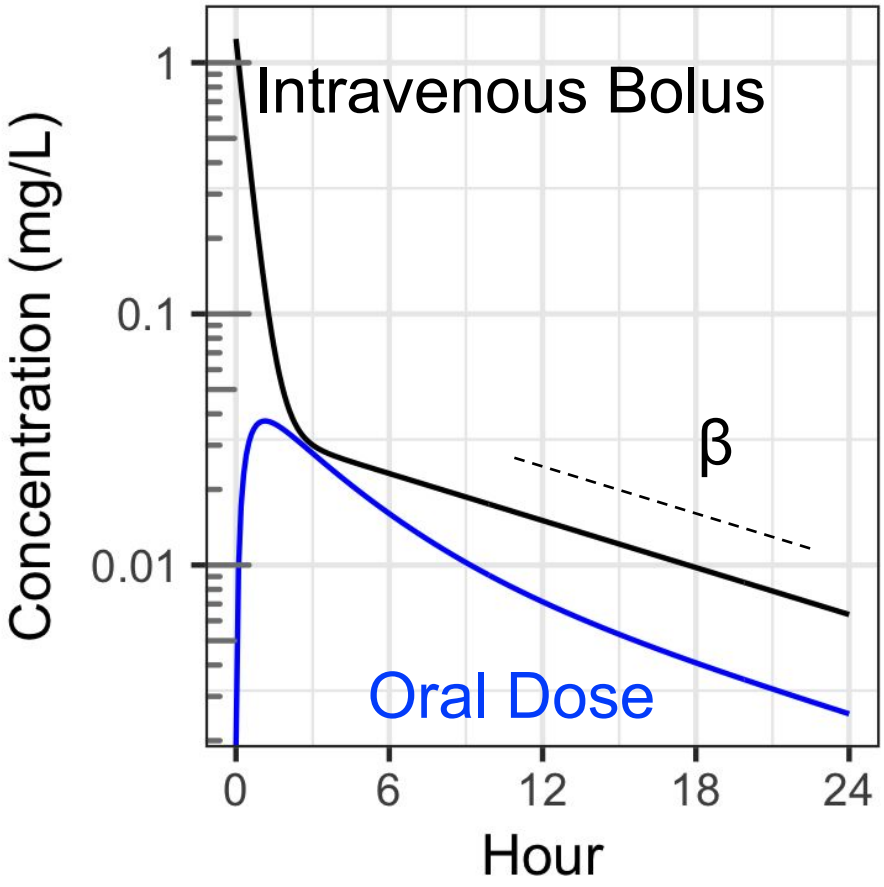
Oral Absorption	Intestinal First Pass Elimination	Hepatic First Pass Elimination

Subcutaneous dose biologic

Subcutaneous Absorption	Inject Site First Pass Elimination	Lymphatic First Pass Elimination



Oral dose vs intravenous dose



	IV Bolus	Oral
Absorption	No	Yes
Initial conc. (C0)	Dose/V1	0
Time of max conc.	0	>0
$AUC_{0-\infty}$	Dose/CL	< Dose/CL
Terminal slope	β	β

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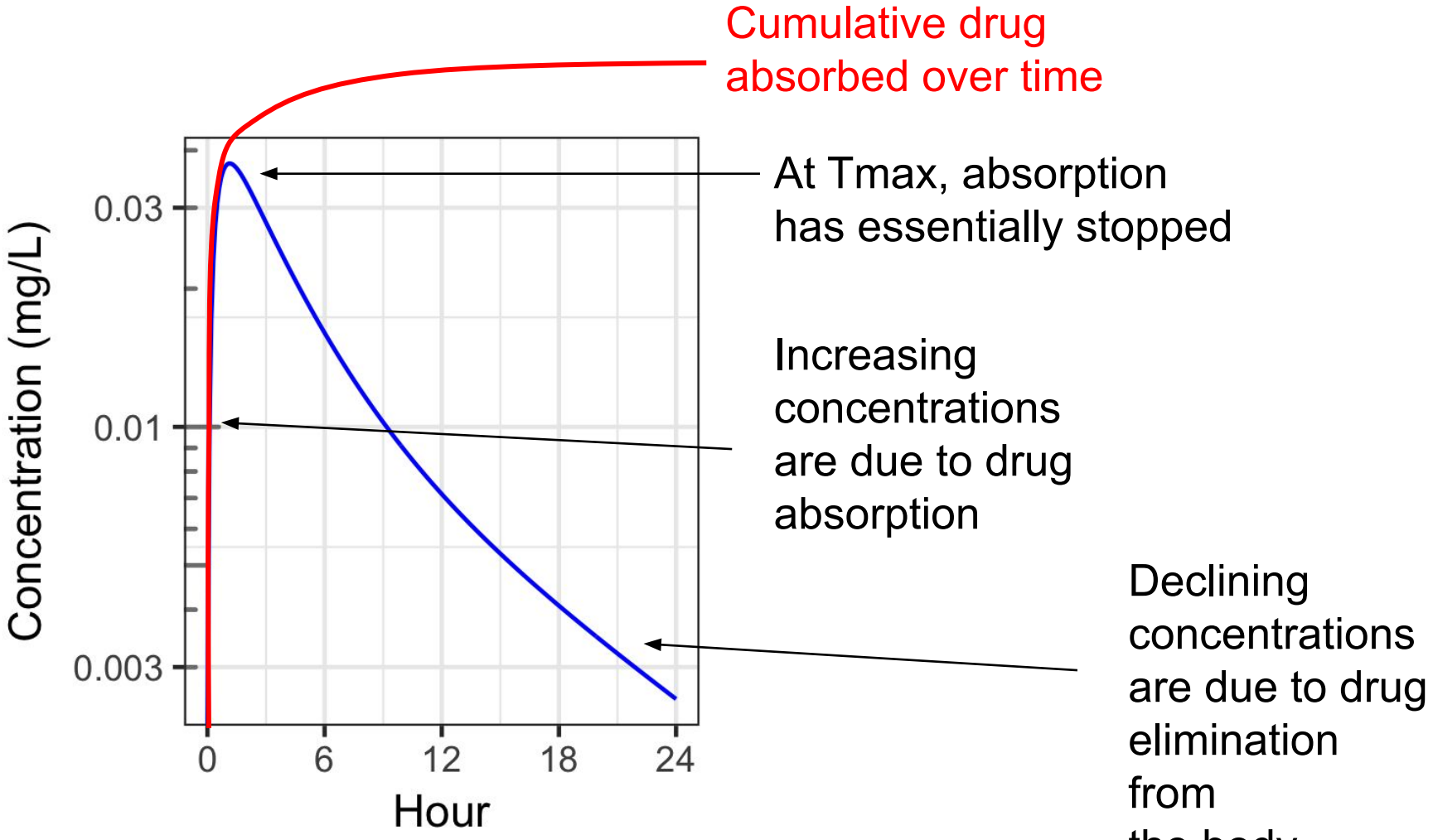
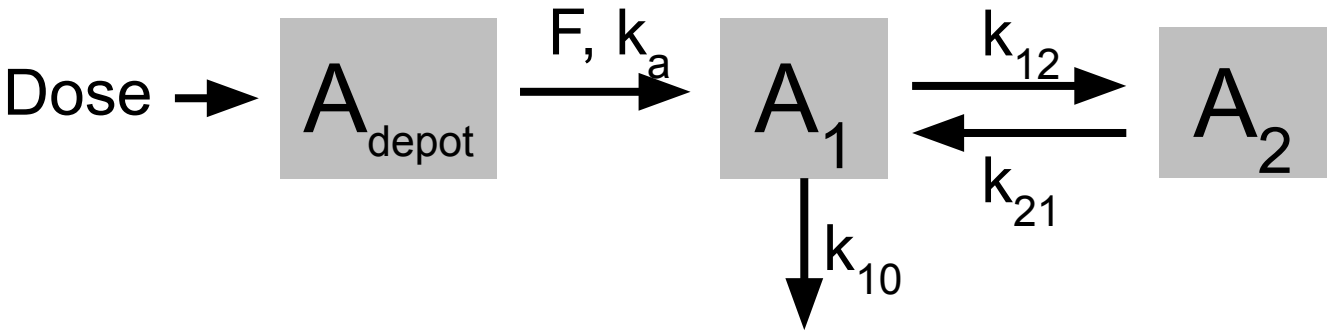
Oral Dose


Cumulative drug absorbed over time
At Tmax, absorption has essentially stopped
Increasing concentrations are due to drug absorption
Declining concentrations are due to drug elimination from the body
Concentration (mg/L)
0.03
0.01
0.003
0
6
12
18
24
Hour

Compartment Model with Absorption



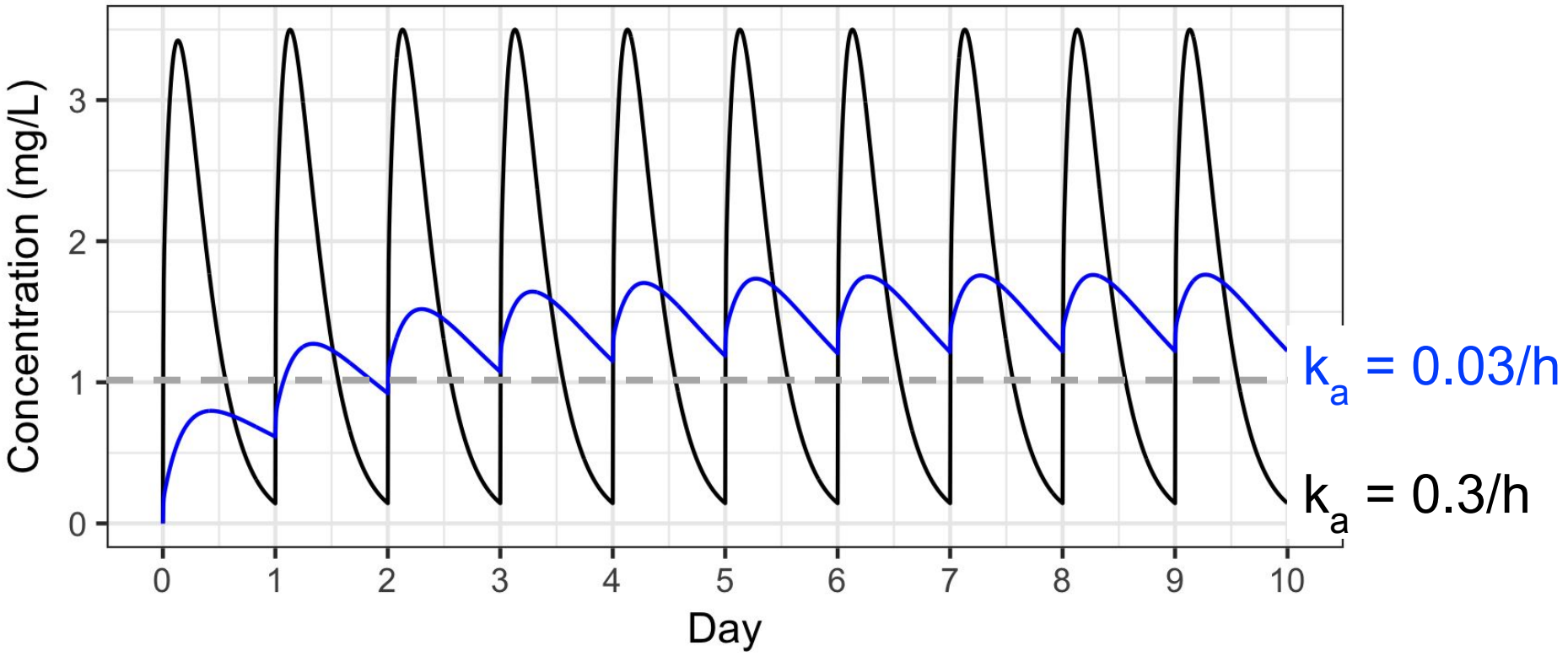
absorption elimination distribution

$$\frac{dA_{depot}}{dt} = -k_a \cdot A_{depot}$$

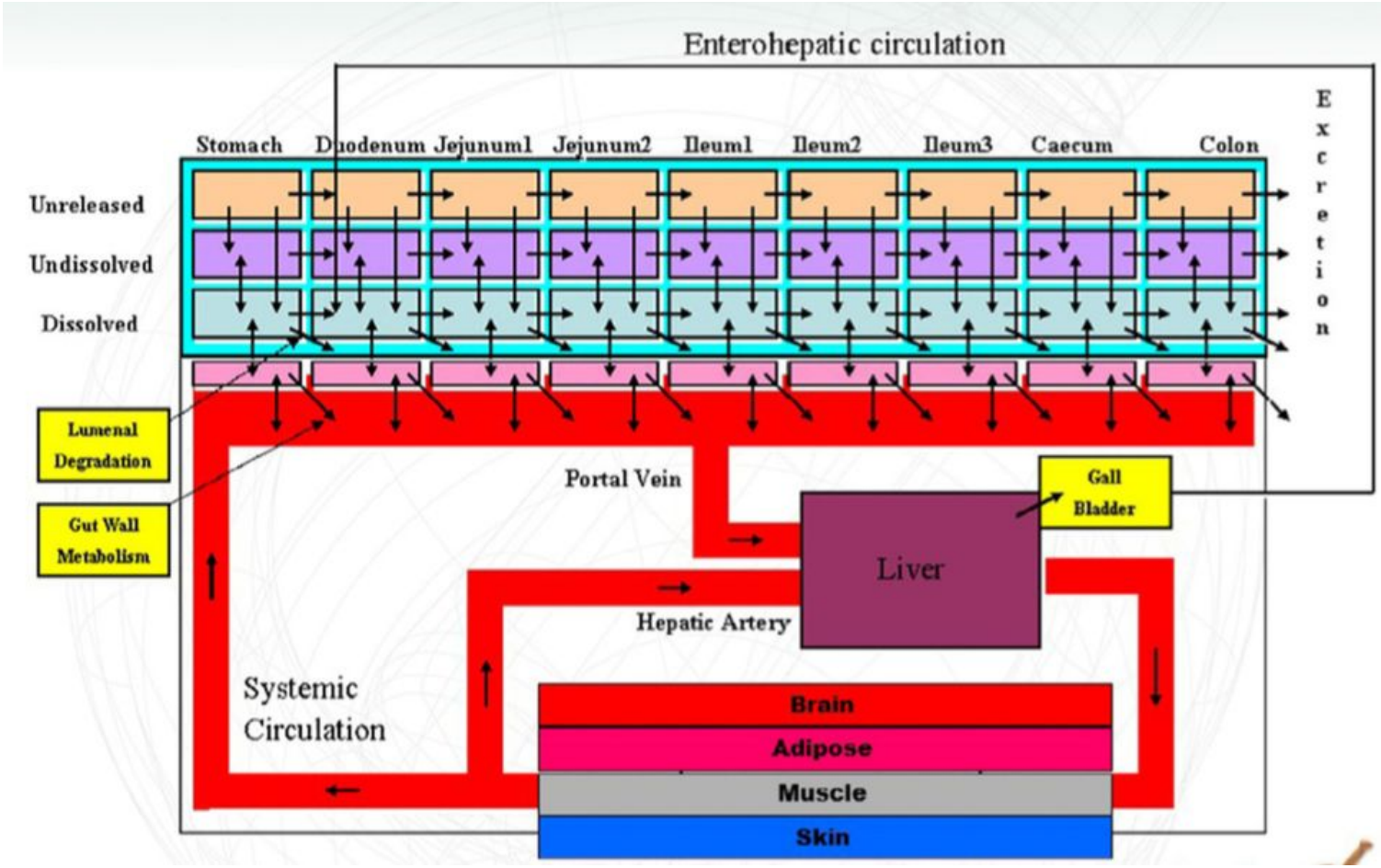
$$\frac{dA_1}{dt} = F \cdot k_a \cdot A_{depot} - k_{10} \cdot A_1 - k_{12} \cdot A_1 + k_{21} \cdot A_2$$

$$\frac{dA_2}{dt} = k_{12} \cdot A_1 - k_{21} \cdot A_2$$

Application – extended release prolongs exposure and can improve safety (reduce peak-trough ratio)



More complex absorption models can be developed



Abuhelwa, Ahmad Y., et al. "Food, gastrointestinal pH, and models of oral drug absorption." European Journal of Pharmaceutics and Biopharmaceutics 112 (2017): 234-248.

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Question

- How would you expect changing the rate of absorption(ka) to affect the average drug concentration at steady state?

- How does changing the bioavailability affect the average drug concentration

Updating average concentration formula

Total drug in = Total drug out

$$F \cdot \text{Dose} = \int_{n\tau}^{(n+1)\tau} CL \cdot C(t)dt$$

If clearance is linear

$$F \cdot \text{Dose} = CL \cdot \int_{n\tau}^{(n+1)\tau} C(t)dt$$

$$F \cdot \text{Dose} = CL \cdot AUC_{\tau}$$

$$AUC_{\tau} = \frac{F \cdot \text{Dose}}{\text{CL}}$$

$$\boldsymbol{C_{avg,ss} = \frac{AUC_{0-\infty}}{\tau} = \frac{F \cdot \text{Dose}}{\text{CL} \cdot \tau}}$$

Formula doesn't depend on absorption, but it does depend on F

Key Lessons

- When drugs are given by alternative routes to intravenous (e.g. oral, subcutaneous, etc.), they must be absorbed before entering blood stream.
- Some of the drug may be lost before entering the blood.

Allometric Scaling

Effect of body size on PK parameters

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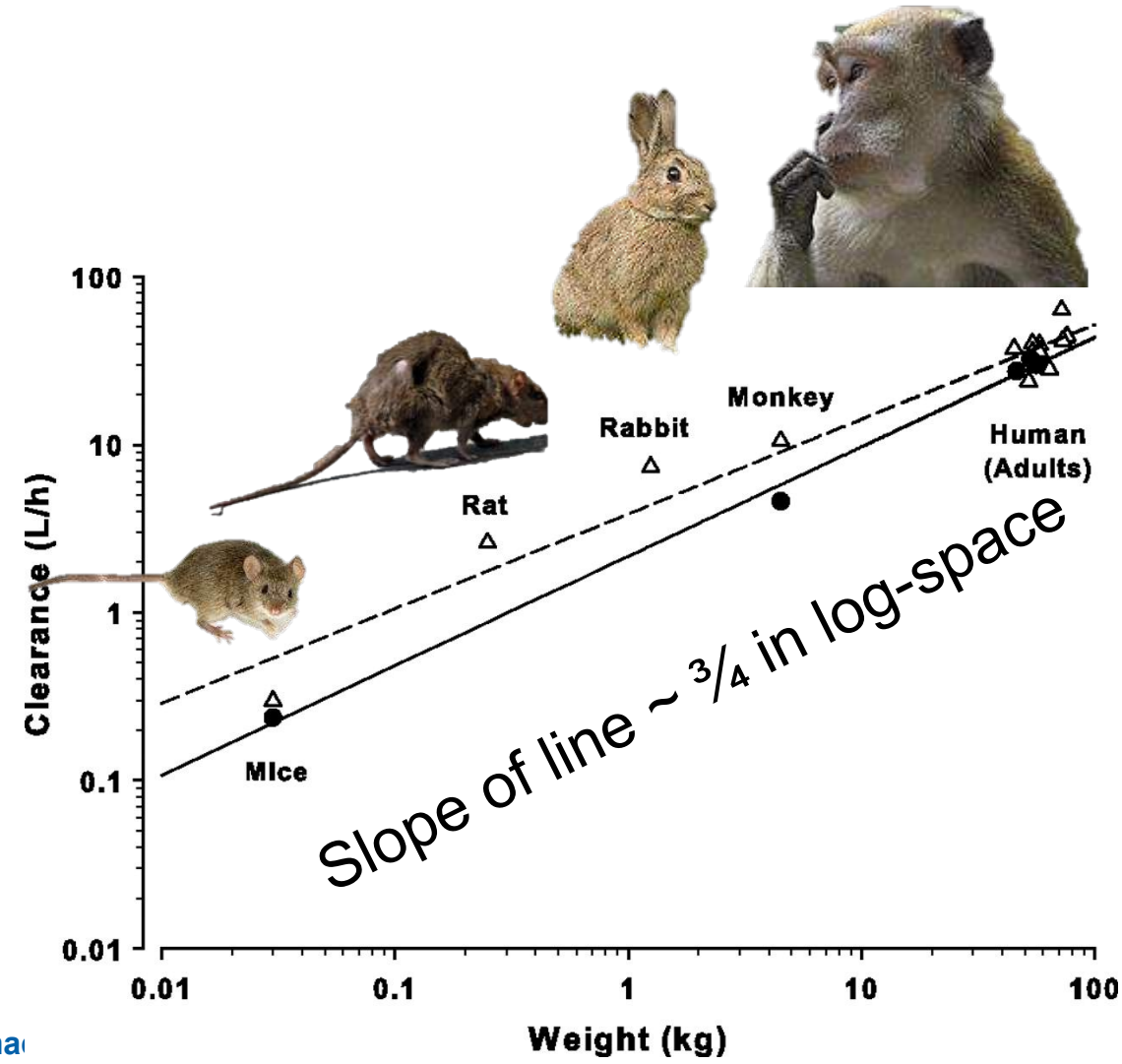
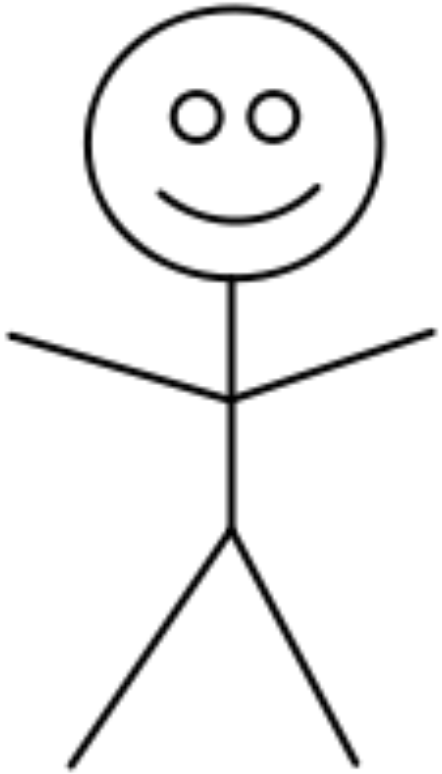
Often, we want to predict PK in humans from animal data





Moore, Brioni R., et al. "Pharmacokinetics, pharmacodynamics, and allometric scaling of chloroquine in a murine malaria model." *Antimicrobial agents and chemotherapy* 55.8 (2011): 3899-3907. Pictures from wikipedia

Many biological processes scale with body weight

- The weight of lifeforms spans 21 orders of magnitude:
  - Smallest microbe ~ 10^{-13} grams
  - Largest whales ~ 10^{8} grams
- Many fundamental biological processes scale with weight (WT) in a surprisingly simple way.
  - Volume ~ WT
  - Metabolic Rate ~ $WT^{3/4}$
  - Lifespan ~ $WT^{1/4}$
  - Heart rate ~ $WT^{-1/4}$
  - Length of aorta ~ $WT^{1/4}$
  - Height of tree ~ $WT^{1/4}$

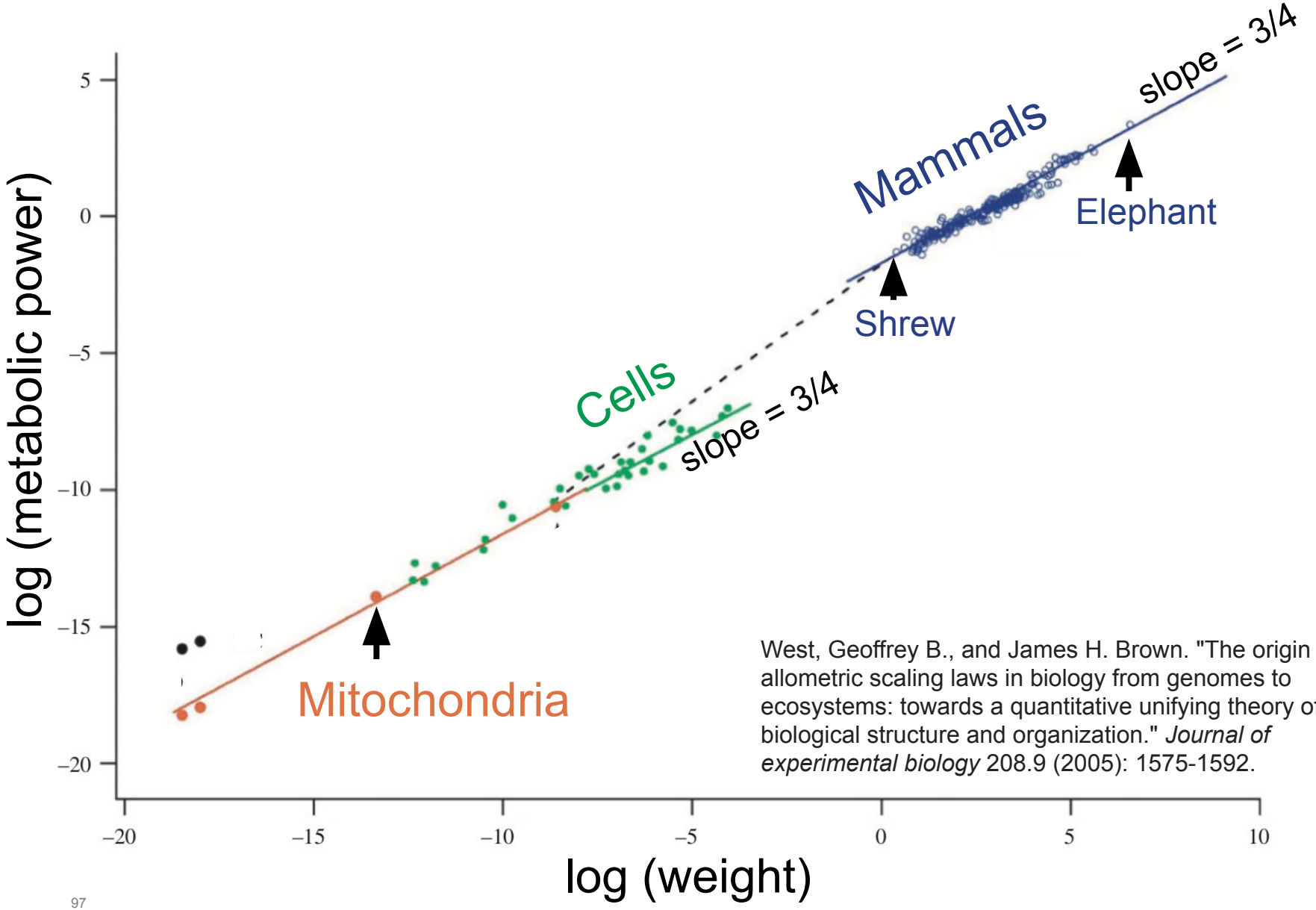
Total number of heart beats before death is independent of weight:

(Heart rate)·(Lifespan) = WT^{0}

Mammals get about 1 billion heart beats in their lifetime (from hamster to elephant)

West, Geoffrey B., and James H. Brown. "The origin of allometric scaling laws in biology from genomes to ecosystems: towards a quantitative unifying theory of biological structure and organization." *Journal of experimental biology* 208.9 (2005): 1575-1592.

Metabolic rate ~ $WT^{3/4}$

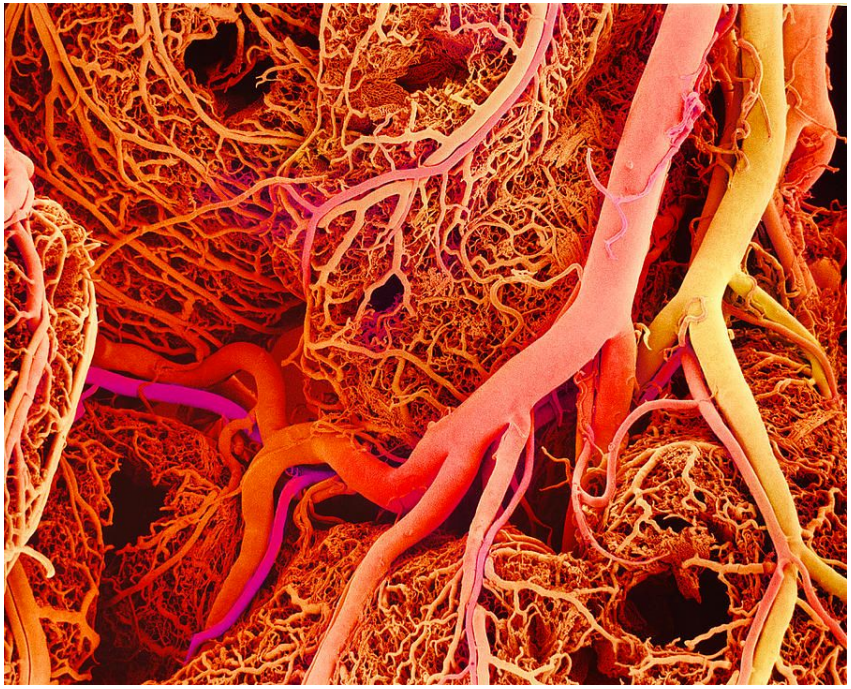


West, Geoffrey B., and James H. Brown. "The origin of allometric scaling laws in biology from genomes to ecosystems: towards a quantitative unifying theory of biological structure and organization." *Journal of experimental biology* 208.9 (2005): 1575-1592.

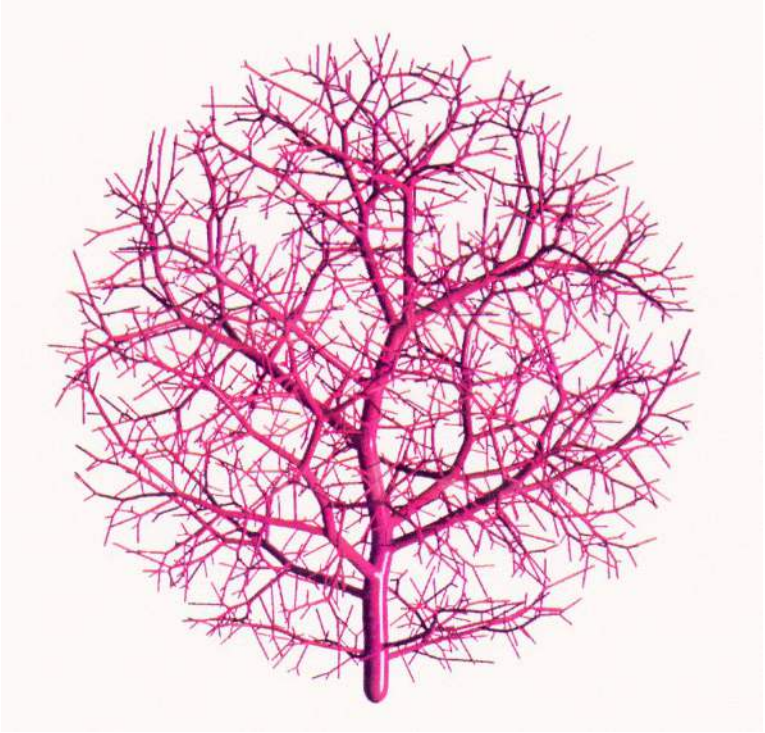
The reason for metabolism ~ $WT^{3/4}$ is to maximize surface area (SA)

- Evolution maximizes surface area (SA), in order to maximize nutrient absorption and metabolism.
- For standard geometries (cube, sphere), surface area relates to length (L), volume (V), and weight (WT) by:
  - $SA \sim L^2$
  - $V \sim L^3$
  - $SA \sim V^{2/3} \sim WT^{2/3}$ (because volume is proportional to weight)
- Because evolution pushes life to maximize surface area and a little more area can be obtained using the "fractal dimension" The maximum possible exponent is ¾.
- Therefore, $SA \sim WT^{3/4} > WT^{2/3}$

Blood vessels follow fractal patterns



https://blogs.uoregon.edu/artofnature/2013/12/03/fractal-of-the-week-blood-vessels/



https://dejavouz.wordpress.com/reflections/tree2/

What is the optimal fractal dimensions to maximize surface area?

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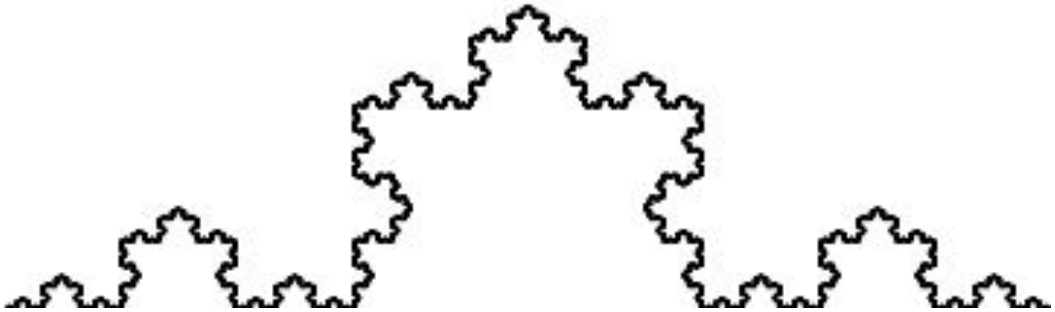
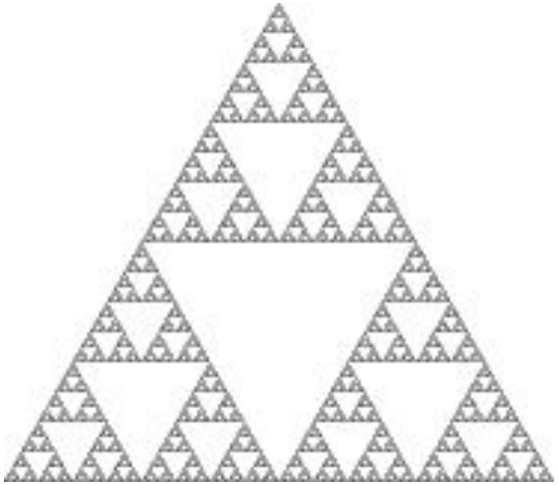
A fractal is a self similar as you zoom in to smaller scales





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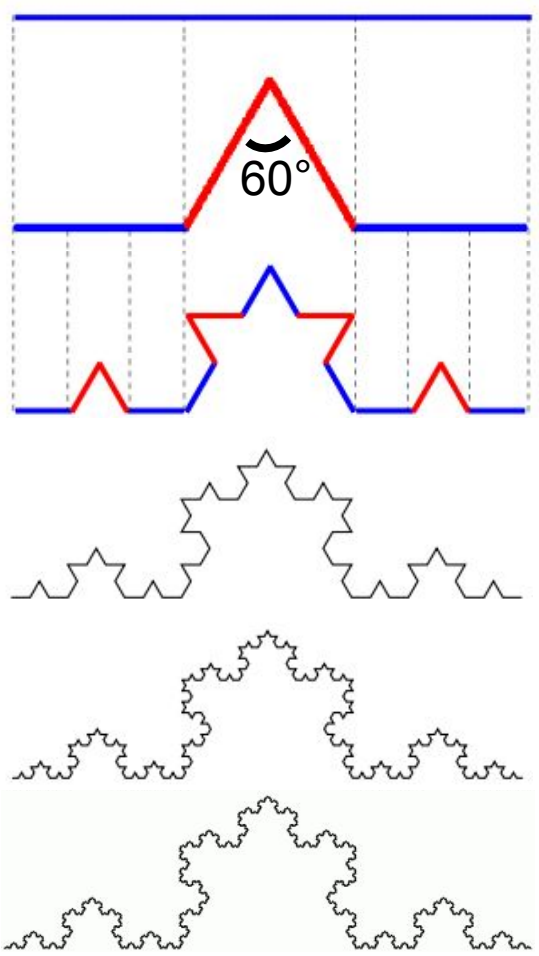
An example of building a fractal

Koch Curve



each line is 1/3 the size of the original line. But now there are 4 segments (instead of 3)

Length

1

4/3 = 1.3

16/9 = 1.8

64/27 = 2.4

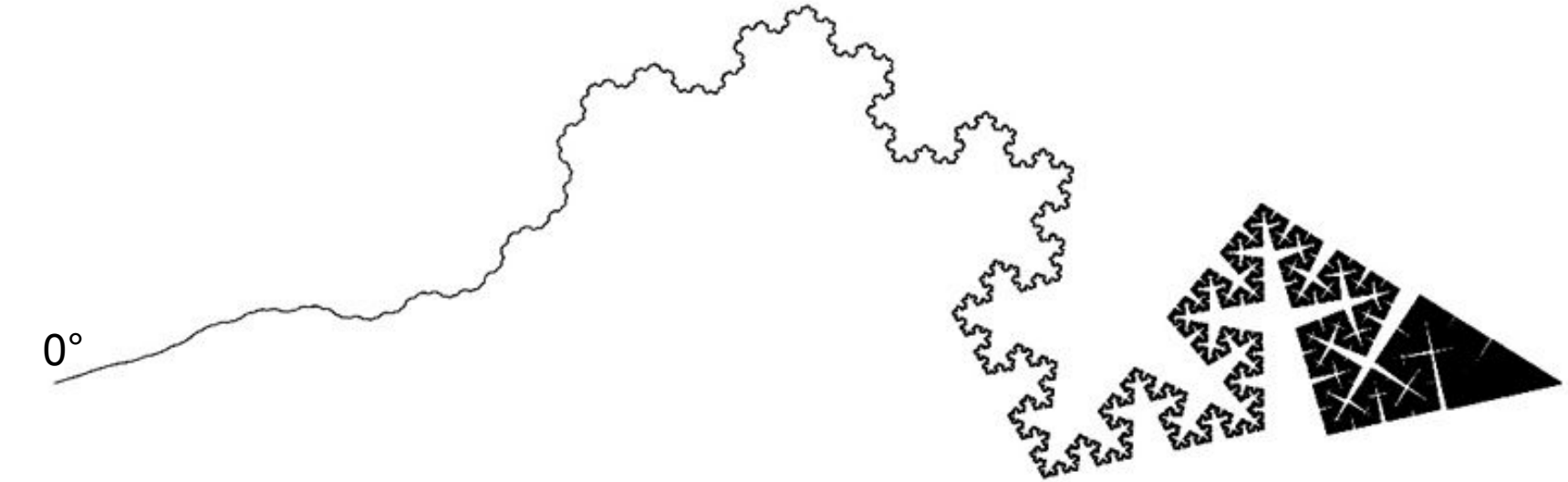
256/81 = 3.2

$4^n/3^n \rightarrow \infty$

fractal dimension = log(4)/log(3) = 1.26

Fractal

Fractal geometry can increase the dimensionality of the space

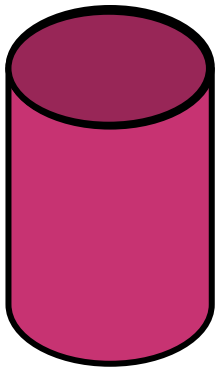


The largest a fractal dimension can be is 1 + spatial dimension
The surface area can go from 2 □ 3 dimensions

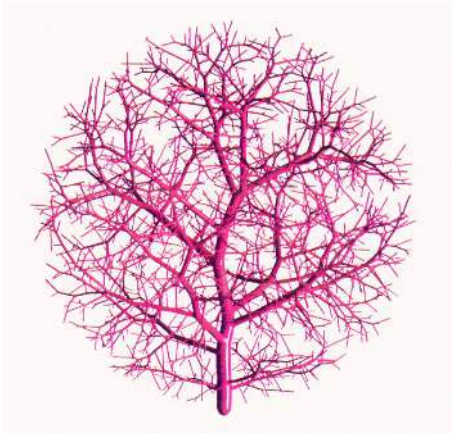
https://www.researchgate.net/figure/Von-Koch-curve-with-bend-angle-from-0-to-90-degrees_fig1_309391846

Life has found a 4th dimension using fractal geometry! This is why CL ~ $WT^{3/4}$

- For "normal" shapes:
  - $SA \sim L^2$
  - $V \sim L^3$
  - $SA \sim V^{2/3} \sim WT^{2/3}$



- For blood vessels
  - $SA \sim L^3$
  - $V \sim L^4$
  - $SA \sim V^{3/4} \sim WT^{3/4}$



1. West, Geoffrey B., James H. Brown, and Brian J. Enquist. "The fourth dimension of life: fractal geometry and allometric scaling of organisms." Science 284.5420 (1999): 1677-1679.

Key Lessons

- Generally
  - Clearance scales with CL ~ $WT^{3/4}$
  - Volume scales with V ~ WT
- This is a rule of thumb and does not always apply. Important caveats:
  - Differing mechanisms of drug metabolism across animals
  - Difference between “lean body weight” and total body weight
  - Differences in metabolism with age, especially under 1 year old.
- In practice, estimating the exponent for a particular drug can be challenging due to the limited range in weights that are tested. So often, the ¾ exponent is assumed.

Where PK measurements and models are used

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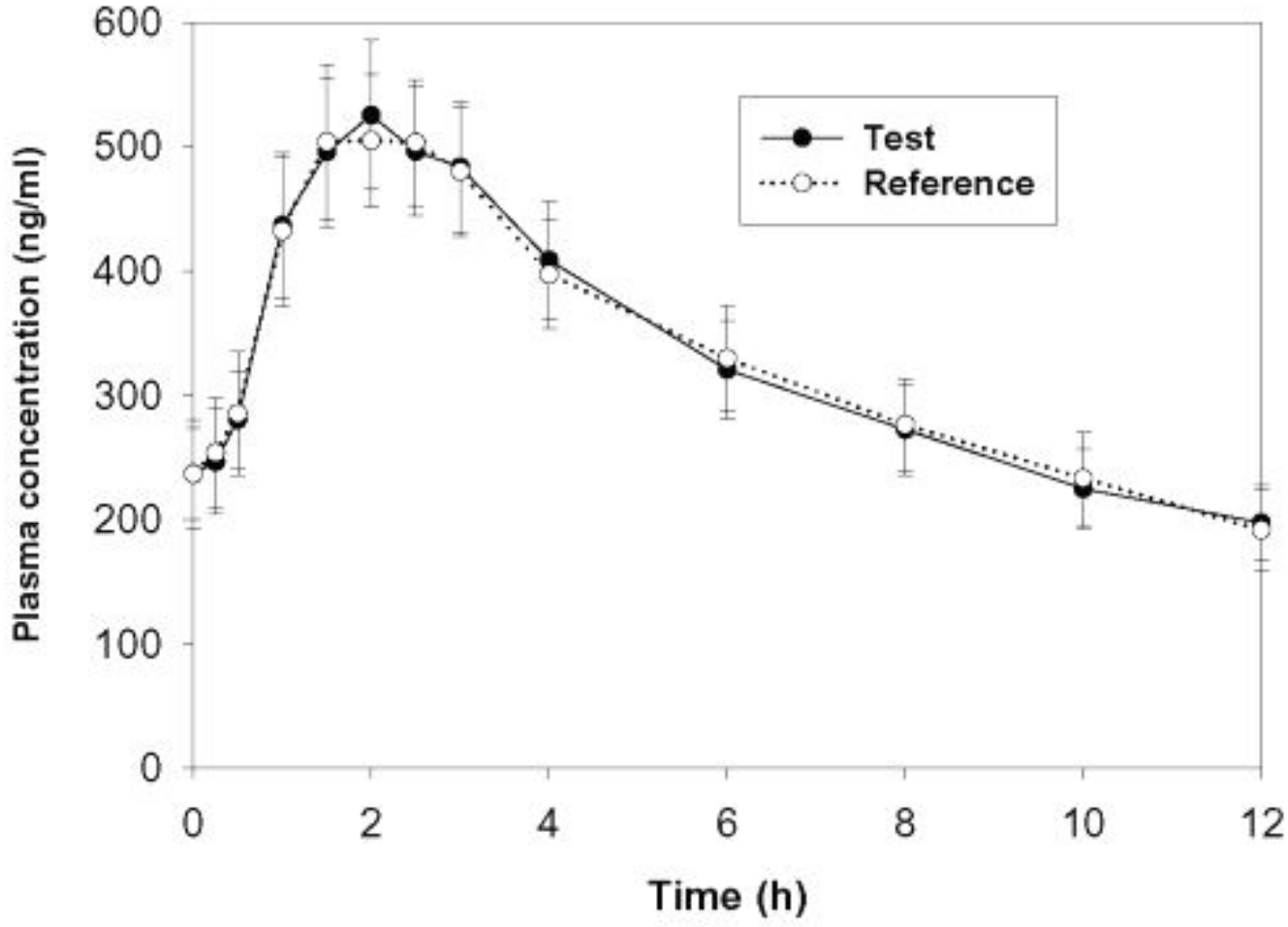
Bioequivalence Postulate

- If the concentration-time profiles for two drugs or dosing conditions are the same then efficacy and toxicity should be the same
  - Basis for generic drugs
  - Basis for formulation changes
  - Basis for examination of drug interactions, food effects, etc.

From Pete Bonate

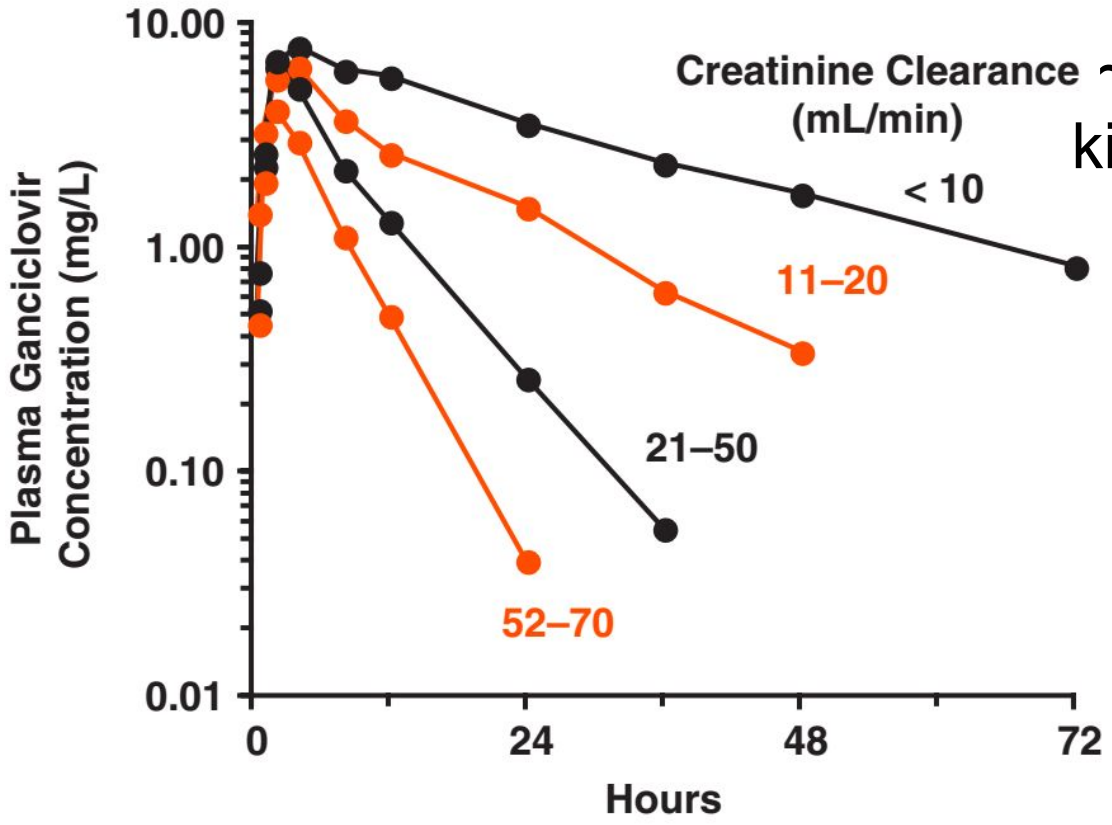
Mean clozapine plasma concentrations after 7 days of 100 mg BID for 2 formulations in 18 schizophrenic subjects



Tassaneeyakul W et al. Steady-state bioequivalence of clozapine tablet in schizophrenic patients. J Pharm Pharmaceutic Sci 8, 47, 2005

From Pete Bonate

For drugs that are cleared by kidney, kidney function will affect exposure



~ Measure of kidney function

Roland and Tozer, Figure 13-14

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Some factors that may impact drug concentrations

Factor	Parameter	Mechanism
Liver and kidney function	CL	Small molecules that are cleared by liver and kidneys
Weight	CL, V	Relates to size of patient (V) and metabolizing tissue (CL)
Comedications (e.g. CYP inhibitor)	CL	Affects function of metabolizing enzyme
Comedications (proton pump inhib)	F, ka	Affects gut pH and how well it absorbs drugs
Taken with food	F, ka	impacts how
Genetics (CYP variants)	CL	Some CYPs are polyclonal

Backups

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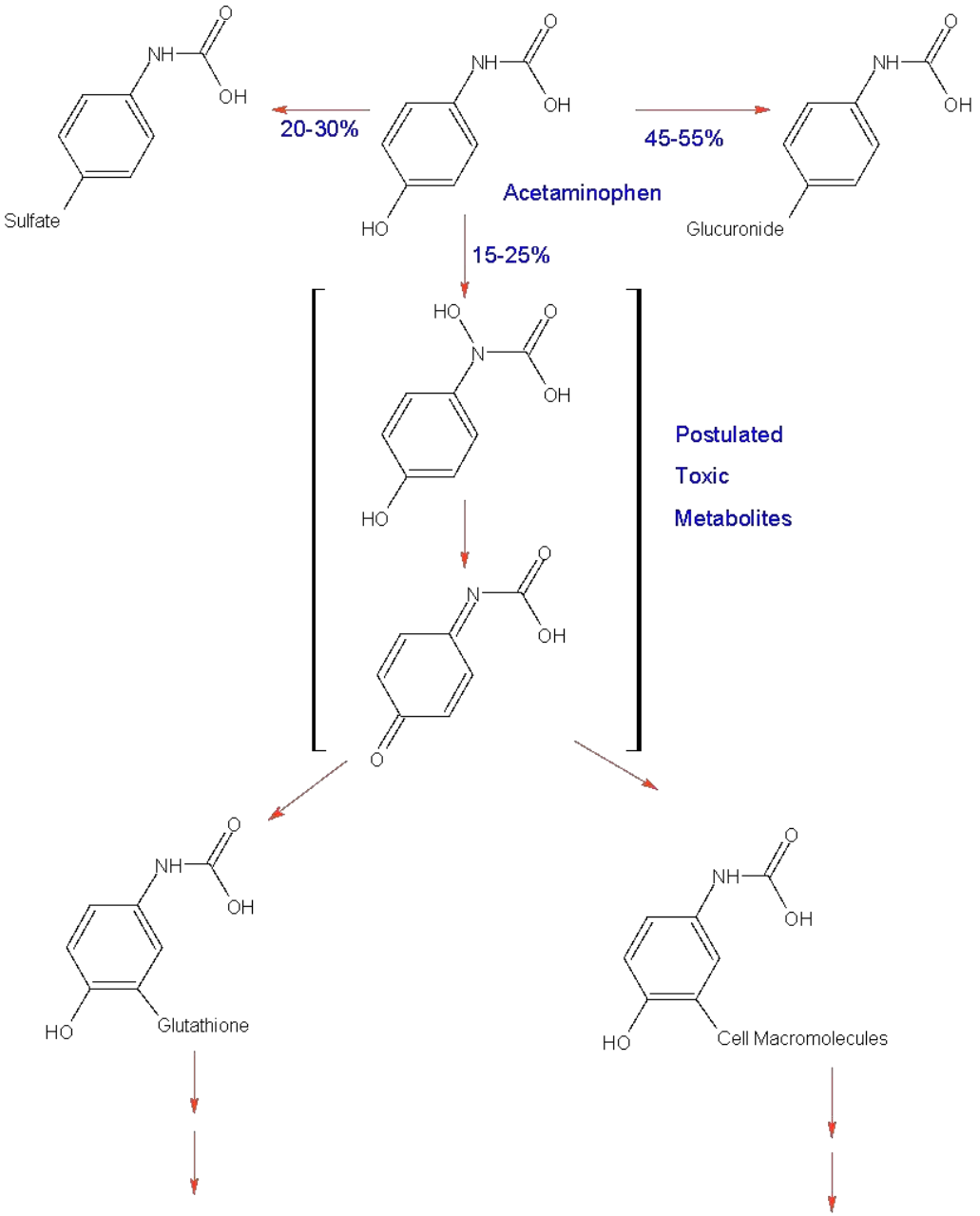
Acetaminophen Overdose

- Acetaminophen is Phase 2 conjugated by glutathione
- Large doses deplete the glutathione and sulfate pools
- Toxic metabolite then binds to cellular macromolecules
- Clinical course:
  - Nausea, vomiting (Day 1)
  - Hepatic enzymes ↑, right upper quadrant sensitive to touch (Day 2 to 3)
  - Hepatic necrosis, possibly renal failure, and cardiac abnormalities (Days 3 to 5)

From Pete Bonate



- Smallest dose recorded for hepatotoxicity in adults is 5.4 g
- 10 g is lethal
- Therapy is targeted at repleneshing sulfate pools

From Pete Bonate

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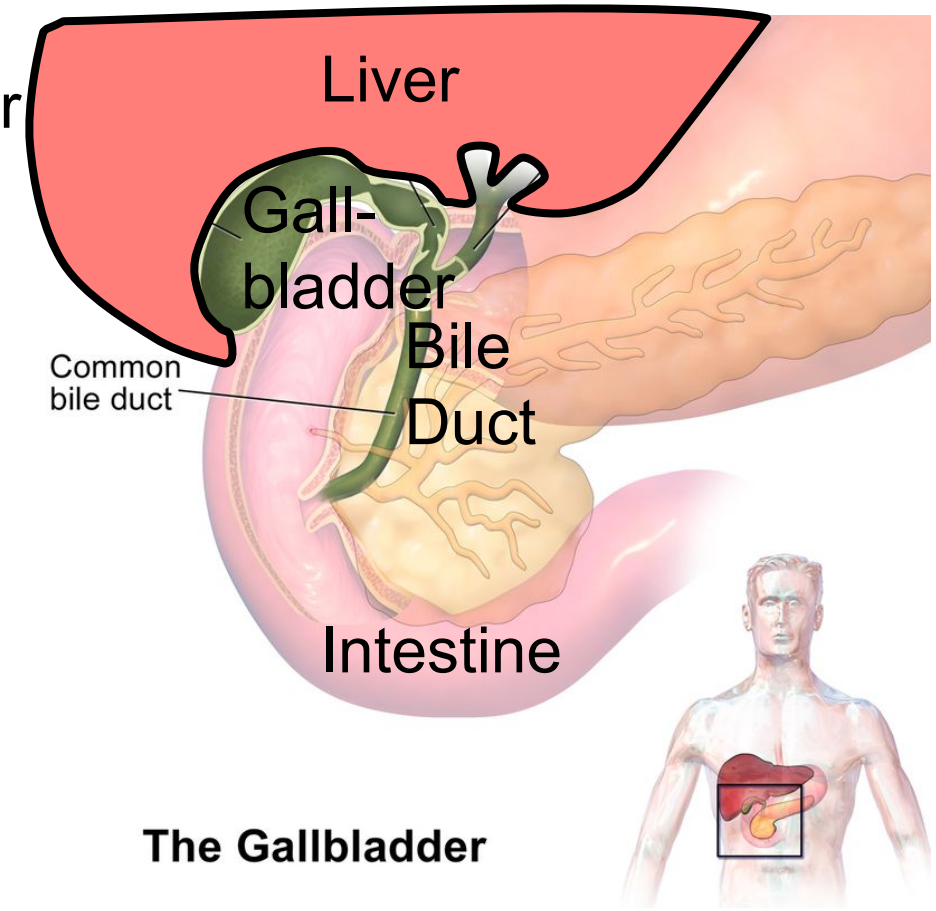
Biliary Elimination

- Bile is secreted from the liver to the gallbladder and to the the intestine
- Bile aids absorption of fats
  - breaks down large fat globules into smaller ones
- Drugs may be excreted by biliary route



From Pete Bonate and wikipedia

In the two compartment model, "volume" is a function of time

- Recall that volume relates amount in body to concentration measured in circulation.
- For 1 compartment model:
  - $C(t) = A(t)/V$
  - There is only one volume.
- For a two compartment model with central CL, there are:
  - Two volume parameters: V_1 and V_2.
  - There is also a volume function: $C(t) = A(t)/V(t)$
  - At time 0, $C(0) = A(0)/V_1$
  - After a single dose, at long times, $C(t) = A(t)/V_z$ where $V_z = CL/\beta$
  - At steady state after multiple doses:
    - $C(t_{ss}) = A(t_{ss})/V_{ss}$ where: $V_{ss} = V_1 \cdot [1 + k_{12}/k_{21}]$

Sketch of derivation of V_z and V_{ss}

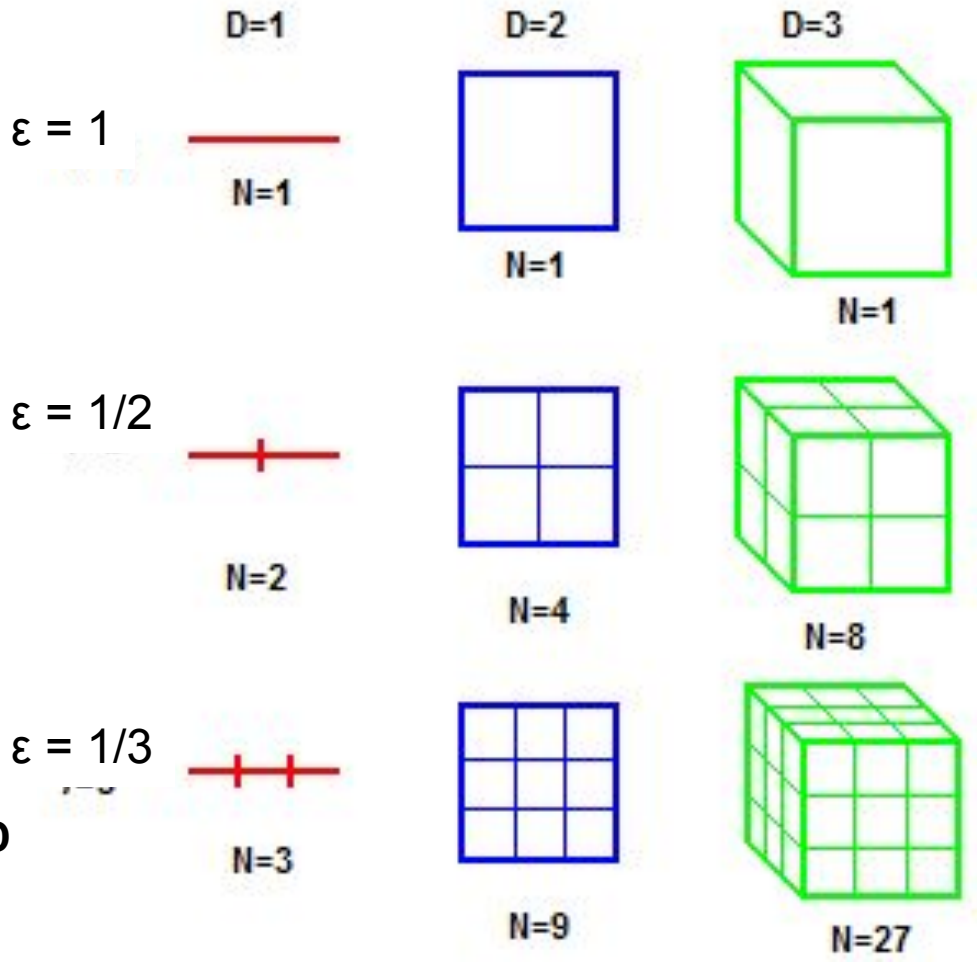
- For the derivation, we start with the definition of V(t)

$$V(t) = \frac{A(t)}{C(t)} = \frac{Dose - CL\int_0^t C(t)dt}{C(t)} = \frac{CL}{C(t)}\int_t^\infty C(t)dt$$

- To derive V_z and V_{ss}, we then:
  - Use the analytic expression for C(t) for the either single dose (V_z) or multiple dose (V_{ss})
  - Take the limit as t□∞

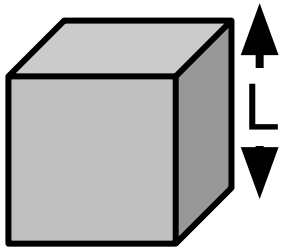
Definition of a dimension

- Let N = number of shapes (sticks, squares or cubes) needed to cover a big shape.
- Now reduce the length of each side of shape by a factor ε (e.g. 1/3)
- Then the dimension (D) is such that: $\mathbf{N \sim \varepsilon^{-D}}$



For normal shapes, surface area relates to weight by 2/3 power

- Cube



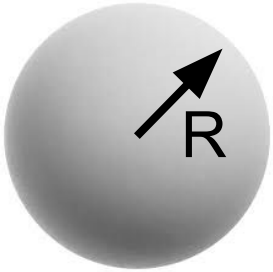
$SA = 6L^2$

$V = L^3$

$SA = c_1 \cdot V^{2/3} \sim WT^{2/3}$

c_1 is a constant

- Sphere



$SA = 4\pi R^2$

$V = (4/3)\pi R^3$

$SA = c_2 \cdot V^{2/3} \sim WT^{2/3}$

c_2 is a constant

- As V increases, SA increases too, but the SA:V ratio decreases.
- This 2/3 ratio holds at the macroscale, but on the microscale, it can be possible for SA to have > 2 dimensions.