Intro to PK-PD Concepts

Cancer Bioinformatics Data Science Bootcamp, 2025

Mitch Phelps

June 24, 2025

The Ohio State University
College of Pharmacy

Data Science in the Pharmaceutical Sciences

- Computer-aided drug design and discovery via molecular modeling of drug-receptor interactions
- Computational modeling of biological systems and drug pharmacology
- Model-informed drug development, translating from preclinical animal models into humans
- Population modeling/simulation to identify individual factors influencing drug pharmacokinetics and pharmacodynamics (PK/PD)
- Personalized medicine, identification of patient-specific factors (e.g. pharmacogenetics) that influence PK/PD and outcomes from drug therapy
- Translating drug therapies across patient populations (pediatrics, geriatrics, racial/ethnic minorities, patients with organ dysfunction, etc.)
- Pharmacoepidemiology, how the use of medications influences human health within various populations

Outline for Tuesday Afternoon and Wednesday Morning in the College of Pharmacy

- Intro and brief overview of PK-PD concepts
- Physiology as a system of compartments
- Hands-on
  - Clinical trial PK/PD data visualization
  - Inter-individual variability in PK and PD
  - Modeling PK, PD and variability in a clinical dataset
  - Simulating to achieve individualized therapy
- Tour of the College of Pharmacy Instrumentation Facility
- Lunch!

Homework -
Create a Posit Cloud account

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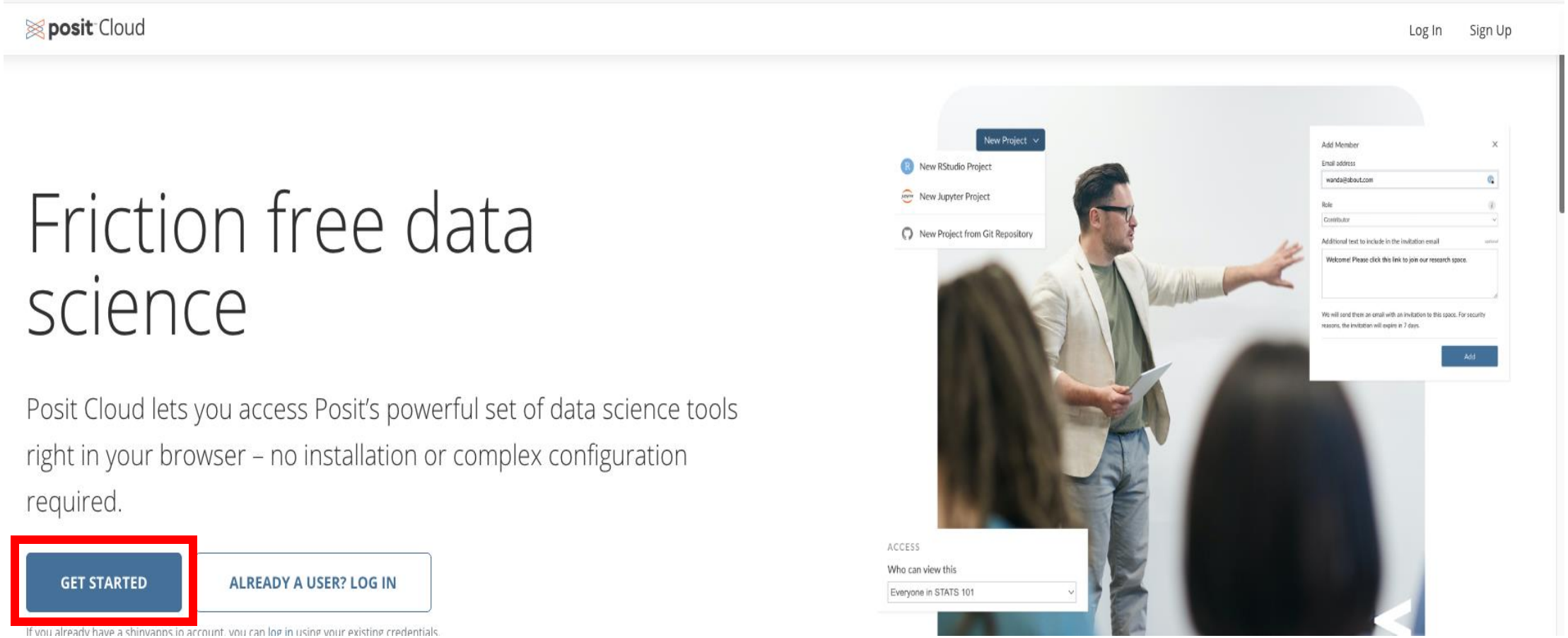

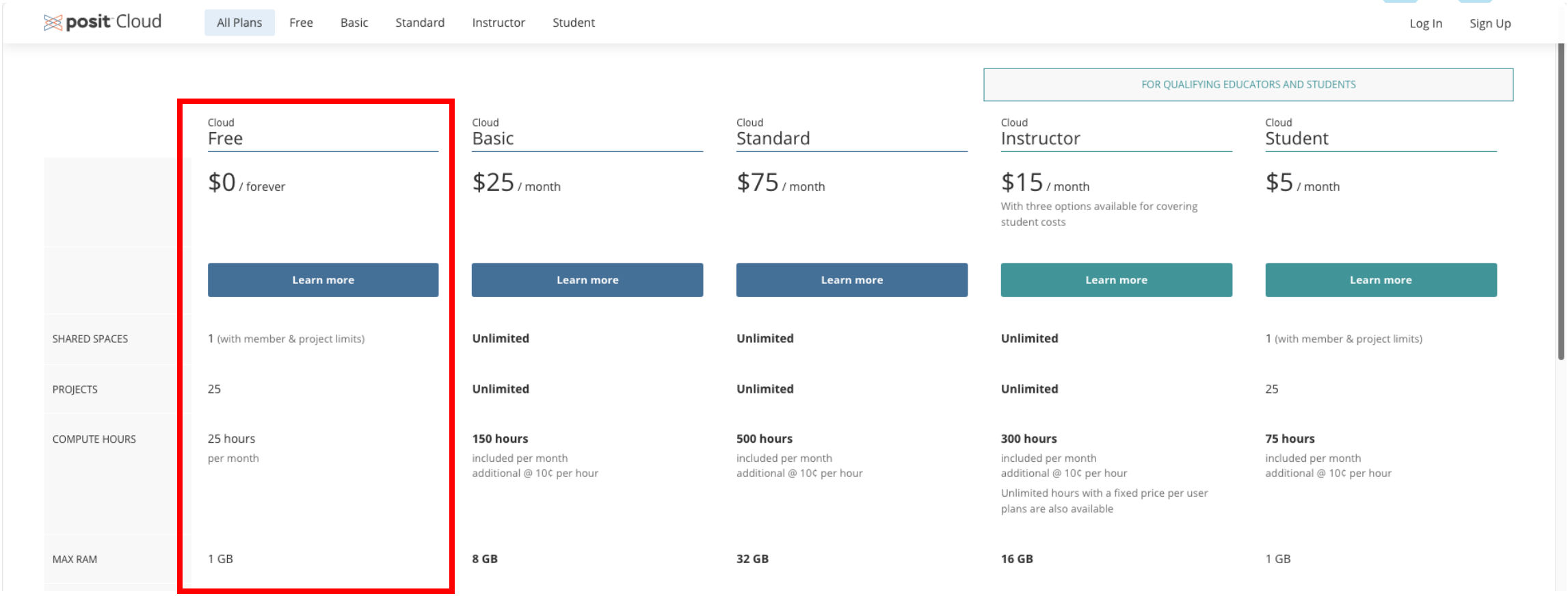
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MAX CPU	**1 CPU**
MAX EXECUTION	**1 hour**
CONCURRENT PROJECTS	**3**

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Questions? **Contact Us.**

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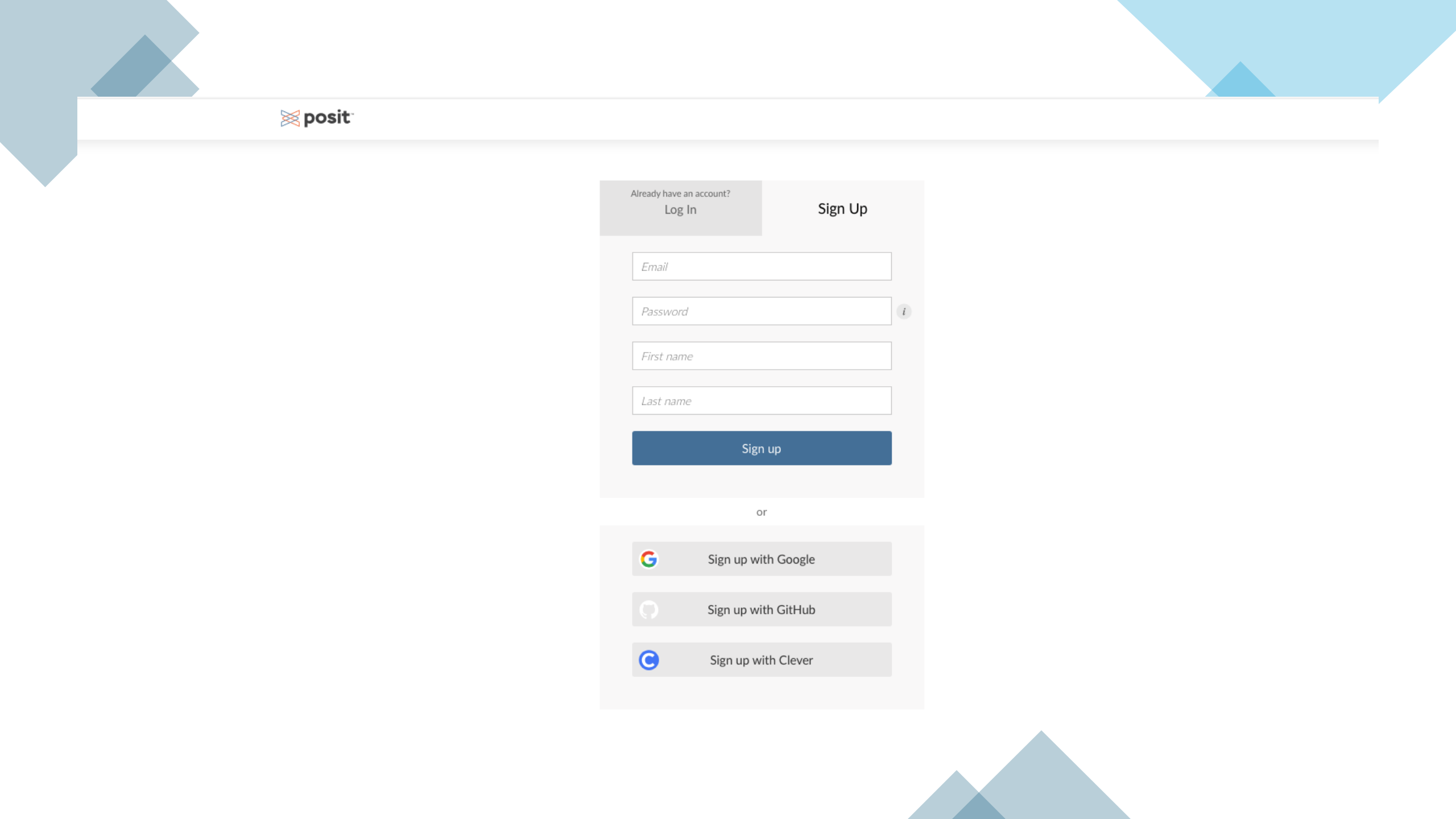
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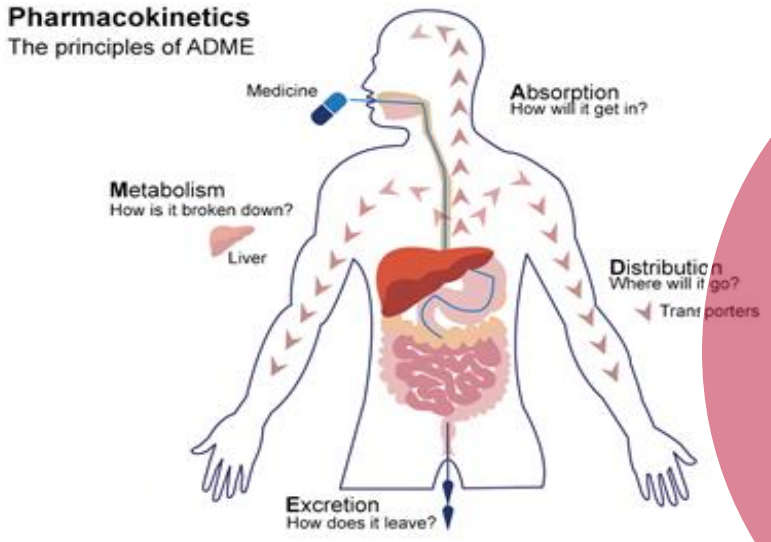
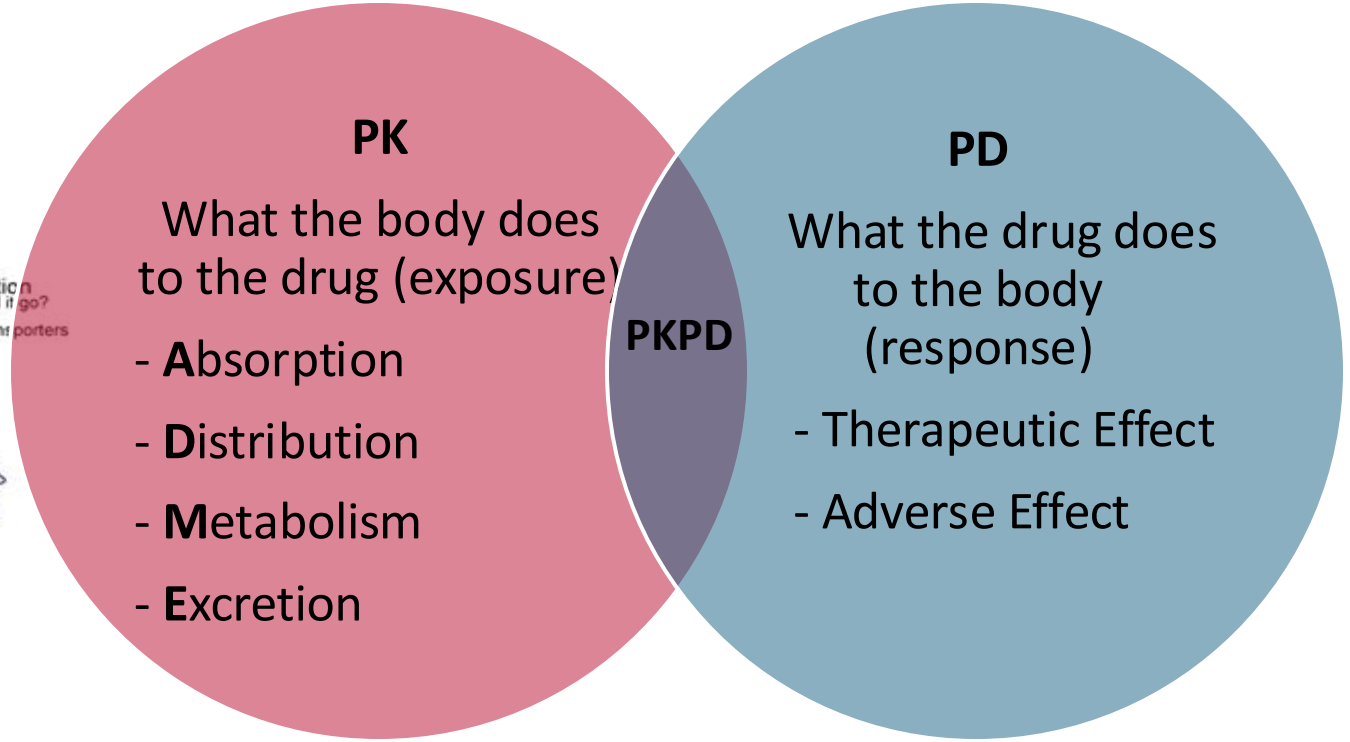
Question: What happens when you take a drug?

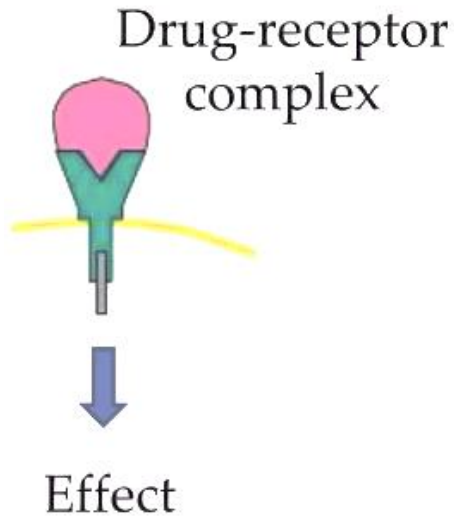
- What does it mean to “take a drug”? How is the drug taken? What are the different routes for drug administration?
- What are the different forms of a drug? Drug formulations?
- After a drug is administered, what happens to it?
  - Absorption, Distribution, Elimination
- How does the drug work? What is the drug’s target? How does the drug “find” its target?
- What happens to the drug target after it is bound by the drug? Does each individual have the same drug target? Same quantify of drug target? Is the target “expressed” in the same location(s) in each individual?
- Does the drug only bind to its intended receptor? Does the drug bind to and affect other targets or receptors? What will happen if this occurs?

Pharmacokinetics and Pharmacodynamics

- Pharmacokinetics (**PK**) is defined as the study of the time course of drug **A**bsorption, **D**istribution, **M**etabolism, and **E**xcretion (ADME).
- Pharmacodynamics (**PD**) refers to the relationship between drug concentration at the site of action and the resulting effect, including the therapeutic and adverse effects.



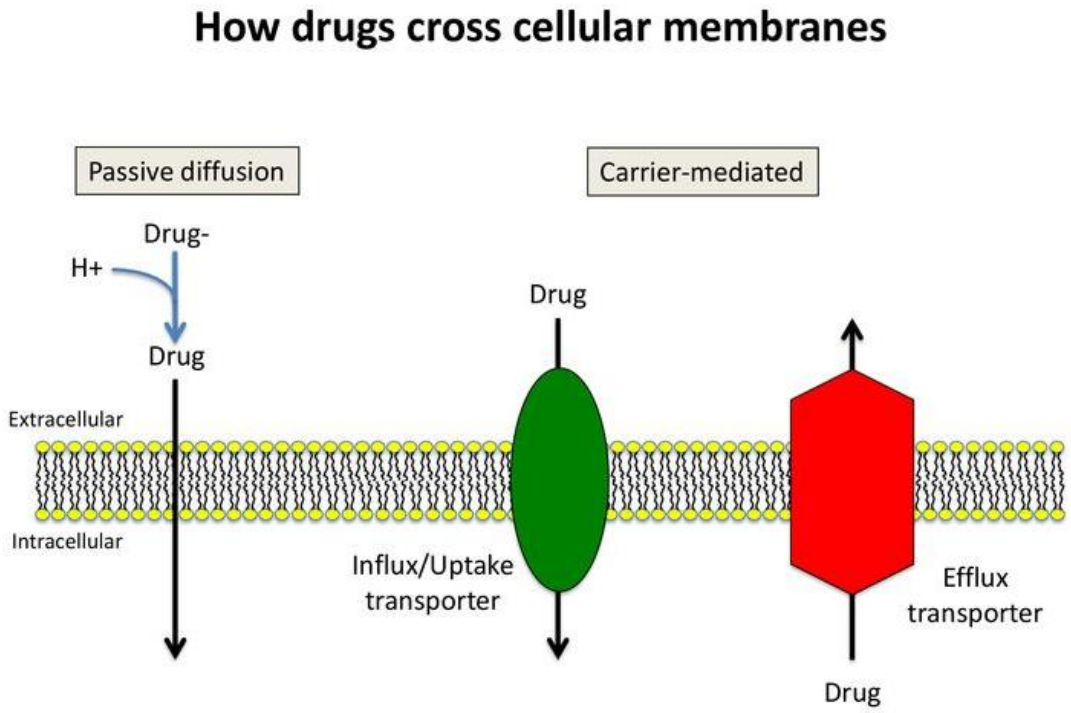




PKPD: Response to the drug as a function of drug concentration over time.

PK: Absorption (the “A” in ADME)

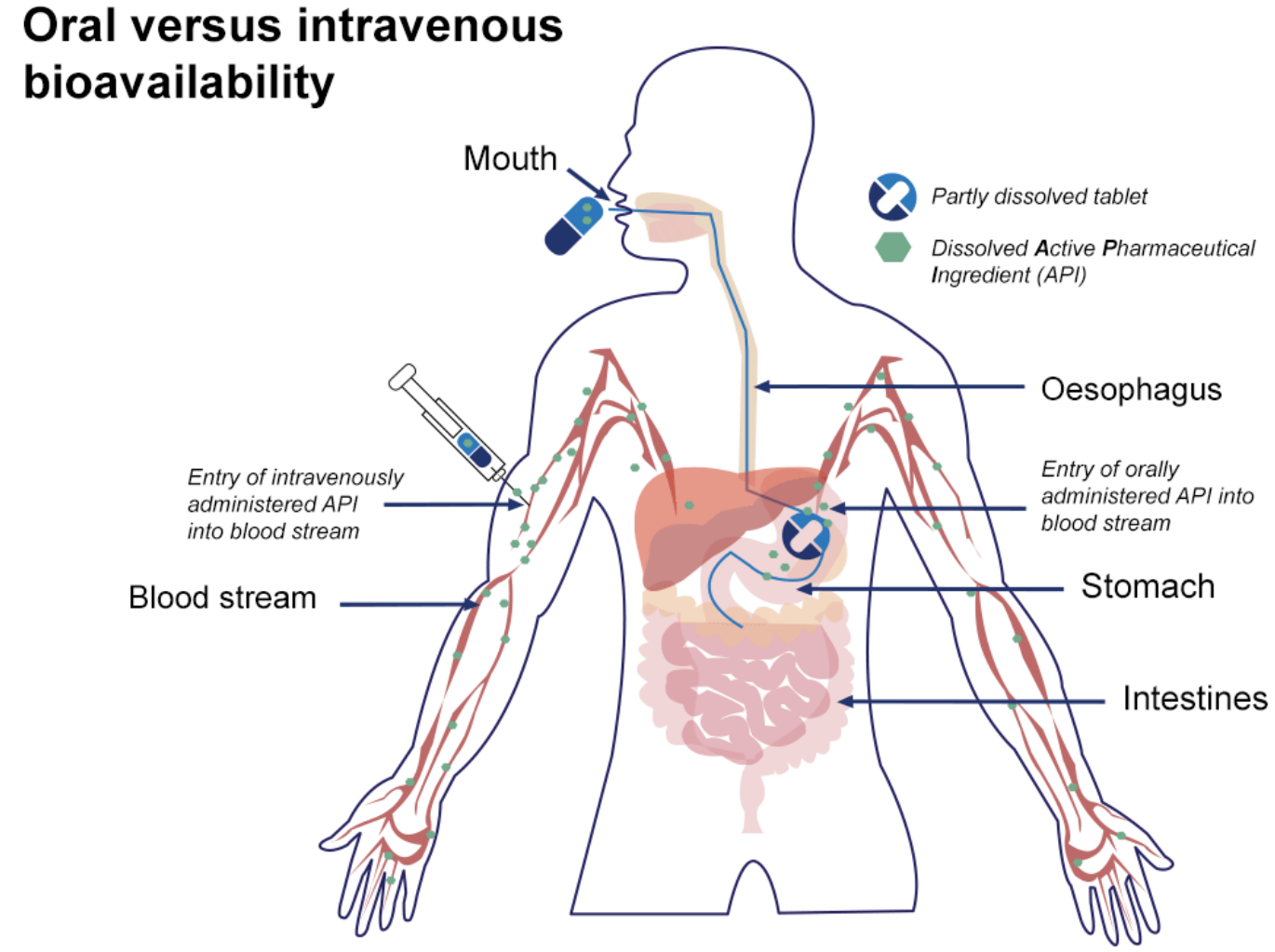
- **Absorption:** The movement of the drug from the site of administration to the blood circulation.
- It takes place from different routes of administration (Oral, intravenous IV, intramuscular IM, etc.)
- We are generally interested in both the rate (i.e. how fast does absorption occur) and extent (i.e. how much of the active drug is absorbed).
- Biological membranes are the first barrier the drug has to move across.
- Movement of drug molecules past this first barrier (and all other biological barriers) is governed by two processes:
  - Diffusion
  - Transport



Kavanagh, R.P., Trout, L.C., Brummel, G.L. (2021). Pharmacology. In: Lucking, S.E., Maffei, F.A., Tamburro, R.F., Zaritsky, A. (eds) Pediatric Critical Care . Springer, Cham.

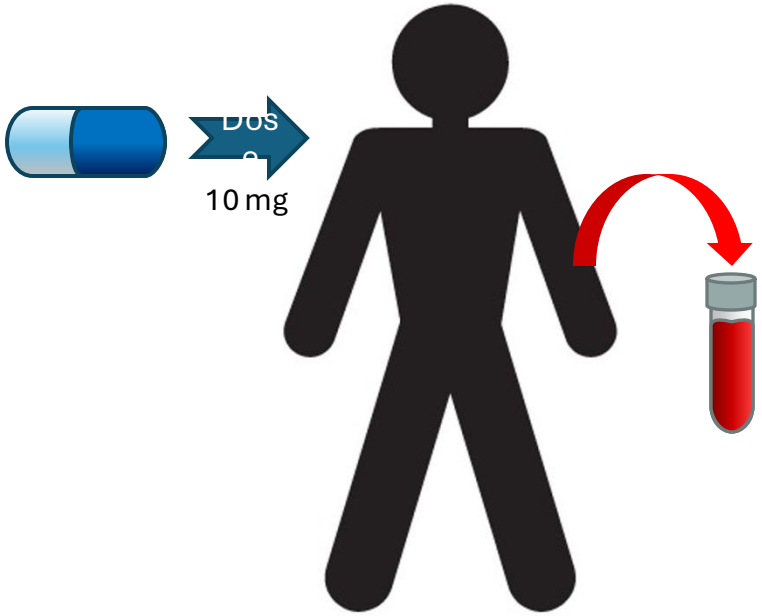
PK: Bioavailability (F)

- **Bioavailability:** the extent of absorption, or the fraction (F) of the drug dose that is absorbed and makes it into systemic circulation (i.e. the blood stream)
- By definition, F = 1.0 (100%) for intravenously (IV) administered drugs
- The main processes impacting how much of an orally administered drug gets into systemic circulation are:
  - Dissolution (for solid dosage forms)
  - Membrane penetration (diffusion and transport)
  - Metabolism – in the gastrointestinal tract (gut wall, microbiota) or liver
  - Biliary excretion
- Bioavailability is an important consideration for all routes of administration.



PK: Distribution (the “D” in ADME)

- Distribution refers to the movement of a drug through a biological system, and key parameter for this process is the volume of distribution (V).
- **Definition of V:** Simply, the volume into which a drug distributes.
- Pharmacokinetic volumes of distribution can be true volumes with physiological meaning, though often they are non-physiological and simply represent a theoretical volume.
- It is useful to know the volume of distribution - how can we measure or estimate V?
  - One method > give an intravenous (IV) “bolus” dose, and immediately measure the blood concentration.
  - $V=Dose/C_0$, where C_0 is the drug concentration in the blood at time zero (immediately after dosing)



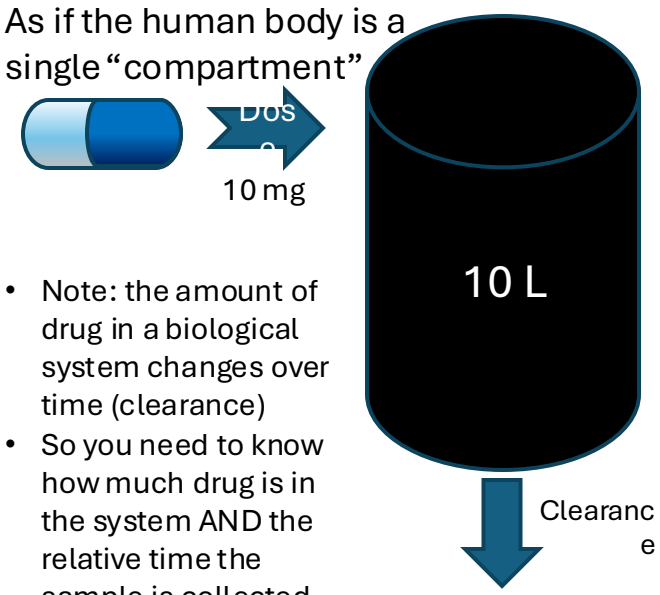
Measure Drug Concentration

= 1 ug/mL (1 mg/L)

Therefore,

V = 10 mg/1 mg/L = 10 L

As if the human body is a single “compartment”



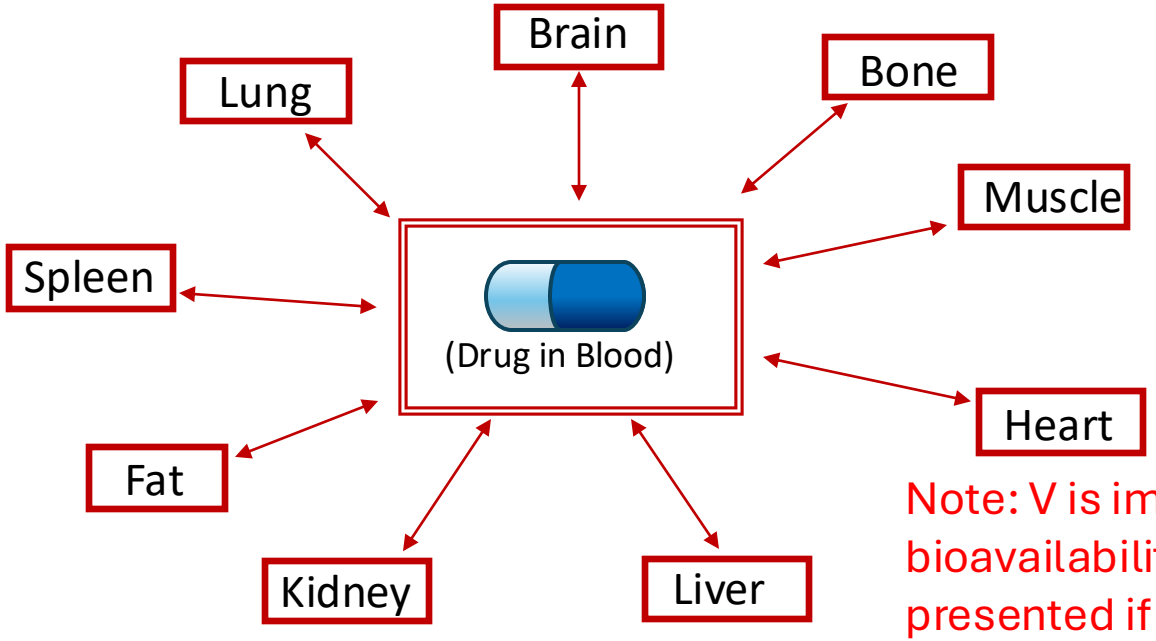
- Note: the amount of drug in a biological system changes over time (clearance)
- So you need to know how much drug is in the system AND the relative time the sample is collected after dosing.

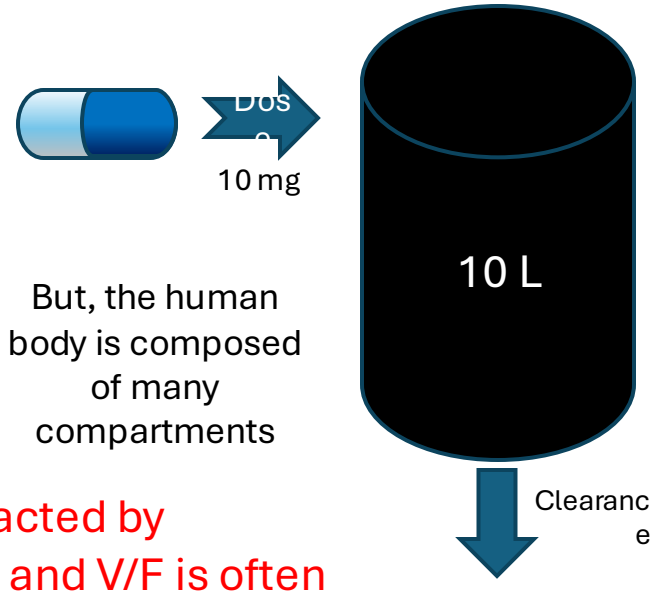
PK: Distribution (cont'd)

- The more a drug distributes into other compartments (organs, tissues), the less drug that will remain in the blood compartment
- The less drug in the blood compartment, the lower will be the concentration measured in a blood sample
- The lower the concentration measured in the blood sample, the larger will be the calculated (apparent) volume of distribution.

V = 10 mg/1 mg/L = 10 L

V = 10 mg/0.1 mg/L = 100 L!



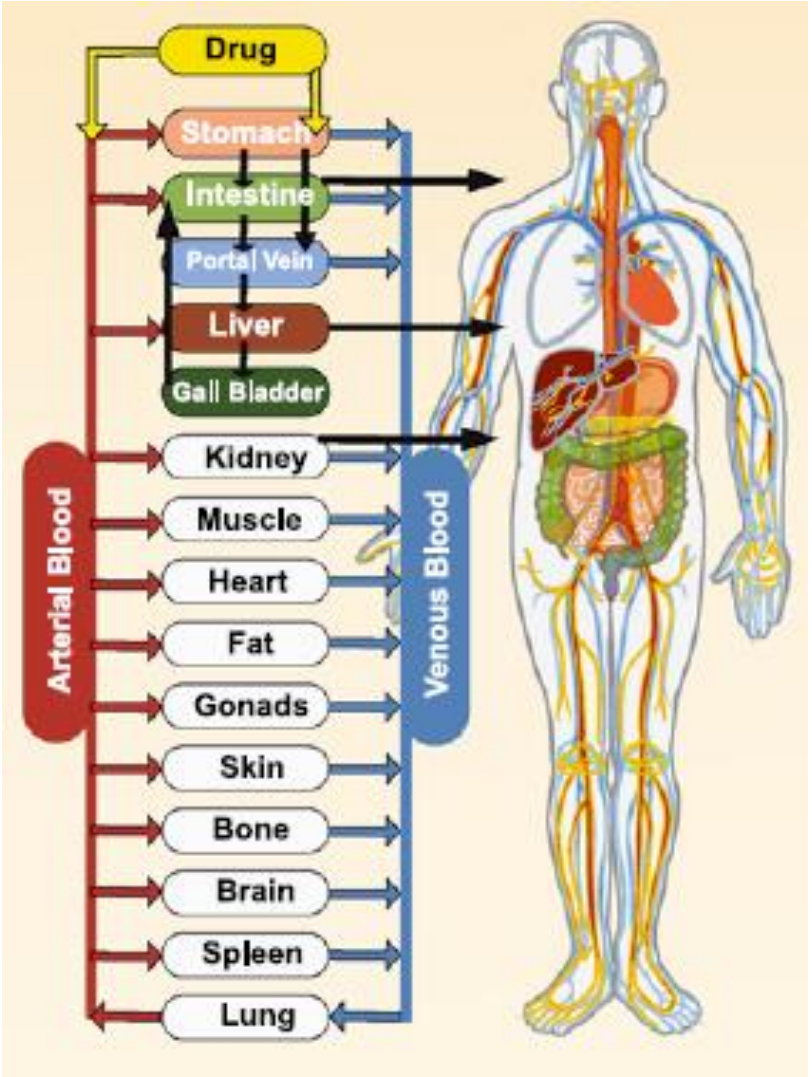


But, the human body is composed of many compartments

Note: V is impacted by bioavailability, and V/F is often presented if F is not known.

Physiologically-Based PK (PBPK)

- PBPK models incorporate many tissue compartments to describe the body.
- PBPK models are therefore extensions of simpler compartmental models.
- These more complex models require solving larger systems of differential equations to estimate parameters.
- The parameters in these models are increasingly relevant physiologically – i.e. they relate to actual physiological volumes (organs, tissues, cells, interstitial fluids, etc.) and clearance processes.

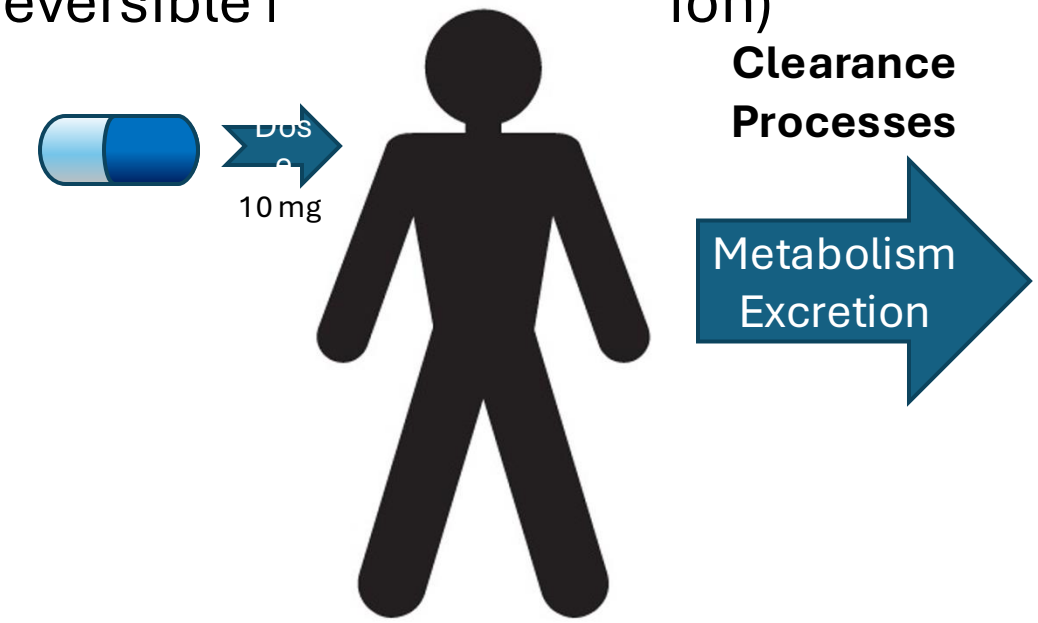


Cordes, et al. Integration of genome-scale metabolic networks into whole body PBPK models shows phenotype-specific cases of drug induced metabolic perturbation. npj Systems Biology and Applications (2018)4:10

PK: Metabolism + Excretion (the “M” and “E” in ADME) = Elimination

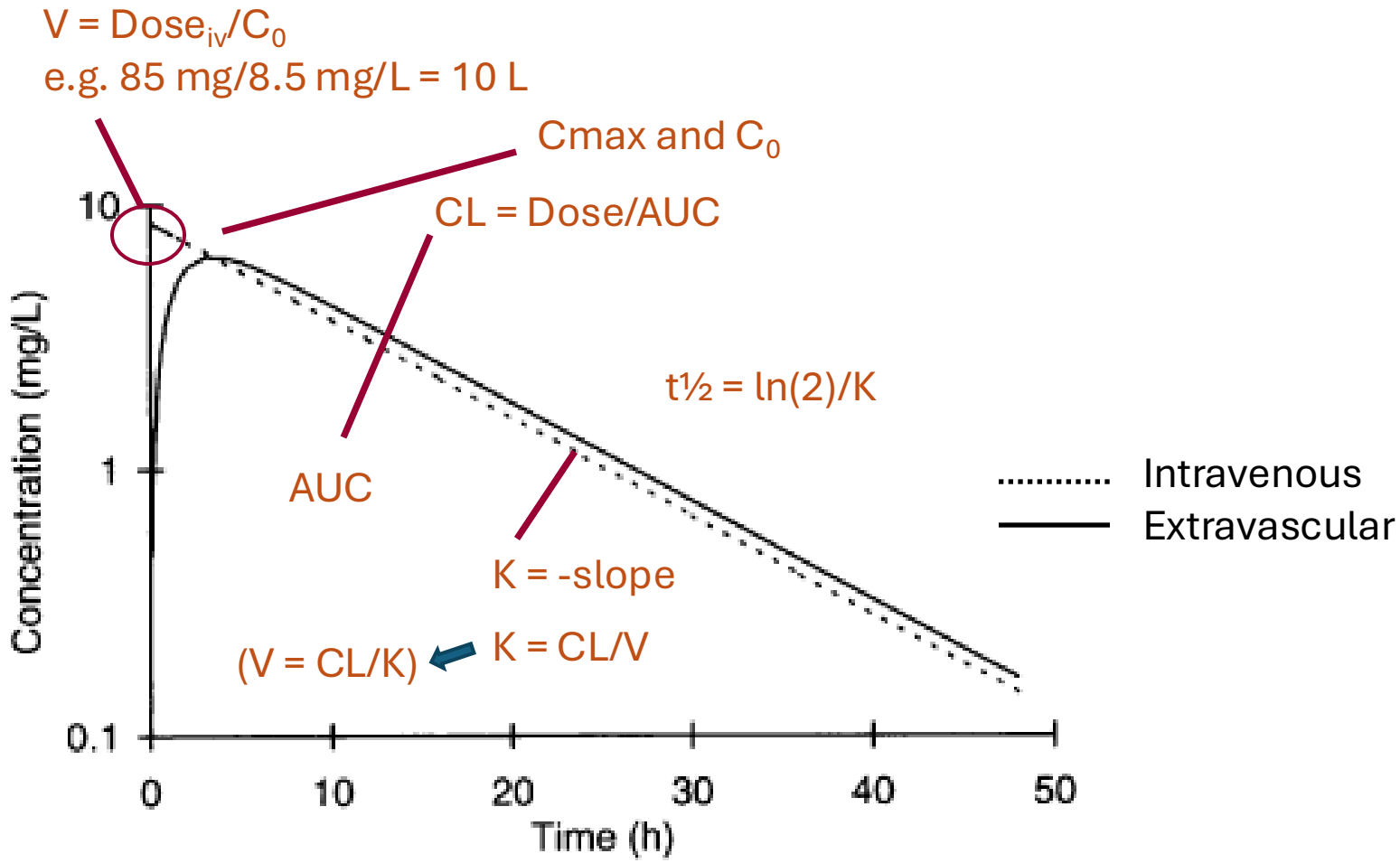
- We can measure elimination in various ways, and a common way is to refer to drug **clearance (CL)**, which is the rate of removal of a drug from a volume of distribution per unit time
  - In other words, CL is the volume from which a drug is completely removed per unit of time.
  - Units = volume/time
- Elimination is any mechanism that removes or clears drug from the body (including metabolism, non-reversible [illegible] ion)

Note: Calculated CL is also impacted by bioavailability, F. CL/F is often presented if F is not known.



PK Parameters – The Very Basics

Note the Semi-Log plot with a log Y-axis



Bauer LA: Applied Clinical Pharmacokinetics, 2nd Edition.
https://accesspharmacy.mhmedical.com/content.aspx?bookid=1374&sectionid=74719450#74719451

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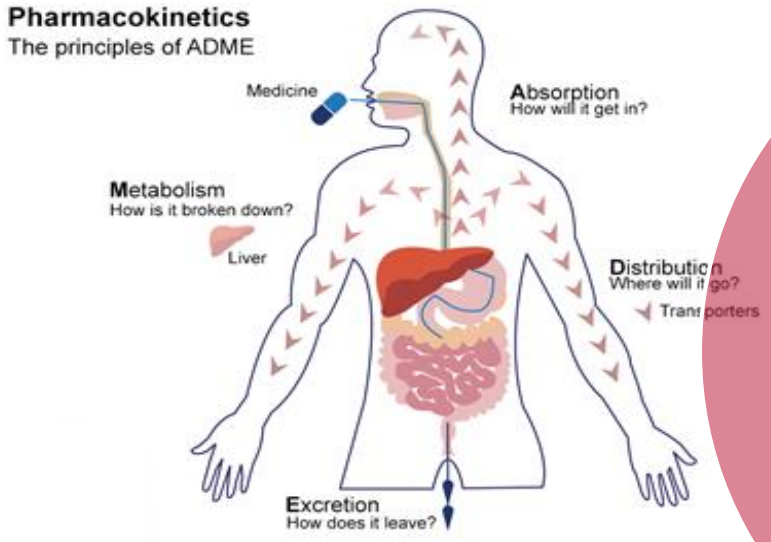


PK

What the body does to the drug (exposure)

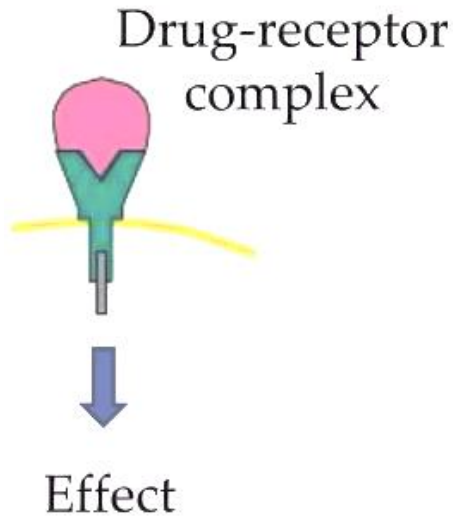
- **A**bsorption
- **D**istribution
- **M**etabolism
- **E**xcretion

PKPD

PD

What the drug does to the body (response)

- Therapeutic Effect
- Adverse Effect



PKPD: Response to the drug as a function of drug concentration over time.

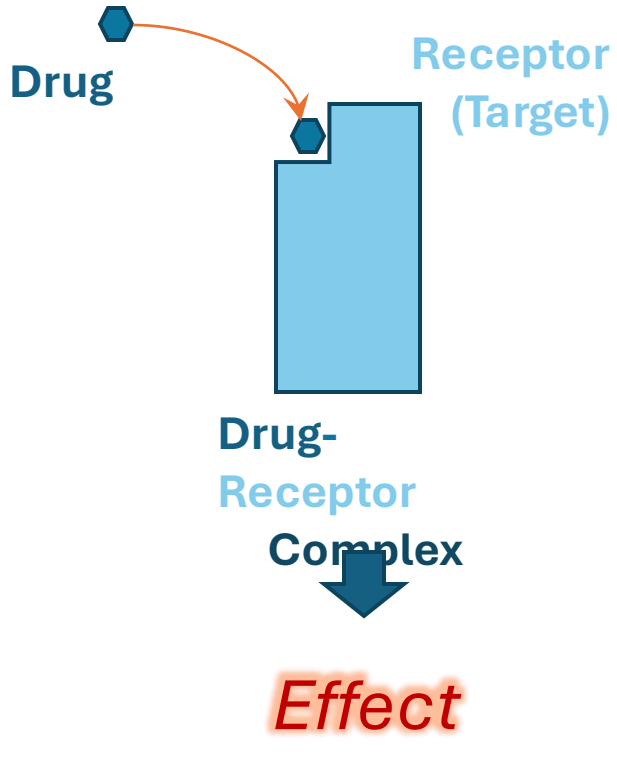
Pharmacodynamics

PD-PK Link

$$[Drug]+[\mathrm{Re}ceptor]\underset{k_{-1}}{\overset{k}{\leftrightarrow}}[Drug-\mathrm{Re}ceptor]\rightarrow Effect$$

- **Pharmacodynamics (PD)** is the discipline that quantifies the relationship between **drug concentration** at the site of drug action and the drug's **pharmacological effect**.
- This involves drug-receptor interactions, post-receptor effects, and chemical interactions.

- Unbound drug concentration [Drug], at the site of its receptor
- Unbound receptor concentration [Receptor]
- Bound drug-receptor complex [Drug-Receptor]



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- This involves drug-receptor interactions, post-receptor effects, and chemical interactions.

- A drug's pharmacological effect can be **monitored and quantified at several levels**, including at a molecular or cellular level *in vitro*, in a tissue or organ *in vitro* or *in vivo*, or in the whole organism.

- Studying pharmacodynamics helps explain the relationship between the **dose and response**.

- Unbound drug concentration [Drug], at the site of its receptor
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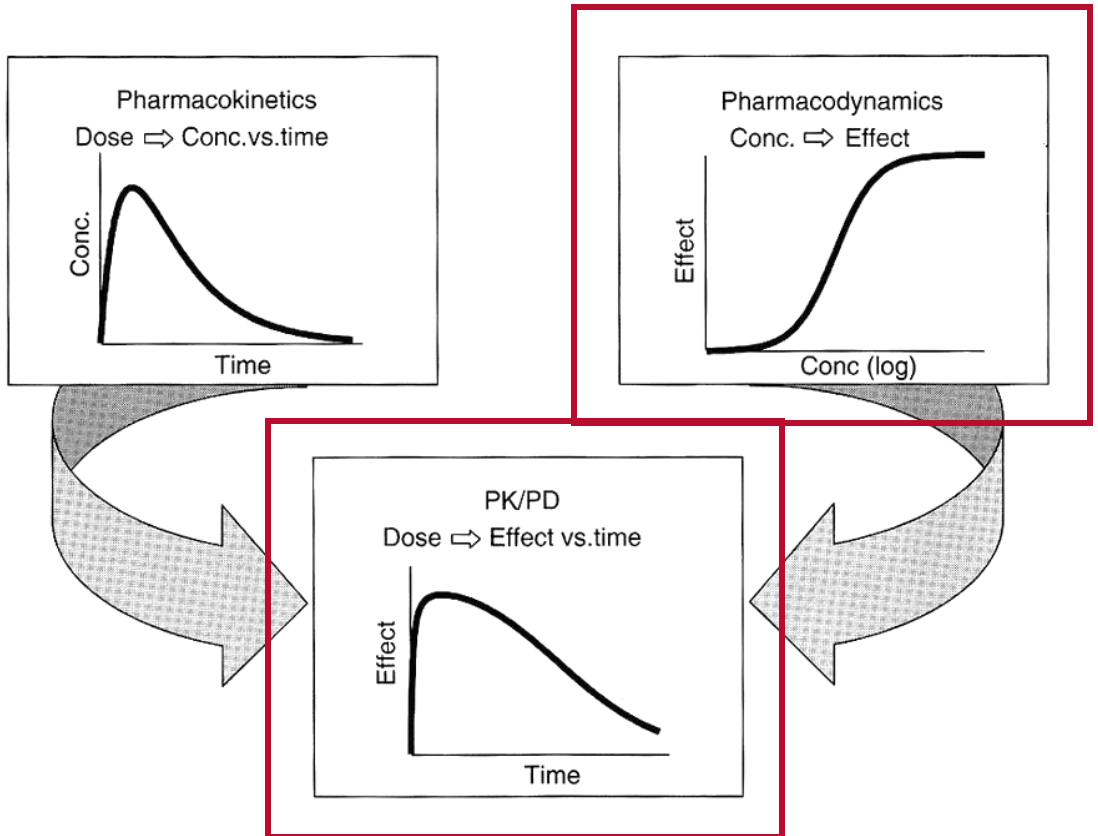
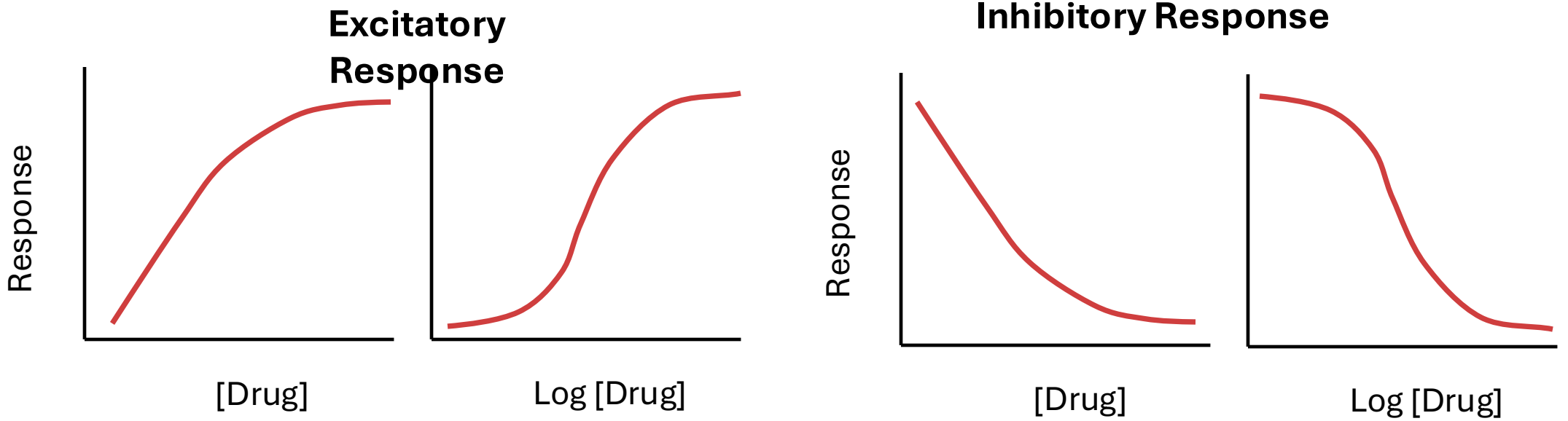


PD: Exposure-Response (E-R) Relationships

$$[Drug] + [Receptor] \rightleftarrows [Drug \cdot Receptor] \rightarrow \boldsymbol{Effect\ or\ Response}$$

The higher the drug concentration [*Drug*] or exposure (AUC), the greater the *Effect* or *Response; Basis of dose selection*



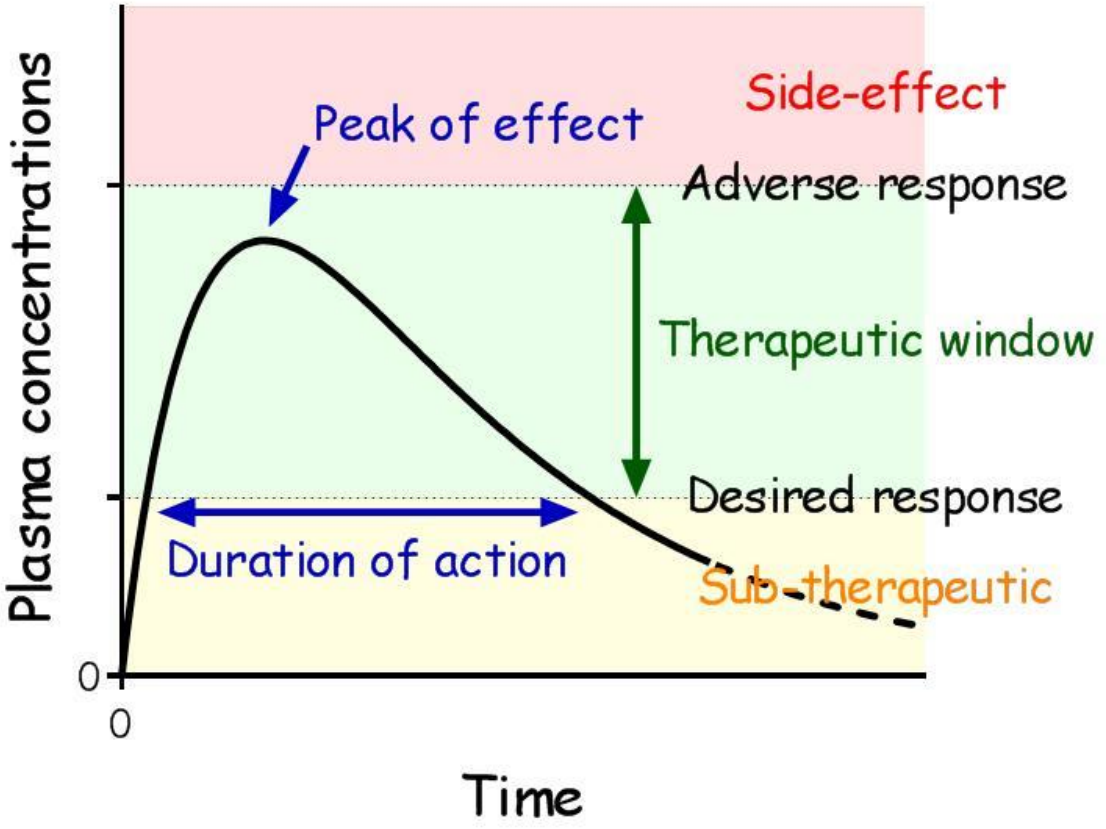
Questions?

The Challenge

We're working with a new cancer drug: KRT-232 aka Navtemadlin

We need to know:

- How much KRT-232 to give patients to achieve the maximum tolerated dose (MTD)
- Which patients will respond to KRT-232
- Which patients when given KRT-232 will have a response of its biomarker, MIC-1, within its therapeutic window

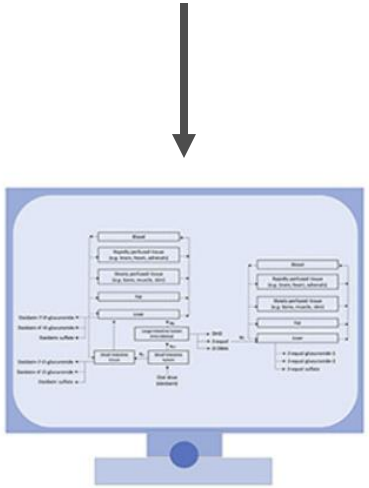


If we have data from 100 patients given KRT-232 and their PK Curves and their PD Curves, **can we predict the PK/PD curves of patient #101 in response to KRT-232?**

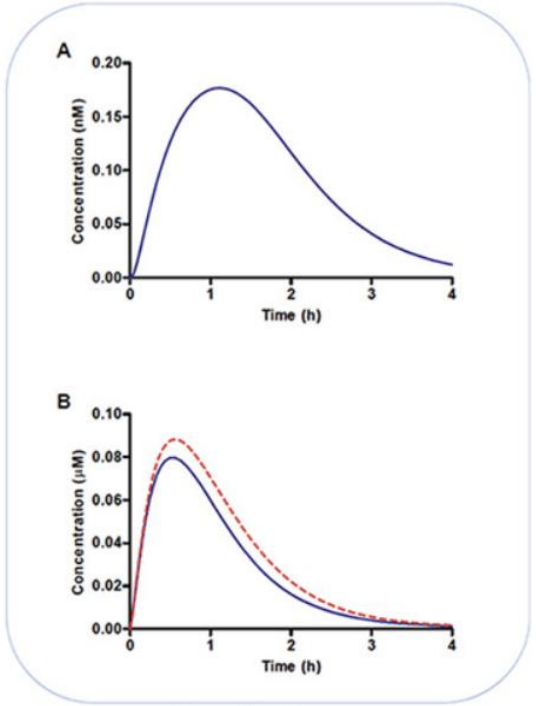
PK/PD Model

Constructed based on observations to capture key biologic processes

Age, Gender, Race, Body weight, Disease related factors (Kidney/liver function, protein levels), Drug properties



PBPK model



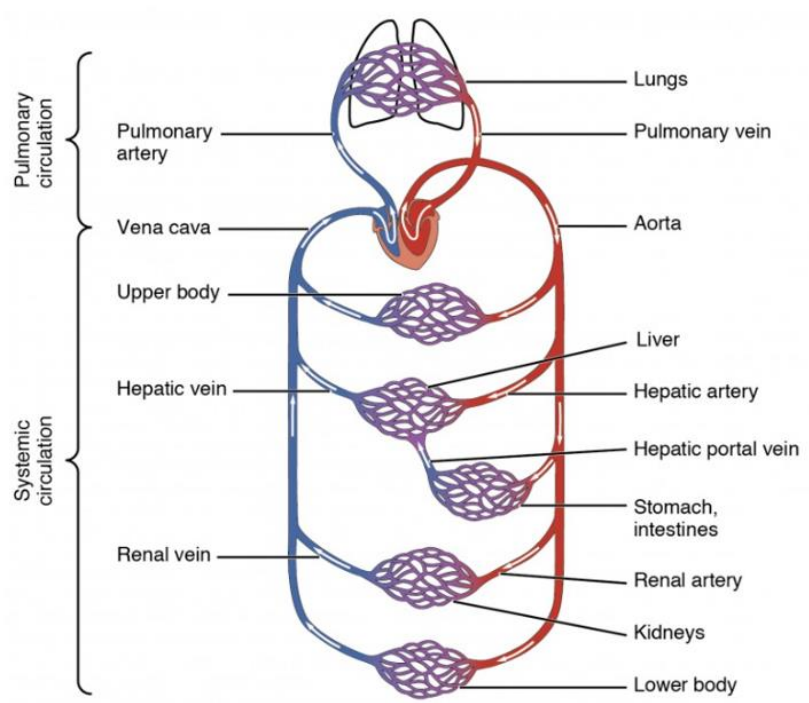
Input **Prediction**

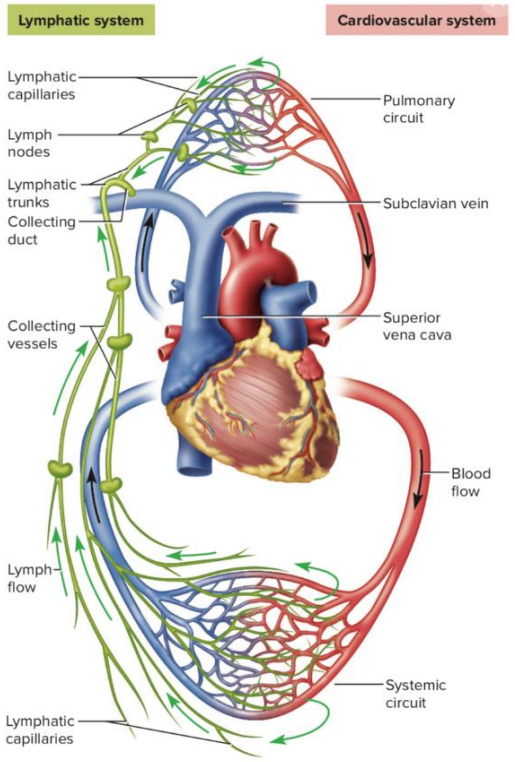
A tool to quantitatively understand a biologic or disease process and their impact on the drug PK and efficacy.

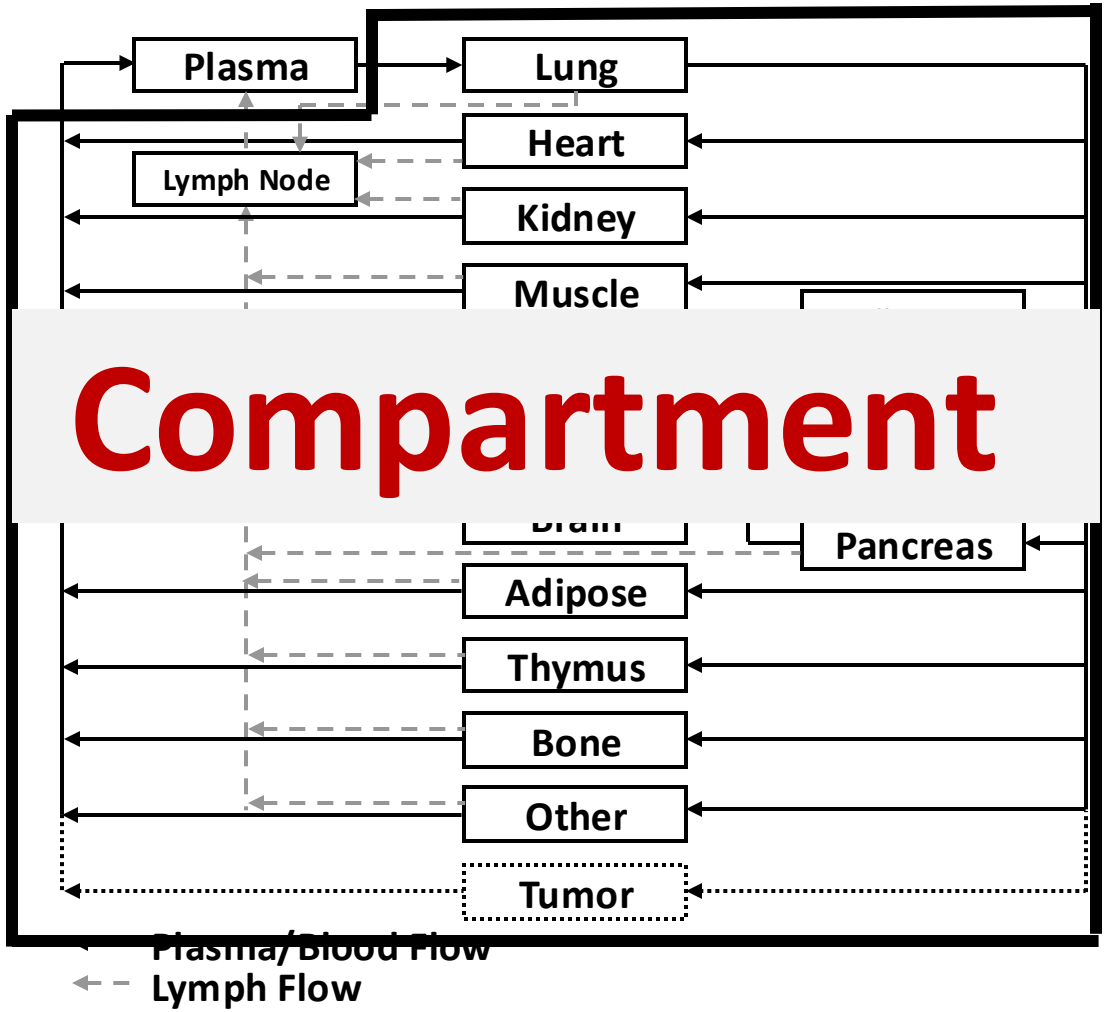
PK/PD Model

Goal: Predict PK/PD parameters for an untreated individual(s) based upon known factors

Anatomy of the Circulatory and Lymphatic Systems







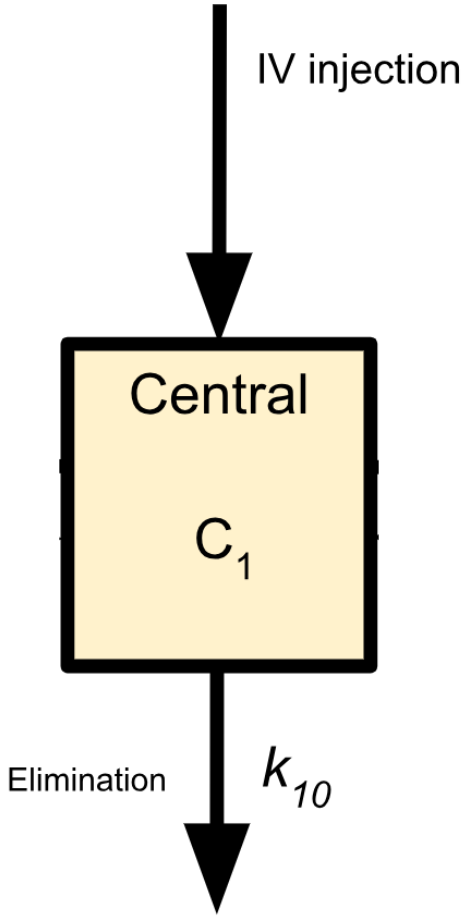
1 & 2 Compartment PK/PD Model

1 Compartment IV model

Central: Blood

k: rate constants

C: concentration of drug



1 & 2 Compartment PK/PD Model

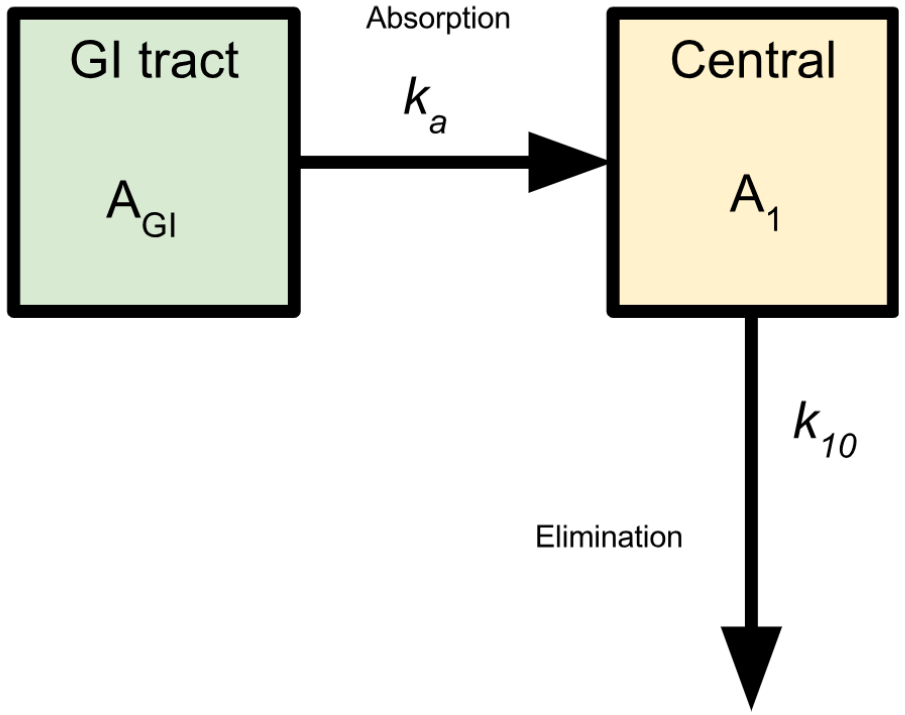
1 Compartment Oral model

Central: Blood

k: rate constants

C: concentration of drug

A: amount of drug



1 & 2 Compartment PK/PD Model

2 Compartment IV model

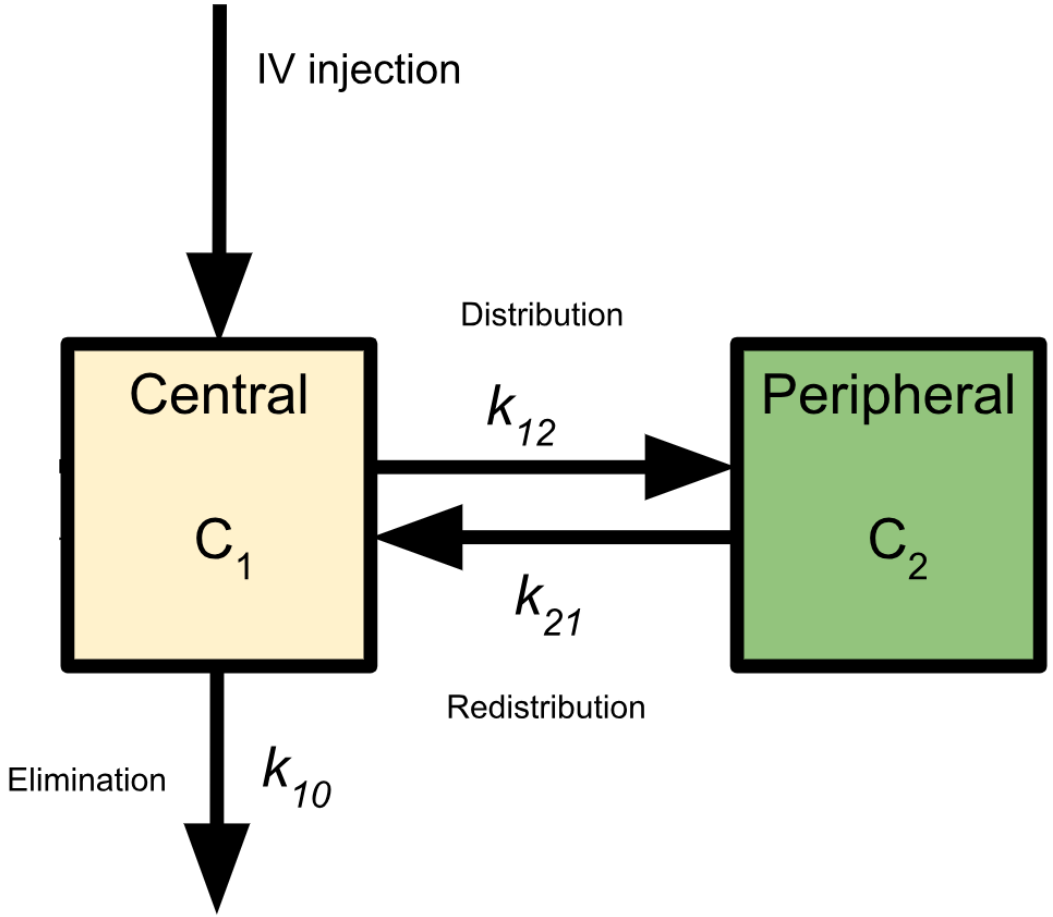
Central: Blood

Peripheral: Tissue

k: rate constants

C: concentration of drug

A: amount of drug



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2 Compartment Oral model

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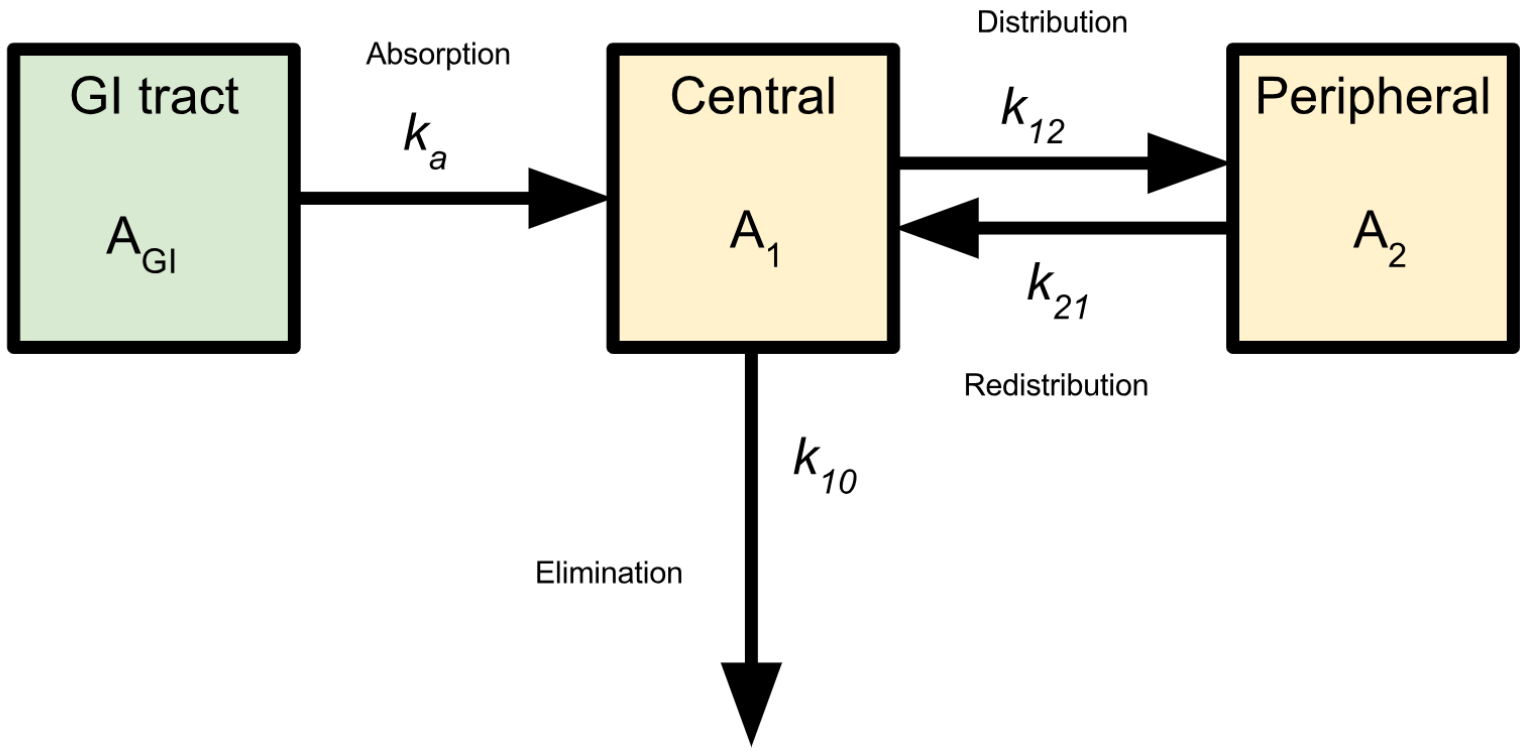
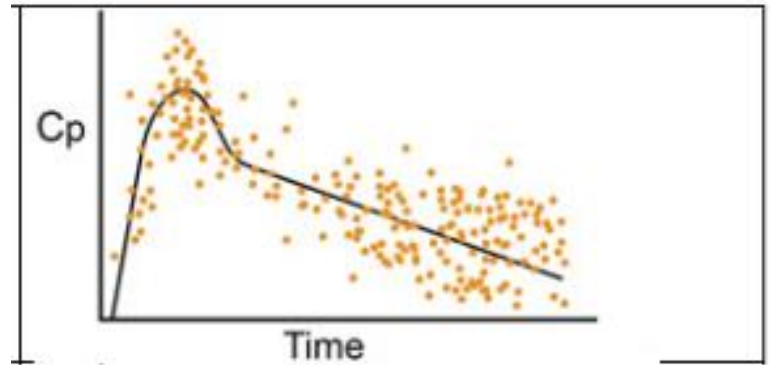


Covariates:
Inter- & Intra Individual Differences



Can we assume that every patient given the same dose will respond the same?

Nope! Every observation and every person is different! We need data to back this assumption.

Covariates – any 2+ variables that vary in a correlated way

For example:

Clearance and weight

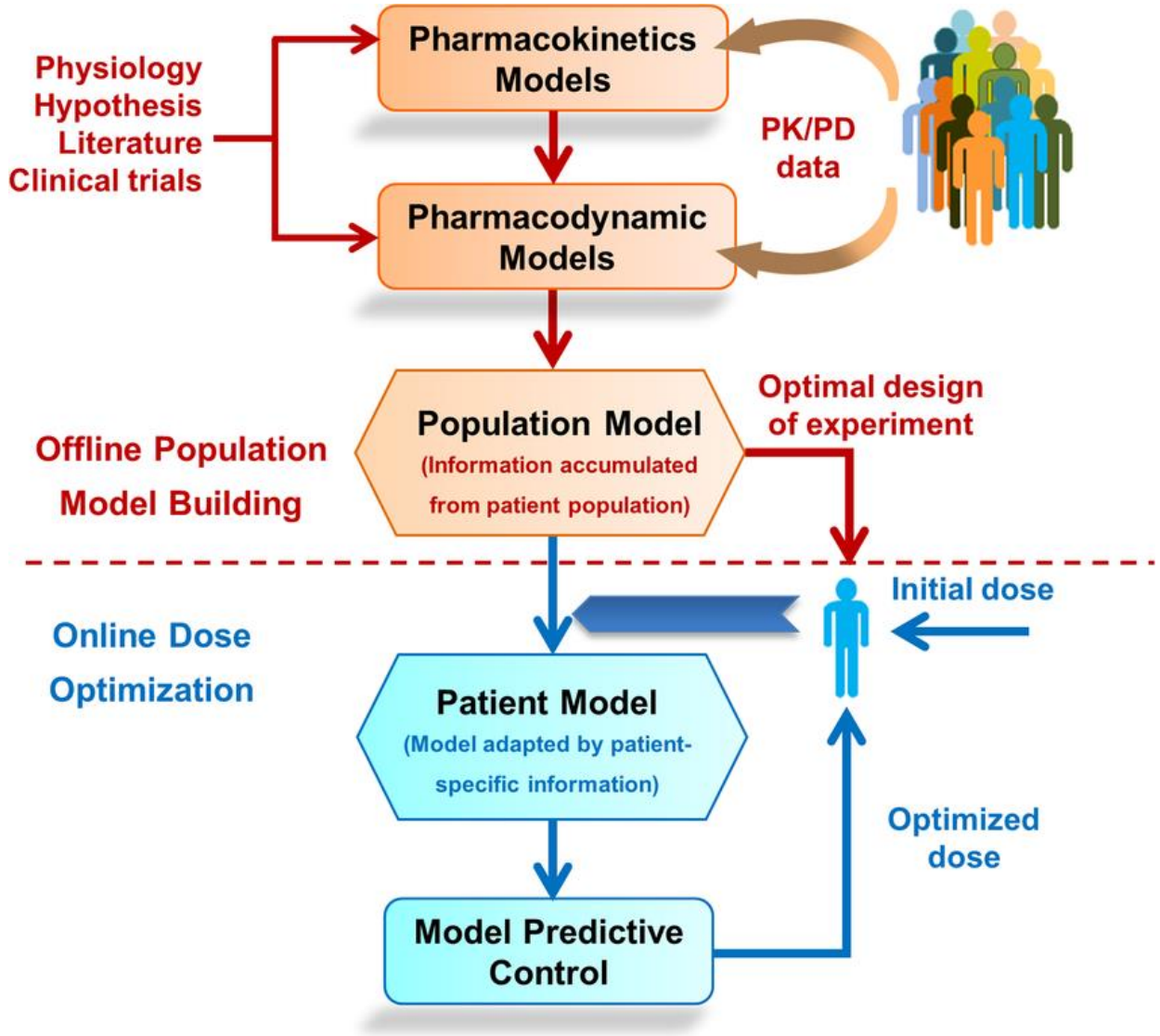
Individualized Medicine

Literature informs models

Models inform trials

Trials inform models

Models inform patient optimized dose



Questions?