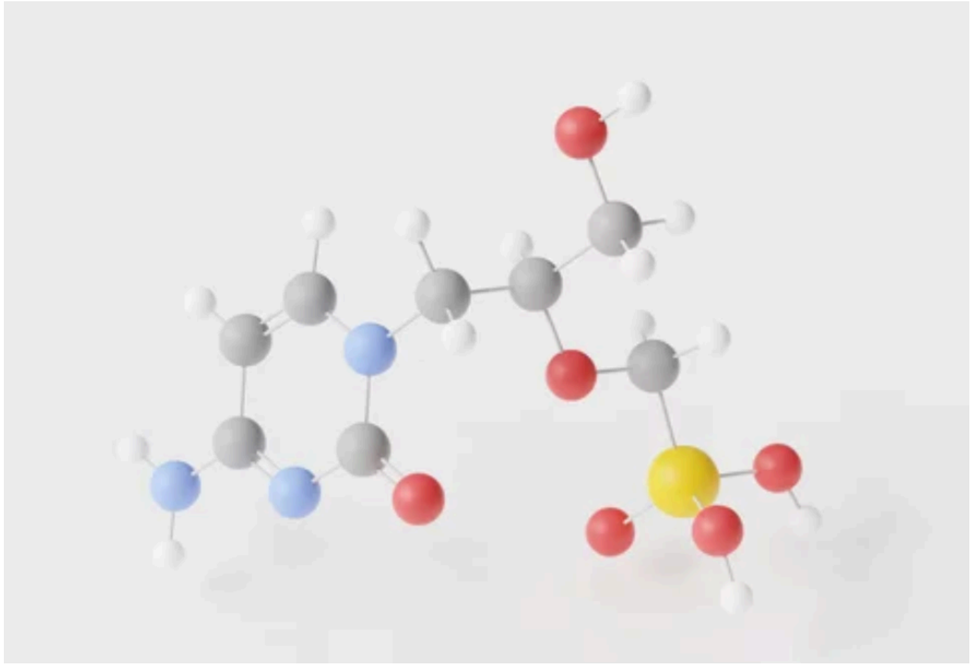
Lecture 6

Application of conservation of mass: Pharmacokinetics

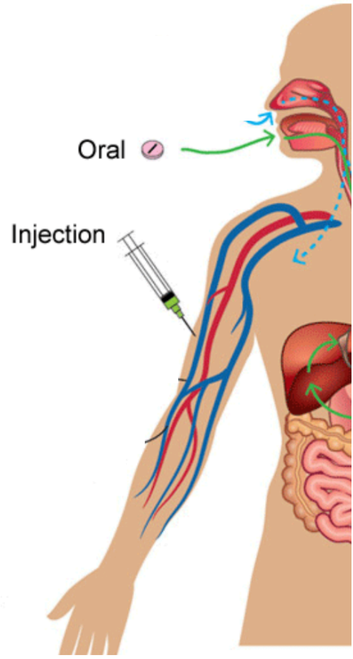
Background:

The Journey of Drugs in Our Body:

Drugs are “traditionally” chemicals designed to interact with biological systems to treat diseases, relieve symptoms, or support physiological functions.



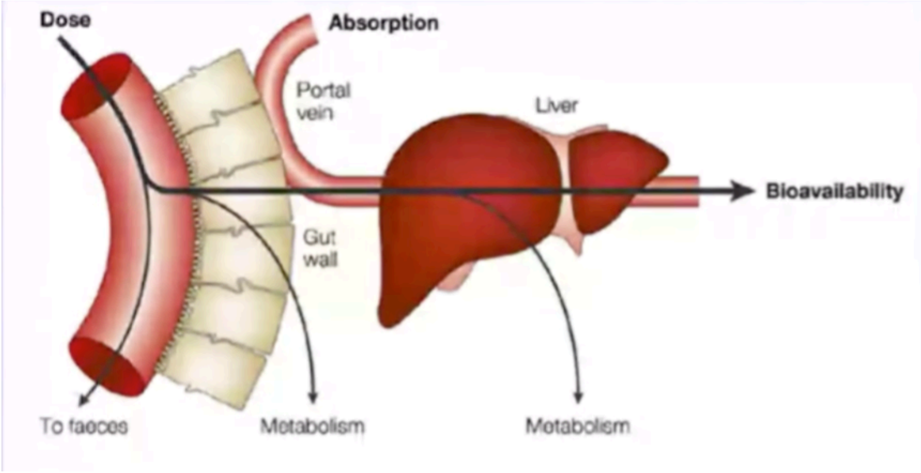
A) Administration and absorption: Two main routes of delivering drugs to the body are oral and injection, though other routes exist as well.



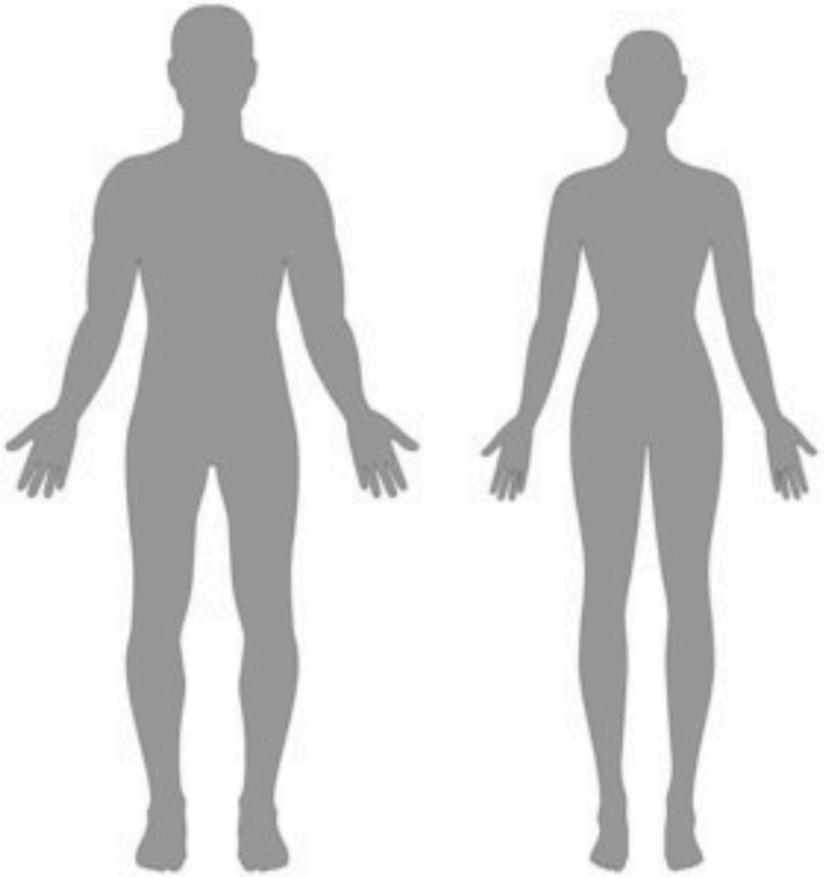
Oral administration: In this route, the drug is taken by mouth and absorbed through the gastrointestinal tract. From there, it enters the **bloodstream** and is distributed to the target tissues.

Injections: In this route, the drug is administered directly into the **bloodstream**, muscle, or beneath the skin.

Note that only a fraction of orally delivered drug reach the bloodstream . This fraction is defined by a term called bioavailability. Bioavailability is the percentage of the administered drug dose that successfully reaches systemic circulation in an active form.



B) Drug distribution: Drugs distribute from the blood into other parts of body, including the target site(s)



Three factors are important in drug distribution into the target site:

1-Concentration gradient between blood and target organ/compartment.

2- Solubility of the drug in target (water/fat solubility).

3-Blood flow to target.

Not all target tissues and organs are the same, when it comes to receiving the drug, but we can group them as below:

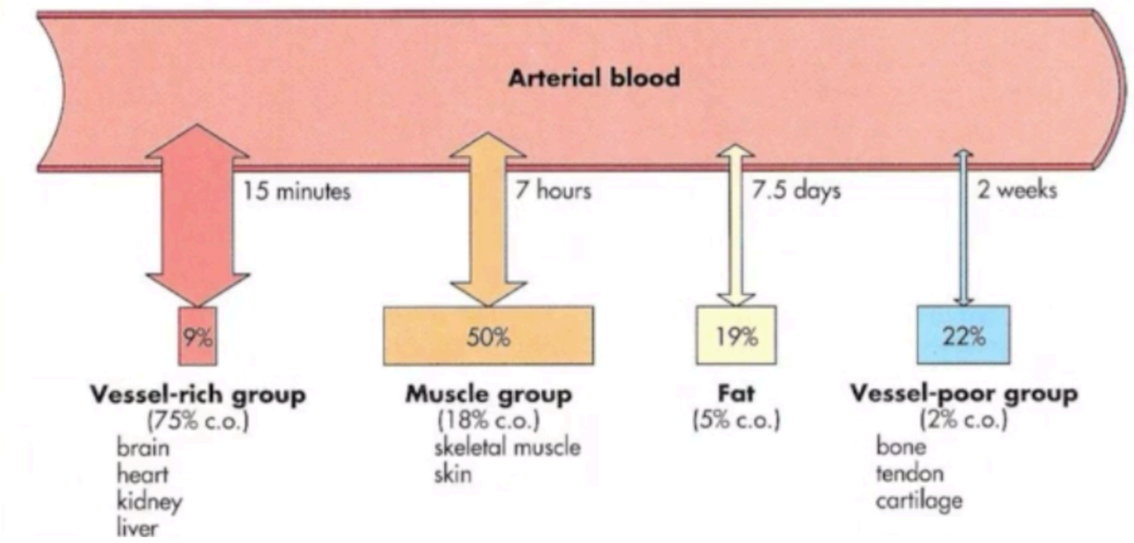
Not all target tissues and organs are the same, when it comes to receiving the drug, but we can group them as below:

Drugs distribute from the blood into three main compartments:

Viscera : highly perfused organs, including the brain – distribution is rapid.

Muscle : well-perfused, large mass, leading to quick distribution despite low lipid content.

Fat : drugs with high-lipid solubility will accumulate in fat though distribution into this compartment is slow because of poor blood supply.



Human Pharmacology - Molecular to Clinical" 3rd Ed. (1998) -E.G.
Time for general anesthetics to equilibrate with the brain is very short compared to other tissues.

C) Elimination

After the drug has been distributed the body begins the process of elimination by Metabolism and Excretion.

Understanding how drugs are absorbed, distributed, metabolized, and excreted is crucial for developing precise and effective treatments. By predicting drug behavior, we can optimize dosing, improve delivery methods, and reduce side effects, leading to better therapeutic outcomes.

In the next part of this lecture, we'll explore how mass balance and solving ordinary differential equations help develop mathematical models to explain changes in drug concentrations. This field, known as **Pharmacokinetics (PK)**, studies how drugs are processed by the body and how their concentrations change over time. We will be using simple models to illustrate key concepts of pharmacokinetics modelling.

Cell

Leading Edge

Commentary

Partnering with Big Pharma—What Academics Need to Know

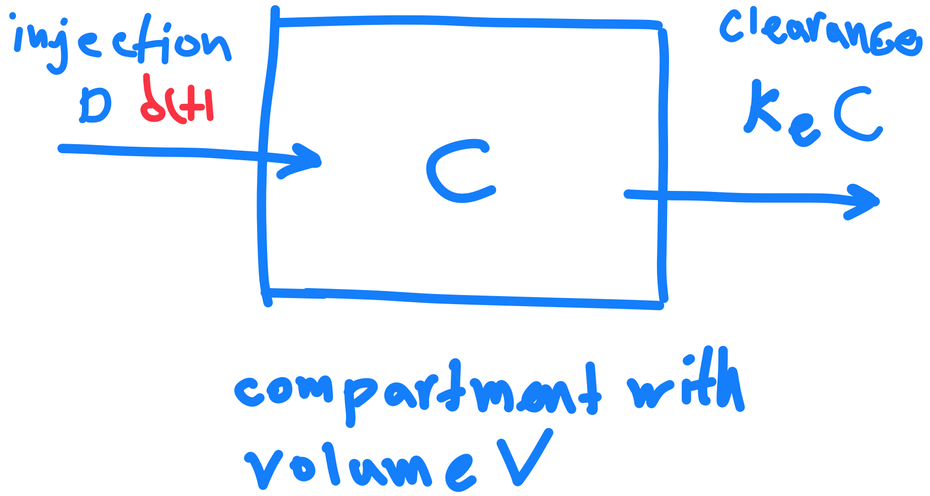
Stuart A. Lipton[1,2,3,*] and Christer Nordstedt[4]
[1]Scintillon Institute, San Diego, CA 92121, USA
[2]The Scripps Research Institute, La Jolla, CA 92037, USA
[3]School of Medicine, University of California, San Diego, La Jolla, CA 92093, USA
[4]Eli Lilly and Company, Indianapolis, IN 46285, USA
*Correspondence: slipton@ucsd.edu
http://dx.doi.org/10.1016/j.cell.2016.04.021

Knowledge of the parameters of drug development can greatly aid academic scientists hoping to partner with pharmaceutical companies. Here, we discuss the three major pillars of drug development—pharmacodynamics, pharmacokinetics, and toxicity studies—which, in addition to pre-clinical efficacy, are critical for partnering with Big Pharma to produce novel therapeutics.

Simple Compartment models in pharmacokinetics analysis

In pharmacokinetic (PK) models, a "compartment" is a theoretical space in the body where a drug or substance is assumed to distribute uniformly. These compartments are used to simplify the complex processes of drug absorption, distribution, metabolism, and excretion.

1) One compartment model: Assuming drug is uniformly and quickly distributes in the body



mass balance: $\frac{dm}{dt} = r_i - r_o + r_g - r_c$ → for concentration

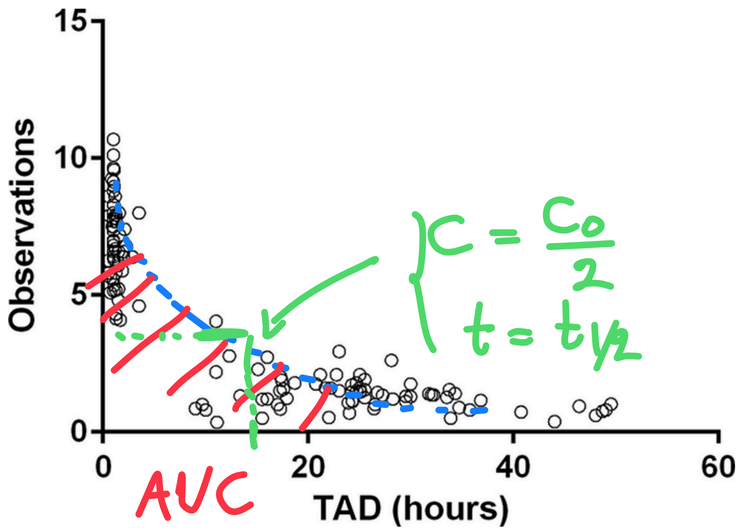
$$\frac{dC}{dt} = -k_e C \quad , \begin{cases} t = 0 \\ C(t=0) = \frac{D}{V} \end{cases}$$

Solve

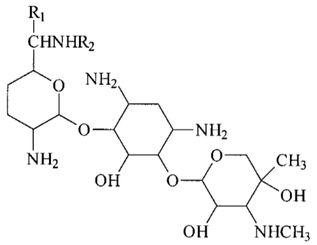
$$\Rightarrow \begin{cases} C(t) = C_0 \, e^{-k_e t} \\ C_0 = \frac{D}{V} \end{cases}$$

Example: Gentamicin

(mg/liter)



Bijleveld, Yuma A., et al. "Population pharmacokinetics and dosing considerations for gentamicin in newborns with suspected or proven sepsis caused by gram-negative bacteria." *Antimicrobial Agents and Chemotherapy* 61.1 (2017): 10-1128.



$R_1 = R_2 = CH_3$ Gentamicin C_1

$R_1 = CH_3$ $R_2 = H$ Gentamicin C_2

$R_1 = R_2 = H$ Gentamicin C_{1a}

Fig. 1. Chemical structures of gentamicins C_1, C_{1a}, and C_2.

$t_{1/2}$: when C reaches half of initial value

$$C(t_{1/2}) = \frac{1}{2} e^{-k_e t_{1/2}}$$

$$\Rightarrow t_{1/2} \downarrow = \frac{\ln(2)}{k_e} \approx \frac{0.7}{k_e} \uparrow$$

AUC: meswes total drug exposure

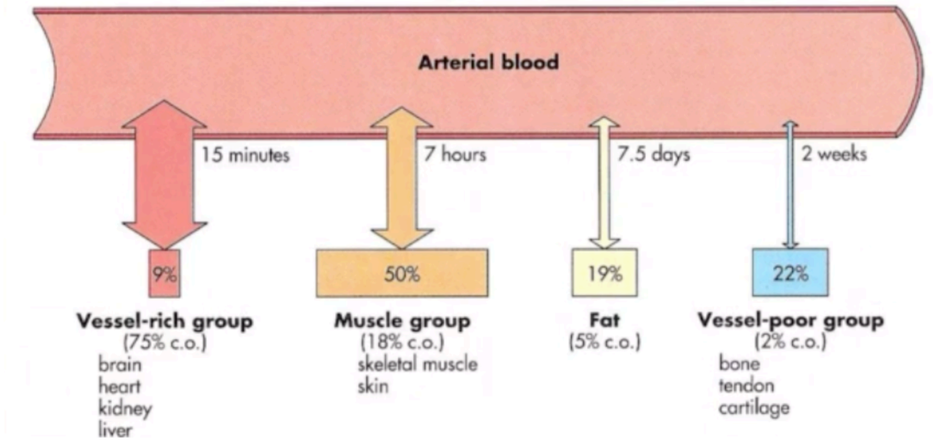
$$AUC = \int_0^\infty C \, dt = \frac{C_0}{k_e} = 1.4 \, C_0 t_{1/2}$$

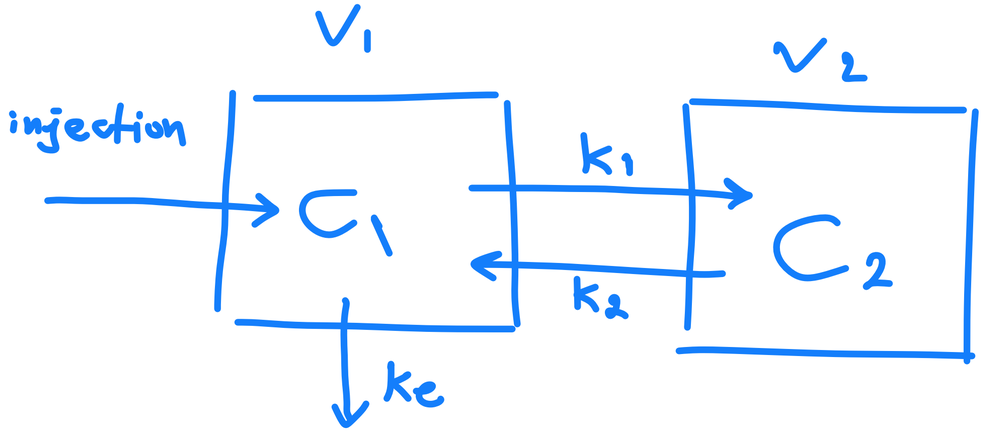
Note that few drugs can be modelled as one compartment in the body. Distribution in tissues is different from plasma. Aminoglycosides distributes 'mainly' into the extracellular fluid compartment

2) Two compartments model:

A one-compartment model is insufficient for analyzing most drugs, as drug transport in plasma differs significantly from other tissues. Therefore, at least a two-compartment model is often required to describe drug distribution in the body.

In this model, the first compartment, called the central compartment (volume V1), represents the plasma's distribution volume. The drug's plasma concentration (C1). The second compartment is the peripheral compartment (V2, C2)





The mass balance eq: note that mass = C × V

$$\begin{cases} V_1 \dfrac{dC_1}{dt} = -k_1 V_1 C_1 - k_e V_1 C_1 + k_2 V_2 C_2 \quad (1) \\ V_2 \dfrac{dC_2}{dt} = +k_1 V_1 C_1 - k_2 V_2 C_2 \quad (2) \end{cases}$$

and $\begin{cases} C_1(t=0) = \dfrac{D}{V_1} \equiv C_0 \\ C_2(t=0) = 0 \end{cases}$

⟶ define $\xi = V_2/V_1$ →

(1) $\dot{C}_1 = -k_1 C_1 - k_e C_1 + \xi k_2 C_2$

(2) $\xi \dot{C}_2 = k_1 C_1 - \xi k_2 C_2$

① $\frac{d}{dt}$ $\longrightarrow$ $\frac{dC_1^2}{dt^2} = -k_1 \frac{dC_1}{dt} + \xi k_2 \frac{dC_2}{dt} - k_e \frac{dC_1}{dt}$ ①.②

$\frac{dC_1^2}{dt^2} = -k_1 \frac{dC_1}{dt} + k_2 (k_1 C_1 - \xi k_2 C_2) - k_e \frac{dC_1}{dt}$ ①

$\frac{dC_1^2}{dt^2} = -k_1 \frac{dC_1}{dt} - k_e \frac{dC_1}{dt} + k_2 \left(\frac{dC_1}{dt} + k_e C_1\right) \Rightarrow$

$$\frac{d^2 C_1}{dt^2} + (k_1 + k_2 + k_e) \frac{dC_1}{dt} + k_2 k_e C_1 = 0 \;,\; C_1(t=0) = C_0$$

second order ODE ...

$$\frac{d^2 y}{dx^2} + a_1 \frac{dy}{dx} + a_2 y = 0 \qquad r_{1,2} = \frac{-a_1 \pm \sqrt{a_1^2 - 4a_2}}{2}$$

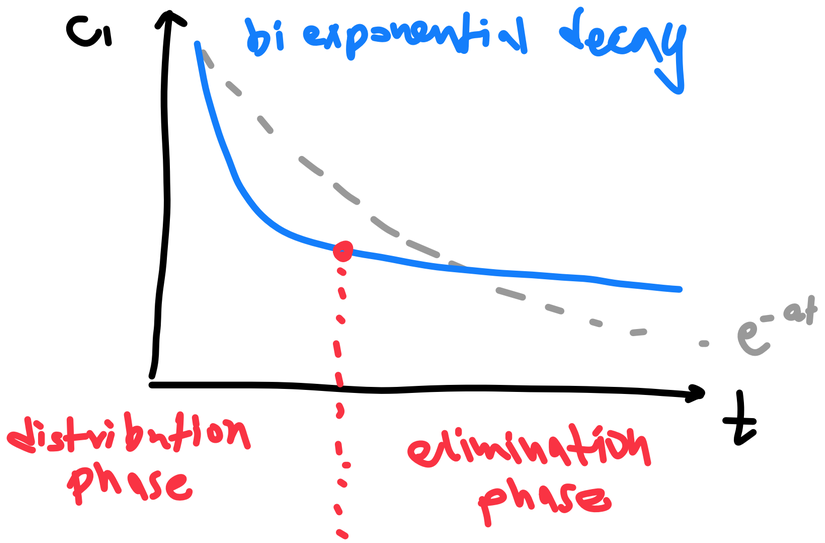
$$\Rightarrow \quad C_1 = C_0\left(\alpha e^{-\lambda_1 t} + (1-\alpha) e^{-\lambda_2 t}\right)$$

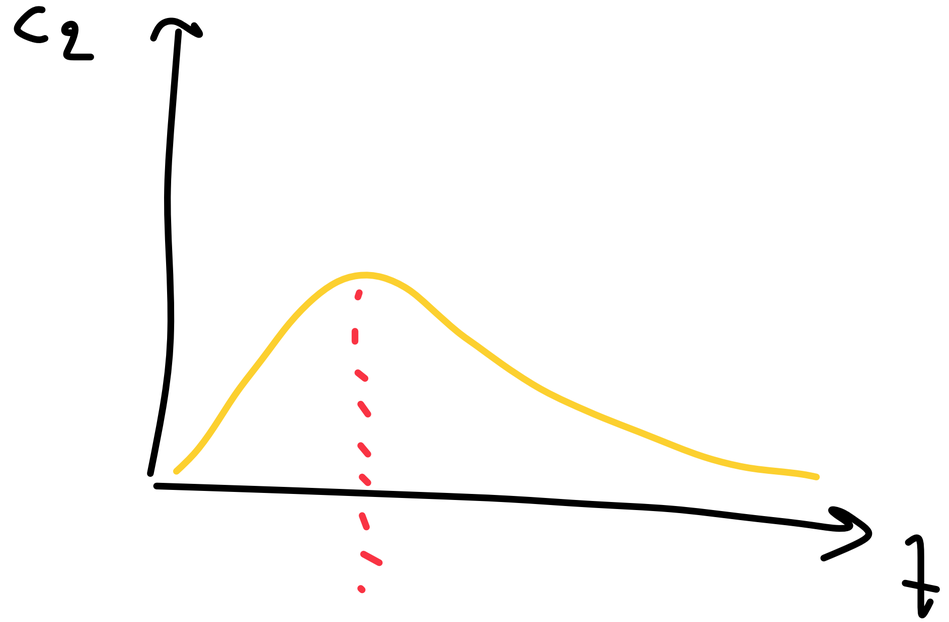
$$\lambda_{1,2} = \frac{(k_1+k_2+k_e) \pm \sqrt{(k_1+k_2+k_e)^2 - 4k_2k_e}}{2}, \quad \alpha = \frac{-\lambda_2 + k_1 + k_e}{\lambda_1 - \lambda_2}$$

and for C_2, we replace the somtion in ①:

$$C_2 = C_0 \frac{\alpha(1-\alpha)(\lambda_2-\lambda_1)}{\S((1-\alpha)\lambda_1 + \alpha\lambda_2)}\left(e^{-\lambda_1 t} - e^{-\lambda_2 t}\right)$$

C1 a follows a bi-exponential decay regime. It means the drug concentration will deplete with a different dynamics than Exp(-at). Many drugs show this behaviour.





Example: Fentanyl

Anesthesiology
55:369–375, 1981

Tissue Redistribution of Fentanyl and Termination of Its Effects in Rats

Carl C. Hug, Jr., M.D., Ph.D.,* and Michael R. Murphy, M.D.†

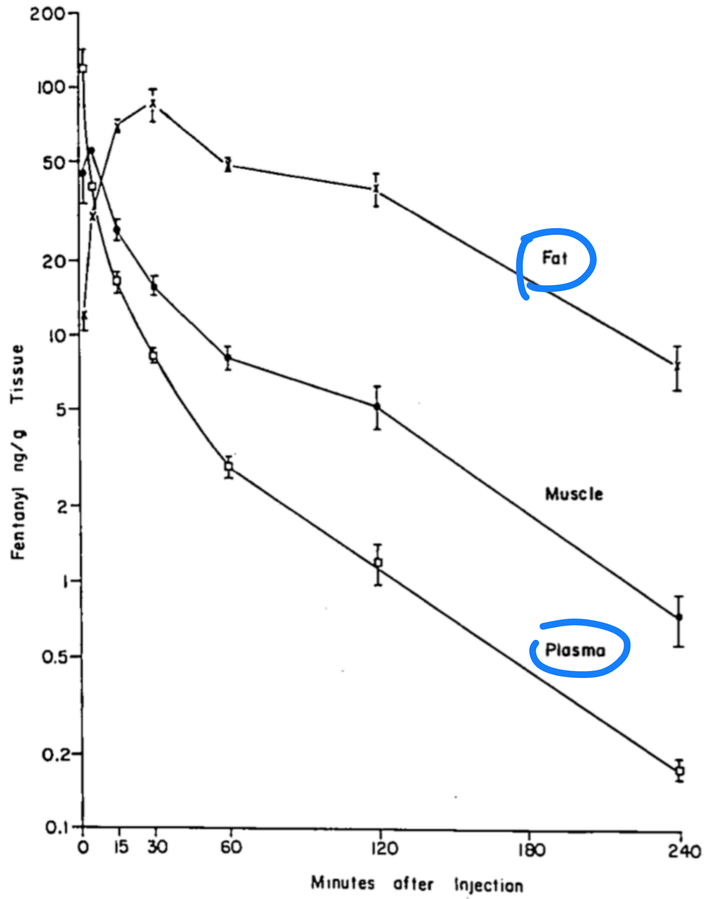
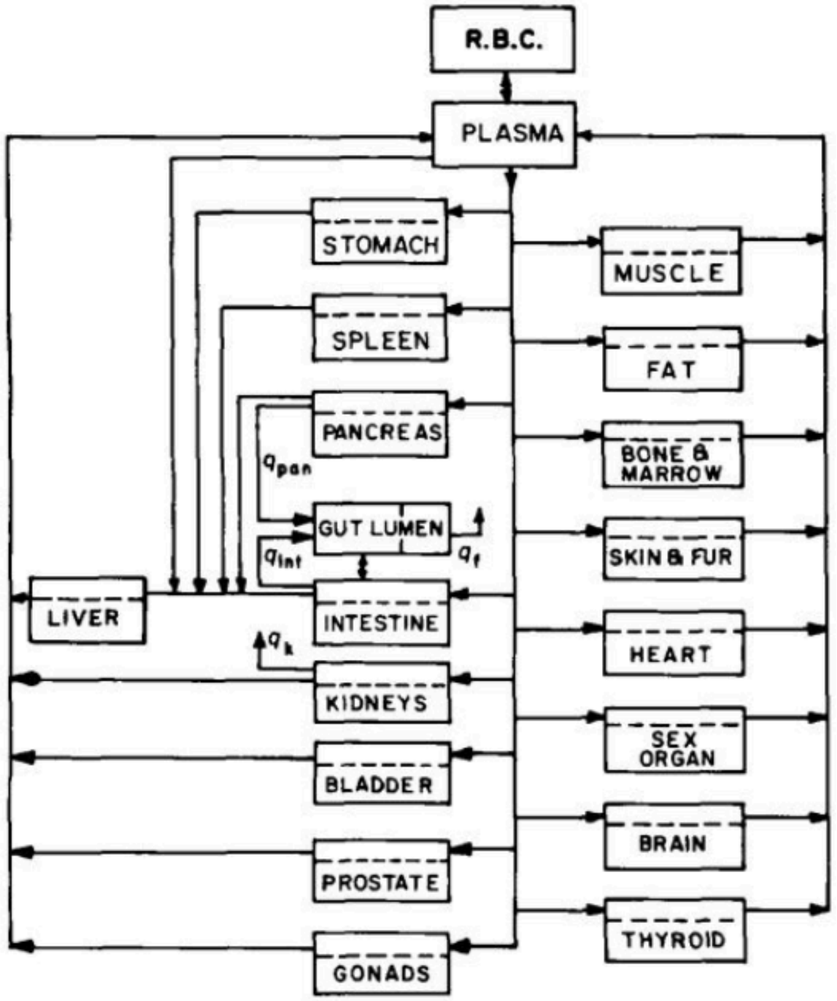


FIG. 4. Concentrations of unchanged ^{3}H-fentanyl in muscle, fat, and plasma following an intravenous injection of 50 μg/kg. Each data point represents the mean ± SEM for six rats.

Activity: hydraulic analogy: the compartments represent different parts of a system where fluid flows between them, similar to how substances move between different compartments in a biological model.

3) multi compartments models:



Limitation, challenges and the future of PK models:

Challenges:

Complexity of biological systems and variability among individuals

Difficulty predicting drug behavior in **diverse populations** (age, sex, genetics, disease states)

Nonlinear pharmacokinetics complicating model development

...

future:

-**person to person** variation for personalized medicine, how to collect data effectively

-**living drugs**: for example car-Tcells, PK models should meet systems biology and **big data**

-**Leveraging AI** in model development and tuning

...

Read more:

Basic models:

Pharmacokinetics made easy

Pharmacology for Anaesthesia and Intensive Care

Example of PK in living therapeutics:

Kirouac, Daniel C., et al. "Deconvolution of clinical variance in CAR-T cell pharmacology and response." Nature Biotechnology 41.11 (2023): 1606-1617.