NATIONAL UNIVERSITY OF PHARMACY
Department of Educational and Information Technologies

BIOPHYSICS, PHYSICAL METHODS OF ANALYSIS

Lecture 9

Mathematical Biophysics.

Plan of the Lecture

1. Mathematical Modeling.
2. Principles of Modeling.
3. Transfer Function, Feedback.
4. Drug Distribution Mass Transport Modeling.
5. Pharmacokinetics, Pharmacodynamics.
6. Pharmacokinetic Models.
7. Compartment Models.
8. Linear and Non-linear Kinetics.

Purpose of the lecture is

- to form the general concepts of mathematical modeling in biophysics.
- to give an example of mathematical modeling application in pharmacokinetics.

Mathematical Biophysics

- Main goal: analysis and modelling of regulatory and control systems of living organisms under physiological and pathological conditions (pathological processes are seen as a distortion of the normal regulatory mechanisms present in the organism)
- It also involves:
  - Support of medical decisions in diagnostics and therapy planning
  - Healthcare management
- Fundamental property of living systems: multiple interaction with surroundings
- ambient variables which act on the system = **input**
- variables by which the system acts on surroundings = **output**
- Input variables for describing the system *must be chosen to be* independent.
- The output ones depend on the input variables and the inner parameters of the given system.

Mathematical Modeling

A model is any representation of a real system.

- May deal with structure or function
- May involve words, diagrams, mathematical notation, physical structure
- May have the same meaning as “hypothesis”
- Must always involve simplification of the real system
- A mathematical model may be as simple as a single equation relating a single dependent variable (*y*) to another independent variable (*x*) such as: $y = ax + b$
- May be multi-component involving the interaction of many equations having several mutually dependent variables

$$a_{11}x_1 + a_{12}x_2 + \ldots a_{1n}x_n = b_1$$
$$a_{21}x_1 + a_{22}x_2 + \ldots a_{2n}x_n = b_2$$
$$a_{n1}x_1 + a_{n2}x_2 + \ldots a_{nn}x_n = b_n$$

$$\frac{dy_1}{dt} = f_1(t, y_1, y_2, \ldots, y_n); y_1(t_0) = y_{1,0}$$
$$\frac{dy_2}{dt} = f_2(t, y_1, y_2, \ldots, y_n); y_2(t_0) = y_{2,0}$$
$$\frac{dy_n}{dt} = f_n(t, y_1, y_2, \ldots, y_n); y_n(t_0) = y_{n,0}$$

Building Models

Stepwise replacement of a system component with a model equation.

1. Conceptual model of the real system. Without an understanding of the real system and the interaction of the system with its environment, no model can be developed.
2. Design experiments and collect “good” data that accurately represents the real system.
3. Examine the data to determine the parameter set that defines the system *f(x,y,t,a,b,c…).*
4. Define an equation based on the data (empirical) and/or based on the characteristics of the system (theory based). For example, $y = ax + b$. y and x are variables. a and b are parameters.
5. Find the optimal (most correct) values for the parameters a and b.
6. Implement the model to “experiment” with new concepts.

Principles of modelling

- Theoretical cognitional process which goal is to recognise properties of certain original on the basis of its representation. The way of re-presentation is given by the purpose of the model.
- **Each model is a simplification of reality.**
- Main principle of modelling is the **abstraction of identification**. We take into account only identical properties of the objects. A model sufficiently representing the properties of the original object can be a source of information about that object and its interactions.
- **Analogy** - structural or functional similarity of objects, processes and phenomena (events). **Structural analogy** is based on partial or total structural identity of two systems.
- **Functional analogy** (more important) - identity in functional properties of two systems - the character of both systems can be quite different (e.g. functional analogy of natural and artificial kidney).
- **Isomorphism** is a special case of analogy - the systems in question are of the same mathematical description

Types of models

- Formal: **real** (physical, chemical) and **abstract** (mathematical).
- According to the presence of accidental features, these can be divided into **stochastic** and **deterministic**.
- According to the way of origin: **induction** models (from empirically obtained information) and **deductive** ones (on the basis of supposed relations)
- According to the purpose: **descriptive** (serving for description of properties of the original) and **explanatory** (serving for verification of hypotheses)
- The choice of modelled hypotheses must be **representative** - the non-modelled properties must not disable to draw general conclusions.

Process of model construction and utilisation

- Observation of certain phenomenon
- Its experimental verification and, if possible, its quantification
- Designing the model
- Its comparison with experimental results
- **Simulation** = specific kind of modelling. Principle: The original system is re-placed by the simulation model. Regressive verification of knowledge obtained by means of the simulation model in the original system is done. The simulation is often performed using computers.
- Mathematical modelling of biological and physiological processes (stimulated, e.g., by development of radionuclide methods - substance distribution and kinetics in organism is studied).

Analysis and synthesis of a system

- **System analysis** - we know structure - we have to determine its behaviour
- **System synthesis** - the structure is to be determined - behaviour is known
- Black box - system of unknown structure and behaviour. **Identification of the system** is done on the basis of relations between input and output data.

Transfer Function

- **TRANSFER function** - Dependence of the values of an output parameter on values of an input parameter
- We can distinguish:

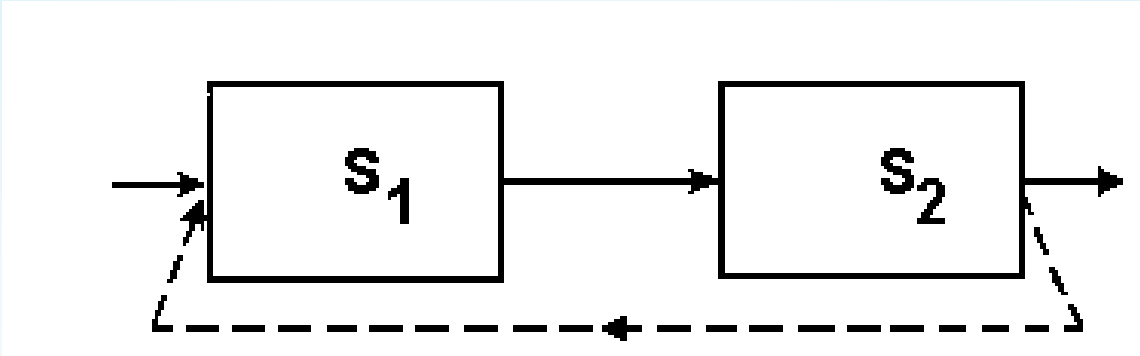
  - linear systems (an ideal case)

  - non-linear
- linearization of a non-linear system - an approximation by a straight line

Transfer Function

- Basic forms of transfer:
  - Amplification or attenuation of the input parameters
  - Their time-delay
  - Performing simple logic operations
  - Selective permeability
  - Generation of specific time-courses etc. (also deformation of input parameters)
- All these forms are encountered in biological systems
- The transfer function need not to be constant. Dynamic systems are capable of adaptation and learning.

Feedback



- **Feedback:** changes in a system output parameter leads to changes an input parameter of the same system
- In **positive feedback** an increase / decrease of the output parameter from its normal value leads to an increase / decrease in the input parameter - the change of the input parameter in this way increases in an uncontrolled manner - positive feedback is therefore unsuitable for controlling dynamic systems.
- In **negative feedback** an increase / decrease of the output parameter from its normal value leads to a decrease / increase (i.e., vice-versa) in the input parameter - the change of the input parameter is in this way minimised hence allowing regulation. Homeostasis in the body is based on negative feedback.

Forms of control in living organisms:

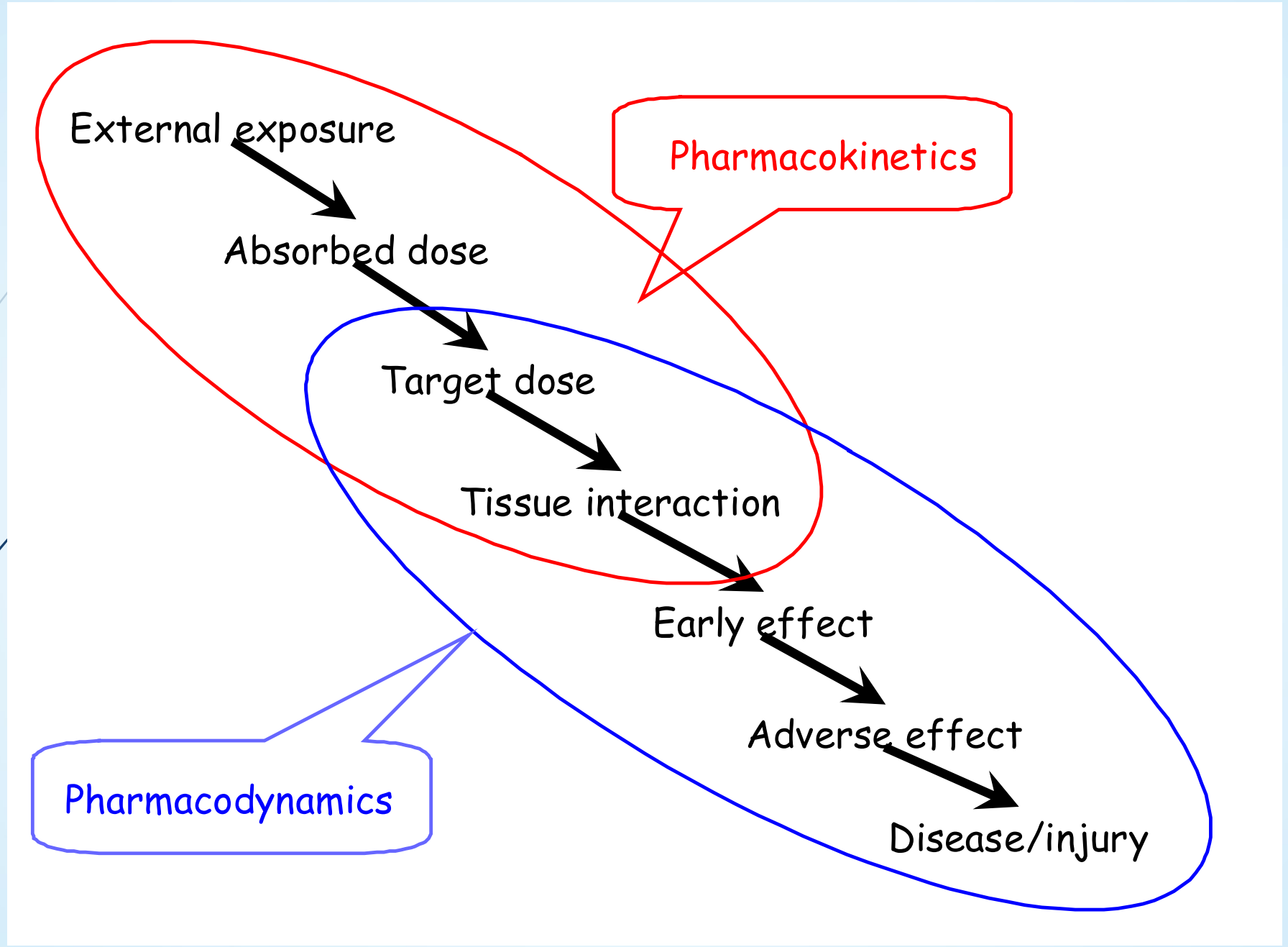
1) Direct control - control commands are transmitted directly from the controlling to the controlled unit.
2) Control with autonomous response. The control commands are only a triggering mechanism for switching over the system states (humoral control - e.g. by hormones).
3) Differentiated control - it involves both the previous forms. It is performed by the controlling system with a complex feedback net (CNS)

An Example: Drug Distribution
Mass Transport

Pharmacology – The history, source, physical and chemical properties, biochemical and physiological effect, mechanisms of action, absorption, distribution, biotransformation and excretion, and therapeutic and other uses of drugs.

Pharmacokinetics – The activity or fate of drugs in the body over a period of time, including the processes of **A**bsorption, **D**istribution, localization in tissues, **M**etabolism (biotransformation) and **E**xcretion (**ADME**).

Pharmacodynamics – The study of the biochemical and physiological effects of drugs and the mechanisms of their actions, including the correlation of action and effects of drugs with their chemical structure; also, the relationship between drug concentration and effect.


External exposure
Absorbed dose
Target dose
Tissue interaction
Early effect
Adverse effect
Disease/injury
Pharmacokinetics
Pharmacodynamics

Pharmacokinetic Parameters

1. Peak Plasma Concentration (Cmax)

   The peak plasma level depends upon – The administered dose, Rate of absorption and Rate of elimination.

2. Time of Peak Concentration (tmax)
3. Area Under the Curve (AUC)

Pharmacodynamic Parameters

1. Minimum Effective Concentration (MEC)
2. Maximum Safe Concentration (MSC)
3. Onset of Action
4. Onset Time
5. Duration of Action
6. Intensity of Action
7. Therapeutic Range
8. Therapeutic Index

More Definitions

Exposure: A measure for the amount of drug that an organism has really "seen"

Bioavailability: A measure for the proportion of the dose that reaches the systemic circulation (not the same as exposure)

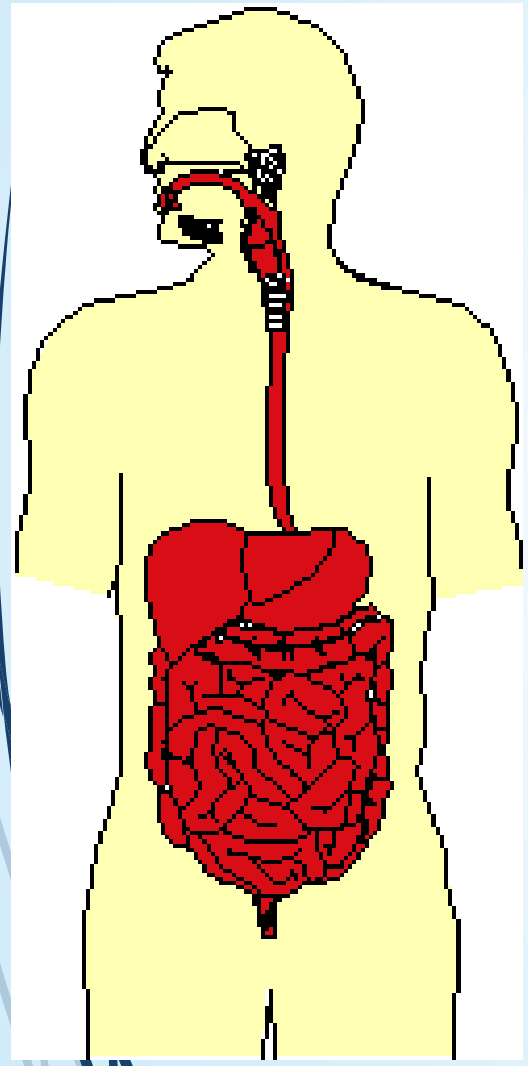
Clearance: A measure of the elimination of a compound from the blood given as volume cleared/time

Volume of Distribution: A measure of the theoretical volume that a compound distributes to.

Unbound Fraction: The fraction of drug not bound to proteins: $C_{unbound} = f_u \times C_{total}$

Half-Life: A measure of the time it takes for the organism to decrease the concentration of the drug by 50%

Absorption



- Most Drugs administered orally as pills
- Absorbed largely from small intestine
  - Some Sublingual absorption
  - Rectal Absorption (suppository)
  - Some Absorption from stomach (rare)
- Molecules need to be near the intestinal mucosa to be absorbed
  - Compound should be soluble in gut contents or in vehicle
- Crystals are not well absorbed
- Gummy stuff is not well absorbed

Distribution

Site of action of most compounds can be related back to the concentration of the compound in the plasma, though the relationship is not always clear.

- Compounds distribute differentially within body.
- Plasma protein binding may limit distribution
- Lipophilic compounds may accumulate in fatty tissues
- Liver, kidneys and other excretory organs often show high concentrations of compounds.
- Concentrations in brain are often very different from plasma concentrations
- Distribution can be studied using ^{14}C-labeled compounds

Metabolism

Metabolism occurs in liver, gut wall, lungs, kidneys and other organs:

Phase I:

- Hydroxylation
- Dealkylation
- Sulfoxide and Nitroxide formation
- etc.

Phase 2 (Conjugation)

- Glucuronide formation
- Sulfation
- Glutathione Conjugation
- Cysteine Conjugation
- Acetylation
- etc.

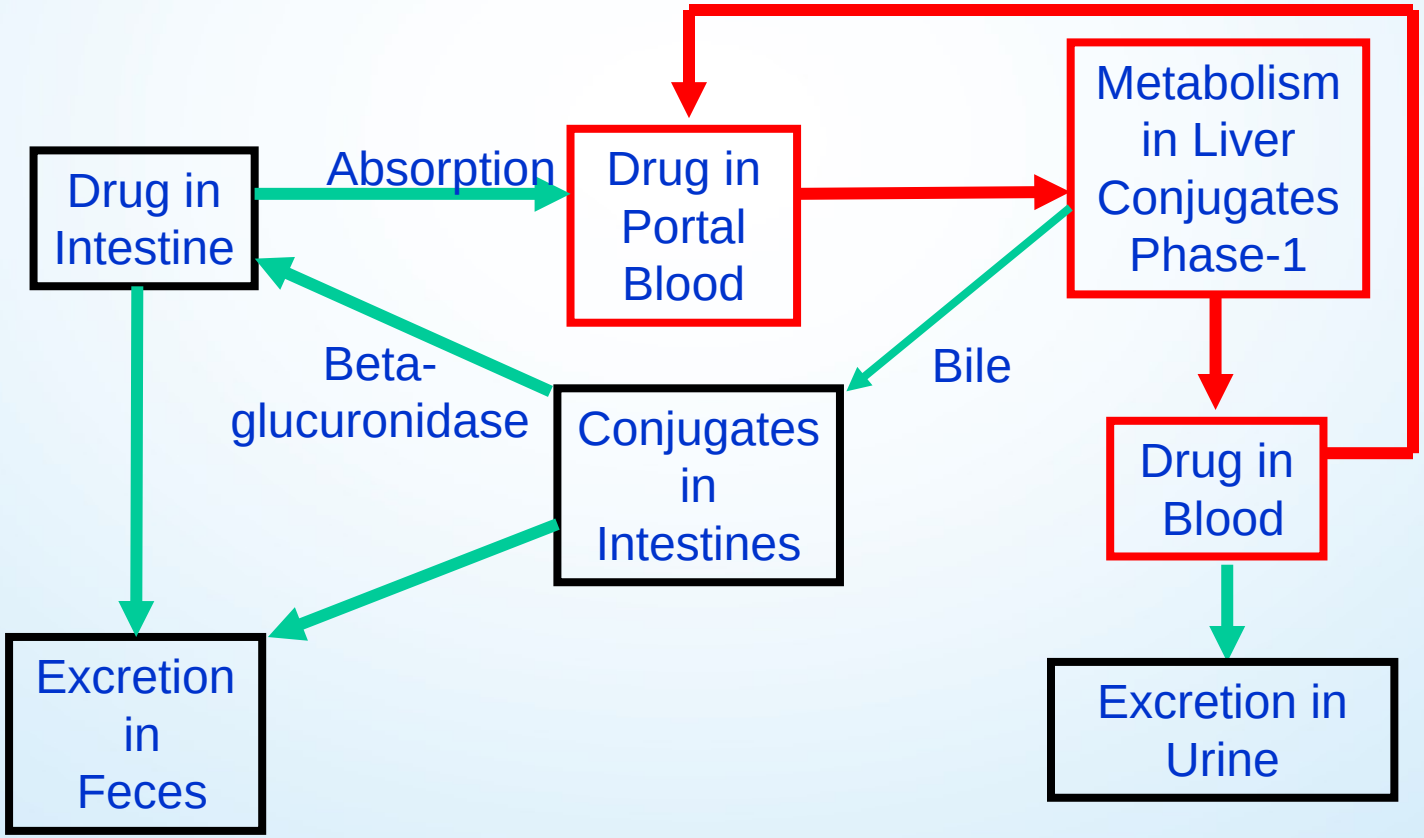
Liver is the major metabolizing organ in the body:

- Sits between Gut and rest of the circulation
- Removes toxic substances and drugs from the blood.
- Hepatic clearance of some drugs approaches or exceeds liver blood flow.
- Cytochrome P450s are the major drug metabolizing enzymes, they are found in every organ in the body.
- The body generally makes compounds more polar so they are more readily excreted in the kidney.

Excretion

Most compounds are excreted in the urine or feces (parent and metabolites, difficult to quantitate without radiolabel).
Some excretion through lungs, in saliva or in sweat, residues may remain in tissues for extended periods.

Routes of Excretion



Pharmacokinetics

The study of the quantitative relationships between the absorption, distribution, metabolism, and eliminations (A-D-M-E) of chemicals from the body.

In practice, pharmacokinetic parameters are determined experimentally from a set of drug concentrations collected over various times known as **data**.

Parameters are also called as **variables**. Variables are of two types:

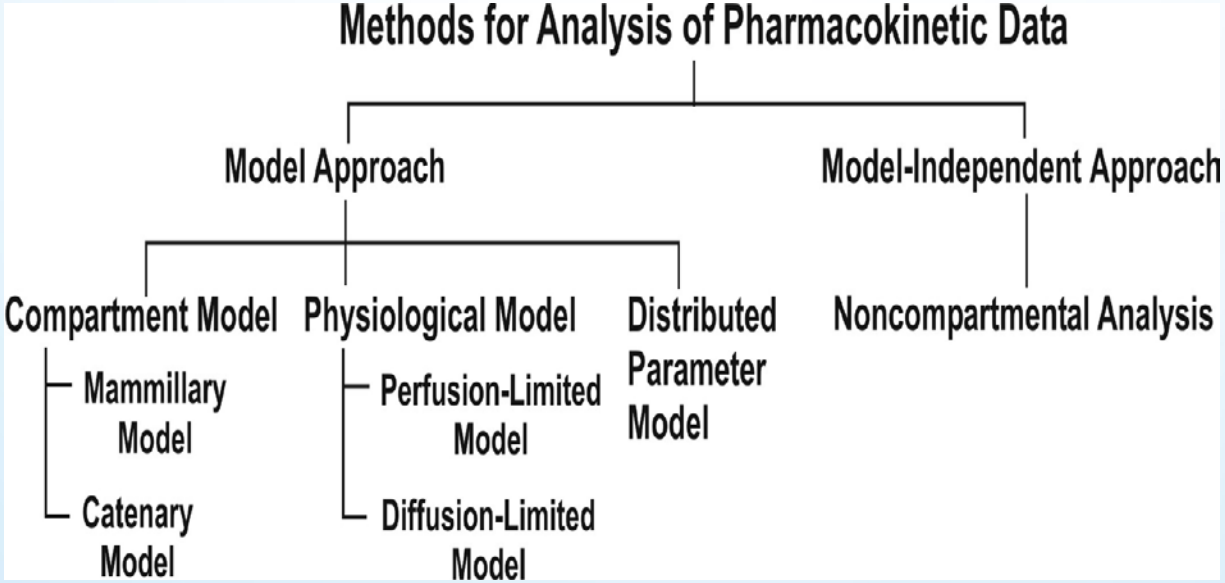
Independent variables, which are not affected by any other parameter, for example time.

Dependent variables, which change as the independent variables change, for example, plasma drug concentration.

Pharmacokinetic Models

Drug movement within the body is a complex process. The major objective is therefore to develop a generalized and simple approach to describe, analyse and interpret the data obtained during *in vivo* drug disposition studies. The two major approaches in the quantitative study of various kinetic processes of drug disposition in the body are

1. Model approach, and
2. Model-independent approach (also called as non-compartmental analysis).



Pharmacokinetic Model Approach

*A **model** is a hypothesis that employs mathematical terms to concisely describe quantitative relationships*. **Pharmacokinetic models** provide concise means of expressing mathematically or quantitatively, the time course of drug(s) throughout the body and compute meaningful **pharmacokinetic parameters**.

Applications of Pharmacokinetic Models:

1. Characterizing the behaviour of drugs in patients.
2. Predicting the concentration of drug in various body fluids with any dosage regimen.
3. Predicting the multiple-dose concentration curves from single dose experiments.
4. Calculating the optimum dosage regimen for individual patients.
5. Evaluating the risk of toxicity with certain dosage regimens.
6. Correlating plasma drug concentration with pharmacological response.
7. Evaluating the bioequivalence/bioinequivalence between different formulations of the same drug.
8. Estimating the possibility of drug and/or metabolite(s) accumulation in the body.
9. Determining the influence of altered physiology/disease state on drug ADME.
10. Explaining drug interactions.

Types of Pharmacokinetic Models

Pharmacokinetic models are of three different types –

Compartment models – are also called as ***empirical models***, and

Physiological models – are *realistic models*.

Distributed parameter models – are also *realistic models*.

Compartment Models

Compartmental analysis is the traditional and most commonly used approach to pharmacokinetic characterization of a drug. These models simply interpolate the experimental data and allow an *empirical formula* to estimate the drug concentration with time.

Depending upon whether the compartments are arranged parallel or in a series, compartment models are divided into two categories —

1. Mammillary model
2. Catenary model.

Since compartments are hypothetical in nature, compartment models are based on certain ***assumptions***:

1. The body is represented as a series of compartments arranged either in series or parallel to each other, that communicate reversibly with each other.

2. Each compartment is not a real physiologic or anatomic region but a fictitious or virtual one and considered as a tissue or group of tissues that have similar drug distribution characteristics (similar blood flow and affinity). This assumption is necessary because if every organ, tissue or body fluid that can get equilibrated with the drug is considered as a separate compartment, the body will comprise of infinite number of compartments and mathematical description of such a model will be too complex.

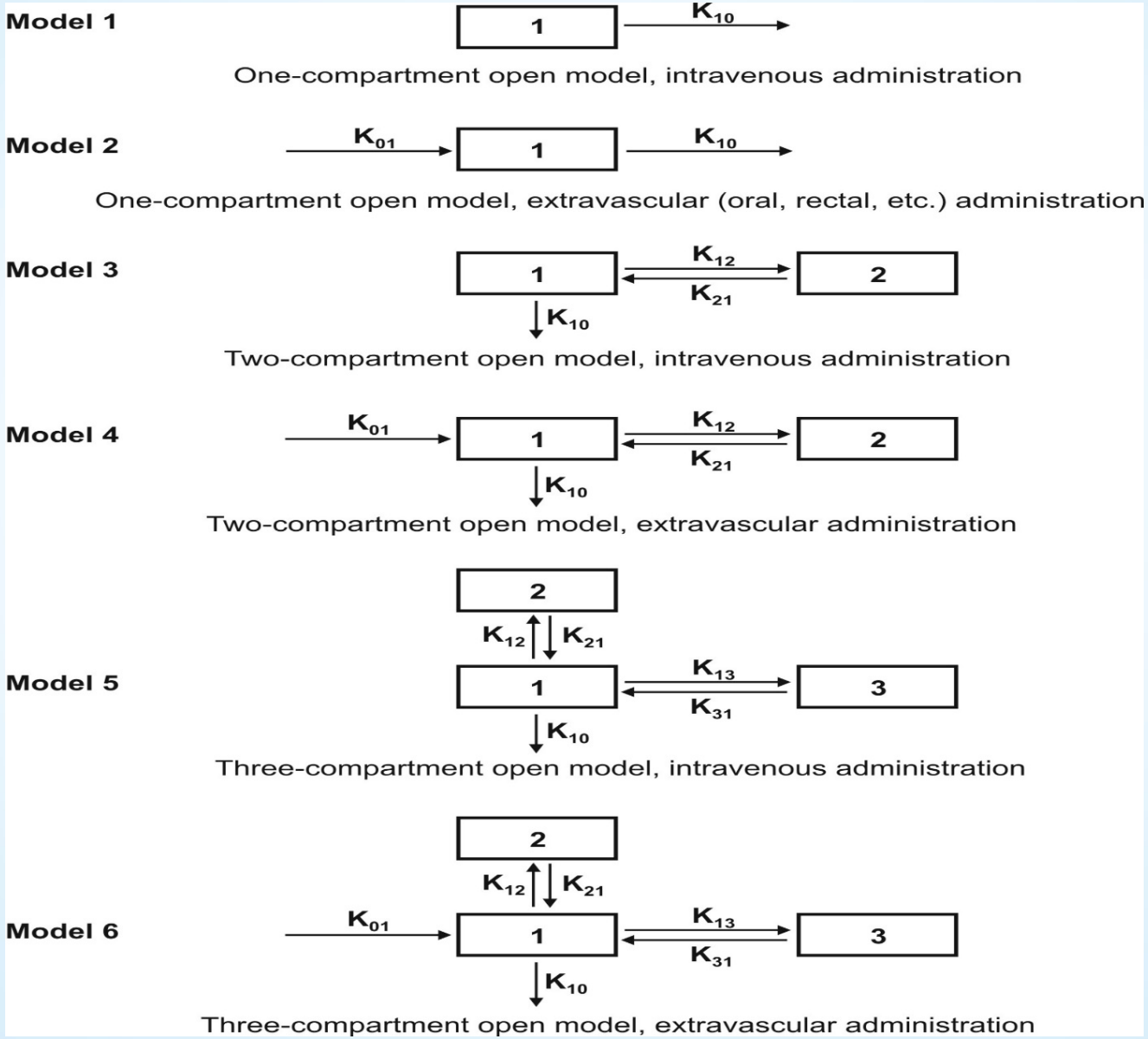
3. Within each compartment, the drug is considered to be rapidly and uniformly distributed i.e. the compartment is *well-stirred*.

4. The rate of drug movement between compartments (i.e. entry and exit) is described by first-order kinetics.

5. Rate constants are used to represent rate of entry into and exit from the compartment.

Mammillary Model

This model is the most common compartment model used in pharmacokinetics.



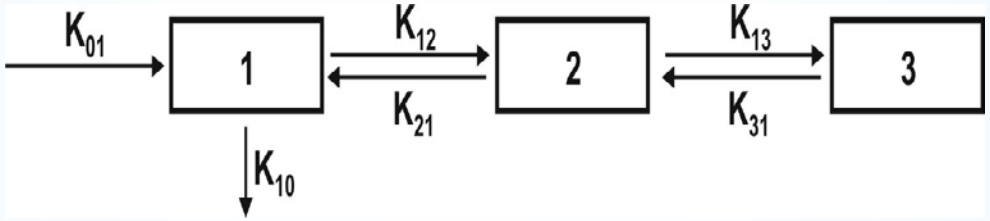
The number of rate constants which will appear in a particular compartment model is given by R.

For intravenous administration, $R = 2n - 1$

For extravascular administration, $R = 2n$

where n = number of compartments.

Catenary Model



Physiological Models

These models are also known as *physiologically-based pharmacokinetic models* (***PB-PK models***). They are drawn on the basis of known anatomic and physiological data and thus present a more realistic picture of drug disposition in various organs and tissues. The number of compartments to be included in the model depends upon the disposition characteristics of the drug. Organs or tissues such as bones that have no drug penetration are excluded.

The physiological models are further categorized into two types –

Blood flow rate-limited models – These models are more popular and commonly used than the second type, and are based on the assumption that the drug movement within a body region is much more rapid than its rate of delivery to that region by the perfusing blood. These models are therefore also called as ***perfusion rate-limited models***. This assumption is however applicable only to the highly membrane permeable drugs i.e. low molecular weight, poorly ionised and highly lipophilic drugs, for example, thiopental, lidocaine, etc.

Membrane permeation rate-limited models – These models are more complex and applicable to highly polar, ionised and charged drugs, in which case the cell membrane acts as a barrier for the drug that gradually permeates by diffusion. These models are therefore also called as ***diffusion-limited models***. Owing to the time lag in equilibration between the blood and the tissue, equations for these models are very complicated.

Example of Simple Kinetic Model: One-compartment model with bolus dose

- **Basic assumption:**
  - Well stirred, instant equal distribution within entire compartment
- **Volume of distribution = A/C**
  - In this classical model, V is an operational volume
    - V depends on site of measurement
- **This simple calculation only works IF:**
  - Compound is rapidly and uniformly distributed
  - The amount of chemical is known
  - The concentration of the solution is known.

Describing the Rates of Chemical Processes - 1 Chemical in the System

- Rate equations:
  - Describe movement of chemical between compartments
    - The previous example had instantaneous dosing
    - Now, we need to describe the rate of loss from the compartment
- Zero-order process:
  - rate is constant, does not depend on chemical concentration

  $rate = k \times C^0 = k$
- First-order process:
  - rate is proportional to concentration of ONE chemical

  $rate = k \times C^1$

Describing the Rates of Chemical Processes - 2 Chemical Systems

- Second-order process:
  - rate is proportional to concentration of both chemicals

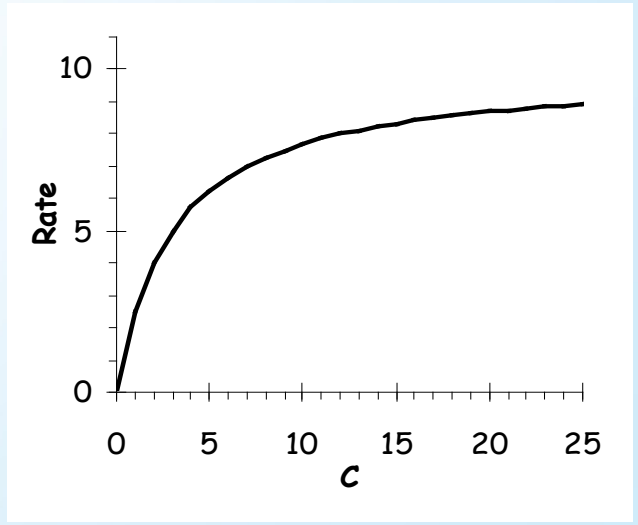
    Rate = k x C_1 x C_2
- Saturable processes*:
  - Rate is dependent on interaction of two chemicals
  - One reactant, the enzyme, is constant
  - Described using Michaelis-Menten* equation

Rate = (V_{max}x C) / (C + K_m)

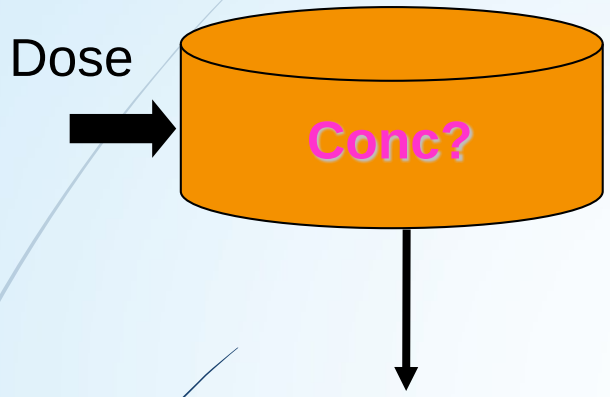
*Michaelis-Menten kinetics can describe:

- Metabolism
- Carrier-mediated transport across membranes
- Excretion

M-M kinetics



1-Comp model with bolus dose and 1st order elimination



Purpose: Examine how concentration changes with time

Mass-balance equation (change in C over time)

- $dA/dt = -k_e \times A$, or
- $dC/dt = -k_e \times C$

where k_e = elimination rate constant

Concentration

- Rearrange and integrate above rate equation

$$C = C_0 \times e^{-ke \cdot t}, \text{ or}$$

$$\ln C = \ln C_0 - k_e \cdot t$$

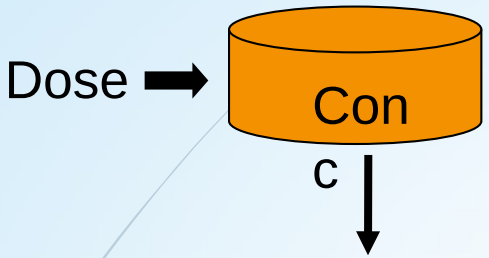
Half-life ($t_{1/2}$)

-Time to reduce concentration by 50%

-replace C with $C_0/2$ and solve for t

$$t_{1/2} = (\ln 2)/k_e = 0.693/k_e$$

1-Comp model with bolus dose and 1st order elimination



Clearance: volume cleared per time unit

- if k_e = fraction of volume cleared per time unit,

$k_e = CL/V$ $(CL=k_e*V)$

Calculating Clearance using Area Under the Curve (AUC):

AUC = average concentration

- integral of the concentration
- $\int C\,dt$

CL = volume cleared over time (L/min)

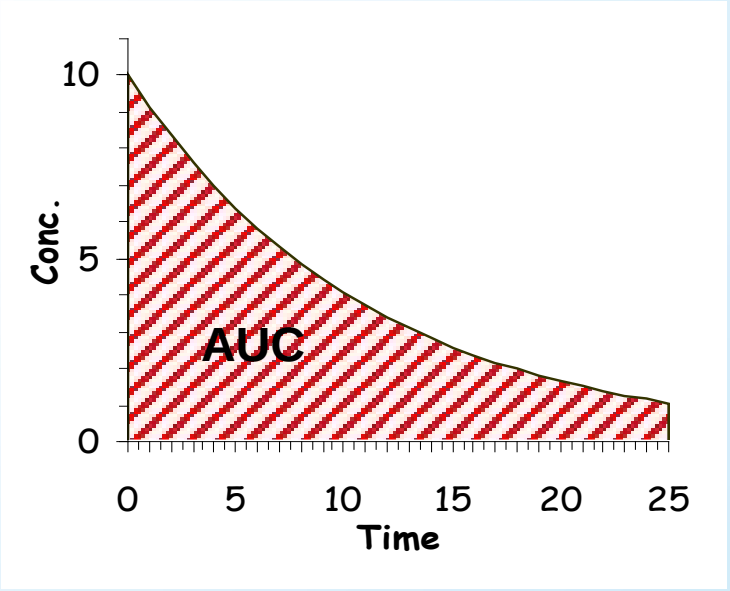
$dA/dt = - k_eA = -k_e\ V\ C$

$dA/dt = - CL \cdot C$

$\int dA = - CL \int C\,dt$

$Dose = CL \cdot AUC$

CL = Dose / AUC



1-Comp model with continuous infusion and 1st order elimination

Calculating Clearance at Steady State:

- At steady state, there is no net change in concentration:

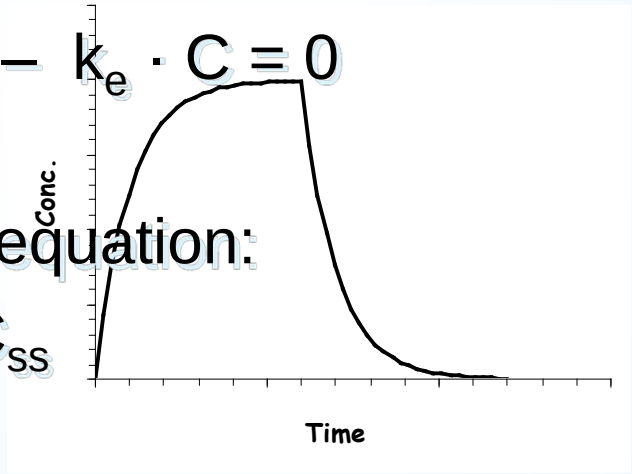
$$dC/dt = k_0/V - k_e \cdot C = 0$$

- Rearrange above equation:

$$k_0/V = k_e \cdot C_{ss}$$

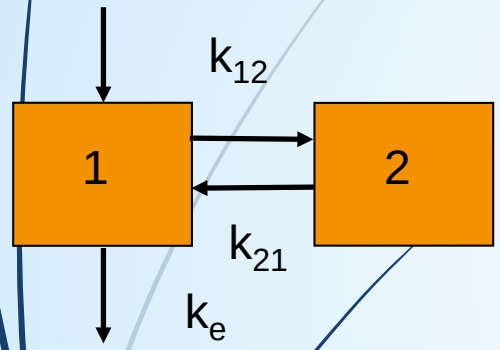
- Since $CL = k_e \cdot V$,

$$\mathbf{CL = k_0/C_{ss}}$$



Steady State

2-Comp model with bolus dose and 1st order elimination



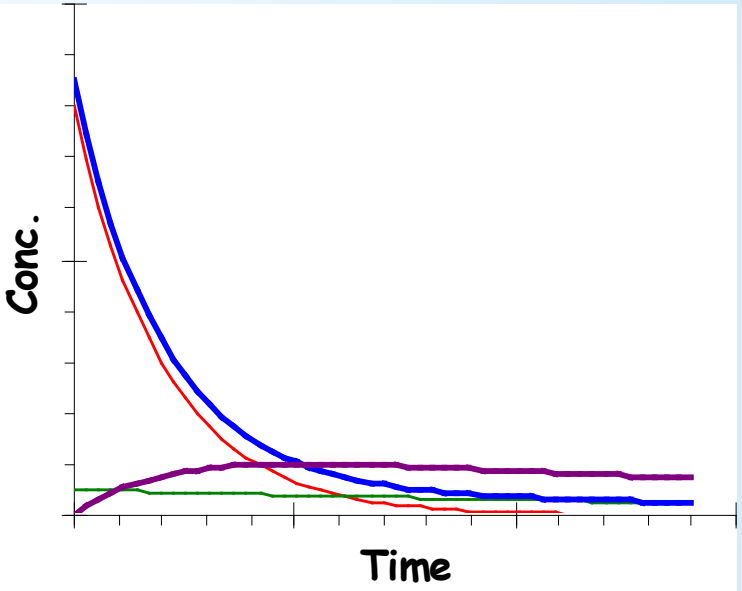
Calculating Rate of Change in Chemical:

– Central Compartment (C1):

$$dC1/dt = k_{21} \cdot C_2 - k_{12} \cdot C_1 - k_e \cdot C_1$$

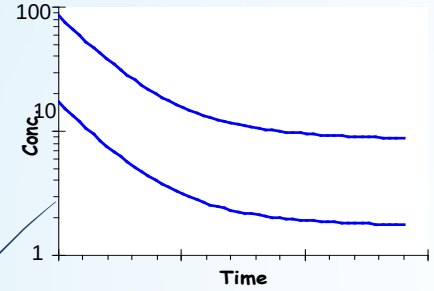
– Peripheral (Deep) Compartment (C2):

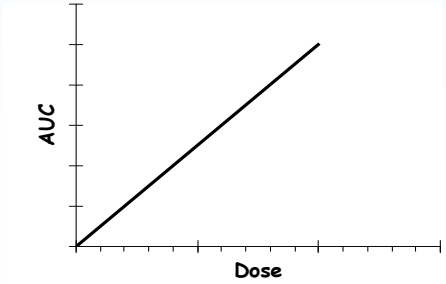
$$dC2/dt = k_{12} \cdot C_1 - k_{21} \cdot C_2$$

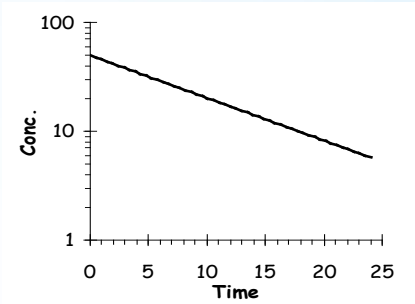


Linear and Non-linear Kinetics

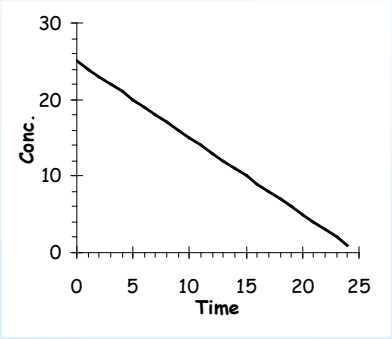
- **Linear:**
  - All elimination and distribution kinetics are 1st order
    - Double dose ➡ double concentration

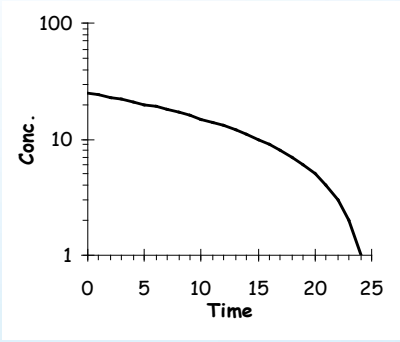






- **Non-linear:**
  - At least one process is NOT 1st order
    - No direct proportionality between dose and compartment concentration





Control Questions

1. Building Models.

2. Positive and Negative Feedback.

3. Relationships between the absorption, distribution, metabolism, and eliminations (A-D-M-E) of chemicals from the body.

4. Mammillary Model.

5. 1-Compartment model with bolus dose and 1st order elimination.

6. 2-Compartment model with bolus dose and 1st order elimination.

Recommended literature:

Basic:

1. Vladimir Timanyuk, Elena Zhivotova, Igor Storozhenko. Biophysics: Textbook for students of higher schools / Kh.: NUPh, Golden Pages, 2011.- 576p.
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Support:

1. Eduard Lychkovsky. Physical methods of analysis and metrology: tutorial / Eduard Lychkovsky, Zoryana Fedorovych. – Lviv, 2012. – 107 p.
2. Daniel Goldfarb. Biophysics DeMYSTiFied. – McGraw-Hill Professional, 1st Edition, 2010. – 400 p.


Thanks for
your attention