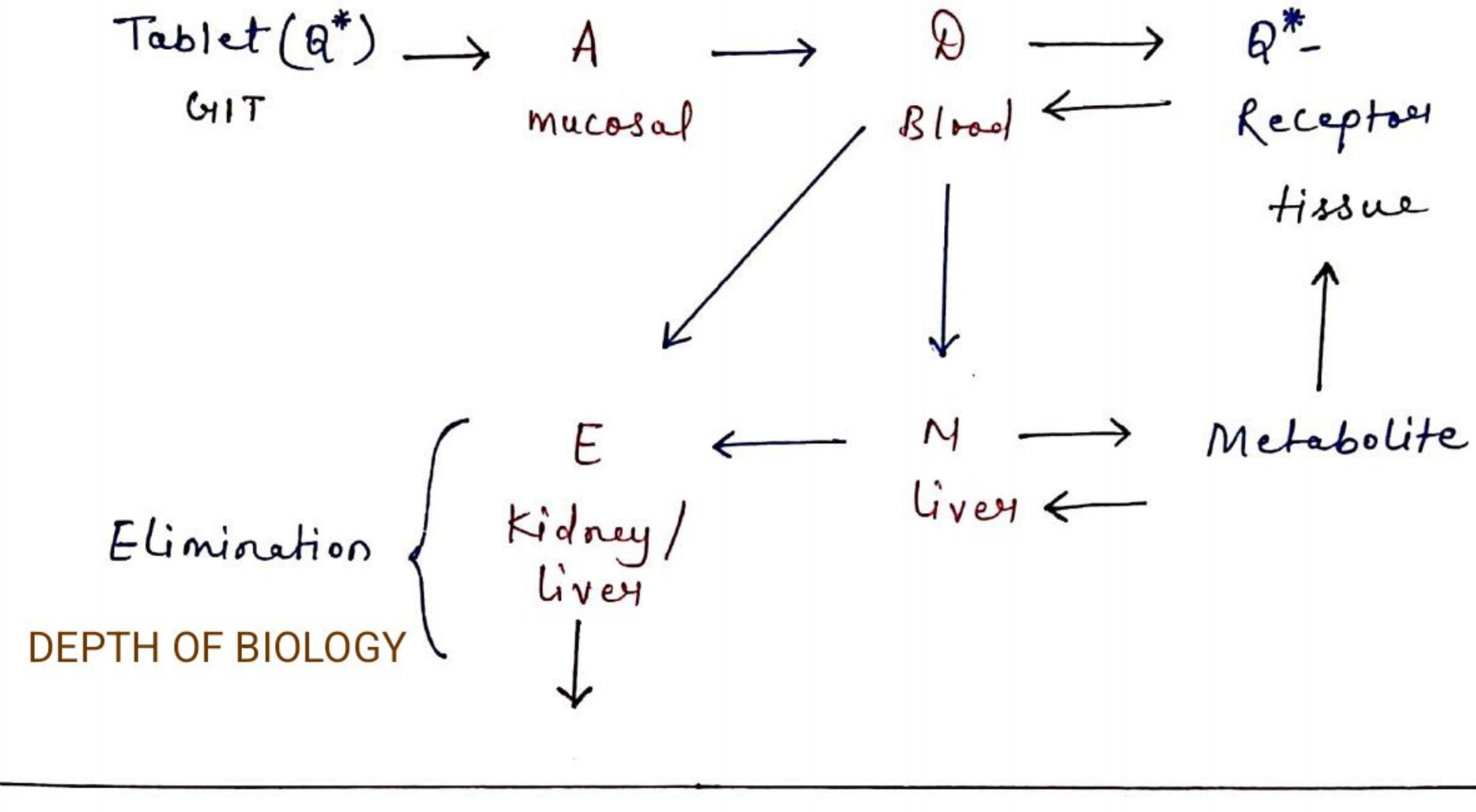
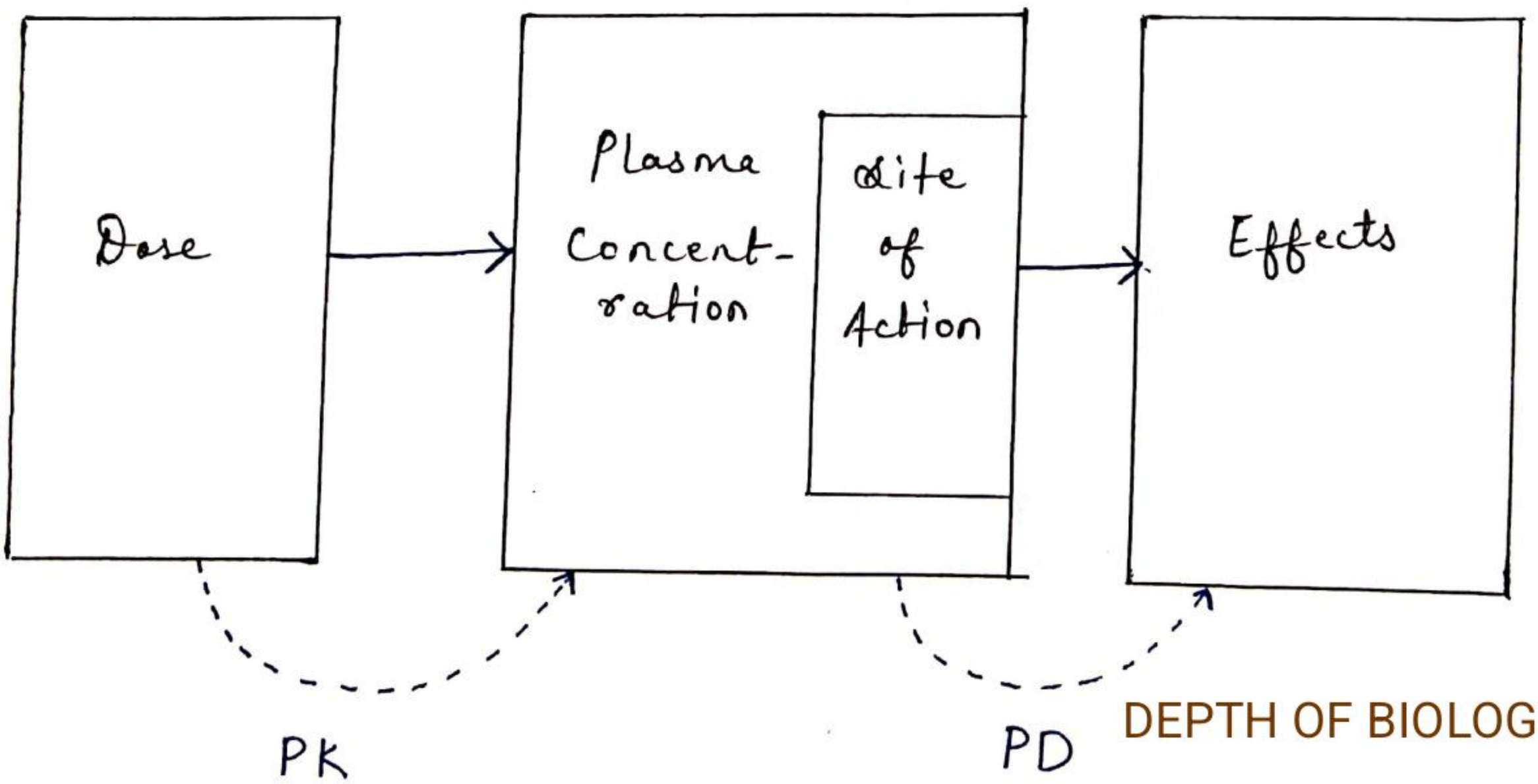
THE PHASES

1 BIOPHARMACEUTICS | 2 PHARMACOKINETICS | 3 PHARMACODYNAMICS





DEPTH OF BIOLOGY → **DEFINITIONS**

Pharmacokinetics is defined as the kinetics of drug absorption, distribution, metabolism and excretion (ADME) and their relationship with the pharmacological, therapeutic or toxicological response in humans

> **Absorption** is defined as the process of movement of unchanged drug from the site of administration to systemic circulation (or to the site of measurement i.e. plasma).

- **Distribution** is *reversible transfer of a drug between the blood and the extra vascular fluids and tissues. (or, we can say Movement of drug from One Compartment to other).

Elimination is the major process for removal of a drug from the body and termination of its action.

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- It is defined as the irreversible loss of drug from the body. Elimination occurs by two processes viz. biotransformation and excretion.

Metabolism (Biotransformation) of drugs is defined as the chemical conversion of one form to another.

Excretion is defined as the process whereby drugs and/or their metabolites are irreversibly transferred from internal to external environment.

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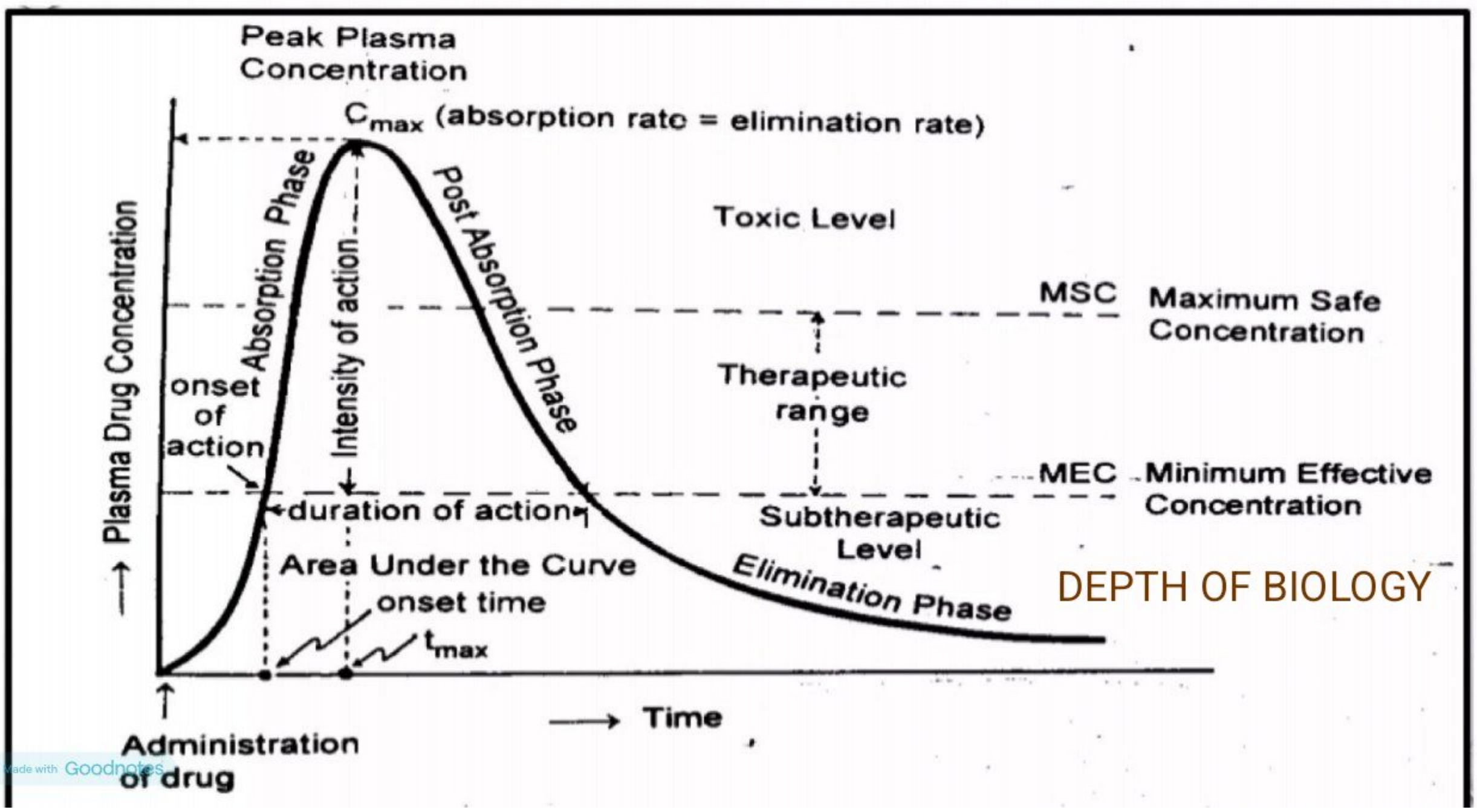
Pharmacokinetics Parameters



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The various Pharmacodynamic parameters are-

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1. Minimum Effective Concentration (MEC): 👇

It is defined as the minimum concentration of drug in plasma required to produce the therapeutic effect.

It reflects the minimum concentration of drug at the receptor site to elicit the desired pharmacological response. The concentration of drug below MEC is said to be in the sub-therapeutic level.

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In case of antibiotics, the term minimum inhibitory concentration (MIC) is used. It describes the minimum concentration of antibiotic in plasma required to kill or inhibit the growth of micro organisms.

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2. Maximum Safe Concentration (MSC)

Also called as minimum toxic concentration (MTC)
It is the concentration of drug in plasma above which adverse or
unwanted effects are precipitated.
Concentration of drug above MSC is said to be in the toxic level.

3. Onset of Action

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The beginning of pharmacological response is called as onset of action.

It occurs when the plasma drug concentration just exceeds the required MEC.

4. Onset Time

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It is the time required for the drug to start producing pharmacological response.

It corresponds to the time for the plasma concentration to reach MEC after administration of drug.

5. Duration of Action

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The time period for which the plasma concentration of drug remains above the MEC level is called as duration of drug action

It is also defined as the difference between onset time and time for the drug to decline back to MEC.

6. Intensity of Action

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It is the maximum pharmacological response produced by the peak plasma concentration of drug.
It is also called as peak response.

7. Therapeutic Range

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The drug concentration between MEC and MSC represents the therapeutic range.

It is Also known as therapeutic window.

8. Therapeutic Index

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The ratio of MSC to MEC is called as therapeutic index

It is also defined as the ratio of dose required to produce toxic or lethal effects to dose required to produce effect

Here, we assumed Body as a Compartment

Pharmacokinetic Models

To, describe the drug behaviour in the body.

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A basic type of model used in pharmacokinetics is the compartmental model.

Compartmental models are categorized by the number of compartments needed to describe the drug's behavior in the body.

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There are one- compartment, two-compartment and multi-compartment model

The compartments do not represent a specific tissue or fluid but may represent a group of similar tissues or fluids.

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These models can be used to predict the time course of drug concentrations in the body.

- This model is only appropriate for drugs which rapidly and readily distribute between the plasma and other body tissues. (Uniform distribution).

When, We Consider Body a Single Compartment →

One compartment model

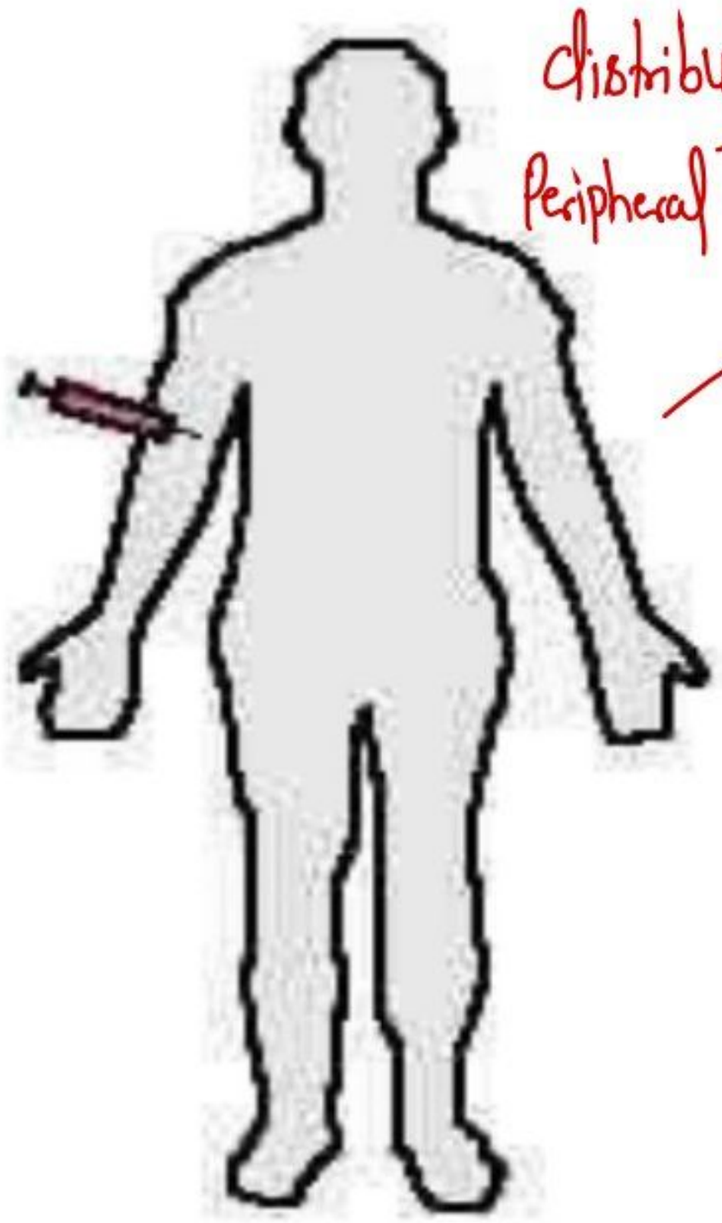
Before Administration

After Administration

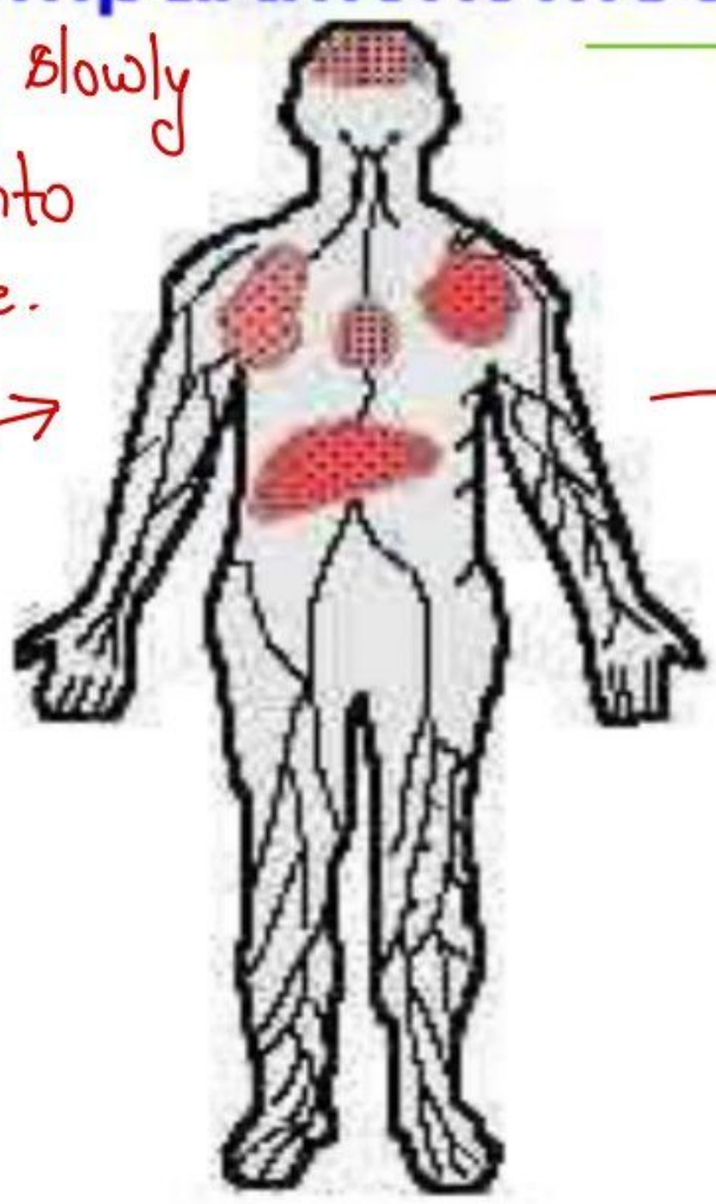
Two compartment model

Drug → Plasma → & then Slowly Slowly distributed into Peripheral Tissue.

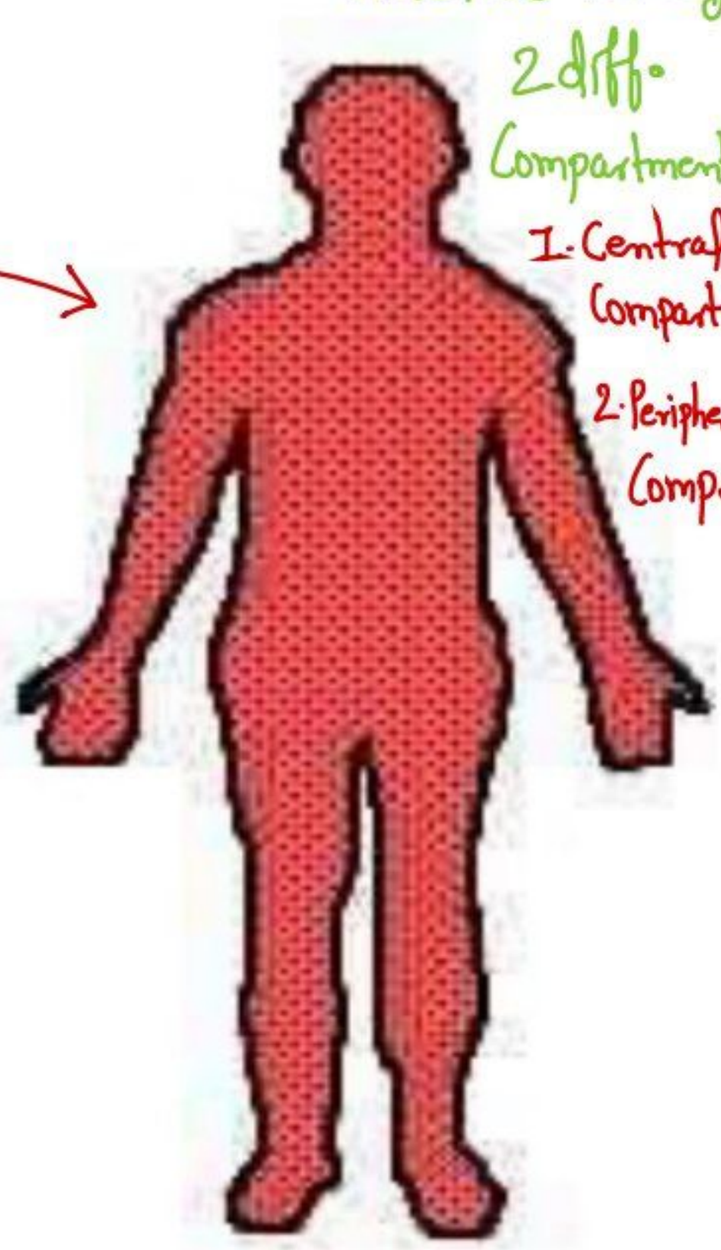
(Not rapidly distributed) → Here, We Study 2 diff. Compartment
1. Central Compart.
2. Peripheral Comp.



Before Administration

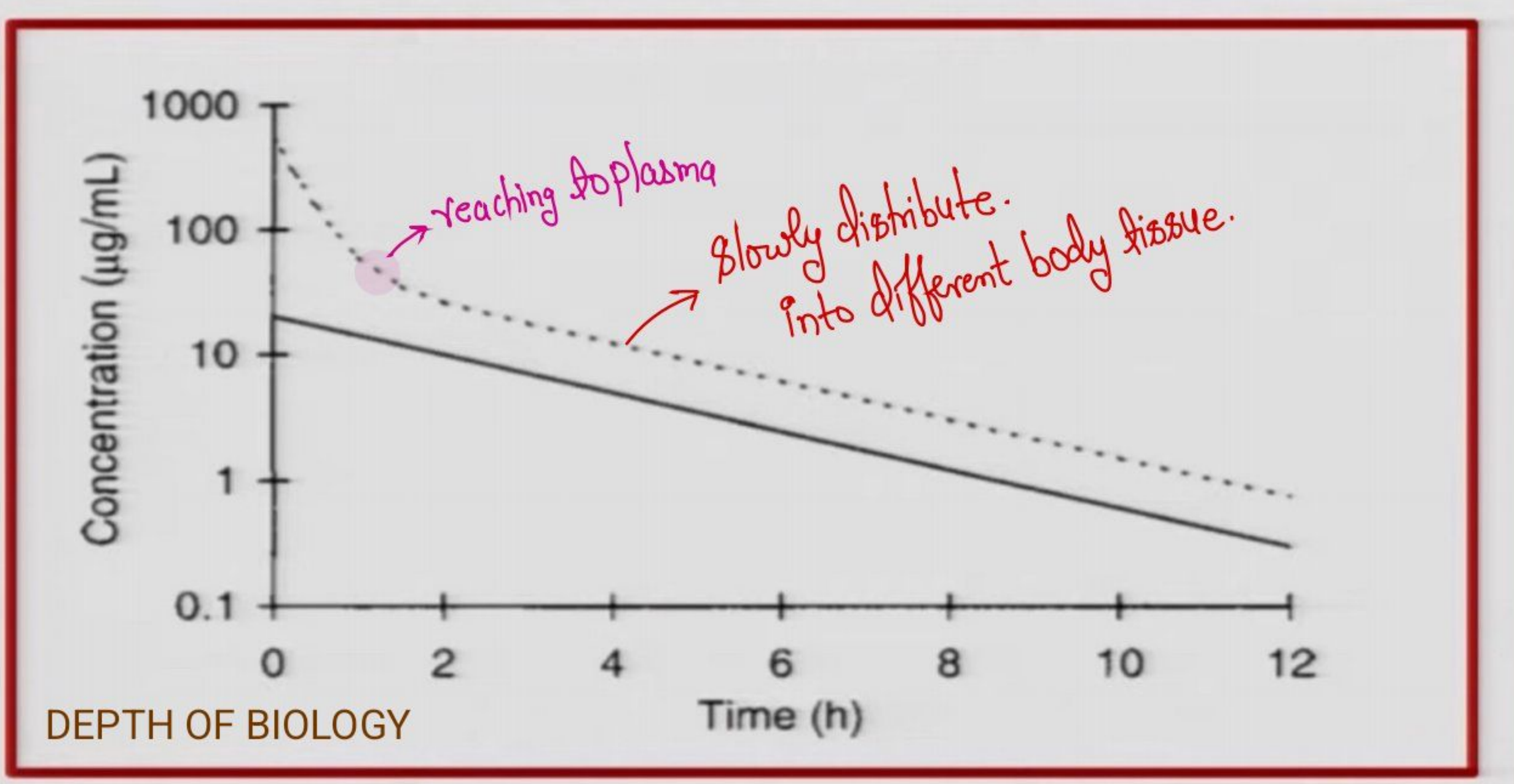


Immediately after Administration



After distribution equilibirum

Drugs which exhibit a slow equilibration with peripheral tissues, are best described with a two compartment model. DEPTH OF BIOLOGY



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The solid line shows the serum concentration/time graph for a drug that follows one-compartment model pharmacokinetics. (Uniform drug distribution).

The dashed line represents the serum concentration/time plot for a drug that follows two- compartment model pharmacokinetics after an intravenous bolus is given. DEPTH OF BIOLOGY

Large dose of drug
Over a short Period of time

Drug movement within the body is a complex process. (ADME).

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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.

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The two major approaches in the quantitative study of various kinetic processes of drug disposition in the body are-

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1. Model approach / Model Dependent Approach
2. Model-independent approach (also called as non-compartmental analysis).

PHARMACOKINETIC MODEL APPROACH

- MODEL:- A model is a hypothesis that employ mathematical terms to concisely describe quantitative relationship.

How, drug reaching to target site.

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PHARMACOKINETIC MODEL:- 👇

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It provide concise means of expressing mathematically or quantitatively, the time course of drug(s) throughout the body and compute meaningful pharmacokinetic parameters.

Give, a lot of information.

Calculate

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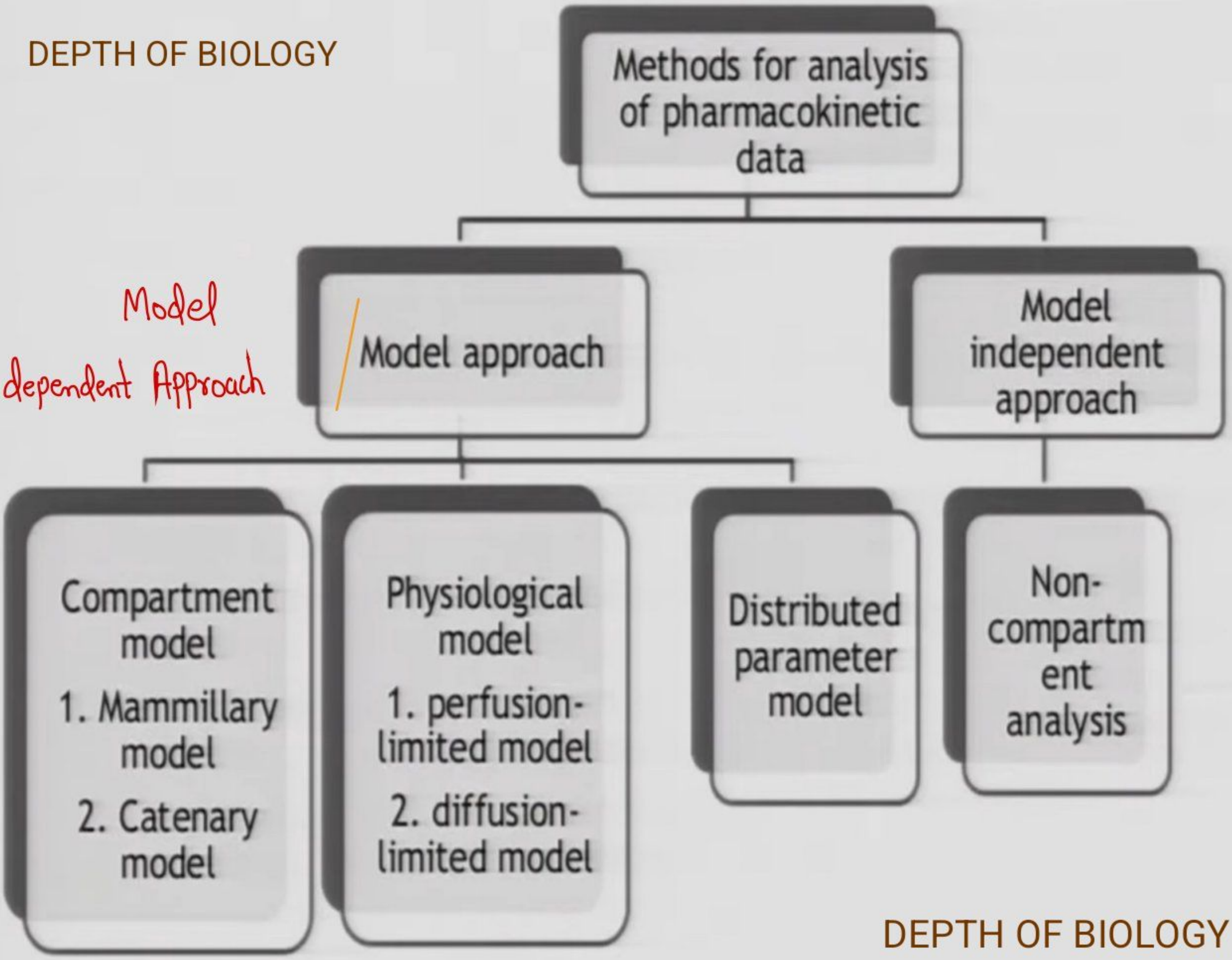
Model dependent Approach



COMPARTMENT MODELS / Empirical Model.

- Compartment analysis is the traditional and most commonly used approach to pharmacokinetic characterization of a drugs.

Insert.

- These models simply interpolate the experimental data and allow an empirical formula to estimate the drugs concentration with time

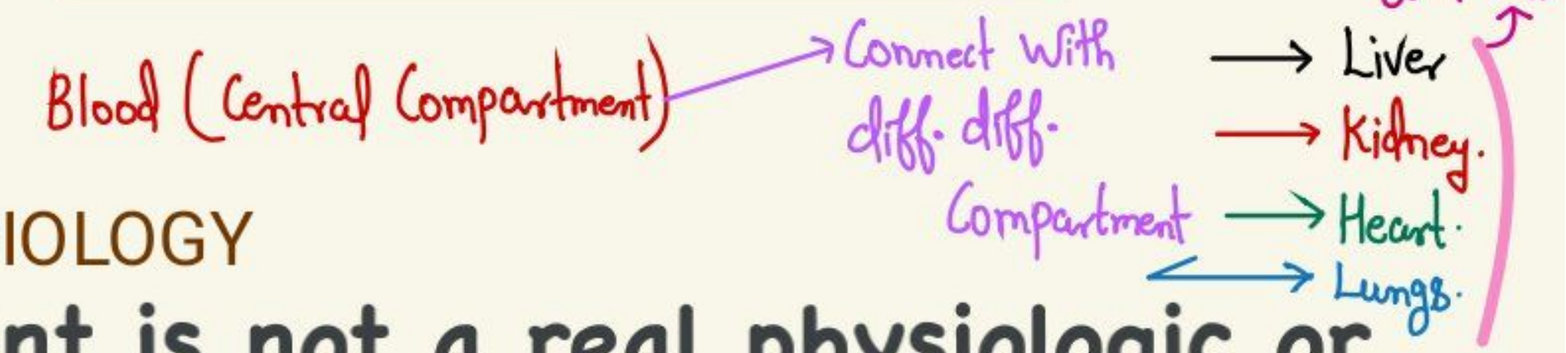
- Since compartments are hypothetical in nature ,compartments models are based on certain assumptions.

Compartmental analysis is commonly used to estimate the pharmacokinetic characters of a drug.

↳ Like AUC, Cmax., tmax., Vd, Clearance etc.

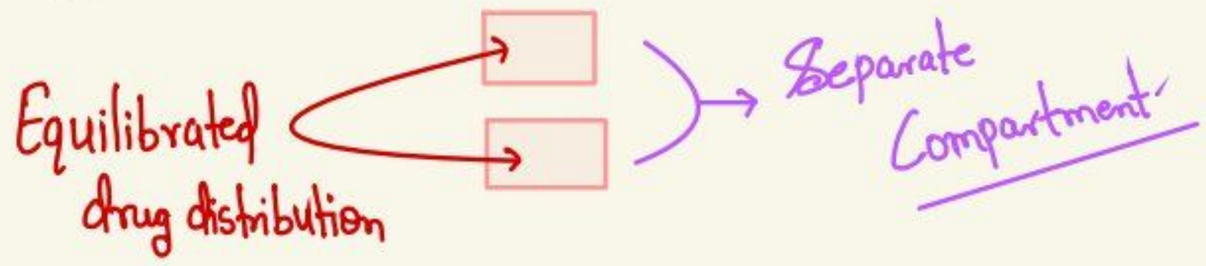
The compartments are hypothetical in nature

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 and considered as a tissue or group of tissues that have similar drug distribution characteristics (similar blood flow and affinity).

3. Every organ, tissue or body fluid that can get equilibrated with the drug is considered as a separate compartment.



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

↳ from Central Compartment / Blood Compartment to Peripheral Compartment

5. Rate constants are used to represented to entry and exit from the compartment.

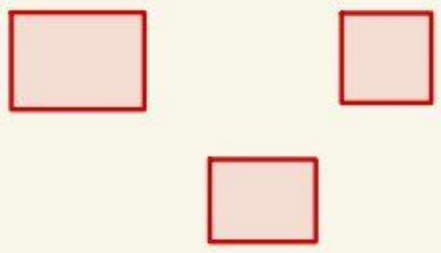
The compartment models are divided into two categories-

A. Mammillary model

B. Catenary model.

DEPTH OF BIOLOGY

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



DEPTH OF BIOLOGY

2. Each compartment is not a real physiological or anatomical region but fictitious (Not real/True.) or virtual one and considered as a tissue or group of tissue that have similar drug distribution characteristics

3. Within each compartments the drugs is considered to be rapidly and uniformly distributed

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4. The rate of drug movement between compartments described by first order kinetics

COMPARTMENTS

Binding affinity of drug is High.

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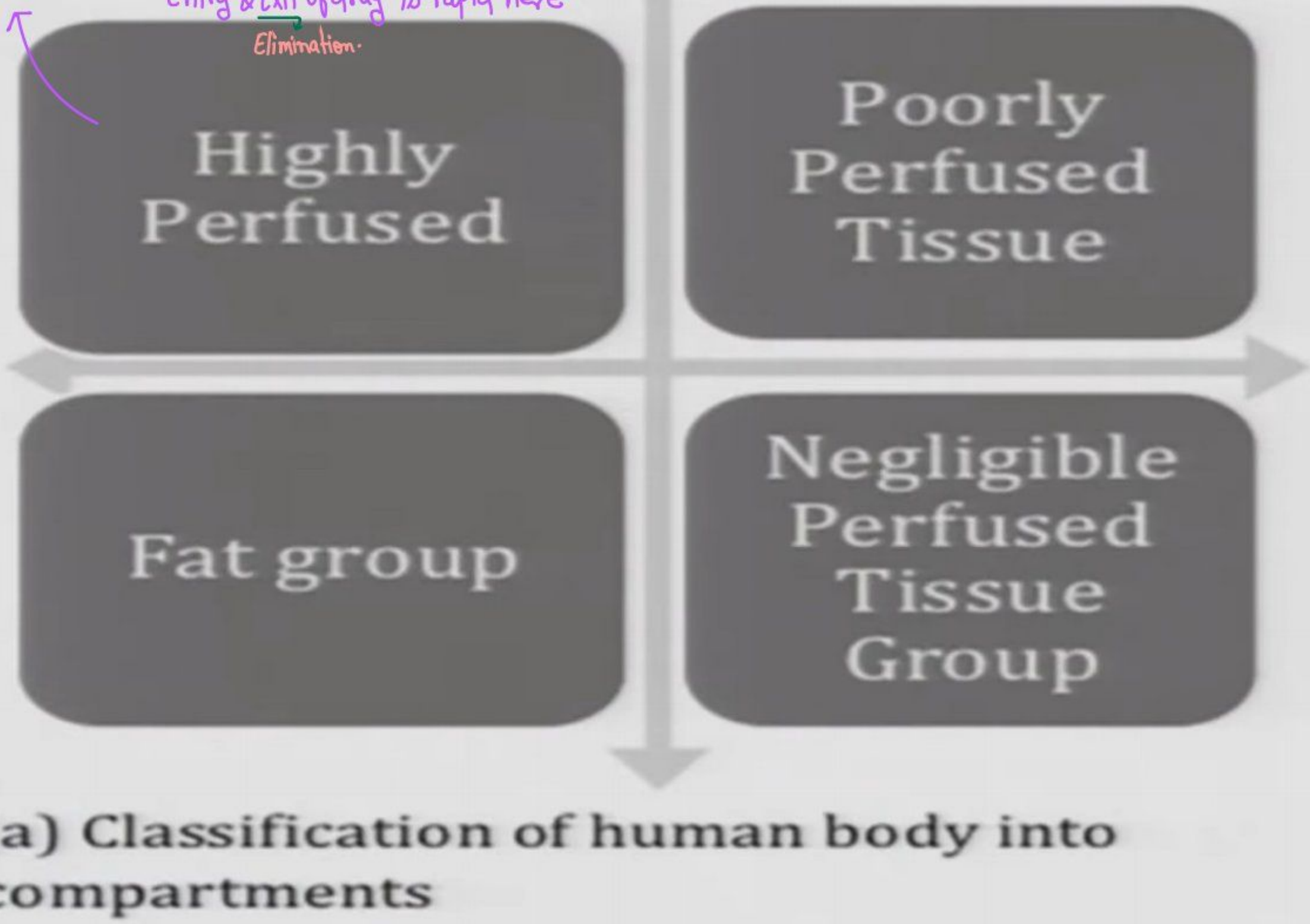
Entry & Exit of drug is rapid here

Elimination.



(a) Classification of human body into compartments

MODEL DEPENDENT APPROACH →

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The model dependent approaches are divided into two categories-

1. Compartment model-

a. Mammillary model
b. Catenary model

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2. Physiological model

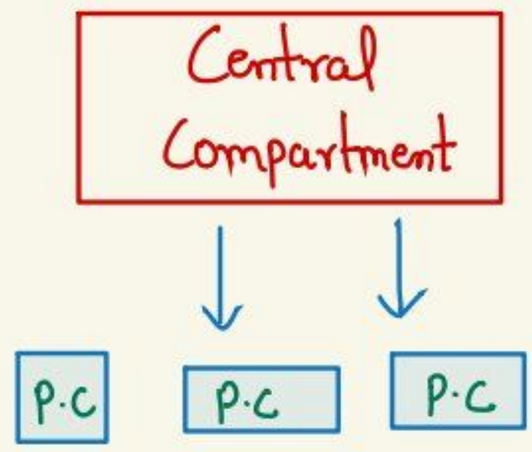
TYPES- COMPARTMENT MODELS-

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

-Mammillary model

-Catenary model

1. MAMMILLARY MODEL-



.It consists of one or more peripheral compartments connected to the central compartment.

.The central compartment comprises of plasma and highly perfused tissues such as lungs, liver, kidneys, etc. which rapidly equilibrate with the drug.

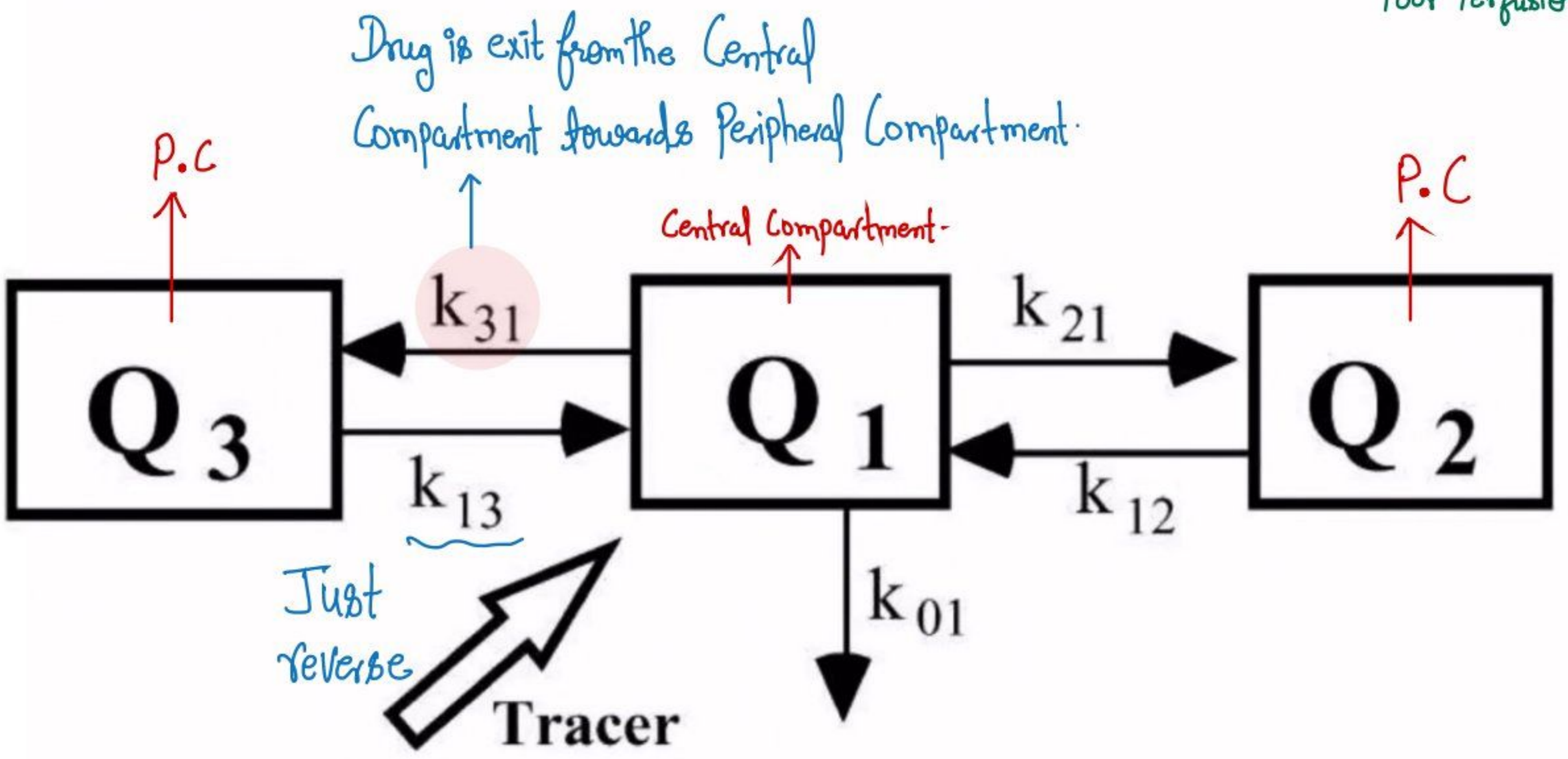
.The drug is directly absorbed into this compartment (i.e. blood). (Central Compart./Blood Compart.) Elimination too occurs from this compartment since the chief organs involved in drug elimination are liver and kidneys, the highly perfused tissues and therefore presumed to be rapidly accessible to drug in the systemic circulation.

-The peripheral compartments or tissue compartments (denoted by numbers 2, 3, etc.) are those with low vascularity and poor perfusion.

Central Compartm. → denoted by 1.

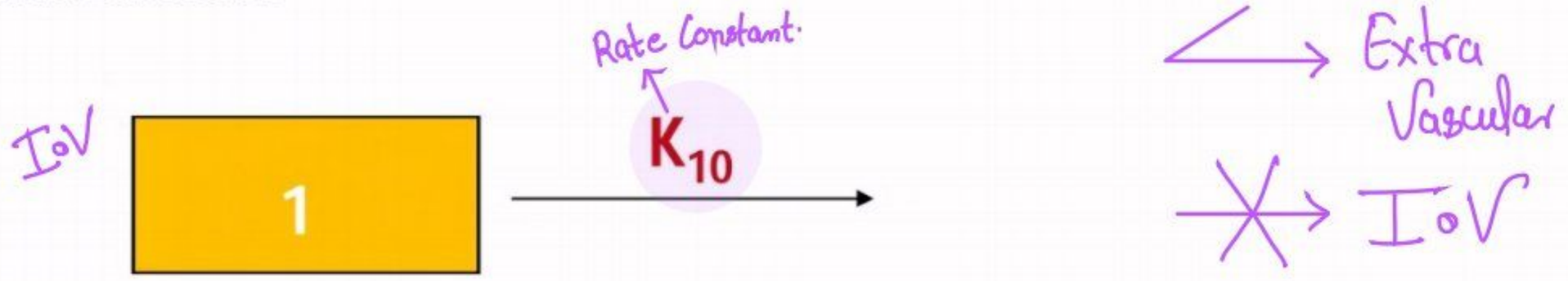
MAMMILLARY MODEL-

Q_2 & Q_3 → Low Vascularity & Poor Perfusion.



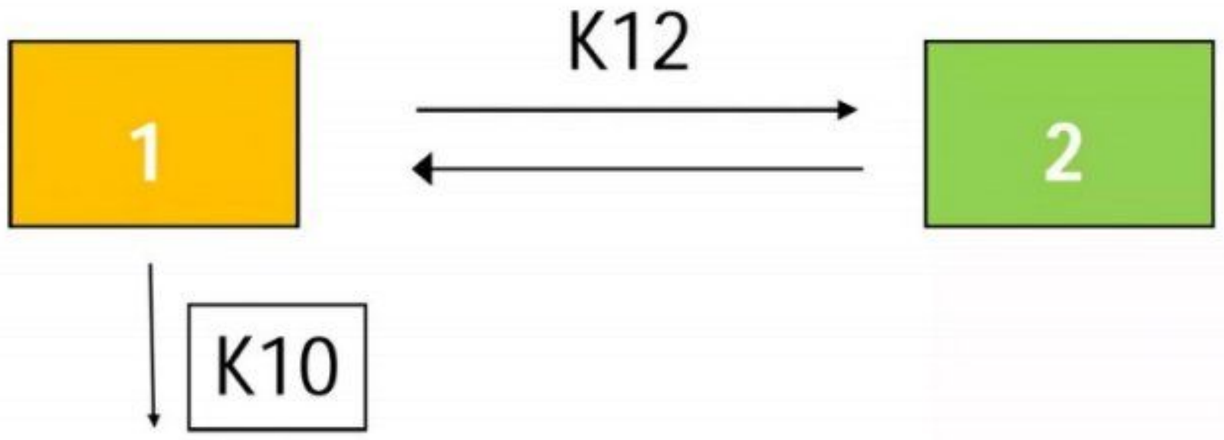
Central compartment

Model 1 One-compartment open model, ⟶ intravenous bolus administration.

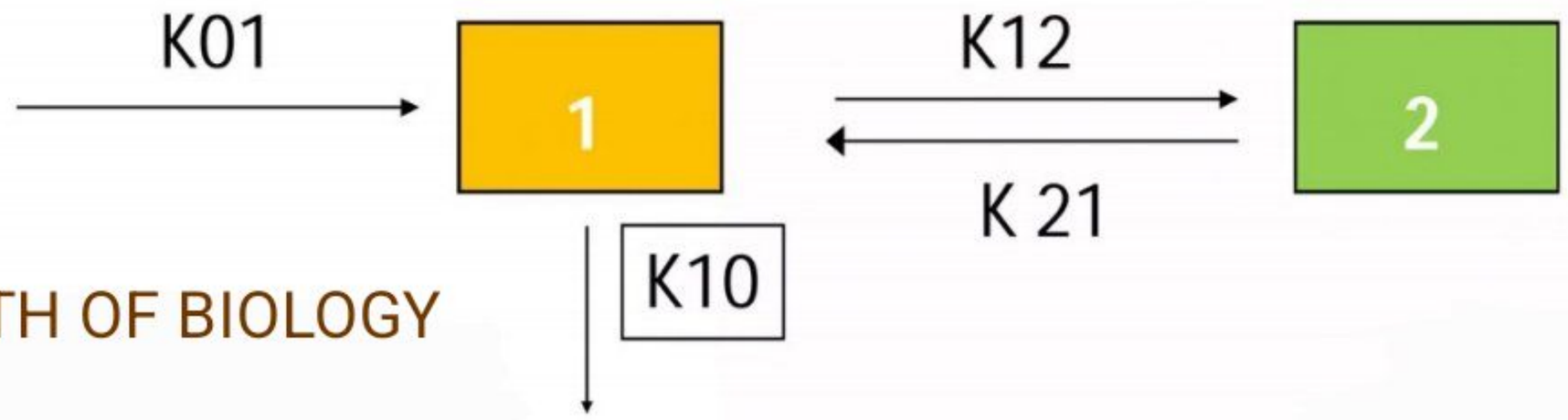


Model 2 One-compartment open model, extravascular administration.

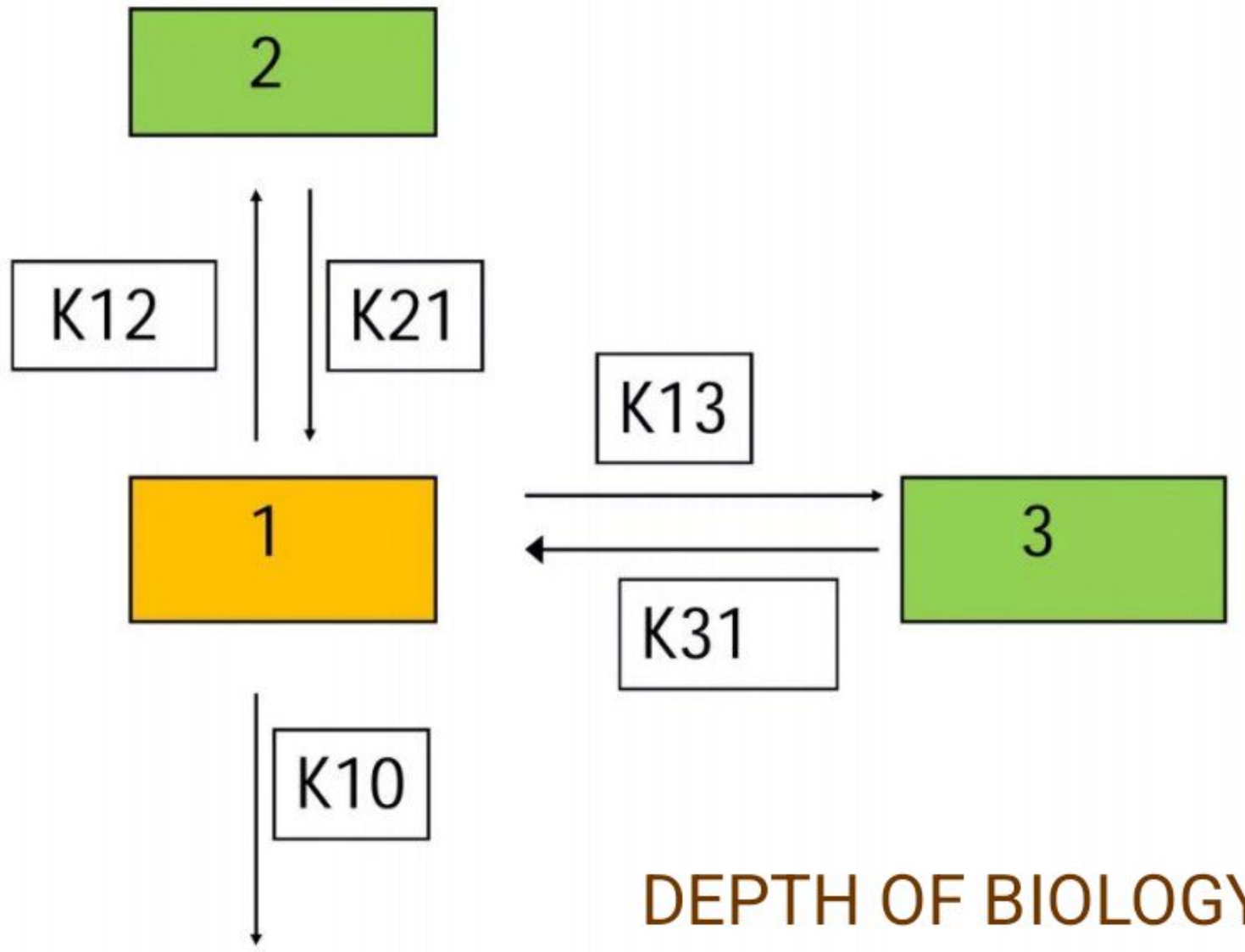
Model 3 Two-compartment open model , intravenous bolus administration.



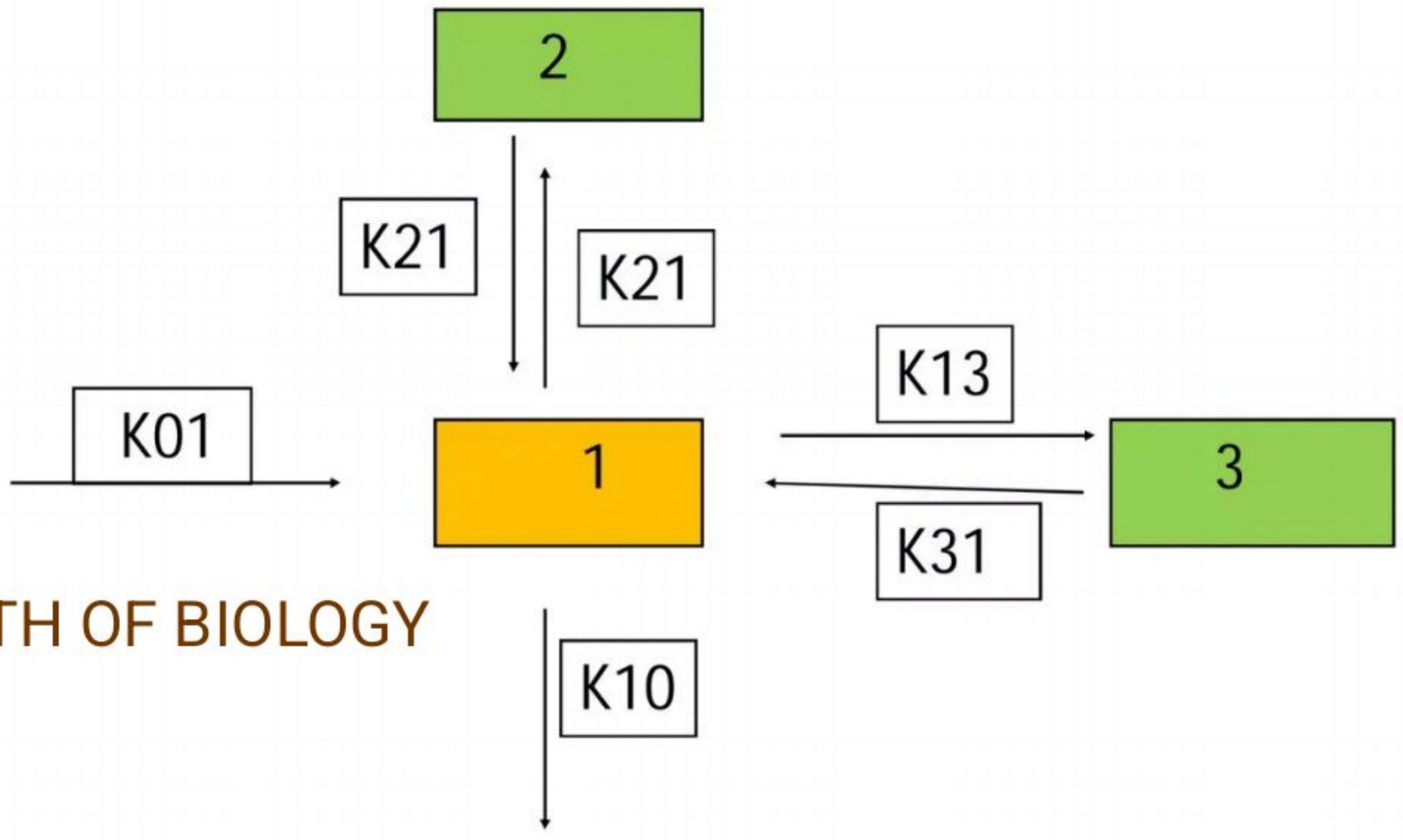
Model 4 Two-compartment open model , extravascular administration.



Model 5 Three-compartment open model, intravenous administration.



Model 6→Three-compartment open model, extravascular administration.



CATENARY MODEL

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- In this model, the compartments are joined to one another in a series like compartments of a train.

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This is however not observable physiologically/anatomically as the various organs are directly linked to the blood compartment. Hence this model is rarely used.

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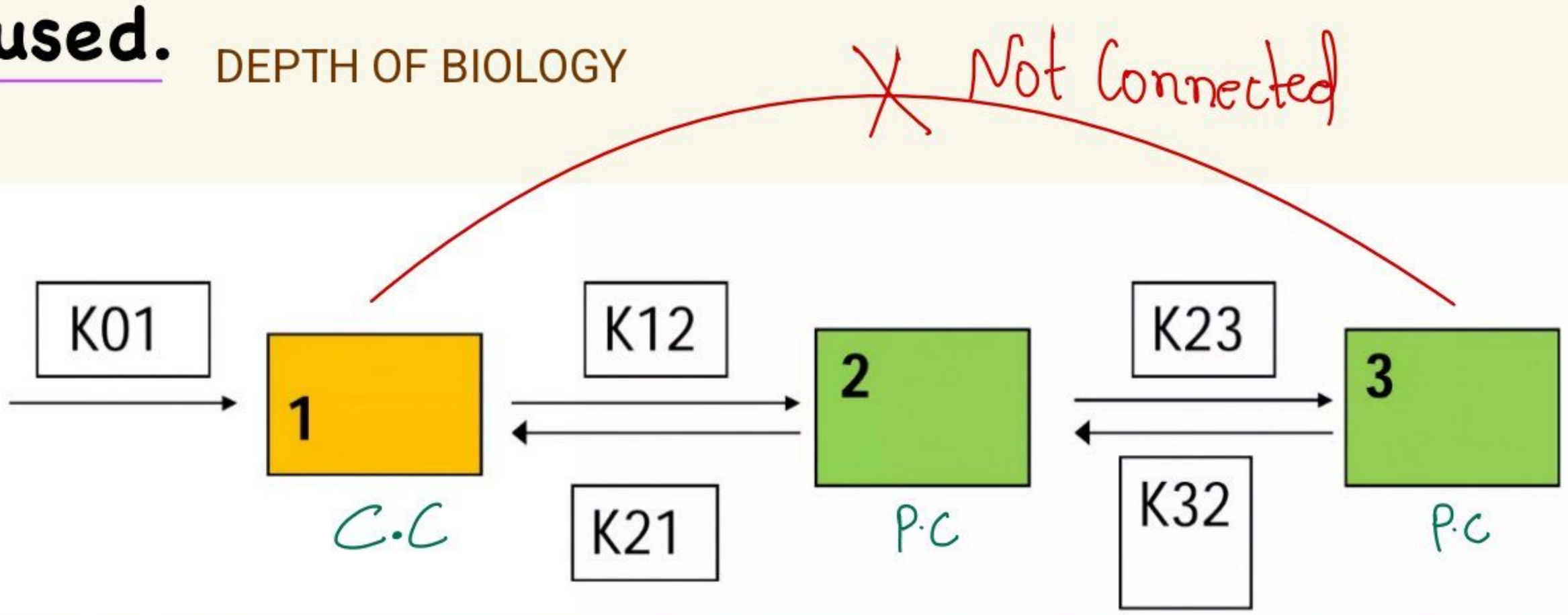

The compartment modelling approach has several advantages and applications –

1. It is a simple and flexible approach and thus widely used. Fundamentally, the principal use of this approach is to account for the mass balance of drug in plasma, drug in extravascular tissues and the amount of drug eliminated after its administration. It often serves as a –first-modelll.

2. It gives a visual representation of various rate processes involved in drug disposition.

3. It shows how many rate constants are necessary to describe these processes.

4. It enables the pharmacokineticist to write differential equations for each of the rate processes in order to describe drug-concentration changes in each compartment.

5. It enables monitoring of drug concentration change with time with a limited amount of data. Only plasma concentration data or urinary excretion data is sufficient.

6. It is useful in predicting drug concentration-time profile in both normal physiological and in pathological conditions.

7. It is important in the development of dosage regimens.

8. It is useful in relating plasma drug levels to therapeutic and toxic effects in the body.

9. It is particularly useful when several therapeutic agents are compared. Clinically, drug data comparisons are based on compartment models.

10. Its simplicity allows for easy tabulation of parameters such as Vd, t½, etc.

Disadvantages of compartment modelling include —

1. The compartments and parameters bear no relationship with the physiological functions or the anatomic structure of the species; several assumptions have to be made to facilitate data interpretation.

2. Extensive efforts are required in the development of an exact model that predicts and describes correctly the ADME of a certain drug.

3. The model is based on curve fitting of plasma concentration with complex multiexponential mathematical equations.

4. The model may vary within a study population.

5. The approach can be applied only to a specific drug under study.

6. The drug behaviour within the body may fit different compartmental models depending upon the route of administration.

7. Difficulties generally arise when using models to interpret the differences between results from human and animal experiments.

8. Owing to their simplicity, compartmental models are often misunderstood, overstretched or even abused.

Because of the several drawbacks of and difficulties with the classical compartment modelling, newer approaches have been devised to study the time course of drugs in the body. They are — physiological models and noncompartmental methods.

PHYSIOLOGICAL MODEL

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- They are drawn on the basis of known anatomical and physiological data

- So it present more realistic picture of drug disposition in various organs and tissues.

- Tissues with similar perfusion properties are grouped into a single compartment

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- e.g. lungs, liver, brain and kidney are grouped as rapidly equilibrating tissues (RET)

- While muscles and adipose as slowly equilibrating tissues (SET).

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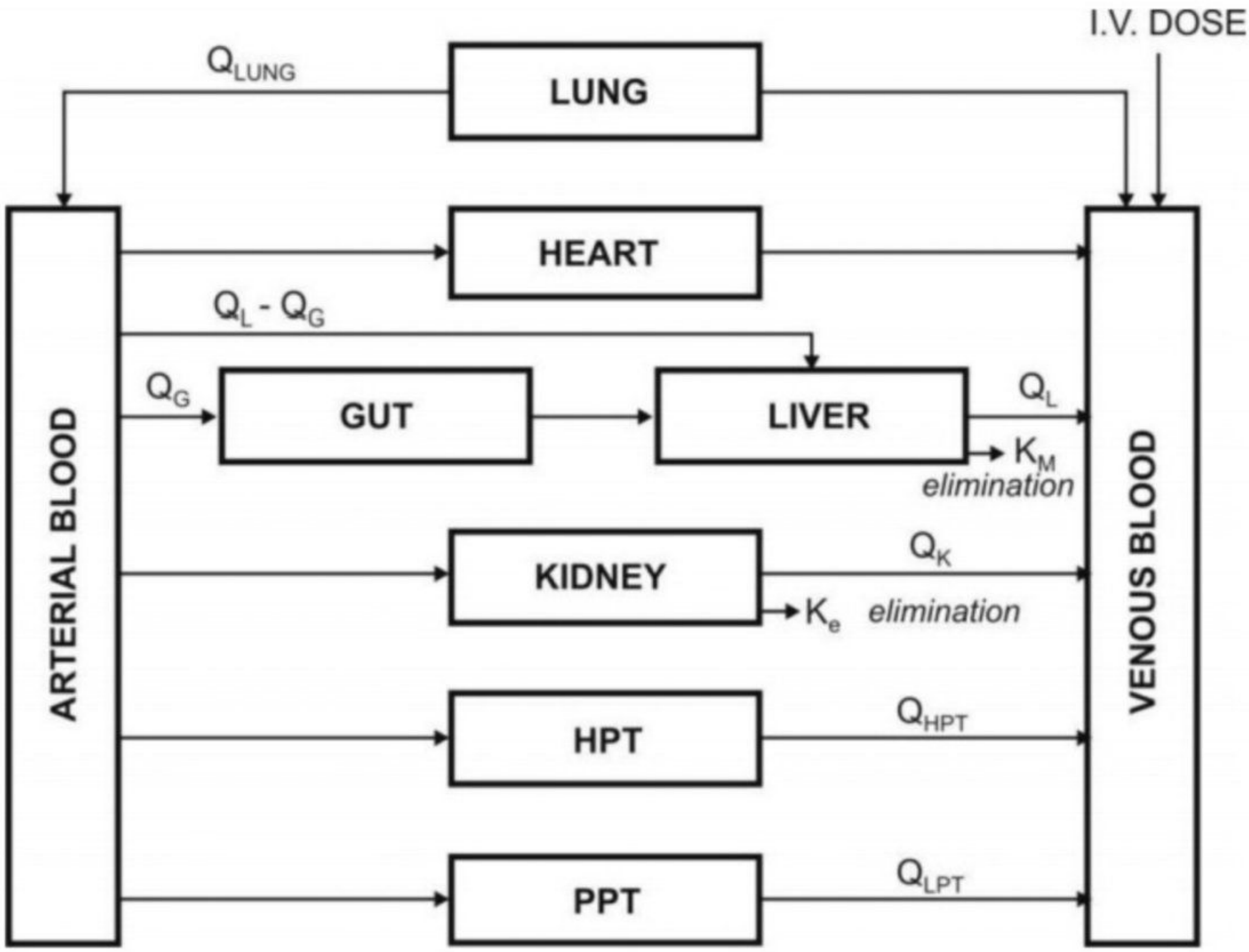

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Schematic representation of a physiological pharmacokinetic model. The term Q indicates blood flow rate to a body region. HPT stands for other highly perfused tissues and PPT for poorly perfused tissues. Km is rate constant for hepatic elimination and Ke is first-order rate constant for urinary excretion.

Since the rate of drug carried to a tissue organ and tissue drug uptake are dependent upon two major factors- DEPTH OF BIOLOGY

DEPTH OF BIOLOGY

- Rate of blood flow to the organ, and
- Tissue/blood partition coefficient or diffusion coefficient of drug that governs its tissue permeability,

The physiological models are further categorized into two types -

1. 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.

2. 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.

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Physiological modelling has several advantages over the conventional compartment modelling –

1. Mathematical treatment is straight forward.

2. Since it is a realistic approach, the model is suitable where tissue drug concentration and binding are known.

3. Data fitting is not required since drug concentration in various body regions can be predicted on the basis of organ or tissue size, perfusion rate and experimentally determined tissue-to-plasma partition coefficient.

4. The model gives exact description of drug concentration-time profile in any organ or tissue and thus better picture of drug distribution characteristics in the body.

5. The influence of altered physiology or pathology on drug disposition can be easily predicted from changes in the various pharmacokinetic parameters since the parameters correspond to actual physiological and anatomic measures.

6. The method is frequently used in animals because invasive methods can be used to collect tissue samples.

7. Correlation of data in several animal species is possible and with some drugs, can be extrapolated to humans since tissue concentration of drugs is known.

8. Mechanism of ADME of drug can be easily explained by this model.

Disadvantages of physiological modelling include —

1. Obtaining the experimental data is a very exhaustive process.

2. Most physiological models assume an average blood flow for individual subjects and hence prediction of individualized dosing is difficult.

3. The number of data points is less than the pharmacokinetic parameters to be assessed.

4. Monitoring of drug concentration in body is difficult since exhaustive data is required

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