UNIT- V

07 Hours

Nonlinear Pharmacokinetics: a. Introduction, b. Factors causing Non-linearity.

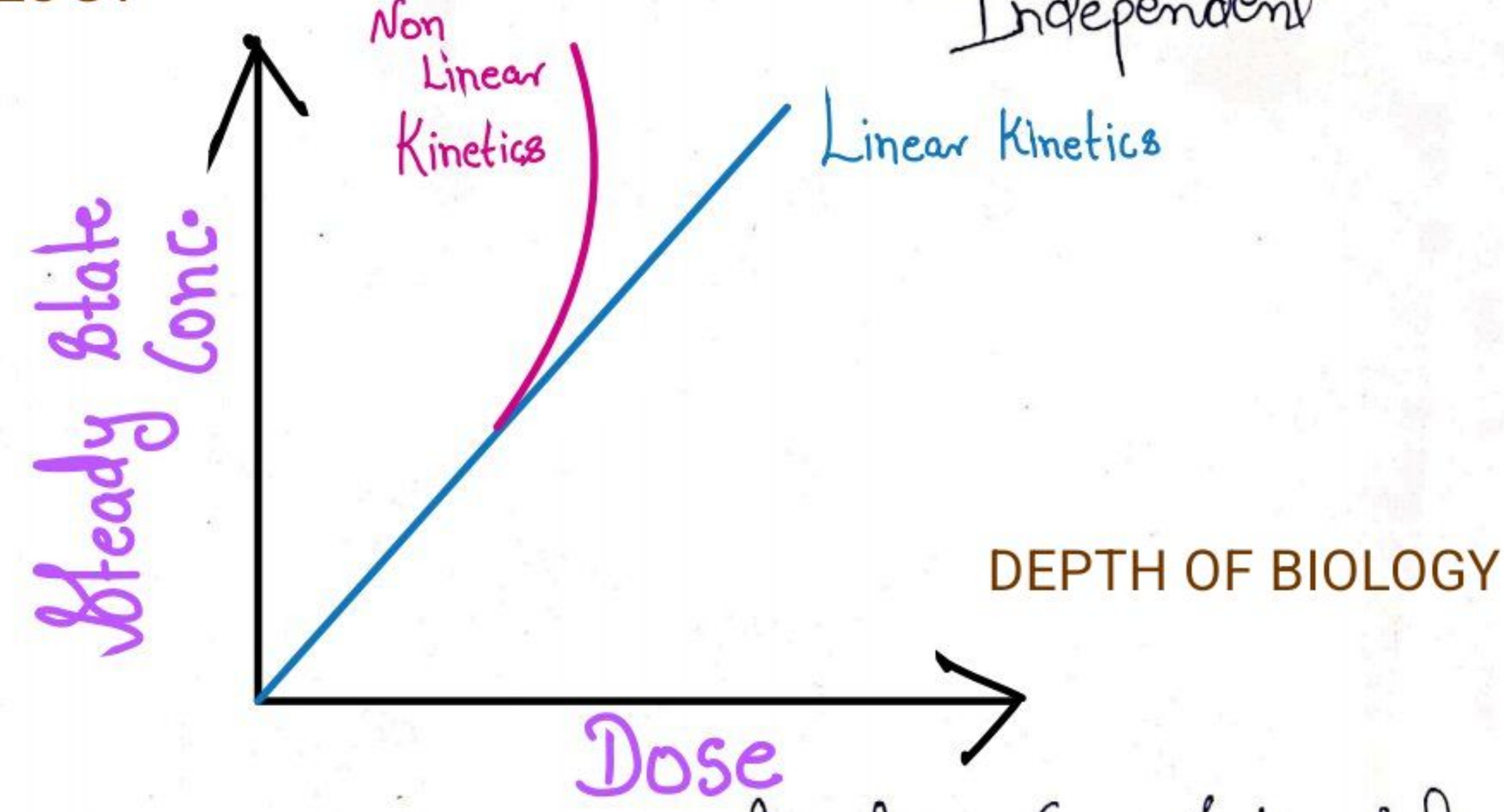
c. Michaelis-menton method of estimating parameters, Explanation with example of drugs.

☆ Linear Pharmacokinetic → follow First Order Kinetics.

Here plasma drug Conc. ∝ Dose (either Single or Multiple dose)

☆ In this Case the Pharmacokinetic parameter like K_E, Ka, Vd, Cl_R, Cl_H which describe the time Course of drug in body → remain Unaffected by dose

So, the Linear Pharmacokinetic is ☆ Dose Independent.



#Non-Linear Pharmacokinetic or Mixed order, Capacity Limited Kinetics, Dose dependent.

☆ Here Pharmacokinetic Parameter Change with the Size of the administered Dose.

Non-Linear Pharmacokinetics.

OR

Dose Dependent Pharmacokinetics.

Linear Pharmacokinetics →

In Most Cases at Therapeutic dose →

→ Change in amount of drug in body

→ Change in it's plasma Concentration due to

-Absorbtion -Distribution -Metabolism

-Binding. -Excretion.

is directly propotional to dose (administered as a single dose Or as Multiple dose).

In this Case First Order or Linear kinetics follow.

☆ And in this Case all Semi-Log plot C v/s t are Super Imposable.

In Some Cases ⇒ (Non linear Pharmacokinetics).

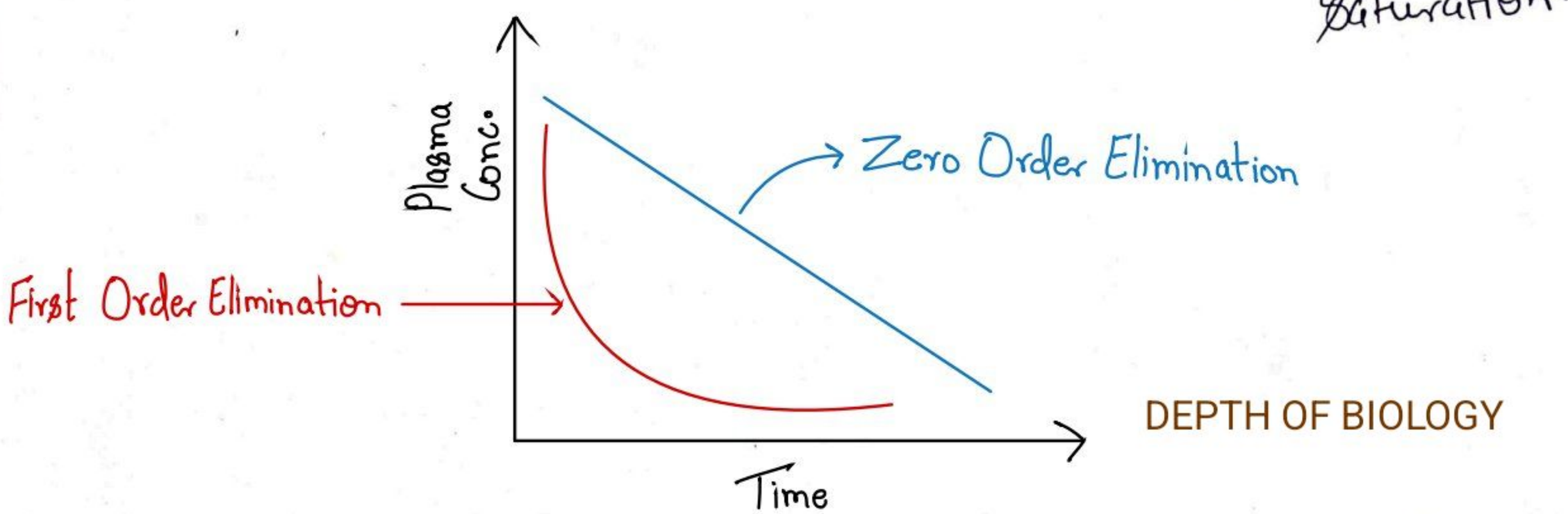
The Rate process of drug A,D,M,E (depends on Carrier or Enzyme).

☆ This Enzyme are Substrate Specific. (substance on which enzyme act).

☆ This Enzyme are Susceptible to Saturation at High drug Concn.

In Such Cases, when enzyme are susceptible to saturation at High drug Concentration. First Order kinetics transform into a Mixture of first Order & zero Order rate processes.

↳ Seen after Enzyme Saturation.



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& the Pharmacokinetic parameter Change with Size of administered dose. that's why it is also known as Dose dependent. The Pharmacokinetic of Such drug are dose dependent. & drug show Variability in their Pharmacological response.

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Characteristics of drug that show Saturation Kinetics

1. Elimination of drug does not follow Simple 1st Order kinetics i.e Elimination Kinetics are Non-Linear.

2. Elimination Half Life Changes as dose is ↑ed. (enzyme saturation)

3. Composition & ratio of the Metabolite of drug (affected by change in dose)

Examples →

(a) Phenytoin (b) Warfarin (c) Methotrexate

(d) Carbamazepine (e) Acetaminophin.

Test to detect Non-Linearity in Pharmacokinetic

1. Determination of Steady state. plasma Concentration at diff. doses.

If Steady State Concentration are directly Propotional to the dose then Linearity in kinetic Exist.

& Such proportionality is not observed when there is Non-Linearity

2. Determination of some of the Important Pharmacokinetic Parameter Such as. Elimination Half Life, Cl_T at different dose of drug any Changes in these parameters.

Indicate Non-Linearity.

Factors causing Non-linearity.

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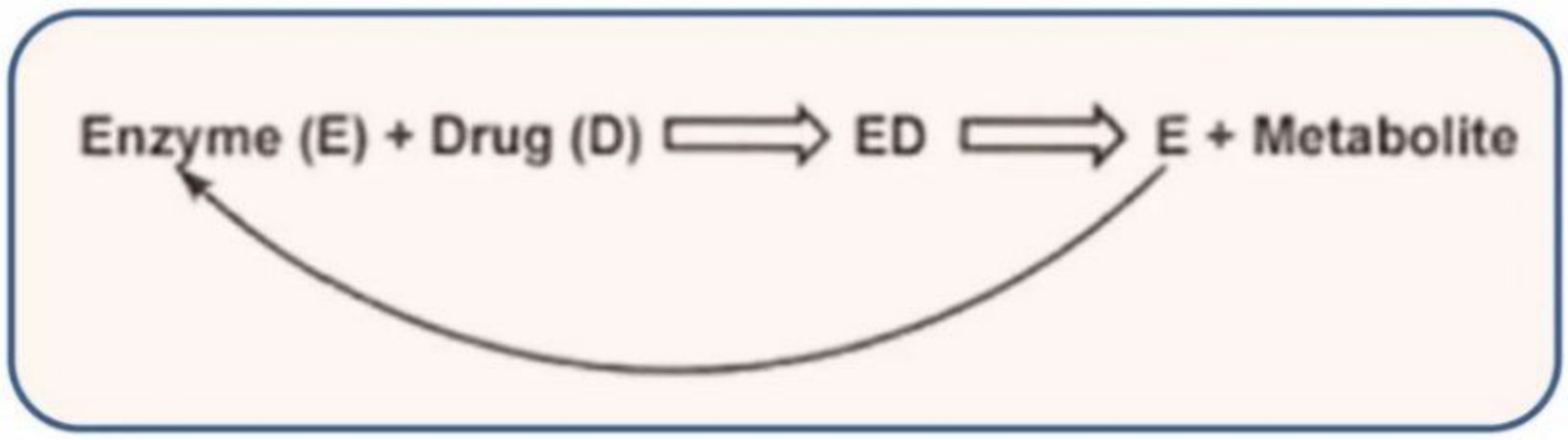
- Capacity-Limited Metabolism:
  - Capacity-limited metabolism is also called saturable metabolism, Michaelis-Menten kinetics, or mixed-order kinetics. The process of enzymatic metabolism of drugs may be explained by the relationship depicted in Figure:



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  - Figure explains Interaction of drug and enzyme based on the MichaelisMenten kinetics.

Factors causing Non-linearity.

- First, the drug interacts with the enzyme to produce a drug-enzyme intermediate. Then, the intermediate complex is further processed to produce a metabolite and release the enzyme. The released enzyme is recycled back to react with more drug molecules

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Causes of Nonlinearity

- Nonlinearity can occur in

1. Drug Absorption
2. Drug Distribution
3. Drug metabolism
4. Drug Excretion

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Causes of Nonlinearity

1. Drug Absorption

Three causes:

I) Solubility / dissolution of drug is rate-limited; Griseofulvin - at high concentration in intestine.

II) Carrier - mediated transport system; Ascorbic acid, - saturation of transport system. → Cause Non-Linearity.

Riboflavin, Cyanocobalamin.

III) Presystemic gut wall / hepatic metabolism attains saturation; Propranolol.

↓ Use Bioavaibility.

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Causes of Nonlinearity

2. Drug Distribution

- At high doses non-linearity due to

Two causes:

I) Binding sites on plasma proteins get saturated; Phenylbutazone.

II) Tissue binding sites get saturated.

- In both cases there is increase in plasma drug concentration.
- Increase in V_d only in (I)

Causes of Nonlinearity

3. Drug metabolism

- Non-linearity occurs due to capacity limited metabolism, small changes in dose administration - large variations in plasma concentration at steady state - large intersubject variability.
- Two imp causes:

I) Capacity - limited metabolism - enzyme &/ cofactor saturation; Phenytoin, Alcohol.

II) Enzyme induction - decrease in plasma concentration; Carbamazepine.

Clearance ↑

C_{ss} ↓

Causes of Nonlinearity DEPTH OF BIOLOGY

4. Drug Excretion

After Saturation of Carrier System → Clearance (↓)se.

Two active processes which are saturable,

I) Active tubular secretion - Penicillin G (Dose ↑).

II) Active tubular reabsorption - Water soluble vitamins & Glucose.

- Saturation of carrier systems - decrease in renal clearance in case of I & increase in II. Half life also increases.
- Other reasons like forced diuresis, change in urine pH, nephrotoxicity & saturation of binding sites.

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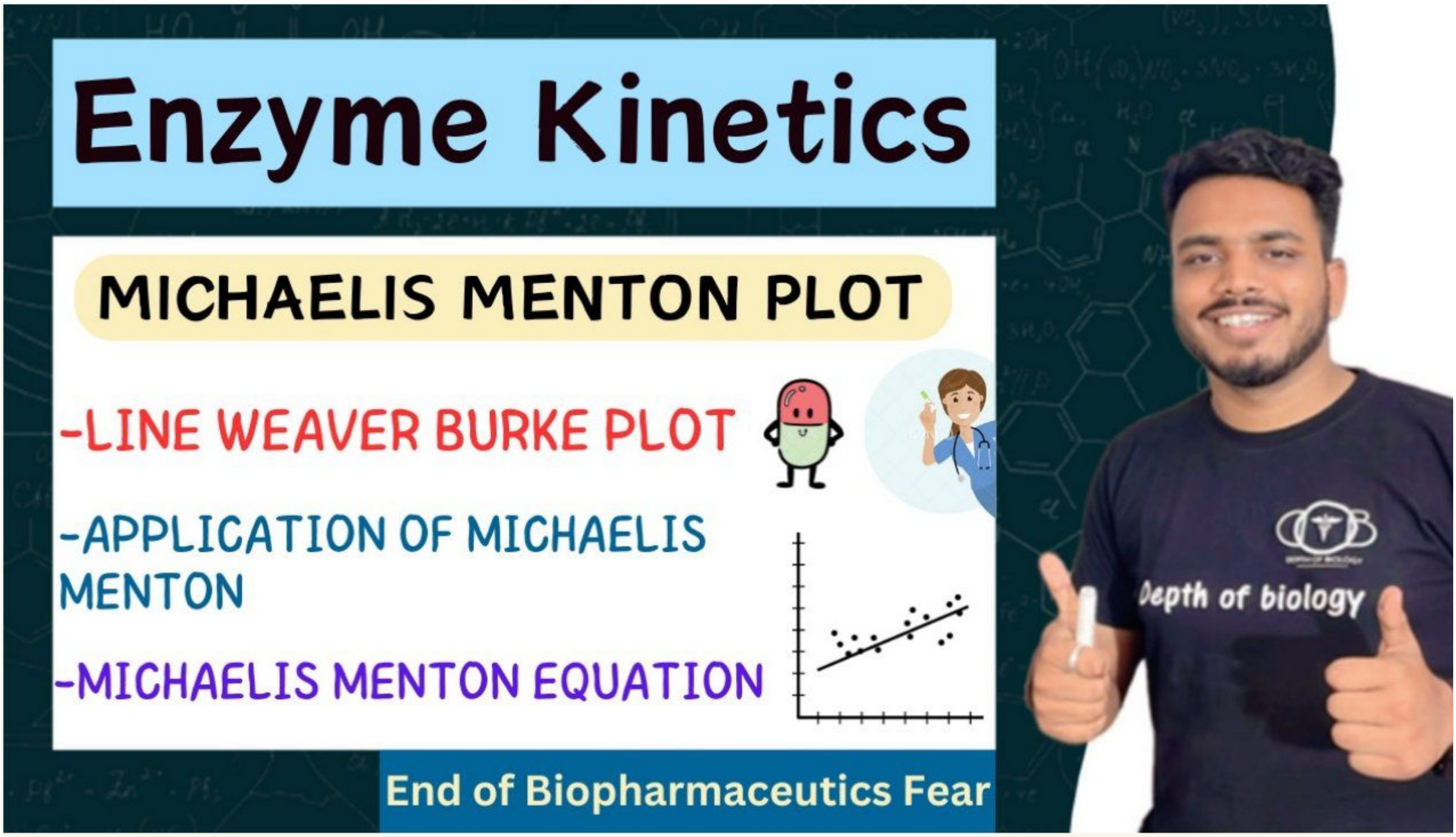


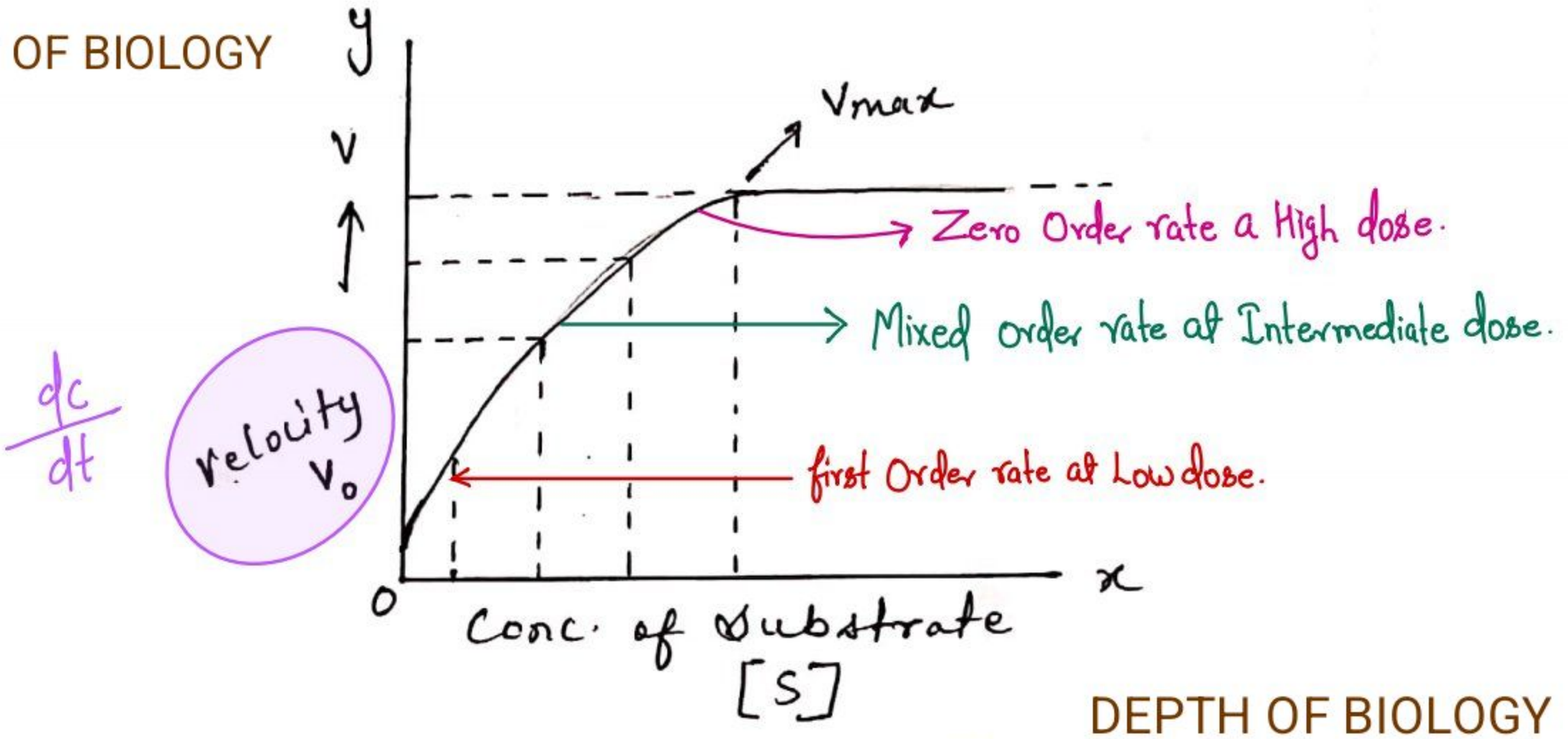
Michaelis Plot :-

With the Help of this We Can easily describe Non-Linear Pharmacokinetics.

Michaelis Menton equation :-

↳ Gives the relationship bet^n the velocity of rxn and the conc. of substrate.

⇒ [velocity ∝ [S] (molar conc. of substrate)]



$$[V_{max} = \text{Maximum velocity}]$$

$$\left[V_0 = \frac{V_{max} \times [S]}{K_m + [S]}\right]$$

- V_{max} → Max. Velocity
- K_m → Michaelis menton const.
- $[S]$ → Conc. of Substrate
- $-\frac{dc}{dt}$ → Rate of decline of drug Conc. With Time - Initial Velocity
- V_0

⇒ If substrate conc. 0 at initial stage then velocity is also 0.

[Initial velocity = V_0]

↓

Rate of rxn starts

and after Vmax, the graph become straight (constant).

⇓

In this condition, if we ↑se substrate conc., nothing will happen because after V_0 stage R.O.R is const.

Reverse the equation ⇒

$$\left[V_0 = \frac{V_{max} \times [S]}{K_m + [S]} \right]$$

$$\frac{1}{V_0} = \frac{K_m + [S]}{V_{max} \times [S]}$$

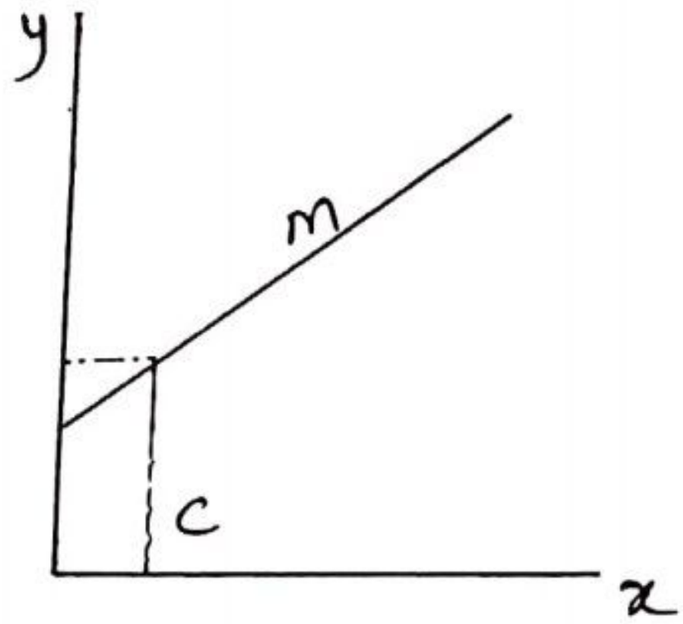
$$\frac{1}{V_0} = \frac{K_m}{V_{max} \times [S]} + \frac{\cancel{[S]}}{V_{max} \times \cancel{[S]}}$$

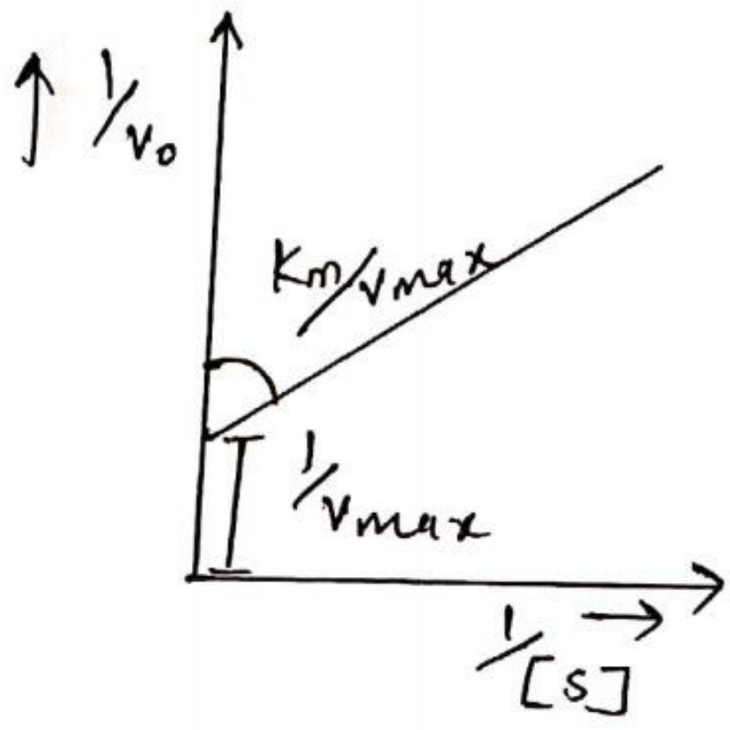
$$\frac{1}{V_0} = \frac{K_m}{V_{max} \times [S]} + \frac{1}{V_{max}}$$

$$\frac{1}{V_0} = \frac{K_m}{V_{max}} \times \frac{1}{[S]} + \frac{1}{V_{max}}$$

Compare this equation with $\Rightarrow [y = mx + c]$

$\left[y = \frac{1}{v_0}\right]$, $\left[m = \frac{K_m}{V_{max}}\right]$, $\left[x = \frac{1}{[S]}\right]$, $\left[c = \frac{1}{V_{max}}\right]$





Line weaver Burke plot :- Double reciprocal plot

$$\frac{1}{V_0} = \frac{K_m}{V_{max}} \times \frac{1}{[S]} + \frac{1}{V_m}$$

If $\left[\frac{1}{V_0} = 0\right]$

$$0 = \frac{K_m}{V_{max}} \times \frac{1}{[S]} + \frac{1}{V_m}$$

$$-\frac{1}{V_{max}} = \frac{K_m}{V_{max}} \times \frac{1}{[S]}$$

$\left(-\frac{1}{K_m} = \frac{1}{[S]}\right)$

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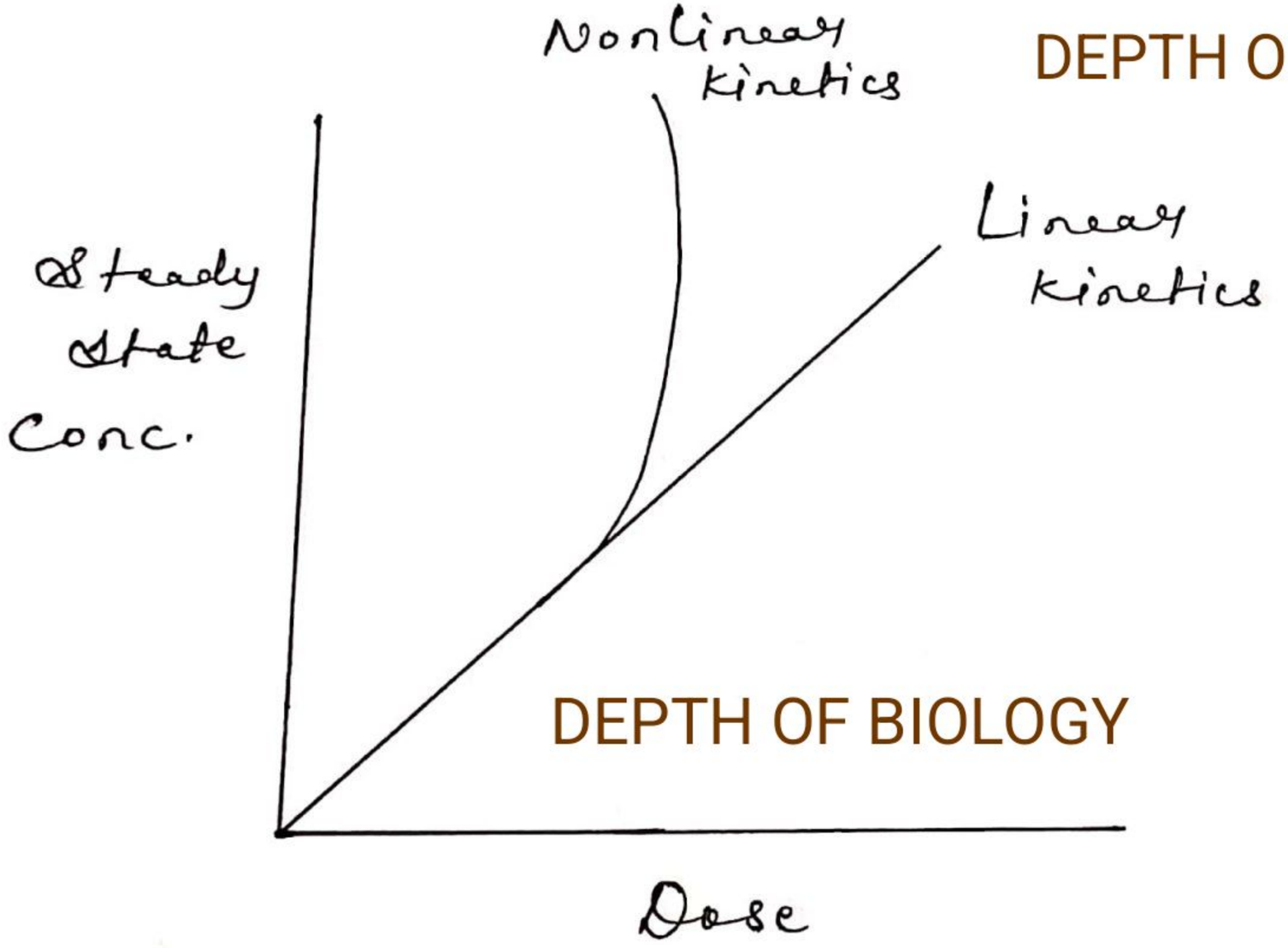

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