PK models and basic PK calculations

PK theory material lecture.2

Importance of PK

* Knowledge of the pharmacokinetic behavior of drugs in animals and human is crucial in drug development, both to make sense of preclinical toxicological and pharmacological data and to decide on an appropriate dose and dosing regimen for clinical trials.

* Drug regulators have developed concepts such as **bioavailability** and **bioequivalence** to support the licensing of generic versions of drugs produced when originator products lose patent protection.

Basic Pharmacokinetics and Pharmacokinetic model

- Drugs are in a dynamic state within the body as they move between tissues and fluids, bind with plasma or cellular components, or are metabolized. The biologic nature of drug distribution and disposition is complex, and drug events often happen simultaneously.

- Such factors must be considered when designing drug therapy regimens. The inherent and infinite complexity of these events requires the use of mathematical models and statistics to estimate drug dosing and to predict the time course of drug efficacy for a given dose.

PK models

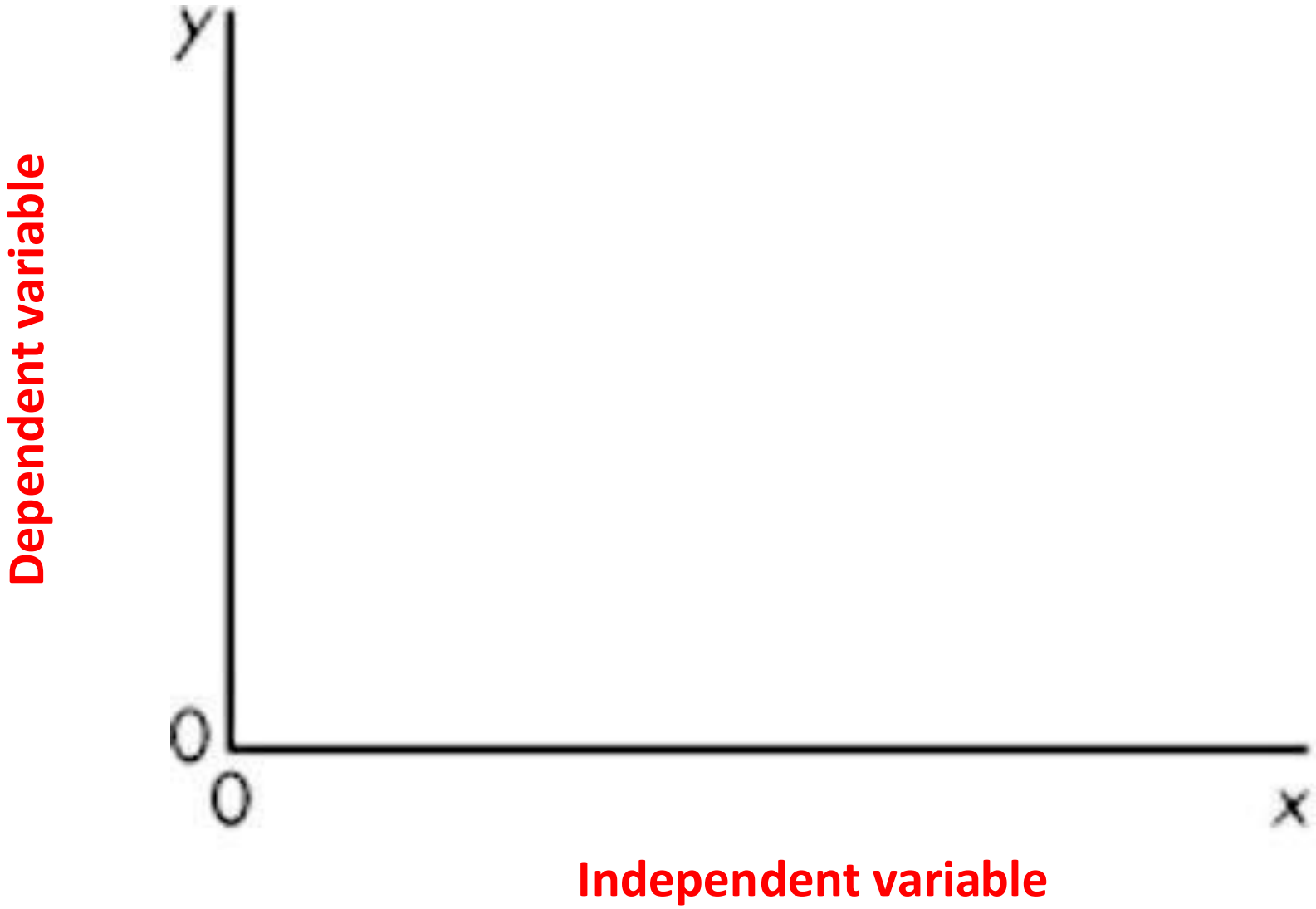
- Model: a hypothesis using mathematical terms to describe quantitative relationships concisely.

- Pharmacokinetic parameter: is a constant for the drug that is estimated from the experimental data.

Basic pharmacokinetics and pharmacokinetic model

- A pharmacokinetic function relates an independent variable to a dependent variable, often through the use of parameters.
- For example, a pharmacokinetic model may predict the drug concentration in the liver 1 hour after an oral administration of a 20-mg dose. The independent variable is the time and the dependent variable is the drug concentration in the liver. Based on a set of time-versus-drug concentration data, a model equation is derived to predict the liver drug concentration with respect to time.
- Such mathematical models can be used to describe and predict drug concentrations in the body as a function of time

Graphs



Compartmental PK

- Theoretically, an unlimited number of models may be constructed to describe the kinetic processes of drug absorption, distribution, and elimination in the body, depending on the degree of detailed information considered.

- A very simple and useful tool in pharmacokinetics is **compartmentally based models**.

- It is common and useful practice to divide objects of scientific interest into smaller conceptual units until the underlying mechanisms become apparent.

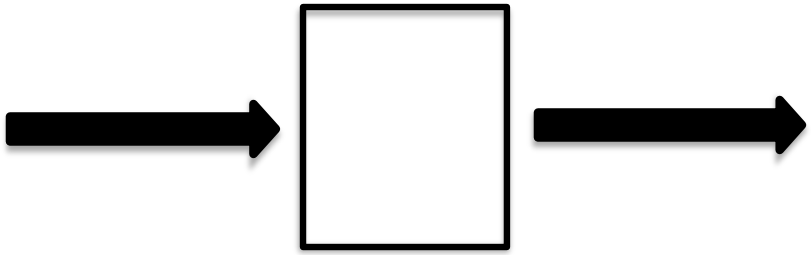
PK models

- Compartmental models are used, and they are simplified models in which the body is conceived to be composed of mathematically interconnected compartments (depicted as boxes)
- **Compartmental model are two types:**

  A. Empirically-based conventional models

  B. Physiologically-based pharmacokinetic (PBPK) models

Compartmentally-based model



* Simple
*The [drug] in the compartment for a given dose is determined by :

1 The fluid volume (V) of the comp.

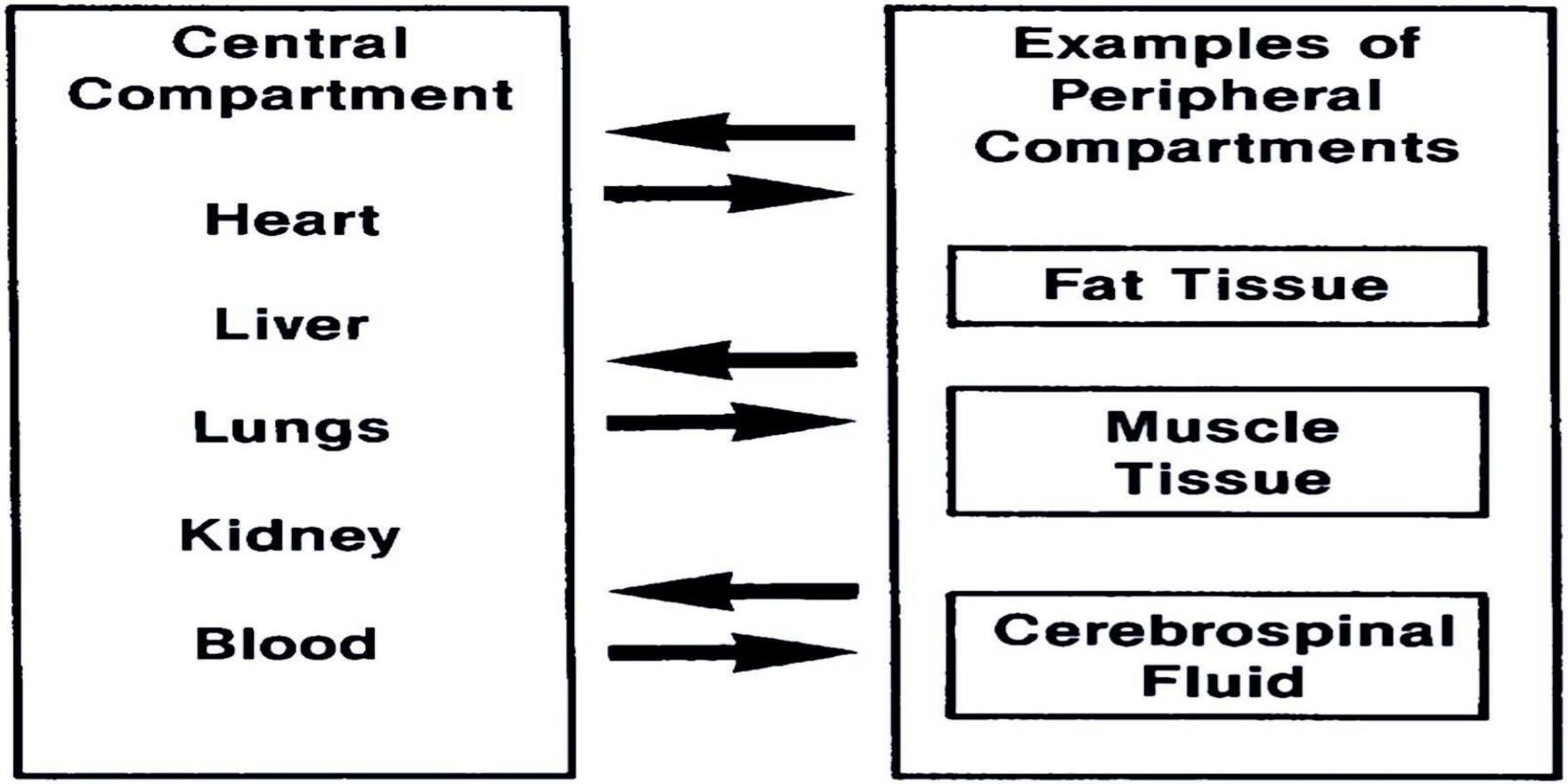
2 The elimination rate of drug per unit of time.

* One-compartment, two-compartment, or multi- compartment model.

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

Cont,

- Organs and tissues in which drug distribution is similar are grouped into one compartment.



Cont,

- Most PK models assume
  - instant homogeneous distribution of drug within each compartment "well-stirred"
  - and elimination rate constant does not change over time
- Model parameters (e.g. V and k) are determined experimentally from a set of drug concentrations collected over various times
- ⇧ parameters → ⇧complexity of the model
  - → ⇧ data needed
- Compartmental PK models are useful esp. when little information is known about the tissues

Mathematical review

- Do you know?/ Can you?
- The units used usually for concentration?
- Calculate the amount of the drug in a solution with a known drug concentration and solution volume? In different volumes?
- **How to convert units?**
- e.g. mg/mL to g/L and µg/µL.
- Calculate the MW of the drug?
- Units of concentration in M?

cont

- If a known amount of drug was added and resulted in 0.6 mg/L (for example) concentration of the solution, what volume of water was in the container?

- For the following equation: (y=1.8x+2)

a.<u>Sketch</u> a plot of the equation.

b.If *x* = 0.5, what is *y*? Y = 2.9

c.If *y* = 4.6, what is *x*? X = 1.44

cont

- What is the slope of the line that connects the following two points?
- 1) x=5, y=8.6
- 2) X=0.6, y=4.5

SLOPE = 0.93

- Solve the following equations for *x*:
  - a. log x = 0.95 X = 8.9125
  - b. $e^{x} = 0.44$ X = - 0.82098
  - c. ln x = 1.22 X = 3.387

Basic exponent laws

- Expression: $N=b^x$

Laws of Exponents	Example
$a^x \cdot a^y = a^{x+y}$	$10^2 \cdot 10^3 = 10^5$
$(a^x)^y = a^{xy}$	$(10^2)^3 = 10^6$
$\frac{a^x}{a^y} = a^{x-y}$	$\frac{10^2}{10^4} = 10^{-2}$
$\frac{1}{a^x} = a^{-x}$	$\frac{1}{10^2} = 10^{-2}$
$\sqrt[y]{a} = a^{1/y}$	$\sqrt[3]{a} = a^{1/3}$

Logarithms

- If $N=b^x$, then $\log_b N= x$
- Common logarithms (log)= logarithms using base 10
- Natural logarithms (ln) use the base *e*

e ≈2.718

2.303 log N= ln N

- A logarithm does not have units = dimensionless

Laws of Logarithms

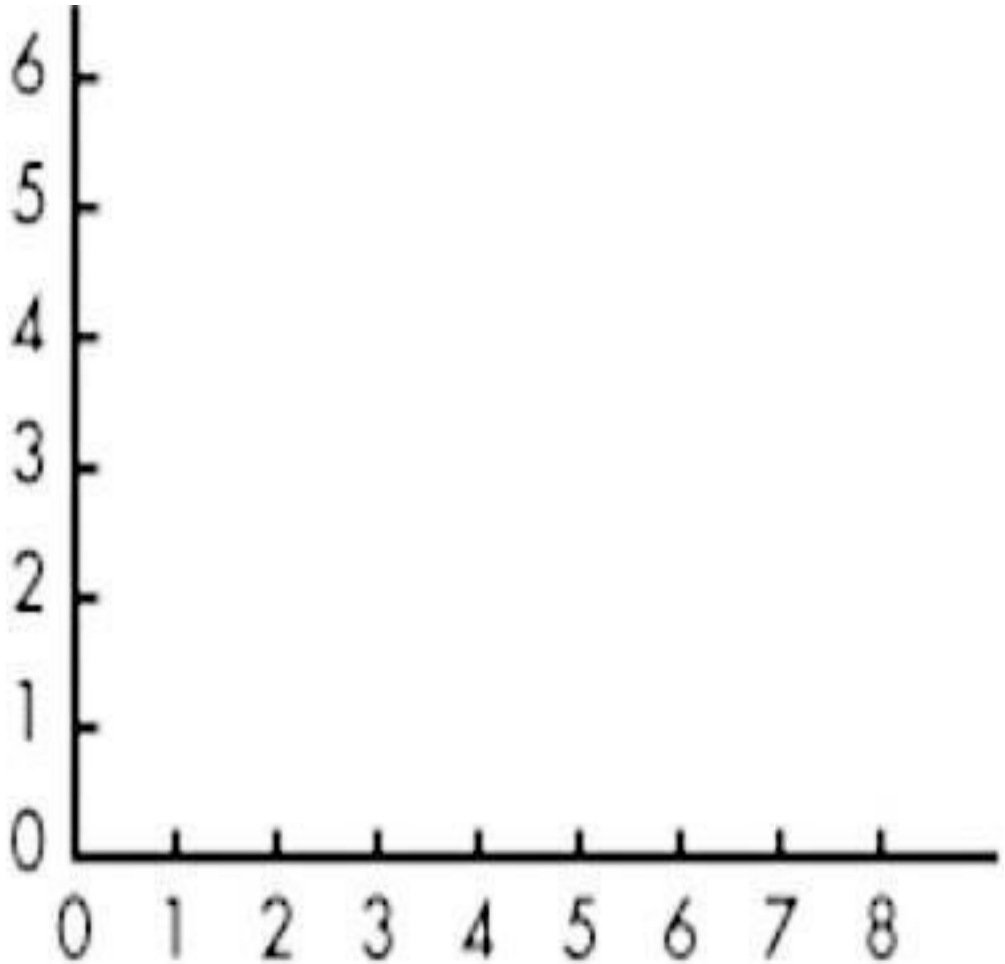
$$\log ab = \log a + \log b$$

$$\log \frac{a}{b} = \log a - \log b$$

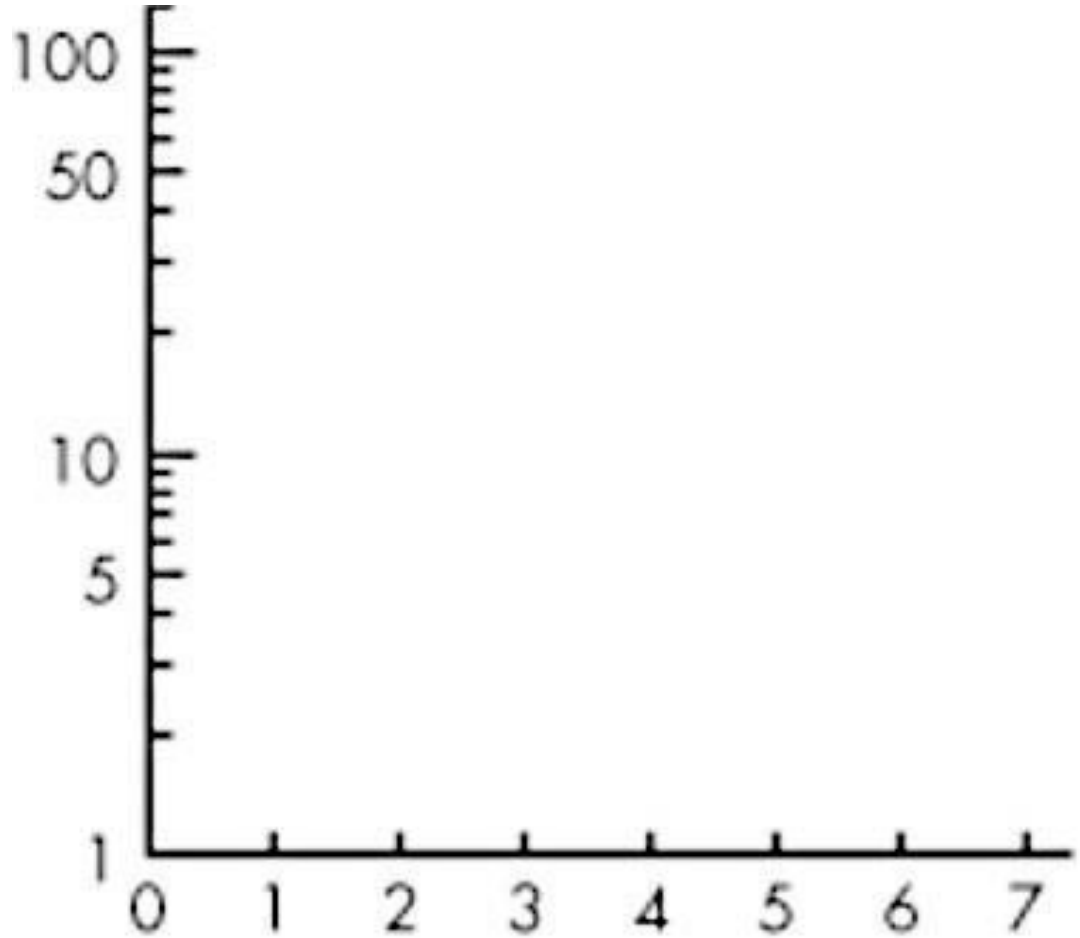
$$\log a^x = x \log a$$

$$-\log \frac{a}{b} = +\log \frac{b}{a}$$

- Your calculator → log, ln, anti-log and anti-ln



Rectangular coordinate graph



Semilog coordinate graph

cont

- Straight line eqt.

$$y = ax + b$$

- Slope? intercept?
- For a given straight line → calculate slope
  (on rectangular or semilog graph)
- **REMEMBER:**

In semilog graphs : the y values are plotted on a logarithmic scale **without** performing actual logarithmic conversions, whereas the corresponding x values are plotted on a linear scale

PK units

PARAMETER	SYMBOL	UNIT	EXAMPLE
Rate	$\frac{dD}{dt}$	$\frac{\text{Mass}}{\text{Time}}$	mg/hr
	$\frac{dc}{dt}$	$\frac{\text{Concentration}}{\text{Time}}$	μg/mL hr
Zero-order rate constant	k_0	$\frac{\text{Concentration}}{\text{Time}}$	μg/mL hr
		$\frac{\text{Mass}}{\text{Time}}$	mg/hr
First-order rate constant	k	$\frac{1}{\text{Time}}$	1/hr or hr^{-1}
Drug dose	D_0	Mass	mg
Concentration	C	$\frac{\text{Mass}}{\text{Volume}}$	μg/mL
Plasma drug concentration	C_p	$\frac{\text{Drug}}{\text{Volume}}$	μg/mL
Volume	V	Volume	mL or L
Area under the curve	AUC	Concentration × time	μg hr/mL
Fraction of drug absorbed	F	No units	0 to 1
Clearance	Cl	$\frac{\text{Volume}}{\text{Time}}$	mL/hr
Half-life	$t_{1/2}$	Time	hr

Rates and Orders of Reactions

- The rate of a chemical reaction of process is the velocity with which the reaction occurs. Consider the following chemical reaction:

Drug A ⇨ Drug B

- If the amount of drug A is decreasing with respect to time (that is, the reaction is going in a forward direction), then the rate of this reaction can be expressed as:

- dA/dt

- Since the amount of drug B is increasing with respect to time, the rate of the reaction can also be expressed as:

+ dB/dt

- The rate of a reaction is determined experimentally by measuring the disappearance of drug A at given time intervals.

Zero order reaction

- **Rate constants and order of Rx**
- Order of the Rx is the way that the [drug] affects the rate of the reaction or process
- Zero-order reactions or first-order reactions

$$- dA/dt = k*A^n$$

n → determine the rate of the reaction

* Zero order reaction

- Drug A is decreasing at a constant time interval t

n =0

$$dA/dt = - k_0*A^0$$

$$dA/dt = - k_0$$

k_0: is the zero-order rate constant

Unit of k_0 : **mass/time** (e.g. g/h)

$$dA/dt = -k_0$$

→Rearrange

→Integrate

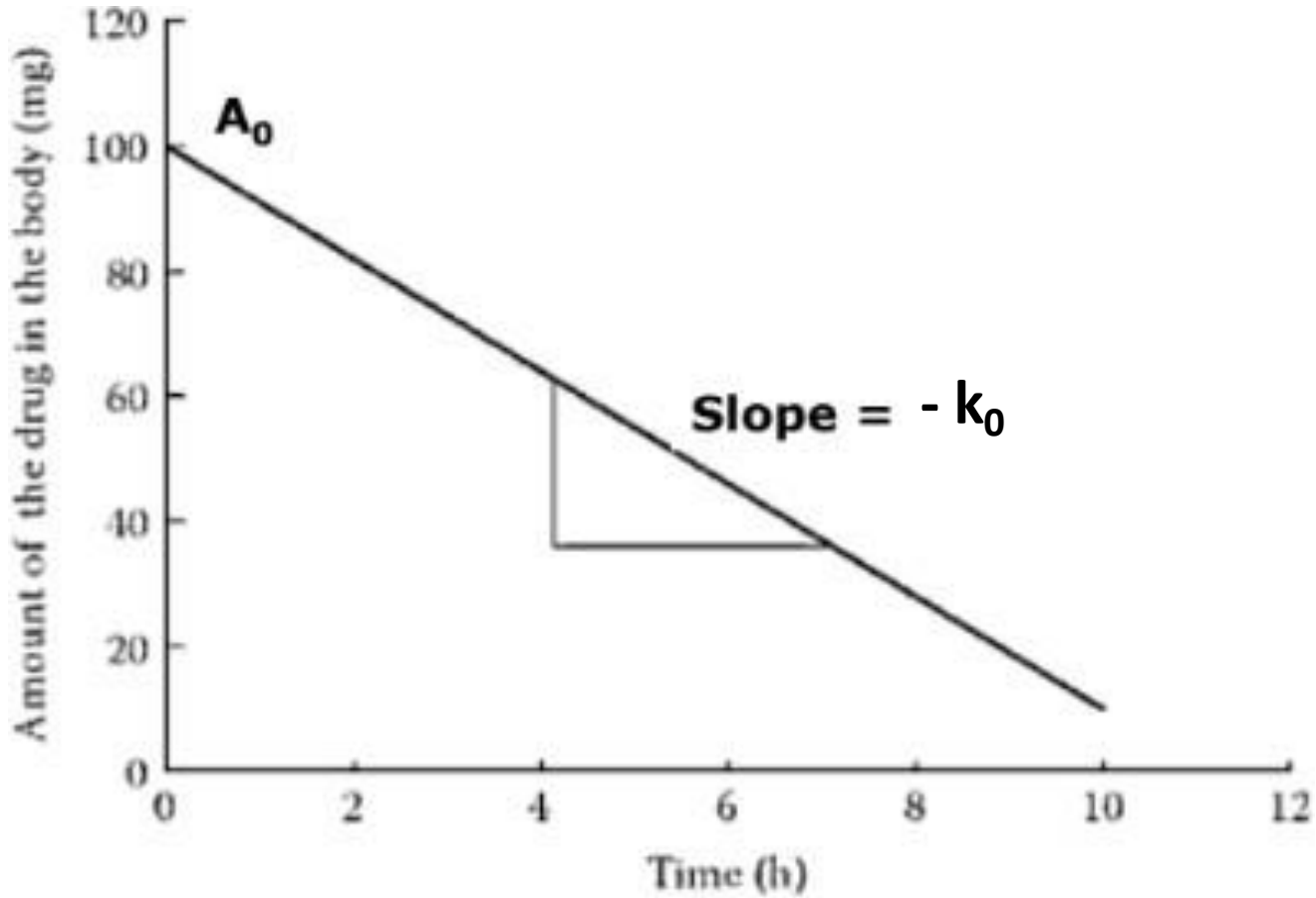
$$\boxed{A = -k_0 t + A_0}$$

A:

k_0:

A_0:

$$A = - k_0 t + A_0$$



Concentration → $C = - k_0 t + C_0$

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

- The period of time required for the amount (A) or concentration (C) of a drug to decrease by one- half.
- Zero-order half-life:

$$t_{1/2} = (0.5\ A_0) / k_0$$

- The zero-order $\mathbf{t_{1/2}}$ is proportional to the initial amount or concentration of the drug ($\mathbf{A_0}$) and is inversely proportional to the zero-order rate constant ($\mathbf{k_0}$).
- **The time required for the amount to decrease by one-half is NOT constant**

Zero-Order Reactions: example

- The administration of a 1000 mg of drug X resulted in the following concentrations:

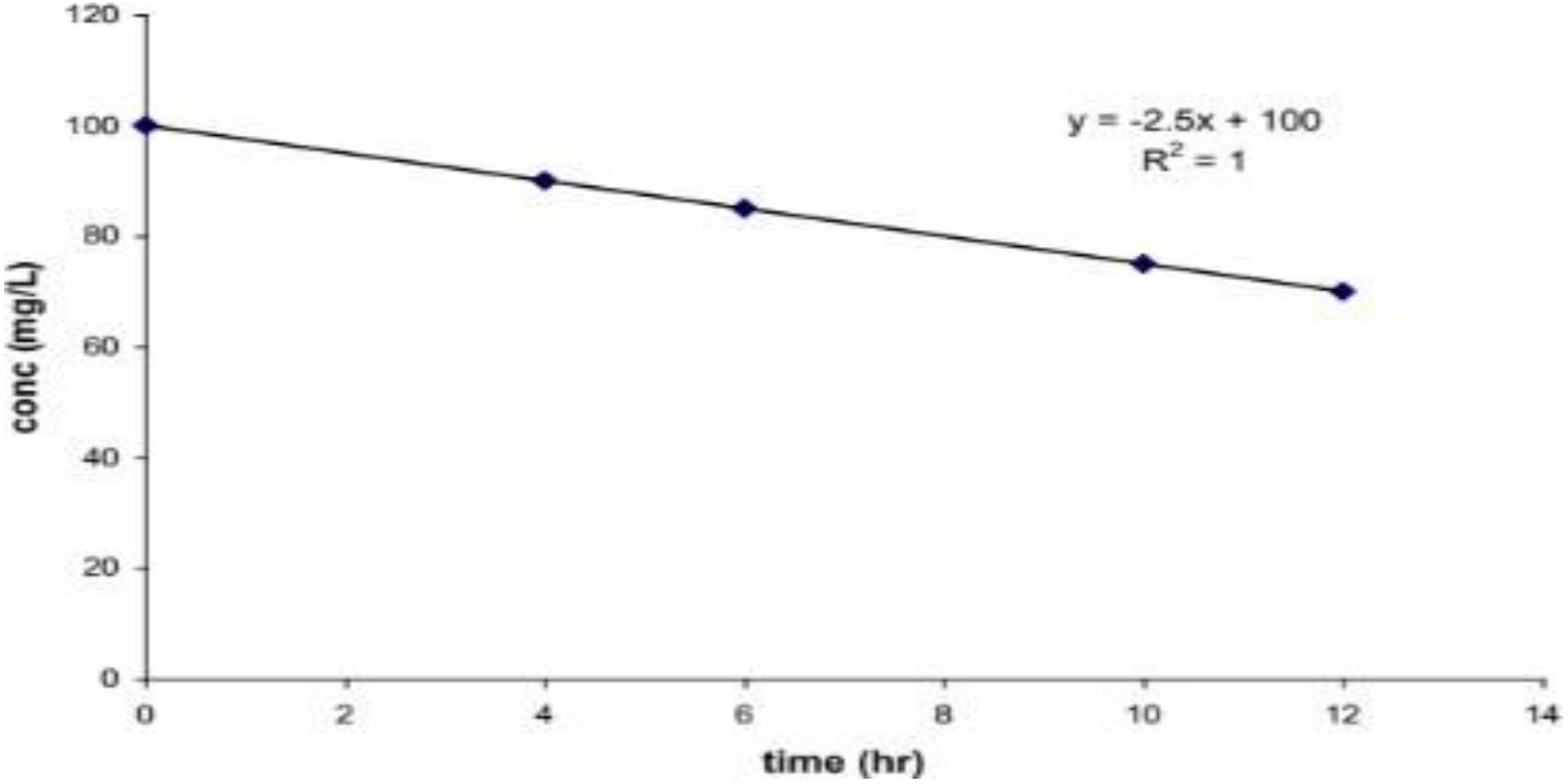
Time	Conc. (mg/L)
0	100
4	90
6	85
10	75
12	70

Zero-Order Reactions: example

- What is the order of the elimination process (zero or first)?

- What is the rate constant?

Zero-Order Reactions: example



Zero-Order Reactions: example

- Since the decline in drug conc. displayed a linear decline on normal scale, drug X has a zero order decline.

- From the equation displayed on the figure (intercept = 100, slope = -2.5)

- The elimination rate constant is 2.5 mg/hr

First order reaction

- If the amount of drug A is decreasing at a rate that is proportional to A, the amount of drug A remaining in the body, then the rate of elimination of drug A can be described as:

$$dA/dt = -k^*A^1$$

  - k: is the 1st order rate constant
  - Unit of k: 1/time (e.g. 1/h or h^{-1})

- The reaction proceeds at a rate that is dependent on the concentration of A present in the body.
- A first-order reaction is a reaction that proceeds at a rate that depends linearly on only one reactant concentration.
- It is assumed that the processes of ADME follow first-order reactions and **most drugs** are eliminated in this manner

First order reaction

- The amount of a drug with first order elimination is described according to the following equation:

$$A = A_0 e^{-k^* \cdot t}$$

where A is the amount of drug in the body, A_0 is the amount of the drug at time zero (equal to the dose in the case of IV bolus)

- This equation is equivalent to:

$$\ln(A) = \ln(A_0) - k^* \cdot t$$

- **$dA/dt = -k*A$**

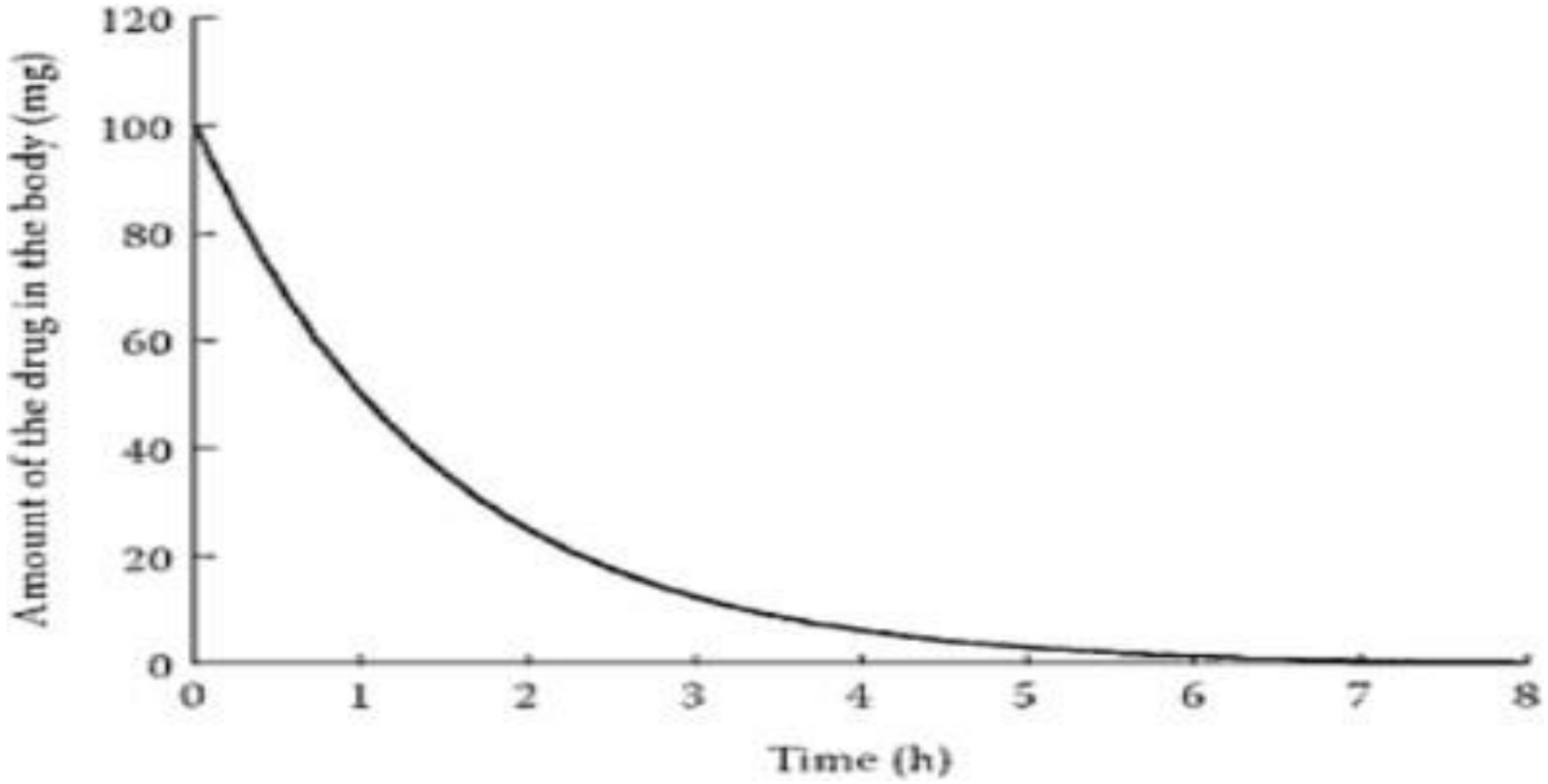
- $A = A_0 * e^{(-kt)}$.....[e]

- $\ln A = -k*t + \ln A_0$.....[ln]

- $\log A = -(k*t/2.303) + \log A_0$.....[log]

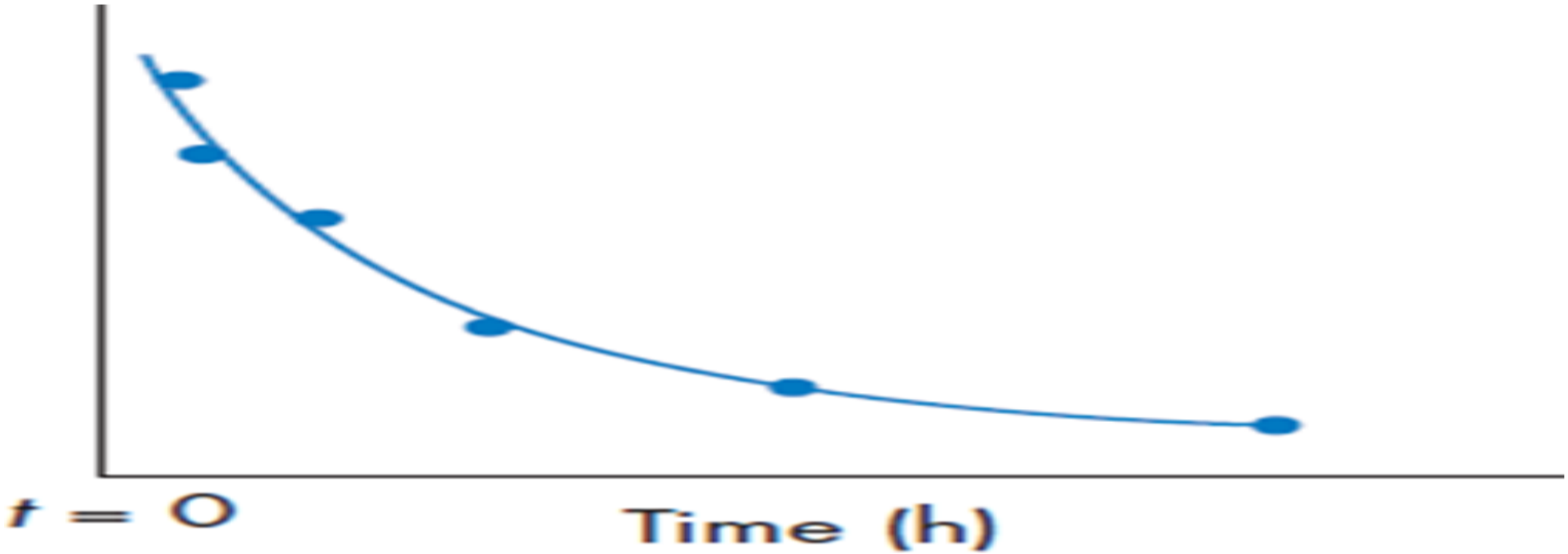
- **A, k, A0:**

Drug with first order kinetic



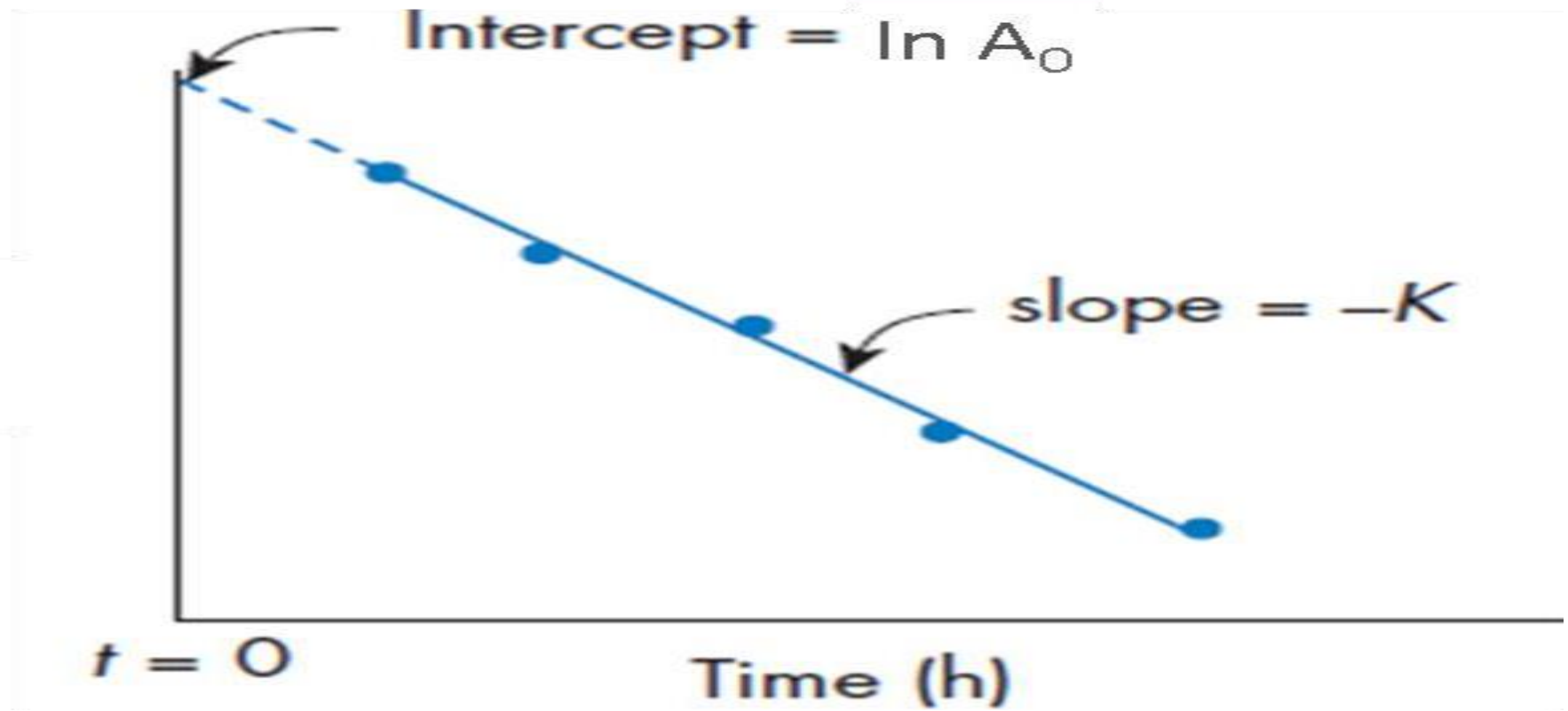
Rectangular coordinate graph

$$A = A_o * e^{(-kt)}$$



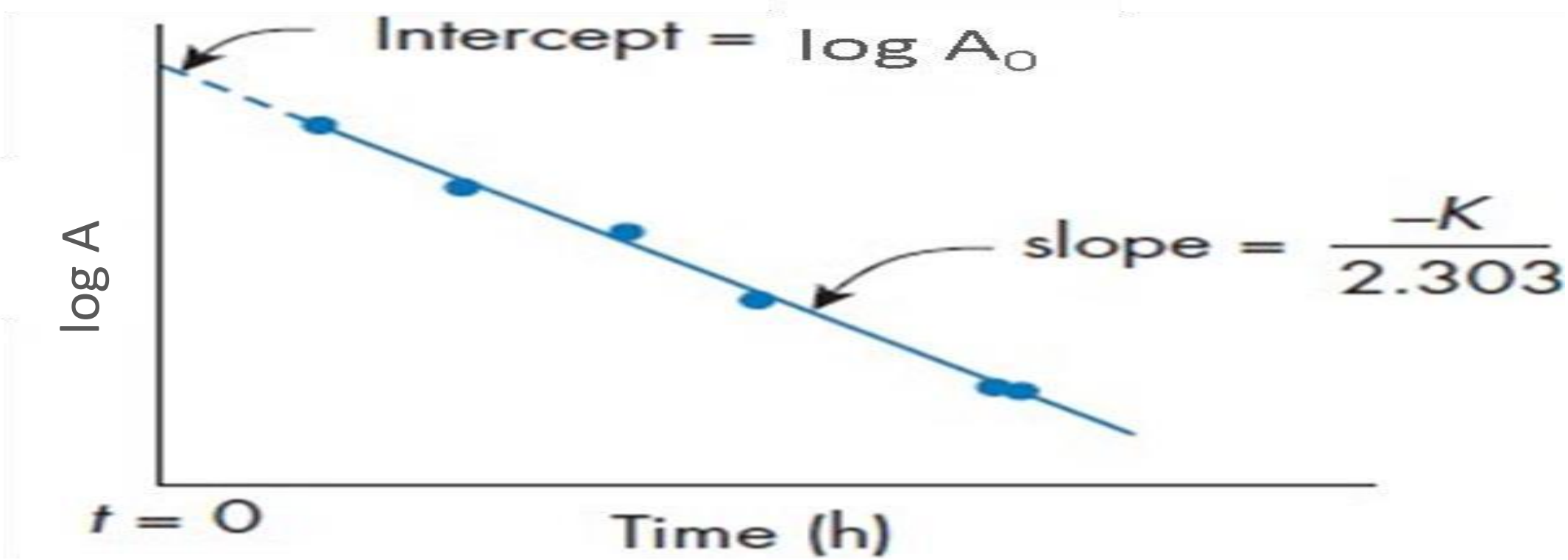
Semilog coordinate graph

$$\ln A = - k^{*}t + \ln A_o$$



Semilog coordinate graph

$$\log A = -(k*t/2.303) + \log A_0$$



cont

$$dC/dt = -k*C$$

$$C = C_0 * e^{(-kt)}$$

$$\ln C = -k*t + \ln C_0$$

$$\log C = -(k*t/2.303) + \log C_0$$

- **C, k, C0:**

cont

- The period of time required for the amount (A) or concentration (C) of a drug to decrease by one-half.

- First-order half-life:

$$t_{½} = 0.693 / k$$

- $t_{1/2}$ is a constant. No matter what the initial A or C
- **The time required for the amount to decrease by one-half is CONSTANT**

BEHIND EVERY SUCCESSFUL PERSON, THERE'S A LOT OF UNSUCCESSFUL YEARS

THANK YOU

ANY QUESTIONS?