Determination of pharmacokinetic parameters from plasma Data

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Introduction

- Most pharmacokinetic parameters can be measured from plasma data after oral or IV bolus dose
- These parameters include :
- AUC
- Cl
- K
- Vd
- F
- Abs. and elimination half life

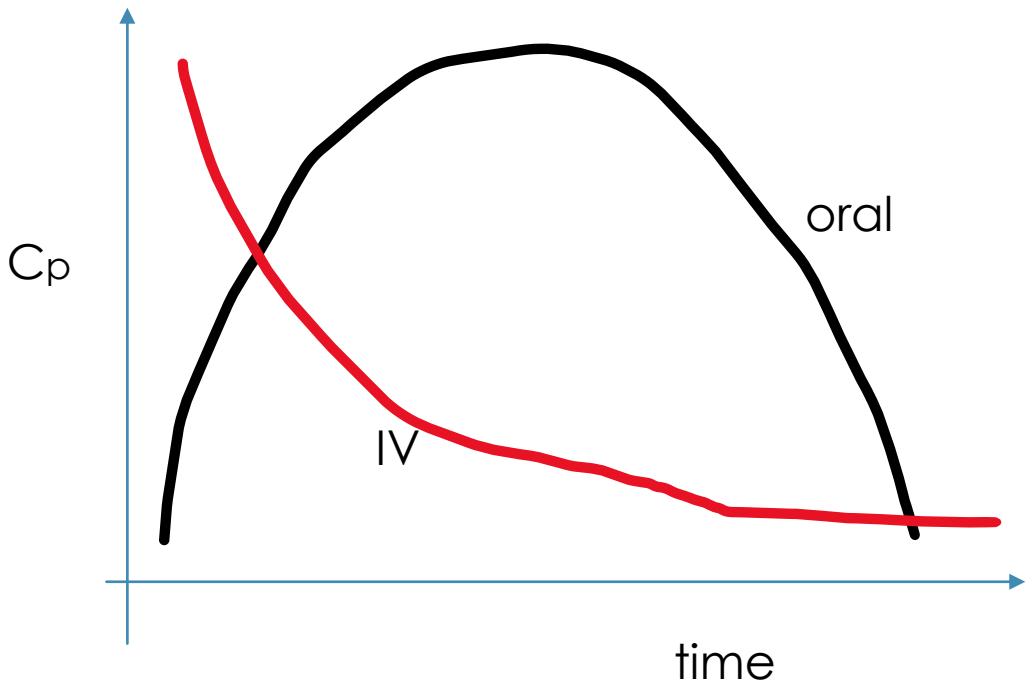
Bioavailability

- It indicates a measurement of the rate and extent (amount) of therapeutically active drug which reaches the systemic circulation

- Why it is important ??

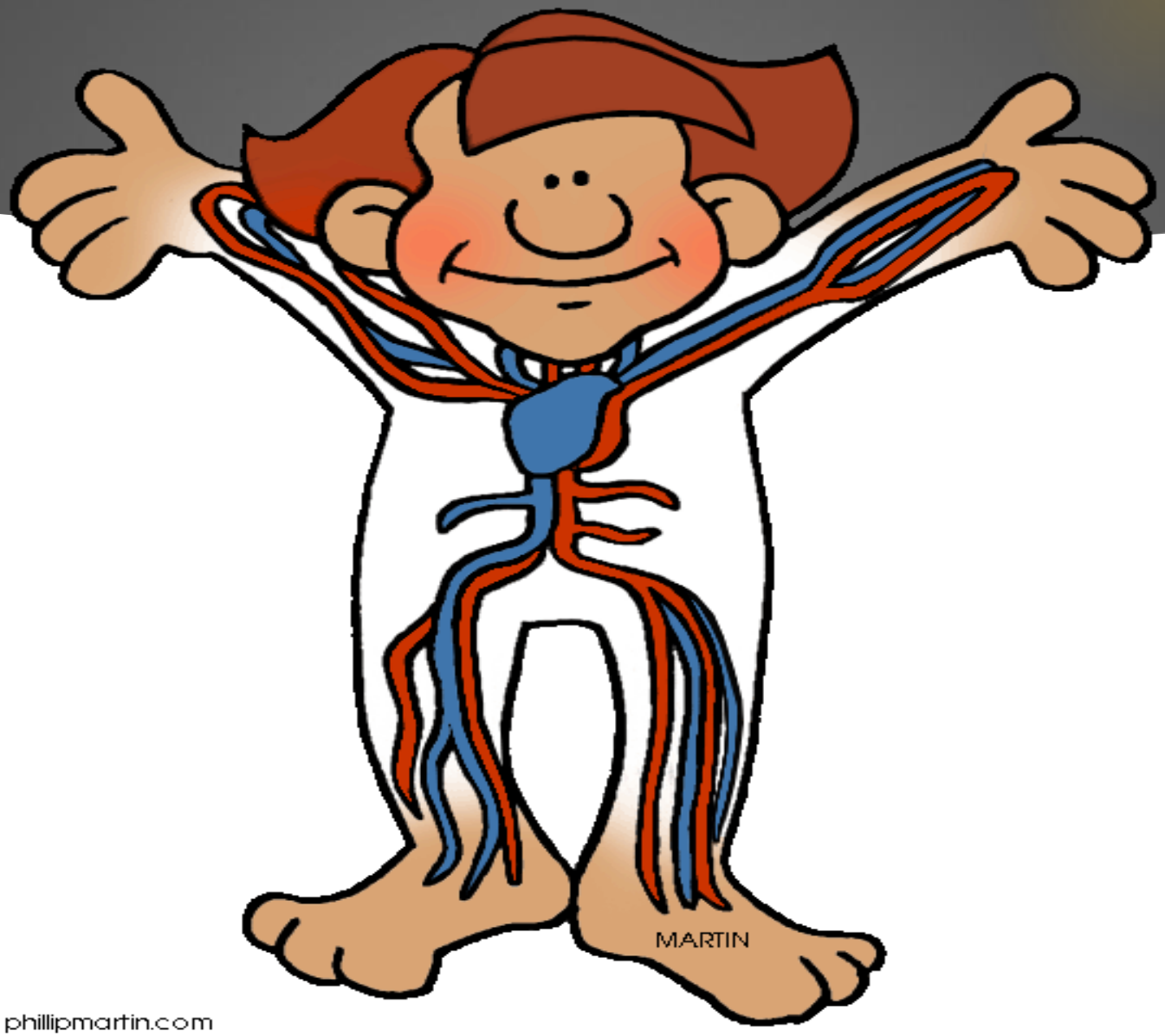
AUC

- To estimate the area under the curve after IV or oral drug conc. In plasma with time
- AUC is measured from time zero to time ∞ because if we give 100 mg drug then after first half life it becomes 50 then after second half life 25 then 12.5 then 6.25 ……etc
- So always there is traces of drug in blood so at time ∞ the plasma conc. Reaches zero



Concept keys

- Difference between oral and IV
- One compartment ?
- Two compartment ?
- ADME !



Methods for estimation of AUC for IV one compartment model

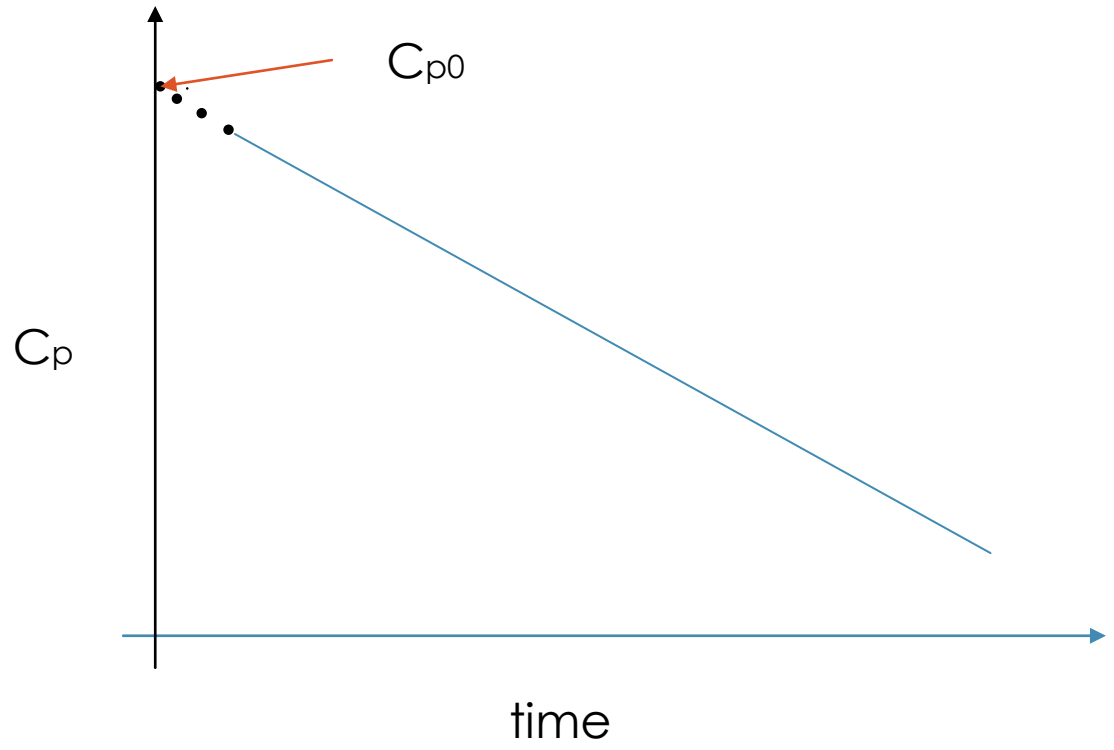
- 1- residual method :

It is used for resolving a curve into its various exponential components

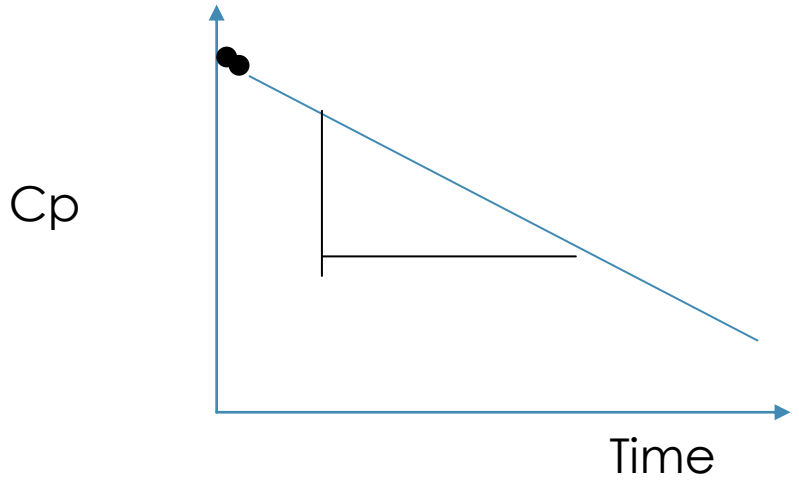
i.e. we use the log to straighten the curve

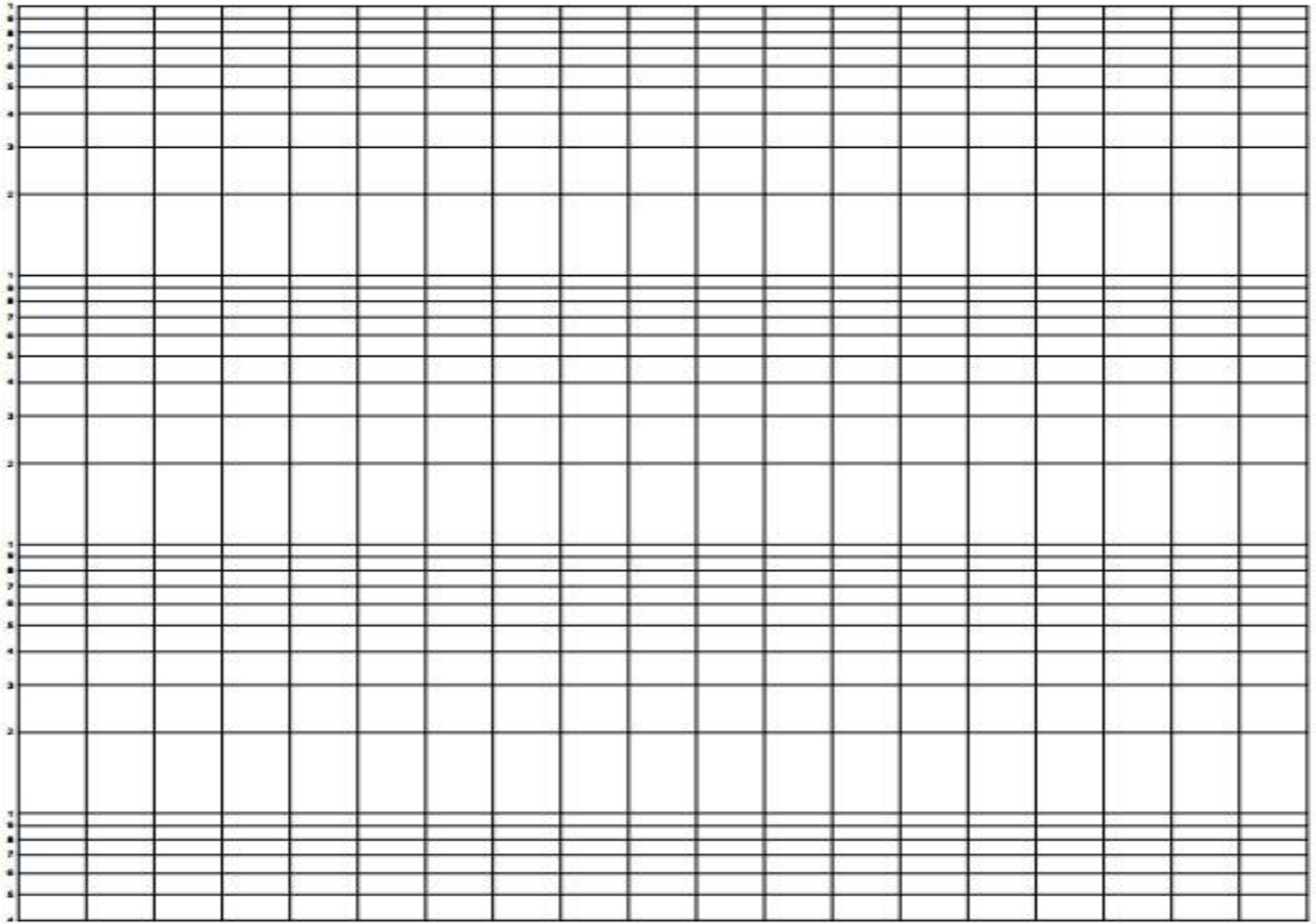
Thus AUC $= \frac{Cp0}{K}$

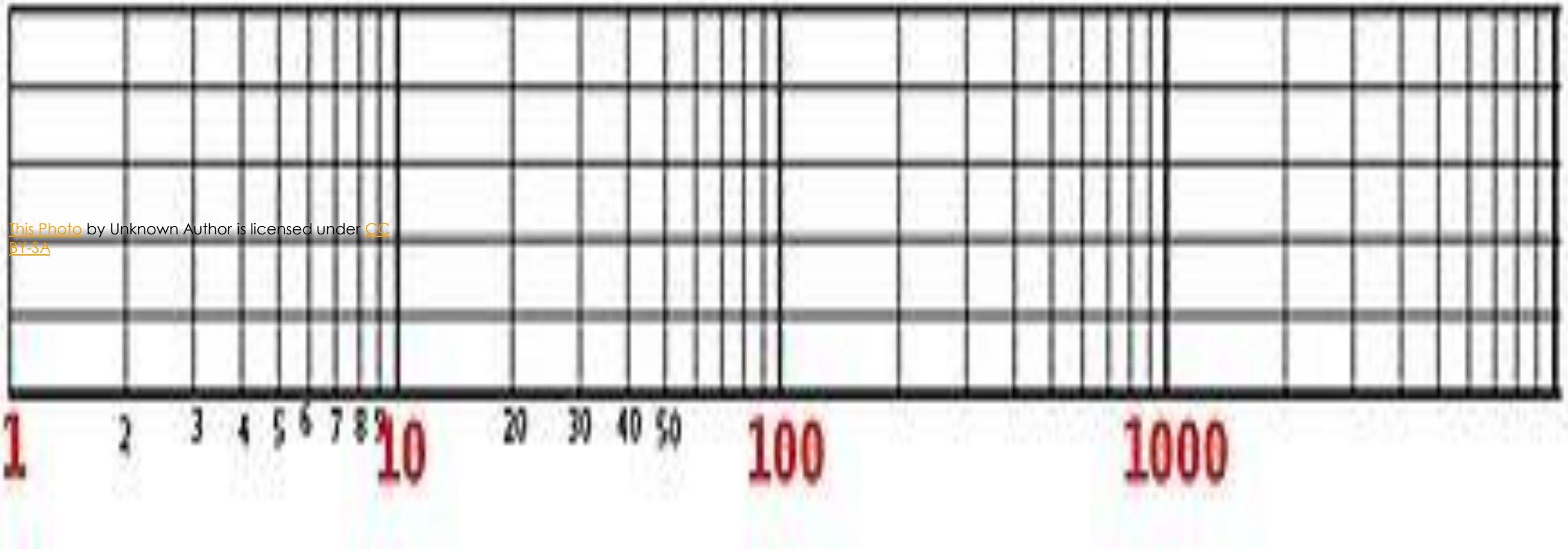
K is equal to slope * -2.303



- 2 Visual method
- By using Semilog paper after curve fitting for the best line , the intercept Is equal to Cpo and to find the slope form the curve we take two points on the straight line as follow
- slope= $\frac{\log Cp2 - Log\ Cp1}{time\ 2 - time\ 1}$
- K = slop * -2.303

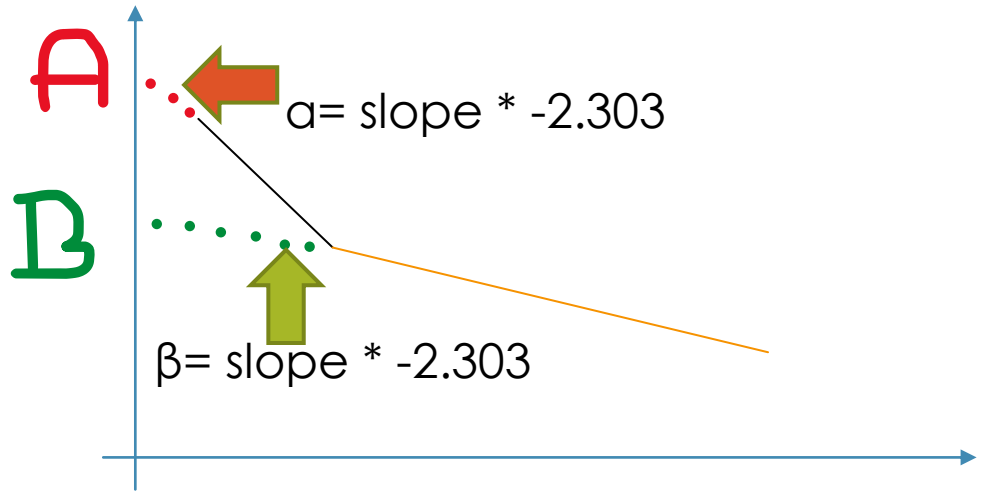






Methods for estimation of AUC for IV two compartment model

- In IV two compartment model we calculate the AUC by dividing the total area into two parts and estimates the area for each one which are elimination phase and distribution phase area
- The biexponential curve shown in the figure is commonly seen after the IV drug administration such curve can be described by the following eq.
- AUC= $\frac{A}{a} + \frac{B}{\beta}$
- A+ B = Cpo



Note

- Generally and commonly after the IV drug administration a (apparent first order fat disposition rate constant , AKA distribution rate constant) is much larger than β (apparent first order slow elimination rate constant , AKA elimination rate constant)
- $t_{1/2} = 0.693/k$
- Unit of K of elimination

$$kel = \frac{-dCp/dt}{Cp}$$

$$\frac{\text{mass}/\text{volume}}{\text{time}} \div \text{mass}/\text{volume} = \frac{1}{\text{time}}$$

1 / hour
Or
Hr^{-1}

Methods for estimation of AUC for oral one compartment model (plasma)

- In this case the drug is given orally and is absorbed by apparent first order process and show a one compartment model in the body
- The following equation is employed to describe the time course of such drug in the body

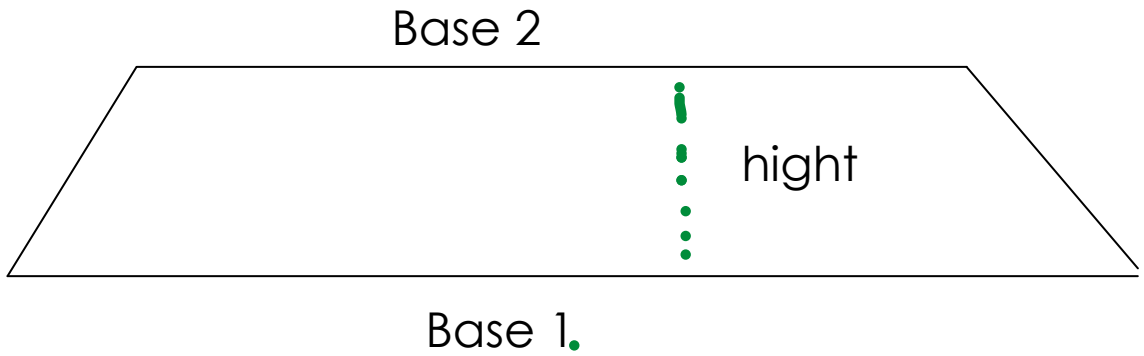
- $Cp = \frac{Ka.F.Dose}{Vd\ (Ka-K)}\ e^{-kt}$
- $Cp = Ae^{-at} + Be^{-bt}$
- AUC after oral dose (extravascular data) is equal to
- $AUC = \frac{B}{K} - \frac{A}{Ka}$

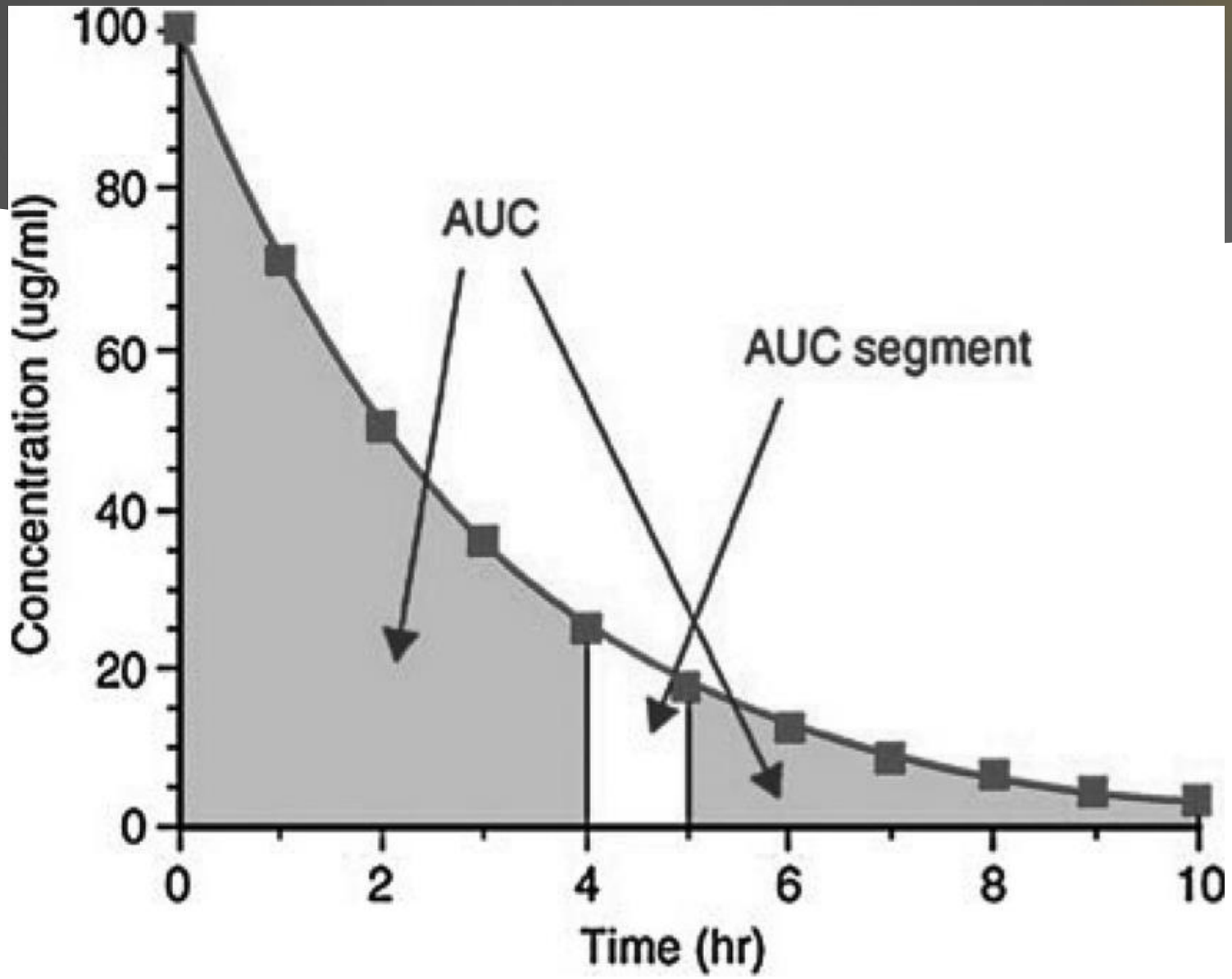
notes

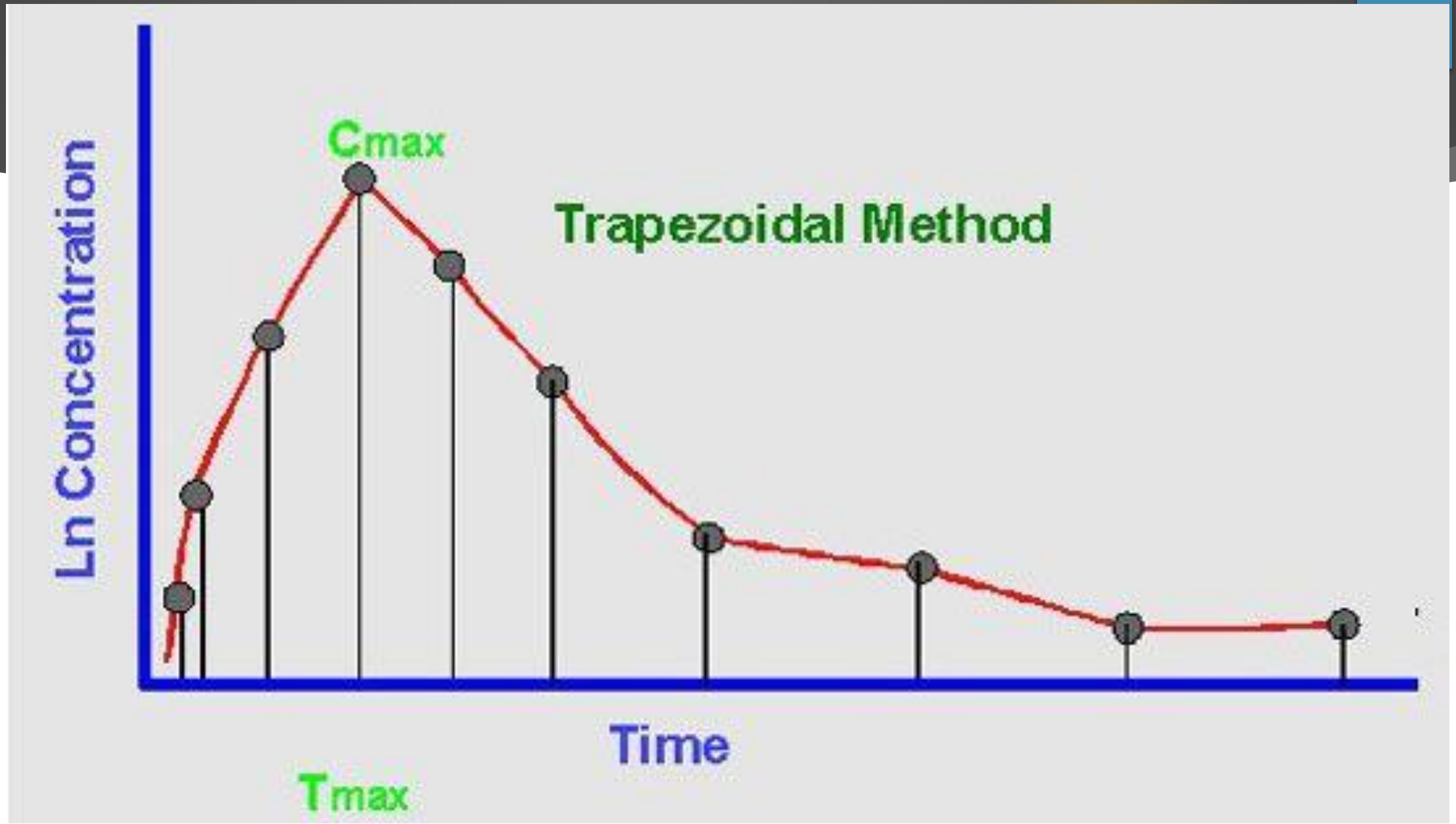
- In general in estimating AUC from time zero to time infinity and to get the best result it should be down the following
- 1- sample early enough
- 2- sampling intervals is short
- 3- sampling for 6-10 half life

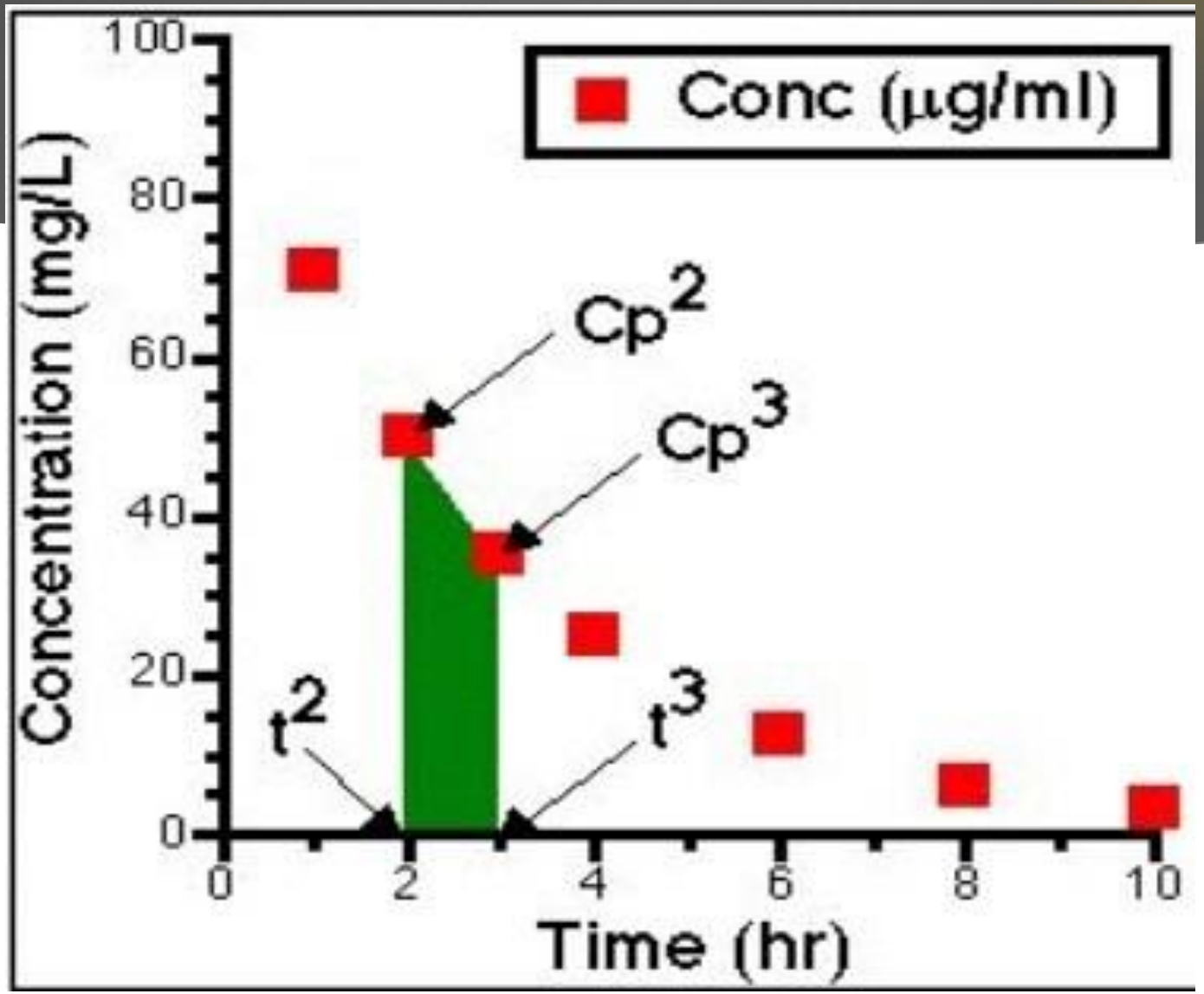
Trapezoidal method

- Area of trapezoid = $\frac{(base\ l+bas\ 2)}{2}.Hight$




100
80
60
40
20
0
Concentration (ug/ml)
AUC
AUC segment
0
2
4
6
8
10
Time (hr)


Cmax
Trapezoidal Method
Ln Concentration
Time
Tmax


Conc (µg/ml)
Concentration (mg/L)
100
80
60
40
20
0
0
2
4
6
8
10
Time (hr)
Cp2
Cp3
t2
t3

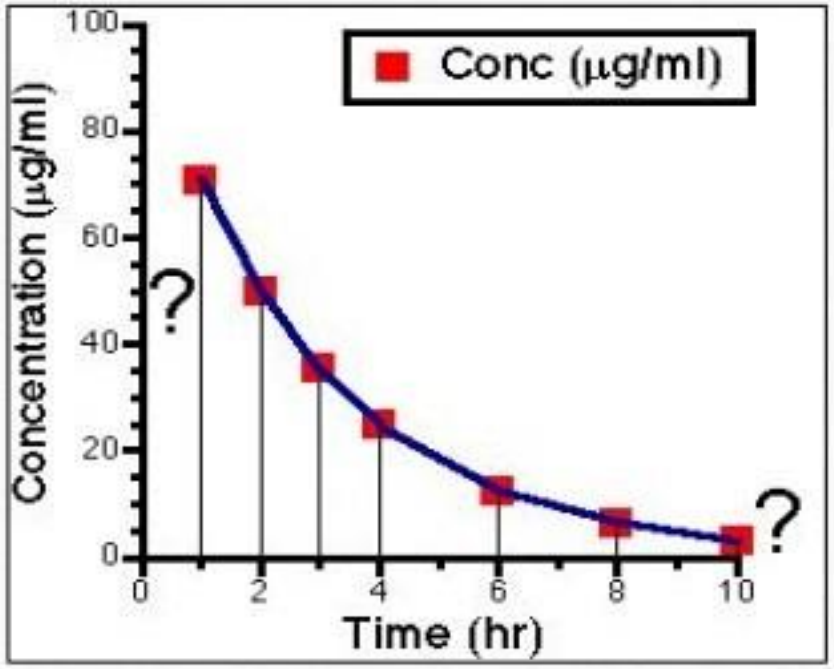
Area of trapezoid

- Area of trapezoid = $\frac{(Cp2+Cp1)}{2}.(t2-t1)$

- *After oral administration the concentration of the drug at zero time is zero thus simply the first area is* $=\frac{(Cp2+0)}{2}.(t2-0)$
- Usually total AUC means the area under the curve from time zero to time t , therefore the area from the last sampling (concentration) to time infinity (usually called residual area) is measured as the last drug concentration divided by the elimination rate constant

- The area from the first to last data point can then be calculated by adding the areas together

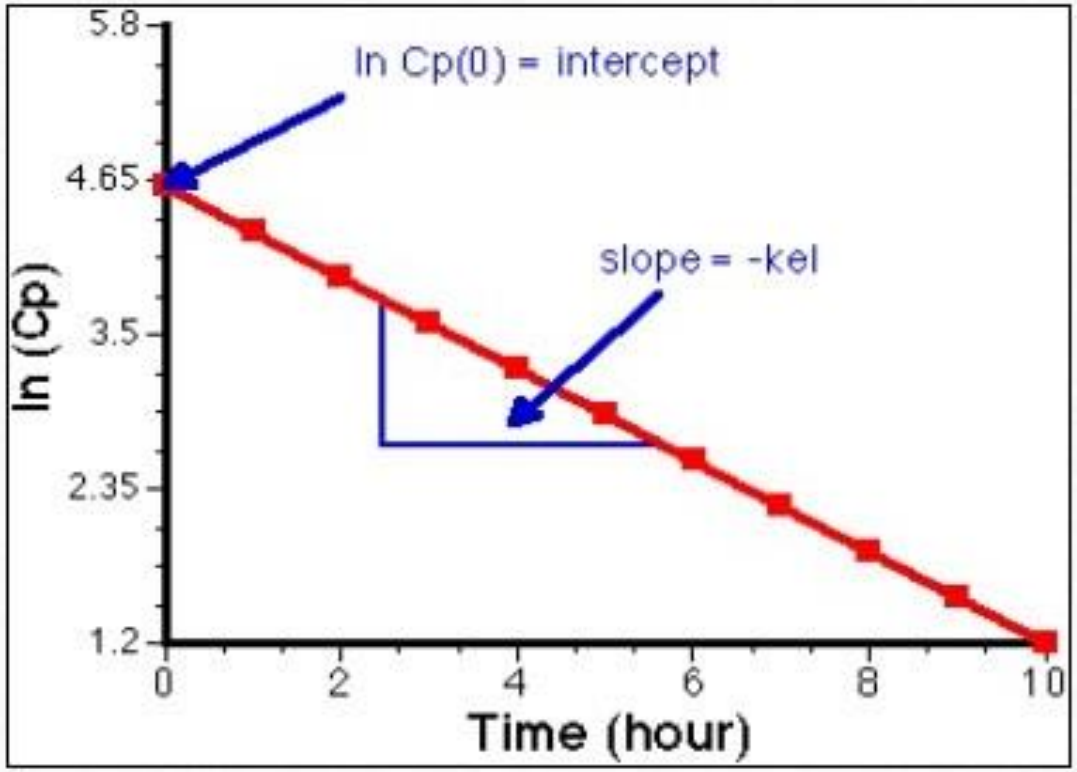
$$AUC_{1-n} = \sum \left\{ \frac{Cp_1 + Cp_2}{2} \bullet (t_2 - t_1) \right\} + \left\{ \frac{Cp_2 + Cp_3}{2} \bullet (t_3 - t_2) \right\} + \ldots$$



Calculation of First Segment

- The first segment can be calculated after determining the zero plasma concentration $\mathbf{Cp_0}$ by extrapolation

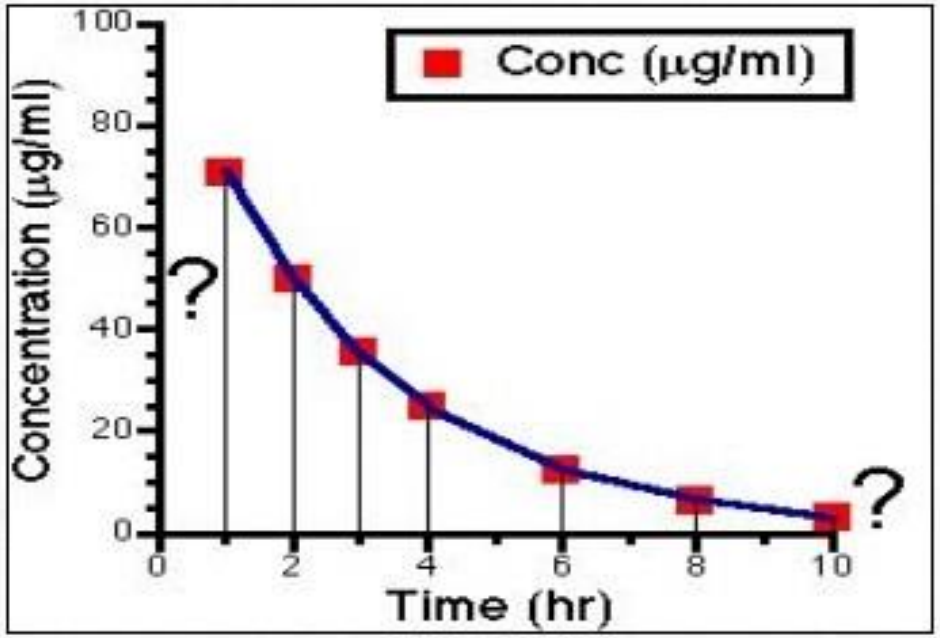
$$AUC_{0\text{-}1} = \frac{Cp_0 + Cp_1}{2} \times t_1$$



Calculation of Last Segment

- Final segment can be calculated from t_{last} to $t_{infinity}$

$$AUC_{t_{last}-\infty} = \int_{t=t_{last}}^{t=\infty} Cp \bullet dt = \frac{Cp_{last}}{kel}$$



Units of AUC

- Con. * time
- Mg. hr / L

- There is an issue !!