BIOPHARMACY

Pharmacokinetics -2-

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Data: Dose = 400 mg, C_p2hr = 4.5 mg/L, C_p6hr =3.7 mg/L

- Question: k and V?
- Equation: $k = (\ln C_{p1} - \ln C_{p2})/ t_2-t_1$

$k = (\ln(4.5) - \ln(3.7))/(6-2) = 0.049\ hr^{-1}$

$$\ln C_p = \ln C_p^0 - kt$$

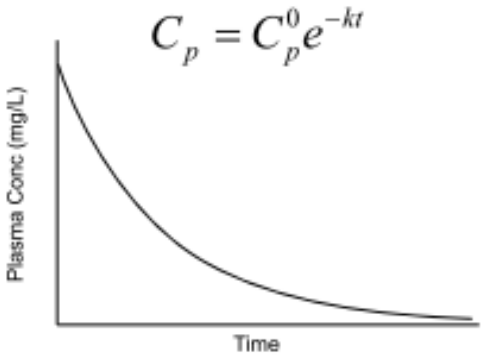
$\ln C_p^0 = \ln(4.5) + 0.049 \times 2 = 1.602$

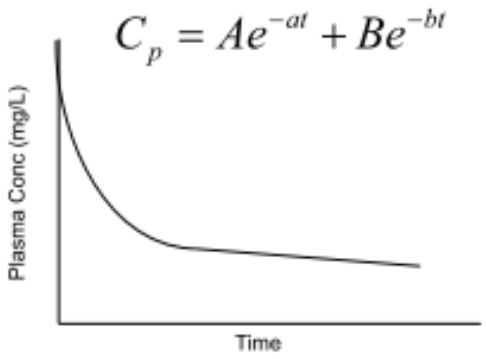
$C_p^0 = 4.96$

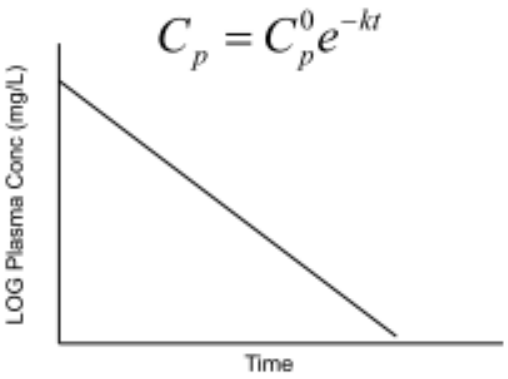
$V = Dose/C_p^0 = 400/4.96 = 80.6\ L$

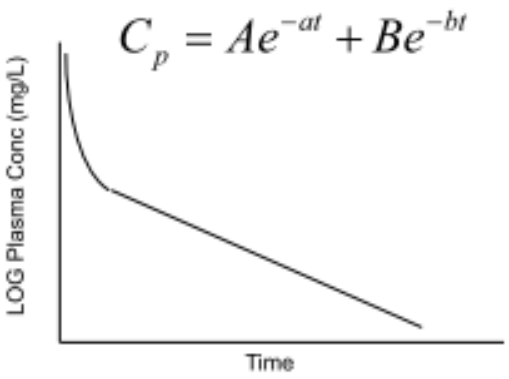
Two Compartment Model – IV

One Compartment	Two Compartment
No absorption	No absorption
Instantaneous Distribution	Distribution phase
Elimination phase	Elimination phase



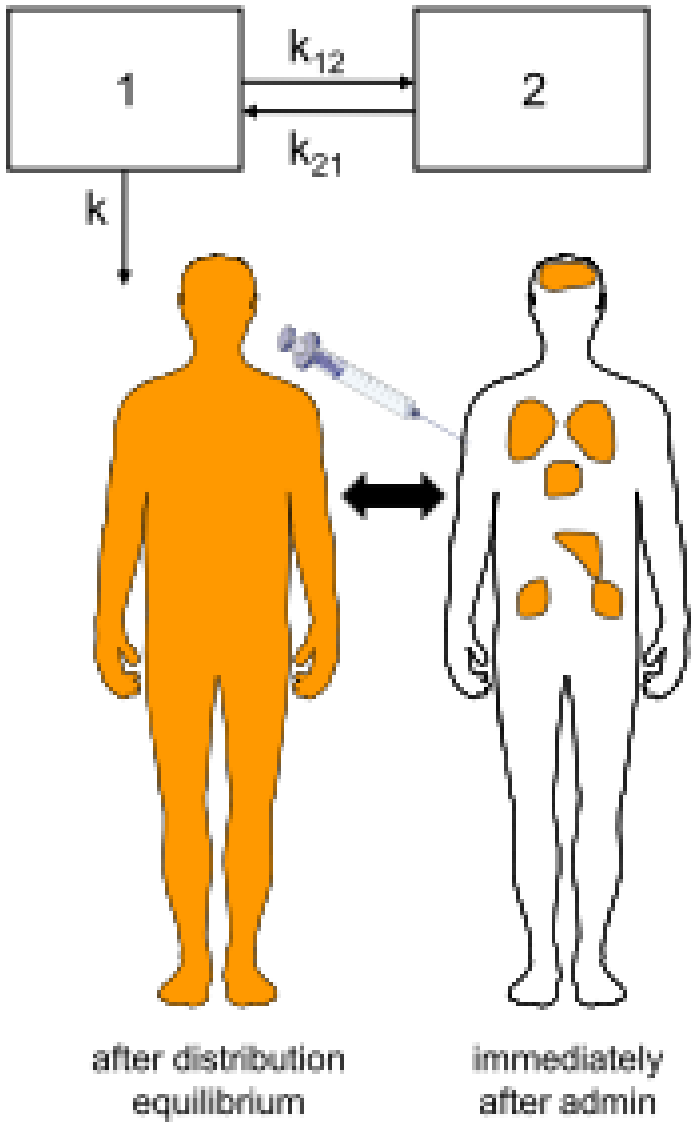


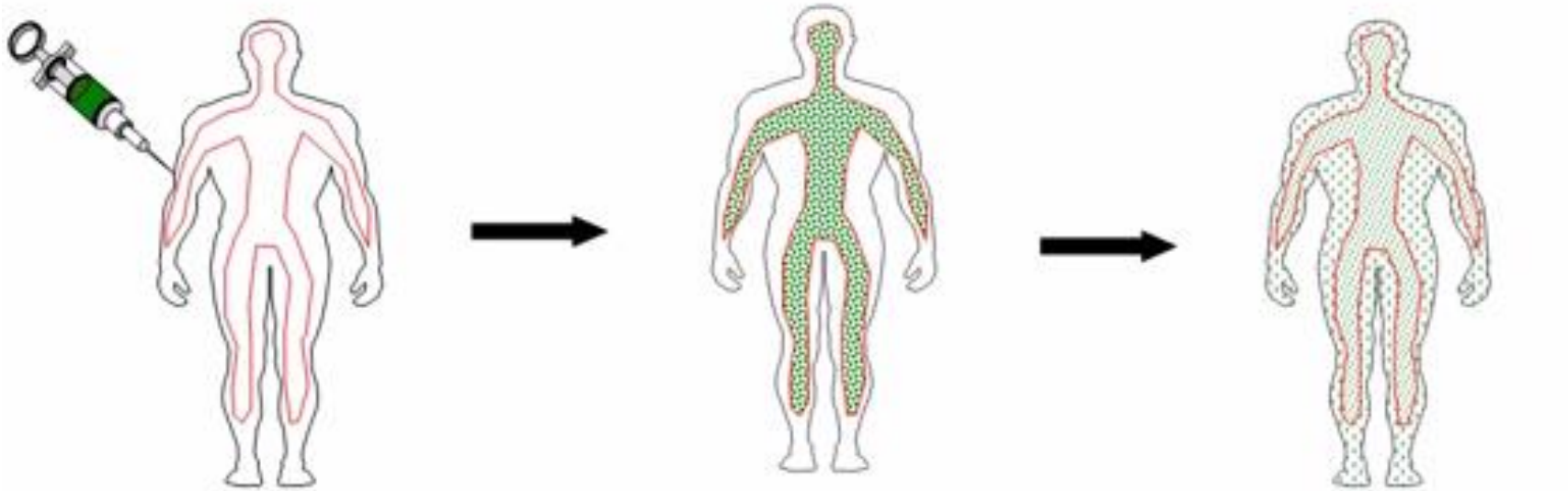




Two Compartment Model - IV

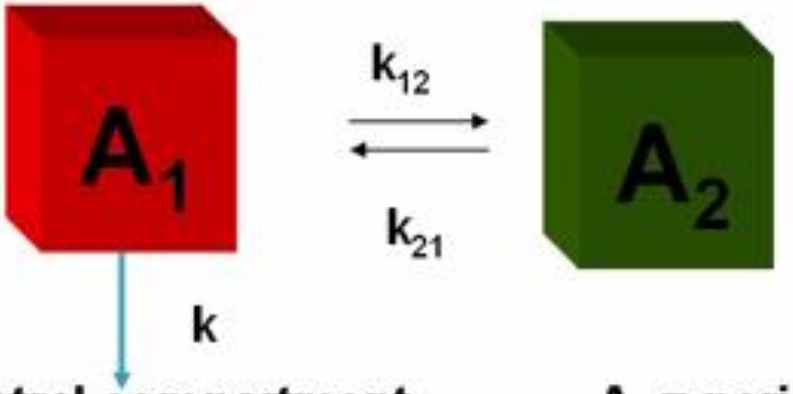
- IV administration
  - no absorption
  - immediate distribution to rapidly perfused organs "central compartment"
  - subsequent distribution into slowly perfused organs "peripheral compartment"
- Assumes all transfer rates are first-order processes
- Tissue uptake depends on lipophilicity, ionization, protein binding





Before distribution

After distribution

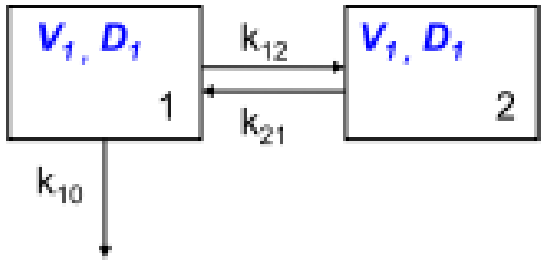


A_1 = central compartment

A_2 = peripheral compartment

Two Compartment Model - IV

- What are the PK parameters to define a 2 compartment model?
- Micro rate constants
  - k_{12}, k_{21}, k_{10}



- Simpler to use biexponential equation
  - a and b are hybrid rate constants
  - $a + b = k_{12} + k_{21} + k_{10}$
  - a = distribution rate constant
  - b = elimination rate constant
  - A and B are intercepts on the y-axis

$$C_p = Ae^{-at} + Be^{-bt}$$

Determination of A, a, B and b

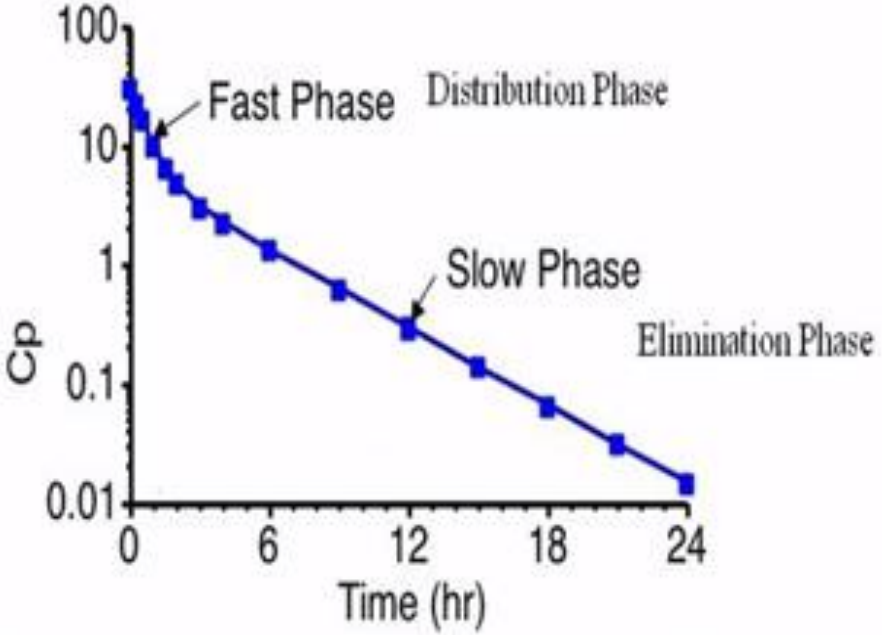
- To calculate values for A and a we need to separate distribution phase from the elimination phase

$$C_p = Ae^{-at} + Be^{-bt}$$

$$\therefore \quad Ae^{-at} = C_p - Be^{-bt}$$

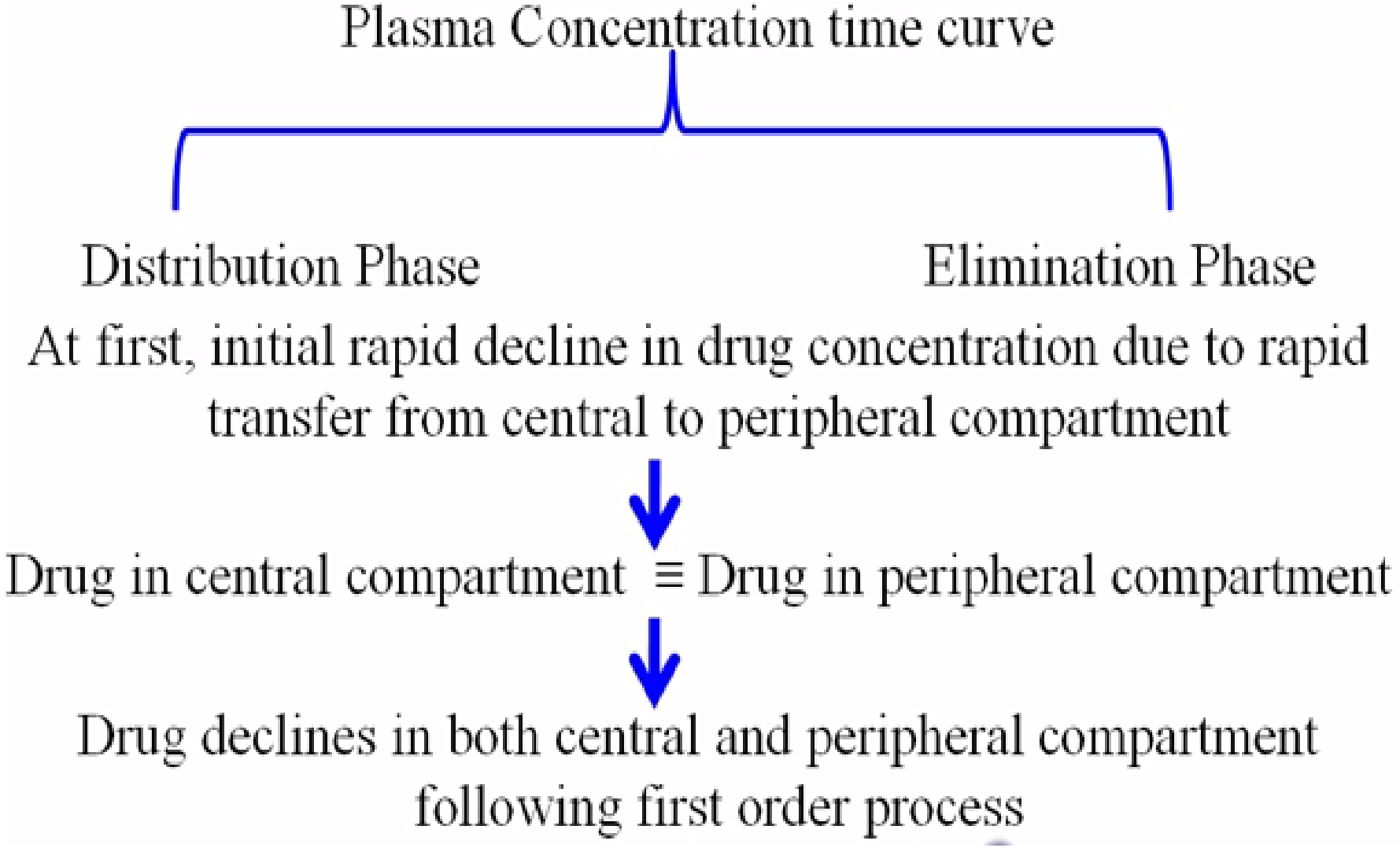
- A is determined from the slope of the 'stripped' curve and a is calculated from the gradient

Plasma concentration time curve for a drug that follows a two compartment model shows that the plasma drug concentration declines bi-exponentially as the sum of two first order processes: distribution and elimination



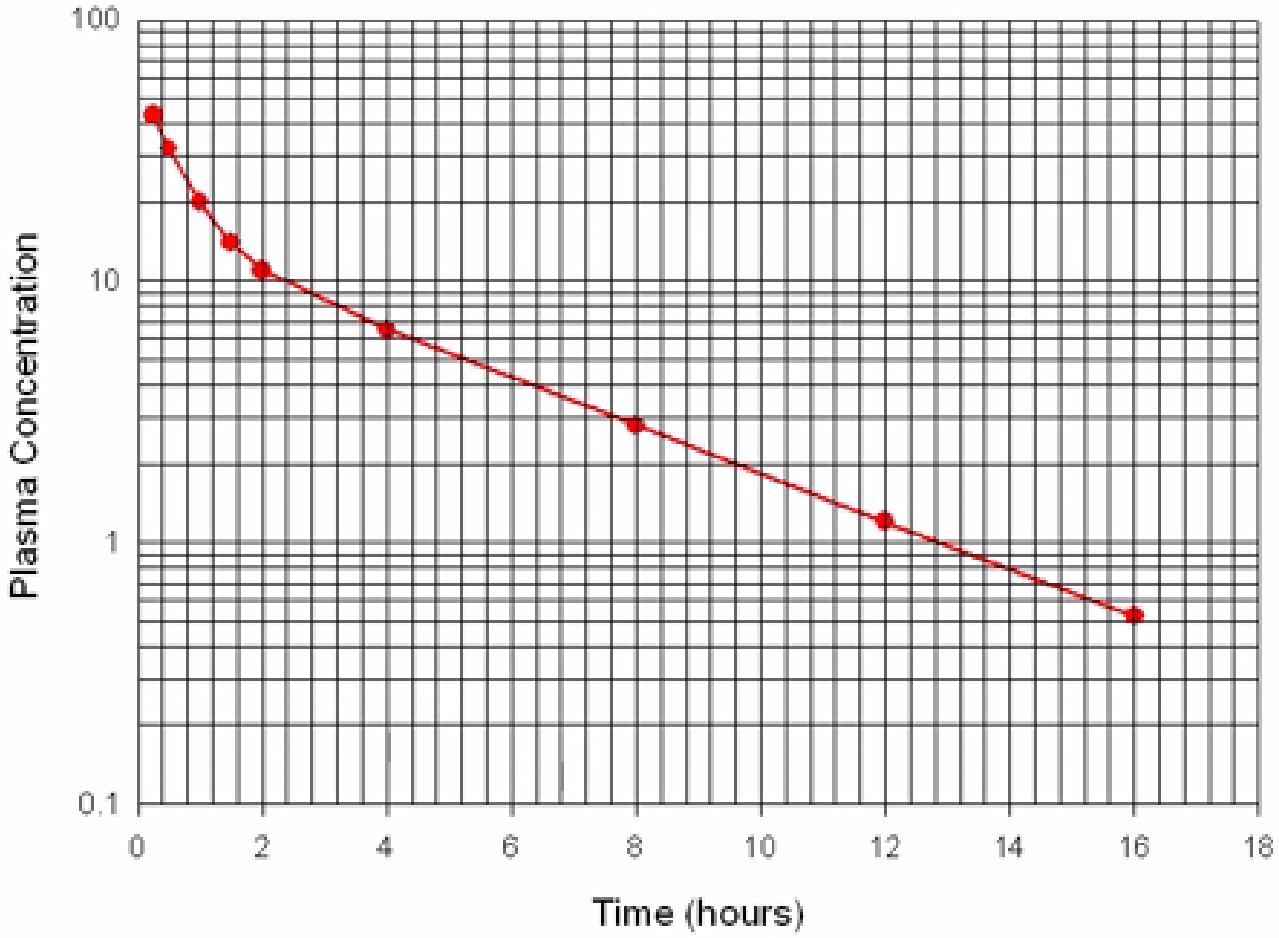
In this model, the drug distributes into two compartments, the central compartment (plasma & highly perfused tissues) and the tissue or peripheral compartment.

The distribution phase may take minutes or hours, and may be missed if plasma samples were taken too late or at wide intervals after the injection.

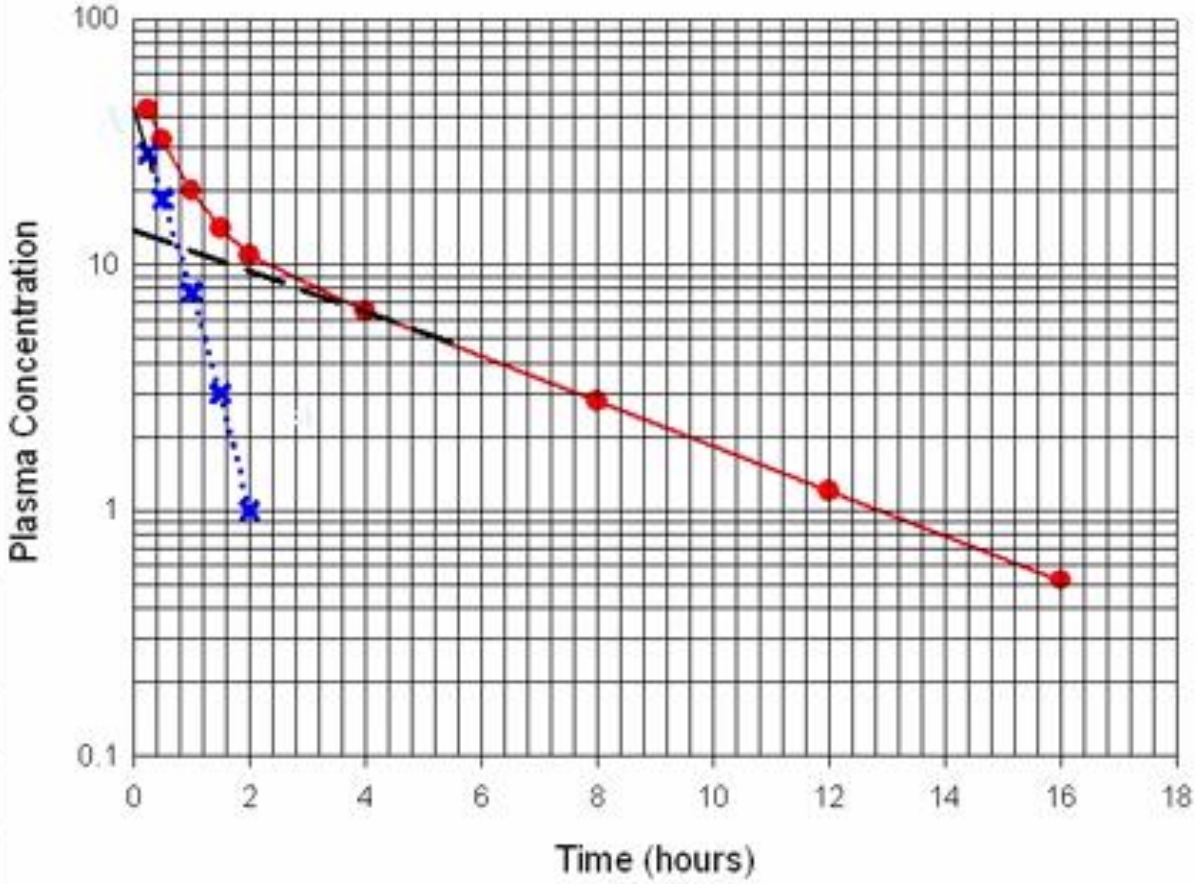

Plasma Concentration time curve
Distribution Phase
Elimination Phase
At first, initial rapid decline in drug concentration due to rapid transfer from central to peripheral compartment
Drug in central compartment ≡ Drug in peripheral compartment
Drug declines in both central and peripheral compartment following first order process

Method of Residuals (Feathering Method)

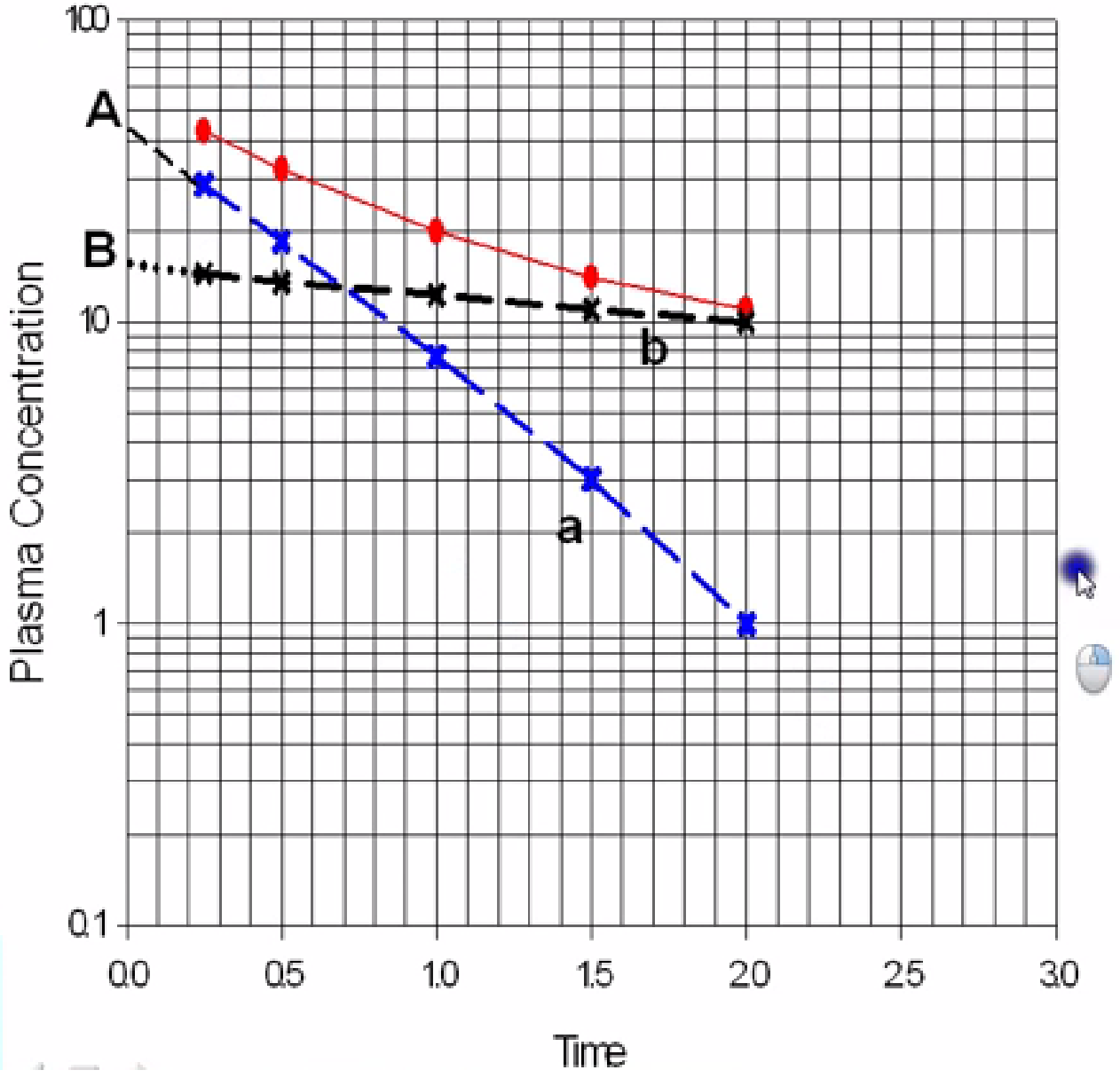
Time	Cp
0.25	43
0.5	32
1	20
1.5	14
2	11
4	6.5
8	2.8
12	1.2
16	0.52



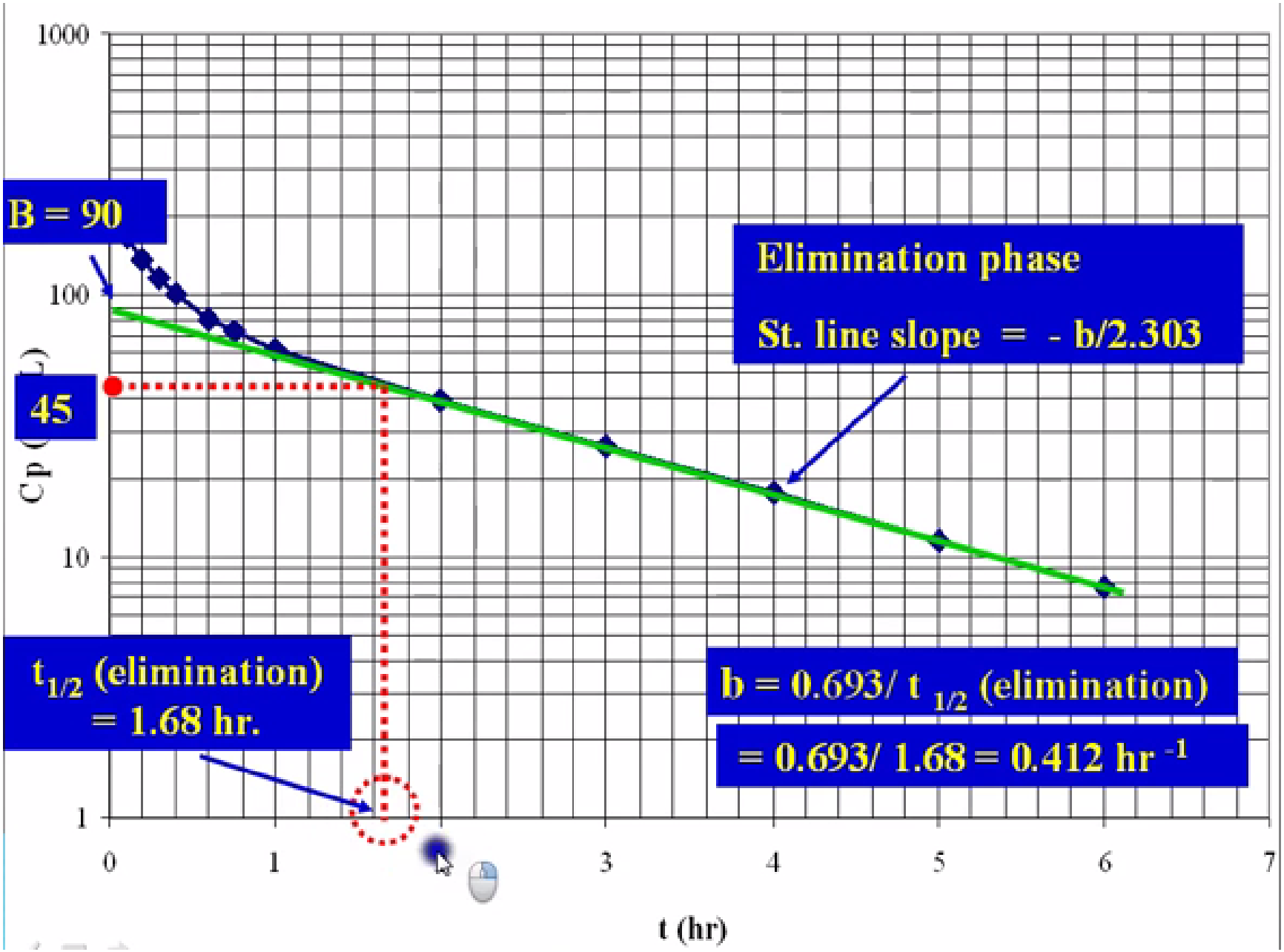
Time	Cp	Cp'	Cp-Cp'
0.25	43	14.5	43-14.5 = 28.5
0.5	32	13.5	32-13.5 = 18.5
1	20	12.3	20-12.3 = 7.7
1.5	14	11	14.-11 = 3.0
2	11	10	11-10 = 1.0
4	6.5		
8	2.8		
12	1.2		
16	0.52		

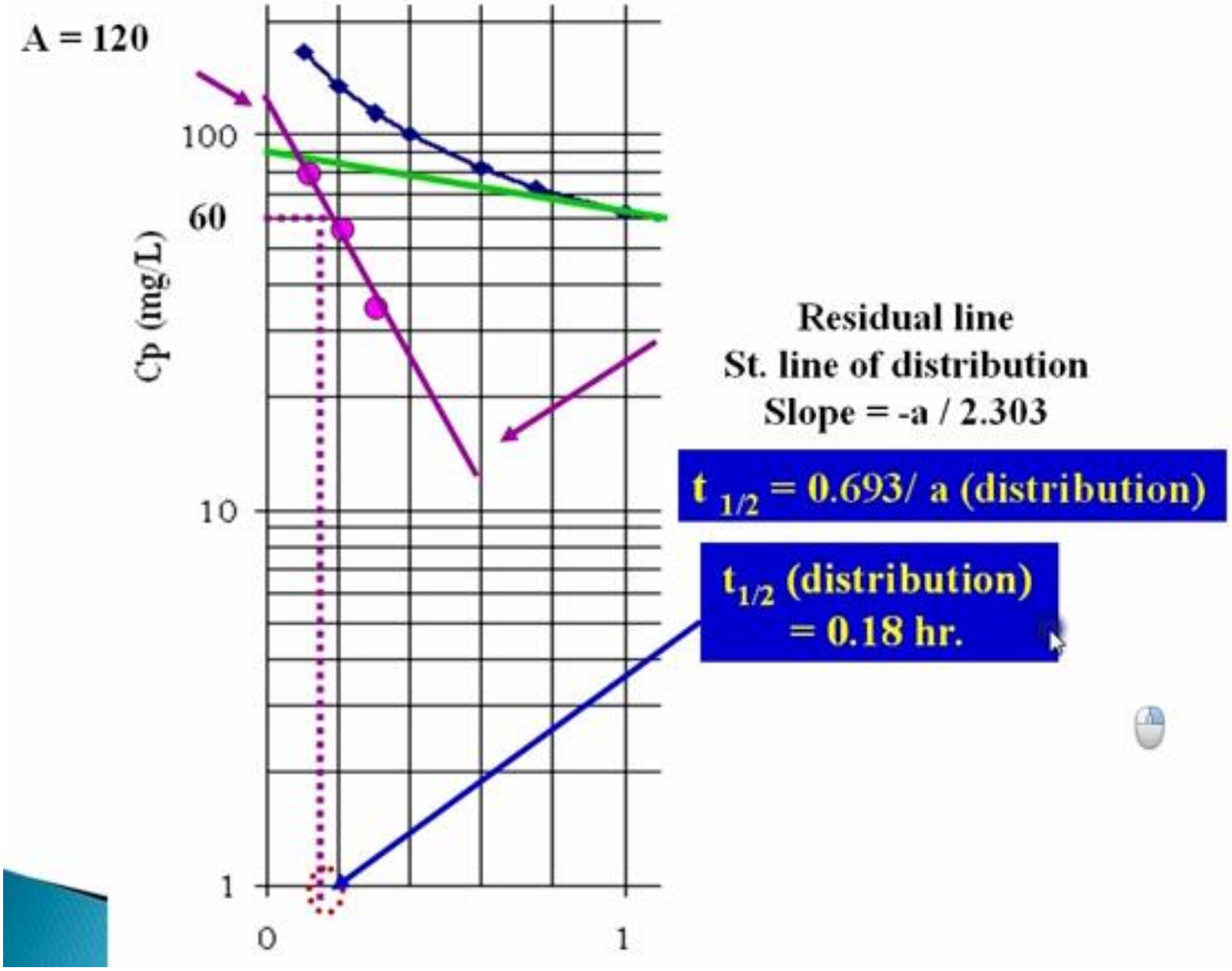


a or α phase



Time	Cp-Cp'
0.25	43-14.5 = 28.5
0.5	32-13.5 = 18.5
1	20-12.3 = 7.7
1.5	14.-11 = 3.0
2	11-10 = 1.0


1000
100
10
1
Cp (
L)
B = 90
45
Elimination phase
St. line slope = - b/2.303
t1/2 (elimination)
= 1.68 hr.
b = 0.693/ t 1/2 (elimination)
= 0.693/ 1.68 = 0.412 hr -1
0
1
3
4
5
6
7
t (hr)


A = 120
100
60
10
1
Cp (mg/L)
0
1
Residual line
St. line of distribution
Slope = -a / 2.303
t 1/2 = 0.693/ a (distribution)
t1/2 (distribution)
= 0.18 hr.

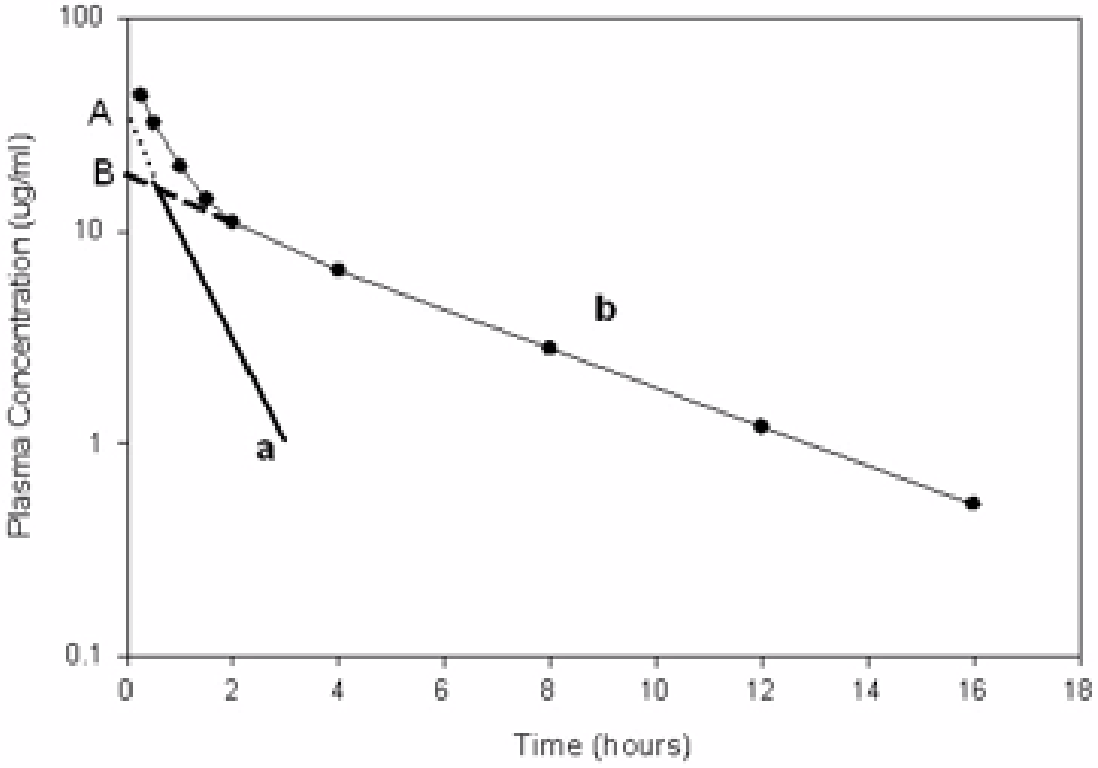
$$Cp = A\, e^{-at} + B\, e^{-bt}$$

$a + b = k12 + k21 + k$

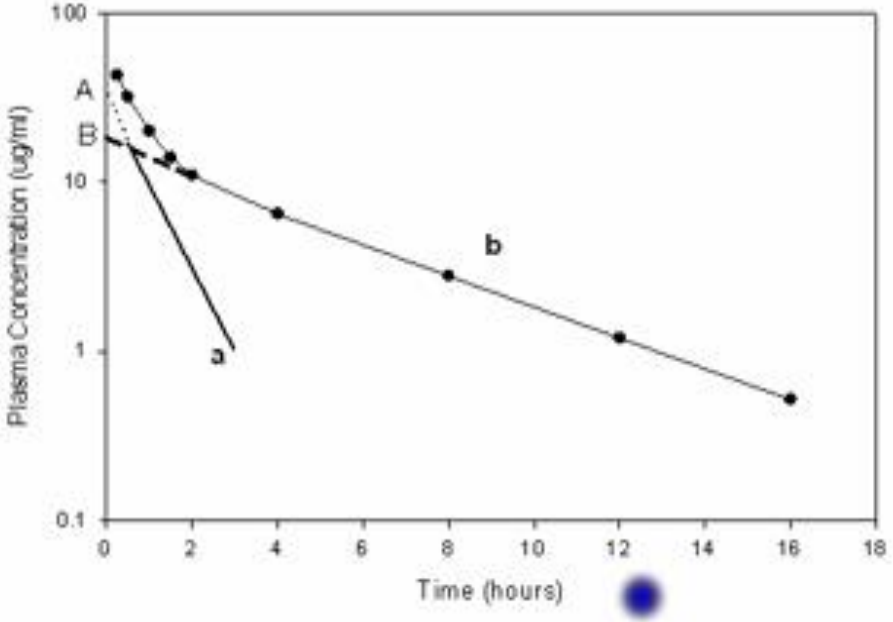
$ab = k21k$

$$A = \frac{D^{\circ}(a - k_{21})}{Vp(a - b)}$$

$$B = \frac{D^{\circ}(k_{21} - b)}{Vp(a - b)}$$



The decline in the initial distribution phase is more rapid than the elimination phase.
The rapid distribution is confirmed by the constant *a* being larger than the rate constant *b*.



$$Cp = B\ e^{-bt}$$

$$\log Cp = \frac{-bt}{2.303} + \log B$$

Rate constant can be obtained from the slope= $(-b/2.3)$

Terminal elimination half-life equals to

$$t_{1/2} = \frac{0.693}{b}$$

Apparent Volumes of Distribution

$$Cp = A\,e^{-at} + B\,e^{-bt}$$

At t= 0, e° =1 therefore

$$Cp^{\circ} = A+B$$

Vp is determined by determining A and B from the residual line.

$$Vp = \frac{D^{o}}{A+B}$$

Elimination rate constant:

- The elimination rate constant k represents the elimination of drug from the central compartment.
- *b* represents drug elimination during the elimination phase only, when distribution is mostly complete.
- Therefore *b* is smaller than k, where k is the true elimination constant.
- While *b* is a hybrid constant that is affected by the rate of drug transfer in and out of the tissue compartment

$$a > b, \quad b < k$$

Determination of Compartment Models:

The observed number of compartments will depend on:

1- The route of drug administration.

2- Sampling intervals (missed compartment if later than distribution phase)

3- The number of samples taken during the collection period (depend on $t_{1/2}$).

4- The assay sensitivity (lower drug concentrations could be missed).