Compartmental Pharmacokinetic Analysis

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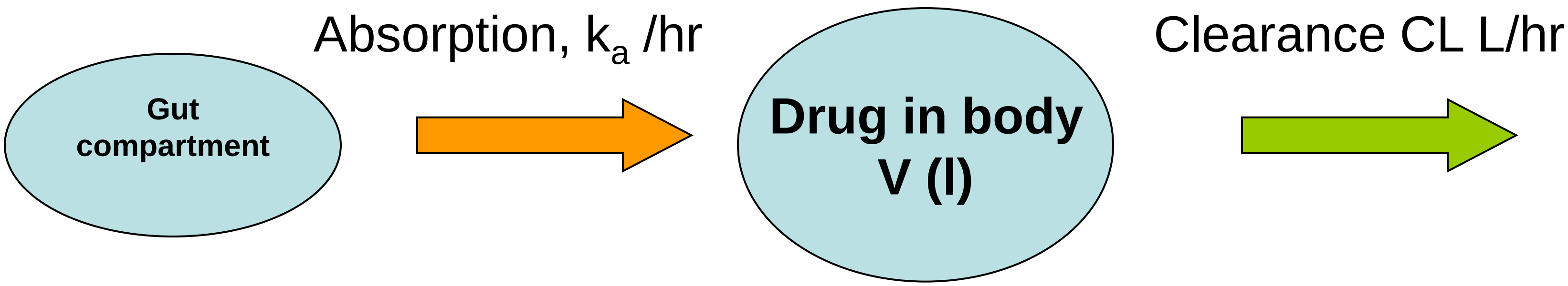
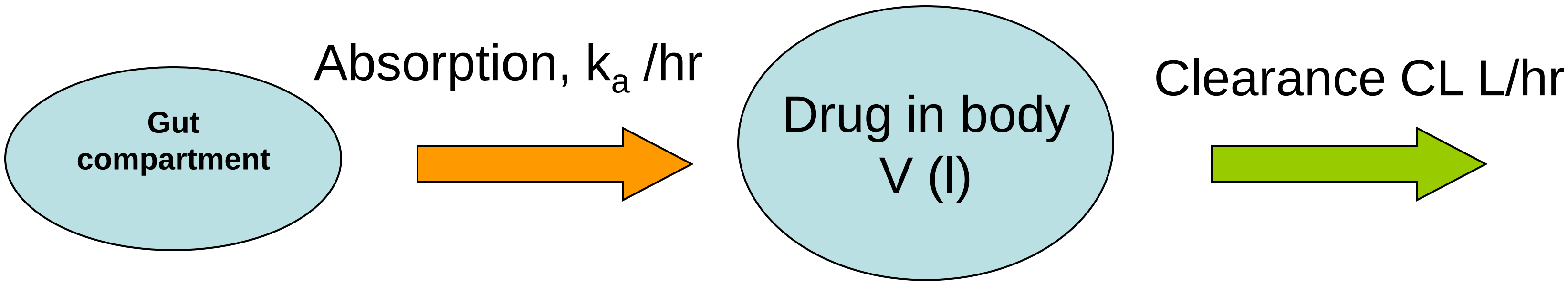
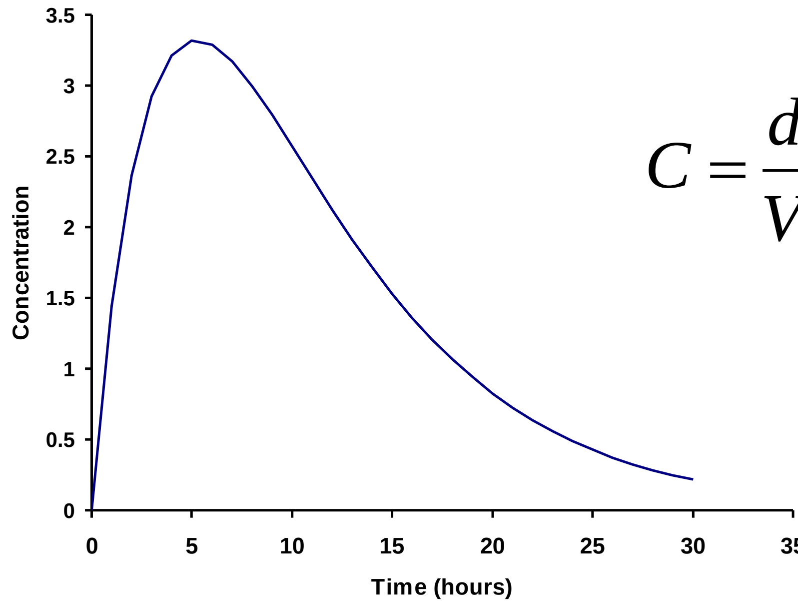
Compartmental PK Analysis

Describes how the drug concentration changes over time using physiological parameters.



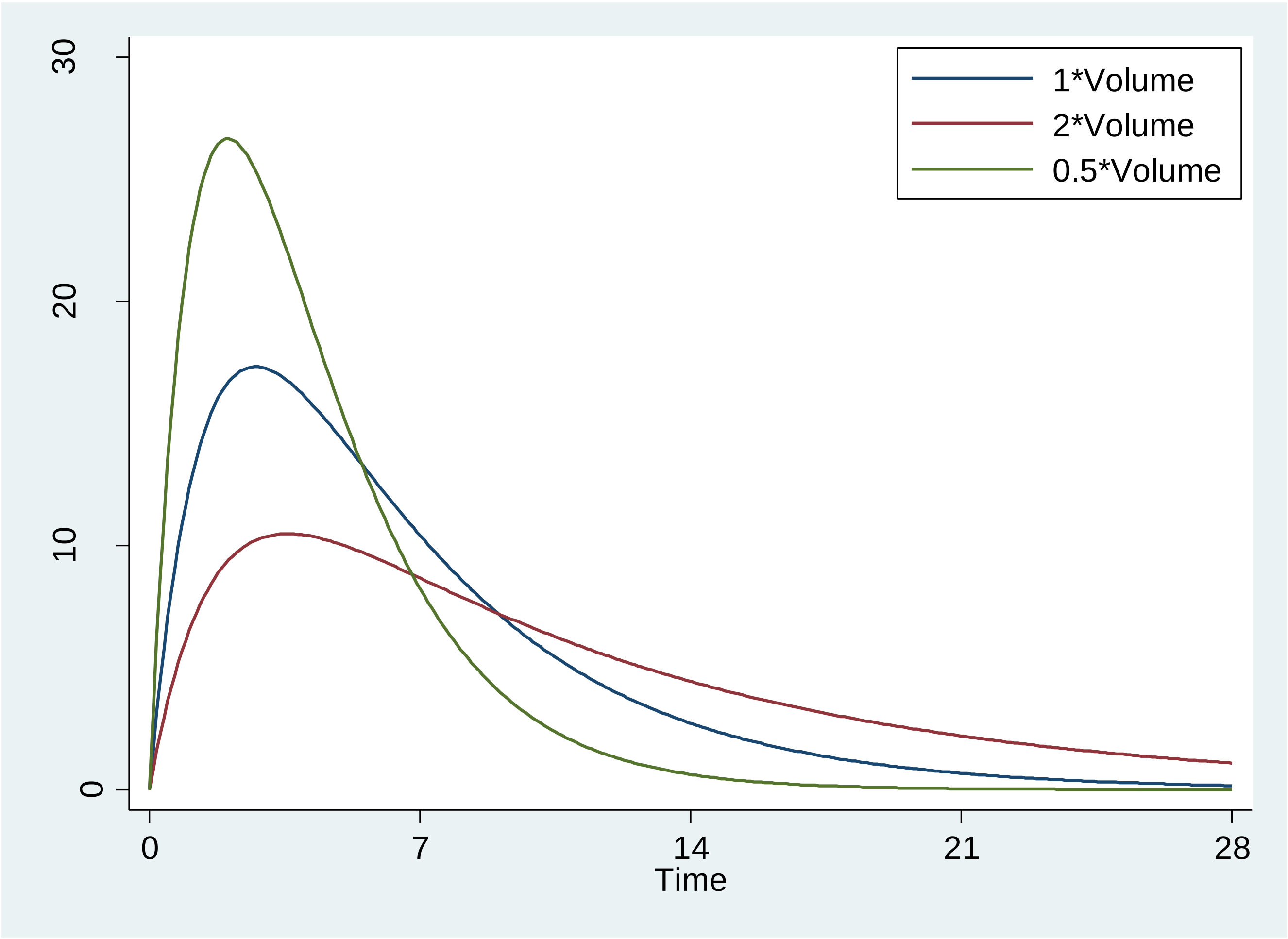
Compartmental PK Analysis



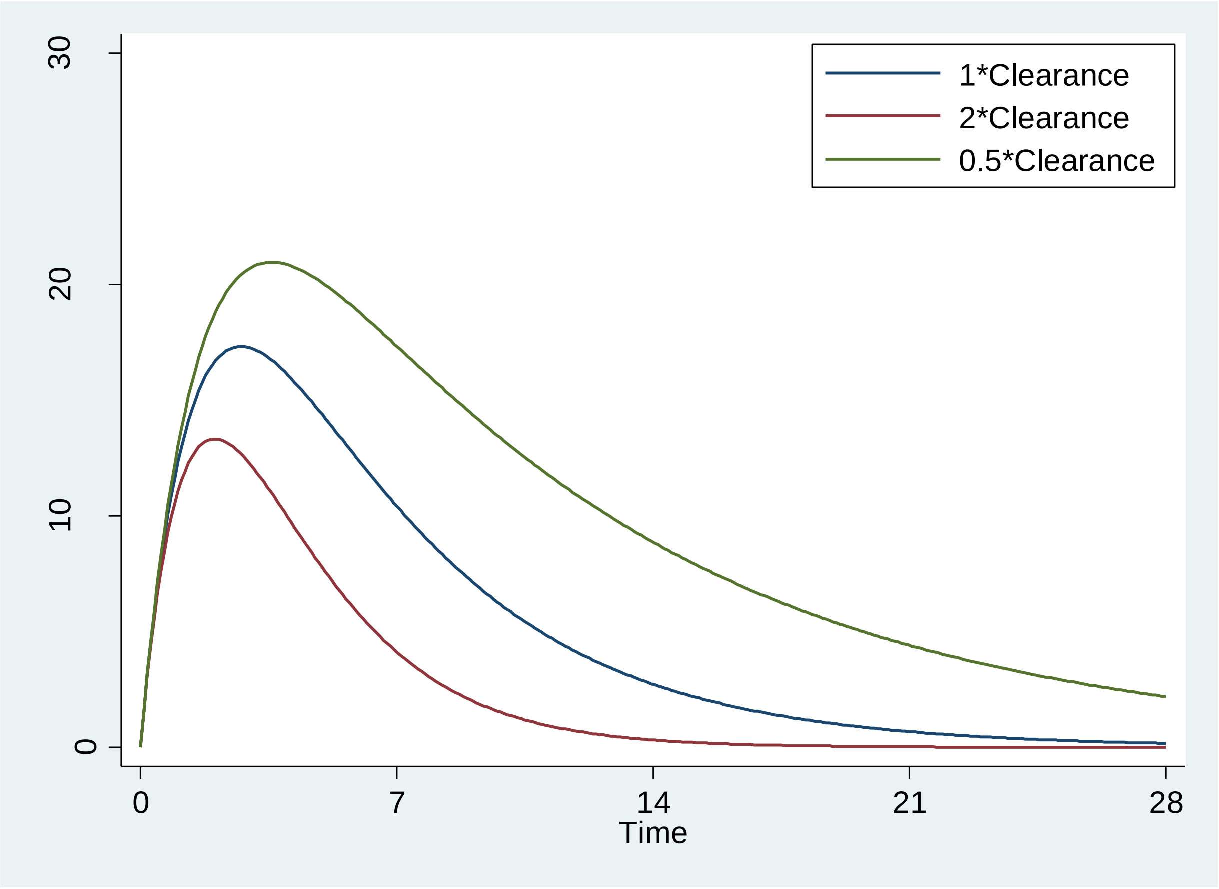


$$C = \frac{dose.k_a.F}{V.k_a - CL}[e^{-(CL/V).t} - e^{-k_a.t}]$$

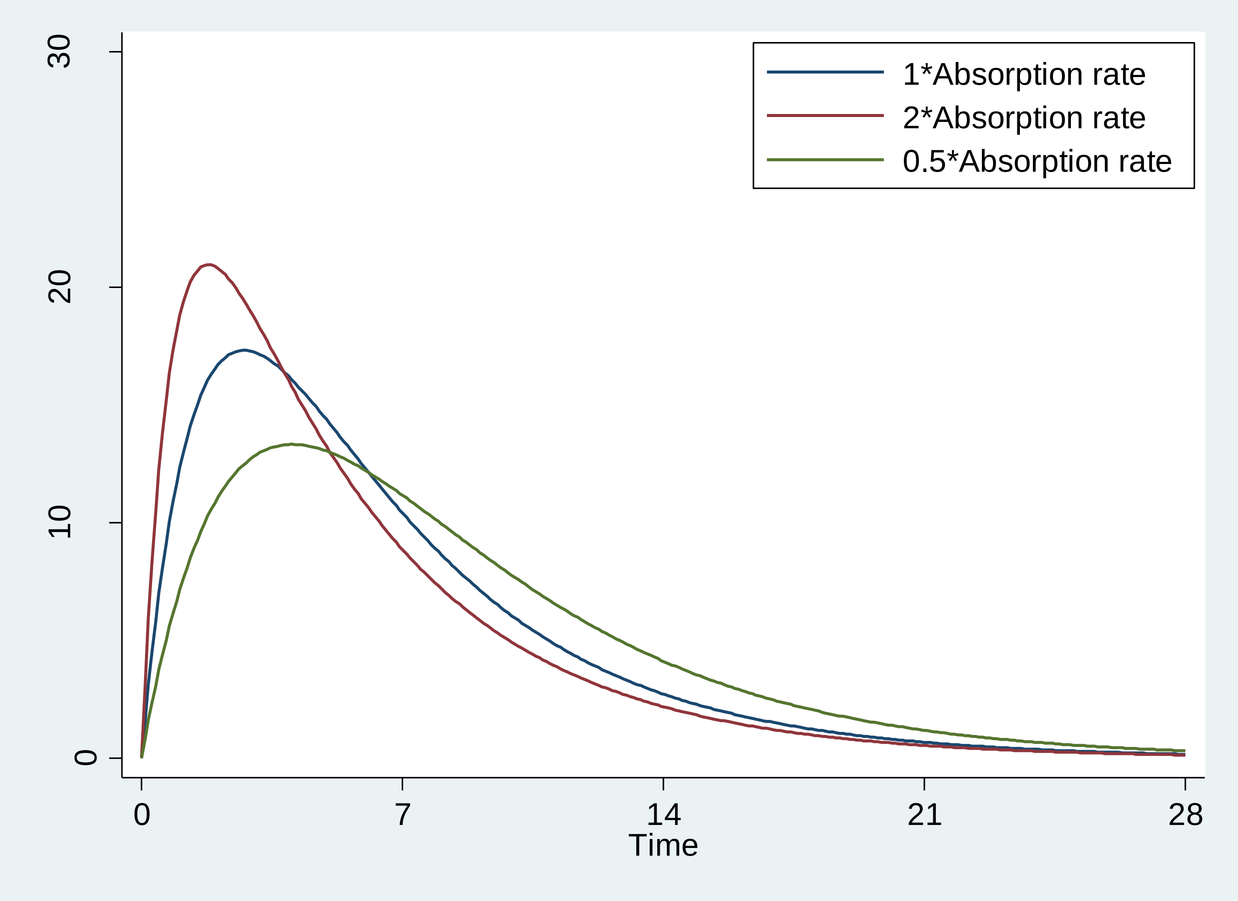
Compartmental PK Analysis – change in PK profile due to V



Compartmental PK Analysis – change in PK profile due to CL



Compartmental PK Analysis – change in PK profile due to k_a



Compartmental PK Analysis *versus* Non-compartmental Analysis

Predict the concentration at any time t using *C(t)=f(p, t)*

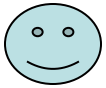
Primary physiological parameters are estimated

k_a, V, CL

Secondary PK parameters can be calculated using the primary physiological parameters

k_{el}, AUC, $t_{1/2}$, C_{max}, T_{max}

Compartmental PK Analysis *versus* Non-compartmental Analysis



- **Fitting of compartmental models can be a complex and lengthy process.**

- **NCA – Assumptions are less restrictive than fitting compartmental models.**

- **NCA – quick and easy to do, and does not require specialist computer software**

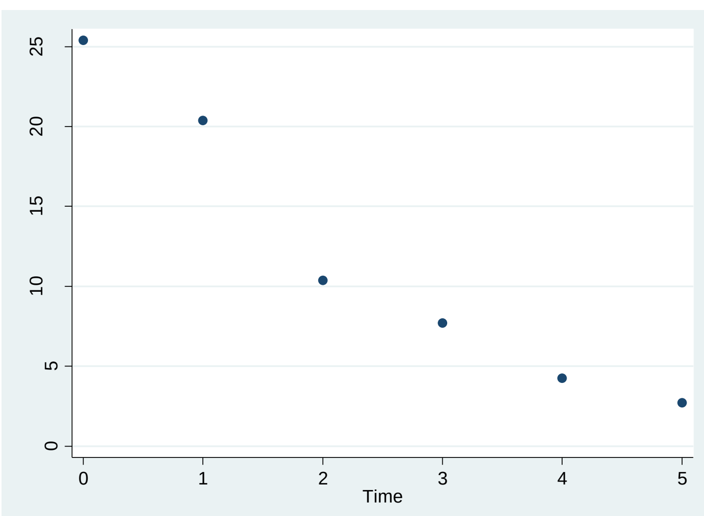
Recommended Steps for compartmental PK analysis

1) Explore concentration-time data visually
2) Select compartmental model(s) to fit to the data using non-linear regression
3) Determine initial values of the PK parameters
4) Estimate the PK parameters using a computer programme with nonlinear regression.
5) Re-run the nonlinear regression with different initial values of the PK parameters to ensure the programme has converged at the global minimum not a local minimum.
6) Assess how well the compartmental PK model(s) explains the individual's concentration-time data:
   - Visually – Observed and predicted concentrations versus time, Residuals versus predicted concentrations;
   - Precision of parameter estimates
   - Goodness of fit – Akaike Information Criteria (AIC) for comparing different compartmental models

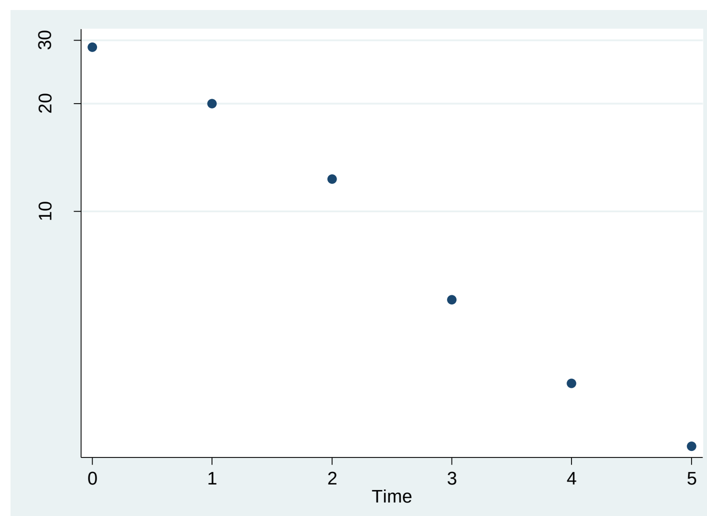
Steps 1 & 2 – Visual inspection of individual's concentration-time data and selection of compartmental PK model

Note: Must have more datapoints than the number of PK parameters to be estimated

Concentration versus time



Concentration ($\log_e$ scale) versus time

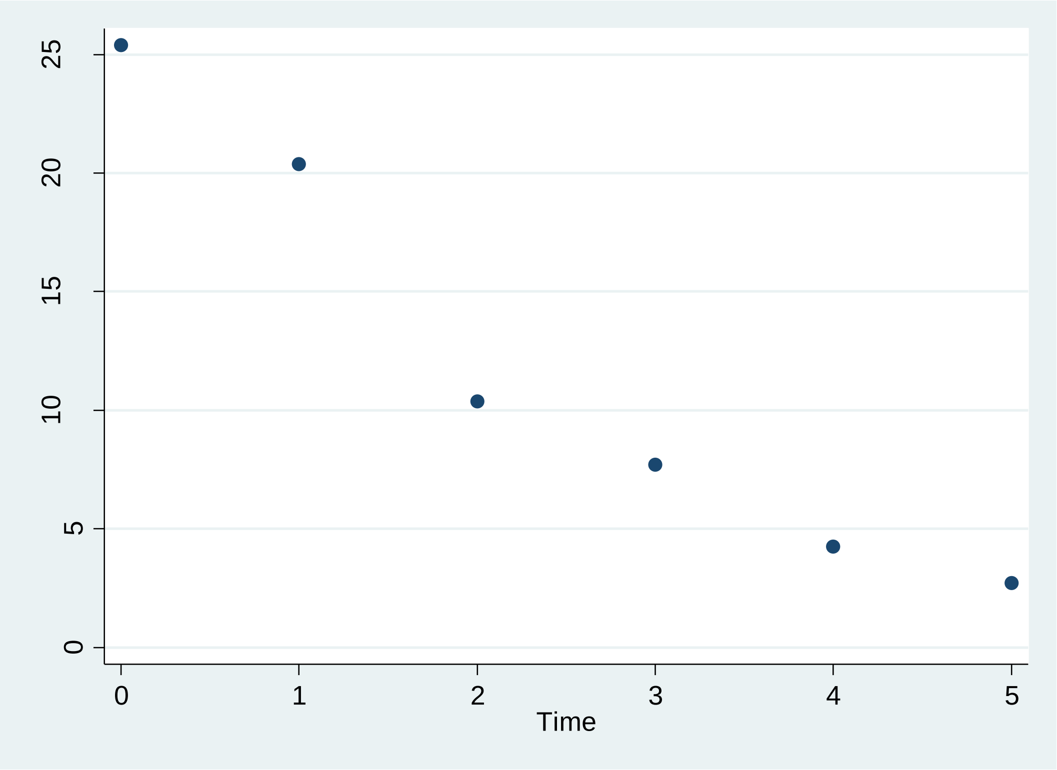


Step 3 - Initial values for PK parameters

One-compartment model, IV administration

$$C = (dose/V) * e^{(-(CL/V)*time)}$$

Dose – 600 mg

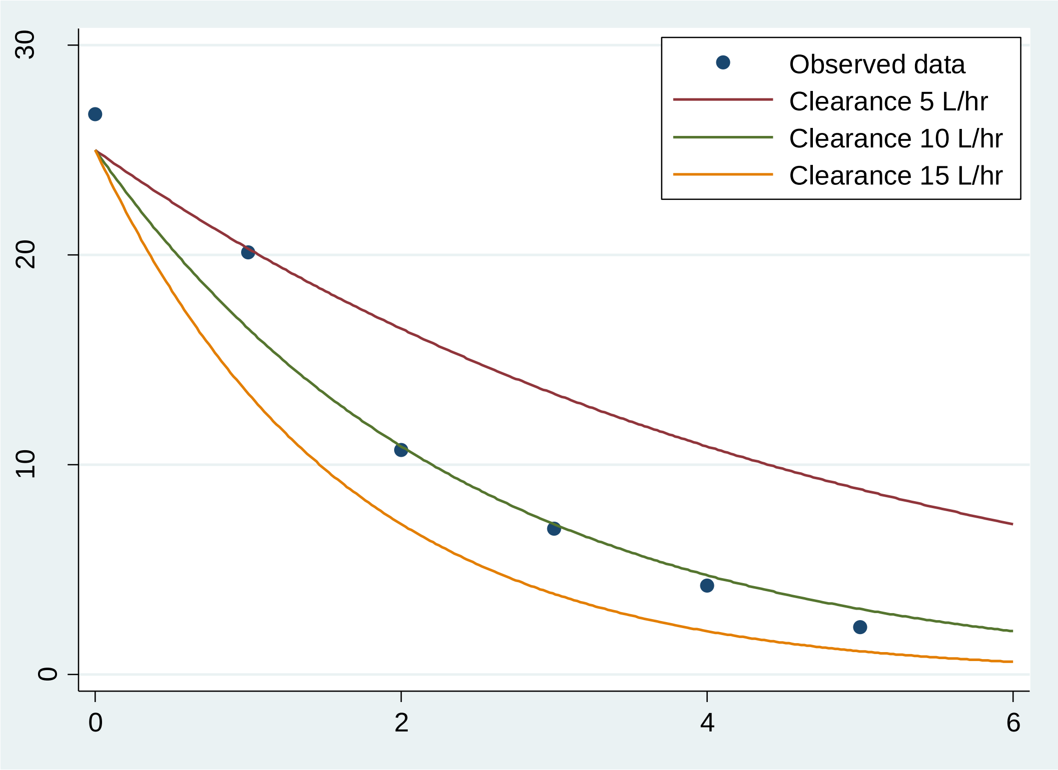


Step 3 - Initial values for PK parameters

$$C = (\text{dose}/V) * e^{(-(CL/V)*\text{time})}$$

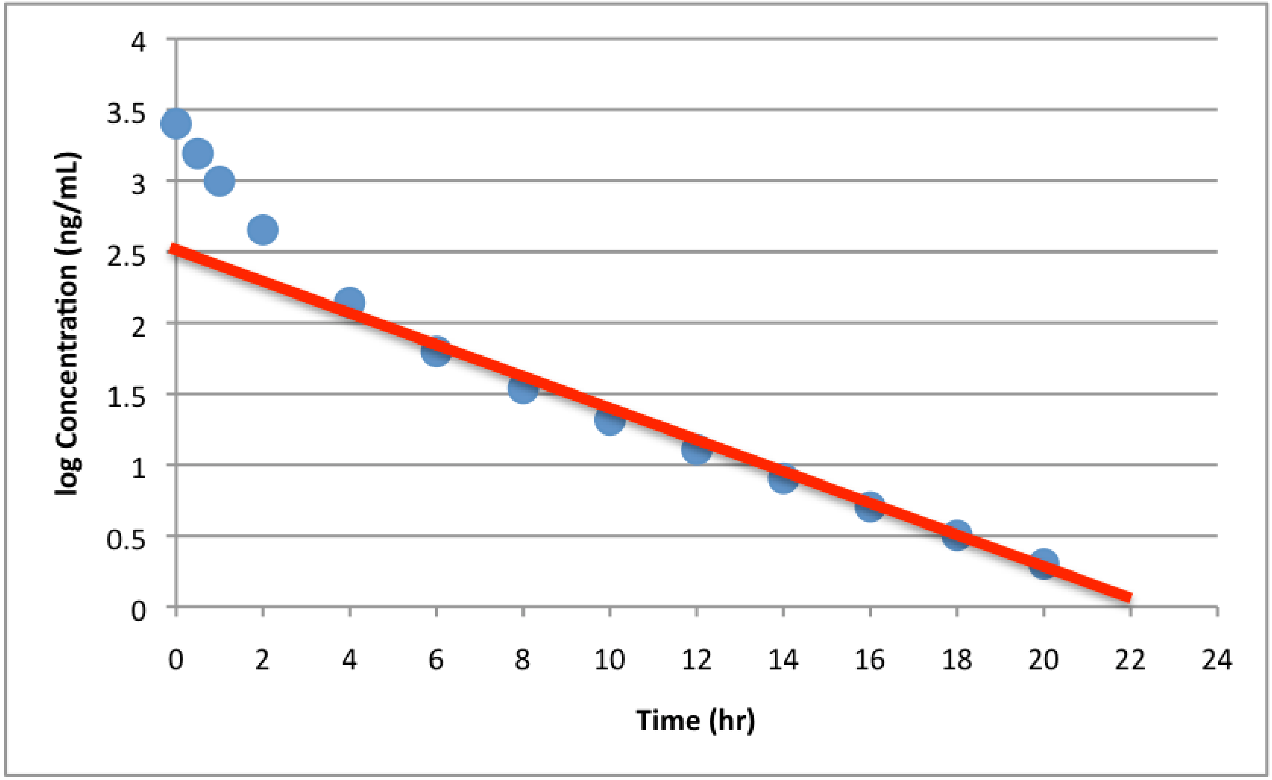
Dose – 600 mg

Try V= 600/25 = 24 & CL= 5, 10, 15



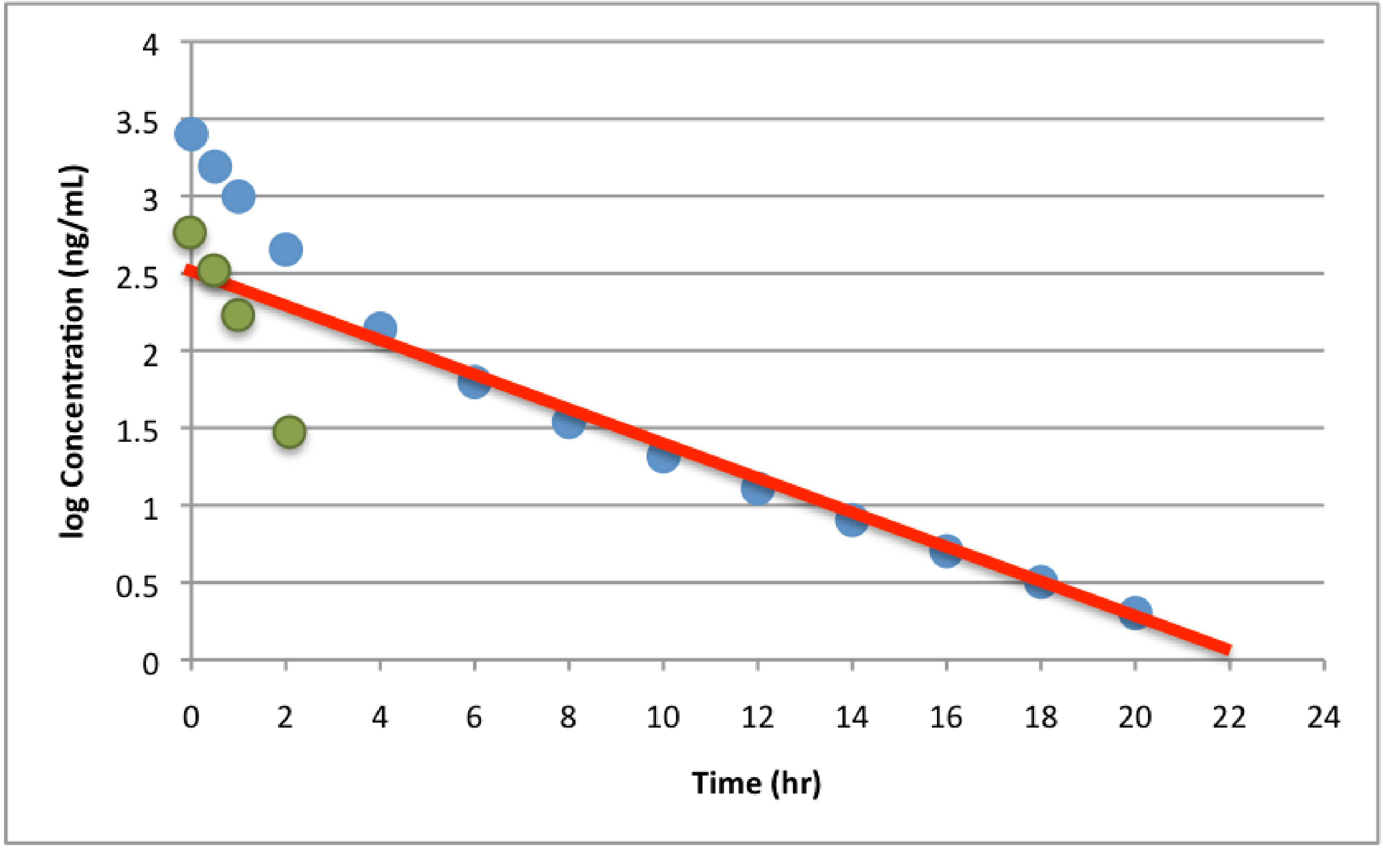
Step 3 - Initial values for PK parameters – Curve Stripping

Two-compartment model, IV administration $C(t)=Ae^{-\alpha t}+Be^{-\beta t}$



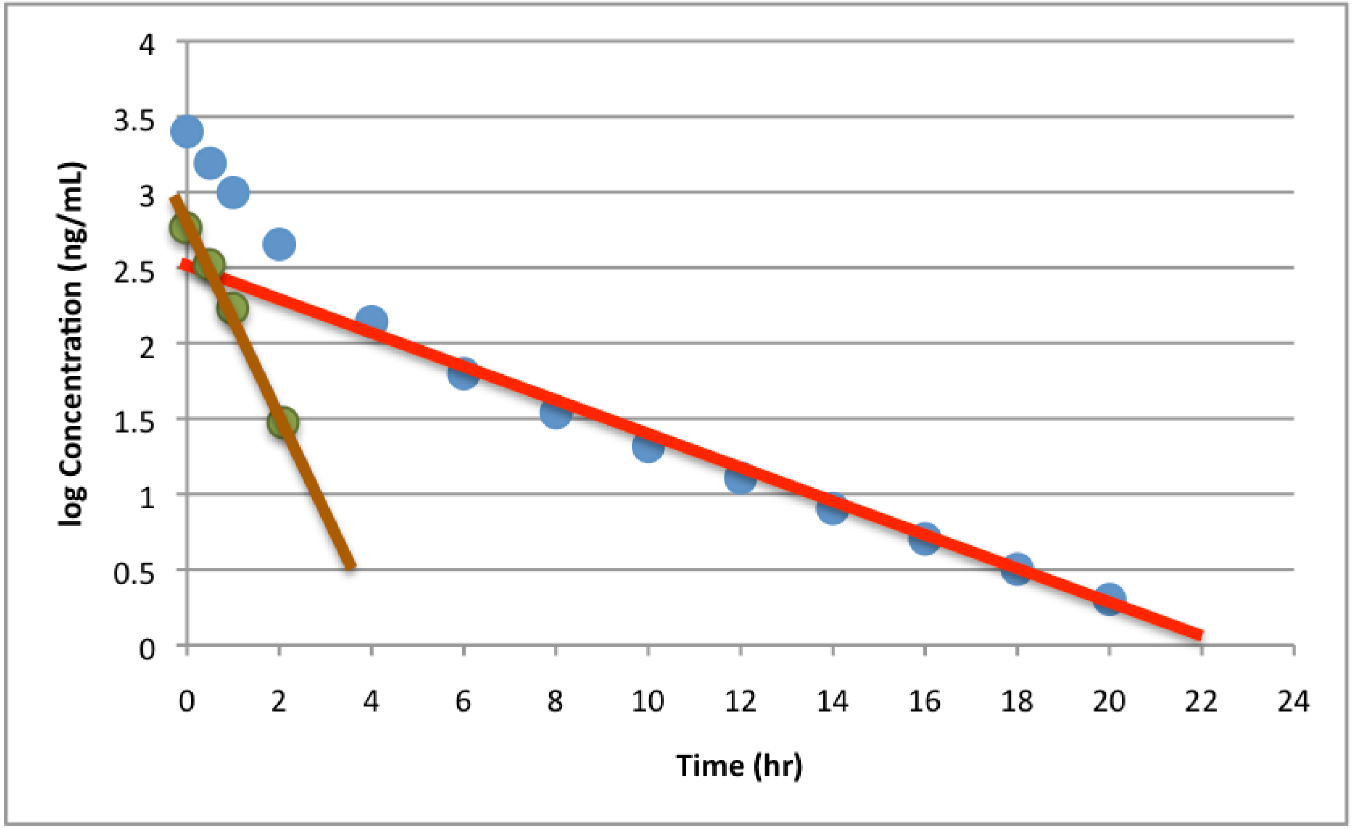
Source: www.learnpkpd.com

Step 3 - Initial values for PK parameters – Curve Stripping



Source: www.learnpkpd.com

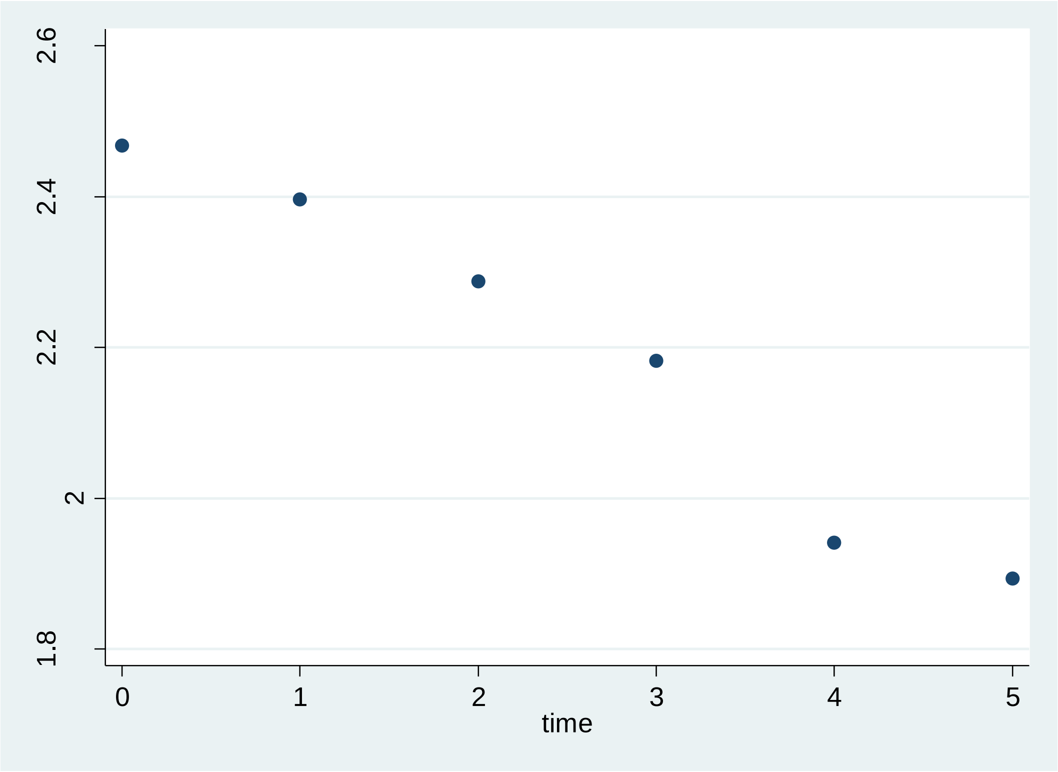
Step 3 - Initial values for PK parameters – Curve Stripping



Source: www.learnpkpd.com

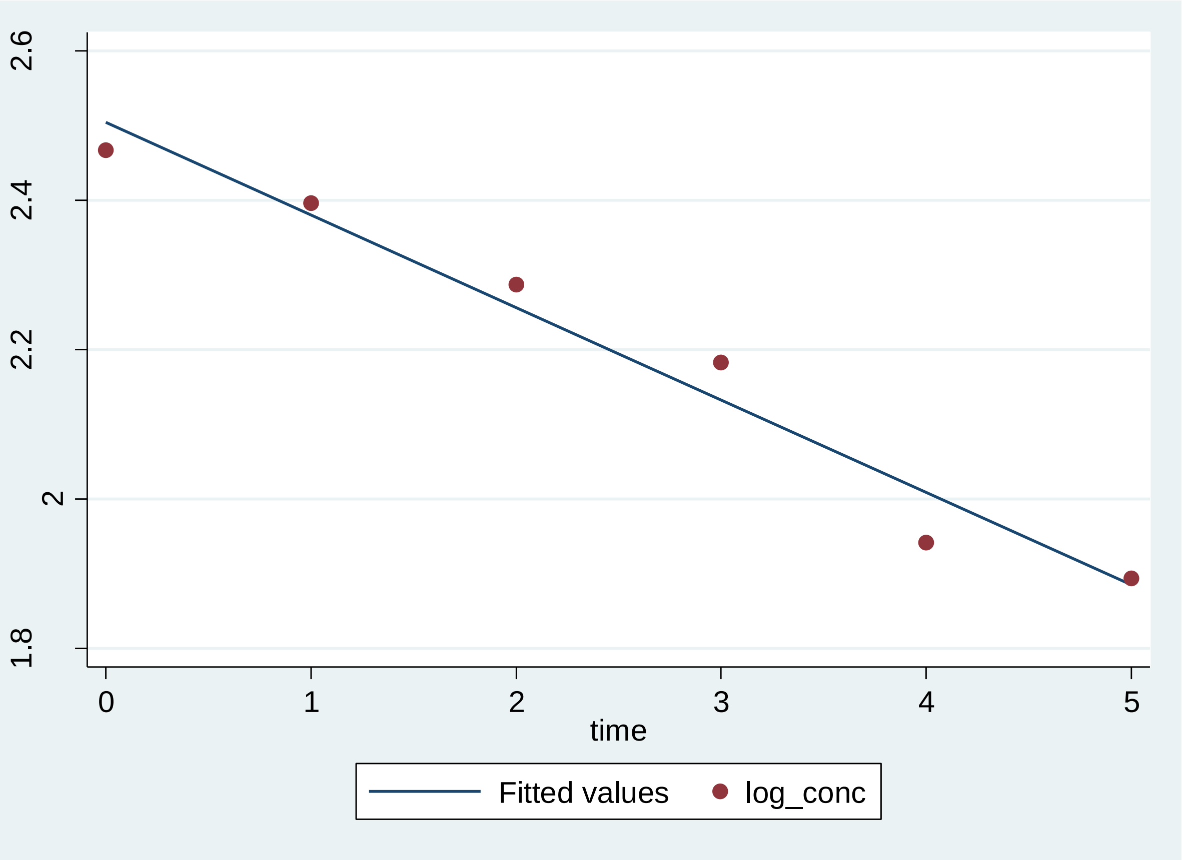
Step 4 – Estimate PK parameters using nonlinear regression

Linear Regression – LC = $\beta_0+\beta_1$*time **(where LC=$\log_e$(C))**



Step 4 – Estimate PK parameters using nonlinear regression

Linear Regression: Line of best fit – determined using method of ordinary least squares (OLS)



Step 4 – Estimate PK parameters using nonlinear regression

Linear Regression - LC = 2.504 – 0.124*time

Stata output

```
reg log_conc time

      Source |       SS       df       MS              Number of obs =       6
-------------+------------------------------           F(  1,      4) =  110.72
       Model |  .269042563     1  .269042563           Prob > F      =  0.0005
    Residual |  .009719381     4  .002429845           R-squared     =  0.9651
-------------+------------------------------           Adj R-squared =  0.9564
       Total |  .278761944     5  .055752389           Root MSE      =  .04929

------------------------------------------------------------------------------
    log_conc |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
        time |  -.1239914    .0117834   -10.52   0.000    -.1567073   -.0912754
       _cons |   2.504657     .035676    70.21   0.000     2.405605     2.60371
------------------------------------------------------------------------------
```

Step 4 – Estimate PK parameters using nonlinear regression

Nonlinear Regression

The relationship between the Y-variable (i.e. Drug concentrations) and the X-variable (time) depends nonlinearly on the model parameters (e.g. k_a, CL and V).

$$C = \frac{dose.k_a.F}{V.k_a - CL}[e^{-(CL/V).t} - e^{-k_a.t}]$$

Step 4 – Estimate PK parameters using nonlinear regression

Nonlinear versus Linear Regression

Linear regression – One unique solution of the model parameters

Nonlinear regression:

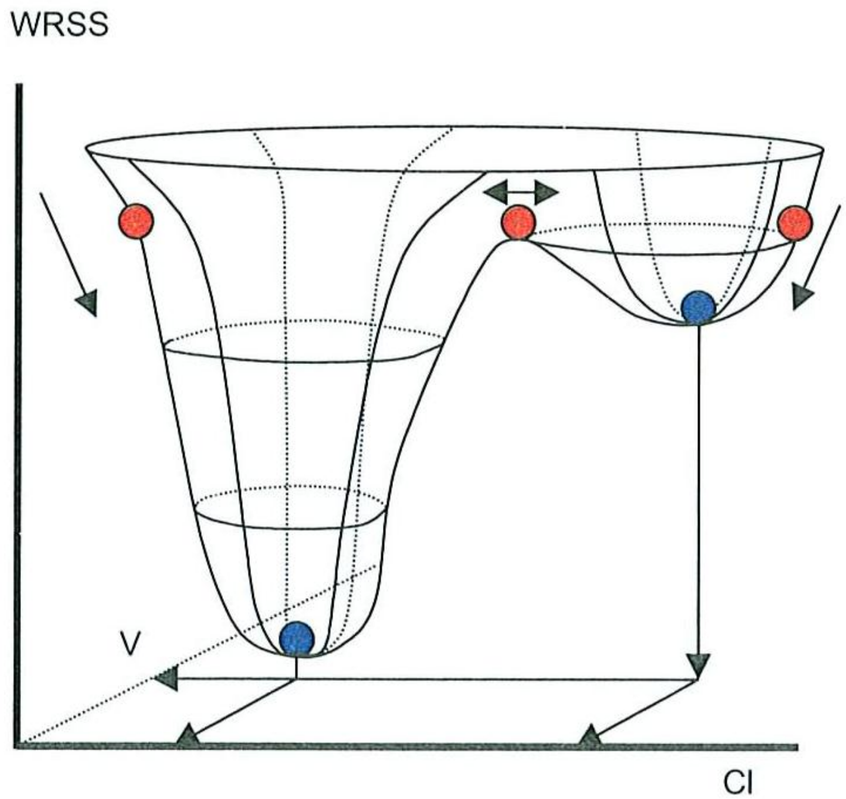
- **Different sets of model parameters can arrive at a false minimum**
- **Need to find the set of model parameters that reach the global minimum**
- **Initial values for each parameter required**
- **Choice of initial values very important**

← **User specifies**

Step 4 – Estimate PK parameters using nonlinear regression

Nonlinear regression:

- **Different sets of model parameters can arrive at a false minimum**
- **Need to find the set of model parameters that reach the global minimum**



Source: **Pharmacokinetic and Pharmacodynamic Data Analysis:*Concepts & Applications.* Johan Gabrielsson & Daniel Weiner**

Step 4 – Estimate PK parameters using nonlinear regression

Estimation Methods

Criteria for best fit (i.e. minimization method)

Ordinary Least Squares (OLS)
Weight Least Squares (WLS)
Maximum Likelihood Estimation (MLE)

Searching algorithms to determine parameter estimates

Newton-Raphson (linearization method)
Marquardt – Levenberg
Nelder-Mead (simplex method)

Step 4 – Estimate PK parameters using nonlinear regression

Estimation Methods (Methods of Minimization)

Example:- Intravenous administration

Statistical package:- Stata

Nonlinear least squares (default algorithm– Gauss-Newton):-

```
nl (conc = (600/{V})*exp(-({CL}/{V})*time)), initial(V 24 CL 15)
```

Output

```
------------------------------------------------------------------------------
        conc |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
          /V |   21.64232    1.01893    21.24   0.000     18.81331    24.47132
         /CL |   9.642787   .7046769    13.68   0.000     7.686291    11.59928
------------------------------------------------------------------------------
```

Step 5 – Sensitivity of PK parameter estimates to different initial values

Example:- Intravenous administration

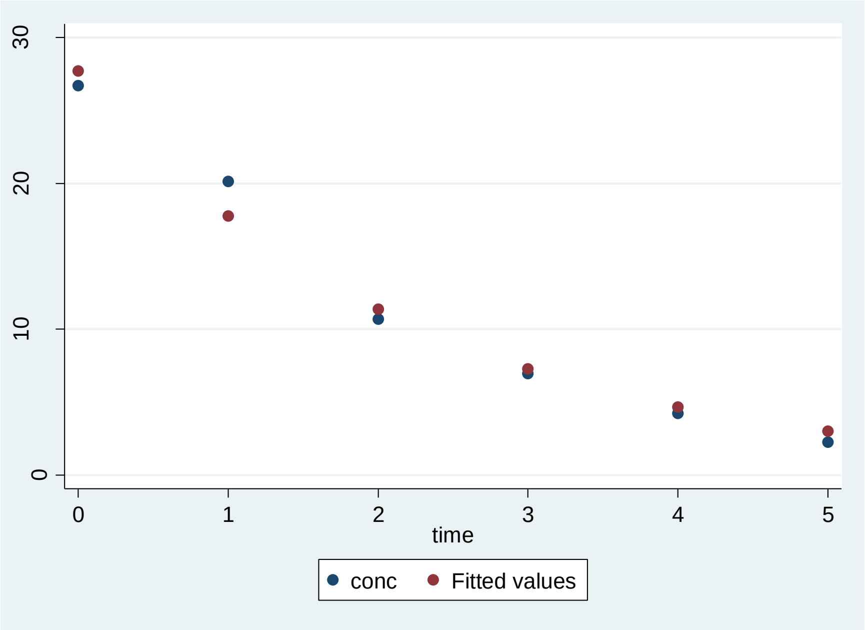
Statistical package:- Stata

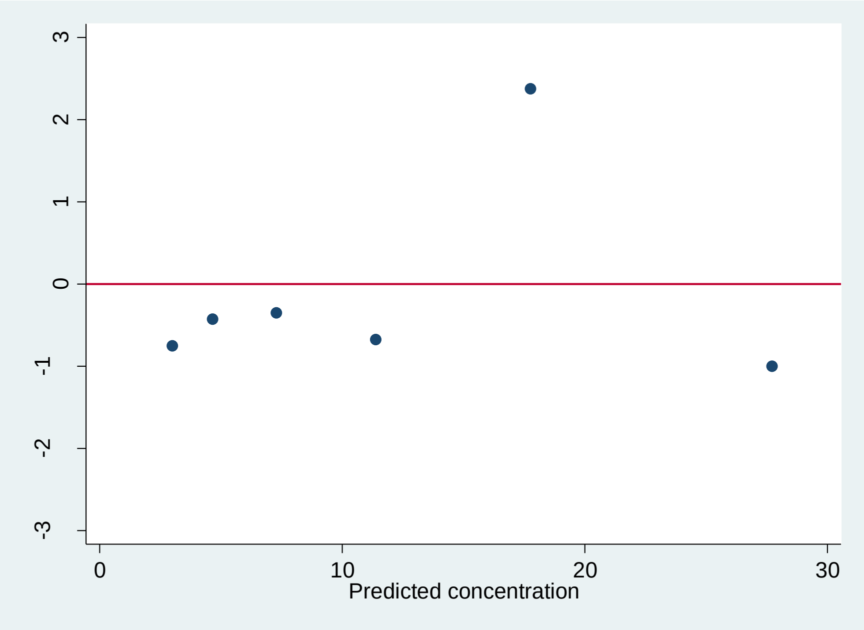
```
nl (conc = (600/{V})*exp(-({CL}/{V})*time)), initial(V 24 CL 15)
------------------------------------------------------------------------------
        conc |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
          /V |   21.64232    1.01893    21.24   0.000     18.81331    24.47132
         /CL |   9.642787   .7046769    13.68   0.000     7.686291    11.59928
------------------------------------------------------------------------------
```

```
nl (conc = (600/{V})*exp(-({CL}/{V})*time)), initial(V 24 CL 5)
nl (conc = (600/{V})*exp(-({CL}/{V})*time)), initial(V 24 CL 50)
```

Step 6 – Assessment of the fit of the PK model to the observed data

Visual assessment





Step 6 - Assessment of the fit of the PK model to the observed data

Precision of the estimates of the PK parameters

Stata Output

```
------------------------------------------------------------------------------
        conc |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
          /V |   21.64232    1.01893    21.24   0.000     18.81331    24.47132
         /CL |   9.642787   .7046769    13.68   0.000     7.686291    11.59928
------------------------------------------------------------------------------
```

Coefficient of variation (%CV)

V = 4.7%   CL = 7.3%

Step 6 - Comparison of different structural PK models

Akaike Information Criterion (AIC)

Example:- Intravenous administration

One versus Two-compartmental model

1-compartment AIC = 22.5

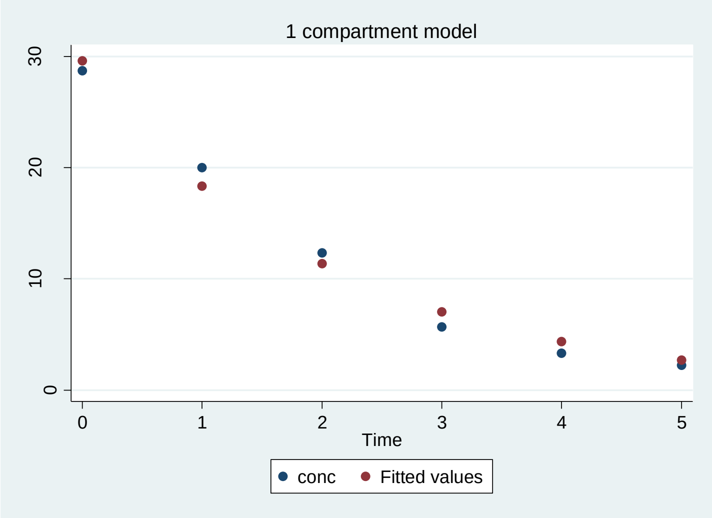
conc	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
/V	20.27007	.8841589	22.93	0.000	17.81525	22.72489
/beta	.4792328	.0389033	12.32	0.000	.3712199	.5872456

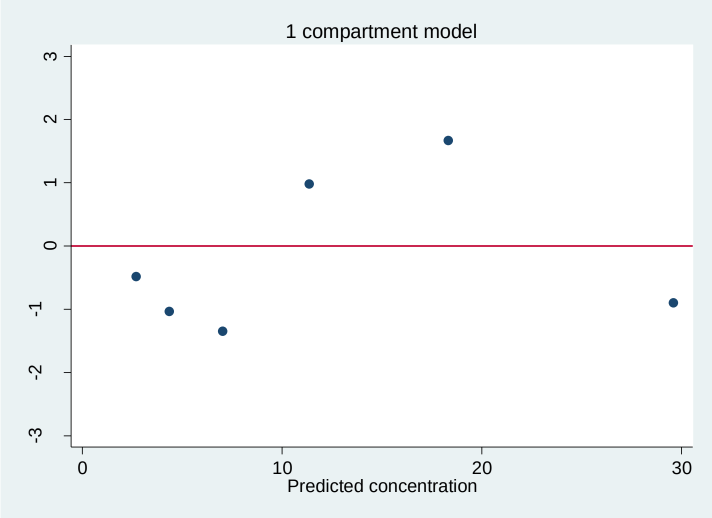
2-compartment AIC = 14.8

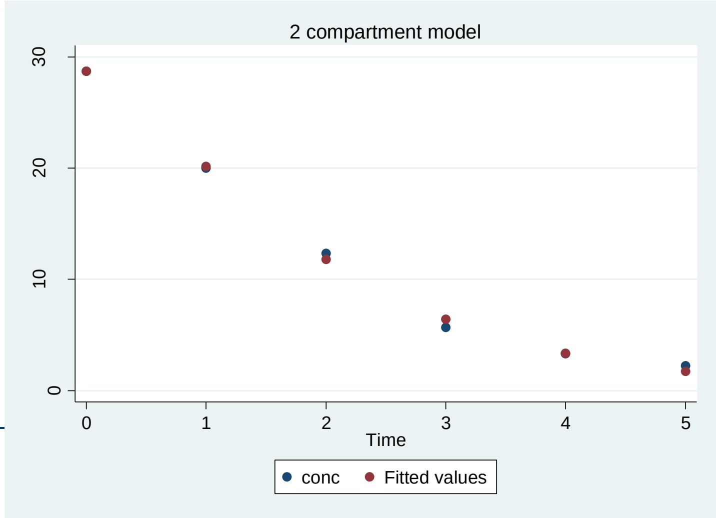
conc	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
/V	20.91251	.5362697	39.00	0.001	18.60513	23.21989
/alpha	.685805	.3467951	1.98	0.187	-.8063339	2.177944
/k21	1.772028	1.569598	1.13	0.376	-4.981405	8.525461
/beta	1.254571	1.67838	0.75	0.533	-5.966915	8.476056

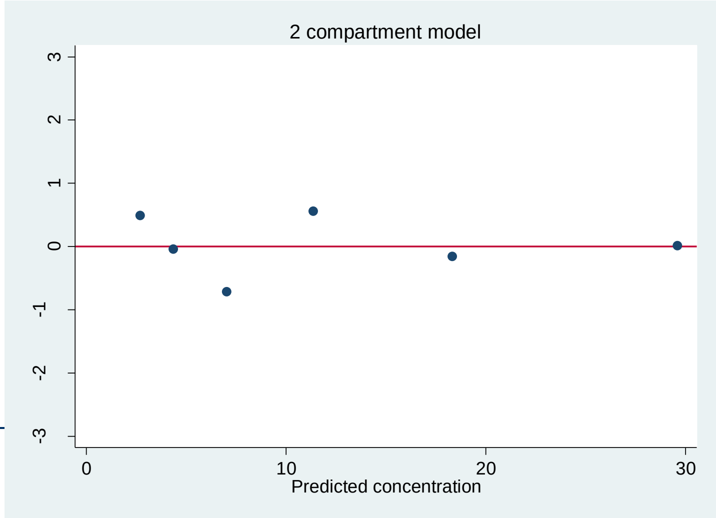
Step 6 - Comparison of different structural PK models

Visual comparison

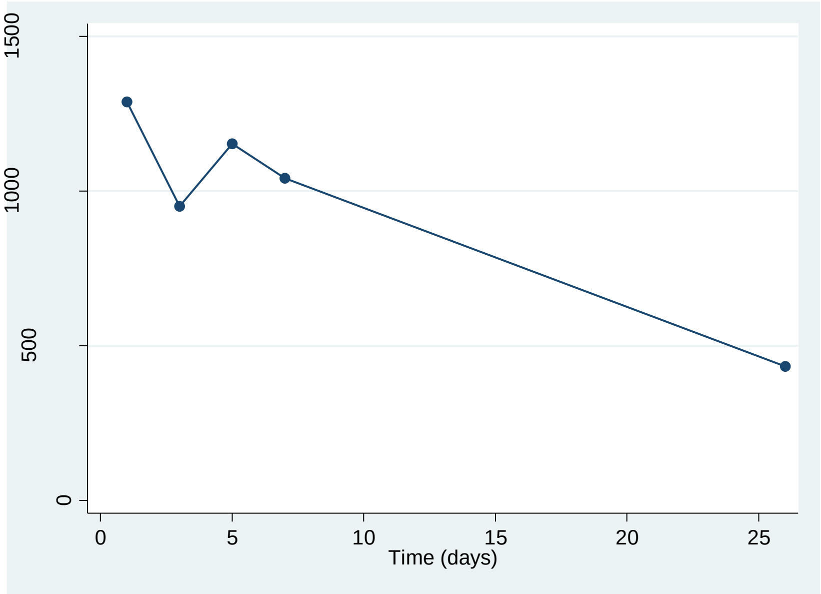


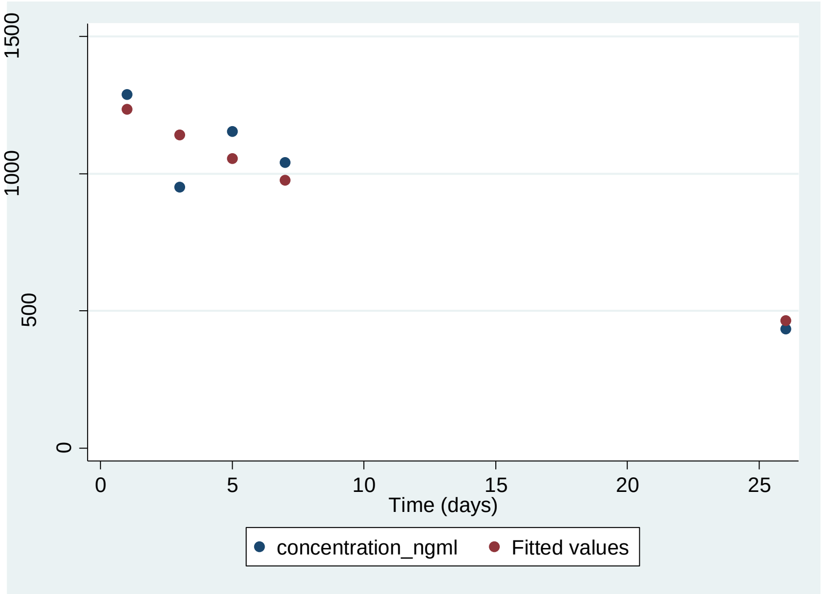






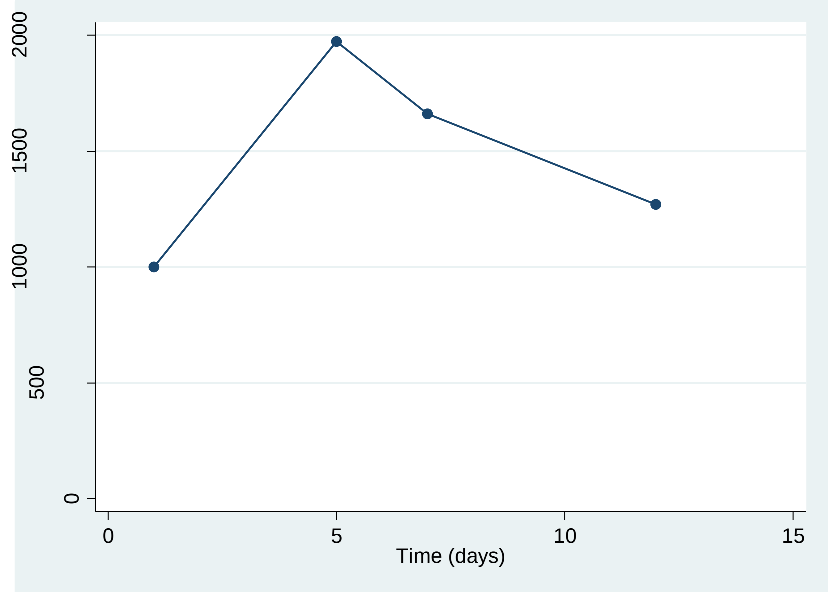
Some more guidelines......

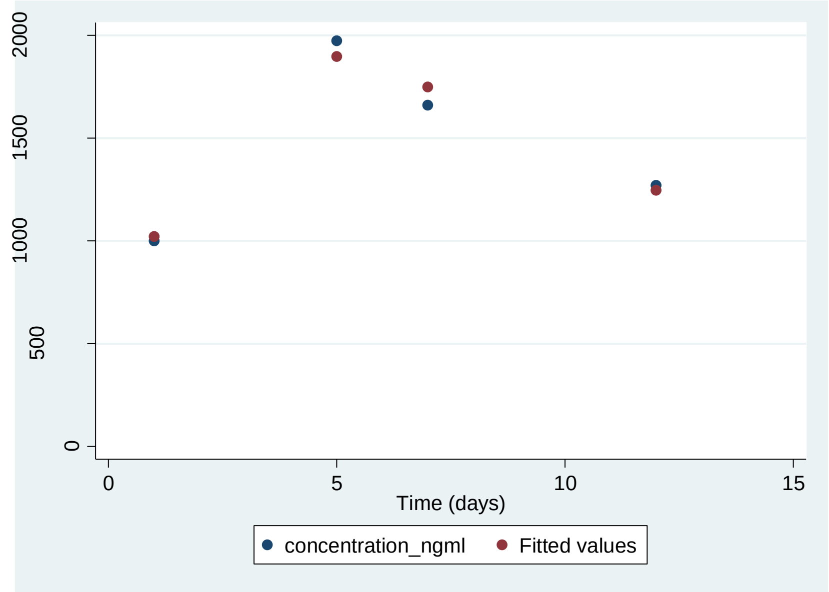




concentrat~l	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
/ka	129.0395	.	.	.	.	.
/v	19.46911	1.566804	12.43	0.001	14.48284	24.45538
/cl	.7621449	.1960614	3.89	0.030	.13819	1.3861

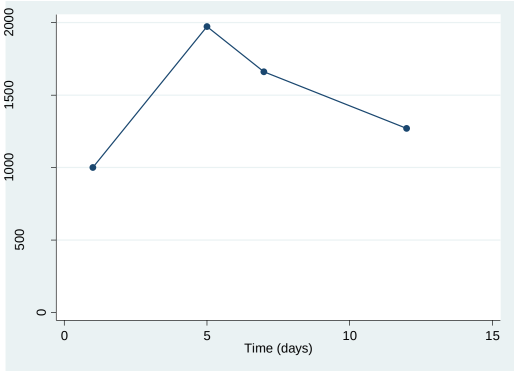
Some more guidelines......

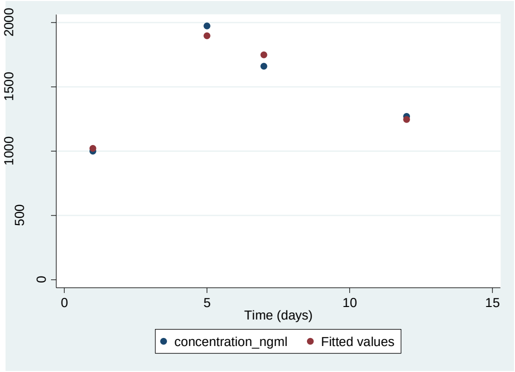




concentrat~l	Coef.	Std. Err.	t	P>|t|	[95% Conf. Interval]	
/ka	.5081871	.1479703	3.43	0.180	-1.371954	2.388328
/v	9.350541	1.546347	6.05	0.104	-10.29766	28.99874
/cl	.7184482	.1482047	4.85	0.130	-1.164672	2.601568

Some more guidelines……

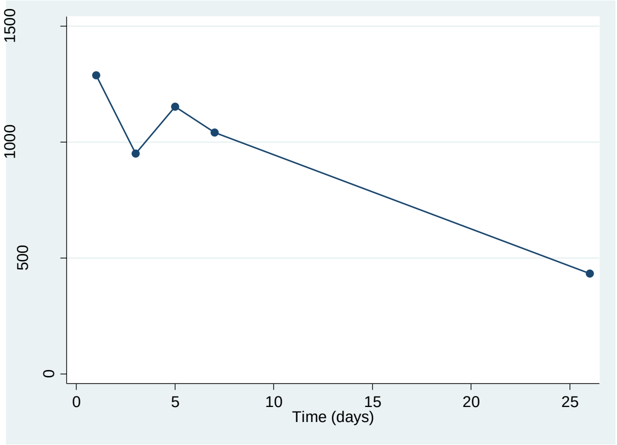


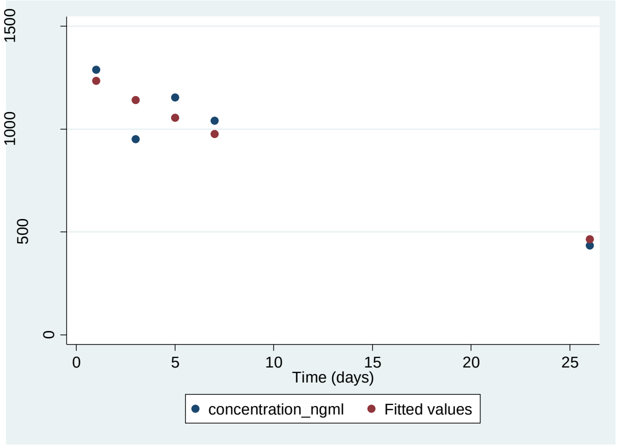


Correlation matrix of coefficients of nl model

e(V)	ka _cons	v _cons	cl _cons
ka _cons	1.0000		
v _cons	0.8710	1.0000	
cl _cons	-0.7647	-0.8814	1.0000

Some more guidelines......






```
Correlation matrix of coefficients of nl model

             | ka        | v         | cl
        e(V) |     _cons |     _cons |     _cons
-------------+-----------+-----------+----------
ka           |           |           |
       _cons |         . |           |
-------------+-----------+-----------+----------
v            |           |           |
       _cons |         . |    1.0000 |
-------------+-----------+-----------+----------
cl           |           |           |
       _cons |         . |   -0.4841 |    1.0000
```

Useful WEBSITES & Textbooks

www.learnpkpd.com

Pharmacokinetic and Pharmacodynamic Data Analysis:
Concepts & Applications
Johan Gabrielsson & Daniel Weiner

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