



## One Phase Association

The objective of this case study is to investigate how plasma drug concentration changes as time increases during constant-rate intravenous infusion and to quantify that relationship using nonlinear curve fitting in **Isalos Analytics Platform**. In this case study, the **One Phase Association** model is used to estimate the **initial concentration**, the **plateau concentration**, and the **apparent rate constant** using a standard exponential association framework.

The dataset used in this case study is a pharmacokinetic dataset describing **plasma cimetidine concentration over time during andante constant-rate intravenous infusion in a beagle dog**, published by *Yu RH et. al(2017)*. The paper presents the measured **time** values and the corresponding **plasma cimetidine concentration**. In this model, the independent variable (X) is **time (h)**, and the dependent variable (Y) is **plasma cimetidine concentration (µg/mL)**.

The **One Phase Association** model describes a saturating exponential relationship in which the response increases rapidly at earlier times and then gradually approaches a limiting plateau at later times. The equation used in this analysis is:

$$Y = Y0 + (\text{Plateau} - Y0) \times (1 - e^{-KX})$$

In this model, **Y0** represents the starting concentration at the beginning of the observed time course, **Plateau** represents the concentration approached at steady state, and **K** represents the apparent first-order rate constant governing the rise toward that plateau.

The purpose of this analysis is to determine whether the observed data are consistent with a one-phase exponential accumulation mechanism and to convert the measured concentration values into biologically meaningful quantitative outputs. The main results obtained from the fit are **Y0**, **Plateau**, and **K**, where **Y0** reflects the initial plasma cimetidine concentration, **Plateau** reflects the steady-state concentration approached during infusion, and **K** reflects the rate at which the drug accumulates toward steady state. These results are useful because they allow direct interpretation of drug accumulation kinetics during infusion and support comparison between compounds or infusion conditions.

*Isalos version used: 2.0.2*

*Scientific Article: <https://www.nature.com/articles/s41598-017-13437-6>*

## Step 1: Import data from file

Right-click on the input spreadsheet panel on the left and choose **“Import from File”**. Then browse to the file containing the XY dataset for this case study and load the sheet in which each row corresponds to one time value and one measured plasma concentration value.

	Col1	Col2	Col3	Col4	Col5	Col6	Col7	Col8
User Header	User Row ID							
1								
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
13								
14								
15								
16								

- Show Spreadsheet Toolbar
- Import from File
- Import from Spreadsheet
- Import from Multiple Spreadsheets
- Adjust Spreadsheet Precision
- Export Spreadsheet Data
- Clear Spreadsheet

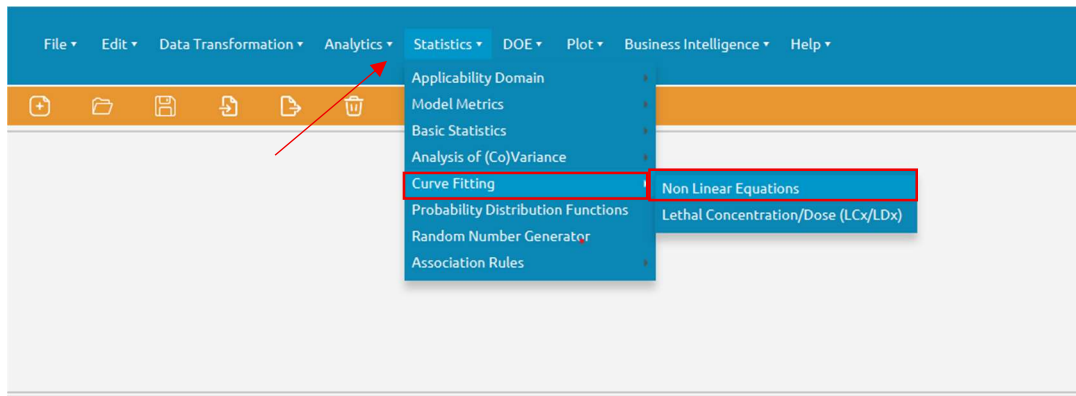
The data will appear on the left spreadsheet.

The screenshot shows the Isalos Analytics Platform interface. At the top, there is a blue header bar with the logo and a menu bar containing 'File', 'Edit', 'Data Transformation', 'Analytics', 'Statistics', and 'DOE'. Below the header is an orange toolbar with icons for adding, deleting, and saving files. An 'Action' button is visible on the left. The main area displays a spreadsheet with the following data:

	Col1	Col2 (D)	Col3 (D)	Col4	Col5	Col6
User Header	User Row ID	Time (h)	Plasma cimetidine concentration (µg/mL)			
1		0.17	1.38			
2		0.5	1.88			
3		1.0	2.31			
4		1.5	2.83			
5		2.0	2.96			
6		3.0	3.73			
7		4.0	4.41			
8		5.0	4.27			
9		6.0	4.42			
10		7.0	4.41			
11		7.5	4.34			
12		8.0	4.06			
13						
14						
15						

## Step 2: Select the Statistic Analysis Model

From the toolbar, open the **Statistics** drop-down list and navigate through **Statistics > Curve Fitting > Non Linear Equations**.



In the category list, select the **Exponential** equations category and then choose **One Phase Association** from the model menu.

Curve Fitting - Non Linear Equations

Category: Exponential

Model: One phase association

Independent Variable: [Empty]

Dependent Variable: [Empty]

Confidence Level (%): Double (0,100), Default: 95

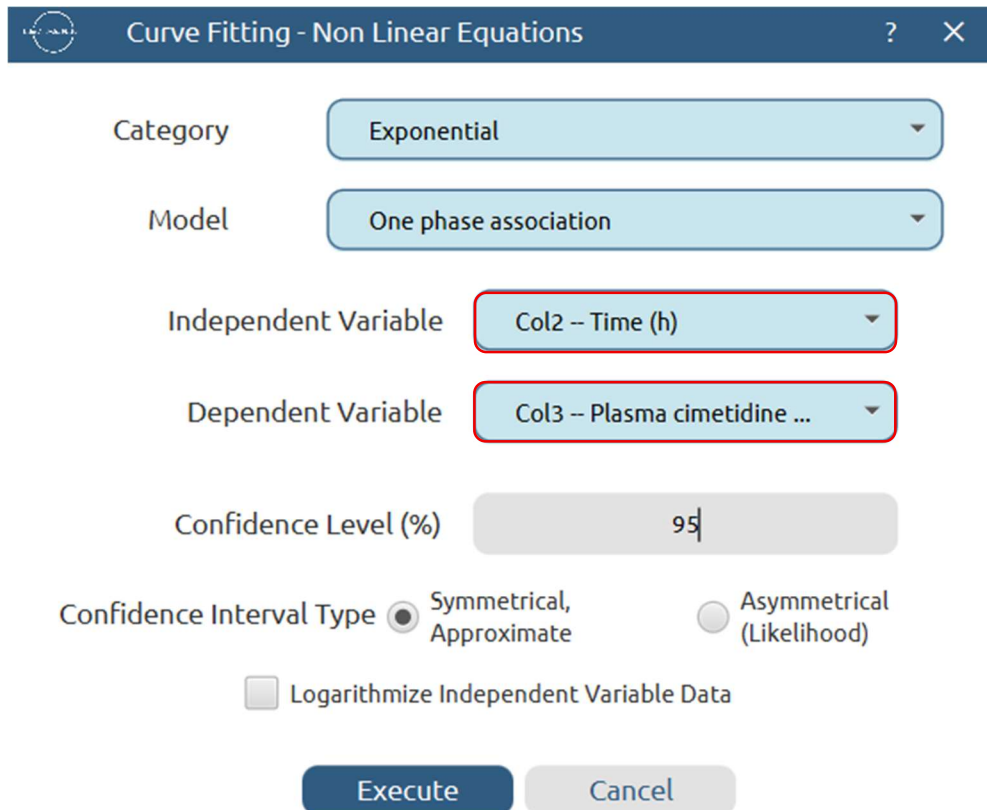
Confidence Interval Type:  Symmetrical, Approximate  Asymmetrical (Likelihood)

Logarithmize Independent Variable Data

Execute Cancel

## Step 3: Configure Variables and Confidence Intervals

Set the column containing the **time** values as the independent variable (X), and set the column containing the **plasma concentration** values as the dependent variable (Y). Set the confidence level to **95%** and choose **Symmetrical Approximate** as the confidence interval type.



Curve Fitting - Non Linear Equations

Category: Exponential

Model: One phase association

Independent Variable: Col2 -- Time (h)

Dependent Variable: Col3 -- Plasma cimetidine ...

Confidence Level (%): 95

Confidence Interval Type:  Symmetrical, Approximate  Asymmetrical (Likelihood)

Logarithmize Independent Variable Data

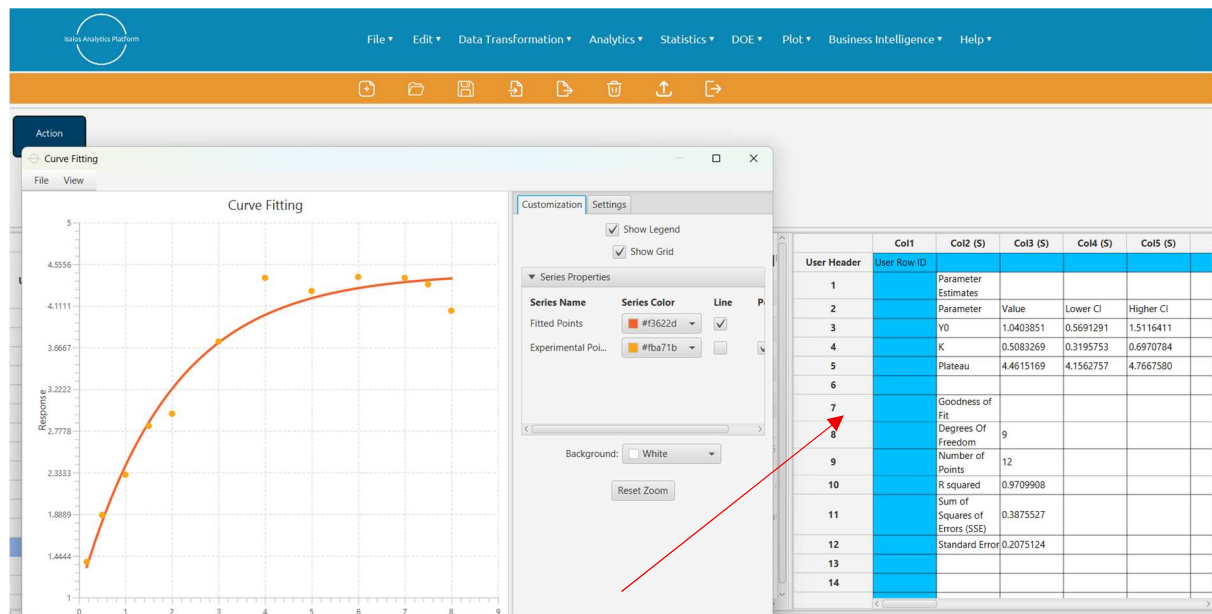
Execute Cancel

## Step 4: Analyzing the Output and Fitted Curves

Once the analysis is completed, Isalos presents the fitted association curve together with the experimental data points, allowing direct visual assessment of how well the model captures the observed pharmacokinetic accumulation pattern. The results page presents the estimated model parameters with their confidence limits, together with goodness-of-fit statistics and the corresponding fitted plot. In the **One Phase Association** model, the main fitted parameters are **Y<sub>0</sub>**, **Plateau**, and **K**, and the graphical output displays an increasing exponential curve in which plasma concentration rises with time and gradually approaches a steady-state plateau.

The **Goodness of Fit** section of the table summarizes key fitting statistics such as the **number of data points used**, **degrees of freedom**, **residual sum of squares**, and the **standard error of the regression**. These outputs should be interpreted together with the fitted plot in order to

evaluate how well the model describes the data and how reliable the estimated parameters are.



The fitted results indicate that plasma cimetidine concentration during constant-rate intravenous infusion is well described by a one-phase association model, in which drug levels rise over time and gradually approach a steady-state plateau. The estimated **Y0** value of approximately **1.04 µg/mL** represents the extrapolated starting concentration at the beginning of the fitted time course, the estimated **Plateau** value of approximately **4.46 µg/mL** represents the concentration approached at long times during infusion, and the fitted **K** value of approximately **0.508 h<sup>-1</sup>** reflects the rate at which plasma cimetidine accumulates toward steady state.

The narrow confidence interval for the plateau estimate, together with the high  $R^2$  value of **0.971** and the relatively low residual error, suggests that the one-phase association model provides a good description of the concentration-time data.

## References:

- (1) Yu, R.H. and Cao, Y.X., 2017. A method to determine pharmacokinetic parameters based on andante constant-rate intravenous infusion. *Scientific reports*, 7(1), p.13279.