NCA

Phoenix's noncompartmental analysis (NCA) engine computes derived measurements from raw data by using methods appropriate for either serially- or sparsely-sampled data. Phoenix provides the following NCA models for different types of input data:

200 Plasma/blood data type, extravascular dose type, requires constants for time of last dose and dose interval (Tau)[a]

201 Plasma/blood data type, IV Bolus dose type, requires constants for time of last dose and dose interval (Tau)[a]

202 Plasma/blood data type, constant infusion dose type, requires constants for length of infusion, time of last dose, dose interval (Tau)[a]

210 Urine data type, extravascular dose type, requires constants for time of last dose

211 Urine data type, IV Bolus dose type, requires constant for time of last dose

212 Urine data type, constant infusion dose type, requires constant for time of last dose

220 Drug effect data type, any dose type, requires constants for time, baseline effect, and threshold (optional)

[a]Tau is required for steady-state data only.

Models 200–202 can be used for either single-dose or steady-state data. For steady-state data, the computation assumes equal dosing intervals (Tau) for each profile, and that the data are from a “final” dose given at steady-state.

Models 210–212 (urine concentrations) assume single-dose data, and the final parameters do not depend on the dose type.

The plasma and urine models support rich datasets as well as sparsely-sampled studies such as toxicokinetic studies. The drug effect model is for analysis of slope, height, areas, and moments in richly-sampled time-effect data.

Use one of the following to add the object to a Workflow:

Right-click menu for a Workflow object: **New > NonCompartmental Analysis > NCA**.
Main menu: **Insert > NonCompartmental Analysis > NCA**.
Right-click menu for a worksheet: **Send To > NonCompartmental Analysis > NCA**.

Note: To view the object in its own window, select it in the Object Browser and double-click it or press **ENTER**. All instructions for setting up and execution are the same whether the object is viewed in its own window or in Phoenix view.

This section contains information on the following topics:

NCA user interface description
Results
NCA computation rules
NCA parameter formulas
NCA examples

NCA user interface description

Main Mappings panel
Dosing panel
Slopes Selector panel
Slopes panel

Partial Areas panel
Therapeutic Response panel
Units panel
Parameter Names panel
Options tab
User Defined Parameters tab
Rules tab
Plots tab

Main Mappings panel

Use the Main Mappings panel to identify how a dataset is used with an NCA object by mapping data types in a dataset to the appropriate contexts. Context associations change depending on the selected NCA model. Required input is highlighted orange in the interface.

None: Data types mapped to this context are not included in any analysis or output.
Sort: Categorical variable(s) identifying individual data profiles, such as subject ID in an NCA study. A separate analysis is done for each unique combination of sort variable values.
Carry: Data variable(s) to include in the output worksheets. Note that time-dependent data variables (those that change over the course of a profile) are not carried over to time-independent output (e.g., Final Parameters), only to time-dependent output (e.g., Summary).

Plasma study

Time: Nominal or actual time collection points in a plasma study.
Concentration: Drug concentration values in the blood of a plasma study.
(Plasma Models with Sparse Sampling also require a single Subject mapping.)

Urine study

Start Time: Starting times for individual collection intervals during a urine study.
End Time: Ending times for individual collection intervals during a urine study.
Concentration: Dependent variable, drug concentration in urine.
Volume: Volume of urine collected per time interval.

Drug effect study

X: Time values for the drug effect data.
Y: Drug effect or response values.

Dosing panel

The Dosing panel allows users to type or map dosing data for the different NCA models.

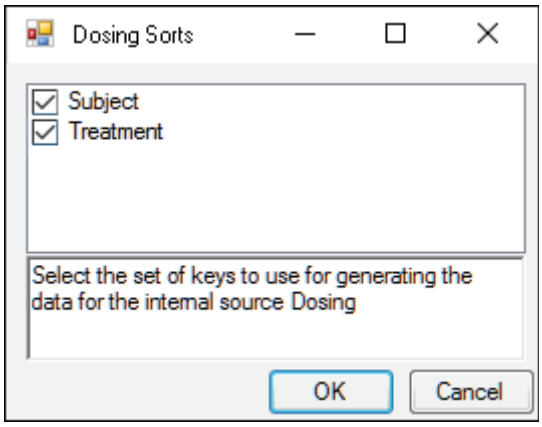
Models 200–202 (plasma) assume that data were taken after a single dose or after a final dose at steady state. For steady state Phoenix also assumes equal dosing intervals.

Models 210–212 (urine) assume single-dose urine data. If dose time is not entered, Phoenix uses a time of zero.

Model 220 (drug effect) uses the same time scale and units as the input dataset. Users enter the time of the most recent dose for each profile.

The Dosing panel columns change depending on the model type and dose type selected in the Options tab.

The first time a user selects the Dosing panel, if sort keys are defined in the Main Mappings panel, Phoenix displays the *Dosing sorts* dialog.



The dialog has all of the currently specified sort variables selected by default. The selected sort variables will be used when creating the internal dosing worksheet. To select a subset of the sort variables, clear the checkbox beside the unwanted variable and click **OK**.

Context associations change depending on the selected NCA model. Required input is highlighted orange in the interface.

None: Data types mapped to this context are not included in any analysis or output.
Sort: Categorical variable(s) identifying individual data profiles. A separate computation is done for each unique combination of sort variable values.
Time: Time of dose administration.
Dose: Amount of drug per profile.
Tau: The (assumed equal) dosing interval for steady-state data. TAU must be a positive number for steady-state profiles and blank for non-steady-state profiles.
Infusion_Length: Total amount of time for an IV infusion.
Dose_Type: Dosing route, if not defined in the Options tab.

Note: The time units for the dosing data must be the same as the time units for the time/concentration data.

Slopes Selector panel

Phoenix attempts to estimate the rate constant, Lambda Z, associated with the terminal elimination phase for concentration data. If Lambda Z is estimable, parameters for concentration data will be extrapolated to infinity. For drug effect models, Phoenix estimates the two slopes at the beginning and end of the data. NCA does not extrapolate beyond the observed data for drug effect models.

The observed times for each profile are displayed in a graph on separate tabs in the Slopes Selector panel. Below are usage instructions. For descriptions of how the NCA object determines Lambda Z or slope estimation settings, see “Lambda Z or Slope Estimation settings”.

Note: Any changes to the settings available in the Slopes Selector panel also affect the Slopes panel and vice versa.

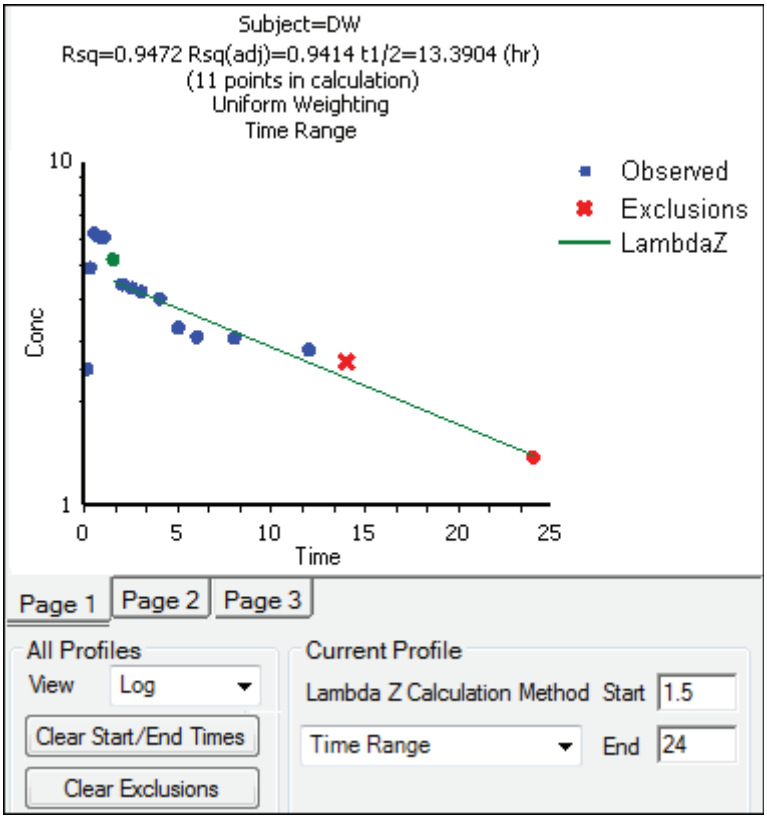
- Use the **View** menu to select a linear (**Lin**) or logarithmic (**Log**) axis scale.
- Use the **Lambda Z Calculation Method** menu to select a method.
  If **Best Fit** is selected, Phoenix calculates the points for Lambda Z estimation for each profile.
  If **Time Range** is selected, users must enter the start and end times for Lambda Z estimation.

- To turn off Lambda Z or slope estimation for all profiles, select the **Disable Curve Stripping** checkbox in the Options tab. For more information see step 4 in "Model settings".

Users can manually select start times, end times, and excluded time points by selecting them on the graph for each profile (this action automatically sets the **Lambda Z Calculation Method** to **Time Range**.

Click a data point on a graph to select the start time.
SHIFT+click a data point on a graph to select the end time.
CTRL+click a data point on a graph to exclude the time point.
Change the start time, end time, and exclusions by selecting new points on the graph using the same key combinations listed above.

When the start time, end time, and exclusions are manually selected, the graph title is updated to show the new R^2 calculation, the graph is updated to show the new slope, and the legend is updated to show the new slope and exclusions, as shown below.



Note: Excluded data points apply only to Lambda Z or slope calculations. The excluded data points are still included in the computation of AUCs, moments, etc.

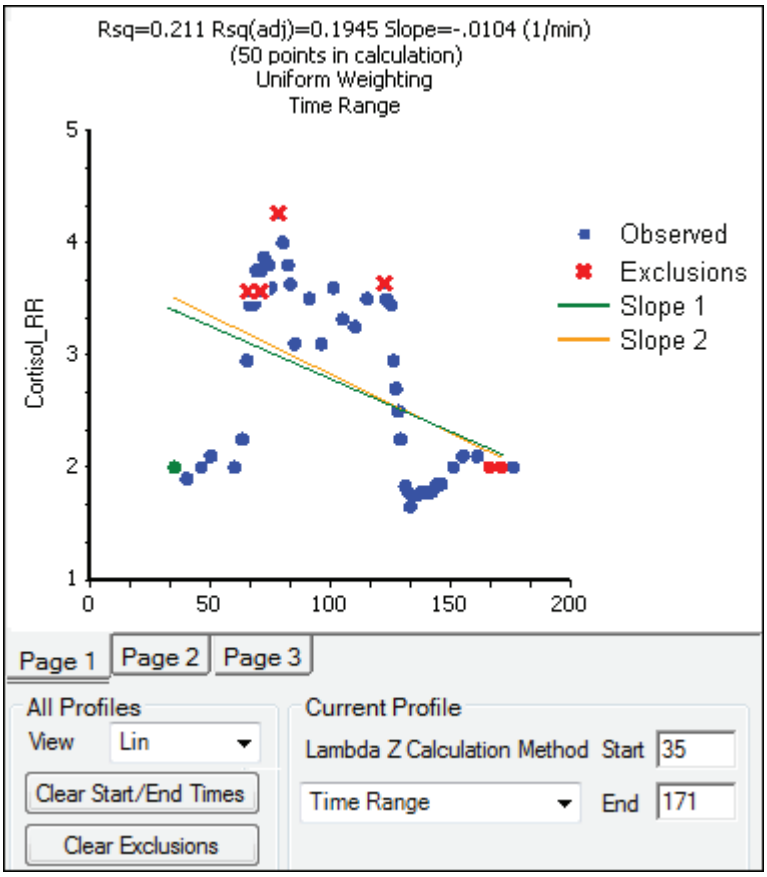
Note: Avoid having excluded or zero-valued points at the beginning or end of the Lambda Z range as this can result in inconsistent reporting of the Lambda Z range.For example, if values range from 0.8 to 2 and points before 1.4 are excluded, some of the output reports the range as (0.8, 2), whereas other output lists the range as (1.4, 2).

- Use the **Clear Start/End Times** button to have previously selected start time and end time points removed from the graphs in the Slopes Selector panel and from the worksheet in the Slopes panel.

- Use the **Clear Exclusions** button to have previously excluded time points included in the graphs in the Slopes Selector panel and in the worksheet in the Slopes panel.

The Drug Effect (220) model calculates two slopes per profile

- Under **Slope Calculation** in the Slopes Selector panel, select **Slope 1** or **Slope 2**.
- Select **Linear** or **Log** to set the slope calculation method for slope 1 or slope 2.
- Use the instructions listed above to select the start times, end times, and exclusions.



Slopes panel

The start time, end time, and exclusions used in the calculation of Lambda Z for each profile are defined in the Slopes panel. Users can type the time points for each profile.

	Subject	Start Time	End Time	Exclusions	Fit Method	Selection
1	DW				Best Fit	
2	GS				Best Fit	
3	RH				Best Fit	

Below are usage instructions. For descriptions of how the NCA object determines Lambda Z or slope estimation settings, see “Lambda Z or Slope Estimation settings”.

Note: Any changes to the settings available in the Slopes panel also affect the Slopes Selector panel and vice versa.

- Type the start and end time values in the **Start Time** and **End Time** columns for each profile.
- Type excluded time points in the **Exclusions** column for each profile.
- Exclude multiple time points for a profile by typing the time points in the same cell and separating the time points with a semicolon.
- Use the **Fit Method** menu to specify the method.
  If **Best Fit** is selected, Phoenix calculates the points for Lambda Z estimation.
  If **Time Range** is selected, users must enter the start and end times for Lambda Z estimation.
- To turn off Lambda Z or slope estimation for all profiles, select the **Disable Curve Stripping** checkbox in the Options tab. For more information see step 4 in "Model settings".

The Slopes panel for the **Drug Effect (220)** model also includes options for the slope calculation method.

- In the **Lin/Log** column, select **Linear** or **Log** to set the slope calculation method.
- Use the same instructions listed above to select the start times, end times, and exclusions.

Partial Areas panel

The Partial Areas panel includes settings for the computation of partial areas under the curve. Partial area computations are optional. It is not necessary to enter or add any start times or end times in this panel. For descriptions of how the NCA object computes partial areas, see "Partial area calculation".

None: Data types mapped to this context are not included in any analysis or output.
Sort: Categorical variable(s) identifying individual data profiles, such as subject ID in an NCA study. A separate analysis is done for each unique combination of sort variable values.
Area #: Number to identify the defined partial area.
Label: Title to use as a label for the defined partial area.
Start Time: The time at which to begin the partial area calculation.
End Time: The time at which to end the partial area calculation.

Some additional notes on partial areas:

- Partial area computations are optional. To skip the computations leave the **Start Time** and **End Time** columns empty.
- Up to 127 partial areas can be computed per subject.
- The start times and end times can be after the last observed time if Lambda Z is estimable.

Therapeutic Response panel

The Therapeutic Response panel allows users to determine the time spent within a therapeutic range, and the AUC within the therapeutic range, by using the lower and upper therapeutic response values. For descriptions of how the NCA object handles therapeutic response data, see "Therapeutic response".

Setting the therapeutic response values is optional for plasma (200–202) and urine (210–212) models. Setting the baseline is recommended for drug effect models (220). The Min Response and Max Response columns show the minimum and maximum concentrations, rates, or responses contained in the datasets.

Caution: When entering or mapping the lower and upper therapeutic ranges of profiles in an NCA urine model, users must enter or map the rate of excretion.

None: Data types mapped to this context are not included in any analysis or output.

Sort: Categorical variable(s) identifying individual data profiles, such as subject ID and treatment in a crossover study. A separate analysis is performed for each unique combination of sort variable values.

Lower (Plasma and Urine study) / **Baseline** (Drug Effect study): The lower concentration, rate, or response for defining the lower boundary of the target range. This is the lower effect value for each profile. It is required when an external worksheet is mapped. If not specified for the drug effect model, a baseline of zero is used.

Upper (Plasma and Urine study) / **Threshold** (Drug Effect): The upper concentration, rate, or response for defining the upper boundary of the target range.

Threshold is the effect value used to calculate additional times and areas. See the "Drug effect data model 220" section.

Units panel

An NCA object's display units can be changed to fit a user's preferences. Each parameter used in a model and the parameter's default units are listed in the Units panel. Required input is highlighted orange in the interface.

For **plasma models** (200–202), the time and concentration data must contain units before users can set preferred units.

For **plasma models** (200–202), the dosing unit must be set before users can set preferred units.

For **urine models** (210–212), the start time, end time, concentration, and volume data must contain units before users can set preferred units.

For the **drug effect model** (220), the time and effect data must contain units before users can set preferred units.

- **None**: Data types mapped to this context are not included in any analysis or output.
- **Name**: Model parameters associated with the units.
- **Default**: The model object's default units.
- **Preferred**: The user's preferred units for the parameter.

Note: if you see an "Insufficient units" message, check that units are defined for time and concentration in your input.

Parameter Names panel

Phoenix provides the option to specify the names for NCA model parameters.

None: (In mapped worksheet only) Rows mapped to this context are not included in any analysis or output.

Parameter Name: In the internal worksheet, Phoenix's default parameter names are listed in this column. For a mapped worksheet, click in the cell to indicate that the name in that row is a parameter name.

Preferred (Name): In the internal worksheet, edit the name that will appear in the output. For a mapped worksheet, click in the cell to indicate that the name in that row is a preferred name.

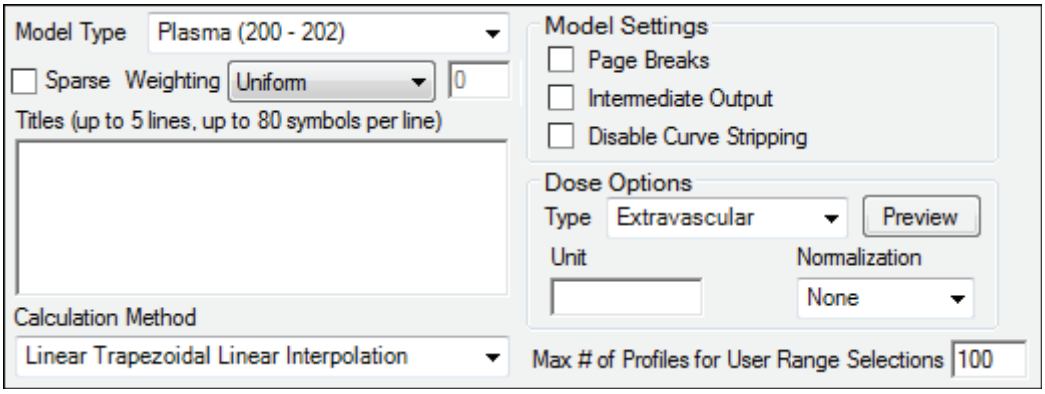
Include in Workbook: Indicate whether or not a parameter is included as final parameter in the workbook output.

Note: Parameter names cannot contain empty spaces. The case of each preferred parameter name is preserved.

For more on NCA output parameters see "NCA parameter formulas".

Options tab

The Options tab allows users to select the NCA model and set options for the selected model.



- Use the **Model Type** menu to select the NCA model type (i.e., whether the input data are from plasma, urine, or drug effect measurements). Select **Plasma (200-202)**, **Urine (210-212)**, or **Drug Effect (220)**.
- Check the **Sparse** checkbox to use analysis methods for sparse datasets. See "Sparse sampling calculation" for more information on using sparse datasets with NCA models.
- Use the **Weighting** menu to select the regression that estimates Lambda Z or slopes. Select **User Defined**, **Uniform**, **1/Y**, or **1/(Y*Y)**.

Note: The relative proportions of the weights are important, not the weights themselves. See "Weighting" for more on weighting schemes.

Rules for using the **Weighting** menu:

- If **User Defined** is selected then users can enter their own Observed to Power N value. The value of N must be typed in the **Weighting** text field.
- **Sparse** data requires **Uniform** weighting.
- When a log-linear fit is done (**Uniform** weighting for Lambda Z), then the fit is implicitly using a weighting approximately equal to $1/Yhat^2$.

Note: If **1/Y** and the **Linear Log Trapezoidal** calculation method are selected, a user might assume that the weighting scheme is 1/LogY, rather than 1/Y. This is not the case, however, since concentrations between zero and one would have negative weights and could not be included in the analysis.

- Use the **Titles** text box to type a title for the analysis. The title is displayed at the top of each page in the Core Output and can include up to 5 lines of text.
- Select a method for calculating the area under the curve from the **Calculation Method** menu.

  The chosen method applies to all AUC, AUMC, and partial area computations. All methods

reduce to the log trapezoidal rule, the linear trapezoidal rule, or both. The methods differ based on when the rules are applied. See “Partial area calculation” for descriptive equations of the calculation methods. Select from:

Linear Log Trapezoidal. This method uses the linear trapezoidal rule up to Cmax and then the log trapezoidal rule for the remainder of the curve, to compute AUCs. Points for partial areas are inserted using the logarithmic interpolation rule after Cmax, or after C0 for IV bolus, if C0 > Cmax. Otherwise, the linear trapezoidal rule is used. If Cmax is not unique, then the first maximum is used.

Linear Trapezoidal Linear Interpolation. This is the default method and recommended for **Drug Effect Data (220)**. It uses the linear trapezoidal rule, which is applied to each pair of consecutive points in the dataset that have non-missing values, and sums up these areas to compute AUCs. If a partial area is selected that has an endpoint that is not in the dataset, then the linear interpolation rule is used to insert a concentration value for that endpoint.

Linear Up Log Down. The linear trapezoidal rule is used to compute AUCs any time that the concentration data is increasing, the logarithmic trapezoidal rule is used any time that the concentration data is decreasing. Points for partial areas are inserted using the linear interpolation rule if the surrounding points show that concentration is increasing, and the logarithmic interpolation rule if the concentration is decreasing.

Linear Trapezoidal Linear/Log Interpolation. This method is the same as **Linear Trapezoidal Linear Interpolation** except when a partial area is selected that has an endpoint that is not in the dataset. In that case, the logarithmic interpolation rule is used to insert points after Cmax, or after C0 for IV bolus, if C0 > Cmax. Otherwise, the linear interpolation rule is used. If Cmax is not unique, then the first maximum is used.

Note: The **Linear Log Trapezoidal**, the **Linear Up Log Down**, and the **Linear Trapezoidal Linear/Log Interpolation** methods all apply the same exceptions in area calculation and interpolation. If a Y value (concentration, rate, or effect) is less than or equal to zero, Phoenix defaults to the linear trapezoidal or linear interpolation rule for that point. If adjacent Y values are equal to each other, Phoenix defaults to the linear trapezoidal or linear interpolation rule.

Model settings

- Check the **Page Breaks** checkbox to include page breaks in the ASCII text output.
- Check the **Intermediate Output** checkbox to add to the text Core Output the values of each iteration during estimation of Lambda Z and for each of the sub-areas in partial area computations.
- Check the **Disable Curve Stripping** checkbox to turn off Lambda Z or slope estimation for all profiles. When this option is selected Lambda Z or slopes are not estimated, parameters that are extrapolated to infinity are not calculated, and the Rules tab is disabled.
- Disable curve stripping for one or more individual profiles:
  - Select **Slopes** in the Setup tab.
  - Enter a start time that is greater than the last time point in a given profile and an end time greater than the start time.

Dose options

Note: Dose Options are not available for the **Drug Effect (220)** model.

- Use the **Type** menu to select the dosing route. Dose type selections determine two things: specific model type and columns available in the Dosing panel. Select **Extravascular**, **IV Bolus**, **IV Infusion**, or **Dosing Defined**.

- Set the dosing unit by clicking the **Units Builder - Dose [...]** button or typing the dosing unit into the **Unit** text field. Only applicable when an internal worksheet is being used for the Dosing data.

  See "Using the Units Builder" for more details.

- Click **Preview** to see a preview of dose option selections in a separate window. Click **OK** to close the preview window.

- Use the **Normalization** menu to select the appropriate factor if the dose amount is normalized by subject body weight or body mass index. Select **None**, **kg**. **g**, **mg**, **m**2**, or **1.73 m**2**.

  If doses are in milligrams per kilogram of body weight, select **mg** as the dosing unit and **kg** as the dose normalization.

  The **Normalization** menu affects the output parameter units. For example, if dose volume is in liters, selecting **kg** as the dose normalization changes the units to L/kg.

  Dose normalization affects units for all volume and clearance parameters in NCA models, as well as AUC/D in NCA plasma models, and Percent_Recovered in NCA urine models.

Other options

- Enter the **Max # of Profiles for User Range Selections** in the field (default is 100).

  If the number of profiles exceeds this value, then the user selection of slopes will be disabled and the engine will calculate the slopes using the Best Fit method. Selecting the Slopes Selector worksheet or Slopes worksheet will display a message notifying the user that the limit has been exceeded and the Best Fit method will be used for all profiles.

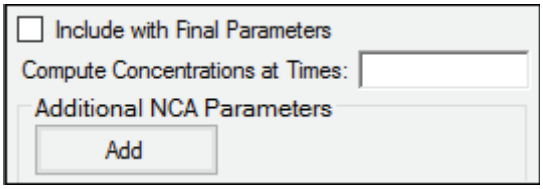
User Defined Parameters tab

The User Defined Parameters tab allows users to include concentrations/Y values at specified times, as well as additional NCA parameters.

- Check the **Include with Final Parameters** box to append the user-defined parameters (both the computed concentrations/Ys and any additional user-defined parameters) to the Final Parameters worksheets, both the pivoted and non-pivoted versions.

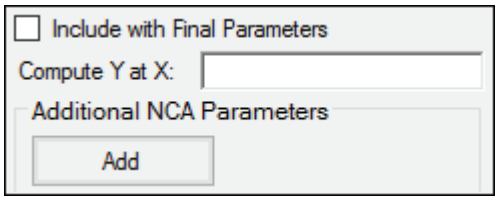
- Enter time or X values at which to compute the concentration or Y value.

  For Plasma models, enter a value(s) in the field to have the NCA object compute the concentration (or the mean concentration, if the **Sparse Sampling** box in the Options tab is checked) at that time and include the result in the output.



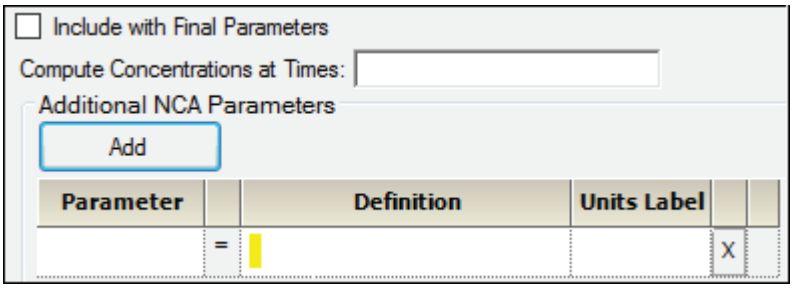
  For Drug Effect models, enter a value(s) in the field to have the NCA object compute the Y value at that X value and include the result in the output.

  Up to 30 values can be entered as a comma-separated list. Values can also be specified by using multiple '`seq`' statements with the format `seq(first_time,end_time,increment)`. For example, `seq(0,6,1),8,12,seq(18,36,6)`.



Note: If a concentration/drug effect value does not exist in the data set for the specified time/X value, it is calculated following the same rules as for computing Y-values for partial area endpoints, see "Partial area calculation".

- Click **Add** to define other NCA parameters to include in the output.



- Enter a name for the parameter in the Parameter column.

  The name is checked for validity as it is entered and a message is displayed in the last column of the table if it is not valid. Since the names become column headers in the output, they must also follow the rules for column headers: start with a letter or underscore; contain only letters, numbers, underscores, and '%'; and not contain spaces, periods, or symbols. The name cannot match any of the following:
  - default names for NCA final parameters
  - preferred names for NCA final parameters
  - previously defined additional NCA parameters
  - names that will be generated by the **Compute concentrations at times** option
  - the words "Dose" and "Sort"
  - names of columns defined as Carry variables
- Enter an equation that defines how the parameter is to be computed in the Definition column. The math function operators +, –, *, /, and ^ can be used in the Definition, as well as ln(x), log(x,base), log10(x), exp(x), and sqrt(x). The parameter can be a function of the following:
  - default parameter names (even if selected to be excluded from the results)
  - preferred names specified on the Parameter Names setup tab (even if selected to be excluded from the results)
  - partial areas
  - if an external dosing worksheet is used, the name of the column mapped to Dose and the name of the column mapped to Tau
  - if an internal dosing worksheet is used, the "Dose" and "Tau" columns
  - Carry variables (names of columns mapped as Carry)
  - previously defined user-defined parameter names (those that are above the current name in the user interface)

Note that:

- If more than one dose amount is specified for a profile, the last dose value will be used when computing the parameter.
- If a carryalong is a time-dependent variable (that is, if the carryalong takes on different values per profile), any user-defined parameters defined in terms of this carryalong will be undefined.
- If any of the values to be used when computing the user-defined parameter are missing (for example, an equation that uses Rsq when the Lambda Z fitting fails or was disabled), the value of the user-defined parameter will be missing (blank) in the results.
- Any names used are case-sensitive (they must be correct in terms of uppercase and lowercase).
- To assist with entering final parameter names in the equation, when the user starts to type a name, a dropdown list provides a list of final parameters that match. **Double-click** an entry from the list to auto-complete typing that name. The list contains only final parameters, even though other names, such as dosing and carryalong names, can be used. The list contains all possible final parameters in NCA, but some may not be applicable to the current selection of model and dosing options.

- In the Units Label column enter the unit name that is to appear when the parameter values are reported. No conversion of units is done for user-defined parameters.
- Click the red X in the row to remove that parameter.

Rules tab

The Rules tab contains optional settings that apply to the Lambda Z calculation in Plasma and Urine models. (The Rules tab does not apply to Slope1 and Slope2 in Drug Effect models.)

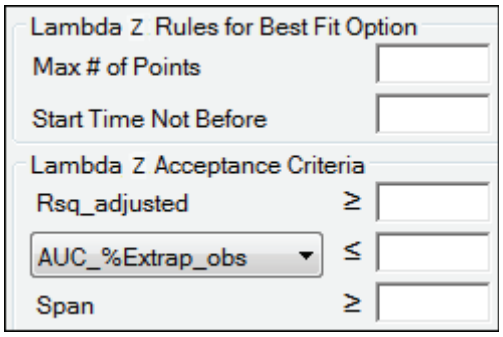


Figure 17-1. Rules tab for NCA object

Lambda Z Rules for Best Fit method: These optional rules are used only in the automatic selection of Lambda Z.

- In the **Max # of points** field, specify the maximum number of points that can be used in the best-fit method for Lambda Z. If a value is specified, the NCA engine will not consider time ranges that contain more than the specified number of points when finding the best Lambda Z. The entered value must be at least 3.
- In the **Start Time Not Before** field, specify the minimum start time that can be used in the best-fit method for Lambda Z. If a value is specified, the NCA engine will not consider time ranges that start before this minimum start time when finding the best Lambda Z.

Lambda Z Acceptance Criteria: These optional acceptance criteria apply to both the Best Fit method and the Time Range method. These rules are used to flag profiles (described further below) where the Lambda Z final parameter does not meet the specified acceptance criteria.

- Specify the minimum value of Rsq_adjusted that indicates an acceptable fit for Lambda Z in the **Rsq_adjusted** field. Value must be between 0 and 1.
- Use the pull-down menu to select whether to use **AUC_%Extrap_obs** or **AUC_%Extrap_pred** (or, for Urine models, **AURC_%Extrap_obs** or **AURC_%Extrap_pred**) when indicating the acceptable fit for Lambda Z. In the field, enter the maximum value to use. Value must be between 0 and 100.
- In the **Span** field, specify the minimum span or number of half-lives needed for the Lambda Z range to be acceptable. Values must be positive.

If a profile does not have an acceptable Lambda Z fit as specified by the acceptance criteria, an output flag value of 'Not_Accepted' is used to flag each of the criterion that is not met by that profile. In addition, a flag value of 'Missing' is used to flag all profiles where the parameter used for acceptance cannot be computed. Note that all computed results for flagged profiles are still included in the output, but the final parameters for these profiles will be marked by the flags. All profiles that have an acceptable Lambda Z fit (i.e., meet the acceptance criterion) will have the flag value of 'Accepted'.

The flags appear in columns in the Final Parameters Pivoted output worksheet immediately after the column for the parameter used for the acceptance criterion. The flag column names are 'Flag' appended with the parameter name used for acceptance, e.g., Flag_Rsq_adjusted, Flag_Span. If the user wants to remove the profiles failing to meet the acceptance criteria from the output, the Final Parameters Pivoted worksheet can be processed by the Data Wizard to delete these profiles, by filtering on the flag values of 'Not_Accepted' and excluding these rows. Note that the Flag columns do not appear in the output when there are no flagged profiles, that is, when all profiles meet the acceptance criterion or when the acceptance criterion is not set.

In the Final Parameters output worksheet and in the Core Output text, where the final parameter output is stacked, the flag names and values appear below the acceptance parameter. If the acceptance parameter is selected to not be included in the worksheet output in the "Parameters Names" setup, the corresponding flag will also not be included in the worksheet.

See "Data checking and pre-treatment" for a list of cases that also produce flagged output.

Plots tab

The Plots tab allows users to select individual plots to include in the output.

- Use the checkboxes to toggle the creation of graphs.
- Click **Reset Existing Plots** to clear all existing plot output.

  Each plot in the Results tab is a single plot object. Every time a model is executed, each object remains the same, but the values used to create the plot are updated. This way, any styles that are applied to the plots are retained no matter how many times the model is executed. Clicking **Reset Existing Plots** removes the plot objects from the Results tab, which clears any custom changes made to the plot display.
- Use the **Enable All** and **Disable All** buttons to check or clear all checkboxes for all plots in the list.

Results

After an NCA object is executed, the output is displayed on the Results tab in Phoenix.

- Worksheet output: worksheets listing input data, output parameters, as well as execution summary.
- Plot output: plots of observed and predicted data.
- Core Output: text version of all model settings and output, including any errors that occurred during modeling.
- The Settings text file lists the user-specified settings in the NCA object.

Worksheet output

Worksheet output contains summary tables of the modeling data and a summary of the information in the Core Output. The worksheets present the output in a form that can be used for reporting and further analyses. The results worksheets are listed on the Results tab underneath Output Data.

Note: The worksheets produced depend on the analysis type and model settings.

Dosing Used: The dosing regimen specified in the Dosing panel.

Exclusions: Any excluded data points specified in the Slopes panel.

Final Parameters: Estimates of the final parameters for each level of the sort variable, including times and areas above ("TimeHigh"), in ("TimeBetween") and below ("TimeLow") the therapeutic response (AUCHigh, AUCLow, etc.). Parameter names that include "Inf" are extrapolated to infinity using estimated Lambda Z.

Final Parameters Pivoted: The same as Final Parameters, but with one parameter per column, in order to conveniently perform further analysis on individual parameters.

Partial Areas: Lists start and end times used to define the partial areas under the curve.

Plot Titles: The title of each graph in the output.

Slopes Settings: The settings for the user specified for the Terminal elimination phase.
It includes the start and end time for each defined time range, excluded points, fit method used and whether the time range was set by the System or the User.

Summary Table: The sort variables, X variable, points included in the regression for Lambda Z (noted with *), Y variable, predicted Y for the regression, residual for the regression, area under the curve (AUC), area under the moment curve AUMC and the weight used for the regression.

Therapeutic Response: Lists the lower and upper boundaries used to define the therapeutic response windows.

User Defined Computed Y: List of user-entered time or X values and the concentration or Y values. The Type column indicates if the value was Observed or Computed by interpolation.

User Defined Parameters: List of any parameters defined by the user in the User Defined Parameters tab.

User Defined Parameters Pivoted: The same as User Defined Parameters, but with one parameter per column, in order to conveniently perform further analysis on individual parameters.

Plot output

Executing an NCA object generates an 'Observed Y and Predicted Y vs X' plot for each subject. Plot output is listed underneath Plots in the Results tab.

Note: Hovering over a regression line in the NCA plot result (Observed Y and Predicted Y vs X plot) displays [time, conc] value pairs. However only coordinates of the predicted value at the nearest observed time points are displayed. In other words, hovering over the regression line does not give continuous predicted coordinates.

NCA computation rules

Computational rules for the NCA engine are discussed in sections:

Time deviations in steady-state data
Data checking and pre-treatment

NCA computations are covered under the headings:

Lambda Z or Slope Estimation settings
Therapeutic response
Partial area calculation
Sparse sampling calculation
Drug effect calculation
Weighting

Time deviations in steady-state data

When using steady-state data, Phoenix computes AUC_TAU from dose time to dose time+tau, based on the tau value set in the Dosing panel. However, in most studies, there are sampling time deviations. For example, if dose time=0 and tau=24, the last sample might be at 23.975 or 24.083 hours. In this instance, the program will estimate the AUC_TAU based on the estimated concentration at 24 hours, and not the concentration at the actual observation time. For steady state data, Cmax, Tmax, Cmin and Tmin are found using observations taken at or after the dose time, but no later than dose time+tau.

Data checking and pre-treatment

Prior to calculation of pharmacokinetic parameters, Phoenix institutes a number of data-checking and pre-treatment procedures as follows.

- **Sorting**: Prior to analysis, data within each profile is sorted in ascending time order. (A profile is identified by a unique combination of sort variable values.)
- **Inserting initial time points**: If a PK profile does not contain an observation at dose time, Phoenix inserts a value using the following rules. (Note that, if there is no dosing time specified, the dosing time is assumed to be zero.)

  Extravascular and **Infusion** data: For single dose data, a concentration of zero is used; for steady-state, the minimum observed during the dose interval (from dose time to dose time +tau) is used.

  IV Bolus data: Phoenix performs a log-linear regression of first two data points to back-extrapolate C0. If the regression yields a slope >= 0, or at least one of the first two y-values is zero, or if one or both of the points is viewed as an outlier and excluded from the Lambda Z regression, then the first observed y-value is used as an estimate for C0. If a weighting option is selected, it is used in the regression.

  Urine data: A rate value of zero is used at dose time.

  Drug Effect data: An effect value equal to the user-supplied baseline is inserted at dose time (assumed to be zero if none is supplied).

  The inserted point at dose time is needed to compute the initial trapezoid from dose time to the first observation for the AUC final parameters and to compute partial areas or therapeutic response parameters that depend on times from the dose time to the first observation. The inserted point is never used in Lambda Z computations.

Only one observation per profile at each time point is permitted. If multiple observations at the same time point are detected, the analysis is halted with an error message. No output is generated.

- **Data exclusions**: NCA automatically excludes unusable data points meeting the following criteria:

  Missing values: For plasma models, if either the time or concentration value is missing or non-numeric, then the associated record is excluded from the analysis. For urine models, records with missing or non-numeric values for any of the following are excluded: collection interval start or stop time, drug concentration, or collection volume. Also for urine models, if the collection volume is zero, the record is excluded.

  Data points preceding the dose time: If an observation time is earlier than the dosing time, then that observation is excluded from the analysis. For urine models, the lower time point is checked.

  Data points for urine models: In addition to the above rules, if the lower time is greater than or equal to the upper time, or if the concentration or volume is negative, the data must be corrected before NCA can run.

- **Flagging data deficiencies in the Final Parameters output**: After exclusion of unusable data points as described in the prior section, profiles that result in no non-missing observations, and profiles that result in only one non-missing observation where a valid point at dose time cannot be inserted, have a flag called “Flag_N_Samples” in the Final Parameters output. More specifically, these cases are:
  - Profile with all missing observations (N_Samples=0) for any NCA Model Type. No Final Parameters can be reported.
  - Urine model profile with all urine volumes equal to zero. This is equivalent to no measurements being taken (N_Samples=0). No Final Parameters can be reported.
  - Profile with all missing observations, except one non-missing observation at dose time, for Plasma or Drug Effect models (N=1 and a point cannot be inserted at dose time because the one observation is already at dose time). All Final Parameters that can be defined, e.g., Cmax, Tmax, Cmin, Tmin, are reported. (This case does not apply to Urine models — the midpoint of an acceptable observation would be after dose time.)
  - Bolus-dosing plasma profile with all missing observations, except one non-missing observation after dose time (N=1 and a point cannot be inserted at dose time because NCA does not back-extrapolate C0 when there is only one non-missing observation). All Final Parameters that can be defined, e.g., Cmax, Tmax, Cmin, Tmin, are reported.

  Each of these cases will have a ‘Flag_N_Samples” value in the Final Parameters output that is ‘Insufficient’. This flag allows these profiles to be filtered out of the output worksheets if desired, using the Data Wizard.

Note: A non-bolus profile with all missing observations, except one non-missing positive observation after dose time is not a data deficiency, because a valid point is inserted at dose time – (dose time, 0), or (dose time, Cmin) for steady state – which provides a second data point.

Lambda Z or Slope Estimation settings

This section pertains to NCA and IVIVC objects.

Phoenix will attempt to estimate the rate constant, Lambda Z, associated with the terminal elimination phase for concentration data. If Lambda Z is estimable, parameters for concentration data will be extrapolated to infinity. For NCA drug effect models, Phoenix estimates the two slopes at the beginning and end of the data. NCA does not extrapolate beyond the observed data for drug effect models.

Lambda Z or slope range selection

Phoenix will automatically determine the data points to include in Lambda Z or slope calculations as follows. (The exception to this is if the time range to use in the calculation of Lambda Z or slopes is not specified in an NCA object and curve stripping is not disabled, as described under "Options tab".)

For concentration data: To estimate the best fit for Lambda Z, Phoenix repeats regressions of the natural logarithm of the concentration values using the last three points with non-zero concentrations, then the last four points, last five points, etc. Points with a concentration value of zero are not included since the logarithm cannot be taken. Points prior to Cmax, points prior to the end of infusion, and the point at Cmax for non-bolus models, are not used in the Best Fit method (they can only be used if the user specifically requests a time range that includes them). For each regression, an adjusted R^2 is computed:

$$Adjusted\ R^2 = 1 - \frac{(1 - R^2) \times (n - 1)}{(n - 2)}$$

where n is the number of data points in the regression and R^2 is the square of the correlation coefficient.

Lambda Z is estimated using the regression with the largest adjusted R^2 and:

– If the adjusted R^2 does not improve, but is within 0.0001 of the largest adjusted R^2 value, the regression with the larger number of points is used.

– Lambda Z must be calculated from at least three data points.

– The estimated slope must be negative, so that its negative Lambda Z is positive.

For sparse sampling data: For sparse data, the mean concentration at each time (plasma or serum data) or mean rate for each interval (urine data) is used when estimating Lambda Z. Otherwise, the method is the same as for concentration data.

For drug effect data: Phoenix will compute the best-fitting slopes at the beginning of the data and at the end of the data using the same rules that are used for Lambda Z (best adjusted R-square with at least three points), with the exception that linear or log regression can be used according to the user's choice and the estimated slope can be positive or negative. If the user specifies the range only for Slope1, then in addition to computing Slope1, the best-fitting slope for Slope 2 will be computed at the end of the data. If the user specifies the range only for Slope2, then the best-fitting slope for Slope 1 will be computed at the beginning of the data.

The data points included in each slope are indicated on the Summary table of the output workbook and text for model 220. Data points for Slope1 are marked with "1" in workbook output and footnoted using "#" in text output; data points for Slope2 are labeled "2" and footnoted using an asterisk, "*".

Calculation of Lambda Z

Once the time points being used in the regression have been determined either from the Best Fit method or from the user's specified time range, Phoenix can estimate Lambda Z by performing a regression of the natural logarithm of the concentration values in this range of sampling times. The estimate slope must be negative, Lambda Z is defined as the negative of the estimated slope.

Note: Using this methodology, Phoenix will almost always compute an estimate for Lambda Z. It is the user's responsibility to evaluate the appropriateness of the estimated value.

Calculation of slopes for effect data

Phoenix estimates slopes by performing a regression of the response values or their natural logarithm depending on the user's selection. The actual slopes are reported; they are not negated as for Lambda Z.

Limitations of Lambda Z and slope estimation

It is not possible for Phoenix to estimate Lambda Z or slope in the following cases.

- There are only two non-missing observations and the user requested automatic range selection (Best Fit).
- The user-specified range contains fewer than two non-missing observations.
- Automatic range selection is chosen, but there are fewer than three positive concentration values after the Cmax of the profile for non-bolus models and fewer than two for bolus models or the slope is not negative.
- For infusion data, automatic range selection is chosen, and there are fewer than three points at or after the infusion stop time.
- The time difference between the first and last data points in the estimation range used is approximately < 1e –10.

In these instances, the curve fit for that subject will be omitted. The parameters that do not depend on Lambda Z (i.e., Cmax, Tmax, AUClast, etc.) will still be reported, but the software will issue a warning in the text output, indicating that Lambda Z was not estimable.

Therapeutic response

For non-compartmental analysis of concentration data, Phoenix computes additional parameters for different time range computations, as listed below. The parameters included depend on whether upper, lower, or both limits are supplied. See "Therapeutic response windows" for additional computation details.

Time range from dose time to last observation
Additional parameters:

TimeLow: Total time below lower limit. Included when lower or both limits are specified.
TimeBetween: Total time between lower/upper limits. Included when both limits are specified.
TimeHigh: Total time above upper limit. Included when lower or both limits are specified.
AUCLow: AUC that falls below lower limit: Included when lower or both limits are specified.
AUCBetween: AUC that falls between lower/upper limits. Included when both limits are specified.
AUCHigh: AUC that falls above upper limit. Included when lower or both limits are specified.

Time range from dose time to infinity using Lambda Z (if Lambda Z exists)
Additional parameters:

TimeInfBetween: Total time (extrapolated to infinity) between lower/upper limits. Included when both limits are specified.
TimeInfHigh: Total time (extrapolated to infinity) above upper limit. Included when lower or both limits are specified.
AUCInfLow: AUC (extrapolated to infinity) that falls below lower limit: Included when lower or both limits are specified.
AUCInfBetween: AUC (extrapolated to infinity) that falls between lower/upper limits. Included when both limits are specified.
AUCInfHigh: AUC (extrapolated to infinity) that falls above upper limit. Included when lower or both limits are specified.

Therapeutic response windows

For therapeutic windows, one or two boundaries for concentration values can be given, and the program computes the time spent in each window determined by the boundaries and computes the area under the curve contained in each window. To compute these values, for each pair of consecutive data points, including the inserted point at dosing time if there is one, it is determined if a boundary crossing occurred in that interval. Call the pair of time values from the dataset (t_i, t_{i+1}) and called the boundaries y_{lower} and y_{upper}.

If no boundary crossing occurred, the difference t_{i+1}, t_i is added to the appropriate parameter $TimeLow$, $TimeBetween$, or $TimeHigh$, depending on which window the concentration values are in. The AUC for (t_i, t_{i+1}) is computed following the user's specified AUC calculation method as described in the section on the "Options tab". Call this AUC^*. The parts of this AUC^* are added to the appropriate parameters $AUCLow$, $AUCBetween$, or $AUCHigh$. For example, if the concentration values for this interval occur above the upper boundary, the rectangle that is under the lower boundary is added to $AUCLow$, the rectangle that is between the two boundaries is added to $AUCBetween$ and the piece that is left is added to $AUCHigh$. This is equivalent to these formulae:

$$AUCLow = AUCLow + y_{lower}(t_{i+1} - t_i)$$

$$AUCBetween = AUCBetween + (y_{upper} - y_{lower})(t_{i+1} - t_i)$$

$$AUCHigh = AUCHigh + AUC^* - y_{upper}(t_{i+1} - t_i)$$

If there was one boundary crossing, an interpolation is done to get the time value where the crossing occurred; call this t^*. The interpolation is done by either the linear rule or the log rule following the user's AUC calculation method as described in the section on the "Options tab", i.e., the same rule is used as when inserting a point for partial areas. To interpolate to get time t^* in the interval (t_i, t_{i+1}) at which the concentration value is y_w:

Linear interpolation rule for time:

$$t^* = t_i + \left[\frac{y_w - y_i}{y_{i+1} - y_i}\right](t_{i+1} - t_i)$$

Log interpolation rule for time:

$$t^* = t_i + \left[\frac{\ln(y_w) - \ln(y_i)}{\ln(y_{i+1}) - \ln(y_i)}\right](t_{i+1} - t_i)$$

The AUC for (t_i, t^*) is computed following the user's specified AUC calculation method. The difference $t^* - t_i$ is added to the appropriate time parameter and the parts of the AUC are added to the appropriate AUC parameters. Then the process is repeated for the interval (t^*, t_{i+1}).

If there were two boundary crossings, an interpolation is done to get t^* as above for the first boundary crossing, and the time and parts of AUC are added in for the interval (t_i, t^*) as above. Then another interpolation is done from t_i to t_{i+1} to get the time of the second crossing t^{**} between (t^*, t_{i+1}), and the time and parts of AUC are added in for the interval (t^*, t^{**}). Then the times and parts of AUC are added in for the interval (t^{**}, t_{i+1}).

The extrapolated times and areas after the last data point are now considered for the therapeutic window parameters that are extrapolated to infinity. For any of the AUC calculation methods, the AUC rule after tlast is the log rule, unless an endpoint for the interval is negative or zero in which case the linear rule must be used. The extrapolation rule for finding the time t^* at which the extrapolated curve would cross the boundary concentration y_w is:

$$t^* = \left(\frac{1}{Lambda\_z}\right)(Lambda\_z\_intercept - \ln(y_w))$$

If the last concentration value in the dataset is zero, the zero value was used in the above computation for the last interval, but now ylast is replaced with the following if Lambda Z is estimable:

$$y_{last} = \exp(Lambda\_z\_intercept - Lambda\_z(t_{last}))$$

If ylast is in the lower window: $InfBetween$ and $InfHigh$ values are the same as $Between$ and $High$ values. If Lambda Z is not estimable, $AUCInfLow$ is missing. Otherwise:

$$AUCInfLow = AUCLow + (y_{last} / Lambda\_z)$$

If ylast is in the middle window for two boundaries: $InfHigh$ values are the same as $High$ values. If Lambda Z is not estimable, $InfLow$ and $InfBetween$ parameters are missing. ***Otherwise:*** Use the extrapolation rule to get t^* at the lower boundary concentration. Add time from $tlast$ to t^* into $TimeInfBetween$. Compute AUC^* from $tlast$ to t^*, add the rectangle that is under the lower boundary into $AUCInfLow$, and add the piece that is left into $AUCInfBetween$. Add the extrapolated area in the lower window into $AUCInfLow$. This is equivalent to:

$$t^* = (1/Lambda\_z)(Lambda\_z\_intercept - \ln(y_{lower}))$$

$$TimeInfBetween = TimeBetween + (t^* - t_{last})$$

$$AUCInfBetween = AUCBetween + AUC^* - y_{lower}(t^* - t_{last})$$

$$AUCInfLow = AUCLow + y_{lower}(t^* - t_{last}) + y_{lower} / Lambda\_z$$

If ylast is in the top window when only one boundary is given, the above procedure is followed and the $InfBetween$ parameters become the $InfHigh$ parameters.

If there are two boundaries and y_{last} is in the top window: If Lambda Z is not estimable, all extrapolated parameters are missing. Otherwise, use the extrapolation rule to get t^* at the upper boundary concentration value. Add time from tlast to t^* into $TimeInfHigh$. Compute AUC^* for tlast to t^*, add the rectangle that is under the lower boundary into $AUCInfLow$, add the rectangle that is in the middle window into $AUCInfBetween$, and add the piece that is left into $AUCInfHigh$. Use the extrapolation rule to get t^{**} at the lower boundary concentration value. Add time from t^* to t^{**} into $TimeInfBetween$. Compute AUC^{**} from t^* to t^{**}, add the rectangle that is under the lower boundary into $AUCInfLow$, and add the piece that is left into $AUCInfBetween$. Add the extrapolated area in the lower window into $AUCInfLow$. This is equivalent to:

$$t^* = (1/Lambda\_z)(Lambda\_z\_intercept - \ln(y_{upper}))$$

$$t^{**} = (1/Lambda\_z)(Lambda\_z\_intercept - \ln(y_{lower}))$$

$$TimeInfHigh = TimeHigh + (t^* - t_{last})$$

$$TimeInfBetween = TimeBetween + (t^{**} - t^*)$$

$$AUCInfHigh = AUCHigh + AUC^* - y_{upper}(t^* - t_{last})$$

$$AUCInfBetween = AUCBetween + AUC^* + (y_{upper} - y_{lower})(t^* - t_{last}) + AUC^{**} - y_{lower}(t^{**} - t^*)$$

$$AUCInfLow = AUCLow + y_{lower}(t^* - t_{last}) + y_{lower}(t^{**} - t^*) + y_{lower} / Lambda\_z$$

Partial area calculation

Linear trapezoidal rule

$$AUC\Big|_{t_1}^{t_2} = \delta t \times \frac{C_1 + C_2}{2}$$

$$AUMC\Big|_{t_1}^{t_2} = \delta t \times \frac{t_1 \times C_1 + t_2 \times C_2}{2}$$

Logarithmic trapezoidal rule

$$AUC\Big|_{t_1}^{t_2} = \delta t \times \frac{C_2 - C_1}{\ln\left(\frac{C_2}{C_1}\right)}$$

$$AUMC\Big|_{t_1}^{t_2} = \delta t \times \frac{t_2 \times C_2 - t_1 \times C_1}{\ln\left(\frac{C_2}{C_1}\right)} - \delta t^2 \times \frac{C_2 - C_1}{\ln\left(\frac{C_2}{C_1}\right)^2}$$

where δt is $(t_2 - t_1)$.

Note: If the logarithmic trapezoidal rule fails in an interval because C_1 <= 0, C_2 <= 0, or C_1=C_2, then the linear trapezoidal rule will apply for that interval.

Linear interpolation rule (to find C^* at time t^* for $t_1 < t^* < t_2$)

$$C^* = C_1 + \left|\frac{t^* - t_1}{t_2 - t_1}\right|(C_2 - C_1)$$

Logarithmic interpolation rule

$$C^* = \exp\left(\ln(C_1) + \left|\frac{t^* - t_1}{t_2 - t_1}\right| \times (\ln(C_2) - \ln(C_1))\right)$$

Note: If the logarithmic interpolation rule fails in an interval because C_1 <= 0 or C_2 <= 0, then the linear interpolation rule will apply for that interval.

Extrapolation (to find C^* after the last numeric observation)

Additional rules for plasma and urine models

The following additional rules apply for plasma and urine models (not model 220 for Drug Effect):

- If a start or end time falls before the first observation and after the dose time, the corresponding Y value is interpolated between the first data point and $C0$. $C0$=0 except in IV bolus models (model 201), where $C0$ is the dosing time intercept estimated by Phoenix, and except for models 200 and 202 at steady state, where $C0$ is the minimum value between dose time and tau.
- If a start or end time falls within the range of the data but does not coincide with an observed data point, then a linear or logarithmic interpolation is done to estimate the corresponding Y, according to the AUC Calculation method selected in the NCA Options. (See "Options tab".) Note that logarithmic interpolation is overridden by linear interpolation in the case of a non-positive endpoint.
- If a start or end time occurs after the last numeric observation (i.e., not "missing" or "BQL") and Lambda Z is estimable, Lambda Z is used to estimate the corresponding Y:

  $$Y = \exp(Lambda\_z\_intercept - Lambda\_z(t))$$
  $$= [\exp(Lambda\_z\_intercept - Lambda\_z(t_{last}))]$$
  $$[\exp(-Lambda\_z(t - t_{last}))]$$
  $$= (\text{predictedConcAtTlast})\exp(-Lambda\_z(t - t_{last}))$$

  The values $Lambda\_z\_intercept$ and $Lambda\_z$ are those values found during the regression for Lambda Z. Note that a last observation of zero will be used for linear interpolation, i.e., this rule does not apply prior to a last observation of zero.
- If a start or end time falls after the last numeric observation and Lambda Z is not estimable, the partial area will not be calculated.
- If both the start and end time for a partial area fall at or after the last positive observation, then the log trapezoidal rule will be used. However, if any intervals used in computing the partial area have non-positive endpoints or equal endpoints (for example, there is an observation of zero that is used in computing the partial area), then the linear trapezoidal rule will override the log trapezoidal rule.
- If the start time for a partial area is before the last numeric observation and the end time is after the last numeric observation, then the log trapezoidal rule will be used for the area from the last observation time to the end time of the partial area. However, if the last observation is non-positive or is equal to the extrapolated value for the end time of the partial area, then the linear trapezoidal rule will override the log trapezoidal rule.

The end time for the partial area must be greater than the start time. Both the start and end time for the partial area must be at or after the dosing time.

Sparse sampling calculation

The NCA object provides special methods to analyze concentration data with few observations per subject. The NCA object treats this sparse data as a special case of plasma or urine concentration data. It first calculates the mean concentration curve of the data, by taking the mean concentration value for each unique time value for plasma data, or the mean rate value for each unique midpoint for

urine data. For this reason, it is recommended to use nominal time, rather than actual time, for these analyses. The standard error of the data is also calculated for each unique time or midpoint value.

Using the mean concentration curve, the NCA object calculates all of the usual plasma or urine final parameters listed under "NCA parameter formulas". In addition, it uses the subject information to calculate standard errors that will account for any correlations in the data resulting from repeated sampling of individual animals.

The NCA sparse methodology calculates PK parameters based on the mean profile for all the subjects in the dataset. For batch designs, where multiple time points are measured for each subject, this methodology only generates unbiased estimates if equal sample sizes per time point are present. If this is not the case, then bias in the parameter estimates is introduced.

Note: In order to create unbiased estimates, the sparse sampling routines used in the NCA object require that the dataset does not contain missing data.

For plasma data (models 200–202), the NCA object calculates the standard error for the mean concentration curve's maximum value (Cmax), and for the area under the mean concentration curve from dose time through the final observed time (AUCall). Standard error of the mean Cmax will be calculated as the sample standard deviation of the y-values at time Tmax divided by the square root of the number of observations at Tmax, or equivalently, the sample standard error of the y-values at Tmax. Standard error of the mean AUC will be calculated as described in Nedelman and Jia (1998), using a modification in Holder (2001), and will account for any correlations in the data resulting from repeated sampling of individual animals. Specifically:

$$\mathrm{SE}(\hat{AUC}) = \sqrt{\mathrm{Var}(\hat{AUC})}$$

Since AUC is calculated by the linear trapezoidal rule as a linear combination of the mean concentration values,

$$\hat{AUC} = \sum_{i=0}^{m} w_i \bar{C}_i$$

where:

$\bar{C}_i$ = the sample mean at time i

$$w_i = \begin{cases} (t_1 - t_0)/2, & i = 0 \\ (t_{i+1} - t_{i-1})/2, & i = 1, \ldots, m-1 \\ (t_m - t_{m-1})/2, & i = m \end{cases}$$

m=last observation time for AUCall, or time of last measurable (positive) mean concentration for AUClast

it follows that:

$$Var(\hat{AUC}) = \sum_{i=0}^{m} \frac{w_i^2 s_i^2}{r_i} + 2\sum_{i<j} \frac{w_i w_j r_{ij} s_{ij}}{r_i r_j}$$

where:

r_{ij} = number of animals sampled at both times i and j

r_i = number of animals sampled at time i

s_i^2 = sample variance of concentrations at time i

s_{ij} = sample covariance between concentrations c_{ik} and c_{jk} for all animals k that are sampled at both times i and j

The above equations can be computed from basic statistics, and appear as equation (7.vii) in Nedelman and Jia (1998). When computing the sample covariances in the above, NCA uses the unbiased sample covariance estimator, which can be found as equation (A3) in Holder (2001):

$$s_{ij} = \sum_{k=1}^{r_{ij}} \frac{(C_{ik} - \overline{C}_i)(C_{jk} - \overline{C}_j)}{(r_{ij} - 1) + \left(1 - \frac{r_{ij}}{r_i}\right)\left(1 - \frac{r_{ij}}{r_j}\right)}$$

For urine models (models 210–212), the standard errors are computed for Max_Rate, the maximum observed excretion rate, and for AURC_all, the area under the mean rate curve through the final observed rate.

For cases where a non-zero value $C0$ must be inserted at dose time t_0 to obtain better AUC estimates (see "Data checking and pre-treatment"), the AUC estimate contains an additional constant term: $C^*=C0(t_1 - t_0)/2$. In other words, w_0 is multiplied by $C0$, instead of being multiplied by zero as occurs when the point (0,0) is inserted. An added constant in AÛC will not change $Var(\hat{AUC})$, so $SE\_AUClast$ and SE_AUCall also will not change. Note that the inserted C0 is treated as a constant even when it must be estimated from other points in the dataset, so that the variances and covariances of those other data points are not duplicated in the $Var(\hat{AUC})$ computation.

For the case in which r_{ij}=1, and r_i=1 or r_j=1, then s_{ij} is set to 0 (zero).

The AUCs must be calculated using one of the linear trapezoidal rules. Select a rule using the instructions listed under "Options tab".

Drug effect calculation

NCA for drug effect data requires the following input data variables:

Dependent variable, i.e., response or effect values (continuous scale)

Independent variable, generally the time of each observation. For non-time-based data, such as concentration-effect data, take care to interpret output parameters such as "Tmin" (independent variable value corresponding to minimum dependent variable value) accordingly.

It also requires the following constants:

Dose time (relative to observation times), entered in the Dosing worksheet

Baseline response value, entered in the Therapeutic Response tab of the Model Properties or pulled from a Dosing worksheet as described below

Threshold response value (optional), entered in the Therapeutic Response tab of the NCA Diagram

If the user does not enter a baseline response value, the baseline is assumed to be zero, with the following exception. When working from a Certara Integral study that includes a Dosing worksheet, if no baseline is provided by the user, Phoenix will use the response value at dose time as baseline, and if the dataset does not include a response at dose time, the user will be required to supply the baseline value.

If there is no response value at dose time, or if dose time is not given, see "Data checking and pretreatment" for the insertion of the point (dosetime, baseline).

Instead of Lambda Z calculations, as computed in NCA PK models, the NCA PD model can calculate the slope of the time-effect curve for specific data ranges in each profile. Unlike Lambda Z, these slopes are reported as their actual value rather than their negative. See "Lambda Z or Slope Estimation settings" for more information.

Like other NCA models, the PD model can compute partial areas under the curve, but only within the range of the data (no extrapolation is done). If a start or end time does not coincide with an observed data point, then interpolation is done to estimate the corresponding Y, following the equations and rules described under "Partial area calculation".

For PD data, the default and recommended method for AUC calculation is the Linear Trapezoidal with Linear Interpolation (set as described under "Options tab".) Use caution with log trapezoidal since areas are calculated both under the curve and above the curve. If the log trapezoidal rule is appropriate for the area under a curve, then it would underestimate the area over the curve. For this reason, Phoenix uses the linear trapezoidal rule for area where the curve is below baseline when computing AUC_Below_B, and similarly for threshold and AUC_Below_T.

Weighting

Phoenix provides flexibility in performing weighted nonlinear regression and using weighted regression. Weights are assigned using menu options or by adding weighting values to a dataset. Each operational object in Phoenix that uses weighted values has instructions for using weighting.

There are three ways to assign weights, other than uniform weighting, through the Phoenix user interface:

Weighted least squares: weight by a power of the observed value of Y.
Iterative reweighting: weight by a power of the predicted value of Y.
Reading weights from the dataset: include weight as a column in the dataset.

Weighted least squares

When using weighted least squares, Phoenix weights each observation by the value of the dependent variable raised to the power of n. That is, WEIGHT=Y^n. For example, selecting this option and setting n= –0.5 instructs Phoenix to weight the data by the square root of the reciprocal of observed Y:

$$1/\sqrt{Y}$$

If n has a negative value, and one or more of the Y values are less than or equal to zero, then the corresponding weights are set to zero.

The application scales the weights such that the sum of the weights for each function equals the number of observations with non-zero weights. See "Scaling of weights".

Iterative reweighting

Iterative Reweighting redefines the weights for each observation to be F^n, where F is the predicted response. For example, selecting this option and setting n= –0.5 instructs Phoenix to weight the data by the square root of reciprocal of the predicted value of Y, i.e.,

$$1/(\sqrt{Y})$$

As with Weighted least squares, if N is negative, and one or more of the predicted Y values are less than or equal to zero, then the corresponding weights are set to zero.

Iterative reweighting differs from weighted least squares in that for weighted least squares the weights are fixed. For iteratively re-weighted least squares the parameters change at each iteration, and therefore the predicted values and the weights change at each iteration.

For certain types of models, iterative reweighting can be used to obtain maximum likelihood estimates. For more information see the article by Jennrich and Moore (1975). Maximum likelihood estimation by means of nonlinear least squares. *Amer Stat Assoc Proceedings Statistical Computing Section* 57–65.

Reading weights from the dataset

It is also possible to have a variable in the dataset that has as its values the weights to use. The weights should be the reciprocal of the variance of the observations. As with Weighted Least Squares, the application scales the weights such that the sum of the weights for each function equals the number of observations with non-zero weights.

Scaling of weights

When weights are read from a dataset or when weighted least squares is used, the weights for the individual data values are scaled so that the sum of the weights for each function is equal to the number of data values with non-zero weights.

The scaling of the weights has no effect on the model fitting as the weights of the observations are proportionally the same. However, scaling of the weights provides increased numerical stability.

Consider the following example:

X	Y	Y^{-2}	Weight from Phoenix
1	6	0.0278	1.8430
10	9	0.0123	0.8190
100	14	0.0051	0.3380
Sum		0.0452	3.0000

Suppose weighted least squares with the power –2 was specified, which is the same as weighting by 1/Y*Y. The corresponding values are as shown in the third column. Each value of Y^{-2} is divided by the sum of the values in the third column, and then multiplied by the number of observations, so that:

(0.0277778/.0452254)*3=1.8426238, or 1.843 after rounding.

Note that 0.0278/0.0051 is the same proportion as 1.843/0.338.

NCA parameter formulas

Plasma or serum data
Urine data
Sparse sampling (pre-clinical) data
Drug effect data model 220
User defined parameters
References

See also "NCA" and, for additional reading, see "References".

Plasma or serum data

Data structure: NCA for blood concentration data requires the following input data:

- Time of each sample
- Plasma or serum concentrations

Output: Models 200–202 estimate the parameters in the following lists.

Plasma parameters that do not require Lambda Z estimation

Plasma parameters that are estimated when Lambda Z is estimated

Plasma parameters that are estimated when at steady-state

Plasma parameters that do not require Lambda Z estimation

Dosing time: Available as 'Time' in the Dosing Used results. Time of last administered dose. It is assumed to be zero unless otherwise specified. This parameter is used mainly with steady-state data, where time may be coded as the time elapsed since the first dose, or the elapsed time since the time of the first dose.

N_Samples: This parameter reports the number of non-missing observations used in the analysis of the profile (time is at or after dosing time, the observation is numeric, and the volume is positive for urine models). It does not count points inserted by engine, e.g., inserted at dosing time.

Dose: Amount of last administered dose. This is assumed to be zero if not specified.

No_points_Lambda_z: Number of points used in computing Lambda Z. If Lambda Z is not estimable, zero.

Tlag: Time of observation prior to the first observation with a measurable (non-zero) concentration. For plasma models, Tlag is only computed when the dosing type is extravascular.

Tmax: Time of maximum observed concentration. For non-steady-state data, the entire curve is considered. If the maximum observed concentration is not unique, then the first maximum is used.

Cmax: Maximum observed concentration, occurring at time Tmax, as defined above.

Cmax_D: = $Cmax/Dose$

C0: Initial concentration. Given only for IV Bolus dosing. It is equal to the first observed concentration value if that value occurs at the dose time. Otherwise, it is estimated by back-extrapolating (see AUC_%Back_Ext below).

Tlast: Time of last measurable (positive) observed concentration.

Clast: Observed concentration corresponding to Tlast.

AUClast: Area under the curve from the time of dosing to the time of the last measurable (positive) concentration (Tlast).

AUClast_D: = $AUClast/Dose$

AUCall: Area under the curve from the time of dosing to the time of the last observation. If the last concentration is positive, AUClast=AUCall. Otherwise, AUCall will not be equal to AUClast, as it includes the additional area from the last measurable (positive) concentration down to zero or negative observations.

AUMClast: Area under the moment curve from the time of dosing to the last measurable (positive) concentration.

MRTlast: Mean residence time from the time of dosing to the time of the last measurable concentration.

For non-infusion models: = $AUMClast/AUClast$
For infusion models: = $(AUMClast/AUClast) - (Tinf/2)$
where $Tinf$ is the length of infusion.

Plasma parameters that are estimated when Lambda Z is estimated

The following list includes several parameters that are extrapolated to infinity. These parameters are calculated two ways: based on the last observed concentration (indicated by "_obs" appended to the parameter name), or based on the last predicted concentration (indicated by "_pred" appended to the parameter name), where the predicted value is based on the linear regression performed to estimate Lambda Z.

Rsq: Goodness of fit statistic for the terminal elimination phase.

Rsq_adjusted: Goodness of fit statistic for the terminal elimination phase, adjusted for the number of points used in the estimation of Lambda Z.

Corr_XY: Correlation between time (X) and log concentration (Y) for the points used in the estimation of Lambda Z.

Lambda_z: First-order rate constant associated with the terminal (log-linear) portion of the curve. Estimated by linear regression of time vs. log concentration.

Lambda_z_intercept: Intercept on log scale estimated via linear regression of time vs. log concentration.

Lambda_z_lower: Lower limit on time for values to be included in the calculation of Lambda Z.

Lambda_z_upper: Upper limit on time for values to be included in the calculation of Lambda Z.

HL_Lambda_z: Terminal half-life: = $\ln(2)/\lambda_z$

Span: = $(Lambda\_z\_upper - Lambda\_z\_lower)/HL\_Lambda\_z$

Clast_pred: Predicted concentration at $Tlast$:

= $exp(Lambda\_z\_intercept - Lambda\_z*Tlast)$

AUCINF(_obs, _pred): AUC from time of dosing extrapolated to infinity, based on the last observed concentration (_obs) or last predicted concentration (_pred).

= $AUClast + (Clast/Lambda\_z)$

AUCINF_D(_obs, _pred): = $AUCINF/Dose$

AUC_%Extrap(_obs, _pred): Percentage of AUCINF(_obs, _pred) due to extrapolation from Tlast to infinity:

= $100[(AUCINF - AUClast)/AUCINF]$

AUC_%Back_Ext(_obs, _pred): Computed for IV Bolus models. Percentage of AUCINF that was due to back extrapolation to estimate C0 when the first measured concentration is not at dosing time.

Vz(_obs, _pred), **Vz_F(_obs, _pred)**[a]: Volume of distribution based on the terminal phase.

For non-steady-state data: = $Dose/[Lambda\_z(AUCINF)]$

Cl(_obs, _pred), **Cl_F(_obs, _pred)**[a]: Total body clearance for extravascular administration.

= $Dose/AUCINF$

AUMCINF(_obs, _pred): Area under the first moment curve (AUMC) extrapolated to infinity, based on the last observed concentration (obs) or the last predicted concentration (pred).

$$= AUMClast + \frac{tlast \cdot Clast}{Lambda\_z} + \frac{Clast}{Lambda\_z^2}$$

AUMC_%Extrap(_obs, _pred): Percent of AUMCINF(_obs, _pred) that is extrapolated.

= $100[(AUMCINF - AUMClast)/AUMCINF]$

MRTINF(_obs, _pred): Mean residence time (MRT) extrapolated to infinity. For non-steady-state data:

For non-infusion models: = $AUMCINF/AUCINF$
For infusion models: = $(AUMCINF/AUCINF) - (Tinf/2)$
where $Tinf$ is the length of infusion.
(Note that, for extravascular dosing (oral model 200), MRTINF includes Mean Input Time as well as time in systemic circulation.)

Vss(_obs, _pred): For non-steady-state data: An estimate of the volume of distribution at steady-state based on the last observed (obs) or last predicted (pred) concentration.

= $(MRTINF)(C)$

Computed for IV Bolus and Infusion dosing only. Not computed for extravascular dosing (oral model 200), as MRTINF for oral models includes Mean Input Time as well as time in systemic circulation and therefore is not appropriate to use in calculating Vss.

[a]For extravascular models (model 200), the fraction of dose absorbed cannot be estimated; therefore Volume and Clearance for these models are actually Volume/F or Clearance/F where F is the fraction of dose absorbed.

Plasma parameters that are estimated when at steady-state

Tau: Available in the Dosing Used results worksheet for steady-state data. The (assumed equal) dosing interval for steady-state data.

Tmax: Time of maximum observed concentration. For steady-state data, based on observations collected during the dosing interval, that is, at or after the dosing time, but no later than the dosing time plus Tau, where Tau is the dosing interval. If the maximum observed concentration is not unique, then the first maximum is used.

Cmax: Maximum observed concentration, occurring at time Tmax, as defined above.

Tmin: Time of minimum observed concentration. For steady-state data, based on observations collected during the dosing interval (i.e., after the dosing time, but no later than dosing time plus Tau, where Tau is the dosing interval). If the minimum observed concentration is not unique, then the first minimum is used.

Cmin: Minimum observed concentration occurring at time Tmin as defined above.

> ***Note:*** Regulatory agencies differ on the definition of Cmin: some agencies define Cmin the same as Ctau is defined below. Both Cmin and Ctau are included in the output so that users can use the correct parameter for their situation.

Ctau: Concentration at dosing time plus Tau. Observed concentration if the value exists in the input data; otherwise, the predicted concentration value. Predicted concentrations are calculated following the same rules as for computing inserting missing endpoints needed for partial areas, see "Partial area calculation".

Cavg: Average concentration, computed = AUC_TAU/Tau

Swing: = $(Cmax - Cmin)/Cmin$

Swing_Tau: = $(Cmax - Ctau)/Ctau$

Fluctuation%: = 100[$(Cmax - Cmin)/Cavg$] where $Cmin$ and $Cmax$ were obtained between dosing time and dosing time plus Tau.

Fluctuation%_Tau: = 100[$(Cmax - Ctau)/Cavg$]

CLss, **CLss_F**[a]: An estimate of the total body clearance, computed for IV Bolus and Infusion dosing only.

$$= \frac{Dose}{AUC|_0^\tau}$$

MRTINF(_obs, _pred): Mean residence time (MRT) extrapolated to infinity based on AUCINF(_obs, _pred).

For non-infusion: $$\frac{AUMC|_0^\tau + \tau(AUCINF - AUC|_0^\tau)}{AUC|_0^\tau}$$

For infusion: $$\frac{AUMC|_0^\tau + \tau(AUCINF - AUC|_0^\tau)}{AUC|_0^\tau} - \frac{TI}{2}$$

where TI represents infusion duration. (Note that, for oral model 200, MRTINF includes Mean Input Time as well as time in systemic circulation.)

Vz, Vz_F[a]: = $$\frac{Dose}{\lambda_z \cdot AUC|_0^\tau}$$

Vss(_obs, _pred): An estimate of the volume of distribution at steady-state based on the last observed (obs) or last predicted (pred) concentration. Computed for IV Bolus and infusion dosing only.

= $MRTINF(CLss)$

Not computed for extravascular dosing (oral model 200), as MRTINF for oral models includes Mean Input Time as well as time in systemic circulation and therefore is not appropriate to use in calculating **Vss**.

Accumulation Index: = $\frac{1}{[1 - e^{-Lambda\_z\tau}]}$

AUC_TAU: The partial area from dosing time to dosing time plus Tau. See "Partial area calculation" for information on how it is computed.

AUC_TAU_D: = $AUC\_TAU/Dose$

AUC_TAU_%Extrap: Percentage of AUC_TAU that is due to extrapolation from Tlast to dosing time plus Tau.

$$= 100 \cdot \frac{AUC\_TAU - AUClast}{AUC\_TAU}, \text{ if } Dosing\_Time + \tau > Tlast$$

$$= 0, \text{ if } Dosing\_Time + \tau \leq Tlast$$

AUMC_TAU: Area under the first moment curve from dosing time to dosing time plus Tau. See "Partial area calculation" for information on how it is computed.

AUClower_upper: (Optional) User-requested area(s) under the curve from time "lower" to "upper".

[a]For extravascular models (model 200), the fraction of dose absorbed cannot be estimated; therefore Volume and Clearance for these models are actually Volume/F or Clearance/F where F is the fraction of dose absorbed.

Urine data

Data structure: NCA for urine data requires the following input data:

Starting and ending time of each urine collection interval
Urine concentrations
Urine volumes

From this data, models 210–212 compute the following for the analysis:

Midpoint of each collection interval=(Starting time+Ending time)/2
Excretion rate for each interval (amount eliminated per unit of time)=(Concentration*Volume)/(Ending time-Starting time)

Output: Models 210–212 estimate the following parameters.

The worksheet will include the Sort(s), Carry(ies), parameter names, units, and computed values. A User Defined Parameters Pivoted worksheet will include the pivoted form of the User Defined Parameters worksheet.

Urine parameters that do not depend on Lambda Z

Dosing time: Available as 'Time' in the Dosing Used results. Time of last administered dose. It is assumed to be zero unless otherwise specified. This parameter is used mainly with steady-state data, where time may be coded as the time elapsed since the first dose, or the elapsed time since the time of the first dose.

Dose: Amount of last administered dose. This is assumed to be zero if not specified.

N_Samples: Number of non-missing observations in the analysis. Does not include missing or non-numeric observations, observations before dosing time, or urine observations where volume is zero. Does not include the point at dosing time if it was not observed but was inserted by the engine.

No_points_lambda_z: Number of points used in the computation of Lambda Z. If Lambda Z cannot be estimated, this is set to zero.

Tlag: Midpoint of the collection interval prior to the first collection interval with measurable (non-zero) rate. Computed for all urine models.

Tmax_Rate: Midpoint of the collection interval associated with the maximum observed excretion rate. If the maximum observed excretion rate is not unique, then the first maximum is used.

Max_Rate: Maximum observed excretion rate, at time Tmax_Rate as defined above.

Mid_Pt_last: Midpoint of collection interval associated with last measurable (positive) observed excretion rate.

Rate_last: Last observed measurable (positive) rate at time Mid_Pt_last.

AURC_last: Area under the urinary excretion rate curve from time of dosing to Mid_Pt_last.

AURC_last_D: = $AURC\_last/Dose$

Vol_UR: Sum of Urine Volumes (urine)

Amount_Recovered: Cumulative amount eliminated.

$$= \sum Concentration\_Volume$$

Percent_Recovered: = 100($Amount\_Recovered/Dose$)

AURC_all: Area under the urinary excretion rate curve from the time of dosing to the midpoint of the interval with the last rate. If the last rate is positive, AURC_last=AURC_all.

Urine parameters that are estimated when Lambda Z is estimated

The following list includes some parameters that are extrapolated to infinity. These parameters are calculated two ways: based on the last observed excretion rate: Rate_last (indicated by "_obs" appended to the parameter name), or based on the last predicted excretion rate: Rate_last_pred (indicated by "_pred" appended to the parameter name), where the predicted value is based on the linear regression performed to estimate Lambda Z.

Rsq: Goodness of fit statistic for the terminal elimination phase.

Rsq_adjusted: Goodness of fit statistic for the terminal elimination phase, adjusted for the number of points used in the estimation of Lambda Z.

Corr_XY: Correlation between midpoints and log excretion rates for the points used in the estimation of Lambda Z.

Lambda_z: First-order rate constant associated with the terminal (log-linear) portion of the curve. This is estimated via linear regression of midpoints vs. log excretion rates.

Lambda_z_intercept: Intercept on log scale estimated via linear regression of midpoints vs. log excretion rates.

Lambda_z_lower: Lower limit on midpoint for values to be included in Lambda Z estimation.

Lambda_z_upper: Upper limit on midpoint for values to be included in Lambda Z estimation.

HL_Lambda_z: Terminal half-life=ln(2)/$Lambda\ Z$

Span: = ($Lambda\_z\_upper - Lambda\_z\_lower$)/$HL\_Lambda\_z$

Rate_last_pred: Predicted rate at Mid_Pt_last.

AURC_INF(_obs, _pred): Area under the urinary excretion rate curve extrapolated to infinity, based on the last observed excretion rate (_obs) or the last predicted rate (_pred), i.e., the excretion rate at

the final midpoint estimated using the linear regression for Lambda Z. Note that AURC_INF is theoretically equal to Amount_Recovered, but will differ due to experimental error.

AURC_%Extrap(_obs, _pred): Percent of AURC_INF(_obs, _pred) that is extrapolated.

Sparse sampling (pre-clinical) data

When an NCA model is loaded with the Sparse Sampling option (see "Options tab"), the data are treated as a special case of plasma or urine concentration data. The NCA engine computes the mean concentration or rate at each unique time value or interval. Using the mean concentration curve across subjects, it estimates the same parameters normally calculated for plasma or urine data, plus those listed below. See "Sparse sampling calculation" for additional details of NCA computations with sparse data.

Note: The names of some of the output worksheets change when the data is sparse: Final Parameters becomes Mean Curve Final Parameters, and Summary Table becomes Mean Curve Summary Table.

Plasma or serum concentration parameters

Sparse sampling methods for plasma data (models 200–202) compute the following parameters in addition to those listed in "Plasma or serum data".

SE_Cmax: Standard error of data at Tmax (time of maximum mean concentration).

SE_AUClast: It is the standard error of the area under the mean concentration curve from dose time to Tlast, where Tlast is the time of last measurable (positive) mean concentration.

SE_AUCall: Standard error of the area under the mean concentration curve from dose time to the final observation time.

Note: SE_AUClast and SE_AUCall provide a measurement of the uncertainty for AUClast and AUCall, respectively, and are usually the same. Differences between these parameter values will only be observed if some of the measurements were flagged as BQL (below the quantitation limit).

Note: With Sparse Sampling, since SE for AUC computations depend on AUC being a linear combination of the mean concentrations, SE_AUClast and SE_AUCall are not included in the output when the output when log trapezoidal rules are specified as the method for computing AUC.

Urine excretion rate parameters

Sparse sampling methods for urine data (models 210–212) compute the following parameters in addition to those listed under "Urine data".

SE_Max_Rate: Standard error of the data at the time of maximum mean rate.

SE_AURC_last: Standard error of the area under the mean urinary excretion rate curve from dose time through the last interval that has a measurable (positive) mean rate.

SE_AURC_all: Standard error of the area under the mean urinary excretion rate curve from dose time through the final interval.

Individuals by time

This sheet includes the individual subject data, along with N (number of non-missing observations), the mean and standard error for each unique time value (plasma data) or unique midpoint value (urine data).

References

Holder (2001). Comments on Nedelman and Jia's extension of Satterthwaite's approximation applied to pharmacokinetics. *J Biopharm Stat* 11(1-2):75–9.

Nedelman, Gibiansky and Lau (1995). Applying Bailer's method for AUC intervals to sparse sampling. *Pharm Res* 12:124–8.

Nedelman and Jia (1998). An extension of Satterthwaite's approximation applied to pharmacokinetics. *J Biopharm Stat* 8(2):317–28.

Yeh (1990). Estimation and Significant Tests of Area Under the Curve Derived from Incomplete Blood Sampling. *ASA Proceedings of the Biopharmaceutical Section* 74–81.

Drug effect data model 220

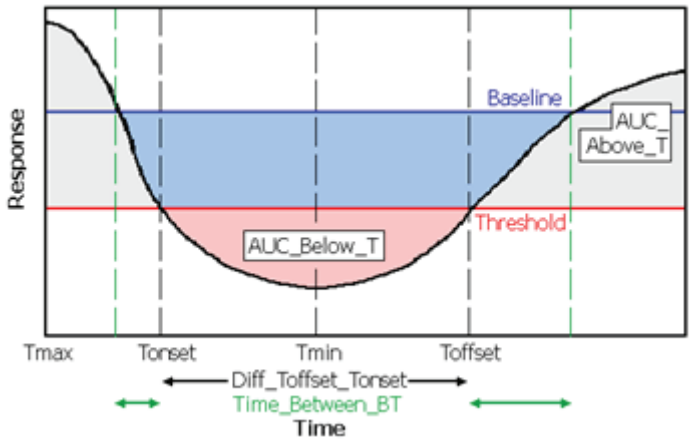


Figure 20-1. Illustration of a time-effect curve with AUCs highlighted

Output parameter names use the following conventions:

B is the baseline effect value (discussed above).
T is the user-supplied threshold effect value.
“Above” means towards increasing Y values, even for inhibitory effects.

Estimated parameters for model 220

N_Samples: This parameter reports the number of non-missing observations used in the analysis of the profile (time is at or after dosing time, the observation is numeric, and the volume is positive for urine models). It does not count points inserted by engine, e.g., inserted at dosing time.

Slope1 (or **2**): Slope of the first (or second) segment of the curve. See “Lambda Z or Slope Estimation settings”.

Rsq_Slope1 (or **2**): Goodness of fit statistic for slope 1 or 2.

Rsq_adj_Slope1 (or **2**): Goodness of fit statistic for slope 1 or 2, adjusted for the number of points used in the estimation.

Corr_XY_Slope1 (or **2**): Correlation between time (X) and effect (or log effect, for log regression) (Y) for the points used in the slope estimation.

No_points_Slope1 (or **2**): The number of data points included in calculation of slope 1 or 2.

Slope1_lower or **Slope2_lower**: Lower limit on Time for values to be included in the slope calculation.

Slope1_upper or **Slope2_upper**: Upper limit on Time for values to be included in the slope calculation.

Tmin: Time of minimum observed response value (Rmin).

Rmin: Minimum observed response value.

Tmax: Time of maximum observed response value (Rmax).

Rmax: Maximum observed response value.

Baseline: Baseline response (Y) value supplied by the user, (assumed to be zero if none is supplied) or, for Certara Integral studies with no user-supplied baseline value, effect value at dose time.

AUC_Above_B: Area under the response curve that is above the baseline (dark gray areas in the above diagram).

AUC_Below_B: Area that is below the baseline and above the response curve (combined blue and pink areas in the above diagram).

AUC_Net_B: = $AUC\_Above\_B - AUC\_Below\_B$. This is likely to be a negative value for inhibitory effects.

Time_Above_B: Total time that Response is greater than or equal to Baseline.

Time_Below_B: Total time that Response is less than Baseline.

Time_%Below_B: = 100*$Time\_Below\_B/(Tfinal - Tdose)$, where $Tfinal$ is the final observation time and $Tdose$ is dosing time.

When a threshold value is provided, model 220 also computes the following.

Threshold: Threshold value used.

AUC_Above_T: Area under the response curve that is above the threshold value (combined light and dark gray areas in the above diagram).

AUC_Below_T: Area that is below the threshold and above the response curve (pink area in the above diagram).

AUC_Net_T: = $AUC\_Above\_T - AUC\_Below\_T$

Time_Above_T: Total time that Response >= Threshold.

Time_Below_T: Total time that Response < Threshold.

Time_%Below_T: = 100*$Time\_Below\_T/(Tlast - Tdose)$
where Tlast is the final observation time and Tdose is dosing time.

Tonset: Time that the response first crosses the threshold coming from the direction of the baseline value, as shown in the above diagram. $Tonset$=$Tdose$ if the first response value is across the threshold, relative to baseline. The time will be interpolated using the calculation method selected in the model options. (See "Options tab".)[a]

Toffset: Time greater than Tonset at which the curve first crosses back to the baseline side of threshold, as shown in the diagram above.[a]

Diff_Toffset_Tonset: = *Toffset – Tonset*

Time_Between_BT: Total time spent between baseline and threshold (sum of length of green arrows in diagram).

AUClower_upper: (Optional) user-requested area(s) under the curve from time “lower” to time “upper”.

[a]Use caution in interpreting *Tonset* and *Toffset* for noisy data if Baseline and Threshold are close together.

User defined parameters

Any user defined parameters will be computed and reported in the User Defined Parameters and User Defined Parameters Pivoted worksheets. The worksheets include entries for Sort, Carry, parameter name, unit, and estimated value. A User Defined Parameters Pivoted worksheet will include the pivoted form of the User Defined Parameters worksheet.

C<time value>: For Plasma models with user-defined times only, one column per requested time value. (For plasma models, a computed concentration at time zero will be reported as the parameter C0_0, since C0 is already used for the initial concentration measurement.)

Y<x-value>: For Drug Effect models with user-defined x-values only, one column per requested x-value.

<user-defined name>: Parameter defined using the User Defined Parameters tab.

References

Holder (2001). “Comments on Nedelman and Jia's extension of Satterthwaite's approximation applied to pharmacokinetics.” *J Biopharm Stat* 11(1–2):75–9.

Nedelman and Jia (1998). “An extension of Satterthwaite's approximation applied to pharmacokinetics.” *J Biopharm Stat* 8(2):317–28.

NCA examples

This section presents several examples of the NCA operational object usage within Phoenix. Knowledge of how to do basic tasks using the Phoenix interface, such as creating a project and importing data, is assumed.

The examples include:

Analysis of three profiles using NCA
Exclusion and partial area NCA example
Sparse sampling NCA example
Urine study NCA example
Drug effect NCA example
Multiple profile analysis using NCA

Analysis of three profiles using NCA

Suppose a researcher has obtained time and concentration data following oral administration of a test compound to three subjects, and wants to perform noncompartmental analysis and summarize the results.

The completed project (`NCA.phxproj`) is available for reference in …`\Examples\WinNonlin`.

Set up the project and data for the three profiles

1. Create a new project named `NCA`.
2. Import the file …`\Examples\WinNonlin\Supporting files\Bguide1 single dose and steady state.dat`.

Note: Units must be added to the time and concentration columns before the dataset can be used in a noncompartmental analysis.

3. With **Bguide1 single dose and steady state** selected in the Data folder, go to the Columns tab (lower part of the Phoenix window) and select the **Time** column header in the Columns box.
4. Clear the **Unit** field and type `hr`.
5. Select the **Conc** column header in the Columns box.
6. Clear the **Unit** field and type `ng/mL`.
   Or
   Click the **Units Builder** button and use the *Units Builder* dialog tools

Note: Units added to ASCII datasets can be preserved if the datasets are saved in `.dat` or `.csv` file format. Phoenix adds the units to a row below the column headers. To import a `.dat` or `.csv` file with units, select the **Has units row** option in the *File Import Wizard* dialog.

Set up the NCA object for analysis of the three profiles

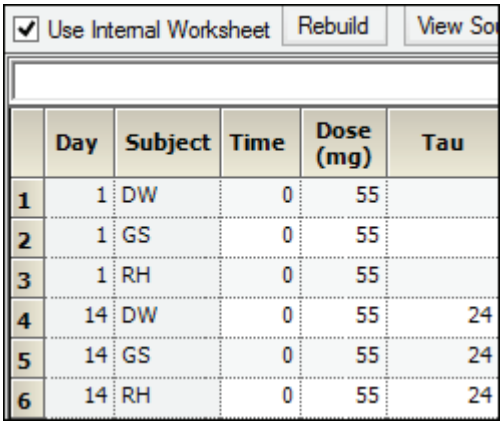
Noncompartmental analysis for extravascular dosing is available as Model 200 in the Phoenix model library. Phoenix displays the model type (Plasma, Urine, or Drug Effect) in the Options tab of an NCA object.

Note: The exact model used is determined by the dose type. Extravascular Input uses Model 200, IV-Bolus Input uses Model 201, and Constant Infusion uses Model 202.

1. Select **Workflow** in the Object Browser and then select **Insert > NonCompartmental Analysis > NCA**.
2. Drag the **Bguide1 single dose and steady state** worksheet from the Data folder to the NCA object's Main Mappings panel.
3. Map the data types as follows:
   Day to the **Sort** context (make sure to map **Day** first)
   Subject to the **Sort** context
   Time mapped to the **Time** context
   Conc to the **Concentration** context

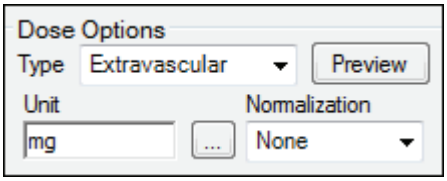
Prepare the dosing information from the profiles

1. Select **Dosing** in the NCA object's Setup list.
2. In the Dosing panel, select the **Use Internal Worksheet** checkbox.
3. Click **OK** in the *Select sorts* dialog to accept the default sort variables.
4. For each row:
   In the Time column, enter `0`.
   In the Dose column, enter `55`.
   In the Tau column, enter `24` for the three Day 14 rows (rows 4, 5, and 6).



	Day	Subject	Time	Dose (mg)	Tau
1	1	DW	0	55	
2	1	GS	0	55	
3	1	RH	0	55	
4	14	DW	0	55	24
5	14	GS	0	55	24
6	14	RH	0	55	24

5. In the Dose Options area of the Options tab, type `mg` in the **Unit** field and press the **Enter** key. The units are immediately added to the column header.
6. **Extravascular** is selected by default in the **Type** menu. Do not change this setting.



Set up the terminal elimination phase for the analysis

Phoenix attempts to estimate the rate constant Lambda Z, associated with the terminal elimination phase. Although Phoenix is capable of selecting the times to be used in the estimation of Lambda Z, this example provides Phoenix with the time range.

Specify the times to be included.

1. Select **Slopes** in the Setup list.
2. For each row:
   In the Start Time column, type `8`.
   In the End Time column, type `24`.
   Do not type any values into the **Exclusions** column.
3. Select **Slopes Selector** in the Setup list.

   The **Time Range** is selected in the **Lambda Z Calculation Method** menu. The **Start** and **End** times have been specified for each subject. A line is displayed on each graph that shows the Lambda Z time range.

   In this example, no points are excluded from the specified Lambda Z time range. The example "Exclusion and partial area NCA example" demonstrates Lambda Z exclusions.

Specify therapeutic response options

The next step is to define a target concentration range to enable calculation of the time and area located above, below, and within that range.

Note: See "Exclusion and partial area NCA example" for an NCA example that includes computation of partial areas under the curve.

1. Select **Therapeutic Response** in the Setup list.
2. Select the **Use Internal Worksheet** checkbox.
3. Click **OK** in the sorts dialog to accept the default sort variables.
4. For each row:
   Type `2` in the **Lower** column.
   Type `4` in the **Upper** column.

Set preferred units for the analysis

The next step in setting options is to specify preferred output units. The independent variable, dependent variable, and dosing regimen must have units before preferred output units can be set.

1. Select **Units** in the Setup list.

   The Units worksheet lists both the Default units and the Preferred units for each parameter. The new preferred volume unit needs to be set to L (liter).
2. Select the cell in the **Preferred** column for Volume (Vz, Vz/F, Vss).
3. Type `L` and press **ENTER**.

Specify NCA model options for the analysis

Four methods are available for computing the area under the curve. The default method is the linear trapezoidal rule with linear interpolation. This example uses the **Linear Log Trapezoidal** method: linear trapezoidal rule up to Tmax, and log trapezoidal rule for the remainder of the curve.

Use the Options tab to specify settings for the NCA model options. The Options tab is located underneath the Setup tab.

1. Select **Linear Log Trapezoidal** in the **Calculation Method** menu.
2. In the **Titles** field type `Example of Noncompartmental Analysis.`

Set an acceptance criteria rule

Acceptance criteria for Lambda Z, which are applicable to both the **Best Fit** method and the **Time Range** method, can be specified on the Rules tab. These rules are used to flag profiles where the Lambda_z final parameter does not meet the specified acceptance criteria.

1. Select the **Rules** tab.
2. In the **Rsq_adjusted** field, type `0.97` to flag any profile with an Rsq_adjusted value greater than or equal to this value.

Profiles that break the rule are flagged in the output and can be quickly filtered out of the results. The process will be illustrated later in this example.

Execute and view the results of the analysis

At this point, all of the necessary commands have been specified.

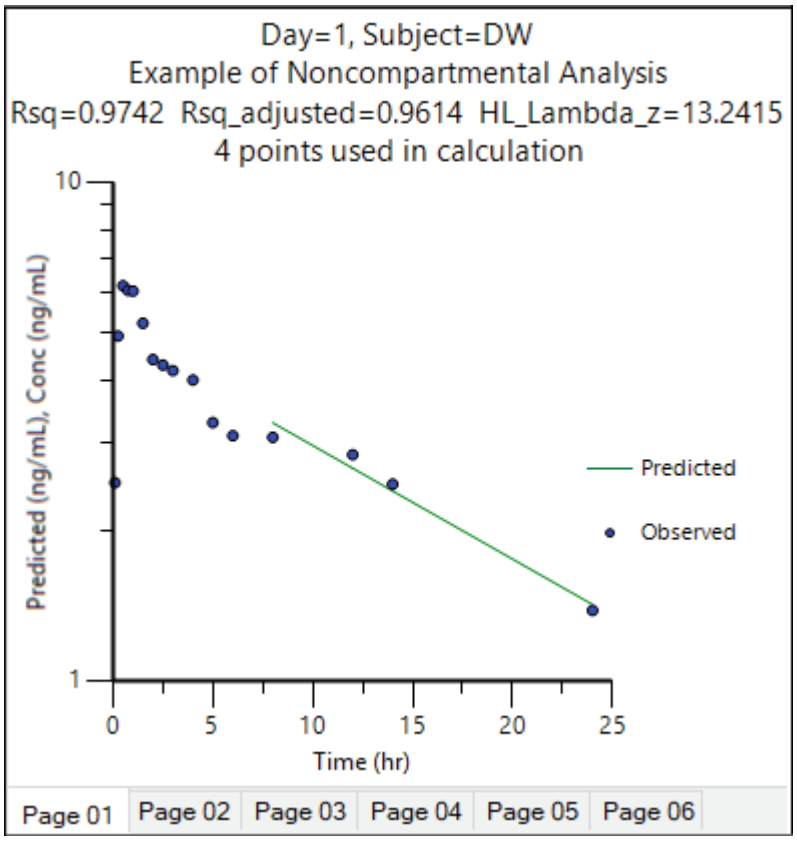
1. Click  (**Execute** icon) to execute the object.
2. In the Results tab, select **Final Parameters** in the list.

   Subject DW's concentrations were within the theoretical therapeutic range for just over 13.8 hours, as reflected in the parameter TimeBetween.

	Day	Subject	Parameter	Units	Estimate
41	1	DW	MRTINF_pred	hr	19.187241
42	1	DW	TimeLow	hr	6.3652263
43	1	DW	TimeBetween	hr	13.811328
44	1	DW	TimeHigh	hr	3.8234453
45	1	DW	TimeInfBetween	hr	13.811328

3. In the Results tab, select **Observed Y and Predicted Y vs X** in the list.

   The NCA object's plot output includes Observed Y and Predicted Y vs X graphs for each subject (switch between the plots using the tabs below the graph).



4. In the Results tab, select **Core output** in the list.

   The NCA object's Core Output text file contains user settings, a brief summary table, and final parameters output for each subject.

```
Settings
--------
Model:  Plasma Data, Extravascular Administration
Number of nonmissing observations:   16
Dose time:      0.00
Dose amount:       55.00
Calculation method:  Linear/Log Trapezoidal
Weighting for lambda_z calculations:  Uniform weighting
Lambda_z method:  User-specified lambda_z range,  Log regression
User's lambda_z bounds:      8.00,     24.00
Lower bound for therapeutic window:    2.00
Upper bound for therapeutic window:    4.00
Lambda_z Acceptance Criterion, Min Rsq_Adjusted:  0.9700
```

Figure 21-1. Settings portion of the Core Output

Filter out flagged profiles

1. In the Results tab, select **Final Parameters Pivoted** in the list.

	Day	Subject	N_Samples	Dose (mg)	Rsq	Rsq_adjusted	Flag_Rsq_adjusted	Corr_XY	No_points_lambda_z
1	1	DW	16	55	0.97423895	0.96135842	Not_Accepted	-0.98703543	4
2	1	GS	16	55	0.98383816	0.97575725	Accepted	-0.99188616	4
3	1	RH	16	55	0.99441626	0.9916244	Accepted	-0.99720422	4
4	14	DW	16	55	0.98659088	0.97988632	Accepted	-0.99327281	4
5	14	GS	16	55	0.99108753	0.98663129	Accepted	-0.99553379	4
6	14	RH	16	55	0.99666853	0.9950028	Accepted	-0.99833288	4

Figure 21-2. Part of the Final Parameters Pivoted worksheet

For this example, a rule was set for the value of Rsq_adjusted (see "Set an acceptance criteria rule"). The output indicates that the profile for DW broke this rule with a value of 'Accepted' in the Flag_Rsq_adjusted column.

To remove any profiles failing to meet acceptance criteria from the output, the Final Parameters Pivoted worksheet can be processed by the Data Wizard to delete these profiles. The worksheet is filtered on the flag values of 'Not Accepted' and identified rows are then excluded.

Note: The `NCA.phxproj` file does not include processing by the Data Wizard, but the information is included here as a reference.
a) Insert a Data Wizard object.
b) In the Options tab, set Action to **Filter** and click **Add**.
c) Click the **Select Source** icon in the Mappings panel and select the NCA Final Parameter Pivoted worksheet.
d) In the Options tab, click the **Add** button to the right of the **Specify Filter** field.
e) In the *Filter Specification* dialog, define the filter to **Exclude** rows that have a value of **Not Accepted** in the **Flag_Rsq_adjusted** column (or other "Flag_" column on which you want to filter profiles).
Once the filter is defined, execute the Data Wizard object.

Summarize the analysis output with statistics

At this point, it is convenient to summarize the results of the noncompartmental analysis using a Descriptive Statistics object. This example summarizes parameter estimates across subjects.

1. Select **Workflow** in the Object Browser and then select **Insert > Computation Tools > Descriptive Statistics**.
2. In the Descriptive Statistic's Main Mappings panel click the **Select Source** icon.
3. Under the **NCA** node, select the **Final Parameters** worksheet and click **OK**.
4. In the Main Mappings panel, map the data types to the following contexts:
   Map **Day** to the **Sort** context (make sure to map **Day** first).
   Leave **Subject** mapped to **None**.
   Map **Parameter** to the **Sort** context.
   Leave **Units** mapped to **None**.
   Map **Estimate** to the **Summary** context.

Note: Mapping Day and Parameter to Sort computes statistics on the parameter estimates for each day and mapping Estimate to Summary computes one statistic per parameter per day.

5. In the Options tab, check the **Confidence Intervals** and **Number of SD Statistics** checkboxes, but do not change the default values for these two items.
6. Execute the object.

The three subjects spent an average of 13.6 hours within the therapeutic concentration range on Day 1, as shown by the parameter TimeBetween.

41	Estimate	1	Rsq_adjusted	3	0	3	0.97624669
42	Estimate	1	Span	3	0	3	1.3132153
43	Estimate	1	TimeBetween	3	0	3	13.627457
44	Estimate	1	TimeHigh	3	0	3	3.4122411
45	Estimate	1	TimeInfBetween	3	0	3	13.627457

Use ratios to compare data

The Ratios and Differences object can be used to quickly setup ratios and/or differences between parameter values in order to compare data. A description of the object can be found in "Ratios and Differences".

1. In the Object Browser, click the NCA object.
2. In the Results list, right-click **Final Parameters Pivoted** and select **Send To > Computation Tools > Ratios and Differences**.
3. In the Main Mappings panel of the Ratios and Differences object, map the data types to the following contexts:
   Map **Day** to the **Filter** context.
   Map **Subject** to the **Sort** context.
   Map the rest of the data types to the **Carry** context by first mapping **N_Samples** to **Carry** and then drag the corner of the selected cell all the way to the bottom of the grid. It may take a few seconds.
4. In the Options tab, set up two ratios as shown in the following image. Use the **Add** button to add the second row of options to the table.

	X		Y		
Comparison	Column	Filter Value	Column	Filter Value	New Column Name
X/Y	Cmax	14	Cmax	1	Ratio_Cmax14_Cmax1
X/Y	AUC_TAU	14	AUClast	1	Ratio_AUC_TAU14_AUClast1

5. Execute the object.
6. In the Results tab, select **Ratios Differences** and compare the ratios for each subject.

	Subject	Ratio_Cmax14_Cmax1	Ratio_AUC_TAU14_AUClast1
1	DW	1.2559716	1.2609336
2	GS	1.0863854	1.2330284
3	RH	1.2174045	1.2203516

This concludes the multiple profile example.

Exclusion and partial area NCA example

This example demonstrates the exclusion of points in the terminal elimination phase and computation of partial area under the curve in the Phoenix NCA object. The time-concentration data is for a single subject and the data is provided in `NCA2.csv`, which is located in the Phoenix examples directory.

Noncompartmental analysis for extravascular dosing is available as model 200 in Phoenix's noncompartmental analysis object. Phoenix always displays the model type in the NCA object's Options tab.

Note: The exact model used is determined by the dose type. Extravascular Input uses Model 200, IV-Bolus Input uses Model 201, and Constant Infusion uses Model 202.

The completed project (`NCA_PartialAreas.phxproj`) is available for reference in `…\Examples\WinNonlin`.

Set up the NCA object

1. Create a project called `NCA_PartialAreas`.
2. Import the file `…\Examples\WinNonlin\Supporting files\NCA2.csv`.
   In the *File Import Wizard* dialog, make select the **Has units row** option.
   Click **Finish**.
3. Select **Workflow** in the Object Browser and then select **Insert > NonCompartmental Analysis > NCA**.
4. Drag the **NCA2** worksheet from the Data folder to the NCA object's Main Mappings panel to map it as the input source.
   Leave **Time** mapped to the **Time** context.
   Map **Conc** to the **Concentration** context.

Prepare the dosing information

In this example, one dose of 70 mg was administered at time zero.

1. Select **Dosing** in the Setup list.
2. In the Dosing panel, check the **Use Internal Worksheet** checkbox.
3. In the first cell in the **Time** column type `0`.
4. In the first cell in the **Dose** column type `70`.
5. Do not enter any values in the **Tau** column.
6. **Extravascular** is selected by default in the **Type** menu in the Options tab. Do not change this setting.
7. In the **Unit** field type `mg` and press the **Enter** key.

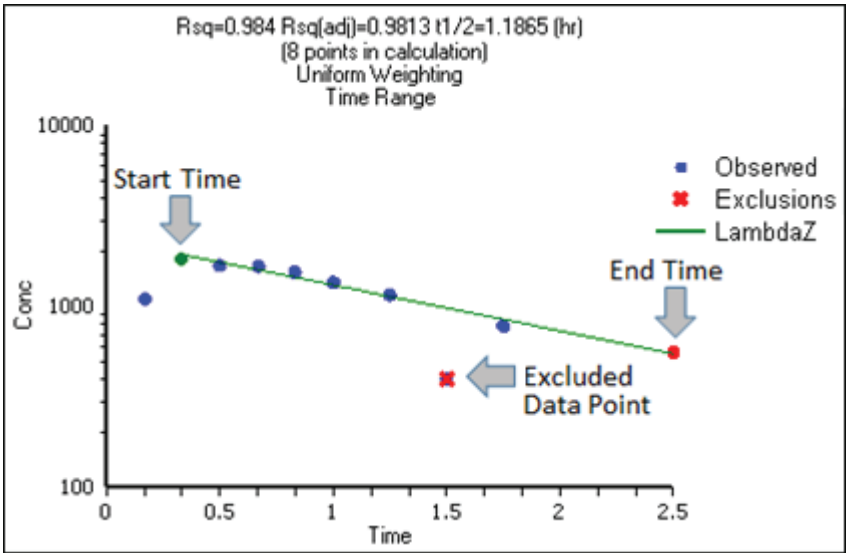
Set up the terminal elimination phase

Phoenix attempts to estimate the rate constant Lambda Z associated with the terminal elimination phase. Although Phoenix is capable of selecting the times to be used in the estimation of Lambda Z, this example provides Phoenix with the time range.

1. Select **Slopes** in the Setup list.
2. In the Slopes panel, type `0.33` in the **Start Time** column.

3. Type `2.5` in the **End Time** column.
4. Exclude the data point at 1.5 by typing `1.5` in the **Exclusions** column and press the **Enter** key.
5. Select **Slopes Selector** in the Setup list.

The Start and End times and the Exclusion are marked on the graph display.



Specify the AUCs to calculate

Partial areas under the curve are computed for zero to 3.0 hours and 1.25 to 2.5 hours.

1. Select **Partial Areas** in the Setup list.
2. Select the **Use Internal Worksheet** checkbox.
3. In the Options tab, change the **Max # of Partial Areas** pull-down menu to **2**.
4. In the first row, type `0` in the **Start Time** column and type `3` in the **End Time** column.
5. In the second row, type `1.25` in the **Start Time** column, type `2.5` in the **End Time** column and press the **Enter** key.

Specify the NCA model options

This example includes titles in the graph output and uses the Linear Log Trapezoidal method to calculate areas under the curve.

Use the Options tab to specify settings for the NCA model options.

1. The default setting for **Model Type** is **Plasma (200-202)**. Do not change this setting.

Note: The exact model type (200, 201, or 202) is determined by the dose type.

2. Select **Linear Log Trapezoidal** in the **Calculation Method** menu.
3. In the **Titles** field type `A Second NCA Example`.

Request a concentration at a specified time

Set up a request to calculate the concentration at time 0.25 and include the information in the results.

1. Select the User Defined Parameters tab.
2. Check the **Include with Final Parameters** check box.
3. In the **Compute Concentrations at Times** field, enter `0.25`.

Define a new parameter

Add a new dose-normalized parameter.

1. In the User Defined Parameters tab, click the **Add** button.
2. Enter `AUCall_D` in the **Parameter** column.
3. Enter `AUCall/Dose` in the **Definition** column.
4. Enter `hr*ng/mL/mg` in the **Units Label** column.

Execute and view the NCA results

All necessary settings are complete.

1. Click  (**Execute** icon) to execute the object.
2. In the Results tab, click **Final Parameters**.

	Parameter	Units	Estimate
1	N_Samples		12
2	Dose	mg	70
3	Rsq		0.98395394
4	Rsq_adjusted		0.9812796
5	Corr_XY		-0.99194452
6	No_points_lambda_z		8
7	Lambda_z	1/hr	0.58421637
8	Lambda_z_intercept		7.7694401
9	Lambda_z_lower	hr	0.33
10	Lambda_z_upper	hr	2.5
11	HL_Lambda_z	hr	1.1864563
12	Span		1.828976
13	Tlag	hr	0

Figure 22-1. Part of the Final Parameters worksheet

Note the partial area estimates near the bottom of the Final Parameters.

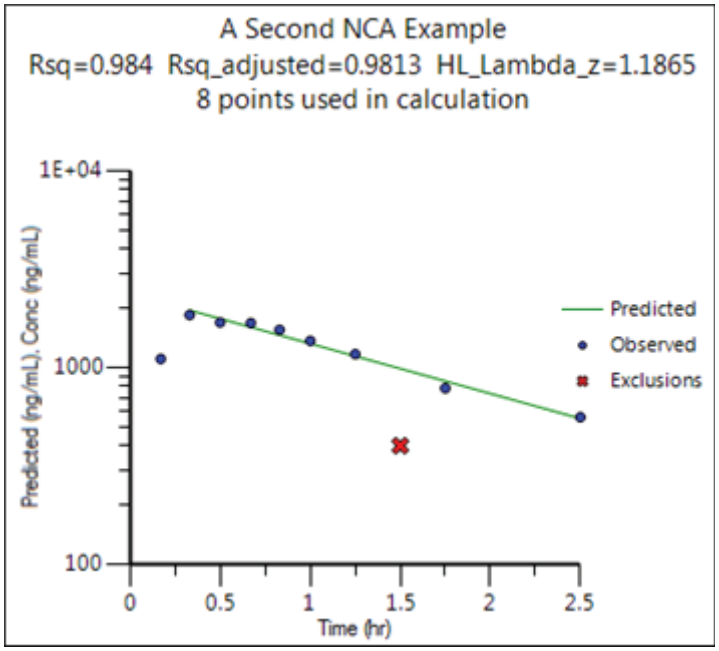
41	AUC0_3	hr*ng/mL	2538.0832
42	AUC1.25_2.5	hr*ng/mL	559.24056

3. Click **Summary Table** in the Results list.

	Time (hr)	lambda_z _Incl	Conc (ng/mL)	Predicted (ng/mL)	Residual (ng/mL)	AUC (hr*ng/mL)	AUMC (hr*hr*ng/mL)	Weighting
1	0		0			0	0	0
2	0.17		1105			93.925	15.96725	0
3	0.33	*	1845	1952.076	-107.07599	329.925	79.70325	1
4	0.5	*	1691	1767.5186	-76.51858	630.29487	203.98591	1
5	0.67	*	1681	1600.41	80.589999	916.91403	371.63404	1
6	0.83	*	1552	1457.5912	94.408775	1175.4167	565.23588	1
7	1	*	1364	1319.7845	44.215529	1422.9329	791.26056	1
8	1.25	*	1167	1140.4402	26.559775	1738.668	1145.4369	1
9	1.5		400			1917.7519	1387.7568	0
10	1.75	*	784	851.55275	-67.552746	2060.4085	1621.5589	1
11	2		0			2158.4085	1793.0589	0
12	2.5	*	558	549.43977	8.5602281	2297.9085	2141.8089	1

Note that values used in the calculation of Lambda Z are marked with an asterisk in the column Lambda_z_Incl. The data point corresponding to time 1.5, which was excluded manually, is not marked with an asterisk. The observation at time 2.0, with a value of zero, was automatically excluded.

4. Click **Observed Y and Predicted Y vs X**.



The excluded data point is marked on the Observed Y and Predicted Y vs X plot output of observed and predicted data.

This concludes the partial areas example.

Sparse sampling NCA example

This example demonstrates how to model with sparse sampling. The time-concentration data is provided in `SparseSamplingChaioYeh.xls`. The dosing and therapeutic response data are stored in `SparseSamplingChaioYeh_sources.xls`. These files are located in the Phoenix examples directory.

The completed project (`NCA_SparseSampling.phxproj`) is available for reference in `…\Examples\WinNonlin`.

Set up the NCA object

1. Create a project called `NCA_SparseSampling`.
2. Import the two files `…\Examples\WinNonlin\Supporting files\SparseSamplingChaioYeh.xls` and `SparseSamplingChaioYeh_sources.xls`.
   In the *File Import Wizard* dialog, select the **Has units row** option for Sheet 1 and Dosing worksheets.
3. Select **Workflow** in the Object Browser and then select **Insert > NonCompartmental Analysis > NCA**.
4. Rename the NCA object just added as `SparseSamplingChaioYeh`.
5. Drag the **SparseSamplingChaioYeh** worksheet from the Data folder to the SparseSamplingChaioYeh object's Main Mappings panel. Map the context as follows:
   Subject set to **None** context
   Time to **Time** context
   Conc to **Concentration** context

Set up for sparse sampling

1. Select **Dosing** in the Setup list.
2. Expand the **SparseSamplingChaioYeh_sources** item in the Object Browser Data folder and drag the **Dosing** item to the Dosing panel.
   Type is already mapped to the **None** context.
   Dose is already mapped to the **Dose** context.
   Time is already mapped to the **Time** context.
3. Select **Therapeutic Response** in the Setup list.
4. In the expanded **SparseSamplingChaioYeh_sources** item in the Object Browser Data folder, drag the **TherapeuticResponse** item to the Therapeutic Response panel.
   Lower is already mapped to the **Lower** context.
5. In the Options tab, check the **Sparse** check box.

Execute and view the NCA results

All necessary settings are complete.

1. Click  (**Execute** icon) to execute the object.
2. In the Results tab, click **Final Parameters**.

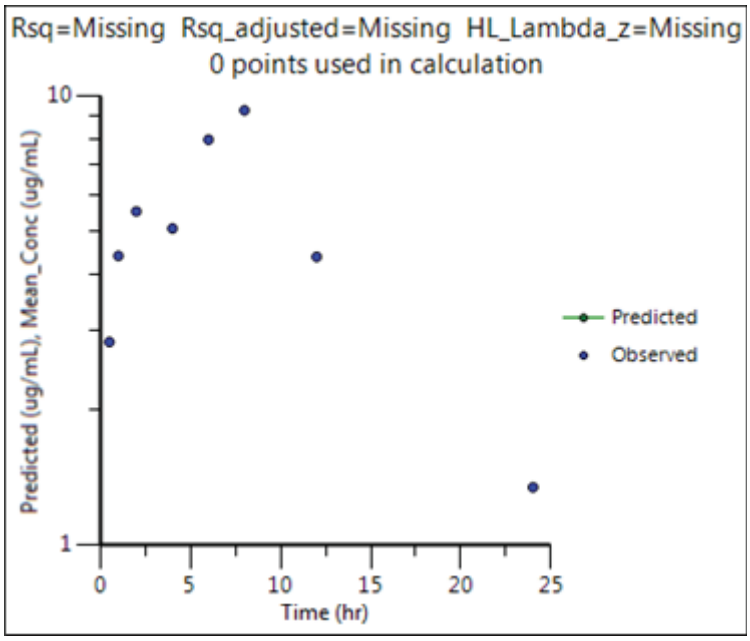
	Parameter	Units	Estimate
1	N_Samples		9
2	Dose	mg	1
3	Rsq		
4	Rsq_adjusted		
5	Corr_XY		
6	No_points_lambda_z		0
7	Lambda_z	1/hr	
8	Lambda_z_intercept		
9	Lambda_z_lower	hr	
10	Lambda_z_upper	hr	
11	HL_Lambda_z	hr	
12	Span		
13	Tlag	hr	0
14	Tmax	hr	8
15	Cmax	ug/mL	9.28

Figure 23-1. Part of the Final Parameters worksheet

3. Click **Summary Table**.

	Time (hr)	lambda_z _Incl	Mean_Conc (ug/mL)	Predicted (ug/mL)	Residual (ug/mL)	AUC (hr*ug/mL)	AUMC (hr*hr*ug/mL)	Weighting
1	0		0			0	0	0
2	0.5		2.8333333			0.70833333	0.35416667	0
3	1		4.4033333			2.5175	1.8091667	0
4	2		5.53			7.4841667	9.5408333	0
5	4		5.0666667			18.080833	40.8675	0
6	6		7.9866667			31.134167	109.05417	0
7	8		9.28			48.400833	231.21417	0
8	12		4.3833333			74.514576	485.88311	0
9	24		1.3456667			105.38204	1005.8655	0

4. Click **Observed Y and Predicted Y vs X**.



This concludes the sparse sampling example.

Urine study NCA example

This example demonstrates how to model a urine study. The time range, concentration, and data is provided in `urine.xls`. The dosing data are stored in `urine_sources.xls`. These files are located in the Phoenix examples directory.

The completed project (`NCA_UrineStudy.phxproj`) is available for reference in …`\Examples\WinNonlin`.

Set up the NCA object

1. Create a project called `NCA_UrineStudy`.
2. Import the two files …`\Examples\WinNonlin\Supporting files\urine.xls` and `urine_sources.xls`.
   In the *File Import Wizard* dialog, select the **Has units row** option for both worksheets.
3. Select **Workflow** in the Object Browser and then select **Insert > NonCompartmental Analysis > NCA**.
4. Rename the NCA object just added as `urine`.
5. In the Options tab, set the Model Type to **Urine (210-212)**.
6. Drag the **urine** worksheet from the Data folder to the urine object's Main Mappings panel to map it as the input source.
7. In the Main Mappings panel, map the data types to the following contexts:
   Map **Lower** to the **Start Time** context.
   Map **Upper** to the **End Time** context.
   Leave **Concentration** mapped to the **Concentration** context.
   Leave **Volume** mapped to the **Volume** context.
8. Select **Dosing** in the Setup list.
9. Drag the **urine_sources** item from the Data folder to the Dosing panel.
   Type is already mapped to the **None** context.
   Dose is already mapped to the **Dose** context.
   Time is already mapped to the **Time** context.
10. Select **Therapeutic Response** in the Setup list.
11. In the Therapeutic Response panel, check the **Use Internal Worksheet** checkbox.
12. In the first cell of the **Lower** column, enter `4`.

Execute and view the NCA results

All necessary settings are complete.

1. Click  (**Execute** icon) to execute the object.
2. In the Results tab, click **Final Parameters**.

	Parameter	Units	Estimate
1	N_Samples		6
2	Dose	mg	10
3	Rsq		0.96100841
4	Rsq_adjusted		0.92201683
5	Corr_XY		-0.98031037
6	No_points_lambda_z		3
7	Lambda_z	1/hr	0.15445199
8	Lambda_z_intercept		7.4848291
9	Lambda_z_lower	hr	8
10	Lambda_z_upper	hr	21
11	HL_Lambda_z	hr	4.487784
12	Span		2.8967526
13	Tlag	hr	0

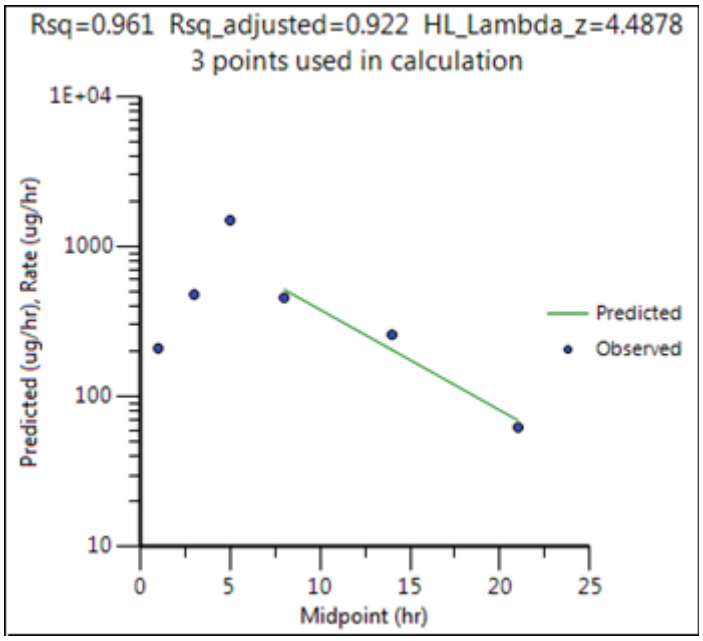
Figure 24-1. Part of the Final Parameters worksheet

3. Click **Summary Table**.

	Midpoint (hr)	lambda_z _Incl	Rate (ug/hr)	Predicted (ug/hr)	Residual (ug/hr)	AURC (ug)	Amount (ug)	Weighting
1	0		0			0	0	0
2	1		210			105	420	0
3	3		478.5			793.5	1377	0
4	5		1497.6			2769.6	4372.2	0
5	8	*	456.45	517.6054	-61.155403	5700.675	6198	1
6	14	*	258.7875	204.89573	53.891767	7846.387	8268.3	1
7	21	*	62.4	69.500732	-7.1007323	8970.543	8642.7	1

Values used in the calculation of Lambda Z are marked with an asterisk in the Lambda_z_Incl column.

4. Click **Observed Y and Predicted Y vs X**.



This concludes the urine study example.

Drug effect NCA example

This example demonstrates how to model a urine study. The time range, concentration, and data are provided in `nca_pd.xls`. The dosing data are stored in `nca_pd_sources.xls`. These files are located in the Phoenix examples directory.

The completed project (`NCA_DrugEffect.phxproj`) is available for reference in `…\Examples\WinNonlin`.

Set up the NCA object

1. Create a project called `NCA_DrugEffect`.
2. Import the two files `…\Examples\WinNonlin\Supporting files\nca_pd.xls` and `nca_pd_sources.xls`.
   In the *File Import Wizard* dialog, select the **Has units row** option for Sheet 1.
3. Select **Workflow** in the Object Browser and then select **Insert > NonCompartmental Analysis > NCA**.
4. Rename the NCA object just added as `nca_pd`.
5. In the Options tab, set the Model Type to **Drug Effect (220)**.
6. Drag the **nca_pd** worksheet from the Data folder to the nca_pd object's Main Mappings panel to map it as the input source.
   Map **Time** to the **X** context.
   Map **Cortisol_RR** to the **Y** context.
7. Select **Dosing** in the Setup list.
8. Expand the **nca_pd_sources** item in the Object Browser Data folder and drag the **Dosing** item to the Dosing panel.
   Type is already mapped to the **None** context.
   Time is already mapped to the **Time** context.
9. Select **Partial Areas** in the Setup list.
10. In the expanded **nca_pd_sources** item in the Object Browser Data folder, drag the **PartialAreas** item to the Partial Areas panel.
    Map **Curve** to the **Area #** context.
    Map **Lower** to the **Start Time** context.
    Map **Upper** to the **End Time** context.
11. Select **Parameter Names** in the Setup list.
12. In the expanded **nca_pd_sources** item in the Object Browser Data folder, drag the **Names** item to the Parameter Names panel.
    Map **Name** to the **Parameter Name** context.
    Leave **Preferred** mapped to the **Preferred** context.
    Map **Include** to the **Include in Workbook** context.
13. Select **Slopes** in the Setup list and enter the following information:
    For the first row:
    `60` for **Start Time**
    `67` for **End Time**
    Time Range for **Fit Method**
    Linear for **Lin/Log**

    For the second row:

125 for **Start Time**
133 for **End Time**
Time Range for **Fit Method**
Linear for **Lin/Log**

14. Select **Therapeutic Response** in the Setup list, check the **Use Internal Worksheet** box and enter the following information:
    2.5 for **Baseline**
    5 for **Threshold**

Execute and view the NCA results

All necessary settings are complete.

15. Click  (**Execute** icon) to execute the object.
16. In the Results tab, click **Final Parameters**.

	Parameter	Units	Estimate
1	N_Samples		47
2	Slope1		0.24058442
3	Rsq_Slope1		0.91798688
4	Rsq_adj_Slope1		0.89064917
5	Corr_XY_Slope1		0.95811632
6	No_points_Slope1		5
7	Slope1_lower		60
8	Slope1_upper		67
9	Slope2		-0.21335456
10	Rsq_Slope2		0.95772862
11	Rsq_adj_Slope2		0.95068339
12	Corr_XY_Slope2		-0.9786361
13	No_points_Slope2		8

Figure 25-1. Part of the Final Parameters worksheet

17. Click **Summary Table**.

	Time (min)	Slope	Cortisol_RR	Predicted	Residual	AUC	AUMC	Weighting
1	60	Slope 1	2	1.8295455	0.1704545	0	0	1
2	63	Slope 1	2.25	2.5512987	-0.3012987	6.375	10.125	1
3	65	Slope 1	2.95	3.0324675	-0.0824675	11.575	31.625	1
4	66	Slope 1	3.45	3.2730519	0.1769480	14.775	49.35	1
5	67	Slope 1	3.55	3.5136364	0.0363636	18.275	72.125	1
6	68		3.45			21.775	98.35	0
7	69		3.75			25.375	129.025	0
8	70		3.55			29.025	163.65	0

This concludes the drug effect example.

Multiple profile analysis using NCA

Data for noncompartmental analyses can include one or more ***sort variables***. Sort variables have discrete values that identify time-concentration profiles to be analyzed individually. Input datasets should be stacked (long and skinny) rather than unstacked (short and wide).

Stacking simply means moving information stored in column headings into the rows. For example, matrix data such as plasma or urine can be placed in one row, and all associated data are arranged in rows beside the matrix data. This means that all measurements appear in a single column, with one or more additional columns flagging which data belong to which matrix. The data for one matrix must be listed first, then all the data for the other matrix.

For noncompartmental analysis data, this means that time (the independent variable) and concentration (the dependent variable) data for all individuals should occupy only one column each, with one or more additional columns (sort variables) used to identify individual profiles.

This example demonstrates the general steps to summarize a dataset using noncompartmental analysis. The dataset contains time-concentration profiles from a two period crossover study with six subjects.

The study data for this example are contained in `Profiles.CSV`, which is located in the Phoenix examples directory. This crossover study includes two sort variables: Subject (subject identifiers) and Form (formulation). There are six subjects, each of whom was tested with two formulations, for a total of twelve profiles.The completed project (`Multiple_Profiles.phxproj`) is available for reference in `…\Examples\WinNonlin`.

Set up the project

1. Create a new project called `Multiple Profiles`.
2. Import the file `…\Examples\WinNonlin\Supporting files\Profiles.CSV`.
   In the *File Import Wizard* dialog, select the **Has units row** option.

Review profile plots

Before analyzing the data, examine a plot of each profile to confirm the model and scan for outlying data points.

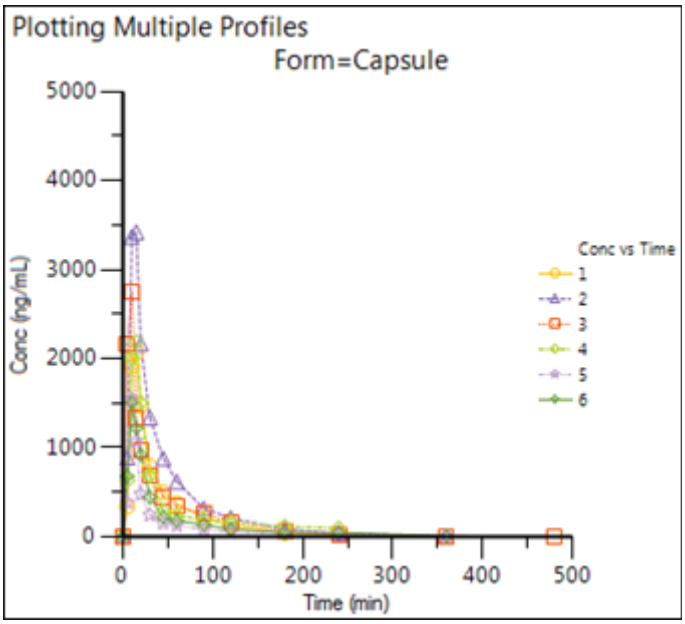
1. Right-click **Profiles** in the Data folder and then select **Send To > Plotting > XY Plot**.
2. In the XY Data Mappings panel:
   Map **Subject** to the **Group** context.
   Map **Form** to the **Lattice Conditions Page (Sort)** context.
   Map **Time** to the **X** context.
   Map **Conc** to the **Y** context.

Note: The plot display options are located in the XY Plot's Options tab. Expand items in the Options menu tree by clicking the (+) signs.

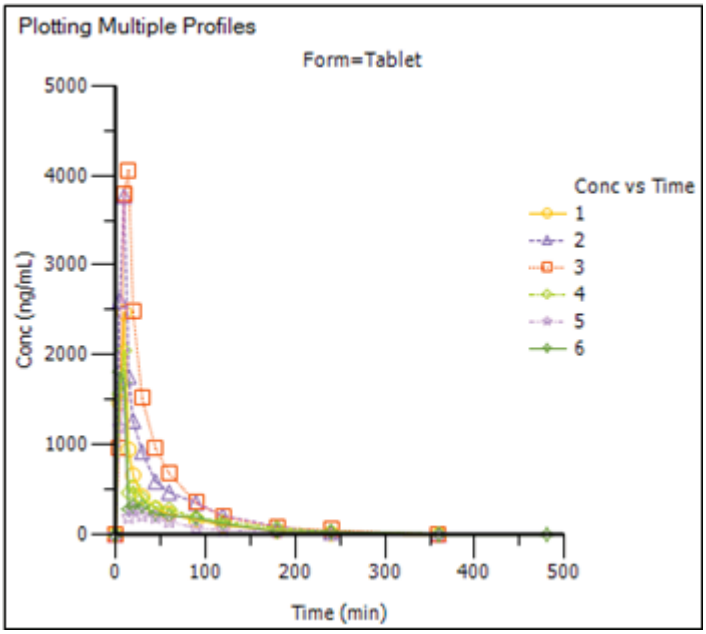
3. In the Options tab, with **Plot** selected in the menu tree, click the **Title** tab.
4. In the Title field type `Plotting Multiple Profiles`.
5. Click  (**Execute** icon) to execute the object.

   There are two formulations in the input dataset. Since Form (formulation) was mapped to the Page

(Sort) Lattice Condition context, two plots are generated, each representing a formulation, and each on a separate tab. The plot for the first formulation (Capsule) is displayed automatically.



6. Click the Page 02 tab to view the plot for the second formulation (Tablet).



Set up the NCA object for the multiple profile analysis

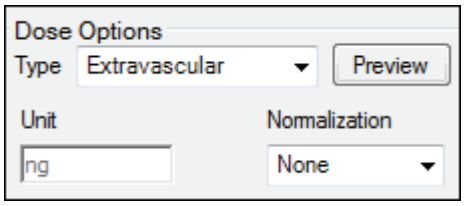
The noncompartmental analysis (NCA) plasma model 200 (extravascular dosing) is suitable for this data. All subjects had a dose of 100 ng at time zero for each formulation. All profiles use uniform weighting, and allow Phoenix to select the terminal elimination phase. The linear trapezoidal method with linear interpolation is used to compute the areas under the curve.

1. Right-click **Profiles** in the Data folder and select **Send To > NonCompartmental Analysis > NCA**.

2. In the Main Mappings panel:
   Map **Subject** to the **Sort** context.
   Map **Form** to the **Sort** context.
   Leave **Time** mapped to the **Time** context.
   Map **Conc** to the **Concentration** context.

Prepare the dosing information from the multiple profiles

1. Select **Dosing** in the Setup list.
2. Check the **Use Internal Worksheet** checkbox.
   Click **OK** in the *Dosing sorts* dialog to accept the default sort variables.
   For each cell in the Time column, enter `0`.
   For each cell in the Dose column, enter `100`.
   Do not enter any value in the Tau column.
3. In the Dose Options area of the Options tab, type `ng` in the **Unit** field and press the **Enter** key.
4. **Extravascular** is selected by default in the **Type** menu. Do not change this setting.



Add a partial area calculation

1. Select **Partial Areas** in the Setup list.
2. Check the **Use Internal Worksheet** checkbox.
   Click **OK** in the *Partial Areas sorts* dialog to accept the default sort variables.
   For each cell in the Start Time column, enter `0`.
   For each cell in the End Time column, enter `120`.

Specify the NCA model options for the multiple profile analysis

1. In the Options tab, the default setting for **Model Type** is **Plasma (200-202)**. Do not change this setting.

Note: The exact plasma model type (200, 201, or 202) is determined by the dose type.

2. The default setting for **Calculation Method** is **Linear Trapezoidal Linear Interpolation**. Do not change this setting.
3. In the **Titles** field type `Processing Multiple Profiles with Model 200.`

Set up a user-defined parameter

1. Go to the **User Defined Parameters** tab.
2. Check the **Include with Final Parameters** checkbox.
3. Enter `75` in the field to compute the concentration at 75 minutes.

Execute and view the results of the multiple profile analysis

At this point, all of the necessary mappings and options have been specified.

1. Execute the object.

   In each Results worksheet, the sort variables Subject and Form are included as columns in the data grid, and the output is presented for each level of the sort variables. See the NCA "Results" for descriptions of the output.
2. Select the **Observed Y and Predicted Y vs X** plot in the Results tab and double-click it. The plot is opened in its own window.
3. In the Options menu tree below the plot, select **Lattice** under **Plot**.
4. Clear the **Bind Lattice to Data** checkbox.
5. Click the up and down arrows in the **Lattice Rows** and **Lattice Columns** boxes to change the number of rows/columns, respectively, that form the lattice.
6. Close the Observed Y and Predicted Y vs X window.

Phoenix can display a maximum of 15 latticed rows and 15 latticed columns, but no more than 200 charts per page. The number of plots that can be displayed per page depends on the monitor size and resolution. If too many plots are placed on one page the axes labels, legends, and other plot information can be difficult to read. Additional information on lattices can be found in "More on latticed plots in Phoenix".

Summarize the multiple profile analysis output with statistics

Phoenix's Descriptive Statistics object is used to summarize several of the output parameters in the Final Parameters Pivoted worksheet. The Descriptive Statistics object generates separate statistics for each formulation.

1. Right-click **Workflow** in the Object Browser and select **New > Computation Tools > Descriptive Statistics**.
2. In the Descriptive Statistics Main Mappings panel click  (**Select Source** icon).
3. In the dialog, under the NCA node, select the **Final Parameters Pivoted** worksheet and click **OK**.
4. Map:
   Form to the **Sort** context.
   Tmax, **Cmax**, and **AUCall** to the **Summary** context.
   Leave all other data types mapped to **None**.
5. In the Options tab, check the **Confidence Intervals** and **Number of SD Statistics** checkboxes, but do not change the default values for these two items.
6. Execute the object.

This example summarizes $AUCall$, the area under the curve through the last measured value, $Cmax$, the maximal concentration of drug in the blood, and $Tmax$, the time at maximal concentration.

	Variable	Units	Form	N	NMis	NOb	Mean	SD	SE	Variance	CV%
1	AUCall	min*ng/mL	Capsule	6	0	6	74440.469	30554.352	12473.762	9.3356842E+08	41.045351
2	AUCall	min*ng/mL	Tablet	6	0	6	76074.068	40833.204	16670.086	1.6673506E+09	53.675589
3	Cmax	ng/mL	Capsule	6	0	6	2243.8556	735.62329	300.31695	541141.62	32.783896
4	Cmax	ng/mL	Tablet	6	0	6	2619.6755	1052.1292	429.52995	1106975.9	40.162578
5	Tmax	min	Capsule	6	0	6	12.5	2.7386128	1.118034	7.5	21.908902
6	Tmax	min	Tablet	6	0	6	10	3.1622777	1.2909944	10	31.622777

Min	Median	Max	Range	Mean Log	SD Log	Geometri	Geometri	Geometri	CI 95% Lo
36783.971	74605.253	126155.16	89371.194	11.146136	0.42073594	69295.571	1.523082	44.006073	-4101.9886
33960.211	59656.625	141616.94	107656.73	11.124524	0.5213256	67813.982	1.6842588	55.883697	-28891.018
1502.9336	2127.4121	3420.6664	1917.7328	7.6725482	0.32076438	2148.5493	1.3781808	32.919485	352.87587
1546.903	2263.3	4058.75	2511.847	7.8053539	0.39327544	2453.7036	1.4818265	40.898353	-84.908561
10	12.5	15	5	2.5053176	0.22208239	12.247449	1.2486742	22.484904	5.4601721
5	10	15	10	2.2546381	0.3552637	9.5318429	1.4265568	36.677377	1.871107

CI 95% Up	CI 95% Lo	CI 95% Up	CI 95% Lower	CI 95% Upper	CI GEO 95	CI GEO 95
152982.93	42375.645	106505.29	3.6375152E+08	5.6157084E+09	23496.346	204366.94
181039.16	33222.251	118925.89	6.4965919E+08	1.0029639E+10	17754.844	259013.05
4134.8354	1471.8664	3015.8449	210848.06	3255137.5	941.99232	4900.5328
5324.2596	1515.5337	3723.8173	431317.24	6658808.9	892.83984	6743.2716
19.539828	9.6260023	15.373998	2.9222672	45.114865	6.9201451	21.675846
18.128893	6.6813933	13.318607	3.8963563	60.153154	3.8244082	23.756886

CI 95% Lo	CI 95% Up	Lower 1S	Upper 1SI	GEO Low	GEO Upp
44560.407	107761.05	43886.117	104994.82	45496.939	105542.84
39238.985	117198.14	35240.864	116907.27	40263.398	114216.3
1534.449	3008.4183	1508.2323	2979.4789	1558.9749	2961.0895
1623.9823	3707.3443	1567.5463	3671.8047	1655.8643	3635.963
9.7012669	15.461898	9.7613872	15.238613	9.8083617	15.293074
6.5653887	13.838637	6.8377223	13.162278	6.6817129	13.597715

Create a Cmax plot with error bars

This section will illustrate how to use the means and SDs of data, computed by the Descriptive Statistics object, to create an overlaid plot with error bars. The Descriptive Statistics results obtained in the previous section will be filtered so that the output for only one variable (Cmax) remains. The data will then be used to create the error bars for a plot of Cmax values.

First filter the Descriptive Statistics results:

1. Right-click **Workflow** in the Object Browser and select **New > Data Management > Data Wizard**.
2. In the Options tab, select **Filter** from the Action menu and click **Add** right below the menu.
3. Click the **Select Source** icon in the Mappings panel.
4. In the *Select Source* dialog, under the **Descriptive Statistics** node, select **Statistics**, and click **OK**.

5. In the Options tab, click the **Add** button to the right of the **Specify Filter** field.
6. In the *Filter Specification* dialog, select **Include** as the Action.
7. Type `Cmax` in the **Select Column or Enter Value** field.
8. Make sure the **Apply to entire row** box is checked.
9. Click **OK**.
10. Execute the object.
    The Result worksheet now only contains the rows of Cmax data.

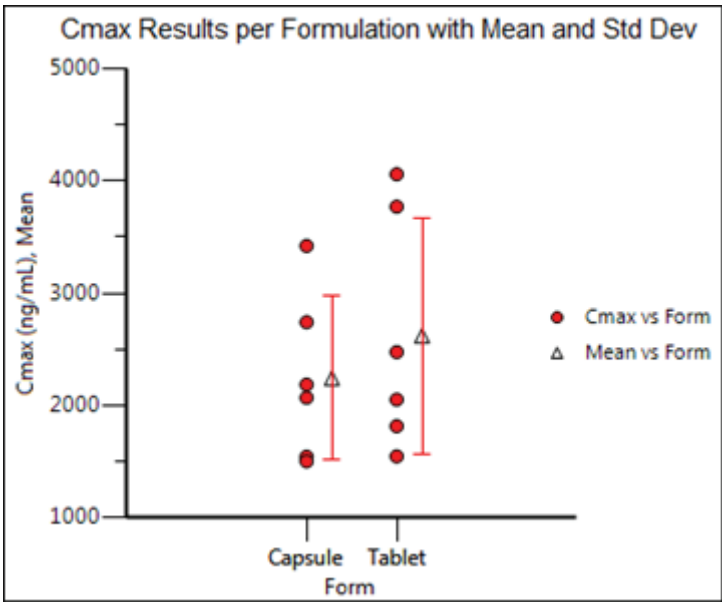
Now set up the X-Categorical XY Plot object:

1. Right-click **Workflow** in the Object Browser and select **New > Plotting > X-Categorical XY Plot**.
2. Click the **Select Source** icon in the Mappings panel and select the **NCA Final Parameters Pivoted** worksheet and click **OK**.
3. Map:
   Form to the **X** context.
   Cmax to the **Y** context.
   Leave all other data types mapped to **None**.
4. In the Options tab, select **Plot** in the menu tree and then the **Graphs** sub-tab.
5. Click the **Add** button.
6. Select the **CategoricalX 1 Data** item in the Setup tab, click the **Select Source** icon.
7. In the *Select Source* dialog, under the **Data Wizard** node, select **Result**, and click **OK**.
8. Map:
   Form to the **X** context.
   Mean to the **Y** context.
   SD to both the **Error Bars Lower** and **Upper** contexts.

Adjust the appearance of the plot:

1. In the Options tab, with **Plot** selected in the menu tree, go to the **Title** sub-tab.
2. Enter `Cmax Results per Formulation with Mean and Std Dev` in the field and click the  icon to center the plot title.
3. In the menu tree, select **Cmax vs Form** under the Graphs node.
4. Change the Marker Color to **Red** and set the Marker Size to **7**.
5. Select **Mean vs Form** under the Graphs node.
6. In the **Content** sub-tab, check the **Offset** checkbox and enter `14` for the number of pixels.
7. Select the **Appearance** sub-tab and set the Marker Shape to **Triangle**.
8. In the menu tree, expand the **Mean vs Form** node and select **Error Bars**.
9. Click the **Appearance** sub-tab and set the Color to **Red** and the Cap Width to **9**.
10. Execute the object.

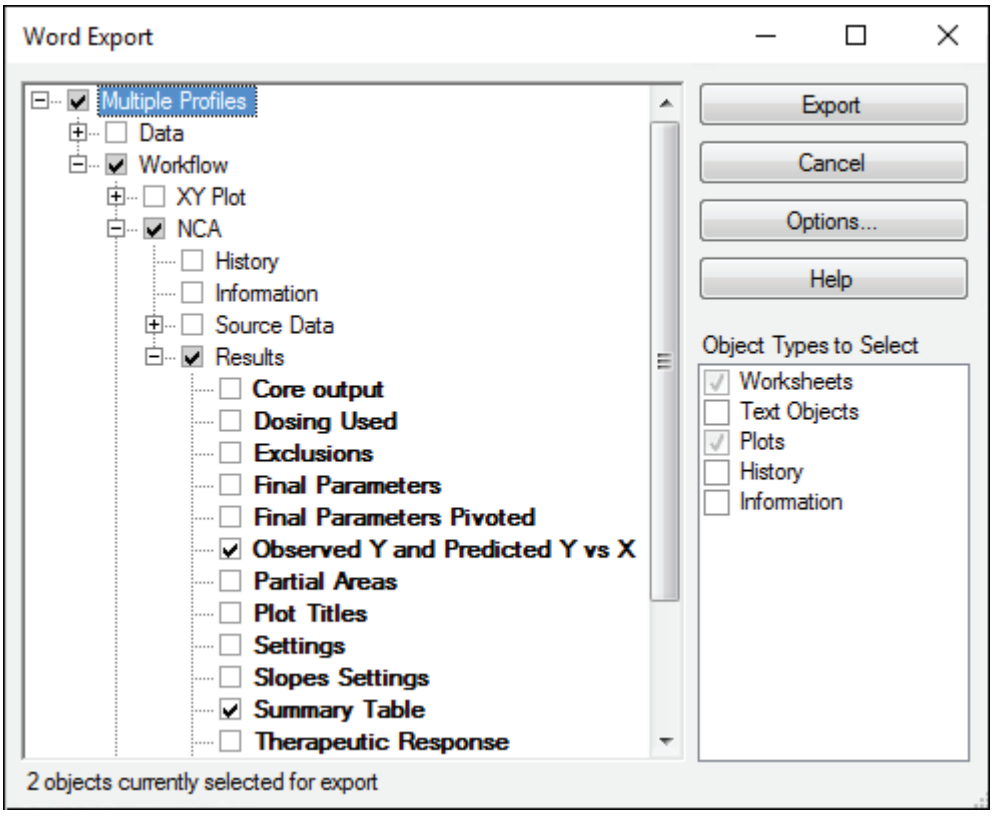
The output is an overlay of two graphs (Cmax vs Form and Mean vs Form) that includes error bars.



Export results to Microsoft Word

The results of any operational object can be exported to a Microsoft Word document. This example shows how to format plot output and export it to Microsoft Word. By default, plots are exported at a resolution of 1024 by 768 pixels.

1. Select **File > Word Export**.
2. In the *Word Export* dialog, click the (+) signs beside **Workflow > NCA > Results** to expand the menu tree.
3. Select the **Observed Y and Predicted Y vs X** checkbox.
4. Select the **Summary Table** checkbox.



5. Click **Options**.
6. Select the **Landscape** option button in the Document tab.
7. Make sure the **Add source line to objects** checkbox is cleared and click **Finished**.
8. Click **Export**.
   Phoenix creates a new Microsoft Word document and exports the selected objects into the document.
9. In the *Export Complete* dialog, click **OK**.
10. Save the Word file and exit Microsoft Word.
11. Close the project by right-clicking the project in the Object Browser and selecting **Close Project**.