Napp Manual

Version 2.01 for Macintosh OS-X

author
Project Associate Professor, Department of Pharmacokinetics, 22nd Century Medical Center, The University of Tokyo Hospital
Akihiro Hizaka
e-mail hisaka-tky@umin.ac.jp

creation-day
September 13, 2010

address (e.g. of house)
Postal 113-8655
7-3-1 Hongo, Bunkyo-ku, Tokyo

About Napp

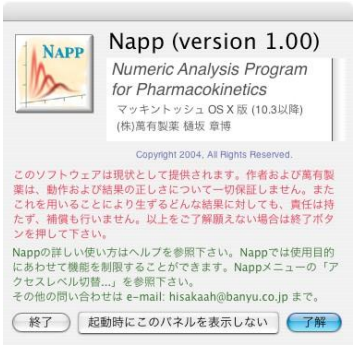
Napp (Numeric Analysis Program for Pharmacokinetics) is a program for simulation, parameter calculation, and numerical analysis of drug disposition.

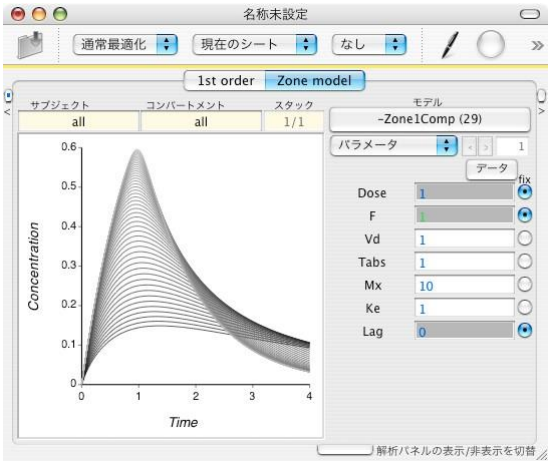
1. In addition to a library of compartmental models commonly used in drug pharmacokinetic analysis, models can be freely defined and combined. Models can be defined in terms of ordinary equations, differential equations, Laplace transform expressions, and partial differential equations (one-dimensional parabolic). This allows for complex physiological, circulatory, and diffusion models.
2. Population analysis (extended least squares) and Bayesian estimation can be performed using all of the above models. A large amount of data can be randomly generated to fit the model. It also has the ability to automatically perform bootstrap analysis.
3. It has many numerical analysis capabilities used in pharmacokinetic analysis, including moment analysis, differentiation, integration, and convolution.
4. It is capable of up to 10th order linear regression analysis of large amounts of data. Numerical transformations such as logarithmic, Lineweaver-Burk, and Logit plots can be performed, which can be used for enzyme reaction rate analysis.

Note: *This program is not intended for commercial use. Although it has been prepared with great care, the author and his/her organization cannot be held responsible for any results that may result from the use of this program, including the correctness of the analysis and the accuracy of this document. Please use this program with this understanding. Please be careful to validate your results by referring to the analysis results of other programs.*

The diagrams in this manual are from an older version and may differ slightly from the current version. Also, locally, the descriptions themselves may not correspond to the latest versions. Please understand.

We do not support this program as the author or his/her organization. However, if you contact the creator directly, he or she may be able to answer your questions.





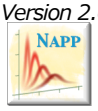
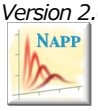
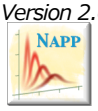
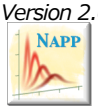


Table of Contents







1. Overview of the operation for short

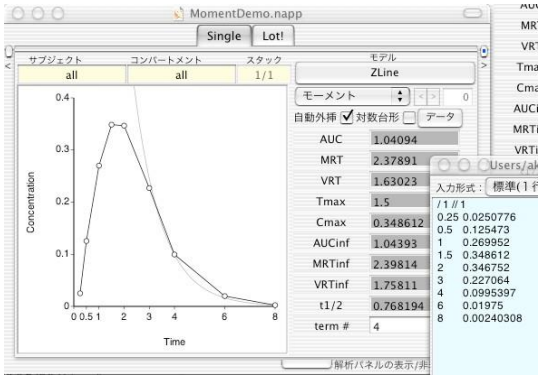
1.1. Introduction to

Napp's application areas include general model analysis including compartmental analysis, population analysis, Bayesian estimation, linear regression analysis, and moment analysis.These are outlined in this section so that the flow of operations can be understood. For detailed explanations, please refer to later chapters. Napp has a function to set the access level according to your usage.When program is launched, it is set to "Expert.

1.2. Moment solution analysis

The following is a general procedure for moment analysis.

1) Prepare data according to a predetermined format using spreadsheet software (e.g. Excel).
2) Press the "Data" button on the nonlinear analysis sheet (the sheet that appears when the program is launched) and paste the data into the input field on the panel that appears.
3) Make sure the model is "Zline" and run a plot on the toolbar.



The results are then displayed on the sheet. All functions of the moment analysis are available at any access level. If you want to extrapolate for infinite time, enter the number of points for the logarithmic vanishing period in the term# field. Alternatively, you can enter the number of points for the logarithmic vanishing period in the
Check the "Auto Extrapolation"switch to automatically poin

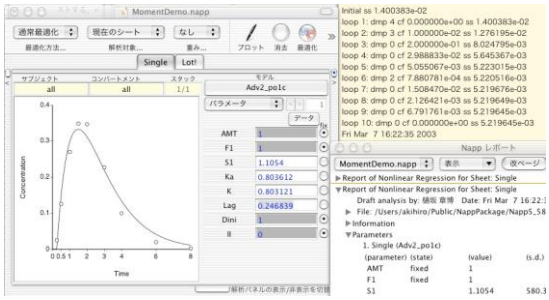
You can also set the number of gates.See 2.8 for details on settings. To output the results to a printer, execute "Report" from the toolbar, followed by "Print" from the "File" menu. See Chapter 6 for more information on reports.

The format of the input data is simply a table of time and concentration. See Chapter 3 for more details. It may also be useful to know the subjectscale, and mark settings for the graphs; see 2.6-7. As an application, y o u can enter data for multiple subjects and get a batch report, as well as calculate averages and correlations from the Properties menu. See 2.4 and 8.7 for more details.

1.3. General model solution analysis

This section presents the procedures for methods such as compartmental model analysis and physiological model analysis, which are generally referred to as optimization calculations using the nonlinear least squares method. As if you wish to perform simulations without optimization, please refer to the instructions in this section. The procedure follows

1) Prepare data in a given format (see Chapter 3).
2) Press the "Data" button on the nonlinear regression sheet and paste the data into the input fields on the panel that appears.
3) Select or create the appropriate model by pressing the button with the model name displayed.
4) Enter initial values in the parameter fields, and if necessary, switch the display of parameters to fix parameters or limit the range of values.
5) Press the Run Optimization button from the toolbar.



At this time, the optimization method shown in the toolbar should be "Normal Optimization" and the target of the analysis should be "Current Stack of Current Sheets" (this is the default). (If access level is learner,it is fixed to this setting). Immediately the calculation is run and the plot and parameter values are updated in real time.When the calculation converges, the results are reported in a new window (you can also choose not to output a report in the preferences). Nonlinear optimization is described in detail in section 4.1-8.

To adjust the initial values, enter a number as desired, then perform a plot on the toolbar, visually judging from the graph drawn, change the parameter values accordingly. To simulate a step-by-step change in the value of a parameter, open the context menu (CTRL-click or right-button click) where the name of the parameter is displayed and run the multisimulation (see 4.4).

Compartment model analysis requires a good understanding of which model is appropriate for the analysisFor a normal compartment model, see 4.14.

See Chapter 7 for details on model creation. Creating, modifying, and deleting models requires a certain level of knowledge

Rather, it is necessary,the access level is set to Expert or Administrator only. Also, to prevent inadvertent modification and analysis of the model, administrators are not allowed to output reports, and experts have a "Draft" proviso on their reports. When using a new model, you as an expert must fully validate the model before recording the model.

Please leave and change the access level to user to perform this analysis.

Napp allows multiple sheets to be defined in a single file, and unless otherwise specified, the data for each sheet's analysis is completely independent. When performing optimization under various conditions for comparison, if you repeat the analysis on the same sheet, the information on the sheet will be overwritten by the new analysis, so if necessary, you can try a new analysis on the duplicated sheet by executing "Insert Duplicate of Current Sheet" from the "Sheet" menu,see 8.3.8.3.

Stacks can be used to repeat the analysis on the same model with different data. Data can also be combined according to the model. For more information on these, see

See 1.6 and 4.12.

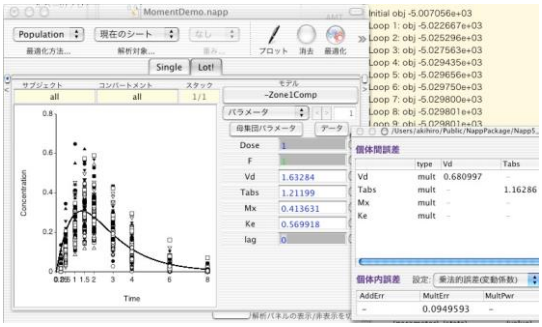
1.4. Population solution analysis

Population analysis is a method of analyzing a large number of data in detail, including the parameters, their error estimates, and the sources of error.This is a complex analysis, so it is recommended that you first become familiar with the compartment model analysis described in the previous section.The basic operations are similar.

1) Set the "Optimization Method" on the toolbar to "Population". This will display the "Population Parameters" button, which allows you to display and enter the standard deviation, variance, etc. of the parameters.
2) Data is entered using spreadsheet software according to a predetermined format.
3) Press the "Data" button to paste the data into the panel's input field.
4) Select or create an appropriate model.
5) Enter initial values in the parameter fields.
6) Press the "Population Parameters" button and enter the initial values for inter-individual and intra-individual errors in the panel that appears. If necessary, toggle the settings for the off-diagonal component of the inter-individual error or the intra-individual error.
7) Error parameter fixation or value limitation as needed

The "Parameters" menu button is used to perform the following. Fixation is done from the context menu, and limitation is done by toggling the "Parameters" menu button.

8) Press the "Optimize" button from the toolbar.



See the description in section 4.10 for more details. napp automatically assumes inter-individual variation corresponding to all (fixed effects) parameters.If you do not want to assume inter-individual variation, fix this to 0.Note that the Population Analysis function cannot be selected when the access level is learner.

To analyze NONMEM data, see the description of the NONMEM format input format (3.8). only data can be imported from NONMEM.A model must be set up separately. to export data to NONMEM, use the data generation (1 To export data to NONMEM, use the data generation (1.6 and 4.12).

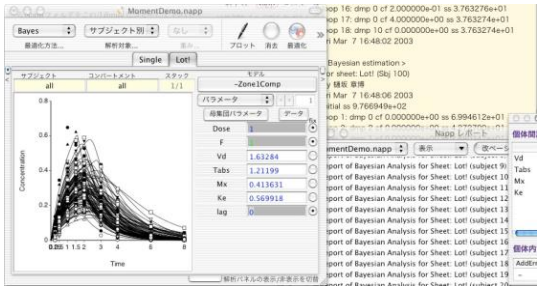
1.5. Bayesian Inference constant

Bayesian estimation is a method of reproducing blood concentration trends from a small sampling of subjects based on information obtained from a population analysis.To perform Bayesian estimation independently, follow these steps

1) Set "Optimization Method" in the toolbar to "Bayes".
2) Select or create an appropriate model.
3) Fixed effects of population parameters as well as population analysis, variance of inter-individual and intra-individual errors

Or enter the standard deviation.

4) Enter appropriate data in the data list.
5) Perform optimization from the toolbar.

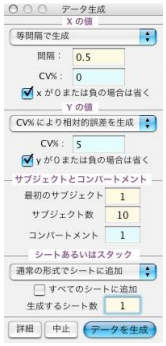


Continued after running the population analysis (To perform Bayesian estimation (in posthoc), set the optimization method in the toolbar to "Bayes" and perform the optimization. Note that during Bayesian estimation, the analysis is automatically switched to "By Subject". In this case, the analysis is repeated for as many subjects as there are in a single sheet. To refer to individual subject values after analysis, enter the number in the subject field of the sheet or use the function in the Properties menu.

As with the population analysis, each of the Bayesian estimation functions cannot be performed when the access level is learner.

1.6. Data Raw Composition

Napp allows you to generate data by selecting a model and plotting some curve, then adding random error to that curve. From the "Tools" menu, select "Generate Data..." in the "Tools" menu. A panel appears where you can set the conditions for the generation, see 4.12.



You can also generate large amounts of data based on the population model, and if you choose to generate in NONMEM format, you can generate on a sheet or create a file in a format that NONMEM can use. and DV are not a problem, but parameters such as AMT, RATE, CMT, II, etc. may not be appropriate and should be checked thoroughly before actual analysis in NONMEM.

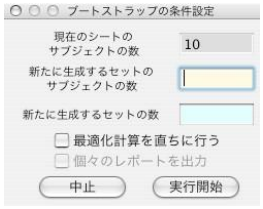
The function of data generation also requires a certain level of knowledge and cannot be performed when the access level is that of a learner.

To validate a population analysis, large amounts of data are often randomly generated and analyzed. It is not uncommon to have hundreds or even thousands of data sets. In this case, generating a sheet for each piece of data is a time-consuming process. A single sheet is used in a stack. In a stack, the model is the same, but the parameter values and data can be set independently. Data can be switched instantly by entering a number in the stack field on the sheet. The "Analysis Target" in the toolbar can be set to "All Stacks" to analyze all stacks at once.

1.7. Bootstrap

Bootstrapping is a method of verifying the reproducibility of an analysis by randomly re-extracting subject data and repeating the analysis. For simplicity, after performing a population analysis, select "Bootstrap Analysis..." from the "Tools" menu. Bootstrap Analysis..." from the "Tools" menu after performing a population analysis. Here, the number of subjects and the number of

Specify the number of tacks and check "Optimize Immediately" to execute.



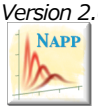
Depending on the model, it may take a considerable amount of time to calculate a large number of data. It is possible to stop the calculation in the middle of the process. It is not recommended to output individual reports, as this will slow down the operation.

It is safer to not perform the optimization immediately, but to store the generated data in a file and then run the optimization. In this case, the "Target for Analysis" on the toolbar should be set to

All stacks" is used. It is also possible to generate multiple sheets without using a stack. See also 4.13 for bootstrapping.

1.8. Its and others

For linear analysis, see Chapter 5. Functions such as compolation, deconvolution, numerical differentiation, and integration are performed in the analysis panel, see 2.9.



2. General Manipulation Created by

2.1. Napp installation and removal, operating environment

To install Napp, you need to open the application file that is displayed with the Napp icon. Copy it to /Applications. This is the "Applications" folder in the Japanese environment. You must have administrator privileges on your computer to do this. Napp uses /Library/Napp in your personal folder to store models. This path is displayed as the "Library" folder in your home folder in Japanese environment. If a folder with models is attached to the distribution with the name Napp, copy it under /Library.

This folder will be automatically created once executed. If the folder already exists, copy the necessary model files (with .eq or .bundle extension) into the appropriate folder. See Chapter 7, "Creating Napp Models," for more information on creating models.

Models stored above can only be used by the currently logged in user. If a model is to be shared by multiple users, the model can be saved to /Library/Napp, directly under the local drive. To do this, set the access level as administrator, select the model you wish to share, and press the "Share" button.

Currently, Napp supports both Japanese and English environments. The menus and tips are set to display according to the environment. This switching is done from System Preferences, Regional Information in the Apple menu. For details, please refer to the OS-X manual.

To remove Napp, delete the /Library/Napp folder along with the application files.

Napp runs on Apple Macintosh OS-X (version 10.5 or later). The OS version and CPU type on which Napp runs are subject to change.

Please note that the current version runs without problems under OS-10.5 and 10.6. The current version runs without problems under OS-10.5 and 10.6, and works on G4 or G5 CPUs as well as Intel-based ones.

Napp was first developed on the workstation NEXTSTEP around 1992. This was before the release of Windows 95. Later, when the technology of NEXTSTEP was used in OS-X for the Mac, Napp was ported to OS-X and has been used to this day. Napp is written in the Objective-C programming language, and we are often asked if there is a Windows version, but there is no Objective-C development environment for Windows, so we have to start all over again. Therefore, it will be difficult to support Windows in the future.

Now that general-purpose programs such as Microsoft Office run on both Mac and Windows, and data can be easily transferred between Napp and these programs, the disadvantage of limiting Napp's operating environment to the Mac is lessened.

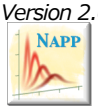
We recommend using a two-button mouse to operate Napp. Some operations may use context menus. To display the context menu, click the right mouse button on the object to be operated. If your mouse does not have a right button, hold down the CTRL key while clicking the button.

2.2. Napp start and end end

To start Napp, double-click on the Napp application or data file icon.

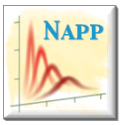
Exit is performed from the "Napp" menu, but in rare cases a forced exit may be necessary. To force termination, use the Apple menu in the left corner of the screen or press the option-apple-ESC keys simultaneously.

Napp as a whole does not implement Undo functionality. Also, unfortunately, it is possible to lose control of the system due to calculation errors, etc.



In some cases, this may result in the loss of valuable data. Therefore, to avoid losing valuable data, be sure to save data as you go along.

Napp application and data icons



2.3. Help and tips s

In Japanese environment, this manual is available from the Help menu. Also, if you hover the mouse cursor over an appropriate location in the active window, a brief explanation (tips) will appear. The model creator can create his/her own tips for the model and each parameter.

2.4. Access leve le

Napp offers four access levels to choose from, "Learner,""User," "Expert," and "Administrator," depending on the purpose of use. The choices are
This is done from the "Napp" menu under "Access Level Switching... ". Currently, since most users with sufficient knowledge use Napp, this version of Napp limits the access level functionality. Immediately after launching the program, you will always be set to "Expert," so you can basically use the program as is. Only when editing a shared model, it is necessary to set the user to Administrator.

2.5. Model and data structure

A model is generally thought of as a function that defines a drug's blood concentration, and data as its realization. More generally, a model is a set of functions and data is a set of structured numbers. A model contains an accompanying realization of the value of a parameter.

Napp analysis data is saved in one file for each window.A toolbar is displayed at the top of each window. In the case of different windows or files, Napp's model and data are completely independent. Therefore, it is not possible to analyze different files with any kind of relationship between them.

Multiple sheets can be set up in a single file, and each can be toggled by clicking on its own tab. Each sheet can have completely independent models and data, but unlike in the case of files, it is also possible to share parameter values among multiple sheets by specifying them in particular a performing closely related analyses. Sheets can also be easily duplicated s a similar analyses can be compared. There are two types of sheets: one for nonlinear analysis, i.e., general model analysis, and one for linear analysis.

Each sheet for nonlinear analysis can have m u l t i p l e stacksEach stack can have separate data and different parameter values (including population parameters) However, i s only one model type can be defined p r sheet t model type is the same among the stacks within a sheet. Using stacks can be challenging, so it is recommended that you become familiar with Napp before using them. To switch between stacks, enter the stack number in the field in the upper right corner of the plot.

Let's discuss the models in a little more detail. Programmatically, Napp has two types of models: interpreted and bundled. T former is less fast than the latter, h has the advantage of being easily modifiable.Creating a bundled model requires programming knowledge.Specifically, bundles must be created in the Objective-C programming language using Xcode, Apple's software development environment. Please contact the creator individually for more details.

Mathematically, Napp's model includes analytical expressions, differential equations

equations, Laplace transform equations, and partial differential equations. The latter are more complicated, so the bundle type is more advantageous, but the interpreter type is almost always acceptable, especially for analytical expressions. Partial differential equation models can only be created with the bundle type.

In both cases, the functions of the model itself are stored in a library, independent of the data file. Only the model and parameter names are saved in the data file. If Napp is run in multiple environments, be careful not to inadvertently change the model from one environment to another.

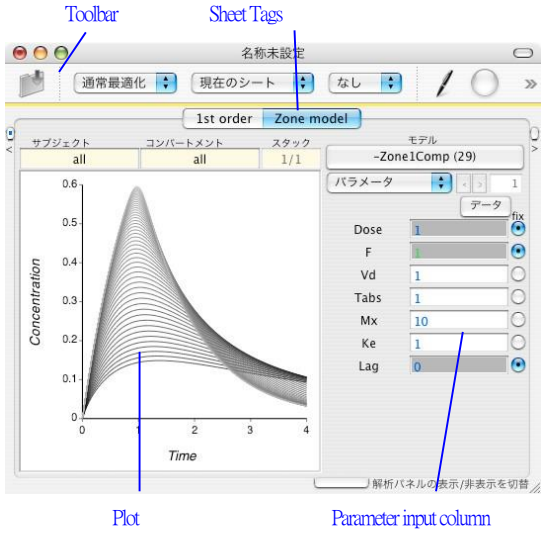
The data is most simply a set of drug blood concentrations corresponding to the time of blood collection. However, in kinetic analysis, it is common for there to be more than one target for analysis of concentration trends at each time. To accommodate this, Napp can store data on concentration trends for multiple compartments. In this case, the compartment number is an integer starting from 1, and there is no programmatic limit on the number of compartments. However, compartment numbers should always be consecutive to avoid missing compartments.

In addition to supporting multiple compartments, Napp can also hold data for several more individuals. This is managed as a subject. Subject numbers do not have to be consecutive. In some cases, it may be desirable to maintain specific information for analysis, such as different doses for different subjects, and Napp allows each subject to maintain a named constant, called a property, to accommodate such a situation. The number of subjects can be as large as 1000, for example. This is a feature that is useful for population analysis.

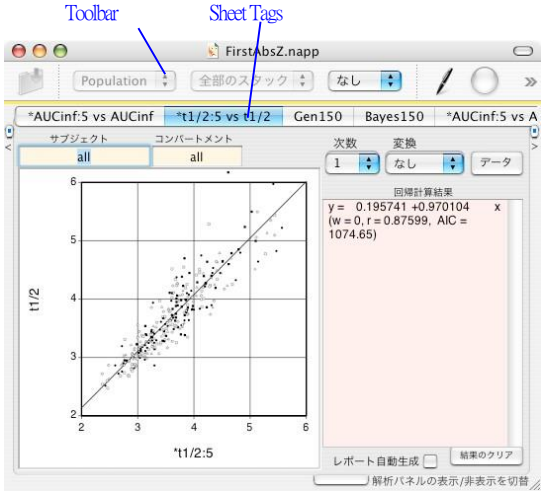
To hold and manage such complex structured data, Napp has several data formats. For details, see "Chapter 3 Input Data Formats".

Please refer to the following. All data formats are in tabular form, so it would be convenient to prepare them in Excel or other formats, and then enter them into Napp as a batch.

Nonlinear Analysis Sheet



Linear Analysis Sheet

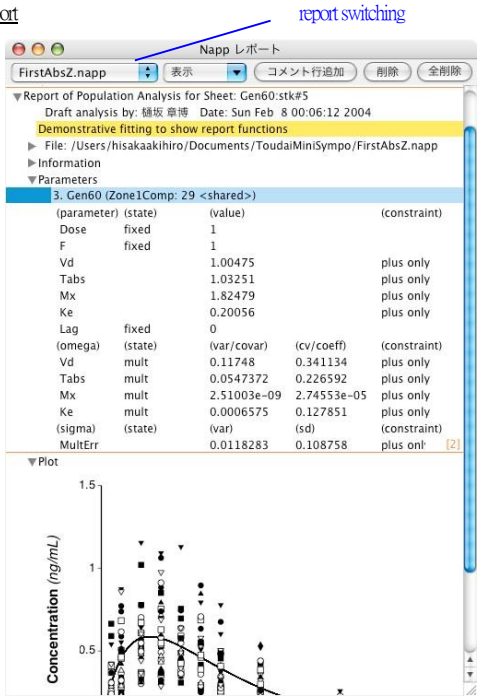


In the analysis, please be sure to name the sheets appropriately. The sheet names will be output to the report to facilitate later data processing. Sheet names can be entered from the toolbar.

The results of the analysis are output to a dedicated report window, which can be printed or turned into a PDF file. The report output is saved in a file along with the sheet data. Data in multiple files

are handled, reports are differentiated by file and switched within the report window.

Report



2.6. Toolba ー

Basic operations such as plotting and deleting plots in Napp can be performed from the toolbar buttons at the top of the window. The toolbar can be turned on and off with the button in the upper right corner of the window. You can also select the display options from the context menu or from the "Napp" menu under "Set Toolbar...". in the context menu or in the "Napp" menu.

The functions of the buttons on the toolbar can also be selected from the "Operations" menu, and many operations have shortcut key definitions. The settings in the pop-up menu on the left side of the toolbar are important, especially the "Analysis Target" and "Optimization Method" settings. The default settings are "Current Stack of Current Sheet" and "Normal Optimization".

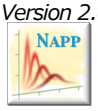
2.7. Proc t

Enter data and execute plots in the operation menu and if the model is a "ZLine", a line graph is immediately plotted and a moment analysis is performed. This area of the graph is called the plot.

The scale of the graph axes is set automatically, but can also be set manually from the "Axis Settings" menu in the context menu of the plot, and the X log and Y log context menus can be pressed to set the graph axes to one or two logarithms. Marks, line types, colors, etc. can be modified from the "Advanced" contextual menu. Similarly, coordinates can be displayed and plots can be independently saved to a PDF file for use in other plotting software.

The graph scale settings include "Auto," "Equal interval," and There are three types of "Manual". In "Manual", you can specify any increments in the input field. In the logarithmic scale, "equal intervals" cannot be specified. There are two types of tick marks: main tick marks that draw numbers and sub-tick marks that do not do so.

To specify a color in the advanced settings of the graph, click on the part of the frame (color well) where the color is to be specified, and a panel for setting the color will appear. If there are multiple subjects or compartments, specify these to set colors and marks. For marks, numbers can be selected in addition to ○●□■△▲▽▼. Line type can be selected from straight line, dotted line, dashed line, single-dash line, double-dash line, etc. The spacing between dotted and dashed lines can be set using "Step". For drawing error lines, you can select upward, downward, or both, and there is also a "fine-tune position" function to avoid overlapping error lines when drawing multiple profiles with error lines, making them difficult to see.



2.8. Subjects and compartmen g

Napp allows you to assign subject and compartment numbers to your data. These can be specified in the subject or compartment setting fields on the sheet to limit the scope of the plotting and analysis.

To specify multiple subjects in this field, for example, use commas to separate them, such as "1,5" or a range, such as "3-5." 3-5,12" or any combination of the two. all" or 0 to show all groups. Compartments are specified in the same way. After entering a value, press the line break to reflect the result in the plot. Also, the values of the moments and parameters will correspond to the subject or compartment as needed.

2.9. Moment solution analysis

Moment analysis is a model-independent method for obtaining AUC and MRT, and Napp performs moment analysis as soon as the data is entered and plotted from the toolbar. If you cannot see the results of the moment analysis, you can switch the display of parameters as needed.

For infinite time extrapolation, enter the number of points for the logarithmic vanishing period in term# and press return to indicate the parameters for infinite extrapolation. Napp calculates the number of points based on the AIC. The maximum number of points for this automatic setting calculation is

You can change the settings in the "Expert Settings..." in the "Napp" menu. Expert Settings..." in the "Napp" menuNote that the access level for this setting must be Expert or Administrator. The default extrapolation line for infinite extrapolation is the line obtained by regressionThis line does not necessarily pass through the actual final measurement pointTo force it to pass through, select "Expert Settings..." in the "Napp" menu. In the Set the settings in the panel that appears.These settings are described in the report.If unlimited extrapolation is difficult because the data continues to rise or for some other reason, the extrapolation setting will be automatically cancelled.

If multiple subjects or compartments are plotted,moments of the lowest numbered group will be displayed.You can also specify the subject of the plot in the manner described in the previous section, andcorresponding moment values will be shown.Note that the report output will show the results for all groups specified.

If the "log trapezoid" switch is checked, the moment is calculated by connecting the points with a straight line when ascending andexponential curve when descending. Even if the data repeat ascending and descending, it will always be a straight line when ascending and an exponential curve when descending. If the data contains 0, the logarithmic trapezoidal method is automatically disabled.

If the "Extrapolated lines" switch is checked, extrapolated lines will be plottedColor of the extrapolated lines can be changed in the "Set Details" section of the plot.

2.10. Analysis Panes Le

Click the "Show/Hide Analysis Panel" button at the bottom right of the sheet to bring up the Analysis PanelThis panel allows you to perform overlay and plot operations based on the information on the sheet.

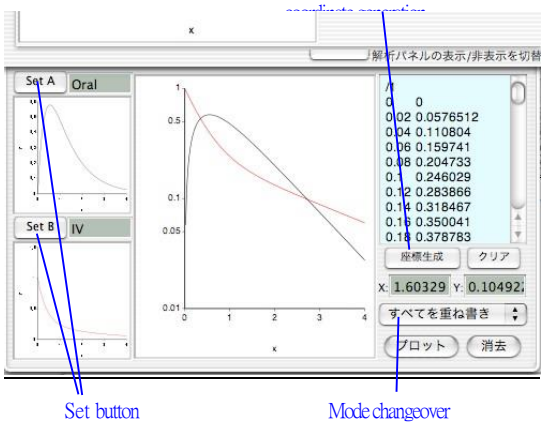
(quadrature, calculus, convolution, deconvolution, etc.).

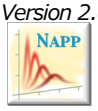
When the analysis panel is first opened, it is in "Overlay All" mode. In this mode, the plots for all sheets in the window are overlaid. If you want to exclude some sheets, disable this mode. You can enable or disable it in the "Sheets" menu. Ifset the graph axis settings for an overlaid plot, the settings will be applied to all sheets in the window.

When the mode is switched to other than overlay, the small plot on the left side of the panel shows the result of the calculation using the data set in the small plot on the left side of the panel. The plot on the left side of the panel displays the result of the calculation using the data set in the

To set the data, plot the appropriate data on the sheet and press the Set button. If you want the numbers of the calculated results, press the Generate Coordinates button.

Analysis Panel





3. Form of input data Expression

Napp offers the following three types of data input formats, which should be used according to your needs.

1) Standard format (one subject per line)
2) Condensed format (multiple subjects per line)
3) NONMEM Format

You can choose between tabular and textual formats for the display of each data type. These can be converted to each other at any time using the buttons in the lower left corner.
In tabular format, moving between cells is done horizontally with the tab key and vertically with the enter keyUse the context menu to insert, add, and delete rows and columns. Copy-paste to and from Excel and other applications is also possible. In tabular format, column titles can be dragged to change the order of columns. Note that if you have multiple stacks, the data sets will be completely different and independent between the stacks.

3.1. Standard format base book

The basic input to the data list is [x value, blank (or comma, tab), y-value, newline] in that order. For example The shaded area is optional and should be entered if necessary.

```
/1 //1
Age 23
BW 46
.5      3.2     1.2     .2
1       4.8     1.6     .31
2.3     3.78    .93     .12
8       1.23    .64     .032
```

The details are explained below.

Note: *When copying and pasting into the Data list, make sure that enough significant digits are shown to maintain accuracy. Double-byte characters are not allowed.*

In general, the use of double-byte characters in variable or property names, comments, etc. is not an error, but double-byte spaces and double-byte numbers are not properly recognized and may cause confusion.

3.2. Subject number in standard format No.

Enter a slash "/" immediately following a new line. A space between the slash and the number is permitted. Subject numbers must be at least 1, but do not have to start with 1 or be consecutive. However, duplicate definitions of the same subject number will result in an error.

3.3. Standard format compartment number No.

Enter a new line immediately followed by a series of slashes "//". Whitespace between the slash and the number is permitted. It is also possible to define a subject number followed by "//" on the same line. Compartment numbers must be consecutive values beginning with 1. What each compartment represents depends on the model definition.

3.4. Standard Format Error Input Power

If there are two first data in a row, they are recognized as x and y values, respectively. If there are three or four, the third and fourth data are recognized as errors in the y and x directions, respectively, and a plot will plot the error bars. Note that when optimizing data with errors in the y direction, the toolbar weight settings are disabled and the weighting of the data depends on the individual error values.

3.5. Enter property Power

Napp allows each subject to have its own constants, which we call properties. Properties can be entered from the datalist in the following order: property name, blank, numeric, and newline. Properties entered from the datalist are covariates of the population analysis
(COVARIATE).

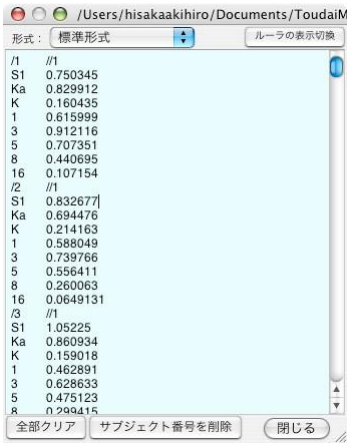
If the property name is the same as the parameter name and the parameter is set to fix, the value of the property is used for parsing for the corresponding subject. In this way, the parameter value can be set subject-specific. This allows, for example, data from multiple subjects with different doses to be analyzed together.

Note that when subject-specific analysis is performed, the obtained parameter values and moments are also automatically registered as properties. Property values can be grouped together in the property menu to calculate averages or subject them to regression analysis. To avoid confusion between the property name entered from the data list and the property name obtained as a result of the analysis, the entered property name is prefixed with @. The variance of the parameters obtained from the population analysis is indicated by $, and the standard deviation is indicated by $$.

3.6. Standard format comen g

The parts of a line enclosed in curly brackets {} are ignored as comments. A semicolon; is considered a comment until the end of the line.

Comments are generally used to note explanations of data, but they can also be used for the purpose of analyzing some data as comments and omitting them.



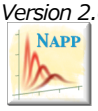
3.7. Data in condensed form data

By switching the input field format to "condensed format", the following types of data are recognized. The shaded area is optional and can be entered when necessary.

Subject 1 3 4 7				
.5	3.2	2.2	1.2	.32
1	4.8	3.6	7.31	1.34
2.3	3.78	2.93	5.12	nicotinamide adenine dinucleotide (ND)
8	1.23	nicotinamide adenine dinucleotide (ND)	2.02	.23

If the first word is "Subject" or "ID," the numbers following that line are interpreted as specifying the subject number. If there is no corresponding line, the subject number is assigned sequentially, starting with 1. The next line will be the X data, followed by the Y data for each subject, in that order. The data cannot be mixed with normal format data on the same sheet. Errors and properties cannot be entered in this format. The advantage of this format is that it provides a compact representation of data when X values are common among subjects.

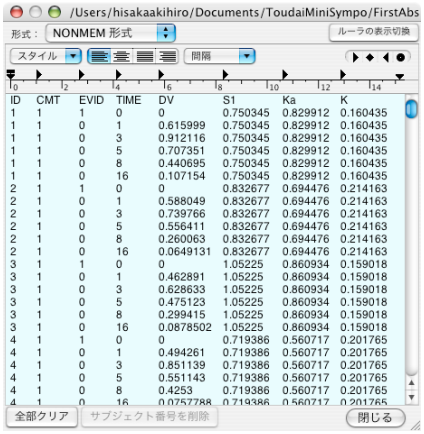
3.8. Data in NONMEM format Ta



By switching the input field format to "NONMEM format", data in NONMEM data record format is recognized.

The first line defines the data item, similar to NM-TRAN's INPUT record. Currently, the recognized Item names are ID, EVID, TIME, DV, MDV, AMT, CMT, PCMT
ID is set as the subject number and CMT as the compartment number. Not all of these work, however: ID is set to the subject number, CMT to the compartment number, TIME and DV are read as x and y values, but rows with EVID or MDV set are ignored. All of these items or user-defined items are stored as properties and can be used as covariates in population analysis using the transform functionality.

Following the above, enter the data record directly. Note that blank lines and lines in which the first character of the record is not a number are ignored; `comments with {, ; are not allowed in NONMEM format data.`



ID	CMT	EVID	TIME	DV	S1	Ka	K
1	1	1	0	0	0.750345	0.829912	0.160435
1	1	0	1	0.615999	0.750345	0.829912	0.160435
1	1	0	3	0.912116	0.750345	0.829912	0.160435
1	1	0	5	0.707351	0.750345	0.829912	0.160435
1	1	0	8	0.440695	0.750345	0.829912	0.160435
1	1	0	16	0.107154	0.750345	0.829912	0.160435
2	1	1	0	0	0.832677	0.694476	0.214163
2	1	0	1	0.588049	0.832677	0.694476	0.214163
2	1	0	3	0.739766	0.832677	0.694476	0.214163
2	1	0	5	0.556411	0.832677	0.694476	0.214163
2	1	0	8	0.260063	0.832677	0.694476	0.214163
2	1	0	16	0.0649131	0.832677	0.694476	0.214163
3	1	1	0	0	1.05225	0.860934	0.159018
3	1	0	1	0.462891	1.05225	0.860934	0.159018
3	1	0	3	0.628633	1.05225	0.860934	0.159018
3	1	0	5	0.475123	1.05225	0.860934	0.159018
3	1	0	8	0.299415	1.05225	0.860934	0.159018
3	1	0	16	0.0878502	1.05225	0.860934	0.159018
4	1	1	0	0	0.719386	0.560717	0.201765
4	1	0	1	0.494261	0.719386	0.560717	0.201765
4	1	0	3	0.851139	0.719386	0.560717	0.201765
4	1	0	5	0.551143	0.719386	0.560717	0.201765
4	1	0	8	0.4253	0.719386	0.560717	0.201765
4	1	0	16	0.0757788	0.719386	0.560717	0.201765

4. Nonlinear Least Squares Solution Analysis

4.1. Setup Setup

A nonlinear least squares analysis requires entering data in the input fields, selecting a model, and setting initial values for parameters. There are a few other things to note, such as selecting parameters, setting parameter range limits, selecting weights, and choosing an algorithm. After reviewing these settings, specify optimization in the toolbar or in the "Operations" menu to run the analysis.

4.2. Creating a model

Pressing the Model Settings button on the Nonlinear Analysis sheet allows you to select a model from the list of registered models. Once the selection is performed, the name of the parameter being set will appear on the sheet. The default value is Zline (meaning line chart); Zline has no parameters and therefore cannot be used for optimization calculations.

A model name prefixed with "@" is a user-specific registered model. Models with a "-" prefix are interpreted not(see Chapter 7), and their contents can be edited if the access level is Expert. Models without "@" are shared models, and only administrators can create or delete them.

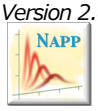
When you select New,Edit or Browse in the Model Selection panel, the "Model Information" panel appears. The contents can be edited in the case of New and Edit.

The function of the model is to give the dependent variable by reference to the value of the parameter when the independent variable is given. Enter the relevant equation in the "Model Equation" field. The "Preliminary Equation" is used when preparatory work is needed to calculate the model equation with parameters and temporary variables. Independent variables cannot be used here.

Model expressions are created according to general mathematical formulas and programming description syntax, but with the following characteristics: expressions are separated from each other by "," and the multiplication symbol "*" can be substituted with a one-byte space. For details, please refer to Chapter 7, "How to Create Napp's Models. After writing the model equation and preliminary equation correctly and pressing the "Check" button, a list of parameters and temporary variables will be automatically created.

The "Description" of the model and parameters is displayed as tips when the mouse hovers over the model name or parameter name on the sheet, so it is best to describe them clearly. Descriptions can be set by language by selecting the language in the lower left corner of the panel.

In Napp, all models can be used commonly for ordinary analysis, population analysis, and Bayesian estimation. Differential equation and Laplace transform equation models are

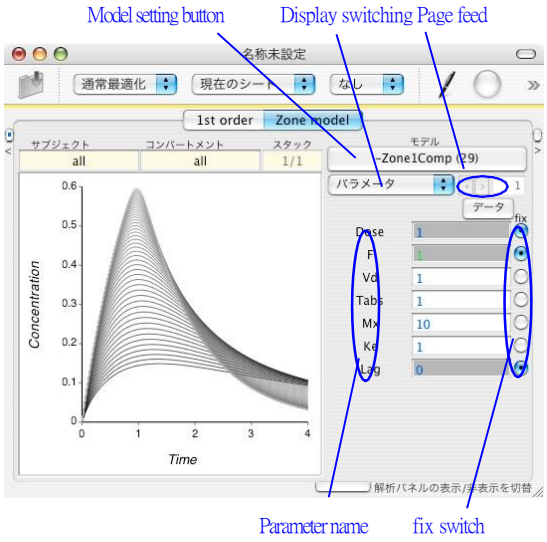


also defined

Can be done.

4.3. Set parameters

Once the model is loaded, the name of each parameter is displayed on the sheet. If the number of parameters exceeds the allowable number in the display column, they cannot be displayed at one time, so enter the number of pages in the pagination cell at the top or use the buttons to change pages.



Enter the appropriate values for the parameters and perform a plot from the operation menu or toolbar to see the results of the model calculations on a graph.

The parameter display columns can be switched as shown below.

Moment" shows the result of moment analysis. If the model is a Zline, you cannot specify any other choice than this one. If you select a general model, such as a compartment model, you can also toggle the parameter display column to show moments. In this case, the moments are based on the curves calculated by the model, unlike when the model is ZLine.

Following "Moments," you can set "Parameters," "Minimum Value," and "Maximum Value," and switch "Previous Initial Value" of the optimization calculation to be performed. To perform optimizationenter an initial value in "Parameters." When optimization starts, the value is copied to the previous initial value, and then the parameter value is updated.

Switching the parameter display changes the numbers in the parameter column, the color of the background, and the function of the buttons to the right of it. After switching the display, enter values as needed and press the right button to set.

When the "fix" switch, which appears in the parameter display, is turned on, the parameter is fixed and excluded from the optimization calculation. This allows, for example, a model with lag time to be used as a model without lag time by setting the lag time to 0 instead of including it in the analysis. Abuse of this feature would effectively change the nature of the model. Therefore, if the access level is learner or user, the "Fix" cannot be changed.

The "plus" button, which appears in the minimum value display, limits the parameter to a positive value (the minimum value in the input field is not valid). The "set" button, which appears in the maximum value display, enables the setting of the maximum and minimum values for the parameter. The settings for the parameter value ranges may be set automatically when the model is selected, as default settings can be defined when the model is created. The button settings for these value limits can be changed independently of toggling the parameter display by bringing up a contextual menu at the button.

Abuse of parameter value restrictions can lead to arbitrary analysis. For this reason, 

the upper and lower ranges of parameters can ented when the access level is learner or user. Restrictions on positive values are always

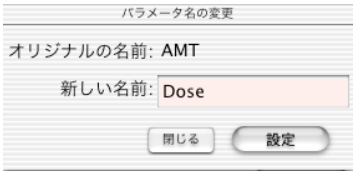
Possible.

The numbers and background colors in the parameter columns have the following meanings

Numbers are black	Editable, no value restrictions
Numbers are blue	Editable and limited to positive values
Number is green	Editable, with maximum and minimum limits
Numbers are red	Not editable (display of analysis results)
White background	Values are valid and subject to optimization calculations
Light gray background	Value is valid but not subject to optimization
	No (or merged with others)
Dark gray background	Value is invalid
Black background	Value is invalid and cannot be edited

4.4. Parameter renaming, multi-simulation sessions, transformations

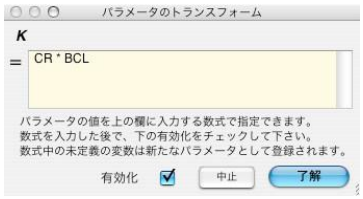
Parameter names can be changed. To do so, open the context menu (CTRL-click or right-click) parameter name display. From this context menu, in addition to changing the parameter name, you can also select the MultiSimulation and Transform functions.



Parameters should be given names that are easy to understand in the analysis, if necessary. As will be explained later, parameter names may define the structure of the model, for example, in simultaneous optimization. Note that parameter renaming cannot be performed when the access level is learner or user.

Multi-simulation is the ability to continuously simulate plots by changing parameter values in small increments. The initial values, final values, and number of calculations are set and

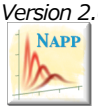
Press the "Run" button. At this time, you can choose whether to change the parameter tolerance-wise or tolerance-wise.



Transforms are used to redefine the values of the relevant parameters in mathematical expressions. This function is mainly intended for population analysis where covariates are incorporated into the model. Transforms are activated only after entering the formula in the field and turning on the activation switch. The formula can have predefined and undefined parameters. For more information on defining functions, please refer to the chapter on how to create a model. Transforms cannot be executed if the access level is learner.

4.5. Default setting Set

Napp does not have the ability to automatically generate initial values. However, it is quite easy for the user to determine by trial and error whether the initial values are appropriate, as a plot can be run to immediately check on the graph.



4.6. Weight selection Selection

The weights are set in a pop-up menu on the toolbar, and in addition to the usual 0, 1, and 2, logarithmic weights can also be selected. The optimization is performed to minimize the absolute error for a weight of 0 and the relative error for a weight of 2. Logarithmic weights are an analysis of the log-transformed values with weight 0. The results are similar to weight 2 when the error is very small, but in general the results are better than with weight 2, since there is less tendency to gravitate toward smaller values.

Note that if the weight is non-zero, a calculation error will occur if the data contains 0.

4.7. Combination of multiple analyses

Napp has the ability to analyze multiple groups of data and multiple analyses together, especially for efficient population analysis. This feature allows the results of many analyses to be correlated and analyzed together.

When "Target of Analysis" in the toolbar is set to "Current Stack of Current Sheets," only the single sheet displayed at the very front is subject to analysis. In this case, if the current sheet contains data for multiple subjects, they will be analyzed together to obtain a single set of parameters. The resulting parameters can be freely edited and used for the next analysis. This mode is generally intuitive and straightforward.

When "All Stacks" is selected, the analysis is repeated for all stacks held by the current sheet. Stacks can be added and deleted from the "Operations" menu. Stacks can also be added and deleted from the "Tools" menu.

Generate Data..." Multiple stacks can also be created at once from "Generate Data...". The stack feature is not available when the access level is learner.

When "Analysis Target" is set to "By Subject," the target sheet remains the same as shown in the foreground, but if there is data for multiple subjects, the analysis is repeated for each subject separately, and the data for each subject is analyzed separately.

The parameter set corresponding to the

The "by subject" analysis is useful for Bayesian estimation (posthoc analysis) after the population analysis. Each parameter is output in the report and can also be viewed on the sheet by specifying it in the subject setting field of the sheet. Correlations between parameters can also be plotted using the "Properties" menu function. This is especially useful for population analysis, as it allows you to output a summary report of correlations between parameters and covariates. However, some care must be taken in this mode, as individual subject parameters cannot be edited on the sheet, and clearing the plot will also clear all values.

To use individual parameters for the following analysis, see the "Use Subject Specific Parameters" item in the "Operations" menu. If you wish to limit the analysis to a subset of the data contained in a sheet, specify it in the sheet's subject settings field before analyzing.

If "Analysis Target" in the toolbar is set to "All Valid Sheets", the analysis is performed for all sheets included in the current window. In this case, the analysis is independent for each sheet, and the analysis is repeated for as many sheets as there are sheets. If you do not want the analysis to be performed on some sheets, you can disable those sheets. Sheets can be enabled and disabled from the "Sheets" menu. Disabled sheets are indicated by a "*" in the name.

When the toolbar's "Analysis Target" is set to "Merge Valid Sheets", the models of all valid sheets in the current window are merged as if they were a single model for simultaneous optimization. The model of each sheet may be different at this time. However, parameters with the same name are considered identical. In order for simultaneous optimization to work properly, the parameters must be well named. Parameters can be renamed by displaying the context menu in the parameter name display.

Simultaneous Optimization

In the "Unify" function, parameters with the same name must be set to the same value and settings even if they are on different sheets. This can be done with "Unify Parameters with Same Name" in the "Operations" menu.

4.8. Optimization options

Performing "Optimize" from the toolbar or the "Operations" menu will start the calculation, and once the results converge, a report will be output on the screen. Whether to output a report at this time, whether to include plots or individual data in the report, and whether to perform correlation plots or residual plots after the analysis, can be set from the "Preferences" in the "Napp" menu.

The size of the plots in the report can also be changed here. If the number of analyses is large and exceeds 100 plots, the report must be simplified or operation will be slow. Even if you do not output a report, you can refer to the analysis results from the properties. Note that the contents of the properties are preserved when the sheet is duplicated and stored in the file. The contents of the properties are erased when the plot is cleared.

The convergence judgment value of optimization can be set in the "Napp" menu.

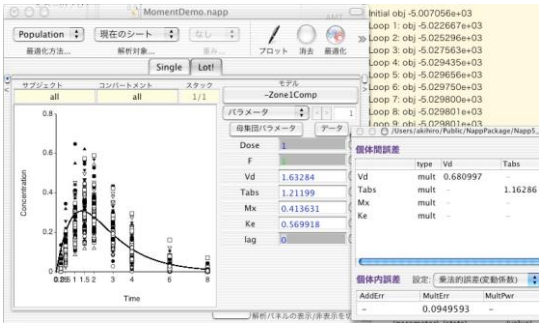
Expert Settings..." in the New Expert Settings..." in the "Expert Settings..." menu. The access level for this panel setting must be Expert or Administrator.

4.9. Optimization Algorithms m

Napp automatically sets up the calculation algorithm for nonlinear least squares. For ordinary nonlinear least squares or Bayesian estimation, the damping Gauss-Newton method is first attempted, and after it converges, the Marquardt method is also calculated again just to be sure. If the damping Gauss-Newton method fails, the simplex method is used to reduce the convergence conditional based on the results, the damping Gauss-Newton method is performed again, followed by the Marquardt method.
Population Analysis
（If the BFGS method fails, the simplex method is attempted and the BFGS method is used again.

4.10. Population solution analysis

Population analysis (extended least squares method) is a method that not only determines the mean value of parameters, but also analyzes the error distribution of parameters and data in detail. It is rapidly gaining popularity in recent years because it enables PK analysis in patients with fewer blood sampling points, and can be used in combination with Bayesian estimation to plan individual dosing.



Population analysis allows for extremely flexible assumptions about factors that can introduce errors in the data. The details are beyond the scope of this manual and should be referred to specialized literature. In particular, it is important to fully understand the meaning of intra-individual and inter-individual errors, additive and multiplicative errors, etc.

In the conventional extended least squares method, the step of creating a model that assumes various error structures is difficult for novice users. Napp allows you to use the same model for Bayesian estimation, so you can effectively use the results of the Extended Least Squares analysis.

To perform a population analysis, switch the "Optimization Method" on the toolbar to "Population". The inter-individual and intra-individual errors of the parameters are set in the panel displayed by pressing the "Population Parameters" button.

The variance,standard deviation, and coefficient of variation of the interindividual error can be entered or displayed in any form. The standard deviation is automatically set to be the square root of the variance. Prior to the analysis, the initial values of the parameters as well as the initial values of these errors must be entered appropriately. In the input field for the inter-individual errors, from the contextual menu, select

If Disable is performed, the error is excluded from the analysis (i.e., fixed at 0).

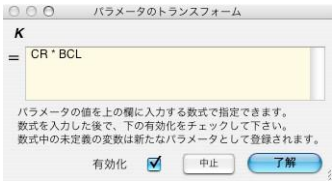
The "Switch Off-Diagonal Components" button allows you to enable or disable the off-diagonal terms in the interindividual error. When the off-diagonal term is enabled, the analysis generally becomes more complicated, and Napp uses a special mathematical process to transform the off-diagonal term in the optimization calculation so that the calculation does not diverge. Therefore, off-diagonal terms cannot be restricted to a range of values, and if they are disabled, they can only be executed sequentially, starting from the end of the table.

The intra-individual error can be set to additive,multiplicative, etc., using the switch buttons, and if F is a fixed effect, the intra-individual variation is modeled by the following equation

$$y = F + MultErr\ F\ ^{\wedge}\ (MultPwr / 2) + AddErr$$

Population analysis examines the relationship between age, gender, weight, and clinical laboratory values of each subject and the pharmacokinetics, efficacy, and safety of a drug. In Napp, covariates can be entered into the data, e.g., "Age 35". To incorporate this into the model, you can rewrite the model itself, or you can click on the parameter name and enter the relationship between the parameter and the covariate as a transform from the input field that appears. For example, if the ability to lose a drug varies with age, and this ability is expressed as a parameter CL, you can define "CL = a * Age + b" and so on. The new parameters a and b will automatically be added to the list of parameters.

to which the appropriate value can be set or an optimization calculation can be used to estimate the appropriate value.



When analyzing with covariates in mind, covariates should be entered as individual subject properties in the data in advance. It is a good idea to first analyze the data with a model that does not include covariates, then analyze the correlation between individual parameters and covariates using the functions in the property menu, and sequentially incorporate those with strong correlations into the model. To incorporate covariates into the model, click on the name of the correlated parameter and activate the transform by entering an expression to calculate the parameter from the covariate. The covariates entered will be added to the parameter list, and if you set this to fix, the values in the data for each subject will be used.

The input covariate is treated as a property in Napp, so even if it is not incorporated into the model or transform, it is possible to perform various types of analysis from the Tools menu. Napp properties are the values that the subject has as attributes, and in addition to covariate, they include parameter values obtained for each subject, moment analysis values, and so on.

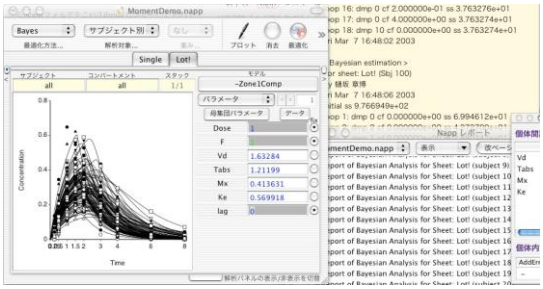
Napp's population analysis is technically only for FO methods based on first-order approximations; it does not support FOCE methods, etc.

4.11. Bayesian Inference constant

Bayesian estimation estimates the parameters of each individual when the population parameters are known. While the usual parameter estimation requires a sufficient number of data for each individual, in the case of Bayesian estimation, the number of data for each individual can be analyzed even if the population parameters are known. Using this method, a dosing plan can be reasonably devised even if, for example, only two or three blood levels are available for an actual patient. For more information on Bayesian estimation, please refer to the technical literature.

To perform Bayesian estimation with Napp, switch "Method of Optimization" to "Bayes" in the control panel. Population parameters are set to Parameter and Standard Deviation or Separate

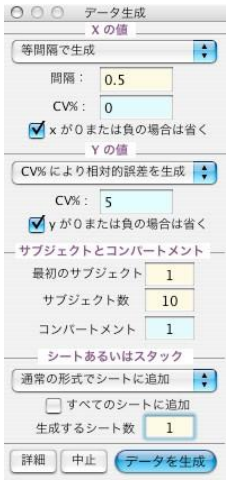
Enter the data in the scatter column. Once the data is entered into the data list and the optimization is run, Bayesian estimation is performed with the population parameters as initial values.



To perform Bayesian estimation continuously after performing a population analysis, switch the "Optimization Method" in the toolbar to "Bayes" and run the optimization making sure that the "Analysis Target" is set to "Individual Subjects".

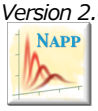
4.12. Random raw of data Composition

By selecting the "Gen" button on the nonlinear analysis sheet or "Generate Data..." from the "Tools" menu on the nonlinear analysis sheet or by selecting "Generate Data..." from the "Tools" menu, the "Generate Data Panel" will appear, allowing you to generate data with random errors from an arbitrary model.



The data generation panel consists of two parts: the upper part of the panel shows how to generate X and Y values, and the lower part of the panel shows the number of data sets to be generated and the output destination.

X values can be set to "Generate equally spaced" and "X-axis ticks".



can be selected "according to". The axis scale can be set manually to any desired value, including unequal intervals. A random error can be added to the X value by setting the CV% column to a value other than 0. This error is relatively small.
(with unequal variance) will be added. If the axis ticks contain 0, setting 'omit x <=0'will suppress the generation of x=0 data.

You can choose between "Follow CV%" and "Follow PPK Parameters" for the value of Y. Follow CV%" adds a relative error to the value simulated by the model equation. In "Follow PPK Parameters," the parameter values are combined according to the inter-individual variation of the PPK parameters, and an error according to the intra-individual variation is added. The synthesized parameter values are also output to the data list so that you can verify how well the values obtained from the analysis match the assumptions of the model. Relative errors are added if the inter-individual variability is specified by the CCV, while additive errors are normally distributed (with equal variance).

If you set the number of subjects to multiple in the number of data sets, multiple data sets will be generated. If the number of sheets is set to multiple, a new sheet is automatically inserted into the window and the combined data is generated there.

If "Output Destination" is set to "Add to sheet in normal format," the combined data will be added to the data list of the sheet.When "Output Destination Settings"is set to "Add in NONMEM format," the output data will be in the format of a NONMEM data file.For more information on this format, please refer to the chapter "Input Data Format. The output data can be cut and pasted for export to NONMEM and other formats. If exporting is your goal from the beginning, you can use the
It is a good idea to set the "Output Destination Settings" to "Store in NONMEM format". In this case, you can specify a file name and then store the data to be output as a text file.

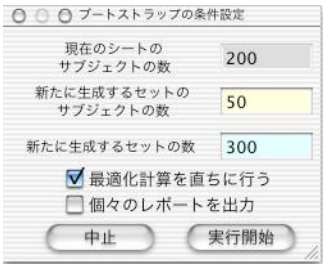
The file name will be automatically numbered after the file name. If the number of sheets at the bottom of the panel is set to multiple, multiple files will be created with the file name automatically followed by a number.

In general, if the error is independent of the value of the parameter (x ± equivalent to 0.5, etc.) and proportional to the value of the parameter (corresponding to a CV value of 15%, for example). The former is described here as absolute and the latter as relative. In general, the lognormal distribution is relative, but the upper and lower fluctuations do not coincide in an unlogarithmic manner. Therefore, the value of the standard deviation differs for the normal distribution and for the lognormal distribution. In the first place, when the variation is large, the difference between the arithmetic mean and the geometric mean becomes significant. In general, the assumption of a normal distribution is often used as a parameter error, but if it is synthesized with the same assumption, negative values are also synthesized, which may cause problems in the analysis. Therefore, in Napp's data generation, the parameters are assumed to have (1) an absolute normal distribution, (2) a lognormal distribution adjusted so that the absolute normal distribution, arithmetic mean, and standard deviation coincide, and (3) a relative normal distribution adjusted so that the relative normal distribution, arithmetic mean, and standard deviation coincide.
Normal distribution, (4) lognormal distribution, and the above four methods of synthesizing data can be selected. Therefore, negative values may be synthesized in (1), but negative values will not occur in (2) through (4). In general, the method (1) may be used to synthesize and exclude negative values, but (2) and (3) are superior in that the arithmetic mean and standard deviation are consistent with the assumptions compared to this method. However, since the distribution that is strictly different from the assumption is synthesized, the data will be highly distorted if the variance is large. In such cases, it should be said that originally it was necessary to deal with such cases by log-transforming the parameters in the analysis, and in the case of simulation, some compromise is necessary.

4.13. Bootstrap

Bootstrap analysis is a method of verifying the reliability of the results of a population analysis.

The analysis is performed by synthesizing a bootstrap analysis set, repeating the same analysis on the synthesized data set, and comparing the results with the original analysis to check the reproducibility of the results. To perform a bootstrap analysis, select "Bootstrap Analysis..." from the "Tools" menu. from the "Tools" menu to bring up the settings panel.



Set the "Number of Subjects in Newly Created Set" and 'Number of Newly Created Sets'and then "Start Execution". The new sheet will duplicate the settings of the current sheet and create a stack of the number of sets to be generated. In general, it is reported that bootstrapping requires a large amount of analysis and should be repeated, for example, about 200 times. If "Perform optimization calculations immediately" is selected, optimization calculations for each stack will begin immediately. If you want to calculate the correlation of the obtained parameters after the optimization calculations are finished, you can do so from the "Properties" menu.

4.14. Default compartment model

4.14.1. Adv1(iv1c)

1-compartment model for instantaneous or continuous infusion. For continuous dosing. It has the following parameters

AMT Dosage

RATE Injection rate.Enter 0 for instantaneous dosing.If a negative value is entered, the absolute value is the dosing time.

F1 Bioavailability

S1 distribution volume, equivalent to

Vd K dissipation rate constant

Lag Ragtime

Dini The number of doses until the first analyzed dose, usually entered as 1. Enter 0for steady state.

II. Inter-dose interval for continuous dosing (inter-dose interval), enter 0 for a single dosedo not set less than RATE;enter 0 for a single dose; do not set less than RATE; enter 0 for a single dose; do not set less than RATE; do not set less than RATE.

4.14.2. Adv2(po1c)

1-compartment model for oral administration. It corresponds to continuous dosing. This model does not cause calculation errors when Ka is equal to K and gives the correct value if Dini is not 0. It has the following parameters

AMT Dosage

F1 Bioavailability

S1 distribution volume, equivalent to

Vd Ka Absorption rate constant

K Disappearance rate constant

Lag ragtime

Dini The number of doses until the first analyzed dose, usually entered as 1. Enter 0for steady state.

II. Inter-dose interval for continuous dosing (inter-dose interval), enter 0 for a single dosedo not set less than RATE;enter 0 for a single dose; do not set less than RATE; enter 0 for a single dose; do not set less than RATE; do not set less than RATE.

4.14.3. Adv3(iv2c)

Two-compartment model for instantaneous or continuous infusion. For continuous dosing. It has the following parameters

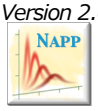
AMT Dosage

RATE Injection rate.Enter 0 for instantaneous dosing.If a negative value is entered, the absolute value is the dosing time.

F1 Bioavailability

S1 distribution volume, equivalent to Vd.

K12. Rate constant from compartment 1 to 2, K



0 means calculation error.

K21 Rate constant from compartment 2 to 1, 0 means calculation error

K Disappearance rate constant

Lag ragtime

Dini The number of doses until the first analyzed dose, usually entered as 1. Enter 0 for steady state.

II. Inter-dose interval for continuous dosing (inter-dose interval), enter 0 for a single dose; do not set less than RATE; enter 0 for a single dose; do not set less than RATE; enter 0 for a single dose; do not set less than RATE; do not set less than RATE.

4.14.4. Adv3a(iv3c)

Three-compartment model for instantaneous or continuous infusion. For continuous dosing. It has the following parameters

AMT Dosage

RATE Injection rate. Enter 0 for instantaneous dosing. If a negative value is entered, the absolute value is the dosing time.

F1 Bioavailability

S1 distribution volume, equivalent to Vd.

K12 velocity constant from compartment 1 to 2 K21 velocity constant from compartment 2 to 1

0 means calculation error.

K13 Velocity constant from compartment 1 to 3, K31 Rate constant from compartment 3 to 1, K31

0 means calculation error.

K Disappearance rate constant

Lag ragtime

Dini The number of doses until the first analyzed dose, usually entered as 1. Enter 0 for steady state.

II. Inter-dose interval for continuous dosing (inter-dose interval), enter 0 for a single dose, not set below the RATE.

4.14.5. Adv4(po2c)

Two-compartment model for oral administration. Corresponds to continuous administration. It has the following parameters

AMT Dosage

RATE Injection rate. Enter 0 for instantaneous dosing. If a negative value is entered, the absolute value is the dosing time.

F1 Bioavailability

S1 distribution volume, equivalent to

Vd Ka Absorption rate constant

K12 Velocity constant from compartment 1 to 2 K21

Velocity constant from compartment 2 to 1 K Vanishing velocity constant

Lag Ragtime

Dini The number of doses until the first analyzed dose, usually entered as 1. Enter 0 for steady state.

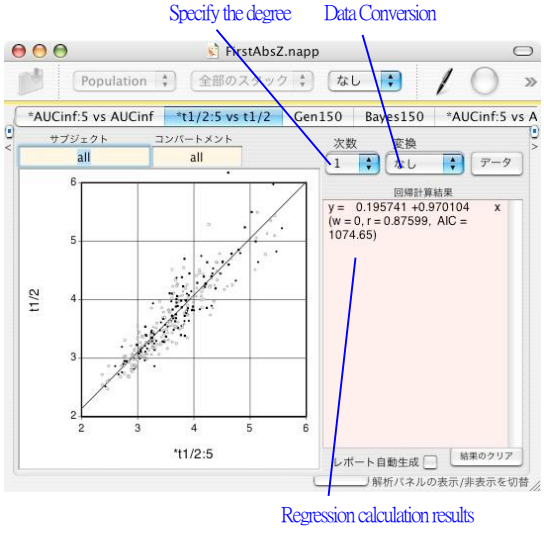
II. Inter-dose interval for continuous dosing (inter-dose interval), enter 0 for a single dose; do not set less than RATE; enter 0 for a single dose; do not set less than RATE; enter 0 for a single dose; do not set less than RATE; do not set less than RATE.

5. Linear least squares solution Analysis

5.1. Linear Analysis Panes Le

To perform a linear least squares analysis, select Insert Linear Regression Sheet from the sheet menu.

After entering the data into the data list in the Linear Regression window, making these settings, and executing Plot from the Operations menu or toolbar, a graph is displayed and the regression equation is output in the text area at the bottom of the linear regression sheet. A detailed report can then be generated by running Report from the Operations menu. The weights of the data for the regression analysis are set in the toolbar. You can specify Order in the Linear Regression window to run linear regression analysis of the first to tenth order. If set to Adj, a linear regression of the first to tenth order will be performed and the results with the lowest AIC will be shown.



Note: *Even in linear regression, the graph axes can be freely set to one-log or two-log. However, the results of linear regression are always shown as a straight line on a normal plot, but as a curve on a one-log or two-log plot. To perform a linear regression after transforming the data to logarithmic, use the following data transformations.*

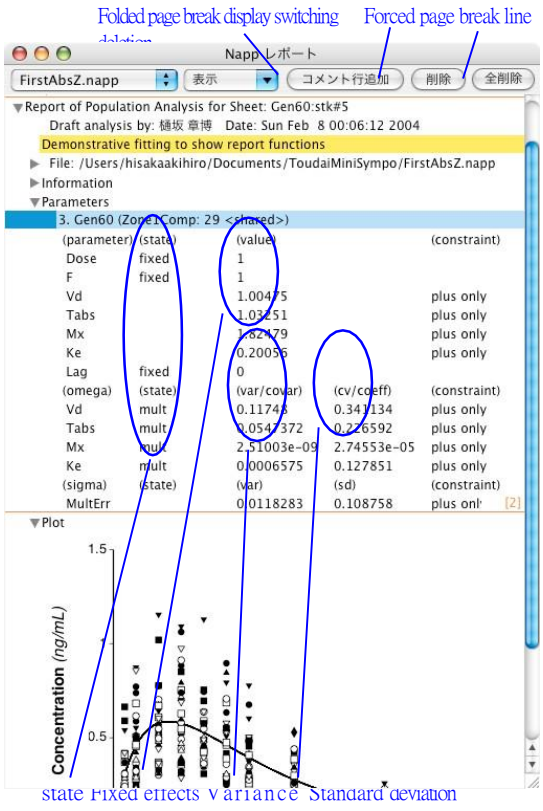
The linear regression window includes a data transformation function.

The mode is set to log - log. For example, if the mode is set here to log - log, the X and Y values are each converted to logarithmic values before linear regression is performed. When the report is output, the transformed values are output in addition to the original variable values. Other conversions include reciprocal and Hill (logit), which can be used to analyze enzyme reaction kinetics.

6. Repo Top

6.1. Foldable table current

Napp reports are presented in a collapsible format. Folding and unfolding can be done by clicking on the triangular symbols as needed. You can also group reports by clicking on the View menu. Note that it may take some time to fold and expand a report if it contains a large number of items. The report will be printed according to the on-screen expansion, so please expand the necessary items in advance.



6.2. Pagen g

The report will be paged accordingly according to its content. Page boundaries are indicated by orange lines. If you need a forced page break in addition to this,select the appropriate line and press the page buttonBoundary with red line

The "Page" field will be shown. To clear a page break, press the page button again.

6.3. Edit and delete Remove

The report headings are basically the proper titles for the sheets, and the report titles will reflect that. However, there are some areas that can be clicked on and modified directly if you wish to edit them laterDeleting rows can only be done on an item-by-item basisdoing so for each row alone can be confusing. To delete a line, select it and press the Delete buttonRows cannot be replaced.

6.4. Figure Repair Correction

The figures on the report can be edited in the report by pressing the button next to the figure to edit the scale, markings, colors, etc. You can also save just the figure as a PDF file by clicking on the Edit button.

6.5. Its and others

For other details, please refer to the figure on the left. Variance and standard deviation are indicated by $ at the beginning of the parameter name, and in the case of the CCV model, CV values are indicated. state indicates whether the parameters are fixed (fixed), merged with other models in simultaneous optimization (merged), CCV model (ccv), or converged in the optimization calculation (NC - not converged). Napp's optimization calculations are basically continued until all parameters have stabilized to the accuracy specified in the advanced settings. If some parameters are unstable, this cannot be achieved and an NC may be indicated.

7. Creation of Napp's model method

7.1. Approximate Summary

When one is trying to examine some property for analysis, it is very helpful to know a mathematical expression that well describes that property. For example, if we are trying to predict the blood concentration of a drug in order to consider its efficacy or safety, we will need some mathematical expression to describe the blood concentration. The basic function of Napp is to use models to analyze the properties of objects. Napp supports a wide variety of models and is designed to make it easy to create new models and modify them.

The Napp model described in this text is relatively simple and can be written like a mathematical equation; we will call it an interpreter-type model. There is another form of Napp model, which is programmable, and has the advantage of being somewhat faster and more flexible, but it requires specialized knowledge to create, so we will not deal with it here. However, it requires specialized knowledge to create, so it is not covered here. This model is called the bundle type. If you have a special model or want to achieve the highest execution speed, you may want to consider the bundle type model.

Professionally...

Napp can perform normal simulation and nonlinear least squares parameter estimation for any model, whether interpreted or bundled, as well as population analysis (extended least squares) and Bayesian estimation.

The bundle type model is created by creating source code in the Objective-C programming language, compiling it to create a bundle of bundles.

Pile, create bundles, and finally dynamic link them.Models of nonlinear partial differential equations must be created in this way.A bundle is a form of application resource as Apple computer jargon.

7.2. Model species 類

In addition to the usual analytical expressions, Napp can handle models for differential equations, Laplace transform expressions, and partial differential equations. The meanings of these are explained below.

7.2.1. analytical expression

The model of an analytical expression is an explicit one.e.g., an equation that returns the value of y when given the value of x. In this case, x is called the independent variable because it can be freely determined, and y is called the dependent variable because it follows x. For example, if plasma concentration is defined according to time t, then t is the independent variable. A simple 1-compartment model after intravenous administration is as follows

$$y = \frac{Dose}{(1)\ Vd}\ e^{-Ke\ t}$$

Dose is the dose, Vd is the volume of distribution, and Ke is the excretion rate. For the meaning of volume of distribution and excretion rate, please refer to a textbook on drug kinetics. Dose, Vd, and Ke are called parameters because they determine the properties of the equation. We can simulate y by changing their values, and vice versa, we can calculate the appropriate parameter values from the measured values of y.However, as is clear from the equation, one of Dose and Vd must be determined before the other can be determined.In this case, since Dose is often known, it would be common to set it as a constant. Entering formula (1) as it is in this form into a computer is complicated by the formatting, so it is written as follows.

$$y = Dose / Vd \exp(-Ke\ t) \qquad (2)$$

The grammar of the description is almost self-explanatory and is omitted here, but will be discussed in detail in later chapters. Note that (2) is an expression number for the purpose of explanation here and is not actually entered. In some models, more than one dependent variable may be defined. For example, if we want to describe the amount excreted in equation (2), let y1 be the plasma concentration and y2 be the amount excreted, and let

$$y1 = Dose / Vd \exp(-Ke\ t)$$
$$y2 = Dose\ (1 - \exp(-Ke\ t)) \qquad (3)$$

In Napp, there is no limit to the number of dependent variables, and in the case of equation (3), y1 is interpreted as the value of compartment 1 and y2 as the value of compartment 2. Here, 1 and 2 in y1 and y2 are indices, and it is easy to understand that they are interpreted as subscripts.

7.2.2. analytical expression

For simple equations, simply enter the model equation in a straightforward manner and you are done setting up the model. For example, for a simple 1-compartment model, enter equation (2) described earlier as is. However, for calculations that do not depend on independent variables, it is more efficient to enter that part as a preliminary formula, so it can be set up as follows. (In practice, the increase in calculation efficiency in this case is negligible, but it is included as an illustrative example.)

Preliminary Formula

a = Dose / Vd

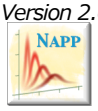
model expression

y = a exp(-Ke t)

The variable a is uniquely determined by the parameters Dose and Vd and is not related to the independent variable t. Since such variables are used only temporarily during the calculation of the model, they are not included in the parameters and are referred to as temporary variables. If you want to know the value of a temporary variable after the analysis, capitalize its first letter and its value will be printed in the report.

After entering the preliminary and model formulas, press the check button to automatically identify and list the defined parameters or temporary variable names to check for any inconsistencies. If there is an obvious definition error in the formula, an error message will appear and the line with the error will be selected for correction. Note that even if there is no error message, an unintended parameter or temporary variable name may appear in the list if the syntax of the formula is incorrect. Also, make sure that the distinction between parameters and variables is appropriate.

A list of parameters and temporary variables allows you to set initial values, limits on possible values, etc. for each. However, these settings can be freely changed again at the time of actual use.



In the case of the above model, Dose is known, so it is normal to assume that it is fixed. In the case of the above model, Dose is known, so it is normal to assume that it is fixed. The order can be changed by entering a number to the left of the list. Enter a description of the list as needed to make it easier to understand the meaning of the model or formula. Pressing the Return key while entering a list moves the cursor down, and pressing the Tab key moves it to the right.

The following is a detailed description of the syntax of formulas allowed in model expressions. In addition to being expressed as simple mathematical expressions, model expressions can, when necessary, combine multiple expressions and perform somewhat programmatic conditional branching such as if ~ then ~. If you do not envision a complex model, you may skip the latter feature and its syntax.

A. Grammar of Mathematical Descriptions

i. Spaces, line breaks

Mathematical expressions can be written across multiple lines.Whitespace and line breaks are ignored.

ii. Comment

You can freely write comments as notes in the formulas. There are two ways to write comments: one is after the semicolon ";" until the end of the line, and the other is enclosed in {}. It is good practice to include comments appropriately to make the meaning of models and formulas easier to understand.

iii. operator

Addition, subtraction, multiplication, and division are represented by + - * /. However, the multiplication sign is optional and can be substituted with a one-byte space. Note that one-byte spaces are always required and that full-width spaces are not used.Use both ^ and ** for powers.

The following is an example of a product that can be used to achieve this goal.

iv. computation sequence

Function calculations are performed with multiply-divide precedence. ^ and ** are computed before addition and division, and even more so in the case of the operator -, which represents a negative.That is, -1^2 is (-1)^2
= 1. In this case, it is better to use () to specify the order in which functions are calculated. () may be nested, and there is no limit to the number of (). The use of [], {} to specify the order of computation is not allowed.

v. assignment

Substitution uses =. Thus, a = a + 1 means a plus 1. Instead of this expression, a
+= 1 can also be used (this is the same syntax as in the programming languages C and Java).Similarly, -=, *=, /=, ^= can be used. Equivalence can be determined by using == as described below.

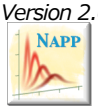
vi. constant

Constants are expressed in terms of ordinary real numbers. Also, 1.23-04e,
-.23+18e, etc. Exponential expressions are also possible. All constants are evaluated as floating-point real numbers.

vii. Parameter and temporary variable names

Parameters and temporary variable names can basically be defined as arbitrary character strings, and double-byte characters such as Kanji characters can be used. However, no superscripts or other formatting is allowed. Case-sensitive alphabetic characters are used, so ke and Ke are considered to be separate variables. There are no restrictions on the length of variable names, but if they are too long, it is inconvenient because not all of them will be displayed on the sheet.

Half-width symbol characters (!") |$%&'()=~^¥{+*}<>? @[;:],. /) cannot be used as part of a variable name. The underline _ can be used.Also, # is a predefined constant#PI and #E
(pi, exponent e) can only be used as The number is 2



It can be included after the first letter, but cannot be used as an initial letter. Dependent variable names should not contain numbers in the name itself, since a number is added after the dependent variable name to indicate the number of the compartment.

Avoid reserved words (if, then, else, elsif, endif, not, and, or, xor, for, to, while, loop, endloop, break, continue, but not all reserved words are functional in the current version) and predefined function names listed below. If you mistakenly use a predefined function name as a parameter name, you will know because it will not be registered as a parameter name. The same applies to temporary variable names.

viii. Dependent variable name

It is recommended that dependent variable names should basically have their first letter in lower case. This is a requirement especially in the case of Laplace transform models. If a dependent variable name is followed by a number (e.g. y1, y2...) the value is considered to be in the compartment corresponding to the number. However, if a number is skipped (e.g. y0, y3...) Compartment numbers are set sequentially from 1 without skipping.

ix. predefined function

Predefined functions include the following. Please note that function names should be written in lower case (this has changed since earlier versions of the development).

Square root, cube root: sqrt(x),
cbrt(x)Natural logarithm: ln(x) or
log(x)Ordinary logarithm:
log10(x)
Exponent: exp(x)
Rounding up, rounding down, rounding off: ceil(x), floor(x),
rint(x)
Trigonometric functions: sin(x), cos(x), tan(x), asin(x), acos(x),
atan(x), atan2(a, b), sinh(x), cosh(x), tanh(x)
asinh(x), acosh(x), atanh(x)
special function
gamma(x): Gamma function
lgamma(x): natural logarithm of the
gamma function signgam(0): sign of
the gamma function igamma(a, b):
incomplete gamma function ibeta(a,
b): incomplete beta function erf(x):
error function
erfc(x): Complementary error
function rand(0): uniform
random number in [0, 1)
normrand(mean, sd): normal
random number
lnormrand(mean, sd): lognormal random
number tdist(a, n): distribution function of
t-distribution with n degrees of freedom
strange(a): discriminant of infinite,
infinitesimal, and indefinite

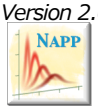
Special functions do not support complex numbers.Therefore, they should not be used in models with Laplace transform expressions. In the example above, the argument 0 has no numeric meaning.

x. Solution formulas for linear equations

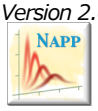
Napp can be solved by solution formulas up to the fourth order. Since these solutions are not numerical, they are fast and relatively error-free. Note, however, that they can produce errors in special cases, such as when the solution is very close to a multiple solution. Also, complex numbers cannot be used as arguments. It has been proven that the solution formulas for equations of the fifth degree or higher cannot be obtained.

solve2eq(b, c, x1, x2)
2 Solve the quadratic equation y = x^2 + b x + c and assign the solutions to x1 and x2. The function body returns the number of real solutions, i.e., 0 or 2. If it is 0, the imaginary solution is x1 ± x2 i.

solve3eq(b, c, d, x1, x2, x3)
3 Solve the cubic equation y = x^3 + b x^2 + c x + d using Cardano's formula and assign the solutions to x1, x2, and x3. The body of the function returns the



number of real solutions, i.e., 1 or 3. If it is 1, the real solution is x1; if it is imaginary



The number solution is x2 ± x3 i.

solve4eq(b, c, d, e, x1, x2, x3, x4)

4 Solve the cubic equation y = x^4 + b x^3 + c x^2 + d x + e using the Ferrari formula and assign the solutions to x1, x2, x3, x4. The body of the function returns the number of real solutions, i.e., 0, 2, or 4. If it is 0, the solutions are x1 ± x2 i and x3 ± x4 i; if it is 2, the solutions are x1, x2 and x3 ± x4 i.

x. Newton-Raphson method for solving the equations

Any equation can be solved numerically by giving initial values using the Newton-Raphson method. Note that this method does not support imaginary solutions.

newton_solve(equation, init, x)

Returns the value of variable x for which equation is 0. The equation can be any mathematical expression whose value varies with the variable x. init is the initial value of x.

newton_min(min)

Sets the minimum value of variable x to be searched. Initially, no minimum value is set.

newton_max(max)

Sets the maximum value of variable y to be searched. In the initial state, no maximum value is set.

newton_free(0)

Removes restrictions on the range of variables to be searched. Argument 0 has no meaning.

newton_init(loopMax)

Set an upper limit on the number of searches for variables and reset all calculation settings except for the upper limit on the number of searches for the Newton-Raphson solution method to their default settings. The maximum number of searches is 3000. The initial value for the maximum number of searches is 3000.

newton_abs(flag)

When searching for a variable, set whether the change is relative or absolute. Relative changes are more stable if the change in the variable does not cross zero. Set flag to 0 for relative and flag to 1 for absolute. Initially, it is relative.

newton_delta(delta)

Sets the initial value of the difference by which the variable is changed when searching for variables. The difference is automatically adjusted, but you set its initial value. The initial value is 0.0001.

newton_criteria(criteria)

The end of the search for a variable is defined as when the improvement in the function value is less than or equal to criteria. The default value is 0.0000001.

newton_error(errorValue)

Sets the value to be returned if variable traversal fails. The initial value is 0.

B. Grammar for combining multiple expressions

i. Combining multiple expressions

The boundary between expressions is indicated by a comma ",". However, it is not necessary at the end of an expression.

ii. conditional branch

It is possible to select and execute an expression by determining the conditions in the following format.

```
if t < Lag then
        y = 0
elsif t < T then
```

```
        y = Dose A / Vd
else
        y = Dose / Vd Exp(- Ke (t -
endif   Lag))
```

When using if, then and endif cannot be omitted. In contrast, elsif and else are used only when necessary. Note that the comma "," is necessary to separate expressions, but is not necessary immediately before or after the control words then, elsif, else, and endif. In this case, from if to endif is considered a single expression. The above example can also be written as follows (i.e., the if statement has a value as an expression)

```
y =     if t < Lag then     0
        elsif t < T then Dose A / Vd
        else                Dose/Vd Exp(-Ke(t -
        Lag)) endif
```

iii. loop

Looping by conditional decision is possible in the following format.

```
c = 0,
while a < b and c < 100
    loop a += d,
    c += 1
endloop
```

When using while, loop and endloop must be placed. Loops can run indefinitely and get out of control if the conditions are not properly set. In the example above, c checks the number of times the loop is executed and exits the loop when the limit is reached in order to avoid such a danger. In the current version, there is no structure equivalent to for, do ~ while in the C programming language, for example. Also, functions equivalent to break and continue are not supported.

No, I don't.

iv. Conditions

Conditional decisions can be made using ==, <, >, <=, >=, <>, where a > b means a is greater than b, a >= b means a is greater than b, etc.

If a <> b, then a and b are equal or greater than a. If a <> b, then a and b are not equal. If if a then... and a variable in the condition is used, if a <> 0 then... if a <> 0 then... means the same as if a

==b then, if a and b are equal, then it is valid.

but this is written incorrectly as if a = b then

Note that this is interpreted to mean that a is satisfied if b is assigned to a and its value is not zero.

v. Combining conditions

The conditions are and, or and xor. and is when both A and B are true, and B is not evaluated unless A is true. and is the case where both A and B are true, and B is not evaluated unless A is true; or is the case where either A or B is true, B is not evaluated if A is true, xor is the case where only either A or B is true (exclusive or), and both A and B are always evaluated.

7.2.3. differential equation

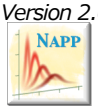
For the basics of defining expressions in differential equations, see the section on analytical expressions. In this section, we will discuss descriptions specific to differential equations.

A. Representation of Differentiation

In differential equations, if the dependent variable is y, it is necessary to define its derivative and to give an initial value for y. The derivative is expressed by appending a " to the name of the dependent variable, so it is basically entered in the form of equations (5)~(7).

B. @ statement

To give an initial value, we need to define a block of formulas to be executed only at time 0. Thus, a block of formulas to be executed only when time satisfies a certain condition



The following @ statements are used to delimit blocks. The @ statement begins with @ and ends with:. A valid block for an @-sentence is from the @-sentence to the @-sentence or from the @-sentence to the end.

i. @At T:

It will be executed only if the time is equal to T. Thus, the initial condition is @At 0:. Also, if instantaneous dosing occurs at time T, for example, it can be expressed as follows.

```
@At T:
  y += dose
```

The value of the derivative (y') cannot be referenced or assigned in the block of the @At statement.Note that if no initial value is given in the @At statement, the initial values of all compartments are assumed to be 0.

ii. @From T1 to T2:

It is only executed if the time is between T1 and T2. [to T2] can be omitted if not needed. In the @From: block, basically, the value of the dependent variable (y) is referenced and its derivative value (y') is defined. However, in a PK-PD model, it is also possible to define the value of the dependent variable itself. For example, compartments 1 and 2 could be defined as the blood and drug site compartments, respectively, and the concentration in compartment 1 could be given by a normal analytical expression, while the transition to compartment 2 would follow a non-linear differential equation.

For differential equations, from this block

It is essentially possible to refer to the value of an independent variable (e.g., t). It is also possible to set the lag time with the with statement as in the case of the Laplace transform equation, which will be discussed later. For example, @From T1 to T2 with time -= Lag: will shift the time axis by the amount of Lag.

time value can be referred to. Note that when the name of the independent variable is, for example, t, be careful not to set it like "with t -= Lag:".

7.2.4. Laplace transform equation

For the basics of defining expressions in Laplace transform equations, see the section on analytical expressions. This section describes the specifics.

A. Auxiliary Variable (s)

In a Laplace transform, the independent variable in the analytical expression (e.g., time t) undergoes a transformation and does not appear directly in the equation. Instead, a transformed auxiliary variable (e.g., s) is used. In other words, the Laplace transform equation defines the Laplace transform (Y) of the dependent variable (y) by the value of the apparent independent variable s. When performing the inverse Laplace transform calculation, s is treated as a complex number, but since Napp automatically performs the conversion to complex numbers and the computation of complex functions, the user is rarely aware o f this. However, the user is rarely aware of this, since Napp automatically performs the conversion to complex numbers and the computation of complex functions.

Anything special with numbers is not feasible with complex numbers. Normal quadratic calculations, exponents, logarithms, and trigonometric functions are not a problem.

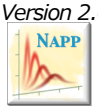
The following special functions can be used in Laplace transform expressions

dispersionModelClosed(Dn, s)

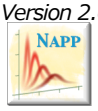
Define a diffusion model with a diffusion constant Dn. The boundary conditions are closed conditions (Dankwerts). Let s be s + K, where K is the vanishing rate constant.

B. @ statement

It is not possible to refer directly to the original independent variable (such as time t) in the Laplace transform equation. However, sometimes you may want to change the function defined by this value. This may be the case when a continuous dose is completed, or when the rate of disappearance changes. In this case, the



differential



You can use the same block definition by @From ~ to ~ : as described in the Cheng section.

Also, when considering lag time in the Laplace transform equation, it can be written as follows

@From T1 to T2 with time -= Lag:

This is a somewhat complicated issue that we will not go into in depth, but in general, the inverse Laplace transform is not good at computing models with lag time, which is both time consuming and computationally inaccurate. To avoid this, Napp performs the inverse Laplace transform without lag time and then adjusts the result to account for lag time, as described above.

Note that the inverse Laplace transform calculation has the drawback that it cannot compute values for time 0. To avoid this calculation error, Napp returns 0 for time 0 by default. If this is inconvenient for some models and you want to define a separate value for time 0, you can give the value of the dependent variable (y) in the @At 0: block.

8. menu reference

The menu reference describes the functions of the commands specified in Napp's menu.

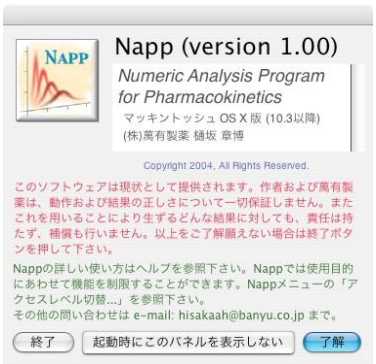
In Mac OS-X, if a shortcut key is defined in the menu, it is shown on the right side of each item. If you are familiar with the operation, try it.

8.1. Napp menu

It has the ability to show information about the program and make basic settings to suit your preferences.

8.1.1. About Napp

Displays an information panel. You can refer to information about the version of the application and its creator.



8.1.2. Preference...

Displays a preference panel for settings tailored to the user's intended use.

8.1.3. Set toolbar...

Shows the toolbar settings panel, which allows customization of the toolbar. Note that the toolbar can be shown or hidden by clicking the button in the upper right corner of the window. You can also change how the toolbar is displayed by clicking this button while holding down the Apple key.

8.1.4. Expert Settings...

This is the setting for the details involved in Napp's numerical analysis. Please be careful when changing this setting. This setting is available only if your access level is Expert or Administrator. For details of the settings, please refer to the tips when you move the cursor over the setting items in the panel.

8.1.5. Access level switching...

Switch access levels according to how Napp is used. Please refer to the panel description for each level.

To switch levels, select from the pop-up buttons, enter the password, and press the "Switch" button. Note that the current version does not have the password function on this screen.

8.1.6. Management...

This feature is not accessible in the current version.

8.1.7. Service

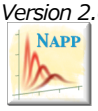
This is used when you want to process the selection with another program other than Napp. The functionality of this part depends on your computer settings.

8.1.8. Hide Napp

Temporarily hides the window related to Napp. To display it again, click on the Napp icon in the dock.

8.1.9. disappear completely, leaving nothing behind

Temporarily hides the windows of running applications other than Napp.



8.1.10. Show all...

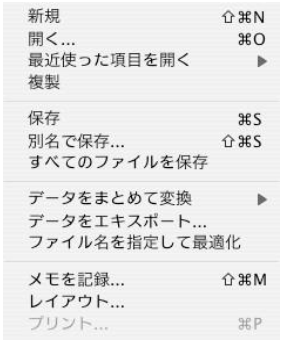
Displays all running application windows.

8.1.11. Exit Napp

Exit NappIf there is data being edited, a panel will appear asking if you want to save it.

8.2. File Menu

Manages the input and output of Napp data to and from files.



8.2.1. new

Open one new blank file.

8.2.2. Open...

Load data from an existing file. If the amount of data is large, loading may take a considerable amount of time.

8.2.3. Open recently used items

Select a recently saved file to load data.

8.2.4. duplication

Create a new file with the same contents as the file currently displayed in the foreground.

8.2.5. Save...

Saves information on the file currently displayed in the foregroundIf no file name is specified, you will be prompted to enter a file name.

8.2.6. Save as...

Saves the information of the file currently displayed in the foreground with a new file name.

8.2.7. Save all files...

Save all currently open files.

8.2.8. Optimize by file name

The software opens, optimizes, and saves the specified file(s). Multiple files can be specified, so it can be used to calculate a large number of filesBe careful to free up disk space when running the programIt is safer to have a few GB available, taking into account the amount of virtual memory used by the system.

8.2.9. Layout...

You can set the layout for report printing.

8.2.10. Print...

Prints the contents of the currently selected report. Allows you to set page and printer detailsA PDF file can be created by selecting an output destination. A preview can also be selected.

8.3. Sheet menu

Create new Napp sheets, enter titles, etc.

8.3.1. Insert new linear analysis sheet

Insert a new empty sheet for linear analysis next to the sheet currently displayed in the foreground.

8.3.2. Insert new nonlinear analysis sheet

Insert a new empty sheet for nonlinear analysis next to the sheet currently displayed in the foreground.

8.3.3. Insert a duplicate of the current sheet

Inserts one sheet with the same contents as the sheet currently displayed in the foreground.

8.3.4. Delete current sheet

Deletes the sheet currently displayed in the foreground. Note that this cannot be undone.

8.3.5. Separate the current sheet as a separate file

Opens a new window and moves the sheet currently in the foreground into it. The sheet will not remain in the current file.

8.3.6. Separate duplicates of the current sheet as separate files

A new window is opened and a duplicate of the sheet currently in the foreground is moved into it. The sheet will remain in the current file.

8.3.7. Separate the current sheet and its right side as separate files

Open a new window, including the sheet that is currently in front of it and (on the right).

sheets together and move them to a new location.

8.3.8. Separate all sheets into separate files

Separates each sheet contained in the file currently displayed in the foreground into a separate window. All will be treated as independent files. Although they are independent as files, they can be displayed simultaneously, but they cannot be analyzed together.

8.3.9. Merge all files into one file

Merge all files currently being edited into one. This is the reverse of the function described in the previous section, but at present this function has a bug and the titles will be displayed incorrectly after merging. Therefore, we do not recommend its use.

8.3.10. Separate sheets by subject

If the current sheet is populated with data from multiple subjects, this will be separated and assigned to separate sheets. The title of the sheet will be the subject number.

8.3.11. Merge all sheets in the current file into one sheet

Combines the data of the current file on a single sheet. This is the reverse of the function in the previous section. The model of each sheet must be identical.

8.3.12. Move the current sheet to the left edge

8.3.13. Move the current sheet one position to the left

8.3.14. Move the current sheet one position to the right

8.3.15. Move the current sheet to the right edge

It is used to move the currently displayed sheets to their respective locations and to arrange their order.

8.3.16. Enable/disable the current sheet

8.3.17. Enable the current sheet and its left side

8.3.18. Invalidate the current sheet and its left side

8.3.19. Enable the current sheet and its right side

8.3.20. Invalidate the current sheet and its right side

Enables or disables the specified sheets collectively. If disabled, the sheets will be excluded from overlays and also excluded from optimization calculations. The name of the disabled sheet is indicated by a prefix "*".

8.3.21. Enter the title of the sheet...

Set the title of the sheet. The entered title will be output in the report.

8.3.22. Go to the sheet on the specified page

Specify a page and navigate to the specified page.

8.4. Editing menu -

The Edit menu allows you to set up cut-and-paste and other functionsAll functions in this menu are OS-X standard.

8.4.1. cancel

Cancels the last edit operation performed on the data list.The name of this menu item changes depending on the type of operation performed.

8.4.2. redoing

Redo an edit operation on a data list that has just been undone. The item name in this menu is the name of the The type of operation depends on the type of operation that has been performed.

8.4.3. copy

Select to duplicate the selection.

8.4.4. cut

Cut out the selection and prepare for duplication.

8.4.5. paste

Paste (paste) the copied portion.

8.4.6. deletion

Delete the selection.

8.4.7. Select All

Selects the entire object. Useful for selecting the entire text.

8.4.8. font

Shows the submenu for font settings. Font and color settings are available for editable portions of the report.

8.4.9. Color panel...

Shows the color panel and sets the color settings.

8.4.10. Start reading out

Starts reading the selected text out loud. For more information about text-to-speech, see the Apple menu in the upper left corner of the screen.
System Preferences..." Speech" in the "System Preferences..." section.

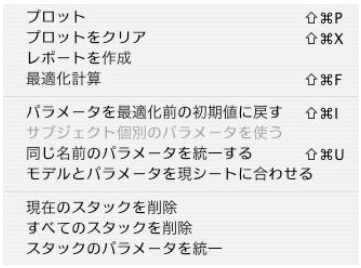
8.4.11. Stop reading

Stops the reading of running text.

8.5. Operation menu

Basic Napp operations such as plottingoptimization calculations, etc.

The main items in this menu can also be executed from the toolbar.
The main items in this menu can also be executed from the toolbar.



8.5.1. plot

If a sheet is the target, the graph is plotted according to the sheet's model, and the moment analysis results are output on the sheet. If the model is a Zline, a line graph is plotted.

In the case of the linear regression window, a linear regression calculation is performed and the results are output.

8.5.2. Clear Plot

Clear the plots of the target sheet. Clearing a plot clears the parameters, if any, that have been registered for each individual. If you have restricted the subjects or compartments to be displayed, this function will clear only the restricted subjects.

8.5.3. Clear all plot information

Erase all plots on the subject sheet, regardless of subject or compartment limits.

8.5.4. Create a report

The results of the analysis for the target sheet are output to the report panel. Note that for nonlinear least-squares optimization, a report is automatically output as soon as the calculation is completed. The contents of the report after the optimization calculation and other reports are different. The latter report focuses on the moment analysis.

8.5.5. Optimization calculation

Performs a nonlinear least squares parameter optimization (linear least squares is performed if the main linear regression window is selected). The current parameter values are registered as initial values and parameters will change during the optimization calculations. It is recommended to save the data once in a file before performing this operation, as the analysis may fail in some cases. Before proceeding, check that the settings for weights, algorithm, initial values of parameters, limits and fixes, etc. are correct.

Note the "Analysis Target" and "Optimization Method" settings in the toolbar.

8.5.6. Restore parameters to their initial values before optimization

Resets the parameter values modified by the optimization calculation to their initial values. The previous initial values can be viewed by toggling the parameter display on the sheet.

8.5.7. Use subject-specific parameters

To perform an optimization calculation with the "Analysis Target" in the toolbar set to an individual subject, you can calculate the parameters for that subject. However, these values are only for reference and cannot be edited or used in subsequent analyses. This command sets the value of the currently displayed parameter to a common value, rather than an individual subject value, and makes it available for use.

8.5.8. Unify parameters with the same name

If the "Target of Analysis" in the toolbar is set to "All Valid Sheets" or "Merge Valid Sheets", sheets that are not currently visible on the screen may be included in the analysis. Parameters with the same name must have the same value set for all these sheets, especially in the case of simultaneous optimization. This command unifies the values and settings of parameters with the same name for this purpose.

8.5.9. Match model and parameters to current sheet

The model and parameter values for all sheets in the current file are identical to those in the current sheet.

8.5.10. Delete current stack

Deletes the displayed stack of the current sheet.

8.5.11. Delete all stacks

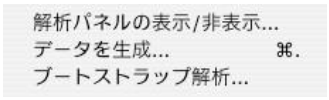
Deletes all stacks set up on the current sheet.

8.5.12. Unify stack parameters

Unify all stack parameters set on the current sheet with those shown.

8.6. Tools menu

The Tools menu contains a collection of functions that assist or extend Napp's functionality.



8.6.1. Show/hide analysis panel...

Shows or hides the analysis panel for the current file.This function can also be performed with the buttons at the bottom of the file's window.

8.6.2. Generate data...

Here is the panel for synthesizing the data with normal error according to the current model, see 4.12.

8.6.3. Bootstrap Analysis...

Compose data for bootstrapping by random sampling according to the data in the current sheet.

8.7. Property menu

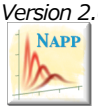
The Properties menu provides functions for outputting sheet properties in various formats.Properties include subject-specific variables (covariates) entered from the data list, parameter values and objective function values obtained from the analysis, AIC values, moment values, sheet number (page), and subject number. Variables entered from the data list are indicated with @ at the beginning of the word. Variance and standard deviation are also indicated by

The $, $$ prefixes the word.

If a sheet is targeted, only the current stack of the current sheet is searched for properties. Properties are searched by subject, and if limited by the subject field of the sheet, output is for valid subjects. When selecting a property

If "Use standard values for missing" is checked, the value of the corresponding property for a subject with no entry in the data list will be the value entered in the parameter field if the variable entered from the data list is identical to the parameter and the parameter is fixed (fix).

When targeting stacks, all stacks in the current sheet are searchedSubject properties are ignoredFile targets the valid nonlinear analysis sheets in the current fileSubject properties are ignored.



8.7.1. Report individual values...

Outputs individual property values to the report.

8.7.2. Reports mean and standard deviation...

Calculates the mean and standard deviation and CV of a property and outputs the results in a report.

8.7.3. Report correlations between each other...

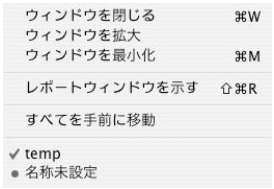
Select multiple properties, analyze the correlations between them in a round-robin fashion, output the results in a report. It also outputs the mean and standard deviation for each property.

8.7.4. Plot a pair of correlations...

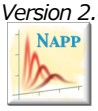
Select two properties and create a new linear analysis sheet to show the correlation between them.

8.8. Window menu

This menu controls the window display.



The function of this menu is obvious and will not be explained here. Note that when a new file is opened, an item is added here that shows the window in front of it, so if a window is missing, you can use this menu to find it.

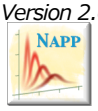


9. thanks

We would like to thank Professor Yuichi Sugiyama and Associate Professor Yoshiyuki Kusuhara of the Department of Molecular Pharmacokinetics, Faculty of Pharmaceutical Sciences, the University of Tokyo, Professor Yusuke Tanigawara of Keio University School of Medicine, and Dr. Hidefumi Kasai, currently at Bellsystem 24, as well as many others, for their advice in preparing this program. I would like to express my sincere gratitude to all of them. I am also grateful for the cooperation of many people at the former Drug Metabolism Research Institute and Clinical Pharmaceutical Research Institute of Banyu Pharmaceutical Co. I would like to take this opportunity to express my gratitude. I would also like to express my deepest gratitude to Professor Hiroshi Suzuki and his staff for their strong support of my research after I moved to the University of Tokyo Hospital.

Napp's numerical routines were created by referring to the books and other reference materials listed in the referencing section. We would especially like to thank Associate Professor Kiyoshi Yamaoka of the Faculty of Pharmaceutical Sciences, Kyoto University, for his pioneering work in this area of analysis programming, as well as all those involved.

Some of the icons used in this program were obtained from the Internet. Thanks to Samuel Krueger (http://homepage.mac.com/pixeljerk link is currently disabled) and Adrian Jean (http://mac.axonz.com).



10. About the creator

Akihiro Hisaka

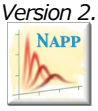
Associate Professor, Department of Pharmacokinetics, 22nd Century Medical Center, The University of Tokyo Hospital

7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan e-mail: hisaka-tky@umin.ac.jp

http://www.h.u-tokyo.ac.jp/research/center22/contribute/yakuri.html

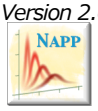
He graduated from the Faculty of Pharmaceutical Sciences, Hokkaido University in 1982 and received his M.D. in 1984, and worked for Banyu Pharmaceutical Co. In 2005, he became a lecturer at the Department of Pharmacy, University of Tokyo Hospital, and in 2007 he was appointed to his current position. He has been actively engaged in research activities, including 27 original papers in English cited in PubMed and about 10 presentations at academic conferences per year while engaged in medical care and education.

Lives in Moriya City, Ibaraki Prefecture.



11. reference

1. Kiyoshi Yamaoka and Yusuke Tanigahara, "Introduction to Drug Kinetics by Microcomputer," Nankendo
2. Kiyoshi Yamaoka, "Drug Kinetic Analysis by Microcomputer" (1984), Nankendo
3. Masatake Mori, "Numerical Programming" (1986) Iwanami Shoten
4. Numerical Fluid Dynamics" edited by Mitsuru Yasuhara and Hisaaki Omiyaji (1992) University of Tokyo Press
5. Ryohei Hori (ed.), Introduction to **Population Pharmacokinetics** (1988), Yakuji Jihosha Co.
6. Manabu Hanano (ed.) "Pharmacokinetics: An Introduction" (1987) Nanzando
7. Manabu Hanano (ed.), Pharmacokinetics, Applications (1989) Nanzando
8. Sugiyama, Yuichi, ed. "Pharmacokinetics: Methods and Techniques of Research" (1993) Japanese Society for Pharmacokinetics and Pharmacodynamics
9. S. L. Beal, L. B. Sheiner, A. J. Boeckmann, "NONMEM User's guide", NONMEM Project Group: University of California, San Francisco, (1998).
10. A. Hisaka and Y. Sugiyama, "Analysis of nonlinear and nonsteady state hepatic extraction with the dispersion model using the finite difference method", Journal of Pharmacokinetics & Biopharmaceutics, (1998), **26**, 495-519.
11. T. Iwatsubo, A. Hisaka, H. Suzuki and Y. Sugiyama, "Prediction of in vivo non-linear first-pass hepatic metabolism of YM796 from in vitro metabolic data ", Journal of Pharmacology & Experimental Therapeutics (1998), **286**, 122-7.
12. A. Hisaka, T. Nakamura and Y. Sugiyama, "Analysis of nonlinear hepatic clearance of a cyclopentapeptide, BQ-123, with the multiple indicator dilution method using the dispersion model", Pharmaceutical Research (1999), **16**, 103-9.
13. A. Hizaka, T. Yasumori, and Y. Tanigahara, "Absorption kinetic analysis by the drug kinetics program **Napp**," Clinical Pharmacology (2002), **33**, 137-8S.



12. Update record

Version 2.00: September 1, 2010　　September 1, 2010

Used in demonstrations at the 3rd Japan Pharmacometrics Research Meeting

Version 2.00 → 2.01 : September 13, 2010　　September 13, 2010

Fixed bug when inserting duplicate sheets for non-linear models with no parameters Fixed colors for parameter tilt simulations
Fixed a bug that prevented deleting the first stack of drawing options for moment extrapolation lines.
Fixed a bug that prevented stack information from being read from files
Organize "optimization method" and "analysis target" options
Allows direct reference to independent variables from differential equations