

PLT Tools

A Graphical Interface for the NONMEM System

Examples

Version 4

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Introduction

PLT Tools is a set of utilities to run NONMEM,* manage files, create diagnostic graphics, and manage projects. **PLT Tools** does not replace NONMEM. The user must install NONMEM (which must be preceded by installation of a Fortran compiler). NONMEM software can be licensed from Globomax (www.icondevelopment.com). Fortran compilers are available commercially or *via* free download (g95.org, sourceforce.net).

The First Installation and Upgrade downloads for **PLT Tools** include examples so that the user can run **PLT Tools** immediately. There are five folders, each of which illustrates different features of **PLT Tools**. The folders and subfolders are listed in Table 1.

In one folder NORMALNONMEMEXECUTION, NONMEM has been run on all the control streams; the user can review the file structure to see the various outputs. In addition, the Compare Runs and Create Archive procedures have been run. The user can review the outputs of these procedures in the POSTPROCESSING subfolder.

The remainder of this document takes the user through a step-by-step approach to using **PLT Tools**. Throughout this manual, files, folders, and operating system commands are displayed in a fixed-width font, Courier. **Buttons** in the GUI are displayed in a box with a yellow background. Note that graphics that appear in this document are obtained from the OS X version of the software. The application will appear slightly different in Windows and Linux.

Before running these examples, three steps must be performed:

1. A Fortran compiler must have been installed.
2. NONMEM must be installed. If NONMEM is already installed successfully on your computer, step #1 is also complete.
3. **PLT Tools** must be installed on your computer. See PLT Tools – Installation Manual for step-by-step instructions for Installation.

* NONMEM is a trademark of the Regents of the University of California.

Table 1. Examples provided for **PLT Tools**.

1. PLTTOOLS.FIRST.RUN: This folder contains a single control stream. The user should run this control stream to confirm that **PLT Tools** is installed correctly.
2. NORMAL.NONMEM.EXECUTION: This folder contains control streams for a simulation and for analysis using a one-compartment model and a two-compartment model.
3. VISUAL.PREDICTIVE.CHECK: This folder contains a control stream that is similar to the 2-compartment model in NORMALNONMEMEXECUTION; however, the initial estimates have been changed to the final estimates from the analysis. In addition, \$SIMULATION is used instead of \$ESTIMATION.
4. BOOTSTRAP-JACKKNIFE: This folder contains two control streams that are similar to the 2-compartment model in NORMALNONMEMEXECUTION.
6. LIKELIHOOD.PROFILE: The folder contains a different control stream and a different dataset from the folders above.
6. FEATURES: This folder contains three sub-folders:
 - A. AUTOMATION: Two scripts are provided to automate the use of **PLT Tools**. Note that there are separate folders for Windows and OS X/Linux.
 - B. CONTROLSTREAMandDATAISSUES: This folder contains three control streams. Two of these illustrate situations in which NONMEM creates ambiguous information in tables that prevents **PLT Tools** from creating graphics. A third control stream demonstrates how **PLT Tools** displays error messages from NMTRAN in a separate window.
 - C. GRAPHICSISSUES: This folder contains eight subfolders:
 - i. ChangingXLabelYLimits: This example demonstrates two features:
 - a. The default x-label for graphics in PLT Tools is typically “Time (units)”. However, if appropriate, this can be changed.
 - b. Limits for the y-axis are generated using rules generally appropriate for PK data (lower limit is zero in linear graphics, LOQ/2 in log graphics; upper limit is determined from the data). If these limits are not appropriate (*e.g.*, PD data in which the range of values is narrow and not close to zero), modifications of the control stream can signal PLT Tools to adjust these limited. Sample code is provided.
 - ii. CrossoverExperiment-DifferentFormulations: The graphics script for **PLT Tools** is designed to accommodate crossover experiments, *e.g.*, comparison of formulations or food effect studies. Sample code is provided.
 - iii. Dataset-ADDL-II. Doses indicated via “ADDL” records, are displayed differently by **PLT Tools** compared to doses entered in the normal manner. An example is provided.

- iv. DisplayIDSinCertainGraphics: Goodness of fit graphics, in which data from multiple subjects are displayed, typically do not display subject IDs. An option in the Graphics Editor allows **PLT Tools** to create additional graphics in which IDs are displayed. These graphics are useful for identifying outlier subjects.
- v. DisplayTimeAfterDose: Spaghetti plots typically reference sample time using the TIME entries in the dataset or to the beginning of a period (if the Multiple Periods option is selected).
- vi. TakeLogBothSides: If an analysis is performed in which the (natural or base 10) log is entered in the dataset, PLT Tools can transform these logged values to the linear domain, then display them on linear \pm log scales. An example is provided.
- vii. UseOfPeriodsInGraphics: Graphics for **PLT Tools** are designed to optimize the display of data from a variety of study designs. If each of two or more doses are followed by intense sampling but the doses are separated by a length interval (*e.g.*, doses on day 1 and 10, 24 hours of sampling at each of these doses), then typical graphics will have extensive white space. **PLT Tools** can create graphics in which the sampling intervals occupy an entire panel, thereby minimizing white space. An example is provided.
- viii. UserDefinedGraphics: A user may need graphics other than those in the large suite of graphics provided the **PLT Tools**. These graphics can be created as part of the routine process for **PLT Tools** and can have the same general format, include headers, footers, and timestamps. This is accomplished with “User-Defined Graphics” in which the user write a script in R / S-Plus. An example is provided; if a user is not facile with the use of R / S-Plus, scripts can be provided by PLTsoft on a contractual basis.

Setting Up **PLT Tools**

These steps must be performed before NONMEM can be run *via* **PLT Tools**.

1. Open the graphical interface for **PLT Tools**.
2. In the File menu, open Preferences and navigate to the Settings tab. Use the Select button to navigate to the correct path for R or S-Plus, then select the appropriate "Language to Use". Details are provided in the Installation Manual.
3. Decide whether to use the automated or manual approach to **PLT Tools**.
4. The first time that **PLT Tools** attempts to run NONMEM, it will search for a file nmfe6.bat (nmfe in OS X/Linux). If the file is located in the default location, the procedure will be rapid and messages will be sent to the user communicating that installation was completed successfully. However, if the file cannot be located and/or copied to the PLTTools folder, NONMEM cannot be executed. Messages will be provided to the user to explain how to complete the installation.

Running NONMEM – Automated Approach

PLT Tools includes an "automation" tool. This tool is designed to allow users to create lists of runs, then perform these runs in sequence. The automation tool is also useful for introducing a user to the many features of **PLT Tools**. Automation also allows the user to see **PLT Tools** "in action" and to learn of its many features. To "take a tour" of **PLT Tools**, do the following:

1. Make sure that the folder PLTTools-Examples is on your Desktop. This was the default destination during the installation procedure.
2. Open the folder PLTTools-Examples, then navigate to the folder FEATURES/AUTOMATION. In addition to a Word document describing use of automation, you will find two folders containing automation scripts, one for Windows, the other for OS X and Linux. Open the folder appropriate for your platform.
3. Right-click (option-click in OS X) on either of the files. Select "Open With" from the dialog box, then navigate to (and select):

Windows:	C:\Program Files\PLTTools\PLTTools.exe
OS X:	/Applications/PLTTools/PLTTools.app
Linux:	/Applications/PLTTools/PLTTools
4. Two windows should appear: the main **PLT Tools** window and a window showing the contents of the automation script. The automation script should then be executed. When a NONMEM run completes, dialog boxes sometimes appear to communicate messages to the user. These dialog boxes need to be dismissed before **PLT Tools** continues to the automation step.

Running NONMEM – Manual Approach

1. Return to the Workspace/Options window. Pull-down the Working Folder, then navigate to:
Windows: [DESKTOP FOLDER]\NORMALNONMEMEXECUTION\WORKING
Linux, OS X: [DESKTOP FOLDER]/NORMALNONMEMEXECUTION/WORKING
where [DESKTOP FOLDER] is your Desktop folder. Once you have done this, the path will be remembered, permitting to you select that path from the pull-down menu.
2. Examine the Output window at the bottom of the interface; look for error messages.
3. Move to the Project Controller tab. Pull down the “Control Stream” menu to select a control stream.* If the folder contains only one control stream, that file will be selected automatically by **PLT Tools**. You can examine the control stream by clicking the **Edit** button.
4. Optional: Pull-down the “Graphics Script” menu. Select `GraphicsScript.pltg` (depending on your system settings, the extension may not appear). If the folder contains only one Graphics Script, that file will be selected automatically by **PLT Tools**. If a Graphics Script is not selected, **PLT Tools** will attempt to prepare default graphics. These default graphics can be replaced by user-specified graphics at a later time by clicking the "Graphics Only" button.
5. Click the button **NONMEM + Graphics**. NONMEM should run. At completion, three files should open automatically, graphics, an abbreviated version of the NONMEM outputfile, and a brief summary of the parameters of the NONMEM run. These files may not open automatically in Linux installations. In they do not open automatically in Windows, it is likely that you do not have Acrobat Reader installed on your computer.
6. Using tools appropriate for your operating system, examine the files that were created in the TEXTFILES, TABLES, PDF, and GRAPHICS folders in the project folder NORMALNONMEMEXECUTION.
7. Return to the Project Controller. Select the second control stream, `Analyze-2Compartment.txt`.
8. Return to the Project Controller and repeat step 7. You have now completed two runs using **PLT Tools**. You can repeat these steps with two additional control streams:
`Analyze-2CompartmentWithCovariate.pltc`
`Simulate-2Compartment.txt`.


* All text files will be listed, regardless of their extension (NONMEM requires that the control stream be a text file). Thus, control streams can be named with an extension, e.g., .ctl, .con, or .txt.

Comparing Runs

1. Once two or more runs are complete, one can evaluate the Compare Runs tool. Click on the Compare Runs tab.

2. Click the **Edit Run Listing** button. This will open the Run Listing Editor. Populate the Run Listing Editor in the following manner:

Row 1: In the first column, use the pull-down menu to select the timestamp of your first run (*e.g.*, the 1-compartment model). Add a comment to the third column (*e.g.*, “One-compartment model”). It is appropriate to omit entries in the second and third columns.

Row 2: Use the  button on the upper right to add a row. In the first column of that row, use the pull-down menu to select the timestamp of the second run (*e.g.*, the 2-compartment model). In the second column, select the timestamp of the first run (*i.e.*, so that you compare the 2-compartment model to the 1-compartment model). In the third column, enter 4 (there are four additional parameters in the 2-compartment model, 2 *thetas* and 2 *omegas*; if you disagree with that assessment, you are welcome to enter any other integer value). In the fourth column, enter text such as “Two-compartment model”.

Close the Run Listing Editor.

3. Click Compare Runs. Examine the Output window for messages.

4. Once the comparisons are complete, a folder containing the results should open automatically. If not, access your file system using appropriate system tools to examine:


Windows: NORMALNONMEMEXECUTION\POSTPROCESSING\COMPARE

Linux, OS X: NORMALNONMEMEXECUTION/POSTPROCESSING/COMPARE

Creating an Archive

1. Once two or more runs are complete, one can evaluate the Create Archive tool. Click on the Create Archive tab.
2. This step is not needed if you performed it already (see #2 in “Comparing Runs”). Click the **Edit Run Listing** button. This will open the Run Listing Editor. Populate the Run Listing Editor in the following manner:

Row 1: In the first column, use the pull-down menu to select the timestamp of your first run (the 1-compartment model). Add a comment to the third column (*e.g.*, “One-compartment model”). It is appropriate to omit entries in the second and third columns.

Row 2: Use the  button on the upper right to add a row. In the first column of that row, use the pull-down menu to select the timestamp of the second run (*e.g.*, the 2-compartment model). In the second column, select the timestamp of the first run (*i.e.*, so that you compare the 2-compartment model to the 1-compartment model). In the third column, enter 4 (there are four additional parameters in the 2-compartment model, 2 *thetas* and 2 *omegas*; if you disagree with that assessment, you are welcome to enter any other integer value). In the fourth column, enter text such as “Two-compartment model”.

Close the Run Listing Editor.
3. Click Create Archive. Examine the Output window for messages.
4. Once the comparisons are complete, a folder containing the archive should open automatically. If not, access your file system using appropriate system tools to examine:

Windows: NORMALNONMEMEXECUTION\POSTPROCESSING\REPOSITORY

Linux, OS X: NORMALNONMEMEXECUTION/POSTPROCESSING/REPOSITORY

Congratulations. You are now ready to work on your own examples.