NM-Win: A Personal Computer-Based Microsoft® Windows™ Front-End to NONMEM IV

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A Microsoft Windows-based front-end, NM-Win, has been written to provide a more user-friendly environment to do nonlinear mixed effect modeling with the NONMEM program. NM-Win utilizes an object-oriented interface design which allows users to view and edit control, PRED, and/or data files using Windows Notepad. In addition, calls made to the Microsoft FORTRAN compiler and linker which generate the final NONMEN executable are performed simply by clicking the "Run NONMEN" button. During the executive step, iterations can be viewed in a window to check the progress of the run. Errors encountered while NONMEN or NM-TRAN is running are brought to a window for ease in debugging. Advanced options allow the user the flexibility of compiling user-written PRED files and creating linker response files. While the PC platform is not optimal for large data set or complex models, it does permit easier debugging and offers multitasking while Windows is running.

KEY WORDS: NONMEM; front-end; personal computer (PC); Microsoft Windows.

INTRODUCTION

The program NONMEM, a nonlinear mixed effects modeling algorithm, has been developed and made available by the NONMEM Project Group at the University of California at San Francisco since the late 1970s (1). Several other programs which provide some form of nonlinear mixed effect modeling algorithm have been written since then; these include NPML (2), NPEM (3), the EM algorithm with and without the Gibbs sampler routine (4–6), and MIXNLIN (7). New algorithms such as POPKAN (8) and P-Pharm (9), among others, are currently in development and offer more user-friendly interfaces. Of these, however, NONMEM remains the most widely used computational tool to analyze nonlinear mixed effect models. It is well supported, extensively tested, and continuously updated.

While the NONMEM Project Group has done an admirable job of periodically updating the source code, many users still point to difficulties in running the program as a necessary hurdle for new users. To this end the NM-Win program (copyright 1993, Merck & Co.), a front-end to the NONMEM source code, takes advantage of the accessibility and user-friendliness of the modern personal computer (PC) as well as the graphical user interface (GUI) of the Microsoft® Windows™ environment. The speed limitations of the current PCs prohibit the use of this platform for analyzing large data sets or complex models; the goal of this front-end has always been to create an efficient, user-friendly environment for debugging NM-TRAN control and/or NONMEM PRED files and subsequently running the error-free code on a faster platform. As newer PCs are approaching workstation-like speed, the need for alternative platforms may be diminished. The current version of NM-Win is designed to work with NONMEM IV and the Version 1.1 upgrade (with single GENER.FOR file) supplied by the NONMEM Project Group but should work with older versions of NONMEM as well.

METHODS

NONMEM Source Code: Directory Structure

The original NONMEM source code is distributed as 12 files—4 double precision-specific files, 4 single precision-specific files, 2 precision-independent versions, and 2 data files. With the exception of the two data files, each individual file contains several subroutines (over 150 in some cases). The file SEP.FOR (10) is included with the source code to separate these files easily into their individual subroutines. To compile NONMEM for use with the Microsoft FORTRAN compiler, the source files were first separated and placed in subdirectories for organizational purposes. Figure 1 shows an example directory structure. The batch files included with NM-Win use the subdirectory names listed in Fig. 1 to find the source code, but the files can be placed in any directory if the batch files are not used or changed.

NONMEM Source Code: Compilation Using Microsoft FORTRAN v. 5.1

The subroutines in these files, including all the files needed for the NONMEM executable and the NM-TRAN executable (the NONMEM preprocessor), are written in FORTRAN 77. These files may be compiled with any FORTRAN compiler that supports the ANSI FORTRAN 77 standard. The files included are specific for a UNIX system, but the documentation provided by the NONMEM Project Group (10) outlines the necessary changes required to port to another platform. The main changes needed to be made when porting from one system to another are machine-specific constants, which are easily located in the BLKDAT.FOR file for NONMEM and the ABLOCK.FOR file for NM-TRAN. The platform specific constants in these two files were modified to be specific for the PC.

Further modifications were necessary to allow NONMEM and NM-TRAN to run as a Microsoft Windows application. Changes were made to the files BLKDAT.FOR, CFILES.FOR, NONMEM.FOR, OBJ.FOR, and OFILES.FOR in the NONMEM subdirectory and the files ABLOCK.FOR, CFILEX.FOR, ERRMSG.FOR, NMTRAN.FOR, and OFILEX.FOR in the NMTRAN subdirectory. These changes were necessary to permit NONMEM and NM-TRAN to use Microsoft FORTRAN QuickWin libraries. The QuickWin

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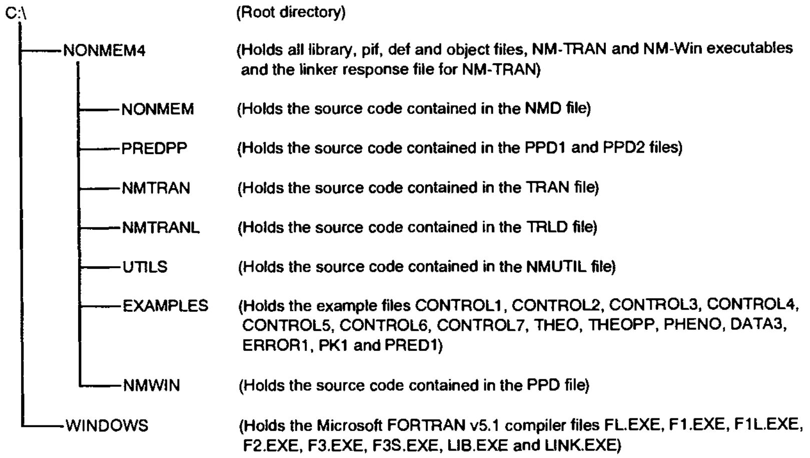


C:\ (Root directory)

NONMEM4 (Holds all library, pif, def and object files, NM-TRAN and NM-Win executables and the linker response file for NM-TRAN)

NONMEM (Holds the source code contained in the NMD file)

PREDPP (Holds the source code contained in the PPD1 and PPD2 files)

NMTRAN (Holds the source code contained in the TRAN file)

NMTRANL (Holds the source code contained in the TRLD file)

UTILS (Holds the source code contained in the NMUTIL file)

EXAMPLES (Holds the example files CONTROL1, CONTROL2, CONTROL3, CONTROL4, CONTROL5, CONTROL6, CONTROL7, THEO, THEOPP, PHENO, DATA3, ERROR1, PK1 and PRED1)

NMWIN (Holds the source code contained in the PPD file)

WINDOWS (Holds the Microsoft FORTRAN v5.1 compiler files FL.EXE, F1.EXE, F1L.EXE, F2.EXE, F3.EXE, F3S.EXE, LIB.EXE and LINK.EXE)

Fig. 1. Directory structure for NM-Win installation on the PC.

libraries allow normal FORTRAN programs to be quickly converted and compiled to run as Windows applications.

To avoid conflicts in file name references, all files in the NM-TRAN library subdirectory had "TR" appended to the prefix of their filename. Other significant modifications and/or optimizations are slightly harder to make due to the fact that the source code is mostly undocumented. Once the changes were made, the source code was compiled using the Microsoft FORTRAN v. 5.1 compiler FL.EXE. When compiling, several compiler options were used to help speed up execution and minimize executable and run-time size, although speed optimization was stressed. The compiler switches that were used are described in Table I. It must be noted that the file GENER.FOR was compiled with special switches and used a different part of the compiler to deal with the subroutine's excessive size. The "/Ox" switch was replaced with the switches "/Od" and "/B3" as indicated in Table I. The "/B3" switch is an undocumented switch suggested by Microsoft Support personel to use a larger capacity compiler for the third pass of the compile process.

Table I. Microsoft FORTRAN Compiler Switches Used to Compile the NONMEM Source Code on the PC

Switch	Function
/c	Compiles the subroutine without linking it
/G2	Generates 80286 chip instructions
/Gt	Places data items greater than or equal to 256 bytes in a new segment. This option is needed since NONMEM uses large data items that occasionally cause compilation and linking problems
/Gw	Creates Windows-compatible object code
/MW2	Creates a Windows-like program with yield statements inserted on subprogram entry
/nologo	Suppresses displaying of the Microsoft logo during compilation
/Ox	Enables full optimization including loop optimization and improved consistency of floating-point results and removes stack probes from the program
/W0	Suppresses warning messages when compiling
/Od[a]	Disables all optimizations and leaves stack checking on
/B3[a]	Invokes a different phase of the compiler to deal with the huge size of the GENER.FOR subroutine

[a] Used only for compilation of the GENER.FOR file.

After the files were compiled, a library was created for NONMEM, which contained all the files in the NONMEM subdirectory except NONMEM.OBJ and BLKDAT.OBJ. These files are not placed in the library since they are required in the linker response file. The NONMEM.OBJ file contains the entry point to the executable and the BLKDAT.OBJ file contains constants used by almost all the NONMEM files. Libraries were also created for each individual file in the PREDPP and NM-TRAN Library directories. These libraries were used to help group related subroutines together, separate subroutines with identical entry points, minimize the number of lines needed in the linker response file, and also minimize the size of the final executable by not including routines that are not needed for the final NONMEM executable (but might be for other NONMEM executables). The Microsoft library utility, LIB.EXE, was used to create these libraries.

Finally, NM-TRAN was linked into an executable using the Microsoft Linker, LINK.EXE. The linker options used to create the executable are listed in Table II. Batch files were created to automate the task of compiling the files, building the libraries, and creating the executables. Using these batch files helps speed both the initial setup and the rebuilding of the files if changes are made to the source code. A linker response file was also created for the NM-TRAN executable and Windows PIF (Program Information Files) files were created for using the compiler and linker in DOS windows.

NM-Win Code: Form and Structure

NM-Win is a Microsoft® Windows™ application that acts as a front-end to NONMEM as mentioned previously. NM-Win was written using Microsoft® QuickC v. 1.0 for Windows™. Once the control file and data file have been created, NM-Win handles running NM-TRAN, compiling the user-written and NM-TRAN-generated subroutines, creating a linker response file, linking the final executable, and running the final executable. The individual steps required for a complete NONMEM run are minimized to pushing a

Table II. Microsoft® FORTRAN™ Linker Switches Used to Create NM-TRAN Executable on the PC

Switch	Function
/BATCH	Suppresses prompts for library or object files not found and instead generates warning and error messages
/NOD	This option was used with "LLIBFEW" after it to specify that the linker is to ignore default libraries named in .OBJ files when link is searching libraries to resolve references
/NOF	Turns off far call translation which interferes with segmented executable files
/PACKC	Packs neighboring code segments together into one segment if the combined size is less than 64k minus 36 bytes
/PACKD	Packs neighboring data segments together into one segment if the combined size is less than 64k
/SEG:512	Sets the maximum number of segments to 512 from the default 128; more segments are needed to link larger segments but also slows down linking

few buttons. These steps can also be completed individually and with full flexibility using the Advanced Options.

Most code was written automatically by using QuickCase:W, a CASE (Computer Aided Software Engineering) tool for designing the windows, menus, linked resources, and general appearance. The Dialog Editor was also used to design the dialog boxes and child windows used in the application. Once the dialog boxes and menus were designed and the code was generated by QuickCase:W, the remaining code was written and expanded as needed. While the source code and subsequently generated compiled code is comprised of the 23 files shown in Table III, only the final executable, NMWIN.EXE, is needed to run NM-Win.

RESULTS AND DISCUSSION

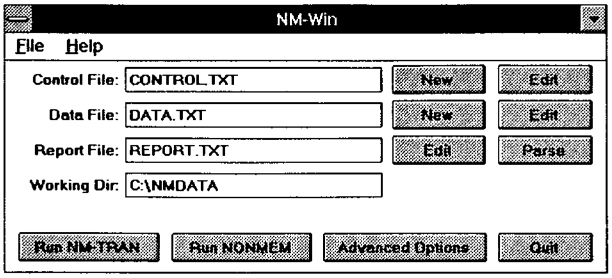
Using NM-Win

After starting NM-Win from the Windows Program Manager, the user is presented with the main NM-Win dialog box as shown in Figure 2. This dialog box will allow the user to handle most steps of completing a NONMEM run with the push of a few buttons. First, the control and data files must be written. After typing the names of the control file, data file and working directory, clicking on the new button next to either the control file or the data file will bring up Windows Notepad and allow the user to enter the file. Then, by saving the file and exiting from Notepad, the user is returned to the dialog box. After specifying a report file in the text box next to the report file label, the user is ready to run NM-TRAN.

By clicking on the "Run NM-TRAN" button, NM-Win loads NM-TRAN and passes the control and data file through it. If no errors are found in either file, NM-TRAN creates the files FCON.DAT, FDATA.DAT, FLIB.DAT,

Table III. List of Files in NM-Win

File	Description
NMWIN.C	Main C source code file created by QuickCase:W and expanded for improved usability
NMWINSUB.C	C source code file that contains subroutines used by NMWIN.C
NMWIN.DEF	Module definition file containing a list of modules to import and export
NMWINABT.DLG	Description file for the "About Box" dialog box
NMWINADV.DLG	Description file for the "Advanced Options" dialog box
NMWINRUN.DLG	Description file for the main NM-Win dialog box
NMWIN.EXE	Executable that is run to load NM-Win
WINSTUB.EXE	Windows stub file to display an error message if the file is loaded under DOS
NMWIN.H	Header file for declaring constants, global variables, and function prototypes
NMWIN.ICO	Application icon; also used in "About Box"
MERCK.ICO	Icon used in "About Box"
NMWIN.MAK	Makefile used by the QuickC compiler to decide which files to compile, in which order, and with which options
NMWIN.MAP	File containing memory locations of the various functions in the NM-Win executable
NMWIN.MDT	File used to store incremental compile information
NMWIN.OBJ	Compiled object file for NMWIN.C
NMWINSUB.C	Compiled object file for NMWINSUB.C
NMWIN.RC	Windows resource script file used to hold information on various resources used by NM-Win such as bitmaps, icons, etc.
NMWIN.RES	Compiled resource file for NMWIN.RC
NMWINABT.RES	Compiled resource file for NMWINABT.DLG
NMWINADV.RES	Compiled resource file for NMWINADV.DLG
NMWINRUN.RES	Compiled resource file for NMWINRUN.DLG
NMWIN.WIN	A file containing the window and menu prototypes
NMWIN.WIR	Compiled window and menu prototype file for NMWIN.WIN



Control File: CONTROL.TXT

Data File: DATA.TXT

Report File: REPORT.TXT

Working Dir: C:\NMDATA

Fig. 2. The initial NM-Win dialog box presented to the screen when the program is launched.

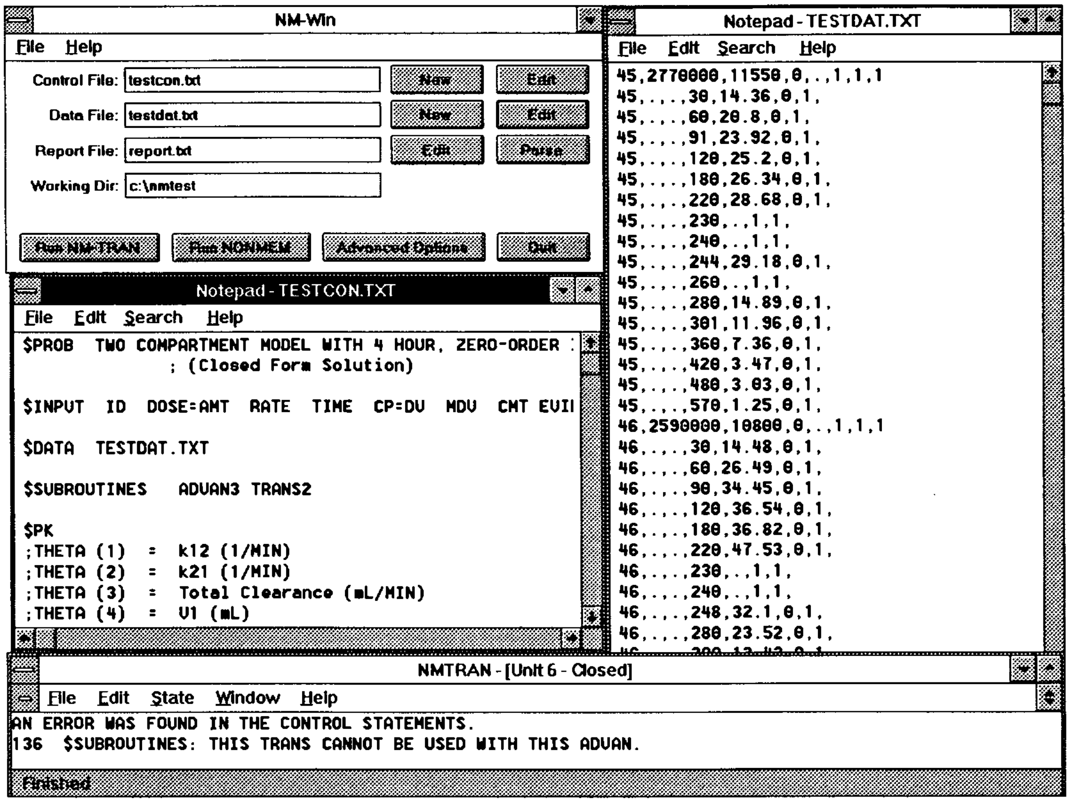
FREPORT.DAT, FSTREAM.DAT, AND FSUBS.FOR, all of which are used to create and run the final NONMEM executable. When NM-TRAN finishes execution, the QuickWin libraries present the user with a dialog box giving the choice of leaving the application on the screen or removing it from both the screen and memory. The user should now close the NM-TRAN window by clicking on the "Yes" button.

If errors are encountered in either the control file or the data file, the user can easily edit these files. The user should first click "No" in the QuickWin message box and then resize the window to take up only part of the screen. By reactivating the NM-Win dialog box (by using one of Windows several methods of switching applications) and then clicking on the edit button next to the file that has errors, NM-Win will load the file into Notepad. Then, as shown in Fig. 3, by resizing Notepad to another part of the screen than NM-TRAN, the user can edit the control and/or data files and view the error message at the same time. Once the errors have been corrected, the user can save the modified files, exit Notepad, close the NM-TRAN window, and try running NM-TRAN again by clicking on the "Run NM-TRAN" button.

Once the control and data files have been debugged, the user is ready to construct a NONMEM executable and run it. By clicking on the "Run NONMEM" button shown in Fig. 3, several steps are completed as shown in Fig. 4. First, the FSUBS.FOR file is compiled by the Microsoft FORTRAN compiler into an object file. Second, NM-Win analyzes FREPORT.DAT to determine which libraries and object files need to be included in the NONMEM executable. From this information, NM-Win constructs a linker response file which tells the Microsoft Linker which files to include and how to build the NONMEM executable. Once the executable has been linked, NM-Win loads the executable and passes the name of the modified control file, FCON.DAT in most cases, and the name of the report file to it. The NONMEM executable will now run until complete. Run times can be substantial, depending on the model used and the speed of the processor.

NM-Win's Advanced Options

NM-Win also contains an "Advanced Options" dialog box, shown in Fig. 5, which allows the user to complete most steps individually. These features allow the creation of user-written PRED files, bypassing NM-TRAN. The "Edit" and "Compile" buttons next to the subroutines text box allow you both to edit the user-created and NM-TRAN-



Control File: testcon.txt

Data File: testdat.txt

Report File: report.txt

Working Dir: c:\nmtest

```
$PROB  TWO COMPARTMENT MODEL WITH 4 HOUR, ZERO-ORDER :
                ; (Closed Form Solution)

$INPUT  ID  DOSE=AMT  RATE  TIME  CP=DV  MDV  CMT EVII

$DATA  TESTDAT.TXT

$SUBROUTINES   ADVAN3 TRANS2

$PK
;THETA (1)  =  k12 (1/MIN)
;THETA (2)  =  k21 (1/MIN)
;THETA (3)  =  Total Clearance (mL/MIN)
;THETA (4)  =  V1 (mL)
```

```
45,2770000,11550,0,.,1,1,1
45,....,30,14.36,0,1,
45,....,60,20.8,0,1,
45,....,91,23.92,0,1,
45,....,120,25.2,0,1,
45,....,180,26.34,0,1,
45,....,220,28.68,0,1,
45,....,230,.,1,1,
45,....,240,.,1,1,
45,....,244,29.18,0,1,
45,....,260,.,1,1,
45,....,280,14.89,0,1,
45,....,301,11.96,0,1,
45,....,360,7.36,0,1,
45,....,420,3.47,0,1,
45,....,480,3.03,0,1,
45,....,570,1.25,0,1,
46,2590000,10800,0,.,1,1,1
46,....,30,14.48,0,1,
46,....,60,26.49,0,1,
46,....,90,34.45,0,1,
46,....,120,36.54,0,1,
46,....,180,36.82,0,1,
46,....,220,47.53,0,1,
46,....,230,.,1,1,
46,....,240,.,1,1,
46,....,248,32.1,0,1,
46,....,280,23.52,0,1,
```

```
AN ERROR WAS FOUND IN THE CONTROL STATEMENTS.
136  $SUBROUTINES: THIS TRANS CANNOT BE USED WITH THIS ADVAN.
```

Fig. 3. Data, NM-TRAN control, and error files viewed simultaneously as DOS windows for ease in debugging.

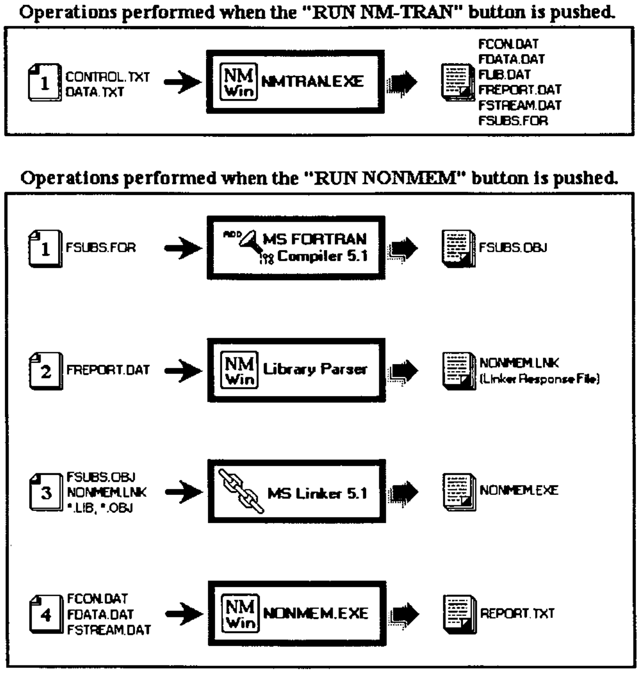
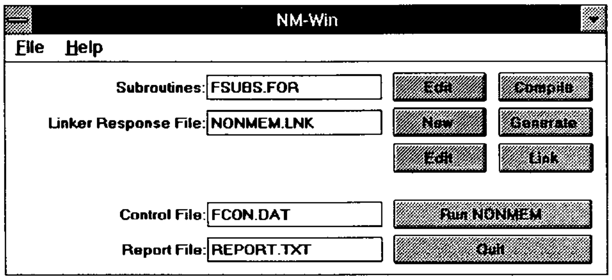


Fig. 4. File operations performed when the "Run NM-TRAN" and Run NONMEM" buttons are selected.

generated FORTRAN subroutines with Notepad and to compile them. The buttons next to the linker response file text box allow you to create a new file, generate a file from the FREPORT.DAT file, edit the file, or pass the file to the Microsoft Linker for creating an executable. The "Run NONMEM" button will pass the listed control file name and report file name to an existing NONMEM executable. This button can be used to restart a NONMEM execution without recompiling and linking if a previous run was canceled.

Windows Resources and Memory

The amount of systems resources that NM-Win and NONMEM use is minimal. The systems resource consist of mainly cursors, icons, bitmaps, strings, and fonts, of which NM-Win and the resulting NONMEM executable do not use much. String resources for NM-Win are read in from the NM-Win executable as needed and the few icons and bitmaps used in both programs make very little impact. Both programs together used less than 1% of the resources in the test case.



Subroutines: FSUBS.FOR

Linker Response File: NONMEM.LNK

Control File: FCON.DAT

Report File: REPORT.TXT

Fig. 5. Dialog box with additional features made available when the "Advanced Options" button on the main dialog box (Fig. 2) is selected.

The amount of memory used by NM-Win and the NONMEM executables was a factor. NM-Win, while a 51k executable, used only 42k of memory, a 9k savings from disk size. However, NONMEM, which in our test case was a 811k executable, used 1183k, which is a 372k increase in size. Most of this extra memory use came from temporary space in which NONMEM does all of its calculations. Even with this 1225k total size, a PC with only 4 MB of RAM should be able to efficiently run NONMEM, even without a swap file. For users who want to run NONMEM in the background and other programs in the foreground, 8 MB of RAM would be more reasonable.

The Notepad editor included with Microsoft Windows 3.x is the default editor called by NM-Win for creating and editing all text files. Notepad is limited, however, in the size of a file it can read, and frequently, the report files will exceed this size. Other small text editors, such as the one included with Norton Desktop, or word processors, such as Microsoft Word or Microsoft Write, which comes bundled with Microsoft Windows, can be used in its place in these cases where the size is too big. If another text editor is desired to be the default editor, it can easily be requested in the NMWIN.H header file. It is not recommended that a word processor be used as the default editor due to the usually longer time in loading the program. Word processors can be used to edit and print files when appearances are important.

Speed

The benchmarking of various personal computer configurations was completed by adding statements to OFILES.FOR and CFILES.FOR to print the system time just after the report file was opened and just before it was closed, which is a reasonably accurate, although a somewhat shorter time then the total NONMEM run. Table IV lists the results of some benchmark comparisons. A test case involving a data-rich example (nine subjects administered iv infusions, 121 total records) with a simple two-compartment model (ADVAN 3 TRANS 1) was used on each PC platform. All results were obtained on computers with similar setups of 8 MB of RAM with an approximately 4-MB permanent swap file using 32-bit access. NONMEM was run under Windows alone, with all other programs, such as screen savers and virus interceptors, removed from execution (i.e., no

Table IV. NM-Win with NONMEM Benchmark Results on Various PC Platforms

Processor	Norton index	Execution time (min)
Intel 386DX/40 ISA	43.4	88.8
Intel 486SL/25 PCMCIA	48.2	17.7
Intel 486DX/33 EISA	72.4	6.5
Intel 486DX/33 ISA	72.4	5.9
Intel 486DX/66 EISA	72.4	3.7

[a] Reflects the speed of the machine in comparison to standard platforms using System Information Version 2.2 included in Norton Desktop Version 2.2

other programs running in the background). The command used to run NONMEM was as follows:

```
C:\NMTEST\win nonmem.exe fcon.dat report.txt
```

As expected, these times indicate that it is to the users advantage to run NONMEM on the fastest system available (11). In comparison to the final NONMEM execution, the times of NM-Win, NM-TRAN, and the Microsoft Compiler and Linker are nominal. It should be noted that running NM-Win in the background will take a significantly longer time to complete. However, the user can still continue to run other programs in the foreground.

Several improvements in speed are planned in the near-future. Watcom's F77/386 v. 9.0 compiler, which is 32-bit compiler in comparison to Microsoft's 16-bit FORTRAN compiler, is currently being explored to further the development of NM-Win. The speed increase from switching from a 16-bit to a 32-bit compiler should improve execution times, possibly as much as twofold. NONMEM running under Windows NT should also improve speed, although probably only slightly more than using a 32-bit compiler with regular Windows. Additionally, with the final release of Window NT near, a few Windows NT-specific FORTRAN compilers are slowly reaching the market. Future hardware improvements should make the biggest impact. Users of Intel's new Pentium chip, which has been released in very limited quantities as of this writing, can expect anywhere from a 200 to 500% increase in speed over an Intel 486DX2/66 for math-intensive (i.e., NONMEM) programs.

The modifications made to the NONMEM source code are minimal and do not, in any way, interfere with the integretity of the parameter estimates generated by the NONMEM source code. The NM-Win code (compiled executable and source code) is available from the corresponding author on request. Requests for code should include two 1.44-MB 3.5-in. formatted DOS disks. Suggestions for modifications and/or improvements to NM-Win are also welcome.

ACKNOWLEDGMENTS

The NONMEM Project Group was consulted on many of the early difficulties with the initial design of the front-end and has been extremely supportive of this effort. Allison Boeckmann's suggestions have been invaluable.

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