

PKPD Tools for Excel

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Preface

It is hard to believe that it is fifteen years since we first released our *PKPD Tools for Excel* at at Prof. Steven Shafer's International Pharmacokinetic Modeling Workshop in Palo Alto (December 1994).

Since then, there have been several complete rewrites of the *Tools*, with incremental improvements in stability. Our 'oldest' users will recall that with the first versions it was necessary to copy a DLL file (the library of functions) to the windows system directory and a XLA file (for the function registrations) to the Excel Add-Ins directory. Although this approach worked, it caused many headaches, particularly with the links created between the spreadsheets and the XLA file. These links were often problematic when they were unexpectedly encountered by users who prepared a spreadsheet on one computer and tried to open it on another computer with a different directory structure.

In order to improve the user experience (specifically to avoid the 'link headaches') we have completely rewritten the *Tools* and compiled them as an XLL, which is a special type of DLL written for Excel (for Windows). This means that this version (and all future versions) of our *Tools* does not require a separate XLA file for function registration. The good news is that there is now no issue with 'link headaches,' i.e., spreadsheets created on one computer can be used on any computer on which our *Tools* are installed without worrying about editing links to the Add-In.

Please feel free to distribute the software and this booklet. In addition, if you would like to receive the updated software as it continues to evolve or if you have any difficulties or suggestions, please visit our website—pkpdtools.com.

Finally, special thanks once again to Dr. Pedro Gambús (Anesthesiologist, Spain) for his continued work as our 'beta-tester' and for his help running our workshop at the *Second World Congress in Total Intravenous Anaesthesia-TCI* in Berlin.

Thomas Schneider
Charles Minto
April, 2009

Preface 1995

Nowadays, pharmacokinetic and pharmacodynamic (PKPD) modeling without computers is unimaginable. On the other hand, the usefulness of computers relies to some extent on the software. Innumerable tools are already available which can be used in pharmacokinetic and pharmacodynamic modeling. In addition, each program requires a slightly different data format, and if the program has a built in programming language, this language is likely to be completely different from the language of another tool. Even the terminology with respect to pharmacokinetics and pharmacodynamics can be different. Lots of old tools run under DOS, others run under Windows and still others run under UNIX.

Not everyone who is interested in PKPD modeling has the background of an experienced programmer. Consequently, the prospective expert in the field often faces a large number of undocumented tools, which work very efficiently for the programmers, but they may not work so efficiently for others.

Why develop Tools for Excel? Spreadsheet programs are becoming very popular for data handling in research. All of them offer features for graphically displaying the data, which is clearly helpful. Many of them have an appealing user interface, and with extensions (such as Excel's Solver—a powerful optimizer) they become a very interesting tool for serious researchers.

The built in programming languages are very useful in simplifying tedious and repetitive data manipulation tasks. The first tools we developed for Excel were pure Excel 4.0 macro language programs. We realized at an early stage, that it was more logical to reprogram some of the functions in another language. After several months of struggling with the C interface to Excel, we succeeded in rewriting and extending our *PKPD Tools*. We find these tools very useful for exploring pharmacokinetic and pharmacodynamic data. The *PKPD Tools* Version 1.02 are only a part of the tools that we have developed so far—the others are not yet completely finished (either algorithmically or they don't fulfill the criteria of user friendliness).

The first version of these tools was released at Steven Shafer's International Pharmacokinetic Modeling Workshop in Palo Alto, December 1994. Depending on how you perceive these tools, we would be motivated to refine and extend them. Eventually, the *PKPD Tools* will cover most of the tasks relevant for PKPD modeling in anesthesia. Comments and suggestions are very welcome.

We would like to acknowledge the help and support of all the members of Don Stanski's and Steven Shafer's group while we worked on these tools. Two scientists deserve special mention. It is not possible to find words to describe Keith Gregg's unique ability to explain complex statistical concepts. Keith is a statistician, who makes statistics not only intelligible, but fascinating—a tall order indeed! Without Russell Wada, PhD, the implementation of population analysis (XLMEM) would never have been possible. He succeeded in unwiring the complexity of the first order approximation and the matrix mathematics, so that the topic became comprehensible for us. Additional thanks must go to Dr. Pedro Gambús (Anesthesiologist, Spain) and Dr. Andrew Donner (Anesthesiologist, Austria) for their helpful comments as our "beta release" users.

The best way to learn about PKPD modeling is by "playing with the data," whether simulated or real, so start playing! We hope that you find our *PKPD Tools* a helpful and interesting addition to Excel.

Thomas Schnider
Charles Minto
June, 1995

Introduction

Philosophy

Why *Excel*?

Microsoft Excel was developed to compete in the lucrative business software market, so you may wonder if the program is suitable for pharmacokinetic (PK) pharmacodynamic (PD) simulation and modeling. Can a business program perform the types of calculations that are required in PK/PD simulation and modeling? The answer, of course, is ‘yes!’

With many software programs you prepare the data, run the program, then wait while it performs some magic and spits out the result. Using such programs, you see only the beginning and the end of a calculation and miss out on the middle. With a spreadsheet implementation, you get to see the whole problem. For example, on one occasion, we were struggling to understand why NONMEM was crashing with certain starting estimates. It proved ‘easy’ to find the reason why with Excel. Firstly, we wrote an ordinary differential equation solver for Excel in C to implement the rather complicated PK model. Secondly, we set up a mixed-effects analysis (based on our XLMEM code). Finally, it proved easy to graphically examine the predicted concentrations for different starting estimates and to examine every value in each matrix used in the calculation of the extended least squares objective function during the optimisation process. Once we could see the whole problem, the answer was obvious!

Why XLL?

An XLL is an Add-In for *Microsoft Excel* that you can build with any compiler that supports building dynamic link libraries (DLLs). Many programmers who write Add-In functions for Excel prefer to do so completely in C or C++ rather than in Visual Basic for Applications (VBA) for any number of good reasons. Although we frequently prototype our functions in VBA, we have implemented the *Tools* in the C language, because the execution is much faster particularly for the analysis of large data sets. Furthermore, we find that coding in C is more efficient for complicated functions. We also discovered that we could not solve some problems without using this approach, because we reached memory limitations in Excel.

The Microsoft Excel 2007 Software Developer’s Kit (SDK) contains the necessary header and library files to build an XLL. Programming with the Excel SDK is a tedious and error-prone task that requires specialised skills and expe-

rience. In recent years, we have used the XLW* project, which is a C++ wrapper for the Excel C Application Programming Interface (API), making the XLL development significantly easier.

Why *Windows*?

Like it or not, Windows is still the dominant operating system, holding about 88% of the desktop market share.[†] Although we are not fans of *Windows Vista*, we have gone to considerable lengths to ensure that the new version works with *Excel 2007/2008*. Because most programs have their own special way of internally representing data, the DLLs which come with various applications are specifically written for those applications. So it is with our XLLs—they are specifically written for *Excel for Windows* and will not work for *Excel for Mac*.

Why *Tools*?

We would like to emphasize that when we start a simulation, we usually start with a *blank* spreadsheet. That is, we start with nothing other than our *Tools*, then proceed to “build” a simulation. We are entirely flexible about how we construct the simulation. Usually, there is some thinking about the particular problem, some scribbling on a piece of paper, a rough sketch of a design to solve the problem. Similarly, when we start PK/PD modeling, we start with a *blank* spreadsheet, import and examine the PK/PD data, then begin to “build a model.”

Just as it is obvious that simply having access to a master builder’s tools does not enable one to build a beautiful home, installing our *Tools* will not make you a PK/PD expert. In fact, it is quite likely that you will manage to shoot yourself in the foot, or worse in the eye, with a pneumatic nailer. Perhaps you will not even know how to use some of the builders tools. Indeed, we regularly get emails from people who find themselves in trouble after they have downloaded one of our example spreadsheets, which they have tried to modify, complaining that “Your hammer is hopeless at cutting wood.” We hope that this booklet will help you with some basic building.

However, *please* understand, we do not provide these examples with the intention that you can collect your own data and somehow just copy your data onto the spreadsheet, and magically develop a new PK/PD model that you can publish. The “Tools” will not make you a PK/PD modeler! Just as a master builder’s tools do not make you a master builder! If you want to become a PK/PD modeler, you need many years of training—there is a lot to learn about pharmacokinetics, pharmacodynamics, statistics, computing, programming, . . . there is no shortcut! You cannot expect to simply download an example spreadsheet, run Excel’s Solver and write a manuscript!

This booklet is still in the process of being written. It is offered in its present form to the registrants of our workshop in Berlin (23 April 2009).

*<http://xlw.sourceforge.net>

†<http://marketshare.hitslink.com>

Part I

The Basics

Chapter 1

Array Formulae

Array formulae are a feature of Excel and are not specific to *PKPD Tools*. Most users have some familiarity with functions which return a single value to one cell on a spreadsheet. For example, the formula `=AVERAGE(A1:A5)` will return the average value of the numbers entered in the first five rows of column A (i.e., one value is returned to the sheet).

Array formulae are required when the function returns an array of values to the spreadsheet (i.e., the answer appears in a range of cells, rather than a single cell). For example, the formula `=MMULT(A1:B3,A5:C6)`, when entered as an array formula (see fig. 1.1), will return the product of the 3x2 matrix entered into cells A1:B3 and the 2x3 matrix entered into cells A5:C6, which is a 3x3 matrix (i.e., nine values are returned to the sheet).

1.1 Entering an Array Formula

To enter an array formula use either of the following two methods:

Method A

1. Select the first cell of the range into which you want to enter the array formula.
2. Type the formula.
3. Press **Enter**.
4. Select the range into which you want to enter the array formula (which must begin with cell into which you entered the formula).
5. Press **F2**.
6. Press the **Ctrl**, **Shift** and **Enter** keys at the same time.

Method B

1. Select the range of cells into which you want to enter the array formula.
2. Type the formula.

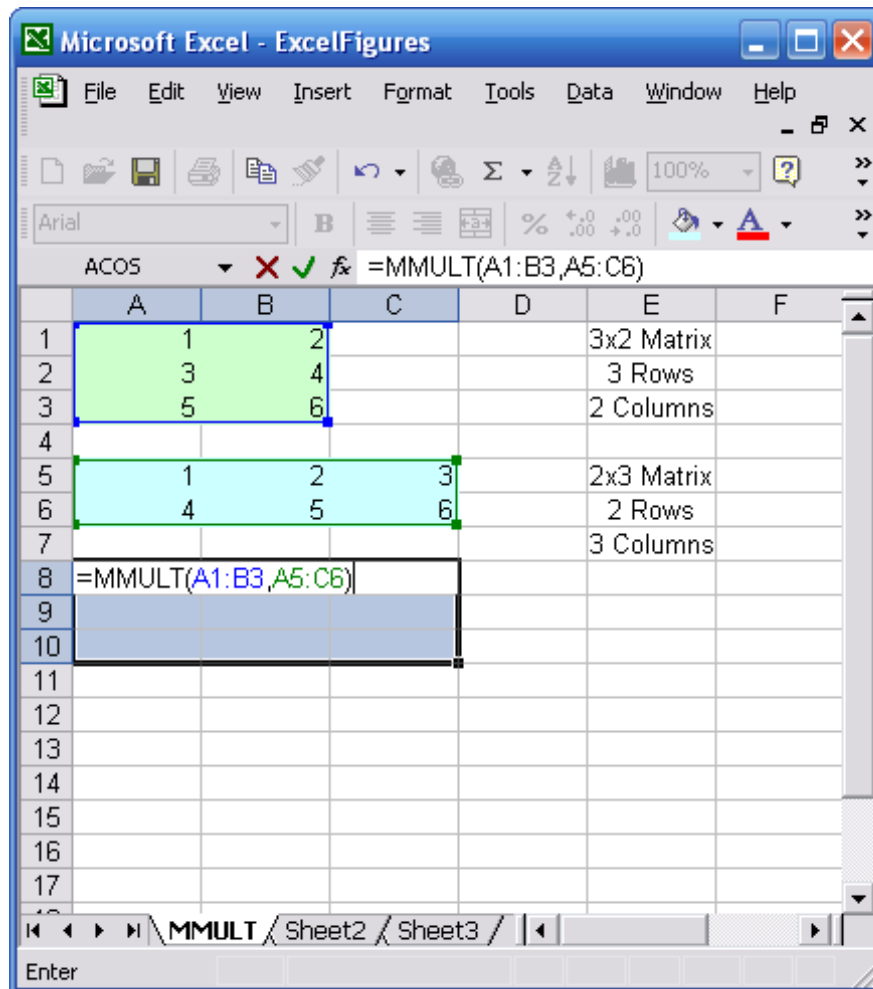


Figure 1.1: Multiplication of two matrices using the Microsoft Excel MMULT function. There are several ways to enter the formula `=MMULT(A1:B3,A5:C6)`. i) The user can simply type the whole formula. ii) The user can type `=MMULT(` then use the mouse to select the range A1:B3, then type a comma, then use the mouse to select the range A5:C6, then type the closing bracket. iii) The formula can be entered using the Function Wizard (see chapter 2). The screenshot is taken just before the user presses the `Ctrl`, `Shift` and `Enter` keys at the same time. After these three keys have been pressed, the formula bar will show that all the cells in the range A8:C10 contain `{=MMULT(A1:B3,A5:C6)}`. The curly braces are added by Excel (not typed by the user) and show that this is an array formula. The ExcelFigures.xls spreadsheet is available on the accompanying CD in the 'figures' folder.

3. Do not press the **Enter** key!
4. Press the **Ctrl**, **Shift** and **Enter** keys at the same time.

1.2 Editing an Array Formula

To edit an array formula use the following method:

1. Select any cell in the the formula array.
2. Press **F2** (to edit the formula).
3. Use the left and right arrow keys or the mouse to move to the part of the formula that you want to edit.
4. Edit the formula.
5. Press **Ctrl**, **Shift** and **Enter** at the same time.

Tip: hold down the Ctrl key while you use the left and right arrow keys to jump to each new cell reference

You cannot simply edit the formula in one cell of the range. If you attempt to do so, you will get the message “You cannot change part of an array.” If you hit the **Enter** key to say ‘OK’ to this message, then try to hit the **Enter** key again, you will find yourself in the never-ending “You cannot change part of an array” loop. You should instead hit the **Esc** key to ‘escape’ this situation.

Increasing the Range of an Array Formula

To increase the range of an array formula use the following method:

1. Select the extended range (i.e., the current range and additional empty cells).
2. Press **F2**.
3. Edit the formula, if necessary.
4. Press **Ctrl**, **Shift** and **Enter** at the same time.

Decreasing the Range of an Array Formula

To decrease the range of an array formula use the following method:

1. Select the entire array. (i.e., all the cells returned by the function).
2. Press the **Delete** key.
3. Start again!

Tip: Save some time by copying the formula in the first cell of the range to another empty cell. After deleting the formula array, copy the formula back to the original cell, then start at step 4 of Method A (see page 3).

1.3 Deleting an Array Formula

To delete an array formula use the following method.

Tip: To select the entire array, select any cell in the array, then press Ctrl and / at the same time.

1. Select the entire array.
2. Press the **Delete** key.

You cannot simply delete one cell in the range. If you attempt to do so, you will get the message “You cannot change part of an array.” If you hit the **Enter** key to say ‘OK’ to this message, then try to hit the **Enter** key again, you will find yourself in the never-ending “You cannot change part of an array” loop. You should instead hit the **Esc** key to ‘escape’ this situation.

1.4 Array Formulae and VBA

Visual Basic for Applications (VBA) can be used to enter array formulae on a spreadsheet.*

Tip: Press the Alt and F11 keys at the same time to open the VBA editor.

We recommend the use of VBA, particularly for large projects or repetitive tasks. The potential time savings are enormous. More importantly, for repetitive tasks, there is the potential for the reduction in errors associated with manually setting up complex spreadsheets. Some simple VBA code, which will enter the array formula shown in figure 1.1, is given below.

```
Option Explicit
Sub WriteArray()
    Range(Cells(8, 1), Cells(10, 3)).Select
    Selection.FormulaArray = "=MMULT(R1C1:R3C2,R5C1:R6C3)"
End Sub
```

*VBA was used extensively in the XLMEM project.

Chapter 2

The Function Wizard

Formulae can be entered onto an Excel spreadsheet in several different ways. The user can type the formula directly or take advantage of the ‘automated’ assistance provided by Excel. Even for a simple function such as `=SUM(A1:A5)` these possibilities exist. For example, the user can select cell **A6** and simply type this formula, press the **Enter** key, and the function returns the result of the sum of the numbers in the first five rows of column **A**. Alternatively, the user can select cell **A6** and click the Σ button on the standard toolbar, and a clever little Excel macro will enter the formula into the cell automatically.

Excel provides a multitude of functions for your use. While this ensures that functions exist for most of your needs, it can also make it very difficult to find a particular function. To make functions easier to find, they are divided into categories (e.g., Financial, Math & Trig functions, Statistical, etc). The Function Wizard ‘Insert Function’ dialog box provides a short description of what each function does, as well as a link to a help file with more detail about each function (see fig. 2.1).

Tip: After installing our Tools two new ‘PKPD’ categories are added to the drop down list.

After the user has selected the function they want to use, the Function Wizard ‘Function Arguments’ dialog box appears. The word argument is used in several differing contexts in mathematics, however the most common usage refers to the argument of a function. An argument of a function $f(x_1, \dots, x_n)$ is one of the n parameters on which the function’s value depends. For example, Microsoft Excel’s `DATE(Year,Month,Day)` function is a three-argument function. In other words, the value returned by the `DATE` function depends on three arguments; `Year`, `Month` and `Day` (see fig. 2.2).

2.1 How to start the Function Wizard

2.1.1 Microsoft Excel 2002/2003

- From the ‘Insert’ menu item, choose ‘Function.’

2.1.2 Microsoft Excel 2007/2008

- From the ‘Ribbon,’ select the ‘Formulas’ command tab.
- In the ‘Function Library’ group, click ‘Function Wizard.’

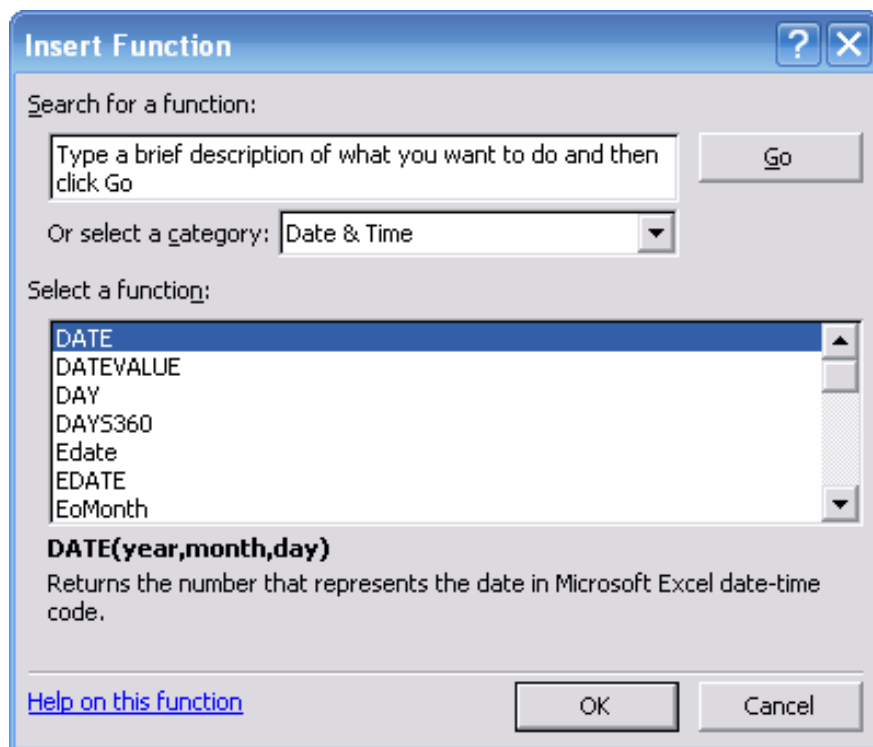


Figure 2.1: The Function Wizard 'Insert Function' Dialog Box. After starting the Function Wizard, you can search for a function or select a category to scroll through the list of available functions. In this example, the 'Date & Time' category is selected, from which the DATE function is selected. After clicking the OK button, the 'Function Arguments' dialog box appears (see fig. 2.2).

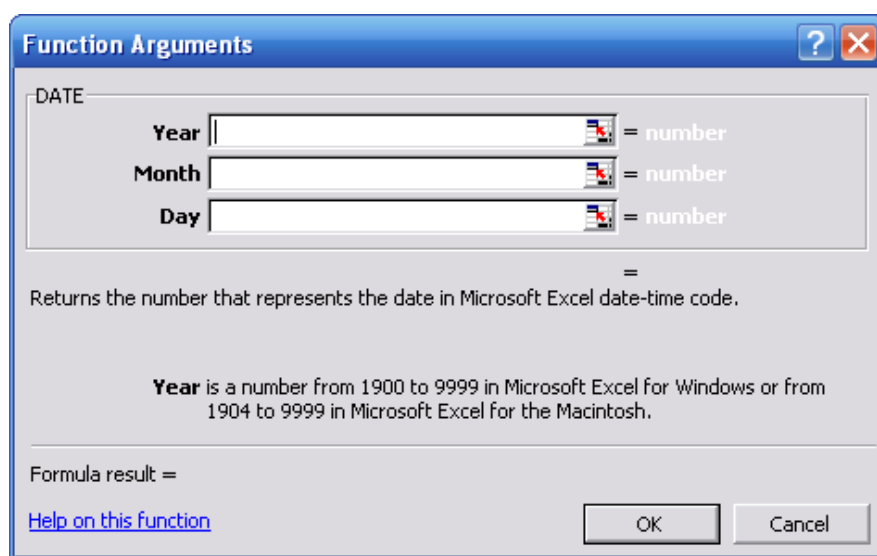


Figure 2.2: The Function Wizard 'Function Arguments' Dialog Box. The Function Wizard provides a brief description for each argument and, importantly, ensures that the function arguments (in this example; Year, Month and Day) are entered in the correct order. The value for each argument can be entered in several ways; e.g., for the Year argument, the user could i) type the value 2009 directly, ii) type the reference to a cell on the spreadsheet containing the year 2009, e.g., cell A1, or iii) click on the cell A1 with the mouse.

2.1.3 Shortcuts

The Function Wizard can be started using various shortcuts.

- Click the f_x button to the left of the ‘Formula Bar.’
- Press the **Shift** and **F3** keys at the same time.
- If you know the name of the function that you want to use, type its name (e.g., =DATE), then press the **Ctrl** and **A** keys at the same time. This will skip the ‘Insert Function’ dialog box (fig. 2.1) and call up the ‘Function Arguments’ dialog box (fig. 2.2) directly.

Chapter 3

Installation

In the past, we have used an ‘installation’ program to detect previous installations, remove them, set up the new directory structure and install the *Tools* automatically. However, with this and future installations, we only provide instructions of how to install the *Tools* manually. We believe that installing the *Tools* manually should be easily managed by anyone who plans to use the *Tools* for simulation or modelling. Also—we hope you agree—our time is better spent developing the *Tools* than maintaining the installation program.

This version of the *PKPD Tools for Excel* consists of two* files, which can be downloaded from the web as a zipped file (pkpdtools.zip).

See <http://pkpdtools.com/doku.php?id=downloads:downloads>.

- pkpddrugs.xll—a new library of functions, which returns the volumes and clearances for a selection of published PK/PD models.
- pkpdtools.xll—a library of PK/PD functions, which builds upon previous releases of the *PKPD Tools for Excel*.

3.1 Visual C++ 2008 Redistributable Package

Before installing our software, you should first install the Microsoft Visual C++ 2008 Redistributable Package (x86). We have placed a zipped copy of the `vcredist_x86.exe` file on the `pkpdtools.com` website. This step is not necessary if you already have Visual C++ installed on your system.

See <http://pkpdtools.com/doku.php?id=downloads:downloads>.

3.2 First Time Installation

In a typical Office/Excel installation, Excel will expect Add-Ins to be placed in either of two locations. These locations vary depending on the version of Excel and the version of Windows.[†] It is not required, however, that an Add-In reside

*The focus of this booklet is on simulation rather than modelling. Thus, we do not describe the use of the log likelihood objective function or `xlmem` software, nor of the use of our software for numerical calculation of standard errors on parameter estimates.

[†]These two locations are accessible with Visual Basic for Applications using the `Application.LibraryPath` and `Application.UserLibraryPath` properties.

in one of those folders. An Add-In may be placed anywhere in any folder on your computer. It is our preference to install the *Tools* in an alternate location of our choosing.

The steps required for a first time installation are:

- Create a directory (folder) for the *Tools* on your computer, for example `d:\pkpdttools`.
- Copy `pkpddrugs.xll` and `pkpdttools.xll` to this new directory (folder).
- Follow subsection 3.2.1 for Excel 2002/2003 (Windows XP).
- Follow subsection 3.2.2 for Excel 2007/2008 (Windows Vista).

3.2.1 Microsoft Excel 2002/2003

- Start Microsoft Excel for Windows.
- See figure 3.1.
- From the Tools menu, choose Add-Ins.
- The Add-Ins dialog box appears.
- Click the Browse button.
- The Browse dialog box appears.
- Browse to the new folder created above, e.g., `d:\pkpdttools`.
- Select the `pkpddrugs` file.
- Click the OK button.
- You are now returned to the Add-Ins dialog box.
- Click the Browse button again.
- The Browse dialog box appears.
- Browse to the new folder created above, e.g., `d:\pkpdttools`.
- Select the `pkpdttools` file.
- Click the OK button.
- The Add-Ins box now has two new (checked) Add-ins available.
- See figure 3.2.
- Click the OK button.
- You have now successfully added in the *PKPD Tools for Excel*.

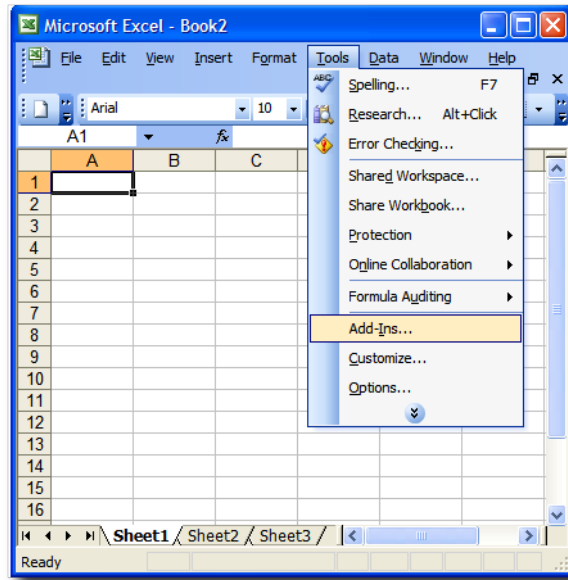


Figure 3.1: Excel 2002/2003 Tools Add-In menu item.

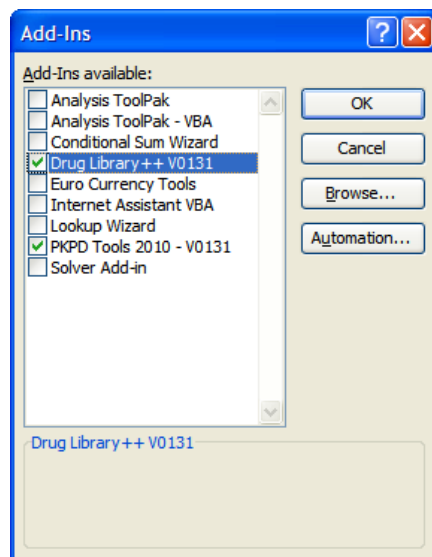


Figure 3.2: Excel Add-Ins dialog box.

3.2.2 Microsoft Excel 2007/2008

- Click the Office button.
- Click the Excel Options button.
- The Excel Options dialog box appears.
- See figure 3.3.
- Click the Add-Ins tab in the left pane. (The Add-Ins tab contains a list of *all* the Add-Ins installed on your computer.)
- Select Excel Add-Ins from the Manage drop-down list (at the bottom).
- Click Go.
- The Add-Ins dialog box appears.
- Choose the Browse button.
- The Browse dialog box appears.
- Browse to the new folder created above, e.g., `d:\pkpdttools`.
- Select the `pkpddrugs` file.
- Choose the OK button.
- You are now returned to the Add-Ins dialog box.
- Choose the Browse button again.
- The Browse dialog box appears.
- Browse to the new folder created above, e.g., `d:\pkpdttools`.
- Select the `pkpdttools` file.
- Choose the OK button.
- The Add-Ins box now has two new (checked) Add-ins available.
- See figure 3.2.
- Choose the OK button.
- You have now successfully added in the *PKPD Tools for Excel*.

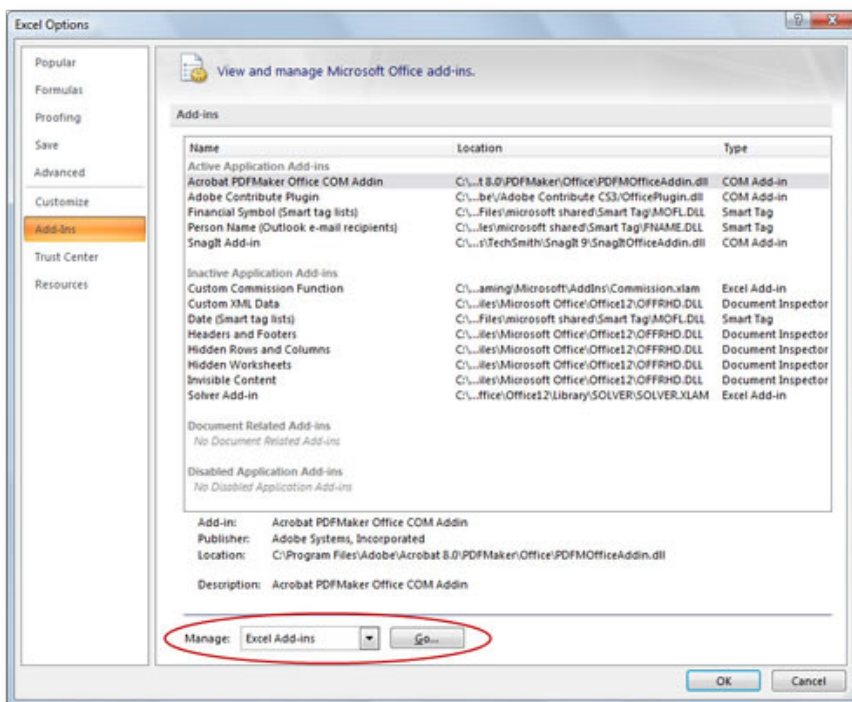


Figure 3.3: Excel 2007/2008 Options Dialog box.

3.3 Deleting the Add-Ins

Removing an existing Add-In is a multi-step process. The details are slightly different with the different versions of Excel, but the following description outlines the main steps.

- Close Excel.
- Delete the `pkpddrugs.xll` and `pkpdttools.xll` from the directory (folder) created above.
- Start Excel.
- If Excel complains that e.g., ‘`pkpddrugs.xll` could not be found. Please check the spelling of the file name, and check that the location is correct ...’ Click OK.
- If Excel complains that e.g., ‘`pkpdttools.xll` could not be found. Please check the spelling of the file name, and check that the location is correct ...’ Click OK.
- Open the Add-Ins dialog box (as described above according to your version of Excel).
- Attempt to check/uncheck the box beside the *PKPD Drugs* Add-in.
- Excel will prompt you with a message ‘Cannot find add-in ‘`pkpddrugs.xll`’. Delete from list?’
- Click Yes to delete the Add-In from Excel’s list of available Add-Ins.
- Attempt to check/uncheck the box beside the *PKPD Tools* Add-In.
- Excel will prompt you with a message ‘Cannot find add-in ‘`pkpddrugs.xll`’. Delete from list?’
- Click Yes to delete the Add-In from Excel’s list of available Add-Ins.

3.4 Upgrading

The safest approach is to delete *all previous versions* of the *Tools* according to the general instructions given in section 3.3 before following the installation instructions given in section 3.2.

However, when we provide a new version of the current `pkpdttools.xll` or `pkpddrugs.xll`, you can upgrade by first quitting Excel, copying the new version of the xll ‘over the top’ of the previous version and then restarting Excel.

Part II

The Add-Ins

Chapter 4

pkpddrugs.xll

The pkpddrugs.xll is a dynamic link library for *Microsoft Excel* for *Windows*. The library contains a collection of functions written in the C programming language. These functions provide easy access to some of the better known pharmacokinetic models used for simulation purposes in anaesthesia. We implemented these functions to minimise the chance of typographical errors (and to save time) when transcribing these models from the publications to a spreadsheet. The functions are described below in alphabetical order.

4.1 Diprifusor(Age, Weight)

This function takes two arguments; age (years) and weight (kg). It returns seven parameters; V_1 , V_2 , V_3 , Cl_1 , Cl_2 , Cl_3 and k_{e0} as a range object (one column, seven rows). These parameters are calculated with the following equations.

$$V_1 \text{ (l)} = 0.228 \cdot \text{weight} \quad (4.1)$$

$$k_{10} \text{ (min}^{-1}\text{)} = 0.119 \quad (4.2)$$

$$k_{12} \text{ (min}^{-1}\text{)} = 0.114 \quad (4.3)$$

$$k_{13} \text{ (min}^{-1}\text{)} = 0.0419 \quad (4.4)$$

$$k_{21} \text{ (min}^{-1}\text{)} = 0.055 \quad (4.5)$$

$$k_{31} \text{ (min}^{-1}\text{)} = 0.0033 \quad (4.6)$$

$$k_{e0} \text{ (min}^{-1}\text{)} = 0.26 \quad (4.7)$$

It is with a little humour that we included age as an argument in this function. As is obvious from the set of equations, age is not used in the model. However, we included age to put a limit on the age range of the model according to the Diprifusor implementation. Note that the parameter k_{12} has a value of 0.114 min^{-1} . The value given in the paper by Marsh *et al.*[7] is given incorrectly as 0.112 min^{-1} .*

See the sheet named 'Diprifusor' in the file `pkpddrugs.xls` located in the `xls` folder on the accompanying CD.

*Personal communication Dr. Iain Glen.

4.2 PropMarsh(Weight)

This function takes one argument; weight (kg). It returns six parameters; V_1 , V_2 , V_3 , Cl_1 , Cl_2 and Cl_3 as a range object (one column, seven rows). These parameters are calculated with the following equations published by Marsh *et al.*[7].

$$V_1 \text{ (l)} = 0.228 \cdot \text{weight} \quad (4.8)$$

$$k_{10} \text{ (min}^{-1}\text{)} = 0.119 \quad (4.9)$$

$$k_{12} \text{ (min}^{-1}\text{)} = 0.112 \quad (4.10)$$

$$k_{13} \text{ (min}^{-1}\text{)} = 0.0419 \quad (4.11)$$

$$k_{21} \text{ (min}^{-1}\text{)} = 0.055 \quad (4.12)$$

$$k_{31} \text{ (min}^{-1}\text{)} = 0.0033 \quad (4.13)$$

The value for k_{12} given in the paper by Marsh *et al.*[7] is given incorrectly as 0.112 min^{-1} . However, this value has been used for other implementations of ‘The Marsh Model’ so we have implemented the model as published for simulation purposes.

See the sheet named ‘PropMarsh’ in the file `pkpddrugs.xls` located in the `xls` folder on the accompanying CD.

4.3 PropPaedfusor(Age, Weight)

This function takes two arguments; age (years) and weight (kg). It returns seven parameters; V_1 , V_2 , V_3 , Cl_1 , Cl_2 , Cl_3 and k_{e0} as a range object (one column, seven rows). These parameters are calculated with the following equations as given in Table 1 of the publication by Absalom and Kenny[1].

$$\text{If age=1–10 yr. } V_1 \text{ (l)} = 0.4584 \cdot \text{weight} \quad (4.14)$$

$$\text{If age=13 yr. } V_1 \text{ (l)} = 0.4 \cdot \text{weight} \quad (4.15)$$

$$\text{If age=14 yr. } V_1 \text{ (l)} = 0.342 \cdot \text{weight} \quad (4.16)$$

$$\text{If age=15 yr. } V_1 \text{ (l)} = 0.284 \cdot \text{weight} \quad (4.17)$$

$$\text{If age=16 yr. } V_1 \text{ (l)} = 0.22857 \cdot \text{weight} \quad (4.18)$$

$$\text{If age=1–10 yr. } k_{10} \text{ (min}^{-1}\text{)} = 0.1527 \cdot \text{weight}^{-0.3} \quad (4.19)$$

$$\text{If age=13 yr. } k_{10} \text{ (min}^{-1}\text{)} = 0.0678 \quad (4.20)$$

$$\text{If age=14 yr. } k_{10} \text{ (min}^{-1}\text{)} = 0.0792 \quad (4.21)$$

$$\text{If age=15 yr. } k_{10} \text{ (min}^{-1}\text{)} = 0.0954 \quad (4.22)$$

$$\text{If age=16 yr. } k_{10} \text{ (min}^{-1}\text{)} = 0.119 \quad (4.23)$$

$$k_{12} \text{ (min}^{-1}\text{)} = 0.114 \quad (4.24)$$

$$k_{13} \text{ (min}^{-1}\text{)} = 0.0419 \quad (4.25)$$

$$k_{21} \text{ (min}^{-1}\text{)} = 0.055 \quad (4.26)$$

$$k_{31} \text{ (min}^{-1}\text{)} = 0.0033 \quad (4.27)$$

$$k_{e0} \text{ (min}^{-1}\text{)} = 0.26 \quad (4.28)$$

Note that the parameters for V_1 and k_{10} are changed according to the child's weight, with a different equation according to the child's age. Note also that the other parameters have the same value as those in the *Diprifusor* (including the value for k_{12}).

See the sheet named 'PropMarsh' in the file `pkpddrugs.xls` located in the `xls` folder on the accompanying CD.

4.4 PropSchnider(Age, Weight, Height, LBM)

This function takes four arguments; age (years), weight (kg), height (cm) and lean body mass (kg). It returns seven parameters; V_1 , V_2 , V_3 , Cl_1 , Cl_2 , Cl_3 and k_{e0} as a range object (one column, seven rows). These parameters are calculated with the following equations published by Schnider *et al.*[10, 11].

$$V_1 \text{ (l)} = 4.27 \quad (4.29)$$

$$V_2 \text{ (l)} = 18.9 - 0.391 \cdot (\text{age} - 53) \quad (4.30)$$

$$V_3 \text{ (l)} = 238 \quad (4.31)$$

$$\begin{aligned} Cl_1 \text{ (l}\cdot\text{min}^{-1}) &= 1.89 + 0.0456 \cdot (\text{weight} - 77) \\ &\quad + 0.0264 \cdot (\text{height} - 177) \\ &\quad - 0.0681 \cdot (\text{LBM} - 59) \end{aligned} \quad (4.32)$$

$$Cl_2 \text{ (l}\cdot\text{min}^{-1}) = 1.29 - 0.0024 \cdot (\text{age} - 53) \quad (4.33)$$

$$Cl_3 \text{ (l}\cdot\text{min}^{-1}) = 0.836 \quad (4.34)$$

$$k_{e0} \text{ (min}^{-1}) = 0.456 \quad (4.35)$$

Note that this function returns the 'carefully developed k_{e0} ' of 0.456 min^{-1} , which results in an age adjusted value for t_{peak} (the time of the peak effect-site concentration after an intravenous bolus).

See the sheet named 'PropSchnider' in the file `pkpddrugs.xls` located in the `xls` folder on the accompanying CD.

4.5 PropWhite(Age, Weight, Gender)

This function takes three arguments; age (years), weight (kg) and gender (male=1, female=0). It returns six parameters; V_1 , V_2 , V_3 , Cl_1 , Cl_2 and Cl_3 as a range object (one column, six rows). These parameters are calculated with the following equations published by White *et al.*[13]. Note that parameters k_{12} , k_{13} , k_{21} and k_{31} are the same as the original model by Marsh *et al.*[7] (without the typographical error in k_{12}).

$$\text{If male } V_1 \text{ (l)} = \text{weight} \cdot (175.5 + 0.046 \cdot \text{age})/1000 \quad (4.36)$$

$$\text{If female } V_1 \text{ (l)} = \text{weight} \cdot (191.8 - 0.669 \cdot \text{age})/1000 \quad (4.37)$$

$$\text{If male } Cl_1 \text{ (l} \cdot \text{min}^{-1}\text{)} = \text{weight} \cdot (26.88 - 0.029 \cdot \text{age})/1000 \quad (4.38)$$

$$\text{If female } Cl_1 \text{ (l} \cdot \text{min}^{-1}\text{)} = \text{weight} \cdot (37.87 - 0.198 \cdot \text{age})/1000 \quad (4.39)$$

$$k_{12} \text{ (min}^{-1}\text{)} = 0.114 \quad (4.40)$$

$$k_{13} \text{ (min}^{-1}\text{)} = 0.0419 \quad (4.41)$$

$$k_{21} \text{ (min}^{-1}\text{)} = 0.055 \quad (4.42)$$

$$k_{31} \text{ (min}^{-1}\text{)} = 0.0033 \quad (4.43)$$

See the sheet named ‘PropWhite’ in the file `pkpddrugs.xls` located in the `xls` folder on the accompanying CD.

4.6 RemiMinto(Age, LBM)

This function takes two arguments; age (years) and lean body mass (kg). It returns seven parameters; V_1 , V_2 , V_3 , Cl_1 , Cl_2 , Cl_3 and k_{e0} as a range object (one column, seven rows). These parameters are calculated with the following equations published by Minto *et al.*[8].

$$V_1 \text{ (l)} = 5.1 - 0.0201 \cdot (\text{age} - 40) + 0.072 \cdot (\text{LBM} - 55) \quad (4.44)$$

$$V_2 \text{ (l)} = 9.82 - 0.0811 \cdot (\text{age} - 40) + 0.108 \cdot (\text{LBM} - 55) \quad (4.45)$$

$$V_3 \text{ (l)} = 5.42 \quad (4.46)$$

$$Cl_1 \text{ (l} \cdot \text{min}^{-1}\text{)} = 2.6 - 0.0162 \cdot (\text{age} - 40) + 0.0191 \cdot (\text{LBM} - 55) \quad (4.47)$$

$$Cl_2 \text{ (l} \cdot \text{min}^{-1}\text{)} = 2.05 - 0.0301 \cdot (\text{age} - 40) \quad (4.48)$$

$$Cl_3 \text{ (l} \cdot \text{min}^{-1}\text{)} = 0.076 - 0.00113 \cdot (\text{age} - 40) \quad (4.49)$$

$$k_{e0} \text{ (min}^{-1}\text{)} = 0.595 - 0.007 \cdot (\text{age} - 40) \quad (4.50)$$

See the sheet named ‘RemiMinto’ in the file `pkpddrugs.xls` located in the `xls` folder on the accompanying CD.

Chapter 5

pkpdtools.xll

The `pkpdtools.xll` is a dynamic link library for *Microsoft Excel for Windows*. The library contains a collection of functions written in the C programming language. These functions can be used for PK/PD simulation and modeling. Unfortunately, this booklet does not describe those functions whose primary purpose is related to PK/PD modeling (due to the authors time constraints prior to the *Second World Congress of Total Intravenous Anaesthesia-TCI* Meeting in Berlin, 23–25 April 2009).

Some of the functions contained in the `pkpdtools.xll` are based on the three-compartment mammillary model. Some of these functions take arguments called `A1`, `A2`, `A3`, `L1`, `L2`, `L3`. These refer to the coefficients and hybrid rate constants given as A_i and λ_i in the following equation (which calculates the plasma concentration after a single intravenous bolus dose for a three compartment mammillary model).

$$C(t) = \text{Dose} \cdot (A_1 \cdot e^{-\lambda_1 \cdot t} + A_2 \cdot e^{-\lambda_2 \cdot t} + A_3 \cdot e^{-\lambda_3 \cdot t}) \quad (5.1)$$

Some of the functions are based on the effect compartment concept. These functions take an argument called `ke0`. This refers to the rate constant out (k_{e0}) of the effect compartment, as conceived by Hull *et al.*[4] and Sheiner *et al.*[12].

Some of the functions take a range argument called `DeltaTimes`. Back in the early 1990's when we started writing the *Tools*, we decided to use the 'delta' times rather than the actual time as the input for the functions. At the time we were using the *Tools* for PK/PD modeling. Several of the functions use the 'state variables' of Bailey and Shafer[2] to update the model from one time interval to the next. We found that it was more efficient to calculate the time interval (`DeltaTimes`) on the spreadsheet and give this value directly to the function, than to calculate the time interval with every iteration of the optimisation procedure. Thus, when you build a spreadsheet to calculate the predicted plasma and effect-site concentrations after a bolus, you will need to have one column for time (e.g., minutes after bolus, or clocktime) and another column for `DeltaTimes`.

It is important that you are consistent with your units. For example, if you have a set of pharmacokinetic parameters with volumes given as litres (l), and clearances given as $\text{l} \cdot \text{min}^{-1}$, and if your bolus dosing unit is mg and your infusion rate is $\text{mg} \cdot \text{min}^{-1}$, then your concentrations will be $\text{mg} \cdot \text{l}^{-1}$ or equivalent (e.g., $\mu\text{g} \cdot \text{ml}^{-1}$).

The notes below provide a brief description of the arguments for each function in alphabetical order. They are not intended as an explanation the PK/PD concepts.

5.1 BMI

BMI calculates the body mass index according to the following equation, where `Weight` is in kg, and `Height` is in metres. The function returns a value with units of $\text{kg}\cdot\text{m}^{-2}$.

$$\text{BMI} = \frac{\text{Weight}}{\text{Height}^2} \quad (5.2)$$

BMI Arguments

Please note that BMI takes the height in cm and *not* in m. We implemented this function, for ease of use (and compatibility) with other functions often used on the same spreadsheet, such as `JLBM` and `JanLBM`, which require that height is given in cm. BMI is a two argument function—none of the arguments are optional.

Weight: Mass in kg. This can be the value of the `Weight` or the cell reference with the value of the `Weight`.

Height: Height in cm. This can be the value of the `Height` or the cell reference with the value of the `Height`.

5.2 CalcRate

Note that this function has been replaced by the new function `TciCp` (see below).

5.3 Cl2Hyb

`Cl2Hyb()` converts the volumes and clearances of a three-compartment mammillary model into the coefficients and hybrid rate constants. `Cl2Hyb()` is a one argument function.

Cl2Hyb Arguments

Parameters: A one column range of six pharmacokinetic parameters; V_1 , V_2 , V_3 , Cl_1 , Cl_2 and Cl_3 . The volume and clearance parameters must be given in this order. To specify a two-compartment model V_3 and Cl_3 should be zero. To specify a one-compartment model V_2 , V_3 , Cl_2 and Cl_3 should be zero. The parameters are returned in the following order; A_1 , A_2 , A_3 , λ_1 , λ_2 and λ_3 (Eq. (5.1))

5.4 CsdTce

`CsdTce()` calculates the context sensitive decrement time for the effect compartment. The function simulates a target controlled infusion pump maintaining an arbitrary constant effect-site concentration for different times (durations). It then calculates the time required for the effect-site concentration to fall by a specified percentage. `CsdTce()` is a nine argument function—none of the arguments are optional.

CsdTce Arguments

- Times:** A one column range of times, which represent the duration (or context) of the effect-site TCI simulation. The first row does not need to be zero. Indeed, if any times are entered that are earlier than the peak effect-site concentration after an intravenous bolus (t_{peak}), the function returns the value zero.
- A1:** The first coefficient for a one-, two- or three-compartment mammillary model (A_1 , eqn. 5.1). This can be the value of the A1 parameter or the cell reference with the value of the A1 parameter.
- A2:** The second coefficient for a two- or three-compartment mammillary model (A_2 , eqn. 5.1). This can be the value of the A2 parameter or the cell reference with the value of the A2 parameter. For a one-compartment model this coefficient should be zero.
- A3:** The third coefficient for a three-compartment mammillary model (A_3 , eqn. 5.1). This can be the value of the A3 parameter or the cell reference with the value of the A3 parameter. For a one- or two-compartment model this coefficient should be zero.
- L1:** The first hybrid rate constant for one, two or three compartment mammillary model (λ_1 , eqn. 5.1). This can be the value of the L1 parameter or the cell reference with the value of the L1 parameter.
- L2:** The second hybrid rate constant for two or three compartment mammillary model (λ_2 , eqn. 5.1). This can be the value of the L2 parameter or the cell reference with the value of the L2 parameter. For a one- or two-compartment model this hybrid rate constant should be zero.
- L3:** The third hybrid rate constant for three compartment mammillary model (λ_3 , Eq. (5.1)). This can be the value of the L3 parameter or the cell reference with the value of the L3 parameter. For a two-compartment model this hybrid rate constant should be zero.
- ke0:** The rate constant out of the effect compartment (k_{e0}).
- Decrement:** The percentage decrement, e.g., 50 for 50%, 80 for 80%. The time for 80% decrement will be longer than for 50% decrement.

5.5 CsdCp

`CsdCp()` calculates the context sensitive decrement time for the plasma. The function simulates a target controlled infusion pump maintaining an arbitrary constant plasma concentration for different times (durations). It then calculates the time required for the plasma concentration to fall by a specified percentage. `CsdCp()` is a eight argument function—none of the arguments are optional.

CsdCp Arguments

Times: A one column range of times, which represent the duration (or context) of the plasma TCI simulation. The first row does not need to be zero. Indeed, if any times are entered that are earlier than the peak plasma concentration after an intravenous bolus (t_{peak}), the function returns the value zero.

A1: The first coefficient for a one-, two- or three-compartment mammillary model (A_1 , eqn. 5.1). This can be the value of the A1 parameter or the cell reference with the value of the A1 parameter.

A2: The second coefficient for a two- or three-compartment mammillary model (A_2 , eqn. 5.1). This can be the value of the A2 parameter or the cell reference with the value of the A2 parameter. For a one-compartment model this coefficient should be zero.

A3: The third coefficient for a three-compartment mammillary model (A_3 , eqn. 5.1). This can be the value of the A3 parameter or the cell reference with the value of the A3 parameter. For a one- or two-compartment model this coefficient should be zero.

L1: The first hybrid rate constant for one, two or three compartment mammillary model (λ_1 , eqn. 5.1). This can be the value of the L1 parameter or the cell reference with the value of the L1 parameter.

L2: The second hybrid rate constant for two or three compartment mammillary model (λ_2 , eqn. 5.1). This can be the value of the L2 parameter or the cell reference with the value of the L2 parameter. For a one- or two-compartment model this hybrid rate constant should be zero.

L3: The third hybrid rate constant for three compartment mammillary model (λ_3 , Eq. (5.1)). This can be the value of the L3 parameter or the cell reference with the value of the L3 parameter. For a two-compartment model this hybrid rate constant should be zero.

Decrement: The percentage decrement, e.g., 50 for 50%, 80 for 80%. The time for 80% decrement will be longer than for 50% decrement.

5.6 JanLBM

`JanLBM` calculates the lean body mass (LBM) according to the equations by Janmahsatian *et al.*[6]. `JanLBM` is a three argument function—none of the arguments are optional.

JanLBM Arguments

Weight: Mass in kg. This can be the value of the `Weight` or the cell reference with the value of the `Weight`.

Height: Height in cm. This can be the value of the `Height` or the cell reference with the value of the `Height`.

Gender: Male = 1, Female = 0. This can be the value of the `Gender` or the cell reference with the value of the `Gender`.

5.7 JLBM

JLBM calculates the lean body mass (LBM) according to the James equations[5]. Note the ‘odd behaviour’ of the James equations in the obese[3].

$$\text{If male, then } LBM = 1.1 \cdot \text{Weight} - 128 \cdot \left(\frac{\text{Weight}}{\text{Height}}\right)^2 \quad (5.3)$$

$$\text{If female, then } LBM = 1.07 \cdot \text{Weight} - 148 \cdot \left(\frac{\text{Weight}}{\text{Height}}\right)^2 \quad (5.4)$$

The equations describe an inverted parabola, which result in a decreasing LBM (eventually negative!) with increasing total mass above a BMI of approximately 36 (females) and 42 (males) $\text{kg} \cdot \text{m}^{-2}$. JLBM is a three argument function—none of the arguments are optional.

JLBM Arguments

Weight: Mass in kg. This can be the value of the `Weight` or the cell reference with the value of the `Weight`.

Height: Height in cm. This can be the value of the `Height` or the cell reference with the value of the `Height`.

Gender: Male = 1, Female = 0. This can be the value of the `Gender` or the cell reference with the value of the `Gender`.

5.8 Hyb2Cl

`Hyb2Cl()` converts the coefficients and hybrid rate constants of a three-compartment mammillary model into the volumes and clearances. `Hyb2Cl()` is a one argument function.

Hyb2Cl Arguments

Parameters: A one column range of six pharmacokinetic parameters; A_1 , A_2 , A_3 , λ_1 , λ_2 and λ_3 (Eq. (5.1)). The coefficients and hybrid rate constant parameters must be given in this order. To specify a two-compartment model A_3 and λ_3 should be zero. To specify a one-compartment model A_2 , A_3 , λ_2 and λ_3 should be zero. The parameters are returned in the following order; V_1 , V_2 , V_3 , Cl_1 , Cl_2 and Cl_3 .

5.9 PredCp

`PredCp()` calculates the predicted plasma concentration (C_p) at each time based on any number of boluses and infusions. `PredCp` is a nine argument function—none of the arguments are optional.

PredCp Arguments

DeltaTimes: A one column range of ‘delta’ times. The first row should be zero. All other rows should be greater or equal to zero. If your basic time units are minutes (i.e., the units of λ_1 , λ_2 and λ_3 are min^{-1}) then the `DeltaTimes` units should also be minutes. Thus, if you want the function to update the infusion rate every six seconds, you should enter zero in the first row and 0.1 in every subsequent row.

Rate: A one column range of intravenous infusion rates. According to our convention, the infusion rate at time zero is zero. At every other time, the infusion rate runs from the previous time (given on the previous row) up to the current time (given on the current row). If there are no infusions, all rows should be zero.

Bolus: A one column range of intravenous bolus doses. If there are no bolus doses, all rows should be zero. The dose in any row is assumed to be given ‘instantaneously’ at that time.

A1: The first coefficient for a one-, two- or three-compartment mammillary model (A_1 , eqn. 5.1). This can be the value of the `A1` parameter or the cell reference with the value of the `A1` parameter.

A2: The second coefficient for a two- or three-compartment mammillary model (A_2 , eqn. 5.1). This can be the value of the `A2` parameter or the cell reference with the value of the `A2` parameter. For a one-compartment model this coefficient should be zero.

A3: The third coefficient for a three-compartment mammillary model (A_3 , eqn. 5.1). This can be the value of the `A3` parameter or the cell reference with the value of the `A3` parameter. For a one- or two-compartment model this coefficient should be zero.

L1: The first hybrid rate constant for one, two or three compartment mammillary model (λ_1 , eqn. 5.1). This can be the value of the `L1` parameter or the cell reference with the value of the `L1` parameter.

L2: The second hybrid rate constant for two or three compartment mammillary model (λ_2 , eqn. 5.1). This can be the value of the `L2` parameter or the cell reference with the value of the `L2` parameter. For a one- or two-compartment model this hybrid rate constant should be zero.

L3: The third hybrid rate constant for three compartment mammillary model (λ_3 , Eq. (5.1)). This can be the value of the `L3` parameter or the cell reference with the value of the `L3` parameter. For a two-compartment model this hybrid rate constant should be zero.

5.10 PredCe

`PredCe()` calculates the predicted effect-site concentration (C_e) at each time based on any number of boluses and infusions. `PredCe` is a ten argument function—none of the arguments are optional.

PredCe Arguments

DeltaTimes: A one column range of ‘delta’ times. The first row should be zero. All other rows should be greater or equal to zero. If your basic time units are minutes (i.e., the units of λ_1 , λ_2 and λ_3 are min^{-1}) then the `DeltaTimes` units should also be minutes. Thus, if you want the function to update the infusion rate every six seconds, you should enter zero in the first row and 0.1 in every subsequent row.

Rate: A one column range of intravenous infusion rates. According to our convention, the infusion rate at time zero is zero. At every other time, the infusion rate runs from the previous time (given on the previous row) up to the current time (given on the current row). If there are no infusions, all rows should be zero.

Bolus: A one column range of intravenous bolus doses. If there are no bolus doses, all rows should be zero. The dose in any row is assumed to be given ‘instantaneously’ at that time.

A1: A single cell giving the value of the first coefficient for a one-, two- or three-compartment mammillary model.

A2: A single cell giving the value of the second coefficient for a two- or three-compartment mammillary model. For a one-compartment model this coefficient should be zero.

A3: A single cell giving the value of the third coefficient for a three-compartment mammillary model. For a one- or two-compartment model this coefficient should be zero.

A1: The first coefficient for a one-, two- or three-compartment mammillary model (A_1 , eqn. 5.1). This can be the value of the **A1** parameter or the cell reference with the value of the **A1** parameter.

A2: The second coefficient for a two- or three-compartment mammillary model (A_2 , eqn. 5.1). This can be the value of the **A2** parameter or the cell reference with the value of the **A2** parameter. For a one-compartment model this coefficient should be zero.

A3: The third coefficient for a three-compartment mammillary model (A_3 , eqn. 5.1). This can be the value of the **A3** parameter or the cell reference with the value of the **A3** parameter. For a one- or two-compartment model this coefficient should be zero.

L1: The first hybrid rate constant for one, two or three compartment mammillary model (λ_1 , eqn. 5.1). This can be the value of the **L1** parameter or the cell reference with the value of the **L1** parameter.

L2: The second hybrid rate constant for two or three compartment mammillary model (λ_2 , eqn. 5.1). This can be the value of the L2 parameter or the cell reference with the value of the L2 parameter. For a one- or two-compartment model this hybrid rate constant should be zero.

L3: The third hybrid rate constant for three compartment mammillary model (λ_3 , Eq. (5.1)). This can be the value of the L3 parameter or the cell reference with the value of the L3 parameter. For a two-compartment model this hybrid rate constant should be zero.

ke0: The rate constant out of the effect compartment (k_{e0}).

5.11 PredEff

`PredEff()` calculates the predicted effect based on the sigmoidal E_{\max} model (Eq. (5.5)). `PredEff()` is a five argument function—none of the arguments are optional.

$$E(t) = E_0 + (E_{\max} - E_0) \frac{C_e^\gamma}{C_e^\gamma + C_{50}^\gamma} \quad (5.5)$$

PredEff Arguments

Ce: A one column range of effect-site concentrations (C_e , Eq. (5.5)).

Ezero: The baseline effect (E_0 , Eq. (5.5)). This can be the value of the **Ezero** parameter or the cell reference with the value of the **Ezero** parameter.

Emax: The maximum effect (E_{\max} , Eq. (5.5)). This can be the value of the **Emax** parameter or the cell reference with the value of the **Emax** parameter.

C50: The concentration associated with half the maximum effect ($(E_{\max} - E_0)C_{50}$, Eq. (5.5)). This can be the value of the **C50** parameter or the cell reference with the value of the **C50** parameter.

Gamma: The ‘steepness’ parameter (γ , Eq. (5.5)). This can be the value of the **Gamma** parameter or the cell reference with the value of the **Gamma** parameter. Sometimes called the Hill coefficient, n .

5.12 TciCe

`TciCe()` calculates the infusion rate required during each time interval to keep the effect-site concentration (C_e) constant. When C_e is within 3% of the targeted concentration, the algorithm switches to target the plasma. According to our convention, the infusion rate at time zero is zero. At every other time, the infusion rate returned by the function runs from the previous time (given on the previous row) up to the current time (given on the current row). `TciCe()` is a ten argument function—none of the arguments are optional.

TciCe Arguments

DeltaTimes: A one column range of ‘delta’ times. The first row should be zero. All other rows should be greater or equal to zero. If your basic time units are minutes (i.e., the units of λ_1 , λ_2 and λ_3 are min^{-1}) then the **DeltaTimes** units should also be minutes. Thus, if you want the function to update the infusion rate every six seconds, you should enter zero in the first row and 0.1 in every subsequent row.

Target: A one column range of target effect-site concentrations. The first row should be zero. All other rows can be greater or equal to zero.

MaxRate: The maximum pump rate in units of amount of drug per unit time. This can be the value of the **MaxRate** or the cell reference with the value of the **MaxRate**. The units of amount should be the same as **Bolus** units and the units of time should be the same as the **DeltaTimes** units. This is not the same as the maximum pump rate in $\text{ml}\cdot\text{h}^{-1}$. However, if you know the maximum pump rate in units of $\text{ml}\cdot\text{h}^{-1}$, and you know the concentration of the drug, then you can easily calculate the **MaxRate**.

A1: The first coefficient for a one-, two- or three-compartment mammillary model (A_1 , eqn. 5.1). This can be the value of the A1 parameter or the cell reference with the value of the A1 parameter.

A2: The second coefficient for a two- or three-compartment mammillary model (A_2 , eqn. 5.1). This can be the value of the A2 parameter or the cell reference with the value of the A2 parameter. For a one-compartment model this coefficient should be zero.

A3: The third coefficient for a three-compartment mammillary model (A_3 , eqn. 5.1). This can be the value of the A3 parameter or the cell reference with the value of the A3 parameter. For a one- or two-compartment model this coefficient should be zero.

L1: The first hybrid rate constant for one, two or three compartment mammillary model (λ_1 , eqn. 5.1). This can be the value of the L1 parameter or the cell reference with the value of the L1 parameter.

L2: The second hybrid rate constant for two or three compartment mammillary model (λ_2 , eqn. 5.1). This can be the value of the L2 parameter or the cell reference with the value of the L2 parameter. For a one- or two-compartment model this hybrid rate constant should be zero.

L3: The third hybrid rate constant for three compartment mammillary model (λ_3 , Eq. (5.1)). This can be the value of the L3 parameter or the cell reference with the value of the L3 parameter. For a two-compartment model this hybrid rate constant should be zero.

ke0: The rate constant out of the effect compartment (k_{e0}).

5.13 TciCp

`TciCp()` calculates the infusion rate required during each time interval to keep the plasma concentration constant. According to our convention, the infusion rate at time zero is zero. At every other time, the infusion rate returned by the function runs from the previous time (given on the previous row) up to the current time (given on the current row). `TciCp()` is a nine argument function—none of the arguments are optional. This function differs from the `CalcRate` function in that there is no `Bolus` argument.

TciCp Arguments

DeltaTimes: A one column range of ‘delta’ times. The first row should be zero. All other rows should be greater or equal to zero. If your basic time units are minutes (i.e., the units of λ_1 , λ_2 and λ_3 are min^{-1}) then the `DeltaTimes` units should also be minutes. Thus, if you want the function to update the infusion rate every six seconds, you should enter zero in the first row and 0.1 in every subsequent row.

Target: A one column range of target plasma concentrations. The first row should be zero. All other rows can be greater or equal to zero.

MaxRate: The maximum pump rate in units of amount of drug per unit time. This can be the value of the `MaxRate` or the cell reference with the value of the `MaxRate`. The units of amount should be the same as `Bolus` units and the units of time should be the same as the `DeltaTimes` units. This is not the same as the maximum pump rate in $\text{ml}\cdot\text{h}^{-1}$. However, if you know the maximum pump rate in units of $\text{ml}\cdot\text{h}^{-1}$, and you know the concentration of the drug, then you can easily calculate the `MaxRate`.

A1: The first coefficient for a one-, two- or three-compartment mammillary model (A_1 , eqn. 5.1). This can be the value of the `A1` parameter or the cell reference with the value of the `A1` parameter.

A2: The second coefficient for a two- or three-compartment mammillary model (A_2 , eqn. 5.1). This can be the value of the `A2` parameter or the cell reference with the value of the `A2` parameter. For a one-compartment model this coefficient should be zero.

A3: The third coefficient for a three-compartment mammillary model (A_3 , eqn. 5.1). This can be the value of the `A3` parameter or the cell reference with the value of the `A3` parameter. For a one- or two-compartment model this coefficient should be zero.

L1: The first hybrid rate constant for one, two or three compartment mammillary model (λ_1 , eqn. 5.1). This can be the value of the `L1` parameter or the cell reference with the value of the `L1` parameter.

L2: The second hybrid rate constant for two or three compartment mammillary model (λ_2 , eqn. 5.1). This can be the value of the `L2` parameter or the cell reference with the value of the `L2` parameter. For a one- or two-compartment model this hybrid rate constant should be zero.

L3: The third hybrid rate constant for three compartment mammillary model (λ_3 , Eq. (5.1)). This can be the value of the L3 parameter or the cell reference with the value of the L3 parameter. For a two-compartment model this hybrid rate constant should be zero.

5.14 TPeak

`TPeak()` calculates the time of the peak effect-site concentration after an intravenous bolus[9]. `TPeak()` is a seven argument function—none of the arguments are optional.

TPeak Arguments

A1: The first coefficient for a one-, two- or three-compartment mammillary model (A_1 , eqn. 5.1). This can be the value of the A1 parameter or the cell reference with the value of the A1 parameter.

A2: The second coefficient for a two- or three-compartment mammillary model (A_2 , eqn. 5.1). This can be the value of the A2 parameter or the cell reference with the value of the A2 parameter. For a one-compartment model this coefficient should be zero.

A3: The third coefficient for a three-compartment mammillary model (A_3 , eqn. 5.1). This can be the value of the A3 parameter or the cell reference with the value of the A3 parameter. For a one- or two-compartment model this coefficient should be zero.

L1: The first hybrid rate constant for one, two or three compartment mammillary model (λ_1 , eqn. 5.1). This can be the value of the L1 parameter or the cell reference with the value of the L1 parameter.

L2: The second hybrid rate constant for two or three compartment mammillary model (λ_2 , eqn. 5.1). This can be the value of the L2 parameter or the cell reference with the value of the L2 parameter. For a one- or two-compartment model this hybrid rate constant should be zero.

L3: The third hybrid rate constant for three compartment mammillary model (λ_3 , Eq. (5.1)). This can be the value of the L3 parameter or the cell reference with the value of the L3 parameter. For a two-compartment model this hybrid rate constant should be zero.

ke0: The rate constant out of the effect compartment (k_{e0}).

5.15 TPeak2ke0

`TPeak2ke0()` calculates the k_{e0} that would result in the desired time of the peak effect-site concentration after an intravenous bolus[9]. `TPeak2ke0()` is a seven argument function—none of the arguments are optional. The functions `TPeak2ke0()` and `Tpeak()` can be used to interconvert t_{peak} and k_{e0} .

TPeak2ke0 Arguments

- A1:** The first coefficient for a one-, two- or three-compartment mammillary model (A_1 , eqn. 5.1). This can be the value of the A1 parameter or the cell reference with the value of the A1 parameter.
- A2:** The second coefficient for a two- or three-compartment mammillary model (A_2 , eqn. 5.1). This can be the value of the A2 parameter or the cell reference with the value of the A2 parameter. For a one-compartment model this coefficient should be zero.
- A3:** The third coefficient for a three-compartment mammillary model (A_3 , eqn. 5.1). This can be the value of the A3 parameter or the cell reference with the value of the A3 parameter. For a one- or two-compartment model this coefficient should be zero.
- L1:** The first hybrid rate constant for one, two or three compartment mammillary model (λ_1 , eqn. 5.1). This can be the value of the L1 parameter or the cell reference with the value of the L1 parameter.
- L2:** The second hybrid rate constant for two or three compartment mammillary model (λ_2 , eqn. 5.1). This can be the value of the L2 parameter or the cell reference with the value of the L2 parameter. For a one- or two-compartment model this hybrid rate constant should be zero.
- L3:** The third hybrid rate constant for three compartment mammillary model (λ_3 , Eq. (5.1)). This can be the value of the L3 parameter or the cell reference with the value of the L3 parameter. For a two-compartment model this hybrid rate constant should be zero.
- tpeak:** The time of the peak effect-site concentration after an intravenous bolus (t_{peak}).

5.16 VdPeak

VdPeak() calculates the apparent volume of distribution at the time of the peak effect-site concentration after an intravenous bolus[9]. Vdpeak() is a seven argument function—none of the arguments are optional.

VdPeak Arguments

- A1:** The first coefficient for a one-, two- or three-compartment mammillary model (A_1 , eqn. 5.1). This can be the value of the A1 parameter or the cell reference with the value of the A1 parameter.
- A2:** The second coefficient for a two- or three-compartment mammillary model (A_2 , eqn. 5.1). This can be the value of the A2 parameter or the cell reference with the value of the A2 parameter. For a one-compartment model this coefficient should be zero.
- A3:** The third coefficient for a three-compartment mammillary model (A_3 , eqn. 5.1). This can be the value of the A3 parameter or the cell reference with the value of the A3 parameter. For a one- or two-compartment model this coefficient should be zero.

- L1:** The first hybrid rate constant for one, two or three compartment mammillary model (λ_1 , eqn. 5.1). This can be the value of the L1 parameter or the cell reference with the value of the L1 parameter.
- L2:** The second hybrid rate constant for two or three compartment mammillary model (λ_2 , eqn. 5.1). This can be the value of the L2 parameter or the cell reference with the value of the L2 parameter. For a one- or two-compartment model this hybrid rate constant should be zero.
- L3:** The third hybrid rate constant for three compartment mammillary model (λ_3 , Eq. (5.1)). This can be the value of the L3 parameter or the cell reference with the value of the L3 parameter. For a two-compartment model this hybrid rate constant should be zero.
- ke0:** The rate constant out of the effect compartment (k_{e0}).

Part III

Appendices

Appendix A

Quotations

A. W. Astin

As long as faculty in the research universities are expected simultaneously to perform research, teaching, advising, university service, and outside professional activities, teaching and advising will continue to receive low priority.

Aaron Levenstein

Statistics are like a bikini. What they reveal is suggestive, but what they conceal is vital.

Abraham Lincoln

Give me six hours to chop down a tree and I will spend the first four sharpening the axe.

Things may come to those who wait, but only the things left by those who hustle.

Albert Einstein

I think and think for months and years, ninety-nine times the conclusion is false. The hundredth time I am right.

Things should be made as simple as possible, but not simpler.

The significant problems we face cannot be solved at the same level of thinking we were at when we created them.

Education is that which remains when one has forgotten everything he learned in school.

How do I work? I grope.

It is a miracle that curiosity survives formal education.

If we knew what it was we were doing, it would not be called research, would it?

Science is a wonderful thing if one does not have to earn one's living at it.

As far as the laws of mathematics refer to reality, they are not certain; and as far as they are certain, they do not refer to reality.

Do not worry about your problems with mathematics, I assure you mine are far greater.

Alexander Hamilton

Men give me some credit for genius. All the genius I have lies in this: When I have a subject in hand, I study it profoundly. Day and night it is before me. I explore it in all its bearings. My mind becomes pervaded with it. Then the efforts that I make are what people are pleased to call the fruits of genius. It is the fruit of labour and thought.

Alvin Toffler

The illiterate of the 21st century will not be those who cannot read and write, but those who cannot learn, unlearn, and relearn.

Amerigo Vespucci

Rationally, let it be said in a whisper, experience is certainly worth more than theory.

Amos Bronson Alcott

Our bravest and best lessons are not learned through success, but through misadventure.

Andrew Carnegie

No man will make a great leader who wants to do it all himself or get all the credit for doing it.

Andy Capp

I've learned one thing—people who know the least anyways seem to know it the loudest.

Anthony Hope

Unless one is a genius, it is best to aim at being intelligible.

Aristotle

It is the mark of an educated mind to be able to entertain a thought without accepting it.

Arthur Balfour

Most people prefer the existence of a problem which they cannot understand, to an explanation of it which they cannot understand.

Arthur C. Clarke

New ideas pass through three periods: It can't be done; it probably can be done, but it's not worth doing; I knew it was a good idea all along!

Auguste Rodin

What makes my *Thinker* think is that he thinks not only with the brain, with his knitted brow, his distended nostrils, and compressed lips, but with every muscle of his arms, back and legs, with his clenched fist and gripping toes.

Benjamin Disraeli

There are three kinds of lies: lies, damned lies, and statistics.

Bertrand Russell

Although this may seem a paradox, all exact science is dominated by the idea of approximation.

Bill Cosby

I don't know the key to success, but the key to failure is trying to please everybody.

Bill Vaughan

People learn something every day, and a lot of times it's that what they learned the day before was wrong.

C. J. Bradfield

Statistics is the art of never having to say you're wrong. Variance is what any two statisticians are at.

C. S. Lewis

In any fairly large and talkative community such as a university there is always the danger that those who think alike should gravitate together where they will henceforth encounter opposition only in the emasculated form of rumour that the outsiders say thus and thus. The absent are easily refuted, complacent dogmatism thrives, and differences of opinion are embittered by the group hostility. Each group hears not the best, but the worst, that the other group can say.

Cardinal De Retz

Nothing sways the stupid more than arguments they can't understand.

Charles Buxton

You will never "find" time for anything. If you want time, you must make it.

Charles Dickens

Whatever I have tried to do in life, I have tried with all my heart to do well; whatever I have devoted myself to, I have devoted myself to completely.

Charles P. McCormick

Two men working as a team will produce more than three men working as individuals.

Charles Proteus Steinmetz

There are no foolish questions and no man becomes a fool until he has stopped asking questions.

Chinese Proverb

One who asks a question is a fool for five minutes; one who does not ask a question remains a fool forever.

Colin Wood

In many cases it is those calling other people control freaks who are really the people who wish to call the shots.

Dag Hammarskjöld

Only he deserves power who every day justifies it.

Time goes by: reputation increases, ability declines.

Dale Carnegie

A country preacher once asked Henry Ward Beecher how to keep an audience awake on a hot Sunday afternoon, and Beecher told him to have an usher take a sharp stick and prod the preacher.

Daniel Goleman

Emotional competence is particularly central to leadership, a role whose essence is getting others to do their jobs more effectively. Interpersonal ineptitude in leaders lowers everyone's performance: It wastes time, creates acrimony, corrodes motivation and commitment, builds hostility and apathy. A leader's strengths or weaknesses in emotional competence can be measured in the gain or loss to the organization of the fullest talents of those they manage.

Darrel Huff

(*How to Lie with Statistics, 1954*) It's like the tale of the roadside merchant who was asked to explain how he could sell rabbit sandwiches so cheap. "Well," he explained, "I have to put some horse-meat in too. But I mix them 50:50. One horse, one rabbit."

David Brent, The Office

If at first you don't succeed, remove all evidence you ever tried.

You have to be 100 per cent behind someone before you can stab them in the back.

Eagles may soar high, but weasels don't get sucked into jet engines.

There may be no 'I' in team, but there's a 'me' if you look hard enough.

If your boss is getting you down, look at him through the prongs of a fork and imagine him in jail.

Accept that some days you are the pidgeon and some days you are the statue.

Remember that age and treachery will always triumph over youth and ability.

Dwight Morrow

The world is divided into people who do things and people who get the credit. Try, if you can, to belong to the first class. There's far less competition.

E. H. Harriman

Much good work is lost for the lack of a little more.

Edmund Burke

Never despair, but, if you do, work on in despair.

Elbert Hubbard

The recipe for perpetual ignorance is to be satisfied with your opinions and content with your knowledge.

Pray that success will not come any faster than you are able to endure it.

Eleanor Roosevelt

Great minds discuss ideas. Average minds discuss events. Small minds discuss people.

Elizabeth Dew

Too often travel, instead of broadening the mind, merely lengthens the conversation.

Émile-Auguste Chartier

(*La Lumière*) Nothing is more dangerous than an idea, when it's the only one we have.

Encyclopaedia Britannica

Nine readers out of ten take a lucid statement for a true one.

Enrique Jardiel Poncela

When something can be read without effort, great effort has gone into its writing.

Ernest Rutherford

If your result needs a statistician then you should design a better experiment.

Eugène Labiche

(*Le Voyage de M Perrichon*) Before doing someone a favour, make sure that he isn't a madman.

Evan Esar

Statistics: The only science that enables different experts using the same figures to draw different conclusions.

Extreme Programming Pocket Guide: O'Reilly

In pair programming, two developers work together to accomplish a single task. The person with the keyboard—the driver—focuses on the details of the task. He thinks tactically. The other person—the navigator—keeps the entire project in mind, ensuring that the task fits into the project as a whole and keeping track of team guidelines.

Francis Bacon

Reading maketh a full man, conference; a ready man, and writing; an exact man.

Frank Tyger

Getting an idea should be like sitting down on a pin; it should make you jump up and do something.

Franklin Delano Roosevelt

Happiness lies not in the mere possession of money; it lies in the joy of achievement, in the thrill of creative effort. The joy and moral stimulation of work no longer must be forgotten in the mad chase of evanescent profits.

Franklin Jones

Experience is that marvelous thing that enables you to recognize a mistake when you make it again.

Franklin P. Adams

I find that a great part of the information I have was acquired by looking up something and finding something else along the way.

G. K. Chesterton

Without education we are in a horrible and deadly danger of taking educated people seriously.

G. N. Lewis

But perfection is rare in the science of chemistry. Our scientific theories do not as a rule spring full-armed from the brow of their creator. They are subject to slow and gradual growth.

Science has its cathedrals, built by the efforts of a few architects and of many workers.

Galileo Galilei

In questions of science, the authority of a thousand is not worth that humble reasoning of a single individual.

George Bernard Shaw

Education is . . . a succession of eye-openers each involving the repudiation of some previously held belief.

Few people think more than two or three times a year. I have made an international reputation for myself by thinking once or twice a week.

It is the mark of a truly intelligent person to be moved by statistics.

George Patton

A leader is a man who can adapt principles to circumstances.

Ginger Meggs

Experience is what you get when you should have known better.

Gottfried Wilhelm Leibnitz

It is unworthy of excellent men to lose hours, like slaves, in the labors of calculation.

Gregg Easterbrook

Torture numbers, and they'll confess to anything.

H. G. Wells

Statistical thinking will one day be as necessary a qualification for efficient citizenship as the ability to read and write.

H. Poincaré

Experiment is the sole source of truth. It alone can teach us something new; it alone can give us certainty.

H. Tom Collard

Success is a journey—not a destination.

Hal Abelson

If I have not seen as far as others, it is because giants were standing on my shoulders.

Harry F. Banks

If at first you do succeed—try to hide your astonishment.

Henry Clay

Statistics are no substitute for judgement.

Henry Ford

Thinking is the hardest work there is, which is probably why so few engage in it.

Nothing great was ever achieved without enthusiasm.

Coming together is a beginning; keeping together is progress; working together is success.

Hilary Billings

There is a growing realisation that we're all becoming victims of the technological devices that were supposed to make our lives simpler. The proliferation of laptops, PDAs and pagers means that we're working harder and harder to keep up with our own inventions. The price of being available 24-7 is the loss of time for reflection, creative thinking and connections with our loved ones—the things that are really important for our emotional and spiritual lives.

Hippocrates

There is no authority except facts. These are obtained by accurate observation. Deductions are to be made only from facts.

Homer Adkins

Basic research is like shooting an arrow into the air and, where it lands, painting a target.

Irish Proverb

You'll never plough a field by turning it over in your mind.

Isaac Newton

I see a man must either resolve to put out nothing new or to become a slave to defend it.

If I have seen further than others, it is by standing upon the shoulders of giants.

J. Clarétie

Any man who leads, who does something, has against him those who would like to do the same thing, those who do precisely the opposite, and mostly the great army of people much more critical, who do nothing.

J. K. Lindsey

Doing statistics is exciting. In the analysis of any new data set, surprises, both good and bad, will always occur. The results can never be fully predicted in advance—or the study would not have been carried out in the first place.

J. Houston

A normal person is just someone you don't know very well.

Jessamyn West

Writing is so difficult that I feel that writers, having had their hell on earth, will escape all punishment hereafter.

Johann Wolfgang von Goethe

Everything has been thought of before, but the difficulty is to think of it again.

John G. Shedd

I like the man who bubbles over with enthusiasm. Better be a geyser than a mud puddle.

John Grier Hibben

The power to grasp the essential features of problems is the great differentiation between the educated and the non-educated man. Undoubtedly the greatest advantage to be gained from a college education is the acquisition of a disciplined mind.

John Holt

Students in school are too busy to think.

John Huxley

Records of the entire present period of history are jeopardised by precisely the technology, and the pace of the technological change, that characterised it.

John Louis von Neumann

If people do not believe that mathematics is simple, it is only because they do not realize how complicated life is.

John Maynard Keynes

The difficulty lies, not in the new ideas, but in escaping the old ones, which ramify, for those brought up as most of us have been, into every corner of our minds.

John McPhee

If at first it doesn't fit, fit, fit again.

John Steinbeck

It is a common experience that a problem difficult at night is resolved in the morning after the committee of sleep has worked on it.

John von Neumann

The sciences do not to try to explain, they hardly even try to interpret, they mainly make models. By a model is meant a mathematical construct, which, with the addition of certain verbal interpretation, describes observed phenomena. The justification of such a mathematical construct is solely and precisely that it is expected to work.

John Walkenbach

Old spreadsheets never die; they just lose some of their functions.

The spreadsheet industry is a race between software engineers striving to build bigger and better idiot-proof programs, and the Universe trying to produce bigger and better idiots. So far, the Universe is winning.

If Excel were a car . . . it would crash two or three times per day for no apparent reason. The driver is often hurt, but the car itself receives no permanent damage. You'd just accept this fact, restart the car, and begin your trip again.

Spreadsheet Solver: A spreadsheet tool usually used by geeks who want to bring their computer's processor to its knees. No valid data is ever obtained, but it makes you feel good that you forced your computer to think for more than half a second.

Spreadsheet general protection fault: What happens when you finally get your spreadsheet working correctly; but before you've had a chance to save it.

Spreadsheet formula: A mathematical equation that displays as #NAME?, #ERR!, #DIV/0! or #N/A!

A spreadsheet wizard: An interface enhancement that enables you to create complex and sophisticated errors at unprecedented speeds.

If Excel were a car . . . before engaging, the airbag system would display a message, "Are you sure?"

You might be a spreadsheet junkie if . . . your wife says "If you don't turn off that damn machine and come to bed, then I am going to divorce you!"—and you chastise her for omitting the "else" clause.

You might be a spreadsheet junkie if . . . your doctor recommends an IV—and you think of the last column in a worksheet.

Kenneth A. Bollen

When evaluating a model, at least two broad standards are relevant. One is whether the model is consistent with the data. The other is whether the model is consistent with the "real world."

Kenneth G. Johnson

Education is . . . man's going forward from cocksure ignorance to thoughtful uncertainty.

Konrad Lorenz

It is a good morning exercise for a research scientist to discard a pet hypothesis every day before breakfast. It keeps him young.

Laplace

The theory of probabilities is at bottom nothing but common sense reduced to calculus.

Laurence Peter

If a cluttered desk is the sign of a cluttered mind, what is the significance of a clean desk?

Lawrence Peter ‘Yogi’ Berra

In theory there is no difference between theory and practice. In practice there is.

Leonardo Da Vinci

As every divided kingdom fails, so every mind divided between many studies confounds and saps itself.

Linus Torvalds

Do you pine for the nice days of minix-1.1, when men were men and wrote their own device drivers?

Lloyd Alexander

We learn more by looking for the answer to a question and not finding it than we do from learning the answer itself.

Louis Pasteur

In the field of observation, chance favors only the prepared mind.

Ludwig Wittgenstein

A man will be imprisoned in a room with a door that’s unlocked and opens inwards; as long as it does not occur to him to pull rather than push.

Lynn Harold Hough

Soak yourself full of the world’s best literature so that you will have words, strong words, clear words, for your speaking.

Malcolm Forbes

It’s the less-bright students who make teachers better.

He who says he never needs help, most does.

Mark Twain

Most writers regard truth as their most valuable possession, and therefore are most economical in its use.

I was gratified to be able to answer promptly, and I did. I said I didn’t know.

Max Gluckman

A science is any discipline in which a fool of this generation can go beyond the point reached by the genius of the last generation.

Max Gyll

Eventually, everything we currently believe will be revised. What we believe, then, is necessarily untrue. We can then only believe in things that are not the truth ... I think.

Michael Barber

(The Learning Game) Teacher to pupil: “What are you doing?” Pupil to teacher: “I’m thinking.” Teacher to pupil: “Well, stop it and get on with your work.”

Microsoft Excel Developer's Kit

Writing DLLs is slightly more complex than writing normal Windows code, which in turn is more complex than writing normal C programs. Make sure you understand both before you begin.

Nathaniel Hawthorne

Easy reading is damn hard writing.

Nicholas Murray Butler

An expert is one who knows more and more about less and less.

Niels Bohr

Anyone who is not shocked by quantum theory has not understood it.

Norbert Wiener

A professor is one who can speak on any subject—for precisely fifty minutes.

Paul A. Meglitsch

Nearly every great discovery in science has come as the result of providing a new question rather than a new answer.

Paul Getty

No man's opinions are better than his information.

Penny Chapman

The only interesting thing about baggage is the little bits and pieces you can take out of it. The thing is, there's no point in your past blighting you. What it can do is inform you and educate you about yourself and the rest of the world.

Phil Jauncey

There are four reasons you fail; you don't know what to do, you don't know how to do it, you don't have the ability to do it, you don't want to do it.

Rafy Marootians

Logic is a systematic method for getting the wrong conclusion with confidence. Statistics is a systematic method for getting the wrong conclusion with 95% confidence.

Ralph Richardson

I like talking to engineers best. They build bridges, they're very precise, very disciplined, yet I find they have roving minds.

Ralph Waldo Emerson

Our best thoughts come from others.

Richard Evans

History cannot create laws with predictive power. An understanding of the past might help in the present insofar as it broadens our knowledge of human nature, provides us with inspiration—or a warning—or suggests plausible, though always fallible arguments about the likely possibilities of certain things happening under certain conditions. None of this, however, comes anywhere near the immutable predictive certainty of a scientific law.

Richard Foster

Our tendency is to highly overestimate what we can accomplish in one year and highly underestimate what we can accomplish in ten years.

Richard P Feynman

It is my task to convince you not to turn away because you don't understand it. You see my physics students don't understand it . . . That is because I don't understand it. Nobody does.

Robert Frost

The brain is a wonderful organ; it starts working the moment you get up in the morning and does not stop until you get into the office.

Robert Sutton

Achieving innovation often means getting out of the way of superperformers. That means allowing them to defy corporate protocol, miss meetings, or work in their offices undisturbed 12 hours a day essentially doing whatever's necessary to stimulate and support the creative process.

Ronald G. Pearl

Since that visit, I have recognized that departments create their own culture by making choices and that the culture which develops tends to be self-perpetuating.

H. H. Munro

(*Saki, The Square Egg*) A little inaccuracy sometimes saves tons of explanation.

Samuel Johnson

He who wants to do a great deal at once will never do anything.

Samuel Karlin

The purpose of models is not to fit the data, but to sharpen the questions.

Scott Zeger

Statistical models for data are never true. The question whether a model is true is irrelevant. A more appropriate question is whether we obtain the correct scientific conclusion if we pretend that the process under study behaves according to a particular statistical model.

Seneca

My joy in learning is partly that it enables me to teach.

Sherlock Holmes

Data! Data! Data! I can't make bricks without clay!

Sigmund Freud

In the small matters trust the mind, in the large ones the heart.

Stephen Jay Gould

The invalid assumption that correlation implies cause is probably among the two or three most serious and common errors of human reasoning.

Stephen Senn

Multivariate analysis: A means of finding the answer when you don't know the question.

Equivalence: Proving that apples are pears by comparing the weight.

Sequential analysis: A means of stopping a trial before it becomes useful.

Successful drug: One in which the maximum tolerated dose is higher than the minimum effective one . . . with the exception of alcohol.

Pharmacovigilance: A game of hunt the thimble, in which you are not sure if it is a thimble you are looking for, you don't want to find it anyway and the only time anyone shouts "warm" is when you have already burned your fingers.

Project prioritisation: A scientific means of continuously ranking drugs in development until the chief executive officer's favourite project comes out on top.

If we see further than we did in the past it is because we stand on the shoulders of giants and sometimes this causes us to bang our heads on the ceiling.

Bayesian: One who, vaguely expecting a horse and catching a glimpse of a donkey, strongly concludes he has seen a mule.

A frequentist statistician asked his boss why he was only being paid for one day in twenty. He was told that this was the going rate for doing nothing.

Bayesian: One who asks you what you think before a clinical trial in order to tell you what you think afterwards.

Medical statistician: One who will not accept that Columbus discovered America . . . because he said he was looking for India in the trial plan.

The difference between a surrogate and a true endpoint is like the difference between a cheque and cash. You can often get the cheque earlier but then, it may bounce.

Pharmacokinetics: One of the magic arts of divination whereby needles are stuck into dummies in an attempt to predict profits.

Sydney A. Feldman

Kinetic modeling has become the Pop-Art of anaesthesia—stridently provoking but adding little to the understanding of clinical problems. This paper reaches a zenith of incomprehensibility in this pseudo-science. It begins by making assumptions (probably only half-truths), incorporating them in complex formulae which are adjusted to make the end result conform with the original assumption. This contrived formula is then presented as primary fact.

T. S. Eliot

Old men ought to be explorers.

Thomas A. Edison

Genius is one percent inspiration and ninety-nine percent perspiration.

Thomas B. Macaulay

Half knowledge is worse than ignorance.

Thomas E. Wilson

This is the foundation of success nine times out of ten—having confidence in yourself and applying yourself with all your might to your work.

Thomas H. Huxley

If a little knowledge is dangerous, where is the man who has so much as to be out of danger?

The great tragedy of Science: the slaying of a beautiful hypothesis by an ugly fact.

Thomas Lodge

Men, in teaching others, learn themselves.

Victor Hugo

Great blunders are often made, like large ropes, of a multitude of fibers.

Voltaire

Better is the enemy of good.

Judge a man by his questions rather than his answers.

W. C. Holman

Genius is intensity. The man who gets anything worth having is the man who goes after his object as a bulldog goes after a cat—with every fibre in him tense with eagerness and determination.

W. H. Auden

A professor is someone who talks in someone else's sleep.

W. Somerset Maugham

Only a mediocre writer is always at his best.

Walter Bagehot

One of the greatest pains to human nature is the pain of a new idea.

Wernher von Braun

Research is what I'm doing when I don't know what I'm doing.

Will Durant

Education is . . . a progressive discovery of our ignorance.

Will Rogers

There is nothing so stupid as an educated man, if you get him off the thing he was educated in.

William Cobbett

Men fail much oftener from want of perseverance than from want of talent.

William Lowe Bryan

Education is . . . one of the few things a person is willing to pay for and not get.

William Shakespeare

(As You Like It) And so, from hour to hour, we ripe and ripe, And then, from hour to hour, we rot and rot; And thereby hangs a tale.

William Strunk, Jr.

Omit needless words. Vigorous writing is concise. A sentence should contain no unnecessary words, a paragraph no unnecessary sentences, for the same reason that a drawing should have no unnecessary lines and a machine no unnecessary parts.

Winston S. Churchill

. . . man will occasionally stumble over the truth, but usually manages to pick himself up, walk over or around it, and carry on.

It is always wise to look ahead, but difficult to look farther than you can see.

I am always ready to learn, but I do not always like being taught.

The greatest lesson in life is to know that even fools are right sometimes.

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