Description of programs to implement methods described in Matthews JNS, Matthews DSF and Eyre JA, "A Statistical Method for the Estimation of Cerebral Blood Flow using the Kety-Schmidt Technique" *Clinical Science*, 1999, volume 97 (herein MME)

You are welcome to use these programs free of charge. While they have been extensively used in our research group and appear to work properly no liability is accepted for any errors that may occur as a consequence of their use.

Instructions for Use

Installation

As you are reading this file it is presumed that you have successfully downloaded and opened the self-extracting ZIP file KS_ARCH.EXE from the web site. The files you have obtained are:

manual.doc	Word 7 version of this file
manual.txt	Plain text version of this file
manual.pdf	Adobe Acrobat PDF version of this file
KS_STAT.EXE	Program to fit model I from MME
example.dat	example data set for KS_STAT
example.log	Results from running KS_STAT on example file
PROFLIK.EXE	Program to find profile likelihood interval

The executable files need to be run in a DOS box under Windows 95 or later. You can either double-click on the executable or open a MS-DOS prompt, change to the appropriate directory and type KS_STAT followed by return. They will also run under MS-DOS (alone or through Windows 3.1 etc.): they require at least a 386 processor with a 387 co-processor. Any Pentium chip will run the programs, as will any 486 DX chip.

By default files are read and written to the current directory.

Data Entry

You need to enter the data on the number of points observed on the arterial and venous curves and the times and concentrations of the marker for each of these points. It is important that the times are recorded accurately, especially for the first few points on each curve. To this end times are entered in whole numbers of minutes and seconds. It is important that you do not attempt to enter times as minutes and fractions of a minute. Internally the program converts the times to minutes and works in this unit of time throughout.

When you run KS_STAT.EXE you are asked if you wish to enter data from a file or from the terminal.

Entry from terminal: you will be prompted for the required quantities. You will be allowed to review your input to check it is correct and amend it as necessary. You will be given the opportunity to save the data to a file. The format of the file will be as used for the 'input from file' option. Indeed, entering some data from the terminal and saving it to file is probably the easiest way to discern the file format used.

Entry from file: You simply enter the name of the file containing the data. The length of this filename should be no more than eight characters plus a three character extension. For example, NUMBERS1.DAT would be allowed. The file is a plain text file. The first row comprises two integer numbers, namely the numbers of points on the arterial (n_a) and venous (n_v) curves, in that order. The rest of the file comprises n_a+n_v lines each of three columns, the first two columns being the minutes and seconds at which the concentration in the third column was observed. The first n_a of these rows are for the arterial curve and the last n_v rows apply to the venous curve. An example file is supplied as EXAMPLE.DAT.

Numerical methods

The program minimises the residual sum of squares with respect to the parameters k_a, k_v and A using the Nelder-Mead simplex algorithm (*Computer Journal*, 1965, 7, 308-313) implemented using a FORTRAN subroutine. The subroutine is based on O'Neill (Applied Statistics Algorithm AS47, *Applied Statistics*, 1971, 20, 338-345) but as amended by Wedderburn and Miller. The amended version can be obtained from the file containing AS47 in the archive maintained at STATLIB (UK mirror at www.hensa.ac.uk/Subject/num/statlib.html).

The routine requires starting values for the parameters and these are obtained by fitting, separately for each of the arterial and venous curves, a linear regression of log(1-x/A*) against t with no intercept, where x is the marker concentration at time t. The slope is used as the estimate of the respective k parameter. A* is 0.1+max(x). The initial estimate for A is the larger of the two A*s. These initial values are printed by the program.

Each time the program is run a file called NMFIT.RES is produced. This contains information on the progress of the fitting routine and can be inspected by anyone interested. Those not interested can delete the file. When the program is run any existing file called NMFIT.RES will be overwritten.

Output

In addition to the initial estimates of the parameters the program prints the final estimates and their standard errors (labelled ses), as computed from the expected information matrix. In addition the correlation between the estimates of the k parameters is also printed but can be ignored for most purposes. An indicator variable is also printed to allow the user to see if the simplex algorithm determined that it found a minimum. A non-zero value could indicate an unsatisfactory solution has been computed. The estimate of cerebral blood flow computed from the estimated k parameters is printed, in ml/100g/min and assuming a blood:brain partition coefficient of 1 ml/g. Its standard error computed using the delta method is also printed.

Graphics

The program will produce a plot of points and the fitted model on screen: arterial points are marked with a diagonal cross and venous points with a plus sign. The graph is very crude: it cannot easily be printed or moved to other applications and the axes are not labelled. However, it is useful to allow the analyst to inspect quickly the fit of the model. To facilitate the production of better quality graphs you can write out some useful quantities. You can save the observed points (in the format x,y) to a file (called POINTS.DAT), with the first n_a rows being the arterial points and the remainder being the venous points. The file SMOOTH.DAT will hold the co-ordinates (in the order x, y) of 302 points along the fitted curves. In a graphics package plotting the points in the former and joining the points in the latter with straight lines should give the basis of a much better plot. The names POINTS.DAT and SMOOTH.DAT are not wholly under the control of the user. If files with these names do not exist in the current directory then the program proceeds to create these two files and the user has no choice in their naming at this stage (they can, of course, be renamed outside of the program). If they do already exist then they may be over-written, although the user is asked if they wish to do this: if they do not then, and only then, will the user be invited to enter different names for these files.

Cerebral metabolic rates

On occasion it may be convenient to use the cerebral blood flow to determine various cerebral metabolic rates. The program will calculate cerebral metabolic rates for oxygen, glucose and lactate provided the user supplies appropriate extra information.

If the user asks to calculate cerebral metabolic rates then they are prompted to enter arterial and cerebrovenous measurements of quantities needed for the calculations. For the rates for glucose and lactate these are simply the arterial and cerebrovenous glucose and lactate concentrations in mmol/l. The cerebral metabolic rate for glucose, CMR(G), is found as:

$$\text{CMR(G)} = (\text{arterial glucose concentration - cerebrovenous glucose concentration}) \times \text{CBF}$$

in mumol/100g/min. The calculation for lactate is entirely analogous.

The computation for oxygen is slightly more complicated. The user must enter the haemoglobin concentration (in g/dl), the arterial and cerebrovenous oxygen saturations (as percentages) and the arterial and cerebrovenous partial pressure of oxygen PO_2 (in kPa). The cerebral metabolic rate for oxygen is calculated, in mumol/100g/min, as

$$\text{CMR(O)} = (\text{AO - VO}) \times \text{CBF}$$

where AO and VO are, respectively, the oxygen contents of arterial and cerebrovenous blood in mmol/l. These are found as

$$\text{AO}=0.393 \times \{0.0138 \times \text{arterial saturation} \times \text{haemoglobin concentration} + 0.023 \times \text{arterial } PO_2\}$$

The factor in {} gives the mls of oxygen per 100ml of blood (see, for example, *Energy Metabolism, Indirect Calorimetry, and Nutrition*, Bursztein, Elwyn, Askanazi and Kinney, Baltimore, Williams & Wilkins, 1989, p. 193) and the factor 0.393 converts this to mumol/ml at 37 celsius. There is a corresponding equation for cerebrovenous blood, namely

$$VO=0.393 \times \{0.0138 \times \text{venous saturation} \times \text{haemoglobin concentration} + 0.023 \times \text{venous } PO_2\}$$

Log file

The program allows the user to record the text output (not the graph) in a log file. The user is prompted for a name for the log file and also for an identifier (such as a patient identifier) that is recorded in the log-file: the identifier must have nine characters or fewer.

The log file records the raw data, the initial estimates of the parameters defining the saturation curve, the final estimates and their standard errors, the CBF and its standard error calculated using the delta-method. If the user has chosen to compute cerebral metabolic rates then the data on which these are based are recorded, as are the final metabolic rates. If the user has not chosen to compute metabolic rates then this part of the log file records zero values.

The log file also records the estimate of the residual variance σ^2. This is of limited practical use and does not appear on the screen when KS_STAT.EXE is run; it is recorded in the log file for completeness and specialist use.

Profile likelihood

Profile-likelihood-based interval estimates for cerebral blood flow are described in the Appendix to MME and can be calculated using the program PROFLIK.EXE. In order to use this program the data must be saved in a file in the format described in ***Data Entry*** above. The program KS_STAT.EXE must be run on the data and then the user runs PROFLIK. The user will be prompted for the name of the file containing the data. It is essential that this file contains the same data that has just been analysed by KS_STAT.EXE. The program also asks the user for the confidence level, values of 90, 95 and 99 are allowed and a profile likelihood interval is printed. Occasionally, when the arterial and venous curves are close the upper bound will be infinite (internally the program actually calculates an interval estimate for the reciprocal of the CBF and an infinite upper bound for CBF results from a lower bound of zero for its reciprocal).

The profile likelihood method requires the data and the estimates of k_a and k_v. The latter are not calculated by PROFLIK.EXE, so that is why KS_STAT.EXE must be run first. Whenever KS_STAT.EXE is run the estimates of k_a and k_v are written to 10 d.p. to the file 2prflk.dat and PROFLIK.EXE obtains the estimates by reading this file. Every time KS_STAT.EXE is run a new 2prflk.dat is written and PROFLIK.EXE does not attempt to check that the estimates of k_a and k_v it reads from 2prflk.dat are the ones that correspond to the data set specified when PROFLIK.EXE is run. It is the responsibility of the user to ensure that no conflict occurs.

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