

Help for SPAMALIZE's FDG Quantitation Tool

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I. Introduction

A. Basics

SPAMALIZE's FDG quantitation tool (SPW_FDG.PRO) converts raw [¹⁸F]-FDG PET data to metabolic rate images. These are called "quantitated" or "metabolic" images in the vernacular, and are commonly used to compare the local cerebral metabolic rate of glucose consumption (ICMRglu) between different subjects, or between the same subject scanned on different occasions.

This program implements a variation of the Sokoloff method as presented in Phelps's landmark 1979 paper:

Phelps ME, Huang SC, Hoffman EJ, Selin C, Sokoloff L, Kuhl DE,
"Tomographic measurement of local cerebral glucose metabolic
rate in humans with (F-18)2-fluoro-2-deoxy-D-glucose:
Validation of method", Ann Neurol 6:371-388, 1979.

There are 3 main parts in this program:

- 1) Create a time-activity curve (TAC) from measured blood data;
- 2) Calculate the correction factors to convert PET data from units of radioactivity concentration to metabolic rate.
- 3) Apply the correction factors to the PET data.

This program is designed to read GE/Advance PET data. Formats from other scanners could be easily incorporated with a bit of programming. Intermediate results can be saved and applied to other analysis if desired. The default behavior is to run through in one fell swoop. This program has been tested (successfully!) on SUN/unix and PC/Windows98 platforms. PC/Linux and MacIntosh success is highly probable but has not been tested.

This program was written by Terry Oakes in December 1999 at the Lab for Affective Neuroscience in the Psychology Department, University of Wisconsin-Madison. Information in this help file supercedes any other information.

Examples of the GUI interface can be found on the SPAMALIZE website:

http://psyphz.psych.wisc.edu/~oakes/spam/spam_frames.htm

B. Interface Overview

There are 5 distinct menus in this program.

1) Main control and raw image display. This menu is on the left-hand side of the GUI and is always visible. The original (raw) PET images are displayed here, and there are also a few buttons for moving through the other 4 menus. Pressing the "Write Log" button will cause a log-file to be written containing the current parameters and status.

Only one (1) of the other four (4) menus is visible at a time. These 4 "Action" menus can be seen in the right-hand side, and are accessed by the dropdown menu "Show" at the top of the left-hand menu.

The Action menus are:

- 2) Filenames: Shows required input filenames, lets user browse for and load files, and lets user override default names for output files. This is the menu which is visible when you begin.
- 3) Blood TAC: Display and manipulate measured blood data.
- 4) FDG Model: Displays the FDG model and its parameters, and allows you to see the effect on typical data values.
- 5) Metabolic Images: Displays metabolic images and average values.

Moving between any of the four Action menus causes the appropriate values to be calculated. For instance, moving from the Filenames to the Blood TAC menu causes the blood data to be read in and a new TAC is created. Moving from the Filename to the Metabolic Images menu causes all of the intermediate steps to be run, i.e. a new TAC is created, the FDG model is run, and finally the metabolic images are created and displayed.

C. Run It!

It is simple to create a set of metabolic images using SPW_FDG. If your data are in the default locations and in the expected formats, you only need to do three (3) things:

- 1) Browse for a GE/Advance raw PET file;
- 2) Move to the Metabolic Images menu;
- 3) Select the "Write Metabolic Images" button.

That's it!

You will automatically progress through the Blood TAC and the FDG Model menus. It is wise to stop at each of these menus to examine your input data, but this is not required.

II. Data Input

A. Overview

Four files are required by SPW_FDG. Two of these are standard files that are the same for every analysis and are stored in SPAMALIZE's data directory. The other two files are the raw PET data and the blood file you are interested in.

Explicitly, the four (4) required data files are:

- 1) 18F-FDG PET scan, currently from a GE/Advance PET scanner;
- 2) Blood file, in the format defined in this help document;
- 3) Composite or ideal blood TAC on a 1-second grid;
- 4) Kinetic model parameter file.

B. PET data

This program uses data from the GE/Advance PET scanner. Other file formats could be used with some modification (see comments in program). The data should be the result of a "IEEE Unarchive" operation. At the LfAN, Robert Pyzalski or Joni Hanson usually do this.

Previous protocols named GE/Advance PET files something like:

a1234.mac128

where:

- 1234 is the patient scan number

- mac stands for "measured attenuation correction", the alternative is cac, which stands for "calculated attenuation correction".
- 128 is the size of the reconstructed images, i.e. 128x128 pixels.

Current protocols should use a naming convention like:
a1234_mac128.pet

In their native format, GE/Advance images are stored with the top of the head in plane #1, with the anterior portion (nose) stored first in each image, and in the radiological convention (patient's left appears on the right-hand side of the image). If the images are displayed by starting to draw from the bottom of a window (which is the default for SPAMALIZE, IDL, and many image display programs) the images will appear upside-down. This program (SPW_FDG) begins drawing from the top, so the images will appear right-side up. However, there is no flipping of any sort to the data itself (either top/bottom or left/right), so subsequent display programs may show the data as upside down.

The GE/Advance data can include a single frame or multi-frame data. The standard approach used by GEMS in creating a PET file is to decay-correct each image to the scan_start, which is the time of the beginning of the scan (not necessarily the frame). The program used to read the GE/Advance data (SPAM_READ_GE) spits out images that have all corrections applied and are in units of radioactivity concentration (microCi/cc).

C. Blood data

The blood data should be in an ASCII text file, in a format defined elsewhere in this Help document. Typically the blood data are named something like:

a1234_blood.txt or a1234

where "1234" is the scan number of the corresponding PET scan.

The blood data are needed as the link between how much radioactivity is measured in each brain pixel, and the opportunity that each brain pixel had to store that radioactivity. In general, brain regions that store more activity for a given opportunity are said to have a higher metabolic activity. This is relevant to the blood data, because if the blood values are e.g. too low, it will appear that a given brain pixel was very active, since it took up a large amount of radioactivity relative to its opportunity to do so (~ number of FDG molecules it saw).

Typically we measure as fast as possible for the first 2 minutes (1 sample/10 sec), then 1 sample/30 sec for 2 min, then 1 sample/min out to 10 min, then 1 sample/5 min out to 30 minutes. The whole blood is spun in a centrifuge, and 0.5 ml of plasma is drawn off and counted in a gamma- (or well-) counter.

Usually the gamma-counter decay-corrects the counts to the injection time using the program "halflife", but occasionally this does not happen. The decay-correction attempts to remove the effect of radioactive decay from the detected counts, i.e. the goal is to "normalize" the counts so that it does not matter how long after injection the samples were actually counted. If the "Decay_corrected" field in the blood file is "yes", this means the samples have all been decay-corrected to the indicated "Injection_time", using the appropriate half-life (109 min) and branching ratio (0.97) for ¹⁸F positron decay. If the "Decay_corrected" field is "no", SPAMALIZE will perform the decay correction using the elapsed time from injection to the time when each sample was counted. If SPAMALIZE performs the decay-correction, you need to make absolutely sure that the gamma counter did not already try to do this automatically.

The data from the well-counter are reported as "counts per minute" (CPM). The samples are usually counted for 30 seconds, but nevertheless since the counts are reported as CPM, the count duration entered into the blood file should be 60 seconds.

D. Ideal blood curve

Most people have a blood time-activity curve (TAC) with a similar and reproducible SHAPE (not value) after approximately 30 minutes. Also, most (>75%) of the FDG uptake has already occurred by 30 minutes, so the subsequent values are only marginally important to the overall computed ICMR_{glu}. We take advantage of this by only

sampling blood out to 30 minutes, and then using a composite TAC (created from ~6 normal subjects) for the time from 30 minutes to the end of the PET scan.

The ideal curve we use extends out to 2 hr, 10 min (or, 7800 seconds). If you have acquired PET data which extends beyond this time, you cannot use this curve. The file is stored in:

/local/progs/spamalize/data/fdg_avg_bloodcurve.txt (unix)

or

W:\local\progs\spamalize\data\fdg_avg_bloodcurve.txt (Windows)

If you are not at the LfAN, look in your SPAMALIZE installation directory:

../spamalize_main_directory/data/fdg_avg_bloodcurve.txt

The ideal curve gets scaled to the measured curve in order to make a smooth transition after the last measured blood point. If your last measured point looks like an outlier, you might want to consider changing it to create a reasonably smooth blood curve.

E. Model parameters

The model parameters are simply the rate constants (k_1 - k_4) and the Lump Constant (LC) that describe the kinetics of the FDG model, as given in [Phelps, 1979]. There are actually different values appropriate for different tissue types (i.e. gray and white matter). However, we do not know ahead of time which tissue corresponds to a given pixel. Since we are primarily interested in the gray matter values, we use the rate constants for gray matter throughout the entire brain.

The file containing the rate constants and Lump Constant is stored in:

/local/progs/spamalize/data/fdg_model_params.txt (unix)

or

W:\local\progs\spamalize\data\fdg_model_params.txt (Windows)

If you are not at the LfAN, look in your SPAMALIZE installation directory:

spamalize_main_directory/data/fdg_model_params.txt

F. Blood File example

Following is an example of a blood file. It should be a simple ASCII text file. There is one row per blood sample. The headings for each column are: number, draw-time, measurement time, counts, counting duration (seconds), and sample volume (ml). The values in the first column (number) MUST start at 1 and increments of 1. If you missed a sample, do NOT indicate this by omitting its designated sample number. Also, the injection time MUST be the same as or earlier than the first blood sample time.

If "Decay_corrected" is "yes", this means the samples have all been decay-corrected to the indicated "Injection_time", using the appropriate half-life (109 min) and branching ratio (0.97) for ^{18}F positron decay. If decay-correction has been performed properly, including running the "half-life" program, the values in the fourth column (measurement time) should all be the same. They are different in the example below.

The text between the dotted lines is a sample file:

```
-----  
Ecat_calibration_factor      1  
Decay_corrected              yes  
Glucose_1                    102  
Glucose_2                    108  
Glucose_3                    107  
Counter_type                 gamma  
Dose                         5.2  
Patient_mass                 240  
Injection_time               11.33.02  
1  11.33.08  12.44.16      18.3   60  0.5  
2  11.33.19  12.45.10       0.0   60  0.5  
3  11.33.28  12.45.52    30122.3  60  0.5  
4  11.33.38  12.46.40   791403.5  60  0.5  
5  11.33.48  12.47.28   590763.5  60  0.5  
6  11.33.58  12.48.16   331228.0  60  0.5  
7  11.34.09  12.48.58   279327.2  60  0.5  
8  11.34.20  12.49.46   204265.8  60  0.5  
9  11.34.52  12.50.34   145213.6  60  0.5  
10 11.35.30  12.51.22   151695.6  60  0.5  
11 11.36.01  12.52.04   150084.4  60  0.5  
12 11.36.38  12.52.46   129319.6  60  0.5  
13 11.37.33  12.53.34   119060.7  60  0.5  
14 11.38.27  12.54.16   109360.3  60  0.5  
15 11.39.28  12.54.58    97636.3  60  0.5  
16 11.40.24  12.55.52    92918.8  60  0.5  
17 11.42.31  12.56.34    81399.7  60  0.5  
18 11.44.34  12.57.16    73857.4  60  0.5  
19 11.46.46  12.58.04    69253.2  60  0.5  
20 11.48.30  12.58.46    65463.9  60  0.5  
21 11.51.31  12.59.34    60141.3  60  0.5  
22 11.54.37  13.00.16    55347.8  60  0.5  
23 11.57.31  13.00.58    51808.6  60  0.5  
24 12.00.33  13.01.52    48941.4  60  0.5  
25 12.03.28  13.02.34    45760.2  60  0.5  
-----
```

III. Interface Menus

A. Filenames

The first menu you encounter manages the filenames needed by this program. Four files are required by SPW_FDG. Two of these are standard files that are the same for every analysis and are stored in SPAMALIZE's data directory. The other two files are the raw PET data and the blood file. You will be unable to proceed to any of the other menus until you indicate valid filenames for each of these four data sources.

Before you can do anything else, you need to find the PET data. Most of the buttons are de-sensitized until a PET file has been successfully read in. Select the "Find" button in the Filename menu next to the PET filename box. Browse through your menu system until you find a GE/Advance data file. Double-click on the file or select "OK" in the browser menu. A menu for reading GE/Advance files will appear. Select the button, "Read all Images in Data Set", unless for some reason you only want a subset of the images. You can select any combination of images with the file selection menu, but if you do this you are on your own!

At this point, SPW_FDG will read the PET data and store it all in memory (RAM). This implies you need to be working on a computer with enough RAM to store the entire PET file, which these days is not uncommon. You will get complaints if you cannot read the file, if the file is not a GE/Advance PET file, etc. You must fix any complaints before proceeding.

SPW_FDG will then search for a blood-file in the same directory as the PET scan. It will look for a file named "a1234_blood.txt" or "a1234", where "1234" corresponds to the PET scan number contained in the PET filename. If this file cannot be located, SPW_FDG will then look for the blood file in a directory designated as "blood_tac_dir" in the file ".../spam_dir/data/spamalize_defaults_XXX.txt".

At the LfAN this directory is currently /gig/blood/, and is used only for compatibility with older protocols. Do not use this directory for new protocols! If the blood file still cannot be located, you will have to browse for it. You may also browse for and select an alternate blood file after the default file has been located. This is how you would use a blood file you had created from a previous session in SPW_FDG.

The standard files contain the ideal blood curve and the FDG model kinetic parameters. You may browse for and select alternate files if you wish. If the files are not suitable, SPW_FDG will complain when you try to move to the Blood File menu.

You can check to see if the input files exist and are readable (by you!) by clicking on the "Filename Rollcall" button in the Filename menu. This also checks the validity of the output files, e.g. if one of the output files currently exist, and you have write-permission for the designated directory. Copious checking is performed at each step of the analysis to make sure the files have the correct format, that the values make sense, etc., in an attempt to keep you out of trouble. If your data are OK, you will not even notice any of these background checks.

B. Blood TAC Menu

This menu displays the values from the blood-file relevant to creating a time-activity curve (TAC). The goal is to create a TAC with 1-second increments (sometimes referred to as a 1-second grid) suitable for use with the PET data. This means that the blood and PET units must be the same, decay-correction must correspond, etc.

You may edit the values in the top window. The three (3) values that have an effect are:

- Decay-corrected: if "yes", indicates that the blood data have already been decay-corrected to the Injection time.
- Detector Eff: This is the detector efficiency, defined as the ratio of:
(# decays detected / (# actual radioactive decays) per second.
Do not change this value unless you have reliable information!
- Time (hh.mm.ss): This is the injection time. If you need to change this, you should probably change the value in your blood file instead, and start over.

The other values in the top menu are for informational purposes only.

The table in the bottom menu displays the blood values from the blood file. You may edit these if you wish. To do so, you must double-click on the desired cell. If the first entry in the blood-file has a draw-time after the injection time, a row is inserted at the beginning of the table with counts=0 and a draw time equal to the injection time. Attempts to change the draw-time in this row will be rebuffed- do not try this!

The Plot-window in the middle displays the measured blood points (red "plus" sign), the ideal curve scaled to the last measured blood value (green dots), and the resulting 1-sec gridded TAC (pink dots). There should be a smooth transition between the measured and ideal TAC at the last measured blood point. The dropdown menu "Plot" lets you examine each of the components individually.

You can import a secondary blood file to compare its TAC to your current TAC by selecting the "Show Secondary TAC" button. This is useful if you have two TACs from the same subject and you want to compare them to see if you may have missed an important time-point in the peak region.

Changing ANY of the values mentioned above causes a new TAC to be calculated. The TAC you see displayed will definitely be the TAC that is used for producing the metabolic PET images. If you make some changes you are unsure of, you can read the original blood data by selecting the "Read Original Data" button. This (naturally) will result in a new TAC.

You can easily create a new blood file with any changes you made by selecting the "Write Log" button from the left-hand menu. The current blood values are placed into one of the sections in the resulting text log-file, and can be copied and pasted into a new file and used, as-is, for subsequent analysis.

C. Kinetic Model

This menu shows:

- parameters for the FDG 3-compartment model;
- the resulting estimates of the concentration in each compartment;
- the ICMRglu values for a single specified PET value.

This is a rich menu, enabling you to investigate various aspects of your data. This can be particularly useful if you want to see the effect on ICMRglu due to small changes in the blood data.

The top portion contains the rate constants for this model. The rate constants, designated as k_1 - k_4 , govern how much radioactivity passes from one compartment to another in a given time. For instance, k_1 governs what fraction of the plasma radioactivity passes from the blood and into the tissue in 1 minute. Likewise, k_3 governs the fraction of FDG in the tissue that is metabolized into 6-P-FDG in one minute. Since FDG competes with glucose, we need to know the (non-radioactive) glucose level in the plasma. There are usually 3 glucose values, measured throughout the course of the uptake of radioactivity.

The bottom menu shows information for the current PET frame, and summarizes the average, minimum, maximum, etc. values for this frame. You can investigate different frames by typing the desired number in the "Frame" box, or by clicking at the corresponding time in the plot-window.

The "Model results" menu shows the ICMRglu value that results from using the current specified PET value, $C_i(T)$, for a time T which usually corresponds to the middle of the current PET frame. In this menu, $C_i(T)$ is a SINGLE representative value. It is usually the average PET value for pixels above the threshold, but you can type in any value you want.

$C_e(T)$ and $C_m(T)$ show, respectively, the values calculated from the model at the time T for the concentration of radioactive unmetabolized FDG and metabolized 6-P-FDG in the tissue. You can change the values for T and $C_i(T)$ by typing in their text-box, or select the time T by clicking in the plot-window. If you select a time T that is within the current PET frame, the time is automatically set to the middle of the frame. The value of $C_i(T)$ is frequently updated to correspond to the average PET value above the indicated threshold for the current PET frame. The time duration of the current PET frame is indicated by a green rectangle in the plot window. Other PET time frames are indicated by vertical blue lines. The current time is indicated by a vertical red line.

The image in the bottom menu shows a single plane, usually the central one. You may display other planes by clicking on the desired image in the left-hand window. The white outline indicates the location of the threshold values used to calculate the average value.

You can view a histogram of the current raw PET image by selecting "Histogram of Image" from the Plot pulldown menu. Click on the histogram to move the threshold (not the average value!) to the current location.

D. Metabolic Images

This menu displays the metabolic PET images. To save your work, select the "Write Metabolic Images" button. Note that the metabolic images are NOT automatically written- you must select this button! In order to change the name of the PET file, you must start over at the Filename Menu.

The metabolic images shown in this menu can be compared to the original raw PET images. Clicking in either of the "en masse" display windows will cause a larger version of that particular image to be displayed on the right-hand side. By moving the cursor over the single-slice images you can see the location and values for both the raw and metabolic images. Clicking on either of the images will place a crosshair, which can be convenient for comparing locations.

The threshold here is the same percentage value as for the raw images, but the average value will not correspond to the ICMRglu in the FDG Model menu, since there the average refers to the average raw value, and here it refers to the average metabolic rate value.

IV. Data Output

A. Overview

Two files are produced for each analysis:

- 1) An ANALYZE file containing the metabolic PET data;
- 2) An ASCII-text log-file containing a record of the parameters used and the actions taken.

The rollcall procedure checks to make sure that you have write- permission in the desired output directory, that the disk is not full, and that the desired filename does not already exist. If the file does exist, you will be asked if you want to over-write the existing file. If you answer "No", a modified filename will be suggested.

The ANALYZE file actually consists of two (2) files, an image file (with extension .img) and a header file (with extension .hdr). If you copy the PET data to another directory, make sure to copy both the .img file and the .hdr file, or else you will be unable to use your quantitated PET data!

The log-file generally has a similar name as the ANALYZE PET file. Both output filenames normally incorporate a date/time stamp, so you will have to work pretty hard to overwrite existing data. On the other hand, if you run this program several times in a row, you will have created a large number of files...

B. Printing Data

You can send most of the plots and most of the images to a color printer via the "Print..." buttons sprinkled throughout the GUI. To use these, you must make sure that SPW_FDG knows how to talk to your color printer.

If you are on a unix computer, the printer commands must be set correctly in the SPAMALIZE defaults file, `../../spamalize/data/spamalize_defaults_unix.txt`

If you are using a non-unix computer (PC/Windows98, MacIntosh, etc.) you will be prompted to browse for the desired computer. You should use a color printer if one is available.

The log-file is a simple text file and can be printed using any common text-editor, or with simple printer commands.

C. Log File

The logfile contains all of the parameters that were actually used to calculate the metabolic images. Note these values may not be the same as the values originally in the blood and model data files, since you have the opportunity to change them within SPW_FDG.

For each frame, a series of parameters (min, max, avg, etc.) are given for the raw data and for the metabolic data, along with their units and a typical range of values. The ranges are fairly liberal, so if any of your values fall outside of its corresponding range you should investigate why. Frequently there will be a simple reason (the person was very large so the radioactivity concentration was lower, the scan did not begin until 2 hours after injection, etc.), but occasionally some sleuthing will be required. This usually means that something non-standard happened to the data, and although it may be painful to track down, you must!