
Users' Manual

For

IDAE: The Integrative Data Analysis Environment for Brain PET

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Abstract

This document is the users' manual for our IDAE tool (The Integrative Data Analysis Environment for Brain PET). IDAE is a user-friendly GUI-based comprehensive data analysis system for brain research using PET (and MRI). To use it, users need to install Matlab and FreeSurfer tools in advance.

Download our environment codes at: <https://github.com/IDAEteam/The-Integrative-Data-Analysis-Environment-for-Brain-PET>

This manual is an yet-updating version, which is last updated on 12/May/2022.

To make interactions with IDAE enjoyable:

- Sometimes users could be frustrated by the behavior of IDAE
- Most of them are caused by users' unexpected behaviors in our experience.
- Thus, keep in mind:
 - GUIs are often left 'active' after a GUI is clicked. Thus, MATLAB (and IDAE) will be confused if any GUI is hit before on-going instruction is completed.
 - So, please be patient until the emitted task is completed.
 - The development team try to include 'be patient .. ' messages as much as possible
 - MATLAB command window shows the 'busy' sign at the bottom
 - When questionable, hit 'return' in the command window. The sign may appear if it is processing. If you do not see the 'busy' sign, you are good to emit the next command

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1 Introduction to IDAE

- The integrative data analysis environment (IDAE) is a comprehensive data analysis system for brain research using PET (and MRI):
 - Users can generate / manage (customize) analysis packages (a.k.a., pipelines), carry out the analyses, and summarize the results, all via **GUI and clickable, organized menus** alone.
 - IDAE is primarily intended to aid non-technical researchers such as neurologists, psychiatrists, and neuroscientists to perform PET data analyses, and thus presents the user with a step-wise procedure
 - IDAE is project oriented: Analysis packages interact with the study's database to perform analyses on groups of subjects, which made result-summary functions possible:
 - A 'study' (a.k.a. 'project') refers to studying groups of subjects to address scientific hypotheses
 - Final products from IDAE for a study will be tables and figures for publications
 - IDEAS modular programming makes it easy to for technical scientists to incorporate free-ware or their own codes to analysis package bases
 - IDAE is built upon MATLAB (thus, independent to operating systems)
 - Analyses are carried out as outlined in the Flowchart, as seen in Figure 1.
 - Users select / customize IDAE-supplied analysis package bases as needed for a study using GUIs alone
 - Stage 1 packages deal with preparation of PET, MRI, and VOIs (volumes of interest)
 - Each study typically has a few Stage 1 packages
 - Stage 2 packages deal with everything else. a few/several Stage-2 packages per Stage-1 package
 - Users prepare / update a database file (one per study) using GUI-based modules.
 - The database interacts with user-managed packages when carrying out the analyses.
 - Users can summarize the results (tables / figures) and perform statistics via GUIs alone
 - Local managers are required to local adaptor codes using a template to cope with site-specific data archive conventions (paths) and other settings.

2 Analysis Flowchart

- Flowchart showing major analysis components of brain PET studies. In IDAE, the database of the study interacts with a few Stage 1 Packages and several Stage 2 packages to carryout analyses on groups of subjects.

** VOI: Volume of interest; TAC: Time-activity curve

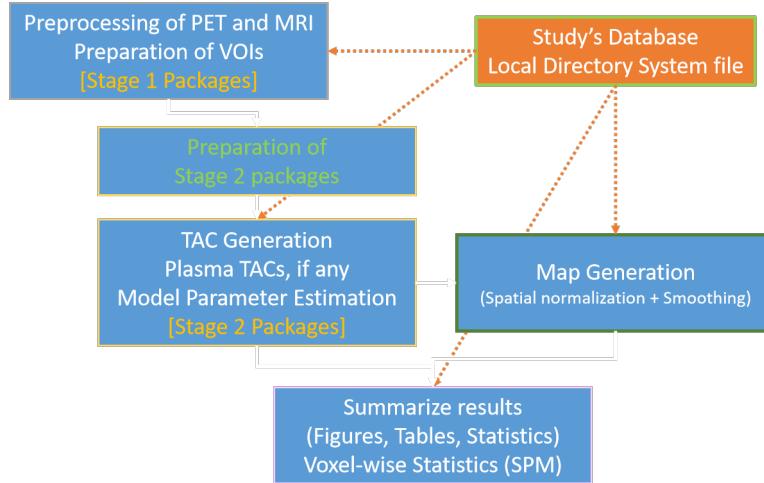


Figure 1: Flowchart

3 Performing Analyses with IDAE

- To start a session of a desired package of a desired ‘project’:
 - Type as follows in Matlab command window:
 - *startIDAE yourUserName*
 - Hit intended GUIs in successive GUI windows (three clicks alone)
 - Then the Level 1 Window of the intended package will pop up.
- Now, observe the L1W for completion statuses of subject-analysis block GUIs (the main GUI matrix)
 - Visit the subject-analysis block GUI that shows the lowest completion percentage
 - In the Level 2 Window that pops up, look for interactive (=i; darker green) and quality control (=c; lighter green) processes that display ‘r’ (=ready) on GUIs. Just visit/complete the process. Then, ‘r’ turns to ‘c’ for completed.
 - Once interactive and/or quality control processes are completed on intended subjects, highlight their subject GUIs (hit GUIs) on L1W and hit the ‘Perform’ GUI.
 - IDAE will stop processing at the first interactive or quality control (QC) process to work on in individual subjects

- Repeat the sequences until all processes are done on all subjects / scans.
- Above performance principles apply to all IDAE packages that are shown in ‘Analysis Flowchart’

3.1 Starting an IDAE Session

- Shown in Figure 2 are the sequences for starting an analysis package of a project (Indicated by blue arrows; 3 clicks alone):
 - Hit ‘Start Analysis’ in the IDAE Control Module (left)
 - Hit the GUI of the intended project in the Project Selector window (middle)
 - Select the intended package from the package list of the project (lower panel)
 - Then, the Level 1 Window of the package (prepMPfsx) will be generated (in Figure 3)

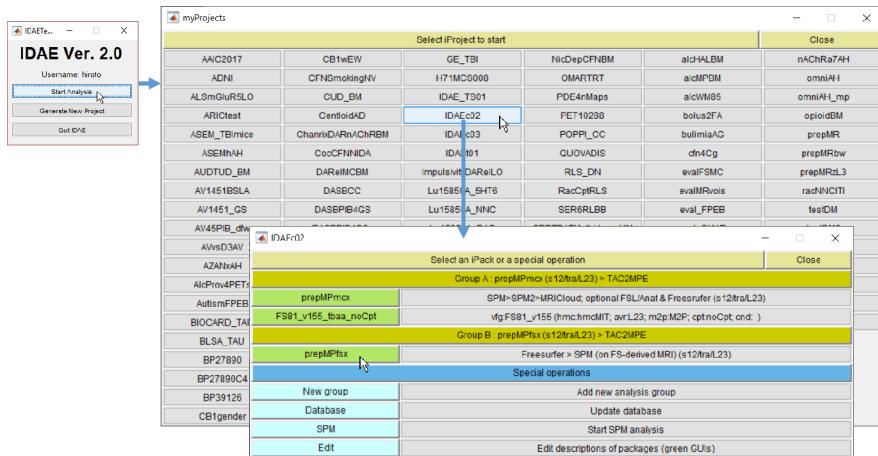


Figure 2: Sequences for starting an analysis package of a project

3.2 Carrying on Analyses with IDAE

- General sequences of performing analyses with IDAE are (in Figure 3):
 - Observe the Level 1 Window (left) for completion statuses of subject-analysis block GUIs (the main GUI matrix)
 - Hit the subject-analysis block GUI that shows the lowest completion percentage to get the Level 2 Window (right)
 - Look for interactive (=i; darker green) and quality control (=c; lighter green) processes that display ‘r’ (=ready) on GUIs.
 - Just visit/complete the process. Then, ‘r’ turns to ‘c’ for completed.

- Once interactive and/or quality control processes are completed on the intended subjects, highlight their subject GUIs (hit GUIs) on L1W and hit the ‘Perform’ GUI (above ‘Subjects’ GUI).
- IDAE will stop processing at the first interactive or quality control process to work on in individual subjects
- Repeat the sequences until all are done

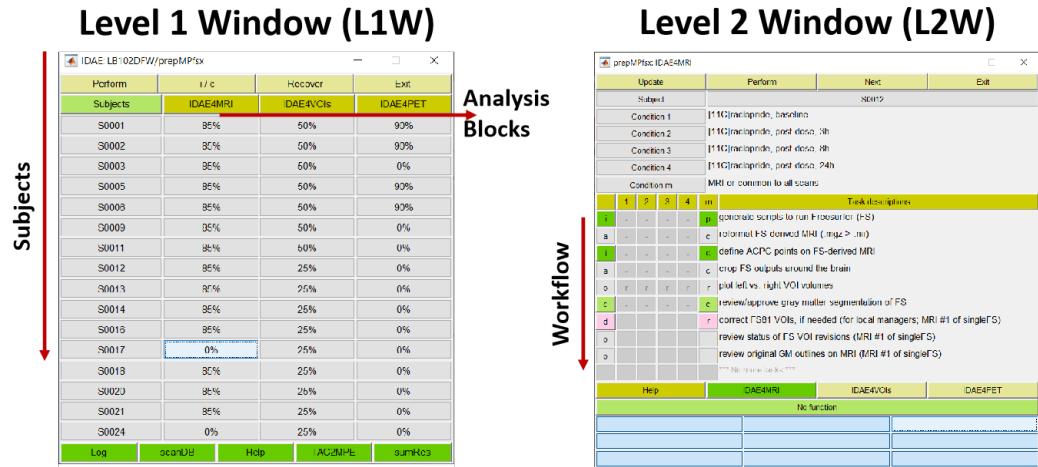


Figure 3: Carrying on Analyses with IDAE

3.3 Installation of IDAE

- Plan & create the following folders for IDAE:
 - One folder for IDAE codes (e.g., C:/idae; referred to as ‘IDAE folder’)
 - Folders (one per user) for execution of IDAE (e.g., C:/users/UserName)
 - One folder to dump intermediate files (e.g., C:/tmp)
 - Place ‘scratch.m’ (any content; using MATLAB editor) in the dump folder
- Download the IDAE package from GitHub to the code folder and unzip it (unzip ‘here’)
 - Look for patches/additional releases occasionally. Do the same for them.
- Prepare a startup.m using IDAE-supplied template and place it to the directory where MATLAB looks when it is stated
 - See the section of ‘Preparation of startup.m’ for details
- Prepare the local adaptor file in the dump folder
 - See the section of ‘construction of local adaptor file’ for details

3.4 Construction of the Local Adaptor File

- IDAE assumes the following 4 computer classes:

Computer classes	Descriptions	Supported OS
Users' workstation	PCs or workstations to run IDAE	Windows 10 / Linux
Local file server	To store outputs from IDAE <ul style="list-style-type: none"> • will be generated by IDAE • organized by subjects and PET & MRI scans 	Windows / Linux
PET & MRI server	To provide reconstructed PET and MRI files	Windows / Linux
Linux machine	To run Linux-based applications for IDAE	Linux

Figure 4: Construction of the Local Adaptor File

- They could be physically identical (e.g., local file server = PET & MRI server)
 - The local IDAE manager is requested to generate the local adaptor file:
 - Once alone
 - Starting template: `inq_windows10.m` (if Window to Linux) or `inq_Linux.m` otherwise
 - Once the template is done, submit it to `iv2_gen_dxetc4xxx.m` as follows:
 - `iv2_gen_dxetc4xxx('inq_whichever', 'dxetc4whatever')`
 - where the second input is the name of local adaptor file of your choice.
 - Setting for Freesurfer
 - Set `dxetc4xxx` such that `-x = dxetc4xxx('fsd', 'avatar948')` returns:
 - `x.fs.home`: the full path of the folder to place IDAE-generated scripts to run Freesurfer
 - `x.fs.linux`: the same as `x.fs.home` but the full path in the Linux system where Freesurfer is installed
 - `x.fs.subj`: the full path of the Freesurfer's working directory (e.g., `/home/avatar948/freesurfer/subjects`)
 - Place a text file (name: `FSdone.txt`; *anycontents*) in your `x.fs.subj`
-UNFINISHED

4 Setting the first project

- The IDAE team suggest to set the first project in a manual approach
 - Why manual approach? To help users understand the basic mechanisms better
 - Users can find GUI-based approaches here

- Hypothetical strings of this manual. Need to replace them by actual strings
 - ‘dxetc4xxx’ stands for your local adaptor file.
 - ‘avatar948’ stands for a hypothetical IDAE user.
 - ‘IDAEc01’ stands for a demonstration project.
- Type (and hit return) as follows MATLAB command (- indicate MATLAB command lines):
 - *iv2_serFolders(‘dxetc4xxx’, ‘avatar948’, ‘IDAEc01’, n);*
 - n stands for the number of PET scans per subject in the project
 - Note that quotation marks are often not copied correctly to MATLAB command window
 - Don’t forget to create the user folder (See Installation of IDAE).
 - The database template (X:/users/avatar948/idae/IDAEc01_scanDB.m in this manual) will be generated and opened for editing
- Edit the scanDB.m as instructed therein:
 - Once completed, save & index it as follows:
 - *iv2_register X:/users/avatar948/idae/IDAEc01/IDAEc01_scanDB.m*
 - Again, need to replace hypothetical strings with actual ones
 - If the indexing is successful, move on the next step.

4.1 Setting Stage 1 Package for Projects

- Enter as follows in the command window:
 - *startIDAE avatar948 dxetc4xxx*
- To open the myProject module (left)
 - The module display one project alone since this is the first project
 - The number will grow as more projects are accumulated (See ‘Starting an IDAE Session’).
- Hit the project GUI (‘IDAEc01’).
 - It is ‘as-expected’ to get a warning sign (right panel).
 - Just hit ‘OK’ to proceed to composing the first Stage 1 package for the project (next section)



Figure 5: Setting Stage 1 Package for Projects

4.2 Preparation Stage 1 Packages

- Just 7 clicks (less than 10 s) to get ready to start the analysis with a Stage-1 package
- Select ‘prepMPfsx’, the only Stage-1 package in this release and hit ‘Done’ (upper panel)
- Select parameters in the 4 sections in the next module (lower panel) and hit ‘Done’
 - Read ‘Information’ tabs (light green)
 - Averaged PETs are used for obtaining a global TAC to understand if individual scans have any problems (such as early termination, scan breaks)
 - Available options are convenient for this purpose which may need to cope with different durations of scans
 - For example, L23 will use 30-45 min frames if the scan terminated prematurely at 45 min instead of the planned 90 min
 - Note that ‘sum’ is a good option as well
 - The local IDAE manager needs to set the last two sections (reconstruction cropping) in the local setting file (dxetc4xxx.m)
- Then, Level 1 Window (L1W) will pop up. Users are ready to start the analyses.

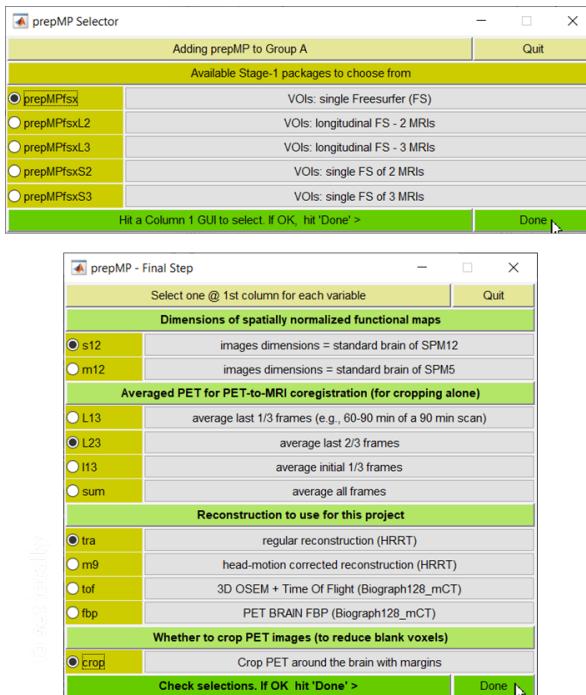


Figure 6: Preparation Stage 1 Packages

4.3 Completing Stage 1 Packages

- Just 7 clicks to the completion of a Stage-1 package:
 - Select ‘prepMPfsx’, the only Stage-1 package in this release and hit ‘Done’
 - Select recommended parameters in the next module (right panel) and hit ‘Done’
 - Read ‘Information’ tabs (light green)
 - Averaged PET is primarily used for cropping PET in Stage-1 (not so critical)
 - Then Level 1 Window will pop up (left bottom). You are set to start the analysis.

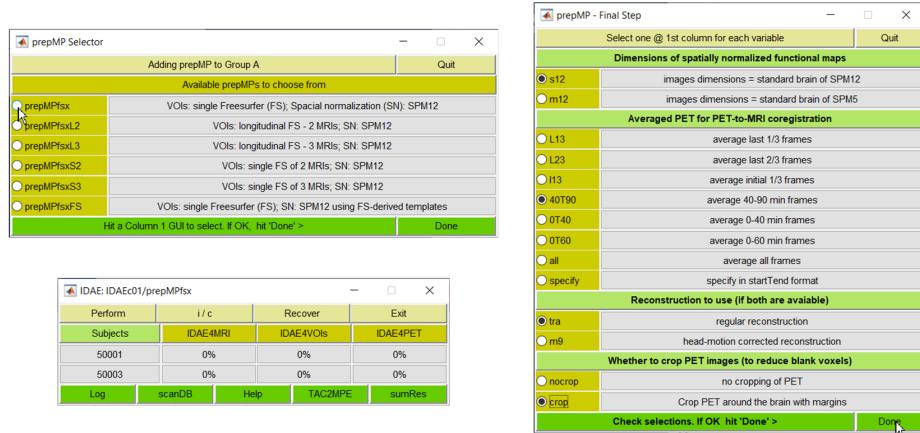


Figure 7:

5 Outlines of ‘prepMPfsx’

Three analysis blocks in prepMPfsx:

- Automated parcellation of brain regions using the Freesurfer software* for (block name: IDAE4MRI). Major steps include:
 - Generation of scripts for running Freesurfer outside IDAE (to avoid stalling MATLAB)
 - Visual confirmation of the outputs using outlines of gray matter regions
 - Manual correction of insufficiencies, if any (optional)

* Available at: <https://surfer.nmr.mgh.harvard.edu/fswiki/FreeSurferWiki>

- VOI-related operations (IDAE4VOIs) (VOI = volume of interest):
 - Selection of VOIs to refine (to focus) and reference regions

- Manual refinement of above-mentioned (and added non-Freesurfer) VOIs
- PET-related operations (IDAE4PET):
 - Cropping of PET frames around the brain with margins, if selected.
 - Initial coregistration of averaged PET to the Freesurfer-derived MRI
 - Visual evaluation/correction, if needed of the coregistration
 - Visual evaluation of head motion

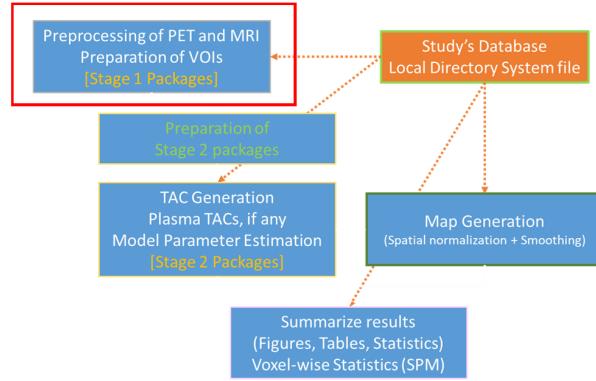


Figure 8: Outlines of ‘prepMPfsx’

5.1 Generate scripts to run Freesurfer (FS)

General sequences of performing analyses apply here as well:

- Visit the subject-analysis block with the lowest complete percentage in L1W
- Visit the first interactive (=i; darker green) or quality control (=c; lighter green) processes that displays ‘r’ (=ready)
 - The application opens with files selected
 - In this step, the command line to submit to your Linux machine (→) will be displayed on MATLAB command line (bottom row). Just copy and paste/submit it.
 - Up to 3 MRIs were submitted at one time
 - [Some technical notes]
- information on the access to Freesurfer, etc. is defined in your local adaptor file.
- IDAE chose to run Freesurfer outside IDAE to avoid stalling MATLAB while execution of Freesurfer (6 hours per MRI)

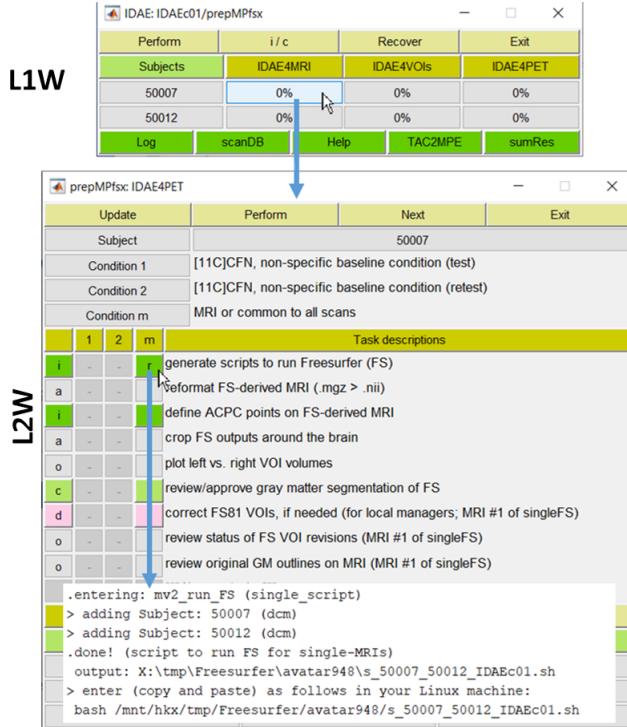


Figure 9: Generate scripts to run Freesurfer (FS)

5.2 Define ACPC Points

- Assume that the Freesurfer script was submitted yesterday, and the user revisited the project/package
 - The percent completion statuses increased on GUIs under IDAE4MRI.
 - So, highlight subject GUIs (now deep blue) and hit the ‘Perform’ GUI in L1W to perform available automatic processes (= ‘a’ in L2W)
 - Completion statuses increased on the first subject (15 to 23%) but not for the second subject [i.e., Freesurfer not completed yet].
 - Open L2W (middle then bottom panels)
 - Look for the first dark or light green GUI with ‘r’ (=ready) which is ‘define ACPC points on FS-derived MRI’ (right column) in this example
 - Hit the ‘r’ GUI to open the application, VOILand with files selected (next slide).
- Define the anterior and posterior commissure points (AC and PC) on the MRI To be consistent with SPM12 which assumes the AC as the origin of the image coordinate system
- Procedures: Navigate images to display the AC point in all orthogonal images (middle panel)

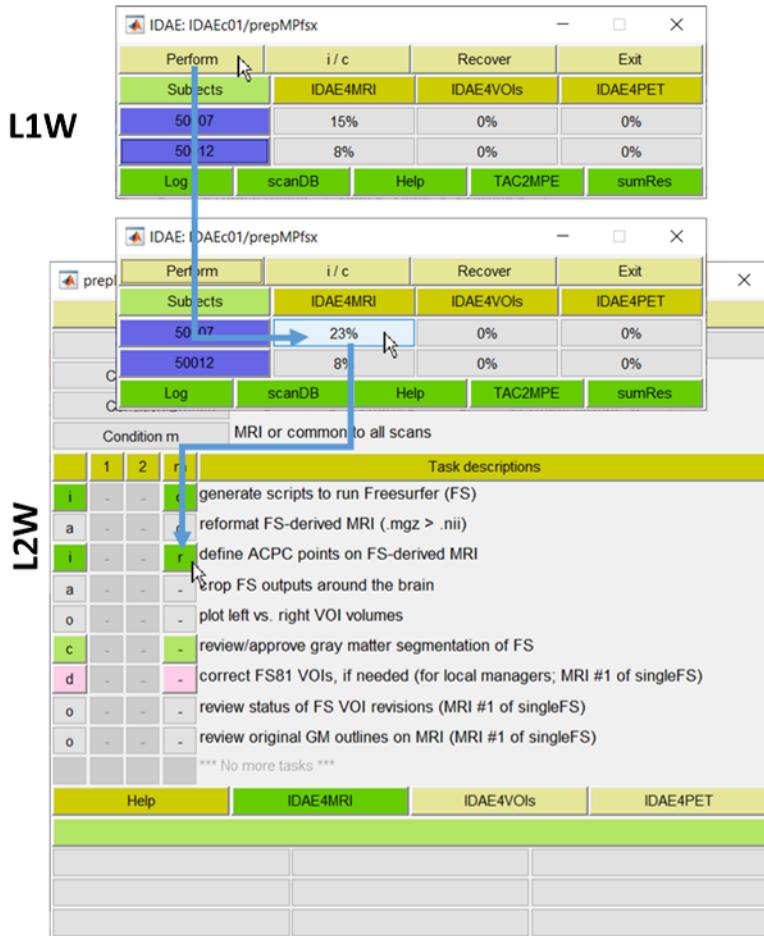


Figure 10: Define AC/PC Points.a

- Image navigation: Hit u/n keys (for up/down in axial direction), i/m keys (towards the inion/nasion, but m), </>keys (towards your left/right)
 - Click at any point on the colormap bars when above keys do not respond
 - Hit at the AC point (arrow in the trans-axial image) to display red dots (one per view)
 - Fine adjustments using number keys: Hit 8/2 keys to displace the dots in anterior/posterior directions, 4/6 to keys to towards your left and right, and 9(Pg Up)/3(Pg Dn) in the up(=cranium)/down directions
 - Target: Slightly above the center of the AC point (See upper panel)
Hit ‘save AC’ GUI when done
 - Repeat the same for the PC points

- But at the middle of PC (bottom panel)
- Make sure to click on ‘Save’ then ‘Exit’ GUIs (after seeing ‘safe to exist’ message).

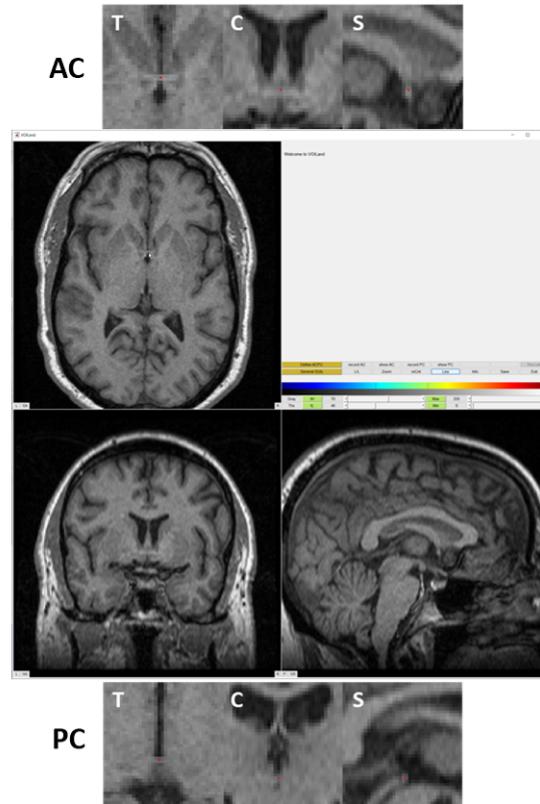


Figure 11: Define AC/PC Points.b

* Not sure about ACPC? Try https://people.cas.sc.edu/rorden/anatomy/na_ac.html

5.3 Review/Approve GM segmentation of Freesurfer

- The percent completion status increased since the ACPC points were set.
- Hit the ‘Perform’ GUI on L1W to run automatic processes through the next interactive or QC process.
- Once done with increased percentages, hit the subject-block GUI again.
- Now, the first dark or light green GUI with ‘r’ (=ready) says it’s time to ‘review/approve gray matter segmentation of FS’
- Hit the GUI to open the application (snOLs.m) for visual inspection (See next section).

- Consequences:
 - Move on to the next block (for this subject) if you approve the outputs from Freesurfer
 - If not (i.e., some problems), move on the correction of Freesurfer-derived VOIs
 - Only trusted users (defined in dxetc4xxx) are allowed to access this optional step (pink)

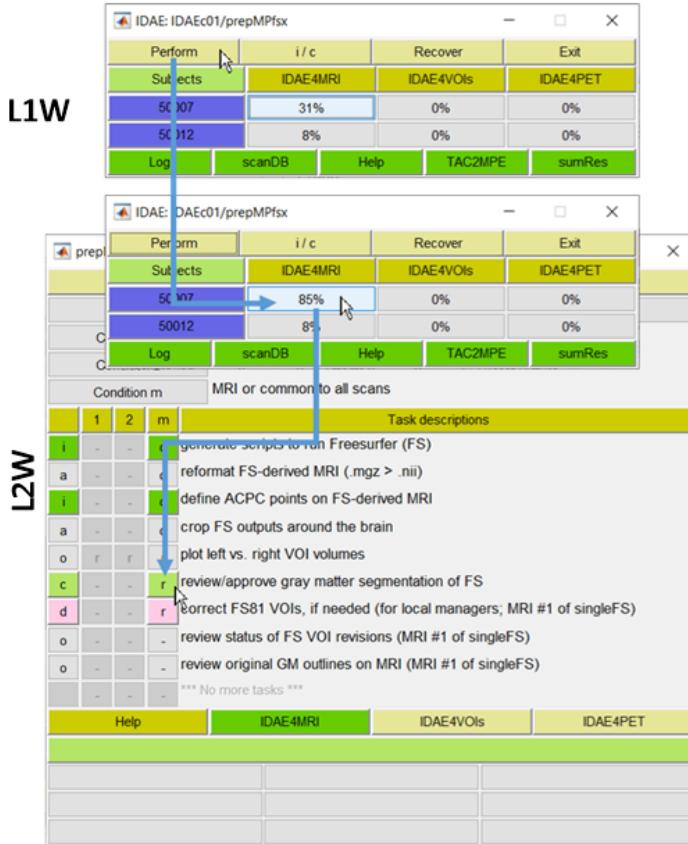


Figure 12: Review/Approve GM segmentation of Freesurfer.a

The outlines of gray matter (with all GM VOIs merged) from Freesurfer are projected on MRI in three orthogonal views in turn (5 s per view)

- Evaluate if GM outlines agree with GM of the MRI. Hit ‘Approve’ GUI if OK (arrow)
 - Use T (trans-axial), S (sagittal), and C (coronal) GUIs under ‘view’ to change views.
 - Use arrow GUIs under ‘Images’ to navigate ‘slices’

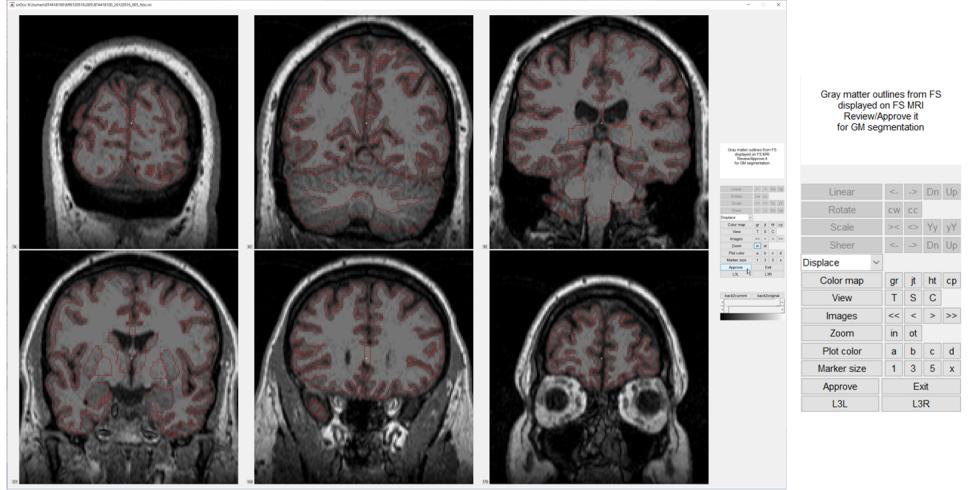


Figure 13: Review/Approve GM segmentation of Freesurfer.b

6 IDAE4VOIs

- Set VOIs to refine/define for the project
 - Background: IDAE makes use of Freesurfer-generated VOIs. It appears to be practically impossible to refine all the VOIs (>85) in every MRI.
 - IDAE provides two sets of VOIs for the sake of convenience: **FS81** that are almost identical to original Freesurfer VOIs; and **FS45** with VOIs re-organized to be conventional larger VOIs.
 - IDAE's strategies to cope with the issue:
 - To set refine a subset of the VOIs that are critical for the project (denoted as ‘S’ VOIs)
 - To set define from scratch those VOIs that are not generated by Freesurfer (= ‘S’ VOIs also)
 - To set refine/define reference regions (target-free regions; need one even none) (= ‘R’ VOIs)
 - Set the S/R VOIs at ‘set VOIs for this project’ (the first task of IDAE4VOIs)
 - Hit the GUIs of intended VOIs (toggles among ‘no-mark’, ‘S’, and ‘R’) in the module which pops up when the task GUI is hit on L2W.
 - Record the selections when done (See next slide) as a set of VOIs
 - Users can add ‘S’ and ‘R’ VOIs later as needed (changes from ‘S’/‘R’ to ‘no-mark’ are not allowed). The displayed selections will be saved as a new set upon completion of the saving processes.
 - Refine/Define ‘S’ and ‘R’ VOIs, separately for FS81 and FS45

- Visit FS81 and/or FS45 versions according to the setting of ‘S’ and ‘R’ VOIs

6.1 IDAE4VOIs: ‘Set VOIs for this project’

- Popup the VOI setter module
 - Hit the first GUI (arrow orange rectangle)
- Columns are for:
 - FS81: almost identical to Freesurfer VOIs
 - FS45: a reorganized version of FS81 into conventional larger VOIs
 - Colored GUIs indicate available VOIs from Freesurfer
- Hit the GUI of the intended VOI in the module
 - Toggles among ‘no-mark’, ‘S’, and ‘R’
 - Hit a ‘(add)’ GUI to add non-Freesurfer VOIs
 - Selections shown in this manual are for demonstration purpose alone
- Once all intended VOIs are marked:
 - Check if all ‘S’ VOIs are marked (none is OK)
 - Check if all ‘R’ VOIs are marked (at least one)
 - Then, hit ‘Done’
- Make use of 2nd and 3rd tasks (‘display VOI... ; marked by a orange bar) of L2W to monitor completion status of the ‘S’ and ‘R’ VOIs in individual subjects
 - It’s convenient to know which MRI to work

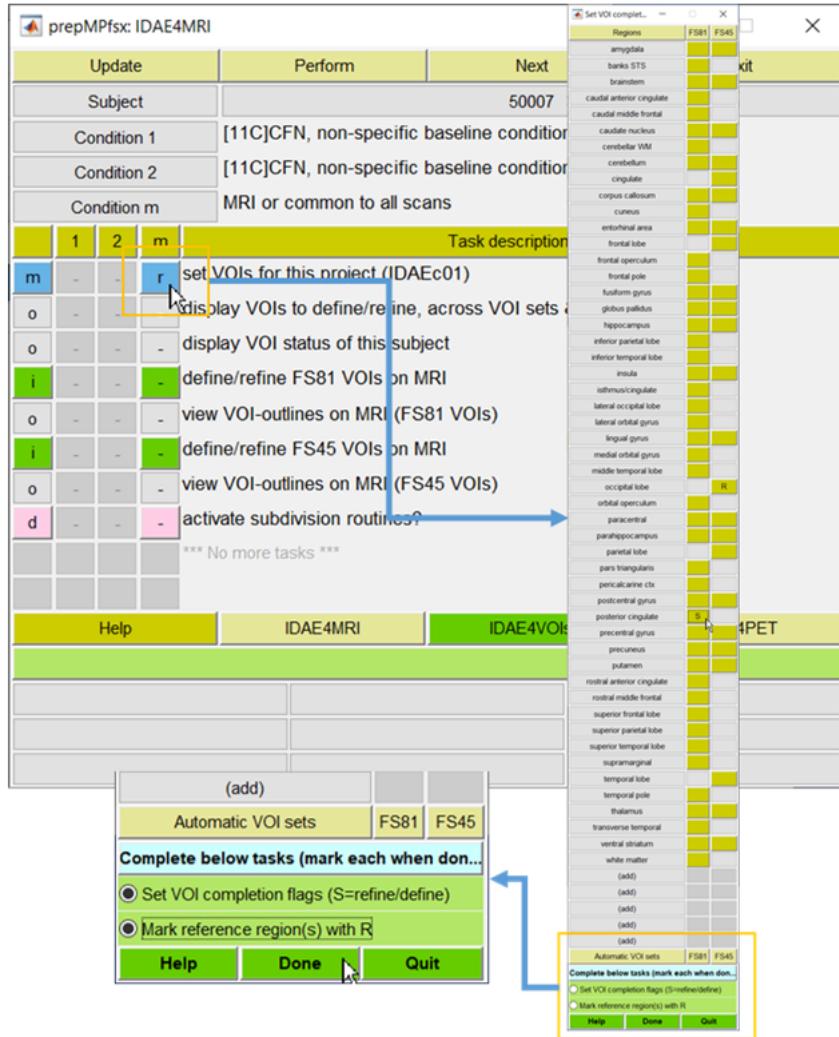


Figure 14: IDAE4VOIs: ‘Set VOIs for this project’

6.2 Define/Refine VOIs

- Hit the green (One each for FS81 or FS45 VOIs) GUI (left orange circle):
 - The application, VOILand will open with input (MRI) and output (VOI) files selected.
- Hit ‘start a VOI’ GUI on the VOILand window to open the VOI selector (inset)
 - The ‘S’ and ‘R’ VOIs will be listed here.
 - The occipital lobe in this example which is defined in FS45 set alone. Therefore, the FS45 set was hit (the second green GUI).
 - ‘y’ means not worked yet.

- See the VOILand manual to learn how to refine/define VOIs.
- Good to know:
 - IDAE generates one set each of FS81 and FS45 VOIs to be shared by users.
 - Users are not allowed to edit the shared sets
 - User-defined ‘S’ and ‘R’ VOIs were copied from the shared sets to users’ personal files, if present.
 - Both shared and personal VOI files are used when to generate time-activity curves, TACs.

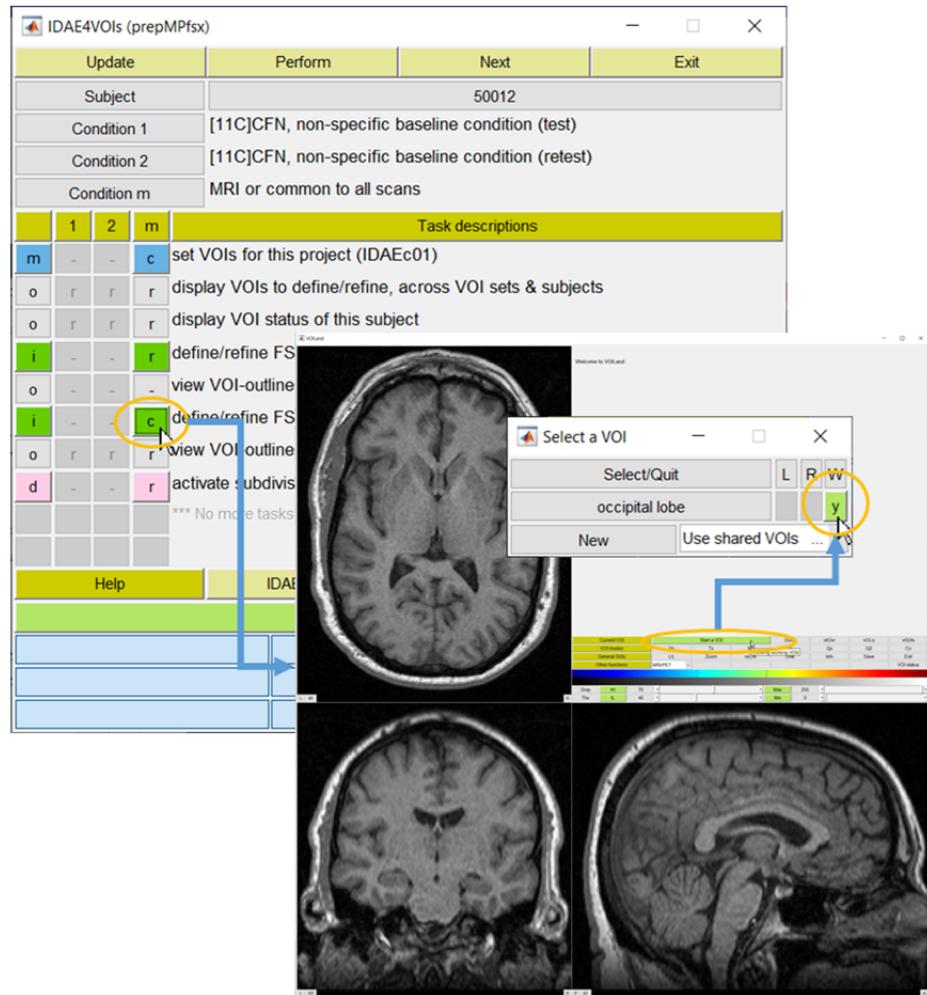


Figure 15: Define/Refine VOIs

6.3 Convenient Option Processes for VOIs

- Two optional processes could be very useful to know which VOIs of the ‘S’ and ‘R’ VOIs are left incomplete
- ‘Display VOIs to define/refine, across VOI sets subjects’ (upper GUI)
 - Will list of VOIs to define/refine (i.e., ‘S’ + ‘R’) and completion statuses of individual subjects (- if left incomplete; * if completed with date/time of completion)
 - Thus, the user can visit those incomplete sets and subjects.
- ‘Display VOI status of this subject’ (lower)
 - Will list VOIs to define for this subject, separately for FS45 and FS81 VOI sets.
- In sum, know which subject to work from the upper GUI, and which VOIs to work for the subject from the lower GUI
 - In addition, a GUI (VOI status) is provided to display VOI completion statuses of the ‘S’ and ‘R’ VOIs on the VOILand window.

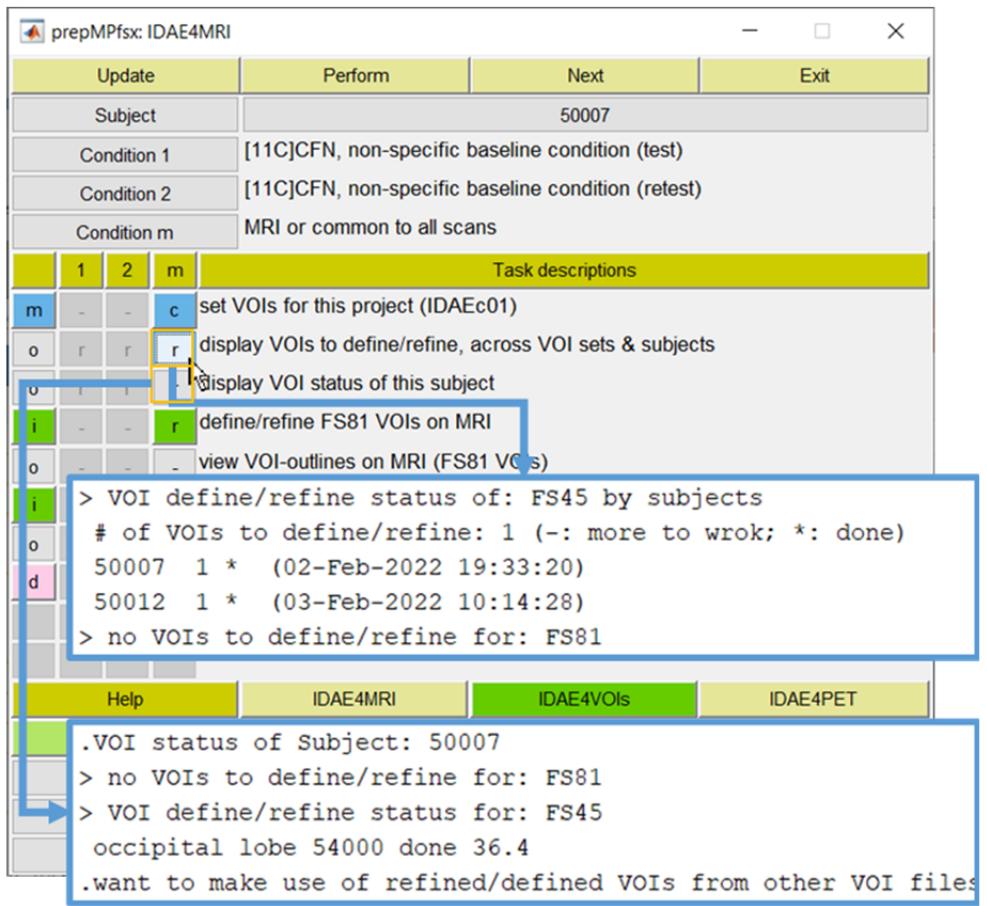


Figure 16: Convenient Option Processes for VOIs

7 IDAE4PET: Mean Cortex TACs

- Review/approve cortex mean TAC
 - Derivation of the cortex mean TAC
 - Marginal voxels of gray matter (red dots of the inset) were transferred to the PET according to the PET-to-MRI coregistration parameters and applied to successive PET frames
 - The user of marginal voxels is expected to be sensitive to head motion, if any
 - Hit the first light green GUI (arrow in orange circle) of L2W to display the plot
 - Look for any sudden dips (often suggestive of bathroom breaks), or shorter than expected scans (early termination).
 - If no such problems, ‘approve’ it (arrow)
 - Otherwise, visit ‘Correct’ GUI. Note that the local IDAE managers need to set this section according to local conventions
- Once it is approved:
 - Highlight those subjects for whom mean TACs are newly approved in L1W and hit ‘Perform’ GUI to process a group of subjects, or
 - Hit ‘Perform’ GUI of L2W (top row) to process ready-to-run automatic processes of current subject

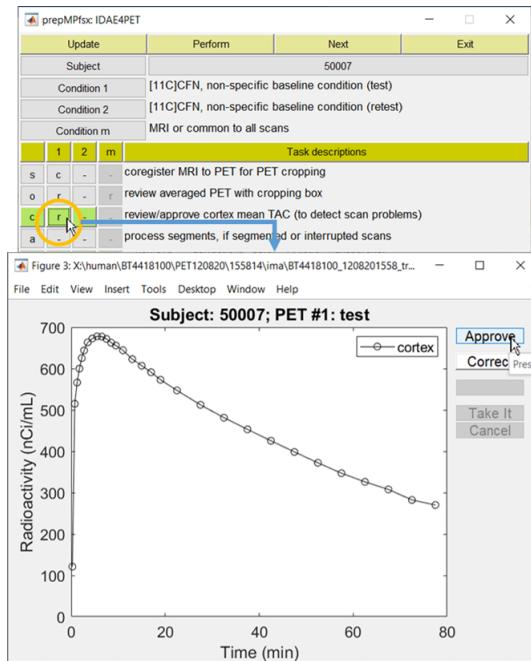


Figure 17: IDAE4PET: Mean Cortex TACs

7.1 Correction of Potential Scan Problems

- Some of scan problems can be ‘corrected’ at this stage, if any
- In this example, the mean cortex TAC had a dip at the last frame and lesser dips just before 50 min (vertical arrow).
- The dip at the last frame may not be ‘corrected’ but it is possible to eliminate the last frame from further analysis.
- It may be possible to ‘correct’ the lesser dips by the head motion correction approaches So, let’s eliminate the last frame
- Procedures:
 - Hit ‘Correct’ GUI (upper orange circle) Respond to successive inquiries
 - Correction approaches for segmented (by e. g., bathroom breaks) or interrupted (often planned) scan are site-specific (reconstruction approaches). Thus, those approaches are not included in the distribution set.
 - Point at the last frame to keep (red triangle) and hit ‘Take It’ GUI, if OK
 - The frames up to the red triangle (inclusive) will be used in subsequent analyses.

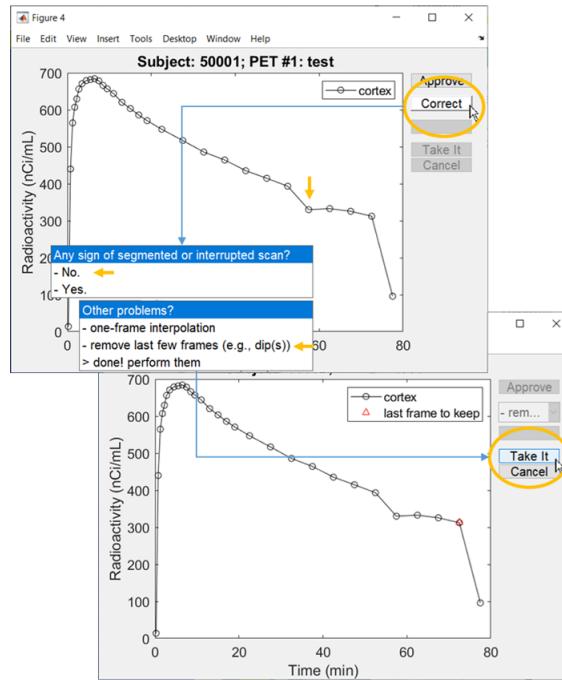


Figure 18: Correction of Potential Scan Problems

7.2 IDAE4PET: Coregistration QC

The outlines of gray matter (from MRI) are projected on the averaged PET volume

- Evaluate if GM outlines agree with the PET volume. Hit ‘Approve’ GUI if OK (arrow)
- Use T (trans-axial), S (sagittal), and C (coronal) GUIs under ‘view’ to change views.
- Use arrow GUIs under ‘Images’ to navigate ‘slices’

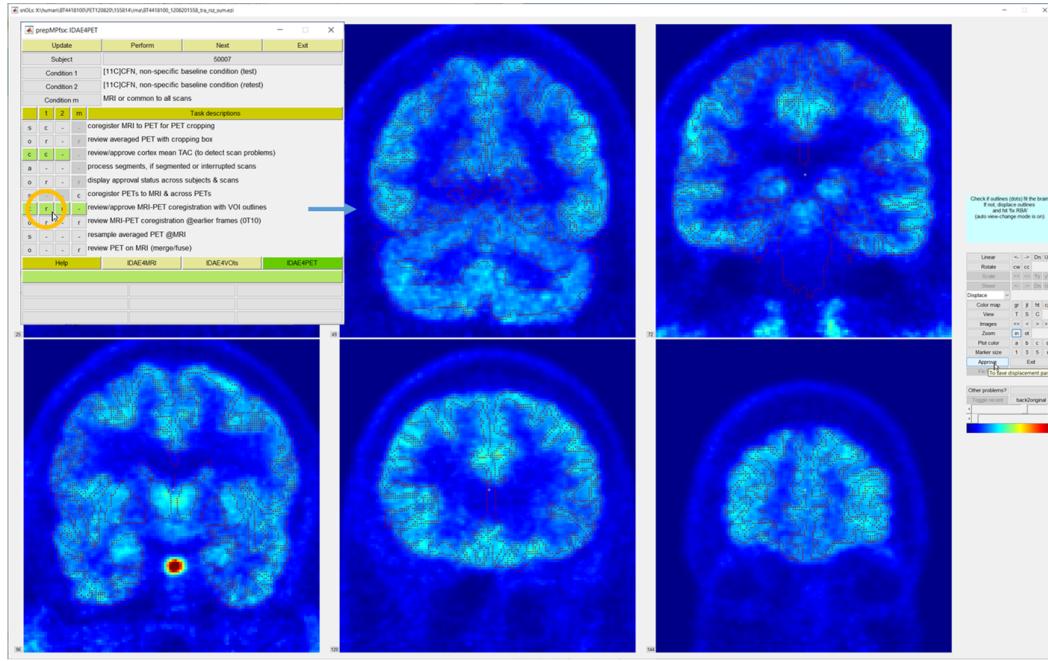


Figure 19: IDAE4PET: Coregistration QC

8 Preparation of Stage 2 Packages

- Stage-2 packages are to generate TACs and perform model parameter estimation (MPE)
 - Usually there will be several Stage-2 packages per prepMPfsx due to:
 - Revisions of ‘S’ and ‘R’ VOIs
 - Selections of the parameters in the next step
- Start the preparation with ‘TAC2MPE’ GUI of L1W (upper orange circle)
- Two potential scenarios (lower GUIs of L2W)
 - To define ‘VOI sets’, select ‘Select/rank VOI sets’ tab (lower orange circle)

- Move on to understand what are ‘VOI sets’
- To apply a new set of ‘other’ parameters to a VOI set, hit ‘Generate TAC2MPE’ GUI

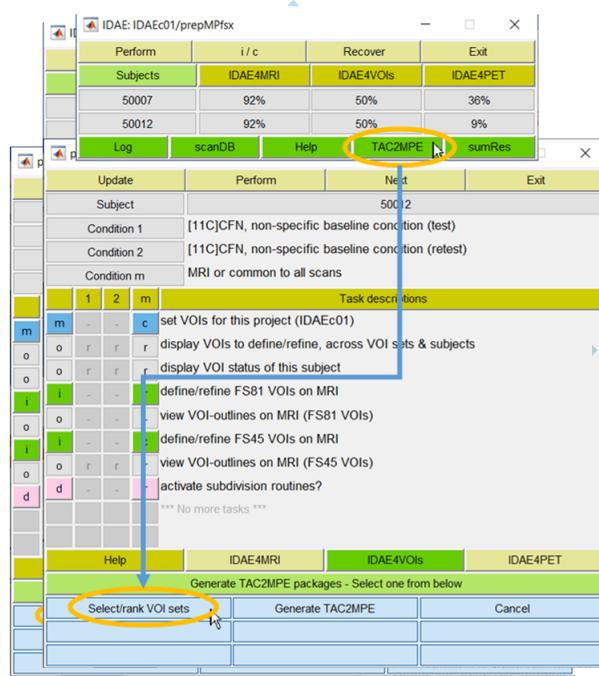


Figure 20:

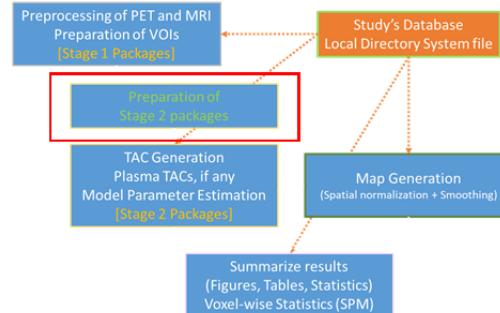


Figure 21: Preparation of Stage 2 Packages

8.1 Setting VOI Sets

- When the ‘Select/rank VOI sets’ tab was hit in L2W, the VOI selector module pops up
 - Previously defined VOIs to refine/define and VOIs for reference regions are indicated by ‘S’ and ‘R’, respectively
 - It is OK to have no ‘S’ VOIs as in this example.

- But there must be at least one ‘R’ VOI
- Dark gold regions are available VOIs. No revisions are allowed in this stage
- Recall that F45 is consisted of merged VOIs from FS81.
- It is strongly recommended to select the F81 set.
- A later function allows calculation of the values of any outcome variables for merged VOIs as weighted means (by volumes) of FS81 VOIs.
- In this example:
- The FS81 set was selected (as 1 and only 1; bottom left circle)
- Then, the FS81 VOIs are shown in light green (right panel)
- The VOI for the occipital lobe, reference region for the tracer was set to refine in the F45 set since it is available on this side alone.
- Just hit the VOI’s GUI to include the VOI to the VOIs to report (orange circle, right panel) (hit it one more time to deselect).
- Hit the ‘Done’ GUI to set the next module

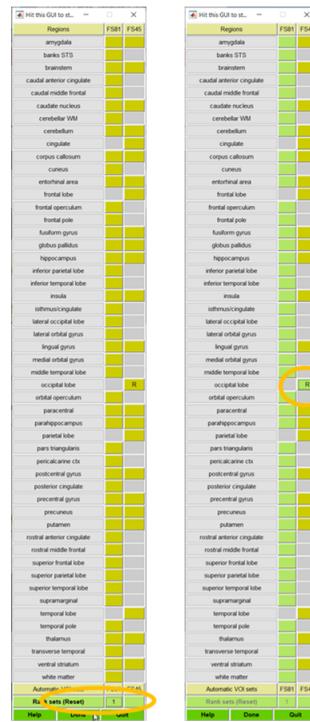


Figure 22: Setting VOI Sets

8.2 Adding Unlisted VOIs

- Instructions for adding VOIs that are not listed under FS81 or FS45 using the pons as an example
 - Hit an (add) GUI (upper orange circle) in the VOI selector module to open the VOIID Utility module
 - Hit the key ‘p’ to list structures starting with p (middle panel)
 - Middle column: Brain structures
 - Right column: Non-brain structures
 - Hit ‘pons’ GUI to bring up the structure
 - Leave ‘whole’ on
 - Hit ‘Done’ GUI (right upper, middle panel)
 - The added structure will appear in the VOI selector module (lower panel)
- The newly added VOIs are not defined by Freesurfer. Therefore ..
 - The user must specify it to ‘S’ or ‘R’, i.e., to define manually from scratch as a target (‘S’) or reference ‘R’ region, respectively
 - The VOI could be included in ‘FS81’ (orange circle) or ‘FS45’ set, depending on which is going to be the primary VOI set.

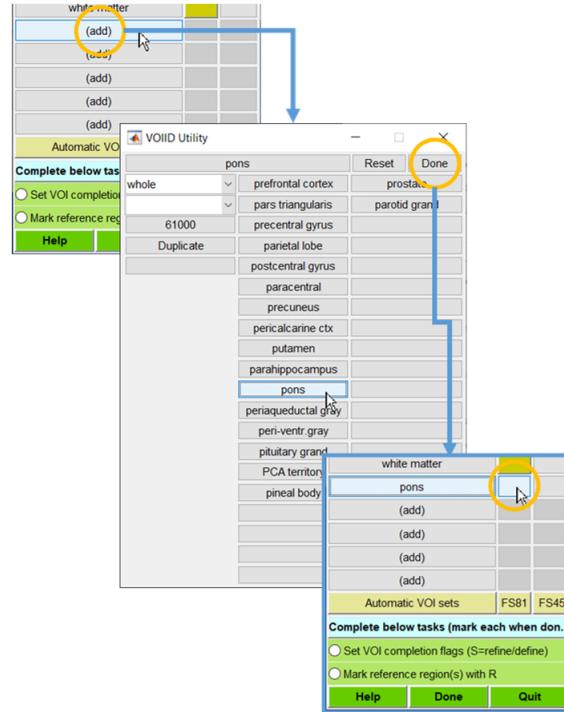


Figure 23: Adding Unlisted VOIs

8.3 Setting Options for TAC2MPE: 1

- TAC2MPE Generator module list the VOI sets the user has for this project
 - The name ‘FS81-v2’ (orange circle) was assigned to the VOI set that was set in the last slide
 - Next GUI explains the set: 47 VOIs from FS81 and FS45 (the occipital lobe alone) sets with 0 ‘S’ and 1 ‘R’ VOIs
 - Most VOIs have left and right VOIs
 - Hit the VOI GUI, and confirm the VOIs to start selecting options in succession
- HMC: Head motion correction
 - No HMC or select one from the mutual information theory-based approaches using SPM12’s coregistration module.
- ‘avr. PET’: Frames to average for PET-to-MRI coregistration (second round)
 - ‘40T90’ and ‘all’ are generic, suggestive choices
 - Consult with the study’s framing protocol (See next slide, if applicable)
- MRI2PET: Approaches for PET-to-MRI coregistration (second round)
 - M2P is strongly recommended



Figure 24: Setting Options for TAC2MPE: 1

8.4 Specify Start/End Times for Frame Averaging

- Aim: To specify PET frames to average for the purpose of PET-to-MRI-coregistration To transfer VOIs from MRI to PET spaces
- Factors to consider:
 - Planned scan durations may be consistent across scans most studies but may be variable to learn the best scan durations for the tracers
 - There could be a common frames to use even in the latter case
 - To take earlier (e.g., 0-10 min frames; close to CBF images higher counts) or later segments (e.g., 40-90 min frames; images are closer to the distributions of target molecule, thus critical for modeling)
- How to specify frames in the module:
 - Select ‘- specify ..’ tab (upper orange circle). It turns to be editable.
 - Remove sTe (middle orange circle; to remind users to use the start-Tend format; e.g., 30T60 to mean to average 30-60 min frames) and enter yours (40T80 in the example; lower orange circle)
 - Make sure to hit return when done. Then, the next selection will appear



Figure 25: Specify Start/End Times for Frame Averaging

8.5 Setting Options for TAC2MPE: 2

- Plasma TAC:
 - Select ‘noCpt’ if no plasma data
 - Select one of generic flags or enter the user’s own flag (postpended to the plasma files)

- Note the descriptions of individual flags using the ‘NoteLine’ function of IDAE (add later)
- Which PET:
 - Indicate which PET scans to apply this TAC2MPE package using check boxes of PET 1 and so on
 - Check scans to apply, and select ‘done’
- Add SN: Whether to add spatial normalization of functional PET volumes
 - SPM12’s unified segmentation method
 - Templates: SPM-supplied or IDAE-supplied
 - Sampling distances for SPM12’s special normalization routine
 - MRI-based spatial normalization + PET-to-MRI coregistration will be used for spatial normalization of PET volumes
- Review selections
 - Hit a GUI (e.g., 40T80 under avr. PET) to revise the selection
 - Hit ‘Done’ if all are as intended. Then, the package will be generated. Restart the project



Figure 26: Setting Options for TAC2MPE: 2

8.6 Starting Stage-2 Packages

- The newly added Stage-2 Package will be listed under group A (=prepMPfsx) when the project is revisited (upper panel)
 - Selected options are listed on the right GUI (upper horizontal arrow) in the order of selection items in TAC2MPE Generator (arrow in bottom panel)
- Level 1 Window of the package (middle panel) pops up when it is selected
 - It may be a good idae to review individual blocks by opening them at this point
- Newly generated Stage-2 packages will be listed in TAC2MPE Generator (lower panel) when the user revisit the TAC2MPE routine

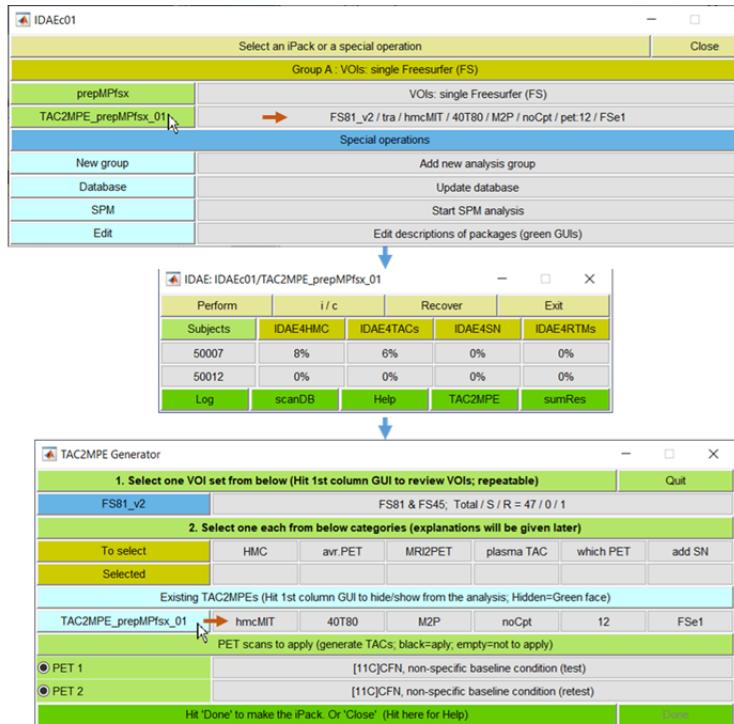


Figure 27: Starting Stage-2 Packages.a

- Stage-2 Packages will be listed under group A (=prepMPfsx) when the project is revisited (upper panel)
 - Selections of options are listed on the right GUI in the order of selection items in TAC2MPE Generator (hmc, avr, m2p, cpt, pet, and SN)
- Level 1 Window of the package (middle panel) pops up when it is selected
 - It may be a good idae to review individual blocks by opening them at this point

- Newly generated Stage-2 packages will be listed in TAC2MPE Generator (lower panel) when the user revisits the TAC2MPE routine

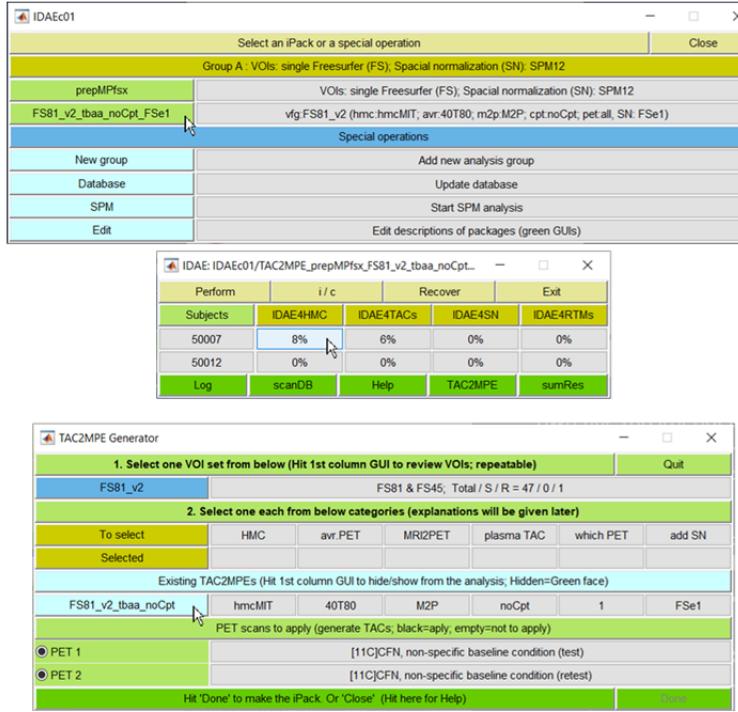


Figure 28: Starting Stage-2 Packages.b

8.7 Managing Stage-2 Packages

- It is very common to have several Stage-2 packages. IDAE
- Major reasons for multiple Stage-2 packages:
 - Revisions of VOIs to refine / define ('S' and 'R' VOIs). Newly added VOI sets will be listed under current FS81_v2
 - Changes in any of option items
- Explanation by example (totally hypothetical)
 - The user wanted to try averaging 0-10 min frames (0T10) for PET-to-MRI coregistration.
 - The resulting package was 'TAU2MPE_prepMPfsx_02' since this is the second package
 - Later, the user wanted to try 30T60 to see if this performed any better than 40T80 (upper panel)
 - Now, the user has 3 Stage-2 packages (lower)
 - Comparing results from the 30T60 and 40T90 sets, the user chose not to use the 40T90 set

- Hit the tab to remove (arrow, lower panel). It toggles between green (disabled) and black (enabled) face colors.
- Disabled package will not show on the selection of packages (no 01 package, lower panel)
- Apply the same procedures to any types of changes (i.e., major reasons), if any



Figure 29: Managing Stage-2 Packages

9 Carrying on with TAC2MPE (a.k.a., Stage-2 Packages)

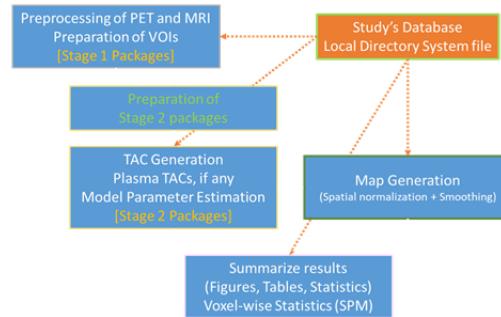


Figure 30: Carrying on with TAC2MPE (a.k.a., Stage-2 Packages)

9.1 Automatic Processes of TAC2MPE with HMC

- Frame-by-frame head motion correction using SPM12's coregistration module with the user-selected cost function (optional)
- Coregistration of PET to the MRI:
 - Averaging PET frames as selected during the generation of TAC2MPE
 - PET-to-MRI coregistration with SPM12's coregistration module
 - In the QC process, the gray matter outlines from the MRI are projected on the averaged PET volume (See 'Coregistration QC at IDAE4TACs')
 - If the coregistration is not acceptable, the user can displace the GM outlines to fit with gray matter of the PET volume to repeat the coregistration using the current guesses as the initial guesses for the optimization process
- Generation of regional TACs:
 - Specified VOIs will be transferred from the MRI to PET spaces according to the PET-to-MRI coregistration parameters, and applied to successive PET frames to obtain regional TACs
- Spatial normalization of the MRI
 - All spatial normalization processes will be performed the unified segmentation method of SPM12
 - In the QC process, the gray matter outlines in the MNI space (generated using the probabilistic maps of spatially normalized gray matter VOIs) are projected on the spatially normalized MRI of the subject
 - No correction measures are available. The user can eliminate the subjects with failed spatial normalization
- Lastly, perform MPE and summarize results.

9.2 TAC2MPE with HMC

- Just follow the principle of IDAE-managed analyses: Perform automatic processes first
- Highlight the subject to perform (upper panel) and hit ‘Perform’ GUI (arrow)
 - In this case, frame-by-frame head motion correction will be performed using SPM12’s coregistration module with the specified cost function
- When done, visit the first subject x analysis-base GUI with an increased completion status % (orange circle at 33%)
- Look for the first light green GUIs with ‘r’ (=ready) or ‘p’ (=pending). Hit it
 - The plot of mean cortex TAC will appear
- Approve it, if the TAC is reasonably smooth
 - No further correction measures at after HMC except removing the last (or a few last) frames.
- The ‘d’ process (special processes that are applicable to certain cases) are not applicable without ‘correction’ approaches for the scans with ‘interrupted’ or ‘segmented’ frames
- Once the QC process is done, repeat processing automatic processes
 - * Note that IDAE4SN (spatial normalization) will be processed as well since the block involves MRI alone

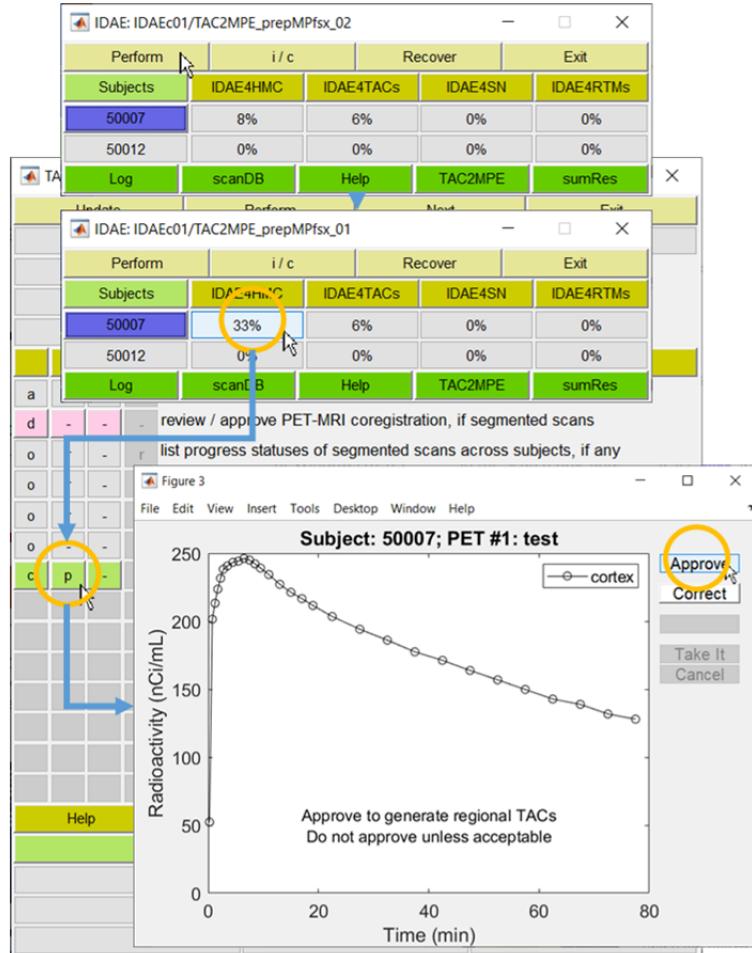


Figure 31: TAC2MPE with HMC

9.3 TAC2MPE without HMC

- TAC2MPE without HMC is identical in the core structure to the version without HMC except that this version lacks IDAE4HMC
- Again, just follow the principle of IDAE-managed analyses
 - Perform available automatic processes
 - Visit the first subject x block GUI what is expected to have an interactive process (upper)
 - Visit the first light-green GUIs displaying ‘r’ (middle circle)
 - Then, the QC process of PET-to-MRI coregistration opens (the same as the next slide)
 - When it is done, hit ‘Perform’ GUI in L1W.

- Then the second row of light-green GUIs (lower circle) will show ‘r’
(See the slide of ‘Review/approve regional TACs’ downstream)

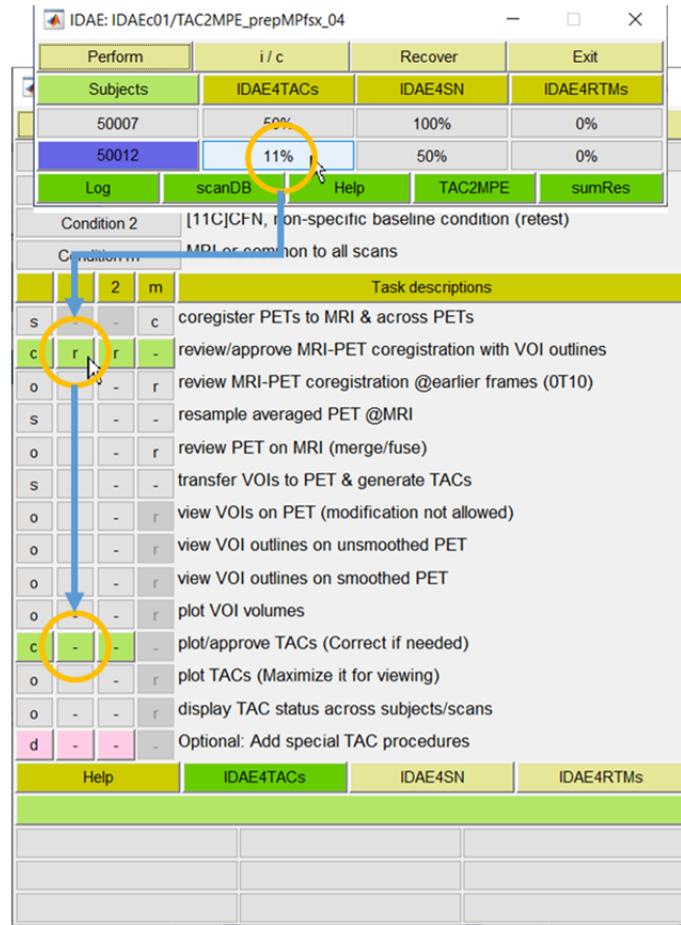


Figure 32: TAC2MPE without HMC

9.4 Coregistration QC IDAE4TACs

- Evaluate if the outlines of gray matter (from MRI) agree with gray matter of the averaged PET volume
 - Use T (trans-axial), S (sagittal), and C (coronal) GUIs under ‘view’ to change views.
 - Use arrow GUIs under ‘Images’ to navigate ‘slices’

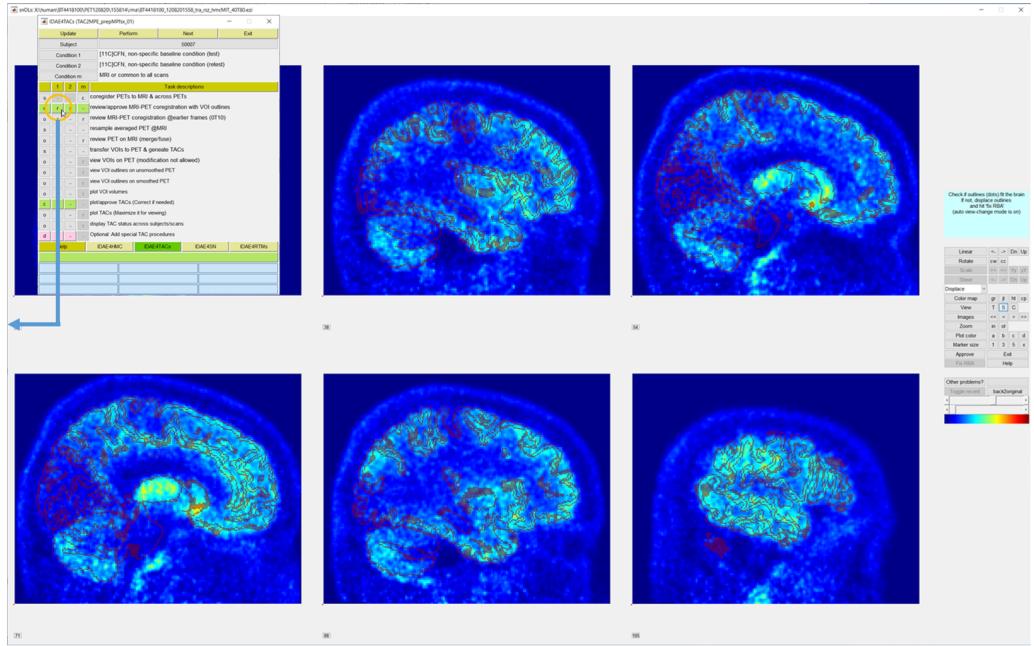


Figure 33: Coregistration QC for IDAE4TACs

9.5 Review/Approve Regional TACs

- Again, hit the first subject x block GUI with ‘increased’ completion status % (orange circle), and visit the first QC (light green) GUI with ‘r’ (or ‘p’) on it.
- Then, plots of regional TACs will pop up
 - Approve it if TACs look OK (orange circle)
 - ‘Correct’ GUI has no functions at this stage
 - Users can set regions to display. See the next section for the procedure

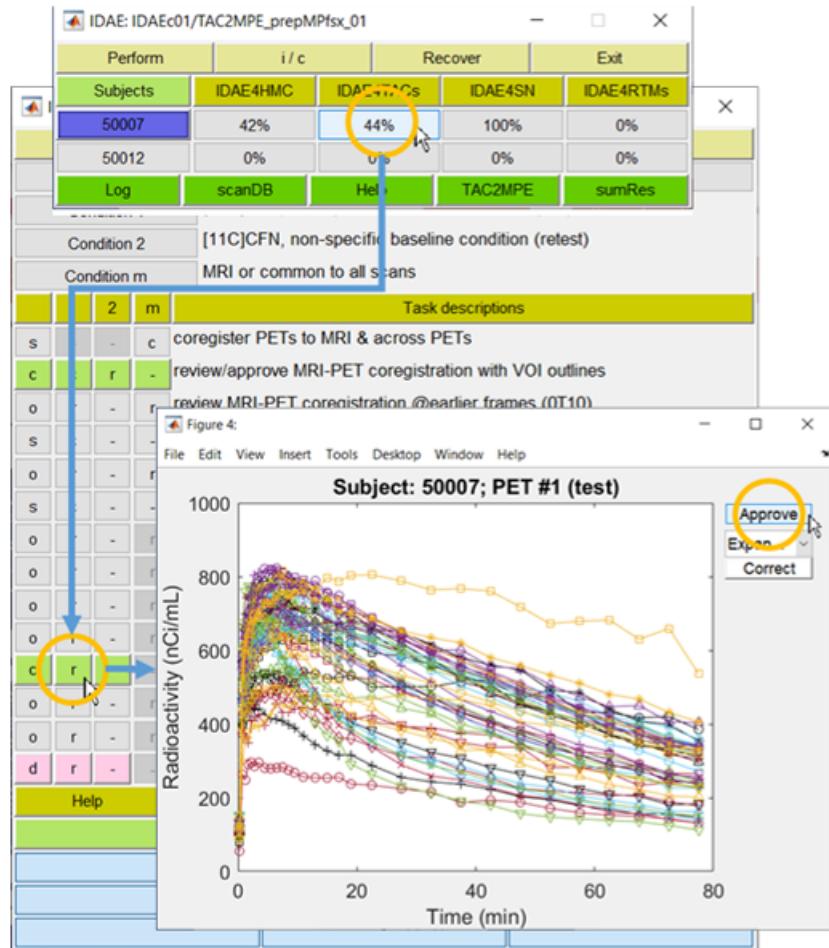


Figure 34: Review/Approve Regional TACs

9.6 Using VOI Selector Module

- The VOI selector module pops up together with plots of regional TACs
- Users can control which regions to include the plots via the VOI selector module:
 - Anatomical labels of all available VOIs are listed in 4 primary columns
 - Each primary column (the first column magnified) lists 3 secondary columns for the left (L), right (R), and whole (W; left-right merged) regions (orange circle)
 - The columns of L and R are disable for those VOIs that are defined for the left-right merged VOIs alone, as for the brainstem (orange arrow)
 - Current selections are checked (black fill)

- Users can change the selection statuses by clicking on the checkboxes
- Users can change the statuses of all regions of respective categories using ‘L’, ‘R’, and ‘W’ GUIs

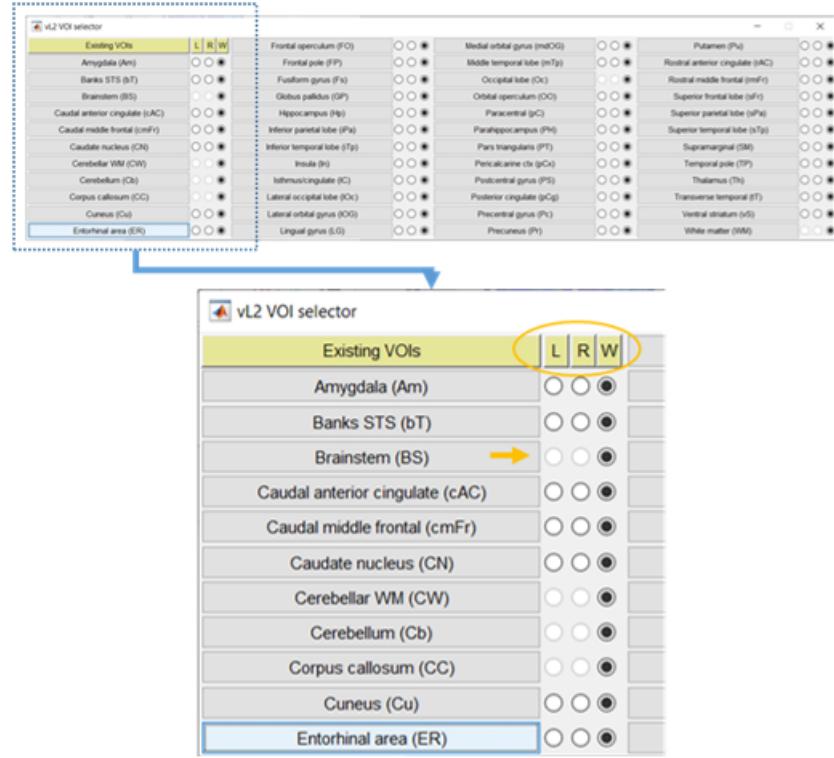


Figure 35: Using VOI Selector Module

9.7 When TACs Are Not Generated

- After performance of automated regions, the step of ‘transfer VOIs to PET & generate TACs’ could remain incomplete (‘r’ is ready to perform). Two major reasons for such instances
 - The mean cortex TAC has not been approved for the scan.
 - That may not be the case if the MRI-to PET coregistration is performed (in this case)
- Not all VOIs od specified VOI sets are not ready.
 - Users will get a summary of the problems IDAE found for the VOIs in MATLAB command window (insert)
 - Two types of VOI files
 - Shared VOI sets: VOIs that are straight from Freesurfer and shared by local users. Only local manage is allowed modify defective VOIs.
 - Personal VOI sets: User-defined ‘S’ or ‘R’ VOIs. The user must complete them as ‘complete’ or ‘as good as possible to be used for VOIs. Shared VOIs will be used for non-‘S’ or ‘R’ VOIs.
 - Revisit the steps of define/define VOIs to complete ‘S’ and ‘R’ VOIs and revisit this step.

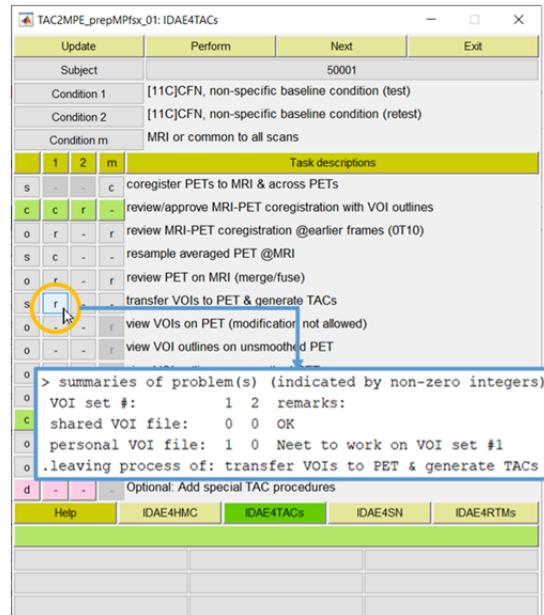


Figure 36: When TACs Are Not Generated

9.8 Optional Processes of IDAE4TACs

- Feel free to visit optional processes ('o' in the first column)
- Review PET on MRI (merge/fuse)
 - Aim: To display the averaged PET images on the MRI for visual inspection.
 - Procedures: Hit 'Fuse' GUI (upper circle), and adjust intensities of the MRI (upper slider) and PET (lower slider, lower circle)
 - Image navigation:
 - Hit at any point on a image to display orthogonal images through that point
 - Hit up/down, i/m (next to u/n), and </>keys to navigate cranium/neck, inion/nasion, and left/right directions, respectively
 - Hit 'q' key to navigate 30 images in the current direction: e.g., 'u' then 'q' to navigate 30 images toward the cranium
- Display TAC status across subjects/scans

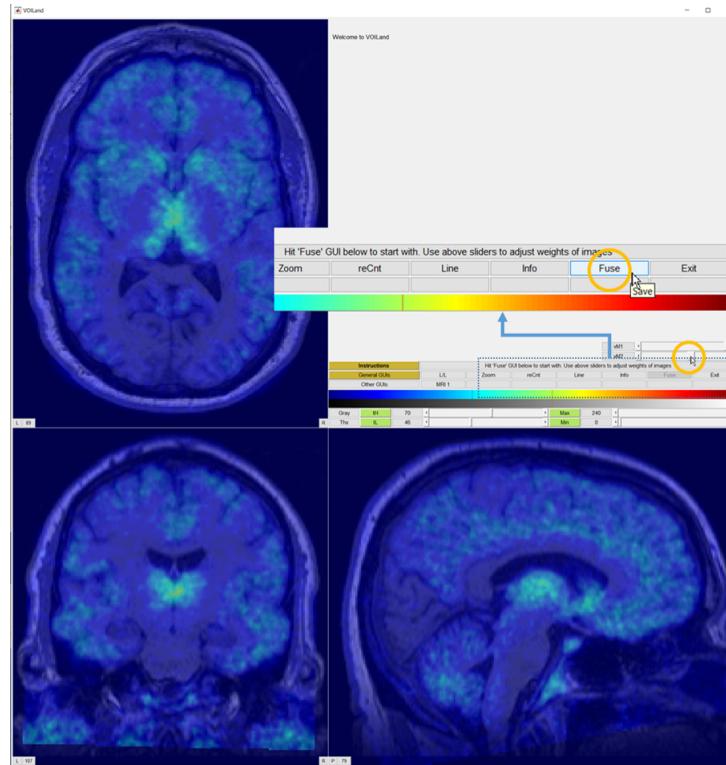


Figure 37: Optional Processes of IDAE4TACs

9.9 QC of Spatial Normalization for IDAE4SN

- Freesurfer-defined gray matter is inserted in this version of MRI. Visit the next step to display SN'ed original MRI

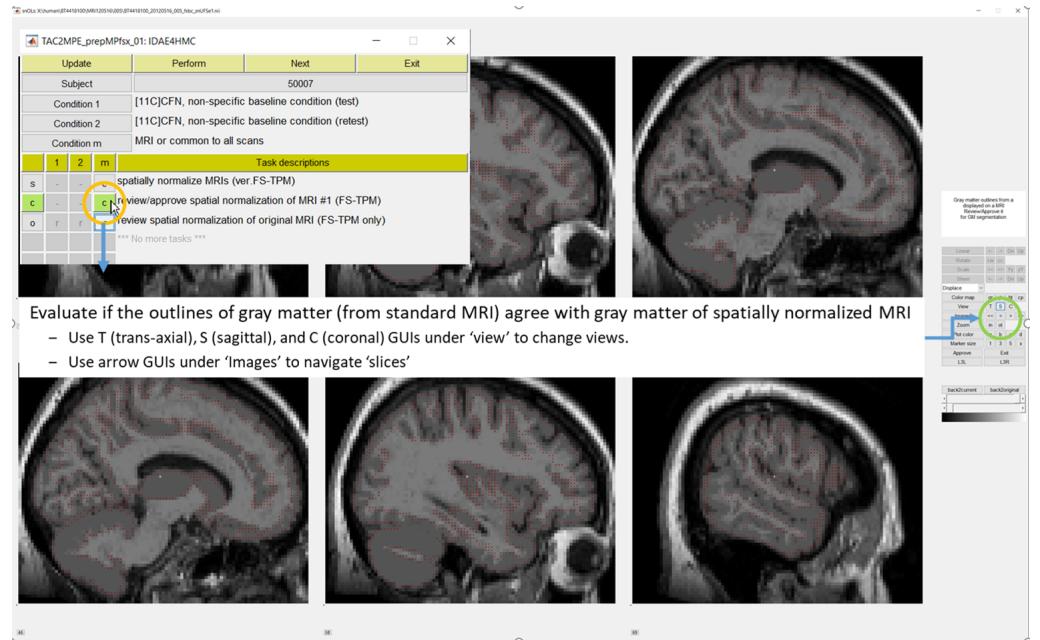


Figure 38: QC of Spatial Normalization for IDAE4SN

10 To Set / Perform RTMs

10.1 Setting RTMs: Overview

- Aim: To set reference tissue methods (RTMs) and their parameters for the package
- Major procedures:
 - First, set the MPE preparation module (lower panel) by clicking the designated GUI (orange circle; upper panel)
 - Follow instructions given in the 1st row
 - Bring in a method from the 1st column GUIs to set relevant parameters (2nd to 4th columns)
 - See the quick guide (next slide) for methods
 - Hit ‘Save this method’ (bottom left) when done to move on to the next method
 - Go inclusive in the first cycle (i.e., for all PETs) to be selective in the second cycle.
 - Hit ‘Save to file’ if no more methods to set (= the end of the first cycle)
 - Visit already-selected (light green) methods one-by-one in the second cycle
 - Adjust applicable PET sans and hit ‘Save this method’ to move on to the next method
 - e.g., 20T90 for PET 1 (tracer A) and 40T90 for PET 2 (tracer B) for PRGA
 - Hit ‘Save to file’ when all methods are done (= the end of second cycle)

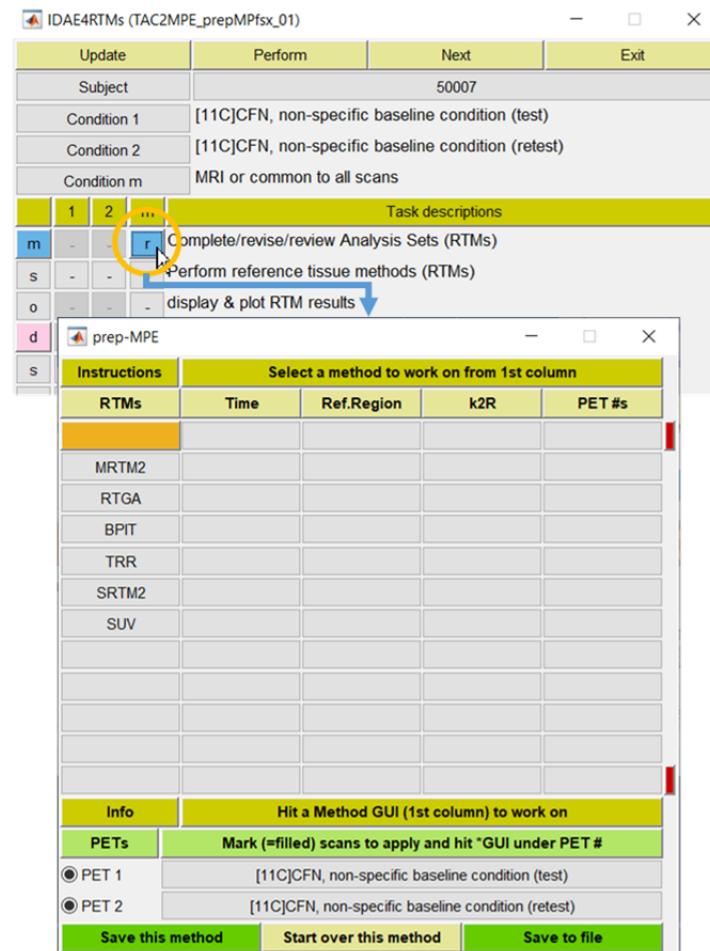


Figure 39: Setting RTMs: Overview

10.2 RTMs: Quick Guide

Methods	Explanations
MRTM2	Multilinear reference tissue method with 2 parameters (Ichise et al., 2003) Treatment of k2R (k_2 , the brain-blood clearance constant of the reference region): <ul style="list-style-type: none"> • Median k2R: Use the median values of k2R (across regions) from the 3-parameter fit • Optimize: Optimize k2R by minimizing the total RSS across regions. Referred to as optk2R here. • Fix as RTGA: fix k2R at the user-entered k2R value(s) for PRGA (need to set)
RTGA	Reference tissue graphical analysis (Logan et al., 1996) <ul style="list-style-type: none"> • RTGA will be performed in two ways: Fixing k2R at the user-entered k2R value(s), and optimizing k2R by minimizing the total RSS across regions (Referred to as optk2R)
BPIT	Bolus-plus-infusion transformation (Kuwabara et al., 2013)
TRR (SUVR)	Target-reference tissue ratio
SRTM2	Simplified reference tissue method with 2 parameters (Lammertsma and Hume, 1996) <ul style="list-style-type: none"> • Not recommended by IDAE because SRTM2 yields practically identical values of BPND to MRTM2, while computationally more demanding. • Wu and Carson, 2002 should be credited for the 2 parameter version
SUV	Standard uptake value
On the circulation times for data analysis	
IDAE's t^*TT_{end} Format	All RTMs assumes the conditions for a method are met a segment of the total scan from the start-analysis time (denoted by t^*) and the end-analysis time (T_{end}). In IDAE, the start- and end analysis can be specified by a t^*TT_{end} format (e.g., 20T80 for a t^* of 20 min, and an end-analysis time of 80 min)

Figure 40: RTMs: Quick Guide

10.3 Setting MRTM2: First cycle

- Hit MRTM2 to start with.
- MRTM2 will be shown in the orange GUI while GUIs for other methods are disabled
- Default parameters will be shown initially. Users can modify them as needed as follows:
 - Time: the circulation time for the analysis in startTend format: 5T90 to use 5-90 min frames
 - Hit an available GUI (5T90 initially) to modify it. The GUI becomes editable. Enter your values and hit ‘enter’ to quit the editable mode.
 - Hit the GUI with * (arrow in left insert) to set another circulation time (by the start time increase by 5 min; thus 10T90) (middle insert)
 - Hit the GUI to modify it as show above. And hit return when done (right insert)
 - Reference region: Pre-selected reference regions (‘R’ regions) will appear here.
 - Go inclusive in the first cycle. For example, select all reference regions when reference regions differ among tracers of the scans (PET 1, 2, etc.).
 - See ‘Quick Guide’ for k2R
 - all checked will be performed
 - Need to add RTGA if to use the ‘fix as RTGA’ option

- Hit ‘Save this method’ GUI when done

prep-MPE

Instructions		Hit filled GUIs to edit, * fore more; Hit next row GUIs for info			
RTMs	Time	Ref.Region	k2R	PET #s	
MRTM2	5T90	<input checked="" type="radio"/> Oc 54000	<input type="radio"/> median k2R	in Step 2	
MRTM2	*		<input checked="" type="radio"/> optimize		
RTGA			<input type="radio"/> fix as RTGA		
BPIT					
TRR					
SRTM2					
	Time	Time	Time		
	5T90	5T90	5T90		
	*	10T90	0T90		
		*	*		
Info		Step 1: Complete Columns from Time through k2R			
PETs	Mark (=filled) scans to apply and hit *GUI under PET #				
<input checked="" type="radio"/> PET 1	[11C]CFN, non-specific baseline condition (test)				
<input type="radio"/> PET 2	[11C]CFN, non-specific baseline condition (retest)				
Save this method		Start over this method	Save to file		

Figure 41: Setting MRTM2: First cycle

10.4 Setting RTGA: First Cycle

- Hit RTGA to start with
 - MRTM2 which was set in the previous slide is marked by light green, although it is disabled along with other non-RTGA methods
- Default parameters are shown initially
 - The values of k2 of the reference region (k2R) must be provided for RTGA. Users can:
 - Use IDAE-recommended values, then edit them if needed
 - If the value is unknown yet, run MRTM2 and obtain mean k2R across subjects
 - When the study involves multiple tracers of different k2R values, enter all in the first cycle and make them tracer-specific in the second cycle
 - An example of RTGA setting is shown in insert
 - Three values for t* (the start of asymptote for RTGA plots) were set to examine which t* is appropriate to [11C]CFN
- Hit ‘Save this method’ GUI when done
 - If no more RTMs to define, hit ‘Save to file’ GUI

Instructions					Hit filled GUIs to edit, * fore more; Hit next row GUIs for info					
RTMs		Time	Ref.Region	k2R	PET #s					
RTGA		10T90	(●) Oc 54000	Recommen... <input type="button" value="in Step 2"/>						
MRTM2		*		Recommended k2Rs:	[11C]CFN 0.104 < select one and edit, if needed					
RTGA										
BPIT										
TRR										
RTMs		Time	Ref.Region	k2R	PET #s					
RTGA		5T80	(●) Oc 54000	0.104	in Step 2					
MRTM2		10T80		*						
RTGA		15T80								
BPIT		*								
TRR										
Info		Step 1: Complete Columns from Time through k2R								
PETs		Mark (=filled) scans to apply and hit *GUI under PET #								
(●) PET 1		[11C]CFN, non-specific baseline condition (test)								
(●) PET 2		[11C]CFN, non-specific baseline condition (retest)								
<input type="button" value="Save this method"/>			<input type="button" value="Start over this method"/>			<input type="button" value="Save to file"/>				

Figure 42: Setting RTGA: First Cycle

10.5 Setting MRTM2: Second Cycle

- Assume that ‘Save to file’ GUI was hit after setting MRTM2 and RTGA
- Then, the module goes into the second cycle (pink instruction GUI)
- Select a method among green GUIs (MRTM2 in this case)
- Now each line shows one set of MRTM2 analysis
- Making analysis set scan-specific (tracer-specific in fact):
 - Note that we cannot do much for making analysis sets to be tracer-specific in this study because the tracer is the same for PET 1 and 2
 - Assume (although very hypothetical) that the 0T90 set is applicable to PET 2 alone. Then, unmark PET 1 alone (orange circle), then hit a GUI under ‘PET #s’ (arrow). It turns now that the 0T90 analysis is ‘applicable to PET 2 alone’
- Hit ‘Save this method’ when all rows are OK
 - Note that the GUI of MRTM2 turns to a darker green color indicating that the second cycle is done for MRTM2

Instructions					Expand mode. Check/Set applicable PETs for each approach				
RTMs		Time	Ref.Region	k2R	PET #s				
MRTM2		5T90	Oc	optk2R	1,2				
MRTM2		0T90	Oc	optk2R	2				
RTGA									
BPIT									
TRR									
SRTM2									
SUV									
Info		Expand mode: One approach per row							
PETs		Mark (=filled) scans to apply and hit *GUI under PET #							
<input type="radio"/> PET 1		[11C]CFN, non-specific baseline condition (test)							
<input checked="" type="radio"/> PET 2		[11C]CFN, non-specific baseline condition (retest)							
Save this method				Start over this method			Save to file		

Figure 43: Setting MRTM2: Second Cycle

10.6 Setting RTGA: Second Cycle

- Again, each row lists an analysis set of RTGA in the second cycle.
- In this example, 6 analysis sets will be performed: 3 user-entered analysis circulation time sets x 2 k2R sets (to fix at 0.104 and to optimize the value for the scan which is automatically added by IDAE).
- Note that we cannot do much in terms of making analysis sets to be tracer-specific in this study because the tracer is the same for PET 1 and 2 H
- It ‘Save this method’ when all rows are OK
- Note that the GUI of RTGA turns to a darker green color indicating that the second cycle is done for PRGA
- Hit ‘Save to file’ GUI if there are no more ‘light green’ GUIs. This is the end of RTM setting.

The screenshot shows the 'prep-MPE' software window. At the top, a message says 'Expand mode. Check/Set applicable PETs for each approach'. Below is a table for 'RTMs' with columns: RTMs, Time, Ref.Region, k2R, and PET #s. The table contains the following data:

RTMs	Time	Ref.Region	k2R	PET #s
RTGA	5T80	Oc	0.104	1,2
MRIIM2	5T80	Oc	optk2R	1,2
RTGA	10T80	Oc	0.104	1,2
BPIT	10T80	Oc	optk2R	1,2
TRR	15T80	Oc	0.104	1,2
SRTM2	15T80	Oc	optk2R	1,2
SUV				

Below the table, an 'Info' section says 'Expand mode: One approach per row'. It includes a 'PETs' section with two radio buttons: 'PET 1' (selected) and 'PET 2'. The 'PET 1' entry is '[11C]CFN, non-specific baseline condition (test)'. The 'PET 2' entry is '[11C]CFN, non-specific baseline condition (retest)'. At the bottom are three buttons: 'Save this method' (green), 'Start over this method' (yellow), and 'Save to file' (green).

Figure 44: Setting RTGA: Second Cycle

10.7 Further on the 2nd Cycle: 1

- In the 1st cycle of this example:
 - Four t₀, the starting time for MRTM2 were entered (but all ending at 90 min)
 - One reference region was entered (CW or the cerebellar white matter)
 - Two approaches for k_{2R}, k₂ of reference region were entered
 - Median k_{2R} in which median of regional k_{2R} values from MRTM3 will be obtained / fixed in MRTM2 (original MRTM3 and MRTM2)
 - Optimize k_{2R} to minimize the total sum of square sums across regions (modified MRTM2)
 - Altogether, 12 modeling approaches (= 4 x 1 x 3) are specified in the 1st cycle In the 2nd cycle:
 - The 12 modeling approaches will be listed one per row
 - Page up / down GUIs (red GUIs) will be activated when more than 12 approaches are present.
 - Since this is a one-scan study, the role of the 2nd cycle is limited to just confirm presence of individual modeling approaches.
 - See the next section for a multi-PET study



Figure 45: Further on the 2nd Cycle: 1

10.8 Further on the 2nd Cycle: 2

- In the 1st cycle (not shown) of this example:
 - Two circulation time pairs were set for RTGA (20T90 and 25T75)
 - One reference region was entered (Cb or the cerebellar)
 - Two approaches for k2R, k2 of reference region were entered
 - Two fixed k2R values for PIB and DASB (0.149 and 0.48 min-1, respectively) were entered
 - Optimize k2R by minimizing the total sum of square sums across regions (denoted as optk2R)
 - Altogether, 6 modeling approaches (= 4 x 1 x 3) were specified for RTGA in the 1st cycle
- Set the applicable PETs in the 2nd cycle:
 - The 6 modeling approaches will be listed one per row to be applicable to all scans (1, 2, 3, and 4) initially (upper panel)
 - Now set the applicable scans for PIB scans
 - Deselect PET 3 and 4 (bottom PET area)
 - Hit GUIs of the rows of k2R = 0.149 min-1 under 'PETs' (e.g., at the cursor) to change applicable PET scans to all to 1 and 2
 - Repeat the same procedures for DASB after activating PET 3 and 4 alone

RTMs	Time	Ref.Region	k2R	PET #s
RTGA	25T90	Cb	0.149	1,2,3,4
MRTM2	25T90	Cb	0.048	1,2,3,4
RTGA	25T90	Cb	optk2R	1,2,3,4
BPT	25T75	Cb	0.149	1,2,3,4
TRR	25T75	Cb	0.048	1,2,3,4
SRTM2	25T75	Cb	optk2R	1,2,3,4

RTMs	Time	Ref.Region	k2R	PET #s
RTGA	25T90	Cb	0.149	1,2
MRTM2	25T90	Cb	0.048	1,2,3,4
RTGA	25T90	Cb	optk2R	1,2,3,4
BPT	25T75	Cb	0.149	1,2
TRR	25T75	Cb	0.048	1,2,3,4
SRTM2	25T75	Cb	optk2R	1,2,3,4

Info		Expand mode: One approach per row		
PETs		Mark (=filled) scans to apply and hit 'GUI under PET #'		
<input checked="" type="radio"/> PET 1		[11C]PIB, PIB scan 1		
<input checked="" type="radio"/> PET 2		[11C]PIB, PIB scan 2		
<input type="radio"/> PET 3		[11C]DASB, DASB scan 1		
<input type="radio"/> PET 4		[11C]DASB, DASB scan 2		

Figure 46: Further on the 2nd Cycle: 2

10.9 Perform / Review RTMs

- It is very simple to perform RTMs
 - Just highlight subjects to perform RTMs (judged from completion status) and hit ‘Perform GUI (lower insert)
 - Once the automatic processes are done, the completion statuses increase (upper insert)
- Users can review results of RTMs of a subject as follows
 - Visit the subject x block GUIs (under IDAE4RTMs) of any subject to open L2W
 - Hit ‘r’ GUI (orange circle) @’display plot RTM results’

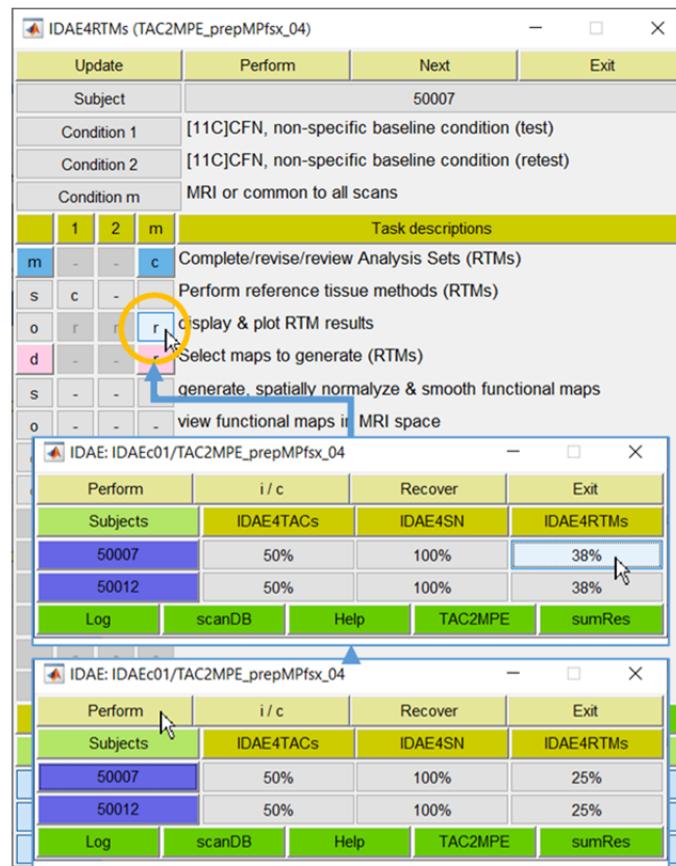


Figure 47: Perform / Review RTMs

10.10 Display / Plot RTM Results

- Hit the ‘r’ GUI @’Display / plot RTM results’ of L2W (IDAE4RTMs) to set the result display module (background)
- Select an output from the menu (top right)
 - Display regional values ... (shown here)
 - Scatter plot of regional data of a variable between scan 1 vs. scan 2 and so on
 - Line plots vs. regions: Spaghetti plots
- Select one analysis approach from the list (left insert)
 - Approaches are shown by 5 elements of ‘method flag’ (acronyms), ‘circulation time for analysis’, ‘acronym of reference region’, ‘treatment of k2R’, and ‘primary variable’.
- Select the variable to display (middle insert)
 - Select ‘show all variables’ to display them all
- Select the scan to display (right insert)
 - Light green = available; darker green = selected
- Set the VOIs to display (bottom)
 - See the section of the VOI selector module
- Hit ‘Perform’ GUI (bottom left)

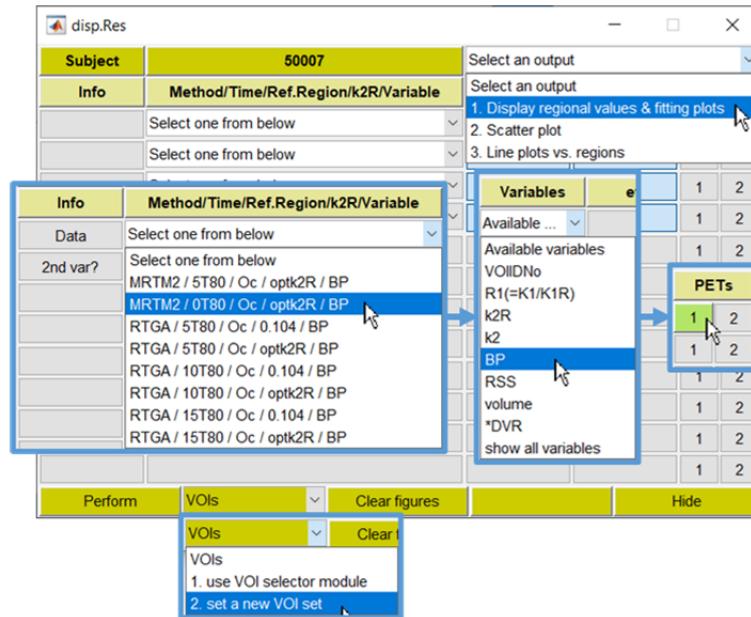


Figure 48: Display / Plot RTM Results

10.11 Example of Observed and Fitted TACs: MRTM2

Plots of observed (o) and model-fitted (-) TACs of all left-right merged regions

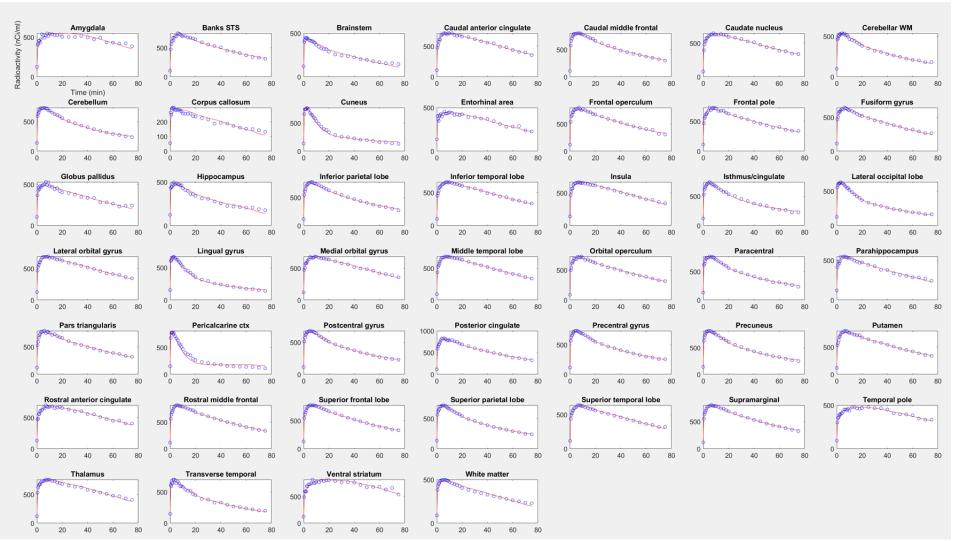


Figure 49: Example of Observed and Fitted TACs: MRTM2

10.12 Display / Plot RTM Results

- First, hit ‘c’ GUI at ‘Complete/revise/review Analyses Sets’ of L2W to bring up the MPE preparation module (upper panel)
 - Previously set RTM approaches will be highlighted in light green
 - Hit a highlighted approach to review / revise
 - Bring in / set a new approaches, as needed
 - Hit ‘Save this method’ to update the working approach
 - Hit ‘Save to file’ when all approaches are done (= the end of the 1st cycle)
 - Leave those approaches not intended to review / revise unattained
- In the 2nd cycle (lower panel):
 - Hit a highlighted approach to review / revise
 - Hit ‘Save this method’ to update the approach
 - Reviewed / revised approaches will be highlighted in darker green (MRTM2 in this example)
 - Hit ‘Save to file’ when done (= the end of the 1st cycle)
 - Leave those approaches not to review / revise unattained

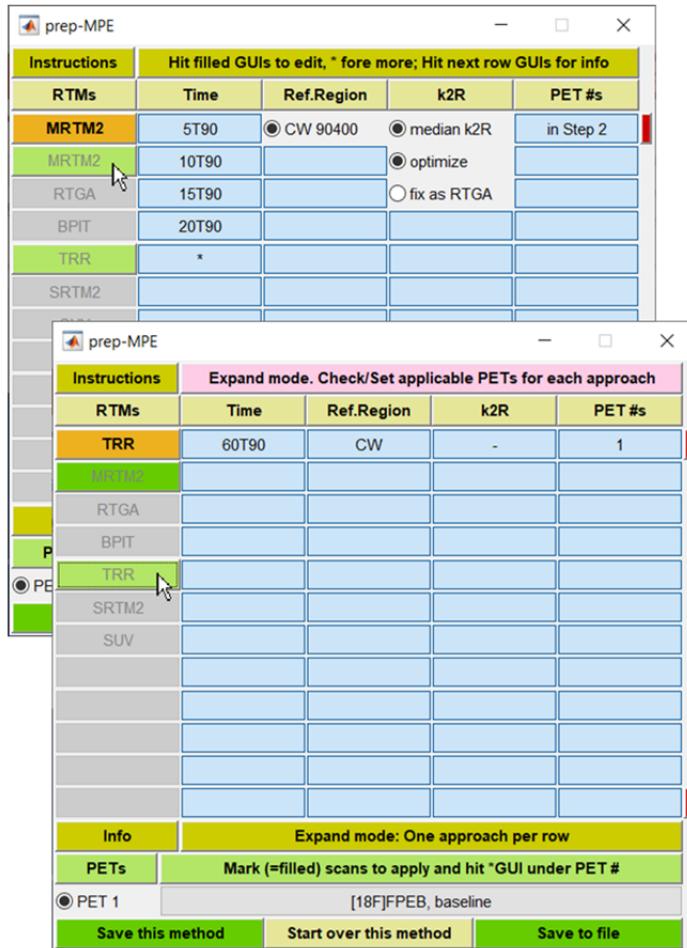


Figure 50: Display / Plot RTM Results

11 To Prepare Plasma and HPLC Data

11.1 Preparation of Plasma HPLC files

- When the ‘preparation’ step is activated (upper orange circle), L2W’s utility GUIs will be set for the purpose (orange rectangle)
 - The function of ‘Plasma’ GUI is to prepare a file of plasma data of this scan of the subject
 - Here, the term ‘plasma data’ refer to a two-column matrix of sampling times and radioactivity values in user-specified unit
 - The function of ‘HPLC’ GUI is to prepare a file of HPLC data. The term ‘HPLC data’ refers to a two-column matrix of sampling times and fractions of metabolites in percentage
- The ‘Plasma’ and ‘HPLC’ GUIs will not function until the local manager set the local system file (dxetc4xxx.m)

- This is to cope with the fact that individual PET centers or Labs prepare plasma and HPLC files in their own formats and store them according to their own conventions.
- To local IDAE managers:
 - See help messages from cv2_getCPT.m
 - See also the next two sections

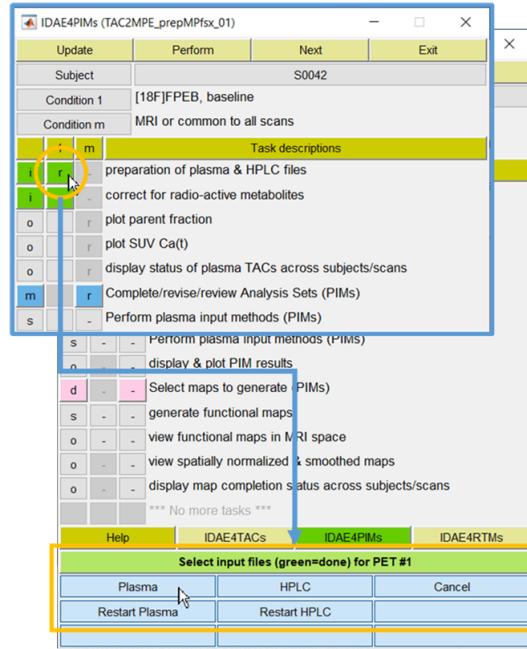


Figure 51: Preparation of Plasma & HPLC files

11.2 Site-Specific Operations: Plasma

- In this example, MATLAB's file selector will pop up when 'Plasma' GUI is hit.
 - Note that the folder was pre-selected
 - Files of target format (*.xls*) alone are listed
 - When the target file is selected (lower orange circle), the plasma data will be extracted and saved in IDAE-requested format
 - The GUI will be marked in darker green
 - Use 'Restart Plasma' GUI to start over
- To local IDAE managers:
 - The callback function of 'Plasma' GUI is:
 - *dxetc4xxx('get_plasma',input_2)*

where input_2.ofl contains the IDAE-generated output plasma file, and input_2.fbc lists [figure of L1W, subject , scan]

- o Set a subfunction ‘local_get_plasma’ in your dxetc4xxx.m and set the following measures:
 - To find the plasma file. A MATLAB function of uigetfile.m was utilized in this example
 - To convert the plasma data into a two-column matrix of sampling times and radioactivity values in user-specified unit
 - To save it to input_2.ofl in 8-digit ASCII format (add ‘-ascii’)
 - To update the Plasma GUI (to green) add the following line just after the ‘save’ line

- `cv2_getCPT('check', 1)`

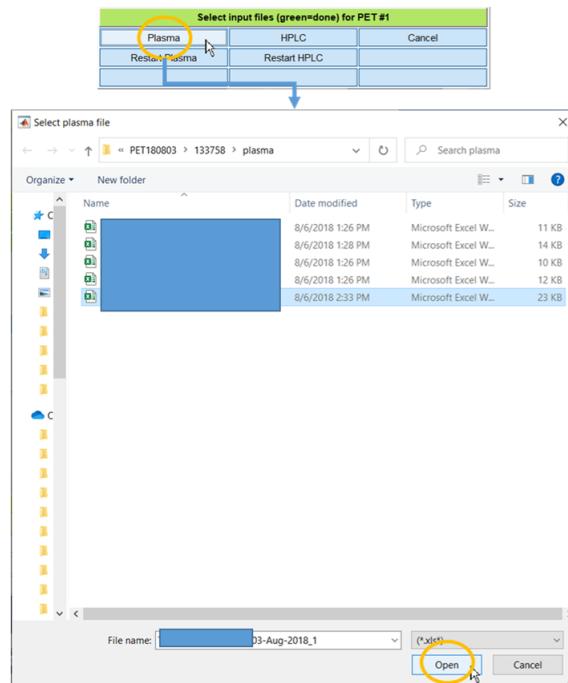


Figure 52: Site-Specific Operations: Plasma

11.3 Site-Specific Operations: HPLC

- o In this example, MATLAB’s file selector will pop up when ‘HPLC’ GUI is hit.
 - o Open the target PDF file (lower panel) as shown in previous slide. Copy / paste time and parent fractions to the MATLAB command as instructed therein
 - The manual method was selected since the function to read PDF requires a specific MATLAB toolbox

- The GUI will be marked in darker green
- Use ‘Restart HPLC’ GUI to start over
- To local IDAE managers:
- The callback function of ‘Plasma’ GUI is:
`dxetc4xxx('get_hplc',input_2)`
 where input_2.ofl contains the IDAEgenerated output HPLC file, and
 input_2.fbc lists [figure of L1W, subject , scan]
- Set a subfunction ‘local_get_hplc’ in your dxetc4xxx.m and set the following measures
 - To find the HPLC file. A MATLAB function of uigetfile.m was utilized in this example
 - To convert the plasma data into a two-column matrix of sampling times and radioactivity values in user-specified unit
 - To save it to input_2.ofl in 8-digit ASCII format (add ‘-ascii’)
 - To update the HPLC GUI (to green) add the following line just after the ‘save’ line

`-cv2_getCPT('check', 2)`

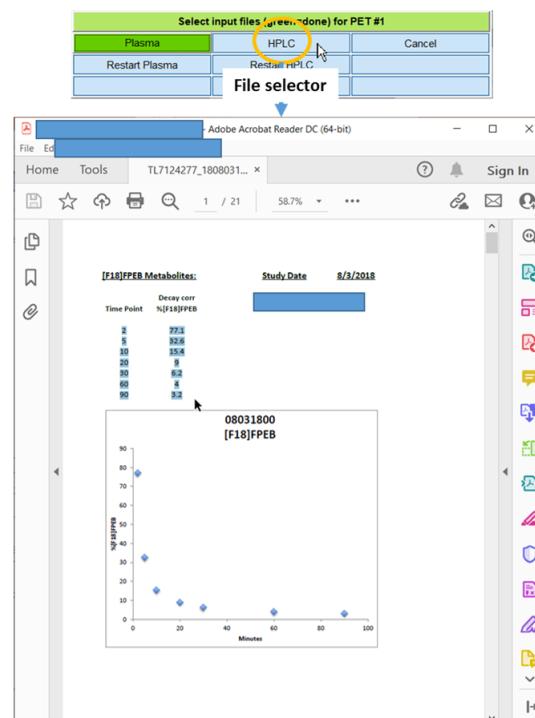


Figure 53: Site-Specific Operations: HPLC

11.4 Correct for Radioactive Metabolites: 1

- The setCPT module will pop-up with plot of the plasma TAC (total) (lower panel) when the GUI of the ‘correct ..’ step is clicked (orange circle)
- Observe the plasma TAC
 - Some corrective measures for the plasma TAC are provided (left insert; under Ca(t))
 - Consult the tabs for functions
 - sumExp2/3 refer to sums of exponential functions
- Import HPLC data, if plasma TAC is OK

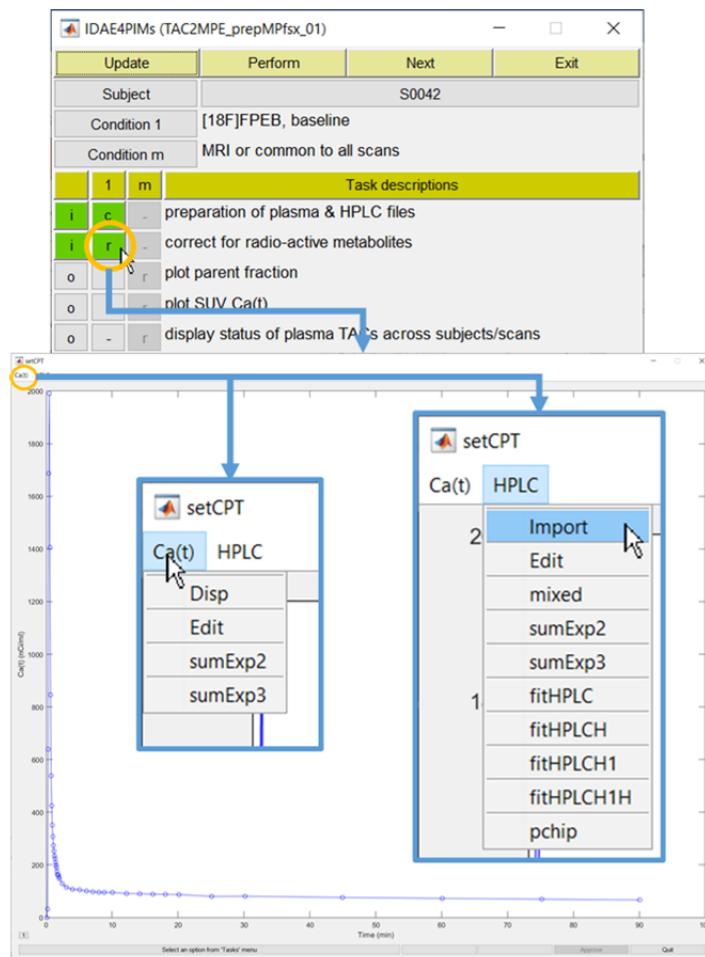


Figure 54: Correct for Radioactive Metabolites: 1

11.5 Correct for Radioactive Metabolites: 2

- Observe plot of the HPLC data (blue circles in lower panel)
 - Note that the HPLC data show total metabolites in percentages (= 100 – parent fraction in percentage)
 - Fit the HPLC data by one of IDAE-supplied functions (3rd tab and on; upper panel)
 - The IDAE team suggest using ‘mixed’, ‘fitHPLC’, one of ‘fitHPLCH*’, or ‘pchip’
 - ‘pchip’ refers to the shape-preserving piecewise cubic interpolation of MATLAB (interp1.m) Employ one approach across scans of a study
 - Hit ‘Take’ (lower orange circle), ‘Apply’, and ‘Approve’ GUIs sequentially. It’s done!
- Associate the fitting approaches with the IDAE-supplied generic terms for plasma data
 - The generic terms including ‘noTAD’ and ‘HPLC*’ are presented during generation of Stage-2 packages (TAC2MPE)
 - The IDAE team recommends to make site-wide rules, for example to use ‘noTAD’, ‘HPLC’, and ‘HPLC1’ for ‘fitHPLC’, one of ‘fitHPLCH*’, and ‘pchip’, respectively.

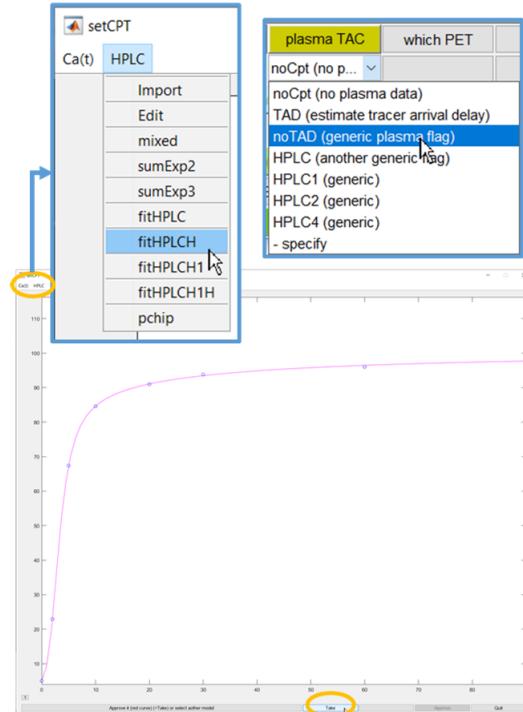


Figure 55: Correct for Radioactive Metabolites: 2

12 To Set / Perform PIMs

12.1 Setting PIMs: Overview

- Aim: To set plasma input methods (PIMs) and their parameters for the package
- Major procedures:
 - First, set the MPE preparation module (lower panel) by clicking the designated GUI (orange circle; upper panel)
 - Follow instructions given in the 1st row
 - Bring in a method from the 1st column GUIs to set relevant parameters (2nd to 4th columns)
 - See the quick guide (next slide) for methods
 - Hit ‘Save this method’ (bottom left) when done to move on to the next method
 - Go inclusive in the first cycle (i.e., for all PETs) to be selective in the second cycle.
 - Hit ‘Save to file’ if no more methods to set (= the end of the first cycle)
 - Visit already-selected (light green) methods one-by-one in the second cycle
 - Adjust applicable PET sans and hit ‘Save this method’ to move on to the next method
 - e.g., 20T90 for PET 1 (tracer A) and 40T90 for PET 2 (tracer B) for PRGA
 - Hit ‘Save to file’ when all methods are done (= the end of second cycle)

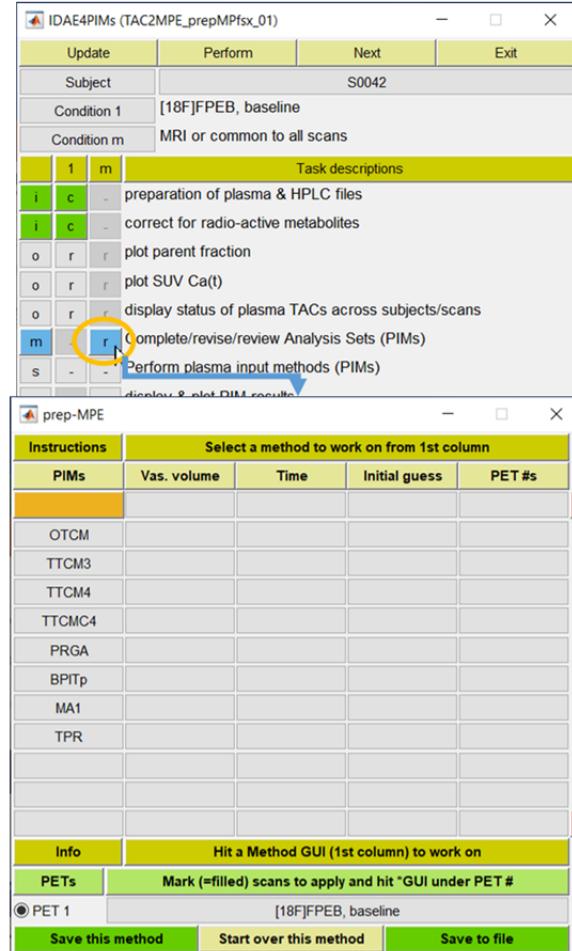


Figure 56: Setting PIMs: Overview

12.2 PIMs: Quick Guide

k_1, k_2 : BBB clearance constants; $k_3 = B_{max}/k_{on}$; $k_4 = k_{off}$; V : tissue vascular volume TTGCM3 etc (yellow highlight): Not working for now (need to fix by submission)

Labels	Descriptions	Parameters	Outcome Variables
OTCM	One tissue compartment model	K_1, k_2', V_0	$V_T = K_1/k_2'$
TTCM3	Two tissue compartment model irreversible (no k_4)	K_1, k_2, k_3, V_0	$K_i = K_1 \cdot k_3 / (k_2 + k_3)$
GPGA	Gjedde-Patlak plot	Slope of asymptote	K_i : slope
TTCM4	Two tissue compartment model reversible (with k_4)	K_1, k_2, k_3, k_4, V_0	$V_T = K_1/k_2 (1 + k_3/k_4)$ $BP_{ND} = k_3/k_4?$
TTCM4C	TTCM with the K_1/k_2 ratio fixed at the reference tissue value	K_1, k_3, k_4, V_0	$V_T = K_1/k_2 (1 + k_3/k_4)$ $BP_{ND} = k_3/k_4$
PRGA	Plasma reference graphical analysis (Logan et al., 1990)	Slope of asymptote	V_T : Slope $BP_{ND} = V_T/V_T^R - 1$
MA1	A multi-linear version of PRGA		
BPITp	Bolus-plus-infusion transformation		V_T : Plateau height

Figure 57: PIMs: Quick Guide

12.3 Setting PIMs: General Points

- Hit a method to set (OTCM in this example)
 - The method will be shown on the ‘Orange’ GUI
 - Suggested entries will be shown in columns of ‘Vas. volume’, ‘Time’, and ‘Initial guesses’
- Complete columns:
 - Hit a filled GUI to modify it, as needed
 - The GUI turns in the ‘edit’ mode (pink)
 - Follow the displayed format: e.g., for the initial guesses, enter ‘K1 = new value, k2 = new value’
 - Empty it to remove the entry
 - Hit the ‘return’ key when done (no longer in pink)
 - Hit a GUI to create a new entry (orange circle)
 - The GUI turns in the edit mode (pink) with a new suggested entry (insert)
 - Follow the displayed format: e.g., ‘fix new value’ to fix the vascular volume at the new value
 - Empty it to remove the entry
- Hit the ‘return’ key when done (no longer in pink)
- Hit ‘Save this method’ GUI when it is done for the method.
- Hit ‘Save to file’ GUI when all intended methods are done
- Repeat the same in the second cycle to individualize the methods to scans

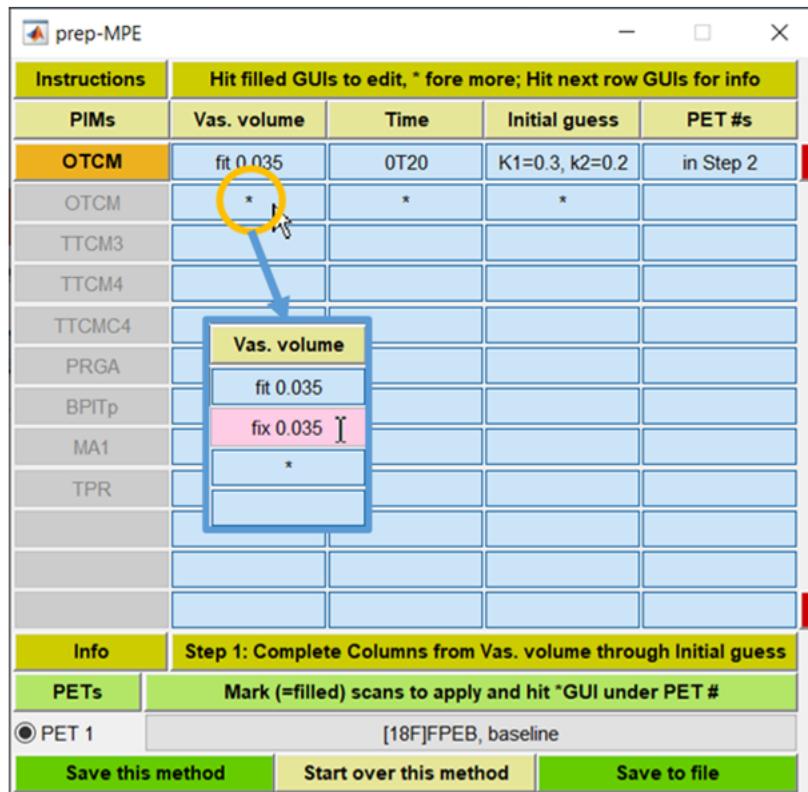


Figure 58: Setting PIMs: General Points

12.4 When to Employ TTCM4 Family

- See the 'Quick Guide' to know IDAE's acronyms for PIMs
- IDAE is set to perform TTCM4 TTCMC4 with regionally adjusted initial guesses of parameters, if OTCM and PRGA are also performed
 - Initial guesses of K1 through k4 will be calculated from the estimates of K1 from OTCM (with a short circulation time such as 0T20) and estimates of V_T from PRGA.
 - In our experience, the measure decreased of outliers of V_T (e.g., $>x5$ of the maximal regional V_T value from PRGA)
 - Thus, IDAE chose to adopt the feature.
- In sum, set OTCM and PRGA if the user intend to set TTCM4 and/or TTCMC4



Figure 59: When to Employ TTGCM4 Family

12.5 Setting OTCM: First Cycle

- Vas. Volume: vascular volume in tissue v0.
 - Default (initial suggestion): ‘fit 0.035’ to fit v0 while setting the initial guess to 0.035 mL/mL
 - ‘fix value’ is also valid to fix v0 at the value (e. g., 0.035 mL/mL)
 - Enter ‘fix 0’ to ignore the vascular volume in tissue
- Circulation time:
 - Start- and end-frame time of the analysis
 - Use the startTend format
 - The initial suggestion is ‘0T20’ specifying to use 0-20 frames for the model parameter estimation
 - This is to obtain regional values of K1 because OTCM can fit TACs very well if initial 20 min of the scan is used (see ‘When to Employ TTGCM Family’)
 - Add other sets (e.g., 0T90) to test OTCM in longer scan durations.
 - The start-frame time should be 0 in OTCM
- Initial guesses:

- The generic one ($K_1=0.3$, $k_2=0.2$) should work well for OTCM
- ‘Save this method’ to move on to set the next method

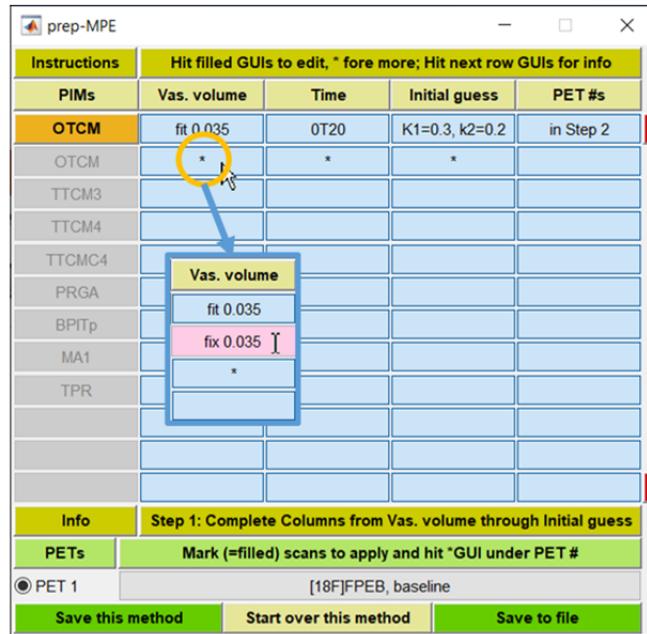


Figure 60: Setting OTCM: First Cycle

* Second (or more) entries for ‘fit’ and ‘fix’ of ‘vas. volume’ (e.g., ‘fix 0.03’ and ‘fix 0.05’) and ‘initial guesses’ work only when they are made scan-specific in the second cycle (e.g., ‘fix 0.03’ for scans 1 & 2 and ‘fix 0.05’ for scans 3 & 4). Otherwise, second (and more) entries will be ignored (due to common output file names).

12.6 Setting TTCM4 and TTGMC4

- Columns of ‘Vas. volume’ and ‘Time’ are accessible for TTCM
 - The entry, ‘OTCM+PRGA’ under ‘Initial guesses’ indicates that initial guesses of K1, k2, k3, and k4 are calculated from outputs of OTCM and PRGA
- Columns of ‘Vas. volume’ and ‘Time’ are accessible for TTGMC4
 - Select applicable reference regions from the list
 - Filled = selected; empty = not to use
 - The K1-k2 ratio of the scan will be obtained from TTGMC4 of the reference region to be fixed to estimate K1, k3, and k4 alone in other regions
- Leave 0 of OTend (e.g., 0T90) for OTCM, TTGMC4, and CCTGMC4 because there is no justification for ignoring the initial portions of TACs in these methods

Instructions					Hit filled GUIs to edit, * fore more; Hit next row GUIs for info				
PIMs	Vas. volume	Time	Initial guess	PET #s					
TTCM4	fit 0.035	0T90	OTCM+PRGA	in Step 2					
OTCM	*	*							
TTCM3									
TTCM4									

Instructions					Hit filled GUIs to edit, * fore more; Hit next row GUIs for info				
PIMs	Vas. volume	Time	Initial guess	PET #s					
TTGMC4C	fit 0.035	0T90	<input checked="" type="radio"/> CW 90400	in Step 2					
OTCM	*	*							
TTCM3									
TTCM4									

Figure 61: Setting TTGMC4 and TTGMC4

12.7 Setting PRGA, MA1, and BPITp

- Complete the column of ‘Time’ alone for PRGA, MA1, and BPITp
 - Again, use the t^*Tend format where t^* stands for the start time of asymptotes and ‘end’ stands for the circulation time for the analyses
 - Hit the GUI with * to start a new entry
 - Edit it (in pink) as needed.
 - Hit an existing GUI to edit it.
- Make sure to include PRGA if to employ TTGCM4 or TTGCMC4

The figure consists of three vertically stacked windows, each titled "prep-MPE". Each window contains a table with the following columns: Instructions, Vas. volume, Time, Initial guess, and PET #s. The rows represent different PIMs: PRGA, OTCM, TTGCM3, and TTGCM4. The "Time" column for PRGA is filled with "10T90". The "Time" column for MA1 is filled with "20T90". The "Time" column for BPITp is filled with "40T90". The "Initial guess" and "PET #s" columns are mostly empty, with some entries like "in Step 2" or "-" visible.

Instructions					Hit filled GUIs to edit, * fore more; Hit next row GUIs for info				
PIMs		Vas. volume	Time	Initial guess	PET #s				
PRGA		-	10T90	-	in Step 2				
OTCM			15T90						
TTGCM3			20T90						
TTGCM4			*						

Instructions					Hit filled GUIs to edit, * fore more; Hit next row GUIs for info				
PIMs		Vas. volume	Time	Initial guess	PET #s				
MA1		-	20T90	-	in Step 2				
OTCM			*						
TTGCM3									
TTGCM4									

Instructions					Hit filled GUIs to edit, * fore more; Hit next row GUIs for info				
PIMs		Vas. volume	Time	Initial guess	PET #s				
BPITp		-	40T90	-	in Step 2				
OTCM			*						
TTGCM3									
TTGCM4									

Figure 62: Setting PRGA, MA1, and BPITp

12.8 Performing PIMs

- To perform PIMs on this subject alone:
 - Hit ‘Perform’ GUI (top orange circle) of IDAE’s Level 2 window
 - Hit ‘r’ GUI of the designated task (middle orange circle)
- To perform PIMs on multiple subjects:
 - Highlight subjects to perform on Level 1 window and hit ‘Perform’ (bottom orange circle)

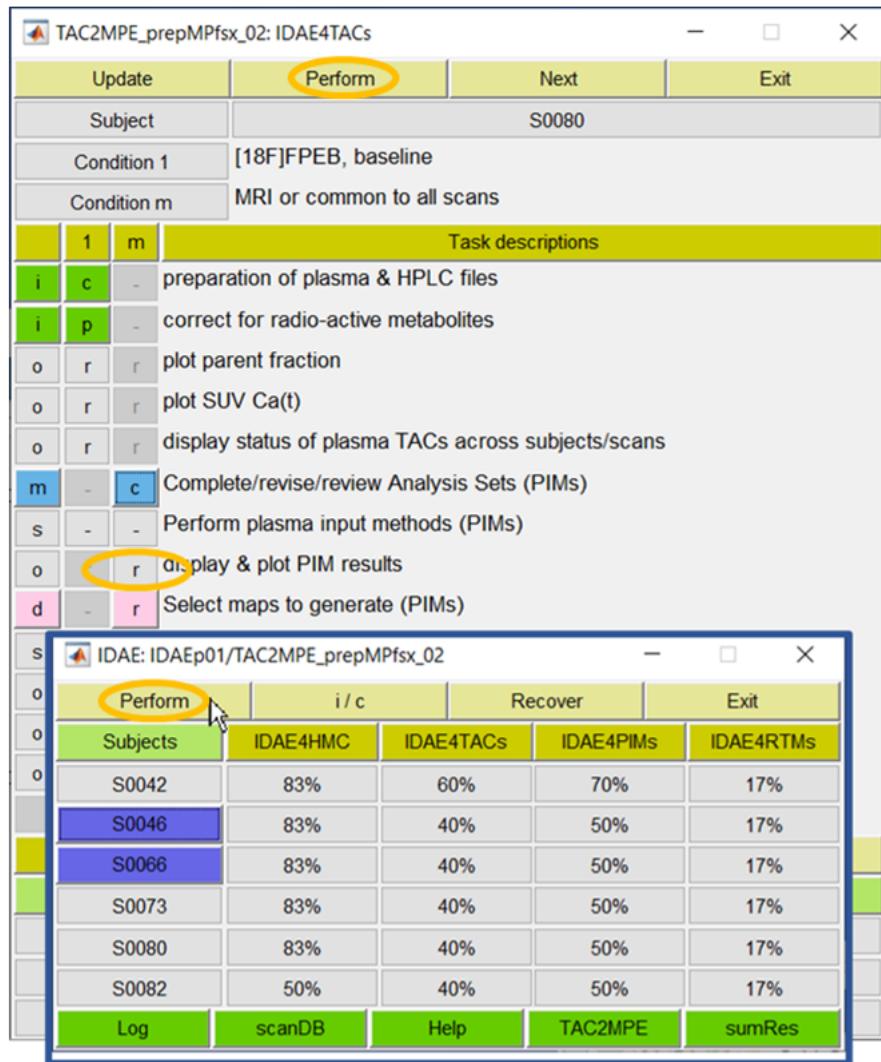


Figure 63: Performing PIMs

12.9 Display / Plot PIM Results

- Hit the ‘r’ GUI @’Display / plot PIM results’ of L2W (IDAE4RTMs) to set the result display module (background)
- Select an output from the menu (top right) Display regional values . . . (shown here) Scatter plot of regional data of a variable between scan 1 vs. scan 2 and so on Line plots vs. regions: Spaghetti plots
- Select one analysis approach from the list (left insert)
 - Approaches are shown by 5 elements of ‘method flag’ (acronyms), ‘fit flag’ (e = to estimate; c = to fix; I = to ignore for K1, k2, k3, k4, and v0), ‘circulation time for analysis’, ‘acronym of initial guesses’, and ‘primary variable’.
- Select the variable to display (right insert)
 - Select ‘show all variables’ to display them all
- Select the scan to display (right insert)
 - Light green = available; darker green = selected
- Set the VOIs to display (bottom)
 - See the section of the VOI selector module
- Hit ‘Perform’ GUI (bottom left)

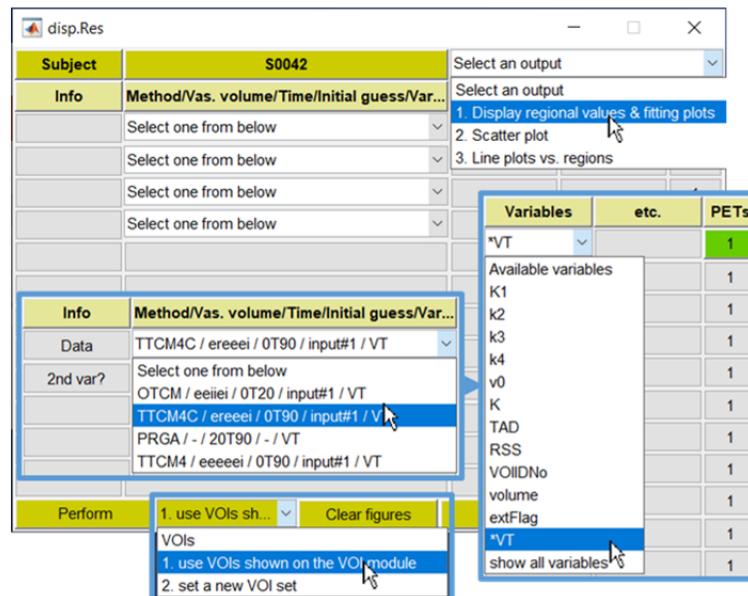


Figure 64: Display / Plot PIM Results

12.10 Example Fitting Plots: TTGCM

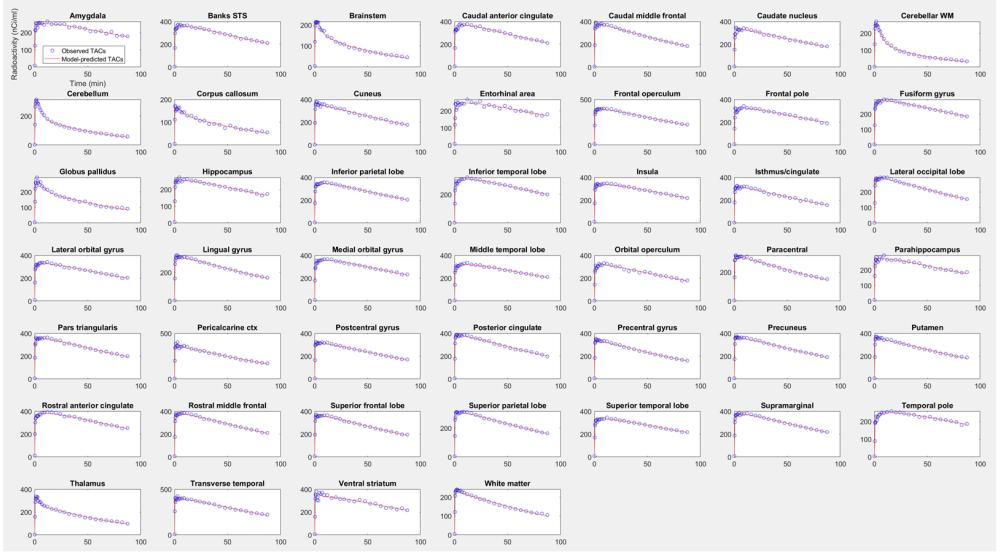


Figure 65: Example Fitting Plots: TTGCM

12.11 Revise / Review PIM Approaches

- To review / revise saved PIM approaches
- Hit 'c' GUI at 'Complete/revise/review Analyses Sets' to bring up the MPE preparation module (upper panel)
 - Previously set PIM methods will be highlighted in light green
 - Hit a highlighted method to review / revise
 - Bring in / set yet-set methods, as needed
 - Hit 'Save this method' to update displayed method
 - Hit 'Save to file' when done (= the end of the 1st cycle)
 - Leave those methods not to review / revise unattained
- In the 2nd cycle:
 - Hit highlighted methods to review / revise
 - Hit 'Save this method' to update displayed method
 - Reviewed / revised methods will be highlighted in darker green (e.g., TTGCM4 in this example)
 - Hit 'Save to file' when done (= the end of the 1st cycle)
 - Leave those methods not to review / revise unattained



Figure 66: Revise / Review PIM Approaches

13 Result Summary

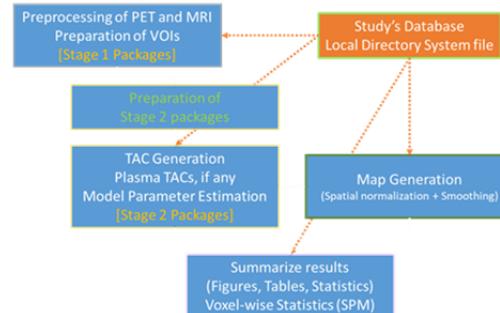


Figure 67: Result Summary

13.1 Introduction

- Aim: To make figures and tables for reports and manuscripts
- One set of outputs (figures or a table) is defined in one cycle of actions that includes:
 - Selection of the output type
 - Available output types are listed on the menu bar (foreground, orange lines) of the disp.Res module (background)
 - Successive selections about details of the outputs, all done by GUIs
 - outlined in the tab, blue lines
 - Execution of so-generated commands
- Management system:
 - IDAE adopt the following system to make it possible to re-generate outputs at will
 - The command lines from one cycle are stored as a ‘subsection’ in the sumRes.m file (plain text) of the study
 - Subsections are organized under sections, both with user-defined titles
 - *The user choose where to place the new subsection in the file at the end of a cycle i.e., such as under which section and above or below which subsection

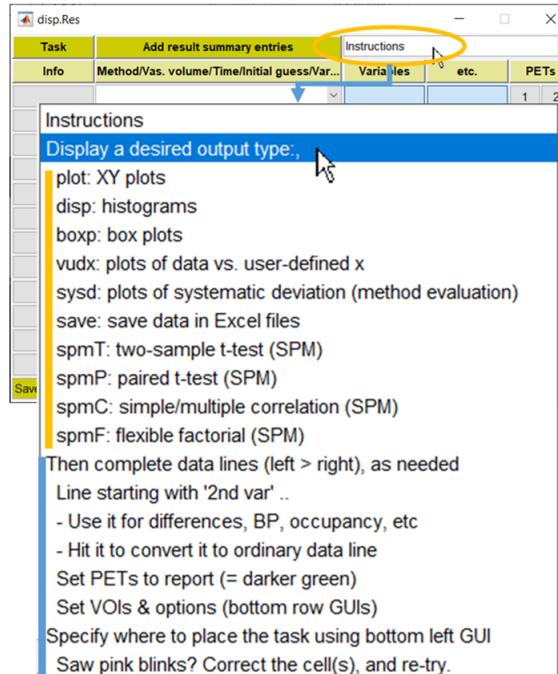


Figure 68: Introduction

13.2 First sumRes Cycle

- Hit the ‘sumRes’ (for result summary) GUI of L1W to start with
- A designated file (referred to as sumRes.m) will be generated / opened
 - It will be organized by sections (start with \$\$\$) which hold several subsections (start with #)
 - Initially, one each alone (second panel)
 - The user manage section/subsection titles while IDAE inserts executable contents
 - Examples of user-edited section and subsection titles are shown in the third panel
 - Make sure to save it before moving on.
- Hit the ‘sumRes’ GUI one more time to display the sumRes module (bottom).
- Select the section to work on first from the upper menu bar (headed by S under orange arrow), then the subsection at SS (subsection)
 - Now the user is ready to add the executable contents (move on to the next slide)
 - Good to remember: Always start with the section first to update the section and subsection titles after revisions.

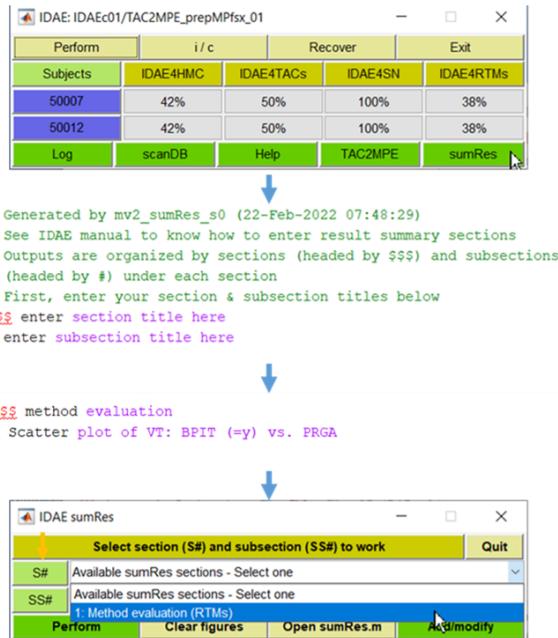


Figure 69: First sumRes Cycle

13.3 Before Setting Outputs

- Hit ‘Add/modify’ of the sumRes module (top) to display the ‘Display Results’ (disp.Res) module (bottom, background)
- The sumRes module indicates that the user is intended to add the executable content for the subsection of the section
 - In this example, ‘Scatter plot of VT: BPIT (=y) vs. PRGA’ under ‘Method evaluation (RTMs)’
- Read the instruction menu carefully
 - Available output types are listed at top under ‘Display a desired output’ (@cursor)
 - Each selection shows the type flag followed by simple description
 - Just display the intended output type
 - *In this example, the user intends to make ‘XY plots’ according to the user-defined subsection title
 - At least one example each output category will be described in this manual.
- Once the intended output type is selected, the main GUI matrix of the disp.Res module become available for selections (next section)

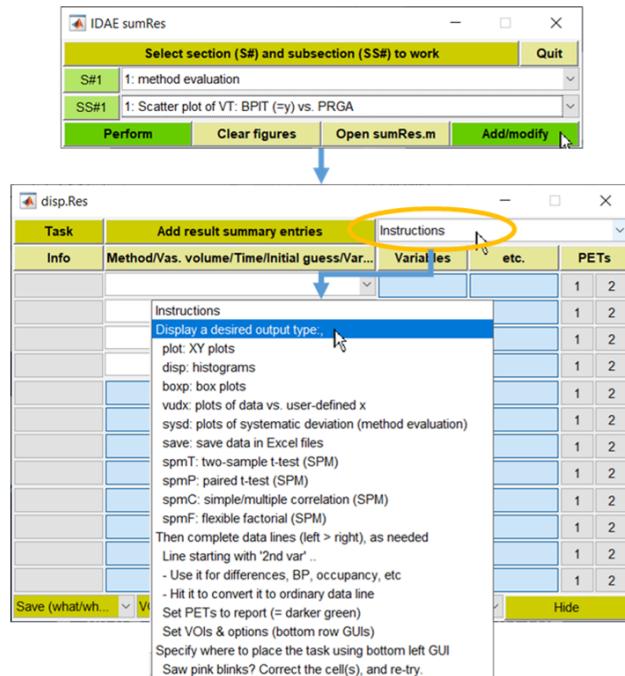


Figure 70: Before Setting Outputs

13.4 Selecting Variables to Report: XY Plots

- Once ‘XY plots’ is selected (top right), GUIs for x- y-data become available (left column)
 - Use the row of 2nd var to specify relational variables such as differences, ratios, or occupancy estimates, as needed
- Complete data lines, one line at a time from left to right (showing for ‘x-data’ first)
 - Select the primary method classification
 - The highlighted selection means ‘regional VT value from this package’ (= VOI-based analysis)
 - ‘Map-value from PIM (from this package) will become available when VT images were generated for this package.
 - Data from ‘other’ packages will become available if other packages are generated / processed
 - Select the method (middle foreground panel)
 - Not sure about the method identification format? Review sections of RTMs and PIMs
 - Select the variable to report (bottom left)
 - Select the groups to report and display ‘done’
 - No need to select groups to report all groups
 - Lastly, select the scans to report
 - Applicable PETs are shown by light green
- Repeat the same for ‘y-data’

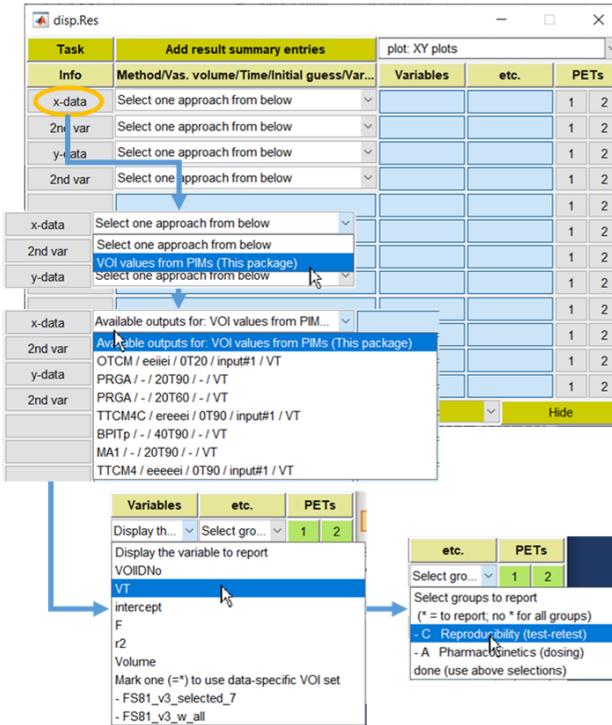


Figure 71: Selecting Variables to Report: XY Plots

13.5 Setting Remaining Parameters: XY Plots

- The user's intention in this example (review):
 - To make a scatter plot of VT data, BPIT (=y) vs. PRGA (@SS#1, upper panel) as a part of 'model evaluation' (@S#1 = section title)
 - Accordingly, it was set that VT data of scan 1 of all subjects were used in the plot (middle panel)
- Set the remaining parameters using bottom row GUIs of the disp.Res module:
 - Set VOIs to report (third panel, right)
 - It is recommended to set VOI sets using VOI selector module to be consistent among trials
 - Review the section of 'Setting a New VOI Set'
 - A previously prepared VOI set was used here
 - Set output options (bottom panel)
 - Each selection shows the option flag followed by simple description
 - Most descriptions are self-explanatory. But ..

- *Need to replace r (= of rows) and c (=# of columns with integers in sumRes.m when to use subplot[r,c] (subplot[3,4] will display 3 rows x 4 columns of subfigures in one figure window.
- Multiple options may be selected, as needed (denoted by *, as the user select)
- Lastly, specify where to place the executable lines
- Select #5 for this example because both section and subsection titles are present (top panel)

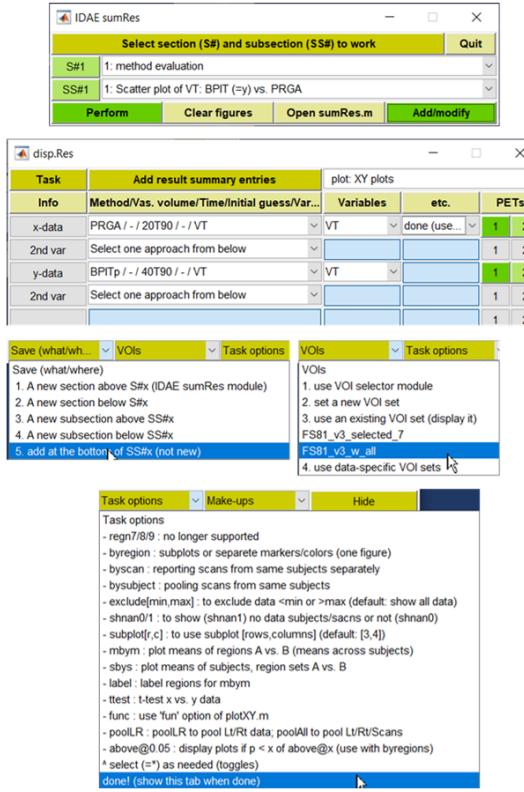


Figure 72: Setting Remaining Parameters: XY Plots

13.6 Setting a New VOI Set

The users can define a VOI set when the ‘display result’ module is in the result summary mode.

- Select the ‘set a new VOI set’ tab under ‘VOIs’
- Check the VOIs to include in the new set: L/R/W GUIs for bulk operations of the left, right, and whole (i.e., left-right merged) VOIs, respectively; Hit a checkbox to set it ‘on’ (filled) or ‘off’ (blank) one-by-one
- Empty the tab (Set a VOI set? ...) and enter a concise name. Note that the name of current VOIs set (FS81_v2) will be prepended automatically (i.e., All_w_noWM alone was entered in this case)

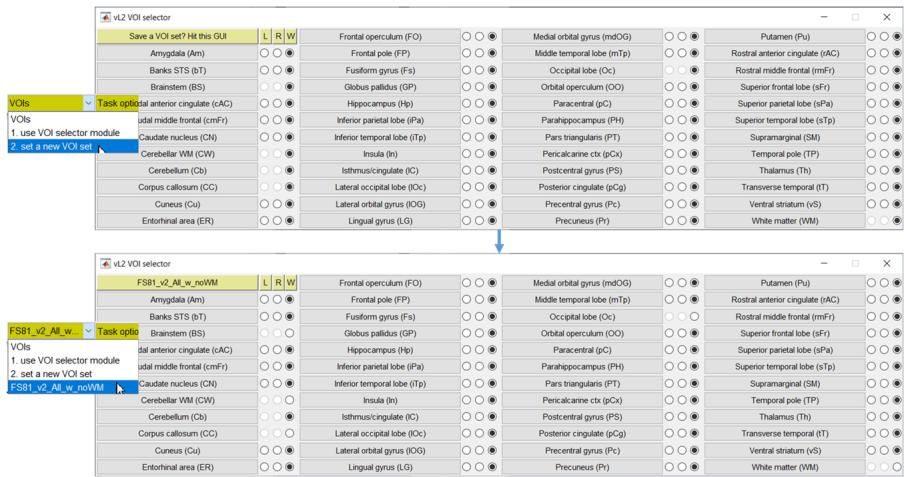


Figure 73: Setting a New VOI Set

13.7 Generation of XY Plots

- Once ‘Save’ is done, ‘Not-right’ GUIs blinks in pink on the disp.Res module
 - Make corrections until the sumRes.m is updated
- If successful, the executable lines will be inserted to the sumRes.m file (and opened)
 - No need to check the executable lines (it’s IDAE’s responsibility)
 - The user can add command lines (second panel) for make-up
 - In this example, command lines for x- and y-labels were added. The third line is to make dots bigger
 - Hit ‘make-ups’ GUI of the disp.Res module to display useful sample command lines

- The users can test / add the command lines after generation of the plot.
- Make sure to save the sum.Res file, if any changes are made
- Hit ‘Perform’ GUI of the sumRes module (arrow, 3rd panel)
- Repeat the sumRes sessions, as needed.

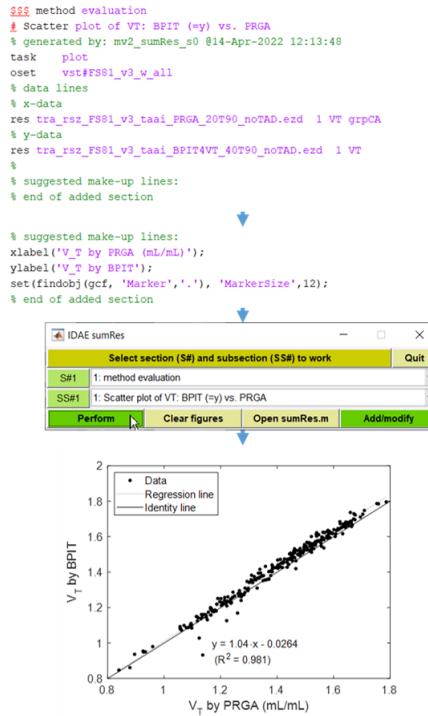


Figure 74: Generation of XY Plots

13.8 Preparation of Histograms

- Presentation of the demonstration case:
 - To generate histograms of regional V_T values of two groups side by side, in an ascending order of Group C under a new section of ‘Figures for Manuscript #1’
- On the disp.Res module:
 - Select ‘histograms’ tab
 - For Data 1 (upper panel):
 - Select the method and variable to report
 - Use the line of 2nd var to calculate relational variables, if needed
 - Select Group C for data #1
 - Select PET #1 (=baseline scan)

- For Data #2 (middle panel):
 - Hit ‘2nd var’ GUI to display ‘data 2’
 - Select Group S this time.
- Options are quite self explanatory
 - Multiple options may be selected (denoted by * if selected). And display ‘done!’ tab (bottom)
- Select ‘2. New section below S#x’ to place the section in the intended location in the file
 - Because it was intended to create a new section in this example
 - Correct errors at GUIs that blink in pink when to ‘Save’ the subsection

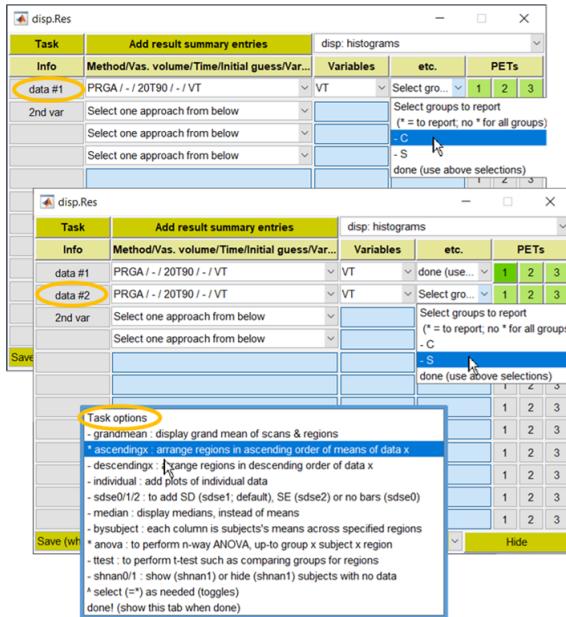


Figure 75: Generation of Histograms

13.9 Generation for Histograms

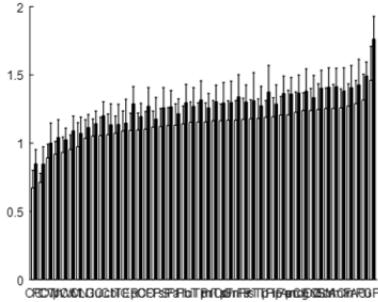
- When successfully saved, the file (sumRes.m) will open for checking / editing
- First, revise the section and subsection titles according to the user’s preferences
- Some option strings require edition as written in the ‘task option’ menu bar
 - In this example, ‘ascendinx’ has to be revised to ‘asending1’ to sort regions by regional mean VT values of Group C (= the intention)

- Warning messages will be issued if option strings that require editions are left unchanged.
- Then, hit ‘Perform’ GUI of the sumRes module to generate the histograms (middle panel)
- Try and error approach for figure make-ups:
 - List points of improvements
 - The y-axis label is missing
 - Region labels are not readable
 - Histograms are too close to each other
 - Legend is missing
 - Hit ‘make-ups’ GUI of the disp.Res module (bottom) to display suggested lines for make-ups
 - Copy / paste the lines for above list to the sumRes.m file and fine tune values
 - Acceptably good make-up lines are shown in bottom panel. See the next slide together with the ANOVA table

```

%%% enter section title here
% enter subsection title here
% generated by: mv2_sumRes_s0 @14-Apr-2022 15:09:35
task    disp    ascendingx    anova
oset   vst#FS81_v3_w_lessBS
% data lines
% data #1
res tra_rsz_hmcMIT_FS81_v3_tbaa_PRGA_20T90_HPLC2.ezd 1 VT grpC
% data #2
res tra_rsz_hmcMIT_FS81_v3_tbaa_PRGA_20T90_HPLC2.ezd 1 VT grpS
%
% suggested make-up lines:
% end of added section

```



```

% suggested make-up lines:
set(gca, 'FontSize',13);
ylabel('V_T (mL/mL)');
pos = get(gcf, 'Position');
set(gcf, 'Position',[200,200,pos(3).*2,pos(4)]);
set(gca, 'XTickLabelRotation',60);
legend('Group C','S', 'location','northwest');
% end of added section

```

Figure 76: Preparation for Histograms

13.10 Example Histograms

- Histograms from the example case after make-ups.
- The ANOVA table shows strong group and region effects in the dataset.

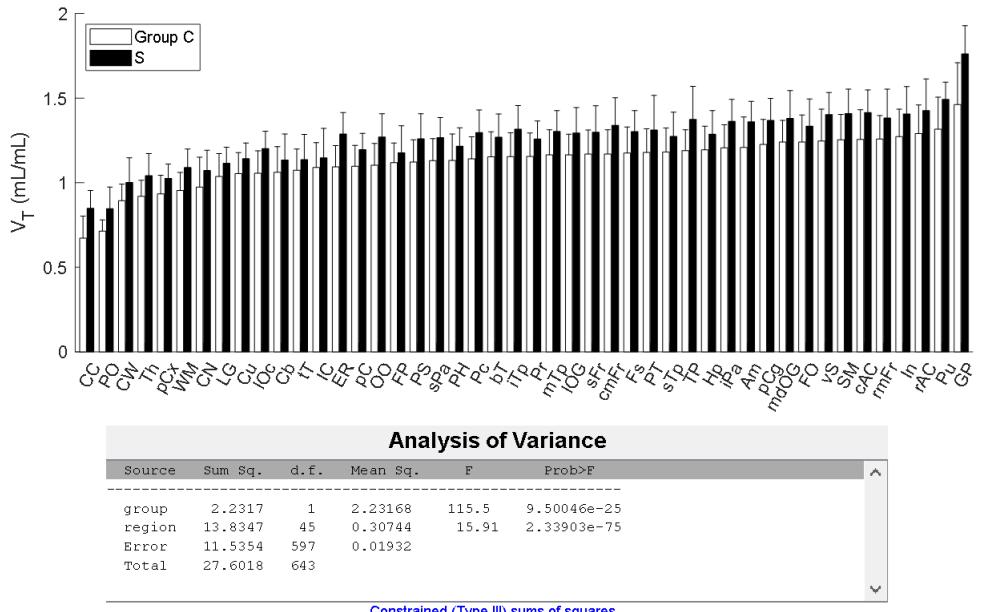


Figure 77: Example Histograms

13.11 Example Box Plots

- For generation of ‘box plots’, follow the procedures of histogram sessions, except that the box plots option have less sub-options.
- The following make-up procedures were used, in addition to those applied to example histograms
 - To find ‘boxes’: `>>h = findobj(gca, 'Tag','Box');`
 - Sorting h from left to right: `hps = cell2mat(get(h, 'XData'));` `[x, is] = sort(hps(:,1));` `h(:) = h(is);`
 - Changing colors of ‘S’ group to red: `set(h(2:2:end),'Color','r');`
 - To add the legend: `legend(h(1:2), 'Group C','S');`

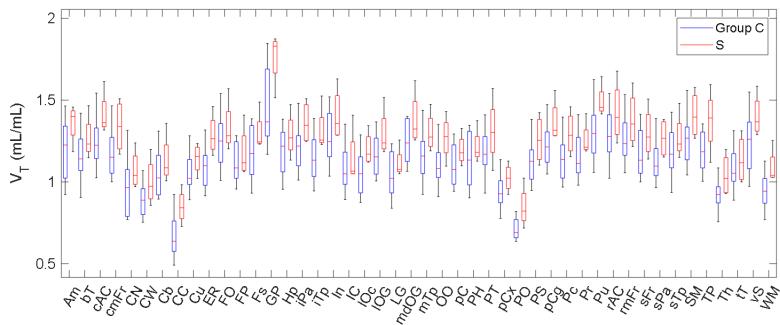


Figure 78: Example Box Plots

13.12 Plots of data vs. user-defined x

- Demonstration case:
 - Subjects had PET scans at baseline and at three time point after a single-dose of drug A.
 - Concentrations of the drug (PK) were measured and entered to the database (scanDB.m)
 - To define occupancy-PK curves for the drug
 - Occupancy values at PET 2, 3, 4, will be calculated using PET 1 (no drug) as reference
 - Most variables may be defined as described before except that:
 - Variables to use for ‘vudx’ must be entered in the scanDB.m file and defined in the info lines
 - ‘PK’ and ‘tD1’ are defined as shown in 2nd panel inf this demonstration example
 - Those variables will be listed in the menu bar of ‘Variables’ of the 1st data row (headed by ‘vudx’)
 - Select all variables to use (* = selected), and display ‘done!’ tab (bottom) (3rd left)
 - Available 2-element variables will be displayed on the menu bar of the ‘2nd var’ row (3rd right)
 - Mark options (* = selected; as needed) and display ‘done!’ tab of the options (bottom)
 - Edit options as needed in sumRes.m file
 - Subplot[r,c]: replace r (# of rows) and c (# of columns with integers for sub-figures in a figure
 - Omax=x%: replace x with a desired value

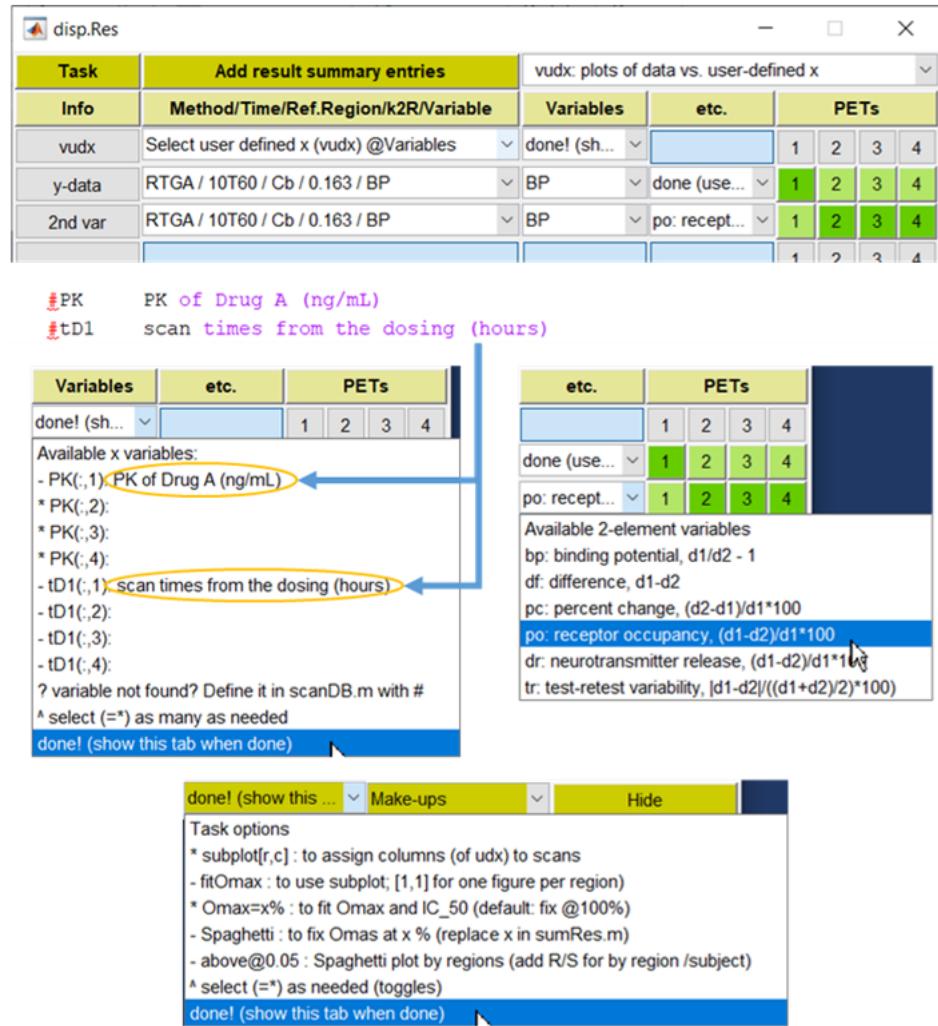


Figure 79: Plots of data vs. user-defined x

13.13 Generation of ‘vudx’ Plots

- Once the subsection of ‘vudx’ plots is completed successfully, the sum-Res.m will be opened.
- Replace titles of the section and subsection
- Edit output options as needed
 - It may be appropriate to make 2 x 2 of sub-figures for the 4 regions
 - It is reasonable to set O_{max} at 100%
 - Always read the option tabs (bottom panel) carefully for the need for manual editions
- Save it

- Display the intended section and subsection titles in the sumRes module (3rd panel)
 - Restart from selection of the section to display updated titles
 - Hit the ‘Perform’ GUI to generate the figure (bottom)
- Post-hoc make-ups:
 - Enter make-ups in the sumRes.m file between ‘% suggested make-up lines:’ and ‘% end of added section’
 - Make use of the ‘make-up’ tab of the disp.Res module to display suggestions

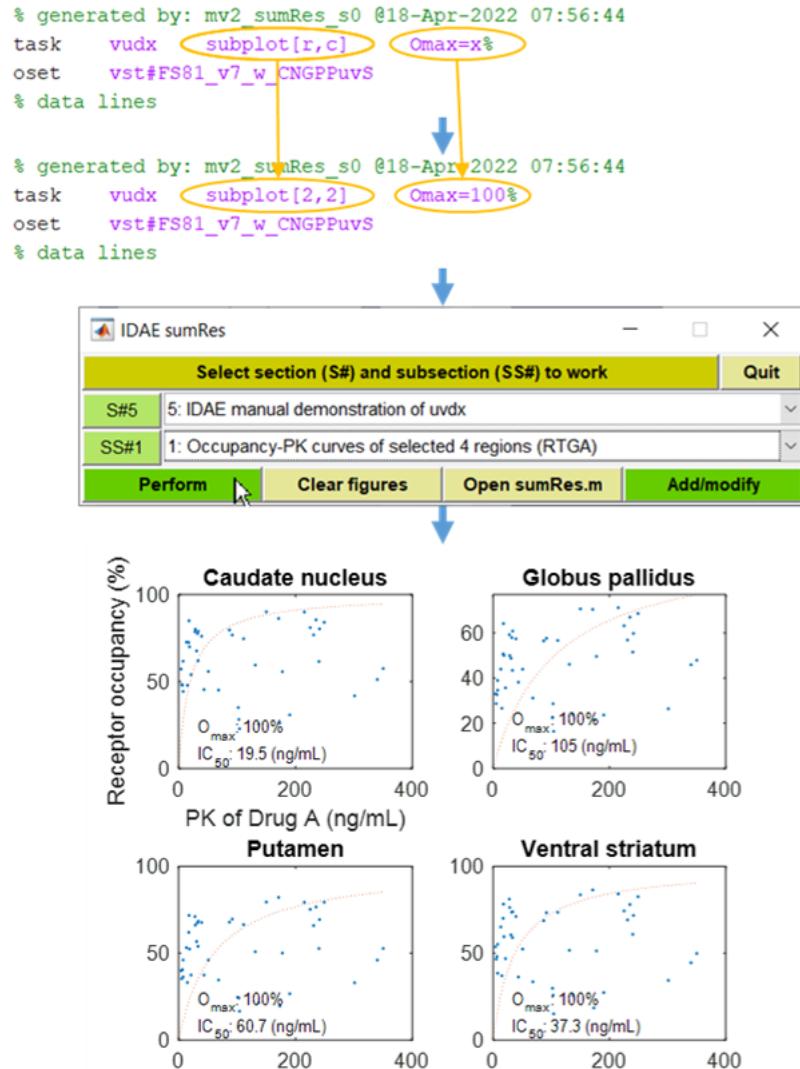


Figure 80: Generation of ‘vudx’ Plots

13.14 Plots of Systematic Deviations

- This result-summary function may be particularly useful for tracer evaluation
- When movements of a tracer in regions of interest are governed by the blood-brain barrier and association to / dissociation from target molecules, the tracer may be useful only when:
 - Time activity-curves are fitted by a two-compartmental tissue model (TTCM) acceptably well, and
 - Plots of the plasma reference graphical analysis (PRGA; Logan et al., 1990) approach asymptotes
- Currently, no solid criteria for above necessary conditions have been established
 - Empirically, the normalized systematic deviations, NSDs of regions (across subjects) fell within $\pm 5\%$ for ‘validated’ (in the literature) tracers ($n > 20$; unpublished data from us)
 - NSDs may be useful for determination of t^* , the start of asymptote for PRGA and other approaches
- It is recommended to make use of NSDs to confirm published t^* for PRGA and other approaches in users’ own data

13.15 Mean Normalized Deviations

Plots of observed and model-fitted TACs of one region by MRTM2 and PRGA.

NSDs are defined as the sum of measured less model-predicted TACs over mean observed TAC in individual regions ($\sum (o - \bar{o}) / \text{mean } o$)

NSD is defined for a regions as the mean across subjects or scans.

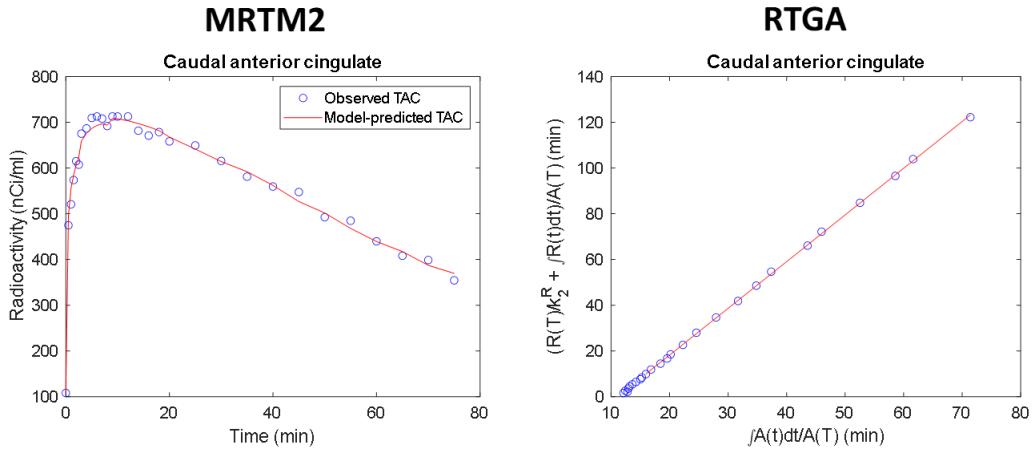


Figure 81: Mean Normalized Deviations

13.16 Procedures for NSD Plots

- Generally, users end up with many analysis approaches (not rate to exceed 100).
- Thus, the search for an approach start with identification of categories
 - The first category is ‘VOI values from RTMs (This package)’ (and the only for this example)
 - ‘VOI values from maps (This package) will be added to the list once the user generate functional volumes (a.k.a., functional maps)
 - Regional values of the variable of the map from the same VOIs
 - ‘VOI values from RTMs (approach ID)’ will be added to the list once other MPE are done
 - In this example, this approach = with HMC; another approach = without HMC
 - ‘VOI values from maps (approach ID)’ will be added when maps are generated for ‘other’ approaches.
- Select intended approach from the list (middle left insert)
- Select the variable to display (middle right)

- Select the group, if applicable
- Display the ‘done’ tab
- Select applicable PET(s)
- Light green GUIs: Set to perform (not by presence)
- Darker green GUIs: Selected.

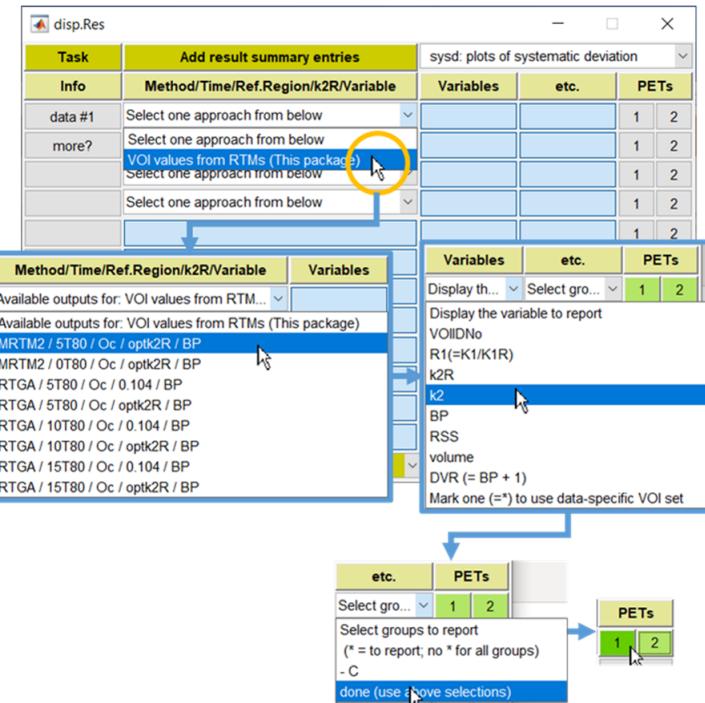


Figure 82: Procedures for NSD Plots

13.17 Setting Other Parameters for NSD Plots

- Once output approaches are defined (background), define ..
- VOIs to report:
 - Use VOI selector module: Report all checked VOIs on the module which may be convenient but hard to reproduce
 - Set a new VOI set: See the slide of ‘Setting a New VOI Set’
 - Make the name descriptive enough to remember
- Set options
 - ‘done!’ tab when done
- Specify where to insert specified set
 - Always relative to the section + subsection combination which is on display on the sumRes module

- In this example, the section (S#1) and subsection (SS#1) titles were defined. So, it is appropriate to insert the output lines ‘at the bottom of SS#x’ (Selection Γ5)
- The process is sort-of fool-proof.
- GUIs with any insufficiency, if any will blink with pink. Visit the GUI and fix the issues.

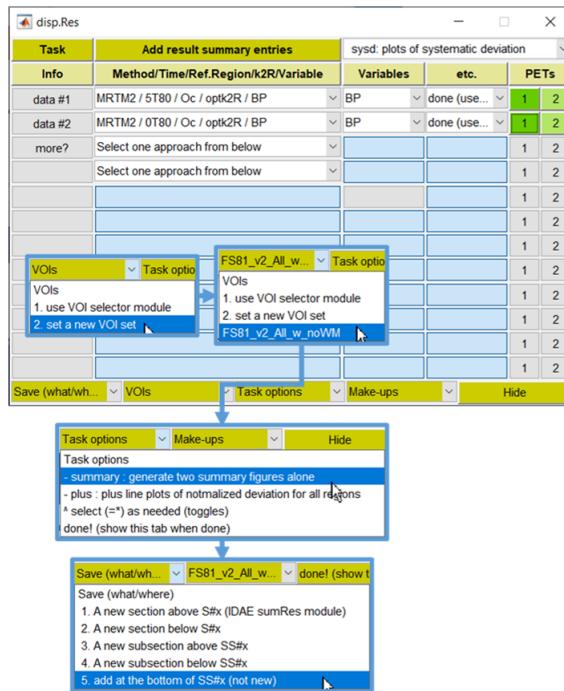


Figure 83: Setting Other Parameters for NSD Plots

13.18 Command Lines in sumRes.m

- Then (i.e., when the ‘at the bottom of SS#x’ tab was selected), command lines will be inserted to the file (studyName.sumRes.m) together with some comment lines (top panel; denoted by vertical orange line)
 - Do not alter the command lines unless the user knows what to do
 - However, the user can insert make-up lines at orange arrow
 - Select ‘coming soon’ tab under the ‘Make-ups’ GUI of the ‘display result’ (disp.Res) module
- Hit ‘Perform’ GUI to generate a figure displaying plots mean normalized deviations of MRTM2.
- Then, a new subsection was added in similar manner for 5T80, 10T80, and 15T80 all with k2R fixed at $0.104 \text{ min}^{(-1)}$.
 - The new request is registered as ‘2: Normalized deviation: RTGA’

- The ‘Perform’ GUI was hit to generate a figure displaying mean normalized deviations of RTGA

```

$## Method evaluation (RTMs)
# Normalized deviation: MRTM2
% generated by: mv2_sumRes_s0 022-Feb-2022 12:11:45
task sysd summary
oset vst#FS81_v2_All_w_noWM
% data lines
% data #1
res tra_rsz_hmcMIT_FS81_v2_tbaa_MRTM2_5T80_Oc.ezd 1 BP grpc
% data #2
res tra_rsz_hmcMIT_FS81_v2_tbaa_MRTM2_0T80_Oc.ezd 1 BP grpc
%
% suggested make-up lines:
% end of added section

```

Figure 84: Command Lines in sumRes.m

13.19 Example Plots of NSDs

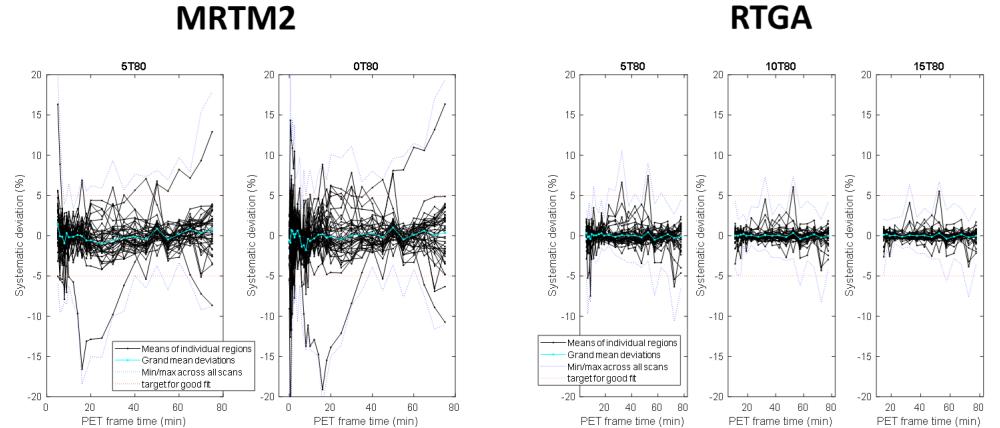


Figure 85: Example Plots of NSDs

13.20 Example NSDs: OTCM vs. TTCM

Plots of observed and model-predicted TACs of the banks of the superior temporal sulci (STS) from a subject of a tracer under evaluation for OTCM (left) and TTCM (upper panels). Plots of regional and grand means of normalized deviations fell within $\pm 5\%$ for TTCM but not OTCM. Thus, the tracer cleared the necessary condition for TTCM.

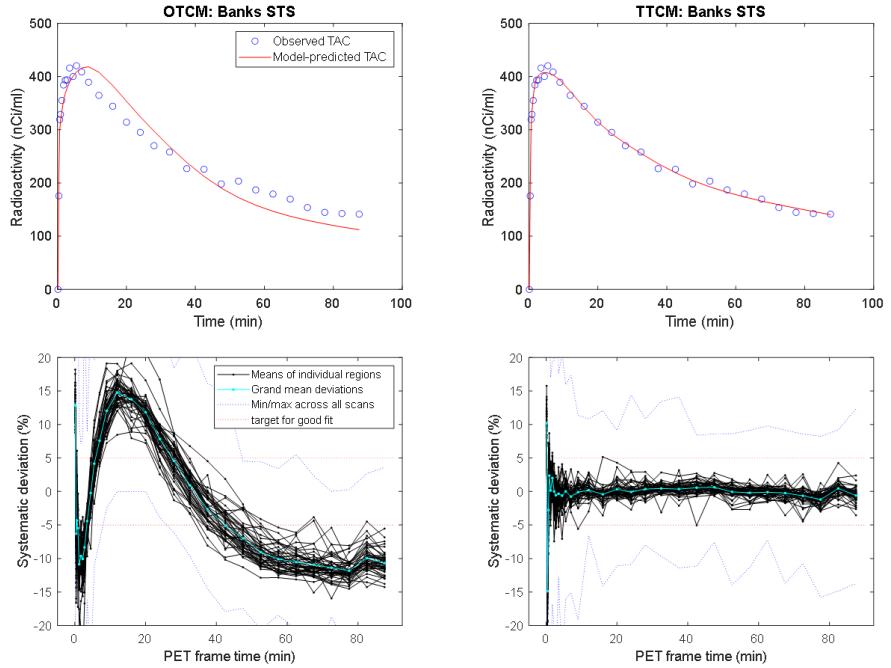


Figure 86: Example NSDs: OTCM vs. TTCM

13.21 Example NSDs: PRGA for t^*

A PRGA plot (open circles) and an asymptote (red line) with t^* , the start of asymptote set at 5 min of the banks of STS from a subject (left panel). Plots of regional and grand means of normalized deviations across the six scans (model-predicted less observed TAC over mean of observed TACs). The plots fell within $\pm 5\%$ for PRGA when t^* was set at 20 min. Thus, t^* was set at 20 min for the tracer.

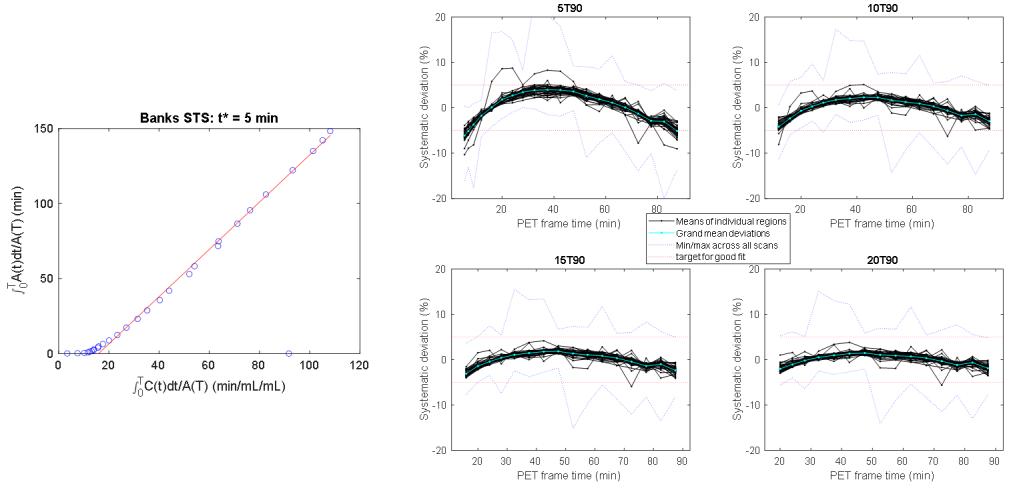


Figure 87: Example NSDs: PRGA for t^*

14 Want to Use IDAE?

- Operating systems:
 - Windows 10 + Linux Subsystem. See <https://docs.microsoft.com/en-us/windows/wsl/install-win10>
 - Mac OS
 - Linux, tested on Ubuntu 18.04
- Matlab 2020a/b
 - Users need to create a script that adds IDAE code paths to the path list
- IDAE codes
 - JHU users: connect to our server for the newest distribution sets
 - Users can obtain the link from anandi1@jhmi.edu
 - Non JHU users: Need to talk to hkuwaba1@jhmi.edu (discouraged)
 - IDAE codes will become available at a public deposit (e.g., GitHub)
 - We look for people who are experienced in this regard
 - Updates will come as zip files per request
 - Users need to create one file dxetc4xxx.m (xxx stands for a site-specific string) to make use of IDAE
 - A sample code is provided (sample_dxetc4xxx.m)
 - This code includes subfunctions to make PET MRI files available to IDAE