A User's Guide to TOPPCAT

Introduction
TOPPCAT stands for **T-O**ne weighted **P**erfusion imaging **P**arameter **CA**lculation **T**oolkit. Its purpose is to create quantitative maps of K^{trans} (volume transfer constant between blood plasma and the extravascular extracellular space) and fV (fractional plasma volume) from dynamic T1-weighted perfusion images. The TOPPCAT package is a set of modular plugins, which runs on the ImageJ platform (rsb.info.nih.gov/ij/). This modular design allows the user flexibility to apply this software to a variety of situations, although ease-of-use can suffer somewhat using this approach.

What is needed to run TOPPCAT?
Hardware
TOPPCAT is designed to run on hardware running an operating system that supports ImageJ, a public domain open source Java-based image processing program authored and maintained by Wayne Rasband at the National Institute of Mental Health (rsb.info.nih.gov/ij/). Supported operating systems include Mac, Windows, Unix and Linux platforms. Be aware that the processing of dynamic T1-weighted perfusion images is a processor and memory intensive task. The resources needed to process these images vary depending on the size of the data sets involved. For large data sets, it helps to set the memory requirements of ImageJ correctly (see Installation paragraph below) and install additional RAM if needed.

Software
TOPPCAT runs as plugins to ImageJ. ImageJ (rsb.info.nih.gov/ij/) must be installed before the TOPPCAT plugins. We recommend installing the version 1.36 of ImageJ bundled with Java 5. This can be obtained from http://rsb.info.nih.gov/ij/download.html. TOPPCAT has been tested on this version of ImageJ. TOPPCAT runs synergistically with other plugins available at the ImageJ website (we will note multiple occasions where the use of these plugins is helpful), but no other plugins are required.

MR imaging data
For typical applications of TOPPCAT, the requirements include:
1) Images from pulse sequences to map T1 and S0 (the equilibrium longitudinal magnetization). We assume a "multi flip angle" approach: that multiple T1-weighted spoiled gradient recalled echo (SPGR) sequence images obtained at identical short TR but with several different flip angles have been obtained to generate these maps. This has been shown to be an efficient and reasonably accurate method to perform T1 mapping[1]. If you have data that uses a "multi TR" approach to T1 mapping, you may be able to use the T1 calculator from Karl Schmidt's MRI Analysis Calculator plug-in (rsb.info.nih.gov/ij/plugins/mri-analysis.html) to calculate your maps. If you already have T1 and S0 maps calculated by another program, then you will not need the source images.
2) Images from a dynamic T1-weighted SPGR perfusion sequences. This software considers the T1 weighted SPGR image set to be a "4D" stack of images in (xy)zt order composed of images repeated at the same number of image locations (n_l) for a certain

number of time points (n_t). In fact, the stack of images in the image set should be composed of (image width) * (image height) * n_l * n_t pixels. It is important that some of the early time points be obtained before the contrast-agent is administered (in our data, we usually obtain seven or eight before contrast agent is administered). The data obtained earliest should begin the stack, with subsets proceeding in order of increasing time so that the data obtained last ends the stack.

NOTE: You need to cover exactly the same anatomy in your images for 1) and 2) above; thus, the slice locations, slice order and number of slice locations should be identical. Likewise the field of view, slice obliquity (if any), and location of the center of the imaging volume should be the same for all image sets.

HINT: If your stack is in (xy)tz order, Michael Abramoff has provided the handy Hypervolume Shuffler (rsb.info.nih.gov/ij/plugins/hypervolume-shuffler.html) that can place these into (xy)zt order.

Image formats
TOPPCAT can handle any image format that can be opened into a stack using ImageJ (TIFF, JPEG, RAW, DICOM). For the purposes of making stacks, it certainly helps to have all of the relevant images in a single directory. One advantage of using DICOM images is that TOPPCAT will take default values of parameters such as flip angle and repetition time from the DICOM header.

Installation

Step 1. Install ImageJ

If you have not already installed ImageJ, download and install this free program by following the instructions at rsb.info.nih.gov/ij/download.html. We recommend installing the version 1.36 of ImageJ bundled with Java 5. TOPPCAT has been tested on this version of ImageJ. We expect it to run smoothly on later ImageJ versions too, but cannot provide any guarantees.

Step 2. Adjust memory

In order to handle large sets of images, maximize the RAM available to ImageJ. To do this, change the memory allocation (-mx option) in the command line launching ImageJ. It often helps to increase the memory allocation option to approximately 2/3 of available RAM (e.g. –mx170m on a 256MB machine). Larger increases may lead to memory thrashing.
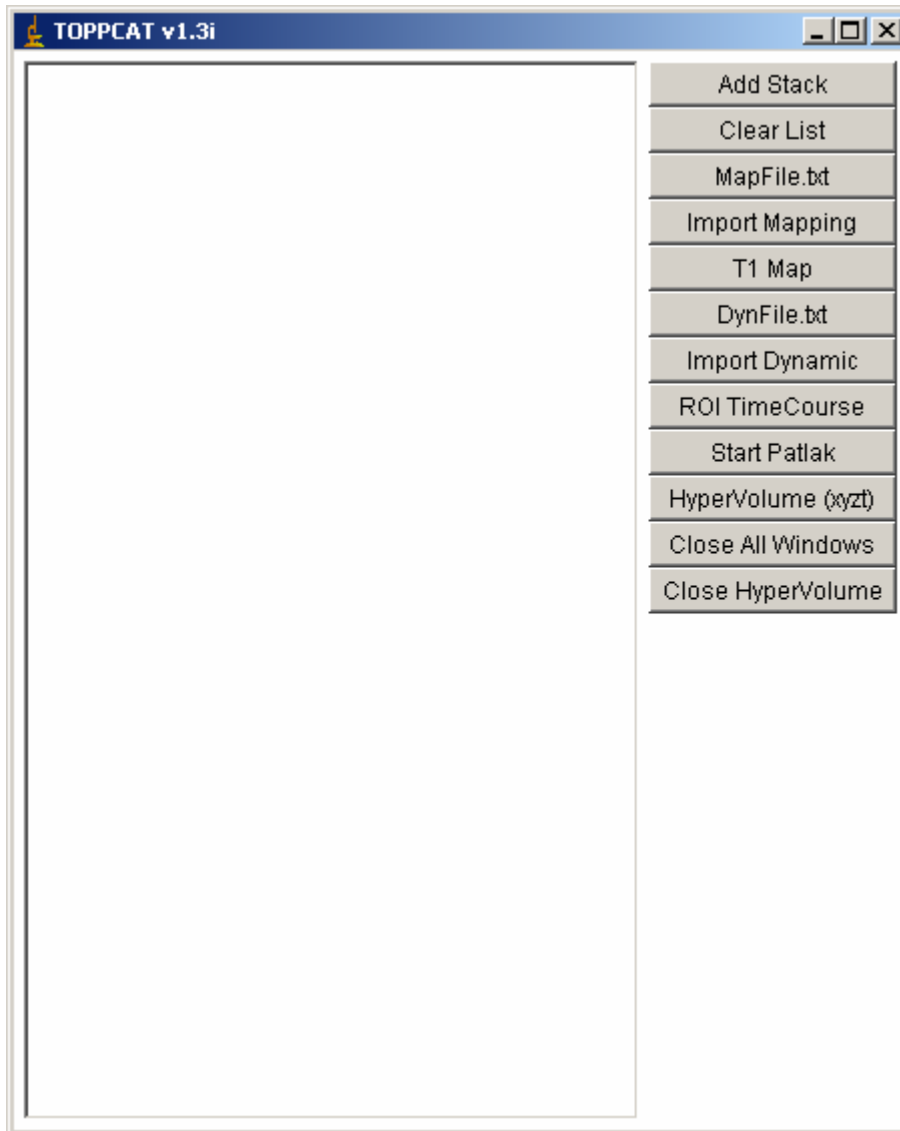
Step 3. Install the TOPPCAT plugins.

Make a directory called TOPPCAT in your ImageJ plugins folder and unzip the downloaded file into this subdirectory, and then restart ImageJ.

TOPPCAT modes of operation

To familiarize yourself with the software and to perform small scale analyses, we suggest using manual mode. Macro mode is useful when you need to perform a number of repetitive analyses.

Manual

The easiest way to use manual mode is to open the TOPPCAT Interface plugin. The functions of this plugin are described below:

TOPPCAT Interface allows ImageJ to import images from multiple directories for T1 mapping or for calculation of gadolinium concentration. In addition, if you are using DICOM images, the images are imported in order of image number.

- Use *Add Stack* to designate the directories from which images will be imported. This button will open a directory browser. Simply double click on any image file in the directory to add the corresponding directory to the list. Repeat until all relevant directories have been listed.
- If you make a mistake in designating the directories, *Clear List* will do just that.
- *MapFile.txt* will look for that file in the ImageJ directory. If found, it will output its contents (directories) to the list.
- If the directories you have designated are multiple flip angle SPGR images for T1 mapping, *Import Mapping* will import images in all of these directories into a single stack with the proper title for processing.
- *T1 Map* will run the T1 Map Sub plugin.
- *DynFile.txt* will look for that file in the ImageJ directory. If found, it will output its contents (directories) to the list.
- If the directories you have designated are T1-weighted SPGR perfusion images, *Import Dynamic* will import images in all of these directories into a single stack with the proper title for further processing.
- *ROI TimeCourse* will run the ROI Time Course plugin.
- *Start Patlak* will run the Start Patlak plugin.
- *Hypervolume* makes use of the most excellent HyperVolume Browser plugin from Patrick Pirrotte and Jerome Mutterer (rsb.info.nih.gov/ij/plugins/hypervolume-browser.html) to display a four dimensional dynamic stack with two slider bars for easy manipulation in both the time and z dimensions.
- *Close all Windows* closes all image windows in ImageJ.
- *Close Hypervolume* closes only a hypervolume if displayed.

Macro mode

All of the plugins in TOPPCAT with the exception of **TOPPCAT Interface** can be run in macro mode. This means that the plugins can be operated using ImageJ's macro language. To experiment with macro language, use the ImageJ command Plugins…Macros…Record, and/or refer to the ImageJ website.
One disadvantage to using the macro mode is that you must explicitly supply all parameters within the macro text. Specifically, the parameters supplied in the macro text override default parameters. It is possible, however, to modify the macro text to supply these parameters in an automated way by using our Query Dicom Header plugin (rsb.info.nih.gov/ij/plugins/query-header.html) within the macro to make the macro text file aware of the Dicom parameters used in the stacks.

What are the plug-in parts of TOPPCAT?

1) TOPPCAT Interface

See paragraphs above.

2) T1 Map Sub

This plug-in uses a linearization of the formula for signal intensity on T1-weighted SPGR images [$S(\alpha) = S_0(1 - e^{-TR/T1}))\sin(\alpha)/(1 - \cos(\alpha)e^{-TR/T1})$, where TR is the repetition time, α is the flip angle, and S_0 is the equilibrium longitudinal magnetization] to calculate T1 and S0 from multi-flip angle T1-weighted SPGR images[2].
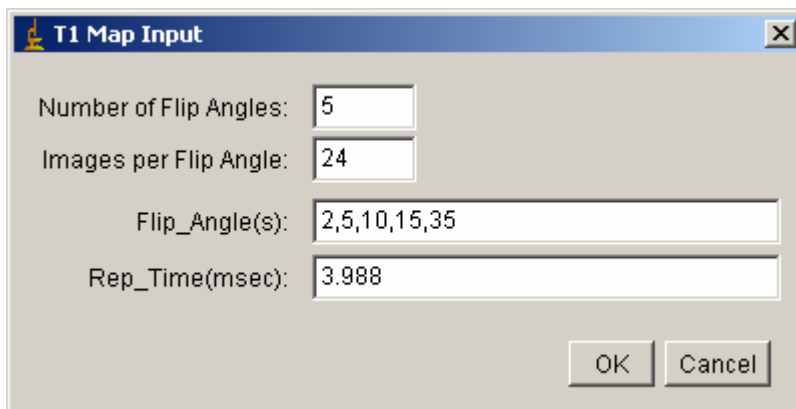
Output:
- T1 (32-bit stack T1 map in units of msec)
- S0 (32-bit stack S0 map)
- Rsq – a map of correlation coefficients for the least squares fit (32-bit stack r^2 map).

Input:
- Multi flip angle SPGR MR 16-bit image data, concatenated into a single stack called "Map Stack." You can create this stack manually using the Concatenator plug-in (rsb.info.nih.gov/ij/plugins/concatenator.html) and renaming the finished stack to "Map Stack." An easier method is to use the TOPPCAT Interface plugin to do this for you (see Manual operation above).

Note: It is advised that you have do not have multiple open stacks called "Map Stack" when you call the T1 Map Sub plugin. This will avoid any confusion about the actual "Map Stack" stack being processed by the plugin.

Control panel:

User input includes the number of flip angles sampled, images for each flip angle, flip angles used (in the order concatenated) and the repetition time (in msec). If DICOM images are used, these values are taken from the DICOM header.
Notes: if there are differences in the repetition time, all values are displayed. Only one value can be used to calculate T1; the operator must choose.
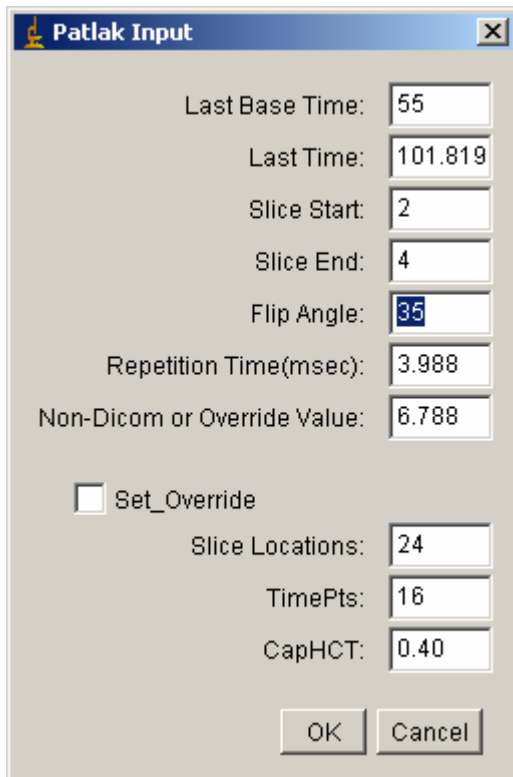
3) Start Patlak

Output:

- ImageTimeTable.txt file containing image times at each time point.
- VascularTimeCourse.txt file containing image times at each time point and concentrations from the venous region of interest.
- K (32-bit stack). Map of K^{trans} (the volume transfer constant between blood plasma and the extravascular extracellular space) for chosen image locations. Window/level default to min of 0, max of 0.1, color lookup table "FIRE."
- FV (32-bit stack). Map of cerebral fractional plasma volume for chosen image locations. Keep in mind that the precise meaning of this map depends on the capillary hematocrit chosen. If the given capillary hematocrit is accurate and the hematocrit is constant for all vascular structures (assumptions that are generally not true), the FV map will reflect the fractional plasma volume. If capillary hematocrit is chosen to be zero, the FV map reflects the fractional blood volume. Window/level default to min of 0, max of 0.2, color lookup table "FIRE."
- Rsq (32-bit stack). Map of r^2 for linear fit of Patlak model. Window/level default to min of 0, max of 1, color lookup table "FIRE."

Input:

- Dyn Stack (16-bit grayscale 4D stack of dynamically acquired SPGR MR images)
- T1 (32-bit stack T1 map)
- S0 (32-bit stack S0 map)
- An ROI placed on a vascular structure on Dyn Stack. In general, we use an ROI overlying the superior sagittal sinus to generate a concentration time curve useful as a surrogate for the capillary plasma concentration time curve.
- Control panel values (see table below. If your imaging data is in DICOM format, default values are extracted from the header if possible).

Note: It is advised that you have do not have multiple open stacks called "Dyn Stack", "T1" or "S0"when you call the Start Patlak plugin. This will avoid any confusion about the actual stacks being processed by the plugin.

Control panel:

Patlak Input

Last Base Time:	55
Last Time:	101.819
Slice Start:	2
Slice End:	4
Flip Angle:	35
Repetition Time(msec):	3.988
Non-Dicom or Override Value:	6.788

☐ Set_Override

Slice Locations:	24
TimePts:	16
CapHCT:	0.40

OK Cancel

Control panel parameters

Note that the last baseline (pre-contrast) time point and the last time point to be used in the Patlak analysis (Last Base Time, Last Time) should be designated in seconds, assuming that the first time point in the data is obtained at 0.0 seconds. The easiest way to choose the Last Base Time parameter is to use the ROI time course plug-in to see visually when contrast appears in a vascular structure or region. For choosing slice locations to include in the Patlak analysis (Slice Start and Slice End), the first location in the stack is designated as location 1. If you have n_t timepoints and n_l locations, then you should have $n_t * n_l$ images in Dyn Stack. You can now add your assumption for capillary hematocrit. The resulting volume images are called "fV." By adjusting the hematocrit, you can get an estimate of fractional plasma volume. If you enter cap hematocrit = 0, you would get the same maps as in the TOPPCAT versions without the capillary hematocrit feature.

- *Last Base Time:* Last time (in seconds) before gadolinium contrast appears in the venous region of interest. Choose this time carefully; if you choose a Last Base Time that is too early, calculated images will be invalid and extremely noisy. If you choose a Last Base Time that is too late, your K^{trans} map will be inaccurate, and the fV may be overestimated in areas of gadolinium leakage.
- *Last Time:* Last time (in seconds) to be included in the analysis. In general, Patlak analysis is more valid the lower this number is; maps are less noisy, however, as this number increases.

- *Slice Start* and *Slice End:* Because of limitations in RAM, your computer may not be able to create a 32-bit data of gadolinium concentrations for every location and time point as an intermediate step for perfusion map calculation. Use Slice Start and Slice End to choose the first and last locations to be included in the outputted maps. If you would like to include the entire range of slice locations, choose 1 and n_l, respectively.
- *Flip Angle:* Flip angle (in degrees) of the dynamic SPGR sequence.
- *Repetition Time (msec):* TR (in msec) of the dynamic SPGR sequence.
- *Non-Dicom or Override Value:* Average time (in seconds) between time points. In GE images, trigger times are used. In Siemens or Philips, acquisition times are used. In non-Dicom images, update the default value of 1.0 seconds. The updated value is automatically used in calculations.
- *Set Override:* If this checkbox is checked, the value in the previous field will be used in calculations as a fixed time interval. If checked, this value will override values taken from the DICOM header.
- *Slice Locations:* Number of slice locations (n_l).
- *TimePts:* Number of time points (n_t).
- *CapHCT:* Your assumption for hematocrit in the vessel you choose as the vascular region of interest. Default is 0.4. Note that your choice of hematocrit affects both the K and FV maps.

4) ROI Time Course

For a region of interest on the Dyn Stack, ROI Time Course creates an ImageTimeTable.txt file and a plot window showing the variation in the mean signal intensity within the location specified by the region of interest over all time points. Useful for calculating the proper last baseline time point before the arrival of the contrast bolus. The x-axis is designated in seconds, the y-axis is signal intensity.

Usage guide

Standard

Most users will probably perform their perfusion analysis in two steps in this order:
1) Use T1 Map Sub plugin to calculate T1 and S0 maps from multi-flip angle SPGR images.
2) Use the Start Patlak plugin along with the output of step one and a region of interest placed on a venous structure on the dynamic SPGR sequence to create a ImageTimeTable.txt file, VascularTimeCourse.txt file, K^{trans} and fV maps.

Notes

This program uses the curve of contrast concentrations in a vascular structure (for example, the superior sagittal sinus) as a surrogate for capillary plasma concentrations. How the vascular blood concentrations in the superior sagittal sinus should be adjusted to reflect plasma concentrations in capillary structures is somewhat controversial since hematocrit is not constant in all vascular structures and may be altered by pathology.

This version of TOPPCAT converts blood concentrations to plasma concentrations by adjusting for the hematocrit provided by the user (CapHCT).

REFERENCES:

1.   Deoni SC, Rutt BK, Peters TM. Rapid combined T1 and T2 mapping using gradient recalled acquisition in the steady state. Magn Reson Med. Mar 2003;49(3):515-526.
2.   Bluml S, Schad LR, Stepanow B, Lorenz WJ. Spin-lattice relaxation time measurement by means of a TurboFLASH technique. Magn Reson Med. Sep 1993;30(3):289-295.