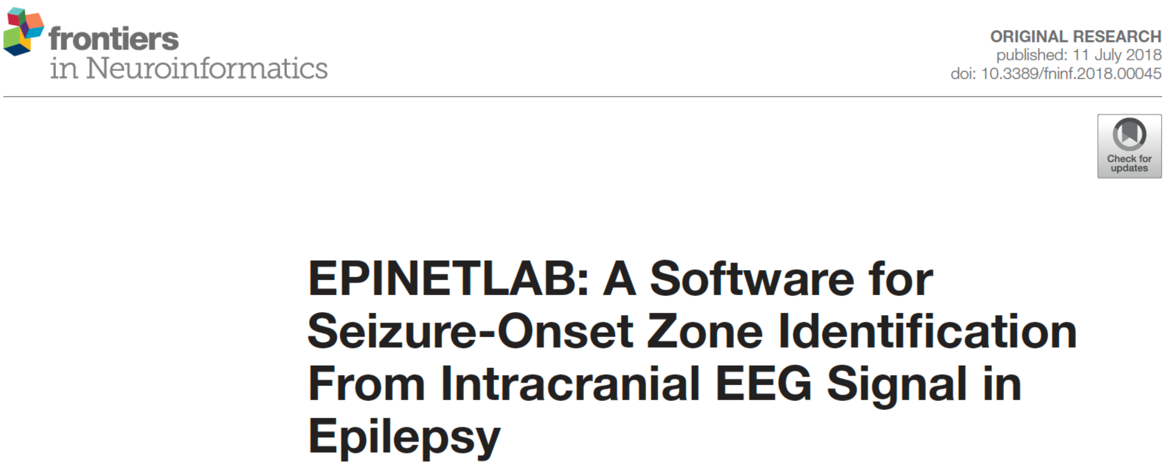
[1]EPINETLAB USER MANUAL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EPINETLAB: A Software for Seizure-Onset Zone Identification From Intracranial EEG Signal in Epilepsy


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EPINET — Result In Brief

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Country: United Kingdom
Domain: Health, Fundamental Research , Industrial Technologies

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EpiNetLab is a post-processing analysis platform for automatic identification and quantification of High Frequency Oscillations (HFO) contained in EEG signal. The tools are accessible from within EEGLab, an interactive MATLAB toolbox for processing continuous and event-related EEG, MEG and other electrophysiological data incorporating independent component analysis (ICA), time/frequency analysis, artefact rejection, event-related statistics, and several useful modes of visualization of the averaged and single-trial data. EEGLAB runs under Linux, Unix, Windows, and Mac OS X (https://sccn.ucsd.edu/eeglab/index.php).

While EpiNetLab was designed with intracranial EEG (iEEG) data in mind, the platform can in principle be used to analyze scalp EEG as well both in signal and source space, provided the dataset can be imported in its higher order framework EEGLab. MEG data import for Elekta Oy ".fif" format has also been developed as part of the project.

The toolbox can be requested from Lucia Quitadamo (l.quitadamo@aston.ac.uk); enquiries on clinical application can be directed to Stefano Seri (s.seri@aston.ac.uk)

The software can be also be downloaded from https://github.com/quitadal/EPINETLAB.

Installation tips: In order for EpiNetLab software to be visible within the EEGLab GUI, the folder containing all its functions has to be copied to the folder "plugins" of EEGLab. When this is done, starting EEGLab from the MATLAB prompt delivers the following screen with "EPINETLAB (HFO)" menu item visible, see Fig.1:

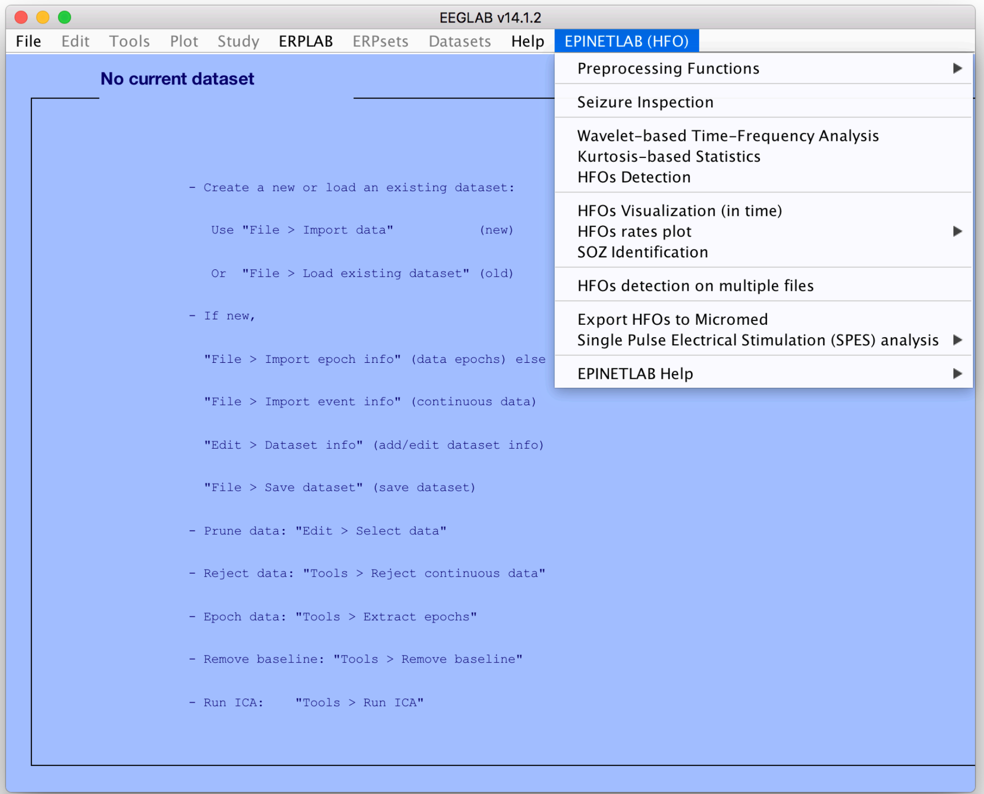


Figure 1: EEGLAB with EPINETLAB installed.

Getting Started

We will assume here that you have been able to export from your clinical EEG system the iEEG data you wish to analyze in a format that EEGLab is able to read.
The preliminary clinical validation was performed on peri-ictal data and on interictal as described in the 2 initial publications:

- Quitadamo, LR, Foley, E, Mai, R, De Palma, L, Specchio, N & Seri, S 2018. 'EPINETLAB: a software for seizure-onset zone identification from intracranial EEG signal in epilepsy' *Frontiers in Neuroinformatics*. DOI:10.3389/fninf.2018.00045
- Quitadamo, LR, Mai, R, Gozzo, F, Pelliccia, V, Cardinale, F & Seri, S 2018, 'Kurtosis-based detection of intracranial high-frequency oscillations for the identification of the seizure onset zone' *International Journal of Neural Systems*, vol. In press, 10.1142/S0129065718500016, pp. 1850001. DOI:10.1142/S0129065718500016

In particular, we tend to analyze:

1. Peri-ictal data: two seizure episodes. An EEG segment containing 10 min before and 2 min after the electrographic onset of each seizure was extracted and was considered as the period of interest for HFOs identification.
2. Interictal data were extracted from 10 min of iEEG signal collected during stage III sleep of the second night of the monitoring period.

The ultimate choice however rests with the user. We also remind users that the tool is not intended as a clinical device lacking any regulatory approval from appropriate agencies. We made this available to users for research purposes only. Its use outside of this context is done exclusively under the user's responsibility.

PRE-PROCESSING

1. Data Import: extensions for EEGLAB

These extensions allow to import various type of data. EEGLAB contains native function to import some data formats (Fig.2).

- **BIOSIG data import:** Import/export data in a wide variety of data formats, developed by Alois Schloegl, the creator of the EDF+ data format. For more information about BIOSIG toolbox visit this page.

- **FileIO:** toolbox allowing data import in multiple data formats.

- **CTF data import:** Import CTF MEG data. Available from Darren Weber's EEG sourceforge project, this extension imports MEG data (plus concurrent EEG, if any) plus sensor locations and data events from data in the CTF (Vancouver, CA) data format.

- **ANT data import (v1.03):** Import data files in the EEP format. Contributed by ANT Software (Netherlands) to import data in their format. Email contact: info@ant-software.nl.

- **BVA data import/export:** Import/export files from/to the Brain Vision Software Analyser suite. Contributed by Andreas Widmann of the University of Leipzig (Germany) with Arnaud Delorme.

- **Neuroimaging 4D:** Christian Wienbruch of the University of Konstanz (Germany) has an extension available for loading Neuroimaging 4-D data into EEGLAB.

- **TDT data import:** Adam Wilson at the NITRO Lab at the University of Wisconsin Madison (USA) offers an extension available for loading Tucker-Davis Technology format data into EEGLAB.

- **NeurOne data import:** EEGLAB extension for reading the file format of NeurOne system.

- **Micromed data import:** Micromed (Italy) has an extension available for loading their data format into EEGLAB. Contact Cristiano Rizzo (cristiano.rizzo@micromed-it.com) for details.

  The import menu from EEGLab with appropriate converters installed is shown below:

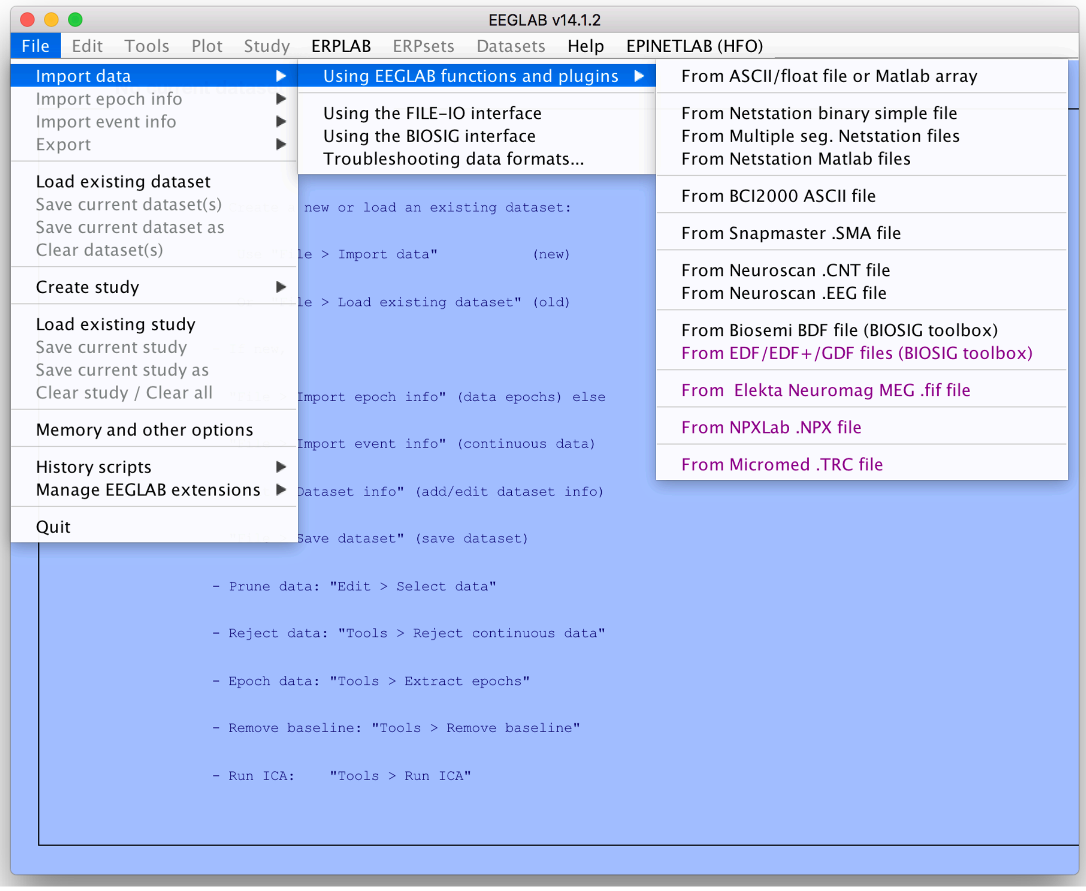


Figure 2: "Import data" functionality in EEGLAB.

2. iEEG channel selection

If your dataset contains a mix of iEEG and scalp EEG or if service channels are present, this is the time to “clean” the dataset from any channel which is not iEEG. In our clinical practice we only connect contacts located in the white matter to be used as reference, after having selected them in the Neuro-inspire planning software from the post-implantation CT co-registered with the patient’s MRI. If you connect all the SEEG contacts you can remove the channels you don’t wish to analyze.
REMEMBER: the statistical thresholding is a critical part of the automated detection; including non grey-matter contacts might affect the final result (please see the paper to understand how/if).
You can exclude contacts using an EEGLab function available from the GUI (Fig.3)

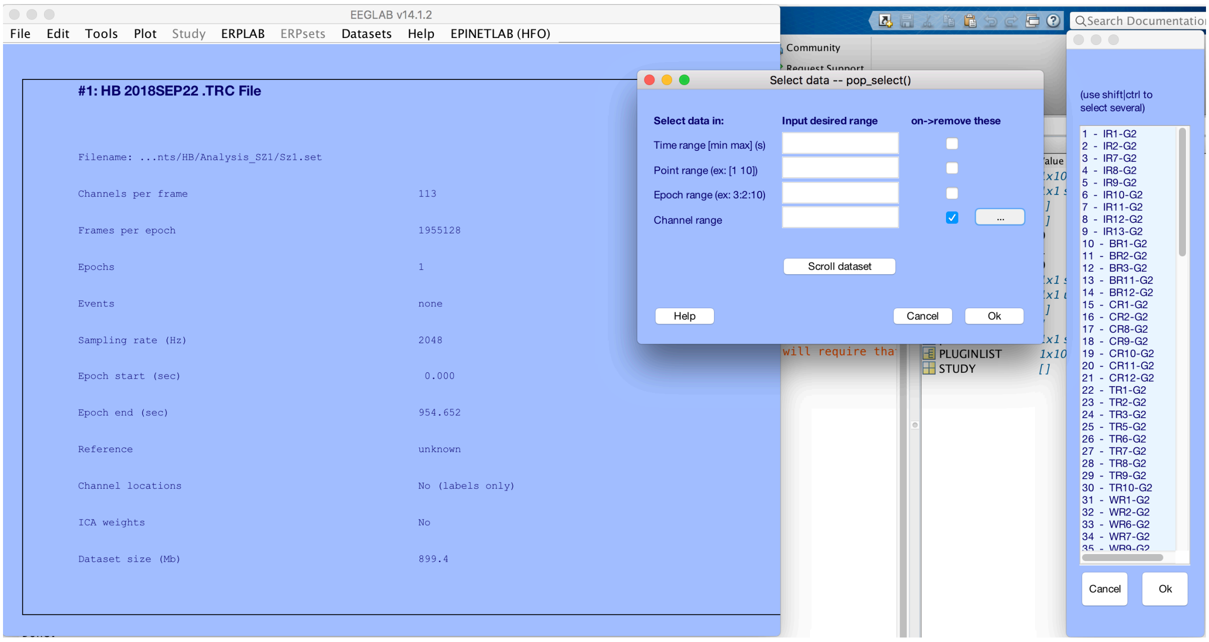


Figure 3: “Select data” functionality in EEGLAB.

Channel range option in the [Edit>Select Data] menu allows you to remove multiple channels from your dataset (command+click for non-continuous or shift +click for contiguous channel selection in the Mac environment).
When you are finished, we advise saving the new file with different name (Fig. 4); it is advantageous to do the same for each step of the GUI-led analysis process to be able to go back to specific intermediate steps in case an error occurs.

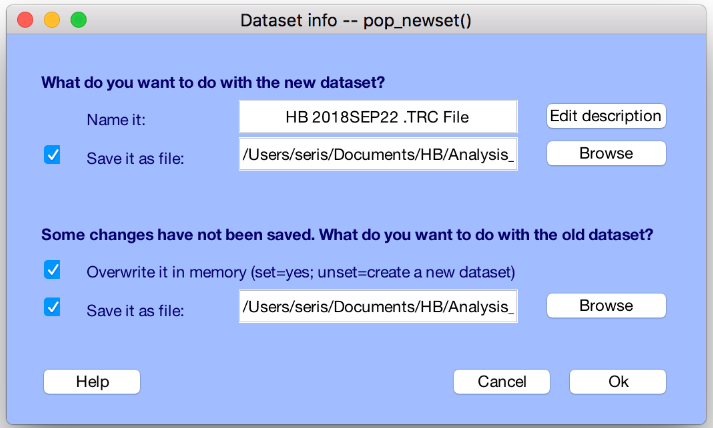


Figure 4: EEGLAB GUI for saving a new dataset.

In this case 12 channels have been removed (113 to 101), Fig. 5.

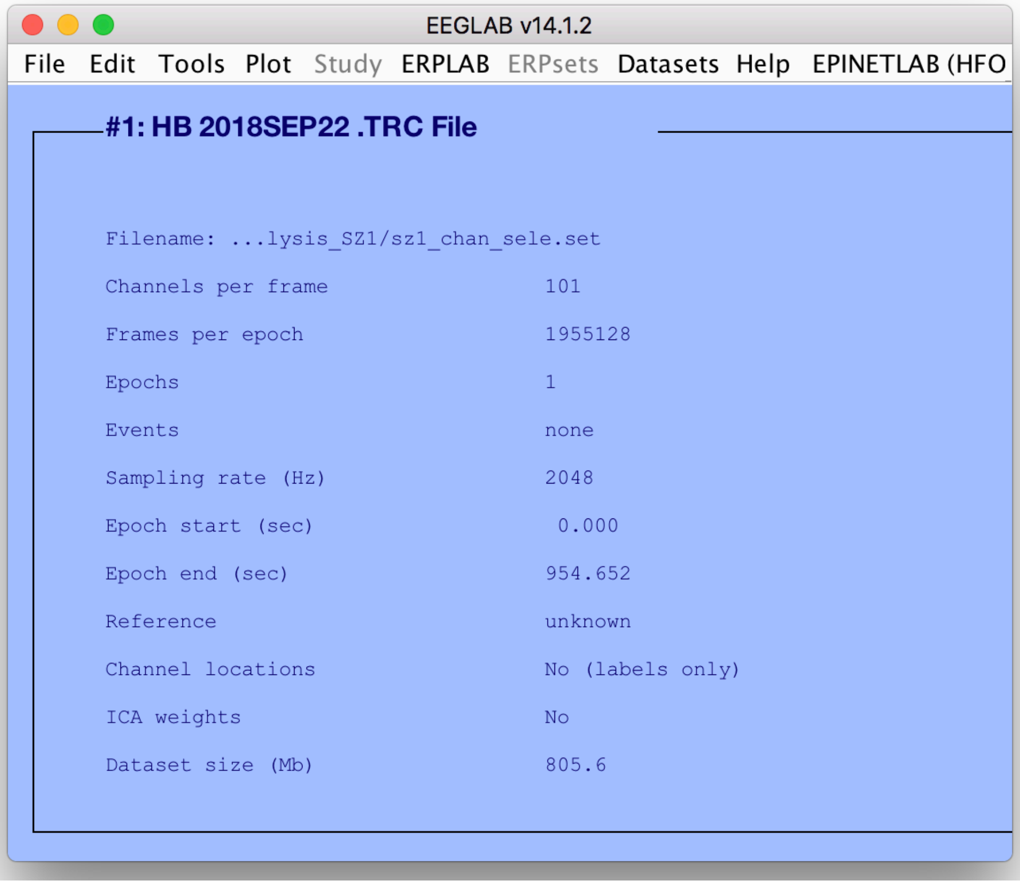


Figure 5: The EEGLAB main window is updated after channel removal.

It is assumed here that the dataset is acquired against a physical reference (in this example against G2 input of the amplifier).

In line with current clinical practice we advise performing iEEG data analysis in bipolar montage using sequential inputs for each electrode or against white matter contacts.

3. Montage Creation

At this stage you will want to create the "montage" in which the analysis will be performed. A bipolar chain option tends to be the preferred option in the clinical literature on sEEG data visualization and we have consequently offered this option. To do this you will have to prepare the montage labels using some text editing functions available in EpiNetLab.

<u>Labels formatting (Fig.6):</u>
Typically, from the example used here, you would want to remove the last 3 characters from the labels (-REF), to allow the bipolar montage label to contain only one – character. This makes it easier for the program to identify channels when processing. EpiNetLab doesn't deal well with the ' (prime) symbol often used in French practice to denote left-side implanted electrodes, therefore replacing the "prime" symbol with the letter "L" for left is advised.

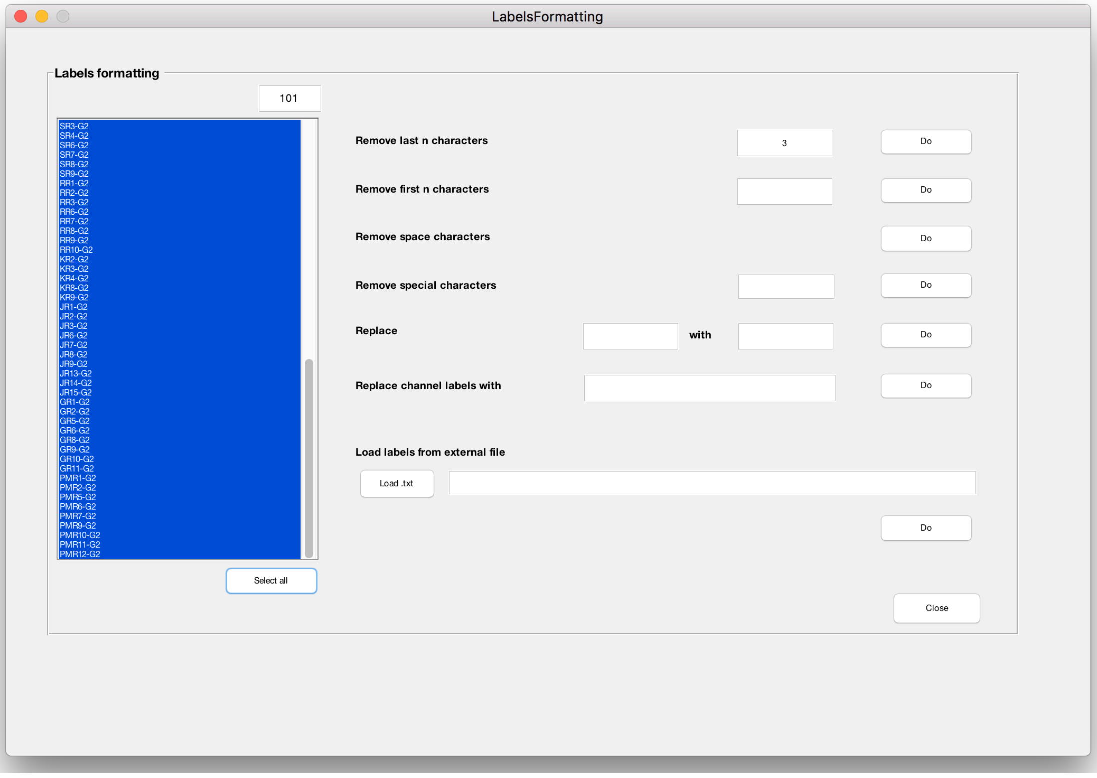


Figure 6: EPINETLAB channel labels formatting GUI.

To do this: [Select all > Remove last n Characters =3 > DO].
Remember that EEGLab asks you to save new file offering you option to give it a different name and/or overwrite in memory the data vs keep both the modified and original. This has memory implications. Please refer to the EEGLab manual for detailed information.

4. BAND-PASS FILTERING

EpiNetLab doesn't require iEEG data to be filtered in the HFO interval of choice. Time-frequency analysis can be performed on the broadband signal, albeit with computational cost. A relatively recent paper has shown that sharp transients and

harmonics of non-sinusoidal signals can produce spurious oscillations after filtering and that these could be confounded with actual oscillatory activity. The aa. advise that high-pass filtering of EEG traces for detection of oscillatory activity should be performed with great care (C.G. Bénar, L. Chauvière, F. Bartolomei, F. Wendling. Pitfalls of high-pass filtering for detecting epileptic oscillations: A technical note on “false” ripples. Clinical Neurophysiology 121 (2010) 301–310).
However, the user can perform re-filtering of the data if they are so inclined by using the EEGLab GUI command [Tools>Filter the data] (Fig.7) and choose the most appropriate filter type and interval (e.g. 80 250 or 250 500).

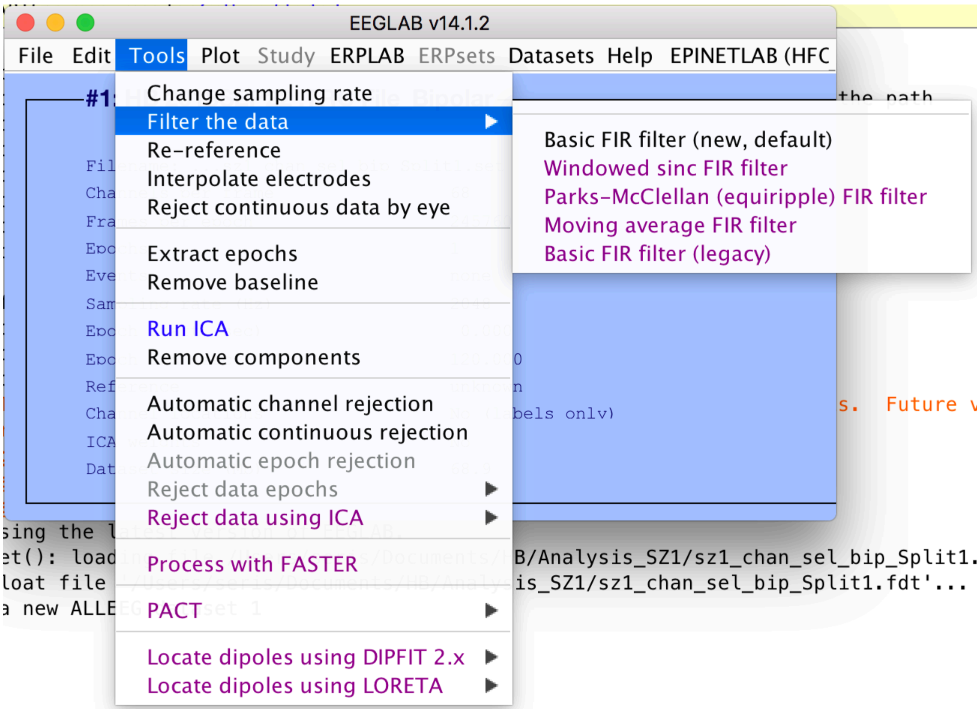


Figure 7: EEGLAB “filtering data” functionality.

5. CREATING BIPOLAR MONTAGE

At this stage you will want to create the montage in which your data will be analyzed. If you chose to work with data referenced to one or more white matter electrodes or any other combination, this can be done from the EEGLab interface [Tools>Re-Reference], see Fig. 8.

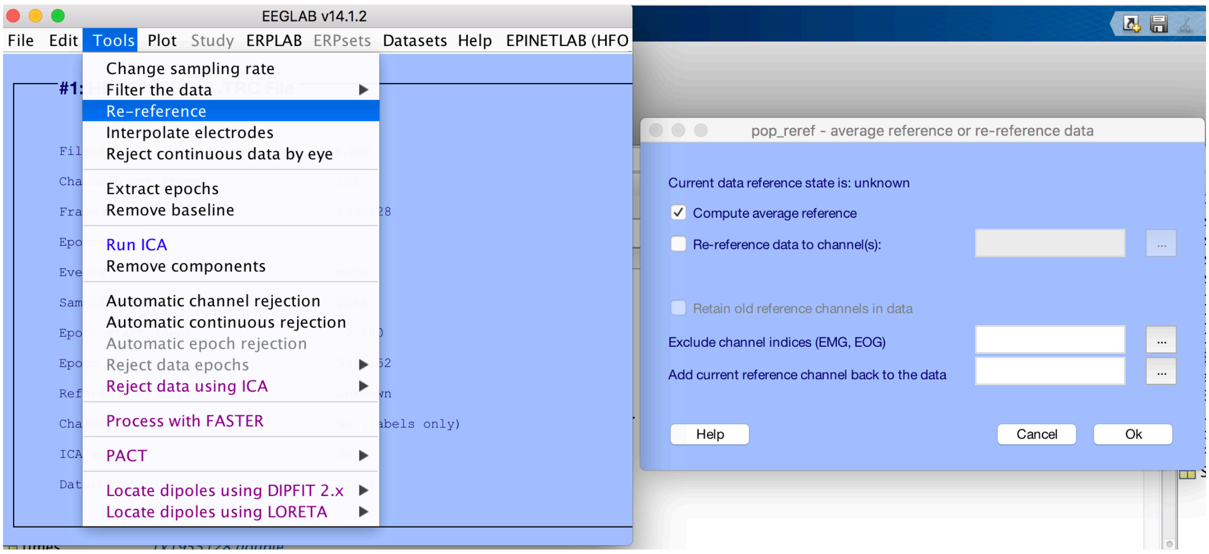


Figure 8: EEGLAB "Re-referencing" GUI.

or from EpiNetLab GUI command [Preprocessing Functions>Average References Creation], in which you will have to select contacts on the left panel and define the number of contacts participating the average reference and their labels. This function was developed for users acquiring data from subdural grids . A full description of the process is in Appendix 1 at the end of this manual.

If bipolar montage is what you want, then the EpiNetLab GUI command: [Preprocessing functions>Bipolar Montage Creation] is available to you (Fig. 9).

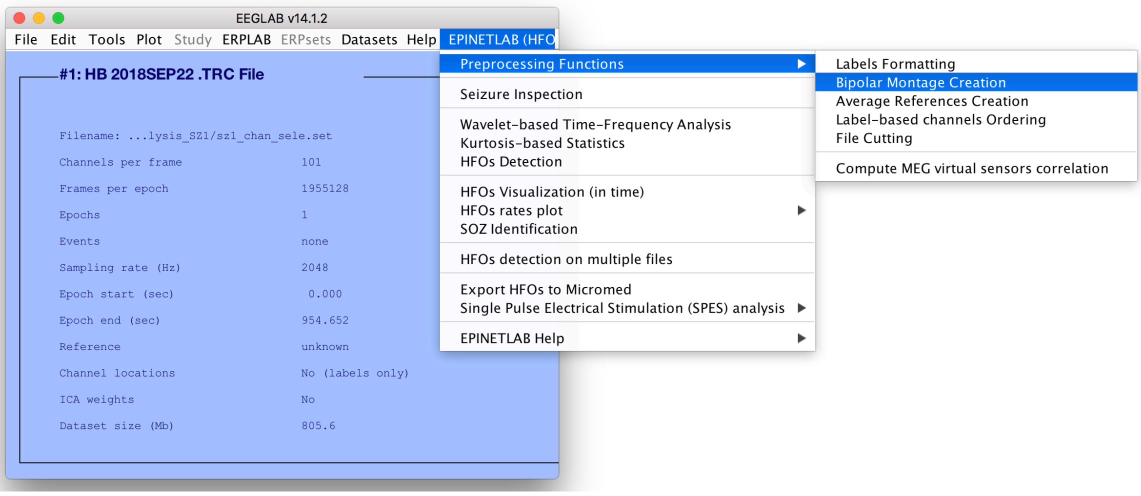


Figure 9: EPINETLAB "Bipolar Montage Creation" functionality.

The menu will offer you the list of the G1 and G2 contact to create your bipolar chain (Fig. 10).

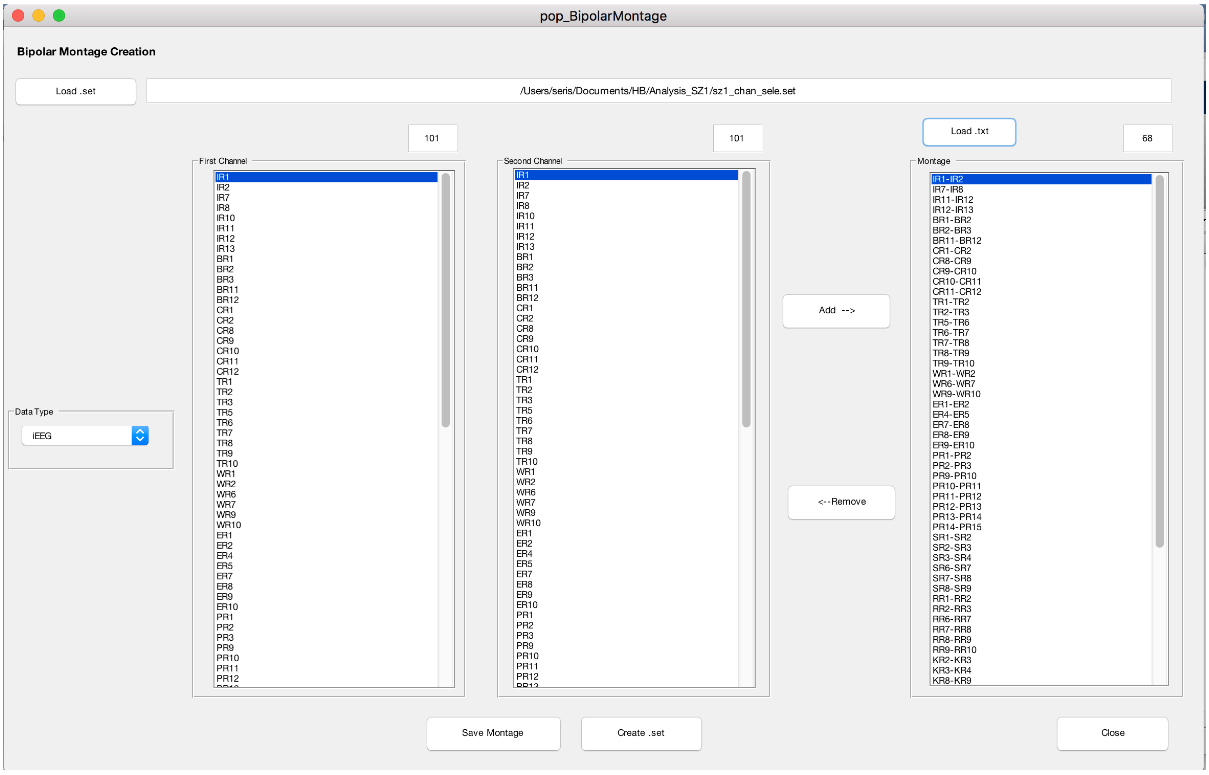


Figure 10: EPINETLAB “Bipolar Montage Creation” GUI.

At the end of this process you should save the bipolar montage as text file in an appropriate location and create the new “.set” (EEGLab format) file in bipolar format. The number of channels will have obviously decreased accordingly.
Again, the EEGLab menu will ask you to save the new file and if you want the old one to be overwritten in memory.

6. FILE PARSING/CUTTING

Now you have a bipolar file; to expedite wavelet coefficient computation and avoid running out of memory on your computer you will want to split the file in smaller segments (2’ chunks in our validation dataset). The example in Fig.11 uses a 954” long file (= ~ 10’); we decided to create 5 consecutive files of 2’ duration.

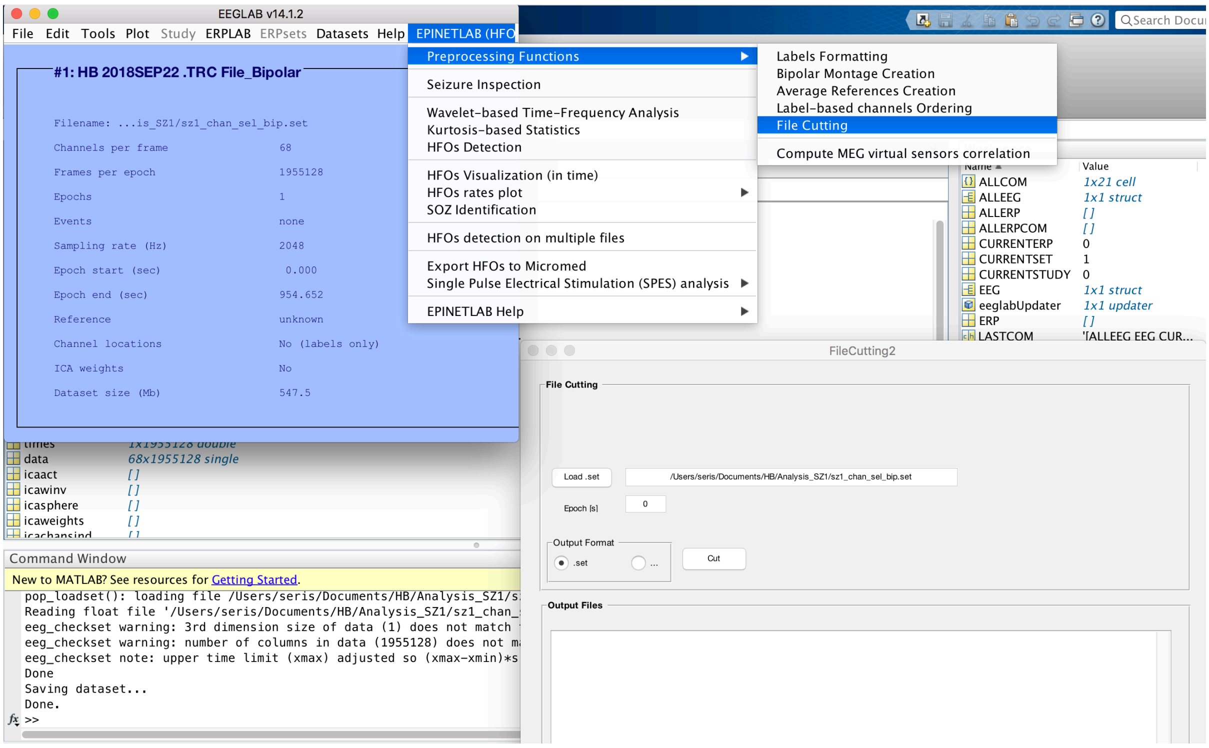


Figure 11: EPINETLAB "File Cutting" functionality.

The menu offers the option of file duration; the seizure file will be divided in N files of the chosen length, in this case 120", see Fig.12.

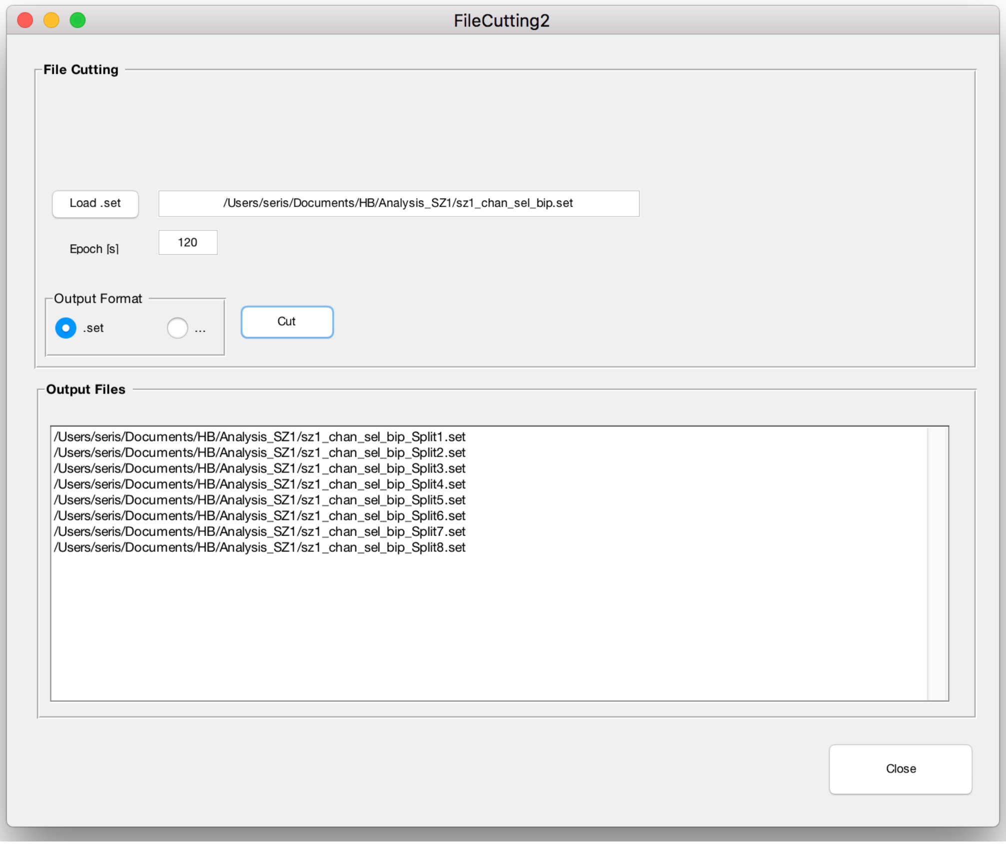


Figure 12: EPINETLAB "File Cutting" GUI.

HFO DETECTION

This stage can be approached by analyzing single or multiple files at the same time. The latter is the most obvious choice; files can be selected from the GUI and parameters for the estimation must be defined in this menu (Fig. 13).
For the full description and scientific bases for each menu choice, please refer to the paper in *Frontiers in Neuroinformatics* mentioned at the beginning of this manual.
Ripples (80-250 Hz) and Fast Ripples (250-500 Hz) must be analyzed separately but the frequency interval can be also set arbitrarily by the user. Other items to choose are:

- Spectral Estimation method: Staba vs Wavelet and if wavelet is chosen as option, which wavelet will be used.
- Detection parameters: Staba method has been implemented here only due to its wider recognition at the time of project inception. More methods have since been published and are not implemented in our software.

If wavelet method is chosen, the user can fine-tune the criteria used by the algorithm to discard as Artefacts events with spectral profile in the chosen HFO window if they meet criteria such as:

1) Present in more than N channels at the same time: this behavior is typical of external artefacts, e.g. muscular artefacts.
2) Power of the event spreading in all the frequency window: this behavior is typical of spikes.

Also the minimum duration of the candidate events can be decided, e.g. 20ms for ripples and 10ms for fast ripples. The default parameters have been used for the validation study, which was focused on the 80-250 Hz interval, and are set as default.

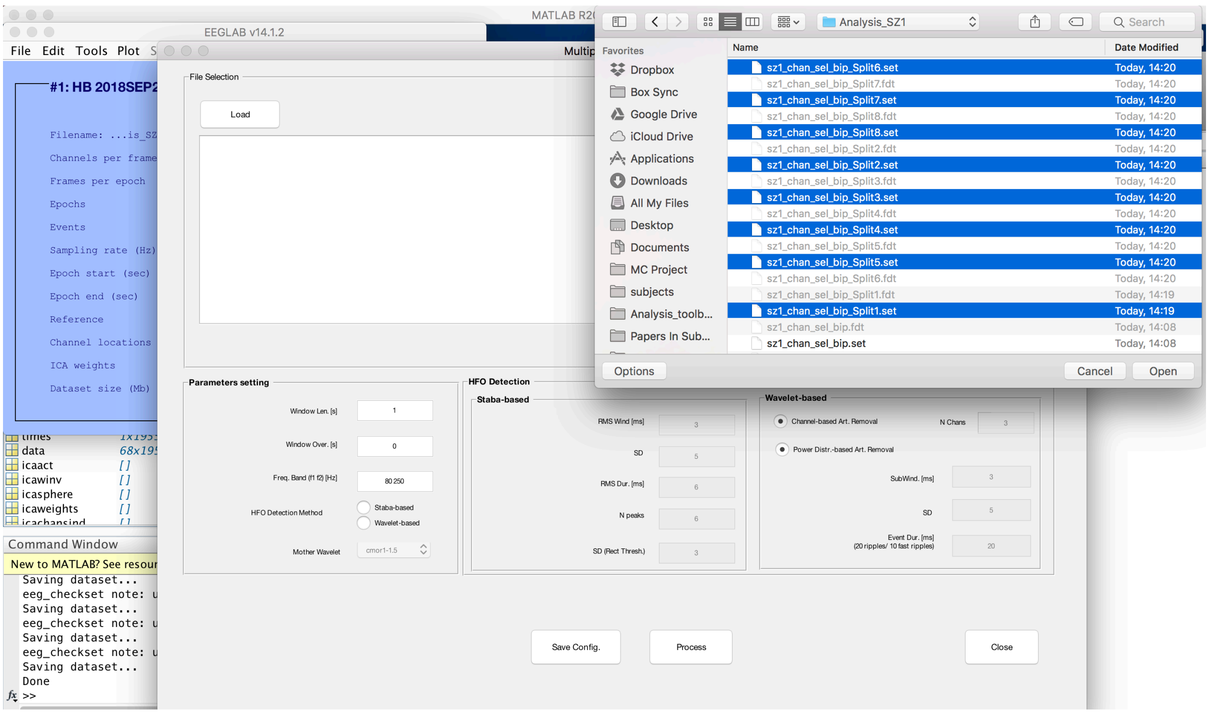


Figure 13: Multiple file selection.

Selecting the Process command, the computation starts and its duration is dependent among others on number of electrodes, sampling rate, number and size of files, frequency interval.
To give a very approximate idea, processing one unfiltered 2' file sampled at 2 KHz with 68 bipolar channels on a Macbook Pro 3.5 GHz Intel Core i7, 16Gb RAM laptop has taken 27 minutes.

7. DISPLAY ANALYSIS RESULTS WITH HFO RATES

After having computed HFO rates for each channel and each epoch file, you will want to produce a figure of HFO rates for each iEEG electrode and display the electrodes as color bars.

- If your dataset contains only stereo-EEG electrode data, select [EPINETLAB(HFO)>HFO rates plot->Plot HFO rates on sEEG channels]. The toolbox will ask you to consecutively load the following objects in this precise sequence:
    - All the files containing HFOs for each channel (text files contained in the WaveletHFO folder) (Fig 14).

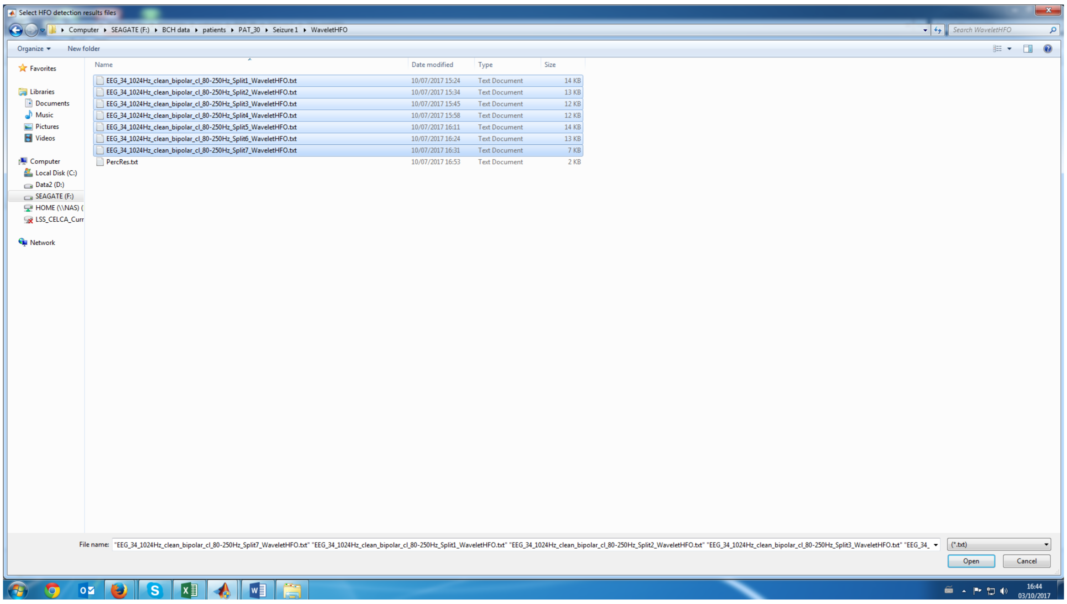


Figure 14: Selection of the files containing detected HFOs in multiple epochs.

    - The bipolar montage.
    - The unipolar montage: this is a text file you can create yourself using any text editor that contains for each row the letter corresponding to each electrode present in the dataset followed by CR/LF.

- If you have SEEG channels and grids (or just grids), select [EPINETLAB(HFO) > HFO rates plot- > Plot HFO rates on sEEG channels AND grids].

The program will ask you to consecutively load the following objects:

- All the files containing HFOs for each channel or grid contacts (text files contained in the WaveletHFO folder). You need to select them all from the folder. Please note that the program will automatically recognize

grids if the labels start with Gd or Gr (if you need more labels to be recognized we can just add new ones).
- The bipolar montage. In case of grids, referencing each contact of the grid to the *Average Reference* can be performed within EEGLAB.
- The unipolar montage.

- Two figures constitute the output of these procedures: one containing the color bars with the HFO rates on each contact (Fig.15) and one containing the distribution of HFO rates in each of the epochs chosen for analysis (Fig. 16).

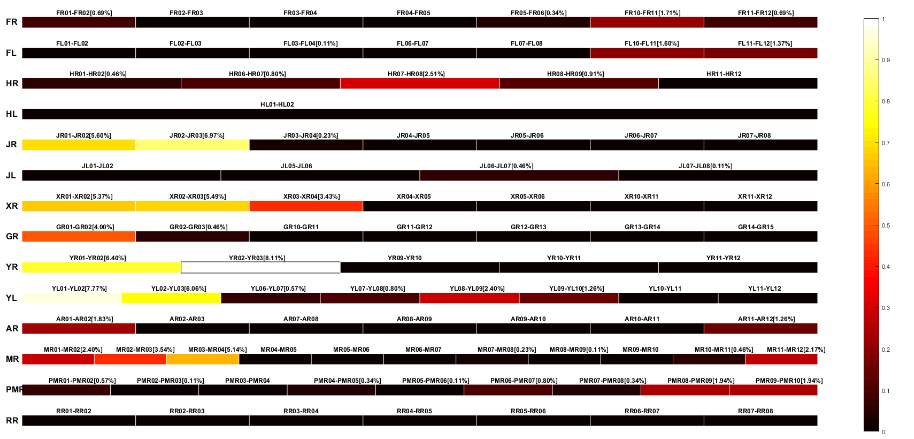


Figure 15: HFO distribution on each contact: black means no HFOs detected, white means maximum HFO rate.

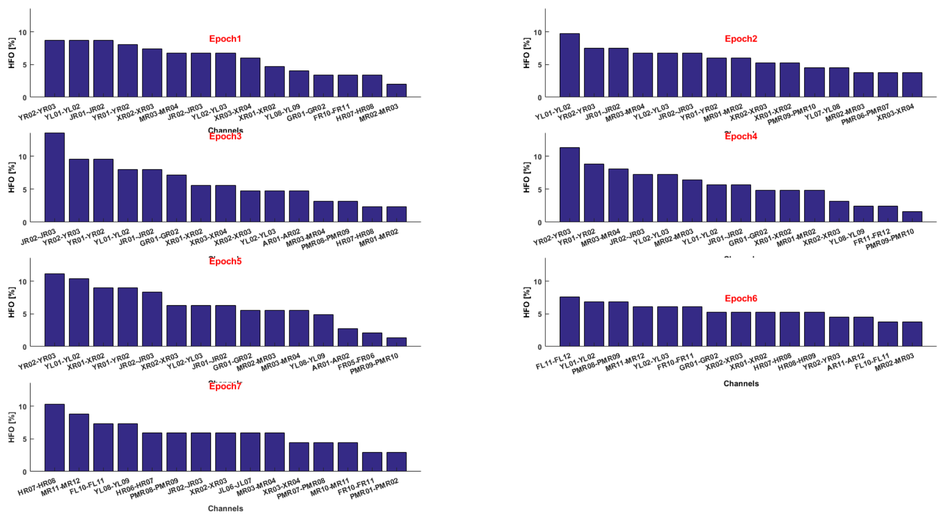


Figure 16: Distribution of HFO rates in each analysed epoch.

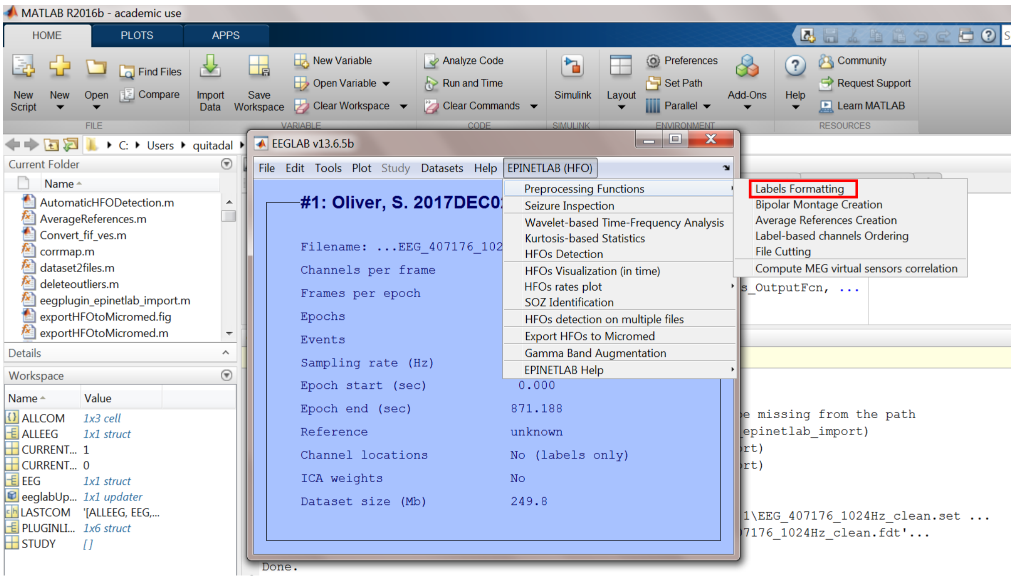
We advise saving the two figures both as bitmap/tiff/jpeg and in the MATLAB format (.fig) if you wish to visualize the figures outside the MATLAB environment.
Also, after you create the figures, a new file **PercRes.txt will be created** in the "WaveletHFO" folder. The file contains the list of the percentages of HFO rates corresponding to each channel.

APPENDIX 1

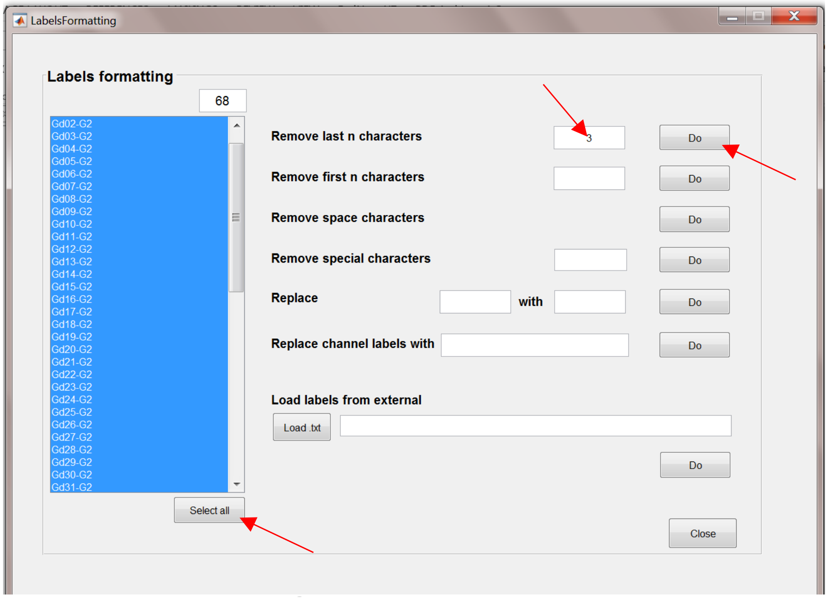
AVERAGE REFERENCE IN EPINETLAB

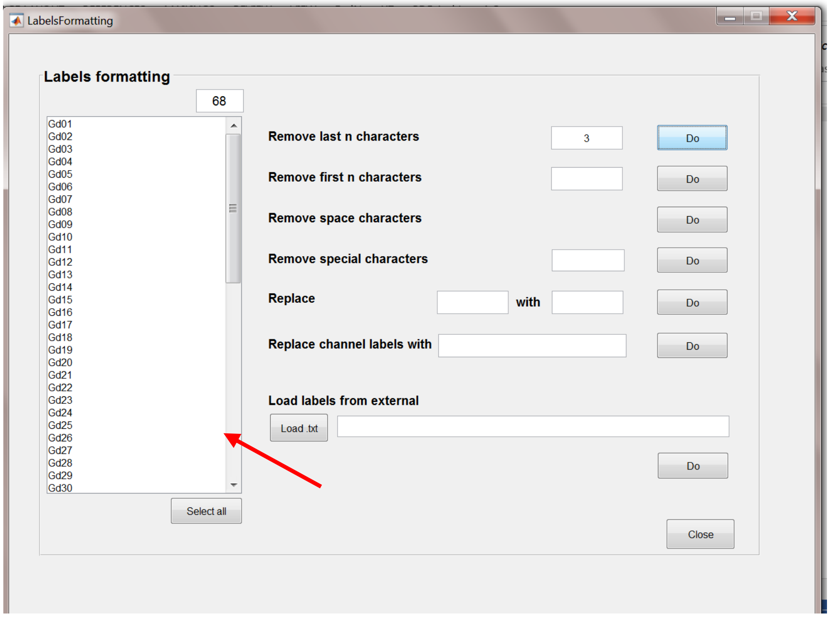
When you have GRIDS besides stereo-EEG electrodes, the best approach for data pre-processing is to refer each contact of the grid to the average reference (AR) of the grid itself, while using bipolar montage just for SEEG.
A new functionality was added to EPINETLAB, under the "Preprocessing Functions" tab, which is called "Average Reference Creation" and allows you to add to the signal a new channel which contains the average reference of the grid. This channel is added at the end of the channel list. If you have many grids, you can add many average references to the file, the important thing is to call them with different names, e.g. AR1, AR2, AR3, REF1, REF2, etc.

Below you find an example of how to use this new functionality (patient O.S., file EEG_407176).
First thing to do with Micromed files is to format labels in order to remove the "–G2" string from each channel label.

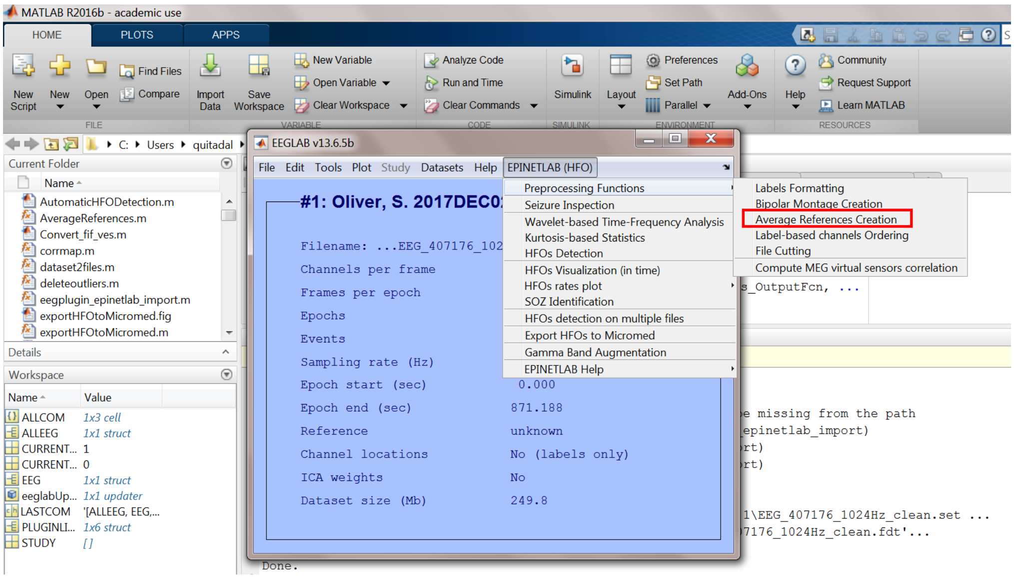


You select the channels after having removed scalp EEG and EMG/EKG/service channels) and then choose 3 as number of characters to delete from the end of the channel labels. Then press "Do" and the last three characters will be removed from each label.

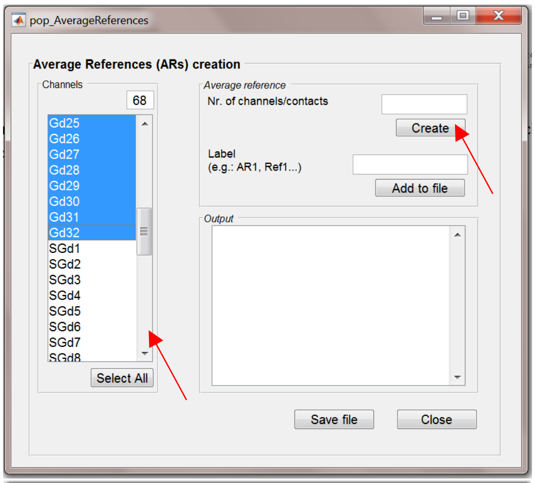


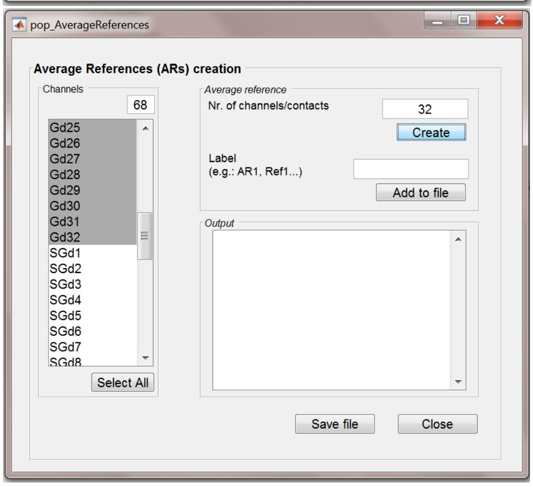


Then we can create the AR channel. We select the "Average References Creation" functionality.

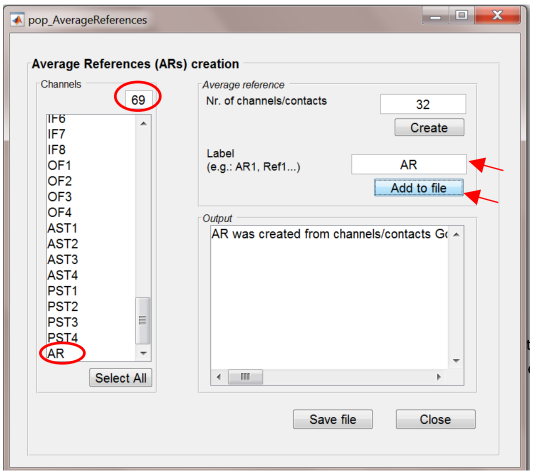


In the GUI that appears, in the channels list we select the contacts on which to perform the AR. In this case from Gd1 to Gd32. Then we press Create and the AR channel is created.

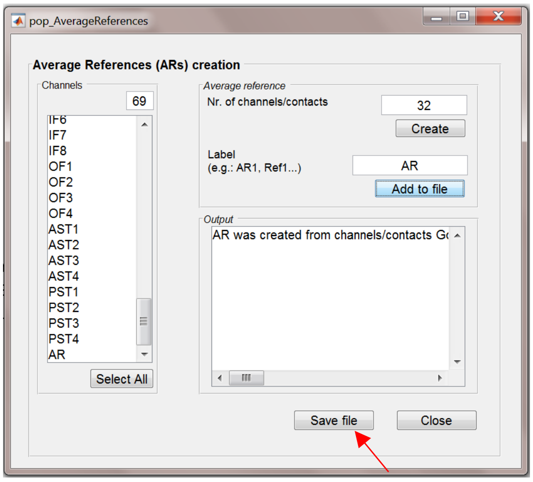


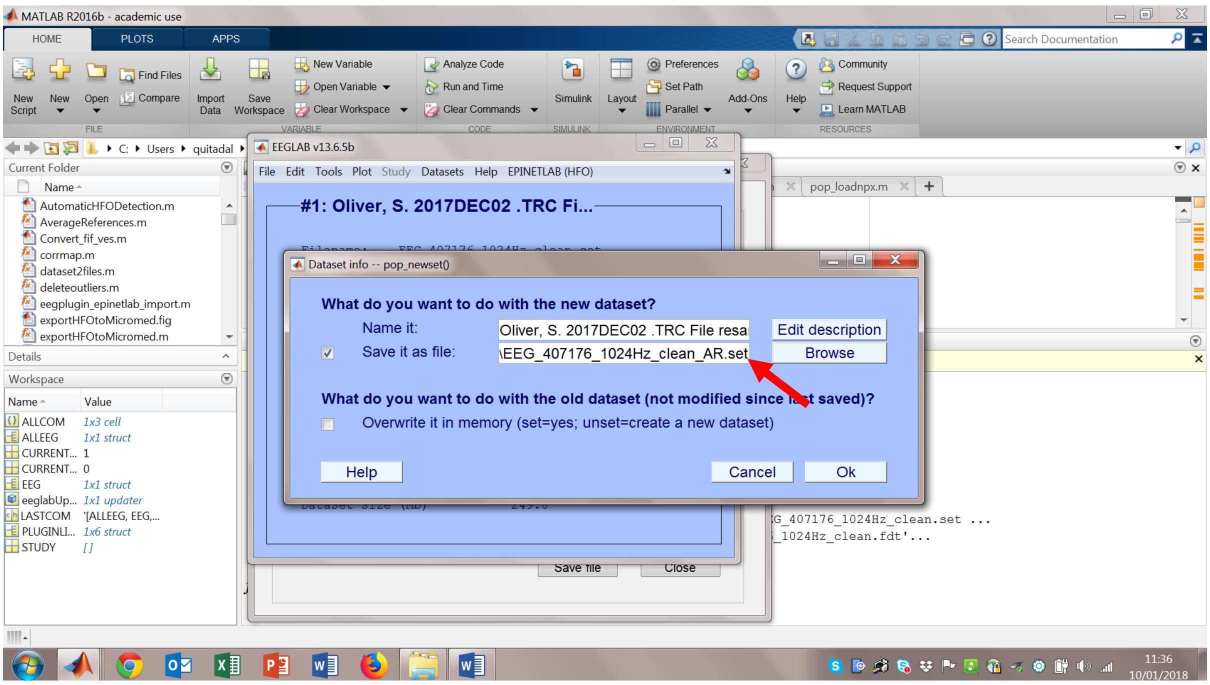


Then we insert a label for the new channel, for example AR and add it to the file. You will see that in the list of channels on the left, AR will appear at the end of the list and the number of channels will change from 68 to 69.

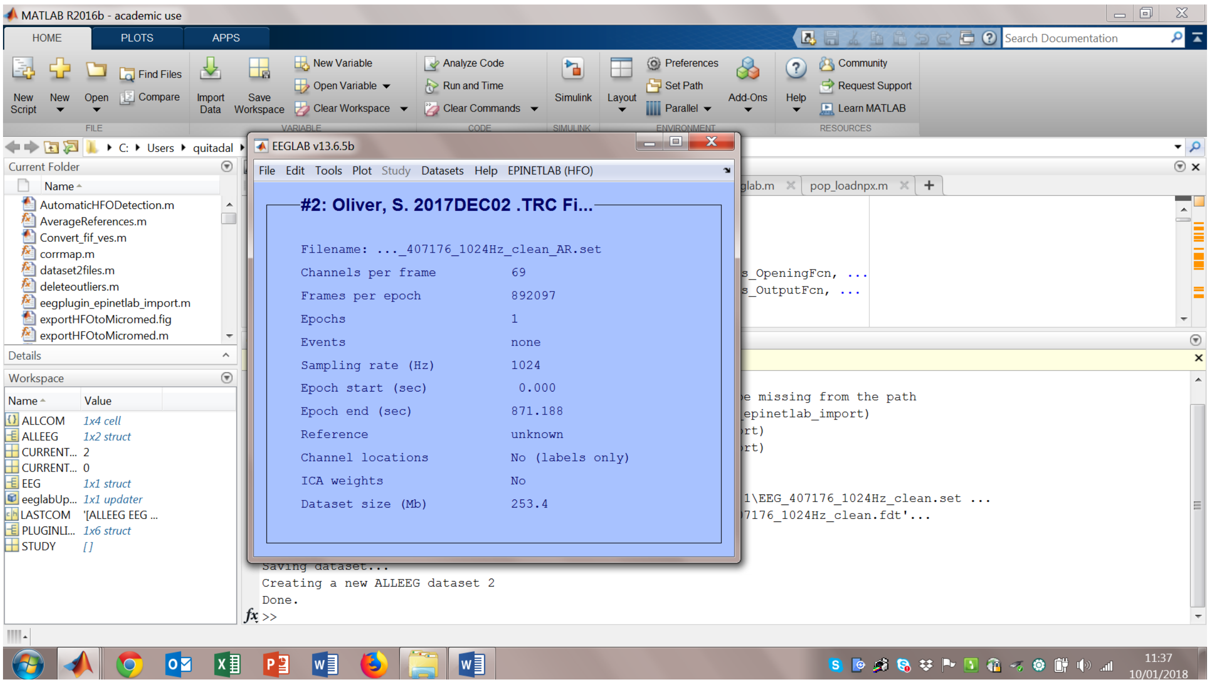


In the Output window, a summary of the operations is reported: “AR was created from channels Gd01, Gd02, …, Gd32”.
Last thing to do is to save the new file.

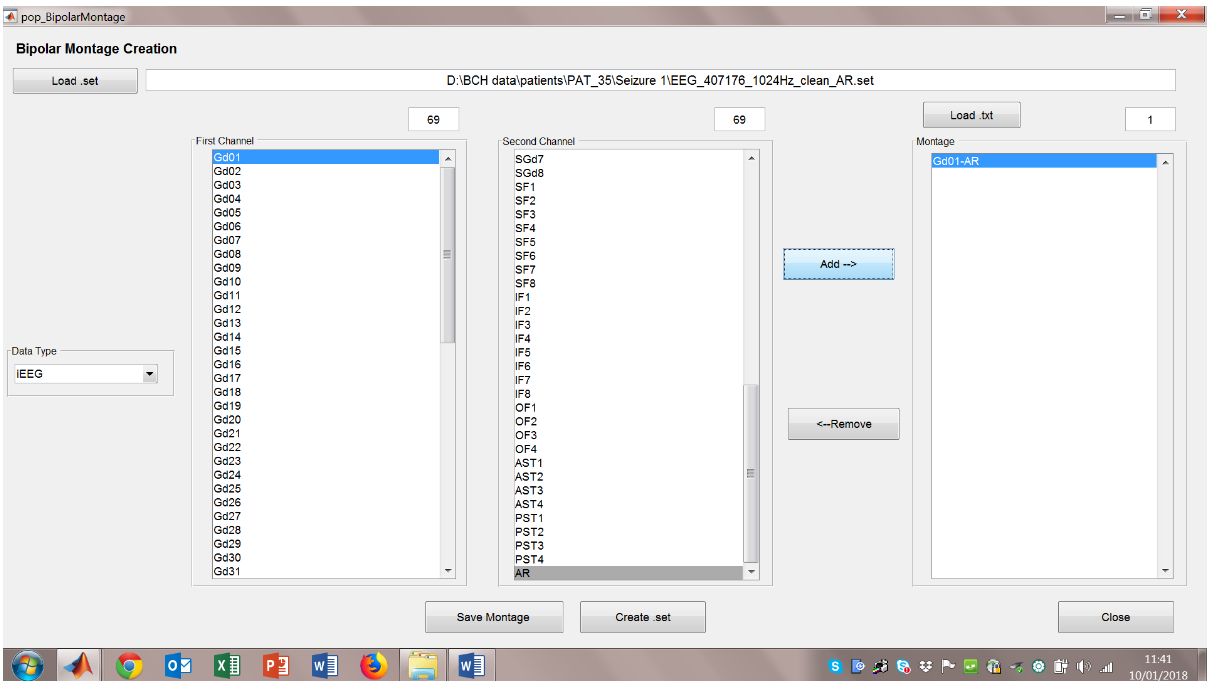


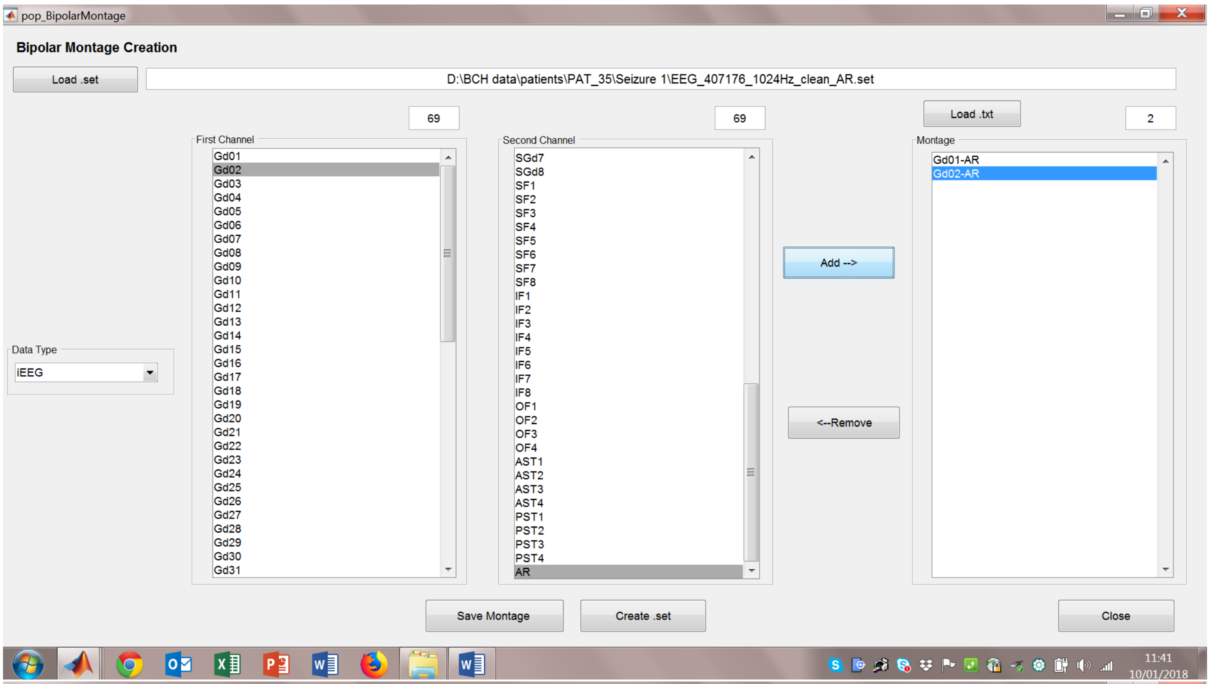


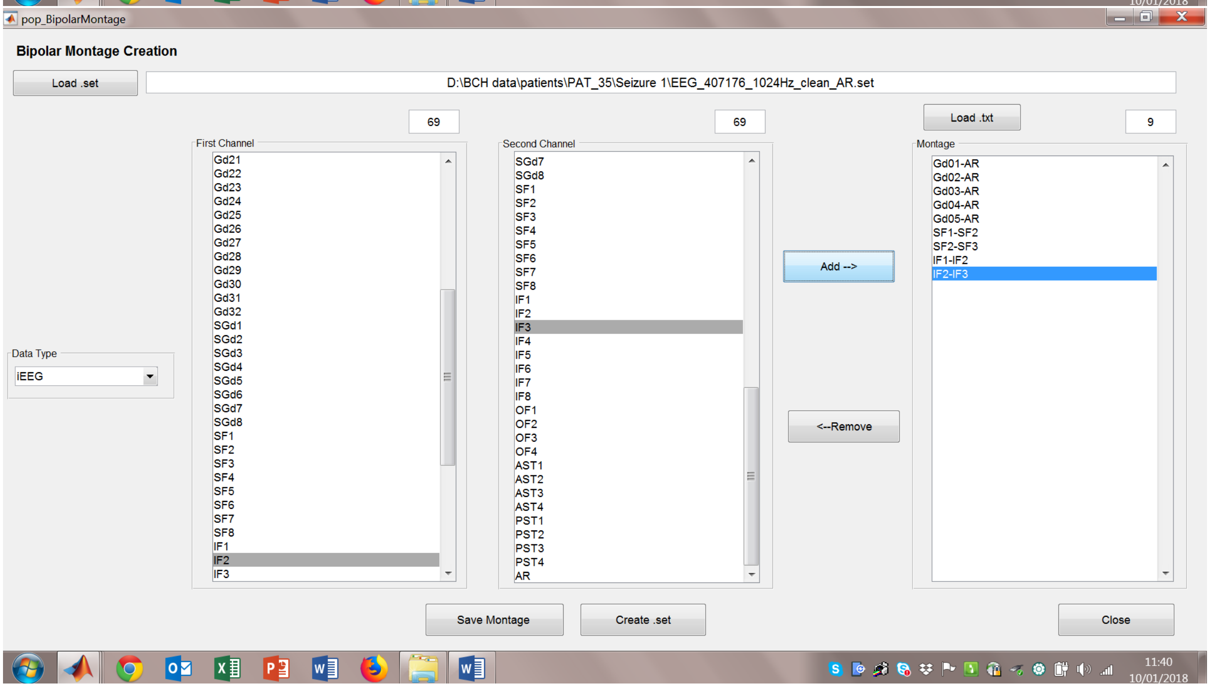
The new file will be automatically added to the EEGLAB interface.



Now the we have the AR relative to the grid, when we create the bipolar montage, each contact of the grid can be referred to the same AR channel, while for the contacts of the SEEG electrodes we still use the classical subtraction between adjacent contacts.







In the end you just need to save the montage in the TXT file and then create the .set file containing the AR/bipolar contacts.