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Aplicacions mèdiques a l'Engininyeria I

Implementing SISCOM technique in a concrete case:

INTRODUCTION

Epilepsy is a chronic brain dysfunction that is caused by various factors and characterized by recurrent, episodic, and temporary central nervous system dysfunction which results due to sudden, disordered, and excessive discharge of brain neurons [1]. These episodes, called seizures, cause involuntary movements that may involve part or all the body.

Under proper pharmacological treatment, up to 60 or 70% of people living with epilepsy may be left without seizures [2]. However, there is still a part of the affected population who still have seizures after having tried various antiepileptic drugs, thus it is not possible to control their seizures with medication. These patients are diagnosed with drug-resistant epilepsy.

Actual treatment for drug-resistant epilepsy is surgical resection of the epileptogenic zone (EZ), which is defined as the "minimum amount of cortex that must be resected to produce freedom from seizures." The success of the surgical treatment is mainly determined by the accuracy of the pre-surgical identification and the prediction of the possible impact of the intervention. Localization of the EZ was classically performed with video-EEG and magnetic resonance (MR). Recently, functional neuroimaging studies of Nuclear Medicine, positron emission tomography (PET) and single photon emission computerised tomography (SPECT) have demonstrated their utility in the localization of the EZ prior to surgery. Ictal SPECT with brain perfusion tracers shows an increase in blood flow in the initial ictal focus, while PET with 18-FDG demonstrates a decrease of glucose metabolism in the interictal functional deficit zone [2].

Various image processing techniques have been described to improve the sensitivity and specificity in the preoperative identification of the area of onset of seizures (SOZ). Subtraction of interictal SPECT from ictal SPECT and RM co-registration (SISCOM), first described by O'Brien et al. [3], is an example that is currently used in the clinical routine thanks to software that integrates it such as FocusDET [4].

The SISCOM technique evaluates the difference in the level of cerebral perfusion or blood flow between a SPECT image obtained during the period of epileptic seizure (or ictal) and a SPECT image obtained during non-altered cerebral activity (or interictal). The increase in neuronal activity triggered by the epileptic seizure leads to an increase in neuronal metabolism and a regional increase in blood flow, which is manifested in ictal SPECT [5].
This report will describe the steps of the SISCOM technique applied to a specific case.

METHODS

The SISCOM workflow consists of the following steps, divided into two parts:

- SPECT-SPECT realignment
- SPECT-RM co-registers

Part I (SPM12)

- Account normalization
- Image difference
- Location of EZ
- Focus Fusion

Part II (python)

Note: The images resulting from Part 1 (realigned and co-registered) are taken from Mireia Aguilar Amorós, with her permission of the teacher's, as SPM12 implemented in the computer used ran too slowly. Therefore, images of the parameters used in the processes inside SPM12 are not available in this report.

Part I: Bring all images to a common space

For this first part SPM12, an add-on on neuroimaging supported by MATLAB, will be used. This software lets us create a common origin of coordinates for all the three images, realign images of the same modality and co-register images of different modalities.
Before starting with the realignment of SPECT images, the origin of coordinates of both images is due to be visually located in the centre of the brain. The Display function allows to perform this action visually.

a) Realigning the Ictal SPECT with the Interictal SPECT

It is possible that the two SPECT images are not aligned, that is, the voxels of one do not correspond to the same area of the brain of the other, as we cannot guarantee that the patient will be placed in the exact same position in both acquisitions. Therefore, the first step will be to realign the SPECT images to ensure that a voxel [1,1,1] corresponds to the same anatomical region in the two images. The Realign (Estimate & Reslice) function allows you to align the ictal SPECT image with the interictal SPECT, taking the Interictal SPECT as the baseline.

b) Co-register the two SPECTs with the MRI

It is also necessary to correctly superpose the two SPECT images with the MRI image so that we can identify the functional information given by the SPECT images into the corresponding anatomical location, given by the MRI image.
In this case, the Co-register (Estimate & Reslice) function will be used, as you want to align images of different modes. The reference image will be the MRI, and the images to be corresponded with respect to the reference, the interictal SPECT and the previously realigned ictal SPECT (rICTAL).

Part II: Mask, Normalize, Subtract, and fuse

Note: For this second part, a Python code has been created with Virtual Studio Code User Interphase, and handling its implementation with a Version Control System, GitHub. The GitHub repository hosts the code, the images analysed and generated, and this report itself. Parallel visualization of the code is recommended for better understanding of Part II procedures. Furthermore, libraries specified at the beginning of the code must be correctly installed for proper execution, and tensorflow version 1.13.1 must be installed for correct functioning of the library deepbrain, as specified in the code [6].

In general terms, the aim of this part is to generate a brain mask, normalize SPECT images in intensity and subtract SPECT images in order to superpose the result with MRI and locate the anatomical structure corresponding to the EZ found. The procedure followed to achieve this is explained below:

a) Libraries and image loading and preliminary evaluation

The first step will be to import all the libraries: nibabel, os.path, numpy, nilearn, deepbrain, and matplotlib.pyplot packages. Subsequently, a function is

created so that, from an input that is the path where the image is located, it returns 5 outputs: the image, the matrix of the image, the dimensions of the matrix, the header of the image and the affine space. The functions provided by the nibabel package are used to obtain all mentioned data. The function is then used to obtain these 5 outputs for the 3 images resulting from part I pre-processing: the RM, the prINTERICTAL, and the pICTAL. A coordinate vector (x,y,z) is defined to plot the images in the same position as shown in Fig. 1. The images are plotted using the nilearn plotting functions plot_epi() and plot_anat().

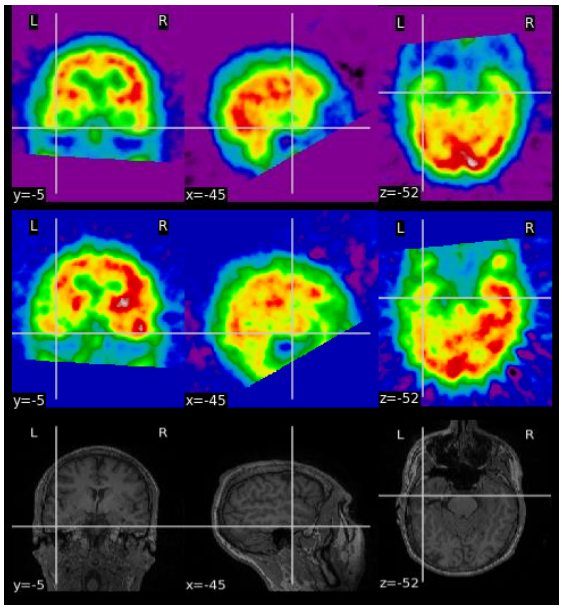

Figure 1: Interictal SPECT, Ictal SPECT and MRI from top to bottom

b) Brain mask implementation

A brain mask is performed in order to exclude the extracerebral voxels from the image, and therefore improve further analysis of the data only using our region of interest, which is the brain. The Extractor() function of the deepbrain package has been used, which contains brain imaging tools that use Deep Learning [7]. This feature extracts brain tissue from T1 MRI images of the brain, running a custom U-Net model trained with a variety of manually verified skull extraction datasets. The output it generates is a 3D array or "matrix of an image" that contains the probability of being brain tissue for each voxel of the image. Then we cast this voxels value over, for instance, 0.5, and generate a Boolean 3D array where the voxels that had a probability matching our criteria are True as of being part of the brain and False when they are not.

This mask is then used to generate an MRI image without the skull, just the brain tissue. In order to do this, a target null matrix is generated, and with an order three for loop we iterate for every voxel of the mask, and if its value is true, we introduce in the null matrix the value of the same index MRI matrix. This way we get only the brain anatomical tissue from the MRI image as shown in Fig. 2.

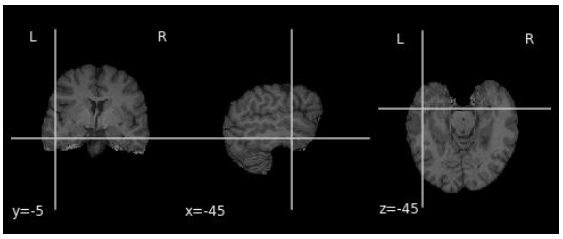

Figure 2: Brain MRI mask

Finally, we apply the mask to the data from the SPECTs to obtain the intensities corresponding only to the brain tissue.

c) Intensity normalization

In order to compare the SPECT brain images it is necessary to normalise their intensities. This is so because we do not know if the patient captured the radiation in the same way in both acquisitions and if the same amount of radiotracer was administered, as shown in Fig 3. Through correct normalisation we can guarantee that differences in intensity between images are due to physiological changes in blood perfusion and not in radiotracer

quantities, calibration, or acquisition variations from the equipment [8].

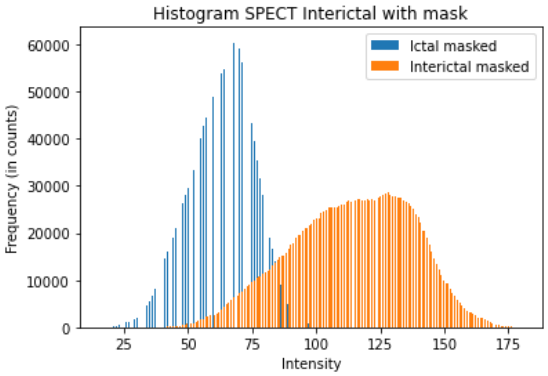

Figure 3: Ictal vs Interictal masked histograms

In this section of the code, we have compared the normalisation factor extracted firstly from dividing the total intensity of the Ictal image (~the total radiotracer quantity) by the total intensity of the Interictal image, in both scenarios: with and without the mask applied.
Secondly, as the two results, masked and unmasked, diverged from each other due to the influence of the EZ, the compute of the same quotient just with the extracerebral voxels was assessed. As the result also diverged from previous ones a more robust approach explained below was selected.

Although there are many different methods and algorithms for normalizing intensity, the conventional method refers to a brain region that is not affected in the ictal and interictal state. Given that for epilepsy this region is not a specific area, but depends on each case, and that SPECT images do not give anatomical information, it will be necessary to use normalization methods that consider the total area of the brain. On the other hand, since in the ictal image there will be the region of the epileptogenic focus with high intensity values, while in the interictal image this area with hyperperfusion will not be there, it would not be optimal to use algorithms that depend on the value of the average of the intensities of the images, as mentioned in the paragraph above.

In light of the above, the proposed solution is to normalise the images from the quotient of the intensity of higher frequency or prevalence in the images, which are visible in the Fig.3, as shown in Eq. 1 [8]. Applying this linear combination to each of the voxels of the transformed image (the normalised one) compacts the intensities of both histograms into the ones of the template histogram, as shown in Fig 4. This normalisation technique that has been widely used in Parkinson image normalisation presenting accurate and reliable results.

$$Ivoxel_{norm} = Ivoxel \frac{Ictal_{Intensity\ of\ higher\ frequency}}{Interictal_{Intensity\ of\ higher\ frequency}}$$

Equation 1: Intensity linear combination

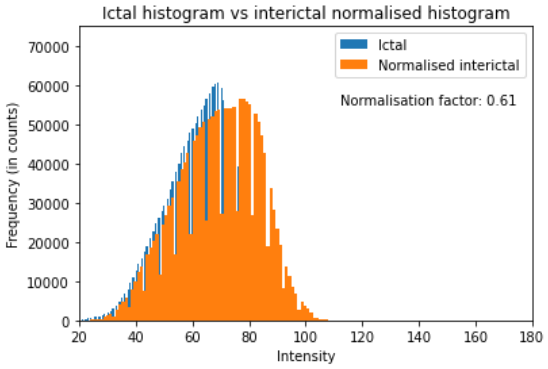

Figure 4: Histograms of normalised and template compared

Furthermore, this normalisation method is not dependant on professionals' skills to choose normalisation parameters nor in anatomical information of the non EZ brain areas, as it is variable in epilepsy and would not be an optimal approach.

d) Image difference

To make the image difference, we subtract the Interictal data image to the Ictal data image once the mask had been applied to both of them as well as the normalisation

factor. We save the image we generated and reload it as seen in Figure 5.

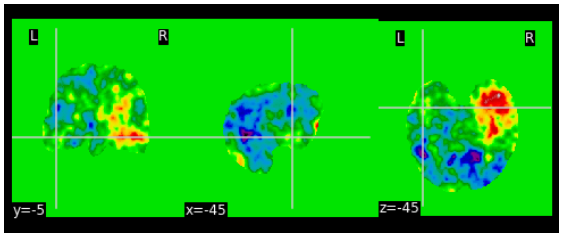

Figure 5: Image difference

e) Location of the epileptogenic zone

Not all difference image values obtained provide information for the ZE, and therefore a threshold should be applied to show only those significant voxels. This threshold is usually (for clinical purposes [9,10]) defined by 2 standard deviations above the mean difference image distribution.
Therefore, it is necessary to first calculate the mean and standard deviation of the difference image. The threshold is typically defined as the sum of the mean and two standard deviations. When this threshold is applied, we see that there is still a lot of residual noise in the image apart from a defined EZ. We increase the threshold to the mean plus 3.8 times the SD. The resulting focus image is saved, and the result is showed in Figure 6.

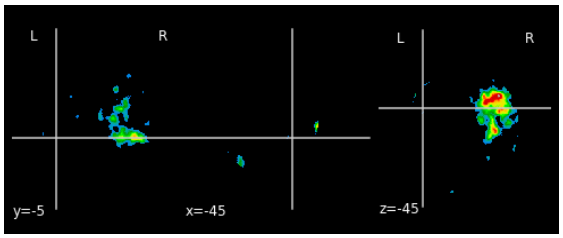

Figure 6: Image difference after threshold application

f) Focus fusion

Finally, the new matrix (focus) is fused to the masked MRI to anatomically locate the EZ. A plot is made with the plotting.plot_roi function of nilearn to show the result, shown in Figure 7.

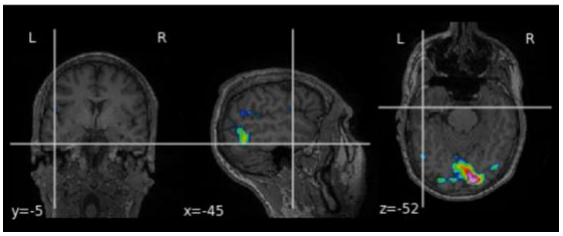

Figure 7: Final image. EZ shown in colour over MRI image.

RESULT

In light of the above, we have found the EZ for a patient with drug-resistant epilepsy, so that the surgical intervention can be correctly prepared to minimise time and associated risks. Even though the approach presents correct results, the pre operatory usefulness of the tool could be greatly improved with the implementation of already existing 3D representation software to further visualize the concrete area. It could be a future improvement of this project to implement such software into the code.

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