Automatic procedure to evaluate a method for epileptogenic zone localisation in drug-resistant epilepsy

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Abstract: The surgical resection of the epileptogenic zone is the indicated treatment in drug-resistant focal epilepsy. For this purpose, an accurate localisation of epileptogenic zone is crucial. A new method combining ictal SPECT and interictal PET is being validated. To this end, we simulated data, implemented the new methodology and validated it. Results show that the development of an automatic procedure to evaluate the presented method can be implemented.

I. INTRODUCTION

Epilepsy is an important disease in the world affecting 50 million people with 2.4 million cases being diagnosed annually [1]. In most patients antiepileptic drugs are beneficial to treat seizures. However, still millions (between 25%-30% of the cases) have drug-resistant epilepsy [2]. This type of epilepsy is known as focal epilepsy and it's generally caused by structural brain lesion. Surgery is the indicated treatment for the resection of the seizure onset zone in those cases [2].

Surgery intervention requires the exact determination of the epileptogenic zone (EZ) in the pre-surgical work-up [3]. Advances in neuroimaging have substantially improved the surgical treatment that we can claim that epilepsy surgery is successful in 70–80% of operated-on patients [4]. Several techniques are used for this purpose, the most relevant being Magnetic Resonance Imaging (MRI), Electroencephalography (EEG), Single Photon Emission Computed Tomography (SPECT) and Positron Emission Tomography (PET).

MRI is a non-invasive high resolution image that provides structural information of the brain. The identification of any type of epileptogenic lesion by MRI leads to a higher surgery success [4]. Unfortunately, in absence of an MRI lesion, epilepsy surgery outcomes are markedly reduced [5].

EEG is the common diagnostic tool for seizure localisation. It consists of electrodes that detect the neurons' ionic current. It is usually complemented with video recording to correlate patient's behaviour with the EEG's signals. EEG's lower sensitivity in respect of other neuroimaging techniques has led to a decrease in the use of invasive EEG [4]. Its spatial limitation means that many patients are not ultimately candidates for surgery [5].

Both SPECT and PET are nuclear medicine techniques consisting in the use of radiopharmatheutical tracers. Those tracers are bounded to a specific molecule, so that the radiotracer distribution follows the molecules behave [6]. On one hand, SPECT technique is based on the detection of gamma rays produced in the decay of the radioactive compound mentioned [6]. On the other hand, PET technique is based on the detection of pairs of gamma rays coming from the annihilation of the positron emitted by the nuclear decay of the radiotracer [6]. The detection involves effects of noise, attenuation, scattering and Point Spread Function (PSF) that need to be corrected. Given its nature, PET provides a better signal-to-noise ratio and a higher spatial resolution than SPECT images [3, 7].

SPECT and PET have risen to be promising tools in the presurgical evaluation of patients with focal epilepsy [2, 5, 7]. The former is unique to map brain perfusion during seizures (ictal state). It consists in ^{99m}Tc-hexamethylpropyleneamine oxime (^{99m}Tc-HMPAO) injection either in the ictal or interictal state (24h period free of seizures). Ictal SPECT shows the increase in regional cerebral perfusion flow in the seizure onset zone compared to interictal SPECT [3]. The latter consists in ^{18}F-fluorodeoxyglucose (^{18}F-FDG) injection in the interictal state and shows hypometabolic zones related to the functional deficit of the ictal onset zone [7].

Qualitative visual analysis of SPECT studies involves comparison of each cerebral region with its contralateral side or between ictal and interictal studies. However, visual comparison can be difficult, because ictal and interictal studies often vary significantly in intensity and image orientation, being observer dependent. As a consequence, several computer-aided methods have been developed to overcome these limitations.

Subtraction of Interictal SPECT from ictal SPECT Coregistered with MRI (SISCOM) is a methodology for the EZ localisation proposed by O'Brien et al. in 1998 [8]. This methodology combines SPECT functional information with the anatomical information that MRI provides. Functional information comes from a parametric image that reflects the differences in regional cerebral blood flow between ictal and interictal studies. O'Brien included the following steps: 1) SPECT-SPECT registration, 2) intensity normalisation, 3) subtraction and thresholding and 4) coregistration of the thresholded image to MRI [8]. Hospital Clínic of Barcelona developed a new software to implement SISCOM called FocusDET.

SISCOM has demonstrated to be a highly valuable

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diagnostic tool in localisation of the seizure-onset zone [3, 9]. However, the role of interictal SPECT has been relegated as a baseline study for ictal SPECT subtraction due to its lower sensitivity [3, 9]. On the other hand, PET studies could provide advantageous information not used in SISCOM analysis due to its better characteristics [3]. This pretext using PET studies in place of interictal SPECT images for SISCOM analysis. The new procedure is named PET Interictal Subtracted from ictal SPECT Coregistered with MRI (PISCOM) [3].

The European Association of Nuclear Medicine Neuroimaging Committee (ENC) provides guidelines for brain neurotransmission SPECT using ^{99m}Tc-HMPAO and PET using ^{18}F-FDG that include recommendations on reconstruction methods, filtering and applied data corrections [10, 11]. According to these guidelines, each centre chooses its own image processing conditions. In particular, it is of paramount importance to analize the influence of the reconstruction parameters on the localisation of the EZ. In this direction, the objectives of this work are:

- Implementation of a pipeline to automatize the processing and validation procedure allowing to vary and validate different parameters involved in the image analysis.
- Development of a validation process to objectively prove the PISCOM technique, without the need of nuclear medicine physician visual validation.

II. MATERIAL AND METHODS

A. Simulation and reconstruction

The determination of the best EZ localisation requires a gold standard that allows to evaluate the differences between the obtained and real localisation. Monte Carlo simulation allows to reproduce a variety of anatomical and tracer uptake cases. Thus, Monte Carlo simulation is used in image processing to generate realistic ^{99m}Tc-HMPAO and ^{18}F-FDG projections from known activity maps with a known EZ and its corresponding attenuation map. Since the ground truth is known, this strategy enables the development of a methodology to optimize reconstruction parameters.

To undergo PISCOM analysis, MRI, SPECT and PET images are needed. Firstly, MRI studies corresponding to 40 subjects free of cerebral abnormalities were selected. Then, these MRI studies were segmented into Grey Matter (GM), White Matter (WM) and Cerebrospinal Fluid (CSF) using Statistical Parametric Mapping (SPM) facilities.

To perform the simulation, activity maps, attenuation map and a theorical focus are needed. The activity maps (see Fig. 1) were obtained by assigning different intensity values to each tissue obtained empirically (GM=100; WM=25; CSF=4). To generate the attenuation maps, threshold segmentation is used to separate the computed tomography image into water and bone. Appropriate attenuation coefficients for bone (0.323 cm^{-1}) and brain (0.155 cm^{-1}) tissue are assigned (see Fig. 1). Nine theoretical focus were defined (with volumes from 8.6 to 10.4 cm^3) by a nuclear medicine physician expert in brain SPECT and PET analysis in the following regions: frontal cortex, occipital cortex, parietal cortex, temporal cortex, hippocampus and amygdala, hippocampus and parahippocampus, insular cortex and orbitofrontal cortex. One of them is shown in Fig. 1. Moreover, for each patient, two groups of focus levels were distinguished for SPECT: low level (ranging from 0 to 0.5) and high level (ranging from 0.5 to 1) in order to evaluate different degrees of hyperperfusion.

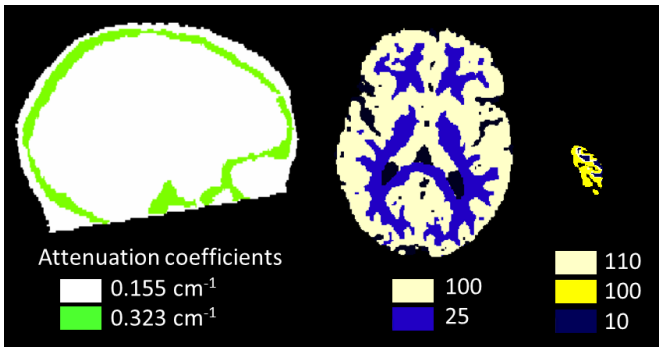

FIG. 1: Maps used in simulation. From left to right: saggital view of attenuation map, axial view of activity map and axial view of a theoretical focus.

Once having activity maps, attenuation maps and the theorical focus, ^{99m}Tc-HMPAO SPECT and ^{18}F-FDG PET projections were simulated by SimSET v2.9 Monte Carlo code considering the Hospital Clínic equipment characteristics. In PET simulation SimSET was configured to obtain sinograms with total counts of around 80 million. The equipment considered was a BGO-based Siemens Biograph scanner consisting in a cylindrical detector with 32 axial rings of 41.2 cm radius. A 3D-mode acquisition with no axial compression was simulated using an energy window of 350-650 keV. Sinogram dimensions were 288 transaxial bins (bin size = 2.2 mm) and 288 angular positions. Photons were separated into true and scatter coincidences, providing an ideal scatter correction. Attenuation map and activity map configured the background image, which was obtained as the interictal maps.

SPECT simulation was configured to generate emission projections from four to six million photons using InfiniaTM HawkeyeTM 4 from GE Healthcare scanner operating with a 35 mm long parallel collimator (hexagonal holes, radius: 0.75 mm, septal thickness: 0.2 mm). SPECT simulation was performed along 120 projections over 360º in a 128 × 54 matrix of 3.32 × 3.32 mm^2 pixel size. The simulation considered an energy window of 20%

centred at 140 keV. Ictal maps were generated from the background image and a theoretical focus.

Once having the projections, 3D images were gererated through Ordered Subset Expectation Maximization (OSEM) reconstruction algorithm. Regarding PET studies, it was used 12 iterations, 8 subsets, an energy window of 350 keV for minimun energy in scatter correction and a gaussian filter of 3.5 mm Full Width at Half Maximum (FWHM). On the other hand, for SPECT studies 10 iterations, 10 subsets and ictal attenuation map were used.

B. PISCOM analysis

The PISCOM method was performed following the same steps as SISCOM analysis but replacing the interictal SPECT image with a preprocessed interictal PET image. ^{18}F-FDG PET images were first degraded to assimilate features of ^{99m}Tc-HMPAO SPECT images as follows: (1) intensity normalisation was applied to ^{18}F-FDG PET images to correct for differences in the total number of photons detected, (2) ^{18}F-FDG PET images were resampled to match ictal SPECT's matrix and voxel size, and (3) ^{18}F-FDG PET images were filtered to achieve similar smoothing between the ictal SPECT and PET images.

To obtain filtered PET image with a degradation equivalent to that of SPECT studies it was assumed that the imaging system is linear. With that assumption, it can be written $f(x,y,z) = h(x',y',z') \otimes \rho(x',y',z')$, where $\otimes$ means convolution and $h(x',y',z')$ is the PSF that degrades the real radiotracer's distribution density $\rho(x',y',z')$ into the resulting image $f(x,y,z)$.

SPECT and PET equipment's PSF were experimentally mesured. Then a convolution between PET images and the inverse PSF of the PET adquisition system followed by a convolution with the SPECT's PSF was applied. Hence, the resulting filter applied was:

$$H_f(\omega) = \frac{H_{SPECT}(\omega)}{H_{PET}(\omega)} \quad (1)$$

Then, preprocessed PET was realigned to ictal SPECT with SPM by previously assigning image origin to its centre of mass. This step ensures PET-SPECT spatial corelation for later subtraction.

The images were then coregistered with patient's MRI, mapping activity images to its anatomical localisation. Firstly, an algoritm developed for coregister was applied on the interictal image and secondly, those transformations were applied on the ictal image. That way, funcional images kept their realignment.

MRI was masked to remove non-brain area. After that, the subtraction image of interictal image from the ictal image was computed for every voxel in the masked MRI following Eq. 2.

$$subtraction[i,j,k] = \frac{SPECT[i,j,k] - PET[i,j,k]}{PET[i,j,k]} \quad (2)$$

where i,j,k are the coordinates of PET, SPECT and subtraction images. Only positive subtraction and $PET[i,j,k] \neq 0$ cases were considered.

Finally, a threshold of two Standard Deviation (SD) over the mean value was applied to the subtraction image. This results in a focus extraction from the subtraction image that is also coregistered with MRI.

All PISCOM analysis was integrated in a Python pipeline using different Python's libraries and external code calls. This way, the script integrated multiple processing platforms in a single automatic procedure that can be replicated anywhere.

C. Validation

Since the theoretical focus prior to simulation is known, an objective PISCOM validation process can be implemented. A Python script compares the fusion image from the PISCOM method with the known theoretical focus. The script binarizes the images and iterates over all voxels. It identifies the region and volume where both image's values are 1 or whether fusion or theoretical focus images are 0. That way, every coincidence case is contemplated. It is important to note that the fusion image from PISCOM analysis will consider a particular region to be true positive even when another region in the same scan is false positive; that is why it is crucial to take all options into consideration.

III. RESULTS

A. Simulation and reconstruction

Simulation and reconstruction processes were performed in a computer cluster. The computational time needed to simulate and compute projection was 3.58 hours for PET studies, whereas the same tasks for SPECT was 24.21 hours. The capacity required was 1.36 MB for simulation, 9.45 GB for projection and 8.3 MB for reconstruction, meaning 9.5 GB used per pacient. Outputs from simulated and reconstructed maps are shown in Figs. 2 and 3 respectively.

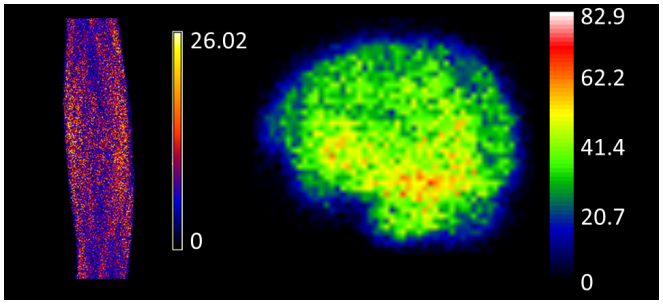

FIG. 2: Simulated results. From left to right: PET axial sinogram and a SPECT projection.

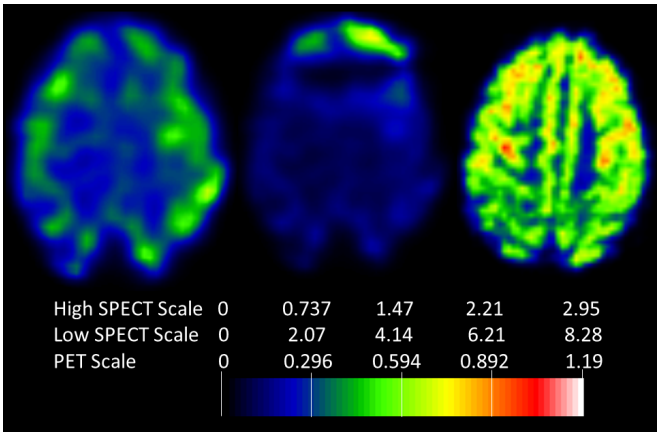

FIG. 3: Axial section of reconstructed images. From left to right: high and low level ictal SPECT and interictal PET studies. Same slice in axial view is shown in Fig. 3 to 6.

B. PISCOM analysis

During PISCOM analysis various images were obtained: the preprocessed PET, the realigned preprocessed PET (Fig. 4B), the ictal SPECT coregistered, the realigned preprocessed PET coregistered and the subtraction image coregistered (Fig. 5A). The final output image from PISCOM method was the fusion image, which is the two SD thresholded subtraction image coregistered to MRI (Fig. 5B).

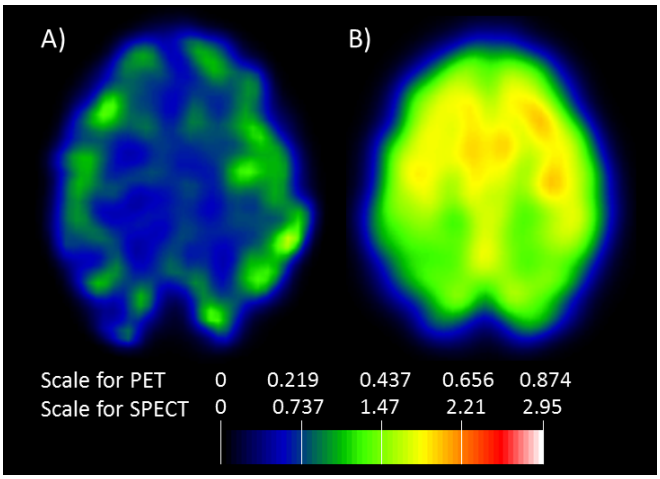

FIG. 4: Axial view of realigned emission images used in PISCOM analysis. Ictal SPECT level high (A) and preprocessed PET (B).

C. Validation

The validation script extracted the number and coordinates of coincident and non-coincident voxels as well as the resulting images. It considered all types of regions: where both are coincident, where only fusion image coincides and where only theoretical focus coincides. Finally, results were summarized in 3 items: volume coincident, % coincident and % non-coincident. Volume coincident refers to the coincident volume between fusion image and theoretical focus. The percentual value coincident is refered to the whole theorical focus volume. The percentual value non-coincident refers to the fusion image percentual volume that isn't explained by the theoretical focus. Fig. 6 shows coregistered fusion image together with the theoretical focus, whereas Tab. I shows some of the results.

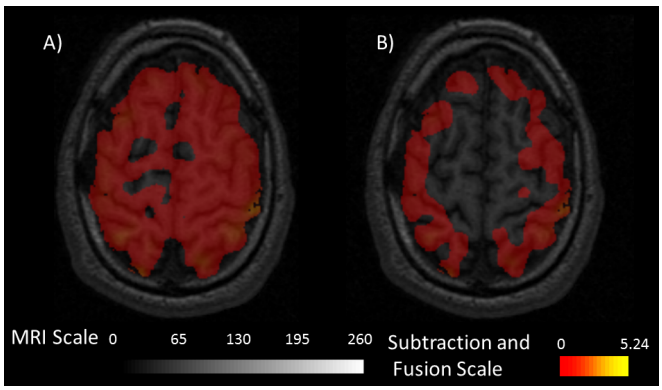

FIG. 5: Axial view for high level subtraction image (A) and fusion image (B) coregisted with MRI.

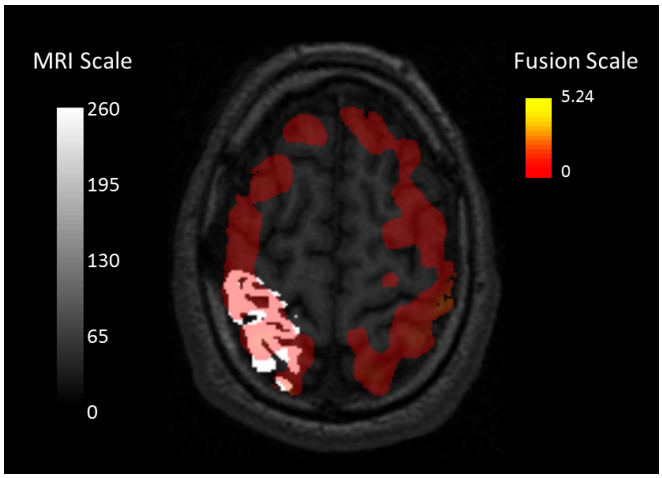

FIG. 6: Axial section of the fusion image from PISCOM analysis and the theoretical focus coregistered with MRI.

IV. DISCUSSION AND CONCLUSIONS

The results of PISCOM analysis (Table I) showed some (2) patients with fairly good (above 70%) of the theoretical focus explaining the fusion image in contrast with 4 patients presenting poor percentage of the theoretical focus explaining the fusion image. Nonetheless, all patients

TABLE I: Coinciding values between fusion image and theoretical focus for some of the patients and for each modality.

Patient	Volume coincident	% coincident	% non-coincident
03 Low	7.1 cm^3	71.21%	98.37%
03 High	7.1 cm^3	71.21%	98.37%
04 Low	5.3 cm^3	70.56%	98.73%
04 High	5.5 cm^3	72.60%	98.72%
05 Low	1.5 cm^3	12.12%	99.63%
05 High	1.6 cm^3	12.34%	99.62%
12 Low	0.0 cm^3	0.00%	100.00%
12 High	0.0 cm^3	0.00%	100.00%
21 Low	1.6 cm^3	22.98%	99.64%
21 High	1.6 cm^3	22.98%	99.64%
36 Low	0.6 cm^3	6.14%	99.87%
36 High	0.6 cm^3	6.14%	99.87%

had a large amount of volume that indicated false positives zones (above 98 % of fusion image volume). Lastly, no big differences were observed between high and low level's SPECT.

The goal of neuroimaging studies in epilepsy is the localisation of a single EZ objectively and unambiguously for epilepsy surgery. The majority epilepsy neuroimaging studies are visually analyzed [2], also taking into account retrospective nature studies. This has many drawbacks, the most dodgy being the neurologist subjectivity but also the lack of quantitative assessment, among others [2]. This complicates the development of a validated image processing method for EZ localisation. However, the present work demonstrates that an objective simulation-based method can be achieved in order to prove whether image processing techinques lead to a successful EZ localisation.

V. FURTHER WORK

The present work lead to a further study to complete the validation of the PISCOM method. For this reason, a larger database of patients and reconstruction parameters variations is needed. Our proposals are:

1. To validate the impact of the reconstruction parameters. For the moment, OSEM with a single set of iterations and subsets was used. In the future we would like to study how these values can affect the EZ localisation in PISCOM.

2. To improve the obtained filter for PET preprocessing. Despite in this work the PSF was obtained experimentally, the aim is to have a simulated PSF.
3. To verify the influence of the z-score used in fusion threshold as it directly affects the output volume pointed.

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