Multimodal Imaging Techniques in Epilepsy: A SISCOM-Based Approach

Medical Applications of Engineering I – Practical Session 7

Marc Biosca, December 2024

Introduction

- **Epilepsy affects 70 million people globally**, with one-third developing drug-resistant epilepsy (DRE). For these patients, surgery is the best chance for a cure, requiring precise epileptogenic zone (EZ) identification [1].
- **Limitations of Structural MRI**: Often fails to localize the EZ when no visible lesions exist.
- **Functional Imaging**:
  - **PET**: Detects hypometabolism during the interictal period.
  - **SPECT**: Identifies hyperperfusion using **99mTc-HMPAO**, which binds to areas of increased perfusion and remains localized post-seizure.
- **SISCOM Method**: Combines **ictal and interictal SPECT with MRI** to highlight hyperperfusion areas, proving highly valuable for pre-surgical evaluations [2], especially when other methods are inconclusive.
- **Objective**: This project uses SISCOM through three normalization methods to precisely localize the EZ in a single subject using MRI, ictal, and interictal SPECT.

Methods

1. SPECT Realignment and Co-Registration: The first step in the SISCOM methodology involved realigning the interictal SPECT to match the ictal SPECT. Both images were then co-registered to the MRI space, ensuring alignment in the same spatial reference. These steps were completed using the *SPM12* toolbox in MATLAB, with the results shown in Figure 1.

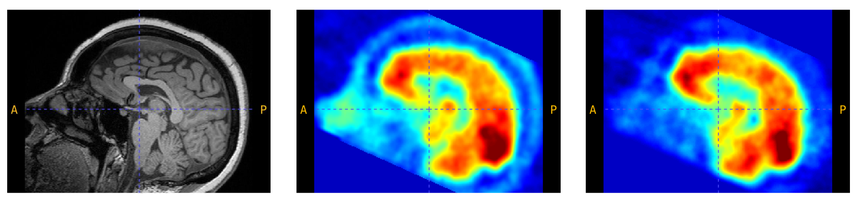

Figure 1. Sagittal cuts of the MRI (left), interictal SPECT (middle) and ictal SPECT (right), realigned and co-registered to the subject's MRI space.

2. Brain Mask using MRI: Before subtraction, a brain mask is applied to reduce SPECT background noise. Generated using FSL's *BET* (Brain Extraction Tool), the mask extracts brain regions from MRI data and sets background intensity to zero, ensuring only brain tissue is analyzed, as seen in Figure 2.

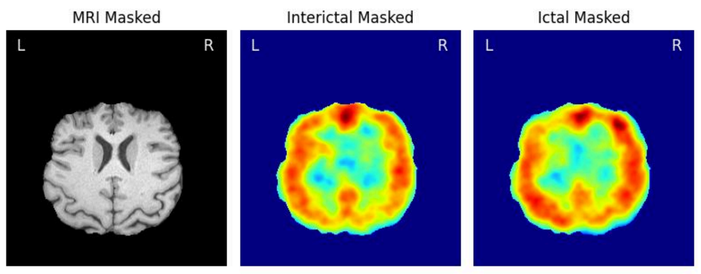

Figure 2. Axial cuts of the MRI, Interictal SPECT, and Ictal SPECT images after masking, all registered to the same spatial reference. Background noise has been reduced to focus on relevant brain regions.

3. Normalization: It ensures the ictal and interictal images are on a similar intensity scale, enabling accurate comparison and subtraction. The methods account for SPECT's Poisson noise by addressing intensity variability and reducing background noise with the mask. These are common methods:

- **Global Intensity Normalization:** Scales pixel values using the mean to adjust for overall intensity variations [2,3]. **Assumes the mean is reliable** but may fail with focal abnormalities or outliers. It is widely used in literature.
- **Z-Score Normalization:** Standardizes voxel intensities to a mean of 0 and standard deviation of 1, highlighting significant deviations. **Assumes a normal distribution**, which may cause misinterpretation for skewed data.
- **Median Scaling:** Divides intensities by the median, **robust to outliers** and skewed distributions. However, it **may not capture global intensity variations** like mean-based methods.

$$X_{mean} = 100 \cdot \frac{x}{\mu} \qquad X_z = \frac{x - \mu}{\sigma} \qquad X_{median} = 100 \cdot \frac{x}{M}$$

- **Other Methods:** Min-Max normalization was discarded due to its high sensitivity to outliers, while reference zone normalization was excluded as defining a consistent pathology-free region can be challenging.

4. Subtraction: In this step, the interictal SPECT is subtracted voxel by voxel from the ictal SPECT, highlighting areas of increased perfusion and the seizure focus. Values corresponding to zero (background) were excluded to ensure only relevant brain regions were analyzed. A threshold of 2.5 standard deviations, a restrictive value commonly used in the literature [4], was applied to display significant positive differences. Refer to the additional material for the *Python* code.

5. Superposition with MRI and Atlas-Based Localization: The identified seizure focus was superposed onto the patient's MRI to enhance anatomical precision. Localization was then performed using the Harvard-Oxford cortical atlas from FSL libraries, which was registered to the subject's image space using FSL's *FLIRT* and *convert_xfm* for linear registration, ensuring accurate alignment and mapping. This is illustrated in Figure 3.

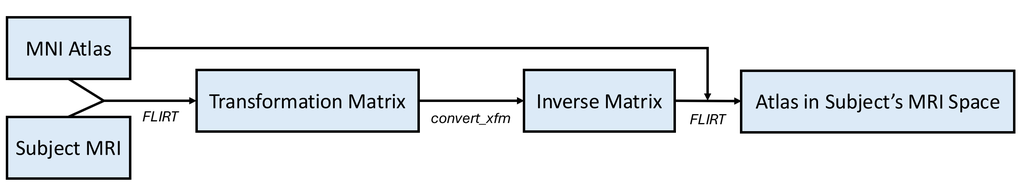

Figure 3. Diagram of the transformation of the atlas from MNI space to the subject's MRI space using FSL tools

Results

Figure 4 shows the histograms of the SPECT images before and after normalization. Normalization aligns intensity scales for comparison; however, histogram differences still exist as the ictal image reflects hyperperfusion from seizure activity, and the interictal image shows baseline perfusion.

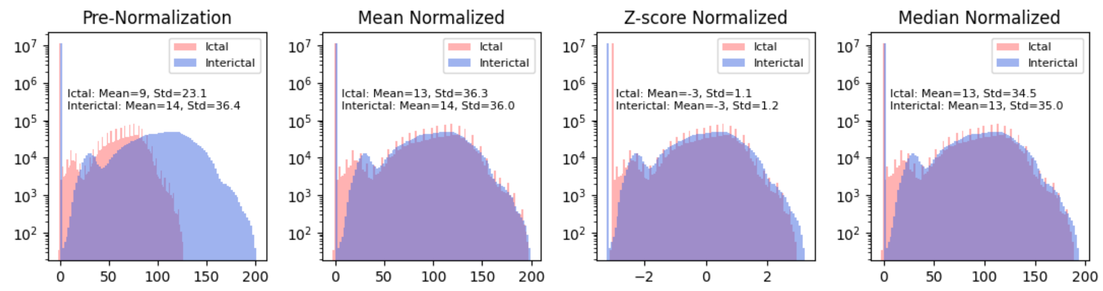

Figure 4. Histograms of voxel intensities for both ictal and interictal images, displayed before normalization and after applying the three normalization methods: mean, z-score, and median normalization. Refer to additional material for more details.

For each of the methods, the normalized ictal and interictal SPECT images were subtracted to highlight regions of increased perfusion. A **threshold of 2.5 standard deviations** was applied to isolate significant differences, reducing noise and focusing on areas linked to seizure activity. These thresholded images were then superposed onto the MRI to provide precise anatomical localization of the hyperperfused regions. The results are presented in Figures 5, 6 and 7.

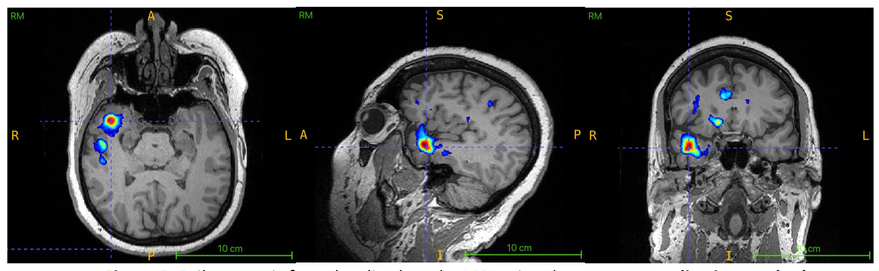

Figure 5. Epileptogenic focus localized on the MRI using the **mean normalization method**.

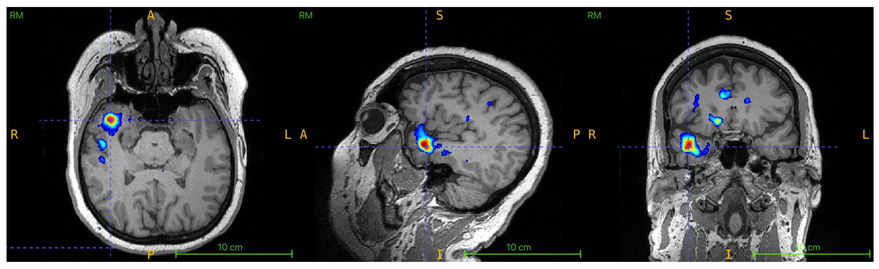

Figure 6. Epileptogenic focus localized on the MRI using the **Z-score normalization method**.

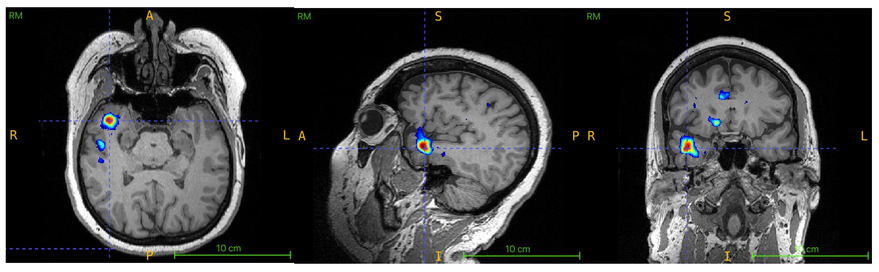

Figure 7. Epileptogenic focus localized on the MRI using the **median normalization method**.

All methods identified the same primary focus, confirming consistency in localization. However, they all also revealed a secondary, smaller focus in white matter, which is not visible in the Figures 5, 6 and 7 and is likely noise. Additionally, lesser intense points passing the threshold were observed, which may also represent **residual noise**. Among the methods, all produced similar results; however, mean and Z-score normalization exhibited more noise compared to the median method. The median normalization provided a more defined and cleaner focus, likely due to its robustness against outliers and noise.

The next step involved anatomically localizing the identified focus. For this purpose, the Harvard-Oxford Cortical Atlas was used. Figure 8 illustrates the focal point identified using the median method overlaid on the atlas, revealing its localization in the **right temporal pole region**.

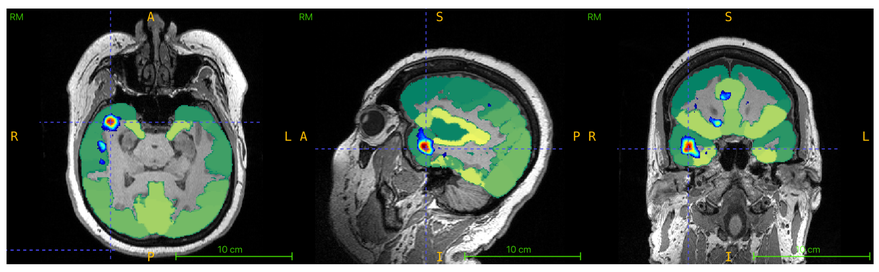

Figure 8. Localization of the epileptogenic focus on the MRI using the median normalization method, overlaid with the Harvard-Oxford cortical atlas in the subject's MRI space. The focus is identified in the right temporal pole region.

Conclusions

- **Robust Focus Identification**: All normalization methods identified the **same primary focus**, indicating their robustness. However, the **median method produced the cleanest** and most well-defined image.
- **Limitations**: This analysis was conducted on a single case, so results may vary across cases. Incorporating ground truth would be crucial for more definitive validation.
- **Importance of Normalization**: Normalization is a key step in this pipeline, as different methods can introduce varying levels of noise. Implementing **noise reduction techniques** or improved preprocessing, such as smoothing filters, could further enhance accuracy.
- **Effectiveness of SISCOM**: Despite its simplicity, SISCOM is a **powerful tool** for localizing the epileptogenic focus, providing crucial information to improve the precision of surgical planning [5, 6].

References

[1] Löscher, W., Potschka, H., Sisodiya, S. M., & Vezzani, A. (2020). Drug Resistance in Epilepsy: Clinical Impact, Potential Mechanisms, and New Innovative Treatment Options. *Pharmacological reviews*, *72*(3), 606–638.
[2] O'Brien, T. J., So, E. L., Mullan, B. P., Hauser, M. F., ... Sharbrough, F. W. (1998). Subtraction ictal SPECT co-registered to MRI improves clinical usefulness of SPECT in localizing the surgical seizure focus. *Neurology*, *50*(2), 445–454.
[3] O'Brien, T. J., So, E. L., Cascino, G. D., Hauser, M. F et. (2004). Subtraction SPECT coregistered to MRI in focal malformations of cortical development: localization of the epileptogenic zone in epilepsy surgery candidates. *Epilepsia*, *45*(4), 367–376.
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Contact

Marc Biosca Marron, Biomedical Engineering Student at University of Barcelona
mbioscma7@alumnes.ub.edu - www.linkedin.com/in/m-biosca

Additional Material (Python code and resultant Images):

https://github.com/mbioscma/P7_Epilepsy_MarcBiosca