Evaluation of Registration of Ictal SPECT/MRI Data Using Statistical Similarity Methods

Christophe Grova[1,2], Pierre Jannin[2], Irène Buvat[3], Habib Benali[3], and Bernard Gibaud[2]

[1] Montreal Neurological Institute, McGill University, Montreal
{christophe.grova}@mail.mcgill.ca
[2] Laboratoire IDM, Faculté de Médecine, Université de Rennes 1, France
{pierre.jannin,bernard.gibaud}@univ-rennes1.fr,
http://idm.univ-rennes1.fr
[3] INSERM U494, CHU Pitié Salpétrière, Paris
{irene.buvat,habib.benali}@imed.jussieu.fr

Abstract. In this study, we evaluated SPECT/MRI registration of ictal data, using similarity based registration methods. An absolute gold standard for registration evaluation was obtained by considering realistic normal and ictal SPECT simulations deduced from a high resolution T1-weighted MRI data set.
Those simulations were also used to study the impact of photon attenuation and Compton scatter corrections on registration accuracy. Evaluation of registration was also performed using inconsistency measurements for six patients with temporo-mesial epilepsy. For these data, as no Gold Standard was available, registration accuracy was assessed using inconsistency measurements involving a registration loop between inter-ictal SPECT, ictal SPECT and MRI data. Five registration methods based on statistical similarity measurements were compared, namely: mutual information (MI), normalized mutual information (NMI), L1 and L2 norm-based correlation ratios (CR) and correlation coefficient (CC). It was found that the simulation context had more influence on registration accuracy than the choice of the similarity criterion. Ictal SPECT as well as correction for uniform attenuation clearly decreased SPECT/MRI registration accuracy.

1 Introduction

Evaluation of SPECT/MRI registration methods is a difficult problem, especially when dealing with pathological data, such as ictal SPECT reflecting extreme perfusion changes occurring during an epileptic seizure. As ictal SPECT is currently the only imaging technique available to explore the ictal state in epilepsy with high sensitivity, achieving accurate registration with the anatomical MRI provides valuable information during the presurgical investigation. The purpose of this study is to perform a quantitative evaluation of SPECT/MRI statistical similarity-based registration methods, especially when dealing with ictal SPECT. Ictal SPECT usually shows large hyperperfusion that is likely

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to occur during a seizure, whereas the anatomical MRI is generally considered as normal. Such situation creates intrinsic dissimilarities between SPECT and MRI data, that may affect registration methods based on statistical similarity measurements.

Quantitative evaluation of a registration method requires a reference geometrical transformation. When it refers to a ground truth, this reference transformation is called a Gold Standard. Although skin fiducial markers were used in some studies [1], the studies evaluating registration involving SPECT data generally lack any accurate gold standard. Evaluation on real data generally uses the result of one or several other registration methods as the reference transformation (e.g., [2]). Absolute gold standard may be obtained using physical phantom [3] or numerical simulations [2,4] of SPECT data. The effect of the dissimilarities introduced by ictal SPECT on registration accuracy has only been studied in the case of SPECT/SPECT registration [3]. The behaviour of registration methods in the presence of hypoperfused pathological areas has been studied under controlled conditions using numerical simulations [2,4]. When using numerical simulations, attention must be paid to the realism of the simulations, and validation bias may be introduced by the simulation method itself.

In the present study, we further investigate a validation methodology we first proposed in [5]. Attention was paid to a standardized description of our validation procedure [6]. Our registration evaluation method consisted in using realistic simulations of SPECT data, obtained from an anatomical MRI. We improved the accuracy of the perfusion model for SPECT simulations, using measurements performed on real data [7]. Pathological simulations mimicking ictal perfusion in temporal lobe epilepsy were added to normal SPECT simulations. Moreover, the simulations were used to assess the effect of attenuation and Compton scatter corrections on registration accuracy. Finally, our results were compared to those obtained on real data by measuring inconsistencies between the registrations of MRI, inter-ictal SPECT and ictal SPECT data of six subjects.

2 Material and Methods

2.1 Statistical Similarity-Based Registration Methods

We considered SPECT/MRI registration as rigid intra-patient registration. The purpose is to assess a rigid geometric T transformation defined by six parameters (three translations and three rotations). Let the reference image R be our SPECT data set and the floating image F our MRI data set. Statistical similarity-based registration methods assume that a similarity measurement $S(R, T(F))$ is optimal when the data sets are perfectly registered. Let us call f the theoretical function that relates intensities of both images, if it exists.

A first class of criteria are obtained by searching the optimal distance measurement on intensity values, given an *a priori* on the nature of f. The correlation coefficient (CC) is thus obtained under the assumption that f is linear. Assuming that there is a functional dependence between R and $T(F)$, without any assumption regarding the nature of f, Roche *et al.* [8] proposed to use

the correlation ratio (CR). Two implementations of CR were studied here using the L1 and L2 norms as metrics in the intensity space. A second class of criteria assess similarity taking into account only information provided by intensity distributions of both images. Relying on entropy measurements, Mutual Information (MI)[9] measures a statistical dependence, making no assumptions regarding the nature of this dependence. Normalized Mutual Information (NMI) [10] is moreover invariant to the region overlapping between the two data sets.

Registration method implementation: All the similarity criteria were maximized according to the rigid transformation T, using Powell's multidimensional direction set method. $\hat{T}$ will denote the result of a registration method. 256-bin histograms and partial volume interpolation [9] were used to compute these similarity criteria. A two-level multiresolution strategy as described by [9] was applied to avoid the pitfall of local optima.

2.2 Validation Procedure

Characterization of the validation objective: We wanted to study the impact of ictal condition on SPECT/MRI registration. This study was performed in a fully controlled environment using simulated normal and ictal SPECT data as well as with real data for which no gold standard was available. The second objective of this study was to assess the impact of attenuation and scatter correction methods on registration accuracy.

Validation data sets: Validation data sets consisted of SPECT simulations generated from one MRI data set. The method to produce realistic SPECT simulations from MRI data was described in [7]. Simulations of SPECT data required an activity map representing the 3D spatial distribution of the radiotracer (^{99m}Tc-HMPAO) and the associated attenuation map describing the attenuation properties of the body. Monte Carlo simulations were used to model the response of a SPECT imaging system. Whereas Monte Carlo techniques are widely recognized to accurately model SPECT data [11], particular attention was paid to the realism of activity maps.

Generation of theoretical perfusion models: Theoretical normal and ictal perfusion models, i.e., activity maps, were deduced from measurements performed on anatomically standardized SPECT data. To perform perfusion measurements, we used Volumes of Interest (VOIs) deduced from an anatomically labelled T1-weighted MRI, Zubal phantom [12] (124 axial slices, matrix: 256×256, voxel size: $1.1 \times 1.1 \times 1.4\ mm^3$). A theoretical map of photon attenuation coefficients was defined by assigning to each VOI a tissue type and an attenuation coefficient μ at $140keV$ for ^{99m}Tc. To define activity maps, an average model of normal perfusion was derived from the analysis of 27 normal SPECT data. Similarly, an average model of ictal perfusion was created from the analysis of 10 ictal SPECT data from patients showing a mesio-temporal epilepsy pattern. Several correction methods were taken into account to derive realistic activity values in the different compartments of our perfusion models. Assuming uniform attenuation

in the head, first order Chang attenuation correction was performed. Scatter correction was only performed for the healthy subjects using the Jaszczak method. To derive a perfusion model as accurate as possible, perfusion measurements were corrected for partial volume effect (see [7] for a detailed description).

Monte Carlo SPECT simulations: Using attenuation and ^{99m}Tc-HMPAO activity maps, Monte Carlo simulations were performed using SimSET[1] [13]. Sixty-four projections over 360° (matrix: 128×128, pixel size: $4.51mm$) were simulated using a 20% energy window centred on 140 keV (126 - 154 keV) and a (111 - 125 keV) Compton window. All SPECT projections were then reconstructed by filtered backprojection using a ramp filter (Nyquist frequency cutoff) followed by 3D Gaussian filtering ($FWHM = 8mm$), leading to a spatial resolution of $FWHM = 12.2mm$ (see Figure 1). To assess the impact of several correction methods on registration accuracy, uniform attenuation correction (AC) and/or Jaszczak scatter correction (SC) methods were used. All simulated data will be referred to using a "simulation context" name (see Table 1).

Table 1. Simulation contexts explored by SPECT/MRI registration evaluation. Attenuation correction refers to first order Chang uniform correction, and scatter correction refers to Jaszczak window subtraction method.

Simulation context	Perfusion model	Correction methods
Normal none	average normal	none
Normal AC	average normal	attenuation correction
Normal SC	average normal	scatter correction
Normal SAC	average normal	attenuation + scatter correction
Ictal none	average ictal	none
Ictal AC	average ictal	attenuation correction
Ictal SC	average ictal	scatter correction
Ictal SAC	average ictal	attenuation + scatter correction

Clinical data for inconsistency measurements: Inconsistency measurements make it possible to study registration performance without any Gold Standard, when more than two data sets are available for each subject [2]. Among the 10 patients with mesio-temporal epilepsy, six subjects were selected, for whom inter-ictal and ictal SPECT, and anatomical MRI were available. Sampling rate, image dimensions and spatial resolution were similar to those used on simulated data.

Reference geometrical transformation:

Estimation of registration absolute errors: Simulated SPECT data being perfectly aligned with the MRI of Zubal phantom, our methodology provided us with an absolute Gold Standard for registration evaluation. $N_t = 50$ theoretical transformations T^* were generated by randomly sampling a 6 parameter vector

[1] Simulation System for Emission Tomography (SimSET) software package: http://depts.washington.edu/∼simset/html/simset_main.html

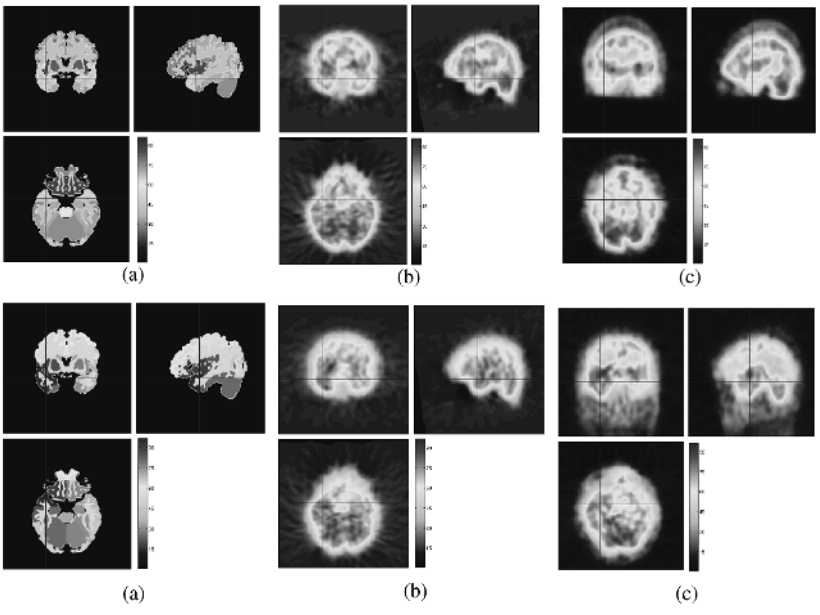

Fig. 1. Theoretical average perfusion model (a), corresponding SPECT simulation (b), and an example of a real SPECT data (c) for normal perfusion (top) and for ictal perfusion characteristic of mesio-temporal lobe epilepsy (bottom).

using a Gaussian distribution (Mean = 0, Standard Deviation = 10 mm or ^{o}). T^* was then applied to the MRI data and new unregistered MRIs were thus created using trilinear interpolation. Registrations were then sequentially performed using each pair of simulated SPECT and unregistered MRI. Let us call $\hat{T}$ the resulting computed geometric transformation.

Estimation of registration inconsistencies: As no Gold Standard was available for clinical data, registration loops allowed us to measure registration inconsistency (see for instance [2]). We assumed that inter-ictal SPECT $\rightarrow$ MRI transformation ($\hat{T}_{12}$) followed by MRI $\rightarrow$ ictal SPECT transformation ($\hat{T}_{23}$) should lead to the same transformation as the one provided by direct inter-ictal SPECT $\rightarrow$ ictal SPECT registration ($\hat{T}_{13}$). Those three registrations were performed using each method, on each of $N_t = 6$ subjects, and on SPECT data being corrected or not from uniform attenuation.

Validation criteria: Spatial registration errors or inconsistencies were estimated on $N_p = 1600$ points $\mathbf{x}_i$ uniformly distributed within the brain. For each registration test j, for each validation data set (cf. Table 1), and for each point $\mathbf{x}_i$ sampled within the brain, a local target registration error (TRE_{ij}) or a local inconsistency (INC_{ij}) was estimated as follows:

$$TRE_{ij} = \left\| \mathbf{x}_i - \hat{T}_j^{-1}\left(T_j^*(\mathbf{x}_i)\right) \right\| \text{ or } INC_{ij} = \left\| \hat{T}_{13}^j(\mathbf{x}_i) - \hat{T}_{23}^j\left(\hat{T}_{12}^j(\mathbf{x}_i)\right) \right\| \quad (1)$$

Table 2. Validation criteria characterizing distributions of registration RMS_j ($Mean$, σ and $Q90$ in mm) for each similarity criterion. Top: SPECT/MRI registration in each simulation context (50 registrations tested in each case). Bottom : Inconsistencies measurement on clinical data using SPECT data with (AC) and without (none) attenuation correction (6 subjects). In each context, most accurate results are in bold.

	SPECT/MRI registration errors									
	MI		NMI		CRL2		CRL1		CC	
Context	$Mean(\sigma)$	$Q90$	$Mean(\sigma)$	$Q90$	$Mean(\sigma)$	$Q90$	$Mean(\sigma)$	$Q90$	$Mean(\sigma)$	$Q90$
Normal none	2.71 (0.166)	2.90	2.72 (0.196)	2.95	**2.45** (0.221)	2.67	2.59 (0.251)	2.89	2.96 (0.229)	3.21
Normal SC	2.74 (0.180)	2.97	2.76 (0.158)	2.97	**2.38** (0.205)	2.59	2.52 (0.219)	2.71	2.65 (0.287)	3.06
Normal AC	3.10 (0.184)	3.28	3.10 (0.204)	3.33	2.98 (0.236)	3.28	**2.95** (0.233)	3.20	3.36 (0.249)	3.67
Normal SAC	3.19 (0.176)	3.46	3.13 (0.210)	3.42	**2.84** (0.199)	3.12	2.98 (0.215)	3.19	3.10 (0.229)	3.33
Ictal none	3.55 (0.189)	3.79	3.55 (0.229)	3.90	3.32 (0.177)	3.53	**3.29** (0.245)	3.51	4.06 (0.304)	4.50
Ictal SC	3.54 (0.235)	3.82	3.55 (0.182)	3.75	**3.22** (0.248)	3.50	3.37 (0.218)	3.55	3.59 (0.237)	3.85
Ictal AC	4.15 (0.212)	4.39	4.17 (0.197)	4.36	**4.05** (0.173)	4.27	4.09 (0.219)	4.29	4.57 (0.244)	4.80
Ictal SAC	4.11 (0.196)	4.30	4.13 (0.180)	4.32	**3.94** (0.157)	4.13	4.10 (0.227)	4.36	4.30 (0.168)	4.52
Correction	Registration inconsistencies on clinical data									
none	9.00 (3.68)	12.6	10.19 (4.55)	14.8	**7.21** (4.65)	11.7	8.03 (2.39)	10.1	11.12 (7.74)	17.6
AC	10.04 (5.33)	16.3	9.35 (5.14)	15.4	7.88 (4.51)	13.1	**7.67** (5.65)	14.8	11.87 (6.25)	17.4

with $i \in < 1, N_p >$ and $j \in < 1, N_t >$. $\| \ \|$ denotes the Euclidian norm in mm. To characterize the spatial distribution of TRE_{ij} or INC_{ij} within the brain, we estimated the root mean square (RMS_j) value of the local errors or local inconsistencies distribution:

$$RMS_j = \sqrt{\frac{1}{N_p}\sum_{i=1}^{N_p} TRE_{ij}^2} \quad \text{or} \quad RMS_j = \sqrt{\frac{1}{N_p}\sum_{i=1}^{N_p} INC_{ij}^2} \tag{2}$$

The validation criteria of a registration method were finally defined as global characteristics of registration errors or inconsistencies over the N_t registrations tested. Empirical mean ($Mean$) and the 90^{th} quantile ($Q90$) of the RMS_j errors were computed to estimate registration accuracy, and standard deviation (σ) of the RMS_j errors was used to assess registration precision.

3 Results

3.1 Simulated SPECT/MRI Registration Errors

Distribution of registration errors RMS_j are summarized on Table 2. All statistical similarity-based registration methods were proved to be very accurate as all mean RMS errors were significantly lower than the SPECT voxel size of 4.51 mm (Student t-test, $pvalue < 0.001$). For each similarity criterion, analysis of variance proved a highly significant effect of the simulation context on registration accuracy (F-test: $pvalue < 0.001$ and adjusted determination coefficient $R^2_{ajust} > 0.86$). Registrations using normal SPECT simulations were more accurate than those involving ictal SPECT simulations, suggesting an effect of the pathology on registration accuracy. Moreover, attenuation correction seemed to decrease registration accuracy, whereas scatter correction slightly improved registration accuracy. Results showed that the effect of the registration method on

accuracy is quantitatively lower than the effect of the simulation context, even if L1 and L2 norm-based correlation ratios (CRL1 and CRL2) were slightly more accurate than the other criteria for each context.

3.2 Registration Inconsistencies on Real Data

Inconsistency measurements are summarized on Table 2. Even if registration seems less accurate than when considering SPECT simulations, inconsistencies RMS_j were most often lower than the SPECT spatial resolution of 12.2 mm. Nevertheless, for non corrected data, few registrations failed and were excluded from the analysis (i.e., $RMS_j > 2 \times 12.2\ mm$): 2 subjects for CRL2, 1 for CRL1 and 3 for CC. CRL1 and CRL2 seemed to be the most accurate methods, whereas no effect of attenuation correction on registration accuracy was observed.

4 Discussion and Conclusion

Our results suggest that statistical similarity-based registration methods may achieve SPECT subvoxel accuracy in SPECT/MRI registration. We used realistic SPECT simulations to study the impact of ictal data, as well as attenuation and scatter corrections, on registration accuracy. To provide realistic SPECT simulations, attenuation, scatter and partial volume corrections were performed on real SPECT data to model realistic activity maps. When comparing simulated data to real data, relative quantification errors less than 20% were found in most anatomical structures, suggesting that our simulated data are quite realistic [7].

The simulation context strongly affected registration accuracy. Registration using normal simulations was more accurate than registration using ictal simulations, suggesting that pathological conditions significantly affected registration accuracy. Moreover, whereas scatter correction slightly improved registration accuracy, attenuation correction decreased registrations performances. Similar findings were observed by Kyme *et al.* [14] in the context of motion correction in SPECT. As Compton scatter has a smoothing effect, scatter correction increased the contrast, which should help the analysis of similarity between SPECT and MRI data. On the other hand, attenuation correction removes information related to the anatomy. Our hypothesis is that such information might be useful for SPECT/MRI registration based on statistical similarity, but this deserves further investigation. Statistical similarity criteria based either on mutual information (MI and NMI) or on correlation ratios (CRL1 and CRL2) seemed to be reliable for ictal SPECT/MRI registration. Even if only slight differences were shown among such methods, criteria based on the correlation ratios (CRL1 and CRL2) seemed to be slightly more accurate.

Using realistic simulations allowed us to study specifically the impact that each parameter may have on registration accuracy. As we did not model inter-individual variability, results might be too optimistic. On the other hand, inconsistency measurements allowed us to evaluate the registration of ictal and inter-ictal data on patients scans. As inconsistency measurements are obtained without any Gold Standard and as they result from the combination of three

independent registration errors, they may over-estimate registration accuracy [2]. All registrations were pretty accurate, RMS_j being significantly lower than SPECT spatial resolution (12.2 mm), but always greater than SPECT voxel size (4.51 mm). Some registrations failed on this small patients group, suggesting that it is definitely not a trivial task to register ictal data. Registration based on the correlation ratios CRL1 and CRL2 seemed to be the most precise and accurate, whereas no effect of attenuation correction was observed. More subjects should be studied to confirm those tendencies.

Quantitative comparison of registration evaluation studies is a delicate task, notably because of the lack of standardization in validation procedures [6]. Our accuracy and precision measurements agree with previous results (e.g.,[1]). Thurjfell *et al.* [2] also simulated pathological data and found no significant effect of the pathological contexts on registration accuracy, but using analytical SPECT simulations. In our study, realistic Monte Carlo SPECT simulations showed an impact of the pathological context on registration accuracy. In [15], we proposed a method to explore functional variability on those data, such models may lead to even more realistic simulations reflecting the functional variability of a population of subjects.

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