Linear intensity normalization of FP-CIT SPECT brain images using the $\alpha$-stable distribution

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Abstract

In this work, a linear procedure to perform the intensity normalization of FP-CIT SPECT brain images is presented. This proposed methodology is based on the fact that the histogram of intensity values can be fitted accurately using a positive skewed $\alpha$-stable distribution. Then, the predicted $\alpha$-stable parameters and the location-scale property are used to linearly transform the intensity values in each voxel. This transformation is performed such that the new histograms in each image have a pre-specified $\alpha$-stable distribution with desired location and dispersion values. The proposed methodology is compared with a similar approach assuming Gaussian distribution and the widely used specific-to-nonspecific ratio. In this work, we show that the linear normalization method using the $\alpha$-stable distribution outperforms those existing methods.

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Introduction

Iodine-123-fluoropropyl-carbomethoxy-3-β-(4-iodophenyltropane) (Fazio et al., 2011; Neumeyer et al., 1991) (FP-CIT; $^{123}$I-ioflupane/DaTSCAN) has been used to differentiate between Parkinsonian syndrome and essential tremors (Benamer et al., 2000; Marek et al., 2001; Seibyl et al., 1995). In addition, its importance has increased more recently when its application range was extended to be used for the differentiation of dementia with Lewy bodies from Alzheimer’s disease (Colloby et al., 2004; Colloby et al., 2008; O’Brien et al., 2009; Walker et al., 2007).

After intravenous injection, $^{123}$I-FP-CIT binds to the dopamine transporters in the striatum. It has been found that patients with PD will exhibit decreased uptake of the tracer (Booij et al., 1997a, 1997b, 1998; Winogrodzka et al., 2001). Imaging with a gamma camera in single photon emission computed tomography (SPECT) mode allows visualization of the transporter distribution.

Previous studies have demonstrated that when $^{[123]}$I-CIT reaches equilibrium binding in the brain, a simple unitless ratio of regional radioactivities is proportional to the binding potential (Laruelle et al., 1994; Scherfler et al., 2005; Van Dyck et al., 1995). Furthermore, specific binding regions (putamen and caudate nuclei) appear more intense in healthy subjects than in PD subjects. Thus, this difference is usually quantified by the so-called binding potential or specific/nonspecific binding ratio (BR).

$$BR_{\text{VOI}} = \frac{C_{\text{VOI}}}{C_{\text{NSB}}}$$

where $C_{\text{VOI}}$ is the count per voxel in the volume of interest and $C_{\text{NSB}}$ denotes the mean count per voxel in the non specific binding region and it is widely used in the literature for normalization purposes in $^{123}$I-FP-CIT SPECT images and also in other functional brain image modalities (Aarts et al., 2012; Andringa et al., 2005; Caretti et al., 2008; Isaias et al., 2006; Rektorova et al., 2008; Sharma and Ebadi, 2008; Zanotti-Fregonara et al., 2008). The occipital cortex is usually selected as the background region because the density of dopamine transporters is negligible in this brain area. In this work, in addition to the occipital cortex, we also consider the whole brain, except the voxel information in the striatum, as nonspecific brain region for comparison purposes.

Furthermore, as Eq. (1) can be written as $BR_{\text{VOI}} = \frac{C_{\text{VOI}}}{C_{\text{NSB}}} - 1$, therefore, from now on, in this document we use the following equivalent expression for the binding ratio:

$$BR_{\text{VOI}} = \frac{C_{\text{VOI}}}{C_{\text{NSB}}}$$

Thus, the bulk of the normalized histogram of intensity values will be placed near 1 instead of 0. In addition, all the normalized values will be positive.

We present a method of automatic intensity normalization of FP-CIT SPECT images. This proposed methodology takes advantage
of the skewed and heavy tailed shape of the distribution of intensities, then it models this histogram using the $\alpha$-stable distribution. Well known properties of the $\alpha$-stable distribution are later used to adapt the shape of this histogram to a new one, also with $\alpha$-stable distribution, but with desired value of its location and dispersion parameters.

This work is organized as follows: the FP-CIT SPECT dataset section presents the dataset used in this contribution and the main differences between healthy controls (NC) and Parkinson’s disease (PD) images. The section on $\alpha$-Stable distribution and FP-CIT SPECT images presents some properties of the $\alpha$-stable distribution. The section on Maximum likelihood estimation of stable parameters shows the maximum likelihood approach used to estimate the $\alpha$-stable parameters. The section on Intensity normalization using the stable property explains the procedure to perform the intensity normalization. The whole procedure is summarized in the Summary section. Results are given in the Results and discussion section and the conclusions are drawn in the last section.

Material and methods

**FP-CIT SPECT dataset**

40 images were obtained after a period of 3–4 h following the intravenous injection of 185 MBq (5 mCi) of $^{123}$I-FP-CIT, after the thyroid was blocked with Lugol’s solution. The SPECT study with [123I]-FP-CIT was carried out using a Siemens Gamma camera, Symbia model, dual head, low energy, high resolution, collimator. A 360-degree circular orbit was made around the skull, at intervals of 3 grades, having 60 images with a 35 second duration per interval, and a 128×128 matrix. Images were reconstructed using filtered backprojection algorithms without attenuation correction and applying a Hanning filter (0.7 frequency). Then, images were acquired according to the transaxial sections and the orbito-meatal line.

The histograms of intensity values of each of the images are superimposed in Fig. 1. This figure reveals that there is a certain degree of variability between the intensity values before normalization. Furthermore, a visual inspection of the histogram of raw data suggests that this variability is not produced by a multiplicative parameter in the data. In addition to multiplicative effects, some histograms are clearly shifted in the x-axis. Therefore, a normalization procedure using only a multiplicative parameter, as the specific to non-specific binding ratio does, is not enough for an accurate intensity normalization procedure.

![Fig. 1. Histogram of the intensity values for the 40 FP-CIT SPECT brain images under study.](image-url)

Fig. 2 shows a slide of the mean normal control (NC) and mean Parkinson’s disease (PD) image (left and right respectively). This figure also shows that NC and PD images are very similar except for the fact that patients with PD exhibit decreased uptake of the FP-CIT SPECT tracer in the striatum. This feature will be used to normalize the intensity of the images considering, as non-specific regions, all the regions of the brain except the striatum.

**$\alpha$-Stable distribution and FP-CIT SPECT images**

A random variable has an $\alpha$-stable distribution if it has a property wherein a linear combination of two independent copies of the variable has the same distribution. Furthermore, the stable distributions are completely described by only four parameters (location, dispersion, characteristic exponent and skewness), the Gaussian distribution is a particular case of $\alpha$-stable distributions and it satisfies the Generalized Central Limit Theorem (Samorodnitsky and Taqqu, 1994). These properties confer to the stable distribution the ability to fit asymmetric and heavy tailed data better than the normal distribution (Salas-Gonzalez et al., 2009; Salas-Gonzalez et al., 2010).

The $\alpha$-stable probability density function $f_{\alpha,\beta,\gamma}(y;\mu)$ has four parameters: $\alpha \in (0, 2]$ is the characteristic exponent which sets the level of impulsiveness, $\beta \in [-1, +1]$ is the skewness parameter, $(\beta = 0$, for symmetric distributions and $\beta = \pm 1$ for the positive/negative stable family respectively), $\gamma > 0$ is the scale parameter, also called dispersion, and $\mu$ is the location parameter.

![Fig. 3.](image-url)

**Fig. 3.** Shows the $\alpha$-stable probability density function for different values of the parameters. We use the distribution with parameters $\alpha = 1.5$, $\beta = 0$, $\gamma = 1$ and $\mu = 0$ as reference. This figure also explains the name of the parameters: $\alpha$ controls the degree of impulsiveness; when $\alpha$ decreases, the degree of impulsiveness increases. $\beta$ controls the skewness and its sign, whether the asymmetry is on the left or the right. $\gamma$ controls the concentration of the samples along the bulk of the distribution: lower values of $\gamma$ correspond with higher concentration of the samples. Lastly, different values of $\mu$ produce similar probability density functions but shifted in the x-axis.

The histogram of intensity values in FP-CIT SPECT images shares some of the properties of the $\alpha$-stable distribution, as it was visually suggested in Fig. 4 when the predicted $\alpha$-stable and the histogram of intensity data were depicted. Some of these common properties are:

- Heavy probability tails due to the existence of a few regions of the brain with high intensity values.
- Peaked bulk because most of the voxels in the brain, the non-specific area, have very similar intensity values (except the striatum, which is the area with greater variability depending on the type of image, PD or NC).
- Positive asymmetry because intensity values are always greater than 0 and the bulk of the distribution reaches very low intensity values compared with the values obtained in the striatum.

On the other hand, Fig. 4 depicts a scheme of the different parts of the histogram of binding values, highlighting the specific and non-specific areas, their typical intensity values and their locations in the brain. This figure also points out the similarities between the histogram of intensity raw data and the $\alpha$-stable distribution with skewness parameter $\beta = 1$ which is superimposed using a continuous red line.

**Maximum likelihood estimation of stable parameters**

The log-likelihood function for an i.i.d. sample $X_1, \ldots, X_n$ is given by

$$
\mathcal{L}(\alpha, \beta, \gamma, \mu) = \sum_{i=1}^{n} \log f_{\alpha,\beta,\gamma}(y_i;\mu).
$$

(3)
The difficulty in evaluating this is that there are no known closed formulas for general stable densities. Nolan (1997) gives reliable computations of stable densities for values of $\alpha > 0.1$ and any $\beta, \gamma$ and $\mu$. His work was improved to give more accurate density calculations on the tails, which were found to be necessary for accurate likelihood calculations. An approximate gradient based search is used to maximize the likelihood. Furthermore, the quantile estimator of McCulloch (1986) is used as an initial approximation to the parameters and then a constrained (by the parameter space) quasi-Newton method is used to maximize the likelihood.

DuMouchel (1973) shows that when the unknown parameters $\theta = \{\alpha, \beta, \gamma, \mu\}$ are on the interior of the parameter space, the maximum likelihood estimator follows the standard theory, so it is consistent and asymptotically normal with covariance matrix given by $n^{-1}B$, where $B = b_{ij}$ is the inverse of the $4 \times 4$ Fisher Information matrix $I$. The entries of $I$ are given by

$$ I_{ij} = \int_{-\infty}^{\infty} \frac{\partial^2 f}{\partial \theta_i \partial \theta_j} \, dx. \quad (4) $$

We use the MatLab Stable toolbox from RobustAnalysis Inc. which numerically computes these integrals. It computes the density $f$ to high accuracy and then it computes the partials. The resulting values for the integrands are then numerically integrated. This allows us to fit a stable distribution to the sample data using a maximum likelihood procedure. In this work, we choose to use a maximum likelihood approach because

![Fig. 2. Left: transaxial mean normal control image. Right: transaxial mean Parkinson’s disease image.](image)

![Fig. 3. $\alpha$-Stable probability density function with reference parameters $\alpha=1.5, \beta=0, \gamma=1$ and $\mu=0$ with changing: (a) characteristic exponent $\alpha$. (b) Skewness parameter $\beta$. (c) Dispersion $\gamma$. (d) Location parameter $\mu$.](image)
this is known to be more accurate for parameter estimation and, in addition, no other estimation method is asymptotically more efficient than maximum likelihood. Any other method of estimating $\alpha$ will likely yield larger confidence intervals. See Nolan (2001) for a comprehensive explanation of the maximum likelihood method and a performance comparison with other existing methods. That work concludes that the maximum likelihood estimates are the most accurate, closely followed by the regression-type estimates, quantile method, and finally, the method of moments. The only disadvantage of the maximum likelihood estimation is that this technique is most computationally expensive, although this is not a problem in the application presented in this work.

Intensity normalization using the stable property

The following properties will be used to perform the normalization task:

- Let $X - f_{\alpha}(y|\gamma, \mu)$ and let $c$ be a real constant. Then, $X + c - f_{\alpha}(y|\gamma, \mu + c)$
- Let $X - f_{\alpha}(y|\gamma, \mu)$ and $c$ be a non-zero real constant. Then, $cX - f_{\alpha}(y|\gamma, \mu) + c$ if $\alpha \neq 1$.

Therefore, the histogram of a vector of intensity data with $\alpha$-stable distribution with parameters $X - f_{\alpha}(y|\gamma, \mu)$ can be easily transformed to another $\alpha$-stable distribution with distribution $Y - f_{\alpha}(y|\gamma', \mu')$ by using the following expression

$$Y = aX + b$$

(5)

where $a = \frac{\gamma}{\gamma'}$ and $b = \mu' - \gamma\mu$.

The goal in this work is to transform all the intensity values for different images $i$ with possibly different dispersion $\gamma_i$ and location $\mu_i$ parameters to another $\alpha$-stable distribution with $\gamma^*$ and $\mu^*$ parameters using the expression in Eq. (5).

Summary

The procedure we follow to perform the intensity normalization is summarized in this section:

- Firstly, we apply a mask in the source images and we consider only those voxels in the brain except the striatum.
- Secondly, we calculate the histogram of the selected voxels (the non-specific region) and we fit a stable distribution to the intensity data. We calculate the $\alpha$-stable parameters for each image $i$ using a maximum likelihood method (Nolan, 1997, Nolan, 2001).
- Then, we calculate $\gamma^*$ and $\mu^*$ as the mean values of the $\gamma_i$ and $\mu_i$ parameters.
- Lastly, we calculate the $a$ and $b$ values for each image and we transform linearly all the intensity values in the brain using Eq. (5).

A related normalization method using Gaussian distribution

In this section, we also introduce a related method assuming that the histogram of non-specific intensity values is Gaussian, which is not the case. Because the normal distribution is also a location-scale family, it is possible to relate all normal random variables to the standard normal using an analogous procedure that we have presented in this work using the $\alpha$-stable distribution. For instance, if $X$ is normal with mean $\mu_c$ and variance $\sigma^2_c$, then

$$Z = \frac{X - \mu_c}{\sigma_c}$$

(6)

has mean zero and unit variance, that is $Z$ has the standard normal distribution. Conversely, having a standard normal random variable $Z$ we can always construct another normal random variable with specific mean $\mu_c$ and variance $\sigma^2_c$:

$$Y = \sigma_c'Z + \mu_c.$$

(7)

Combining Eqs. (6) and (7) we can always transform a Gaussian random variable $X$ with parameters $(\mu_c, \sigma^2_c)$ to a new one $Y$ with parameters $(\mu_c', \sigma^2_c)$ using a similar expression as Eq. (5) for the $\alpha$-stable parametrization.

$$Y = \frac{\sigma_c'}{\sigma_c}X + \left[\mu_c' - \frac{\sigma_c'}{\sigma_c}\mu_c\right]$$

(8)

In this work, we also compared the proposed normalization method with a linear transformation of intensity values assuming Gaussian distribution and using expression (8). Nevertheless, raw intensity data in FP-CIT SPECT brain images is far from the Normal assumption. On the other hand, the Gaussian distribution is a particular case of the $\alpha$-stable distribution (specifically with $\alpha = 2$), therefore, the intensity normalization method assuming Gaussian distribution in the raw intensity data is also a particular case of the proposed $\alpha$-stable approach.

Results and discussion

The proposed methodology has been tested in 40 different SPECT images (16 Controls and 24 with degenerative parkinsonism). The labels of the images in this work are irrelevant, as we do not make use
of them in our normalization method. Nevertheless, they give us certainty that the images under study present a high degree of variability of their values in the striatum. Therefore, this normalization method is suitable for preprocessing of brain FP-CIT SPECT images for diagnosis purposes (where there are NC and PD images). Previously, the images have been spatially normalized to a common template using a general affine model with 12 parameters (Salas-Gonzalez et al., 2008).

Firstly, the non-specific voxels are selected (the whole brain except the voxels in the striatum). The selected voxels are fitted to an $\alpha$-stable distribution. The maximum likelihood method is used (Nolan, 2001). An analysis of the estimated parameter values reveals the following features:

- The characteristic exponent ($\alpha$) ranges from 1.6 to 2. Furthermore, normal control images present, in overall, lower values of $\alpha$, and therefore, lower degree of impulsiveness.
- The skewness parameter ($\beta$) is equal to 1 for all the images except two of them (with $\beta = 0.95$ and $\beta = 0$). The image with $\beta = 0$ has $\alpha = 2$. Take note that for this value of $\alpha$, the $\beta$ parameter is undefined (Samorodnitsky and Taqqu, 1994).
- The dispersion parameter ($\gamma$) ranges from 1 to 3.3. Roughly, the $\gamma$ value is lower for PD images.
- The location parameter ($\mu$) has the greatest range of variability among all (from 5.6 to 25.4).

After normalization using Eq. (5), the dispersion and location parameter of the intensity values of non specific region are the same for all the FP-CIT SPECT images.

Fig. 5 shows the histogram with the intensity values for each of the images after performing the normalization procedure. Take note that the bulk of the histograms of all the images are very similar after normalization.

Fig. 6 shows one transaxial slice for each of the 40 FP-CIT SPECT brain images. Fig. 6a) depicts the intensity values before normalization while Fig. 6b) shows the same information but with the intensity values normalized using the $\alpha$-stable distribution approach presented in this paper. This figure reveals that the intersubject differences in intensity values in the non-specific regions is clearly mitigated after

![Fig. 5. Histograms of the intensity values for the 40 images considered after normalization using the $\alpha$-stable approach.](image)

![Fig. 6. Transaxial slice of each SPECT brain image in the database. (a) Before normalization. (b) After intensity normalization using $\alpha$-stable procedure.](image)
normalization which is, in fact, the main goal of the intensity normalization procedure.

In order to compare the α-stable normalization method with the specific-to-nonspecific ratio approach and the Gaussian method, we plot the mean histogram of intensity values in Fig. 7. In this figure, the intersubject intensity variability is also depicted by means of the error bars which are estimated using the 25th and 75th percentile. BRall denotes the binding ratio calculated using all the brain voxels except those in the striatum as non-specific region, while BRocc considers the occipital cortex as the non-specific binding region. This figure shows that the α-stable normalization method provides lower inter-subject variability than Gaussian, BRocc and BRall methods. Therefore, the α-stable method accomplishes the normalization more accurately, as the processed FP-CIT SPECT brain images present greater degree of homogeneity in their intensity values (smaller error bars).

We also estimate the difference between the probability distributions of each normalized image and the mean normalized brain image using the Kullback-Leibler divergence (KL). Thus, we measure quantitatively the intersubject variability after normalization (Table 1). The error has been calculated by the standard deviation of the estimated Kullback-Leibler divergence. Let see that the lowest KL value (and also lowest standard deviation) is reached for the α-stable normalization procedure presented in this work.

Conclusion

In this work, a procedure to perform the normalization of the intensity values in FP-CIT SPECT images has been presented. The proposed methodology is based on the fact that the shape of the distribution of intensity values is skewed and heavy-tailed, and therefore, it can be modeled in a parsimonious way using the α-stable distribution. The location-scale property is used to transform linearly the intensity values in each voxel. After normalization, the α-stable location and scale parameters of the non specific voxels in each of the FP-CIT SPECT brain images are the same. We have proved that, using this procedure, we are able to obtain brain images with very similar intensity distribution. We compare our method with a similar one assuming Gaussian distribution and the widely used specific-to-non specific ratio. The proposed methodology improves the intensity normalization and reduces the intersubject differences in intensity values in the non-specific regions.

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