Knowledge-based vascular segmentation methods typically rely on a pre-built training set of segmented images, which is used to estimate the probability of each voxel to belong to a particular tissue. In 3D Rotational Angiography (3DRA) the same tissue can correspond to different intensity ranges depending on the imaging device, settings and contrast injection protocol. As a result, pre-built training sets do not apply to all images and the best segmentation results are often obtained when the training set is built specifically for each individual image. We present an Image Intensity Standardization (IIS) method designed to ensure a correspondence between specific tissues and intensity ranges common to every image that undergoes the standardization process. The method applies a piecewise linear transformation to the image that aligns the intensity histogram to the histogram taken as reference. The reference histogram has been selected from a high quality image not containing artificial objects such as coils or stents. This is a pre-processing step that allows employing a training set built on a limited number of standardized images for the segmentation of standardized images which were not part of the training set. The effectiveness of the presented IIS technique in combination with a well-validated knowledge-based vasculature segmentation method is quantified on a variety of 3DRA images depicting cerebral arteries and intracranial aneurysms. The proposed IIS method offers a solution to the standardization of tissue classes in routine medical images and effectively improves automation and usability of knowledge-based vascular segmentation algorithms.

Keywords: Vascular segmentation, Intensity standardization, Image processing, X-ray Angiography

1. INTRODUCTION

3D Rotational Angiography (3DRA) is considered the gold standard modality for the visualization of vascular anatomy in neuroradiology applications, especially for the diagnosis and treatment planning of vascular pathologies. As opposed to Computed Tomography Angiography (CTA) and Magnetic Resonance Angiography (MRA), where the entire head of the patient is typically reconstructed, 3DRA reconstruction focuses on a region of interest (ROI) within the head. Depending on the location and size of the chosen ROI, the reconstructed 3DRA images will contain different types and amounts of tissues, as shown in Figure 1. Another feature of 3DRA imaging is that due to different imaging devices and settings and to the variability of contrast injection protocols a correspondence between an imaged tissue and a range of intensity values can not be established. In particular, image intensities are typically scaled to span the full dynamic range, thus the highest intensity will correspond to the highest attenuating tissue, which might be vessel in one subject or an artificial medical device (stent/coil) in an other subject. The variability of the intensity scale between 3DRA images not only affects automatic image rendering algorithms currently available in modern interventional workstations, but also represents an obstacle to the automatism of vascular image segmentation algorithms. With image segmentation we here refer to the extraction of the boundaries of vascular objects from a 3D image volume. In particular, we are interested in the segmentation of cerebral vessels for the investigation of intracranial aneurysm disease. The aim is to identify those...
phenomena that are more likely to affect the evolution and outcome of the disease, including aneurysm morphological, haemodynamical and wall structural properties. These properties are currently obtained using modeling and simulation techniques, which are applied to subject-specific models of the cerebral vascular anatomy. The reliability of these methods depends on the accuracy of the segmentation output and their clinical application requires the availability of intuitive and user-friendly image segmentation techniques for the processing of large patient samples.

Figure 1: Variability in size and location of typical reconstructed ROIs within the head during 3DRA acquisition.

The segmentation of cerebral arteries from 3DRA images is a difficult task due not only to noise and inhomogeneous image gradients but also to the presence of vessels of a wide range of sizes. In order to facilitate the segmentation process, a model of the intensity distribution corresponding to each tissue class may be introduced. In particular, knowledge-based vascular segmentation algorithms exploit the availability of such models, which can be built from a training set of ground truth segmentations. This approach assumes that tissues such as bone, brain matter and blood are associated with similar image intensity ranges for all images in a data set, which however is not ensured for 3DRA images. As a result, although knowledge-based segmentation algorithms have shown great potential for the extraction of vascular anatomy from 3DRA images of cerebral vessels, the best segmentation results are often obtained when a training set is built specifically for each individual image. The generation of a training set is a relatively expensive operation that requires a substantial level of user interaction, thus limiting the potential integration of knowledge-based segmentation algorithms for the extraction of vascular anatomy in clinical settings.

The standardization of medical images has been previously investigated in applications involving Magnetic Resonance Imaging (MRI). Nyul et al. applied a piecewise linear intensity transformation to align a set of landmarks explicitly selected on the histogram of MRI images of the brain against the corresponding ones selected
on a reference histogram. The process is automatic and the landmarks are simply obtained as the median and quartile locations of the histogram. However, the criteria for the selection of the landmarks showed limitations especially in the presence of variations in image intensity distribution due to pathologies. Madabushi et al. recently proposed an improvement of the method where a single intensity landmark is obtained as the mean intensity of the largest generalized scale. A generalized scale is defined as the largest set of voxels connected to a given voxel that satisfies some homogeneity criteria. As the largest generalized scale region of each MRI image belongs to the same tissue, the new standardization method identifies a single landmark on the histogram that is directly related to a particular tissue of interest. However, both approaches would arguably have a limited success for the standardization of 3DRA images as intensity distribution, types and amounts of tissues may considerably change in different ROIs of the head and the correspondences of generalized scale regions between two images would be difficult to ensure.

This paper presents an Image Intensity Standardization (IIS) method, which has been designed to automatically establish a correspondence between specific tissues and intensity ranges common to every 3DRA image that undergoes the standardization process. The proposed IIS is based on the alignment of 3DRA image histograms using signal registration techniques. The integration of the IIS technique in a well-validated knowledge-based vascular segmentation method is also demonstrated. The IIS technique represents a pre-processing step automatically applied to every image undergoing the segmentation process and to every image belonging to the training set. The viability of the new segmentation approach for the extraction of the geometry of cerebral arteries in the presence of intracranial aneurysms is illustrated for a sample of 8 3DRA images. The segmentation results are compared with the results that would be obtained using either a non-standardized training set or a training set separately built for each image. The impact of the IIS technique on the usability and automation of the segmentation method is illustrated and its potential application to a large database of 3DRA images is discussed.

The paper is organized as follows. In Section 2 we summarize the main components of the adopted vascular segmentation algorithm. In Section 3 we describe the methodology for intensity standardization of 3DRA images. Section 4 illustrates the impact of the IIS technique on the segmentation results of 8 3DRA images. Finally, Section 5 provides concluding remarks and introduces topics for future research.

2. VASCULAR SEGMENTATION ALGORITHM

This section provides an overview of the main properties of the knowledge-based vascular segmentation algorithm that is used in this work. In order to adapt to the topological changes common in the cerebral vasculature, the segmentation is performed using the geometric deformable model technique within the level set framework. The external forces (the speed image) supplied to the deformable model are defined likewise the Geodesic Active Regions (GAR) technique, which combines statistical region-based information with image gradient maps to drive the evolution of the model towards the vascular boundaries. The region-based information contributes to reduce the leakage of the evolving front in areas with weak image gradient and is presented in the form of a probability image map that contains the probability (from 0 to 1) of each image voxel to belong to a certain region (or tissue) R. The estimated probability value can be interpreted as a conditional probability, \( P(x \in R \mid f(x)) \), where \( x \) is a point in the image domain and \( f(x) \) is the feature vector used to characterize the tissue it belongs to. Features are based on differential invariants up to the second order computed at multiple scales to provide a richer description than just voxel intensity. These feature vectors are also expected to be able to differentiate between tissues that cover overlapping image intensity ranges but present different shapes. The set of feature vectors belonging to a specific region are first learned in an interactive, supervised fashion from a set of images used as a training set. During the segmentation, the probability of each image voxel to belong to a particular tissue is then estimated by comparing its feature vector with the set of learned feature vectors. It should also be noted that the availability of a probability image map allows to remove any user intervention in the initialization process since the initial surface of the deformable model can be obtained by thresholding of the probability map corresponding to the vessel region (values close to 1). This methodology has been previously applied for the segmentation of vascular geometries from 3DRA images and has been validated against ground-truth data.

The workflow of the segmentation is shown in Figure 2, where the main components of the method are depicted. An important aspect of the segmentation process is the need of a pre-built training set, which is
obtained from a limited number of template images. In the case that the training set would not well represent the characteristic features of all images undergoing the segmentation process, under- or over-segmentation may occur. In particular, the feature that mainly varies between the same tissues in 3DRA images is the intensity magnitude. A solution could be to include each image presenting erroneous segmentation results in the training set, although the automation of the method would be strongly affected. Our solution is to introduce an image standardization component in the workflow illustrated in Figure 2. The IIS technique is integrated as a pre-processing step to the segmentation process and is applied to all the images used as a training set and to each image that undergoes the segmentation process, thus enabling a generalized use of a representative training set in a fully automatic fashion.

Figure 2: Vascular segmentation workflow as presented in with the inclusion of the IIS component.

3. IIS METHODOLOGY

The purpose of the intensity standardization process is to minimize the variability of the intensity range corresponding to a specific tissue among different images. The basic idea is to establish a correspondence between histograms of images taken from a generic dataset and a histogram taken as a reference. An overview of the proposed method is shown in Figure 3. As a first step, a reference histogram is selected or estimated. The histogram of a new image is then extracted and subjected to a denoising step to allow for further processing. The smooth histogram is then aligned to the reference using a non-linear registration technique. The deformation map that is generated in the registration process is used to apply an intensity transformation to the image volume and achieve a standardization of the intensity scale.

Figure 3: Workflow of the IIS component shown in Figure 2.

3.1 Histogram variability of 3DRA images of the brain

A typical histogram of a 3DRA image of the brain contains four main features. The major peak belongs to the brain soft tissue. The neighboring regions are characterized by two sidelobes: the lower intensity (left) sidelobe corresponds to air and the higher intensity (right) sidelobe corresponds to bone. Depending on the
selected ROI, the sidelobes can be more or less emphasized. The high intensity region of the histogram belongs
to vessels and artificial objects (if present) such as coils and stents. The voxels corresponding to the vascular
lumen typically occupy only 3-4% of the total image volume and cover a broad intensity range. As a result,
the peaks corresponding to the other tissues dominate over the flat vessel region and a logarithmic transform
(log(x + 1)) is typically applied in order to better visualize this area (Figure 4).

\[ \begin{array}{cc}
\text{Image intensity} & \text{Frequency} \\
0 & 0.005 \\
1 & 0.01 \\
2 & 0.015 \\
3 & 0.02 \\
4 & 0.025 \\
5 & 0.03 \\
6 & 0.035 \\
7 & 0.04 \\
\end{array} \]

\[ \begin{array}{cc}
\text{Image intensity} & \text{Log (frequency)} \\
0 & 0 \\
1 & 2 \\
2 & 4 \\
3 & 6 \\
4 & 8 \\
5 & 10 \\
6 & 12 \\
7 & 14 \\
\end{array} \]

Figure 4: Canonical histogram (a) and its logarithmic representation (b).

The variability of types and amounts of the tissues captured in different 3DRA images contributes to a
significant variability in possible histogram shapes. Figure 5 shows examples of histogram shapes that may be
encountered. It should be noted that, as the focus of this work is on the segmentation of cerebral vasculature,
the signal corresponding to all other tissues, including bone, brain and air, will be referred to as background.

3.2 Signal denoising
The noise affecting the histogram, when this is considered as a signal, may be obstacle to further processing,
including the selection of landmarks on the histogram curve or its alignment to the reference. For signal denoising,
a wavelet shrinkage method is adopted. This technique processes the signal at different scales and has the
property of de-correlating the signal in the wavelet domain and reduce it to the large wavelet coefficients only.
In particular, noise is inherently not correlated and is distributed throughout the whole wavelet domain, but
is characterized by small wavelet coefficients. An automatic thresholding technique is therefore applied to the
wavelet coefficients to remove the noise contribution. As opposed to smoothing filters that eliminate all the
high frequency components of a signal, this approach provides an effective denoising of the signal while keeping
relevant high frequency features. An example of the application of such technique to histograms considered in
this work is shown in Figure 6.

3.3 Histogram alignment
The alignment of each image histogram with the reference is performed using a non-linear registration technique.
All histograms are represented in a logarithmic scale so as to avoid the introduction of a bias in the alignment
process due to the dominating peaks in correspondence to the background tissue. The reference histogram has
been selected from a high quality image not containing artificial objects such as coils or stents. In order to verify
the type of bias that the choice of the reference image would introduce, we investigated the effect of changing the
reference histogram on the segmentation results. Only negligible differences were experienced. Regardless, we
are currently pursuing the implementation of a methodology that automatically extracts a reference histogram
from an atlas of template images.

The registration process is divided into the following steps. First, a number of control points is automatically
defined on the histogram undergoing the standardization process. The control points define a deformation map
that is used to deform the whole histogram. The deformation map achieving the optimal alignment with the
reference histogram is obtained through an iterative optimization procedure. This optimization procedure seeks
to minimize the distance between two histograms and is based on a predefined similarity metric.
Figure 5: Examples of histograms corresponding to 3DRA image of the brain. In (d) a logarithmic representation is used to highlight the contribution of the coil mass to the histogram.

Figure 6: Original histogram in the logarithmic scale a) and its filtered version (b).

### 3.3.1 Definition of control points and similarity metric

The control points are obtained by automatically selecting a set of locations equally spaced along the intensity axis of the histogram as shown in Figure 7(a). The aim of the registration process is to obtain a deformation map (Figure 7(b)) that will then move these points along the intensity-direction of the histogram and the rest of the histogram with it. In particular, it is assumed that the deformation map defines a piecewise linear transformation, so the displacement of points on the histogram lying between two control points will be linearly dependent on the corresponding displacements. The movement of each control point is instead independent and is defined as
\[ cp_i^{\text{new}} = cp_i^{\text{old}} \exp(x_i), \]
where \( cp_i \) is the scalar intensity value associated with a control point \( i \) and \( x_i \in \mathbb{R} \) is the parameter optimized for each control point during the registration procedure. A number of control points equal to 10 showed to be a reasonable compromise between speed and effectiveness of the alignment process.

**Figure 7**: Histogram of an image (a), where the 10 control points are depicted, and a possible deformation map (b).

It should be noted that, while the deformation of the histogram is dictated by the control points, the similarity metric takes into account the whole shape of the histogram. In particular, the metric describing the similarity between two histograms is defined as the sum of square differences (SSD) between a dense set of points sampled on them. The lower this value, the more similar the two histograms are.

### 3.3.2 Optimization and initialization

The optimization process seeks a minimum to the energy function associated with the similarity metric, which in turn leads to the deformation field that yields the two most similar histograms. The definition of the energy function is constrained to obtain only monotonically growing deformation maps, thus ensuring that a histogram would not fold over itself. The minimum of the energy function is obtained using the Nelder-Mead simplex algorithm. This is a non-linear optimization algorithm and is particularly efficient when applied to find a local optimal solution. As a result, a good initialization of the two curves is required. This is achieved by exploiting the characteristic background peak that appears in all histograms. In particular, the initial registration parameter vector is chosen to achieve the matching between background peaks. The result of the initialization process is shown in Figure 8.

**Figure 8**: Two histograms before (a) and after (b) the initialization process.

The optimization technique produces a deformation map that best aligns a histogram to the reference one. The results of this process are exemplified for three cases in Figure 9. In particular, Figures 9(g-i) shows an
example where a histogram of an image presenting a coil is registered to the reference one. The registration process satisfactorily identifies the contribution of the coil and has the potential to be used for the segmentation of the coil mass by simple thresholding of the intensity scale.

![Graphs showing histogram registration results](image)

Figure 9: Results of the registration to a reference applied to three histograms. (a,d,g) Pairs of histograms before the registration process. (b,e,h) The pairs of histograms after the registration process. (c,f,i) The corresponding deformation maps.

### 3.4 Intensity transformation

The result of the histogram alignment procedure is a deformation map that defines a piecewise linear intensity transformation between the original and the standardized image. The intensity transformation is applied to all voxels of the image volume and is executed in real-time using a look-up table. A more sophisticated interpolation between the control points could be used, for example using B-splines, but there is no significant improvement in the results of the IIS process to justify the increase in computational effort. The overall effect of the IIS process is further illustrated in Figure 10, demonstrating the effectiveness of the approach in achieving an optimal alignment among a set of image histograms.
4. IMPACT OF IIS ON VASCULAR IMAGE SEGMENTATION

The IIS technique has been applied in combination with the knowledge-based segmentation algorithm introduced in Section 2 to a variety of 3DRA images. This algorithm has been previously applied for the segmentation of vascular geometries from 3DRA images using a suitable training set and has been validated against ground-truth data. Consequently, we use the results of this segmentation method when a specific training set is built for each individual image as reference segmentations. These are then compared to the segmentation results obtained both when a non-standardized training set is used and when the IIS technique is introduced in the whole segmentation process for a sample of 8 images. In particular, the results for two of these cases is shown in Figure 11. The use of a non-standardized training set leads to significant under-segmentation of the vascular geometry, whereas the integration of the IIS technique in the segmentation procedure leads to a result that is equivalent to building a training set specifically for the image being segmented. In addition, possible differences in the segmentation results were quantified using surface to surface distances for all cases. The results are summarized in Table 1. For all cases, the average error introduced by using a standardized training set with the IIS technique proposed in this paper is within the desirable bounds of voxel accuracy.

5. CONCLUSIONS

We have developed an image intensity standardization (IIS) technique for 3DRA images that establishes a correspondence between specific tissues and a range of intensity values common to every image that undergoes the standardization process. IIS is a mandatory pre-processing step to employ a training set built on a limited number of standardized images for the segmentation of standardized images which were not part of the training set. The proposed IIS method offers a solution to the standardization of tissue classes in 3DRA images of the brain and effectively improves automation and usability of knowledge-based vascular segmentation algorithms,
Figure 11: Comparison of the results of different vascular segmentation strategies for two images.
Table 1: Mean, standard deviation (std. dev.), 90% quantile, and maximum of the surface to surface distance between results of the segmentation process using a specifically built training set or the IIS technique (voxel size = 0.15 mm). The histogram of the image corresponding to patient 1 was used as a reference.

<table>
<thead>
<tr>
<th>Surface to surface distance [mm]</th>
<th>mean</th>
<th>std. dev.</th>
<th>90% quantile</th>
<th>max</th>
</tr>
</thead>
<tbody>
<tr>
<td>patient 1</td>
<td>0.16</td>
<td>0.10</td>
<td>0.29</td>
<td>0.48</td>
</tr>
<tr>
<td>patient 2</td>
<td>0.12</td>
<td>0.11</td>
<td>0.28</td>
<td>0.82</td>
</tr>
<tr>
<td>patient 3</td>
<td>0.07</td>
<td>0.08</td>
<td>0.17</td>
<td>0.66</td>
</tr>
<tr>
<td>patient 4</td>
<td>0.1</td>
<td>0.1</td>
<td>0.25</td>
<td>0.8</td>
</tr>
<tr>
<td>patient 5</td>
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<td>0.08</td>
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<tr>
<td>patient 6</td>
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<tr>
<td>patient 8</td>
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<td>0.09</td>
<td>0.31</td>
<td>0.63</td>
</tr>
</tbody>
</table>

thus envisioning their adoption in clinical settings and establishing their viability for the processing of large patient data.

Current work in progress includes the introduction of alternative divergence measures for aligning the histograms and a methodology to automatically extract a reference histogram from an atlas of representative images. Additionally, we are also investigating the possibility of reducing the number of control points used in the image transformation process and introduce techniques to propagate tissue-specific landmarks manually identified on a reference histogram.\(^{10}\)

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