

# Content-aware image smoothing based on fuzzy clustering

Antunes-Santos, F.<sup>1,2,3</sup>[0000-0003-3298-9215], Lopez-Molina,  
C.<sup>1,2,3</sup>[0000-0002-0904-9834], Mir-Fuentes, A.<sup>1,3</sup>[0000-0001-5914-9860], Mendioroz,  
M.<sup>3</sup>[0000-0002-4179-5781], and De Baets, B.<sup>2</sup>[0000-0002-3876-620X]

<sup>1</sup> Dept. of Estadística, Informática y Matemáticas, Universidad Pública de Navarra,  
31006 Pamplona, Spain;

{felipe.antunes, carlos.lopez, arnau.mir}@unavarra.es

<sup>2</sup> KERMIT, Dept. of Data Analysis and Mathematical Modelling, Ghent University,  
9000 Ghent, Belgium;

bernard.debaets@ugent.be

<sup>3</sup> NavarraBiomed, Hospital Universitario de Navarra,  
31008 Pamplona, Spain.

tmendioi@navarra.es

**Abstract.** Literature contains a large variety of content-aware smoothing methods. As opposed to classical smoothing methods, content-aware ones intend to regularize the image while avoiding the loss of relevant visual information. In this work, we propose a novel approach to content-aware image smoothing based on fuzzy clustering, specifically the Spatial Fuzzy *c*-Means (SFCM) algorithm. We develop the proposal and put it to the test in the context of automatic analysis of immunohistochemistry imagery for neural tissue analysis.

**Keywords:** Image smoothing · Fuzzy clustering · Progressive supranuclear palsy

## 1 Introduction

Image regularisation is one of the most basic tasks in computer vision. Initially, its goal was to produce a regularised, a.k.a. smooth, version of the original signal, hence preventing problems due to noise or contamination in the signal. Despite large improvements in understanding image smoothing, e.g. the use of Gaussian filters and the creation of the Gaussian Scale Space [16, 17], it was soon evident that smoothing brought undesired distortions to images. Specifically, such distortions included the removal of small objects, as well as the blurring of certain image artefacts, mainly object boundaries. It then became evident that it was necessary to have smoothing techniques that, while regularising the image

---

The authors gratefully acknowledge the financial support of the Spanish Ministry of Science (Project PID2019-108392GB-I00 AEI/FEDER, UE), as well as the funding from the European Union's H2020 research and innovation programme under Marie Skłodowska-Curie Grant Agreement Number 801586.

content, would not entail any of the drawbacks. In this context, two main families of smoothing techniques can be discriminated: content-unaware (CUS) and content-aware smoothing (CAS) techniques. The former apply the same smoothing operation across the image, while the latter adapt the smoothing operation locally to avoid object removal and boundary blurring.

Content-unaware techniques have historically been based on Gaussian smoothing, especially since the theoretical results by Babaud *et al.* [1]. Large efforts were devoted to understand Gaussian smoothing, develop theories as the anisotropic Gaussian filters or the Gaussian Scale-Space [13, 17]. However, the panorama in content-aware smoothing is significantly richer. Early attempts are due to Saint-Marc [24], who presented a Gaussian-based smoothing technique in which the standard deviation of the Gaussian kernel applied at each pixel is dependent upon local characteristics. A more elaborate proposal was that by Perona and Malik, who presented a discrete schema for the so-called Anisotropic Diffusion model [23]. These pioneering efforts were continued to produce continuous schemas, as well as to customise the smoothing behaviour [26, 28]. For example, Weickert presented Coherence-Enhancing Anisotropic Diffusion [18, 27], which not only aimed at preserving structurally strong objects, but also at improving the visibility of visual structures. Other authors elaborated on theories different from anisotropic diffusion. Examples are bilateral filtering [25], aimed at content-aware smoothing using principles from spatio-tonal filtering, and Mean Shift [8], which incorporates notions from clustering and multivariate analysis. Despite the variability in both inspirations and specific implementations, many of the proposals for content-aware smoothing can be studied under the prism of unifying theories [3, 4].

Among the inspirations for content-aware smoothing, a very promising trend is that based on pixel clustering. The underlying idea behind this trend is as simple as powerful: the pixels in an image can be seen as  $n$ -dimensional feature vectors comprising (a) their position and (b) their (possibly multivalued) tone. Hence, an image becomes a point cloud in either 3D (for grayscale images), 5D (for most colour images), or even larger spaces (for, e.g., multispectral images). By performing clustering in such point cloud, pixels will be grouped according to spatial and tonal similarity. Otherwise said, the tone at each pixel will be influenced by the tones in pixels that are both spatially and tonally close. This shall achieve intra-object regularisation (since tones within an object will be grouped to a single tone) while avoiding object boundary blurring (since nearby pixels will have low influence on each other if they are tonally different). The main representative for clustering-based content-aware smoothing is Mean Shift, as presented by Comaniciu and Meer [8]. However, other clustering techniques are equally valid, e.g. gravitational clustering [20, 31]. Literature contains, to the best of our knowledge, no proposals for content-aware smoothing using fuzzy clustering. This is relatively surprising, given the significant impact of fuzzy clustering techniques in both fuzzy set theory and machine learning.

In this work, we propose a novel method for content-aware smoothing using Spatial Fuzzy  $c$ -Means (SFCM). Our proposal is put to the test in the context

of medical image processing, a field of particular interest for image smoothing given the proneness of such images to noise and external contamination.

The remainder of this work is organised as follows. Section 2 presents the general notions of clustering-based content-aware smoothing. Then, Section 3 depicts our proposal for image smoothing using Spatial Fuzzy  $c$ -Means. Our proposal is experimentally tested in Section 4. Finally, Section 5 lists some general conclusions and future work.

## 2 Clustering-based content-aware smoothing

Among the inspirations for content-aware smoothing, a relevant trend is that inspired by multidimensional clustering. This trend is based on the interpretation of images as datasets to be analysed from a spatio-tonal perspective. Let  $I : \Omega \mapsto \mathbb{T}$  be an image, with  $\Omega = \{1, \dots, N\} \times \{1, \dots, M\}$  representing the set of positions and  $\mathbb{T}$  representing the tonal palette. The image  $I$  can be understood as a dataset in which each pixel becomes an instance  $p \in \{1, \dots, N\} \times \{1, \dots, M\} \times \mathbb{T}$ . Consider a pixel  $I(i, j) = \mathbf{t} \in \mathbb{T}$  with  $\mathbf{t} = (t_1, \dots, t_k)$  a given tone; the instance corresponding to this pixel would be  $(i, j, t_1, \dots, t_k)$ .

The idea behind clustering-based content-aware smoothing is that clustering pixels in the spatio-tonal space will group pixels that are both similar in tone and similar in position. In this manner, pixels that are both spatially and tonally similar will be grouped to similar tones. This shall produce inter-object regularisation. Also, pixels that are spatially similar, but tonally different, shall not be grouped together, preventing inter-object blurring. Hence, the evolution of instances in the clustering process is meant to produce content-aware smoothing.

Nevertheless, the underlying inspiration of these smoothing techniques needs to render into functional algorithms, and such algorithms are dependent upon the specific clustering method. There are two main technical issues to be faced in clustering-based smoothing techniques. Firstly, we need to build an image from the dataset, at each stage of the clustering process, since the result of the process at each stage should be an image. Secondly, since clustering methods are normally based on comparison measures (often, on metrics), it is necessary to design comparison measures able to produce meaningful results in the spatio-tonal universe.

The generation of images at each stage of the clustering process is heavily dependent upon the specific body of knowledge generated in the process itself. In clustering methods that properly evolve the instances in the dataset (e.g., mean shift or gravitational clustering), each instance  $p$  in the image will be modified iteratively. This shall affect the tonal information in  $p$ , but also the spatial information in it. Otherwise said, the positions shall no longer fit the original pixel grid in  $\Omega$ . Hence, when using such clustering methods, positional information is normally reset back to the original values after each iteration in the clustering process. The situation is different for clustering methods that evolve a set of centroids, leaving the instances unaltered. In such cases, it is necessary to work with the membership of each pixel to each of the centroids, regardless of

whether such membership is expressed as probability, a fuzzy membership degree or any other numerical representation. Since each centroid is an element in  $\mathbb{R}^+ \times \mathbb{R}^+ \times \mathbb{T}$ , it does represent a tone. Hence, at each iteration of the clustering process, an image can be reconstructed through linear combination of the tones at each centroid, using as weighting coefficients the *memberships* to such centroids. More image-creating strategies could be designed for clustering methods that shall not fit in any of the previous two descriptions. Still, it is evident that the use of clustering methods for content-aware smoothing requires not only the creation of a dataset incorporating spatio-tonal information. Also, it requires the design of a strategy to create an image from the body of knowledge generated in the clustering itself.

As for the design of comparison operators for the spatio-temporal universe, there is no predefined solution. This is mainly because it is extremely dependent upon the tonal palette  $\mathbb{T}$ , which can vary from grayscale tones (scalar values in  $\mathbb{R}^+$  or  $\mathbb{N}^+$ ) to hyperspectral signatures (vectors in  $(\mathbb{R}^+)^{256}$  or  $(\mathbb{R}^+)^{512}$ ). However, it is typical to produce a metric from the convex combination of two metrics: one in the spatial universe ( $\mathbb{R}^+ \times \mathbb{R}^+$ ), to account for spatial similarity, and another one in the tonal universe ( $\mathbb{T}$ ), to account for the tonal one. Still, the weights in the convex combination must be adjusted to ensure the representativeness of both spatial and tonal information in the spatio-tonal metric. It is remarkable that the design of comparison measures able to work on a spatio-tonal universe is recurrent in image processing literature. For example, it was a key in the evolution of Baddeley’s delta metric [2] from binary images to gray-scale ones [9].

It is relevant to mention that clustering, at final stages, can also be used for both segmentation and hierarchical segmentation. Literature contains different successful examples, such as the graph-based hierarchical clustering method by Felzenschwalb and Huttenlocher [11] and the FCM-based segmentation based by Yang *et al.* [30]. In these segmentation procedures there is no need to produce intermediate images as the clustering evolves, since the only required result is the distribution of pixels in the final partition. However, they do require spatio-tonal comparison measures for the clustering.

An example of the performance of CUS and clustering-based CAS can be seen in Fig. 1. In this figure we display a colour image, together with the result of a Gaussian smoothing with  $\sigma = 2$ . We can also observe the image at its initial state, together with its state after the 10<sup>th</sup> and 100<sup>th</sup> iterations of the gravitational clustering procedure in [20].

### 3 Content-aware Smoothing based on Spatial Fuzzy *c*-Means

The goal of a content-aware smoothing algorithm is to homogenize image regions while maximally preserving the information on regions of interest, which in this case are mainly edges [19]. However, edges are (a) some of the most sensitive areas when performing image smoothing and (b) a naturally color-wise imprecise zone [5]. In order to preserve information about objects on a image, and given



**Fig. 1.** Example of image smoothing performed with content-aware and content-unaware techniques. (a) The original image; (b) the result with content-unaware smoothing (Gaussian smoothing,  $\sigma = 2$ ); (c) the smoothing output from the 10<sup>th</sup> and 100<sup>th</sup> iteration of gravitational (content-aware) smoothing, respectively. For CUS, (b) shows the blurring of the edges and loss of information. For CAS, (c) shows the progressive blending of tones within objects, while preserving their boundaries.

their border properties, fuzzy set theory comes as a natural alternative. We have hence focused on an existing fuzzy clustering algorithm which embodies the expected needs in our approach: the Spatial Fuzzy  $c$ -Means (SFCM) [7].

The SFCM is an unsupervised  $n$ -dimensional clustering algorithm primarily designed for data clustering [7]. Through the image-to-dataset conversion, any image can be seen as a dataset on which clustering can be applied. The SFCM will receive an image  $I$  as input and will output a set of  $N$  cluster centroids  $\mathbf{C} = (C_1, C_2, C_3, \dots, C_N)$ , with  $C_i \in \Omega \times \mathbb{T}$ . However, the result of a smoothing procedure is an image, which means that the information produced at each iteration needs to be used to produce a progressively smoother version of the image. Multiple approaches can be taken to map the clusters back to image, but the process mainly comprises of two phases: pixel-to-cluster assignment and pixel colour definition.

The first phase consists of assigning the pixels to each of the clusters, so as to determine which cluster or clusters (that is, which class centroids) will be used in the determination of the colour at each pixel. A list of alternatives is available. In a simplistic approach, each pixel can be assigned to the cluster to which it has the highest membership degree. Also, a combination of the membership degrees to the clusters can be used to perform the cluster assignment, in a procedure similar to Generalized Mixture Functions [10]. A third alternative is to keep the partial membership to each of the clusters, so as to represent that the pixel is not completely assigned to any of them.

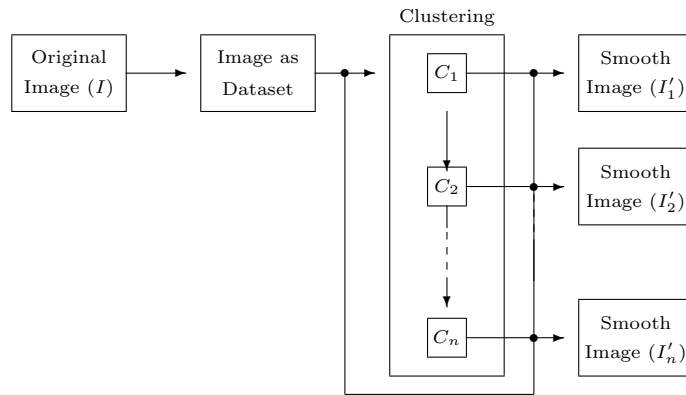
At the second phase, the cluster information at each pixel is used to produce a tonal value for each pixel  $p \in \Omega$ . Surely, this phase depends on the decision made in the former phase. If each pixel is uniquely associated to one cluster, its tone in the smooth image will be that represented in the tonal part of the cluster it is assigned to. If the pixels are considered to have multiple partial membership degrees to all clusters, the tone value can be obtained from the weighted combination of the membership degrees and the tonal information of the clusters.

Although membership degrees shall not be understood as weights to be operated with, we can use the membership functions for each cluster to materialise such weighted combination. Let  $I$  be an image and let  $\mathbf{C}_i = \{C_{i,1}, \dots, C_{i,N}\}$  be the set of class centroids at some iteration of the clustering. From each centroid  $C_{i,j}$ , we can compute a membership function  $\mu_j : \Omega \mapsto [0, 1]$  representing the membership degree of each pixel to the  $i$ -th cluster. The tone of a pixel  $p \in \Omega$  in the  $i$ -th smooth image  $I'_i$  can be computed as

$$I'_i(p) = \sum_{j=1}^N \mu_j(p) \cdot C_{i,j} , \quad (1)$$

where  $C_{i,j}$  represents the tonal information of  $j$ -th cluster at the  $i$ -th iteration.

The overall workflow of the proposal is shown in Fig. 2. From now onward, this algorithm will be referred to as CAS-SFCM.



**Fig. 2.** Schematic representation of content-aware smoothing based on Spatial Fuzzy  $c$ -Means (SFCM). After converting an image  $I$  into a dataset, the clustering procedure iteratively produces cluster centers  $\mathbf{C}_i$ . In order for those centers to be converted into a progressively smoother image, the information from the centers is combined with the data in the original image, as covered in Section 3.

The result of the CAS-SFCM is expected to be an edge-preserving, smoothen version of the image, since the pixels will take colors progressively evolving toward clustering centroids. As such centroids are influenced by groups of (spatio- tonally) similar pixels, they shall evolve to represent highly populated regions in the spatio-tonal space. By applying Eq. (1) in the reconstruction of the images from the clustering data, pixels shall evolve towards the colors represented by such centroids, hence producing a context-aware smoothing behaviour. This shall be put to the test in the upcoming section.

## 4 Experimental results

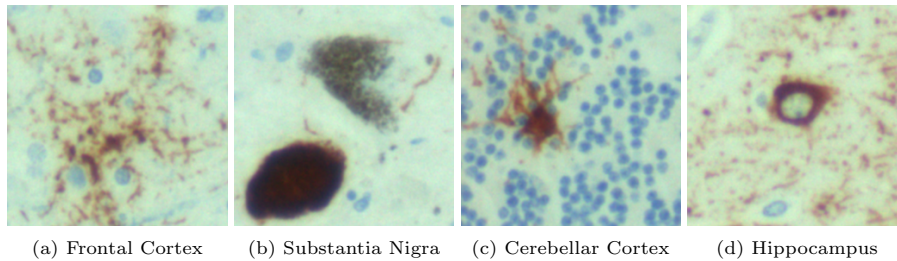
In order to test the applicability of our proposal to realistic scenarios, we put it to the test in a dataset of electronic microscopy for neural tissue analysis. Specifically, we use a dataset of neural biopsies from patients affected by Progressive Supranuclear Palsy (PSP). These images are used to determine how the presence of free protein (in this case, Tau protein) at different areas of the brain affects the degeneration of the brain functionality. The dataset is composed of 188 high resolution images of all brain regions from 14 PSP-affected patients. For better visualisation, patches of the original images will be analysed on this paper. From now onward, the PSP image dataset will be referred to as PSP dataset.

### 4.1 Progressive Supranuclear Palsy

Neurosciences, as well as neurology, is heavily hampered by the fact that few invasive studies can be used to audit the state of a diseased organ. Invasive study methods can permanently damage neural tissues and, are unsuitable for the study of many processes related to neurodegeneration [29]. In this context, scientists have developed strategies for neural tissue analysis that do not involve invasive techniques. For Progressive Supranuclear Palsy, for instance, mislocalized Tau protein is the main study object to understand the condition [14].

The Tau protein is present in all humans in a natural manner. It has the essential function of structurally stabilising the neuron’s microtubules and to regulate some biological processes [22]. For patients with PSP, an anomaly causes the Tau protein to detach from its original place, which in time will cause neural death [12]. The detached Tau protein also acts as a catalyst for the degeneration process. Thus, Tau protein is a key biomarker for PSP and several studies have been performed to relate the quantity, location and form of the free Tau protein to the impact of the disease in a patient [22]. Most of these studies use imaging techniques to either manually or automatically segment the Tau protein and identify its form [6, 15]. However, segmenting, identifying and quantifying the Tau protein are all challenging tasks, as the imaging conditions vary greatly in the few data that exist. One of these conditions is the visual aspect of the Tau protein after immunohistochemistry processing. After tinting the neural tissue, Tau protein tends to take a characteristic colour. Figure 3 contains examples of Tau protein deposits, which are identifiable by the brownish-tone it takes in comparison to other artefacts.

Considering the existing challenges in defining the edges of Tau protein areas due to the tonality variation, a smoother version of the images, in which the tonality change issue is addressed, would greatly improve efficiency and results of future studies, both for automated and non-automated approaches. In addition, given that Tau protein is analysed by experts as regions and not by pixel, the spatio-tonal clustering comes as a natural approach, following the hypothesis that a pixel that belongs to a Tau region is usually near other pixels that belong to the same Tau region.



**Fig. 3.** Patches of biopsies after being tinted to highlight Tau protein, which is identifiable by its brownish tone. Patches are taken from different brain regions, as indicated individually for each column.

## 4.2 Experimental configuration

This section intends to illustrate the specific configuration of our proposal for its application to a realistic dataset. The PSP dataset is used for illustration purposes.

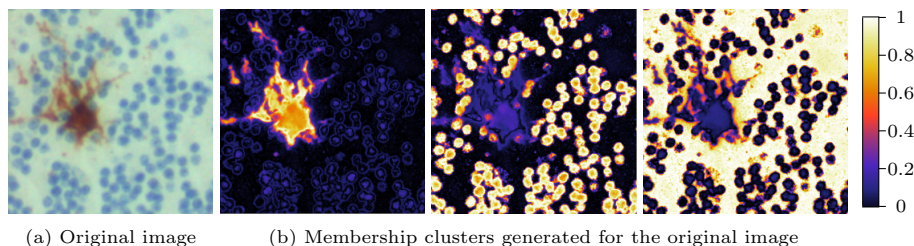
The first relevant decision is related to the tonal palette of the images, which needs to be coordinated with the decision on the metrics to be used in the SFCM. In this case study, we select the CIELab colour space. The main reason is that distances yielded by the Euclidean metric on CIELab tones are consistent with tonal dissimilarities in human perception. Thus, the PSP dataset will contain 5-dimensional instances comprising  $L$ ,  $a$  and  $b$  colour space components, as well as the pixel coordinates.

A second decision of interest is related to the construction of the smooth images from the centroids. In this case, we use the strategy in Eq. (1) so as to combine as much information as possible from all clusters. Figure 4 contains a visual representation of the clusters in an image from the PSP dataset. Specifically, we observe the three clusters generated from the 100<sup>th</sup> iteration of the clustering process. Such visual representations can be used to inspect the actual fitting of the clusters to the different regions or artefacts in the image.

## 4.3 Result evaluation

Ideally, content-aware smoothing should be evaluated in a quantitative way. Certain quantitative measure or strategy should evaluate the results in terms of intra-region smoothing and inter-region contrast enhancement. However, such measures or strategies are absent from the literature. On the one hand, there is no possibility to generate ground truth, since it is unclear which is the optimal final state of a content-aware smoothing procedure. Hence, comparison-based strategies are discarded. On the other hand, standalone image quality strategies (such as BRISQUE [21]) attempt to measure how good an image looks to the Human Visual System, which is not really the goal of content-aware smoothing. Alternative options can be built around the intelligent use of contrast, homogeneity and luminance quantifications. However, the use of multiple metrics or





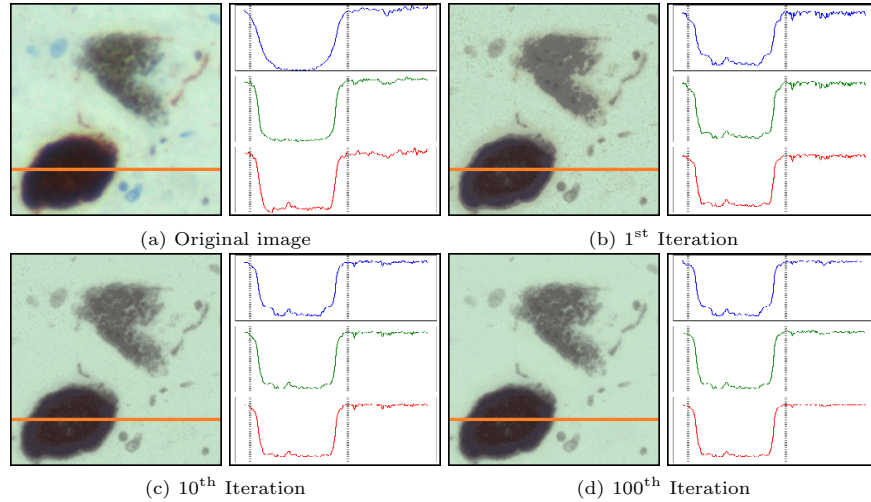
**Fig. 4.** Visual representation of the membership functions modelled after configuring the clustering process with three clusters. (a) The original image on which the smoothing will be performed; (b) the visual representation of the three clusters generated by the clustering for (a). We can observe that each cluster in (b) mainly contains one object area from (a), specifically the tau protein (leftmost cluster), the blueish nuclei (middle cluster) and the background (rightmost cluster).

quantifiers would generate a complex measurement strategy and, as long as all individual strategies are weak by themselves, we might reach a questionable result evaluation.

The indirect evaluation of the CAS-SFCM would be the more natural approach to take, as content-aware smoothing is normally performed to improve the image quality for object segmentation. However, the use of a method or segmentation schema would add another layer of parameters to the CAS-SFCM evaluation. Also, if this indirect strategy is applied, the evaluation would be performed on the output of the method with the smoother images applied and not on the images themselves.

Considering the above-mentioned factors, the direct and indirect evaluations of the CAS-SFCM in our view are unsuitable in the current state of literature. We have hence opted for a visual evaluation of the results. In this manner, we do not intend to identify the best performing set of parameters, or to compare the results of our proposal to that by other proposals in literature. Instead, we intend to illustrate how our proposal actually leads to interesting results in the context of applications.

The first question relates to the ability of our algorithm to perform both intra-region regularisation and inter-region contrast enhancement. In order to illustrate this fact, we present in Fig. 5 the line-based analysis of the evolution of an image path from the PSP dataset. The figure contains the state of the image patch in its original state, after the 1<sup>st</sup>, 10<sup>th</sup> and 100<sup>th</sup> iterations, together with the plot-based representation of one of its rows (highlighted in orange). This plot-based representation displays the red, green and blue channel of the selected row. Although the variation in the image patch itself is subtle, we can observe how the signal evolves in all channels. This evolution is seen in two different aspects. Firstly, we observe a reduction in the rugosity of the quasi-flat areas of the image. Secondly, we see how the contrast at the transition points (between the background and the Tau protein deposit) are sharpened progressively.

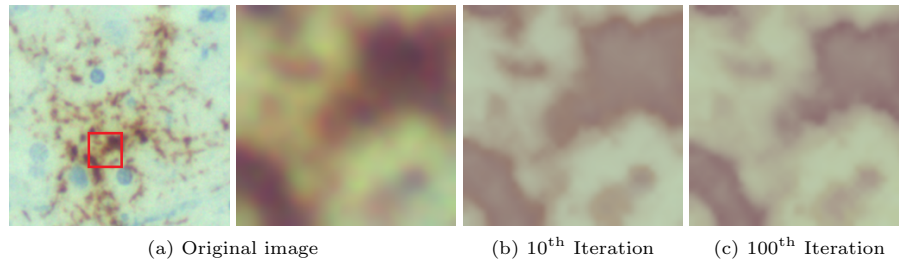


**Fig. 5.** Visual representation of the state of one row in an image patch at different iterations of the smoothing procedure. The figure displays the state of the image patch in its original form, and after the 1<sup>st</sup>, 10<sup>th</sup> and 100<sup>th</sup> iterations, as well as the state of the row marked in orange (individually for each RGB component). We can observe both the intra-region regularisation (reduction of the rugosity inside the objects) and the inter-region contrast enhancement (sharper tonal changes at object boundaries). The vertical grey lines are for better visualisation.

A detailed view of this fact can be seen in Fig. 6. In this figure we present a detailed patch of the image to observe how the regularisation of the image is not only noticeable for individual components, as seen in Fig. 5, but also for multi-valued tones. Fig. 6 displays the original patch (Fig. 6(a)) and the state of the patch after 1<sup>st</sup>, 10<sup>th</sup> and 100<sup>th</sup> iterations (Fig. 6(b)-(c)). We observe in Fig. 6(a) how deposits normally feature smooth and gradual boundaries. However, with content-aware smoothing (as in Fig. 6(b)) the boundary is sharpened. .

## 5 Conclusions

In this paper, we proposed a content-aware image smoothing approach for neural tissue images based on fuzzy clustering. Our proposal is inspired by the problems and limitations that experts have when segmenting regions of interest from neural tissue imagery to perform studies on neurodegenerative diseases. Specifically, the approach is divided in three phases, being: (1) turning images into clusterable data; (2) clustering the data; and (3) generating a smooth version of the input image from the clustering output. For the experimentation and results obtained, our proposal is analysed by the prism of tonality stability, colour distribution and expert feedback, as a direct or indirect analysis is unsuitable for the context. The three analyses yielded positive feedback, showing meaningful and useful improvements through the use of the CAS-SFCM. Nevertheless,



**Fig. 6.** Zoomed-in analysis of the preservation of boundaries and the smoothing behaviour for an image from the PSP dataset. The patch is displayed in both its original state and its state after the 10<sup>th</sup> and 100<sup>th</sup> iterations.

a natural possibility for future work is to delve into means to quantify the results attained by the CAS-SFCM. The comparison of our proposal with other smoothing procedures is another possibility of future work.

## References

1. Babaud, J., Witkin, A.P., Baudin, M., Duda, R.O.: Uniqueness of the Gaussian kernel for scale-space filtering. *IEEE Trans. on Pattern Analysis and Machine Intelligence* **8**(1), 26–33 (1986)
2. Baddeley, A.J.: Errors in binary images and an  $L^p$  version of the Hausdorff metric. *Nieuw Archief voor Wiskunde* **10**, 157–183 (1992)
3. Barash, D.: A fundamental relationship between bilateral filtering, adaptive smoothing, and the nonlinear diffusion equation. *IEEE Trans. on Pattern Analysis and Machine Intelligence* **24**, 844–847 (2002)
4. Barash, D., Comaniciu, D.: A common framework for nonlinear diffusion, adaptive smoothing, bilateral filtering and mean shift. *Image and Vision Computing* **22**(1), 73–81 (2004)
5. Bonnet, A.: On the regularity of edges in image segmentation. In: *Annales de l’Institut Henri Poincaré C, Analyse non linéaire*. vol. 13, pp. 485–528 (1996)
6. Borroni, B., Gardoni, F., Parnetti, L. *et al.*: Pattern of Tau forms in CSF is altered in progressive supranuclear palsy. *Neurobiology of Aging* **30**(1), 34–40 (2009)
7. Chuang, K.S., Tzeng, H.L., Chen, S. *et al.*: Fuzzy c-means clustering with spatial information for image segmentation. *Computerized Medical Imaging and Graphics* **30**(1), 9–15 (2006)
8. Comaniciu, D., Meer, P.: Mean shift: a robust approach toward feature space analysis. *IEEE Trans. on Pattern Analysis and Machine Intelligence* **24**(5), 603–619 (2002)
9. Coquin, D., Bolon, P.: Application of Baddeley’s distance to dissimilarity measurement between gray scale images. *Pattern Recognition Letters* **22**(14), 1483–1502 (2001)
10. Farias, A.D.S., Santiago, R.H., Bedregal, B.: Some properties of generalized mixture functions. In: *2016 IEEE International Conference on Fuzzy Systems*. pp. 288–293 (2016)
11. Felzenszwalb, P.F., Huttenlocher, D.P.: Efficient graph-based image segmentation. *International Journal of Computer Vision* **59**(2), 167–181 (2004)

12. Flament, S., Delacourte, A., Verny, M. *et al.*: Abnormal tau proteins in progressive supranuclear palsy. *Acta Neuropathologica* **81**(6), 591–596 (1991)
13. Florack, L.: *Image structure*, vol. 10. Springer Science & Business Media (1997)
14. Iglesias-Rey, S., Antunes-Santos, F., Hagemann, C. *et al.*: Unsupervised cell segmentation and labelling in neural tissue images. *Applied Sciences* **11**(9), 3733 (2021)
15. Kuiperij, H.B., Verbeek, M.M.: Diagnosis of progressive supranuclear palsy: Can measurement of tau forms help? *Neurobiology of Aging* **33**(1), 204.e17–204.e18 (2012)
16. Lindeberg, T.: *Generalized Gaussian scale-space axiomatics comprising linear scale-space, affine scale-space and spatio-temporal scale-space*. Tech. rep., KTH (Royal Institute of Technology) (2011)
17. Lindeberg, T.: *Scale-Space Theory in Computer Vision*. Ph.D. thesis, KTH (Royal Institute of Technology) (1991)
18. Lopez-Molina, C., Galar, M., Bustince, H., De Baets, B.: On the impact of anisotropic diffusion on edge detection. *Pattern Recognition* **47**(1), 270–281 (2014)
19. Madhulatha, T.S.: An overview on clustering methods. *IOSR Journal of Engineering* **2**(4), 719–725 (2012)
20. Marco-Detchart, C., Lopez-Molina, C., Fernandez, J., Bustince, H.: A gravitational approach to image smoothing. In: *Advances in Fuzzy Logic and Technology*, pp. 468–479. Springer (2017)
21. Mittal, A., Moorthy, A.K., Bovik, A.C.: No-reference image quality assessment in the spatial domain. *IEEE Trans. on Image Processing* **21**(12), 4695–4708 (2012)
22. Nizynski, B., Dzwolak, W., Nieznanski, K.: Amyloidogenesis of Tau protein. *Protein Science* **26**(11), 2126–2150 (2017)
23. Perona, P., Malik, J.: Scale-space and edge detection using anisotropic diffusion. *IEEE Trans. on Pattern Analysis and Machine Intelligence* **12**(7), 629–639 (1990)
24. Saint-Marc, P., Chen, J.S., Medioni, G.: Adaptive smoothing: A general tool for early vision. *IEEE Trans. on Pattern Analysis and Machine Intelligence* **13**(6), 514–529 (1991)
25. Tomasi, C., Manduchi, R.: Bilateral filtering for gray and color images. In: *Proc. of the IEEE International Conf. on Computer Vision*. pp. 838–846 (1998)
26. Weickert, J.: *Anisotropic Diffusion in Image Processing*. ECMI Series, Teubner-Verlag (1998)
27. Weickert, J.: Coherence-enhancing diffusion filtering. *International Journal of Computer Vision* **31**(2-3), 111–127 (1999)
28. Weickert, J.: Nonlinear diffusion scale-spaces: From the continuous to the discrete setting. In: Berger, M.O., Deriche, R., Herlin, I., Jaffré, J., Morel, J.M. (eds.) *ICAOS '96, Lecture Notes in Control and Information Sciences*, vol. 219, pp. 111–118. Springer Berlin Heidelberg (1996)
29. Werner, C.T., Williams, C.J., Fermelia, M.R. *et al.*: Circuit mechanisms of neurodegenerative diseases: A new frontier with miniature fluorescence microscopy. *Frontiers in Neuroscience* p. 1174 (2019)
30. Yang, Z., Chung, F.L., Shitong, W.: Robust fuzzy clustering-based image segmentation. *Applied Soft Computing* **9**(1), 80–84 (2009)
31. Yung, H.C., Lai, H.S.: Segmentation of color images based on the gravitational clustering concept. *Optical Engineering* **37**(3), 989–1000 (1998)