ORIGINAL ARTICLE

Expert Systems WILEY

Combined use of radiomics and artificial neural networks for the three-dimensional automatic segmentation of glioblastoma multiforme

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Funding information

Universidad de Las Palmas de Gran Canaria; Agencia Nacional de Promoción de la Investigación, el Desarrollo Tecnológico y la Innovacion, Grant/Award Number: PICT 2017 3802; Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET); Universidad de Buenos Aires (UBA)

Abstract

Glioblastoma multiforme (GBM) is the most prevalent and aggressive primary brain tumour that has the worst prognosis in adults. Currently, the automatic segmentation of this kind of tumour is being intensively studied. Here, the automatic threedimensional segmentation of the GBM is achieved with its related subzones (active tumour, inner necrosis, and peripheral oedema). Preliminary segmentations were first defined based on the four basic magnetic resonance imaging modalities and classic image processing methods (multithreshold Otsu, Chan-Vese active contours, and morphological erosion). After an automatic gap-filling post processing step, these preliminary segmentations were combined and corrected by a supervised artificial neural network of multilayer perceptron type with a hidden layer of 80 neurons, fed by 30 selected radiomic features of gray intensity and texture. Network classification has an overall accuracy of 83.9%, while the complete combined algorithm achieves average Dice similarity coefficients of 89.3%, 80.7%, 79.7%, and 66.4% for the entire region of interest, active tumour, oedema, and necrosis segmentations, respectively. These values are in the range of the best reported in the present bibliography, but even with better Hausdorff distances and lower computational costs. Results presented here evidence that it is possible to achieve the automatic segmentation of this kind of tumour by traditional radiomics. This has relevant clinical potential at the time of diagnosis, precision radiotherapy planning, or post-treatment response evaluation.

KEYWORDS

artificial neural networks, automatic segmentation, glioblastoma multiforme, image processing, radiomics

INTRODUCTION 1

Gliomas, derived from neuroglial cells or its precursors, are the primary brain tumours most frequent in adults (DeVita et al., 2019; Kannan et al., 2022). Among this group, glioblastoma multiforme (GBM, grade IV astrocytoma) is the most aggressive and of worst prognosis (Chiariello

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et al., 2023; van Solinge et al., 2022). Although it very rarely metastasizes, its high intracranial invasive capacity cannot be completely evidenced by actual medical imaging technology. This is considered to be one of the causes of frequent tumour recurrence observed after the standard Stupp protocol that combines surgery, chemotherapy with temozolomide, and fractional radiotherapy (Stupp et al., 2005). This results in a median overall survival of approximately 15 months and presents an important challenge for current oncology. Image processing by medical radiomics may be of great benefit with this issue, specially when combined with multimodal magnetic resonance imaging (MRI) (Zhang et al., 2022).

Medical radiomics has the goal of acquiring, in a patient-specific way, quantitative information that cannot be obtained by the operator naked eye (Lambin et al., 2012; Mu et al., 2022). It is based on the hypothesis that microscopic tissue, cell, or molecular heterogeneity can be captured at the macroscopic level by quantitative features extracted from the image. Much literature has been produced on the use of radiomics in GBM segmentation, diagnosis, prognosis, treatment evaluation, pseudo-progression detection, and prediction of recurrence/survival (Aftab et al., 2022). Artificial intelligence systems can also provide a great advance in the management of this malignancy, potentially improving its efficiency and efficacy (Vobugari et al., 2022).

Automating tumour segmentation is becoming essential not only as a helpful tool for the clinician during tumour characterization and target treatment volume, but also as a necessary prior step in other more complex radiomic studies. Many methods have been proposed to achieve the automatic MRI-based brain tumour segmentation (Bhalodiya et al., 2022). Among them, U-Net deep learning technologies are cited the most (Bhandari et al., 2020; Feng et al., 2020), with high accuracy scores (Dice coefficients of 90%). The combination of Conditional Random Fields (CRF) with fully Convolutional Neural Networks (CNN); and of CRF with DeepMedic or Ensemble; has been very effective in this field (Wadhwa et al., 2019). More recently, unified frameworks of the UNetFormer type, that combines a CNN with Transformer-based encoders and/or decoders, have also being tested (Hatamizadeh et al., 2022).

Nevertheless, the automatic segmentation of the GBM is a particularly complex task, not yet solved. This is not only due to its great intraand inter-tumour heterogeneity (Martin et al., 2022), but also due to its high invasive capacity into peripheral nervous tissue (Blystad et al., 2017). This implies that a great part of the vasogenic oedema that surrounds the active tumour usually coexists with microscopic tumour infiltration. To consider all relevant tumour regions, this oedematous area, often very extended and with rather diffuse boundaries, has to be also included in the region of interest (ROI) to be segmented. This open problem is at present targeted by the University of Pennsylvania through their annual Brain Tumor Segmentation (BraTS) Challenges (Menze et al., 2015) (https://www.med.upenn.edu/cbica/brats/) (last one, BraTS 2023, still on-going).

Overcoming the challenge of automatic GBM segmentation could lead to the development of advanced clinical tools capable of being integrated into routine clinical practice, improving diagnosis and therapeutics in many critical aspects as: (1) Accurate and differential diagnosis, essential for an early and specific treatment. (2) Personalized treatment, since the delimitation of the oedema extent gives an idea of the degree of infiltration of a given tumour. This information allows for better radiotherapy planning, the identification of areas that could need more aggressive intervention or regions more prone to recurrence. (3) Evaluation of treatment outcome and/or recurrence, since precise segmentation would allow for a better quantification of the tumour response, as well as the existence of resistant or recurrent areas.

We present here a relatively simple algorithm for the automatic three-dimensional segmentation of the GBM combining classic image processing methods with radiomics using an Artificial Neural Network (ANN). First, preliminary segmentations were obtained from the four basic pre-processed MRI modalities of the BraTS challenge database through image-processing. Then, radiomic features extracted and selected from these MRI modalities were used to feed an ANN of the perceptron type with one hidden layer of 80 neurons, that classifies each image voxel into one of four classes: active tumour, necrosis, oedema or normal tissue. After an automatic post-processing step, the preliminary segmentations were corrected by the ANN classification.

The contribution of the proposed work is threefold: (1) Efficient automatic segmentation of the entire tumour and subareas is achieved using standard radiomics. In current methods present in the bibliography, necrosis is not usually differentiated from the active tumour, but rather both areas are segmented as the tumour core. (2) Our algorithm shows similar results to other machine learning techniques but with a lower computational cost. Our neural network does not require a large set of parameters, which also makes it suitable for adaptation to higher-resolution images in the near future. (3) The complete algorithm used is available on GitHub, which makes it reproducible and allows free development of future new versions. For all the above, the three-dimensional segmentation algorithm proposed here has clinical potential in diagnosis, radiotherapy planning, and/or evaluation of post-treatment responses.

The article is structured as follows. First, in Section 2, we explain the design to solve the problem. Then, in the Section 3, we described the dataset used, and the performance evaluation of the ANN and the full algorithm proposed. After a Section 4, some Conclusions and Future Work are outlined.

2 | METHODOLOGY

A general diagram of the entire algorithm proposed in this work is described in Figure 1. Preliminary segmentations of the whole region of interest (ROI) and inner sub-zones were determined applying classic image processing methods (Otsu multithreshold, Chan–Vese active contours, and morphological erosion) in images from the four basic MRI modalities (T1, gadolinium enhanced T1 or T1c, T2 and FLuid-Attenuated Inversion Recovery or FLAIR) pre-processed by the database. Then a supervised ANN was trained to define the final active tumour, necrosis, and oedema segmentations. The algorithms designed to perform these different steps are all coded in Matlab (https://la.mathworks.com/products.html) and

applied to the complete image series of the modality in use to obtain three-dimensional segmentations. Full code applied in this work (GBManalizer) is freely available at GitHub (https://github.com/amulet1989/GBManalizer).

2.1 | Segmentation of the region of interest (ROI)

To achieve a preliminary segmentation of the ROI, which in our case has to include the active tumour, the necrotic core and the peripheral oedema; FLAIR and T2 modalities were in first place combined by a voxel-to-voxel addition to reach a new FLAIR plus T2 image (FLAIR+T2) with a more homogeneous ROI area (Figure 2c,i). This combination allows the dark necrotic areas observed in some FLAIR images (Figure 2a) to be highlighted, and the bright liquid ventricle areas observed in T2 images (Figure 2b,h), to be de-emphasized.



FIGURE 1 General diagram of the whole algorithm proposed for GBM segmentation. First, the four main MRI modalities pre-processed by the database were used to make preliminary segmentations achieved by classic image-processing methods. Then, final subregion segmentations were defined by an ANN feed by extracted and selected radiomic features.



FIGURE 2 Preliminary ROI segmentations. Each row presents a different GBM example case. First column: FLAIR modality. Second column: T2 modality. Third column: FLAIR+T2 modality. Fourth column: Initial ROI seeds. Fifth column: Final ROI seeds. Sixth column: Preliminary ROI segmentations in the FLAIR modality.

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Automation of the ROI segmentation requires the automatic definition of a seed volume (initial volume where the region-growing algorithm will start to work). To automatically find this seed, FLAIR+T2 images were first quantified at nine gray intensity levels (eight thresholds) using the multithreshold Otsu method (Xu et al., 2011), a modification of the original Otsu (Otsu, 1979) that finds the threshold that maximizes the variance between classes σ^2 between two classes (1 and 2), with:

$$\sigma^2 = \omega_1 (\mu_1 - \mu_\tau)^2 + \omega_2 (\mu_2 - \mu_\tau)^2, \tag{1}$$

being μ_1 and μ_2 the median intensity of the class, μ_{τ} the mean intensity of the entire image, and $\omega_1 + \omega_2 = 1$. In Matlab, the method is implemented through the 'multithresh' function from the image-processing toolbox.

Then a three-dimensional binary mask was created that included the five levels of higher intensity. If this mask is larger than a volume threshold (200 cm³, nearly 7 cm in diameter, one sixth of the total volume of the brain), then the lower intensity level is discarded and the new mask will keep the remaining four levels. The described process was repeated until the mask volume was smaller than the threshold-volume. As this mask may be composed of different non-connected volumetric components, the larger one is defined to be the initial ROI seed (Figure 2d,j).

This initial seed was then eroded in the three dimensions by morphological erosion, a procedure that removes floating voxels and thin lines so that only substantive objects remain (Heijmans, 2020). This is achieved using the 'imerode' Matlab function by means of the passage, through the entire image, of a suitably designed structural element. Thus, erosion was able to eliminate objects such as ventricles (Figure 2j) or seizures that do not correspond to the tumour but may be still bright in FLAIR+T2 images. This step gives rise to the final ROI seed (Figure 2e,k).

Then the Chan-Vese active contour method (Chan & Vese, 2001) was applied to make the seed grow in the FLAIR modality. This parametric method makes evolve a contour curve starting from inside the object to be defined until reaching its limits, according to the minimization of a defined energy function. The implementation in Matlab is achieved by the 'activecontour' function with 20 iterations. This iteration level was determined by mesh search, pursuing a better trade-off between segmentation results and computational cost. Finally, inner gaps of the segmentation volume were filled in by the 'imfill' Matlab function. This gives rise to a preliminary ROI segmentation (Figure 2f,I). The method seeks to slightly overestimate the ROI region, in order to let it be corrected later by the ANN to define the final ROI segmentation.

2.2 | Preliminary active tumour and oedema-plus-necrosis segmentations

To achieve active tumour segmentations, ROI segmentations in the T1c modality (Figure 3a) were quantified in six gray intensity levels using the Otsu multithreshold method (Figure 3b). Then an initial three-dimensional mask was extracted using the four higher intensity levels (Figure 3c). If the volume of this mask is higher than a threshold (25% ROI), then the lower intensity level was discarded. This process was repeated until the mask volume was lower than the threshold volume.

At this point, the final mask achieved defines the limits of the preliminary active tumour segmentation (Figure 3d) that will be corrected later by the ANN. The complementary mask (ROI minus active tumour) was defined as the oedema-plus-necrosis (EN) mask. This volume corresponds to the preliminary segmentation of oedema plus necrosis, the ROI volume most difficult to discriminate, as its gray intensity levels are very similar. Finally, this region will be used to feed the ANN.

2.3 | Radiomic feature extraction and selection

In order to obtain final three-dimensional segmentations for the ROI, active tumour, necrosis, and oedema volumes; an ANN was constructed and trained by selected features extracted from the four MRI modalities. Nevertheless, the network did not work with information from the whole image, but only with that from voxels (in each modality) that belong to the EN mask previously defined.



FIGURE 3 Preliminary active tumour segmentation. (a) ROI segmentation in the T1c modality. (b) Quantified ROI segmentation in the T1c modality. (c) Initial mask defined by the four higher gray-intensity levels. (d) Final mask of the preliminary active tumour segmentation.

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The whole process is exemplified for the T1c modality in Figure 4. First, the images of the four modalities were normalized using the *Z*-score method to homogenize the gray intensity ranges between different machines and protocols (Carre et al., 2020; Mizumura & Kumita, 2006) (Figure 4a). This method subtracts from each voxel intensity *x* the mean intensity of the whole image or region of interest μ and divides it from the correspondent standard deviation σ , as follows:

$$z = \frac{(x - \mu)}{\sigma}.$$

Then, each voxel of the EN mask (Figure 4d) was analysed in each pre-segmented image alongside a neighbourhood window of 7×7 voxels (Figure 4b,e) to extract three first-order features of the gray-intensity histogram: maximum, minimum and range.

The same was done, but in this case using quantified images at 32 gray levels, (Figure 4c,f) to extract three first-order global texture features (kurtosis, skewness, and variance) (Vallieres et al., 2015), and nine higher-level Haralick texture features based on the Gray-Level Co-occurrence Matrix (GLCM) (energy, contrast, correlation, homogeneity, variance, average sum, entropy, dissimilarity, and self-correlation). In 1973, Haralick proposed the use of the GLCM matrix as a method to quantify the spatial relationship among neighbour voxels of an image (Haralick et al., 1973). These texture features are widely used at present due to their simplicity and intuitive interpretation (Lofstedt et al., 2019). In brief, 15 features were extracted in each of the four MRI modalities, making a total of 60 features. All of them were normalized by standard normalization to make them comparable.

Feature extraction was performed using the radiomics tool available on Github (https://github.com/mvallieres/radiomics). The main functions used here were equalQuantization, windowMxN, max, min, range, getGlobal-Textures, getGLCM, and getGLCMtextures. In a preliminary search for the optimal feature extraction parameters (window size and image gray level quantification), an ANN was trained to test 5×5 and 7×7 voxels, as well as 32 and 64 gray levels. The best Dice similarity coefficients were achieved by a 7×7 -voxels window and at 32 gray level quantification.

To reduce computational cost and eliminate redundant or not informative features, a feature selection process was performed using the Maximum Relevance/Minimum Redundancy (MRMR) algorithm (Ding & Peng, 2005). Through this algorithm, features can be selected to be mutually far away from each other while still having a 'high' correlation with the classification variable. The MRMR algorithm was implemented by the Matlab 'fscmrmr' function. In this way, 30 features were found to be relevant enough and not redundant to be selected to feed an ANN. This network classifies, with a given probability, each voxel of the EN mask in each MRI modality into one of four classes: active tumour, necrosis, oedema, or healthy tissue; giving a segmented output image (Figure 4g).



FIGURE 4 Feature extraction and ANN architecture. (a) Normalized GBM image in T1c. (b) ROI segmentation in T1c. (c) Quantified ROI segmentation in T1c. (d) EN mask. (e) Zoom of a 7×7 -voxels window from image (b). (f) Zoom of a 7×7 -voxels window from image (c). (g) ANN output segmentation achieved by radiomic features. (h) ANN architecture (30:80:4).

2.4 | Artificial neural network (ANN)

The 30 selected features fed an ANN with a multilayer perceptron architecture of one hidden layer with 80 neurons (Ramchoun et al., 2016), trained to sort voxels in four classes (architecture 30:80:4) (Figure 4h). This architecture was chosen because it is one of the simplest yet capable of achieving good results. The use of only one hidden layer was justified by the universal approximation theorem, which establishes that standard multilayer feedforward networks with as few as one hidden layer are capable of approximating any Borel measurable function (Hornik, 1989). In our case, this layer applied the hyperbolic tangent activation function, as it presented good tolerance to failures and limits. Finally, the output layer applied the 'softmax' activation function, that obtains a representation based on probabilities, which is specially adequate to multi-class outputs, as is our case.

Hyperparameter optimization (neuron quantity and learning rate) was performed, avoiding overfitting, by mesh search and cross-validation using the KFold method with stratification and five partitions of the dataset (K = 5). The network was fitted by the limited-memory quasi-Newton Broyden-Fleter-Goldfarb-Shanno (BFGS) optimizer to minimize the error function of cross-entropy loss (Nocedal & Wright, 2006), through 500 epochs applied to 85 GBM cases from the BraTS database. No batches were used, the entire training dataset was applied as a unique batch in each epoch.

Network parameters used for the different configurations tested never exceeded 4205, which is negligible compared to the quantity of parameters required by CNN architectures usually used for this task. As the network classifies voxels (not images), and considering only voxels present in the EN mask, the 85 training GBM cases generate a dataset of (voxels \times features \times modalities) = (8.437.339 \times 30 \times 4) = 1.012.480.680 data, which can be considered large enough. This dataset was then randomly divided into two groups: training (80%) and validation (20%). Voxel distribution per class in both groups was as following: active tumour: 10.7%, oedema: 58.6%, necrosis: 17.6%, and healthy tissue: 13.1%. Using an AMD Ryzen7 4700u CPU with 16 Gb RAM and Windows 10, network training never was longer than 2 h under a defined configuration. All voxels classified by the network as active tumour were added to the preliminary active tumour segmentation, while those classified as normal tissue were eliminated from all segmentations.

3 | EXPERIMENTAL SECTION

3.1 | Dataset

The results shown here are based on data generated by The Cancer Genome Atlas (TCGA) Research Network (Bakas et al., 2017a) (https://www. cancer.gov/ccg/research/genome-sequencing/tcga). GBM MRI images were obtained from two multicentric databases: the BraTS Challenge 2020 database with 366 GBM cases (Bakas et al., 2018) and The Cancer Imaging Archive (TCIA) database (Clark et al., 2013) (https://www. cancerimagingarchive.net/) (TCGA-GBM collection; Bakas et al., 2017b; Scarpace et al., 2016; https://doi.org/10.7937/K9/TCIA.2016. RNYFUYE9) with 262 cases. BraTS database includes cases from 19 different medical institutions analysed using different MRI scanners and clinical protocols. Of the 120 cases extracted semi-randomly from the BraTS database, 85 were used to train and validate the ANN (71%) and 35 to test the entire algorithm (29%). The algorithm was also tested by other 10 additional cases from the TCIA database. Each GBM case comprises whole sets of images in the four basic MRI modalities, in NIfTI format and pre-processed (with the skull extracted, co-registered to the same anatomical template and with a three-dimensional resolution [voxel] of 1 mm³).

In all cases, each GBM has its own ground-truth segmentation defined by a neuroradiologist with area labels depicted as active tumour, necrotic core, or peripheral oedema.

3.2 | Evaluation of ANN performance

Many metrics can be applied to evaluate the performance of ANN multi-class classification, being those derived from the confusion matrix the most used (Grandini et al., 2020). Among them, we have accuracy, precision, sensitivity (or recall), and F1 score. Being TP = True Positive, TN = True Negative, FP = False Positive, and FN = False Negative, Accuracy is defined as the proportion of the total cases that are correctly classified:

$$Accuracy = \frac{TP + TN}{TP + TN + FP + FN}.$$
(3)

Precision is the proportion of the positive-predicted cases that are really positive:

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	$Precision = \frac{TP}{TP + FP}.$	(4)	
Sensitivity is the proportion of the	he truly positive cases that are positive-predicted:		

$$Sensitivity = \frac{TP}{TP + FN}.$$
(5)

And the F1 score is defined as the harmonic mean between precision (P) and sensitivity (S):

$$F1 \text{ score} = \frac{2^* P^* S}{P + S}.$$
(6)

Table 1 presents the confusion matrix correspondent to the validation group. In this table, rows correspond to real classes and columns to predicted ones. Diagonal values in bold are data (voxels) correctly classified. The precision values are 82.5%, 88.1%, and 73.1% for necrosis, oedema, and active tumour, respectively. The sensitivity values are 76.6%, 92.1%, and 72.8% for the same classes, respectively. The *F*1 score values are 79.5%, 90%, and 72.9% for the same classes, respectively. As the ANN only classifies the voxels present in the EN mask, the values related to oedema and necrosis are the most relevant in this case.

There are also macro- or micro-averages for these metrics. Macro approaches consider each class as a basic element of the calculation, then each class has the same weight in the average, as there is no link to the class size. On the contrary, micro approaches consider each sample as a basic element of the calculation, then each class has a different weight depending on its size. Micro approaches are in this way more informative of unbalanced systems. This is in fact our case, as the necrosis class has many fewer elements (voxels) than the oedema class. Table 2 reports the main overall metrics derived from the confusion matrix, such as macro- and micro-average precision, sensitivity, and *F*1 score. Finally, overall classification accuracy reaches the 83.9%.

3.3 | Post-processing

Figure 5 shows three examples of GBM segmentation achieved by ANN without post-processing. As it can be observed, there are errors in some sub-zone segmentations. In some cases, the inner parts of necrosis are incorrectly classified as oedema (first and third rows, in light grey). In others, as healthy tissue (second row, in black). In general, the presence of oedema or normal tissue inside active tumour or necrotic areas is not correct from the biological/medical point of view. This kind of error is then corrected by a post-processing automatic step in the code that applies the gap filling method inside all active tumour and necrosis gaps and classifies their voxels as necrosis.

TABLE 1 Confusion matrix obtained for the validation dataset.

Class	Pred. healthy tissue	Pred. necrosis	Pred. oedema	Pred. active tumour	Sensitivity
Real healthy tissue	147,934	3304	66,622	4073	66.7%
Real necrosis	4154	227,271	36,582	28,523	76.6%
Real oedema	42,882	19,783	909,492	15,855	92.1%
Real active tumour	4066	25,157	20,096	131,673	72.8%
Precision	74.3%	82.5%	88.1%	73.1%	
F1 score	70.28%	79.46%	90.01%	72.93%	

Abbreviation: Pred, predicted.

set.

MaAv. S	MiAv. S	MaAv. P	MiAv. P	MaAv. F1 score	MiAv. F1 score	Accuracy
77.03%	83.93%	79.49%	83.93%	78.17%	83.93%	83.93%

Abbreviations: MaAv, macro-average; MiAv, micro-average; P, precision; S, sensitivity.

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FIGURE 5 Segmentations before post-processing. Each row shows a different GBM case. Left column: original MRI images. Central column: ground-truth segmentations. Right column: segmentations before post-processing. White: active tumour, dark grey: necrosis, light grey: oedema, and black: healthy tissue.

3.4 | Evaluation of the entire algorithm

To test the efficacy of the entire automatic 3D segmentation algorithm (Otsu + Chan–Vese + ANN + post-processing), 35 new GBM cases from BraTS plus 10 from the TCIA databases were used. Figure 6 presents three examples of final active tumour, necrosis, and oedema segmentations delivered by the complete procedure that show good correspondence with their respective ground-truths. The same is presented in Figure 7, but in this case in three dimensions.

Table 3 shows the main metrics usually applied to quantify the success of this type of medical volumetric segmentation (Taha & Hanbury, 2015). Tumour core (active tumour plus inner necrosis) segmentations as well as winner results reported by recent BraTS challenge 2020 were also included for comparison. The Dice similarity coefficient is calculated as (Dice, 1945):

$$\mathsf{Dice} = \frac{\mathsf{P} \cap \mathsf{T}}{(\mathsf{P} \cup \mathsf{T})/2}.$$
(7)

Being *P* and *T* the predicted and ground-truth segmented volumes, respectively. The Hausdorff distance (HD) ranks each point in a set A based on its distance to the nearest point of another set B and then defines the largest distance obtained as the HD between A and B

0	6

FIGURE 6 Final segmentations presented in 2D. Each row shows a different GBM case. Left column: Original MRI images. Central column: ground-truth segmentations. Right column: final segmentations. White: active tumour, dark grey: necrosis, light grey: oedema, and black: healthy tissue.

(Huttenlocher et al., 1993). Then the greater the HD, the greater the difference between the two groups compared. It can be used to determine the degree of resemblance between two objects that are superimposed to each other. To eliminate the 5% of extreme points (outliers), it is recommended to use HD95 (Fick et al., 2021).

Finally, the Boundary F1 score (BF score) also evaluates segmentation performance as the Dice coefficient, but in this case it is more concerned with boundaries, as it determines the match level between a predicted boundary and the correspondent ground-truth one (Csurka et al., 2013). These values were calculated by using the 'bfscore' Matlab function. Average processing times for the whole segmentation algorithm were about 5.66 min, being the calculation of textures features the most expensive process in terms of time.

4 | DISCUSSION

All metrics analysed achieve, in general, reasonable good scores, with very low processing times for a complete segmentation. The winner results from the last BraTS Challenge 2020 are in the same range as ours, although they were achieved applying more complex algorithms (nnU-Net in first place (Isensee et al., 2020), H2NF-Net (Jia et al., 2020) and modality-pairing learning (Wang et al., 2020) for tied second place). They also apply more computational resources, which may not be available in many hospital settings. Networks related to deep learning, on the other hand, do not make explicit the actual features that are being used for classification, which is somehow a disadvantage from the clinical point of view.



FIGURE 7 Final segmentations presented in 3D. First row: Final segmentations for the first example case. Second row: correspondent ground-truth segmentations. Third row: Final segmentations for the second example case. Fourth row: correspondent ground-truth segmentations. First column: active tumour segmentations. Second column: oedema segmentations. Third column: necrosis segmentations. Fourth column: complete ROI segmentations.

	ROI	Active tumour	Oedema	Necrosis	Tumour core
Dice (%)	89.33	80.69	79.67	66.41	83.72
HD95 (mm)	5.39	7.79	7.17	8.98	7.33
BF score	87.27	90.4	86.49	75.66	77.49
Sensitivity	87.04	82.74	76.11	71.67	87.35
Precision	92.62	80.56	85.24	65.79	82.6
BraTS 1st (Isensee et al., 2020) dice (%)	88.95	82.03	-	-	85.06
BraTS 1st HD95 (mm)	8.5	17.8	-	-	17.34
BraTS 2nd (Jia et al., 2020) dice (%)	88.79	82.77	-	-	85.37
BraTS 2nd HD95 (mm)	4.53	13.04	-	-	16.92
BraTS 2nd (Wang et al., 2020) dice (%)	88.28	81.77	-	-	84.33
BraTS 2nd HD95 (mm)	5.22	13.43	-	-	17.97

 TABLE 3
 Main metrics used to test the whole algorithm in each segmentation volume.

Note: Results corresponding to BraTS challenge 2020 winner algorithms (there was a tie for second place) are included below.

Our method, on the contrary, makes explicit the image features used to feed the network, information that may be translated to clinics in order to correlate to specific tumour characteristics. Moreover, our results have in general much lower HD95 values than BraTS winners, reflecting better correspondence between segmentations and ground-truths. BF scores achieved by our algorithm are also very acceptable. This is specially important in relation to the oedema segmentation, as this means a good definition of oedema contours, a critical clinical aspect for infiltration prediction and radiotherapy planning.

The Dice similarity coefficients corresponding to the necrosis zone are the lower ones, which is probably related to different factors. First, an important group of GBM cases virtually do not have visible necrosis. Second, this zone is usually smaller than the oedema, which means less voxels to train the network. Third, necrosis has much more gray-level heterogeneity among GBM cases and MRI modalities, which may affect feature extraction and the ANN learning rate. This issue may lower the effectiveness of ANN in segmenting this zone and indicate the need of finding new image features with more discrimination power. The use of complex MRI modalities; such as functional MRI (fMRI), diffusion weighted MRI (DWI), perfusion weighted MRI (PWI), or diffusion tensor MRI (DTI); may also be of help in this case. In fact, necrosis segmentation is in general not discriminated in present bibliography, as it is segmented in conjunction with the active tumour as a tumour core.

The databases used in the present study are multicentric, as 19 different institutions contribute MRI images acquired by different scanners and acquisition protocols. Effectively, there is a very strong effect of selecting training data on ANN performance in a multi-institutional setting (AlBadawy et al., 2018), which still represents a challenge to the standardization and generalization of the radiomics analysis (Huang et al., 2023). In this respect, the initial normalization scheme applied showed to be very important, as it may determine that the percentage of stable features vary from 3.4% to 8% (Saltybaeva et al., 2022).

5 | CONCLUSIONS AND FUTURE WORK

Automatic segmentation of the GBM along with its complex subzones is of vital clinical relevance at the time of planning a precision radiotherapy, evaluating post-treatment responses, or even designing more complex radiomics studies related to prognosis. In spite of the great heterogeneity of GBMs in relation to their shape, size, and subregional structure; as well as that derived from different image acquisition equipment and protocols; the results present evidence that it is possible to achieve automatic three-dimensional segmentation of this kind of tumour discriminating its related zones of active tumour, oedema, and necrosis. This may be done based on a combination of basic MRI modalities, classic image-processing methods, and a relatively simple ANN. In this way, preliminary segmentations were achieved, at first, based on information associated to gray-intensity values (first-order statistics). Then, all segmentations of interest were defined using explicit and relatively simple (intensity and texture) features extracted and selected to feed an ANN.

The whole algorithm proposed achieves results in the range of the best reported in the present bibliography with lower computational costs, making it more suitable for its application in the clinical context of a hospital, where informatic resources are often limited. On the other hand, most of the strategies presented in the BraTS 2020 challenge were based on deep learning architectures (Crimi & Bakas, 2021). This type of approximation, though usually very effective, does not make explicit the actual features that are being used for classification, instead working as 'black boxes'. This is somehow a disadvantage from the clinical point of view, as does not add relevant information about the biomedical basis of the phenomena observed. In our approximation, in contrast, the radiomic features determinant for segmentations were made explicit, which opens the possibility of connecting these macroscopic characteristics with microscopic biomedical information of clinical interest.

Some future work directions may be proposed. First, necrosis segmentation may be improved by exploring new algorithms and/or radiomic features extracted from more complex MRI modalities. Second, in order to provide a complete segmentation task, it is necessary to add a previous image pre-processing step similar to that implemented by the BraTS database. Third, the development of a friendly graphic interface and/or application would be a very helpful interaction tool for the clinical expert (neurooncologist, neurosurgeon, and neuroradiologist). This tool must be flexible enough to let him/her adjust any critical step of the process. In summary, we believe that the approach presented here has interesting potential related to its translation to the real clinical context.

ACKNOWLEDGEMENTS

This work was supported by the Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), the Agencia Nacional de Promoción de la Investigación, el Desarrollo Tecnológico y la Innovacion and the Universidad de Buenos Aires (UBA). The authors thank the editor and reviewers for their valuable suggestions that improved the manuscript.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available at requirement in Brain Tumor Segmentation (BraTS) Challenge 2020 at https:// www.med.upenn.edu/cbica/brats/.

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How to cite this article: de los Reyes, A. M., Lord, V. H., Buemi, M. E., Gandía, D., Déniz, L. G., Alemán, M. N., & Suárez, C. (2024). Combined use of radiomics and artificial neural networks for the three-dimensional automatic segmentation of glioblastoma multiforme. *Expert Systems*, e13598. https://doi.org/10.1111/exsy.13598