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Christopher W. Haddad
Karen Drukker
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Christopher W. Haddad,* Karen Drukker, Rebecca Gullett, Timothy J. Carroll, Gregory A. Christoforidis, and Maryellen L. Giger

University of Chicago, Department of Radiology, Chicago, Illinois, United States

Abstract. Patients suffering from ischemic stroke develop varying degrees of pial arterial supply (PAS), which can affect patient response to reperfusion therapy and risk of hemorrhage. Since vessel segmentation may be an important part in identifying PAS, we present a fuzzy c-means (FCM) clustering method to segment major vessels in x-ray angiograms. Our approach consists of semiautomatic region of interest (ROI) delineation, separation of major vessels from capillary blush and/or background noise through FCM clustering, and identification of the major vessel category. This method was applied to a database of x-ray angiograms of 24 patients acquired at various frame rates. The ground truth for performance evaluation was the designation by an expert radiologist selecting image pixels as being vessel or nonvessel. From receiver operating characteristic (ROC) analysis, area under the ROC curve (AUC) was the performance metric in the task of distinguishing between major vessels and blush or background. When clustering data into three categories and performing FCM segmentation on each ROI separately, the AUC was 0.89 for the entire database and ≥ 0.87 for all examined frame-rates. In conclusion, our method showed promising performance in identifying major vessels and is anticipated to become an integral part of automatic quantification of PAS. © 2018 Society of Photo-Optical Instrumentation Engineers (SPIE) [DOI: 10.1117/1.JMI.5.1.014501]

Keywords: vessel segmentation; x-ray digital subtraction angiography; fuzzy c-means; quantitative image analysis; stroke.

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1 Introduction

Acute ischemic stroke, which is induced by a blockage in a cerebral vessel, is experienced by an estimated 795,000 people each year in the United States.¹ Emergency reperfusion treatment can restore perfusion and mitigate cognitive disability.² However, such therapies can often cause intracerebral hemorrhage and herniation, which reduces their risk/benefit profile.³ Therefore, there is an urgent need to effectively identify patients most likely to benefit from reperfusion treatments.

Many adult patients suffering from an ischemic stroke develop varying degrees of flow from pial arteries that can supply affected neural tissue.⁴ During occlusion of the internal carotid artery (ICA) or middle cerebral artery (MCA), this flow—referred to as pial arterial supply (PAS)—serves as a temporary back-road supply to MCA branches, extending the viability of the ischemic (i.e., underperfused) but viable penumbra of neural tissue.^{2,3} In prior clinical studies and animal experiments, observation of PAS using x-ray digital subtraction angiography (DSA) predicted better response to reperfusion treatment and reduced the risk of hemorrhage compared with no PAS.^{2,3,5–10}

Clinical imaging protocols for observing PAS and at-risk neural tissue have used CT angiography, MR angiography, and planar x-ray DSA.^{11–13} Because PAS can be readily observed on planar x-ray DSA and it has superior temporal resolution, setup time, and scan time relative to CT or MR angiographies, planar x-ray DSA is considered the gold standard in patient evaluation during and immediately after reperfusion

treatment.¹⁴ Using this modality, manual scoring systems based on the level of angiographically visible MCA branches have been developed. These scoring systems can reliably predict the outcome of treatment.¹¹ However, these scoring systems also require a certain level of experience and expertise by the radiologist, whose assessment of pial collaterals is relatively coarse and subjective.

A computerized and quantitative assessment of PAS available during interventional imaging can allow for dynamic assessment of at-risk tissue, which may affect treatment decisions during endovascular rescue. This can allow potentially personalized treatment toward each patient and quicker delivery of said treatment. Because of the role that reconstituted MCA vessels (i.e., the MCA branches affected by PAS) play in patient assessment, the ability to segment those vessels will be critical to developing a computerized assessment method of collateral flow.

Because of the role that reconstituted MCA branches (i.e., MCA branches affected by PAS) play in patient assessment, the ability to segment major vessels in angiographic images of stroke will be critical to developing a computerized assessment method of PAS. In current interventional settings, major vessel branches are identified visually on x-ray DSA series by interventional radiologists. However, this involves acquiring image series that run into the late venous phase and identifying multiple major vessel branches across almost all image frames, which is very time consuming. Therefore, manual delineation of vessel boundaries in an interventional setting is highly impractical.

*Address all correspondence to: Christopher W. Haddad, E-mail: chrstphrhaddad@gmail.com

Methods have been developed to segment vessels in DSA images. Frangi et al.¹⁵ developed a vessel enhancement filter using the eigenvalues of Hessian images. However, it was found that this technique did not offer additional utility over digital subtraction of the original angiographic images. More recently, Sang et al.¹⁶ proposed two methods (one developed for computational speed and the other for accuracy) that involve adaptive thresholding based on *a priori* knowledge of the vessels' diameters. In Franchi et al.,¹⁷ a shape recognition algorithm that utilizes anisotropic Gaussian filters, angular mapping, and thresholding schemes was proposed, and it had fewer false positives when compared with the more accurate method described in Sang et al. However, these methods require substantial user input, making them unsuitable in an interventional setting. Furthermore, they focus on segmenting vessels within a given frame in a DSA series and assume a background with little contrast. During acute ischemic stroke, MCA branches affected by PAS may fill over the course of many frames, and the presence of contrast blush due to capillaries violates the assumption of a background with little contrast. Therefore, a technique that is robust over multiple frames in a DSA series and properly handles capillary filling is expected to better segment vessels in the ischemic territory.

Fuzzy c-means (FCM) clustering has been shown to reliably segment breast lesions in dynamic contrast-enhanced (DCE) MRI.¹⁸ As a result, it has found extensive use in this field.^{18–20} The formulation described in Chen et al.¹⁸ makes use of the time-based imaging of DCE-MRI, which can be viewed as an analog to x-ray DSA. Thus, in our study, we proposed and examined the use of FCM clustering to segment reconstituted MCA vessels in x-ray DSA series. The performance is evaluated by comparing vessel pixel classification against radiologists' manual designations on retrospectively acquired DSA series.

2 Materials and Methods

2.1 Database and Image Acquisition

Digitally subtracted angiograms were collected retrospectively under a HIPAA-compliant institutional review board-approved protocol (institutional review board protocol #16-0645). Angiograms were acquired using Philips Allura Xper interventional suites from 24 patients undergoing treatment for stroke at the University of Chicago Medical Center (Table 1). There were a total of 12 females and 12 males with an age distribution of 63 ± 14 years (range of 29 to 86 years). General anesthesia was given to 21 patients to reduce motion during imaging; the remaining three were determined to have minimal motion. We included cases from 2010 to 2016. There were an additional 14 cases that were excluded from analysis: 13 of them had motion, which rendered the angiograms unsuitable for quantification, and 1 had no angiograms in the AP direction.

All patients except one were treated with tPA and/or mechanical embolectomy (Table 1). Among cases treated with both tPA and mechanical embolectomy, three were acquired at 6 frames/s, while five were acquired at the mixed frame-rate protocol. One case had such poor PAS that the attending physicians decided not to proceed with—tPA or mechanical embolectomy. However, because these angiograms were acquired prior to treatment, treatment is not relevant to the design of the segmentation method.

All angiograms were acquired at 75.0 to 103.6 kVp and exposures of 11 to 49 mAs. Image matrix size was 1024×1024 pixels with pixel size ranging from $0.183 \text{ mm} \times 0.183 \text{ mm}$

Table 1 Summary of Clinical Angiographic Database of a total of 24 cases.

	6 frames/s	Mixed frame rate
Number of cases	11	13
General anesthesia	11	10
Range in (number of frames)/case	93–277	12–26
Range in image acquisition times	15.3–46 s	12–26 s
Iohexol injection technique	Hand	
tPA treatment	3	6
Mechanical thrombolectomy	8	8
Female/male ratio	5/6	7/6

to $0.215 \text{ mm} \times 0.215 \text{ mm}$. In each case, the same pixel size was used for providing ground truth and evaluating segmentation accuracy, shown in Sec. 2.2. Iohexol was injected by hand to provide contrast in the vessels. As shown in Table 2, angiograms from 11 cases (dataset A) were acquired at 6 frames/s; the remaining 13 (dataset B) were acquired under a mixed frame-rate protocol (i.e., a dose-sparing protocol) that would start imaging at 3 frames/s, switch to imaging at 1 frame/s 4 to 4.33 s into the acquisition, and then switch to imaging at 2 frames/s 12 to 12.33 s into the acquisition. Also, to better understand how the performance of the proposed method is affected by frame-rate, the 6 frames/s angiograms were sub-sampled to generate a dataset of 3 frames/s angiograms (dataset A_3), a dataset of angiograms acquired at the mixed frame-rate protocol (dataset A_M), a dataset of 1 frame/s angiograms (dataset A_1), and a dataset of 0.5 frame/s angiograms (dataset A_{HIF}).

2.2 Computerized Segmentation of Vessels

2.2.1 Review of fuzzy c-means clustering

FCM clustering is an unsupervised learning method for pattern recognition. Its goal is to find the fuzzy partition of the dataset X comprising N data vectors ($X = \{\mathbf{x}_i, i = 1, 2, \dots, N | \mathbf{x}_i \in \mathbb{R}^m\}$) into N_c categories or classes. The data vector $\mathbf{x}_i$ is an m -dimensional feature vector. The class means are represented by a $N_c \times m$ matrix, V . Each row of V corresponds to the mean feature vector of a class. The partition, or set of class membership scores, for X is given by the $N_c \times N$ matrix U . Each element of matrix U , u_{ki} , represents the membership score of the i 'th data point to the k 'th class and always falls in the range $[0, 1]$. The FCM implementation presented here follows the implementation detailed in Chen et al.¹⁸ for solving for U and V , except that our implementation was performed using a nVidia GeForce GTX Titan graphical processing unit (6.3-GB GPU memory, 867 MHz, 2688 CUDA cores; nVidia Corporation) on a cluster node with 256 GB of memory and is coded in MATLAB R2015b (Mathworks, Inc.).

2.2.2 Vessel segmentation via fuzzy C-means clustering

An angiogram may be represented as $D(x, y, t)$, where D is the contrast concentration, x and y are the spatial pixel coordinates, and t is the time. Therefore, individual angiographic images

Table 2 Description of the datasets. Note that additional datasets were generated by downsampling dataset *A* to 3, 1, and 0.5 frame/s (i.e., datasets *A*₃, *A*₁, and *A*_{1/2}) and according to a mixed frame-rate protocol (i.e., dataset *A*_M).

Case	Datasets					
	<i>A</i> (6 frames/s)	<i>A</i> ₃ (3 frames/s)	<i>A</i> ₁ (1 frames/s)	<i>A</i> _{1/2} (0.5 frame/s)	<i>A</i> _M (mixed frame rate)	<i>B</i> (mixed frame rate)
1	✓	✓	✓	✓	✓	
2	✓	✓	✓	✓	✓	
3	✓	✓	✓	✓	✓	
4	✓	✓	✓	✓	✓	
5	✓	✓	✓	✓	✓	
6	✓	✓	✓	✓	✓	
7	✓	✓	✓	✓	✓	
8	✓	✓	✓	✓	✓	
9	✓	✓	✓	✓	✓	
10	✓	✓	✓	✓	✓	
11	✓	✓	✓	✓	✓	
12						✓
13						✓
14						✓
15						✓
16						✓
17						✓
18						✓
19						✓
20						✓
21						✓
22						✓
23						✓
24						✓
Number of Cases	11	11	11	11	11	13

(Fig. 1) contain data at particular times. For each pixel i , the contrast over time is shown via a contrast-time curve $D_i(t)$. These curves are input directly into the FCM algorithm via the contrast values at each time index.

Using the pixel curves as inputs [i.e., $\mathbf{x}_i = \mathbf{D}_i$, where $\mathbf{D}_i$ is the vector notation of contrast data in $D_i(t)$], FCM clustering then is used to separate pixels into 2 or 3 classes ($N_c \in \{2, 3\}$). When $N_c = 2$, the two classes are (1) background and parenchymal blush due to capillaries and (2) large blood vessels or major vessels; when $N_c = 3$, the three classes are (1) background, (2) parenchymal blush due to capillaries, and (3) major vessels. The steps of the segmenting algorithm are outlined in Fig. 2. The

outputs of FCM are matrices $U = [U_1 \ U_2 \ \dots \ U_{N_c}]^T$ of size $N_c \times N$ and $V = [V_1 \ V_2 \ \dots \ V_{N_c}]^T$ of size $N_c \times M$. Each row of U is the transpose of the column vector representation of a class membership map. Similarly, each row vector of V represents the mean contrast curve of one of the three classes (Fig. 3), with the cluster ordering in V matching that in U . The rows of U and V are then sorted according to peak heights of the mean contrast curves in V .

If $N_c = 3$, the mean contrast curve with the highest peak is identified as belonging to the major vessel class, the mean contrast curve with the median peak is identified as belonging to the capillary blush class, and the mean contrast curve with

Fig. 1 Circle placement in angiographic image series. (a) For MCA occlusions, five circles are placed in the normal-flow ACA ($r = 1$) and reconstituted MCA branches ($r = 2-5$). (b) For ICA occlusions, six circles are placed on the normal-side ACA ($r = 1$), occlusion-side ACA ($r = 1.5$), and reconstituted MCA branches ($r = 2-5$). The back-filling of the MCA branches can extend into the venous phase ($t = 5.50$ and $t = 6.83$ in this figure).

the lowest peak is identified as belonging to the background class. Similarly, if $N_c = 2$, the mean curve with the higher peak is identified as belonging to the major vessel class and the mean curve with the lower peak is identified as belonging to the capillary blush/background class. The ordering for the mean-curve-peak-sorted rows in U , and hence the class membership maps, is the same as for the mean-curve-peak-sorted rows in V . Sample sorted mean contrast curves of the major vessel, capillary blush, and background classes for $N_c = 3$ are shown in Fig. 3, and a corresponding vessel membership map is shown in Fig. 4. A pixel is considered to belong in the major vessel group if its vessel membership score is higher than its membership score for capillary blush or (when $N_c = 3$) background.

As a contrast bolus travels through the vascular tree, it undergoes dispersion and delayed arrival, which broadens a pixel's contrast curve and lowers its height (Fig. 5). Dispersion is

manifested by friction within the vessel walls and with distribution of the contrast bolus among multiple branches; this leads to broadening of the pixel contrast curves and a lowering of their heights. This property is exploited to identify pial collateral arteries. However, in the occluded MCA territory, this delay-and-dispersion effect causes a pixel contrast curve in capillary blush-only region (anterograde filling) to appear similar to a pixel contrast curve in a major MCA branch (retrograde filling) that is further downstream (i.e., within later-filling segments of the MCA territory) in the direction of flow. To reduce the resulting misidentification of anterograde capillary blush as retrograde filling of an arterial branch, circular regions of interest (ROIs) are specified in the direction of flow. For MCA occlusions [Fig. 1(a)], five circular ROIs with indices $r = 1$ to 5 were specified in the direction of retrograde filling. Four ROIs contained the MCA branches, while one ROI was chosen in the anterior cerebral artery (ACA) branches (normal, anterograde filling) for reference. This process was repeated for ICA occlusions; however, because the occlusion-side ACA branches experienced reduced filling, an additional circular ROI was chosen in the normal-side ACA territory [Fig. 1(b)] to act as the reference for normal perfusion. Circular shapes were chosen for these ROIs because they would not intrude into the edge of the calvaria as easily as conventional rectangular shapes. In each case, ROIs were initialized with diameters of 130 pixels, at angular intervals of $\pi/7$, at 367 pixels from the image center, and with the ability for the operator to adjust their size and position. Adjustments were made by the operator (G.A.C.) to ensure the following:

- Distal ROI edges were just inside the calvaria.
- ROIs lay lateral to the longitudinal fissure.
- ROIs covered contrast flowing from distal (unoccluded) ACA branches through the pial collaterals and PAS-affected (i.e., occluded) MCA vessels.
- ROIs avoided covering contrast from normal-flow external carotid branches.

In short, these adjustments are made so that segmentation is isolated as much as possible on the retrograde flow and its immediate source. This meant that ROI centers could be moved by as much as 65 pixels and that the ROI diameters ranged from 55 to 130 pixels.

FCM clustering can then be conducted on each individual circular ROI to reduce the influence of dispersion. FCM clustering was then conducted on (a) each individual circular ROI to reduce the influence of dispersion [input data protocol R_s , see Fig. 6(a) and Table 3] and (b) inputting all ROIs of a given case together [input data protocol R_a , see Fig. 6(b) and Table 3]. When using input data protocol R_s , each ROI is segmented separately and independently, and hence ROI $r = 1$ is not used as a reference for other ROIs. Input data protocol R_a was investigated to better understand the effect of delay-and-dispersion on segmentation performance.

2.3 Evaluation

The FCM algorithm was evaluated using a pixel-based direct comparison with manually determined ground truth (major vessels versus capillary blush and/or background). In this study, pixels in the ROIs for cases in datasets A and B (see Table 2) were labeled by a board-certified neuroradiologist (G.A.C.) as

Fig. 2 Flowchart for the proposed FCM vessel segmentation algorithm with ROC analysis conducted in the task of distinguishing between pixels that are in major vessels and pixels that are not in major vessels.

Fig. 3 Mean curves found by FCM ($N_c = 3$ categories) for input curves from ROI $r = 3$ in the angiogram in Fig. 1(a). The curves are identified with their respective classes (text with arrows) using the peak heights.

belonging to one of the following categories: (1) major vessels or (2) capillaries or background.

For each category, 25 to 40 pixels were manually labeled in each ROI (i.e., ROI-specific truth), although this number may be lower if the prevalence for a category in a particular ROI is small. Using this truth, the task of separating major vessels from capillary blush was assessed using receiver operating

Fig. 4 Class membership map for major vessels in the angiogram in Fig. 1(a).

Fig. 5 Mean contrast curves for each ROI (input separately to FCM) for the case in Fig. 1(a). Note the effect of delay-and-dispersion in the direction of flow for both (a) major vessels class and (b) capillaries class.

Fig. 6 FCM segmentation methods used (see Table 3): (a) implementing FCM using R_s (separate FCM segmentation for each ROI) and (b) implementing FCM using R_a (one FCM segmentation for all ROIs). As a reference, composite angiographic images made from all image frames are shown on the left.

Table 3 Organization of input data for FCM segmentation of major vessels from parenchymal blush due to capillaries.

Input data protocol	FCM inputs	Evaluation databases
R_s	Single ROI	(1) Datasets $A + B$
		(2) Dataset A
		(3) Dataset B
R_a	Angiogram (all 5 and 6 ROIs)	(1) Datasets $A + B$
		(2) Dataset A
		(3) Dataset B

characteristic (ROC) analysis. ROC curves were generated using the major-vessel-membership values as the decision variable. When using input protocol R_s , ROC curves were generated for each ROI using the ground truth pixels within that ROI and then averaged across all ROIs in a case to obtain a case-specific ROC curve; when using input protocol R_a , case-specific ROC curves were generated using all the ground truth pixels in each case. For both protocols, the case-specific ROC curves were averaged across all cases in datasets A and B and across all cases in datasets $A + B$ to yield frame-rate-based ROC curves and an ROC curve for the entire database, respectively. ROI-specific ROC curves generated under R_s and case-specific ROC curves generated under R_a were fitted using the proper binormal ROC model²¹ software package, and the nonparametric Wilcoxon area under the ROC curve AUC was used as the performance metric for this task.

The two-sided 95% confidence interval (CI) for reported AUC values were empirically estimated using bootstrapping (3000 iterations). Performance comparisons for different choices for the number of input categories in FCM (N_c), different input data protocols to FCM (Table 3), and different frame rates (databases A , A_3 , A_M , A_1 and A_{HIF} ; see Table 2) were made by evaluating the differences in AUC (ΔAUC). Any difference in AUC values was also assessed through bootstrapping (3000

Table 4 Database ROC statistics for different numbers of input categories N_c and input protocol R_s [Fig. 7(a)], with 95% CIs in brackets, for datasets $A + B$ (24 cases total; see Table 2).

N_c	AUC	95% CI of ΔAUC	p -value ($\alpha = 0.05$)
3	0.89[0.86; 0.92]	[0:04; 0:08]	<0.001
2	0.84[0.80; 0.87]		

iterations), and two-sided 95% CIs were calculated for superiority testing. One-sided 90% CIs were calculated for noninferiority assessment when superiority testing was inconclusive. Noninferiority was reached if the lower limit of the CI was > -0.02 .²²

3 Results

3.1 Effect of Number of Fuzzy C-Means Categories N_c

In this section, the input data protocol for each administration of FCM was R_s , i.e., each input was restricted to 1 ROI (Table 3). Segmentation of major vessels from parenchymal blush and background using FCM with $N_c = 3$ has favorable performance over using FCM with $N_c = 2$ [Fig. 7(a) and Table 4]. In particular, the bootstrapped 95% CIs for ΔAUC is above zero, indicating a clear separation between $N_c = 3$ and $N_c = 2$. This improved performance for $N_c = 3$ holds between acquired frame-rates as well [Fig. 7(b) and Table 5].

3.2 Comparing Input Data Protocols

In this section, the number of input categories was $N_c = 3$. Using the input data protocol R_s for FCM leads to improved performance across the database compared with using the input data protocol R_a (Table 3) [Fig. 8(a) and Table 6]. The bootstrapped 95% CI of ΔAUC is above zero (Table 6), indicating superior performance when FCM is administered on each ROI separately. The improved performance for inputting curves from

Fig. 7 Fitted binormal ROC curves for the performance in separating vessels from capillary blush and background for number of categories $N_c = 3$ and $N_c = 2$ for (a) datasets $A + B$ (see Table 2) and (b) dataset A (6 frame/s) and dataset B (mixed frame rate). The input protocol to FCM was R_s .

Table 5 Performance in terms of AUC value for datasets *A* and *B* for different numbers of input categories N_c and input protocol R_s [Fig. 7(b)], with 95% CIs in parentheses. The significance level α is adjusted using a Bonferroni correction.

Frame rate (frames/s)	N_c	AUC	95% CI of Δ AUC	p -value ($\alpha = 0.025$)
6 (Dataset <i>A</i> , 11 cases)	3	0.92[0.90; 0.95]	[0.04; 0.08]	<0.001
	2	0.86[0.82; 0.90]		
Mixed (Dataset <i>B</i> , 13 cases)	3	0.87[0.83; 0.91]	[0.02; 0.09]	<0.001
	2	0.82[0.76; 0.87]

Fig. 8 Fitted binomial ROC curves for the performance in separating major vessels from capillary blush and background for different input data protocols (see Table 3) for (a) datasets *A* + *B* (see Table 2) and (b) dataset *A* (6 frame/s) and dataset *B* (mixed frame rate). The number of input categories was $N_c = 3$.**Table 6** Areas under the ROC curve for the different input protocols and $N_c = 3$ categories [Fig. 8(a)], with CI in brackets and p -values in parentheses, for Database *A* + *B* (24 cases total; see Table 2).

Input data protocol	AUC	95% CI of Δ AUC	p -value ($\alpha = 0.05$)
R_s : individual ROIs	0.89[0.86; 0.92]	[0.01; 0.08]	0.01
R_a : all ROIs in case	0.85[0.82; 0.88]		

each ROI one-at-a-time holds for dataset *A* [Fig. 8(b)] but not for dataset *B*; because the bootstrapped two-sided 95% CI of Δ AUC includes zero (Table 7), the comparison of input protocols for dataset *B* fails to show statistical significance. However, since the bootstrapped one-sided 90% CI of dataset *B*'s Δ AUC is above -0.02 , R_s is noninferior to R_a for this dataset.

3.3 Effect of Frame Rate

As shown in Fig. 9 and Table 8, using $N_c = 3$ input categories and input protocol R_s for FCM yielded nearly identical ROC curves and AUC = 0.92 for datasets *A*, A_3 , A_{Mix} , and A_1 (Table 2), indicating that this method is insensitive to frame-rates that may be used in the clinic. Similarly, the 95% CI for AUC for the angiograms taken under the mixed frame-rate

protocol is only slightly wider than the uniform frame-rate angiograms. Only the ROC curve for dataset A_{Hif} differed from dataset *A*'s ROC curve. The robustness for frame-rates >0.5 s is further reflected in the bootstrapped pairwise difference between the datasets AUCs as shown in Table 9. The difference in performance for the different frame-rates failed to reach statistical significance except when comparing datasets *A* and A_{Hif} (Table 9, two-sided 95% CI for Δ AUC). Moreover, the one-sided 90% CI for Δ AUC (Table 9) demonstrated that the performances for frame-rates >0.5 s were noninferior. The P -values were all compared with a Bonferroni-corrected significance level of $\alpha = 0.013$.

3.4 Processing Times

When using input protocol R_s , the segmentation algorithm takes ~ 15 s per case; when using input protocol R_a , the segmentation takes ~ 30 s per case.

4 Discussion

FCM clustering yielded good performance in segmenting major vessels from capillary blush and background. There are two major reasons for this level of performance. The first and most direct reason is that, because of vascular dispersion, there is a higher concentration of contrast in the major vessels about the peak time, leading to higher and wider contrast curves. A second reason is that bone and cranial parenchyma are automatically subtracted out in the cases of angiographic images. This

Table 7 Areas under the ROC curve using the different input protocols and $N_c = 3$ categories, with CIs in brackets and p -values in parentheses, for datasets *A* and *B* [Fig. 7(b)]. The significance level is adjusted to $\alpha = 0.025$ using a Bonferroni correction.

Frame rate (frames/s)	Input data protocol	AUC	95% CI of Δ AUC	90% CI of Δ AUC
6 (Dataset <i>A</i> , 11 Cases)	R_s : individual ROIs	0.92[0.90; 0.95]	[0.03; 0.12] (<0.001)	[0.04; 1]
	R_a : All ROIs in case	0.85[0.81; 0.89]		
Mixed (Dataset <i>B</i> , 13 Cases)	R_s : individual ROIs	0.87[0.83; 0.91]	[-0.03; 0.06] (0.19)	[-0.01; 1]
	R_a : all ROIs in case	0.85[0.81; 0.88]		

removes the corresponding constant offsets in each pixel's contrast curve, allowing only curve values representative of contrast concentration to be input to FCM.

Using input protocol R_s produces favorable performance over protocol R_a for dataset *A* because the effect of having different delay-and-dispersion in each class is mitigated when individual ROIs are input separately into FCM (Fig. 5). In Fig. 5, ROIs 2 to 4 did not show a delay relative to ROI 1. This is prevalent across the entire dataset. This is because the analysis uses two-dimensional (2-D) spatial projections. The delay across ROIs can be seen for vessel branches lying predominantly in the image plane, but many MCA branches in ROIs 2 to 5 (or 2 to 6 for ICA occlusions) are supplied by pial collaterals that lie just medial to those ROIs. Therefore, contrast in vessels arrives and peaks at similar times across all ROIs, and delay is not well presented in 2-D projection images. This means that dispersion is responsible for the differences in contrast curves across the ROIs. Therefore, FCM only needs to segment major vessels from capillaries based on the dispersion within an ROI in x-ray DSA series.

A limitation of this study was the small sample size (24 patients) of our database. In particular, because only three

patients imaged without general anesthesia had minimal motion, our database cannot meaningfully answer whether or not general anesthesia affects the performance of this segmentation algorithm.

Closer examination of five cases in dataset *B* revealed that mild motion artifacts (i.e., more visible bone and parenchyma) are present as contrast moves through the ischemic region. The artifacts are present across the affected ROIs and obscure the effect of delay-and-dispersion on the capillaries, making administration of FCM on separate ROIs less useful than administering FCM on all ROIs per case. Reducing motion would allow for better within-ROI segmentation of major vessel from parenchymal blush and background.

An important finding in these results is that a high frame rate is not necessary to satisfactorily segment major vessels; as long as the frame rate is > 0.5 s, which is well-within the capabilities of modern angiographic suites, performance is expected to be

Table 8 Areas under the ROC curve AUC with 95% CIs in brackets for datasets *A*, A_3 , A_M , A_1 , and A_{Hif} (see Fig. 9 and Table 2) using $N_c = 3$ input categories and input protocol R_s .

Frame-rate dataset	N	AUC
Dataset <i>A</i>	11	0.92 [0.90; 0.95]
Dataset A_3	11	0.92 [0.89; 0.95]
Dataset A_M	11	0.92 [0.90; 0.95]
Dataset A_1	11	0.92 [0.89; 0.95]
Dataset A_{Hif}	11	0.89 [0.83; 0.93]

Fig. 9 Fitted binormal ROC curves for the performance in separating vessels from capillary blush and background for datasets *A*, A_3 , A_M , A_1 , and A_{Hif} (Table 2). The curves for datasets *A* and A_3 are so close that they overlap in the figure. The number of input categories and the input protocol were $N_c = 3$ and R_s , respectively.**Table 9** Pairwise bootstrapped difference in AUC between frame-rate datasets (Table 2) with CIs in brackets and significance values for the 95% CIs in parentheses. The significance level is adjusted to $\alpha = 0.013$ using a Bonferroni correction.

Frame-rate dataset comparison	Δ AUC	Two-sided 95% CI	One-sided 90% CI
<i>A</i> versus A_3	0.001	[0.000; 0.002] (0.04)	[0.00; 1.00]
<i>A</i> versus A_M	-9×10^{-4}	[-0.01; 0.09] (0.56)	[-0.01; 1.00]
<i>A</i> versus A_1	-7×10^{-4}	[-0.004; 0.005] (0.36)	[0.00; 1.00]
<i>A</i> versus A_{Hif}	0.04	[0.02; 0.07] (<0.001)	[0.02; 1.00]

robust. This indicates that the difference between major vessels and capillaries is captured in low-frequency components in pixel contrast curves.

Methods have been proposed for vessel segmentation in angiographic images, but, to our knowledge, there are no gold standards for automatic vessel segmentation that utilize entire angiographic images series. Furthermore, the methods developed by Franchi et al. and Sang et al. only segmented vessels using a single image frame. Furthermore, these methods require *a priori* knowledge or designation of vessel sizes, which limit their utility in time-sensitive interventional imaging. The proposed FCM algorithm requires only the placement of 5 to 6 ROIs after the angiographic series is acquired, which can be done in a timely manner.

In conclusion, an FCM-based method for automatically segmenting MCA vessels in acute ischemic stroke using digitally subtracted x-ray angiograms was developed. This method shows promise in identifying vessel pixels and has robust performance at all clinical angiographic frame-rates examined in this study. It is anticipated that this FCM segmentation method will be an integral part of a method for computerized assessment of stroke.

Disclosures

Christopher Haddad, Rebecca Gullett, Timothy Carroll, and Gregory Christoforidis have no financial interests or other potential conflicts of interest. Maryellen L. Giger is a stockholder in R2/Hologic and cofounder and equity holder in Quantitative Insights and receives royalties from Hologic, GE Medical Systems, MEDIAN Technologies, Riverain Medical, Mitsubishi, and Toshiba. Karen Drukker receives royalties from Hologic.

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Christopher W. Haddad is a recent graduate of the Graduate Program in Medical Physics at the University of Chicago and is currently a medical physics resident in clinical imaging at west physics. His research interests involve quantitative image analysis of neural and cerebrovascular diseases.

Karen Drukker has been actively involved in CAD/radiomics research at the University of Chicago for over a decade. Her work has focused on multimodality detection/diagnosis/prognosis of breast cancer and the performance evaluation of radiomics methods.

Rebecca Gullett is an undergraduate at Benedictine University majoring in computer science and mathematics. Her research interests include medical imaging.

Timothy J. Carroll is a professor of radiology at the University of Chicago, and he has been actively involved in evaluating and quantifying physiologic changes in the brain resulting from neurovascular disease and stroke. His work focuses on advanced magnetic resonance imaging to target changes in arterial vasculature, tissue perfusion, and the arterial wall itself to quantify physiologic changes in patients.

Gregory A. Christoforidis is a professor of radiology and surgery and board-certified neuroradiologist at the University of Chicago. His research focuses on endovascular treatment of acute ischemic stroke.

He is investigating the formation of collateral blood vessels in the pial tissue surrounding the brain and its role in acute ischemic stroke.

Maryellen L. Giger is the A.N. Pritzker professor of radiology and the committee on medical physics at the University of Chicago. Her research interests mainly involve the investigation of CAD and

radiomics methods for the assessment of risk, diagnosis, prognosis, and response to therapy of breast cancer on multimodality (mammography, ultrasound, and magnetic resonance) images. She is also involved in broad-based developments in computer vision and data mining of medical images.