Classification of Spatiotemporal Hemodynamics From Brain Perfusion MR Images Using Expectation-Maximization Estimation With Finite Mixture of Multivariate Gaussian Distributions

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The ability to cluster different perfusion compartments in the brain is critical for analyzing brain perfusion. This study presents a method based on a mixture of multivariate Gaussians (MoMG) and the expectation-maximization (EM) algorithm to dissect various perfusion compartments from dynamic susceptibility contrast (DSC) MR images so that each compartment comprises pixels of similar signal-time curves. This EM-based method provides an objective way to 1) delineate an area to serve as the in-plane arterial input function (AIF) of the feeding artery for adjacent tissues to better quantify the relative cerebral blood volume (rCBV), relative cerebral blood flow (rCBF), and mean transit time (MTT); 2) demarcate regions with abnormal perfusion derangement to facilitate diagnosis; and 3) obtain parametric maps with supplementary information, such as temporal scenarios and recirculation of contrast agent. Results from normal subjects show that perfusion cascade manifests from normal subjects show that perfusion cascade manifests from normal subjects show that perfusion cascade manifests from normal subjects show that perfusion cascade manifests from normal subjects show that perfusion cascade manifests from normal subjects show that perfusion cascade manifests from normal subjects show that perfusion cascade manifests from normal subjects show that perfusion cascade manifests from normal subjects show that perfusion cascade manifests from normal subjects show that perfusion cascade manifests from normal subjects show that perfusion cascade manifests from normal subjects show that perfusion cascade manifests from normal subjects show that perfusion cascade manifests from normal subjects show that perfusion cascade manifests from normal subjects show that perfusion cascade manifests from normal subjects show that perfusion cascade manifests from normal subjects show that perfusion cascade manifests.
been utilized in nuclear medicine to separate cardiac components and extract left ventricular input function from dynamic H$_2$O PET images (15–17). Although the current methods of factor analysis have been considered attractive, additional assumptions of a priori knowledge are needed in order to obliquely rotate PCA eigenvectors to yield factors with physiological significance (12,13,18). Moreover, only one or two physiological factors were determined in past studies, while other factors were not fully explored. Independent component analysis (ICA) (19), which uses the assumption of statistical independence as a constraint to remove rotational factors, has been applied to MR perfusion images to segment out different tissue types (20) and to remove confounding signals of large blood vessels from hemodynamic parametric maps (21). T$_2$-weighted (T$_2$W) and diffusion-weighted (DW) images to separate a portion of noise content within a diffusion tensor imaging (DTI) data set (22), and dynamic H$_2$O PET images to separate the ventricles and myocardium (23).

In this study we employ the expectation-maximization (EM) algorithm (24), one of the most widely used methods for brain MR segmentation (25–29), to classify multitissue hemodynamics. The EM algorithm is often used for estimation problems in which some of the data are “missing”. In this application, what is missing is knowledge of the tissue labels. Since the dimension of dynamic MR data is usually far larger than the number of tissue types, we first apply the PCA (19) to reduce the data dimension and hence facilitate the subsequent EM estimation. The distribution of the reduced data associated with each tissue type is assumed to be a multivariate Gaussian function, and the overall distribution of the reduced data is assumed to be a mixture of multivariate Gaussians (MoMG) (30) in which the model parameters are fitted to the reduced data via the EM algorithm. The number of classes (i.e., tissue types) is determined by minimizing the information criterion of the minimum description length (MDL) (31), which consists of two terms: the log-likelihood function and the model-complexity penalty (see Eq. [A7] in the Appendix). The first term represents the discrepancy between the data predicted by the MoMG model and the actual data, and the second term represents a measure of complexity of the model. A very simple model will be a poor predictor and lead to a large first term. A more complex model will reduce such discrepancies, but will lead to a larger model-complexity penalty. Accordingly, we look for an MoMG model that can accurately predict the data while keeping the model complexity as low as possible. There are two alternating iterative steps in the application of the EM algorithm: the E-step and the M-step. The E-step is to calculate the so-called Q function, which is the expectation of the complete-data log-likelihood, conditional on the observed data and current MoMG model. The M-step is to find the new class parameters (i.e., the mean vectors, covariance matrices of the MoMG, and the proportion of each class) that maximize the Q function. After the values of the resultant posterior probabilities at each pixel are compared, the tissue type that produces the maximal probability will determine the pixel label. Once all tissues of interest are identified, the averaged signal-time curves of each tissue type are computed and the AIF is modeled to compute the rCBV, rCBF, and MTT maps. We applied this algorithm to MR perfusion brain images of normal subjects, as well as a patient with cerebral arteriovenous malformation (CAVM).

MATERIALS AND METHODS

Subjects and Data Recording

Five healthy volunteers (three males and two females, 18–47 years old, 49–70 kg) participated in this study. Written informed consent was obtained from each volunteer before the study was conducted. A multislice gradient-echo EPI pulse sequence (Signa® CV/i; GE Medical Systems, Milwaukee, WI, USA) was used to acquire dynamic perfusion images on a 1.5-Tesla scanner. Transaxial imaging was performed with TE/TR = 60/1000 ms, flip angle = 90°, FOV = 24 cm × 24 cm, matrix = 128 × 128, slice thickness/gap = 5/5 mm for three slices, one acquisition, and 100 images per slice location. Twenty milliliters of Gd-DTPA-BMA (Omniscan®, 0.5 mmol/ml; Nycomed Imaging, Oslo, Norway) followed by 20 ml of normal saline were delivered administratively via a power injector (Spectris®; Medrad, Indianola, PA, USA) at a flow rate of 3–4 ml/s in the antecubital vein. Figure 1 exhibits perfusion images 11–40, which were obtained transaxially through the body of the lateral ventricle encompassing the first pass of circulation in one volunteer (a 47-year-old male). The temporal resolution is 1 s. Since only dynamic images with stable baselines and discernibly temporal signal changes were of interest, we removed the first three and last 27 images from a total of 100 images, and thus retained 70 images per slice location for analysis. In addition, proton density-weighted (PDW) images for each subject were acquired on the same 1.5-Tesla scanner using a fast spin-echo pulse sequence. The scan parameters were: TE/TR = 24.3/2000 ms, echo train length = 7, FOV = 24 cm × 24 cm, matrix = 256 × 256, and slice thickness/gap = 5/5 mm. All routines were implemented using MATLAB (MathWorks, Inc., Natick, MA, USA) code and carried out on a 2 G-Hz Pentium-based personal computer.

Data Preprocessing and Tissue Segmentation by the MoMG Model With the EM Algorithm

We extracted the brain regions from the perfusion images by first setting all pixel values larger than 15% of the maximum intensity to one, and all values smaller than this threshold to zero. We applied an erosion operation with a 3 × 3 structure element to the resultant binary mask, and removed all pixels corresponding to skull and scalp areas. This was followed by a dilation operation with a 5 × 5 structure element filling holes in the brain region. Only the remaining pixels within the extracted brain region were subjected to further classification processing.

If we assume that the brain region for each image consists of N pixels, the observation of 70 temporal images can be represented by a 70 × N matrix, i.e., each row is an image and each column contains signal intensities of a pixel across 70 time points. To facilitate the subsequent segmentation process, we further reduced the dimension of each data set by PCA to retain most of the data infor-
mation by computing the eigenvectors of the covariance matrix of the data and selecting the first $t$-th eigenvectors as a transformation matrix. In this study, $t$ was chosen to be 10 to condense the data size from $70 \times N$ to $10 \times N$ so that the sum of the associated eigenvalues interpreted at least 95% of the data variance.

Let each point in the compressed data be denoted by $x_n$ ($t \times 1$), $n = 1, \ldots, N$. The tissue segmentation was carried out by means of the EM algorithm, which fit the overall distribution of the compressed data to an MoMG consisting of two alternating iterative steps, i.e., the E-step and M-step (see Appendix for details). The E-step is to compute the posterior probabilities of tissue classes $p(i|x_n, \theta^{-1})$ based on the estimation from previous $j-1^{th}$ iteration:

$$p(i|x_n, \theta^{-1}) = \frac{\pi_i^{j-1} g_{\pi_i}(\mu_i^{j-1}, \sum_i^{j-1})}{\sum_{k=1}^{K} \pi_k^{j-1} g_{\pi_k}(\mu_k^{j-1}, \sum_k^{j-1})}$$

where $i = 1, \ldots, K$ represent labels of tissue classes, $g_{\pi_i}(\mu_i, \Sigma_i)$ represents the multivariate Gaussian density with the mean vector $\mu_i$ and covariance matrix $\Sigma_i$ of tissue class $i$, $\pi_i$ denotes the proportion of each class $i$, and $\theta^{-1}$ denotes the parameters $\{\mu_i^{-1}, \Sigma_i^{-1}, \pi_i^{-1}\}$ at the $j-1^{th}$ iteration. The M-step consists of estimating parameters $\theta^j$ as follows:

$$\mu_i^j = \frac{\sum_{n=1}^{N} p(i|x_n, \theta^{-1}) x_n}{\sum_{n=1}^{N} p(i|x_n, \theta^{-1})}$$

$$\Sigma_i^j = \frac{\sum_{n=1}^{N} p(i|x_n, \theta^{-1}) x_n x_n^T}{\sum_{n=1}^{N} p(i|x_n, \theta^{-1})} - \mu_i^j \mu_i^j$$

The number of classes $K$ is determined by the information criterion of the minimum description length (MDL) (31). The tissue label at each pixel was determined by the maximal value of $p(i|x_n, \theta^{-1})$ at that pixel, and therefore each tissue type was classified.

### Calculation of Parametric Images for rCBV, rCBF, and MTT

We calculated pixel-by-pixel parametric maps for rCBV, rCBF, and MTT for areas of classified tissues using concentration-time curves. We then computed the concentration-time curve $c_i(t)$ for a pixel using the linear relationship with the change in the relaxation rate, $\Delta R_2^*(t)$:

$$c_i(t) = \Delta R_2^*(t) = -\frac{k}{TE} \ln \left( \frac{S(t)}{S_0} \right)$$

where $k$ is an unknown constant, and $S(t)$ and $S_0$ are the signal intensities of each pixel at time $t$ and baseline, respectively (5,7,9). Note that the concentration-time curve for the arterial region on the same slice was used as

![Sequential perfusion images](image)

**FIG. 1.** Sequential perfusion images (from left to right, and top to bottom) at an upper slice location encompass the first circulation. The image numbers are shown in the left side of each row of corresponding images. Images 16–38 were used to calculate the rCBV.
an AIF, i.e., \( c(t) \), in the subsequent computation of rCBV and rCBF. According to indicator dilution theory, one can determine the rCBV as a ratio of the area integrating over the first pass of a contrast agent under the concentration-time curve, \( c(t) \), to that under the AIF (1):

\[
\text{rCBV} = \frac{\int_{\text{first pass}} c(t) \, dt}{\int_{\text{first pass}} c(t) \, dt}.
\]

The rCBF at each pixel can be expressed based on the relationship with AIF, concentration-time curve and the residue function, \( R(t) \), for the pixel:

\[
c(t) = \text{rCBF} \cdot c(t) \otimes R(t)
\]

where \( \otimes \) denotes convolution (32). The singular value decomposition (SVD) method (3,7) was employed and implemented to deconvolve Eq. [5] and calculate the \( \text{rCBF} \cdot R(t) \) curve for each pixel. To minimize the oscillation effect on the solution, small singular values in the diagonal matrix produced by SVD were set to zero. The cutoff threshold was set at 20% of the maximum singular value (3,7). The value of rCBF, in theory, can be determined by the initial value of the deconvolved curve, i.e., \( R(t = 0) = 1 \), according to indicator dilution theory. However, the AIF can be affected by time delay and dispersion of the bolus, causing the spreading of the deconvolved curve. Ostergaard et al. suggested that the maximum value of \( \text{rCBF} \cdot R(t) \) curve should be used instead of the value at the initial point in order to avoid underestimation of flow (3). The MTT of contrast-agent particles passing through a pixel can be calculated using the central volume principle (3,5,7,9):

\[
\text{MTT} = \frac{\text{rCBV}}{\text{rCBF}}.
\]

Monte Carlo Simulation

Computer simulations were conducted to assess the performance of the EM-MoMG method. Sets of simulated dynamic images were first created so that each data set consisted of four to nine hypothetical clusters. The pixel number and intensity distribution of each hypothetical cluster were generated based on the region of interest (ROI) on one of the raw data sets so that the statistics of the simulated dynamic images would emulate the actual ones. For example, in the case of seven hypothetical tissue clusters, the selected ROIs on the raw data represented artery (434 pixels), GM (1113 pixels), WM (1182 pixels), sinus (289 pixels), vein and sinus (737 pixels), cerebrospinal fluid (CSF) and choroid plexus (375 pixels), and artifacts (409 pixels). The ROIs were either merged or split to produce less or more hypothetical clusters. Pixels within each hypothetical tissue area were assumed to be spatially independent, and their intensities across time were assumed to be multivariate Gaussian-distributed. The averaged intensity-time curves (each of which was a 70 × 1 vector) and covariance matrices of intensities across time (each of dimension 70 × 70) within ROIs on the raw data were employed as the hypothetical parameters for the MoMG model to create a set of noise-free simulated dynamic images using random number generators. Sets of noise-free simulated dynamic images with different numbers of hypothetical clusters were generated in a similar manner. In addition, Gaussian noise was added to each set of noise-free simulated dynamic images to produce signal-to-noise-ratios (SNRs) of 10, 40, 70, and 100. For each hypothetical cluster number and SNR level, a Monte Carlo simulation of 1000 runs was performed. Accordingly, the total number of simulated image sets was 6 (number of hypothetical clusters) × 5 (SNR levels) × 1000 = 30000. Each set of simulated dynamic images was rearranged into a 70 × 10 matrix before classification, where \( N (N = 4539) \) in the simulation was the number of pixels representing brain area. Next, PCA was applied to condense the 70 × 10 matrix into a 10 × 4 matrix followed by EM-MoMG estimation with number of tissue classes being tested from 3 to 10. After the values of posterior probabilities \( p(x_n | \theta) \) at each pixel were compared, the cluster resulting in the maximal probability was identified and the pixel was labeled accordingly. The classification rate for each cluster, denoted by \( r_i \), was defined by the observed proportion of agreements, i.e., \( r_i = f_i/n_i \), where \( f_i \) is the number of agreements for the \( i \)th cluster, and \( n_i \) is the total number of pixels in the \( i \)th class. The classification rate for a set of simulated dynamic images, denoted by \( R \), was computed by \( R = \frac{\sum r_i}{100} \times r/K \) (percentage), where \( K \) is the number of clusters.

RESULTS

Simulation Results

The simulation results obtained with various SNR levels and numbers of hypothetical tissue clusters are presented in Fig. 2a–f and Table 1. In Fig. 2 the horizontal axis is the number of tissue classes (\( N_o \)) used in the EM-MoMG algorithm; the left vertical axis is the MDL scale for the noise-free condition and SNR = 40, 70, and 100; and the right vertical axis is the MDL scale for SNR = 10. Each mark on a curve was obtained from averaging 1000 resultant values of MDL. The minima on the curves in Fig. 2a–f show that when the signals were noise-free and SNR = 100, 70, and 40, the numbers of classes were accurately determined. However, as the SNR decreased to 10, the data consisting of five, six, seven, eight, and nine hypothetical tissue clusters were incorrectly classified into four, four, four, and six clusters, respectively, except for the data with four hypothetical tissue types. The averages of classification rates (\( R \)) were calculated for the simulated data sets whose cluster numbers were accurately estimated. Table 1 shows that the averaged classification rates ± the averaged standard deviation (SD, percentage) for the data consisting of four, five, six, seven, and eight hypothetical tissue clusters in the noise-free condition were 96.5% ± 0.64%, 95.0% ± 0.92%, 94.0% ± 1.06%, 92.9% ± 1.27%, and 92.3% ± 1.61%, respectively. These values degraded slightly to 95.1% ± 0.78%, 93.0% ± 1.14%, 91.9% ± 1.21%, 90.5% ± 2.27%, and 89.1% ± 1.81%, respectively, when SNR = 40. How-
ever, when the data consisted of nine hypothetical clusters, the mean classification rate reduced from 90.1% ± 4.80% in the noise-free condition to 86.6% ± 5.86% when SNR = 40. As SNR decreased to 10, the mean classification rates for data with various hypothetical clusters were between 86.1% ± 1.44% and 63.4% ± 14.29%.

Results From Normal Subjects
Five normal image data sets were analyzed, and the results of one segmentation are depicted as a color-coded composite image in Fig. 3a, in which each color represents a tissue type. The SNRs of these data sets were 51, 55, 77, 83, and 88, respectively. The distribution of each tissue type corresponded to its anatomical location in the PDW image (Fig. 3b). Note that the areas of artery, vein, and sinus appear to be blooming and are larger than pure ones, since these areas consist of vessels. This exaggeration was caused by the susceptibility effect of gradient-echo EPI. In order to analyze the hemodynamics, we used different colored areas as ROIs to compute the true signal-time...

Table 1
Averaged Classification Rates for Monte Carlo Simulations

<table>
<thead>
<tr>
<th>SNR</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noise free</td>
<td>96.5 ± 0.64%</td>
<td>95.0 ± 0.92%</td>
<td>94.0 ± 1.06%</td>
<td>92.9 ± 1.27%</td>
<td>92.3 ± 1.61%</td>
<td>90.1 ± 4.80%</td>
</tr>
<tr>
<td>100</td>
<td>96.3 ± 0.66%</td>
<td>94.6 ± 0.97%</td>
<td>93.6 ± 1.09%</td>
<td>92.6 ± 1.28%</td>
<td>91.4 ± 1.52%</td>
<td>89.7 ± 4.39%</td>
</tr>
<tr>
<td>70</td>
<td>95.9 ± 0.69%</td>
<td>94.3 ± 1.02%</td>
<td>93.2 ± 1.11%</td>
<td>92.1 ± 1.33%</td>
<td>90.8 ± 1.58%</td>
<td>89.1 ± 4.31%</td>
</tr>
<tr>
<td>40</td>
<td>95.1 ± 0.78%</td>
<td>93.0 ± 1.14%</td>
<td>91.9 ± 1.21%</td>
<td>90.5 ± 2.27%</td>
<td>89.1 ± 1.81%</td>
<td>86.6 ± 5.86%</td>
</tr>
<tr>
<td>10</td>
<td>86.1 ± 1.44%</td>
<td>76.8 ± 8.18%</td>
<td>78.1 ± 12.51%</td>
<td>74.1 ± 10.02%</td>
<td>69.2 ± 12.96%</td>
<td>63.4 ± 14.29%</td>
</tr>
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curves for different tissue types in the perfusion images (Fig. 3c). Based on the arrival order of contrast agent (Fig. 3c) and the PDW image (Fig. 3b), the tissue types can be easily recognized as artery, GM, WM, sinus, vein and sinus, CSF and choroid plexus, and artifacts, respectively. A plot of the relative concentration-time curves of these tissues using Eq. [3] is shown in Fig. 3d, which demonstrates that the bolus of contrast agent arrived first in the artery and then in the GM, WM, sinus, or vein and sinus. In addition, good recirculation was observed in these tissues because of intact blood–brain barriers. It is not easy to separate the “sinus” and “vein and sinus” based on their signal-time curves alone. According to the anatomical atlas, although the areas of veins and sinuses differ, they overlap somewhat. In general, the sinuses locate dorsally in the midline on transaxial images, whereas the veins locate on brain surfaces and periventricular regions, and eventually converge into sinuses. The concentration-time curve of pixels in the artery region was modeled as an AIF for the deconvolution of rCBF. Figure 3e–g display parametric images for rCBV (the first pass includes images 16–38 in Fig. 1, as used in the calculation), rCBF, and MTT for this slice, respectively. They all have good contrast between tissues due to the use of in-plane AIF. Values of rCBV, rCBF, and MTT for different tissues can be easily computed from the associated ROIs on three parametric maps.

Our analysis of the images of five subjects (one upper slice for each subject) showed that arterial areas were reliably extracted out, and the delivery of contrast agent appeared consistently in the order of artery, GM, WM, sinus/vein and sinus, and choroid plexus and CSF. The optimum number of tissue clusters was either seven or eight when the MDL values attained the minimum. The averaged ratios of GM to WM for rCBV, rCBF, and MTT were $2.156 \pm 0.117$, $2.363 \pm 0.113$ and $0.903 \pm 0.052$. 

FIG. 3. Segmentation results and parametric maps. a: The seven tissue types displayed in a composite color-coded image are artery (red), GM (yellow), WM (brown), sinus (purple), vein and sinus (blue), CSF and choroid plexus (green), and artifacts (gray). b: The segmentation result agrees with the anatomical PDW image. c: The averaged signal-time curves of corresponding tissues. d: The relative concentration-time curves of corresponding tissue types demonstrate the sequential phasic order: the bolus of contrast agent arrived first in the artery and then in the GM, WM, vein and sinus or sinus, and CSF with choroid plexus. e: rCBV (scale unit: arbitrary unit (a.u.)). f: rCBF (scale unit: a.u.). g: MTT (scale unit: second).
respectively, which are in good agreement with those reported in the literature (5,6,33,34).

Results From a Patient With CAVM Before and After Treatment

The EM-MoMG method is currently being applied to controlled clinical trials. One of the initial trials was conducted on a 29-year-old female patient with a CAVM in her left motor cortex. The patient was experiencing seizures. The CAVM was treated by radiosurgery with a multiple Co60 irradiation unit (Gamma Knife). The SNRs of the pre- and post-treatment data were 70 and 72, respectively. Prior to the treatment, EM-MoMG-based perfusion imaging quantitatively demonstrated the different hemodynamic components of the CAVM and other brain tissues. To facilitate the identification of the CAVM region from the segmentation result, 3D time-of-flight (TOF) images (Fig. 4b and Fig. 5b) were acquired on the same 1.5-Tesla scanner using a gradient-echo, 3D-TOF pulse sequence (TE/TR = 6.9/40 ms, flip angle = 90°, FOV = 24 cm × 24 cm, matrix = 512 × 256, and slice thickness/gap = 2/0 mm). The perfusion parametric maps showed increased rCBV and rCBF, and decreased MTT of the CAVM and its surroundings compared to the homologous areas of the contralateral hemisphere (Fig. 4).

Six months later, the CAVM was observed to be morphologically smaller than it was prior to treatment. The EM-MoMG-based perfusion maps (Fig. 5) demonstrated the movement of the CAVM and brain hemodynamics toward normalization, with the rCBFs of arterized blood (ar) and CAVM+ar falling from 1259 ± 757 and 857 ± 690, respectively, before radiosurgery to 1130 ± 558 and 596 ± 390, respectively, after radiosurgery. The MTT values increased from 3.3 ± 0.9 and 3.4 ± 0.9 (seconds) to 3.8 ± 0.9 and 3.7 ± 0.5 (seconds), respectively. The GM/WM ratios for (rCBV, rCBF, MTT) of lesion hemisphere and whole hemisphere were improved from (2.84, 3.12, 0.87) and (3.08, 3.27, 0.90) before treatment to (2.74, 2.83, 0.93) after treatment, respectively. Moreover, apparent recirculation recoveries for artery, GM, vein, and sinus, which started at the 23rd to 26th seconds and ended at the 35th to 40th seconds, were observed in their relative concentration-time curves (Fig. 5d) after radiosurgery, also suggesting the normalization of aberrant brain hemodynamics. These results show that the EM-MoMG method can effectively differentiate pathological tissues from nor-
mal tissues, and allows quantitative estimates of hemodynamic parameters to be obtained. In addition, this method supplements DSC-MRI with temporal information, such as sequential phasic order and recirculation information, which is not provided by conventional perfusion maps.

**DISCUSSION**

The mixture of Gaussians (MoMG) is a popular model that is used in many image segmentation methods (25,35,36). The use of this model is based on the assumption that the grayscale intensity value of each pixel is a sample from a finite mixture of Gaussian distributions. Such a model can be extended to parameterize the intensity distribution of multidimensional images. Liang et al. (25) modeled the distribution of 3D image intensities of $T_1W$, $T_2W$, and PDW MR images as a finite MoMG, and used the EM method to classify different tissue regions. Similarly, we adopted the MoMG in this study to fit the multidimensional dynamic data. However, DSC-MR images are much more informative than anatomical images because they encode not only the attributes of the spatial intensities but also those of the temporal bolus profiles in various tissue types. To speed up the estimation process, we reduced the data dimension from $70 \times N$ to $10 \times N$ via PCA so that the number of unknown parameters would decrease greatly from $(70^2 + 3 \times 70 + 2) \times 7/2 - 1 = 17891$ to $(10^2 10 + 3 \times 10 + 2) \times 7/2 - 1 = 461$ when the number of tissue types was seven. Since fitting a large number of class parameters to the high-dimensional raw data is computationally expensive, and the improvement is very limited, the use of reduced data is highly recommended.

We assessed the robustness, accuracy, and sensitivity of the proposed method based on the results of Monte Carlo simulations in Fig. 2 and Table 1 as follows: First, the numbers of tissue classes were correctly estimated for SNR $\geq 40$ (Fig. 2a–f). This demonstrates that the determination of class numbers based on MDL is insensitive to noise. However, it should be noted that as we classified the data into more clusters, the differences between the minimum MDLs and their adjacent MDLs became smaller. For example, when SNR $= 40$, the differences between the minimum MDL and its two adjacent MDLs became smaller. For example, when SNR $= 40$, the differences between the minimum MDLs and their adjacent MDLs became smaller. For example, when SNR $= 40$, the differences between the minimum MDLs and their adjacent MDLs became smaller. For example, when SNR $= 40$, the differences between the minimum MDLs and their adjacent MDLs became smaller. For example, when SNR $= 40$, the differences between the minimum MDLs and their adjacent MDLs became smaller. For example, when SNR $= 40$, the differences between the minimum MDLs and their adjacent MDLs became smaller. For example, when SNR $= 40$, the differences between the minimum MDLs and their adjacent MDLs became smaller. For example, when SNR $= 40$, the differences between the minimum MDLs and their adjacent MDLs became smaller. For example, when SNR $= 40$, the differences between the minimum MDLs and their adjacent MDLs became smaller. For example, when SNR $= 40$, the differences between the minimum MDLs and their adjacent MDLs became smaller. For example, when SNR $= 40$, the differences between the minimum MDLs and their adjacent MDLs became smaller.

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We assessed the robustness, accuracy, and sensitivity of the proposed method based on the results of Monte Carlo simulations in Fig. 2 and Table 1 as follows: First, the numbers of tissue classes were correctly estimated for SNR $\geq 40$ (Fig. 2a–f). This demonstrates that the determination of class numbers based on MDL is insensitive to noise. However, it should be noted that as we classified the data into more clusters, the differences between the minimum MDLs and their adjacent MDLs became smaller. For example, when SNR $= 40$, the differences between the minimum MDLs and their adjacent MDLs became smaller. For example, when SNR $= 40$, the differences between the minimum MDLs and their adjacent MDLs became smaller. For example, when SNR $= 40$, the differences between the minimum MDLs and their adjacent MDLs became smaller. For example, when SNR $= 40$, the differences between the minimum MDLs and their adjacent MDLs became smaller. For example, when SNR $= 40$, the differences between the minimum MDLs and their adjacent MDLs became smaller. For example, when SNR $= 40$, the differences between the minimum MDLs and their adjacent MDLs became smaller. For example, when SNR $= 40$, the differences between the minimum MDLs and their adjacent MDLs became smaller. For example, when SNR $= 40$, the differences between the minimum MDLs and their adjacent MDLs became smaller.
method performed accurately and robustly against the noise, resulting in averaged classification rates higher than 89.1% (Table 1). Specifically, when the noise level increased from the noise-free condition to SNR = 40 for any data set consisting of four to eight clusters, the maximum differences of the averaged classification rates remained less than 3.2%, and the overall SDs of the averaged classification rates were less than 2.27%. However, when the data consisted of nine clusters and SNR ≥ 40, the mean classification rates degraded to 90.1%—86.6%, and the mean SDs increased to 4.31–5.86%. Finally, when SNR = 10, none of the cluster numbers were determined correctly (except for the data with four clusters), and the accuracy rates were not satisfactory. In summary, the simulation results suggest that the present method performed well when the data consisted of less than nine clusters and the SNR was higher than 40.

It can be seen that the red areas (artery) surrounding the brain in Fig. 3a located at an upper slice level have disappeared in Figs. 4c and 5c at a lower slice level, and the blue regions around the brain in Figs. 4c and 5c are not visible in Fig. 3a. From a pathophysiological standpoint, CAVM contains a cluster of abnormal vessels, the so-called nidus, that locate between feeding arteries and draining veins. Due to the pressure gradient between the arteries and veins, arterial-venous shunts occur in CAVM. The shunts cause blood diversion from adjacent and even remote brain areas from the contralateral brain hemisphere to the CAVM, which is known as the cerebral “steal phenomenon” (37). In addition, the shunts and the steal phenomenon result in increasing venous blood and venous pressure in the ipsilateral or contralateral brain hemispheres. Taking this phenomenon into account, the “red” areas in Fig. 4c indicate the nidus consisting of arterized blood (ar) and the “blue” areas (vein + sinus) in Fig. 4c indicate increasing venous blood and venous pressure. The disappearance of red areas surrounding the brain in Fig. 4c was also caused by the steal phenomenon, which modified the arterial hemodynamic patterns in the contralateral hemisphere such that they resembled GM patterns. This resulted in the contralateral hemisphere being classified as GM. Six months after radiosurgery, the nidus decreased in size and the shunts and steal phenomenon gradually diminished. Because of the cerebral hemodynamics recovered toward the normal condition, the overall hemodynamic changes supported the therapeutic effects of CAVM radiosurgery. Accordingly, the hemodynamic mapping appeared more similar to that shown in Fig. 3a (i.e., the ar of the CAVM nidus in Fig. 5c became smaller, whereas the ar in the midline and contralateral brain hemisphere became more evident and the blue part (vein + sinus) was diminished). Several factors may contribute to a difference in segmentation results, such as slice level effects and imaging differences caused by the patient or imaging acquisition heterogeneity. Nevertheless, in the case of CAVM, these factors are minor compared to the arterial-venous shunts and the steal phenomenon.

In the current method, all data points are assumed to be independent samples drawn from a population, and the label of class k is assigned to data point x_n, when the posterior probability p(k|x_n,θ) is maximal among all the K classes. If the spatial correlation among data points is not negligible, the tissue regions can be further assumed to be piecewise contiguous and the current histogram-based method can be modified to take the spatial information into account. Such spatial continuities can be characterized by a Markov random field (MRF) prior (38,39), or the recently developed hidden MRF model (40), which is constructed by the tissue-region membership of the first- and second-order neighborhood. Since we attempt to keep the implementation simple, as long as the results are satisfactory, the incorporation of an MRF prior is optional. However, this will be investigated in future studies.

CONCLUSIONS

We have presented an EM-MoMG method for extracting different spatiotemporal hemodynamics from brain perfusion MR images. This method has several advantages for central hemodynamics studies and clinical applications. First, an AIF can be modeled consistently on the same slice location for the calculation of rCBV, rCBF, and MTT maps. Second, various tissue compartments on perfusion images can be classified systematically. Third, the bolus transit profiles of these tissues can be well separated. Fourth, this pilot study illustrates that the extracted spatiotemporal blood-supply patterns improve differentiation of pathological and nonpathological hemodynamics. Finally, this method provides an effective imaging technique for evaluating treatment effects. This method can be extended to other imaging modalities, such as dynamic CT and PET, and to other organs (e.g., the heart, liver, kidneys, and extremities) in perfusion images.

APPENDIX

Let the compressed data be denoted by a matrix X with size t × N (t = 10). The proposed method assumes that each tissue class has a multivariate Gaussian distribution of data points, and that the overall distribution of the compressed data can be fitted by a linear combination of the distributions of the classes. In other words, each data point x_n (t × 1), n = 1, . . . , N, can be considered as a sample from an MoMG given by

\[ p(x_n|m, \pi) = \sum_{i=1}^{K} p(z = i)p(x_n|z = i) \]

\[ = \sum_{i=1}^{K} \pi_i g_i[m, \sum_i] \]

\[ = \sum_{i=1}^{K} \frac{1}{(2\pi)^{t/2} \det \sum_i^{1/2}} \exp \left[-(x_n - \mu_i)^T \sum_i^{-1} (x_n - \mu_i)/2 \right] \]  [A1]

where z is a variable representing a tissue class that assigns a label (z ∈ {1, . . . , K}) to every data point, p(z=i) denotes
the proportion of each class, and $g_{x_i} [\mu, \Sigma]$ represents a multivariate Gaussian density with the mean vector $\mu_j$ and covariance matrix $\Sigma_j$, $i = 1, \ldots, K$. To simplify notation in the following discussion, we will write $i$ and $\pi_i$ instead of $z = i$ and $p(z = i)$, respectively. Note that the sum of proportions $\pi_i$ is equal to 1, i.e., $\sum_{i=1}^{K} \pi_i = 1$. Since there is no prior information on the labels of the data, we employ the EM algorithm, an unsupervised clustering method, to learn the parameters $\mu_j$, $\Sigma_j$ and $\pi_i$ by fitting a MoMG to $X$, and assign each data point to one of $K$ clusters based on the maximal posterior probability. Let $\theta_i$ denote the parameters $\{\mu_j, \Sigma_j, \pi_i\}$ at the $t$th iteration. The EM algorithm consists of two alternating iterative steps: the E-step and the M-step. The E-step is to compute the posterior probabilities of tissue classes $p(i|x_n, \theta^{t-1})$ based on the Bayesian rule and estimated parameters from previous $t-1$th iteration, which is given by

$$p(i|x_n, \theta^{t-1}) = \frac{p(i)p(x_n|i)}{\sum_{j=1}^{K} p(j)p(x_n|j)}$$

$$= \frac{\pi_i g_{x_n} [\mu_i^{-1}, \Sigma_i^{-1}]^T}{\sum_{j=1}^{K} \pi_j g_{x_n} [\mu_j^{-1}, \Sigma_j^{-1}]^T} \quad [A2]$$

The posterior probability is in turn used to evaluate the so-called Q function:

$$Q(\theta|\theta^{t-1}) = E[\log[p(X, i|\theta)]|X, \theta^{t-1}]$$

$$= \sum_{i=1}^{N} \sum_{j=1}^{K} p(i|x_n, \theta^{t-1})(\log[p(x_n|i, \theta)] + \log[p(i|\theta)])$$

$$= \sum_{i=1}^{N} \sum_{j=1}^{K} p(i|x_n, \theta^{t-1})(\log[g_{x_n} (\mu_j, \Sigma)] + \log[\pi_j]) \quad [A3]$$

It should be noted that the posterior density $p(i|x_n, \theta^{t-1})$ plays a crucial role because its maximal value associated with each data point determines the label at corresponding pixel. The M-step consists of maximizing $Q$ over the parameters $\{\mu_j, \Sigma_j, \pi_j\}$ by taking derivatives of $Q$ with respect to parameters $\mu_j$, $\Sigma_j$, and $\pi_j$, respectively, and equating them to zero to yield

$$\mu_j = \frac{\sum_{n=1}^{N} p(i|x_n, \theta^{t-1})x_n}{\sum_{n=1}^{N} p(i|x_n, \theta^{t-1})} \quad [A4]$$

$$\Sigma_j = \frac{\sum_{n=1}^{N} p(i|x_n, \theta^{t-1})x_n x_n^T}{\sum_{n=1}^{N} p(i|x_n, \theta^{t-1})} - \mu_j \mu_j^T \quad [A5]$$

$$\pi_j = \frac{1}{N} \sum_{n=1}^{N} p(i|x_n, \theta^{t-1}) \quad [A6]$$

The initial-guess $\mu^0$ and $\Sigma^0$ can be randomly generated. Alternatively, in this study we chose the initial guess by first downsampling the images at every 1, 2, ..., $K$ pixels to have $K$ sets of subimages, and then computed the average and covariance matrix from each set of subimages. The optimal number of classes $K$ is determined by the value that minimizes the information criterion of the MDL (31):

$$\text{MDL}(K) = - \log \left( \prod_{i=1}^{N} \sum_{j=1}^{K} \pi_j g_{x_n} [\mu_j, \Sigma_j] \right) + \lambda K \log(N) \quad [A7]$$

where the term $\prod_{i=1}^{N} \sum_{j=1}^{K} \pi_j g_{x_n} [\mu_j, \Sigma_j]$ is the maximum likelihood of $p(x_n|\mu_j, \Sigma_j, \pi_j)$ with parameters $\{\mu_j, \Sigma_j, \pi_j\}$ estimated by the EM algorithm, $J = (t^2 + 3 \times t + 2) \times K/2 - 1$ (i.e., $tK$ parameters of $\mu_j$, $(t+1)K/2$ parameters of $\Sigma_j$, and $K - 1$ parameters of $\pi_j$), and $\lambda = 3/4$ is a scalar factor.

REFERENCES