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Mitochondrial Organelle Movement Classification (Fission and Fusion) via Convolutional Neural Network Approach

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ABSTRACT Mitochondria are highly dynamic cellular organelles with the ability to change size, shape, and position over the course of a few seconds. Mitochondrial organelle movement refers to the problem of finding fission and fusion and generates energy for the cell. In this paper, we proposed a deep learning method [mitochondrial organelle movement classification (MOMC)] for mitochondrial movement classification using a convolutional neural network. We present a three-step feature description strategy, such as local descriptions, which is first extracted via the GoogLeNet, followed by the production of mid-level features by ResNet-50 and global descriptor features by Inception-V3 model and final classification of the position of mitochondrial organelle movement. Our method consists of a deep classification network, MOMC for gathering the organelle position, and a verification network for classification accuracy by removing false positives. Using machine learning methods, logistic regression (LR), support vector machine (SVM), and convolutional neural networks (CNNs), we found that the CNN better classified the shape of mitochondrial organelles (fission and fusion). Employing 24 types (position) of images, a convolutional neural network was trained to identify mitochondrial organelle movement with 96.32% accuracy. This enabled the discovery of position, further advancing the clinical utility of human mitochondrial organelles.

INDEX TERMS Shape movement classification, mitochondrial organelle, deep learning, fission and fusion.

I. INTRODUCTION

Mitochondrial movement, position, and shape are controlled by fission and fusion. Mitochondria have two types of fusion protein mutations, including, mitofusin-2 (MFN2) or optic atrophy protein (Opa1), which has been associated with neurological disorders, that are identified in neurological patients. Mutations in mitofusin-2 and Opa1 have been linked to Charcot-Marie-Tooth disease and optic atrophy, respectively. Optic atrophy is common in hereditary blindness. In this study, we hypothesized that it may be possible to predict mitochondrial movement position specifically fission and fusion (see Fig.1). Prediction of mitochondrial organelle movement position in clinical decision is vital especially in neurological patients showing blindness. Mitochondria play an important role in tumor metabolism [1]. Normal differentiated cells generate energy needed in cellular processes by rewiring cellular metabolism through oxidative phosphorylation in mitochondria whereas cancerous cells rely on aerobic glycolysis, which has been termed as the Warburg effect [2]. The Warburg effect increases metastatic tendency [3] and worsens disease outcome, in certain cancers [4]. Oxidative phosphorylation contributes to tumor growth [5], fuels unique tumor characteristics, including repopulation after oncogene ablation [6], [7] and metastatic dissemination [8], [9]. Recent studies have suggested that the mitochondrial cell is dynamic organelle, which controls the size, shape, and topography of tumor cells [10]. Although the use of image-based features [11] has played a very important role in the clinical diagnosis of breast cancer in the last decade, major advances in the prediction of cancer have mainly relied on molecular methods [12]–[14]. However, these methods are costly and

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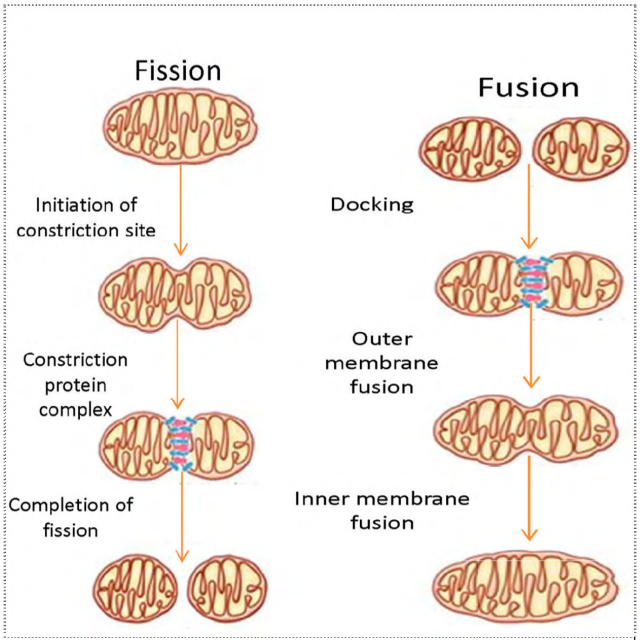

FIGURE 1. **Mitochondrial organelle fission and fusion.**

not routinely performed on all clinical patients, who could benefit from advanced molecular tests. Older approaches have largely relied on handcrafted features, such as color and shape, to capture cell by cell morphology. However, it has been challenging to adapt handcrafted features to new datasets [15], [16]. Previously, automated image classification has been used to determine mitotic counts [17], nuclear atypia [18], and individual tubule formations [19], and other novel features that are commonly identified in breast [20] and other types of cancer [21], [22]. None of these approaches have been used to classify mitochondrial organelle movement (shape 1 to shape 24). However, significant advances in molecular biology, tumor detection techniques [23], [37], metastatic cancer detection [24], mitosis detection [25], tissue segmentation [26] and detection of tissue structures have demanded the use of deep learning method to classify the shape of mitochondria during fission and fusion as shown in Figure.1 [27]. Previously, the deep learning methods were used to detect image-based features but none of these focused on the mitochondrial organelle image analysis. The use of deep learning to predict the movement of the single mitochondrion that is not apparent to mutations, such as fission and fusion or even shape and position of a mitochondrial organelle has not been previously described. Currently, only a few studies have attempted to classify mitochondrial movement [28]. However, these studies have only focused on cell classification but no attempt has been made to study mitochondrial shape and movement. In this study, we classified mitochondrial movement as a unique contribution to effective classification of mitochondria.

Deep learning has gained attention in the biomedical field for resolving medical imaging features, including object classification, recognition and segmentation. Our goal is to propose a new fully automated approach to classify the 24 positions of mitochondrial movement and using the mitochondrial organelle movement classification (MOMC) method. Firstly, an input image dataset was used. Secondly, we propose new mitochondrial organelle movement classification architecture.

In this study, a convolution neural network based classifier was trained to predict the position of mitochondria organelle movement. As a first step, we obtained low level features by using GoogLeNet-22, and the second step middle level features were determined using ResNet-50. Finally, high level features were obtained and used as an inception model to differentiate mitochondrial organelle positions.

The proposed method will be useful in neurology, specifically in blindness. Our proposed method not only achieves higher accuracy but also addresses the clinical relevance. This method will be used in the diagnostic neurology. Furthermore, deep learning techniques are usually used to analyze large amount of data but in this study we sought to achieve higher accuracy with minimal data. These results suggest that our method is useful in helping diagnosing neurological disorders and blindness. The workflow provides a foundation for high throughput analysis of mitochondrial organelle movement.

II. METHOD

A. MITOCHONDRIAL ORGANELLE MOVEMENT CLASSIFICATION (MOMC)

In this study, we used different methods and applied multilayer CNN for understanding mitochondrial organelle movement. In the last five to eight years, CNN has progressed in many fields, such as natural language processing [31]–[33], computer vision [38], and medical imaging [34]–[36], a number of studies have applied CNN and shown that this technique has a powerful ability to extract features. CNN carries out self-learning from the high amount of data without using any hand designed features. Our model did not require the building of complex rules on how the model decides to extract information automatically, forms movement dataset and classifies mitochondrial position and shape. The framework (see Figure 2) takes mitochondrial image as an input and this framework predicted the probability of shape as an output. Briefly, in the first input patches were used to form mitochondrial image and the CNN model was trained by 'GoogNet-22' and used to classify different shapes. In the second model, 'ResNet-50' generated a probability that an image represented shape could change position. In the third model, 'Inception-V3' was contracted to a small CNN stacked on top of ResNet-50. Inception model was trained to generate a score for a full image that indicates the probability contained fission and fusion of mitochondrial organelle. For more details, this method is described below. Figure 2 shows the whole classification system. Three networks were used: the first network was a GoogLeNet like architecture [29]. GoogLeNet is a neural network architecture developed by

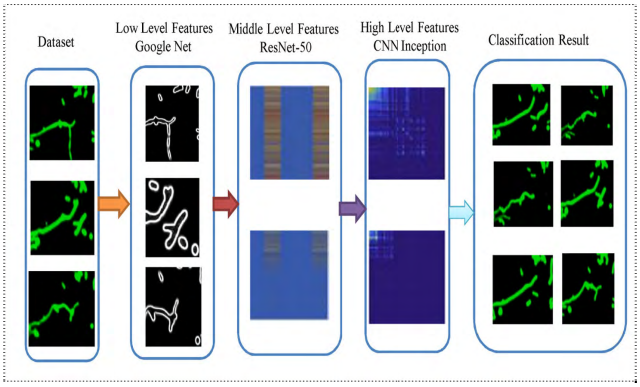

FIGURE 2. The stack of three existing structures: Mitochondria organelle movement classification (MOMC), proposed model framework. We used GoogleNet and ResNet-50 for low-level and middle level features, respectively. Finally, inception model was used for high-level features. Extract the feature vectors of mitochondrial image and map them to the feature map and calculate the probability of each position and select the high probability of the mitochondrial image shape detection.

Szegedy *et al.* [29]. The second network is ResNet-50 and its network architecture was developed by He *et al.* [30]. The details of our network training and configuration are presented in the results section.

B. DESCRIPTION OF CNN INCEPTION-V3 FOR CLASSIFICATION OF DIFFERENT SHAPE OF MITOCHONDRIA (FISSION AND FUSION)

To demonstrate the potential of mitochondrial organelle movement, Inception model was constructed to identify the shape of mitochondrial organelles based on the output of ResNet-50 only. The output features were mapped on the second last layer of ResNet-50 (hidden layer, which output is fed to final layer), which was a solid representation of the input mitochondrial organelle image. Inception model takes the input features from ResNet-50 for 24 non-overlapping shapes. Features were identified by ResNet-50 as protecting the strongest shape-change alterations to predict the different shapes of mitochondria (fission and fusion) (Figure.2). For detailed procedures on mitochondrial organelle shape classification, see the method section. To generate the final classification shape of the mitochondrial organelle, we used both GoogLeNet and ResNet-50 with Inception-V3 and a modified version of Inception-V3 without the last two fully connected layers, and the average probability of two networks was taken as the final shape classification. Furthermore, the shape deviation of the mitochondrial organelle and slide image were compared. The model achieved a good accuracy and classified mitochondrial fission and fusion.

In the training model, we used mitochondrial shape-level labels to predict the class or characteristic group of mitochondrial organelle movement, such as shape 1-24. Mitochondrial organelle images were much larger than the required MOMC input. We resized the image to 800 × 800. Furthermore, CNN (convolutional neural network) was applied to produce features for mitochondrial organelle classification (fission and fusion). Thus, some modification to the MOMC method was necessary because we used three different networks for low, middle and high-level features, and each network had specific requirements and image size as input. We proposed that a new classifier is trained to operate on low-level features from GoogLeNet-22 and a classifier trained for middle-level features from ResNet-50. Finally, a classifier for high-level features was trained by Inception-V3. In this study, a set of mitochondrial organelle image shape 1 to 24 were obtained. Each contained one or more shapes of mitochondrial organelle. We also obtained a label for each shape movement: shape grade, shape 1-24, and fission and fusion. Due to variation in mitochondrial image shape, the learning model label was applied on every image shape change but did not perform well in the initial experiments. In order to account for fission and fusion heterogeneity, a probabilistic model was formed, each image was allocated to class, and aggregated probabilities across the image shapes were formed to predict shape movement (fission and fusion) Figure 6. For training, the image region was generated as (800 × 800) pixel Figure 5. Convolutional neural network computed the features over the region. The linear SVM (support vector machine) was used to predict the probability of each image shape detection.

C. CNN ALGORITHM

Convolutional neural network algorithm was developed using GoogLeNet, ResNet and inception. We have used caffe deep learning frameworks, to train validate and test our newly developed method. It allows the gradient to pass back through layers (backpropagation), without losing information. In the regular convolution neural network, the gradient passes through an activation layer, which diminishes the gradient (backpropagation: following a gradient descent approach that exploits the chain rule). To avoid this problem, the connection was appended within CNN, to allow gradients to pass through, and decrease the effect of information loss. The MOMC had high accuracy and a lower training time in comparison to other methods. We also compared MOMC network framework with other machine learning methods. We used the GoogLeNet-22, ResNet-50 and Inception-V3 pre-trained CNN with the mitochondrial organelle image dataset mentioned in this work for feature extraction. We selected deep GoogLeNet-22, ResNet-50, and Inception-V3, architecture (see Fig. 3) and computed feature vector for each image. In Figure 3, mitochondrial organelle image and convolutional layers were pooled and finally fusion and fission cell images were classified.

D. STATISTICS AND REPRODUCIBILITY

Using the fission and fusion of single cell factures extracted from mitochondrial image data set, we developed the predictive model (MOMC) to predict the movement of mitochondrial organelles. The model was validated on the basis of some traditional machine learning methods (LR, SVM, and LR+SVM) and CNN (GoogleNet-22, ResNet-50, and inception. The curve of predicted accuracy is shown in Fig.8.

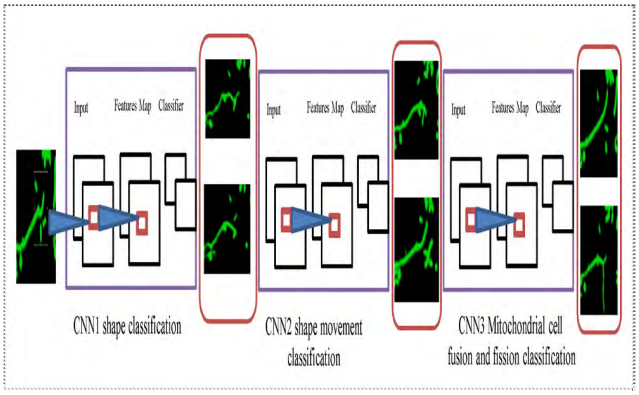

FIGURE 3. The overview of the mitochondrial organelle shape classification, and the system used for classification. Whole slide image, shape1 to shape 24, and fission and fusion. CNN-1 classified the tissue into shape1 to shape 24. CNN-2 operated on regions detected by CNN-1 and was trained to the identified region of shape change. To classify the movement of fission and fusion, CNN-3 took as input patches with high probabilities for shape change identified by CNN-2 and classified the fission and fusion.

We defined some measures to evaluate the accuracy of mitochondrial organelle movement. The evaluation method used several evaluation indicators, which are commonly used in the classification task to evaluate the performance of our model. Their conceptions and formulas are described as follows:

$$\mathbf{Accuracy} = (\mathbf{TP})+(\mathbf{TN})/(\mathbf{TP})+(\mathbf{FP})+(\mathbf{FN})+(\mathbf{TN}) \quad (1)$$

where true positive (TP), a trend is up and it is classified as up. The True Negative (TN), a trend is down and it is classified as down. False Positive (FP), a trend is down but it is classified as up. False Negative (FN), a trend is up but it is classified as down.

III. RESULTS

A. DATA SET

Mitochondria were classified into seven groups [46] (curved, discoid, multiple vase shaped, single-vase shaped, tabular and perforated). The conventional type of mitochondria is tabular and usually observed in the control organelles. Biconcave shape type mitochondria are called discoid, cup-shaped mitochondria are called curved, and vase-shaped are called orifice. Furthermore, vase-shaped mitochondria are classified into two classes (single and multiple). Here, we used the single vase shaped mitochondria (see Fig.4). For single mitochondrial image movement in a few seconds, twenty-four different positions were identified. Twenty-four types of mitochondrial images were obtained by confocal microscopy (classified 1-24). A total of more than 252 images were captured. In Fig.4 (a), images are shown, the first image in all the twenty-four positions.

In this paper, we propose a novel and comprehensive method to classify the shape of mitochondrial organelles (Fig. 2). In our method, we applied twenty-four image-transforms to mitochondrial images in order to extract the mathematical features of the images. The image features are ranked by their Fisher scores according to their statistical importance. These features can be input into any kind of classifier for the purpose of discrimination. Using a dataset of mitochondrial images, we demonstrate that the accuracy and robustness of the classification can increase when using an image pattern rather than an average spectrum representing the cell. Then, we demonstrate that the possibility of combining both methods. The current study provides supporting evidence that our methodology can benefit the analysis of mitochondrial images in biological and biomedical studies.

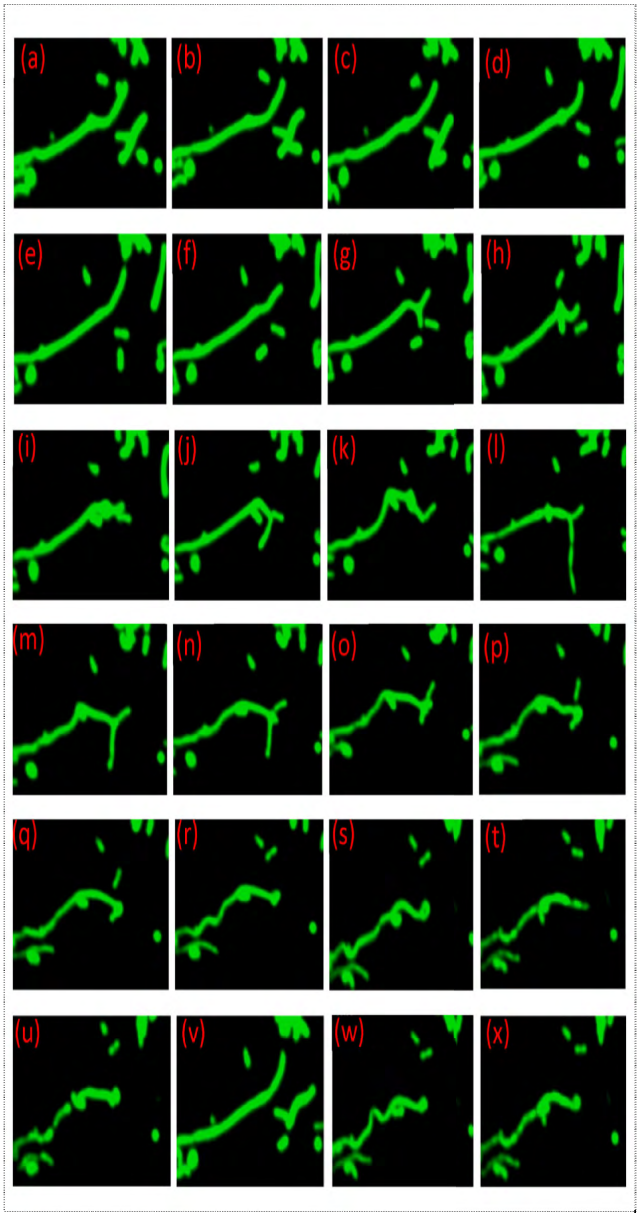

FIGURE 4. Mitochondrial images observed by confocal microscopy. The change of mitochondrial shape (1-24) within a very short time (a-x).

B. MITOCHONDRIAL DYNAMICS

Mitochondria are versatile and highly dynamic organelles that continuously fragment and fuse in response to different

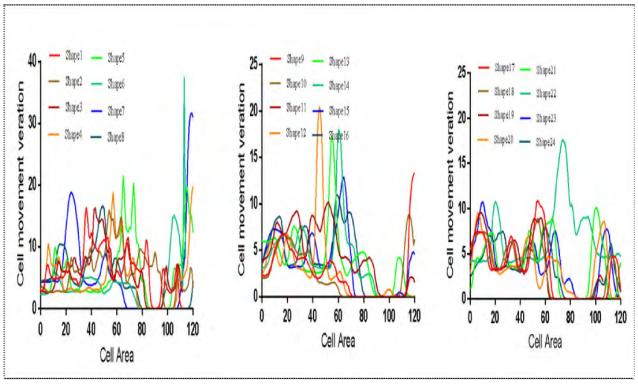

FIGURE 5. Mitochondrial organelle shape deviation.

physiological needs of the cell. The structure of mitochondria is complex and parallel to their functionality. The change in shape of mitochondria plays important roles in vertebrate development, programmed cell death and normal cell physiology [28]. The shape variation (shape1-24) of mitochondrial organelle is shown in Figures 5 (a-c).

C. CLASSIFICATION OF MITOCHONDRIAL SHAPE (WHOLE SLIDE IMAGES)

GoogelNet-22 subdivided the whole slide images into regions consisting of shape 1-24, and achieved the classification accuracy of 96.32%, and computed the subset of marked pixels in the independent test set. Representative examples of shape classification are shown in Figure 6. Figure 6 shows the representative output probability map for a slide containing the shape movement of mitochondria (Figures. 6a–z).

Prediction accuracy and association with clinical characteristics for core-level comparisons, and image region probabilities were calculated for high-grade fission and fusion. Each sensitive variable was determined to compare image analysis classification and mitochondrial shape movement (fission and fusion). To find the shape movement grade for the shape movement tissue as a whole, accurate classification was defined as identical classification on histological image analysis. To determine the accurate characteristics, estimated odds ratios between mitochondrial shapes were determined (see Figure. 7). Figure 7 shows the fission and fusion.

The proposed method (MOMC) based on the GoogleNet, ResNet-50 and Inception-V3 architecture, and some traditional machine learning methods (LR, SVM, and LR+SVM), aimed at detecting the shape of mitochondrial organelles and obtain the region of the interest. The objectives of the study were: 1) to select the shape change in regional features, and 2) to classify with high probabilities features (see Figure 5). To validate the efficiency of our proposed method (MOMC), the comparison was made between the traditional machine learning versus deep learning with SIFT features and BoW model. The statistical significance of our method is shown in Figure 8 and Table 1. There was a statistical difference between the deep learning and non-deep learning methods, the accuracy of MOMC, LR, SVM, and LR+SVM is shown in (Table.1) (96%, 80%, 85%, and 91.5%). The training time

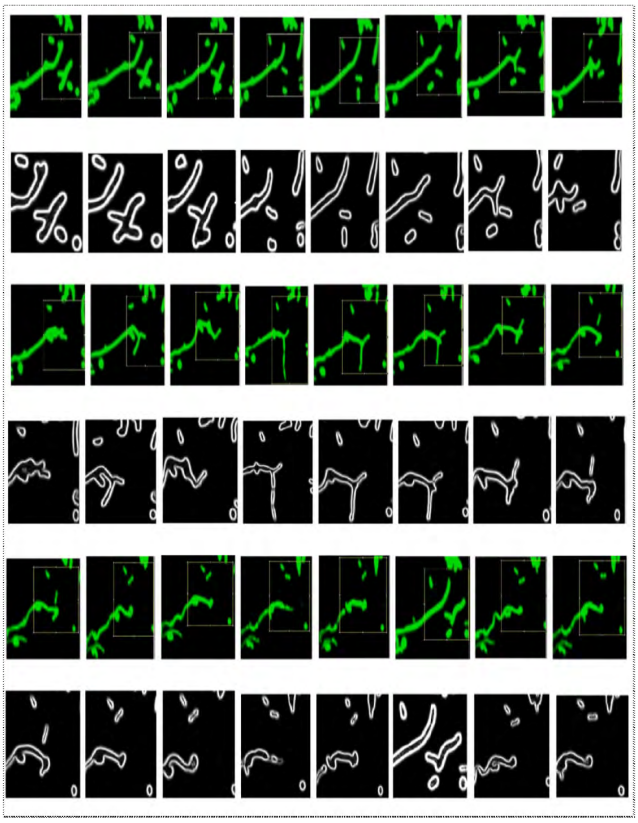

FIGURE 6. Results of mitochondrial shape change (a-x) classification and position identification. A representative of whole slide image containing shape change (a) and other shape change (b-x).

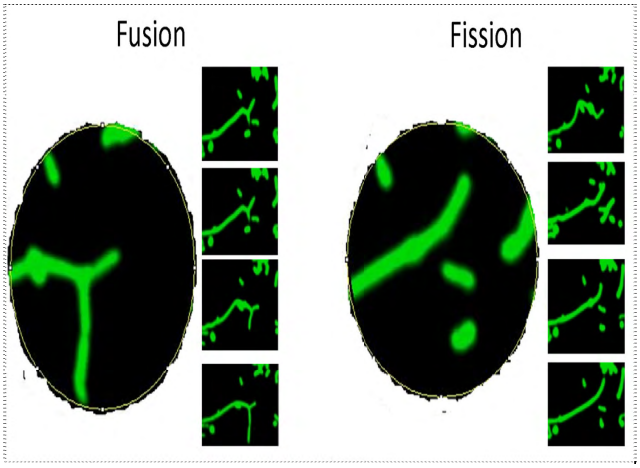

FIGURE 7. The shape classification of the mitochondrial organelles (fission and fusion). The prediction shows the fission and fusion.

of methods are (7, 8, and 9 minutes of 100 epochs, CPU). The results suggest that the MOMC is the best method compared to other machine learning methods. Figure 4 shows total images, which were taken as input and split data in training, test set and predicted classified mitochondrial organelle images. Training, validation, and test data were split by study, and test data were not used for training or validating the model. The model was trained to classify images, with video classification as a majority rule vote on related

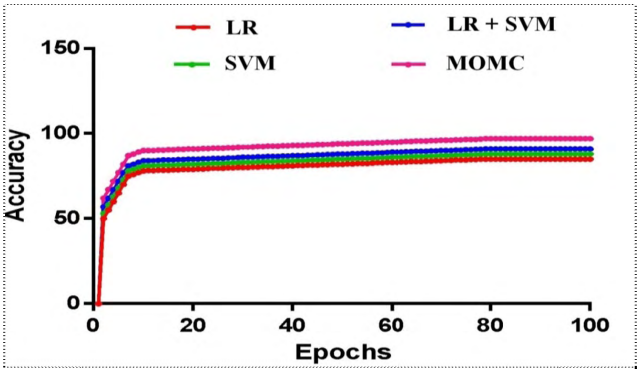

FIGURE 8. We have implemented four different methods, and the accuracy of deep learning performance is much better than other methods.

TABLE 1. Results of different methods, where "CNN" indicates the performance of the proposed model. The CNN is the ResNet-50, and CNN performance is better than all other methods.

Predicted accuracy of diseases & normal mitochondrial organelle images		
Methods	Data types	Accuracy
Logistic Regression	Mitochondrial organelle Images	0.80
SVM	Mitochondrial organelle Images	0.85
LR + SVM	Mitochondrial organelle Images	0.91
CNN (MOMC)	Mitochondrial organelle Images	0.96

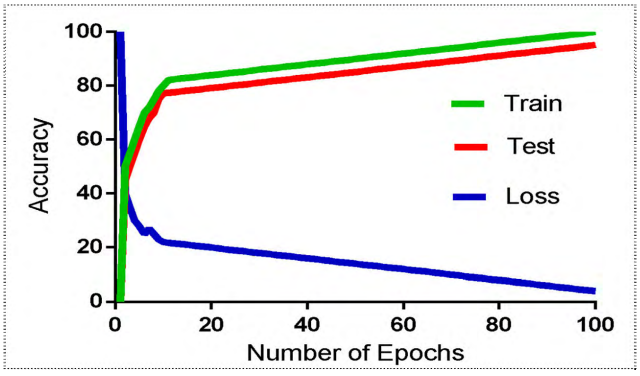

FIGURE 9. The training, test and loss of the MOMC. The test accuracy is 96%. We used 70% data for training, 15% for test and 15% for validation.

image frames. The CNN for mitochondria cell classification (fission and fusion) is illustrated in Figure 9.

IV. DISCUSSIONS

In this study, we developed a novel method for analyzing mitochondrial organelle movement (fission and fusion). Previously mitochondrial imaging methods have been limited to the classification of mitochondrial organelle shapes (seven shapes) [46], but the proposed method is also able to classify the movement of a single mitochondrial organelle. Our work differs from previous work in the use of deep learning, which automatically classifies the mitochondrial shape movement. We were able to analyze different movements of a mitochondrial organelle, and determine the heterogeneity among mitochondrial organelle shapes.

Thus for the first time, we were able to classify mitochondrial shape heterogeneity using machine learning. This MOMC approach extracts automatic useful features from mitochondrial organelle image datasets. We anticipate that the use of MOMC in the analysis of mitochondrial organelle shapes will be useful and valuable for the study of neurological related diseases, including blindness. The current method [39] is based on cell classification in radiology [44], pathology [45], breast cancer [42], and skin cancer [38], [43]. MOMC can also be used to analyze mitochondrial inner membrane fusion [40] and transport kinetics into mitochondrial organelle [41].

In this study, we proposed a method for analysis of mitochondrial organelle movement, including cell fission and fusion using CNN. Comparison of our method (MOMC) with a number of machine learning methods proved that MOMC was superior to the other methods (see Table 1). The high accuracy 96.23% achieved by MOMC suggests that our method has a very low probability of misdiagnosis. From test results, we infer that our model has a significant practical value. The MOMC approach does not require complex rules and large-scale knowledge as model features and parameters are automatically learned from mitochondrial image datasets. MOMC is a practical method, which outperforms other machine learning methods, including LR, SVM LR+SVM and CNN (see Table 1). As the results show in Fig. 2, with MOMC, it was possible to extract low-level, middle-level and high-level features of mitochondrial organelle images and map them into a high dimensional feature space. In this feature space, different shapes of mitochondrial organelle images had a different distribution. Similar types of mitochondrial shape movement gathered together. Analysis of feature space revealed fission and fusion movements, which allowed a better understanding of the clinical diagnosis (neurology and blindness). A novel deep learning method for mitochondrial imaging (MI) is proposed. We modified the CNN according to the features of the mitochondrial image and a target image was obtained through a trained network. A series of simulations results showed that MOMC was faster and accurate for classifying mitochondrial images compared with conventional machine learning method. Our method introduced AI (artificial intelligence) into mitochondrial imaging (MI). In summary, major contributions of this article included designing and implementing a model for mitochondrial organelle movement (fission and fusion) analysis based on CNN (convolutional neural network). This method will be useful in the analysis of neurological diseases and will also help in the classification of mitochondrial fission and fusion shapes. This study revealed that analysis of mitochondrial shape movement dataset by MOMC was 96.23% accurate. We are hoping that our work will serve as a

guide for future work and promote further the development of the mitochondrial organelle movement classification (fusion and fission).

V. CONCLUSION

MOMC was used in mitochondrial organelle shape recognition and prediction based on the shape of mitochondria (fission and fusion). In this article, we have proposed a mitochondrial organelle movement classification, which can be used for classifying cell fission and fusion. This approach allows end to end training to perform on microscopy imaging. The MOMC will be useful in classification of organelles in neurological patients as well as optic atrophy. Our results suggest that systematic mitochondrial organelle shape classification is an effective strategy for analyzing and classifying millions of organelle variants of uncertain significance that currently limits clinical genome interpretation. The accuracy of our deep learning network on both fission and fusion organelles is 96.23%. These results support the assertion that mitochondrial organelles are largely benign in cells with respect to penetrant neurological diseases.

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