Deep Learning-Based Adjunctive Therapy Tool for Mitochondrial Dysfunction

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Abstract

Mitochondrial myopathy is a maternally inherited metabolic disease, the root cause of which is mitochondrial structure and dysfunction due to genetic mutations in mitochondrial DNA (mtDNA) or nuclear DNA (nDNA). Due to complex classification and overlapping symptoms of mitochondrial myopathy, this paper introduces a non-invasive diagnostic tool to help examine patients with mitochondrial dysfunction. This paper first introduces the facial image processing of patients with mitochondrial dysfunction. The Viola-Jones algorithm and the improved Canny Algorithm are used to detect and extract the features of the eyebrows, and then the curvature of the eyebrows is calculated mathematically to describe the facial changes of the patients. The results of our experiments will aid in the patient's treatment record and may help patients detect symptoms earlier. Researchers can remotely and long-term improve the odds of treatment by taking pictures of patients. In addition, experimental data will help to mathematically document treatment improvements.

Keywords: Mitochondrial Dysfunction, Non-invasive, Feature Extraction, Viola-Jones Algorithm, Canny Algorithm.
1. Introduction

Mitochondrial myopathy is a group of diseases caused by mitochondrial DNA (mtDNA) or nuclear DNA (nDNA) defects that result in the functional and structural disorders of mitochondrial and insufficient ATP synthesis \(^1\). It is classified into two types: mitochondrial myopathy and mitochondrial encephalomyopathy. The distinction is whether mitochondrial encephalomyopathy lesions will continue to invade the central nervous system in addition to skeletal muscle. The majority of muscle injury manifests as skeletal muscle fatigue intolerance. Ophthalmoplegia, recurrent epilepsy, and myoclonus are the most common nervous system symptoms. Heart block, cardiomyopathy, and diabetes are examples of other system symptoms.

This paper focuses on the recognition of mitochondrial myopathy and encephalomyopathy with early-onset symptoms of ptosis and external ophthalmoplegia or paralysis, as shown in Fig.1. The most common mitochondrial myopathy is chronic progressive external ophthalmoplegia (CPEO), which manifests as pure extraocular muscle paralysis. In addition to extraocular muscle paralysis, Kearns-Sayre syndrome (KSS) is accompanied by retinitis pigmentosa and/or heart block, as well as short stature and mental retardation. Ptosis can be seen in mitochondrial encephalomyopathies such as Leber's hereditary optic neuropathy (LHON) and subacute necrotizing encephalomyelopathy (SNE or Leigh disease), but because of the complex and varied clinical manifestations, ptosis or extraocular muscle paralysis is only used as an auxiliary judgment condition.
Luft and Holt were the first to identify and propose mitochondrial myopathy and mitochondrial encephalomyopathy in 1962 and 1988, respectively [2]. CPEO was first to be recorded in 1868, and it is more frequent in women [3]. The main criterion is if it is accompanied by encephalopathy symptoms and alterations in brain imaging [4]. The disease usually occurs in children and adolescents, but the diagnosis time is often delayed, the average age of diagnosis in the literature is 18 to 56 years old, with chronic progressive ptosis and eye movement problems as clinical signs [5]. About half of CPEO patients are sporadic, owing to the loss of large mtDNA segments. Another 50 percent of patients have a family history of mitochondrial disease, which can be inherited in autosomal dominant, recessive, or maternal forms [6]. Because mitochondrial dysfunction is uncommon in clinics, it is frequently misdiagnosed as ophthalmic myasthenia gravis (OMG), oculomotor nerve palsy, and oculopharyngeal muscular dystrophy [7]. There is currently no effective treatment for mitochondrial myopathy, mainly using symptomatic treatments such as improving energy metabolism, antioxidants, scavenging free radicals, and promoting energy metabolism, but scholars believe that early treatment can improve prognosis [8], so the goal of this paper is to investigate a non-invasive technique for identifying mitochondrial malfunction. Calculate the eyebrow curvature slope in extraocular myopathy patients, as well as the common law for patients with mitochondrial failure who have this symptom. It aids patients in detecting diseases earlier and faster, receiving prompt treatment and relief as an auxiliary diagnosis and

![Fig. 1 Symptoms of ptosis.](Image)
treatment approach for clinical and telemedicine.

In this paper, eyebrows are selected as the detection subject. First, the position of the eyebrows is judged by the Viola-Jones framework, and then the improved canny algorithm is applied to detect the precise eyebrow edges. Finally, calculate the curvature of the eyebrows when the patient has ptosis symptoms, and record the treatment process in a long-term mathematical way.

2. Proposed method

2.1 Biometric selection

Biometrics are human physical or behavioral characteristics that can be used to digitally identify a person in order to grant access to systems, devices, or data \[^9\]. Traditional mitochondrial dysfunction research relies on patients' conscious and self-reported responses. An integrated camera system with video and a novel computer application were used in this study to capture images of patients' faces. This is a non-invasive biometric technology that collects additional information from photographs taken during patient visits \[^10\]. One of the primary goals of this study was to extract useful features from the face in order to differentiate between obvious and non-obvious differences among patients with mitochondrial dysfunction and others. Ptosis is one of the most common early-onset symptoms in patients with mitochondrial dysfunction. As a result, it is prudent to select the periocular site as a study feature. The periocular region refers to the area of the face near the eyes, including the eyelids, eyelashes, and eyebrows \[^11\]. Although different people have different skin tones, multiple studies have shown that the main difference is their intensity rather than their shade \[^12\], so distinguishing between eyebrow and face color is relatively simple. Therefore, we can get some space to use chromatic aberration to detect eyebrows from human faces and do further experiments, and high-precision eyebrow detection will help in the extraction of eyebrow features.
2.2 Feature segmentation based on Viola-Jones Algorithm

In order to easily and quickly determine the position of the eyebrows in the face, this paper first uses the Viola-Jones framework face detection algorithm, uses the Haar feature to describe the face features, and then uses the feature matrix module integral to represent the face image to realize the initial detection of eyebrows.

The eye area will be darker than the cheek area, and the brightness of the eyes will be darker than the cheeks, according to the characteristics of human face skin color. Similarly, the lips will be darker than the mouth's surrounding area, and the nose will be brighter than both sides of the cheeks. The Viola-Jones framework matrix feature, which is based on this face feature, uses four types of matrix features to represent the face \[^{13}\], as shown in Fig. 2. It also shows how the face image can be represented using the Viola-Jones framework matrix model as various white and black patches. To calculate the Haar feature, all pixels in the rectangle area must be added together. An image is made up of rectangular regions of various sizes and shapes. The integral image approach is used to improve these problems, as shown in the left figure of Fig. 2. The integral image value of any point \( S(x, y) \) of the image is equal to the sum of all pixels placed in the upper left corner of the point, and the formula is as indicated in formula (1):

\[
S(x, y) = \sum_{x \leq x'} \sum_{y \leq y'} f(x', y')
\]  

(1)

Fig. 2 Viola-Jones framework matrix (A and B in the figure are the boundary features; C is
the thin feature; D is the diagonal line feature).

In Fig.3, assuming that $f(x, y)$ represents the integral area of the whole, the area of a certain rectangle can be calculated according to other known rectangular areas, such as area $S(x, y) = f(x, y) - S(x - 1, y) - S(x, y - 1) - S(x - 1, y - 1)$. There is no need to cycle through all of the rectangular areas in the image after utilizing the integral image approach. It only needs to traverse the original image once to calculate the total grey value of the rectangle area, considerably reducing the amount of grey value calculation $^{[14]}$.

![Image Integration](image)

**Fig. 3 Image Integration**

### 2.3 Improved canny algorithms

Since the eyebrow features obtained by the Viola-Jones algorithm are small-scale regional, this paper uses the canny algorithm to further detect the edges of the eyebrows, identify the precise shape of the eyebrows and calculate the curvature. The Canny algorithm is a multi-level edge detection algorithm developed by John F. Canny in 1986 $^{[15]}$. Its purpose is to significantly reduce the data size of the image while preserving the original image properties.

![Flowchart of improved canny algorithm](image)

**Fig. 4 Flowchart of improved canny algorithm**
However, because the traditional canny algorithm performs two-dimensional Gaussian filtering for image smoothing through Gaussian blur, the image smoothing effect is poor, and false edges may be generated due to artificially set high and low thresholds. Therefore, this paper adopts an improved adaptive Gaussian-median filtering algorithm, which solves the problem of a random selection of Gaussian standard deviation $\sigma$ and uses Ostu double thresholds to calculate the connection edges to avoid the limitation of artificially setting high and low thresholds. The main flow of the algorithm is shown in Fig.4.

Traditional Gaussian filtering makes it difficult to preserve both edge information and smooth noise \[16\]. Adaptive median filtering not only effectively reduces the influence of noise on data, but it also better preserves the image's basic edge information \[17\]. After the median filtering process, the image is subjected to adaptive Gaussian filtering to remove Gaussian noise. Then, using the operator, combine Gaussian smoothing and differential derivation to calculate the approximate gradient of the image, and finally, use the Ostu algorithm to automatically determine the threshold, that is, divide the image into two parts: foreground and background, and traverse the entire image to obtain the maximum value of the variance function, indicating when the threshold is the optimal threshold.

3. Experiments with eyebrow features

As previously stated, the eyebrow is a very visible feature that can be used in feature detection. Another physiological reason is that patients with mitochondrial dysfunction will struggle to open their eyes wide because their eye muscles are weaker than those with normal functioning mitochondria. Patients, however, can gradually improve their situation with careful treatment. If the treatment helps the patients get more energy in the cells of the periocular part muscles, the shape of the eyebrow should change when they try to open their eyes wide. As a result, the change
in eyebrow shape can record the treatment process in a unique way. In this experiment, we extract the eyebrow feature in order to obtain the eyebrow curve, which represents the shape of the eyebrow. For the eyebrow curve, we can calculate the curvature of the extracted curve to find the data change. After comparing the curvature data before and after the treatment, we can describe the treatment process mathematically by comparing the curvature data before and after the treatment. If the treatment is successful, the curvature data should change dramatically.

In our experiments, we are unable to get enough face pictures of patients before and after treatment. This is primarily due to the fact that the treatment is usually lengthy and only a few patients are willing to pose for photographs. Fortunately, we can still obtain some face pictures of patients undergoing treatment and extract the left and right brow features to continue our experiments. In this case, feature extraction will be tested, and comparing the curvature of the left and right brow curves can also meet our expectations to a degree.

![Eyebrow Detection](image1)
![Eyebrow Extraction](image2)

**Fig. 5** Eyebrow detection and extraction.

As shown in Fig. 5(a), the eyebrow should be detected first in this experiment. The Viola-Jones algorithm is used to detect brows, and the eyebrow part is extracted from the original images.

Eyebrow Extraction. After detection, a skin color model is constructed, and the segment in the yellow skin colour area is used to perform morphological filtering. A binary image will be created from the grayscale image. Following erosion and dilation, the brow edge shown in Fig. 5(b) is extracted using the improved Canny algorithm. Small objects are removed from the binary image, and the curvature is displayed next.
Intuitively, the curvature describes for any part of a curve how much the curve direction changes over a small distance travelled (for example angle in rad/m), so it is a measure of the instantaneous rate of change of direction of a point that moves on the curve: the larger the curvature, the greater this rate of change. In other words, the curvature measures how quickly the unit tangent vector to the curve rotates (fast in terms of curve position). In fact, it is possible to demonstrate that this instantaneous rate of change is the curvature. Assume that the point is moving along the curve at a constant speed of one unit per second, which means that the position of the point P(s) is a function of the parameter s, which can be thought of as the time or the arc length from a given origin. T(s) is the unit tangent vector of the curve at P(s), as well as the derivative of P(s) with respect to s. The derivative of T(s) with respect to s is then a vector normal to the curve with length equal to the curvature. The following equation are the procedure of this algorithm. Then, let the rectangular coordinate equation of the curve be \( y = f(x) \), and \( y = f(x) \) has the second derivative. The slope of the tangent of the curve at point M is \( y' = \tan \alpha \), so:

\[
\sec^2 \alpha \times \frac{d\alpha}{dx} = y''
\]

(2)

\[
\frac{d\alpha}{dx} = \frac{y''}{1 + \tan^2 \alpha} = \frac{y''}{1 + y'^2}
\]

(3)

\[
d\alpha = \frac{y''}{1 + y'^2}
\]

(4)

\[
ds = \sqrt{1 + y'^2} \, dx
\]

(5)

Therefore, the curve L at the point M is:

\[
k = \frac{|y''|}{(1 + y'^2)^{2/3}}
\]

(6)

Let the curve be given by the parametric equation \( \begin{cases} x = \varphi(t) \\ y = \varphi(t) \end{cases} \). It can be obtained by using the parametric equation derivation method:

\[
k = \frac{|\varphi'(t)\varphi''(t) - \varphi'(t)\varphi''(t)|}{[\varphi'^2(t) + \varphi'^2(t)]^{2/3}}
\]

(7)
It is not a difficult task to show both left and right eyebrow curvature using the curve fitting and two curvature curves are shown below. The abscissa indicates the horizontal space of the eyebrow curve in these representations, while the ordinate shows the curvature of the eyebrow.
curve.

Through the above experiments, the curvature map of the eyebrows can be obtained, so that we can intuitively observe the changes in the eyebrows. The curvature is based on a straight line. In other words, if the patient's eyebrows are a straight line, the curvature is 0. From Fig. 6 it can be seen that the curvature of the eyebrows with the disease is 0 at horizontal positions 30, 70, and 125, which is caused by the patient's eyelid ptosis, and the changing trend of the curvature on both sides is relatively symmetrical around 78. In figure. 7, for the change of normal eyebrows, the phenomenon of asymmetrical change trend of the curvature changes on both sides first appears at the top of the eyebrows, and the curvature of the eyebrows is close to 0 at the horizontal position 120.

Although covid-19 is about to disappear, long-term, uninterrupted recording of treatment progress through recent photos of patients should be of great help in curbing the further progression of the disease. Some mitochondrial dysfunction patients feel hard to make their eyes wildly open, but after treatment, this symptom will be relieved. If they can open their eyes more wildly than before, the shape of the eyebrow should change a lot because the stronger eye muscles will also make their eyebrow raise when they try to open their eyes. Correspondingly, the curvature data should get a lot of change comparing the eyebrow picture before and after treatment. Thus, it should be very useful to record the curvature data of the patients before and after treatment. These curvature data will help researchers to record the improvement of treatment in a completely new way.

4. Conclusion

In this paper, a new non-invasive diagnostic tool to help examine mitochondrial dysfunction patients has been introduced. The experiment results work successfully, and it can be found that
image processing is of great significance in medical research. In this experiment, the eyebrow of patients is used to work as the feature to do image processing, which results can be used to help mitochondrial dysfunction research. It worked out satisfactorily and the results show that the curvature data can describe the shape of the eyebrow in a mathematical way. It can be expected that if the eyebrow detection can be more accurate, the curvature data can exactly describe the slight change of the eyebrow.

In traditional mitochondrial disease treatment progress chase, researchers always feel struggle to learn more about the improvement of the treatment. The records are mainly about intracellular mitochondrial activity detection, which always makes the medical testing cycle long and complicated. However, the records about the clinical manifestations of patients always lack accurate metrics and our experiments can help build the metrics by calculating the curvature of eyebrow feature curve through the face pictures of patients.

Therefore, learning more novel algorithms for feature detection and extraction should be an essential task. Besides improving image processing methods, the collection method of the patient picture is another important task. The experiment results may be affected by the size of the picture and the filming angle. In conclusion, if more good pictures can be obtained, more face features will be used in the future to help with mitochondrial dysfunction research.

**Conflict of interest**

There are no conflicts to declare.
References


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20-word summary:

This paper presents a non-invasive diagnostic tool for mitochondrial dysfunction using facial image processing and mathematical calculations.