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人工智能在眼底病中的应用

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[摘 要] 人工智能是对人类智能的模拟和拓展。基于深度学习的人工智能可以很好地利用图像的内在特征，如轮廓、框架等，来分析图像。研究人员通常利用图像来诊断眼底病，因此将人工智能应用于眼底检查是有意义的。在眼科领域，人工智能通过分析光学相干断层扫描图像、眼底照片和超宽视野图像，已经在检测多种眼底疾病上取得了类似医生的性能。它也已经被广泛应用于疾病进展预测。然而，人工智能在眼科的应用也存在一些潜在的挑战，黑盒问题是其中之一。研究人员致力于开发更多的可解释的深度学习系统，并确认其临床可行性。人工智能在最流行的眼底病中的最新应用、可能遇到的挑战以及未来的道路将一一阐述。

[关键词] 人工智能；深度学习；糖尿病性视网膜病变；青光眼；可解释性

Application of artificial intelligence in ocular fundus diseases

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Abstract Artificial intelligence (AI) is about simulating and expanding human intelligence. AI based on deep learning (DL) can analyze images well by using their inherent features, such as outlines, frames and so on. As researchers generally diagnoses ocular fundus diseases by images, it makes sense to apply AI to fundus examination. In ophthalmology, AI has achieved doctor-like performance in detecting multiple ocular fundus diseases through optical coherence tomography (OCT) images, fundus photographs, and ultra-wide-field (UWF) images. It has also been widely used in disease progression prediction. Nonetheless, there are also some potential challenges with AI application in ophthalmology, one of which is the black-box problem. Researchers are devoted to developing more interpretable deep learning systems (DLS) and confirming their clinical feasibility. This review

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describes a summary of the state-of-the-art AI application in the most popular ocular fundus diseases, potential challenges and the path forward.

Keywords artificial intelligence; deep learning; diabetic retinopathy; glaucoma; interpretability

Ocular fundus disease is complex and challenging. As the population aged, it has posed a major threat to people's health. In China, the most common fundus diseases include diabetic retinopathy (DR), retinal vein occlusion (RVO), glaucoma and so on. Among all kinds of technology, medical image is the most important one for clinical diagnosis and prediction. Ophthalmologists tend to use fundus images, optical coherence tomography (OCT) and so on. At present, the diagnosis based on medical images is quite subjective. For the same image, different ophthalmologists may get different results. In addition, manual analysis will require a lot of time.

Deep learning (DL) is an important part of artificial intelligence (AI). It can learn experience (characteristics of fundus diseases) from data (medical images) and analyze new data. Therefore, AI technology can provide objective results. It can also save time.

In recent years, with the rapid development of AI technology, the automatic fundus diseases diagnosis has attracted worldwide attention. This review is about recent achievements in this area and problems we are meeting with.

1 AI, DL, and convolutional neural networks (CNN)

AI was first proposed by Mccarthy's team[1] in the 1950s. It is a branch of computer science and mainly develops intelligent systems which simulate human thought. Machine learning (ML) is an important part of AI[2]. It is a group of efficient algorithms figuring out laws from data. Traditional ML includes support vector machine (SVM), random forest, and other algorithms. DL, including CNN and artificial neural networks, is a sub-field of ML[3]. DL is far more excellent than classic ML in analyzing images. This is because DL is good at processing large amounts of data, so that the algorithm can better fit the original data. Exceptionally, DL can retain the original features of the data, that is, some components in the image. These components are layered on top of each other and eventually become an image. This is similar to how the human brain processes images. Thanks to the development of computer performance, DL has achieved great progress in image analysis[4], language[5], and other aspects. In the medical field, especially in the ocular fundus disease diagnosis, DL can diagnose a variety of diseases, and the accuracy is close to or even higher than that of experienced doctors[6-8].

2 AI in fundus diseases

2.1 DR

DR is a leading cause of vision impairment and blindness. By 2040, 600 million people worldwide will have diabetes, with a third having DR[9]. The fundus photography is generally recognized as a conventional method of diagnosing DR. As DL performs well in detecting features in fundus photographs, it can be applied to detecting DR. While the DR screening progress meets with difficulties, such as high cost, not enough qualified doctors, DL has totally changed the performance of detecting DR.

In 2016, Gulshan *et al.*[8] showed that DL gave an excellent performance in detecting referable DR. The system achieved 90.3% and 87.0% sensitivity, with 98.1% and 98.5% specificity, when detecting two validation sets of referable DR. It rivaled results of a panel of 7 US board-certified ophthalmologists. Later in 2017, Ting *et al.*[10] showed that deep learning system (DLS) also performed well when detecting DR through retinal images from multiethnic populations. Its sensitivity was 90.5% and specificity was 91.6%.

Recently, researchers are devoted to verifying the application to more advanced technology. Oh *et al.*[11] showed that the DLS based on ultra-wide-field (UWF) outperformed that based on the optic disc and macula-centered image in a statistical sense. Hacisoftaoglu *et al.*[12] applied ResNet50 model to images taken on smartphones to detect DR. The model achieved 98.6% accuracy, with 98.2% sensitivity and 99.1% specificity.

Besides, DLS has achieved remarkable progress in clinical application. In 2018, IDx-DR[13] was the first DLS to be approved for DR detection by Food and Drug Administration. It performed well in the clinical trial, with 87.2% sensitivity and 90.7% specificity. It can be used in primary care and alleviate the demand for human physicians. EyeArt[14] is a DR detection system based on cloud technology. It achieved 91.7%

sensitivity and 91.5% specificity in a retrospective study with 78,685 patients involved. With its potential benefits of efficiency and reproducibility, EyeArt would be useful in reducing the burden from the increased people with diabetes.

2.2 RVO

RVO is one of the major global blinding diseases[15]. After DR, it is the second most common clinical retinal vascular disease[16]. In 2018, Nagasato *et al.*[17] used DLS to detect central retinal vein occlusion (CRVO) in UWF images. The DL technology is superior in sensitivity, specificity and area under curve (AUC), better than SVM. This experiment showed the possibility of automatic CRVO detection with DL. In 2019, Nagasato *et al.*[18] confirmed that DLS has similar advantages in detecting branch retinal vein occlusion (BRVO) through UWF images. At the same time, Nagasato *et al.*[19] used DLS to detect the non-perfusion area through optical coherence tomography angiography (OCTA) images. The results showed that DLS is superior to SVM and human RVO experts. Yeung *et al.*[20] graded the OCTA images of BRVO patients as mild, moderate and severe macular ischemia. DLS detected these images, generated parameters and was compared with OCTA machine. In the images of severe macular ischemia, DLS results of denoised images are more accurate than of original images. The research showed that it is conducive to denoise OCTA images for automatic macular ischemia grading in BRVO eyes.

2.3 The fundus lesion of glaucoma

Glaucoma is a progressive optic neuropathy that can cause retinal nerve fiber layer (RNFL) defect and glaucomatous optic neuropathy (GON)[21]. For people aged 40 to 80, the global prevalence rate of glaucoma is 3.4%. Moreover, it is estimated that by 2040, there will be approximately 112 million affected people worldwide[9].

While glaucoma damage is irreversible, early treatment can usually prevent or slow functional impairment progression. Therefore, researches on detecting potential glaucoma and glaucoma progression have flourished recently. Lee *et al.*[22] developed a DLS to predict glaucoma development through fundus images. The system detected RNFL thickness and predicted the change of it. The study showed that the rate of change of RNFL thickness predicted the conversion to glaucoma. Christopher *et al.*[23] used DL models to predict the progression of glaucoma visual field damage through spectral domain OCT (SD OCT). The study showed that the model based on RNFL en face images performed better than that based on RNFL thickness maps. Garcia *et al.*[6] used Kalman filtering to predict intraocular pressure (IOP) through previous IOP results. The study showed that predicted IOP accorded well with observed IOP.

Besides, some important progress has been made on glaucoma detection. Medeiros *et al.*[24] developed a machine-to-machine DLS without human labeling. The system used a classifier trained by RNFL thickness data which is extracted from SD OCT. In this way, it can avoid mistakes that human markers usually make. For example, it can distinguish eyes with large physiologic cups from those with actual glaucomatous damage. The study has opened new possibilities of surpassing human markers' limitations. Thompson *et al.*[25] developed a DLS without conventional segmentation of RNFL. It performed better than the conventional method in detecting glaucoma. This may be a new approach to improving the accuracy and sensitivity in glaucoma detection. Li *et al.*[26] developed a DLS for GON detection through color fundus photographs. The DLS achieved an AUC of 0.983 to 0.999. It is comparable to that of an experienced ophthalmologist.

2.4 Age-related macular degeneration (AMD)

In developed countries, many patients are blind because of AMD[27-28]. It is the major course of vision impairment in American whites aged over 50[29]. The incidence rate of AMD in China will be increasing because of the aging population[30]. Scientists estimated that there would be 288 million AMD patients by 2040[31].

In 2018, Rohm *et al.*[32] showed that ML performed well in predicting AMD progression. The system predicted subjects' visual acuity (VA) by 41 medical records and OCT features. The prediction results are close to the actual ones.

There is an urgent need for efficient methods of AMD prediction. AI has made excellent progress in this area. Banerjee *et al.*[33] proposed a model to predict the risk of exudation in non-exudative AMD eyes. The system performed well in forecasting in the short term (within 3 months) and long term (within 21 months). While the AUC of 21 months is significantly lower than 3 months, its high performance within 3

months showed the possibility of impacting clinical follow-up. Yim *et al.*[7] used a DLS to predict the AMD progression of patients' one eye, the other eye of whom has been diagnosed as AMD. Its accuracy is better than 5 of the 6 ophthalmologists. Waldstein *et al.*[34] used a DLS to predict early-stage and middle-stage AMD progression to late stage. The system made a prediction by detecting drusen and hyper-reflective foci (HRF) from OCT images. Lee *et al.*[35] developed a DLS to predict visual prognosis. The system made a prediction by analyzing features in OCT images, such as intraretinal fluid, subretinal fluid, and pigment epithelial detachment. Liu *et al.*[36] developed a DLS to predict responses to treatment. The system made a prediction by detecting pretherapeutic OCT images. Researchers compared the prediction with the observed post-therapeutic OCT image and found a strong correlation between them.

Besides, AI has performed well in AMD diagnosis. Liefers *et al.*[37] developed a DLS to detect AMD and evaluated its performance. They trained the system for the segmentation of 13 features associated with atrophic AMD. The system obtained a higher score than experienced human graders on 11 features out of 13.

2.5 Retinopathy of prematurity (ROP)

ROP is a leading cause of childhood blindness worldwide[38]. ROP screening can identify early signs of severe ROP, and with timely treatment it can prevent most cases of ROP blindness[39]. Therefore, researchers have been paying attention to the prediction of ROP. Taylor *et al.*[40] developed a DLS to predict ROP progression. The system proposed the ROP vascular severity score by detecting clinical examination images. And it made a prediction based on these scores. The prediction is associated with clinical progression. Huang *et al.*[41] used a DLS to predict visual prognosis after treatment. The system predicted the VA, best corrected VA (BCVA) and spherical equivalent (SE) of ROP patients. It performed better on predicting SE than on predicting VA and BCVA. Wang *et al.*[42] developed 4 classifiers, including image quality, any stage of ROP, intraocular hemorrhage, and preplus/plus diseases. The platform integrated the results of 4 classifiers and generated the diagnosis results. Its performance is comparable to human ROP experts.

2.6 Central serous chorioretinopathy (CSC)

CSC is one of the most common ocular fundus diseases, affecting middle-aged men mostly[43]. Zhen *et al.*[44] used Inception-V3 to assess CSC depicted on color fundus photographs. The research showed that the performance of DLS is comparable to 2 ophthalmologists. Yoon *et al.*[45] developed a new DL model to diagnose CSC in SD-OCT images, and distinguish chronic from acute CSC. The research showed that the new model is superior to VGG-16 and Resnet-50 in both diagnosis and classification. And it is comparable to human experts.

2.7 Retinal detachment (RD)

According to the cause, RD can be divided into rhegmatogenous retinal detachment (RRD) and non-rhegmatogenous. RRD can lead to blindness without surgical treatment[46]. Li *et al.*[47] developed a DLS that can detect RD based on UWF images. Its performance is comparable to human experts. It can also guide patients to adopt an appropriate position before surgery, which can reduce RD progression. Xing *et al.*[48] developed a weakly supervised two-stage learning architecture to detect and segment RD. They designed a Located-CNN to detect lesion regions in SD-OCT. The results showed that this method is superior to some models trained with stronger supervision. It is a promising method as it reduces the amount of labelling.

2.8 Retinitis pigmentosa (RP)

RP is the most common blinding inherited fundus disease[49]. Masumoto *et al.*[50] used CNN to detect RP through UWF pseudocolor imaging and UWF autofluorescence of retinitis pigmentosa. The research showed that DLS performed well in these two kinds of UWF images. Arsalan *et al.*[51] developed RPS-Net, an automatic RP segmentation network based on DL. This method provided fine segmentation and accurately detected RP even in the case of degraded images. The research showed that RPS-Net is superior to the state-of-the-art methods in segmentation.

2.9 Other optical fundus diseases

Diabetic macular edema (DME), optical neuritis, lattice degeneration, and retinal breaks are common. Wu *et al.*[52] developed a DLS to detect DME based

on OCT images. They train the DLS to detect 3 OCT patterns of DME, including diffused retinal thickening, cystoid macular edema, and serous retinal detachment. The system showed high accuracy, sensitivity, specificity, and AUC in all 3 patterns. It also performed well in external validation. This research emphasized the potential of DL in detecting DME. Abri Aghdam *et al.*[53] used learning decision tree to assess the probability of conversion to multiple sclerosis (MS) in patients with optic neuritis. The DLS also evaluated the factor most related to the conversion. Results showed that the overall conversion rate to MS was 42.2% and the presence of white matter plaque was the most important factor. Li *et al.*[54] developed a DLS to identify lattice degeneration and retinal breaks based on UWF images. They used 4 different DL algorithms (VGG16, InceptionV3, InceptionResNetV2, and ResNet50) with 3 preprocessing techniques (original, augmented, and histogram-equalized images) for the training. The research confirmed that InceptionResNetV2 was the best algorithm and the original image augmentation was the best preprocessing technique.

3 Potential challenges

3.1 The Black-box problem

As AI is widely used in the medical field, the AI black-box has become a critical problem which researchers have to solve. Since AI's neural network algorithm is too complicated for humans, it is difficult for human end-users to know whether the conclusion is reliable. As humans require more accurate algorithms, the system will be more complicated and more difficult to be interpreted. However, when DL is used in medical diagnosis, it is bound to use detection methods which is understandable for humans, in order to judge the reliability.

In recent years, researchers are developing methods to interpret DL algorithms to solve this problem. The most common and simplest method is to perform an occlusion test used for AMD detection on OCT[55]. Recently, Schmidt-Erfurth *et al.*[56] have used statistical indicators to compare the interpretability of different algorithms used to diagnose glaucoma. These studies will significantly promote clinical understanding.

3.2 Poor adaptability to different equipment

When we developed a new DLS, the image data for training and detecting often come from the same equipment. When the AI model is applied to images obtained by equipment different from its training data source, its accuracy will often decrease. This problem is obvious in OCT images.

Different countries, regions and medical institutions have different inspection equipment. And the quality of the pictures needed for training will be unstable, which will ultimately affect the accuracy of AI model.

3.3 Unsophisticated databases

Several databases cannot reflect the real world. The data currently used for AI research are mostly public databases or databases designed for other researches. Most of the data only include the target disease, but many people actually have multiple eye diseases. What's more, the data often include only one single race, which means it cannot reflect the obvious ethnic differences among people. It is extremely urgent for us to develop more sophisticated databases.

3.4 Different diagnostic criteria

In clinical practice, ophthalmologists make a diagnosis based on multiple factors. But in researches, diagnosis from DLS usually bases on one certain factor. This makes a huge difference. Taking glaucoma as an example, ophthalmologists need to consider complicated examination results, such as IOP, OCT images, visual field and so on. While the DLS only consider one of these factors. The ability of AI to make a diagnosis based on multiple factors is unknown.

4 Conclusions

DL is the most advanced AI ML technology. It has shown clinically acceptable performance in many ocular fundus diseases, such as DR, glaucoma, and AMD. AI has helped humans to predict ocular fundus diseases and reduce their prevalence. The progress on AI also shows the possibility of decreasing the incidence rate in low-income and middle-income areas. Especially for glaucoma, a fast and irreversible eye disease, it will vastly change patients' fate. In order to improve the DL system's clinical acceptance, it is essential to use existing and future methods to unlock the black-box nature of DL. Despite the challenges, DL may lead the advance in medicine and ophthalmology for decades.

Footnote

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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