Review

Deep learning for microscopic examination of protozoan parasites

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Abstract

The infectious and parasitic diseases represent a major threat to public health and are among the main causes of morbidity and mortality. The complex and divergent life cycles of parasites present major difficulties associated with the diagnosis of these organisms by microscopic examination. Deep learning has shown extraordinary performance in biomedical image analysis including various parasites diagnosis in the past few years. Here we summarize advances of deep learning in the field of protozoan parasites microscopic examination, focusing on publicly available microscopic image datasets of protozoan parasites. In the end, we summarize the challenges and future trends, which deep learning faces in protozoan parasite diagnosis.

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1. Introduction

Parasitic diseases have far-reaching consequences on public health globally. According to World Health Organization’s Global Health Estimates in 2020 [1], infectious and parasitic diseases are among the main causes of mortality in Africa. There are three main classes of parasites that can cause disease in humans: protozoa, helminths, and ectoparasites. Most parasitic protozoan in humans range less than 50 μm in size [2]. Due to the smaller size, protozoan parasites present a greater challenge to diagnosis from microscopic examination. Best known disease-causing protozoan parasites include *Plasmodium*, *Trypanosoma*, *Babesia*, *Toxoplasma*, *Leishmania*, and *Trichomonad*. Malaria is caused by *Plasmodium*, which destroys the red blood cells, thus causing fatal disease. According to the World Health Organization (WHO), malaria deaths have increased to an estimated 627,000 (±5%) due to disruptions during the COVID–19 pandemic [3]. *Trypanosoma* is the causative agent of trypanosomiasis, which threatens the lives of people in sub-Saharan African countries and is transmitted by the tsetse fly [4]. Chagas Disease is a tropical parasitic disease in Latin America caused by *Trypanosoma cruzi* (T. cruzi) that leads to approximately 14,000 annual deaths [5]. Babesiosis, a malaria-like parasitic disease, affects not only a wide range of domestic and wild animals, but occasionally also people [6]. In the past 20–30 years, the United States has reported increasing numbers of blood transfusion-transmitted cases of *Babesia*, making Babesia infections a major public health problem [7]. *Toxoplasma* is the causative agent of toxoplasmosis that infects over a third of the world’s population [8]. *Toxoplasma* can reach various parts of the body via the bloodstream, leading to a decreased immunity and various symptoms by destroying the brain, heart, and fundus of the eyes [9]. Most infected people have either no symptoms or mild symptoms, but *Toxoplasma gondii* (T. gondii) infection during pregnancy can cause severe nerve damage and even fetal death [10]. *Leishmania* causes leishmaniasis, which is a neglected tropical disease and transmitted by the female phlebotomine sandflies, affecting more than 700,000 people every year [11]. *Trichomonad* parasites in the genitourinary system, intestines and oral cavity cause human diseases, collectively referred to as trichomoniasis [12]. Trichomoniasis is highly epidemic in women, can cause poor perinatal outcomes and infertility [13]. Each year approximately 3.1 million women are infected with *Trichomonas vaginalis* in United States [14].

Mass drug administration programs have significantly reduced the disease burden [15]. To administer the correct drugs and to avoid drug abuse requires first a reliable and efficient diagnosis. Microscopy is one of the most commonly used methods for the diagnosing of the parasitic diseases [16,17]. However, microscopy-based parasite identification and quantification is challenging, time-consuming and labor-intensive, requires microscope and well-trained researchers [19–20]. Parasite examination in microscopic images is challenging for human experts because of the variations and uncertainties in the shape, density and staining color of the parasites [21]. Human infections caused by parasites usually occur in developing and undeveloped countries, which often suffer from a lack of good medical conditions and well-trained microscope operators [22]. Another disadvantage of the microscopic examination of some parasites is the relatively low sensitivity, particularly at low parasite levels [20]. With the increase of computing power and data availability, artificial intelligence has been successfully employed in many applications, such as face recognition, natural language processing and biomedical image analysis [24,44,64]. Biomedical image analysis refers to the characterization, recognition and understanding of biomedical images, with the aid of the prior knowledge in large amount of data and the efficient extraction of data features [25]. As a subfield of machine learning, deep learning uses multi-layer neural networks to extract and characterize the features of input data, which can be divided into supervised, weakly supervised and unsupervised models. As shown in Fig. 1, the main difference between supervised and unsupervised learning is whether the data provided to the model is labeled. Labeled data is usually difficult to obtain, thus requiring labeling personnel, special equipment and additional expenses. Relatively speaking, unlabeled data is cheap and easy to obtain. Deep learning has been applied in the life and health sciences with the aim to improve the accuracy and efficiency of clinical diagnosis [26], and to discover novel biomarkers. From the perspective of biomedical image datasets, neural network with convolutional neural network (CNN) can extract the features of the images of these diseases [28,28]. Furthermore, deep learning has played an important role in the analysis of a wide variety of microorganisms, including bacteria, fungi, parasites, and viruses [29].

2. Microscopic examination of protozoan parasites

Due to its high speed, accuracy, flexibility and low cost [20,30], deep learning has been widely applied in various microscopic image analyses, including microscopic examination of protozoan parasites. This analysis includes detection, segmentation, tracking...
and classification. Detection is used to obtain the distribution and location of individual parasites, clusters and hosts [32,33]. Classification is used for multi-parasites identification in the case of mixed infections [35,36]. Segmentation is used to observe the edges of parasites morphologically [36]. Tracking is a unique task for the dynamic observation of motile parasites [37]. The detection model represented by You Only Look Once (YOLO) series has been improved to detect parasites [38]. CNN-based models are usually used for parasite classification [39]. U-Net-based model is widely used for segmentation [36,40]. In clinical scenarios of these algorithms, researchers use methods such as transfer learning [20,34] and GAN-based model [19] to develop weakly supervised learning and unsupervised learning [31,42], which reduce the volume of annotation needed. Notably, smartphones play an important role in developing parasite diagnosis algorithms, thus greatly reducing the need for well-trained microscope scope [38].

2.1. Malaria microscopic image analysis

*Plasmodium* infects humans through mosquito bites. The malaria parasite *Plasmodium* goes through two life stages in the human host, a clinically silent liver stage followed by a blood stage with clinical manifestation of the malaria disease [42]. Therefore, the examination of the blood smear is essential for the diagnosis of malaria. [43] developed a two-stage method for detecting and counting red blood cells (RBCs) in thin blood smear microscopy images. In the first stage, U-Net is used to superpixel or cell-cluster segmentation. Then, Faster R-CNN is used to detect small cell objects in a connected component cluster. Due to the foreground cell-cluster masks from U-Net adaptively guide the detection stage, this work achieved higher true positive and lower false alarm rates. Inspired by residual and dense networks and the combined attention mechanism, [44] proposed a miniature and effective CNN named Attentive Dense Circular Net (ADCN) for classifying Red Blood Cells in Malaria. It is worth noting that ADCN combines the attention mechanism, which can make CNN focus on critical factors. It has a patient-level accuracy of 97.47% in infected RBCs classification task. Although great achievements have been made in the accuracy of the above algorithms, their application in most of the developing and undeveloped countries with high incidence of Malaria diseases remains difficult, due to their inconvenience, complexity and need for data annotation.

Supervised learning usually requires extensive annotation and is therefore time-consuming and laborious, microscopic image analysis of parasites requires progress in the development of weakly supervised and unsupervised learning strategies. Unlike other weakly supervised algorithms detecting specific objects by using image-level labels, [41] proposed Multiple Objects Features Fusion (MOFF), which is based on the fusion of the convolutional features of multiple objects. This study successfully diagnosed malaria in one hundred high resolution thick blood film (TBF) fields of view by using sample-labels associated with multiple image fields. In evaluation of automated malaria diagnosis in blood films, MOFF outperforms the existing supervised detection in TBF dataset. [30] proposed a graph convolutional network (GCN) based model to recognize various stages of malaria parasites in blood smear images. This model based on unsupervised learning is the first application of GCN on recognition of malaria parasite image. It successfully recognizes multiple stages of malaria parasites with a patch-level accuracy of 95.4 ± 0.05% in the *P. vivax* larger-scale dataset without any image label, which consists of 13,780 testing images with an equal quantity of infected and uninfected images. However, this method has only been evaluated on multiple stages of *Plasmodium*, and its recognition performance for other multi-stage parasites has not been validated.

In addition, other studies have tried to solve the scarcity of highly skilled microscopists in undeveloped countries and remote areas of developing countries by focusing on the diagnosis of malaria using smartphones [38,45,46]. [46] could be among the first to apply deep learning to detect parasites in thick smears and run on smartphones. [45] developed an Android smartphone application for the automated malaria parasites detection method based on CNN architecture. Smartphone is attached to the eyepiece of microscope to obtain the target image. Images are captured with 100x magnification in RGB color space with pixel resolution of 3024 × 4032. Then, Iterative Global Minimum Screening (IGMS) is used to find the parasite candidates. Finally, the classification and detection of *Plasmodium* cells is achieved by running the customized CNN, and the parasite counting results are recorded in the patient database and displayed in the user interface of the mobile-phone applications. [38] reached the state-of-the-art in the detection of small objects such as *Plasmodium* by optimizing YOLO3 and YOLO4. YOLO3 and YOLO4 are state-of-art detectors with simple network structure and great generalization capability, but their drawback is that they are not optimized for detecting small objects. [38] modified the architecture of YOLO3 and YOLO4 to increase their applicability in detecting malaria parasites images captured by smartphone camera over the microscope eyepiece. In this study, feature scales were increased and detection layers were added to enhance capability and speed of detecting small objects. They applied the optimized models to detect malaria parasites from 608 × 608 images, which were captured by smartphone over microscope eyepiece with 1000x magnification. This YOLO based architecture models were shown to have obvious advantages, including high performance of mean average precision (mAP), compared to existing models such as single shot detector (SSD) and two-stage detector Faster R-CNN for *P. falciparum* detection [38].

2.2. Other microscopic image analyses of protozoan parasites

In the absence of treatment, *T. gondii* infection is fatal to human infants and people with the weakened immunity, such as AIDS patients [47]. [19] presented a transfer learning-based method for *T. gondii* microscopic image recognition without any data annotation. The connection between micro and macro objects in this study established by embedding fuzzy C-means cluster into CycleGAN. The algorithm achieved patch-level accuracy of 93.1% and 94.0% in the detection of *T. gondii* microscopic image dataset with magnification of 400x and 1000x respectively. [40] applied U-net to segment *T. cruzi* and detected *T. cruzi* amastigotes nests from histopathological images, thus decreasing the workload of pathologists. The proposed model achieved a segmentation accuracy of 99.19% and Jaccard index of 49.3%, which outperform the results of SVM [40]. However, this research also showed some drawbacks of U-net, such as the network performance can be improved by increasing the number of images and variability, whose result is heavily dependent on the input data. [36] proposed FCN-based system and developed U-net method to segment and classify *Leishmania* into promastigotes, amastigotes and adhered parasites. In order to overcome labor-intensive diagnostic procedures and false negative scores caused by straightforward nature of sample preparation, [4] proposed a ResNet18 based method to detect *T. cruzi* automatically in unstained microscope images. This method can overcome sensitivity limitations related to microscopic examination. [48] proposed an efficient artificial neural network named MCellNet to detect *Giardia* and *Cryptosporidium* from drinking water. In this study, 346 frames per second were captured and processed by the system of MCellNet combined with imaging flow cytometry to increase the high-throughput and efficiency of deep learning. This model achieved a classification accuracy of greater
than 99.6%, but could not handle the data that model did not see.

In clinical diagnosis scenarios, it is very important to identify the parasite species and presence of potentially mixed infections [35]. The multi-parasite algorithm has better practicability and generalization. [37] built a cost-effective mobile instrument to quickly detect the moving parasites of optically dense bodily fluids. The CNN model was used to automatically detect the signals created by motile Trypanosomes. This study showed that this instrument can detect other motile parasites by imaging Trichomonads. [32] proposed a deep-learning approach of geometry-aware and applied geometric-feature spectrum to detect host nucleus, Toxoplasma, Trypanosome, and Babesia by ExtremeNet based architecture without misdiagnosis. Different from ordinary unsupervised learning, [34] proposed a deep cycle transfer learning (DCTL) method for parasite detection. DCTL can avoid tedious data annotation by transferring macro shape knowledge from human experts to replace micro shape knowledge of parasites. DCTL successfully uses the shape information of macro objects that are similar with parasites’ shape such as ring, pear and banana, to detect Plasmodium, Babesia and Toxoplasma. The drawback of DCTL is that highly depend on shape information of macro objects.

3. Parasite datasets and metric

To facilitate the development of deep learning approaches to the diagnostic of parasites, we summarize and describe the publicly available protozoan parasite datasets in Table 1. As shown in the Table 1, most of them are Plasmodium datasets, because malaria diagnosis still remains the main focus of deep learning based parasite research [21]. Studies containing datasets of other parasites, such as Toxoplasma, Babesia, Leishmania, Trypanosome and Trichomonad [20,29,34], are precious because there are only few publicly available datasets of these parasites. Most of the datasets are used for the detection and classification with only few datasets focusing on the segmentation [50].

3.1. Representative dataset

The detailed parameters of representative datasets are displayed in Table 1. Three representative datasets were displayed
in **Fig. 2**. The malaria parasites dataset \[50\] is a representative dataset, which harbors four species of malaria parasites, namely *Falciparum*, *Malariae*, *Ovale* and *Vivax*. For each species, there are four distinct stages of life, namely Ring stage, Trophozoite stage, Schizont stage and Gametocyte stage. The patch image of four stages are shown coming from the specie of *Plasmodium Falciparum*. Each original whole image has corresponding mask, provided and labeled by expert pathologists. 

B: Multiple protozoan parasites dataset \[29\]. This dataset contains six types of protozoan parasites (Plasmodium, Toxoplasma, Babesia, Leishmania, Trypanosome, Trichomonad) and two types of host cells (RBCs and Leukocyte) presented in the cropped image patches. 

C: *Plasmodium falciparum* dataset \[51\]. The dataset contains cropped image patches from parasitized and uninfected RBCs.
Table 2
Standard evaluation metrics for parasite analysis based on deep learning. A is the predicted result and B is the Ground truth. TP: true positive, TN: true negative, FP: false positive, FN: false negative.

| Classification          | Accuracy  |
|-------------------------|-----------|
|                         | $\frac{TP + TN}{TP + TN + FP + FN}$ |
| Recall                  | $\frac{TP}{TP + FN}$ |
| Precision               | $\frac{TP}{TP + FP}$ |
| Specificity             | $\frac{TP}{TP + FN}$ |
| $F_1$ score             | $\frac{2 \times Precision \times Recall}{Precision + \text{Recall}}$ |
| precision-recall curve  | (abscissa = Precision, ordinate = Recall) |
| AP                      | $\frac{1}{N} \sum_{i=1}^{N} AP_i$ |
| ROC curve               | (abscissa = FPR, ordinate = TPR) |
| AUC                     | $\frac{1}{N} \sum_{i=1}^{N} \text{AUC}_i$ |
| IoU                     | $\frac{TP}{TP + FP + FN}$ |
| VOE                     | $1 - \frac{TP}{TP + FN}$ |
| PA                      | $\frac{TP}{TP + FN}$ |
| Dice                    | $\frac{2 \times TP}{2 \times TP + FP + FN}$ |
| ASD                     | $\frac{1}{N} \sum_{i=1}^{N} \min_{b \in B} \| a - b \|_2 + \sum_{b \in B} \min_{a \in A} \| b - a \|_2$ |

### 3.2. Evaluation metrics

To aid parasite classification, detection and segmentation of deep learning, we summarized the algorithms-related formulas for standard metrics in Table 2. The evaluation metrics of classification mainly include Accuracy, Precision, Recall, Specificity, $F_1$ score and Confusion Matrix. The evaluation indicators of object detection mainly include precision-recall curve, average precision (AP), mean average precision (mAP), Intersection-over-Union (IoU), receiver operating characteristic curve (ROC curve) and area under curve (AUC). In order to measure the segmentation task, Pixel Accuracy (PA), Dice, volumetric overlap error (VOE) and average symmetric surface distance (ASD) are usually calculated in medical image analysis.

### 4. Challenges and future trends

Deep learning assists in the analysis of parasites and their hosts. In this paper, we systematically and comprehensively summarized the development and the application of deep learning in microscopic examination of protozoan parasites. Furthermore, we also collected and described the available datasets and model evaluation metrics used in protozoan parasites.

#### 4.1. Pros and cons

There is a number of methods used for protozoan parasite examination. For example, the main methods of malaria diagnosis include rapid diagnostic tests (RDTs) and microscopy [3]. Compared to microscopic examination by human experts, RDTs are quite convenient, effective and fast. However, RDTs is not always available and detectable in all regions with the largest disease burden [3]. According to world malaria report 2021, Nicaragua suffered undersupply of RDTs during a malaria outbreak [3]; between 2020 and 2021, 17 publications from 13 countries have recorded the pहरर2/3 deletions, which made plasmodium undetectable by RDTs [3]. Hence, microscopic examination and other molecular or antigenic diagnostic tests are more complementing than replacing each other. Microscopic examination remains the gold standard for laboratory diagnosis [17], and deep learning represents promising technology for microscopic parasite examination [18]. Compared to parasite microscopic examination by the human experts, microscopic parasite diagnosis employing deep learning is fast, automatable and accurate, while traditional microscopic examination by human experts is usually tedious, time-consuming and labor-intensive, which can lead to misdiagnosis and missed diagnosis [55,56]. Deep learning-based microscopic parasite diagnosis can save a lot of time for doctors, thus reducing the rate of misdiagnosis, missed diagnosis and drug abuse. Using deep learning-based microscopic parasite diagnosis clinicians can spend more time on advanced decision-making tasks. Besides, deep learning has advantages in multi-parasite diagnosis, multi-stage parasite recognition and parasite quantification in real-time, high-throughput and at low parasite density [31,33,48,58].

Although deep learning has made progress in protozoan parasite diagnosis, several challenges remain. As our article highlights, dataset is an important factor restricting the wide application of deep learning for parasite diagnosis. Compared with other fields, the scarcity of publicly available datasets in the field of parasite diagnosis is more prominent, especially in other protozoan parasites other than Plasmodium. In some protozoan parasite examination studies, datasets are too small to give a convincing evaluation about model’s performance. Therefore, collecting existing publicly available protozoan parasite datasets is very important in training model and distinguishing model’s over-fitting, robustness and good generalization [40]. In supervised learning, the lack of labeled data is an important factor hindering the application of deep learning in parasitology. Collecting and labeling large datasets for training models is costly and time-consuming, especially in the pixel-level labeling for segmentation tasks [36,40]. Moreover, some datasets currently use only parts of samples in the microscopy slide, while whole slide image needs to be analyzed [43,45]. This requires additional time, computing resources and more robust models for small objects. Inference speed, model size and accuracy of model need to be compromised in clinics. Parameters of dataset, such as the different staining methods, preparation of samples, color differences, standards of images and digitization devices, need to be unified and be more specific to determine their impact on the performance of deep learning models [58].

To solve the limitation of available labeled datasets, some transfer learning-based methods have been created [20,34]. These methods rely heavily on the selection of specific macro objects to match the parasites, and might be only effectively against specific types of protozoan parasites tested, such as Toxoplasma, Plasmodium and Babesia. These methods might not be able to apply to other parasites which might have no corresponding macro objects, such as Leishmania, Trichomonad and Trypanosoma. Although deep learn-
ing model performs well in the analysis of microscopic parasite images, deep learning is like an opaque black box, which lack convincing interpretability [59]. The complete interpretability of deep learning model would be conducive to the promotion of artificial intelligence in the protozoan parasites diagnosis. The deep learning model has a large number of hyperparameters which usually depends on empirical settings, such as learning rate, batch size and epochs, which are also unexplainable. Although there are currently some automated tuning tools such as Neural Network Intelligence and AutoML [60], the long training time and vast parameter verifications make those newly proposed state-of-the-art models require a large amount of time and computing resources.

4.2. Pay more attention to biological view

Deep learning-based protozoan parasite researches should not only focus on improving model accuracy, but also pay more attention to the biological view. The complex and divergent life cycles of the protozoan parasites make lots of difficulties associated with the diagnosis of these organisms by deep learning. Therefore, deep learning-based protozoan parasite researches need to consider the different growth stages and distinct morphological characteristics of the parasites. Protozoan parasites accomplish their life cycle in different hosts where they adopt completely different morphological stages, which needs to be considered for accurate parasite microscopic examination. Besides Plasmodium [30], it is also true for other protozoan parasites such as T. gondii and Leishmania. T. gondii has three infective stages: tachyzoite, bradyzoite and sporozoite [10]. However, Plasmodium is perhaps the simplest case because it infects non-nucleated cells (RBCs) during blood stage. This is not the case for all protozoan parasites, care must be taken before generalizing the benefits of such deep learning approaches to other protozoa and in the context of medical decision making. Presenting and distinguishing their different morphological stages and divergent life cycles can help us to better understand the difficulties associated with the diagnosis of these organisms by microscopic examination and deep learning.

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CRediT authorship contribution statement

Chi Zhang: Formal analysis. Writing – original draft, Visualization, Implementation. Hao Jiang: Methodology, Writing – original draft, Implementation. Hanlin Jiang: Formal analysis. Hui Xi: Formal analysis. Baodong Chen: Writing – review & editing. Yubing Liu: Writing – review & editing. Mario Julas: Writing – review & editing. Junyi Li: Writing – review & editing. Funding acquisition. Yang Zhang: Conceptualization, Supervision, Resources, Funding acquisition, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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