Automated plasmodia recognition in microscopic images for diagnosis of malaria using convolutional neural networks

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ABSTRACT

Malaria is one of the world's most common and serious tropical diseases, caused by parasites of the genus plasmodia that are transmitted by Anopheles mosquitoes. Various parts of Asia and Latin America are affected but highest malaria incidence is found in Sub-Saharan Africa. Standard diagnosis of malaria comprises microscopic detection of parasites in stained thick and thin blood films. As the process of slide reading under the microscope is an error-prone and tedious issue we are developing computer-assisted microscopy systems to support detection and diagnosis of malaria.

In this paper we focus on a deep learning (DL) approach for the detection of plasmodia and the evaluation of the proposed approach in comparison with two reference approaches. The proposed classification schemes have been evaluated with more than 180,000 automatically detected and manually classified plasmodia candidate objects from so-called thick smears. Automated solutions for the morphological analysis of malaria blood films could apply such a classifier to detect plasmodia in the highly complex image data of thick smears and thereby shortening the examination time. With such a system diagnosis of malaria infections should become a less tedious, more reliable and reproducible and thus a more objective process. Better quality assurance, improved documentation and global data availability are additional benefits.

Keywords: Malaria diagnosis, automated microscopy, image analysis, machine learning, plasmodia recognition, convolutional neural networks

1. INTRODUCTION

Malaria is one of the world's most common and serious tropical diseases, caused by parasites of the genus plasmodia that are transmitted by Anopheles mosquitoes. Various parts of Asia and Latin America are affected but highest malaria incidence is found in Sub-Saharan Africa. Approximately half the world's population is at risk for malaria and the disease is currently endemic in 104 countries. According to estimates by the World health Organization (WHO) in 2015, there are approximately 214 million cases of malaria annually with a death toll of 438,000 (86% were children under age 5).

Five species of the genus Plasmodium are responsible for human malaria infections: P. falciparum, P. vivax, P. ovale, P. malariae and also P. knowlesi a Plasmodium species originally thought to be restricted to macaques. These parasites can be detected and classified by microscopic examinations of stained blood smears which represent the diagnostic gold standard recommended by the WHO. In 2012 there were 188 million microscopic examinations globally, of which 120 million were performed in India and 52 million in Africa. There is a global increase in microscopy with a 42% rise in Africa (2011 to 2012) [1].

To diagnose malaria the so-called thick smear is used for the initial detection of malaria parasites. In addition to that, thin smears are used for species confirmation. As the process of slide reading under the microscope is an error-prone and tedious issue we are developing computer-assisted microscopy systems to support detection and diagnosis of malaria.

Medical Imaging 2017: Digital Pathology, edited by Metin N. Gurcan, John E. Tomaszewski, Proc. of SPIE Vol. 10140, 101400B · © 2017 SPIE · CCC code: 1605-7422/17/$18 · doi: 10.1117/12.2249845

In this paper we focus on a deep learning (DL) method for the detection of plasmodia in thick smears and the evaluation of the proposed approach, as well as the comparison with two further approaches. The proposed classification methods have all been evaluated with more than 180,000 automatically detected and manually classified plasmodia candidate objects. Automated solutions for the detection and morphological analysis of malaria smears could potentially apply such a classifier to detect plasmodia and thereby shortening the examination time. Furthermore, a fully digital documentation and the possibility of getting a second opinion could be provided.

2. METHODS

Fig. 1 depicts the workflow for plasmodia detection from the blood smear (thick blood film) on a microscopic slide (left side) to a visualization of the automatic plasmodia detection (right side). Blood smears are digitized with an automated microscope in several steps. At first the whole slide is captured in low optical magnification to obtain an overview image. For an automatic system and to minimize the scanning duration, detection of the blood smear on the microscopic slide is required. The blood smear region is determined automatically and a region in the center of the smear is selected automatically and scanned in high magnification for plasmodia detection. The high magnification scan thereby consists of image stacks. Each image stack contains 17 z-layers with a distance of 150 nm between each layer.

Figure 1: Workflow for plasmodia recognition in thick smears.

For the detection of plasmodia all image processing steps are applied on extended depth of field images derived from the image stacks. At first a chromatin enhancement step is applied. Then shape filtering, thresholding and artifact removal techniques are used for localization of plasmodia candidates. Afterwards the layer within the image stack is determined that delivers the most sharpen view of the plasmodia candidate. A subimage of this layer representing the plasmodia candidate is used for the subsequent classification steps. All determined candidates are pre-classified into three different classes corresponding to different appearances of plasmodia during the development from ring to schizont or gametocyte. For the subsequent final classification we propose a procedure which is based on convolutional neural networks (CNNs). Two other methods (Support Vector Machines, k-Nearest Neighbors) are also used and evaluated for the final classification step and are used for comparison of the classification results. All three procedures are described in the following subsections.

For training and testing of these classification schemes blood smears that have been drawn from routine work by the Bernhard Nocht Institute for Tropical Medicine (BNITM) were scanned yielding so-called virtual slides. Afterwards experts from BNITM annotated all plasmodia in these virtual slides. Based on this ground truth all detected objects of the first step are assigned as plasmodia object or non-plasmodia object. The training database contains 15,499 plasmodia objects and 39,374 non-plasmodia objects (see Fig. 2 for some examples) from 44 different slides and is disjunctive to the test database. From these 44 slides 21 are from patients with P. falciparum, 22 from patients with P. vivax and one from a patient with a P. malariae infection.

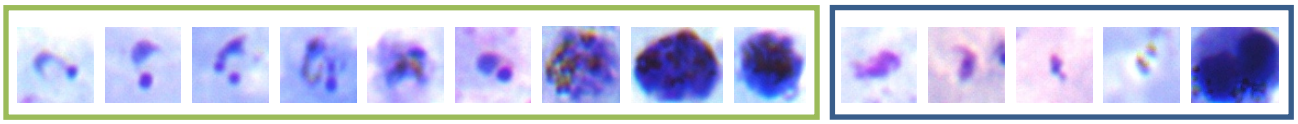

Figure 2: Examples of plasmodia objects (left box) and non-plasmodia objects (right box).

2.1 Plasmodia detection using an image based convolutional neural network (CNN)

The annotated image tiles with candidate objects vary in size due to the segmentation method (bounding box) and therefore are resized to the common size of 70 x 70 pixels in order to use them in a deep learning framework. For this experiment we used Microsoft's Convolutional Network Toolkit (CNTK) [2] with GPU support and 1-bit stochastic gradient decent option on a 64-bit Windows 7 machine. We adapted a convolutional network from the CNTK examples which was originally applied to the 32x32 color images of CIFAR-10 data set [3]. This convolutional network defines a cascade of convolutional / activation layers and max-pooling layers. We use three layers of each type. The kernel width for the convolution layer is 5 and for the max pooling layer is 3 and we use the Rectified Linear Unit (ReLU) as activation function. The architecture of the convolutional neural network is depicted in Fig. 3.

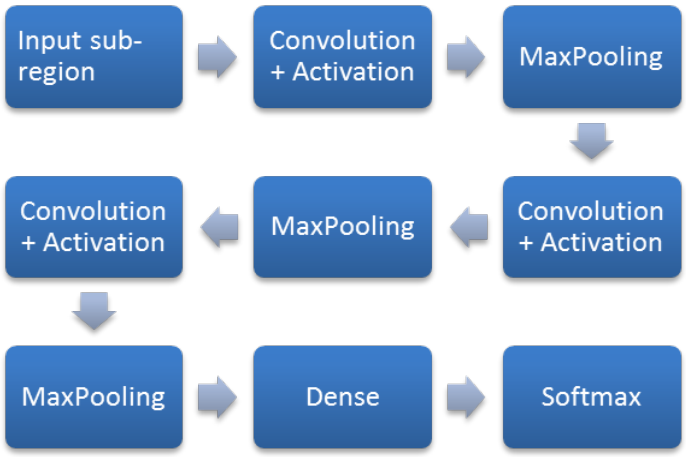

Figure 3: Convolutional neural network for plasmodia detection.

2.2 Plasmodia detection using support vector machines (SVM)

The extracted plasmodia candidates of different development stages are characterized by texture and color features. The texture characteristics can be described by numerous texture features: co-occurrence matrix based features, sum and difference histogram based features, color enhanced texture features, features for the characterization of the heterogeneity and granularity, statistical geometric features, as well as textural features corresponding to visual properties of texture. The color component of the plasmodia candidates is described by central moments in RGB and HSV color space and different moments in HSV color space.

The classification task is obtained by support vector machines (SVMs). For each of three development stages we use a positive and a negative class. Therefore, we make use of 6 two-class classifiers (one-vs.-rest respectively) to determine the class for unseen data. For the binomial learning process we select 100 features for each node by iteratively adding the feature with the most information regarding the label and the least redundancy to the already selected features [4]. From these 100 features we use the features with the highest weights and train a Support Vector Machine (SVM) with a radial basis function. A feature vector is assigned by means of the 6 classifier to the class with the highest class probability.

2.3 Plasmodia detection using k-nearest-neighbors (KNN)

For this approach the same features as for the support vector machines are extracted from the images of the plasmodia candidates.

The classification task is obtained by a K-Nearest Neighbor model. We also use 6 two-class classifiers (one-vs.-rest respectively) to determine the class for unseen data. For the binomial learning process we select 100 features for each node by iteratively adding the feature with the most information regarding the label and the least redundancy to the already selected features [4]. From these 100 features we use the features with the highest weights and train a K-Nearest Neighbor model with K=5. A feature vector is assigned by means of the 6 classifiers to the class with the highest class probability.

3. RESULTS

The test database for P. falciparum contains 2,390 plasmodia objects and 93,324 non-plasmodia objects from 18 different slides. The detection results of the different approaches for this database are visualized in the Fig. 4. The CNN – approach shows the best results with respect to accuracy (98%) and specificity (98%) and the KNN-approach yields to the best sensitivity result (96%).

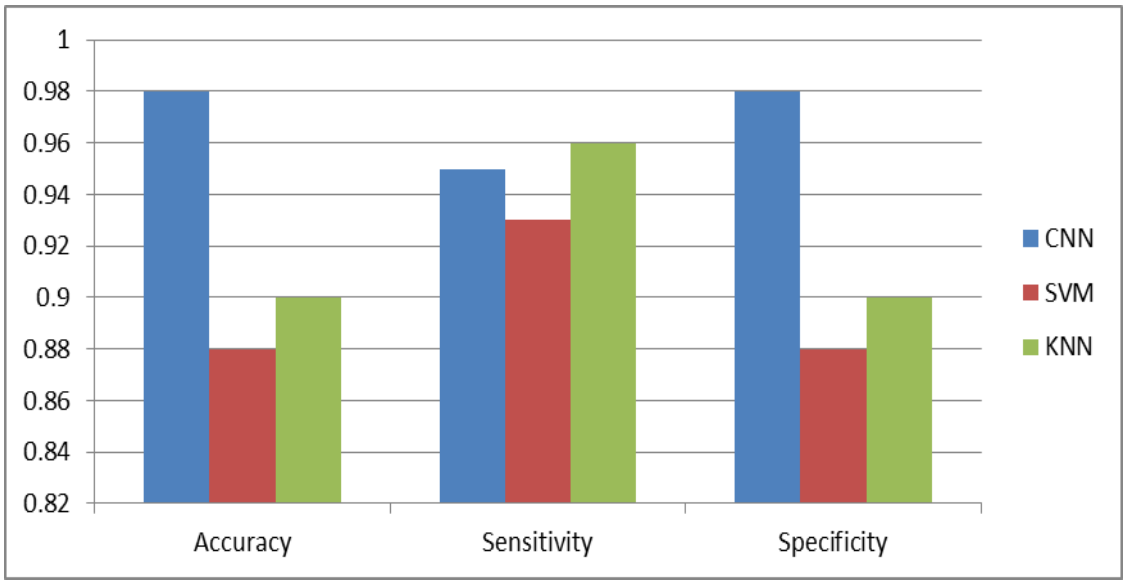

Figure 4: Detection results of the three different approaches for *P. falciparum* test database

The test database for P. vivax contains 3,528 plasmodia objects and 92,277 non-plasmodia objects from 19 different slides. The detection results of the different approaches for this database are visualized in the Fig.5. The CNN – approach shows the best results with respect to accuracy (96%), sensitivity (94%) and specificity (96%) for this dataset.

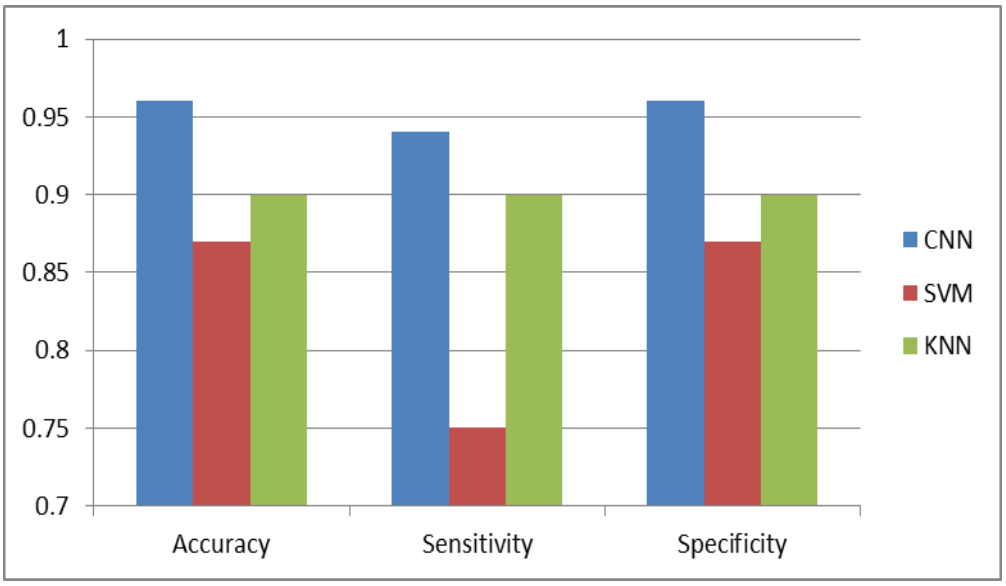

Figure 5: Detection results of the three different approaches for *P. vivax* test database

For the combination of the two datasets the CNN – approach is the best for all three measures (97% accuracy, 94% sensitivity and 97% specificity). The results for the combination are shown in Fig. 6.

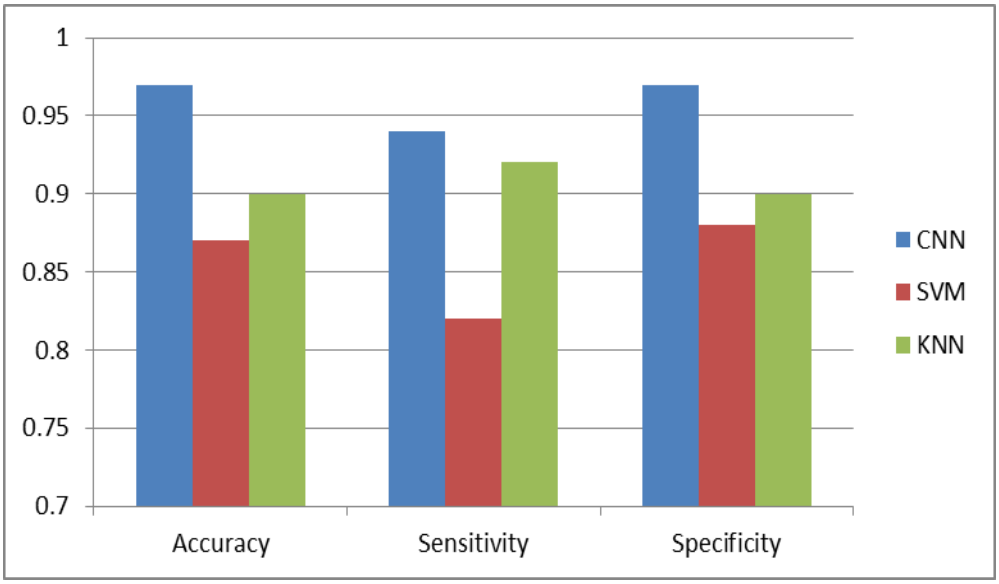

Figure 6: Combined detection results of the three different approaches

4. CONCLUSION

In this paper we present a new approach for the detection of plasmodia in thick blood smears which is based on a convolutional neural network. We have compared this approach with two conventional 1-vs.-rest classification schemes (SVM and KNN). The proposed classification methods have been evaluated with more than 180,000 automatically

detected and manually classified plasmodia candidate objects. The CNN – approach yields better detection results on this dataset with respect to accuracy, sensitivity and specificity than the two alternative approaches (SVM and KNN). Automated solutions for the morphological analysis of malaria smears could apply such a classifier to detect plasmodia and thereby shortening the examination time. With such a system diagnosis of malaria infections should become less tedious, more reliable and reproducible and thus a more objective process. Better quality assurance, improved documentation and global data availability are additional benefits.

5. ACKNOWLEDGEMENT

This work was supported by Fraunhofer Zukunftsstiftung.

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