An application of U-Net for cell detection in fragments of cytological smear images

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Abstract. Cervical cancer is one of the most lethal cancers in women, although early detection may allow successful treatment. Providing computer and automatic support during a diagnosis of cervical smears can accelerate cancer detection time as well as lower its cost. Here we show the first step towards developing such a system: A U-Net-based method for cell detection in small fragments of whole slide images of cervical pap smears. Additionally, two datasets containing 1748 and 1887 cells each were prepared and used to train and test the method. The method yields a 0.88 F1 score and will be used to develop a whole system for automatic support in cervical smear diagnosis

Keywords: biomedical engineering, digital pathology, image detection.

1 Introduction

Cervical cancer is the fourth most common cause of death from cancer in women [1]. However, prevention in the form of evaluation of cytological smears, executed every 3-5 years (depending on a type of smear) can reduce the incidence rate up to 60% [2].

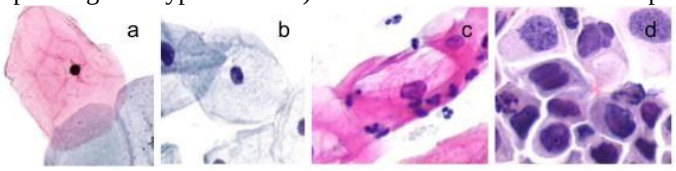

Fig. 1. Examples of normal cells (a and b) and abnormal cells (c and b).

There are two main categories of abnormal epithelial squamous cells (see Fig. 1) found in gynecological cytology smears, low-grade squamous intraepithelial lesions (LSIL) and high-grade squamous intraepithelial lesions (HSIL). Atypical cells are classified into atypical squamous cells of undetermined significance (ASC-US) or atypical squamous cells – cannot exclude HSIL (ASC-H) [3]. The treatment following

a positive result depends on the category of detected abnormal or atypical cells. If LSIL or ASC-US cells are found, an HPV test is done or another smear should be collected after 6 months. If HSIL or ASC-H cells are found, a biopsy should be performed to diagnose the patient [2].
Cytology evaluation is performed manually by highly trained cyto-diagnosticians and physicians and is very time-consuming, therefore numerous machine learning (ML) methods have been developed to support and accelerate the process, the oldest being described in 1981 [4]. A review of the ML methods developed until 2019 can be found in article [4]. Few of ML methods focuse on single category of cells, for example Tao et al. focused on distinguishing high-risk slides form ASC-US slides [5]. This work presents the results of U-Net [6] trained to perform a detection task on a newly-made set of cytological smear WSI fragments (tiles) and evaluation of the task on the testing set using F1 score. The method described in this research is a part of a system of methods being developed for the analysis of pap smears.

2 Materials

Specimens used in this research were collected in a private clinic *Arsmedica* in Bialystok in accordance with a written agreement between the clinic and IBBE, along with ethic permission. The 20 slides were digitized and annotated by cyto-diagnosticians and physicians. Annotations were in a form of color-coded dots, each color symbolized a different cell type. Two sets - training and testing were extracted from the collection.
The training dataset is made of tiles that were chosen and annotated by cyto-diagnosticians in a form of color-coded marks on WSI tiles. Among these tiles, 50 were chosen that contained low-grade squamous intraepithelial lesion (LSIL) or high-grade squamous intraepithelial lesion (HSIL) cells. Tiles, each sized 3500x3500 pixels were cut into 4 smaller fragments and compressed to size 512x512 pixels to meet usual neural networks size requirements. Based on such images ground truth maps were prepared.
Areas of cells belonging to the same group were marked on separate black and white maps using GIMP [7]. An example of cell maps is shown in Fig. 3. In this study, the cell maps were summed to allow differentiation between cell areas and background with noise. 200 tiles were prepared, each containing around 15 cells each. A summary of the types of cells included in the training set is shown in Fig 2.
The testing set consists of 60 images containing approx. 33 cells each, yielding 1887 cells and cell clusters in total. Images were cut out from 20 whole slide images (WSI) and were selected to show a large number of distinguishable cells and diverse backgrounds.

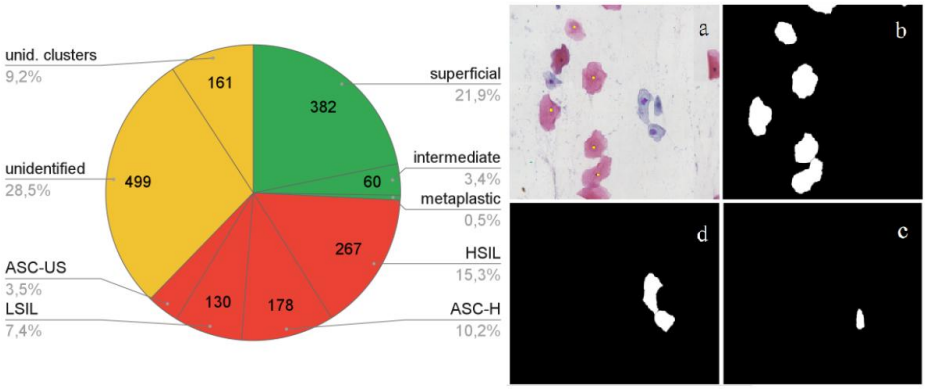

Fig 2. Left: percentages and numbers of cells representing different types in the training set of images. The total number of cells: 1748. Right: marked WSI tile a) and maps derived from it: b) superficial squamous cells, c) ASC-US, d) LSIL.

Cells and cell clusters were annotated by bounding boxes using software called VGG Image Annotator [8]. An example of an annotated image is shown in Fig. 2. Fragments of cells visible on the edges of the tiles were excluded from the annotations since such fragments do not contain full information about the cells.

3 Methods

A convolutional neural network called U-Net (with Inception Network [9] used as a backbone) was trained to perform detection of cell areas. The network's parameters are shown in table 1. The network was pretrained on ImageNet [10] dataset. Transfer learning was done using the training set discussed earlier. Network was tested with the testing set. Then, using the network's output and bounding boxes as a reference, an automatic method for preparing data for the process of evaluation of the method's performance was developed.

Table 1. Parameters of the neural network used in the study.

Parameter	Steps	Epochs	Batch size	Learning rate	Decay	Loss function	Metric function
Value	200	40	4	10^{-6}	10^{-8}	Binary cross-entropy	Binary accuracy

The evaluation method consisted of 3 steps performed on each image:

1. Finding contours in the output of interference with Otsu thresholding and filling them in white.
2. Dilating the white areas and enclosing them with a box.
3. Finding centers of annotating bounding boxes and marking them with a black dot.

If a dot exists on a white background it is treated as a true positive, a dot on a grey background is a false negative, box without a dot symbolizes a false positive.

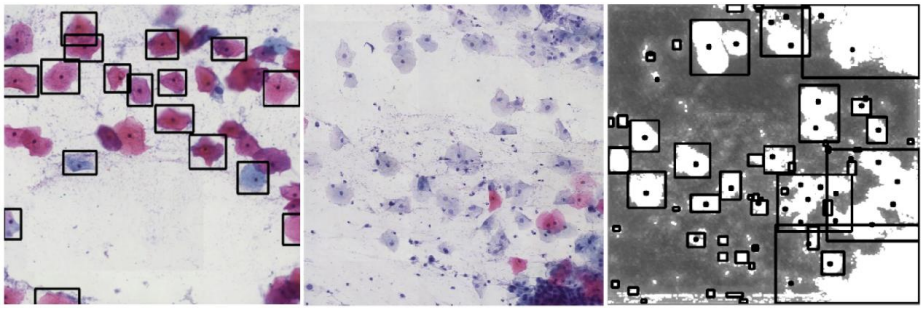

Fig. 3. An example of a bounding box annotation done only on non-clustered cells (left). A tile (middle) and its interference with evaluation marks (right). Dots mark the true position of cells (or cell clusters), white areas - network answers, boxes enclose white areas, serving as an estimation of supposed cell placements.

4 Results and discussion

The interference results were evaluated using the verification method discussed earlier, statistical measures are shown in table 2. Kurnianingsih et al [4] reached similar recall of 0.91 and slightly higher precision (0.92) and F1 (0.91) in their segmentation study. It is clear that our method shows high sensitivity, allowing it to be used in further steps towards developing a cell differentiating method.

Table 2. Summary of measures used to evaluate the network's results.

Measure	All cells	True positives	False negatives	False positives	Sensitivity	Precision	F1 score
Value	1887	1716	171	308	0.91	0.85	0.88

5 Conclusion

Cytology of the uterine cervix is a common screening method, allowing to detect precancerous changes, thus saving women from developing hard-to-treat cancer. The process of developing automation tools for cytology diagnosis is still not finished, however, neural networks seem to be a crucial method of support for physician diagnosis, allowing faster evaluation of specimens. The proposed study focuses on developing the first stage of a method for supporting cytological smear evaluation. The output of this method will be used in the next stage of differentiating normal cells from lesions. Future plans also include use of color normalization and advanced augmentation methods.

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