

**ARTIFICIAL INTELLIGENCE (AI) SOLUTION FOR PLASMA CELLS DETECTION
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The article investigates the application of a neural network detection model to histological images in order to detect plasma cells for chronic endometritis detection. A two-stage algorithm was developed for plasma cell detection. At the first stage, a CenterNet model was used to detect stromal and epithelial cells. The neural network was trained on an open dataset with histological images and further fine-tuned using an additional labeled dataset. A labeling protocol was used, and the coefficient of agreement between two experts was calculated, which turned out to be 0.81. At the second stage, using the developed algorithm based on computer vision methods, plasma cells were identified and their HSV color boundaries were calculated. For the two-stage algorithm the following quality metrics were obtained: precision=0.70, recall=0.43, f1-score=0.53. The model then was modified to detect only plasma cells and trained on a dataset with histological images containing labeled plasma cells. The quality metrics of the modified detection model were obtained: precision=0.73, recall=0.89, f1-score=0.8. As a result of the comparison, the modified detection model approach showed the best quality metrics. Automating the work of counting plasma cells will allow doctors to spend less time on routine activities.

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1. INTRODUCTION

The use of neural network models has recently become extremely important and relevant in many areas. Neural network models help efficiently process and analyze large amounts of data. They are able to automatically extract useful information, uncover hidden patterns, and predict trends to help in making more accurate and automated decisions. In recent years, neural networks and computer vision have played an increasingly important role in the field of medicine. They provide new opportunities for automatic and accurate analysis of medical images. One of the important applications of neural network models in medicine[1] refers to diagnosing various diseases by

analyzing images such as x-rays, computed tomography (CT), magnetic resonance imaging (MRI), and histological slides. They can detect pathologies such as tumors, infections, or other critical markers. In particular, chronic endometritis, a common disease of the female reproductive system, requires accurate diagnosis to be treated effectively. It is characterized by chronic inflammation of the endometrium, which can lead to reproductive disorders, infertility, and increases the risk of endometrial cancer. Early detection of chronic endometritis is crucial for timely treatment initiation and complications prevention. Identification of plasma cells is one of the main criteria for diagnosing chronic endometritis, therefore, automation of the process of detecting plasma cells on histological images

can greatly facilitate the process of diagnosing this disease.

2. PROBLEM STATEMENT

The objective of the study is to count positively stained plasma cells on histological images stained with the CD138 marker (for automatic detection of chronic endometritis).

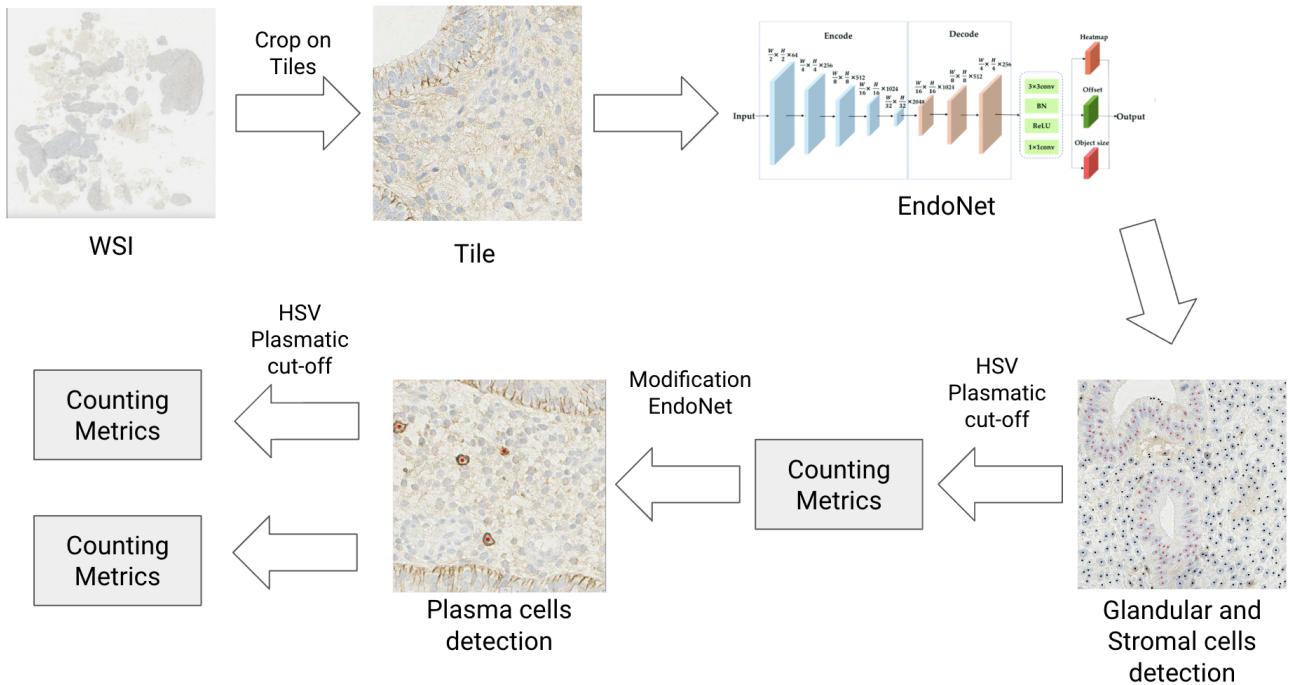


Fig. 1. Pipeline of the AI solution for plasma cell detection.

It is necessary to solve the following subtasks ("fig. 1"):

- Apply the CenterNet[2] neural network model trained on the EndoNuke[3] public dataset to images from histology slides provided by expert doctors.
- Fine-tune[4] the model on histological images labeled by experts.
- Develop an algorithm for searching plasma cell candidates using computer vision methods.
- With the help of experts, collect a dataset of histological images with labeled plasma cells.
- Validate and calculate the accuracy of the plasma cell search algorithm.
- Modify and train the model for plasma cells detection.

- Validate and calculate the accuracy of the modified plasma cell search algorithm.

3. NEURAL NETWORK DETECTION MODEL

To solve the problem of detecting stromal and epithelial cells on histological images, a neural network detection model architecture CenterNet ("fig. 2") is used. The model takes RGB images as input, and the result of its work is a set of classified keypoints. The CenterNet architecture consists of three main components: backbone, heatmap and keypoint extractors.

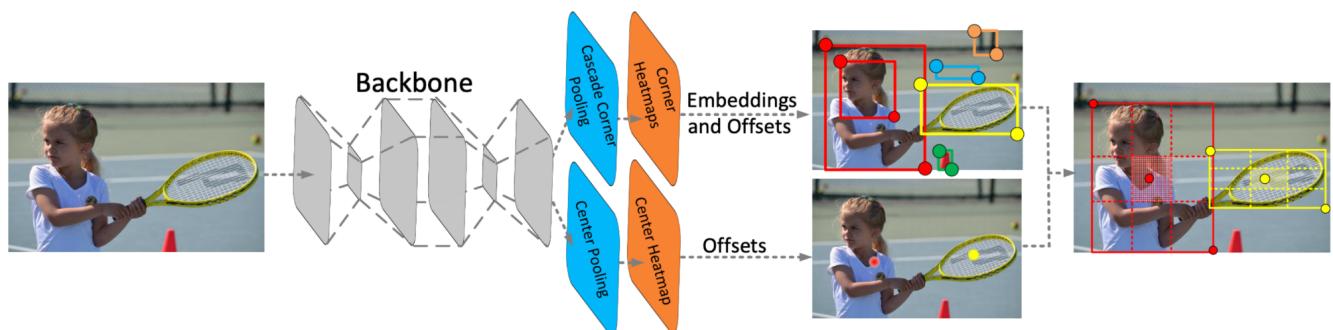


Fig. 2. CenterNet neural network architecture.

CenterNet is a one-step object detector that identifies each object as a triple of keypoints. ISP RAS conducted a study of such models, during which different versions of the models were compared, and the model with backbone UNet++[5] ResNet50[6] showed the best results. During the study, several test samples were formed, an optimal set of augmentations and other hyperparameters was selected, and the optimal optimizer parameters and loss functions were selected. This architecture with

backbone UNet++ ResNet50 and selected optimal parameters was named EndoNet and formed the basis for developing a solution for detecting plasma cells on histological images.

The weighted Huber Loss[7] was used as a loss function. Due to the imbalance of classes, the weight value was 1 for stroma type cells, and 4 for epithelial type cells.

Optimizer options of the used neural network model EndoNet are presented in the table ("table 1"):

Table 1. Parameters of the neural network model EndoNet

Backbone	Optimizer options			
	optimizer	learning_rate	weight_decay	amsgrad
UNet++ ResNet50	Adam	0.0001	0	True

4. RESEARCH AND SOLUTION PROCEDURE

The research and the solution for the stated problem were carried out in several stages, corresponding to the subtasks.

4.1 DATA

The data that was used in solving the problem was provided by doctors from the National Research Center for Obstetrics and Gynecology named after A. Kulakov. Histological samples are a set of 14 histological slides (whole slide images, WSI) in .svs format. The size of each slide is $\sim 100,000 \times 100,000$ pixels and $\sim 25,000 \times 25,000 \mu\text{m}$. The QuPath[8] was used to work with histological slides. To reduce the number of internal parameters of the neural network model, these slides were divided into histological images (tiles) of size 790×790 pixels and $200 \times 200 \mu\text{m}$.

4.2 FINE-TUNING NEURAL NETWORK MODEL

The EndoNet model was trained on an open dataset with histological images EndoNuke. During training accuracy control was assessed with the use of mAP (mean Average Precision).

With the help of experts, images from histological slides were annotated with the use of CVAT, an open

source markup tool. Using the built-in QuPath methods, the area on the histological slide was divided into histological images (tiles). 30 histological tiles (24 unique and 6 matching) of size $200 \times 200 \mu\text{m}$ and 790×90 pixels were prepared for each expert. For the correct stroma and epithelium classification, a context was added to the edges. An annotation protocol was agreed upon. The obtained agreement coefficient Cohen's kappa[9] on matching tiles turned out to be 0.81. This labeled dataset was named as endometrium.

Table 2. mAP metric values when training EndoNet on EndoNuke for the task of detecting stromal cells and epithelial cells on histological images

Backbone	EndoNuke	
	train	valid
UNet++ ResNet50	0.83	0.76

Further, fine-tuning of the EndoNet model was carried out using the labeled endometrium dataset with various pre-trained weights. The labeled dataset endometrium was divided into train/val parts in the ratio 70% / 30%, which corresponds to 37/17 labeled images (tiles). During fine-tuning accuracy control was assessed with the use of mAP (mean Average Precision)

Table 3. mAP metric values during EndoNet fine-tuning on the labeled endometrium dataset with various pre-trained weights for the task of detecting stromal and epithelial cells

Pre-trained weights	first epoch		best epoch	
	train	valid	train	valid
EndoNuke	0.46	0.49	0.84	0.72
Imagenet	0.05	0.09	0.75	0.57

Analyzing the results, we can conclude that the additional annotation and fine-tuning on the labeled histological images increased the accuracy of stromal and epithelial cells detection. Looking at the first epoch using the pre-trained weights from the EndoNuke dataset, we can see that if no fine-tuning was done, the accuracy of stromal and epithelial cells detection is mAP = 0.49. Because of fine-tuning, the accuracy of stroma and epithelial cells detection is mAP = 0.72. It can also be noticed that if just the pre-trained imagenet weights are taken, the accuracy of stromal and epithelial cells detection is mAP = 0.57. Thus, labeling the endometrium dataset and fine-tuning the model EndoNet on this dataset significantly improved the accuracy of stromal and epithelial cells detection on the histological images.

4.3 DEVELOPMENT OF AN ALGORITHM FOR SEARCHING PLASMA CELL CANDIDATES USING COMPUTER VISION METHODS

The median filter and the laplacian filter were applied to histological images (tiles), due to which the contours of candidates for plasma cells were built:

- A median filter was applied to histological images. This filter helped to reduce noise on the image and smooth the edges[10]. Filter window size was validated as a hyperparameter.

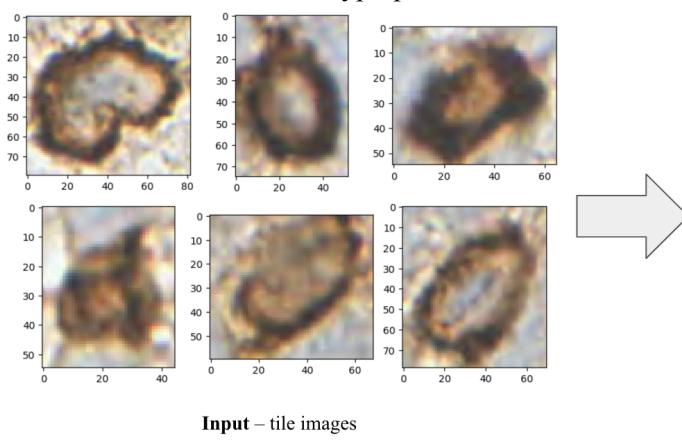


Fig. 3. Contours around plasma cell candidates.

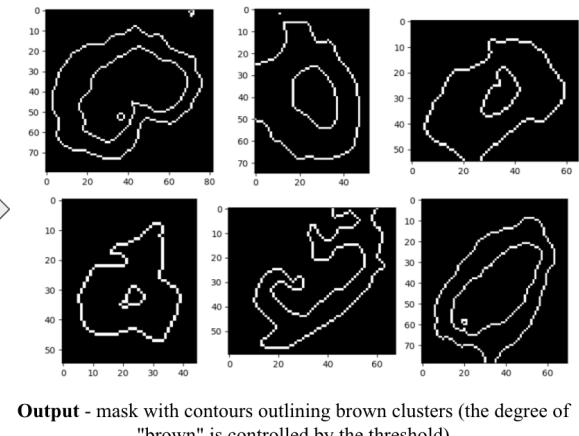
Convex objects were made from the obtained in the previous step contours. These convex objects can be further analyzed ("fig. 4").

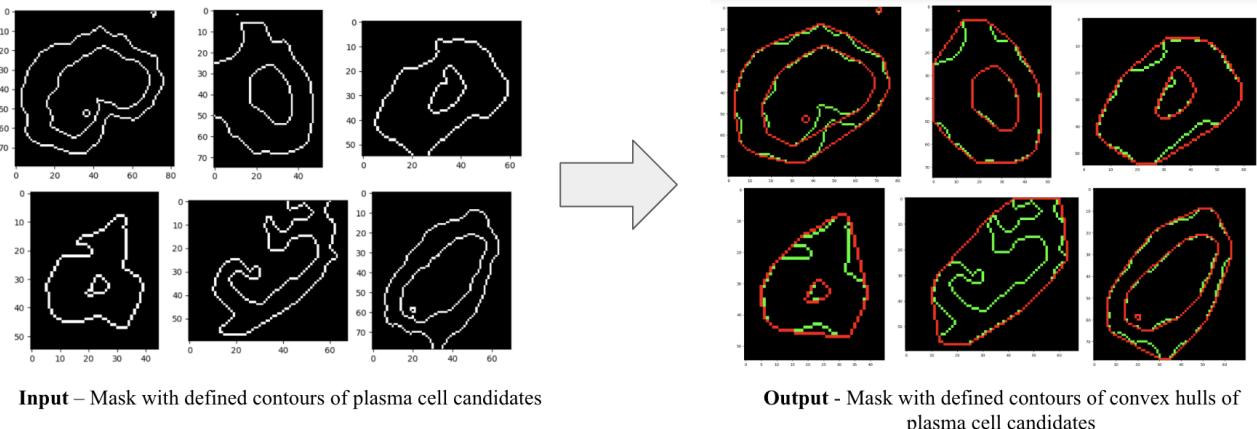
- Next, histological images were converted to grayscale.
- After conversion to grayscale, the histological images were subjected to binarization by a threshold. This helped to highlight objects and contours on the image. The threshold value was validated as a hyperparameter.
- Next, the laplacian filter[11] was applied to the histological images. It helped to highlight the edges and textures of objects, making the outlines clearer and more distinguishable. In this study, a 3x3 kernel is used, which is represented by the following matrix:

$$\text{kernel} = \begin{vmatrix} 0 & 1 & 0 \\ 1 & \text{center_kernel_value} & 1 \\ 0 & 1 & 0 \end{vmatrix}$$

where the "center_kernel_value" was validated as a hyperparameter.

Thus, after performing these steps, contours were built around the plasma cell candidates ("fig. 3").





Input - Mask with defined contours of plasma cell candidates

Output - Mask with defined contours of convex hulls of plasma cell candidates

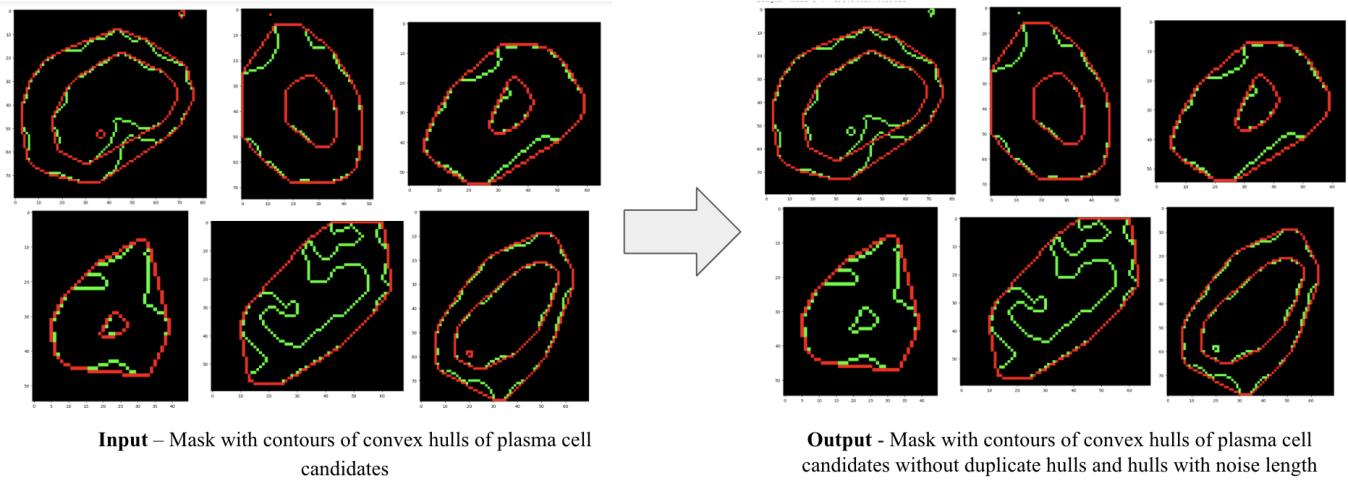
Fig. 4. Creating convex hulls from contours that were built around plasma cell candidates.

Next, the obtained at the previous stage convex hulls were preprocessed ("fig. 5") in two steps:

- Removal of hulls with noise length. The threshold value of contours length, at which it

was considered as noise, was validated as a hyperparameter.

- Elimination of duplicate hulls.



Input - Mask with contours of convex hulls of plasma cell candidates

Output - Mask with contours of convex hulls of plasma cell candidates without duplicate hulls and hulls with noise length

The preprocessed convex hulls were grouped into nested convex hulls in a graph. Each convex hull is considered as a node of the graph, and if one convex hull is completely inside another convex hull, then an edge of the graph is established between them. The structure in the form of a graph is necessary for the correct calculation of the HSV[12] boundaries that plasma cells have, in order to take into account only the color of those pixels that are stained with the CD138 marker and not take into account the color of those pixels that are not stained with this marker ("fig. 6").

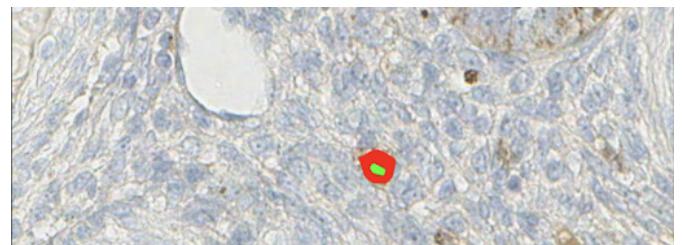


Fig. 6. A CD138-stained plasma cell to illustrate which pixels (marked in red) determine the HSV color of the cell

Thus, using computer vision and image processing methods, objects that are most similar to plasma cells were identified. These objects are candidates for plasma cells.

4.4 PLASMA CELL SEARCH ALGORITHM

A set of histological images were collected and annotated by medical experts, which contain plasma cells: 219 tiles were prepared for each expert (154 unique and 65 matching). In total 373 unique images were collected. Matching tiles were needed to calculate the agreement coefficient Cohen's kappa, which turned out to be 0.89. 826 plasma cells were labeled by the medical experts on these tiles. On 23/373 tiles, the experts did not find plasma cells. This labeled dataset was named plasmatic. The dataset plasmatic was divided into train/val/test in the ratios:

- 35%/15%/50%
- in train 132 images (tiles), 7 empty
- in val 56 images (tiles), 4 empty
- in test 185 images (tiles), 12 empty

For a more correct and generalized definition of quality metrics, 160 more images (tiles) were added to test from histological slides containing no plasma cells. Such images were called "empty". Images that have at least one plasma cell were called "non-empty". Total in test : 345 images (173 non-empty / 172 empty).

There were established conditions under which the cell was considered as plasmatic:

- Color restriction: The HSV color of a plasma cell candidate must be within a certain threshold value.
- Class restriction: Inside the convex hull of a plasma cell candidate, there must be exactly one keypoint, which was determined by the EndoNet and this keypoint was classified as stromal.

Thus, if both conditions: the color restriction and the class restriction are considered, then the cell is defined as a plasmatic.

Based on the labeled plasma cells, the HSV color thresholds bounds for when a cell is considered as

plasmatic were determined: $5 \leq \text{hue} \leq 20$. To validate the hyperparameters of the plasma cell search algorithm, the val part of the dataset plasmatic, consisting of 56 histological images (tiles), was used. The hyperparameters of the plasma cell search algorithm were validated ("table 4").

Table 4. Hyperparameter values of the plasma cell search algorithm

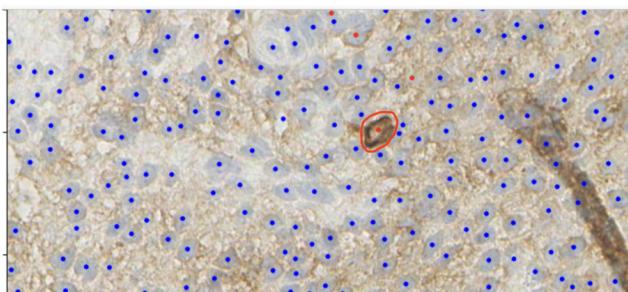
Hyperparameter	Value
Median filter value	17
Image binarization threshold	147
Kernel value for laplacian filter	-20
Hulls threshold length considered noise	23

Also, the quality metrics of the plasma cell search algorithm were counted on 345 tiles (173 non-empty / 172 empty). For the binary classification problem plasma cell/background Precision, Recall and F1-score quality metrics were used ("table 5").

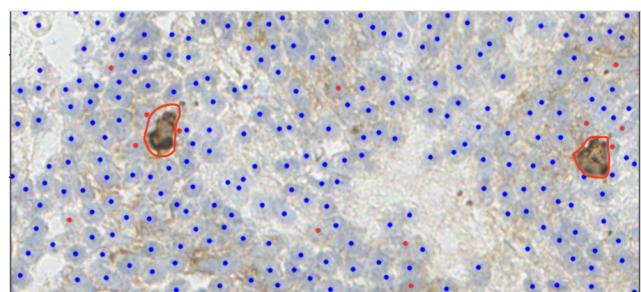
Table 5. Accuracy of the plasma cell search algorithm on a test dataset containing 345 images

Metrics	Value
Precision	0.70
Recall	0.43
F1-score	0.53

The results were analyzed and the low Recall resulted due to the fact that EndoNet did not learn to classify plasma cells as stromal cells ("fig. 7").



A plasma cell is classified as an epithelial cell



A plasma cell is not classified at all

Fig. 7. An example of plasma cells that EndoNet did not classify as stromal cells

As a result, it was decided to modify the EndoNet model, which originally solved the problem of detecting and classifying endometrial cells into stroma and epithelium, to focus on detecting only plasma cells.

4.5 ENDONET MODIFICATION FOR PLASMA CELL DETECTION

In order to modify the EndoNet model to detect only plasma cells, some of its parameters were changed. The architecture and backbone of the model remained

unchanged. The number of classes has been reduced to one class that corresponds to plasma cells. In the loss function Huber, the weight of one class has been removed. Hyperparameters of the heatmap[13] and keypoint extractor have been changed, as well as some augmentation parameters. With the use of Pytorch[14], the last layer of the segmentation head was changed so that the model could work with the new number of classes. These steps were done to use the pre-trained weights of the model with a different number of classes (EndoNet trained on the EndoNuke and endometrium dataset).

Then, the EndoNet, which was modified for plasma cell detection, was trained on the train/val part of the dataset plasmatic. Pre-trained weights from the EndoNuke dataset, the endometrium dataset, and pretrained weights imangenet[15] were used. During training accuracy control was assessed with the use of mAP (mean Average Precision).

Table 6. mAP metric values during EndoNet training on train/val part of the dataset plasmatic with various pre-trained weights for the task of detecting plasma cells

Pre-trained weights	Best epoch	
	train	valid
Imagenet	0.73	0.54
EndoNuke	0.97	0.70
endometrium	0.98	0.75

Based on the results in "table 6", it was concluded that the best quality of plasma cell detection is achieved if pre-trained weights from the dataset endometrium are used. Therefore, the accuracy of EndoNet trained for plasma cells detection with pre-trained weights from the dataset endometrium was counted on 345 tiles (173 non-empty / 172 empty) in standard metrics Precision, Recall and F1-score for binary classification problem plasma cell/background ("table 7").

Table 7. Accuracy of EndoNet trained for plasma cell detection on test containing 345 images.

Metrics	Value
Precision	0.73
Recall	0.89
F1-score	0.80

As a result of the analysis, it became clear that modified EndoNet assigns keypoints to certain cells that are not stained with the CD-138 marker and, therefore, are not considered as plasma cells ("fig. 8").

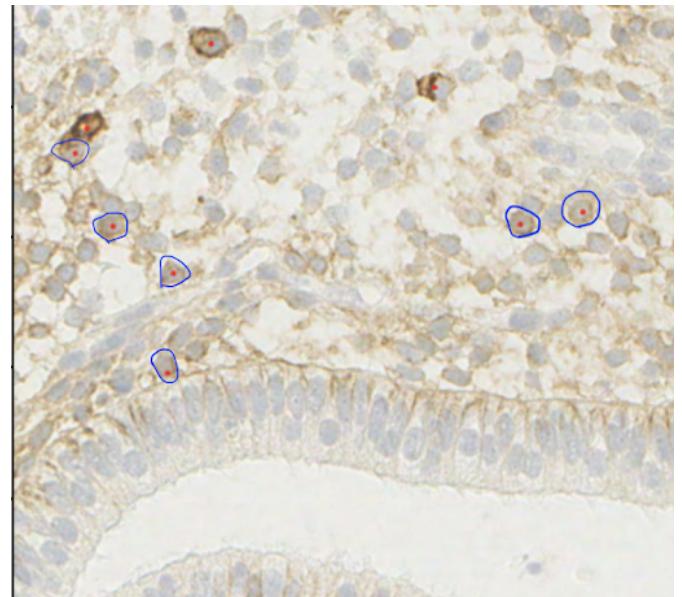


Fig. 8. An example of cells (circled in blue) that are not stained with CD-138 but are identified as plasma cells by the modified EndoNet

To reduce this problem, it was decided to cut detected by EndoNet plasma cells by the HSV color, similar to what was done in the two-stage search plasma cell algorithm.

4.6 MODIFIED PLASMA CELL SEARCH ALGORITHM

There were established conditions under which the cell was considered as plasmatic:

- Color restriction: The HSV color of a plasma cell candidate must be within a certain threshold value.
- Class restriction: Inside the convex hull of a plasma cell candidate, there must be exactly one keypoint, which the modified EndoNet defined as plasma cell.

Thus, if both conditions: the color restriction and the class restriction are considered, then the cell is defined as a plasmatic.

The HSV color thresholds bounds for when a cell is considered as plasmatic were determined: $5 \leq \text{hue} \leq 20$. To validate the hyperparameters of the modified plasma cell search algorithm, the val part of the dataset plasmatic, consisting of 56 histological images (tiles), was used. The hyperparameters of the modified plasma cell search algorithm were validated ("table 8").

Table 8. Hyperparameter values of the modified plasma cell search algorithm

Hyperparameter	Value
Median filter value	17
Image binarization threshold	165
Kernel value for laplacian filter	-8

Hulls threshold length considered noise	20
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Further, the quality metrics of the modified plasma cell search algorithm were counted on 345 tiles (173 non-empty / 172 empty). For the binary classification problem plasma cell/background Precision, Recall and F1-score quality metrics were used ("table 9").

Table 9. Accuracy of the modified plasma cell search algorithm on a test dataset containing 345 images

Metrics	Value
Precision	0.84
Recall	0.76
F1-score	0.80

5. CONCLUSION

In this work, the application of a neural network detection model to histological images was investigated in order to identify plasma cells for chronic endometritis detection. A two-stage algorithm was developed to count positively stained plasma cells on histological images stained with the CD138 marker. At the first stage, a neural network model was used to detect stromal and epithelial cells on histological images. The model was trained on an open dataset and fine-tuned using an additional dataset labeled by two medical experts. Because of the fine-tuning, the detection accuracy of stromal and epithelial cells increased from mAP=0.49 to mAP=0.72. At the second stage, using the developed algorithm based on computer vision methods, plasma cells were identified. The quality metrics of the developed plasma cell search algorithm on test containing 345 tiles are Precision=0.70, Recall=0.43, F1-score=0.53. Because of low Recall it was decided to modify the EndoNet model, which originally solved the problem of detecting stroma and epithelium cells, to detect only plasma cells. The modified model was trained using different pre-trained weights. The comparison of the results showed that the best accuracy of plasma cell detection is achieved when using pre-trained weights from the dataset endometrium, which was labeled by medical experts. The quality metrics of plasma cells detection on test containing 345 tiles increased to Precision=0.73, Recall=0.89, F1-score=0.8. A modified plasma cell search algorithm was defined. For the modified plasma cell search algorithm, the quality metrics turned out to be Precision=0.84, Recall=0.76, F1-score=0.8. Thus, all the subtasks formulated in the problem statement section were completed, and the approach with the modification of the neural network model for only plasma cells detection showed the best results.

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