# Deep Learning-Based Segmentation and Classification of Histological Colon Cells

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## Abstract

Deep neural networks have become important in the research of medical applications, particularly in histology. One of the important research areas is the usage of deep neural networks in the diagnostics of diseases such as Crohn's disease and Ulcerative Colitis. In these types of diseases, the correct detection of specific cell types and cell features is crucial. To integrate this domain-specific knowledge directly from pathologists, we propose a customizable system made of three connected modules: segmentation, filtration, and classification.

The segmentation module uses the AttentionUNET [11] architecture to find cell boundaries. The filtration module contains a stack of filters suitable to specific cell features, such as color, shape, and area. These filters are used to eliminate irrelevant cells from the predicted segmentation mask. The classification module uses the ResNet34 [4] architecture for multi-class classification tasks. Through experimentation involving custom loss functions and attention modules, we found that the filtration module is well-suited for elimination of irrelevant cells from the predicted mask. The segmentation module achieves a Dice score of 84.18% and an F1-score of 90.08%. However, the classification module exhibits an accuracy of approximately 72%, primarily due to limited annotated data. Nonetheless, our solution proves effective in scenarios with constrained training data, as the filtration module aids with process of prediction by filtering out irrelevant cells.

**Keywords:** Deep Learning, Cell Segmentation, Cell Classification, Computer Vision, Medical Image Analysis, Feature Extraction, Histopathology

## 1 Introduction

In recent years deep learning started to be involved progressively more in histology. *Histology images* contain a vast number of features and objects, which need to be precisely detected by doctors. An example of a histology image of the colon can be seen in fig. 1. These images are in a different resolutions in a range from 61440x73728 to 134400x82944 pixels. Because of these resolutions it is sometimes hard to detect abnormalities in them. Because of this, *deep neural networks (DNN)* came in handy. With the help of DNN, mostly convolution neural networks [10], pathologists can save days of work. Specific types of diseases, where deep neural networks can be used is *Ulcerative Colitis* and *Crohn's disease*. The symptom presented in these diseases is inflammation of the colon and small intestine. Starting and long-lasting inflammation can be detected in histology images. In the last 50 years occurrence of these diseases increased 10 to 15 times. This means it became a modern-age disease, which occurs more and more often [9]. Indeed, the complexity of diagnosing diseases in the colon arises from the diverse range of cell types and tissues present in this region. Unlike some other diseases that may affect more homogeneous tissues, conditions affecting the colon often involve interactions between various cell types and tissues, each with its own distinct characteristics and functions. Diagnostic and prediction of disease is extremely important. When a doctor can predict the development of a disease, he can establish less invasive treatment earlier. This can in some situations save a patient's life.

The training of neural network-based system requires a sufficient amount of annotated cell images. However, annotating these cells is time-consuming and can only be done by pathologists. Since creating annotations is not a common task for pathologists, it is crucial to expedite the annotation process. Only pathologists know the exact rules regarding which cells are most important and which features to focus on. This underscores the importance for pathologists to have the option to interact with and modify the annotation tool, as well as access an annotation tool capable of extracting cells based on specific features. Hence, they require an annotation tool capable of minor modifications by individuals who aren't AI professionals.

The contribution of this papers is to provide a system, which is able to perform segmentation and classification of specific areas of histology images chosen by pathologists, with the additional option of modifications of the system

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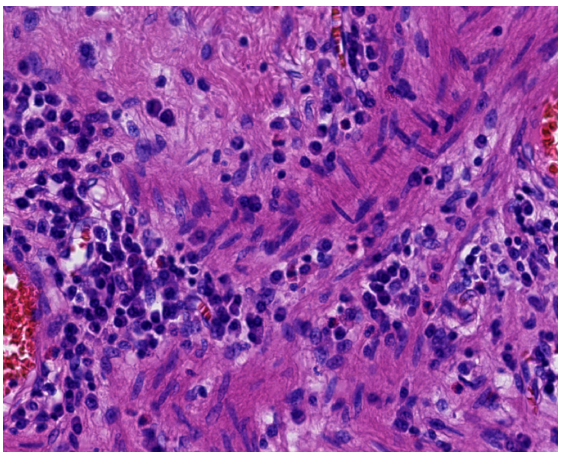


Figure 1: Example of histology image

by the user. Due to the scarcity of training data, the model is pre-trained on the CoNIC dataset [2]. The whole system is meant to be implemented into the custom annotation application as a tool for the acceleration of the pathologist's work. The advantage of this custom annotation application is that it would be easily expandable based on specific requirements.

Mentioned system is made of three connected modules: segmentation, filtration, and classification. These modules work as a pipeline. The main part is the filtration module, which provides necessary modifiability. Implementation of the module into the custom annotation application can increase the speed of histology image examination by a pathologist. Furthermore, it offers the option to implement active learning based on the visualization of predicted masks within the annotation application.

## 2 Related work

Numerous applications have been developed for cell segmentation and classification [17], yet only a limited number specifically target Crohn's disease and Ulcerative Colitis. That is the reason why, it is hard to compare this specific task to other state-of-the-art solutions. Most of the similar solutions focus on the incorporation of additional features with *attention mechanisms* [14] or adjustments to neural network architectures. This is a advantageous option when we want a precisely functioning black box that requires infrequent modification. However, it also increases the system's complexity, making optimization and management more challenging and model less explainable.

Yildiz et. al [18] work with the same CoNIC dataset [2] as used in this paper. However, the paper provides a whole different approach to cell segmentation and classification. The *UNET* architecture mentioned in the paper is used for multi-class segmentation which means they used one model to predict and classify segmentation mask. Validation was performed on five different subsets of images. The average metrics of these tests are *57,08% dice score* and *48,57% IoU*. At first glance, this approach may appear to offer a superior and simpler solution. However, a issue may arise. One model needs to learn how to perform segmentation and also classify individual pixels into correct classes. Handling complex data such as cells can indeed present challenges in this regard. The problem also can be seen in the paper, where the test accuracy metric showed that some of model is not that robust. This is beneficial in situations, when model needs to have fast performance and take up less disk space. Due to the previously mentioned challenges associated with the complexity of performing classification and segmentation on similar types of data such as cells, we opted to use separate models for segmentation and classification.

Iacucci et. al [8] provide neural network architecture adjusted to distinguish between remission and inflammation phases. This can be predicted from histology images based on specific types of cells located in tissue. The method which is used for this problem is a modification of *VGG16 architecture* by use of attention mechanism [8], which results in better focus on *neutrophils*. Input to the attention mechanism is the annotation of the corresponding whole slide image. This modified architecture provides *79% accuracy* and *71% F1-score* for classification. The implementation offers techniques for prioritizing specific types of cells over others.

Zeng et. al [19] provide different sights on the problem and different approaches. In this proposed solution architecture detects the position, shape, scale, and contour of cells. The architecture used in the paper is called *Residual-inception-channel attention-Unet (RIC-Unet)* [19]. It brings the advantage of residual blocks, which helps to extract more representative features. The Inception block [19], also present in this architecture, is renowned for its computational efficiency and its ability to manage large receptive fields. On top of this, an attention mechanism is added for better focus on regions of interest. The combination of these blocks creates the architecture of RIC-Unet. This architecture provides an *80,08% dice score* and *82,78% F1-score*. The biggest advantage of this architecture is its ability to extract features of single cells.

Aziz et. al [3] used different method for feature extraction. In this proposed solution is chosen five different neural network based architectures for feature extraction, following algorithms for feature selection and classification itself. Specific architectures used for feature extraction are VGG16, VGG19, Xception, ResNET50 and ResNET121. Proposed method outperforms state of the art solutions by 95,5% accuracy for multi-class classification and 99,49% accuracy for binary classification. It shows exceptional results, but one problem still persists. The system is challenging to interpret, making it difficult to ascertain which specific features are the most relevant and whether they align with the primary decisive features identified by pathologists.

The mentioned papers [8, 18, 19] are based on attention

mechanism [6]. However, these mechanisms can be modified only by AI specialists, due to their complexity. This could be beneficial in some situations, but when a model needs to be set up for each task specifically, it becomes crucial for the model to be *user-adjustable*.

# 3 Proposed method

The whole concept of developing an AI system for medicine, which we want to follow can be seen in fig. 2. The starting point is often a pathologist who presents the problem to a *UX expert*. This UX expert later introduces the problem to the AI expert in a more technical manner. Afterward, AI experts try to implement solutions and discuss results with pathologists through UX experts. This process is repeated a few times, creating a loop [13]. In our specific problem, pathologists need architecture, which can accurately classify selected classes of cells in colon histology images. These types of cells are often common in Crohn's disease and Ulcerative Colitis. To take advantage of communication with pathologists, we aim to create an architecture, which will be easy to modify. These modifications will enable the integration of additional information provided by pathologists directly into the architecture. The blue part of the diagram in fig. 2 represents the AI system of our proposed solution, which is described in the next chapter.

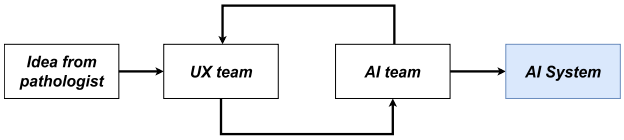



Figure 2: Human in the loop cycle for developing of new AI histology tool

## 3.1 System architecture

The whole system, which can be seen in fig. 3, can be divided into three main modules. Each of these modules is responsible for a different part of the process. The process starts with the extracted histology image patch, which is inserted into the first module. This module is called the *segmentation module*, which is responsible for predicting segmentation masks. The next module is called the *filtration module*. This module is the most flexible part of the system. It contains a stack of filters used for the filtration of the created segmentation mask. It serves as the second module to expedite the process. By filtering out irrelevant cells before passing them to the classification module, we can streamline the validation process and save time. The last module, called the *classification module* is applied for extracting of specific classes of single cells. By combining these modules, we obtain a classified and segmented mask for a specific patch, which is then filtered based on the required cell features. All of these modules are integrated and implemented within the PyTorch [15] framework to optimize the performance of the deep neural network-based application.

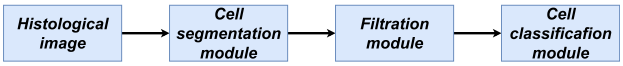



Figure 3: Architecture of system

## 3.2 Segmentation module

The first part of the system is the segmentation module, which can be seen in fig. 4. This module is responsible for the creation of a segmentation mask. The module is consists of two parts: *data preparation* and *cell segmentation*. In the data preparation part, data loading, splitting images into the same size patches, and data preprocessing are performed. The preprocessing stage involves resizing of data and the conversion of data into tensors. Following data preparation, cell segmentation is performed using the *AttentionUNET* [11] architecture, recognized as the state-of-the-art approach for cell segmentation. In our evaluation, we compared Ordinary UNET, AttentionUNET, and Residual AttentionUNET architectures. Despite similar dice scores averaging around 83%, the AttentionUNET architecture outperformed others in accurately segmenting cells and their edges. This determination was made through visual comparison by a pathologist.

The AttentionUNET architecture consists of a combination of two components: the conventional UNET and an attention module. UNET architecture [16] is a convolution neural network-based structure, based on encoder-decoder architecture enriched by skip connections for enhanced feature extraction. These connections aid in retaining fine details during upsampling by concatenating feature maps from corresponding encoder and decoder layers. Furthermore, an attention gate consisting of two inputs is also in the UNET architecture. The first input is from the layer before and the second is from the encoder part. These inputs are then concatenated and passed through ReLU, convolution layer, sigmoid, and then resampled. This model is trained based on transfer learning on *CoNIC* [2] dataset. CoNIC dataset is used due to small amount of annotated data provided by the pathologist.

## 3.3 Filtration module

The second part of the system, which can be seen in fig. 5, is the filtration module. This module is the main part of our proposed solution. The primary objective of this module is to offer pathologists options for interacting with the system and modifying the results based on their preferences. It aims to preserve the accuracy of the outcomes as much as possible. This module is separated into the *data preparation* and *cell filtration* parts. The data preparation

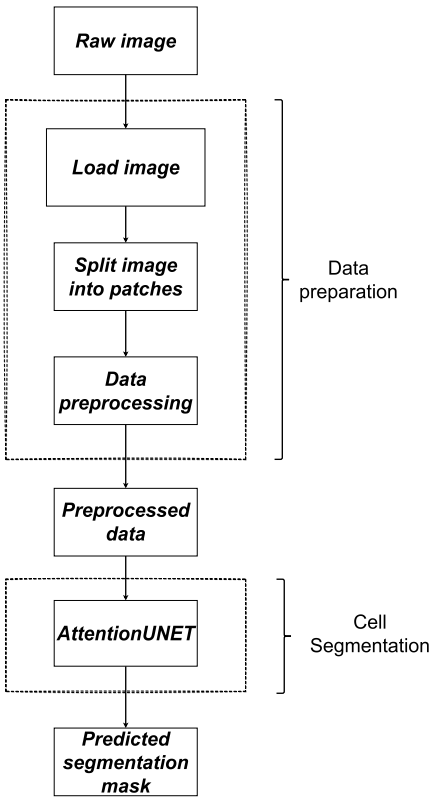



Figure 4: Components of the segmentation module

part is phase involves merging image and mask patches into a single mask and image. This facilitates the subsequent step, which is the usage of a *contour analyzer*. A contour analyzer, implemented using the OpenCV [5] Python library, is utilized to extract single cells from the mask. When we have contours and their positions, we can extract these contours from images. After the extraction of cell contours, we can easily perform filtration. In this stage of development are implemented three filters.

The first filter detects an *area of specific cells*. At first, the area is calculated over each contour. After that, the value of the area is compared to the threshold, and is decided whether the contour passes the test or not.

The second implemented filter is the *shape filter*. This filter also iterates over each contour of the mask and calculates the aspect ratio of elliptic approximation [7]. Using of this calculation solve problem of different cell rotations, because of which cannot be used simple ratio of width and height. The calculation creates value that is used to decide whether the contour is valid or not. Decision is also made by comparison of threshold and calculated ratio, like before.

The third filter is a *color filter*, which is the most complex one. For this filter three input data are crucial. Image, segmentation mask, and sample image. Sample image is one color image, which is set to specific color, based on observations of cells. The first step of the color filter is to extract contours from the mask. Once contours are obtained, specific color pixels of the contour need to be extracted from the image. The next step involves calculating the color ratio by leveraging the difference between two colors in the form of CIE Lab, specifically utilizing the *CIE 2000 method*, across both the image and color sample. This method is implemented with color-science [12] Python library. As the last step, all calculated pixels of the contour are added up and divided by all pixels of the contour. This creates an average color difference value, which is used for filtration.

Mentioned earlier, each of the filters is implemented to work with a specific threshold value. The value tells which cells need to be filtered and which need to be kept. Setting these thresholds directly inside of the annotation tool in which the presented system will be implemented provides the required variance for pathologists. The filtration module is not limited to the mentioned filters; it is designed to allow easy modification and addition of new necessary filters based on the *extraction of cell features*. The choice of these three specific filters is guided by the observations of pathologists during annotation sessions, which highlighted the most important cell features. Further identification of additional filters will involve additional sessions with pathologists.

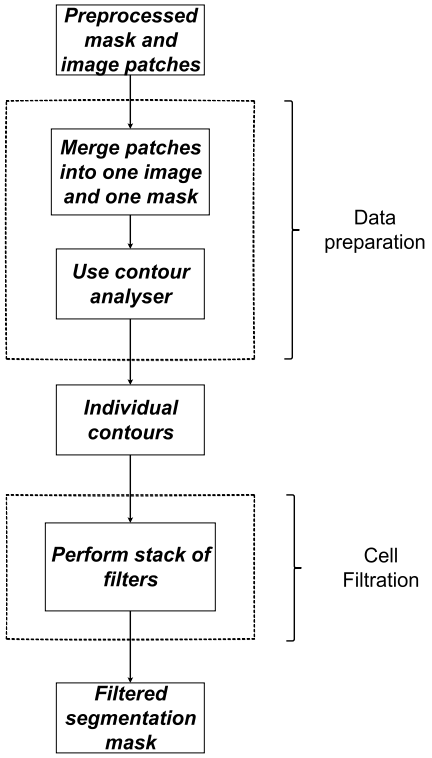



Figure 5: Components of the filtration module

## 3.4 Classification module

The final component of the system is the classification module (fig. 6) tasked with classifying single cells. These

cells must be categorized into six distinct classes: neutrophil, epithelial, lymphocyte, plasma, eosinophil, and connective. Module is divided into two main parts: *data preparation* and *cell classification*. In the data preprocessing part all patches need to be merged into one image, because of the contour analysis. Following this, single cells can be extracted and prepared for classification. These single cells are then passed to the cell classification part, which is made of *ResNET34* architecture [4]. Variations of ResNET and VGG16 architectures with single and multi-input configurations were explored. Despite the similarities in results across the models, attributed to insufficient training data, the ResNET34 architecture currently yields the best performance. However, as more training data becomes annotated, additional experiments with diverse architectures will be conducted.

ResNET34 architecture can be divided into three parts. The first part is residual blocks with skip connections. These residual blocks contain convolution, batch normalization, and ReLU activation function. Between each of these residual blocks are skip connections. The number of residual blocks defines what type of ResNET architecture it is. When increasing the number of residual blocks, the model is able to get more fine-grained features, but on the other hand, it needs bigger computational resources. Global average pooling is located after residual blocks. It is used for reducing of output's spatial dimension to 1x1, which is then fed to the last layer. The last layer is the fully connected layer, which is used for probabilities and prediction extraction. This model is used for the classification of cells and output labels for single cells.

Based on visualization of *class activation map (CAM)* [1], which can be seen in fig. 7, it is evident that the neural network model is sometimes not focusing on important areas. In fig. 7a can be seen CAM of the correct prediction and in fig. 7b can be seen CAM of the incorrect prediction. From the images, it can be observed that the model sometimes encounters difficulties in determining which pixels to focus on. Because of this problem, a custom attention module is added to ResNET34 architecture. This module is implemented into the architecture after the convolution layers extract weights from the segmentation mask, providing additional information to the model. This adds to the model information about the position of important cells and indicates which pixels are important.

## 3.5 Training process

The system contains segmentation and classification modules, which need to be trained. Both models are exclusively trained on the CoNIC dataset, which contains colon histology images. Therefore, because of the same type of data in the dataset, it could be used for *transfer learning*. The training process for each of them is slightly different. The segmentation model is trained with dice loss function and Adam optimizer for 100 epochs. On the other hand, the classification model is trained with cross entropy loss and with Adam optimizer, which was trained for 20 epochs. Both of the trainings were performed on Tesla V100-SXM2-32GB with 8 GPU.

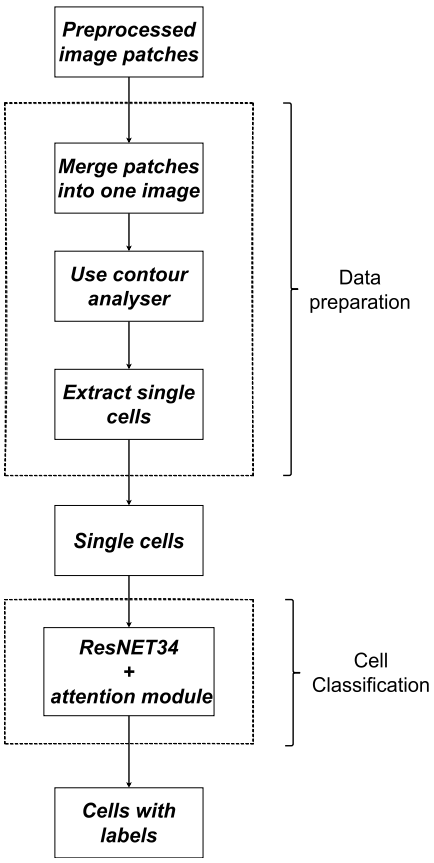



Figure 6: Components of the classification module

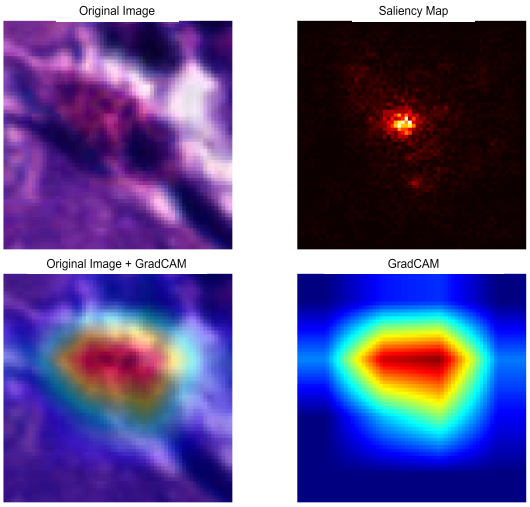
## 3.6 Evaluation methods

Evaluation methods used in the proposed solution can be separated into three parts: quantitative evaluation, visual inspection, and validation by pathologists.

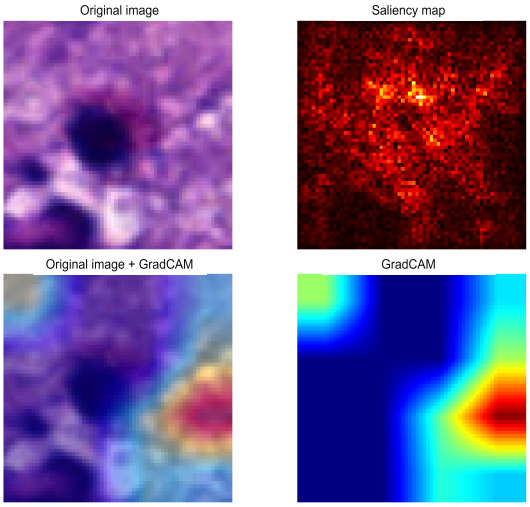
Numeric metrics evaluation can be divided into the segmentation and classification parts, as each task requires distinct metrics for evaluation. For segmentation, *dice score*, *intersection over union*, and *F1-score* are used. On the other hand, classification uses *precision*, *recall*, and *accuracy*. These numeric metrics interpret performance precisely with easily interpretable numeric values.

Visualization, on the other hand, represents graph plots of the training process or exact generated segmentation masks. These can be used as simple methods whether the model is performing well. Another visualization method used in the paper is class activation mapping, which is used for classification. This one is useful to check if the trained neural network is correctly focusing on the important and the most representative areas of the image.

The last evaluation metric used is direct validation by a pathologist. Pathologists review the generated predicted mask and provide feedback on its accuracy and quality.




(a) Class activation mapping of a correct prediction




(b) Class activation mapping of an incorrect prediction

Figure 7: Class activation mapping (CAM)

While this approach is the most informative and useful, its execution frequency is limited by the availability of pathologists' time. The evaluation process can be segmented into two tests: qualitative and quantitative. The first test involves feature extraction for qualitative analysis, where pathologists explain the most significant features during cell annotation. The outcome of this test provides information about important features. The second test is active learning. In this evaluation method, a proposed solution can be also directly integrated into the annotation application, expediting the validation process. For optimal results, specific cells that pose challenges for the classification model need to be provided to the pathologist in an iterative process. The outcome of this approach is a refined predicted mask for our model, which can subsequently be retrained on this problematic data.

# 4 Results

The results of experiments can be categorized into two parts, one is numerical metrics results and the second one is visualization of results. A combination of these two gives the best insight into the evaluation of computer vision solutions, especially the proposed one.

Numeric value metrics provide results of two different modules. These modules are previously mentioned segmentation and classification modules. Results of the segmentation module can be seen in a table 1. These results provide the difference in dice IoU and F1-score metrics between CoNIC dataset and the custom dataset. The *custom dataset* is made up of converted raw data, directly from the pathologist. Data is in a format of *ndpi*, which was converted and used to extract around *600 annotated cells*. These cells are then used as previously mentioned custom dataset. Metrics shown in the table 1 indicate promising results both on CoNIC and on the custom dataset. The fact that the model is trained only on CoNIC and yet, we can achieve sufficient results without additional training on custom data is great. The second evaluated module is the classification module. The results of this module also provide calculated metrics over CoNIC and custom dataset. The metrics used for this experiment are accuracy, precision, and recall. Based on these results, it can be observed that the model performance is not optimal, but it is satisfactory considering the limited availability of annotated data. Increasing of accuracy will be part of the active learning implementation. On the other hand, the filtration module cannot be evaluated like this because only a pathologist can say if cells in the filtration module are correctly removed.

| Segmentation task | | | |
|---|---|---|---|
| Dataset | Dice | IOU | F1-score |
| CoNIC | 84,18% | 72,69% | 90,08% |
| Custom Data | 75,22% | 66,74% | 79,13% |

Table 1: Results of segmentation module

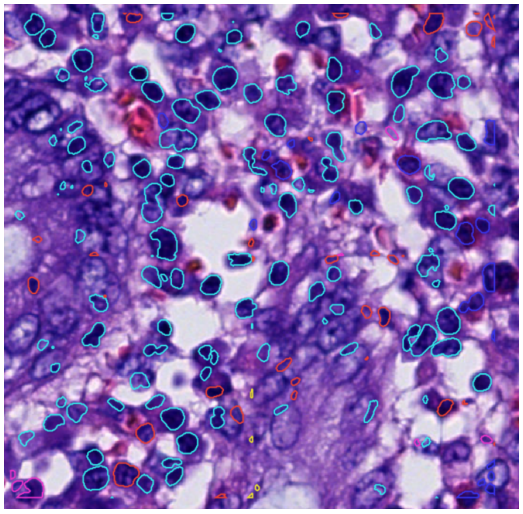
| Classification task | | | |
|---|---|---|---|
| Dataset | Accuracy | Precision | Recall |
| CoNIC | 93,00% | 93,00% | 93,50% |
| Custom Data | 72,00% | 66,00% | 70,05% |

Table 2: Results of classification module

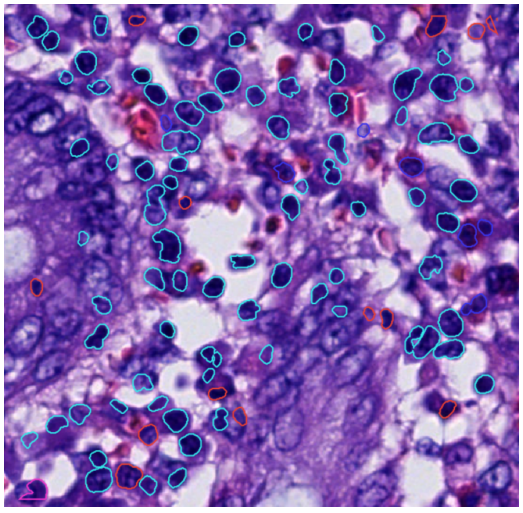
The second result of the visualization of data can be seen in fig. 8. Prediction is performed on histology images never seen by the model. These images have been provided directly by a pathologist. In a comparison of prediction *without filter* in fig. 8a and prediction *with filter* in fig. 8b, it can be observed, that adding of filtration module filtered a significant number of irrelevant cells. When focusing especially on small and oblong cells on a left and

bottom part of the image, it can be seen that in fig. 8b is much less of these cells then in fig. 8a. This filtration is provided with only filters and thresholds, which can be later modified. Modifications can be done anytime without changing neural network model architectures or retraining of models. The advantage of visualization of data is that it is more interpretative. Few results of prediction masks were evaluated directly by pathologists who noted good results, especially with *neutrophils*. These neutrophils are important in the diagnosis of Crohn's disease and Ulcerative Colitis, which makes them one of the most important types of cells for our solution.

The proposed solution of filtration architecture shows that the system can be modified by changing the values of *thresholds* in specific filters. This creates the required modifiability of the system by the user. It shows that it is possible to handle the creation of a prediction mask easily and fast, which was exactly the objective of the research.



(a) Prediction mask without filter module



(b) Prediction mask with filter module

Figure 8: Predicted masks

## 5 Conclusions

Due to the differences and complexity inherent in histology tasks, it is crucial to develop a system that is user-friendly and capable of accommodating modifications by pathologists. It is important in situations when a pathologist need to find cells based on their features. Sometimes pathologists need to find all specific features in areas of histology image. In such scenarios, challenges arise when the prediction system generates a mask with a large number of cells. Lots of the cells are irrelevant for pathologists who need to search in them for specific cells. The proposed solution helps exactly with this. The contribution shows in results that the difference with and without using of filtration module is significant. The filtration module can focus on *specific features based on filters*. What's more, it is designed to be easily expandable by more filters, based on pathologist needs. Tests have demonstrated that merely *adjusting thresholds* can result in significant changes to prediction masks. With a correct setting of threshold and correct knowledge, it is able to extract individual classes of cells, which are sometimes hard to find. The second advantage that comes with this solution is the fastening of the validation process. Directly after the segmentation module, the filtration module removes lots of contours, which significantly decreases the number of single cells prepared for classification. What is more, it can be beneficial for some pathologists, who have problems with using neural networks as black boxes. When they obtain the feeling that they can modify the model by themself, it can build greater trust in the system.

## 6 Future work

Implementation of a filtration module into the system has shown advantages in the classification task of single cells. However, pathologists need to be able to use this system. This involves implementing the system into the *custom annotation tool*, which is currently in development at the faculty. Following the implementation of the system in the annotation tool, the next intriguing approach is to adapt the system for *active learning*. This active learning will be based on output from the pathologist directly using a custom annotation tool. This could help the model with a better understanding of data and enhance the performance of the system. Also, the implementation of *new types of filters* and new methods of feature extractions into the system might be beneficial to try. By offering pathologists a wider array of filters, the system becomes more versatile and adaptable, ultimately enhancing its utility and efficacy in medical image analysis.

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