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Automatic Tumor Cellularity Measurement: AI-Based Pipeline for Multi-Organ Pathology Imaging

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Abstract. Tumor Cellularity (TC) is an important metric for assessing organ tumor burden. However, manual cell counting is not feasible due to large volumes of pathology images and inconsistent measurements between pathologists. The PAIP 2023 Challenge aimed to solve this problem using AI. The challenge presented two main obstacles: the need to evaluate pancreas-trained data for effective use in the colon, and the common miscounting of clustered cells in segmentation results. To address these, we proposed a novel pipeline. It included channel normalization, which standardizes RGB values to ensure consistent model performance across different organs. By introducing CacoX, a specialized model for accurate cell segmentation, we used Coordinate Attention Gates for accurate cell localization and non-local learning. Finally, the implementation of a watershed algorithm allowed the automatic separation of clustered cells. This approach secured 3rd place in the PAIP 2023 Challenge with an impressive ICC score of **95.69%**.

Keywords. Deep Learning, Segmentation, Pathological Imaging

1. Introduction

Tumor Cellularity (TC) is a critical metric used to assess residual tumor burden in various organs such as breast and colon [1]. TC refers to the ratio of tumor cell numbers to the total cell count. It is crucial to accurately identify and classify each cell to count them. However, manual counting and analysis of cells in pathology images is impractical in clinical settings due to the large number of cells and the inconsistent in counts between pathologists. Using AI to automatically and accurately count cells and calculate TC values has the potential to significantly reduce the workload of pathologists. With this goal in mind, the PAIP 2023 Challenge [2] was organized as part of the ISBI 2023.

To accurately count cells, it's essential to precisely locate each cell. Utilizing AI to detect cells in digital pathology images has been the subject of extensive research [1, 3], with problems being addressed using detection models like YOLO [4]. However, these models face issues such as failing to accurately recognize cells at the edges of patches and mistaking clustered cells for a single cell. This problem is particularly prevalent

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when a large number of tumor cells are present, as they tend to cluster together and are often identified as one.

To overcome this, we propose a pipeline that employs a cell segmentation approach to identify cells at the pixel level, using the watershed algorithm to naturally separate clustered cell segmentation results. In this process, we introduced a model optimized for the segmentation of small objects like cells, named CacoX (Coordinate Attention with ConvNext), and utilized channel normalization techniques to enhance model compatibility across different organs. As a result, we achieved **3rd place in the PAIP 2023 Challenge** (Team Hasukmin) with a final ICC score of **95.69%.**

2. PAIP 2023 Datasets

The dataset configuration for the PAIP 2023 Challenge [2] is outlined in Table 1. The dataset includes segmentation annotations for tumor and non-tumor nuclei, all provided in PNG format at a resolution of 1024 X 1024 pixels. Image patches are also provided in PNG format (1024 X 1024 pixels) and were extracted from whole slide images (WSI) scanned with Leica Aperio AT2 or GT450 and stained with Haematoxylin and Eosin.

The training set consists of 50 pancreas images and 3 colon images. A subset of 10 pancreas images is used for the validation phase. In the testing phase, which determines the final results, the dataset consists of 20 pancreas images and 20 colon images. The pancreas data was captured at either 20x or 40x magnification, while the colon data was captured at 40x magnification.

Consequently, this competition highlights the challenge of transferring the knowledge gained from pancreatic data to achieve accurate results in colon data.

TC values from 0 to 100 (without decimals) are provided in an Excel file, along with Microns Per Pixel (MPP) information. And annotations are only available for the training data.

Table 1. Dataset composition of the PAIP 2023 Challenge

Dataset	Pancreas	Colon	Total
Training	50	3	53
Validation	10	-	10
Testing	20	20	40
Total	80	23	103

3. Methods

Our proposed method (depicted in Figure 1) consisted of the following steps. To improve multi-organ compatibility, we start with image pre-processing using channel normalization. Next, our newly proposed network, CacoX, makes predictions for tumor cells and non-tumor cells. These predictions are subjected to the Watershed algorithm [5] to separate clustered cell prediction results, allowing cell counting. The TC is then calculated based on the cell counts.

3.1. Channel Normalization

Colouration in pathology images can vary due to factors such as scanner differences, staining variations or organ-specific characteristics. We've implemented the channel normalization introduced in the NeurIPS 2022 Cellseg Challenge [3] to effectively correct color variations in pathology images.

This calculates percentiles and rescaling for each RGB channel. We applied this normalization to all training data. During inference, the input images are automatically normalized before being fed into the model.

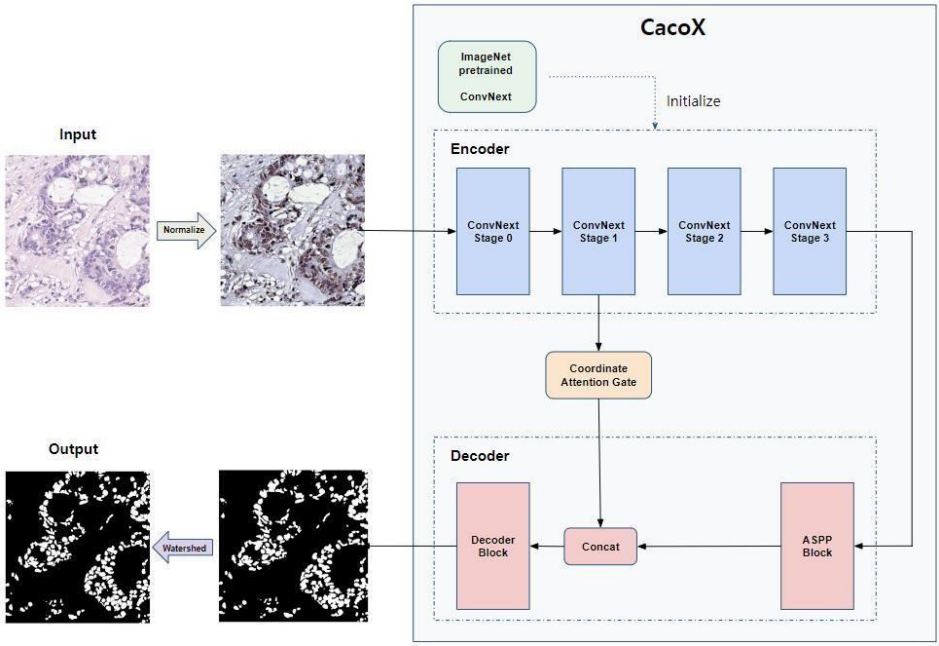

Figure 1. The architecture of the proposed pipeline

3.2. Cell Segmentation using CacoX Network

We propose CacoX, a novel network designed for precise cell segmentation. This network is composed of a U-Net [6] architecture, with a ConvNext [7] encoder pre-trained on ImageNet [8] and a decoder structured from DeepLabV3+ [9]. When experimenting with the provided dataset, we observed that ConvNext [7] encoder delivered the most impressive performance in cell segmentation. And Pre-training the encoder on ImageNet provided better initialization for improved results.

We improved this network structure by integrating the Coordinate Attention Gate [10] into the skip-pathway to effectively acquire a global context information by non-local learning. Through average pooling along both the x and y axes, we represent each coordinate axis as two features, which are then concatenated. By pooling global information along each coordinate axis and fusing them together, the concatenated feature captures the overall information of the image. This global information is

subsequently employed for learning via convolutional operations. As a result, Coordinate Attention Gate provides the global context that lead to extract small object like cell.

3.3. Watershed Algorithm to separate clustered cell prediction

While CacoX is effective at accurately predicting cells in pathology images, accurately counting these cells in the segmentation map is another significant challenge. Due to the close proximity of cells, the predicted results often appear clustered, and counting them as a single entity is a common source of inaccuracy. To address this, we introduced an automatic separation approach using the watershed algorithm [5].

The algorithm uses concepts from watershed hydrology to process the image. The key idea of the algorithm is to identify 'separate basins' corresponding to each object or region in the image. First, local minima in the image are identified and treated as starting points for each object. Then, as "water" is allowed to fill the image, the separate basins are expanded, effectively delineating boundaries between different objects and segmenting the image.

We chose the superior algorithm of ImageJ over the one provided by the cv2 package. We separated the predicted cell results by class and applied the watershed algorithm to the images of each class to effectively separate closely adjacent cells (Figure 2).

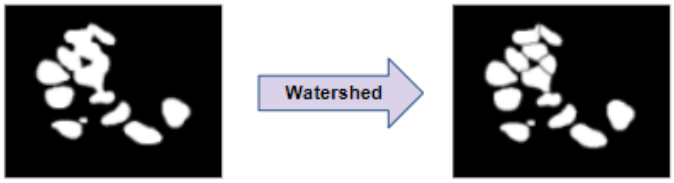

Figure 2. Result of Watershed Algorithm.

3.4. Calculate TC

The CacoX network prediction results are separated by class, clustered cells are separated using the Watershed algorithm [5], and the cells are counted. Using ImageJ's [11] Watershed algorithm, not only is cell separation automated, but the separated cells are also counted. This feature streamlines the cell counting process and allows automatic quantification of cell counts for both tumor and non-tumor classes.TC values are then calculated using the following formula:

$$TC\ (\%) = \frac{Number\ of\ tumor\ cell\ nuclei}{Total\ number\ of\ cell\ nuclei} \tag{1}$$

4. Results

We were unable to run any additional experiments after the competition, as the test dataset was not made available. The experiment results are based on the leaderboard results provided by the challenge. The challenge rankings were determined by the Intraclass Correlation Value (ICC) score [2], a metric that indicates the similarity of

observations within the same group. The ICC score ranges from 0 to 1, with a higher score indicating greater similarity between group observations. In leaderboard, considering that our proposed CacoX achieved an ICC score of 87.57% on the validation dataset without the Watershed algorithm, and later achieved an ICC score of **95.69%** in the testing phase after applying the Watershed algorithm, this suggests a significant impact. As a result, in the final test phase of the PAIP 2023 Challenge [2], we secured 3rd place against 1st a marginal difference of 1.95%.

5. Discussion

To overcome the issue of color variations, we utilized Channel Normalization. However, more sophisticated research has been conducted to address these issues. We expect that employing new research could potentially yield higher performance than our proposed Channel Normalization.

6. Conclusions

We presented new perspectives on automated cell counting using AI. This experiment is expected to help catalyze further advances in various future applications or research.

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