Local and global feature aggregation for accurate epithelial cell classification using graph attention mechanisms in histopathology images

Author name(s) withheld EMAIL(S) WITHHELD
Address withheld

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Abstract

In digital pathology, cell-level tissue analyses are widely used to better understand tissue composition and structure. Publicly available datasets and models for cell detection and classification in colorectal cancer exist but lack the differentiation of normal and malignant epithelial cells that are important to perform prior to any downstream cell-based analysis. This classification task is particularly difficult due to the high intra-class variability of neoplastic cells. To tackle this, we present here a new method that uses graph-based node classification to take advantage of both local cell features and global tissue architecture to perform accurate epithelial cell classification. The proposed method demonstrated excellent performance on F1 score (PanNuke: 1.0, TCGA: 0.98) and performed significantly better than conventional computer vision methods (PanNuke: 0.99, TCGA: 0.92).

Keywords: digital pathology, malignant epithelial cells, cell classification, cell-based graphs, node classification, graph attention, graph clustering

1. Introduction

In the field of digital pathology, recent advances in deep learning have led to the development of cell-level tissue analyses from hematoxylin and eosin (H&E) stained slides, opening the possibility to conduct accurate quantitative analyses on whole slide images (WSI) that might not be possible in a clinical scenario with a microscopic assessment of slides. In the era of personalized medicine, understanding the precise composition and the spatial histologic features of the tissues is a key point to improve our understanding of tumor behavior (Baxi et al., 2022). Automated cell detection and classification on H&E WSI can be used to explore specific cell-cell interactions and global tissue structure and organization (Ahmedt-Aristizabal et al., 2022; Pati et al., 2022).

Although publicly available models and datasets for cell classification in colorectal cancer exist, these often lack the differentiation between normal and malignant epithelial cells, as they are usually grouped together as a single "epithelial" class (Graham et al., 2019, 2021). For downstream cell-based analyses, however, the distinction between these two epithelial categories is of great importance. This task is particularly challenging because of the high morphological heterogeneity of neoplastic epithelial cells. Nevertheless, when looking at the overall epithelial gland architecture, the differentiation between normal and malignant glands is easier to make. Taking advantage of this, we propose a new method based on the aggregation of local cell morphology features together with surrounding gland structure information to learn accurate epithelial-cell level classification from H&E images.

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2. Material and Methods

A subset of patches from the Lizard dataset (Graham et al., 2021) was selected that solely contain either normal or malignant epithelial cells. Additional patches (1000×1000px) from scanned colorectal tissue slides from the Institute's cohort and from TCGA were retrieved and annotated for epithelial cells by experts. The TCGA and PanNuke (a subset of Lizard) patches were kept as test data while the remaining patches were used for training and validation. All patches were extracted at 20X magnification (0.5μm/pixel). The dataset description can be found in Table 1.

First, epithelial cell tiles (128×128px) were extracted around the cell centroids. ResNet18 (He et al., 2016) and ViT16 (Dosovitskiy et al., 2021) were trained for normal versus malignant cell classification as baseline. Since ResNet18 showed a better performance than ViT16 on the TCGA data but a similar one on PanNuke, we opted to use ResNet18 for further analysis (see Table 2).

Epithelial cell graphs were then built on the training patches. Nodes were individual epithelial cells. Node features were extracted from the last hidden layer of the previously trained ResNet18 to describe the cell morphology. Then, edges were added to connect the nodes (epithelial cells) using Delaunay triangulation (Delaunay, 1934). Different graph neural network (GNN) architectures were evaluated and optimized for node classification, exploring the following parameters: number of message passing (MP) layers [2, 3, 4], size of the MP layers [64, 128, 256, 512] for the most common MP functions [GCN, GraphSage, GIN, GATv2] (Kipf and Welling, 2017; Hamilton et al., 2018; Xu et al., 2019; Brody et al., 2022). The edge length threshold was also optimized. All parameters were optimized using a 5-fold cross-validation.

A final post-processing (pp) step was applied to smooth the graph predictions. As individual epithelial glands are expected to be composed of either normal or malignant epithelial cells, single glands were isolated into subgraphs using a short edge threshold of 30px(15μm). For every single epithelial gland, a median filter was applied to all cells in that gland to get the final cell class. Each step is illustrated in Figure 1.

3. Results

The best-performing method was a GNN composed of 4 GATv2 layers of size 256. As shown in Table 2, the cell classification significantly improved when using the GAT GCN model ($p < 0.05$), outperforming the CNN baselines. The final clustering and filtering further improved the cell classification.

datasets	**epithelial type**	**#patches**	**#cells**	**average #cells/patch**
train data (Lizard + Institute)	normal	68	66,034	797
	malignant	107	119,013	1093
test data (PanNuke + TCGA)	normal	14	9,301	664
	malignant	17	12,335	726
	both	5	normal: 3,450	690
			malignant: 5,362	1,072

Table 1: Overview of the number of patches and cell types in the different subsets.

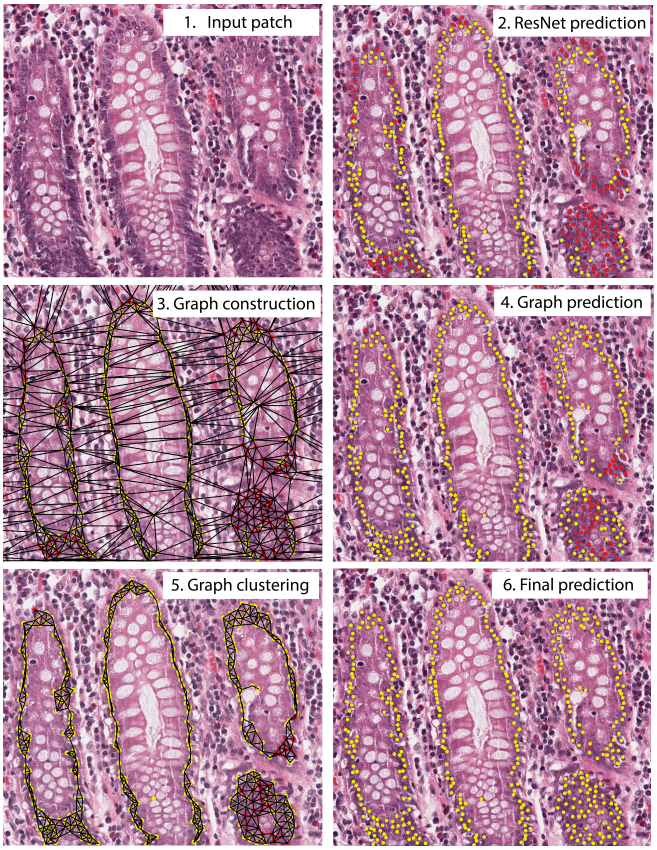

Figure 1: Epithelial cell classification pipeline on a normal epithelial tissue example from TCGA testset. Red dots indicate epithelial cells classified as malignant and yellow dots cells classified as normal. Black lines indicate edges between connected cells when applying graph classification and graph clustering.

Table 2: Weighted F1 score.

Model	PanNuke	TCGA
ViT16	99.099	89.469
ResNet18	99.039	91.716
GAT	99.423	95.074
GAT + pp	**100.0**	**97.847**

4. Discussion and Conclusion

We show that graphs allow us to effectively capture the structural context around the cell of interest for accurate epithelial cell classification in colorectal H&E images. The proposed graph-based model is highly accurate and can be easily applied in addition to any other model detecting epithelial cells to further differentiate between normal and malignant cells.

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