TPMIL: Trainable Prototype Enhanced Multiple Instance Learning for Whole Slide Image Classification

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Abstract

Digital pathology based on whole slide images (WSIs) plays a key role in cancer diagnosis and clinical practice. Due to the high resolution of the WSI and the unavailability of patch-level annotations, WSI classification is usually formulated as a weakly supervised problem, which relies on multiple instance learning (MIL) based on patches of a WSI. In this paper, we aim to learn an optimal patch-level feature space by integrating prototype learning with MIL. To this end, we develop a Trainable Prototype enhanced deep MIL (TPMIL) framework for weakly supervised WSI classification. In contrast to the conventional methods which rely on a certain number of selected patches for feature space refinement, we softly cluster all the instances by allocating them to their corresponding prototypes. Additionally, our method is able to reveal the correlations between different tumor subtypes through distances between corresponding trained prototypes. More importantly, TPMIL also enables to provide a more accurate interpretability based on the distance of the instances from the trained prototypes which serves as an alternative to the conventional attention score-based interpretability. We test our method on two WSI datasets and it achieves a new SOTA. GitHub repository: ***https://github.com/LitaoYang-Jet/TPMIL***

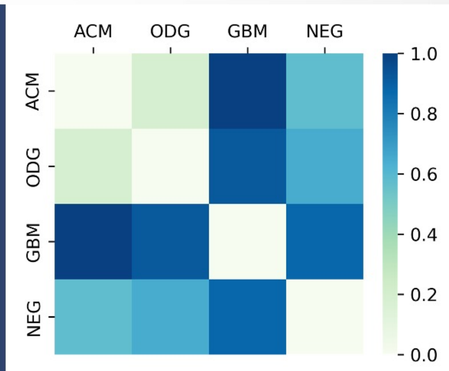

Fig. 2. The distance matrix of TCGA Brain Tumor prototypes after training. Darker color indicates higher distance and lower correlation. (NEG = Negative; ACM = Astrocytoma; ODG = Oligodendroglioma; GBM = Glioblastoma)

Interpretation:

- The distance between ACM and ODG is markedly lower than their distance to GBM, as both ACM and ODG are lower grade gliomas (LGG) whereas GBM is higher grade glioma (HGG), which may have distinct morphological features, such as necrosis and pseudo palisading cells around necrosis.
- NEG is closer to ACM and ODG compared to GBM. This might be attributable to the fact that GBM has more diverse morphological features, and that the NEG prototype accounts for a much smaller proportion of tissues in the WSI.

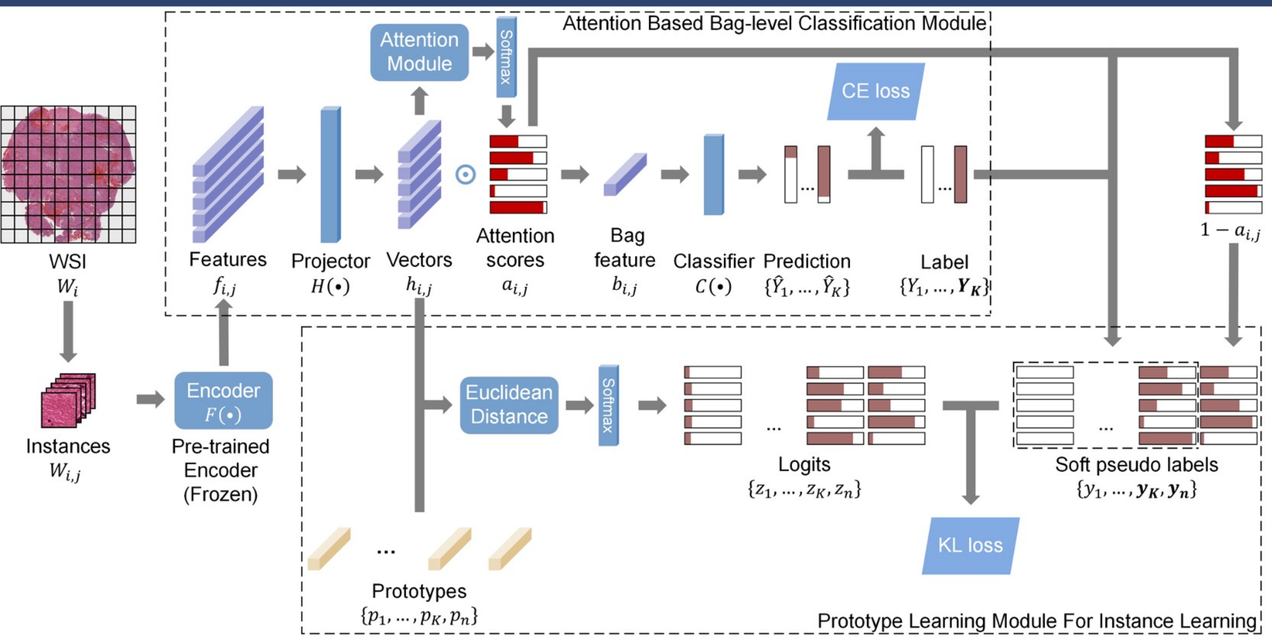

Fig. 1. Overview of TPMIL. The Prototype Learning Module will help to learn an optimal distribution of instances.

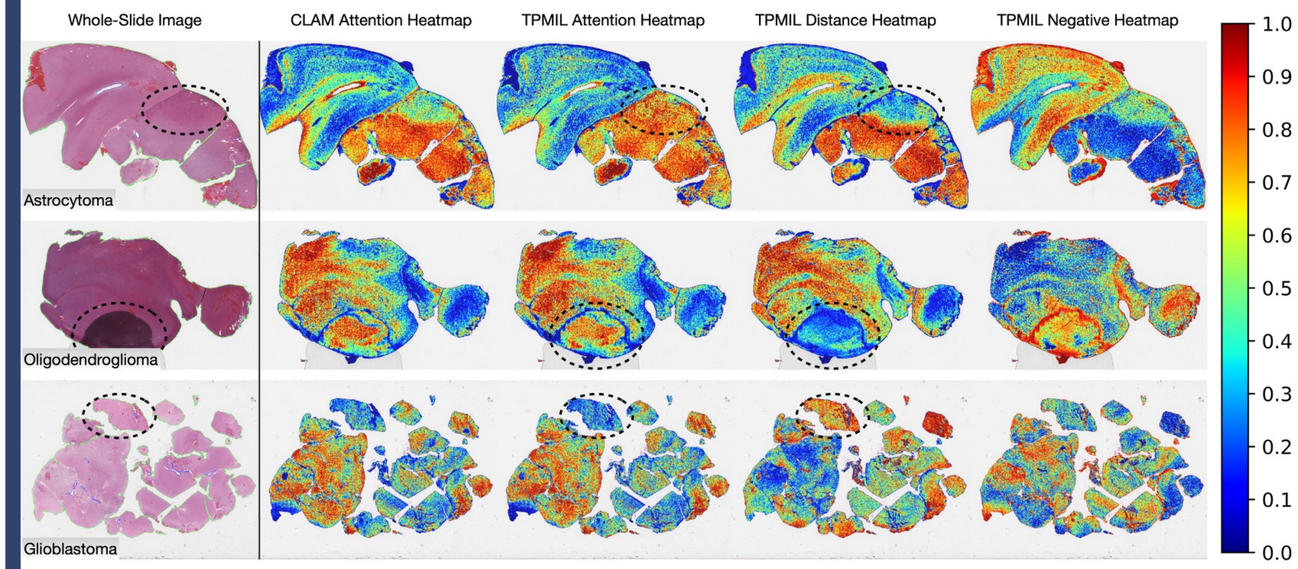

Fig. 3. Interpretability and visualization of heatmaps for brain tumor WSI classification

Dataset	Method	AUC	ACC
TCGA Brain Tumor dataset	Baseline	0.9393	0.8162
	CLAM	0.9394	0.8188
	TPMIL(Ours)	**0.9417**	**0.8316**
TCGA Lung Cancer dataset	Baseline	0.9783	0.9381
	DSMIL	0.9633	0.9190
	DGMIL	0.9702	0.9200
	CLAM	0.9788	0.9286
	TPMIL(Ours)	**0.9799**	**0.9427**

Table. 1. Comparison of performances on TCGA Brain Tumor dataset and TCGA Lung Cancer dataset

Interpretation:

- In Astrocytoma and Oligodendroglioma, the circled regions are artefacts which should not be considered as positively related to the diagnosis, and it can be seen that Distance Heatmap is more robust to artefacts as it doesn't give a dark red color. In Glioblastoma, the circled region is a necrotic area which is a diagnostic feature of glioblastoma and Distance Heatmap successfully captured it by indicating the dark red color.
- In contrast to the distance heatmap from the predicted tumor type, the negative prototype distance heatmaps highlight the regions that are close to the negative prototype, including normal brain tissues and blood vessels, among different artefacts such as the overstained regions in the Oligodendroglioma WSI.

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