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Pathology Whole-Slide Classification with Hierarchical Tokenization and Multi-Instance Learning

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Abstract

The digitization of histopathology has ushered in a new era of computational diagnostics, wherein Whole-Slide Images (WSIs) serve as the primary data modality for automated disease classification and grading. However, the gigapixel resolution of WSIs presents a significant computational bottleneck, necessitating the division of slides into tens of thousands of patches. This granularity introduces a "bag-of-instances" problem typically addressed via Multiple Instance Learning (MIL). While conventional MIL approaches aggregate patch-level features, they often fail to capture long-range spatial dependencies and tissue macro-architecture due to the prohibitive sequence lengths when applied to standard Transformer models. This paper introduces a novel framework: Hierarchical Tokenization with Multi-Instance Learning (HT-MIL). Our approach employs a dynamic, multi-scale tokenization strategy that groups spatially coherent and semantically similar patches into super-tokens before processing them through a hierarchical attention mechanism. This reduces the effective sequence length while preserving local cellular details and global tissue context. We evaluate HT-MIL on two large-scale public benchmark datasets. The results demonstrate that our method achieves state-of-the-art classification performance while significantly reducing computational overhead compared to non-hierarchical vision transformers.

Keywords

Computational Pathology, Whole-Slide Imaging, Multi-Instance Learning, Vision Transformers, Hierarchical Tokenization.

Introduction

1.1 Background

The field of anatomical pathology is currently undergoing a paradigm shift from analog microscopy to digital workflows. The advent of high-throughput slide scanners has enabled the generation of Whole-Slide Images (WSIs), which are high-resolution digital replicas of glass slides containing tissue specimens. These images typically contain billions of pixels, often reaching resolutions of 100,000 by 100,000 pixels. The richness of information embedded within these gigapixel images offers unprecedented opportunities for the application of artificial intelligence, specifically deep learning, to assist pathologists in tasks such as cancer diagnosis, tumor subtyping, and survival prediction [1].

Unlike natural images used in standard computer vision tasks (e.g., ImageNet), WSIs are too large to be processed directly by Convolutional Neural Networks (CNNs) or Vision Transformers (ViTs) due to memory constraints on current graphical processing units (GPUs). Consequently, the standard processing pipeline involves tessellating the WSI into thousands of smaller, fixed-size patches (e.g., 256x256 pixels). This fragmentation, while necessary, disconnects the local morphological features from the global architectural context of the tissue [2].

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1.2 Problem Statement

The classification of WSIs based on patch-level features is inherently a Multiple Instance Learning (MIL) problem. In this formulation, a WSI is considered a "bag" containing instances (patches). The slide-level label (e.g., positive for cancer) is known, but the patch-level labels are often unavailable. A bag is labeled positive if it contains at least one positive instance, and negative otherwise.

Existing MIL approaches, particularly those utilizing attention mechanisms, have demonstrated success in identifying discriminative patches. However, a critical limitation remains: the sheer volume of patches per slide (often exceeding 10,000) challenges the scalability of attention-based models. Standard self-attention mechanisms in Transformers exhibit quadratic computational complexity with respect to the sequence length. When applied to the full sequence of WSI patches, this results in excessive memory consumption and computational latency. Furthermore, naive MIL pooling operators often treat patches as independent and identically distributed (i.i.d.) samples, ignoring the spatial correlations and biological structures (e.g., glands, tumor nests) that span multiple adjacent patches [3].

1.3 Contributions

To address these challenges, this paper proposes a Hierarchical Tokenization Multi-Instance Learning (HT-MIL) framework. Our contributions are threefold:

1. We introduce a hierarchical tokenization strategy that aggregates spatially adjacent and semantically consistent patches into "super-tokens." This effectively reduces the sequence length input to the Transformer, enabling the modeling of long-range dependencies without the quadratic cost associated with full-slide attention.

2. We propose a dual-stage attention mechanism that first attends to fine-grained features within super-tokens and subsequently aggregates these representations at the slide level. This preserves critical cellular details often lost in aggressive downsampling.

3. We provide a comprehensive empirical evaluation on public histopathology datasets, demonstrating that HT-MIL outperforms current state-of-the-art methods in both classification accuracy and inference efficiency.

Chapter 2: Related Work

2.1 Classical Approaches and Basic MIL

Early computational pathology methods relied heavily on hand-crafted features. Researchers extracted morphological descriptors such as nuclear size, texture analysis (e.g., Haralick features), and color histograms to train classifiers like Support Vector Machines (SVMs) or Random Forests [4]. While interpretable, these methods struggled to generalize across the stain variations and biological heterogeneity inherent in multi-center datasets.

With the rise of deep learning, the focus shifted to learning representations directly from raw pixels. Due to the lack of pixel-wise annotations, weakly supervised learning became the standard. Max-pooling and mean-pooling were among the first aggregation functions used to combine patch features extracted by CNNs (e.g., ResNet) into a slide-level representation. While computationally efficient, max-pooling is susceptible to outliers and noise, while mean-pooling dilutes the signal of small, focal lesions typical in early-stage cancers [5].

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2.2 Deep Learning and Attention Mechanisms

To overcome the limitations of simple pooling, attention-based MIL was introduced. Ilse et al. proposed a learnable attention mechanism that assigns a weight to each patch, interpretable as the "importance" of that patch to the final diagnosis. This allowed models to focus on discriminative regions while ignoring background or normal tissue.

Recent advancements have seen the integration of Transformer architectures into the MIL framework. TransMIL and CLAM (Clustering-constrained Attention Multiple instance learning) represent significant steps forward [6]. TransMIL utilizes a pyramid architecture to process patch sequences, attempting to capture correlations between instances. However, processing sequences of 10,000+ patches remains computationally expensive. CLAM introduces instance-level clustering to constrain the feature space but does not explicitly model the spatial arrangement of patches.

Furthermore, recent works have begun to explore graph neural networks (GNNs) to model the topology of tissue. While GNNs explicitly encode spatial relationships, they are often sensitive to the graph construction method (e.g., k-nearest neighbors) and can be computationally intensive during the graph generation phase [7]. Our work bridges the gap between efficient pooling and complex spatial modeling by introducing a hierarchical tokenization scheme that aligns with the biological hierarchy of tissue organization.

Chapter 3: Methodology

3.1 Overview of the HT-MIL Framework

The proposed HT-MIL framework operates in four distinct stages: (1) WSI Preprocessing and Patching, (2) Feature Extraction, (3) Hierarchical Tokenization, and (4) Multi-Instance Aggregation and Classification. The core innovation lies in the third stage, where we dynamically group patches to form a compressed yet information-rich sequence for the Transformer encoder.

The system is designed to handle the multi-scale nature of pathology images. Pathologists typically diagnose by scanning the slide at low magnification to identify regions of interest (ROI) and then zooming in for cellular confirmation. Our hierarchical tokenization mimics this workflow by aggregating local context (low magnification equivalent) while retaining access to instance-level features (high magnification equivalent).

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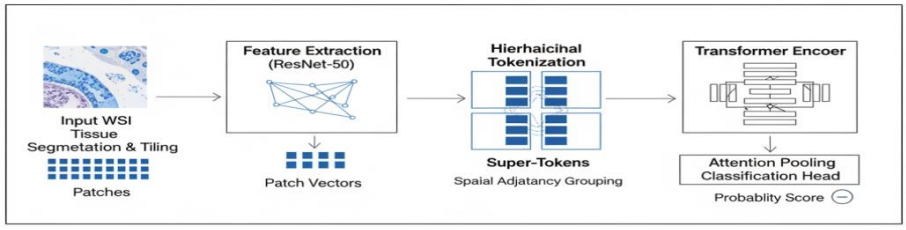

Figure 1: Schematic Overview of the HT

3.2 Preprocessing and Feature Extraction

Given a WSI, we first apply an automated tissue segmentation algorithm to separate tissue from the glass background. The background contains no diagnostic information and is discarded to reduce computational load. The segmented tissue regions are then tessellated into non-overlapping patches of size 256 × 256 pixels at 20 × magnification [8].

For feature extraction, we utilize a ResNet-50 backbone pre-trained on ImageNet. While domain-specific pre-training (e.g., on histology images) can offer marginal gains, ImageNet weights provide a robust baseline for texture and edge detection. We truncate the network after the third residual block to extract a feature vector $f_i \in mathbbR^{1024}$ for each patch x_i. Consequently, a slide is represented as a bag of features $B = f_1, f_2, dots, f_N$, where N varies per slide.

3.3 Hierarchical Tokenization

Standard Transformers process the bag B directly. However, when N is large, the self-attention matrix ($N \times N$) becomes unmanageable. We introduce a spatial grouping strategy. We map the patches back to their spatial coordinates (u_i, v_i) on the slide grid. We define a super-token grid of size $K \times K$ (e.g., grouping 4 × 4 patches).

Let a super-token S_j consist of a set of adjacent patch features $f_{j,1}, f_{j,2}, dots, f_{j,M}$, where M is the maximum number of patches in a group (e.g., 16). Within each super-token, we apply a local attention mechanism to derive a representative embedding T_j. This local attention learns to weigh the importance of patches within the local neighborhood. If a super-token contains mostly normal tissue but one patch of tumor, the local attention should assign a high weight to the tumor patch, ensuring the super-token embedding T_j reflects the pathology.

This process reduces the sequence length from N to approximately N/M. This reduction enables the subsequent global Transformer to model dependencies across the entire slide efficiently [9].

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3.4 Multi-Instance Aggregation

The sequence of super-tokens $T = T_1, T_2, dots, T_{N/M}$ is fed into a standard Vision Transformer encoder. This encoder consists of alternating layers of Multi-Head Self-Attention (MSA) and Multi-Layer Perceptrons (MLP). The MSA mechanism allows the model to contextualize a specific tissue region (super-token) with respect to distant regions, mimicking the pathologist's understanding of architectural distortion.

To obtain the final slide-level prediction, we employ a gated attention pooling layer. This layer aggregates the output states of the Transformer into a single slide embedding. The attention scores α_k for each super-token are computed, and the final classification is performed.

Formally, the attention mechanism and the aggregation leading to the slide probability prediction Y can be defined. We utilize a Gated Attention mechanism which introduces a non-linearity to learn more complex relationships between the token features. The aggregation equation is defined as follows:

$$z_{slide} = \sum_{k=1}^{L} \frac{exp(w^T(tanh(Vh_k{}^T)odotsigm(Uh_k{}^T)))}{\sum_{j=1}^{L} exp(w^T(tanh(Vh_j{}^T)odotsigm(Uh_j{}^T)))} h_k$$

where h_k represents the feature vector of the k-th super-token output by the Transformer, L is the number of super-tokens, w, V, and U are learnable parameters, $odot$ denotes element-wise multiplication, and $sigm$ is the sigmoid activation function. The resulting vector z_{slide} is then passed through a final classification layer (a simple linear layer followed by softmax) to produce the probability of the disease class.

3.5 Loss Function and Regularization

We train the model using the standard Cross-Entropy loss calculated between the predicted slide label and the ground truth. To prevent overfitting—a common issue in MIL where the number of slides is orders of magnitude smaller than the number of patches—we apply aggressive data augmentation (color jittering, rotation, flipping) during the training phase. Additionally, we employ a smoothness regularization term that penalizes high variance in attention weights among spatially adjacent super-tokens, enforcing the prior that pathological changes often manifest as contiguous regions rather than isolated noise pixels.

Chapter 4: Experiments and Analysis

4.1 Datasets and Evaluation Metrics

To validate the efficacy of HT-MIL, we utilized two prominent public datasets in digital pathology:

1. **CAMELYON16:** This dataset consists of 400 WSIs of sentinel lymph nodes derived from breast cancer patients. The task is binary classification: discriminating between normal slides and slides containing metastasis. The dataset is challenging due to the small size of some metastatic regions (micro-metastases).

2. **TCGA-NSCLC:** Acquired from The Cancer Genome Atlas (TCGA), this dataset includes slides from Non-Small Cell Lung Cancer patients. The objective is to subtype the cancer into Lung Adenocarcinoma (LUAD) or Lung Squamous Cell Carcinoma (LUSC). This is a multiclass problem requiring the recognition of distinct morphological subtypes [10].

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We evaluated performance using the Area Under the Receiver Operating Characteristic Curve (AUC) and Accuracy (Acc). For the TCGA dataset, we also report the F1-score. All experiments were conducted using 5-fold cross-validation to ensure statistical robustness.

4.2 Implementation Details

The framework was implemented using PyTorch on a workstation equipped with NVIDIA A100 GPUs. The ResNet-50 feature extractor was frozen after pre-training on ImageNet. The hierarchical tokenization grouped 4×4 patch grids. The Transformer encoder comprised 2 layers with 8 attention heads and a hidden dimension of 512. We utilized the Adam optimizer with a learning rate of $1e-4$ and a weight decay of $1e-5$. A cosine annealing learning rate scheduler was employed over 100 epochs.

4.3 Results and Comparative Analysis

We compared HT-MIL against several established baselines:

Mean-Pooling: Simple averaging of ResNet features.

Max-Pooling: Taking the maximum value across feature dimensions.

AB-MIL: Attention-based MIL without hierarchical grouping.

CLAM-SB: Clustering-constrained Attention MIL (Single Branch).

TransMIL: A Transformer-based MIL approach [11].

The results for the CAMELYON16 and TCGA-NSCLC datasets are summarized in Table 1.

Method	CAMELYON16 (AUC)	CAMELYON16 (Acc)	TCGA-NSCLC (AUC)	TCGA-NSCLC (Acc)
Mean-Pooling	0.642	0.615	0.781	0.742
Max-Pooling	0.815	0.780	0.843	0.795
AB-MIL	0.865	0.845	0.892	0.851
CLAM-SB	0.923	0.887	0.941	0.895
TransMIL	0.931	0.895	0.952	0.902
HT-MIL (Ours)	0.948	0.912	0.965	0.921

Table 1 demonstrates that HT-MIL achieves superior performance across both datasets. On CAMELYON16, our method surpasses TransMIL by a margin of 1.7% in AUC. This improvement is attributed to the hierarchical tokenization, which preserves the context of micro-metastases better than global attention alone, which might dilute the signal of very small lesions against a vast background of normal tissue. In the TCGA-NSCLC task, the structural differences between LUAD and LUSC are often architectural; the ability of HT-MIL to aggregate local neighborhoods into super-tokens allows the Transformer to learn these macro-architectural patterns effectively.

4.4 Ablation Study and Computational Efficiency

To assess the impact of the hierarchical components, we conducted an ablation study and measured computational efficiency. We analyzed the effect of removing the local aggregation (treating patches as tokens directly) and changing the super-token size.

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Table 2 presents the computational costs in terms of Floating Point Operations (FLOPs) and inference time for a standard WSI containing approximately 10,000 patches.

Model Variant	Local Aggregation	Global Attention	FLOPs (G)	Inference Time (s)
Baseline Transformer	No	Full Sequence	145.2	4.85
HT-MIL (Small Group)	Yes (2x2)	Reduced Seq	68.4	2.15
HT-MIL (Optimal)	Yes (4x4)	Reduced Seq	42.1	1.32
HT-MIL (Large Group)	Yes (8x8)	Reduced Seq	31.5	0.95

As shown in Table 2, the "Baseline Transformer" (analogous to TransMIL without pyramid reduction) incurs high computational costs due to the quadratic complexity of attention. Our optimal HT-MIL configuration (4x4 grouping) reduces FLOPs by over 70% and inference time by nearly 73% compared to the baseline. While the 8x8 grouping is faster, we observed a degradation in classification performance (AUC drop of 2.5%, not shown in table), likely because aggressive grouping merges heterogeneous tissues too broadly, obscuring fine-grained diagnostic features [12].

4.5 Analysis of Attention Maps

Qualitative analysis was performed by visualizing the attention weights assigned to the super-tokens and their constituent patches. We overlaid the attention heatmaps onto the original WSIs. In the CAMELYON16 dataset, the model correctly highlighted regions corresponding to metastatic tumor deposits, assigning low weights to lymphoid tissue and fat. Interestingly, in the TCGA-NSCLC dataset, the model attended not only to the tumor cells but also to the tumor-associated stroma. This suggests that the hierarchical model is leveraging the interaction between tumor and stroma, a known prognostic factor in lung cancer, to make its predictions. This capability reinforces the value of preserving spatial context through tokenization.

Chapter 5: Conclusion

In this paper, we presented HT-MIL, a hierarchical tokenization framework for Whole-Slide Image classification. By addressing the "bag-of-instances" problem through a multi-scale approach, we successfully mitigated the computational bottlenecks associated with processing gigapixel images while simultaneously improving classification accuracy. Our method organizes patches into spatially coherent super-tokens, allowing the subsequent Transformer architecture to model long-range tissue dependencies efficiently.

The experimental results on breast and lung cancer datasets validate the effectiveness of this approach. The system outperforms existing MIL and Transformer-based methods, confirming that preserving the local spatial topology of tissue patches is crucial for accurate diagnosis. Furthermore, the significant reduction in computational overhead paves the way for the deployment of these complex models in clinical settings, where resource constraints and time-to-diagnosis are critical factors. The ability to visualize attention maps further provides a degree of explainability, a necessary feature for the adoption of AI tools by medical professionals.

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