# CLASS-M: Adaptive stain separation-based contrastive learning with pseudo-labeling for histopathological image classification

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## Introduction

- Histopathological image classification is an important task in medical image analysis.
- Achieving a highly accurate model requires a substantial amount of training labels, demanding significant time and effort from human experts.
- We propose a semi-supervised patch-level histopathological image classification model: Contrastive Learning with Adaptive Stain Separation and MixUp (CLASS-M), that does not require extensively labeled datasets.
- We apply our novel contrastive learning on Hematoxylin images and Eosin images after performing slide-level stain separation. We also use pseudo-labeling with MixUp to further improve classification accuracy.
- We provide the new Utah clear cell renal cell carcinoma (ccRCC) dataset which has 49 WSIs with patch-level labels, and patch-level labels for 150 WSIs from the TCGA ccRCC dataset.
- We test various state-of-the-art semi-supervised learning and self-supervised learning methods on both ccRCC datasets and demonstrate that CLASS-M outperforms other state-of-the-art models.

## Model design

Contrastive loss:

$$\mathcal{L}_{c.t.}(x_i) = \max\left(\| f_H(x_i) - f_E(x_i) \|_2 - \| f_H(x_i) - f_E(x_k) \|_2 + m, 0\right)$$

Pseudo-labeling:

$$\bar{y}_i = \frac{1}{K} \sum_{1 \le k \le K} P_{model}(x_{i,k}),\ x_i \in U$$

$$y_i = sharpen(\bar{y}_i, T), \text{where } sharpen(y, T)_{(c)} = \frac{{y_{(c)}}^{\frac{1}{T}}}{\sum_{j=1}^{C} {y_{(j)}}^{\frac{1}{T}}}$$

MixUp samples:

$$x' = \lambda' x_i + (1 - \lambda') x_j$$

$$y' = \lambda' y_i + (1 - \lambda') y_j$$

Total loss:

$$\mathcal{L} = \underbrace{\sum_{x_i \in L'} \frac{y_i \log \hat{y}_i}{|L'|}}_{\text{Label prediction loss (labeled set)}} + \lambda_{U'} \underbrace{\sum_{x_i \in U'} \frac{\| y_i - \hat{y}_i \|_2{}^2}{C|U'|}}_{\text{Label prediction loss (unlabeled set)}} + \lambda_C \underbrace{\sum_{x_i \in L' \cup U'} \mathcal{L}_{c.t.}(x_i)}_{\text{Contrastive loss (labeled + unlabeled set)}}$$

- Paper link:
  arxiv.org/abs/2312.06978
- Code link:
  github.com/BzhangURU/Paper_CLASS-M/tree/main

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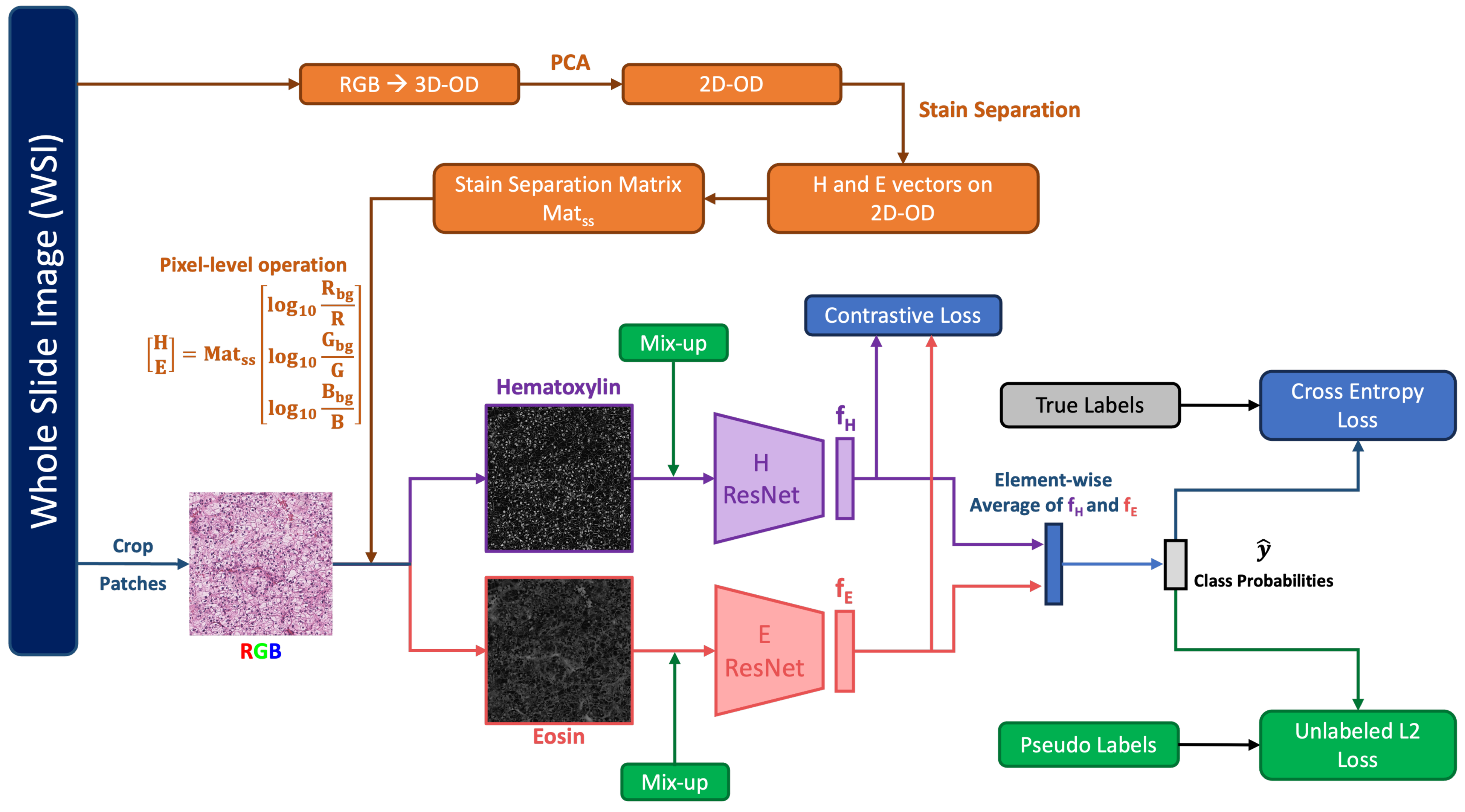
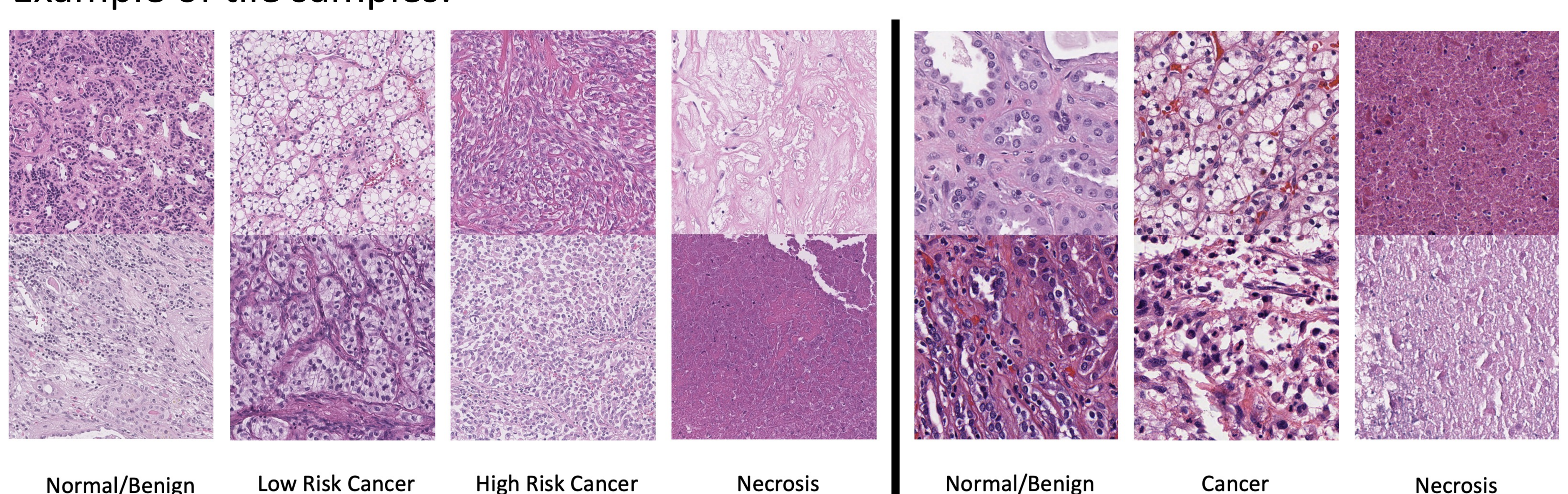



## Experiment settings

Example of tile samples:




(a) Tiles from Utah ccRCC dataset

(b) Tiles from TCGA ccRCC dataset

Details of experiment settings:

Utah ccRCC dataset

| Number of tiles | Normal/Benign | Low Risk Cancer | High Risk Cancer | Necrosis | Unlabeled |
|---|---|---|---|---|---|
| Training | 28,497 | 2,044 | 2,522 | 4,115 | 171,113 |
| Validation | 5,472 | 416 | 334 | 2,495 | |
| Test | 7,263 | 598 | 389 | 924 | |

TCGA ccRCC dataset

| Number of tiles | Normal/Benign | Cancer | Necrosis | Unlabeled |
|---|---|---|---|---|
| Training | 84,578 | 180,471 | 7,932 | 1,373,684 |
| Validation | 19,638 | 79,382 | 1,301 | |
| Test | 15,323 | 62,565 | 6,168 | |

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## Experiment results

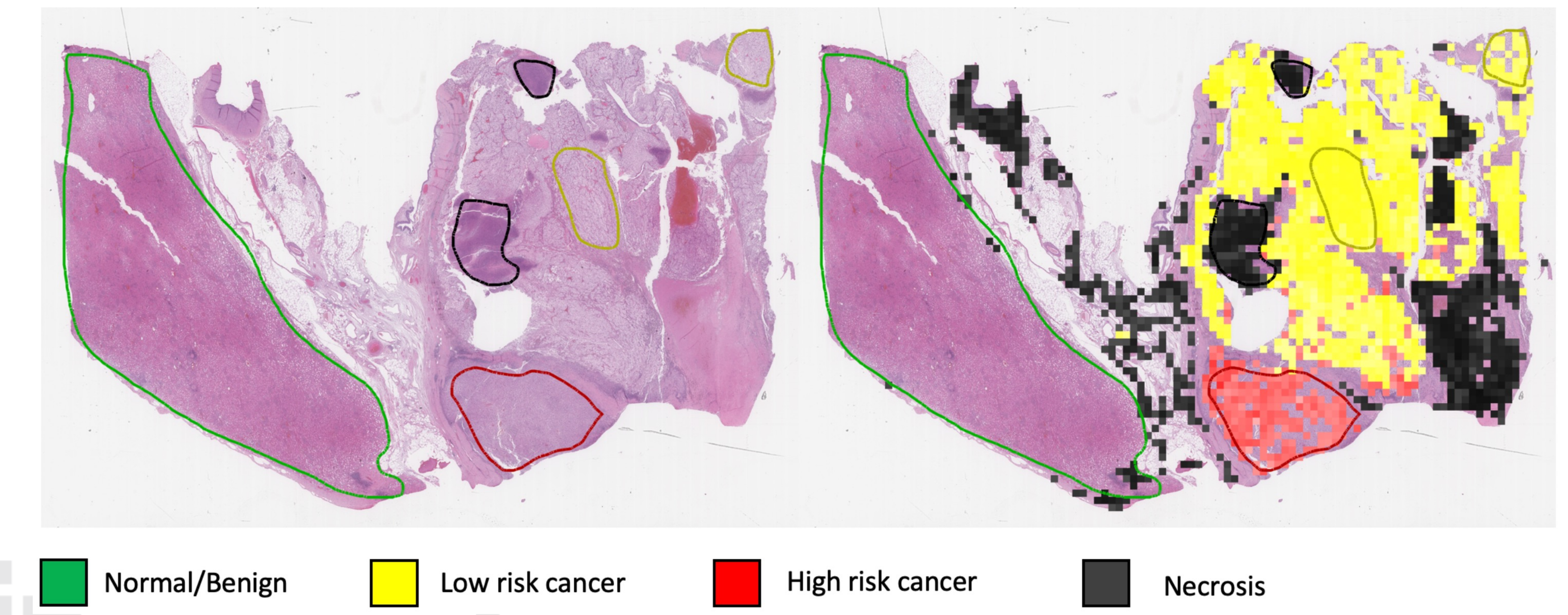
Model comparisons:

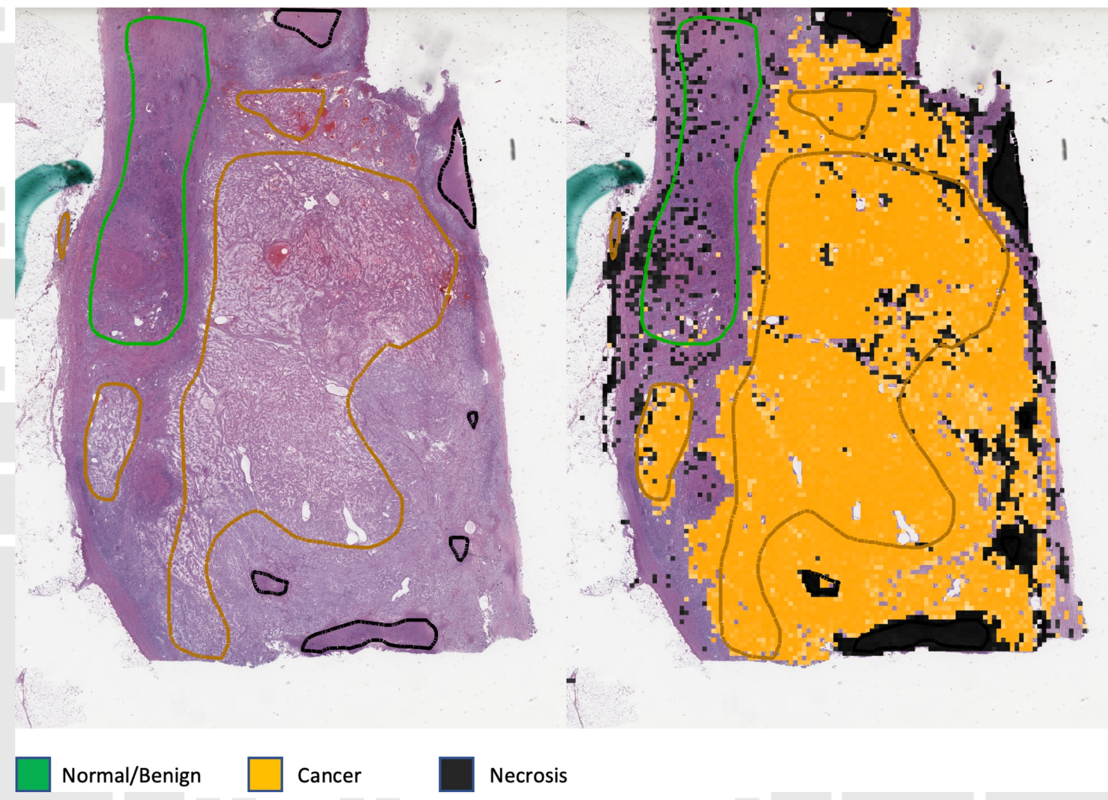
| | Models | Test accuracy (Utah) | Test accuracy (TCGA) |
|---|---|---|---|
| **Supervised** (labeled images only) | ResNet | $88.85 \pm 2.66\%$ | $72.11 \pm 0.41\%$ |
| | ViT | $84.69 \pm 1.33\%$ | $73.50 \pm 0.94\%$ |
| **Self-supervised** (pre-trained on labeled and unlabeled images) | Barlow Twins | $93.42 \pm 0.43\%$ | $77.42 \pm 4.92\%$ |
| | SwAV | $93.87 \pm 0.59\%$ | $82.17 \pm 0.05\%$ |
| | MoCo v3 | $93.91 \pm 0.60\%$ | $78.82 \pm 0.93\%$ |
| | ViT-DINO | $90.53 \pm 1.13\%$ | $79.76 \pm 2.15\%$ |
| **Semi-supervised** (trained on labeled and unlabeled images) | FixMatch | $91.58 \pm 0.65\%$ | $83.34 \pm 2.53\%$ |
| | MixMatch | $92.94 \pm 1.54\%$ | $88.35 \pm 1.39\%$ |
| | CLASS | $94.92 \pm 0.67\%$ | $83.06 \pm 0.47\%$ |
| | CLASS-M | $\mathbf{95.35 \pm 0.46\%}$ | $\mathbf{92.13 \pm 0.89\%}$ |

Ablation studies:

| Contrastive Loss | Augmentations on original RGB | Adaptive stain separation | Pseudo labeling with MixUp | Two views | Test accuracy (Utah) | Test accuracy (TCGA) |
|---|---|---|---|---|---|---|
| ✓ | ✓ | ✓ | ✓ | H/E | **95.35** $\pm$ **0.46** % | **92.13** $\pm$ **0.89** % |
| | ✓ | ✓ | ✓ | H/E | 90.92 $\pm$ 1.18 % | 89.70 $\pm$ 0.77 % |
| ✓ | | ✓ | ✓ | H/E | 94.41 $\pm$ 0.44 % | 91.21 $\pm$ 2.05 % |
| ✓ | ✓ | | ✓ | H/E | 93.97 $\pm$ 0.40 % | 90.97 $\pm$ 1.86 % |
| ✓ | ✓ | ✓ | | H/E | 94.92 $\pm$ 0.67 % | 83.06 $\pm$ 0.47 % |
| ✓ | ✓ | ✓ | | Red/Green | 90.75 $\pm$ 0.13 % | 81.14 $\pm$ 0.34 % |
| ✓ | ✓ | ✓ | | Red/Blue | 89.06 $\pm$ 0.54 % | 80.14 $\pm$ 2.66 % |
| ✓ | ✓ | ✓ | | Green/Blue | 83.43 $\pm$ 3.63 % | 80.25 $\pm$ 1.15 % |
| | ✓ | ✓ | | H/E | 84.57 $\pm$ 2.40 % | 74.46 $\pm$ 2.03 % |
| ✓ | | ✓ | | H/E | 94.99 $\pm$ 0.58 % | 82.78 $\pm$ 1.10 % |
| ✓ | ✓ | | | H/E | 92.43 $\pm$ 0.34 % | 79.89 $\pm$ 0.69 % |
| ✓ | | | | H/E | 91.53 $\pm$ 1.52 % | 75.67 $\pm$ 1.76 % |

Visualization of CLASS-M model prediction on slides:

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