Stain Based Contrastive Co-training for Histopathological Image Analysis

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Introduction

- Deep learning models are widely used in histopathology image classification.
- Expert annotation at tile level for providing labels in model training has very high cost and is infeasible beyond a small number of whole slide images (WSIs).
- Semi-supervised learning (SSL) utilizes unlabeled data in training combined with limited amount of labeled data.
- Co-training approach to SSL achieves excellent results when multiple conditionally independent views of each sample are available, and each view is able to support accurate classification on its own.
- We explored if H&E slides can be color deconvoluted to Hematoxylin (H) and Eosin (E) stain images to fulfill co-training's view requirements.
- A novel contrastive co-training model with H and E views was tested on a clear cell renal cell carcinoma (ccRCC) dataset and a prostate cancer dataset.
- Our co-training model always had the best performance over other state-of-the art SSL methods in both datasets, including consistency regularization, MixMatch and FixMatch.

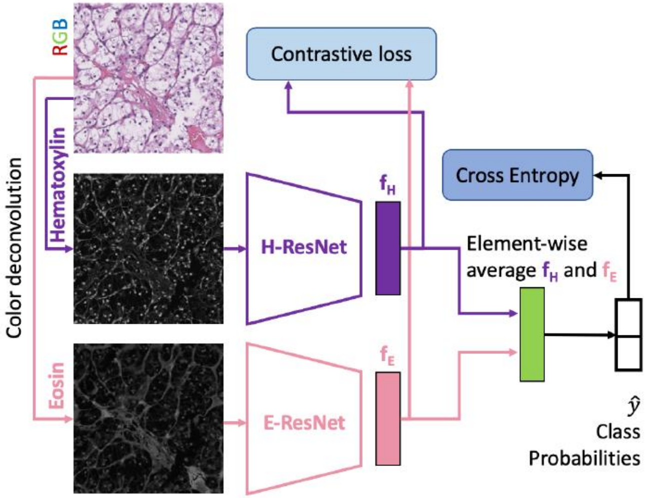
Model design

Stain separation: $\begin{bmatrix} H \\ E \end{bmatrix} = \begin{bmatrix} 1.838 & 0.034 & -0.760 \\ -1.373 & 0.772 & 1.215 \end{bmatrix} \begin{bmatrix} \log_{10} 255/R \\ \log_{10} 255/G \\ \log_{10} 255/B \end{bmatrix}$

Contrastive loss:

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

Total loss: $\mathcal{L} = \sum_{x_j \in L} y_j \log \hat{y}_j + \lambda \sum_{x_i \in L \cup U} \mathcal{L}_{c.t.}(x_i)$



Experiment settings

- In clear cell renal cell carcinoma (ccRCC) dataset*:
  - ✓ Histologic growth pattern (HGP) tiles were cropped from expert annotated polygons from 53 WSIs.
  - ✓ Tiles from same patient are only in same set.
  - ✓ 10% tiles set as labeled data from training polygons in SSL.
  - ✓ Performed nested vs. diffuse (non-nested) classification and compared with other SSL models.
- In prostate cancer dataset*:
  - ✓ 5% tiles set as labeled data from training polygons in SSL.
  - ✓ Performed benign vs. cancer classification and compared with other SSL models.
- Randomly selected labeled data 5 times to calculate mean and standard deviation of classification accuracies.

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Experiment results

ccRCC Model	Test Accuracy	Prostate Model	Test Accuracy
100% label RGB ResNet	$84.8 \pm 2.4\%$	100% label RGB ResNet	$77.5 \pm 2.5\%$
100% label H/E co-train	$\mathbf{92.0 \pm 2.6\%}$	100% label H/E co-train	$\mathbf{79.1 \pm 2.0\%}$
10% label RGB ResNet	$76.9 \pm 5.9\%$	5% label RGB ResNet	$73.4 \pm 1.0\%$
10% label RGB consis	$86.8 \pm 3.3\%$	5% label RGB consis	$74.7 \pm 1.3\%$
10% label RGB MixMatch	$85.9 \pm 5.7\%$	5% label RGB MixMatch	$73.7 \pm 5.0\%$
10% label RGB FixMatch	$88.3 \pm 3.8\%$	5% label RGB FixMatch	$78.2 \pm 3.8\%$
10% label H/E co-train	$\mathbf{92.3 \pm 2.1\%}$	5% label H/E co-train	$\mathbf{78.7 \pm 1.9\%}$

H-only and E-only models' test accuracy for the ccRCC dataset to show each view (H or E) can do classification alone:

Model	Accuracy	Model	Accuracy
100% label H ResNet	$79.4 \pm 3.7\%$	10% label H ResNet	$73.5 \pm 4.0\%$
100% label E ResNet	$94.0 \pm 1.4\%$	10% label E ResNet	$82.3 \pm 7.0\%$

Coefficient of determination(R^2) of image mapping between various channels on ccRCC validation set to show independence between channels:

Experiments	R^2 value	Experiments	R^2 value
$H \Rightarrow E$	0.5223	$E \Rightarrow H$	0.4613
$R \Rightarrow G$	0.8464	$G \Rightarrow R$	0.7833
$R \Rightarrow B$	0.8207	$B \Rightarrow R$	0.7713
$G \Rightarrow B$	0.8522	$B \Rightarrow G$	0.8824

Ablation study on ccRCC (Test set accuracy of ResNet and co-training models taking only 2 channels from RGB as input with 10% labeled data in training):

Model	Accuracy	Model	Accuracy	Model	Accuracy
RB ResNet	$77.5 \pm 6.6\%$	RG ResNet	$80.2 \pm 6.4\%$	GB ResNet	$78.4 \pm 9.7\%$
R/B co-train	$78.2 \pm 4.5\%$	R/G co-train	$79.8 \pm 5.6\%$	G/B co-train	$76.6 \pm 7.3\%$

Conclusion

- The experiments show that our model outperforms all other tested state-of-the-art semi-supervised learning methods in both datasets.
- The experiments prove that the benefit of our model is due to contrastive co-training loss on hidden features combined with more independent H and E view selection.