Classifying whole slide images based on Tumor Infiltrating Lymphocytes using deep learning

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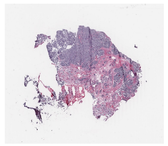
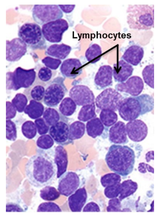
INTRODUCTION

- **Whole slide images (WSI)** are digital representations of tissue sections.
- **Tumor infiltrating Lymphocytes (TILs)** are useful in treating breast cancer patients.
- TILs have prognostic and predictive importance[1, 2].
- TIL score quantifies the # TILs in the tissue.
- Manual TIL scoring is ambiguous.
- Has led to an increasing interest on computational TIL scoring.



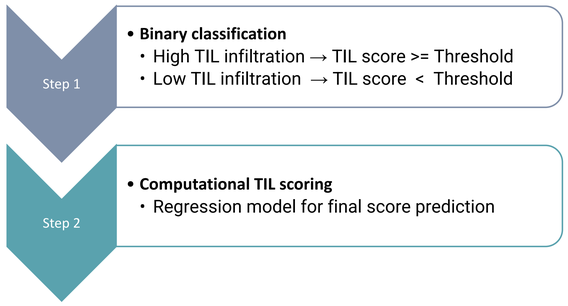
Example of a WSI
(Scaled down by 32 times)



Lymphocyte cells [3]

OBJECTIVES

- Develop a model for computational TIL scoring in WSIs.
- We break down our problem of computational TIL scoring into two steps:

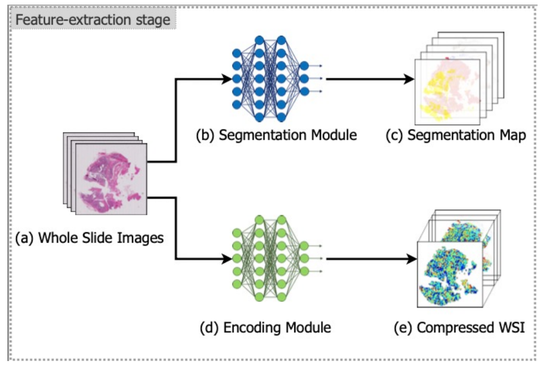


- In step 1, we look at our task from the classification domain
  - We do so by defining a threshold to break the WSIs into two classes as high vs low TIL infiltration.
- In step 2, we achieve our final goal, and move from the classification to the regression domain to predict the numerical TIL score.

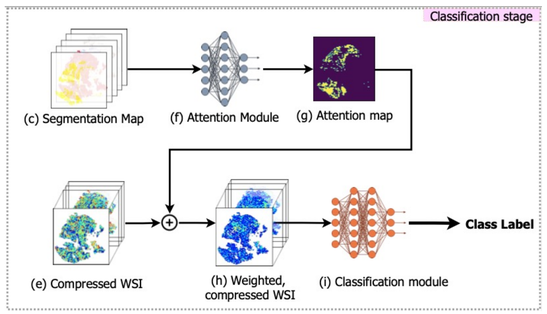
METHOD

A pipeline for **step 1** to distinguish WSIs with High TIL Infiltration vs WSIs with Low TIL Infiltration.

STAGE 1: Compress information in WSI in two ways[4,5].



STAGE 2: Use the outputs from stage 1 to train final classifier.



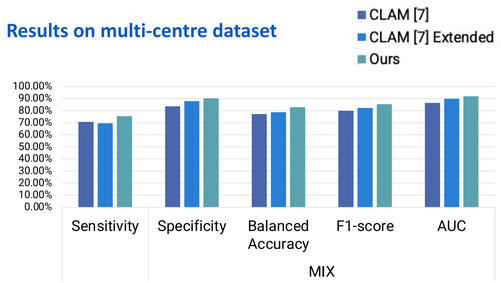
MATERIALS

- We train and validate our pipeline on 3 in-house datasets (CLEOPATRA, MARIANNE, FINHER) and 1 public dataset (TCGA - The Cancer Genome Atlas).
- TCGA, contains only frozen tissues sections whereas all other datasets contain only Formalin-Fixed Paraffin-Embedded(FFPE) tissues.
  - Usually, frozen tissues are more challenging to process in neural networks.
  - So, we test our pipeline on both these formats.
- TIL threshold is defined based on **disease stage** to divide the slides into the two classes of interest.
- Experiments carried out on:
  - Multi-centre combined dataset
  - Each Independent centre specific dataset

RESULTS

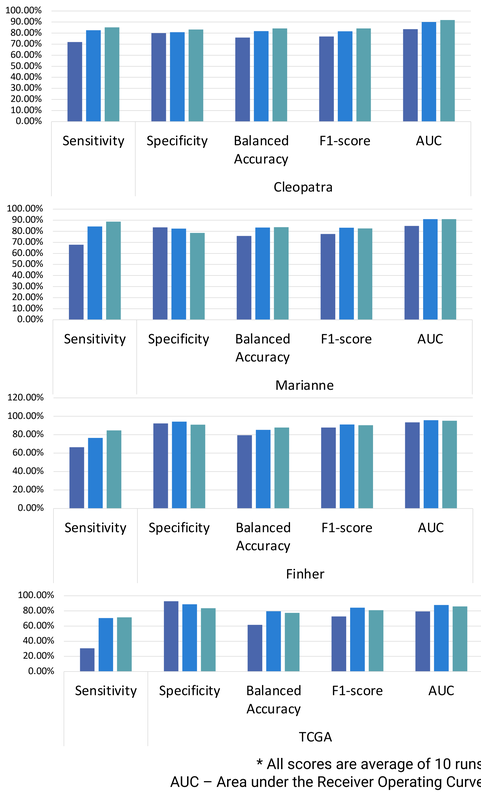
- Evaluated our pipeline against an existing method in literature known as CLAM[6].
- We also proposed and implemented an extension of CLAM, termed as CLAM extended.

Results on multi-centre dataset



- We achieved highest performance in all five metrics comparing favorably to existing methods and extensions of them.

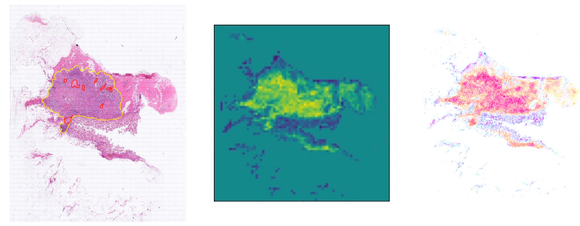
Results on Independent centre specific dataset



* All scores are average of 10 runs
AUC – Area under the Receiver Operating Curve

- In each dataset, we were able to obtain highest performance in sensitivity.
- In terms of balanced accuracy, we obtained highest performance in all datasets except in TCGA.
- However, our model was still able to maintain a more balanced performance for sensitivity and specificity in TCGA.

Visualizing model attention maps



Human annotation of tumor (yellow) and stroma (regions) on original WSI from the CLEOPATRA test dataset.

Attention map generated by our final model.

Heatmap overlay of the generated attention map on top of the original WSI.

CONCLUSIONS

- Low-cost, segmentation information can assist in the binary TIL classification task.
- Segmentation model is not fine-tuned on our dataset which introduces an inevitable error gap.
- For frozen tissue datasets, CLAM extended method is a better choice.

FUTURE WORK

- Moving from binary classification task (step 1) to regression task (step 2).
- Experimenting clinical applicability.

REFERENCES

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