Improving the Accuracy of Melanoma Diagnosis from Whole Slide Images

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Outline

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- Preliminary Work
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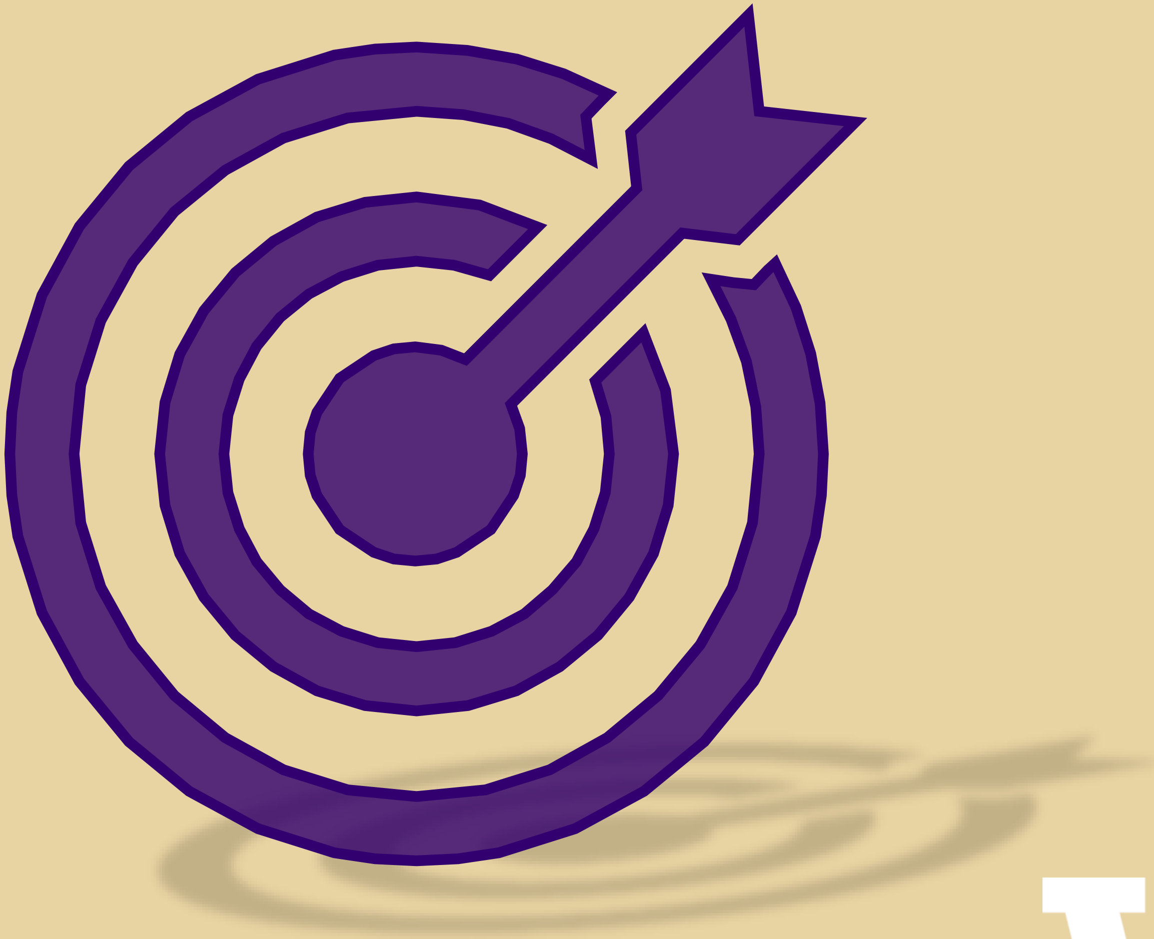
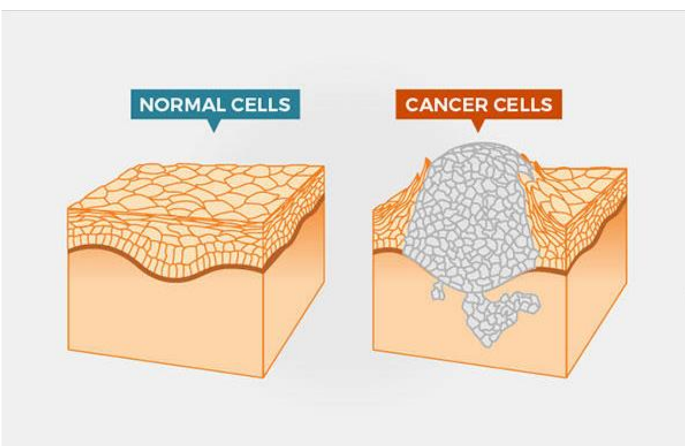
  2. Segmentation using Coarse and Sparse Annotation
- Future work

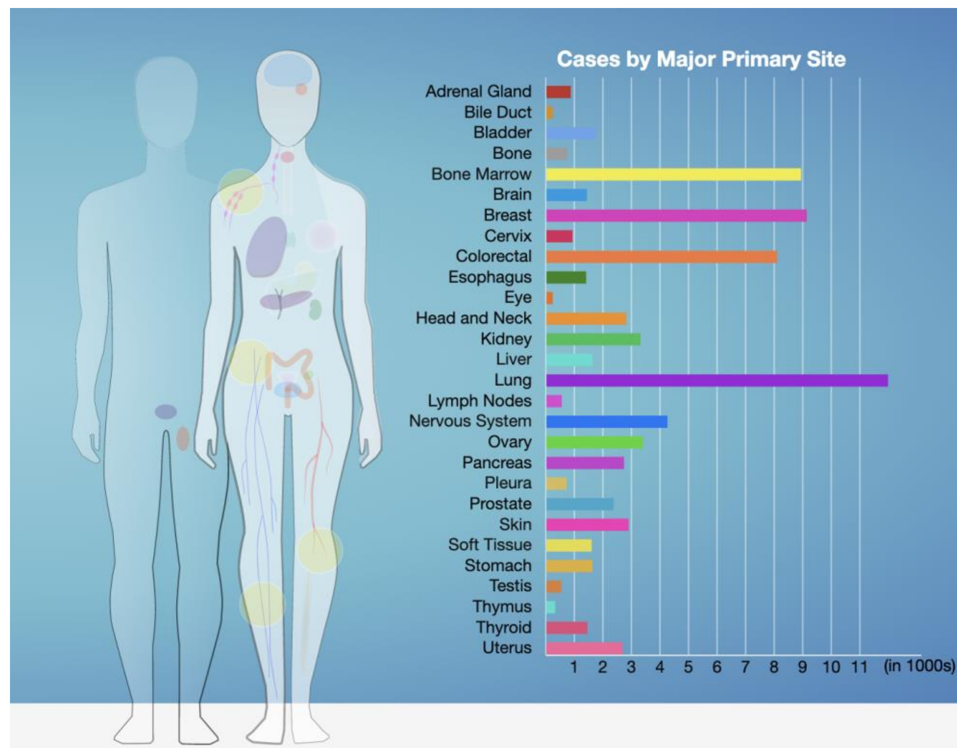
Motivation and Goals



What is Cancer?

Cancer is a disease in which some of the body's cells grow uncontrollably and spread to other parts of the body.

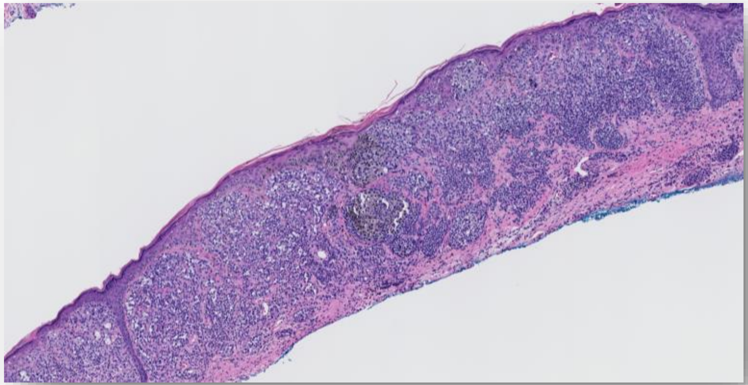




Figures are from National Institute of Cancer website.

What is Melanoma?

- Melanoma is the most aggressive type of skin cancer.
- Pathologists look at a skin biopsy slide and determine if its overall structure is normal, abnormal, or malignant.
- Diagnostic errors are much more frequently than in other tissues and can lead to under- and over-diagnosis of cancer.
- Deep learning image analysis methods may improve and complement current diagnostic and prognostic capabilities.



An example of an Invasive Melanoma T1b in M-Path dataset.

Related Work

- There is various work related to the diagnosis of biopsy images of other types of cancers than melanoma, especially on breast histopathological Whole Slide Images (WSI) [1,2].
- Related work for melanoma diagnosis using skin biopsy WSI is very limited. There are works on staining other than H&E, such as Ki-67 stain [3].
- Most existing work on melanoma diagnosis are either binary classification system or on not very challenging categories to distinguish [4,5,6,7].

Melanoma Diagnosis

Structural entities:

- Dermis
- Epidermis
- Nests

Cellular entities:

- Nuclei
- Melanocyte
- Mitosis

Raw WSI

Diagnosis model

Diagnoses:

Mild Dysplastic

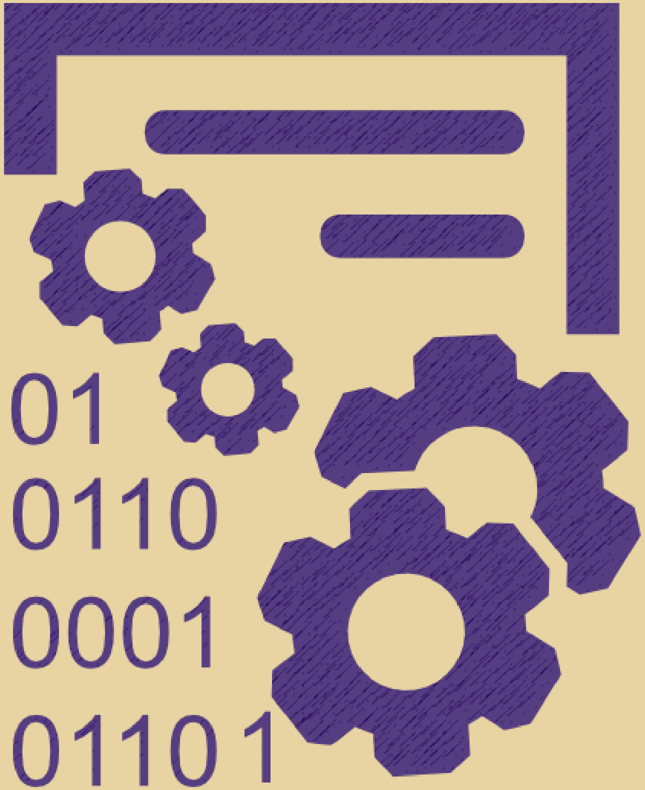
Moderate Dysplastic

Melanoma in situ

Invasive T1a

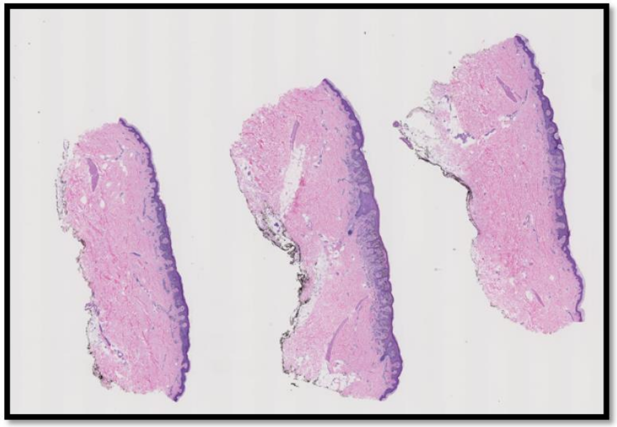
Invasive T1b

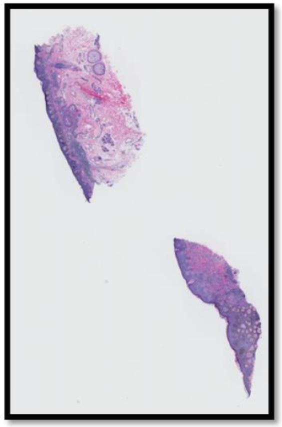
Dataset

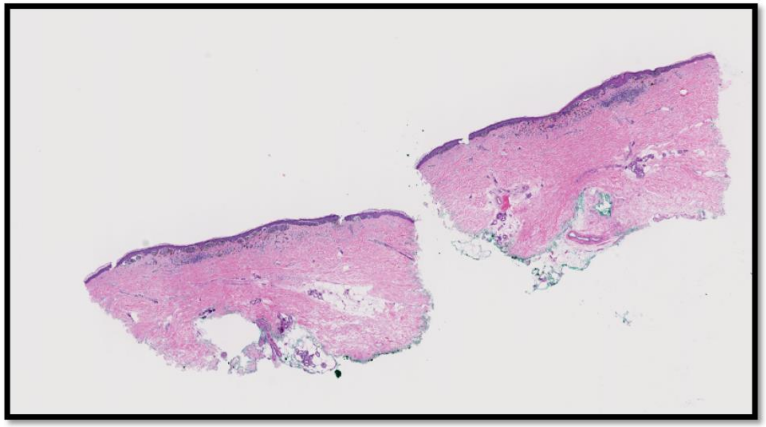


Dataset

Our dataset comes from 240 H&E stained slides of skin biopsy images, acquired by the University of Washington School of Medicine in the MPATH study (R01 CA151306).







Diagnostic Category	**#Cases**
Mildly Dysplastic Nevus	25
Moderately Dysplastic Nevus	36
Melanoma in Situ	60
Invasive Melanoma Stage T1a	58
Invasive Melanoma Stage $\geq$ T1b	61
Total	240

Dataset

- Each class varies in structure of tissues.
- Ground truth comes from 3 expert pathologists.
- For each WSI, we have one rectangular Region of Interest (ROI).

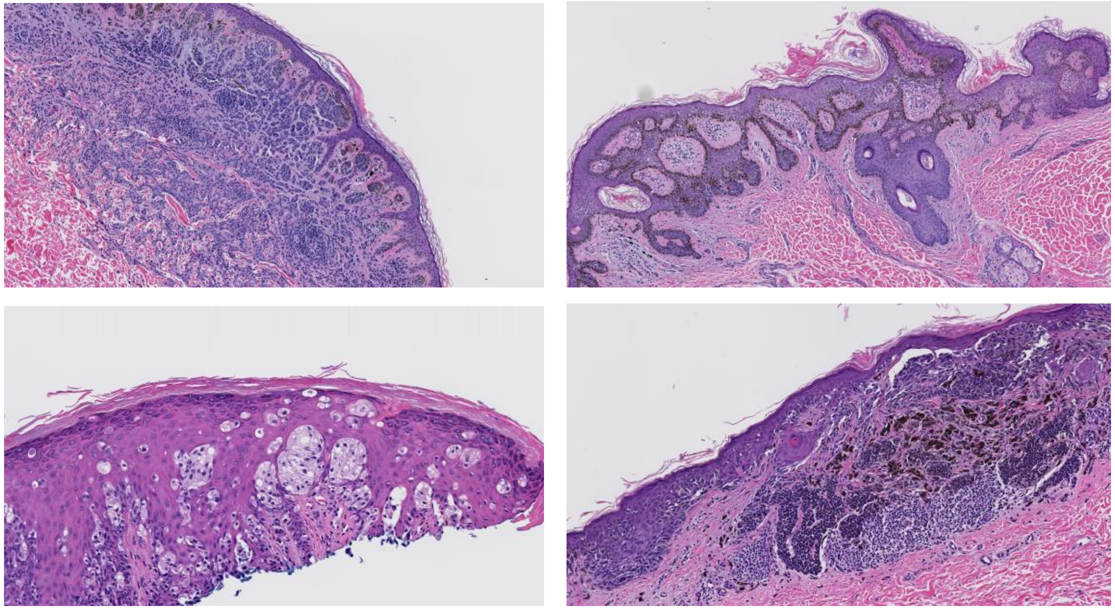
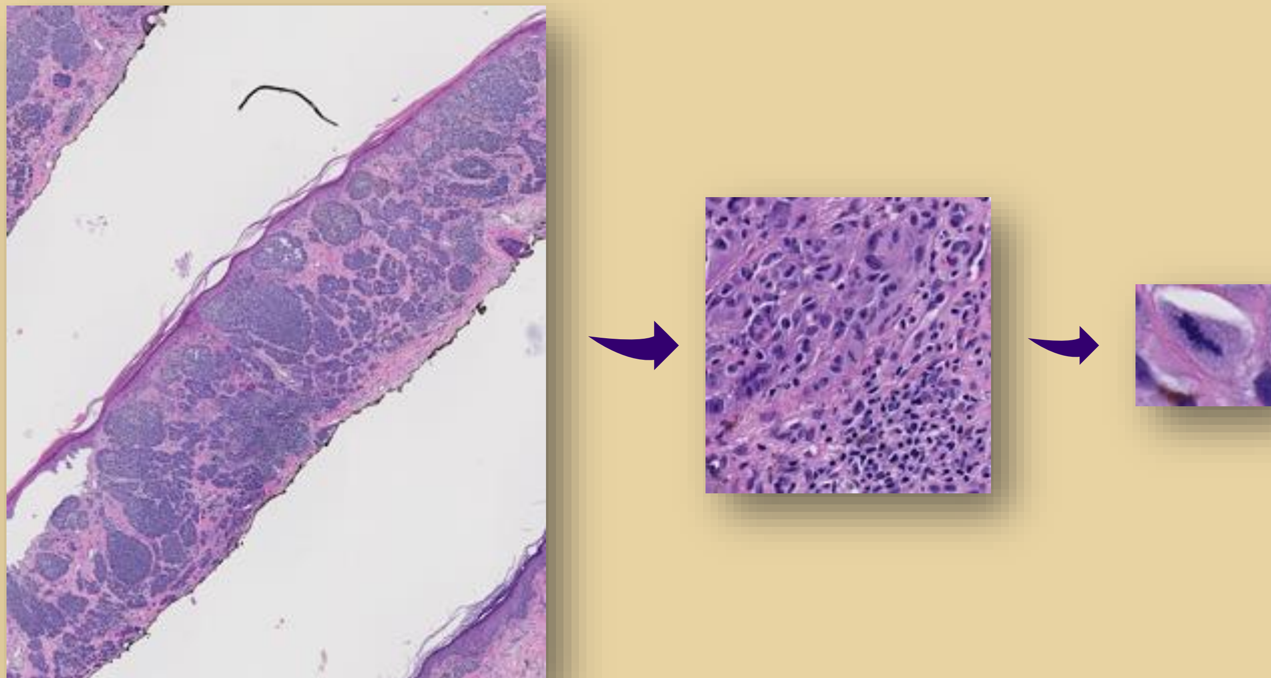


Figure3. Examples of Skin Biopsies with Different Diagnosis. Top Left: Benign.
Top Right: Atypia. Bottom Left: Melanoma in Situ. Bottom Right: Invasive Melanoma (T1a).

1. Mitosis Classification



Paper: Machine Learning Techniques for Mitoses Classification*

*Published in the journal of Computerized Medical Imaging and Graphics

https://doi.org/10.1016/j.compmedimag.2020.101832

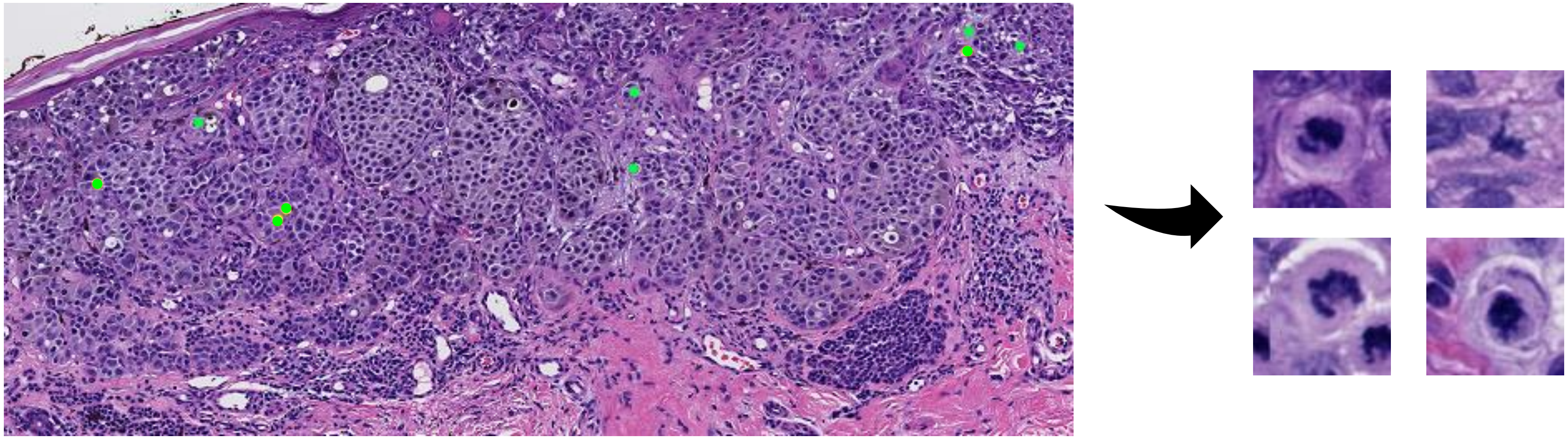
Related Work

- Among the independent predictors of melanoma-specific survival, mitotic rate is the strongest prognostic factor after tumor thickness [8].
- Various approaches have been applied to detect mitotic figures. Probability based methods [9], graph-based multi-resolution approach [10], used morphological features [11], and CNN-based method [12] are some of the approaches in detection of mitosis in biopsy images.
- Most of these methods have been applied on breast biopsy images.

Dataset

Positive samples – class Mitosis

- About 600 mitoses marked by our expert pathologist (Dr. Knezevich).
- We cropped each mitosis in a 101*101 patch centered on the dot placing on the mitotic figure.

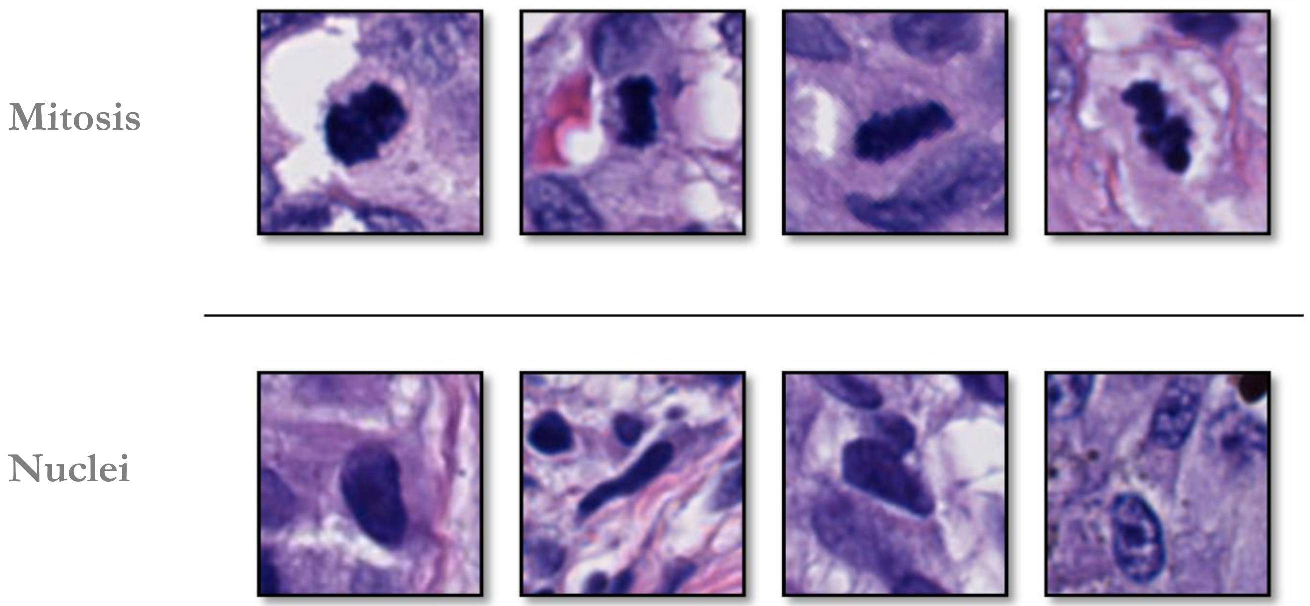


Example of expert pathologist markings of mitoses (Left) and sampled mitoses (Right)

Dataset

Negative samples – class NonMitosis

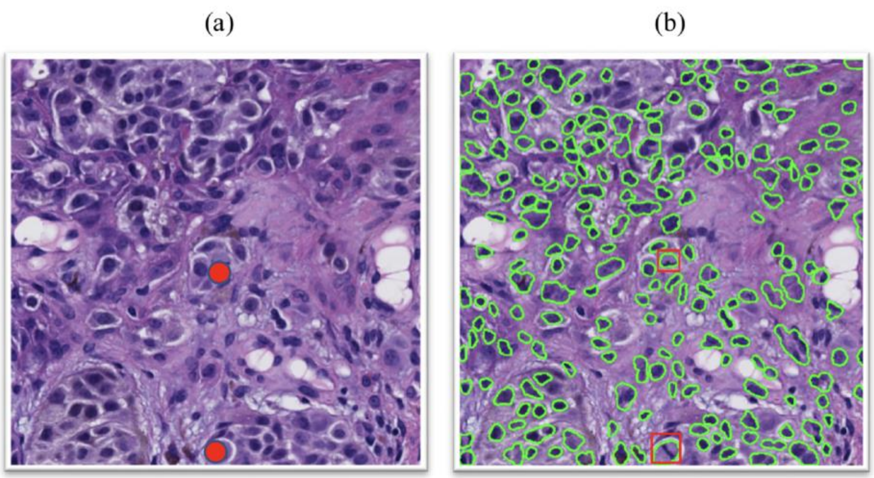
- Distinguishing mitoses from normal nuclei is a challenge.



Dataset

Negative samples – class NonMitosis

- We used a feature-based nuclei detector to find nuclei.
- We sampled them as negative cases for our dataset.



Examples of applying the nuclei segmentation on a crop of skin biopsy image (a) original crop (b) nuclei segmentation result. Two mitoses that are present in the original crop are marked with red dots for Visualization.

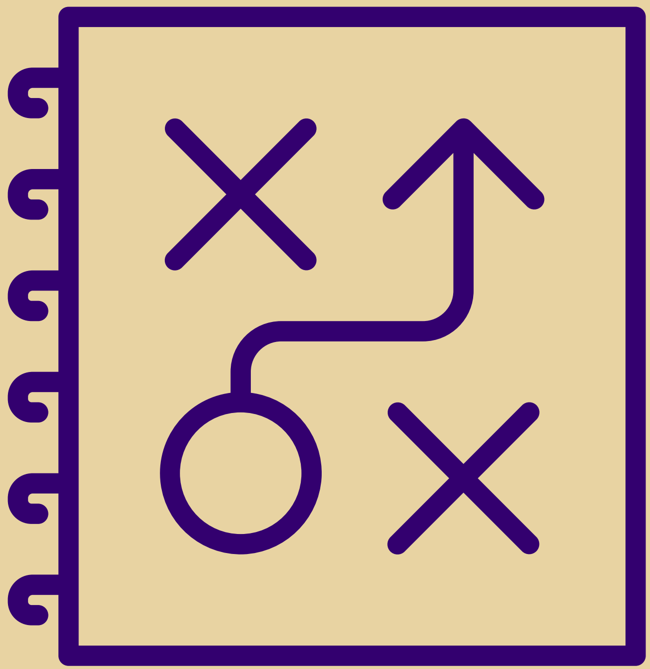
Preprocessing

> **Data augmentation:**
  - Rotations of 45, 90, 135 or 225 degrees.
  - Mirroring horizontal and vertical.

> **The final dataset:**
  - 4364 mitosis samples.
  - 12640 non-mitosis samples.

> **Dataset randomly split:**
  - Training: 60%
  - Validation: 20%
  - Testing: 20%

Method and Model

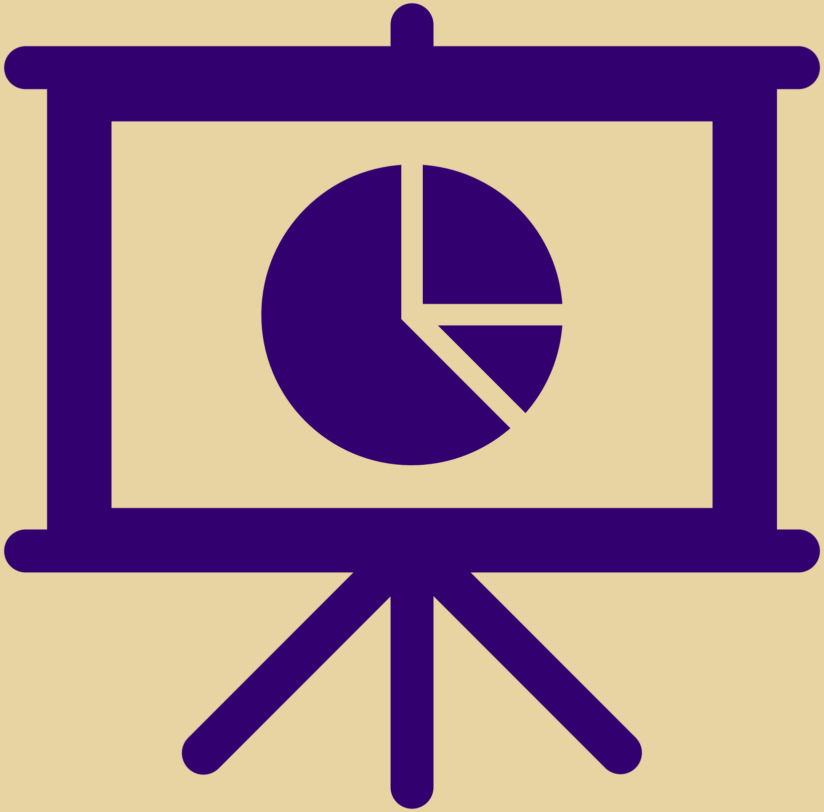


Method and Model

- In recent years, with the development of fast and accessible GPUs, Convolutional Neural Networks (CNNs) have dominated computer vision research due to their impressive performance, and mitosis detection is not an exception.

- We ran two separate experiments on two well-designed CNNs and compared their results:
  1. Efficient Spatial Pyramid of Dilated Convolutions (ESPNet) [13]
     - A light model developed and published by a member of our group.
  2. Densely Connected Convolutional Networks (DenseNet161) [14]
     - One of the well-known model in Deep Learning literature.

Results



Method and Model

- Hyperparameters
  - Adam optimizers.
  - learning rate decay schedule with step size = 5 and $\boldsymbol{\gamma} = 0.1$.
  - 20 epochs.
  - cross-entropy loss function.

- Evaluation Metrics
  - Accuracy = (TP+TN)/(TP+FP+FN+TN)
  - Precision = TP / (TP + FP)
  - Recall = TP / (TP + FN)
  - $\text{F1 score} = 2 \times \frac{(\text{Precision} \times \text{Recall})}{\text{Precision} + \text{Recall}}$
  - Sensitivity = TP / (TP + FN)
  - Specificity = TN / (TN + FP)

Results

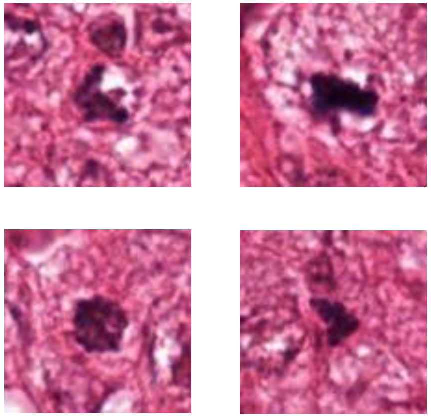
Evaluation results of ESPNet and DenseNet161 on **Melanoma**

Metrics	ESPNet	DenseNet
Accuracy	0.984	0.988
Precision	0.961	0.984
Recall	0.976	0.968
F1 Score	0.968	0.976
Sensitivity	0.976	0.968
Specificity	0.987	0.995
FP, FN	5, 3	2, 4
TP, TN	122, 370	121 , 373
Training time	35m & 6s	106m & 32s

Results

> ## Supplementary Dataset

- There is not a public marked dataset of mitoses in skin biopsies.
- Therefore, we used the MITOS dataset which is a public mitosis dataset of breast biopsies.
  - The MITOS dataset contains 50 images stained with Hematoxylin & Eosin.
  - A total of 800 mitoses are visible in MITOS



Examples of Mitoses in MITOS public dataset of breast biopsy images.

Results

- To generalize on a public dataset, we used MITOS dataset from ICPR12 challenge, which is a breast biopsy dataset for mitosis.

Evaluation results of ESPNet and DenseNet161 on **MITOS**

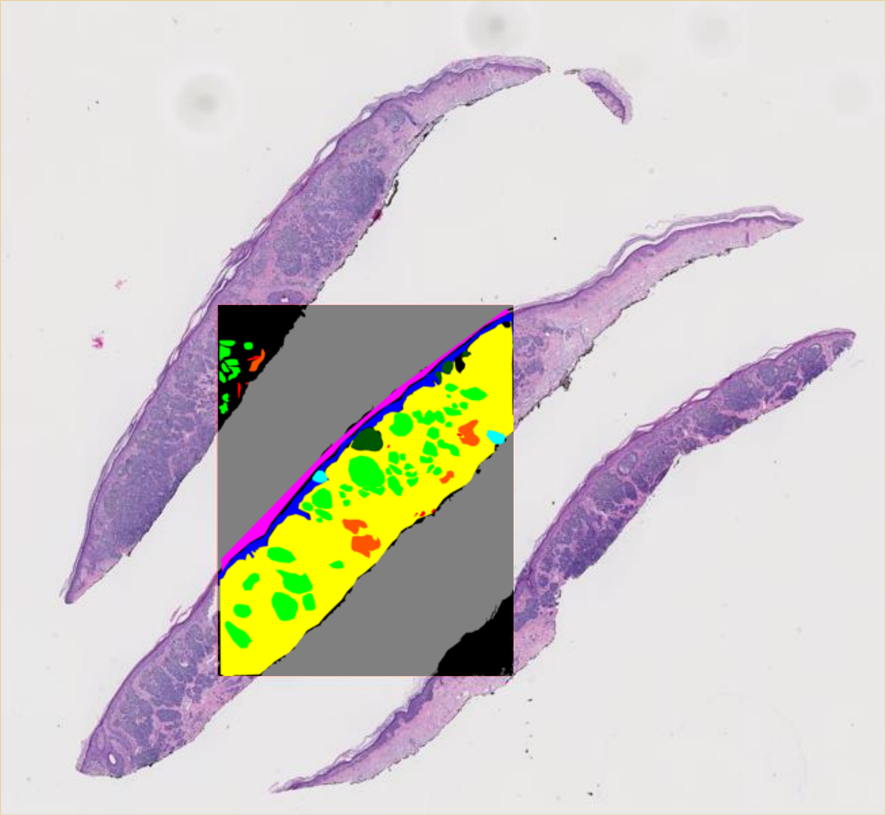
Method	**ESPNet** (Our trained model)	**DenseNet** (Our trained model)	[Saha et al., 2018]	[Dodballapur et al., 2019]	[Li et al., 2018]	[López-Tapia et al., 2019]	[Cireşan et al., 2013]
Precision	0.916	**0.939**	0.92	0.93	0.854	N/A	0.866
Recall	0.866	**0.916**	0.88	0.80	0.812	N/A	0.70
F1 Score	0.890	**0.927**	0.90	0.87	0.832	0.826	0.782

Discussion

Discussion

- We achieved very high scores in both of our experiments.
- **Melanoma:**
  - DenseNet161 performed slightly better than ESPNet.
  - Training time of ESPNet is significantly less than Densenet161.
- **MITOS:**
  - Both of ESPNet and DenseNet performed significantly better than the classifier of ICPR12 winner with significance level of 0.01.
  - DenseNet161 is significantly better than the classifier of the out-performer at significance level of 0.05.
  - ESPNet is not significantly better than the out-performer.

2. Segmentation using Coarse and Sparse Annotation



Paper: Segmenting Skin Biopsy Images with Coarse and Sparse Annotations using U-Net*

*Submitted to the Journal of Digital Imaging

Related Work

Various approaches have been developed to overcome imperfect and limited data annotation and vary with the specific challenges posed by the specific dataset on which they were developed.

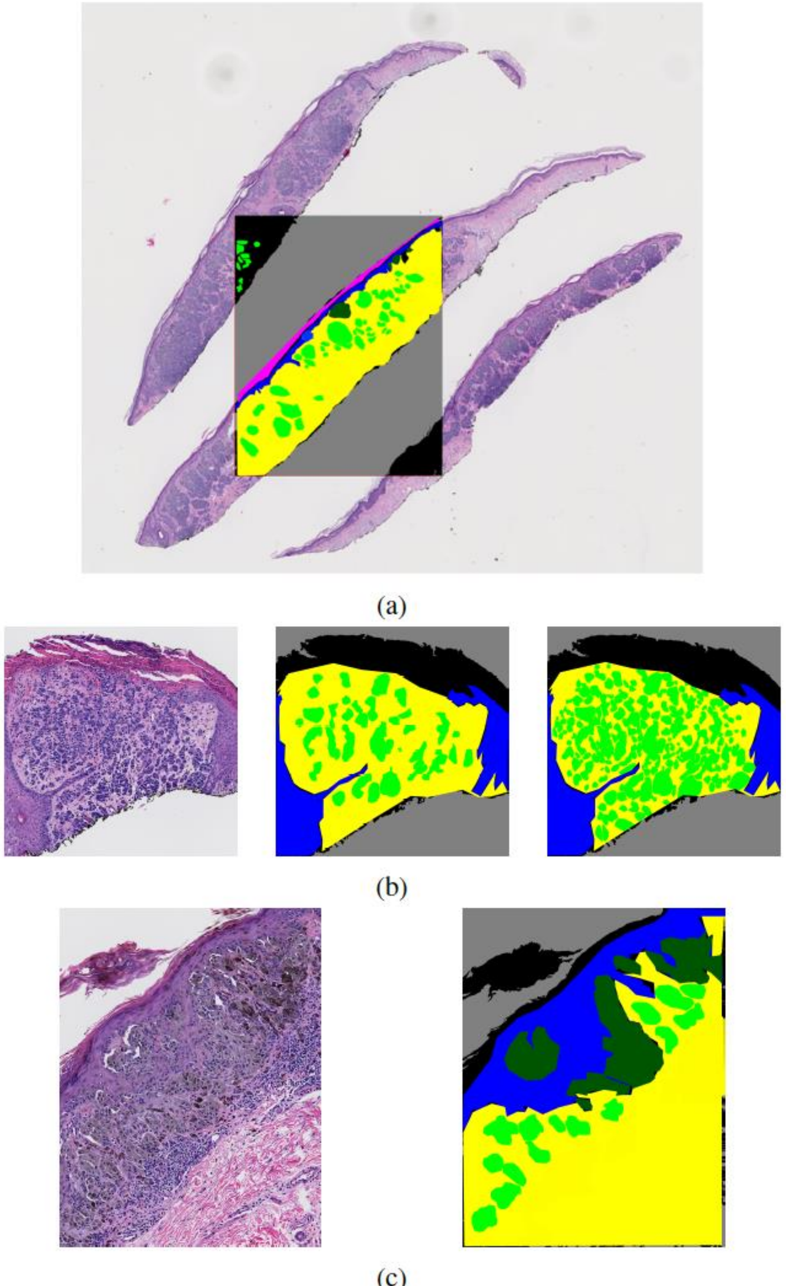
- When a small portion of an image is fully annotated, different methods of augmentation have proven to be helpful [15,16].
- Active learning is another popular method in the case of limited annotation [17,18,19].
- Changing loss function, or using external data also generated promising segmentation result.

Dataset

- We obtained coarse and sparse annotations only on the ROI images by an expert pathologist (Dr. Mokhtari).

- Not only are the annotations not on the full WSI, but they are also sparse within the annotated ROI.

- Moreover, the annotations are coarse, i.e., they are not pixel-level accurate.

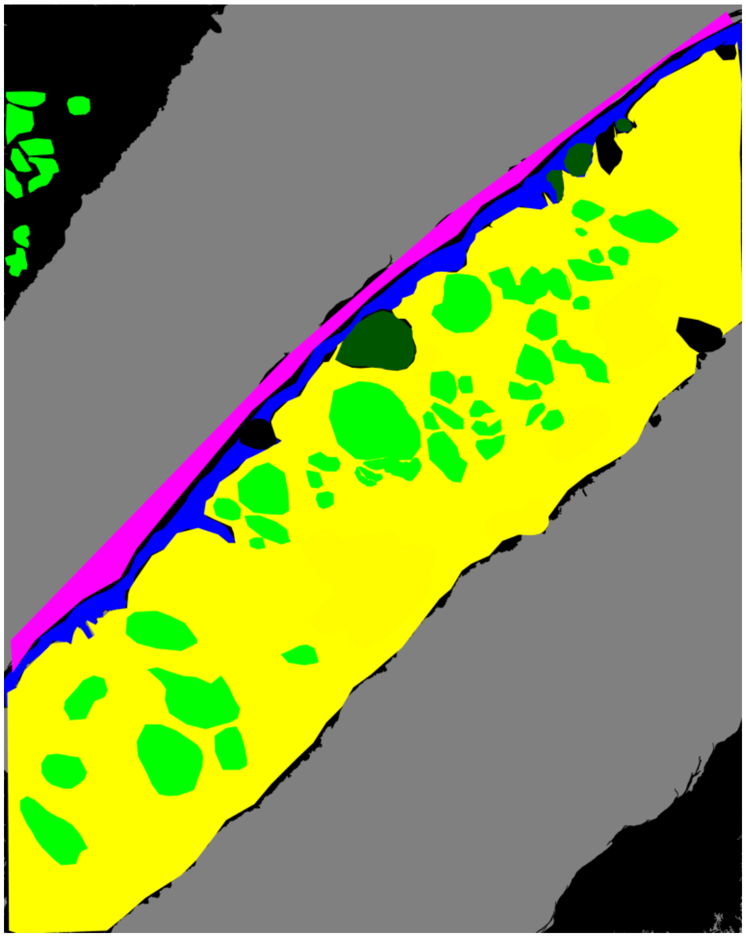


(a)

(b)

(c)

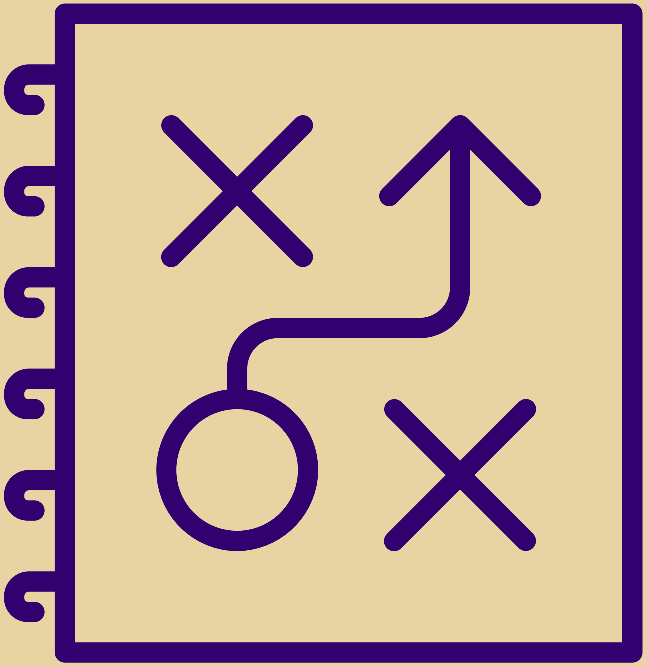
Dataset



Labels and colors:

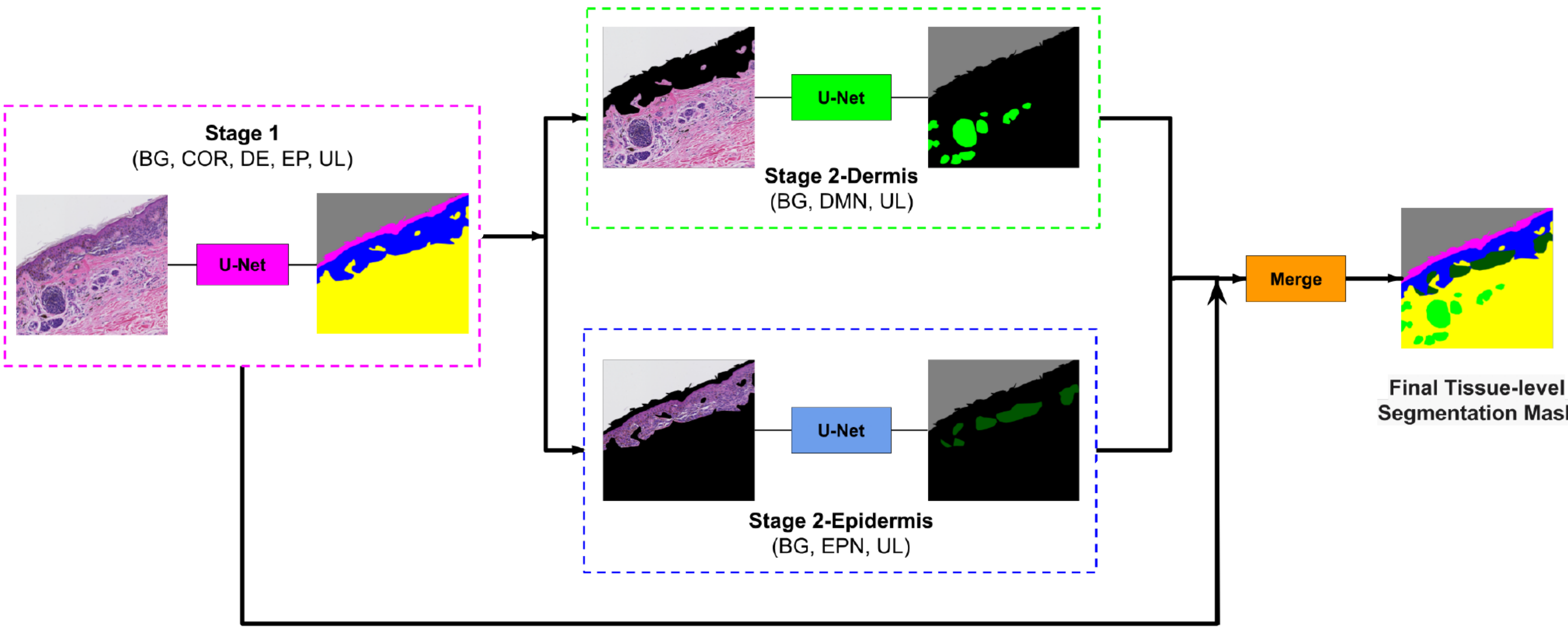
- Corneum (COR)
- Epidermis (EP)
- Epidermal Nests (EPN)
- Dermis (DE)
- Dermal Nests (DMN)
- Background (BG)
- Unlabeled (UL)

Method and Model



Method and Model

Two stage method: first big tissue structures, then smaller tissue structures.



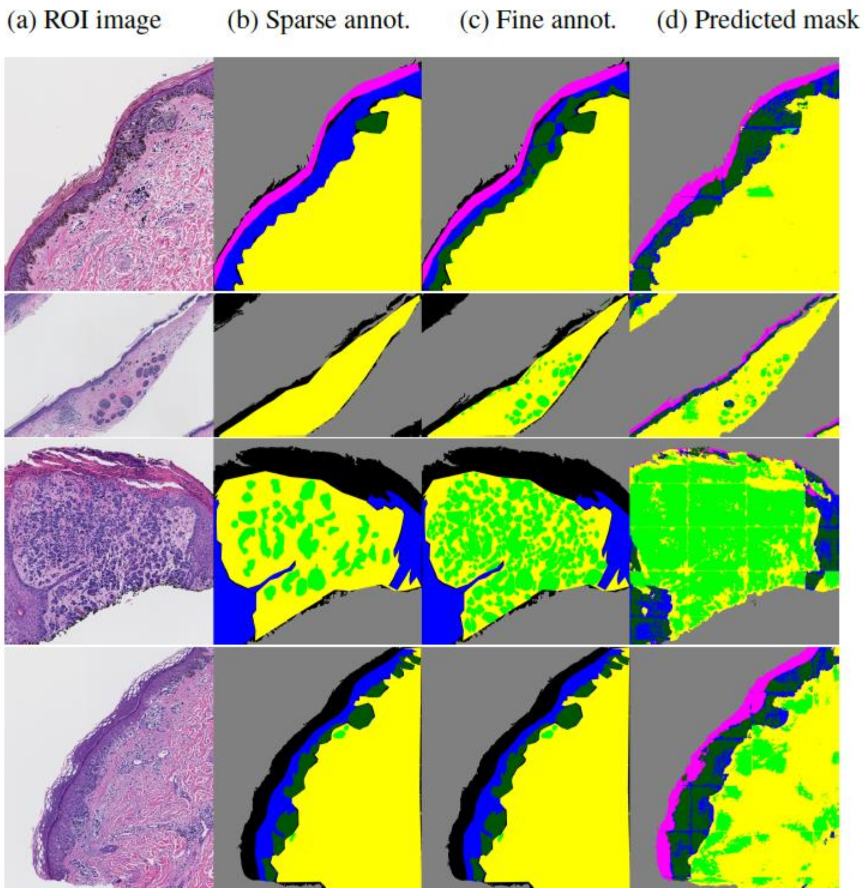
Results

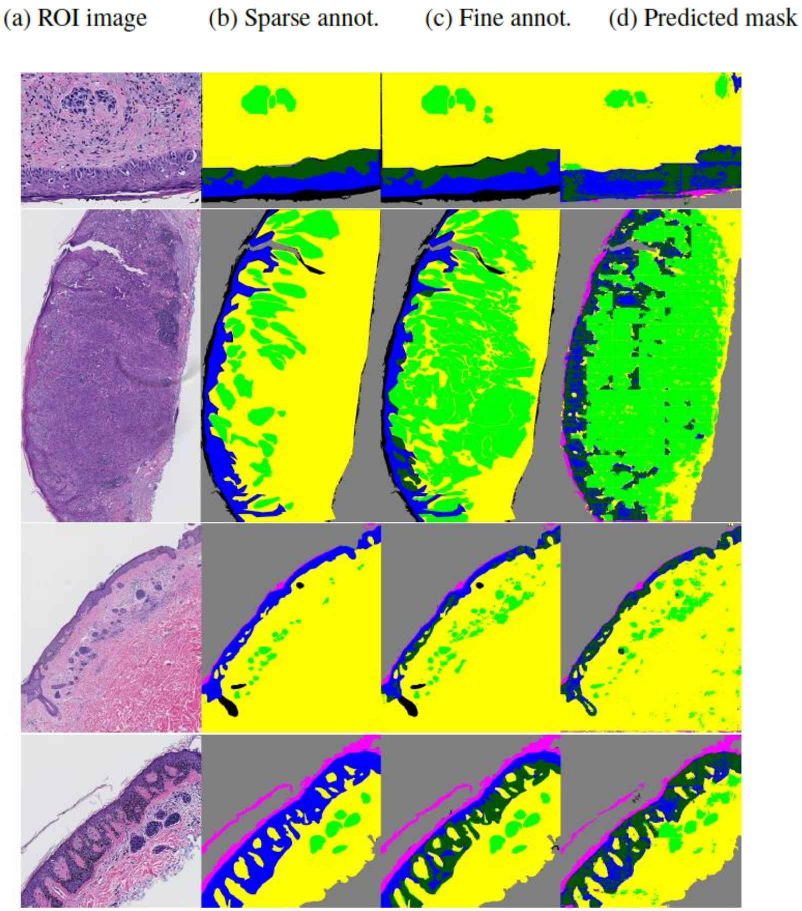
Results

- Evaluation of the segmentation model on **ROI** testing set.

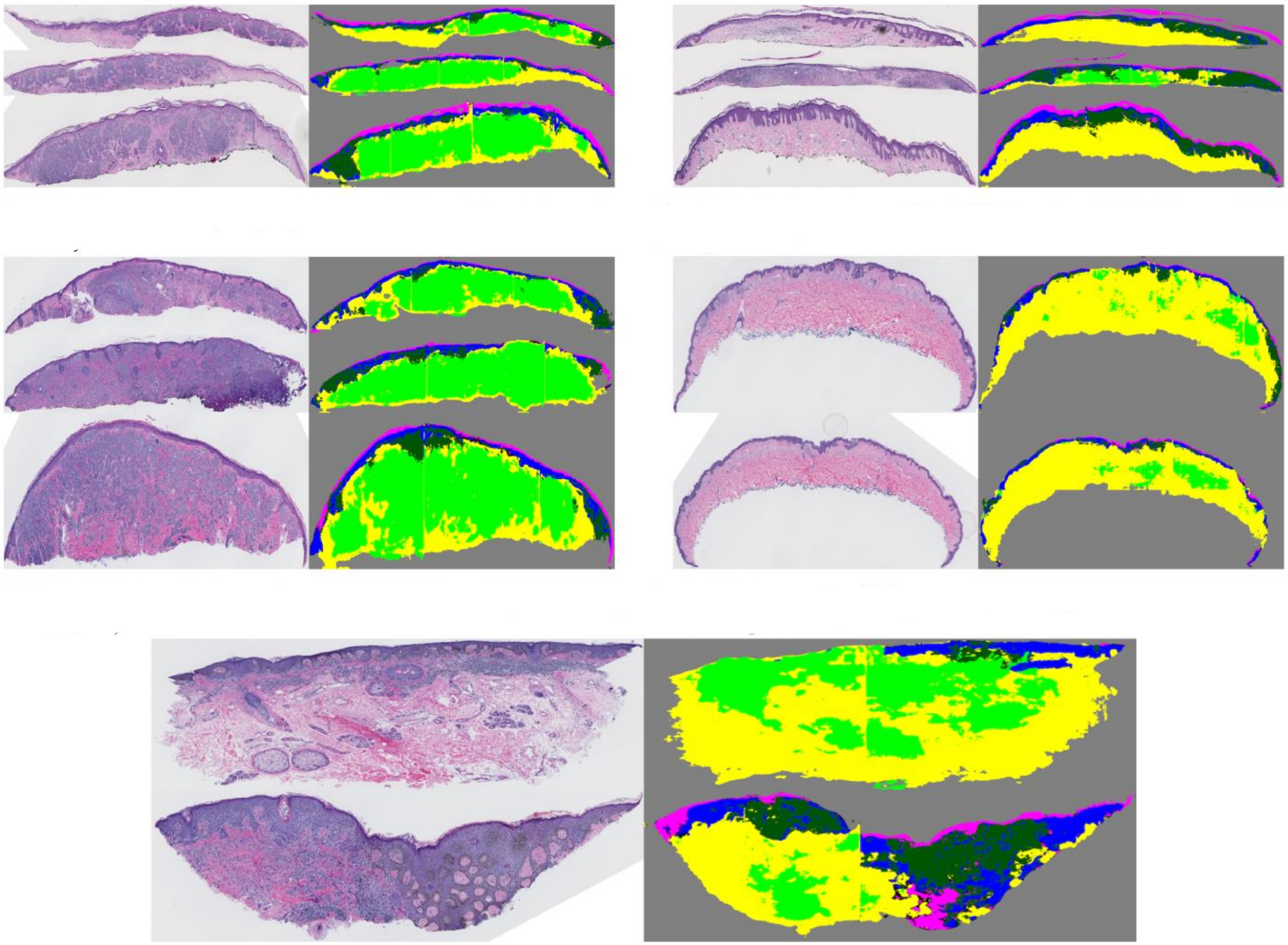
Segmentation stage	Dice score	IoU
Stage 1 (all tissues)	0.942	0.906
Stage 2-Dermis (DMN)	0.558	0.638
Stage 2-Epidermis (EPN)	0.332	0.558

Results - ROI testing set





Results - Generating WSI Segmentation Masks

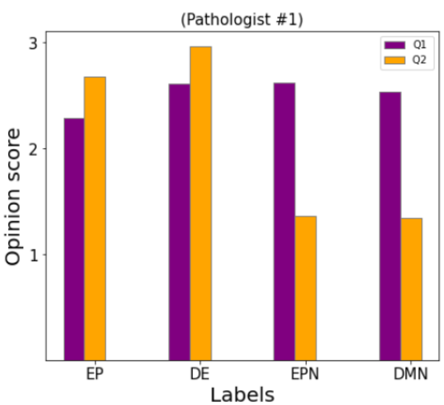


Subjective Assessment with Pathologists

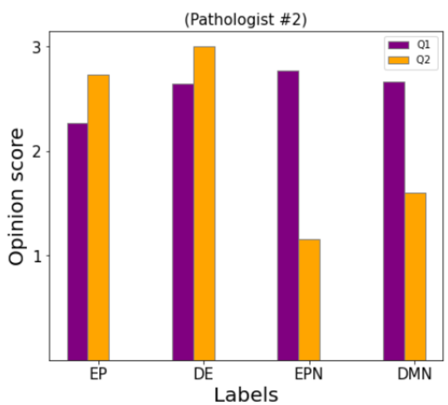
Qualitatively evaluation the WSI segmentation, with these questions:

- **Q1:** How much of the tissue/area that is present in the corresponding WSI has been correctly identified by the model? Rate Low, Medium, or High.

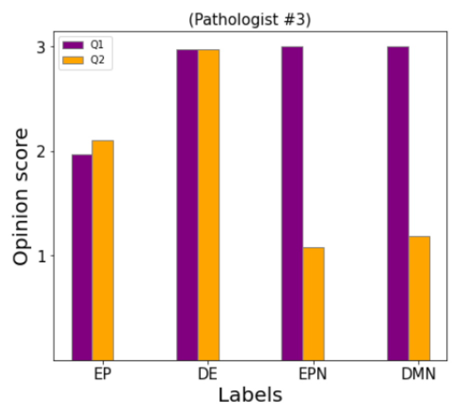
- **Q2:** How much of the label identified by the model is the correct tissue/area? Rate Low, Medium, or High.



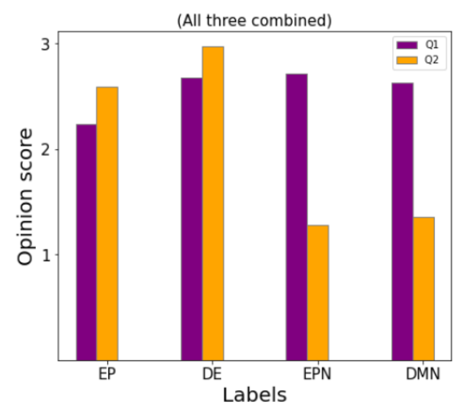
(a) Individual survey #1



(b) Individual survey #2



(c) Individual survey #3



(d) Combination of all three

Discussion

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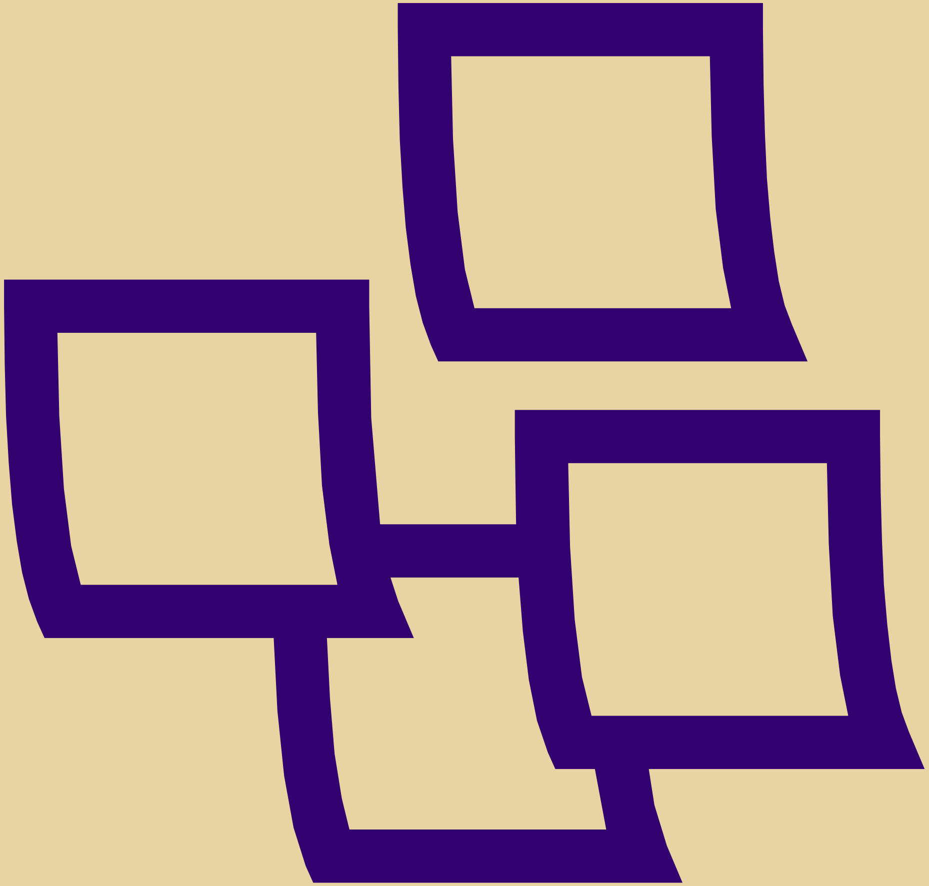
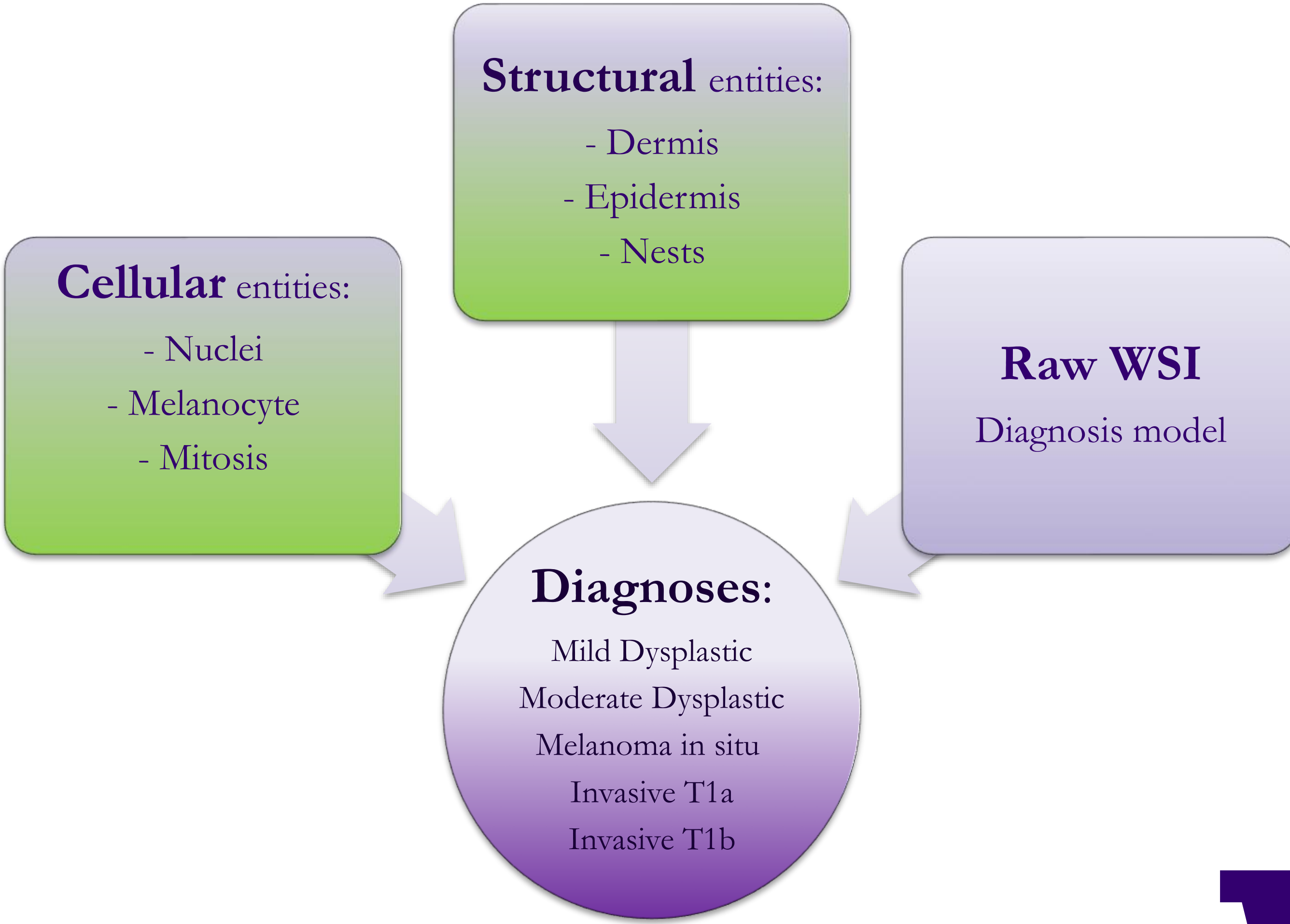
Discussion

- Training a segmentation model generally requires a large, high-quality annotated ground-truth. However, medical datasets require expert-level annotation as ground-truth.
- Our system was able to generate segmentation masks for both epidermis/dermis and nests with high-quality performance, indicating that having **sparse** annotation on important tissues has the potential for producing a useful segmentation model.
- Our results suggest that both the DMN and EPN can be over-labeled by the model, highlighting the problems that **coarse** annotation can cause for the system, especially on a small dataset in which the ground-truth did not clearly distinguish.
- **Sparse, but fine**, annotation on a small region of the WSI may be enough for training a better segmentation model.

Future Work



Melanoma Diagnosis



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deep neural networks. In International Conference on Medical Image Computing and Computer-assisted Intervention, pages 411–418. Springer, 2013.

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Thank you for your attention.

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