Classification of Non-Small Cell Lung Cancer Adenocarcinoma via Interactive Annotation Representation Learning

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Abstract

Background. Studies have demonstrated that the morphology on hematoxylin and eosin (HE) whole slide images can be histologically classified by computer vision algorithms and has the potential to indicate the presence of genetic drivers. But these algorithms need a large amount of annotated data. Whole slide images often have gigapixel resolution which makes it difficult to perform manual annotation. In this work, we employed a GAN via a novel interactive representation learning patch-level annotation framework on whole slide images of NSCLA to classify the lepidic histological subtype pattern. **Methods**. The pre-trained GAN was developed by computational pathologists at the University of Glasgow. The test set data source consisted of 437 lung images obtained from PathLink, which is a tissue and image repository associated with Vanderbilt's data warehouses. Five NSCLA lepidic subtype whole-slide HE images were extracted from this PathLink cohort. These images were then annotated with QuPath segmentation API to establish the ground truth. The images were divided into patches of 224 x 224 with 50% overlap. For data augmentation, the images were rotated. This resulted in 218,000 ground truth patches for the interactive patch-level annotation framework. Foreground annotation selections designated lepidic morphology and background annotation selections designated non-lepidic morphology. The real time classification occurred via logistic regression in the Napari segmentation API. **Results**. Generalization performance of the GAN interactive patch-level annotation model was measured against ImageNet dataset weights derived from a ResNet50 model the original weights of developed GAN. Accuracy, precision, recall, area under the curve and the F1 score were calculated for evaluating performance relative to the number of foreground and background annotations for each trial. Five annotation trials were performed for real time annotation of two lepidic image for each dataset weights. **Conclusion**. Both the GAN and ImageNet models were able to distinguish significant amount of NSCLA lepidic subtype tissue. However, the model with ImageNet based weights was prone to creating more false positives and required more foreground and background patch annotations to reach the target F1 score of 0.70 compared to model with the GAN.

Objective

1. The primary aim is to create an interactive annotation tool using representation learning scheme for histopathology images to minimize the manual work done to produce annotations. Non-small cell lung adenocarcinoma (NSCLA) lepidic subtype is the focus of this work.
2. Exploration of whether this generative adversarial network (GAN) can capture relevant NSCLA tissue structures in the latent space.

Introduction

- Non-small cell lung adenocarcinoma (NSCLA), a malignant epithelial tumor with glandular differentiation and one of the most common neoplasms worldwide, has histological subtypes.
- Studies have demonstrated that the morphology on hematoxylin and eosin (HE) whole slide images can be histologically classified by computer vision algorithms and has the potential to indicate the presence of somatic oncogenic genetic drivers.
- Manual annotation of whole slide images is a bottle neck to training computer vision algorithms.
- An interactive representation learning automated digital pathology solution of tumor classification and gene mutation prediction could lower the workload of pathologists, increase efficiency, reduce turn-around time and decrease subjectivity in diagnosis and improve outcomes.

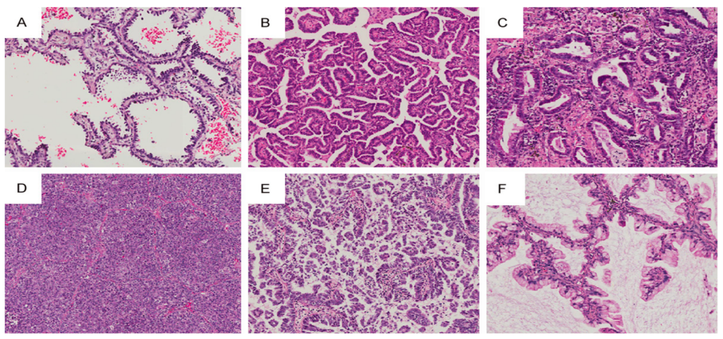

Figure 1. Micrographs of Histological Subtypes of Lung Adenocarcinoma. A. Lepidic; B. Papillary; C. Acinar; D. Solid; E. Micropapillary; F. Mucinous

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Materials and Methods

- GAN was developed on HE breast cancer TMA by computational pathologists at the Univ. of Glasgow.
- Transfer learning data and the test set from 437 lung images obtained from PathLink. 5 NSCLA lepidic whole slide images extracted.
- QuPath API to establish ground truth and NaPari API for interactive annotation framework
- Images were divided into patches of 224 x 224 with 50% overlap
- Rotations of 90◦, 180◦, vertical and horizontal inversion were applied to images patches
- 218,000 ground truth patches for the interactive representation learning patch-level annotation framework
- Foreground annotation selections designated lepidic morphology / positive / green tiles
- Background annotation selections designated non-lepidic morphology / negative / blue tiles
- Real time classification occurred via logistic regression on tile with at least 70% tissue

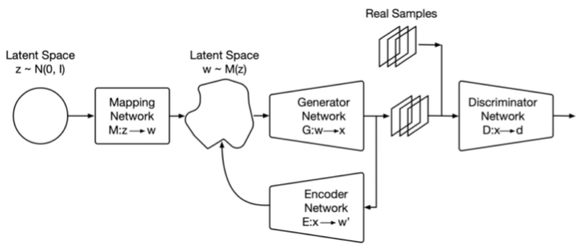

Figure 2. Network Architecture of GAN. Generative Adversarial Networks are models that are able to learn the distribution of the data and produce realistic images.

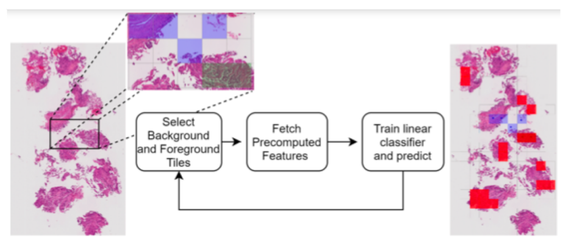

Figure 4. Overview of the Interactive Annotation Framework. Green and blue tiles are user selected foreground and background respectively. Red tiles are the ones the network predicted as foreground.

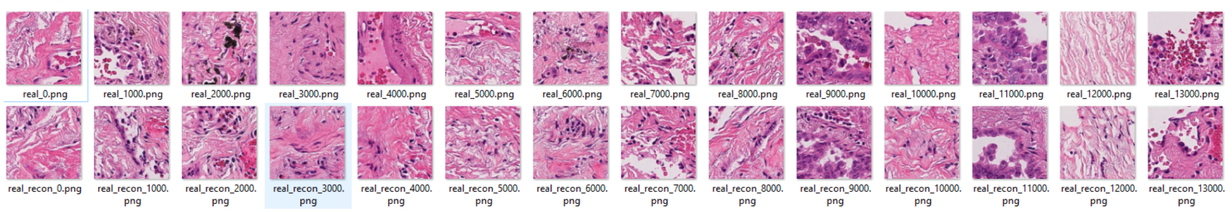

Figure 3. Real Tissue Images and their Reconstructions. 224×224 HE NSCLA lepidic subtype real images and their reconstruction by the GAN.

Results

- Generalization performance of the GAN interactive patch-level annotation model was measured against ImageNet dataset weights derived from a ResNet50 model and the original weights of developed GAN.
- F1 score was the primary metric of performance relative to the number of foreground and background annotations for each trial.
- Five annotation trials were performed for real time annotation of two lepidic image for each dataset weights.
- Transferred learning GAN model performed better than ImageNet model weights and slightly less than model with original GAN weights.

Method	# Clicks to reach F1-70	
	Image 1	Image 2
ImageNet	23.8	21.75
PathologyGAN VGH+NKI	14	8
PathologyGAN PathLink	14.8	8.6

Table 1. Comparison between different feature extraction methods. ImageNet dataset weights derived from a ResNet50 model. Original GAN weights derived from two breast cancer dataset from the Netherlands Cancer Institute (NKI) and the Vancouver General Hospital (VGH) cohorts with 248 and 328 patients, respectively.

Discussion

- Continued research will explore the number of annotations required to reach a F1 score of 0.90.
- The next step will be to explore the relation between morphological phenotypes of lung adenocarcinoma with a corresponding oncogenic somatic driver mutation.
- Ultimately, the goal is to determine if this digital pathology solution that can be generalize to other cancers and improve patient survival.

Conclusion

- GAN based model was used to learn a compressed representation of the histopathological tissue structure of the NSCLA lepidic subtype.
- Representations implemented into an interactive annotation framework to reduce the amount of annotations to learn new NSCLA lepidic subtype images.
- Model out performed traditional neural network in number of annotations required to reach the target F1 score of 0.70.
- This digital pathology solutions can potentially address the issue of limited annotated datasets for training computer vision algorithms.