Image Entropy for Classification and Analysis of Pathology Slides

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Abstract—Pathology slides of lung malignancies are classified using the “Salient Slices” technique described in Frank et al., 2020. A four-fold cross-validation study using a small image set (42 adenocarcinoma slides and 42 squamous cell carcinoma slides) produced fully correct classifications in each fold. Probability maps enable visualization of the underlying basis for a classification.

Frank et al., 2020 describes a training and analysis strategy for convolutional neural networks (CNNs) in which images are sliced into tiled segments and sifted using an information criterion — in particular, only those tiles exhibiting as much information entropy as as the original image are retained. These tiles stand in for the original images for training and testing purposes. To make predictions, a probability aggregation framework is applied to probabilities assigned by the CNN to tiles representing an image.

In facilitating the use of high-resolution images that would be too large to process in unmodified form, the technique seemed well-suited to analysis of medical images. Preliminary experiments with pathology slides — that is, whole-slide histopathology images of cancerous tissue — as described below have been encouraging. These slides can be quite large, often more than 1 GB, precluding direct analysis by a CNN. They may also include considerable empty space irrelevant to classification. As a result, pathology slides have been decomposed into smaller fragments for analysis (Yu et al., 2019).

A longstanding impediment to clinical adoption of machine-learning techniques is the inability of many such techniques to convey the rationale behind a classification, diagnosis or other output (Knight, 2017). Black-box models whose reasoning is opaque or impervious to retrospective analysis may pose clinical dangers that outweigh the benefits of a computational approach (Matheny et al., 2020). Until recently, CNNs have fallen squarely within the black-box category, but techniques such as Grad-CAM (Selvaraju et al., 2017) have pried the box open,
highlighting the image regions important to a CNN classification. Still, identifying which image
regions attract the attention of a CNN does not reveal the underlying rationale for a classification
— only the pixels on which the classification, whatever its basis, depended most strongly.
Described below is an alternative visualization approach that explicitly estimates and displays
classification probabilities at a subimage level.

**Methods**

Forty-two adenocarcinoma slides and 42 squamous cell carcinoma slides were
downloaded from the GDC portal of the National Cancer Institute. These averaged about 1 GB
in size and contained varying amounts of empty, non-image area. The downloaded images were
resized to 6000 pixels along the larger dimension; in some cases a large portion rather than the
entirety of a slide was used, but this did not affect the image resolution. The resized images were
decomposed into sets of square tiles ranging in size from 200×200 to 650×650 pixels in steps of
50. The tiles overlapped by 75%. Sifting these tile sets with the image entropy criterion
eliminated between 52% and 63% of the tiles, but the significant degree of overlap left 28,500
training tiles even at 650×650 pixels. Visual inspection confirmed that tiles with excessive
empty areas were eliminated.

Four cross-validation folds of tiles corresponding to 64 training images and 20 test
images were prepared. In each case the training and test sets were evenly split between
adenocarcinoma and squamous cell histology images. These were analyzed with the five-layer
CNN architecture described in Frank et al., 2020, which contained five convolutional layers and
three dropout layers.

**Results**

At all tile sizes, after 40 epochs of training, the best models successfully classified all
slides in each of the test sets. To classify a slide, the classification probabilities assigned to the
corresponding tiles were averaged. The variance of probabilities among tiles corresponding to a
single slide was small for the best models, ranging from 0.03 to 0.04. Interestingly, as was found
with analysis of artwork, a more complex CNN architecture — specifically, VGG16 — produced
inferior results. In particular, VGG16 assigns the same probability to every slide in a set, usually about 0.53. The fact that no learning takes place (at learning rates of 0.01 and 0.001) suggests that the simpler model is better suited to this classification task, or at least learns more efficiently.

To assess classification probabilities at a subimage level, we created probability maps as representatively shown in Fig. 1(b) below. The probability map color-codes the probabilities assigned to the examined regions of an image using four colors. With a decision boundary at 0.5, red corresponds to high-likelihood \((p \geq 0.65)\) classification as squamous cell carcinoma, gold to moderate-likelihood \((0.5 \leq p < 0.65)\) classification as squamous cell carcinoma; green to moderate-likelihood \((0.5 > p > 0.35)\) classification as adenocarcinoma; and blue to high-likelihood \((p \leq 0.35)\) classification as adenocarcinoma. Gray regions of a probability map correspond to tiles that did not pass the image-entropy selection criterion and were not examined.

To obtain a granular, fine-featured map, tiles were overlapped more substantially at 88%. Each colored pixel represents the classification probability averaged over all tiles containing that pixel.
Fig. 1: (a) Resized histopathology image of lung tissue exhibiting squamous cell carcinoma; (b) color-coded probability map of the classified regions of (a) using 250×250 pixel tiles.

The trained CNN classified most of the test images with probabilities approaching the prediction limits of 0 and 1. Were probability maps created for such images, they would be nearly all red or nearly all blue. In each test set, however, the models that achieved 100% accuracy usually scored 20-25% of the images in the interval 0.2 < p < 0.8; presumably, these correspond to closer cases including tissue not conforming to malignant types in the training images, and produce more interesting probability maps. If a training set is large enough to span the full range of adenocarcinoma and squamous cell carcinoma morphologies encountered by pathologists, variegated probability maps will provide a useful guide to the subtleties underlying a classification and allow clinicians to identify possible sources of error.

Despite the small size of the training set used in this preliminary study, high classification accuracies were achieved across all tile sizes — a departure from our experience with art images, for which a single tile size generally outperforms all others. These classification accuracies, combined with the ability to generate probability maps that indicate the pixel-level basis for a classification, suggests the utility of the Salient Slices technique in the analysis of medical images. Future work will require much larger training and test sets, as well as the involvement of trained clinicians who would actually use this type of system and can evaluate its performance on ambiguous or edge cases.
References

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