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Segmentation of Tumor Regions On Biopsy Slides Using Deep Learning for Microdosimetry Applications

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INTRODUCTION

Tissue response to ionizing radiation varies between different tissue and tumor types, patients as well as different radiation qualities. The identification of the causes of this variability in radiation sensitivity could have essential implications for radiotherapy[1]. The probability of obtaining a certain amount of energy absorbed in a target volume such as the tumor nucleus, depends on the size of the target volume as well as the spread in energy deposition due to the stochastic nature of ionizing radiation interactions with matter[2].
In radiotherapy dosimetry, the presence of this spread in energy deposition, where individual cell nuclei may not receive the same amount of absorbed energy is ignored. This spread may influence the dose-response and affect the treatment outcome. Hence there exists a need for consideration of nuclei and cell size distributions in radiobiological modeling of tissue response in radiotherapy.
Tumor nuclei and cell size distributions can be obtained from patient's digital histopathology images manually contoured by a pathologist in tumor and healthy regions. However, manual contouring of tumor regions is expensive both in time and money. In addition, it presents challenges such as intra-observer discrepancies[3].

AIM

To study the effect of varying nuclei and cells size distributions on radiotherapy dosimetry treatment outcomes, we have verified the use of a fully **automatic** machine learning algorithm to perform **segmentation of tumor and healthy regions in 2D digital histopathological core images**. The contoured images are used in another study to extract nuclei and cell distributions for dosimetry or other applications.

METHOD

- Use of a UNet architecture[4] as presented in Figure 1.
- 57 digital histopathology images contoured by a pathologist were split into 48 training and 9 testing images.
- The images had 3750 x 3750 pixels and an isotropic resolution of 248 nm/pixel.
- 1872 x 1872 pixel patches were extracted from the images due to memory limitations.
- Training was done for 24 hours on a 120 GB GPU cluster.
- Best weights achieved after 52 epochs.
- Batch size: was 8.
- Binary cross entropy was used as the loss function.
- Initial learning rate: 0.001 with learning rate reduction by factor 10 with patience 3
- Testing was done using the average from overlapping patches.

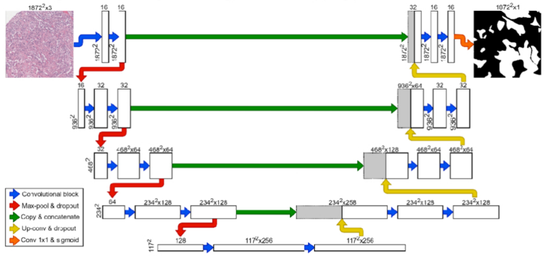

Figure 1: Representation of the UNet algorithm used in this study. A convolutional block consists of a convolution with a 3x3 kernel, batch normalization, and a rectified linear unit (ReLU) activation function.

RESULTS

- It takes a pathologist 20 minutes on average to contour one histopathological core image.
- The UNet segmented 3 images per minute achieving 60 times increased efficiency.
- The reconstruction of the contours done by the UNet appears similar to the manual contours as illustrated in Figure 2. A notable difference between the manual contours and the UNet prediction are the holes in the large tumor regions made by the UNet shown in Figure 2 C-D.
- The algorithm's reconstructed contours were scored against the pathologist's contours. The results are presented in Table 1-2.
- The UNet produces contours in the form of a prediction map. Each pixel has a probability from 0 to 1 of containing tumor. To compare these results to the binary contours made by the pathologist a threshold of 0.5 was applied to the prediction map.

Metric	Score
Accuracy	0.909
Specificity	0.912
Sensitivity	0.900
Precision	0.730
F1-score	0.806
Area under the ROC curve	0.906
Area under the Precision-Recall Curve	0.825
DICE score	0.806

Table 1: Segmentation scores performend on testing data set. For accuracy, specificity, sensitivity, precision, and F1-score a 0.5 threshold was applied to the prediction mask before scoring.

Accuracy $\frac{TP+TN}{TP+TN+FP+FN}$ **Specificity** $\frac{TN}{TN+FP}$ **Sensitivity** $\frac{TP}{TP+FN}$

Precision $\frac{TP}{TP+FP}$ **F1-score** $\frac{2}{sensitivity^{-1}+precision^{-1}}$

Legend
TP: True Positive **TN**: True Negative
FP: False Positive **FN**: False Negative

		Ground Truth	
		Healthy	Tumor
U - Net	Healthy	91 182 031 (TN)	8 825 098 (FP)
	Tumor	2 657 849 (FN)	23 897 522 (TP)

Table 2: Confusion matrix after applying a 0.5 threshold to the reconstructed contours. Ground Truth are the contours made by the pathologist. U-Net are the contours made by the convolutional neural network.

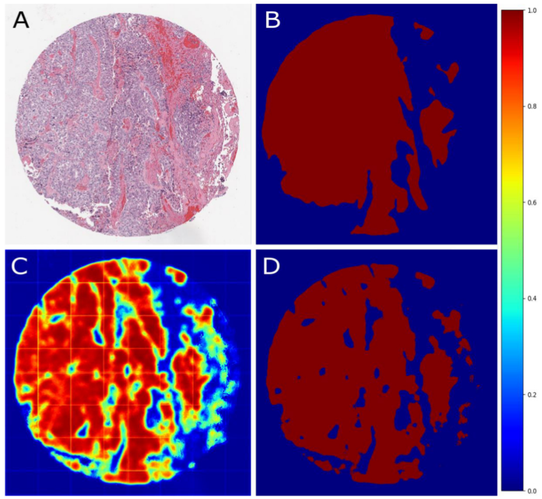

Figure 2: Representative example of a segmentation made by the UNet model. A) the original image. B) the contour made by the pathologist. C) the prediction made by the UNet. D) the prediction made by the UNet after applying a 0.5 confidence threshold. The values 0 to 1 represent the probability of a region containing tumor.

DISCUSSION

- The relatively low precision indicates that the algorithm is labeling too many healthy regions as cancerous.
- After inspection by a pathologist, the holes in the prediction maps from the UNet were identified as stroma. Stroma plays an important role in the progression and growth of cancer.
- The pathologist included the stroma cells in the tumor region, as the relatively small size and abundance of the stroma cells made the delineation too tedious.
- The UNet, however, distinguished between the tumor cells and stroma, and created a more precise contour of the large tumor regions.
- Although identifying the stroma is important, as these cells significantly affect the growth and progression of tumors, the algorithm received a negative score for delineating these regions, which affected the sensitivity of the UNet negatively.
- Delineating the stroma in the contoured ground truth images by the pathologist would increase the algorithms sensitivity.
- The automated reconstruction eliminates errors due to intra-individual differences in manual contours, but cannot eliminate inter-individual variations as the data set was created by a single pathologist.
- The UNet results might be improved by using training data created by multiple pathologists and providing more images.
- The dice score achieved using the UNet is similar to the dice scores produced by deep learning algorithms for tumor segmentation in histopathological core images from the literature.[5]

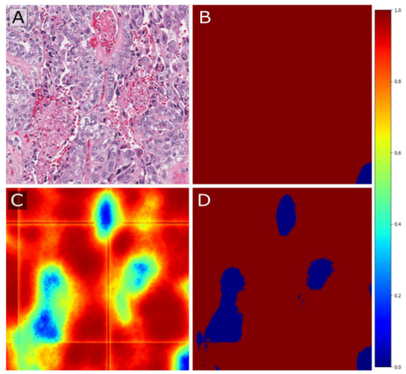

Figure 3: Zoomed in example of the stroma segmented in the image presented in Figure 2. A – The image used as input for the UNet. B – The contour made by the pathologist. Tumor regions are contoured in white. C – Prediction map generated by the UNet algorithm with 1872 x 1872 pixel patches and 500 x 500 pixel strides. D – The prediction map after applying a 50% confidence threshold.

CONCLUSIONS

The proposed UNet algorithm provides a promising method to segment tumor regions in histopathological core images. The automatic segmentation significantly increases the efficiency and reproducibility of tumor segmentation as compared to manual contours. The algorithm could be improved by training on data from multiple pathologists.
The masks produced by the UNet are accurate enough to be used to extract nuclei and cell size distributions for dosimetry or other applications.

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