SegMed : Analysis on Automated Nuclei Segmentation Methods

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Project Proposal

- Nuclei segmentation in high-resolution histopathological images.

- Nuclear segmentation is an important step in the pipeline of many cytometric analyses. Helps in obtaining the detailed information of each nucleus.

- Variation in appearance such as color, shape, and texture, makes nuclei segmentation from histopathological images very challenging.

- Contribute to the Human Biomolecular Atlas Program (HuBMAP). HuBMAP is to develop an open and global platform to map healthy cells in the human body.

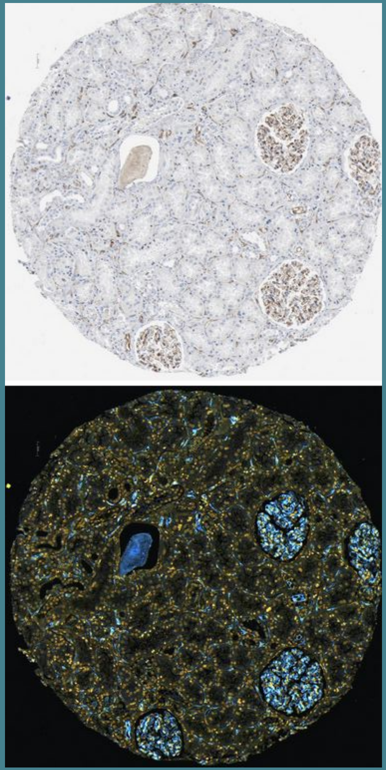


Image source: "Ju Yingnan - https://github.com/juyingnan/IndependentStudy2018SP ".

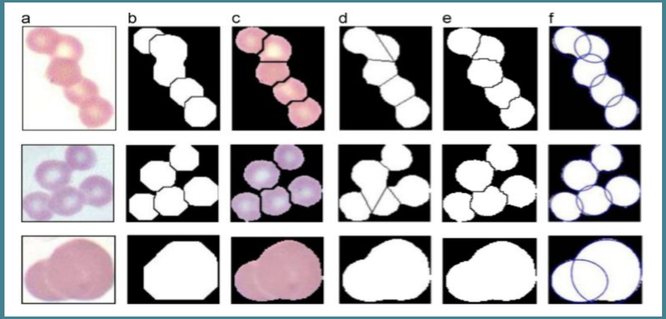
Prior

- Conventional - Otsu's method detects nuclei through intensity thresholding, filtering by utilizing the features of the nuclei, k-means.

- Limitations - they are only effective for one or a few specific types of nuclei or images and are highly sensitive to manually set parameters .

- Supervised Learning - Pixel level classification, splitting overlapped nuclei areas through bottleneck detection and ellipse fitting.

- Deep learning - Advancements in object classification, object detection and segmentation.



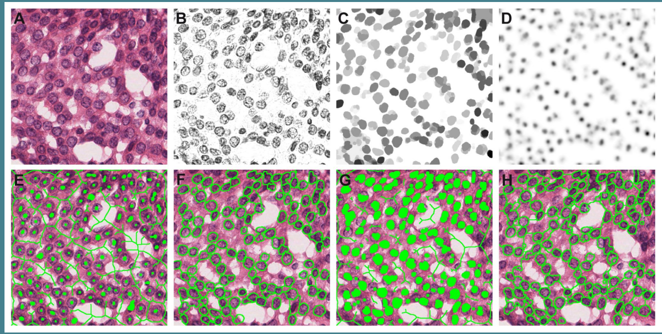


Image source : A. Qu, J. Chen, L. Wang, J. Yuan,"Two-step segmentation of hematoxylin-eosin stained histopathological images for prognosis of breast cancer," in Bioinformatics and Biomedicine (BIBM), 2014 IEEE International Conference on. IEEE, 2014,
Image source: M. Veta, P. J. van Diest, R. Kornegoor, A. Huisman, M. A. Viergever, and J. P. Pluim, "Automatic nuclei segmentation in h&e stained breast cancer histopathology images," PloS one, vol. 8, no. 7, p. e70221, 2013.
Background Source : Yuxin Cui,Guiying Zhang,Zhonghao Liu,Zheng Xiong ,Jianjun Hu -"**A deep learning algorithm for one-step contour aware nuclei segmentation of histopathology images**"

Models

- Nuclei-boundary model
- Unsupervised SegMed Model
- Mask R-CNN
- UNet2

Data Analysis

Datasets from multiple sources :

- MonuSeg - A Multi-Organ Nucleus Segmentation Challenge 2018 .
    - Training data of MoNuSeg contains 30 images and around 22000 nuclear boundary annotations and the test set has 14 images with 70000 nuclear boundary annotations.
- PSB Crowdsource
    - It has crowdsourcing image annotations for nucleus detection and segmentation that includes annotations from experts, automated methods and the crowd.
- TNBC
    - This dataset consists of H&E stained, triple negative breast cancer (TNBC) tissue slide images of 11 different patients.

Data Preprocessing

- H&E stain is the most widely used stain protocol in medical diagnosis.
- The nuclei of cells are stained to blue by Haematoxylin while cytoplasm is colored to pink by Eosin.
- Each of these models have used colour normalization techniques to eliminate the negative interference caused by color variation.
- Some models required for modifying the ground truth images and pixel level classification .
- Manual Annotations for nuclei .

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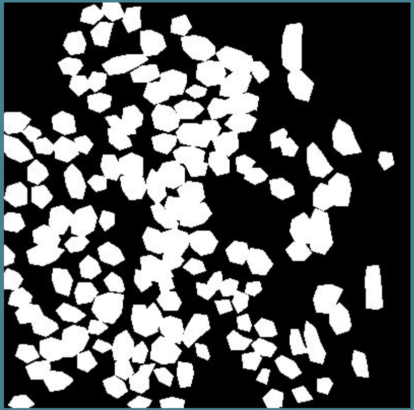
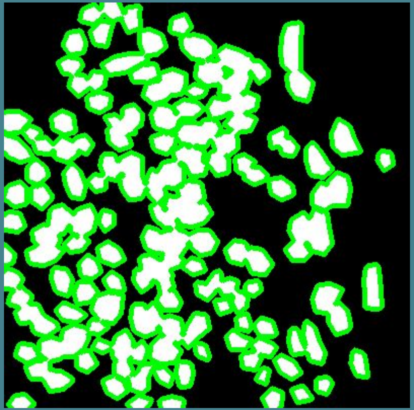
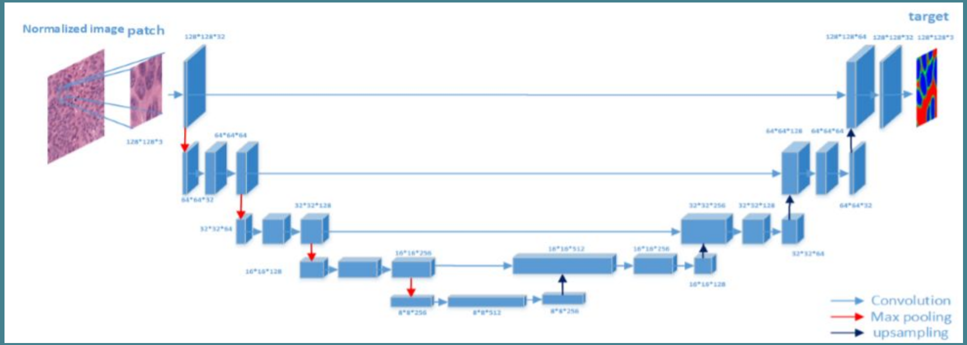




Unet2

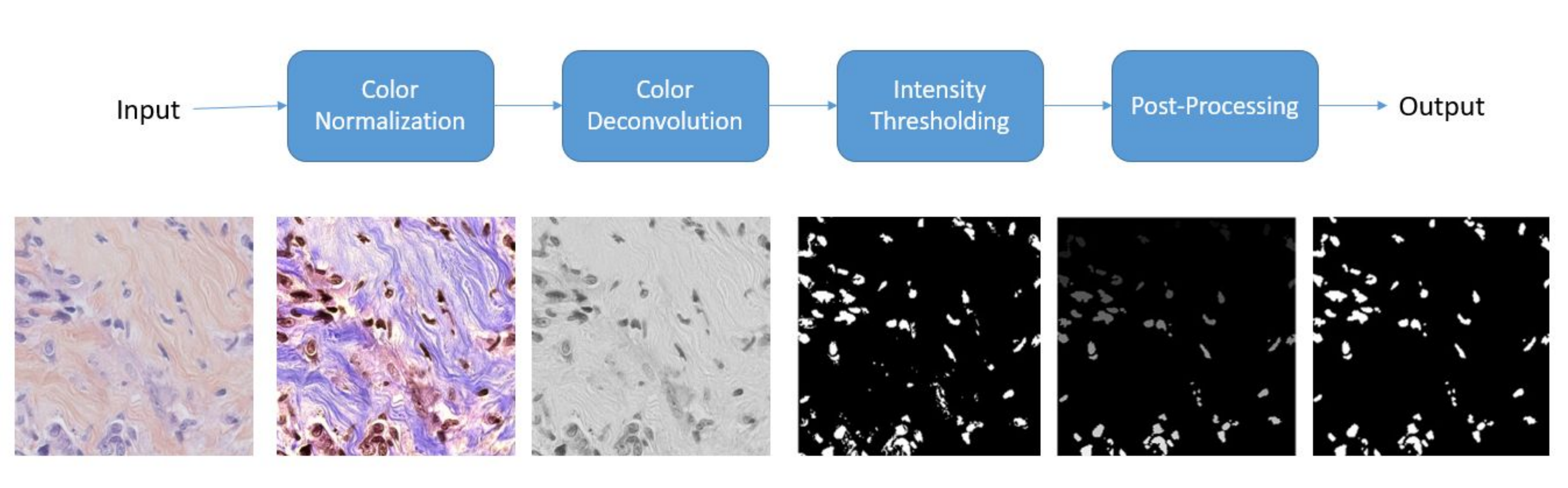
- Unet and Mask-RCNN are some of the highly successful architectures for instance based segmentation problems .
- This model uses the UNET architecture to classify the foreground and backgrounds of medical images .



- The encoding layers are used to extract different levels of contextual feature maps.
- The decoding layers are designed to combine these feature maps produced by the encoding layers to generate the desired segmentation maps.
- Loss Function : Binary Cross Entropy   Evaluation Metrics : Mean IOU

Unsupervised-SegMed Model

- This unsupervised method is done using the library HistomicsTK.
- This Model consists of four stages:

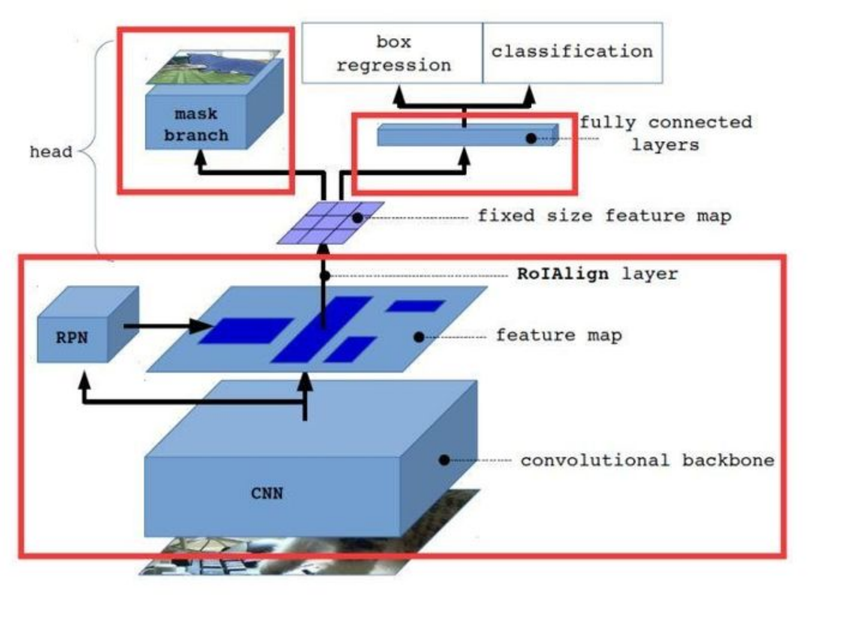


Limitations

- It is specific to H&E stained images.
- Params in post-processing such as minimum nuclei area, foreground intensity threshold should be provided to modulate it for multiorgan histology images.

Mask R-CNN

- backbone+RPN
- Parallel heads for box regression and classification
- RoIAlign



Loss Functions

$$\mathcal{L} = \mathcal{L}_{\text{cls}} + \mathcal{L}_{\text{box}} + \mathcal{L}_{\text{mask}}$$

Classification Loss

- Multiclass cross-entropy loss

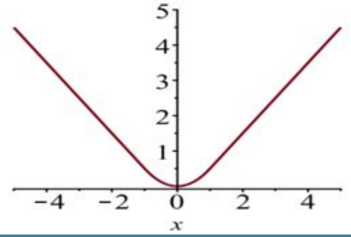
$$\mathcal{L}_{\text{cls}}(p_i, p_i^*) = -p_i^* \log p_i - (1 - p_i^*) \log(1 - p_i)$$

Bounding Box Loss (Top (x,y), Width and Height)

- Smooth L1 loss between ground-truth bounding boxes and predicted bounding boxes
- Smooth L1 loss is a robust L1 loss that is less sensitive to outliers than the L2 loss
  - Prevent gradient explosion

$$L_1^{\text{smooth}}(x) = \begin{cases} 0.5x^2 & \text{if } |x| < 1 \\ |x| - 0.5 & \text{otherwise} \end{cases}$$

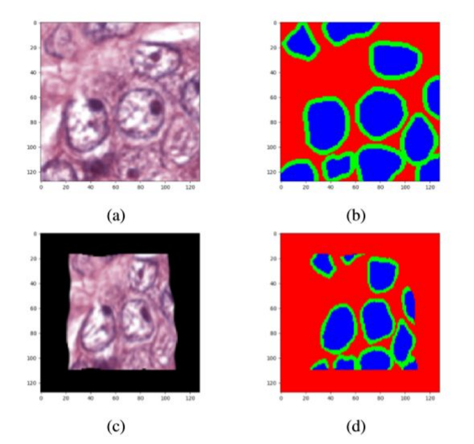
$$\mathcal{L}_{\text{box}}(t^u, v) = \sum_{i \in \{x,y,w,h\}} L_1^{\text{smooth}}(t_i^u - v_i)$$



Background Source : Yuxin Cui,Guiying Zhang,Zhonghao Liu,Zheng Xiong ,Jianjun Hu -"A deep learning algorithm for one-step contour aware nuclei segmentation of histopathology images"

Nuclei-Boundary Model

- This model predicts the category of all the pixels of an image with only one pass.
- This model merges these two stage of extracting the nuclei and their edges at the same time.
- The output of the NB model has three channels, each has the same height and width with of the input image.
- Its values represent the probabilities of each pixel being background, boundary or inside class, respectively.
- Augmentation techniques used random elastic transformation, rescale, affine transformation, shift, flip and rotate.



Weighted loss

- This model has a weighted loss and a scheme for patch extraction and assembling.
- This allows the neural network to predict a segmentation map of equal size without concerning the lack of context issue in the border area.
- The model is trained by minimizing the categorical softmax cross-entropy loss between predictions and target.

$$L = \sum_i \sum_j W_{i,j} log(p_{t(i,j)}(i,j))$$

$$W_{i,j} = \alpha \frac{D^e_{i,j}}{(D^c_{i,j} + D^e_{i,j})}$$

$$\alpha = \frac{h \cdot w}{\sum_{i=1}^{h} \sum_{j=1}^{w} \frac{D^e_{i,j}}{D^c_{i,j} + D^e_{i,j}}}$$

Image source: ”A Deep learning algorithm for one-step contour aware Nuclei segmentation of histopathological images“ by Yuxin Cui, Guiying Zhang et al. 03-07-2018.

Overlapped Patches and Post Processing

- Memory constraints and poor border area accuracy in UNET.
- The patches are extracted by sliding window with a stride. For assembling, a vote mechanism is applied to predict each pixel using P(i,j).
- NB model detects both inside and boundary classes, all we need is the inside class map.
- Inside class map is transformed to a binary map using a constant threshold 0.5.
- In this way, each connected component in the binary image indicates the inside area of one nucleus.

$$P(i,j) = \frac{\sum_k W_{k(i,j)}\, p(k(i,j))}{\sum_k W_{k(i,j)}}$$

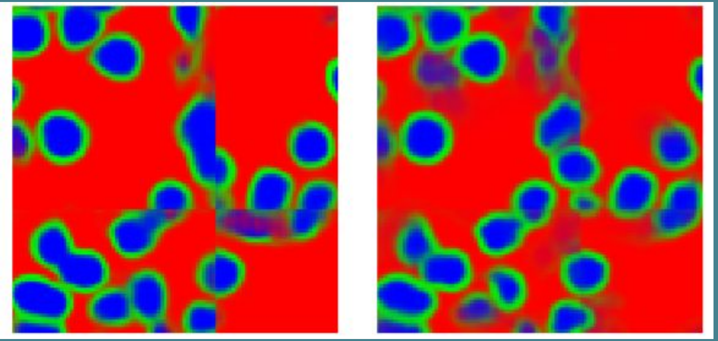
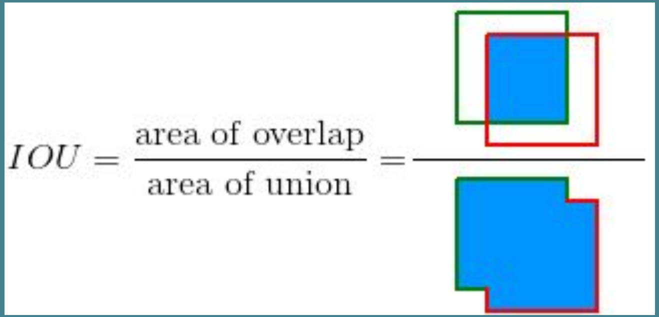


Image source: ”A Deep learning algorithm for one-step contour aware Nuclei segmentation of histopathological images“ by Yuxin Cui, Guiying Zhang et al. 03-07-2018.

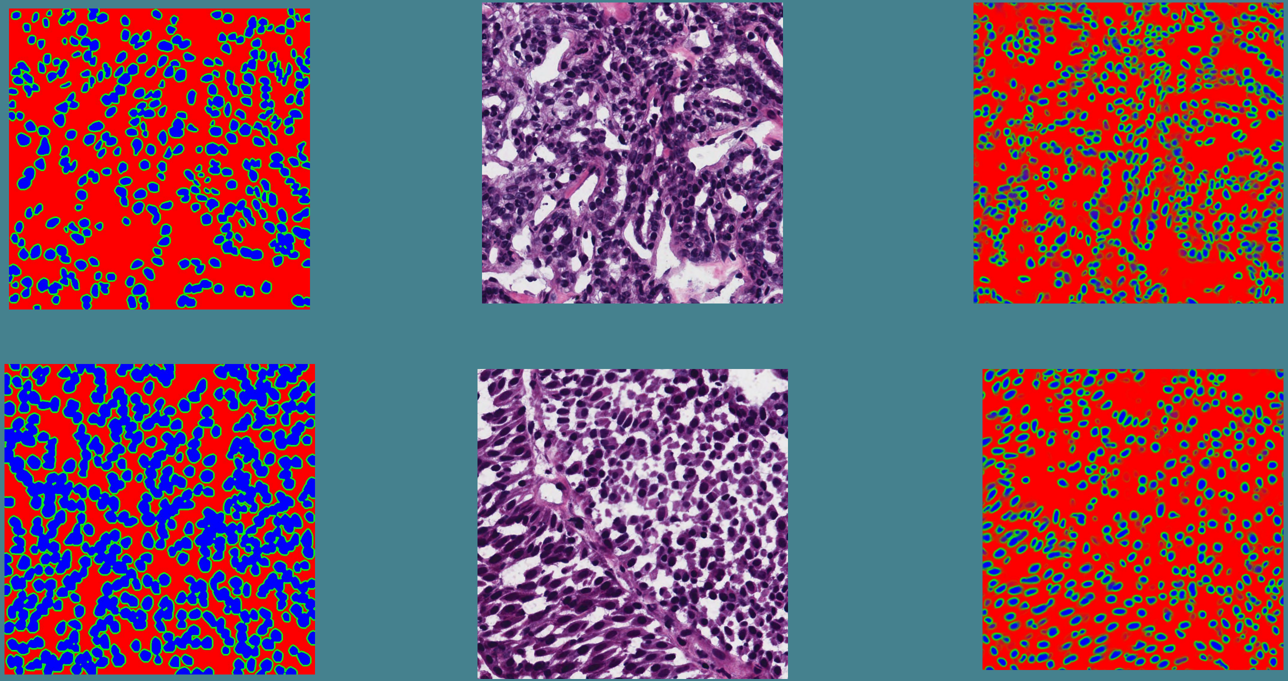
Evaluation

- Evaluation across models, datasets is pretty challenging .
- We used meanIOU - is the area of overlap between the predicted segmentation and the ground truth divided by the area of union between the predicted segmentation and the ground truth.

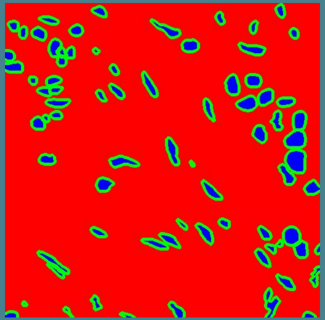


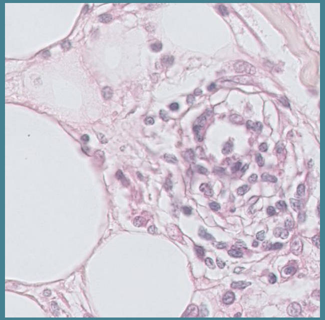
Segmentation Results

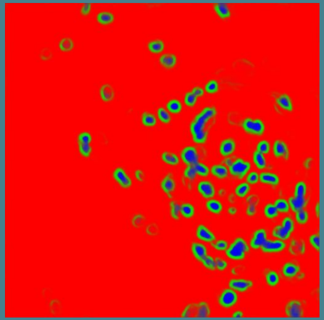
Nuclei Boundary Model - MonuSeg

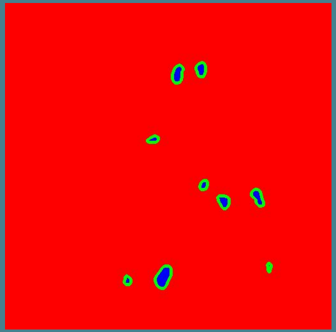


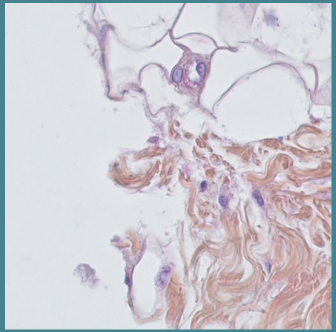
Nuclei Boundary Model - TNBC

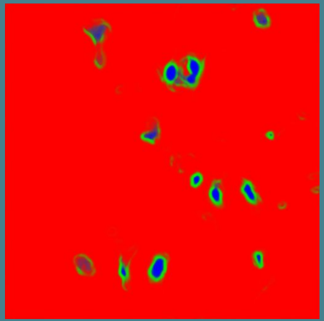




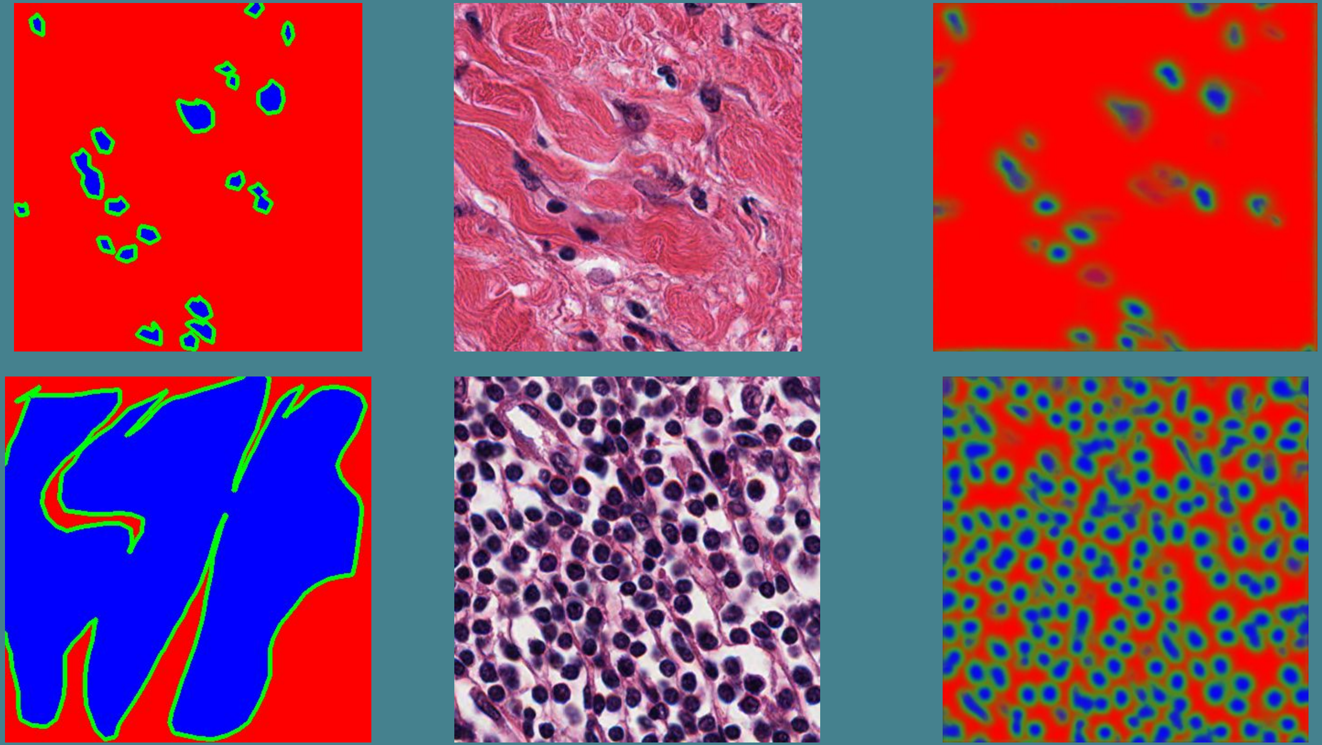




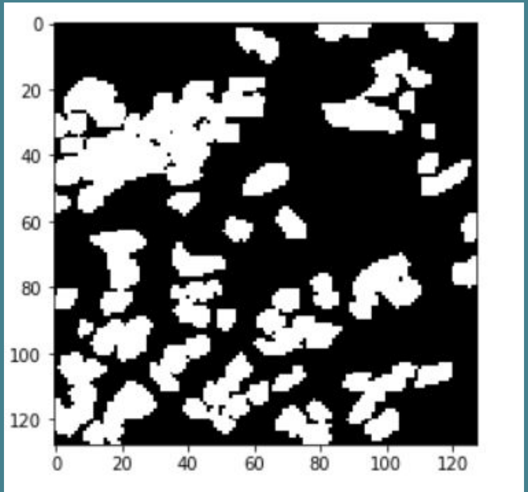




Nuclei Boundary Model - PSB



Unet2 - PSB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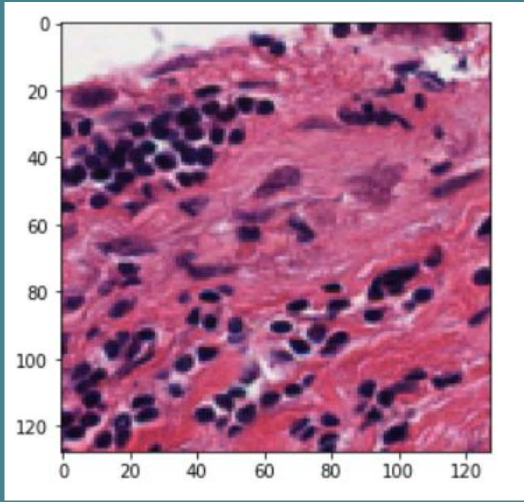
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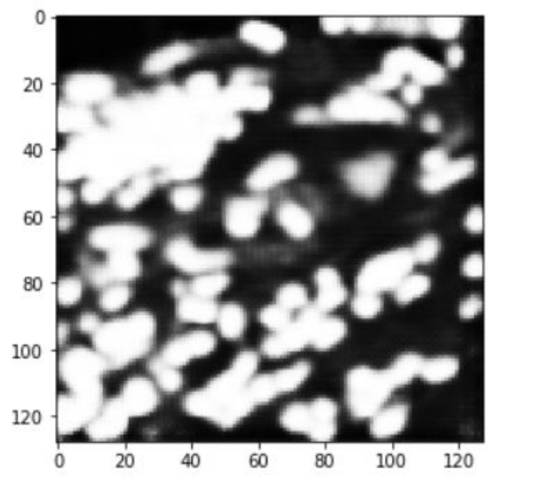
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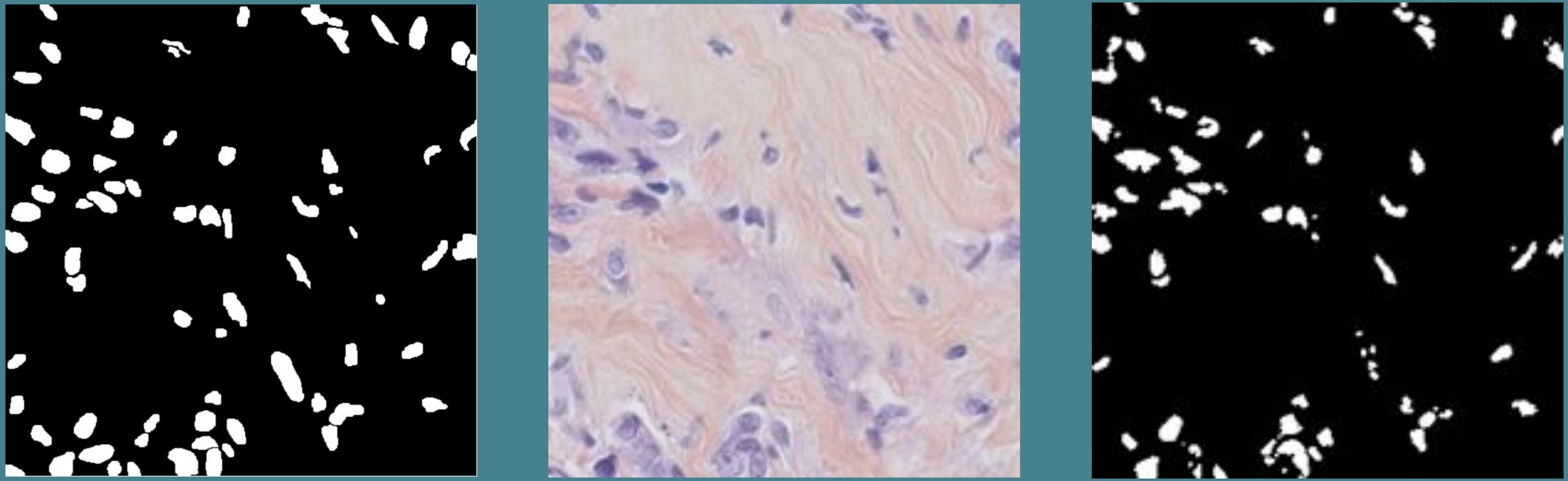
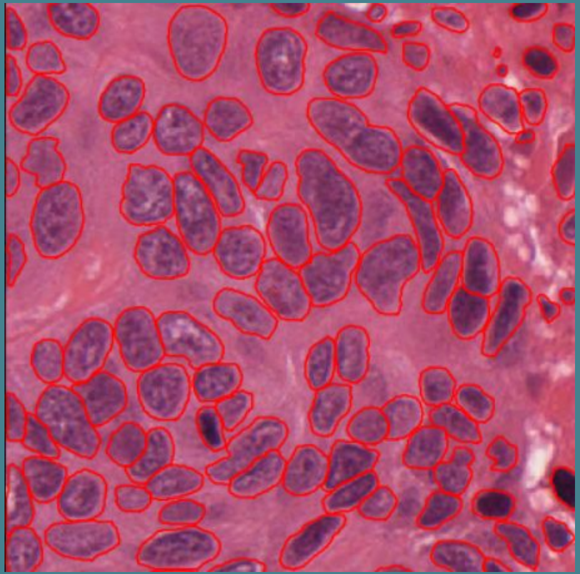
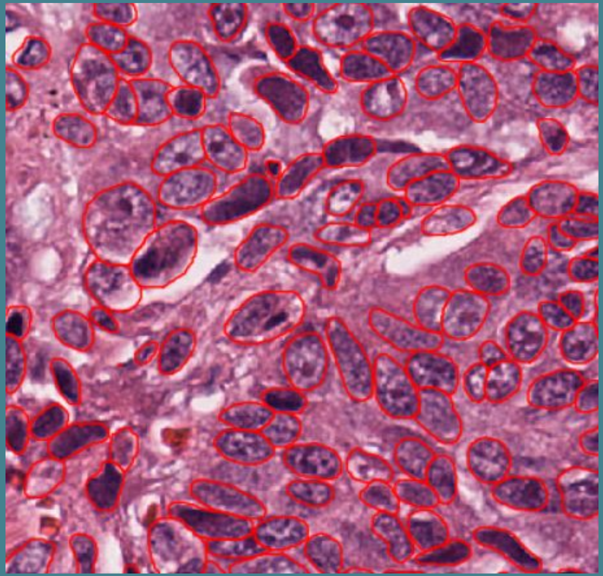
Unsupervised - SegMed Model



Mask R-CNN





Thank you!