Convolutional Neural Network-based Mitosis Detection

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Introduction

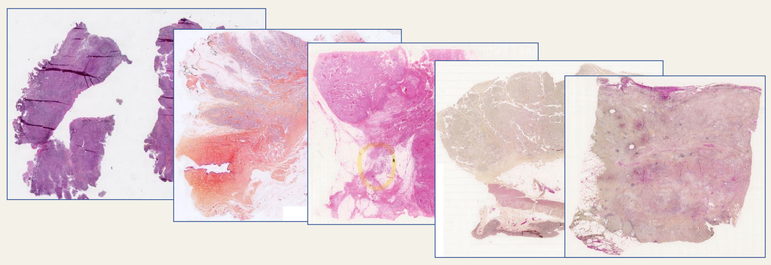
Context:

- The mitotic index is essential for the establishment of many cancer prognosis, namely breast cancer and peritoneal mesothelioma considered in this study.
- The traditional method of manually counting mitosis in histological images is tedious and subject to inter and intra observer variability.

→ Automatic mitosis detection is necessary to standardize and accelerate the mitosis analysis.

Challenges:

- **Stain variability** due to the difference of scanners, difference in sample preparation and image acquisition process e.g. some slides are stained with only H&E stains while others are strained with an additional safran stain.



- **Cell variability** due to the biological development of mitosis. Each mitotic phase (prophase, metaphase, anaphase and telophase) gives rise to a different shape of the nuclei.

Approach and innovation:

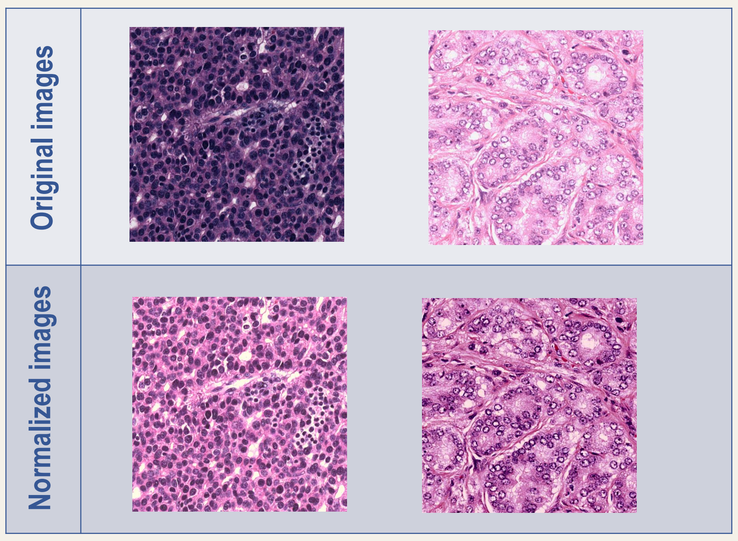
- Complete analysis pipeline accounting for stain variability and structural variability of cells
- Combining different CNN architectures to maximize the detection accuracy
- Unique detection approach for different tumors (breast cancer and peritoneal mesothelioma)

Method

Step 1 : Stain normalization

To uniformize the slide stains along the dataset we use Reinhart's normalization method [1]. The principle of this method is to use one slide as a reference image whose colors will be reproduced on all other slides .

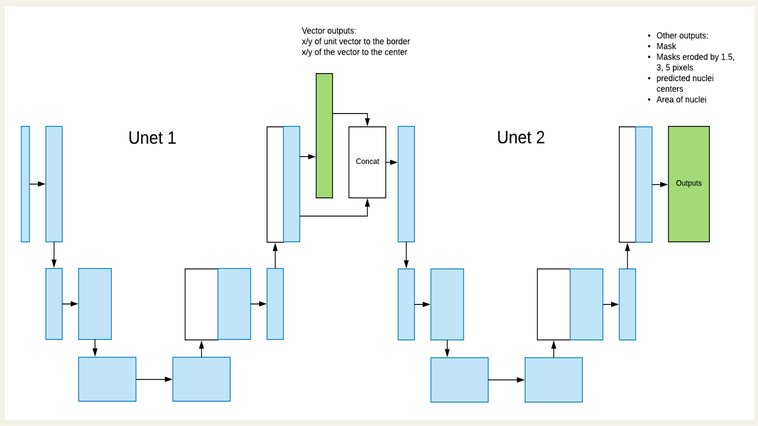
For that, we transfer the images in the lab color space and use a linear transformation so that the color distribution of the transformed image has the same mean and standard deviation as the reference image. The images are set back to the RGB color map so that they can be processed by a detection algorithm.



Results

Step 2 : Cell segmentation

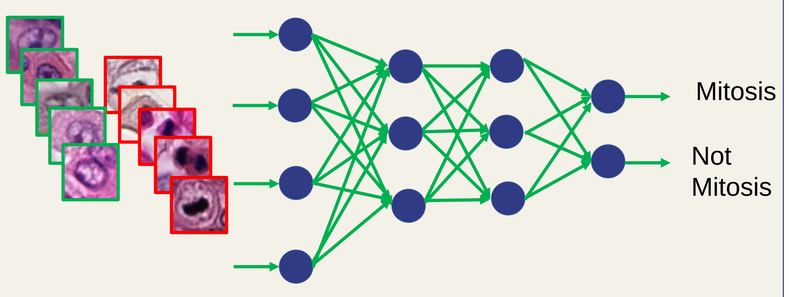
We use a particular architecture of a fully convolutional network called "Vector U-net" inspired from the article [3] for its ability to differentiate very heterogeneous cells in dense clusters by combining different objective functions considering different segmentation components such as the cell centers, the horizontal and vertical gradients, etc. We train the model on the dataset of the MICCAI 2018 challenge labeled « Multi-organ Nuclei Segmentation » containing 30 images with over 22,000 annotated cells.



Vector U-net architecture extracted from
https://www.kaggle.com/c/data-science-bowl-2018/discussion/55118

Step 3 : Cell classification

Each cell detected by the previous step is extracted in a patch of 64 x 64 pixels at a magnification of x40. A binary classification model using a Resnet50 pre-trained on ImageNet dataset was readjusted on a base containing more than 15000 cells with 3492 mitotic ones extracted from different samples (breast cancer and peritoneal mesothelioma).



Experiments & Results

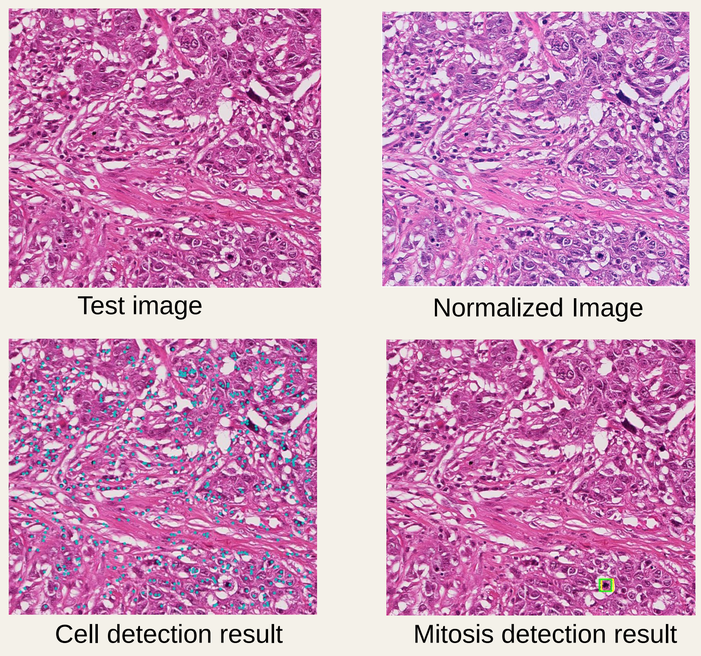
Dataset :

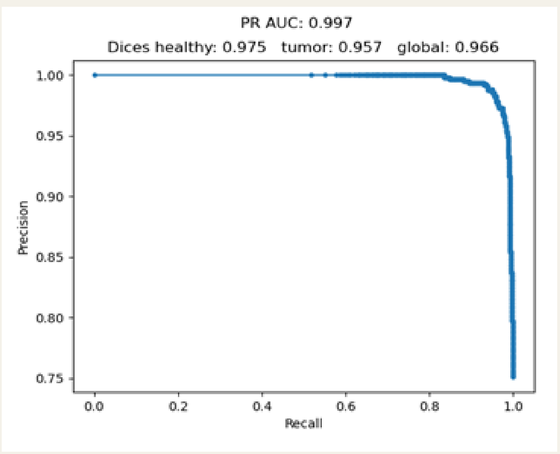
We used data from different sources and mixed different tumors (breast cancer and peritoneal mesothelioma):

- **Gustave Roussy Institute :** 143 peritoneal mesothelioma slides containing 588 annotated mitosis.
- **TUPAC'16** : 73 breast cancer slides collected from different Netherland centers and contains about 1500 annotated mitosis.
- **MITOS'14 :** 22 breast cancer slides aquired with different scanners (Hamamatsu and Aperio) and contain about 1404 annotated mitosis.

The data was split into training and validation sets (80% vs 20%). The model was trained in an iterative hard mining fashion to reduce the false positive rate while keeping a high true positive detection rate. Evaluation is also performed using Precision-Recall curve as well as the AUC value (Area Under the Curve).

Results





$$\text{Precision} : \frac{TP}{(TP+FP)}$$

$$\text{Recall} : \frac{TP}{(TP+FN)}$$

TP : True Positive

FP : False Positive

FN : False Negative

Conclusion

Summary:

- **High precision** model for mitosis detection robust to stain and cell variability
- Novel analysis approach based on the **combination of U-net and Resnet50** architectures.
- **Unique** model for multiple organ analysis

Future work:

- Include other datasets: MITOS12 and AMIDA13
- Extend the model to other organs
- Large scale validation

References

[1] Color normalization in digital histopathology images. D. Magee, D. Treanor, D. Crellin, M. Shires, K. Smith, K. Mohee, and P. Quirke. Citeseer

[2] U- net: Convolutional networks for biomedical image segmentation, Ronneberger, Olaf and Fischer, Philipp and Brox, Thomas, International Conference on Medical image computing and computer-assisted intervention, pp 234-241, 2015.

[3] Deep watershed transform for instance segmentation, M. Bai and R. Urtasun. CoRR, abs / 1611.08303, 2016.

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