Pattern Recognition Lab

Freie Universität Berlin

FRIEDRICH-ALEXANDER UNIVERSITÄT ERLANGEN-NÜRNBERG
FACULTY OF ENGINEERING

Field Of Interest Proposal for Augmented Mitotic Cell Count: A Comparison of Two Networks

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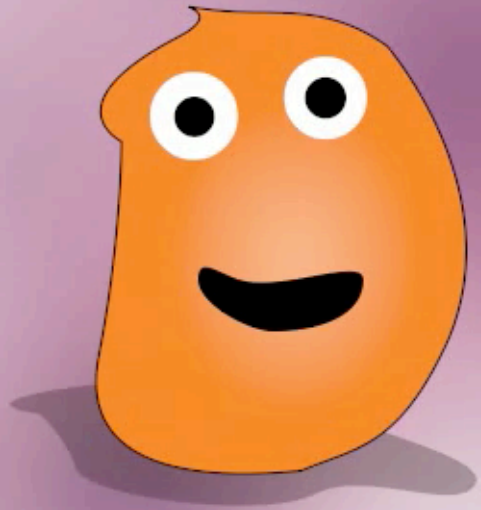
Mitosis [cell division]



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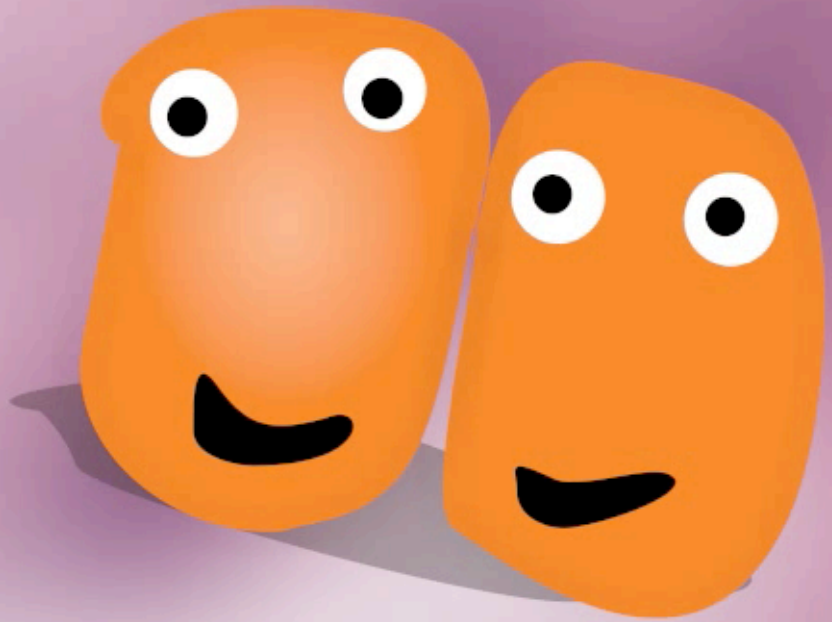
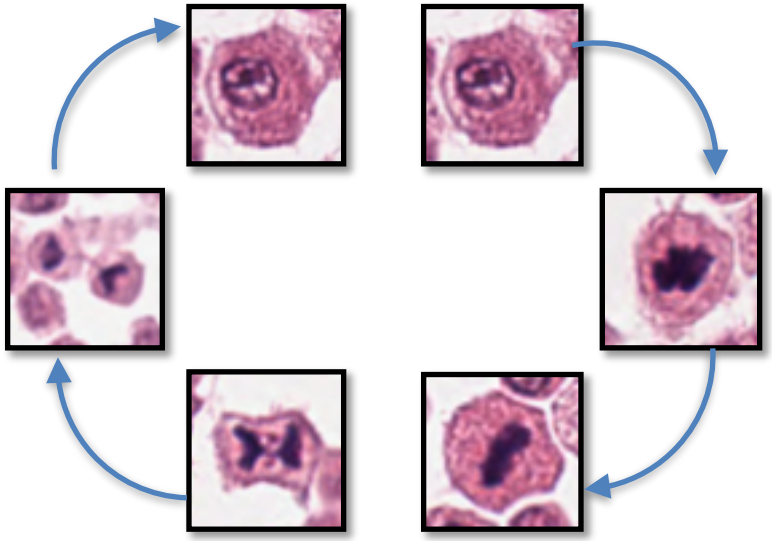


Mitosis
[cell division]

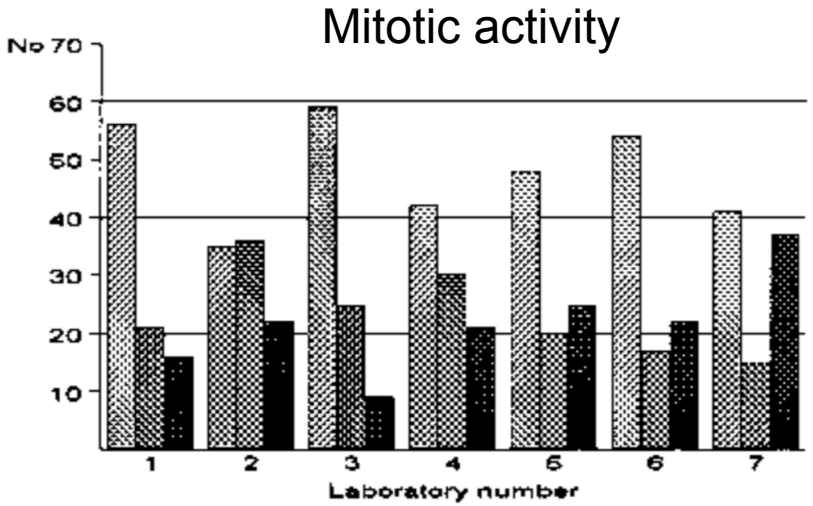
Mitosis
[cell division]

Mitosis and Mitotic Count

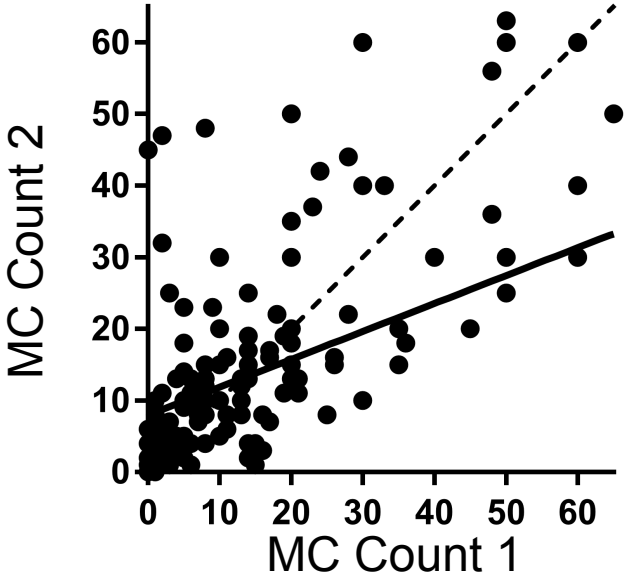
- Mitotic Count (MC) = Count of mitotic figures per area (typically: 10 High-Power-Fields)
- Mitotic activity strongly correlates with cell-proliferation
- Important factor in most grading schemes, e.g: Bloom&Richardson, Kiupel, etc...



Intra- and inter-rater agreement on mitotic count



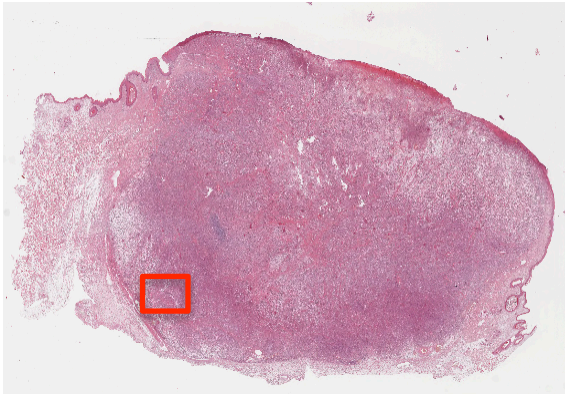
Boiesen, P., et al. (2000). Histologic grading in breast cancer: reproducibility between seven pathologic departments. Acta Oncologica, 39(1), 41–45.



Bertram, C. A., et al. (2018). Validation of Digital Microscopy Compared With Light Microscopy for the Diagnosis of Canine Cutaneous Tumors:. Veterinary Pathology, 55(4), 490–500.

Mitotic Count in Grading Schemes

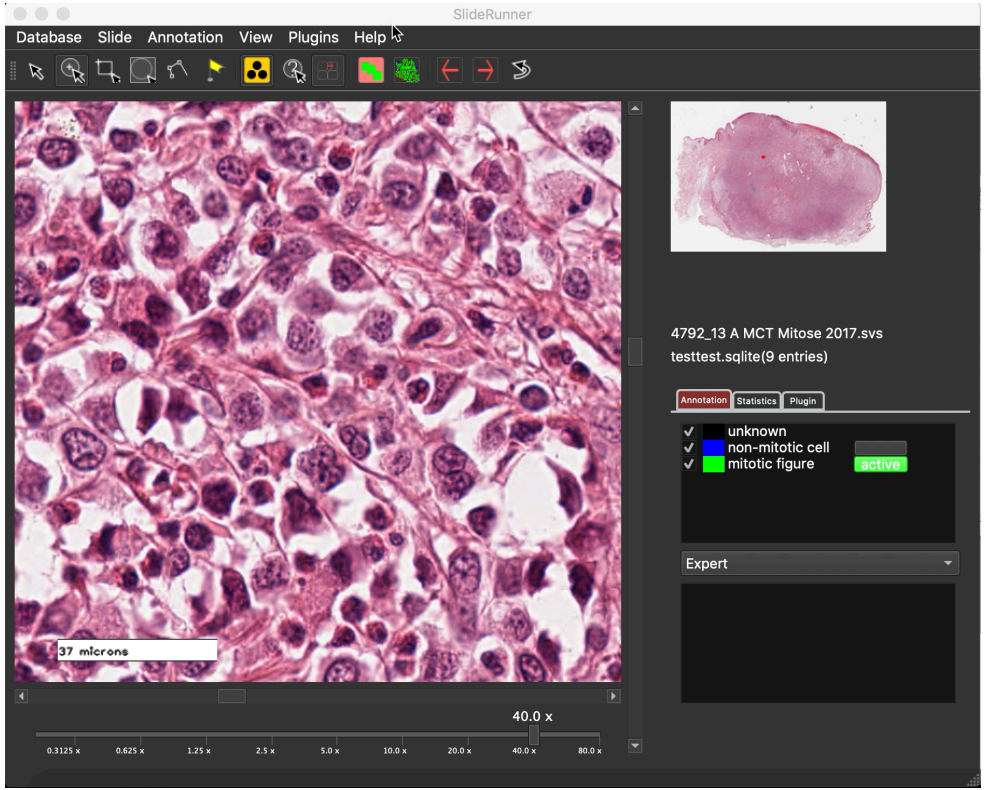
- Typically mitotic figures are counted in the region of highest mitotic activity.
- Aim: Assessing malignancy in most malignant part of the tumor
- Area size for counting is fixed (for our case: 2.37 mm2)
- Determination of area of highest mitotic activity is somewhat fuzzy.



The region recommended is at the periphery; tumor margin with non-neoplastic tissue. This region has the most active cellular proliferation, it is the invasive front, fixation is typically optimal, whereas mitoses are usually less frequent in the center of a tumor[...]

Meuten, D. J. (2016). Appendix: Diagnostic Schemes and Algorithms. In *Tumors in Domestic Animals* (Vol. 23, pp. 942–978). Hoboken, NJ, USA: John Wiley & Sons, Inc. http://doi.org/10.1002/9781119181200.app

Creation of a large-scale mitosis data set



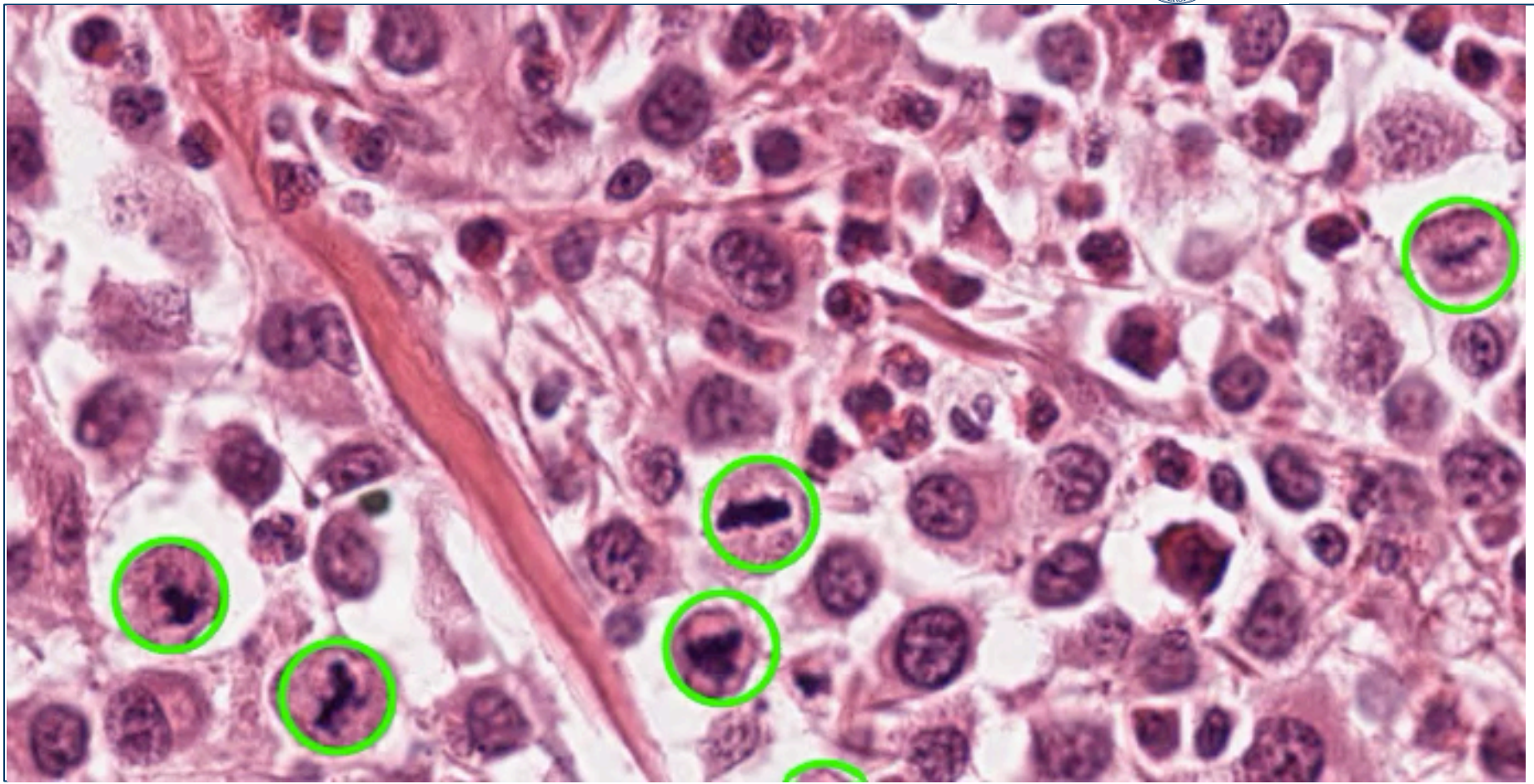
- Open Source software solution SlideRunner

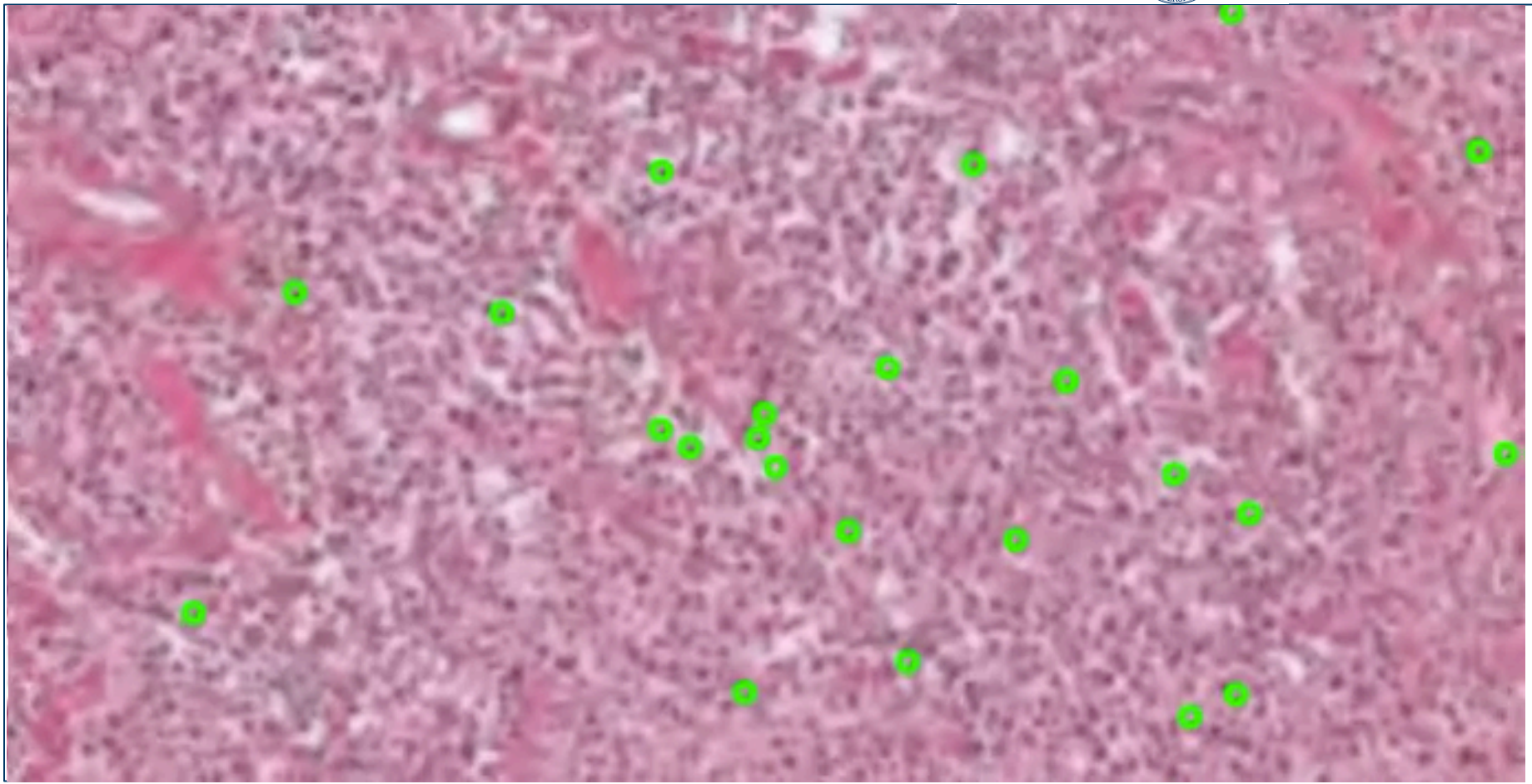
  github.com/maubreville/SlideRunner

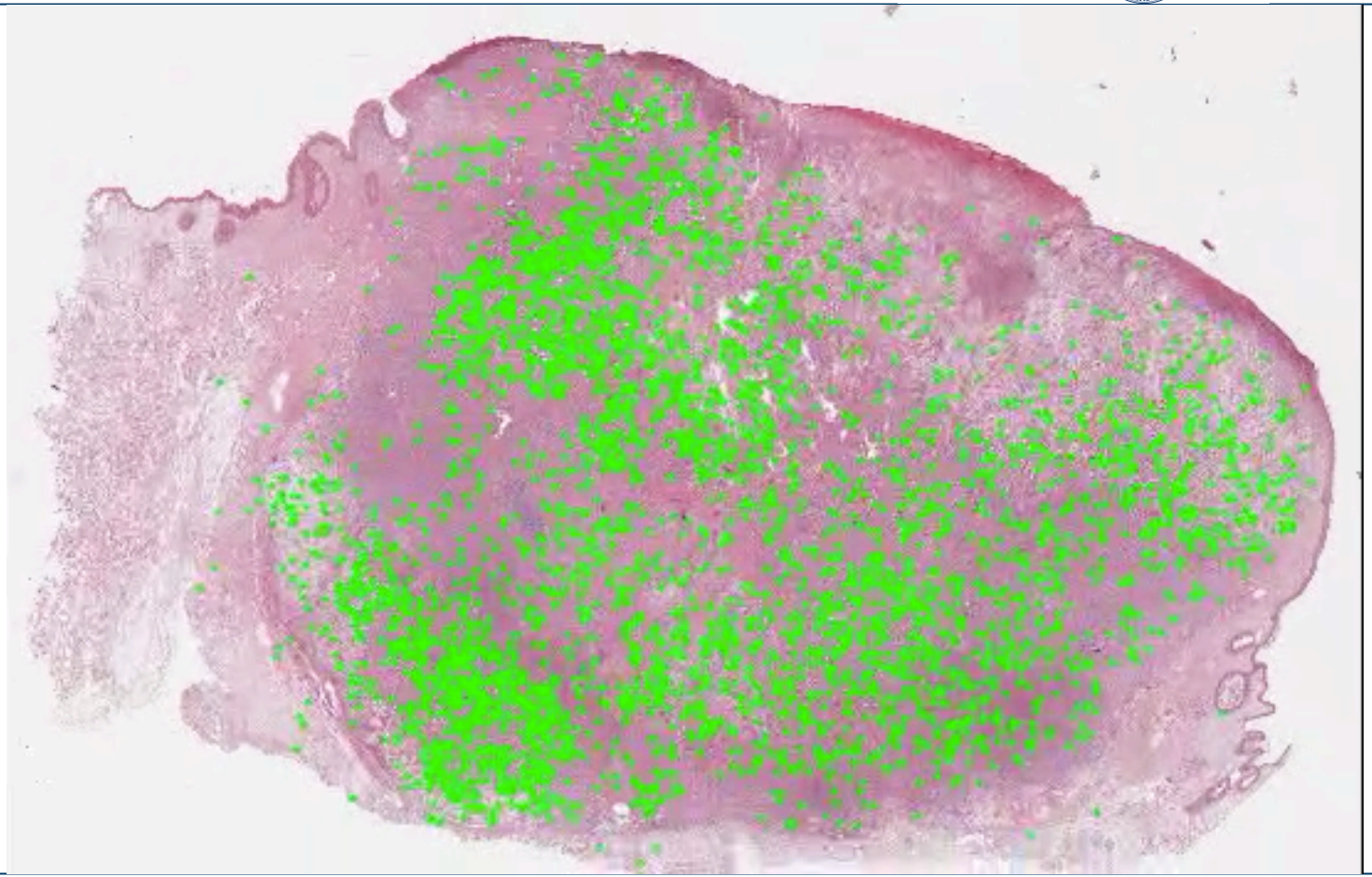
- One click annotations for cells

- Guided screening mode with blind option for multiple experts

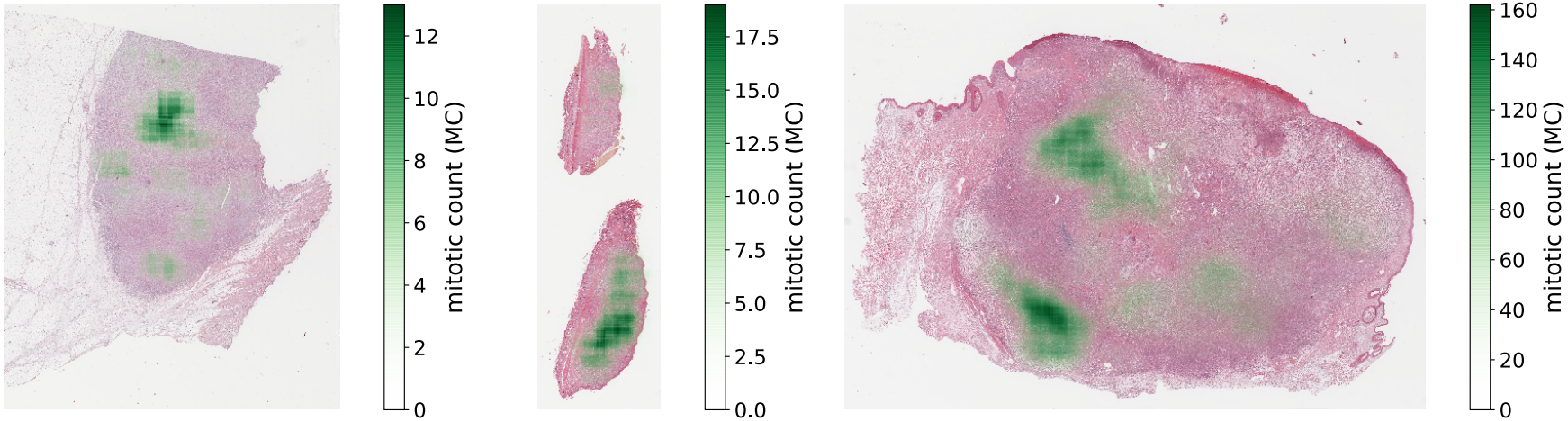
- But it still took some time...







Center vs. Periphery



[Bertram, Aubreville, et al., Vet. Pathol. (in revision)]

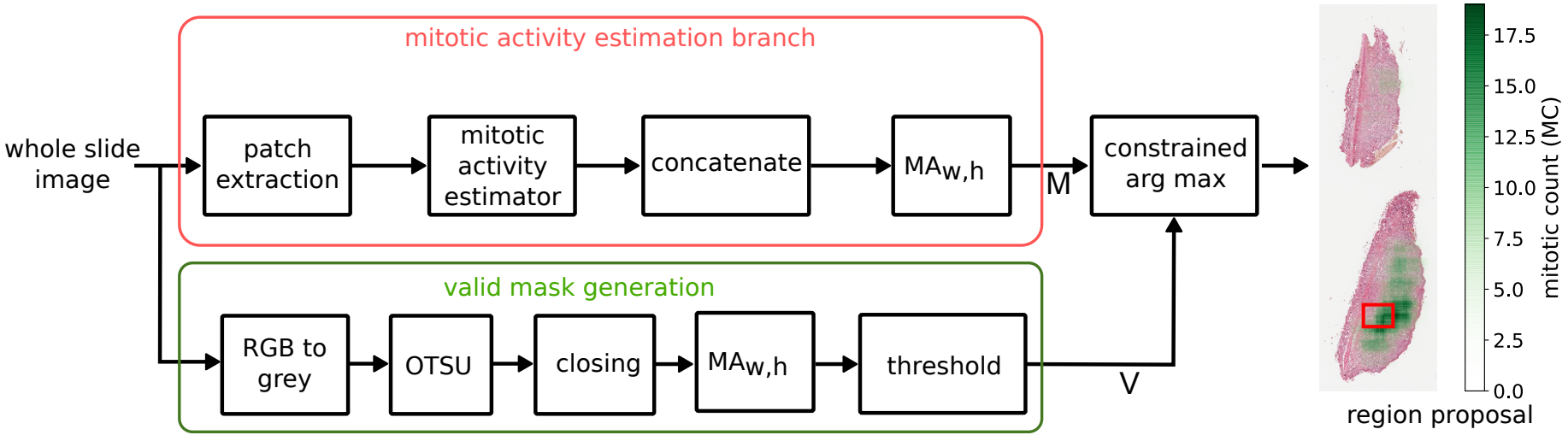
- No statistical difference between center and periphery in mitotic count in our canine cutaneous mast cell tumor data set.
- But certainly a patchy distribution!

Our dataset

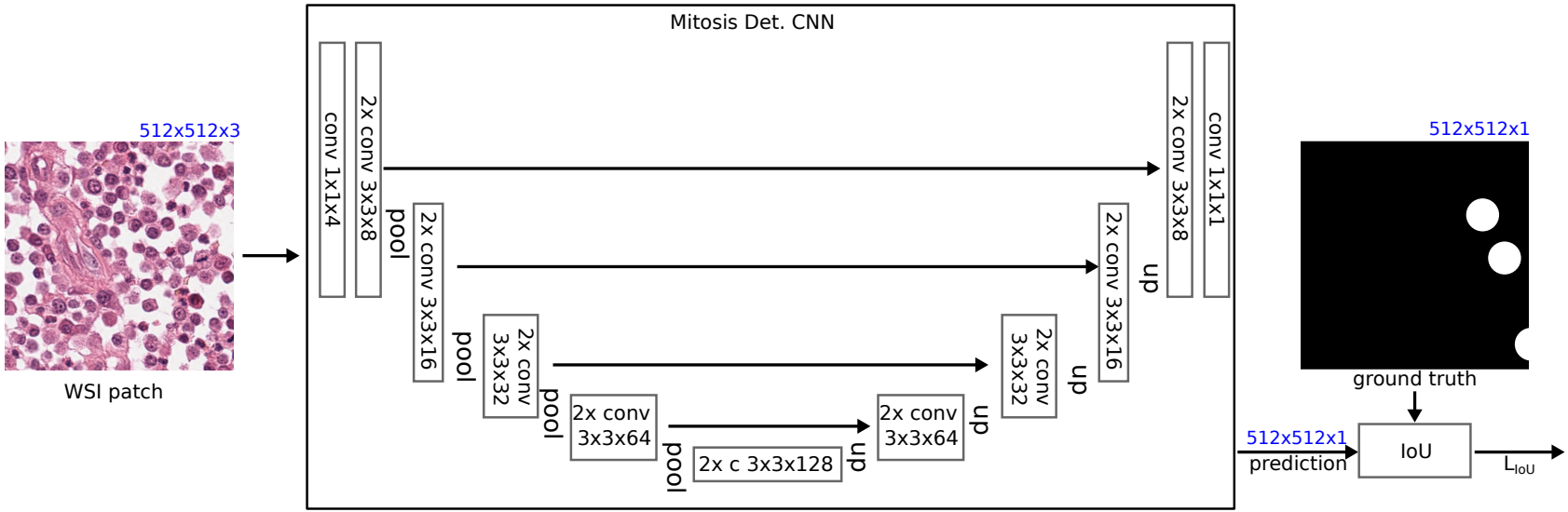
	Our data set	TUPAC16 [Veta et al.]
Number of cases	32	73
Tumor type	canine cutaneous mast cell tumor	human mamma carcinoma
Cases completely annotated for mitosis	32	0
Mitotic figures	42,652	1,552
Area annotated	4,939 mm2	251.5 mm2

Veta, M., Heng, Y. J., Stathonikos, N., Bejnordi, B. E., Beca, F., Wollmann, T., et al. (2018). Predicting breast tumor proliferation from whole-slide images: the TUPAC16 challenge. CoRR (Vol. cs.CV).

General Approach

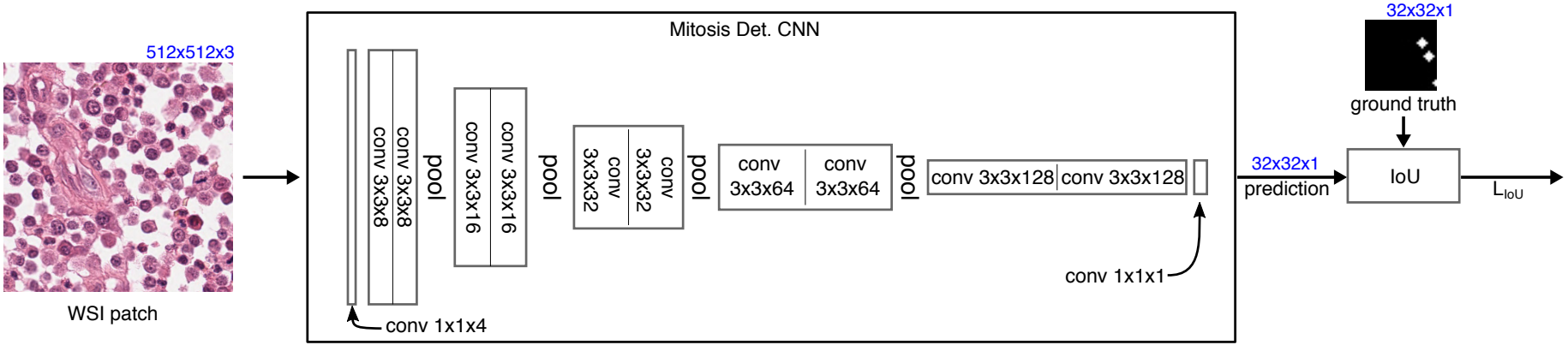


Fine map-based detection (U-Net)



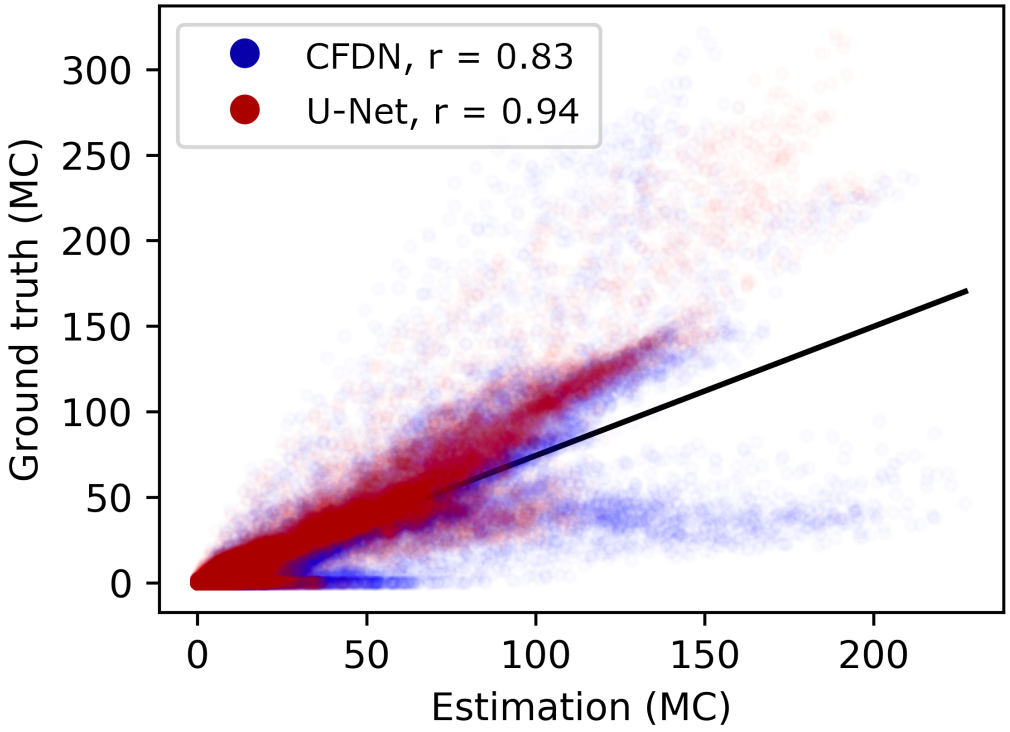
Ronneberger, O., Fischer, P., & Brox, T. (2015). U-Net - Convolutional Networks for Biomedical Image Segmentation. In International Conference on Medical image computing and computer-assisted intervention (Vol. 9351, pp. 234–241). Cham: Springer International Publishing. http://doi.org/10.1007/978-3-319-24574-4_28

Coarse map-based detection (CMDN)

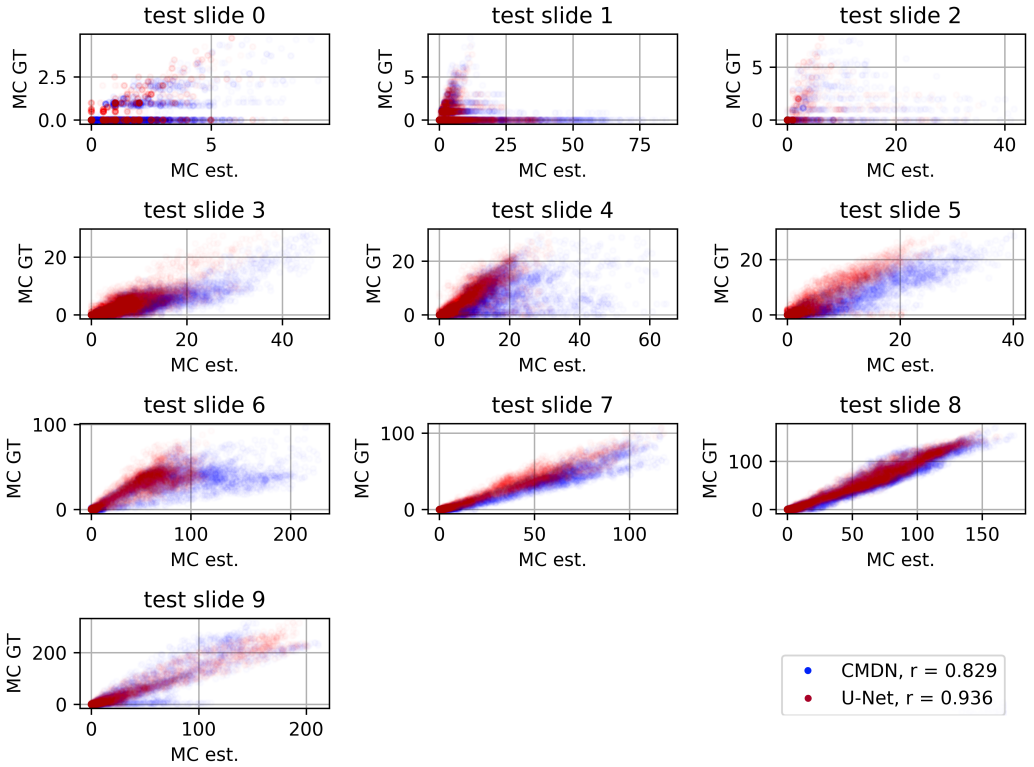


Results: Correlation

- Correlation between ground truth mitotic count and estimated mitotic count



Correlation on single slides

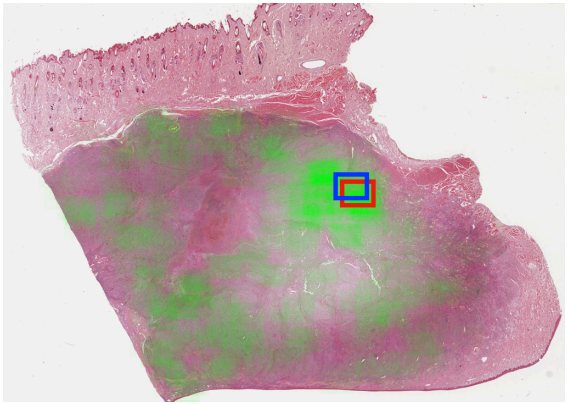
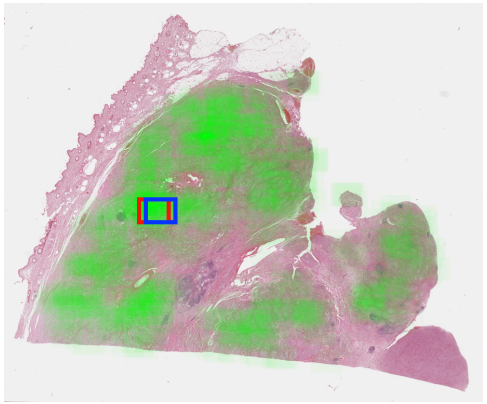
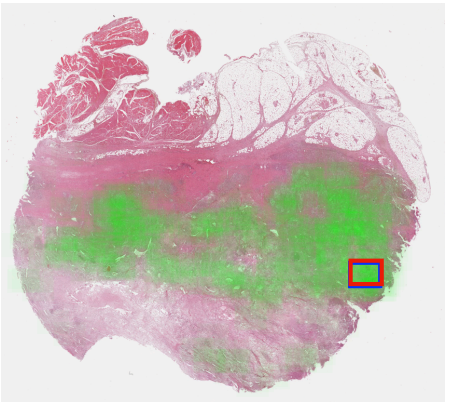


Over-estimation for low MC slides for both detectors

Slight over-estimation of MC by CMDN

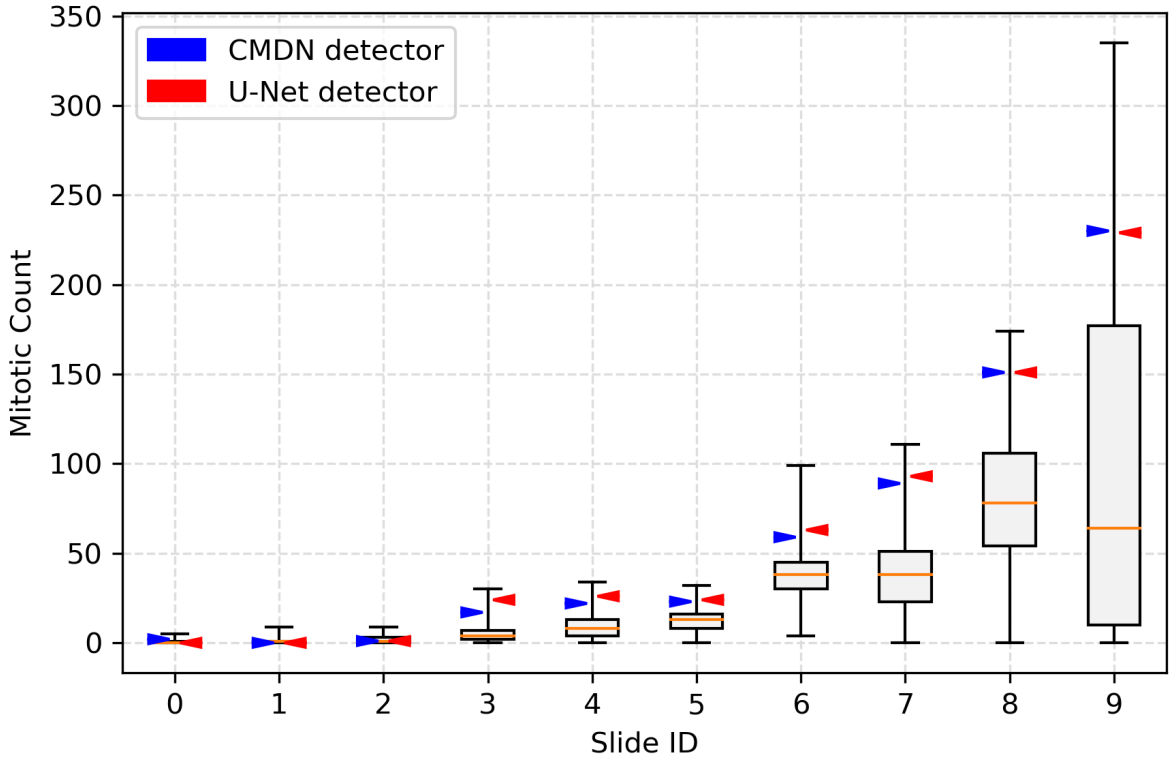
But:
Could be effect of model selection!

Results: Examples

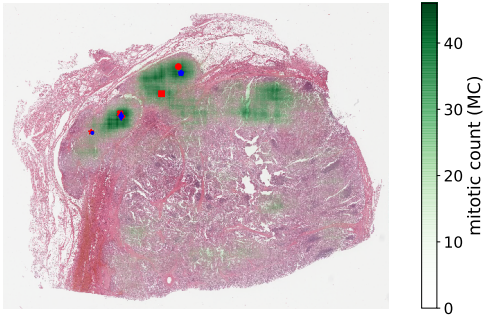




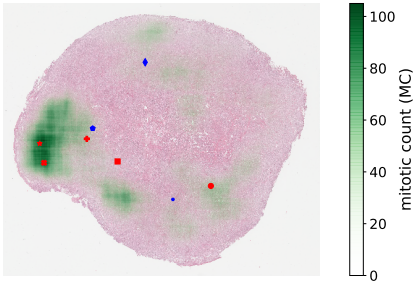
Results: Region of Interest Prediction

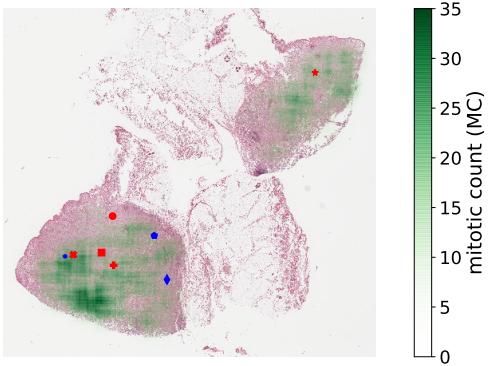
- Ground truth mitotic count based on predicted region of interest

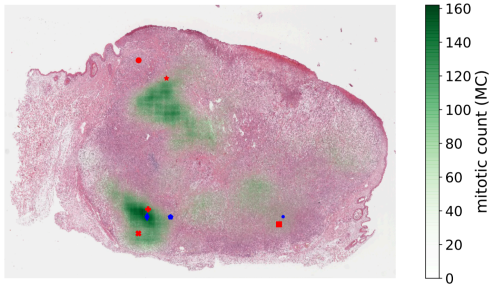


Cross-check: How well can experts predict the field of interest?









pre-published on

arxiv:1902.05414

board certified veterinary pathologists (BCVP)

veterinary pathologists in training (VPIT)

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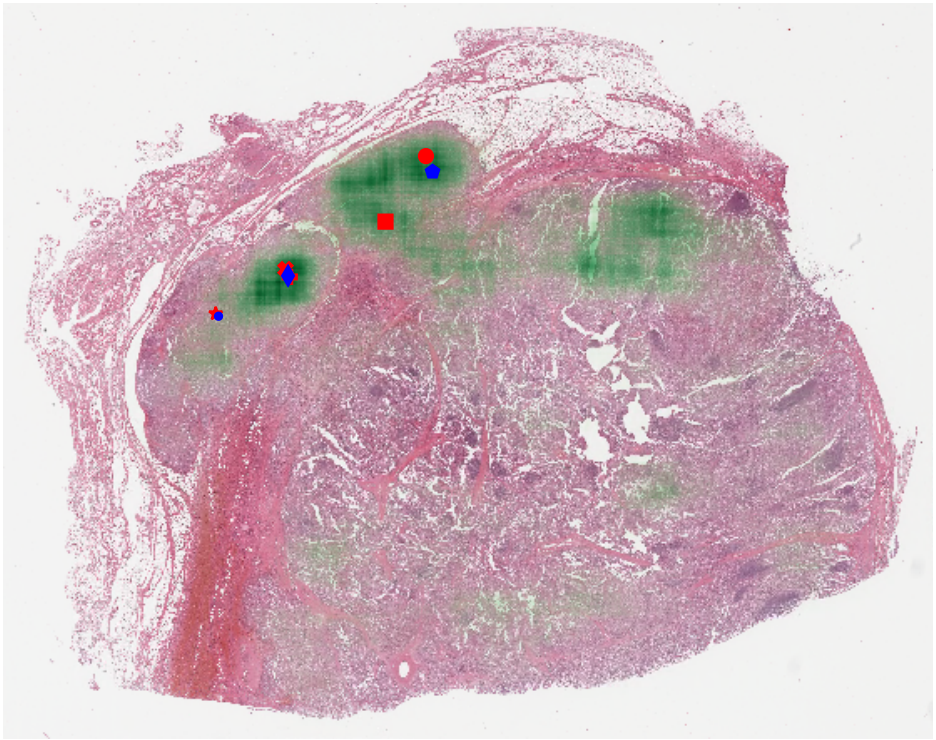

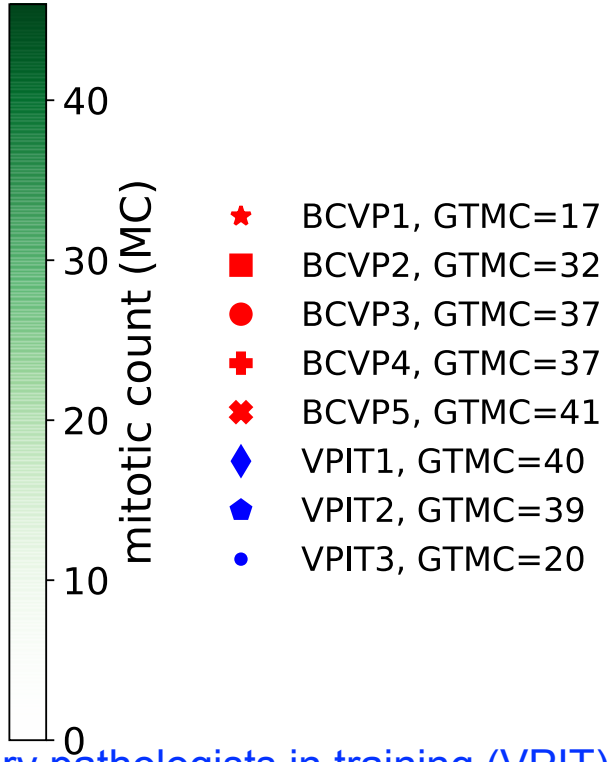

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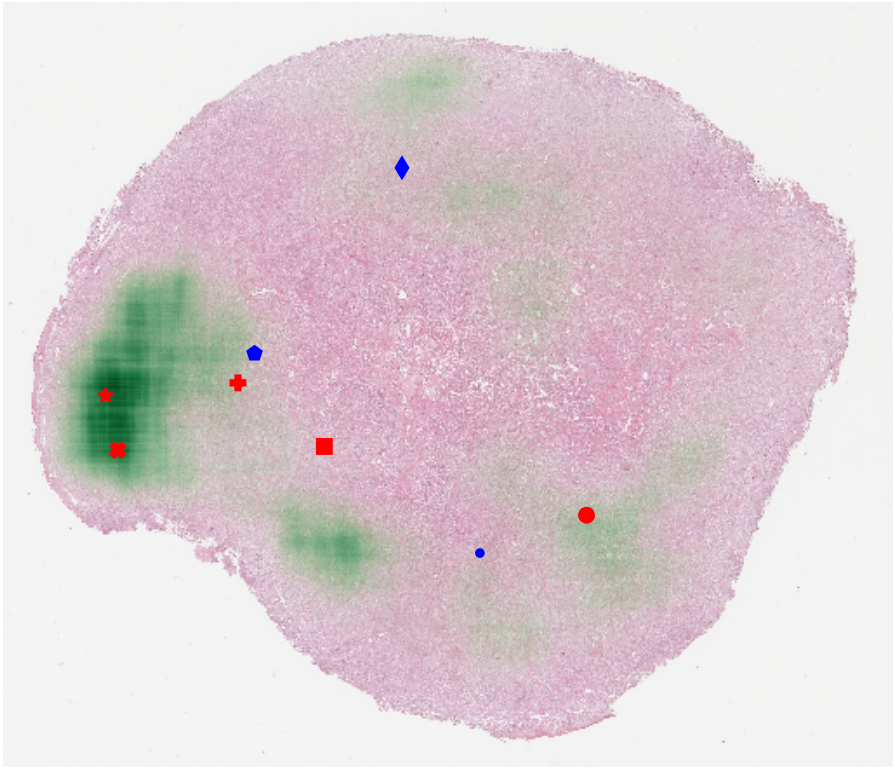

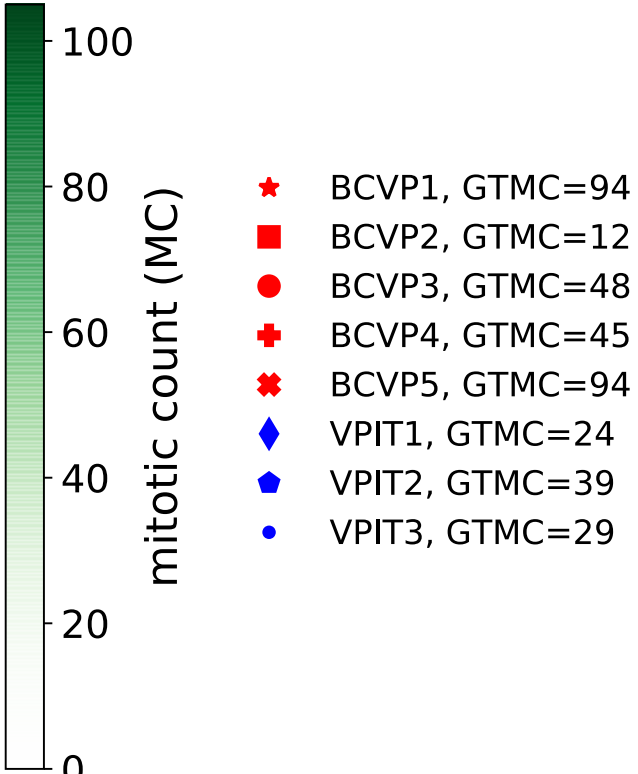

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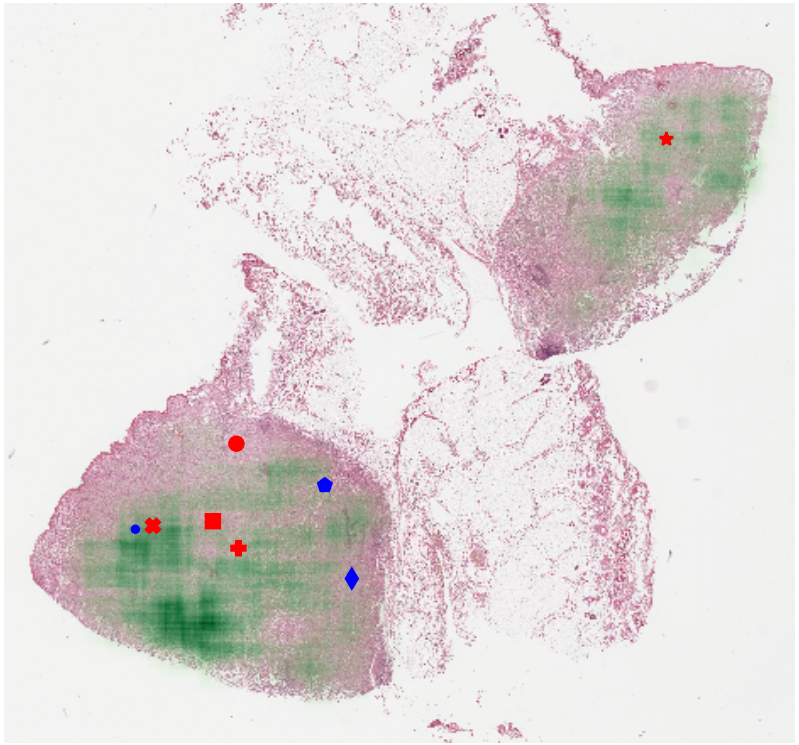

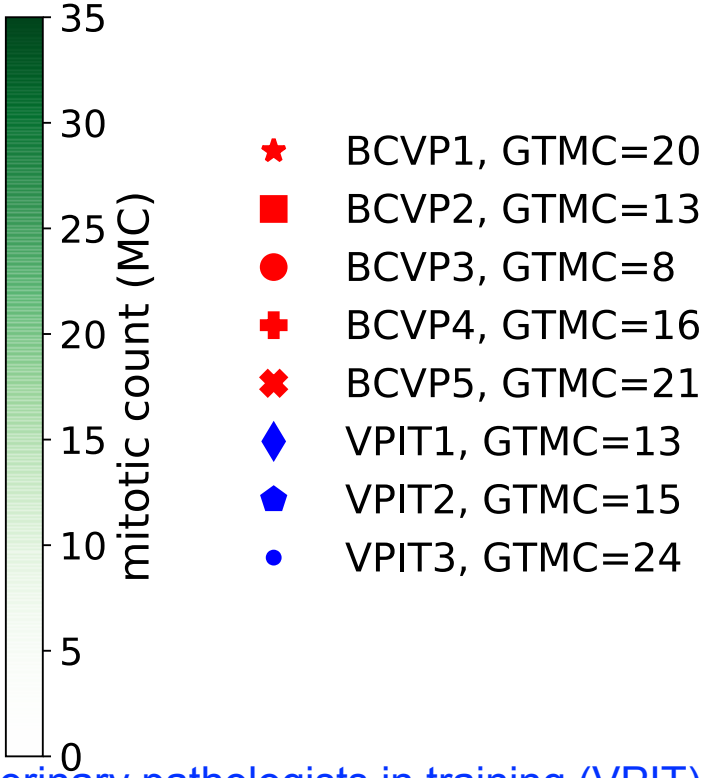

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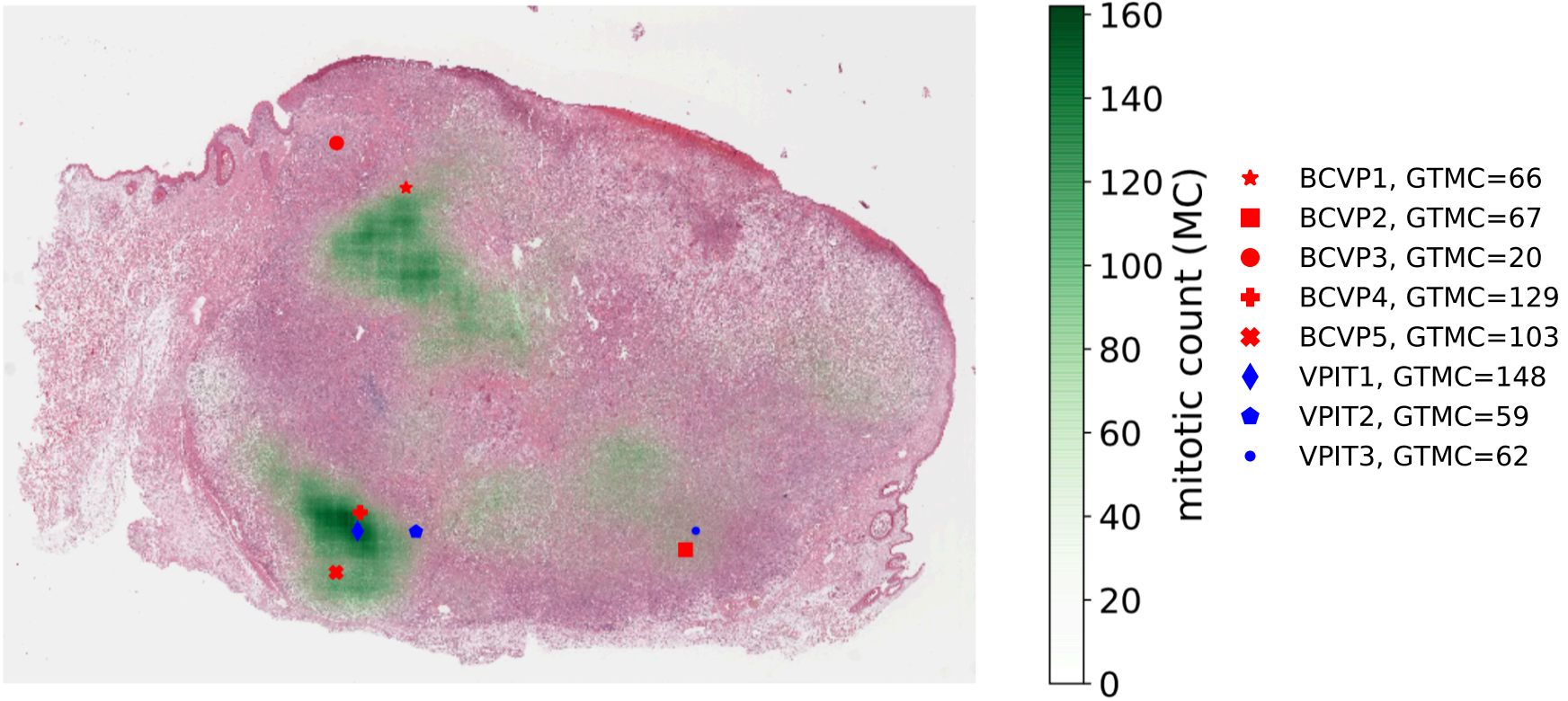

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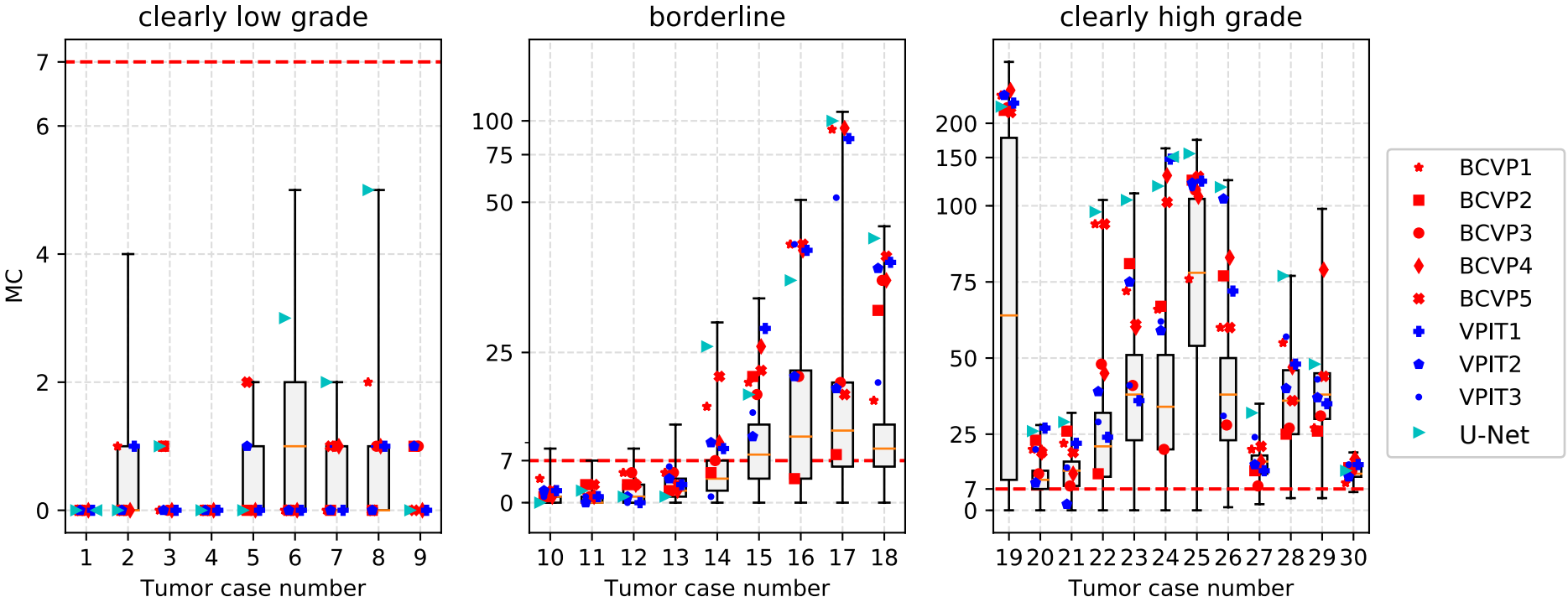
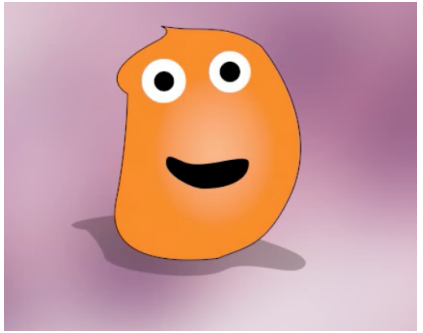
Comparison: Expert vs. Algorithm



Summary

- High inter-rater variance of mitotic count likely cause by high variance in field of interest selection
- Very mixed expert performance, reducing reproducibility.
- Proposed method:
  Deterministic way of finding field of interest
- On average: Better performance than human experts.



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