Dynamically Ranking Urothelial Cells by Malignancy Using Multiple Instance Learning and Attention

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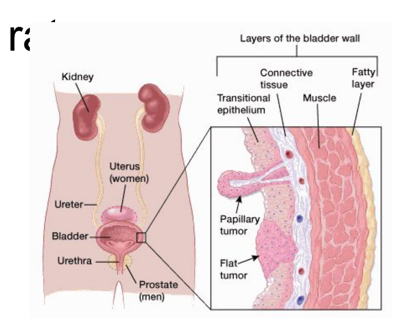
ABSTRACT

Urothelial carcinoma's (UC) heterogeneity complicates diagnosis and treatment. Used AutoParis-X features, including cell morphology and deep-learning features. **Multiple-instance learning** was applied with slides as bags and cells as instances. An attention mechanism ranked cells by malignancy relevance. **Results for the Attention Model:** 79% accuracy, 0.76 AUROC.Results for the Baseline Model: 67% accuracy, 0.66 AUROC.
The Attention Model outperformed the Baseline Model, showing promise for improving UC diagnostics.

INTRODUCTION

Urothelial carcinoma such as Bladder Cancer is the 5th most common non-cutaneous cancer in the U.S., with a 31% recurrence rate. Current cytology is cost-effective but suffers from:

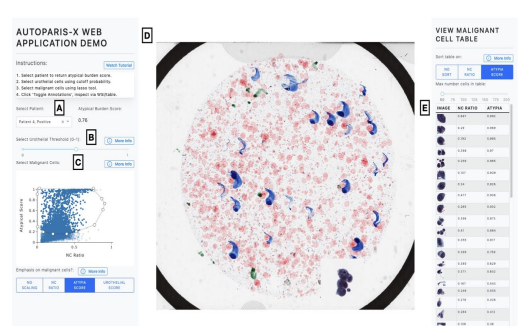
- **Labor-Intensive**: Time-consuming and error-prone.
- **Screening Bias**: Variability and missed patterns.
- **Limited Scalability**: Struggles with high test volumes.



Automating cytology could improve efficiency, accuracy, and consistency while reducing costs and detecting subtle patterns.

AutoParis-X

- Software application with several deep learning models to analyze urine cytology
- Extracts cell and cluster-level features including NC ratio, atypia score, and morphological measures
- ***Does not rank relative malignancy of cells***



Current Approaches

- RankNet, introduced by Burges et al. in 2005, employs neural networks to learn a ranking function by comparing pairs of examples, which can result in computational inefficiency, particularly when working with large datasets.
- Sanghvi et al. developed a semi-autonomous diagnostic decision aid for bladder cancer using deep learning to rank cells based on their likelihood of malignancy, but it faces challenges such as reliance on high-quality labeled data and limited interpretability of the model's predictions.
- Butke et al. proposed an end-to-end multiple instance learning approach for whole-slide cytopathology of urothelial carcinoma, which learns to rank regions of interest within a slide. However, this approach faces challenges such as increased complexity in model training and potential issues with false positives or negatives.

What is Multiple Instance Learning (MIL)?

MIL is a machine learning approach where only bag-level labels are known, not individual instances within the bags.

Why is MIL Useful?

1. **Handles Incomplete Labeling:** Useful for datasets with only overall labels, such as medical images where individual labels are impractical.
2. **Identifies Relevant Instances:** Focuses on important regions within bags, improving detection accuracy, like spotting malignancy in pathology slides.

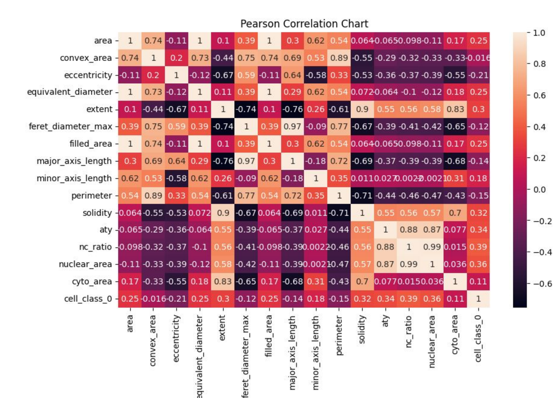
METHODS

Data Collection

- **Slide Acquisition:** Dataset of cytology slides from DH
- **Cell Extraction:** AutoParis-X extracted features
  - Morphological features (e.g., cell shape, size, nuclear morphology).
  - Deep learning-extracted features (e.g., atypia score, NC ratio)
  - Limited to 3000 cells per slide

Feature Selection

- Features were selected based on Pearson correlation and literature review
- Features involving NC ratio and cytoplasmic area showed greater correlation with slide malignancy classification
- Features that shared high correlations had only one feature selected for dimensionality reduction



Multiple Instance Learning (MIL) Framework

- **Bags:** Cytology slides
- **Instances:** Urothelial cells
  - **Malignant slides:** Have at least one malignant cell
  - **Benign slides:** Have no malignant cells

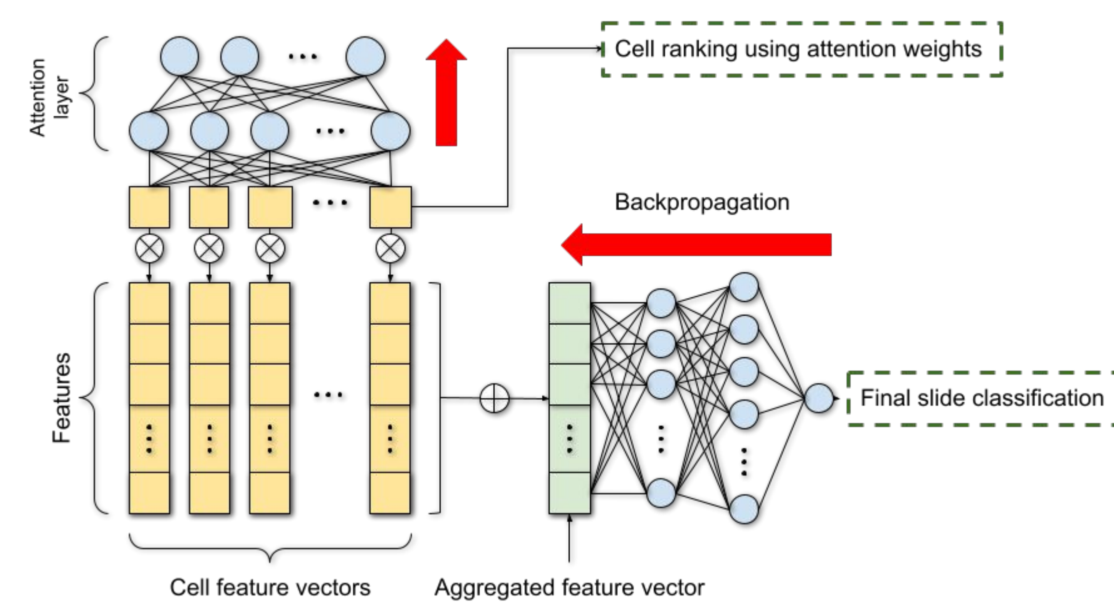


Figure 1: Slide-level Attention Framework

RESULTS

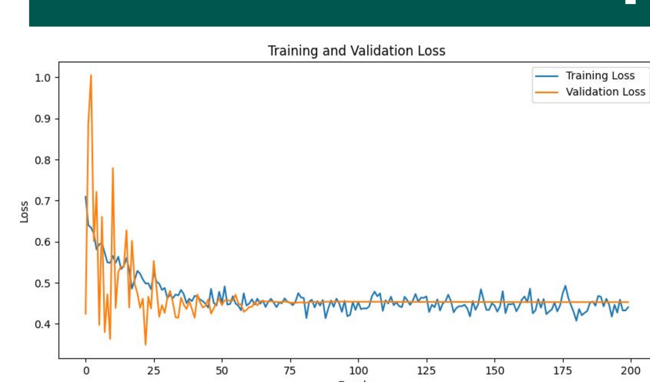


Figure 2: Loss Graph

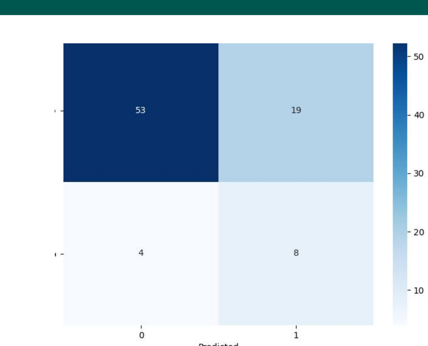


Figure 3: Confusion Matrix

	Accuracy	AUROC	F1
Attention Model	**0.79**	**0.76**	0.36
Baseline Model	0.67	0.66	**0.63**

Table 1:Ablation Study Results

Model Evaluation

Challenge: No predetermined rankings of cells on the slide.
Solution: Our model ranks cells without supervised guidance.
Evaluation:
- **Accuracy:** Measures how well the model's ranking matches the slide's classification.
- **AUROC:** Assesses the model's ability to distinguish between different classes.
- **F1 Score:** Evaluates the balance between precision and recall in the ranking.

Objective: Validate the model's effectiveness by comparing its rankings to the known slide classifications.

DISCUSSION

Model Performance and Loss Analysis

- Training loss decreased and stabilized, showing effective learning.
- Validation loss had initial variability but eventually converged, suggesting good generalization.
- Model with attention outperformed baseline model in accuracy and AUROC
- Loss graph indicates some instance of overfitting due to stagnation after 50 epochs

Confusion Matrix Insights

- Model shows sensitivity to overlapping features between benign and malignant cells.
- Confusion matrix results indicates the model's main classification weakness lies in the false positives category

Ablation Study Results

- Attention model performed better than baseline in accuracy and AUROC.
- Lower F1 score reflects a trade-off between precision and recall.

FUTURE WORK

- Reduce number of false positives by determining a higher threshold
- Develop saliency map to understand which regions of cells are more responsible for slide classifications
- Experiment with different learning weights and a weight scheduler
- Integrate project into web app

CONCLUSION

Enhanced Diagnostic Accuracy

- The integration of the attention mechanism within our multiple instance learning framework substantially improved the model's diagnostic accuracy and AUROC.
- The attention mechanism effectively highlighted the most relevant cells, refining the model's ability to distinguish between benign and malignant urothelial cells.

Precise Cell Ranking

- The model's capacity to dynamically rank cells based on their malignancy is a significant advancement, offering a more nuanced evaluation compared to traditional methods.
- This approach enables more targeted and accurate assessments, contributing to better diagnostic and treatment strategies for urothelial carcinoma.

REFERENCES : American Cancer Society. (2017). Bladder cancer. In Cancer Facts & Figures 2017 (pp. 1-72). American Cancer Society. Retrieved from https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-facts-figures-2017.html

1. Siegel, R. L., Miller, K. D., & Jemal, A. (2017). Cancer statistics, 2017. *CA: A Cancer Journal for Clinicians, 67*(1), 7-30. https://doi.org/10.3322/caac.21387
2. Babjuk, M., Burger, M., Zigeuner, R., Shariat, S. F., van Rhijn, B. W., Comperat, E., ... & Sylvester, R. J. (2013). EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder: Update 2013. *European Urology, 64*(4), 639-653. https://doi.org/10.1016/j.eururo.2013.06.003
3. Murphy, W. M., Soloway, M. S., & Jukkola, A. F. (1984). Urinary cytology and bladder cancer. The cellular features of transitional cell neoplasms. *Human Pathology, 15*(7), 675-684. https://doi.org/10.1016/S0046-8177(84)80003-9
4. Raab, S. S., & Grzybicki, D. M. (2009). Urine cytology and the detection of urothelial neoplasms: A review of the recent literature. *Cancer Cytopathology, 117*(3), 175-181. https://doi.org/10.1002/cncy.20029
5. Compérat, E. M., Burger, M., Gontero, P., Mostafid, A. H., Palou, J., Rouprêt, M., van Rhijn, B. W. G., Shariat, S. F., Sylvester, R. J., Zigeuner, R., & Babjuk, M. (2018). Grading of urothelial carcinoma and the new "World Health Organisation Classification of Tumours of the Urinary System and Male Genital Organs 2016". *European Urology, 73*(2), 240-246. https://doi.org/10.1016/j.eururo.2016.05.041
6. McCroskey, Z., Pambuccian, S. E., Kleitherms, S., Antic, T., Cohen, M. B., & Barkan, G. A. (2015). Accuracy and interobserver variability of the cytologic diagnosis of low-grade urothelial carcinoma in instrumented urinary tract cytology specimens. *American Journal of Clinical Pathology, 144*(6), 902-908. https://doi.org/10.1309/AJCPE1O9YKMRSQKG
7. Burges, C. J. C., Shaked, T., Renshaw, E., Lazier, A., Deeds, M., Hamilton, N., & Hullender, G. (2005). Learning to rank using gradient descent. In *Proceedings of the 22nd International Conference on Machine Learning* (pp. 89-96). ACM. https://doi.org/10.1145/1102351.1102363
8. Sanghvi, A. B., Allen, E. Z., Callenberg, K. M., & et al. (2019). Performance of an artificial intelligence algorithm for reporting urine cytopathology. *Cancer Cytopathology, 127*(10), 658-666. https://doi.org/10.1002/cncy.22162
9. Butke, J., et al. (2021). End-to-end multiple instance learning for whole-slide cytopathology of urothelial carcinoma. In *Proceedings of the MICCAI Workshop on Computational Pathology*. Retrieved from https://link.springer.com/chapter/10.1007/978-3-030-87237-3_11
10. Kather, J. N., Heij, L. R., Grabsch, H. I., Loeffler, C., Echle, A., Muti, H. S., ... & Zöllner, F. G. (2022). Pan-cancer image-based detection of clinically actionable genetic alterations. *Nature Cancer, 3*(4), 395-403. https://doi.org/10.1038/s43018-022-00334-5
11. Sirinukunwattana, K., Raza, S. E. A., Tsang, Y. W., Snead, D. R., & Rajpoot, N. M. (2016). Locality sensitive deep learning for detection and classification of nuclei in routine colon cancer histology images. *IEEE Transactions on Medical Imaging, 35*(5), 1196-1206. https://doi.org/10.1109/TMI.2016.2525803
12. Ilse, M., Tomczak, J. M., & Welling, M. (2018). Attention-based deep multiple instance learning. In Proceedings of the 35th International Conference on Machine Learning (Vol. 80, pp. 2127-2136). PMLR. Retrieved from https://proceedings.mlr.press/v80/ilse18a/ilse18a.pdf

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