Multiple Instance Learning for Heterogeneous Images: Training a CNN for Histopathology

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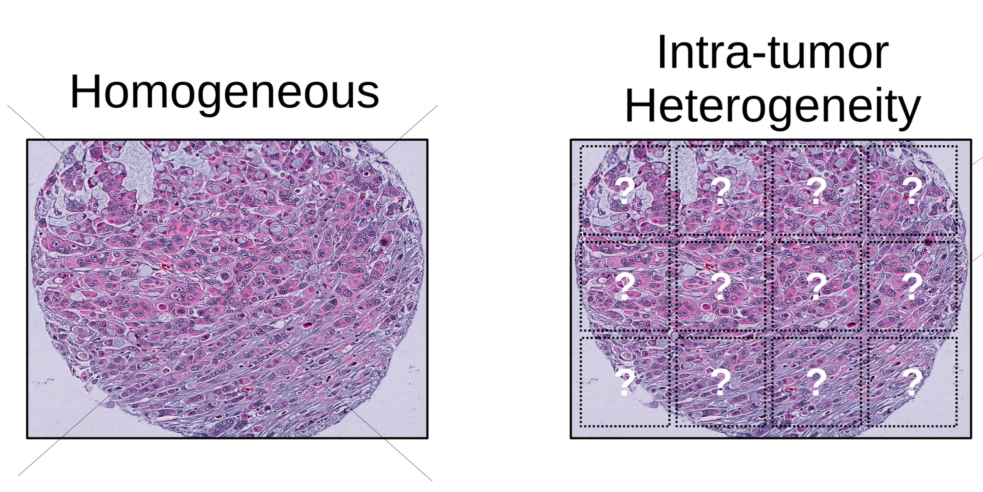
Problem Definition

Goals:

- Classification of large, heterogeneous images with a CNN
- Prediction of molecular properties of tumors that are not visually apparent to pathologists



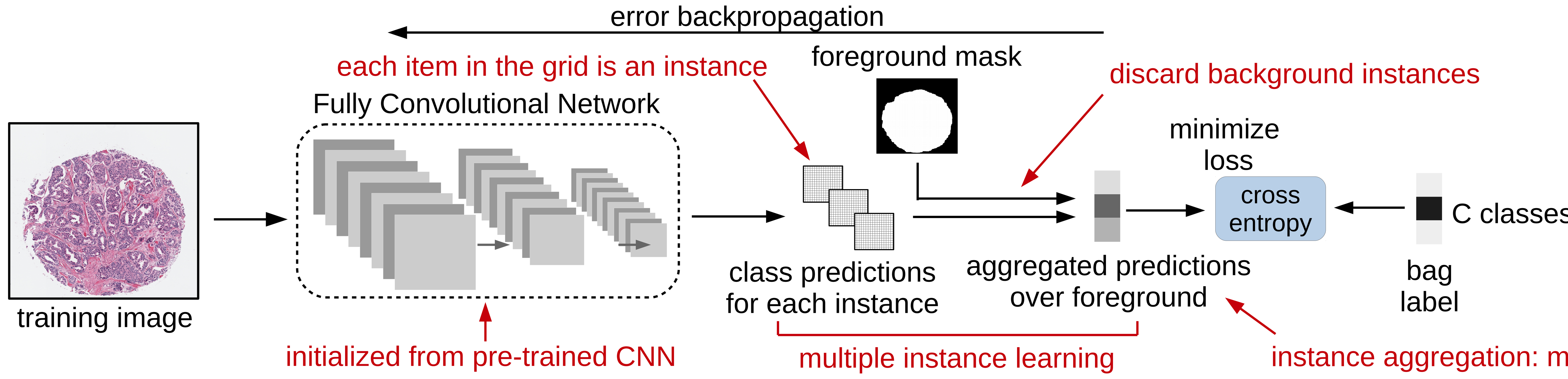
Approach: Multiple Instance (MI) learning with a CNN by adding an MI layer to aggregate instance predictions

Contributions:

1) A more general MI aggregation method that uses the quantile function for pooling and learns how to aggregate instance predictions
2) An MI augmentation technique for training MI methods
3) Exploration of single instance and MI learning on a continuous spectrum, demonstrating the importance of MI learning on heterogeneous images
4) Evaluation on a large data set of patient samples, showing significant gains in classifying breast cancer tissue microarrays
5) A method for visualizing the predictions of each instance, providing interpretability to the method

Multiple Instance Learning with a CNN

A fully convolutional network forms the instance classifier, followed by a global MI layer for instance aggregation



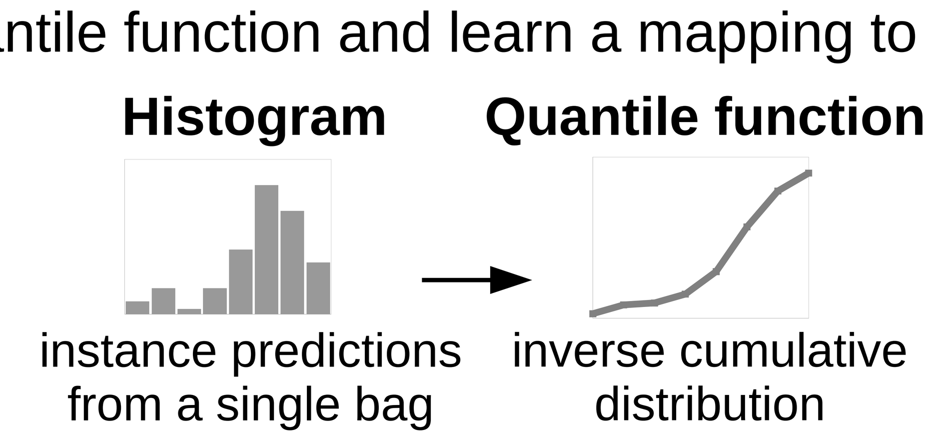
Instance Aggregation

Aggregate instance predictions into bag prediction

Max: maximum of predictions for each class

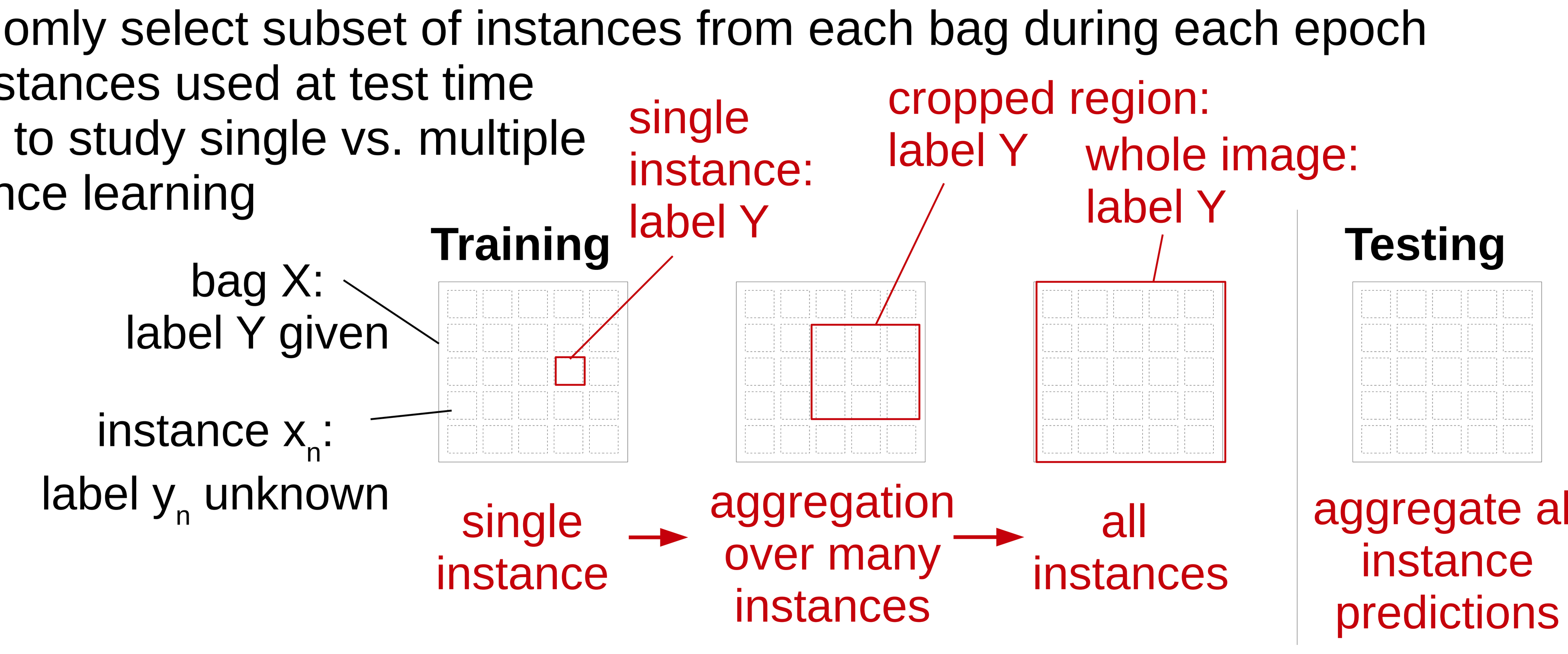
Mean: mean of instance predictions

Quantile: capture full distribution of instance predictions with quantile function and learn a mapping to bag class



Training with MI Augmentation

- Randomly select subset of instances from each bag during each epoch
- All instances used at test time
- Used to study single vs. multiple instance learning



Results: Classification Accuracy

Data set:

- H&E histology tissue microarray
- 1713 patient samples from the Carolina Breast Cancer Study, Phase 3
- 4 images per patient (5970 images total)

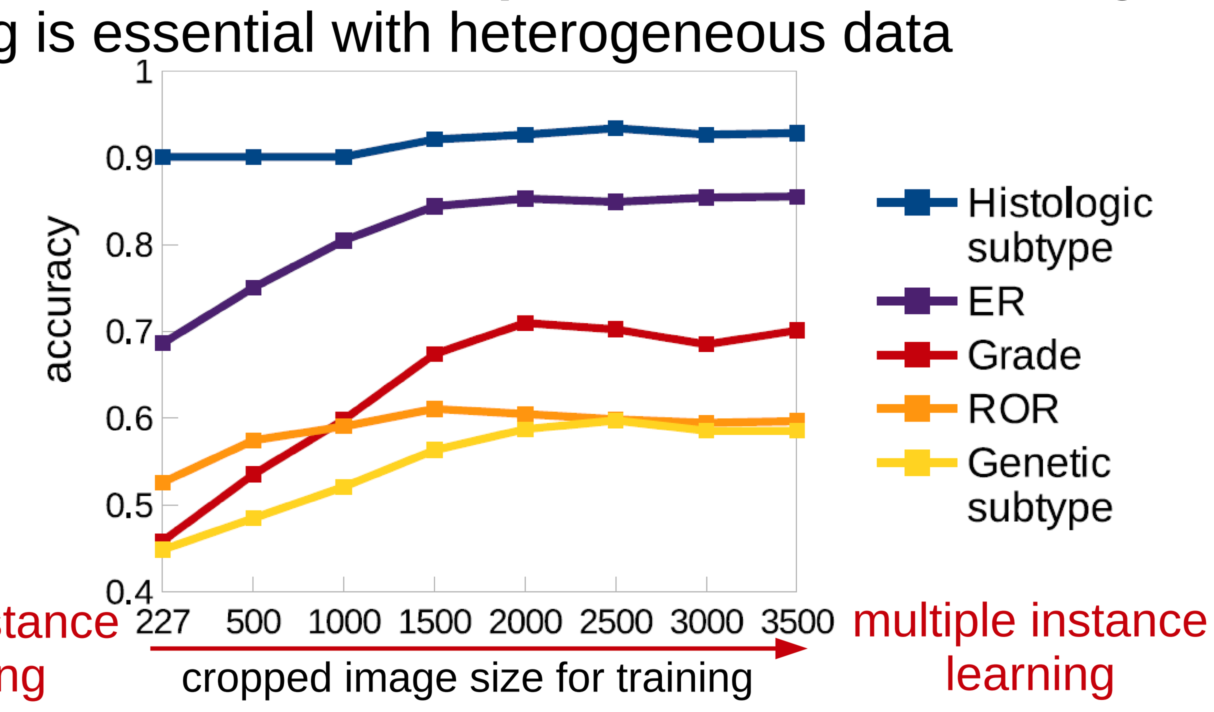
MI Aggregation:

Compare aggregation methods

Task	Max	Mean	Quantile
Histologic subtype	.898 (.004)	.931 (.004)	**.952** (.003)
Estrogen receptor status	.683 (.006)	.833 (.008)	**.841** (.006)
Grade	.408 (.019)	**.680** (.003)	.676 (.006)
Risk of recurrence (ROR-PT)	.542 (.010)	**.595** (.003)	.582 (.008)
Genetic subtype	.321 (.032)	**.548** (.006)	.544 (.003)

MI Augmentation and the Importance of MI Learning:

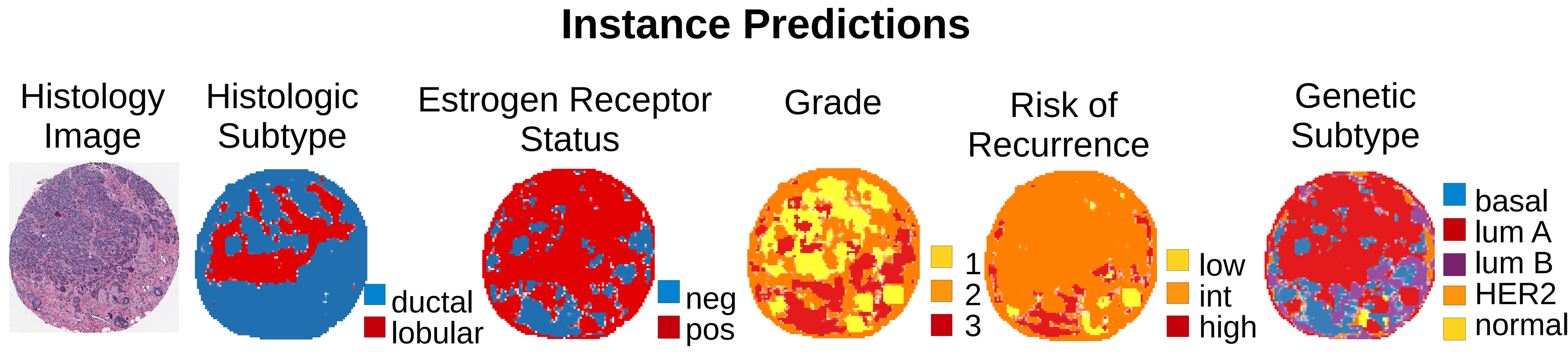
MI learning is essential with heterogeneous data



Application: Tumor Heterogeneity

- Cancer research suggests that heterogeneous tumors might be more aggressive
- Further validation of predicted heterogeneity and association with survival needed
- Could provide biological insights into cancer progression

Instance Predictions



Predicted Heterogeneity