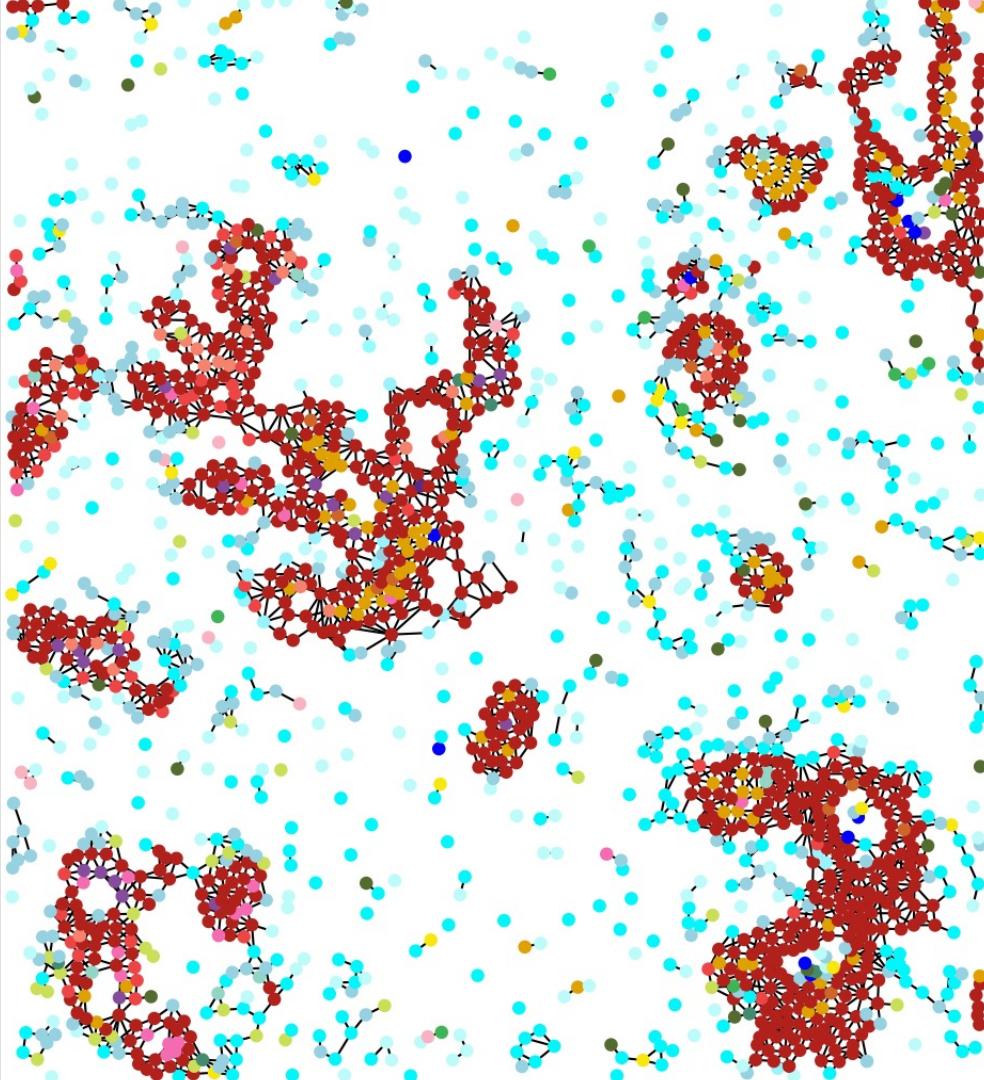
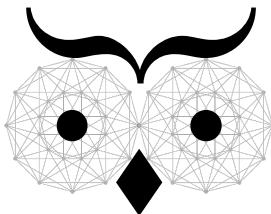


# Assessing Tumor Heterogeneity with Spatial Single-Cell Omics

—  
Marianna Rapsomaniki  
[aap@zurich.ibm.com](mailto:aap@zurich.ibm.com)

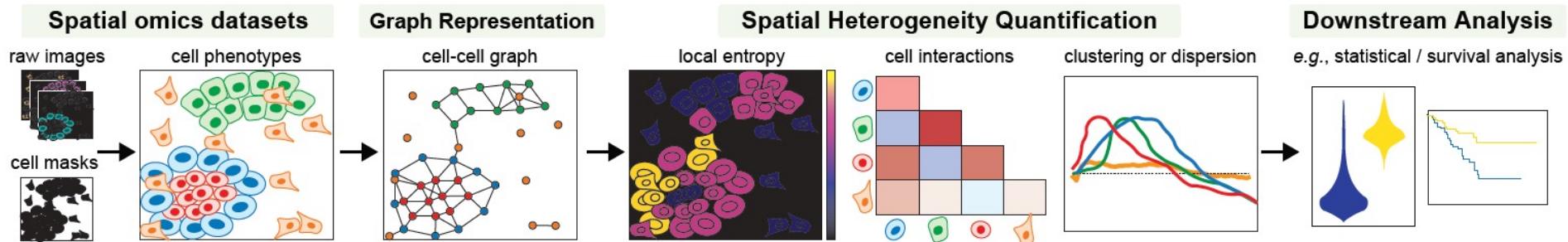
Adriano Martinelli  
[art@zurich.ibm.com](mailto:art@zurich.ibm.com)

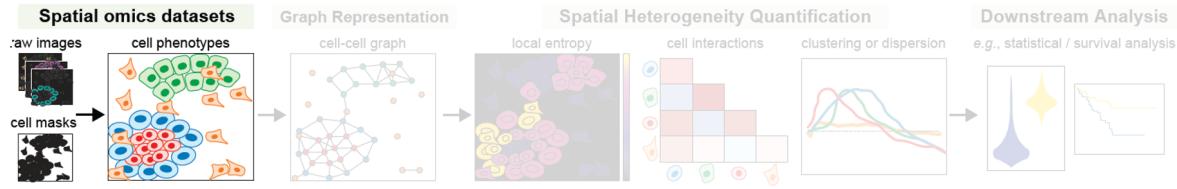
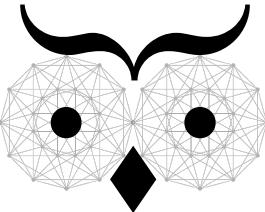




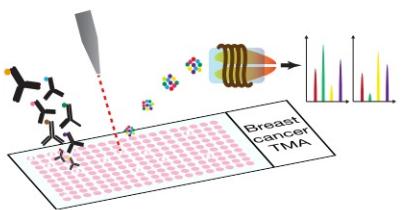
# ATHENA

Analysis of Tumor Heterogeneity from Spatial Omics Measurements



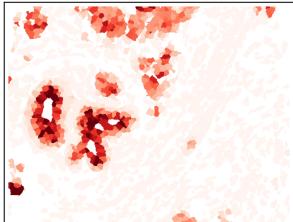


From multiplexed imaging...

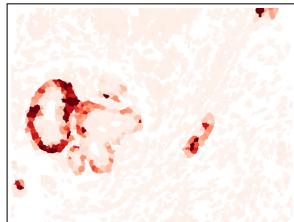


... to single-cell spatial omics

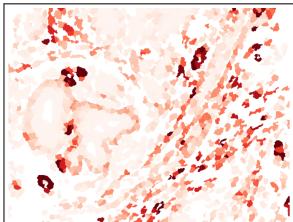
Pan Cytokeratin



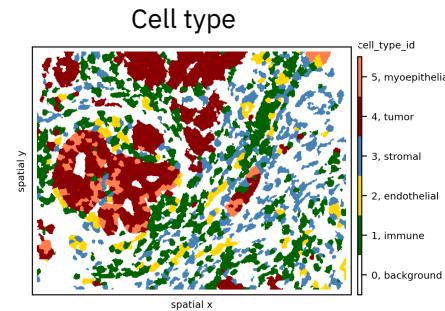
Cytokeratin 5



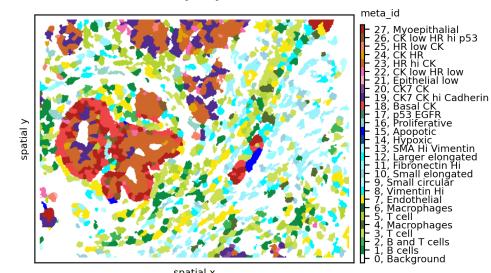
Smooth Muscle Actin

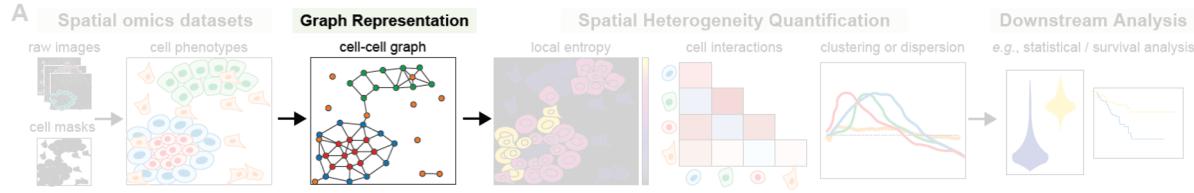
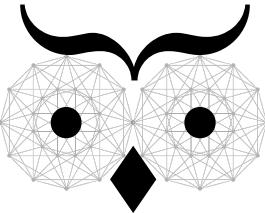


... and cancer ecosystems

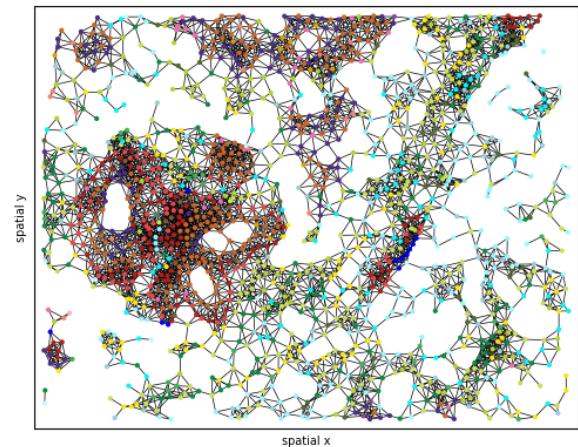


Tumor subpopulation

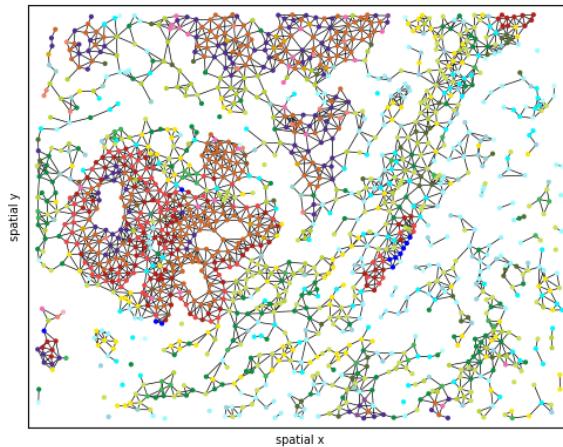




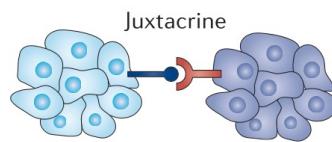
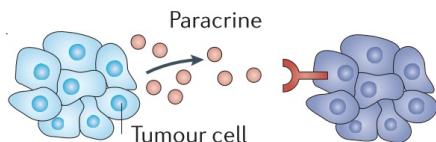
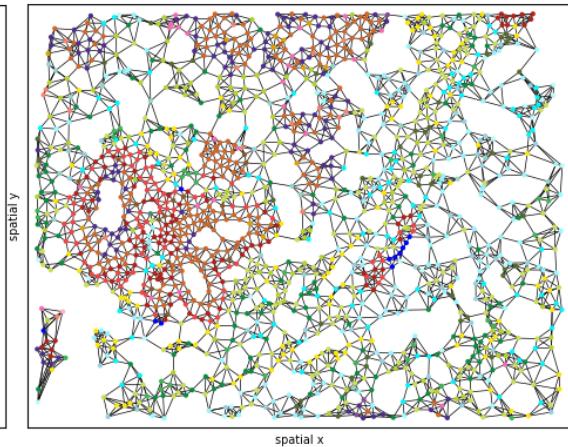
Radius Graph

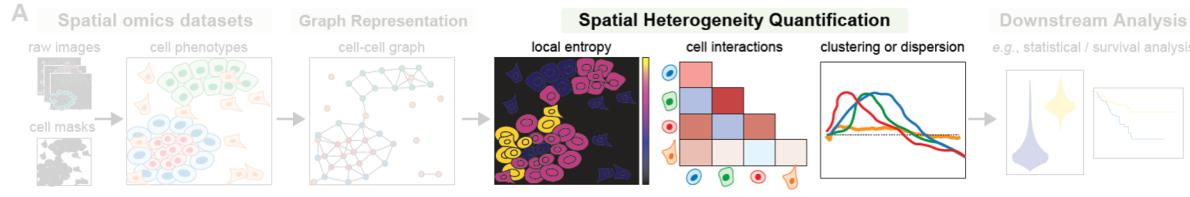
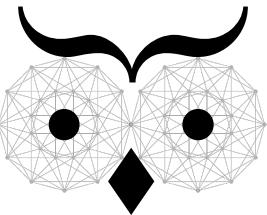


Contact Graph

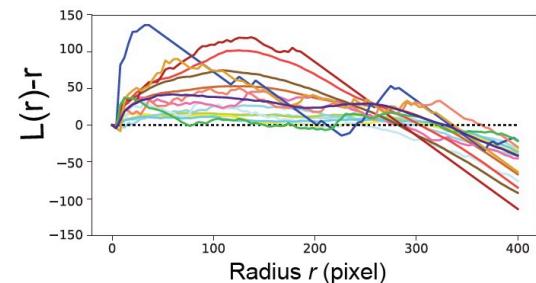
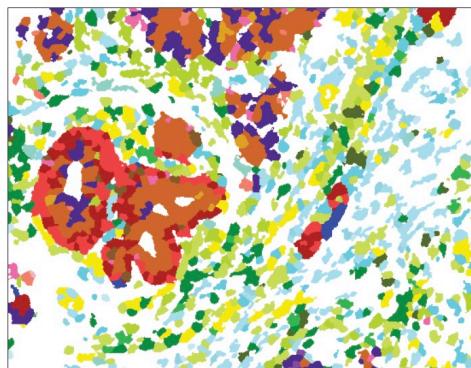
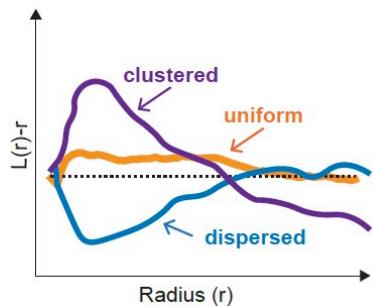
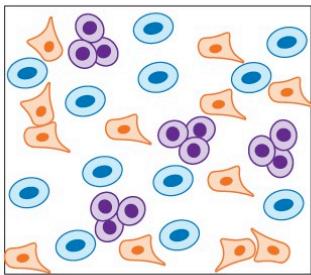


kNN Graph

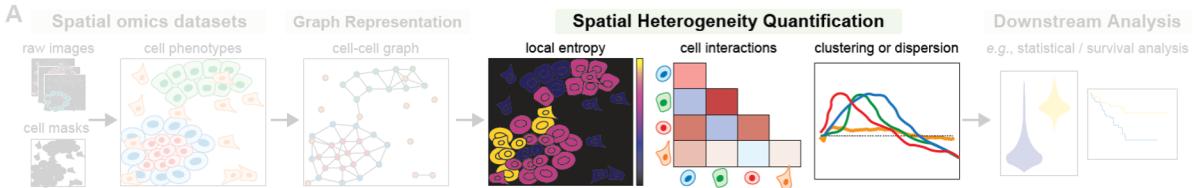
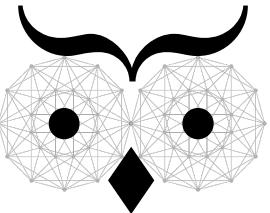




### Spatial statistics scores

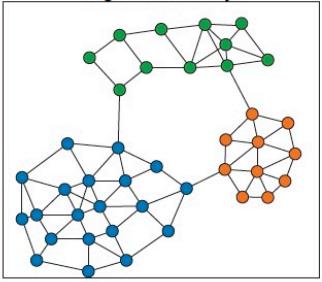


Endothelial	SMA <sup>hi</sup> Vim	CK <sup>low</sup> HR <sup>low</sup>	Myoepithelial
Macrophages	Fibronectin <sup>hi</sup>	CK7 CK <sup>hi</sup> Cadh	CK <sup>low</sup> HR <sup>hi</sup> p53
T cells	Small elongated	Basal CK	HR <sup>low</sup> CK
B and T cells	Vimentin <sup>hi</sup>	Proliferative	CK HR
B cells	Small circular	Apoptotic	HR <sup>hi</sup> CK

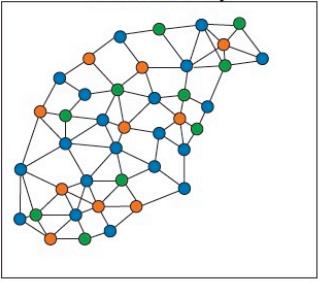


### Graph-theoretic scores

high modularity



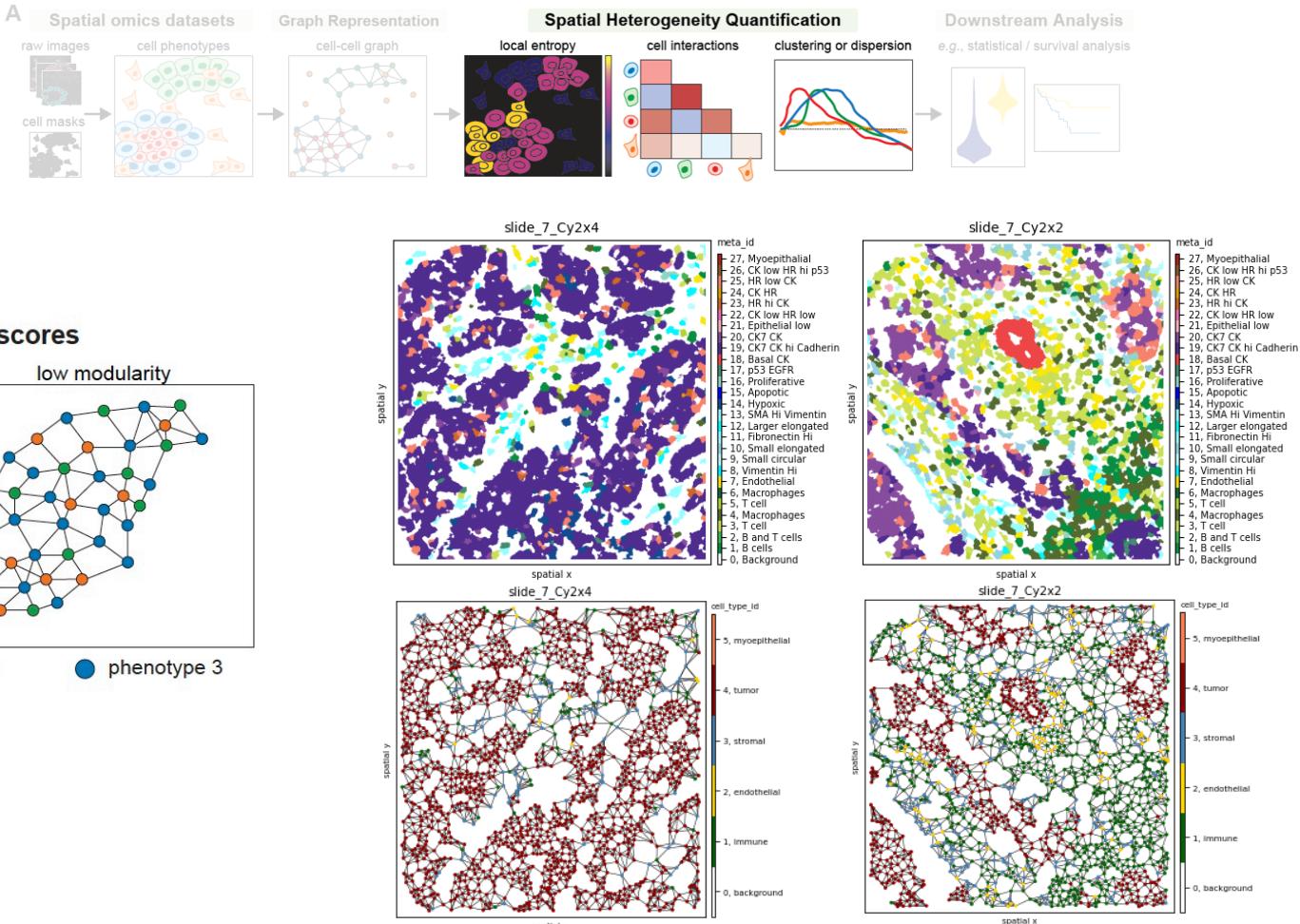
low modularity

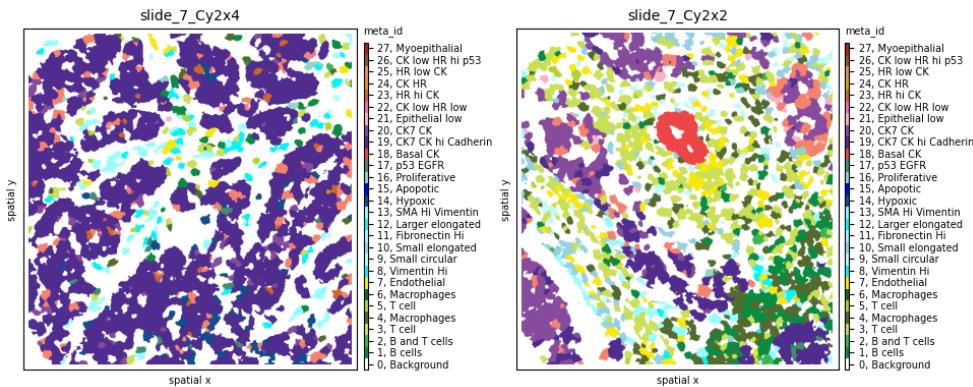
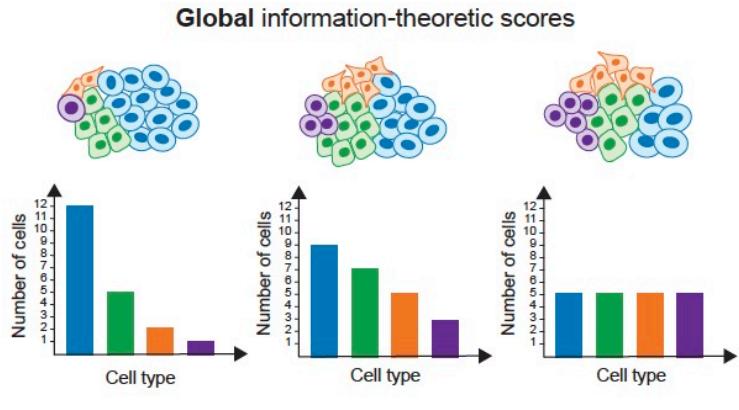
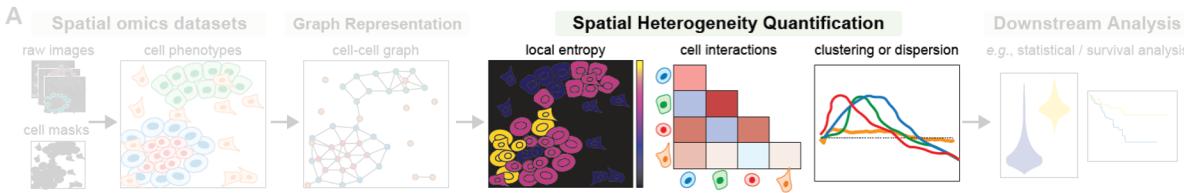
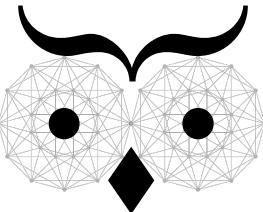


phenotype 1

phenotype 2

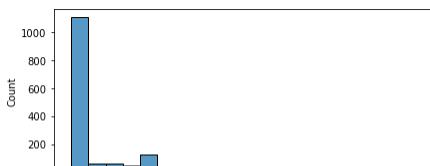
phenotype 3



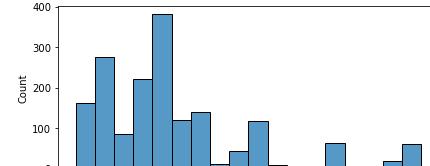


Entropy = low      Entropy = medium      Entropy = high

sample-level



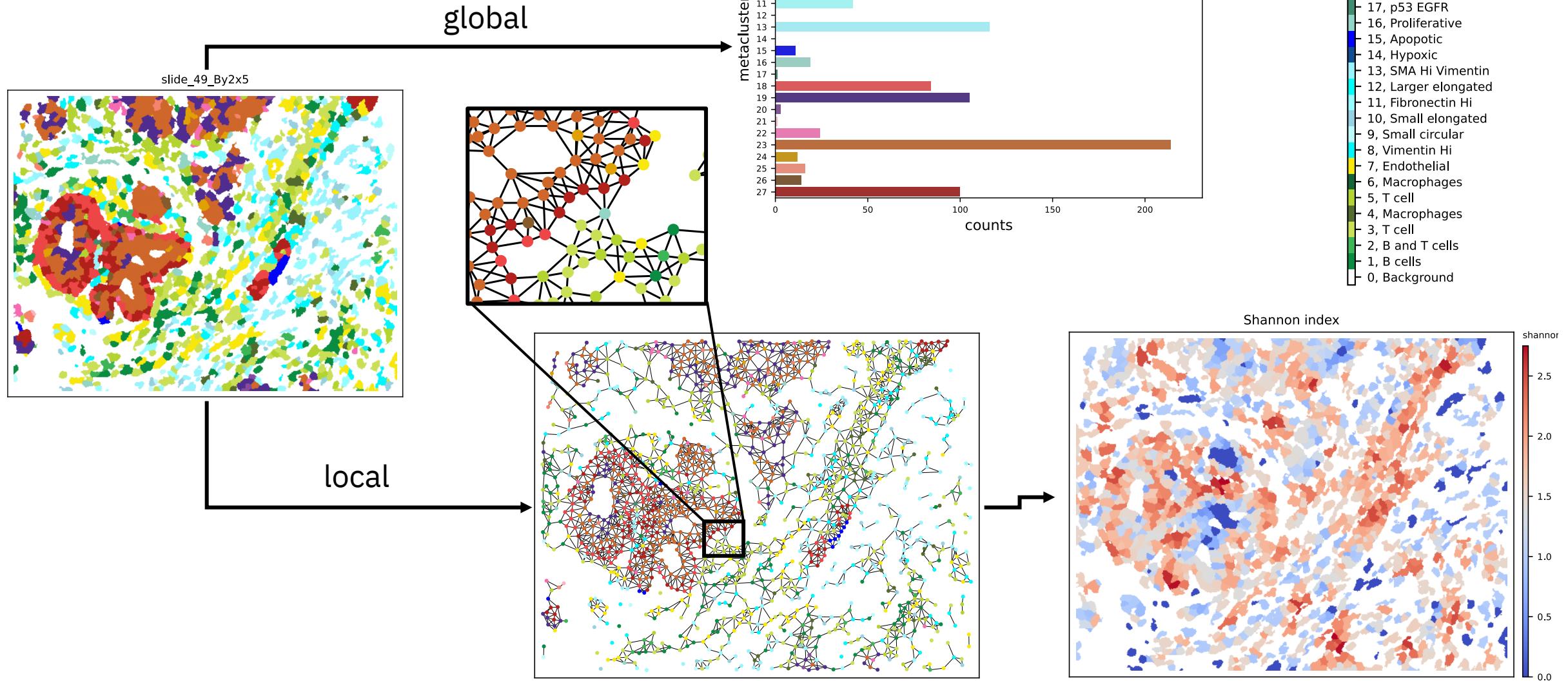
Shannon entropy: 1.95

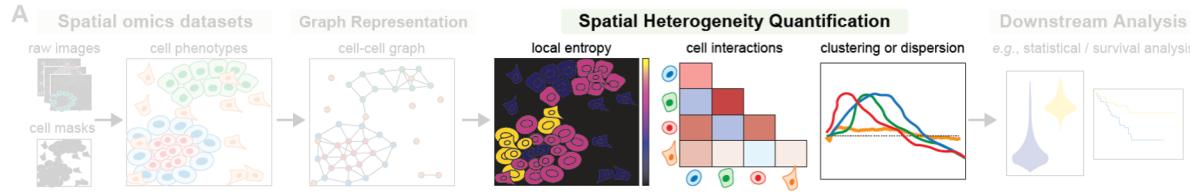
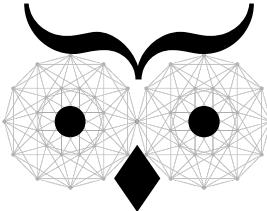


Shannon entropy: 3.41

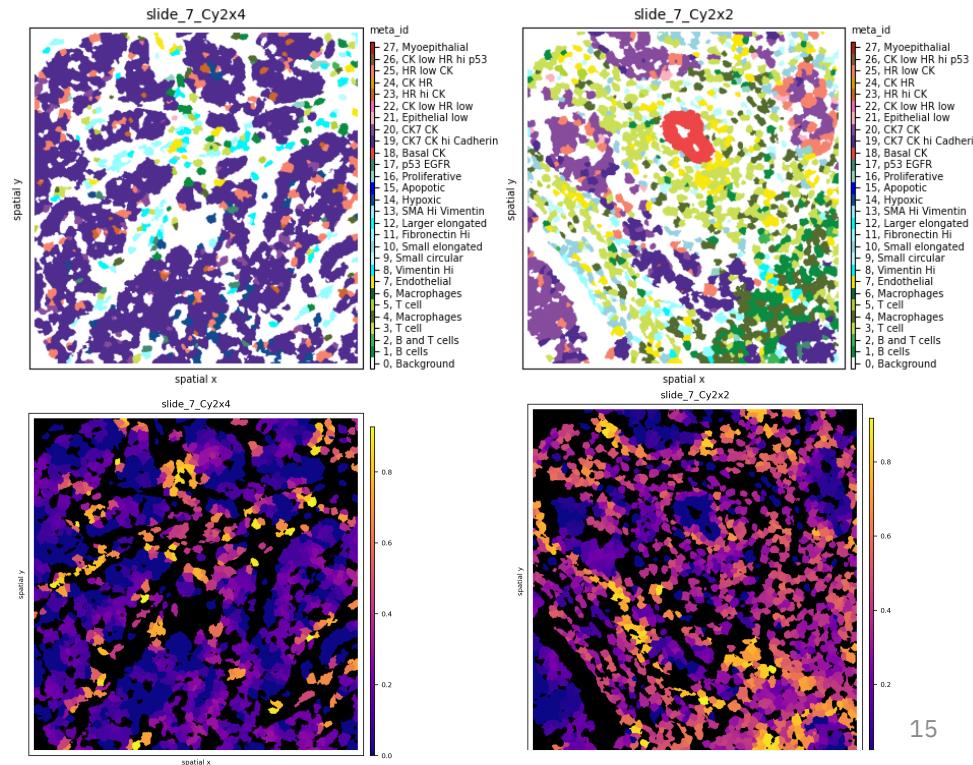
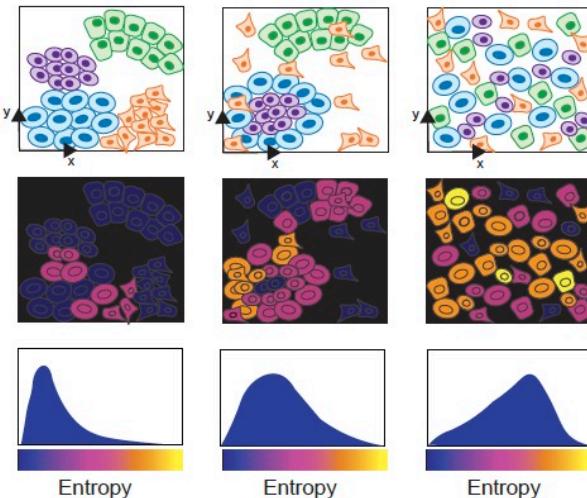
# Computational Framework

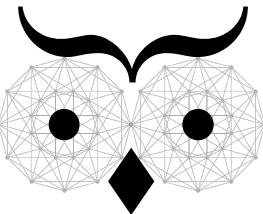
## Quantification: Diversity indices



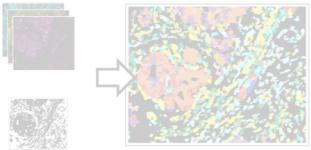


### Local information-theoretic scores





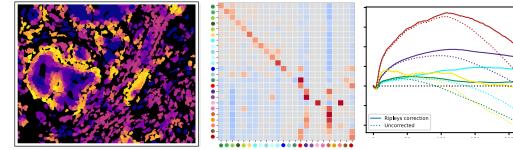
Spatial Omics



Graph Representation

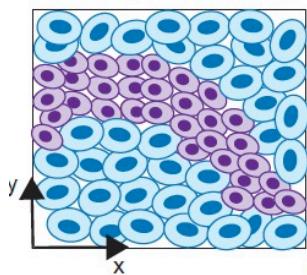


Tumor Heterogeneity Metrics

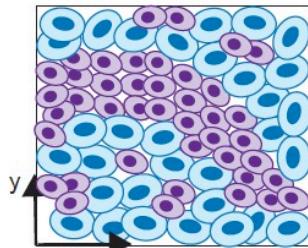


## Infiltration

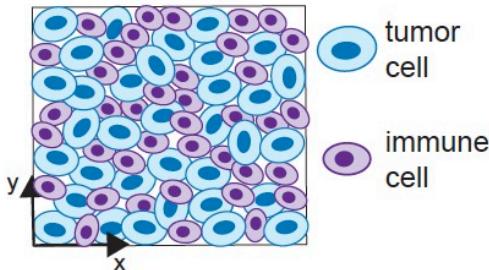
Compartmentalization



Local infiltration

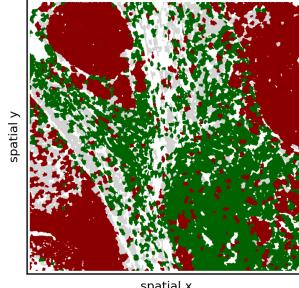


Intermixing

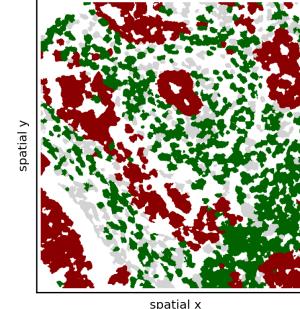


## Global score

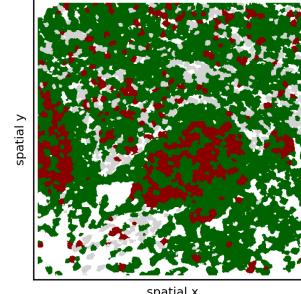
SP43\_116\_X3Y4

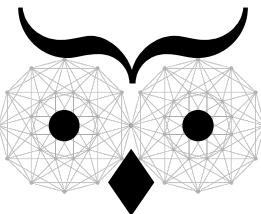


slide\_7\_Cy2x2

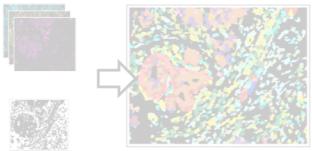


slide\_59\_Cy7x7





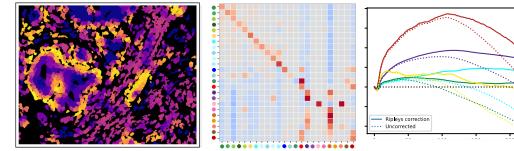
Spatial Omics



Graph Representation

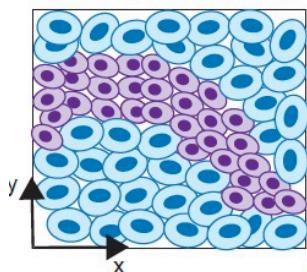


Tumor Heterogeneity Metrics

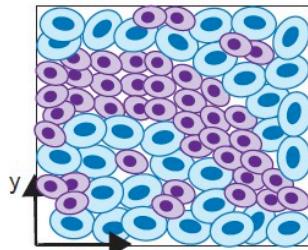


## Infiltration

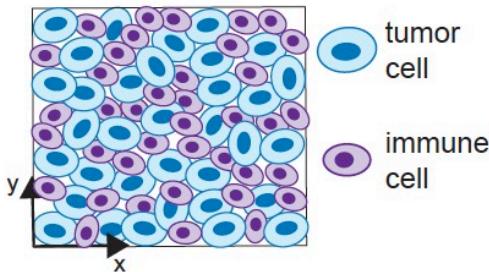
Compartmentalization



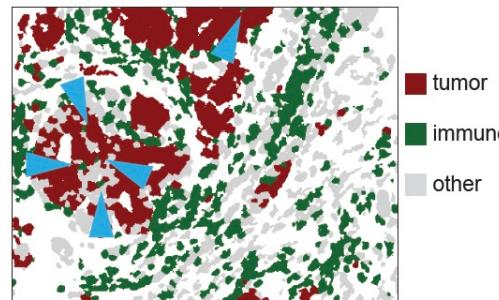
Local infiltration



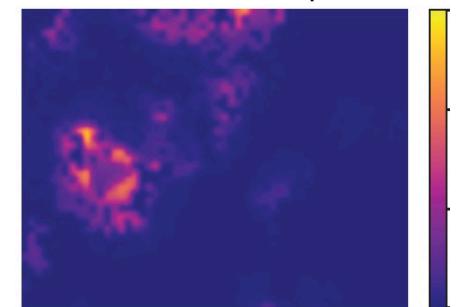
Intermixing

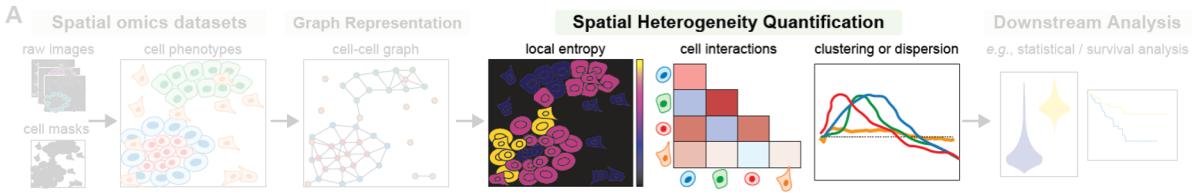
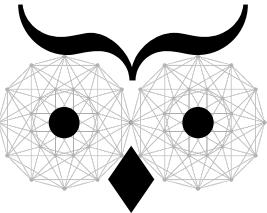


## Local score



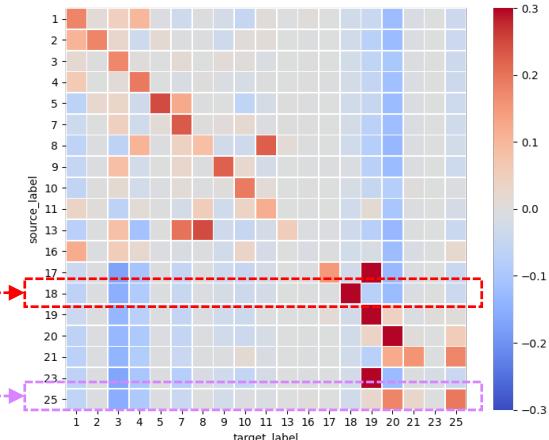
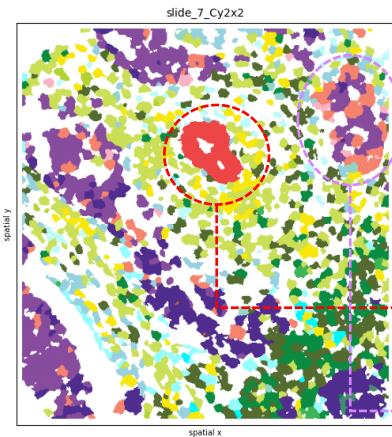
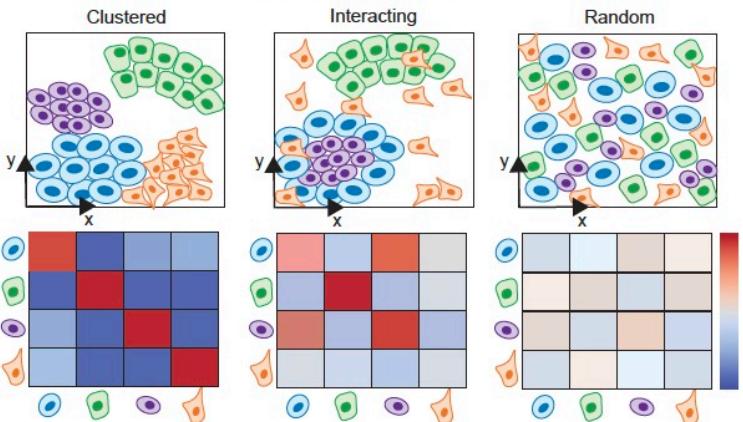
## Infiltration map

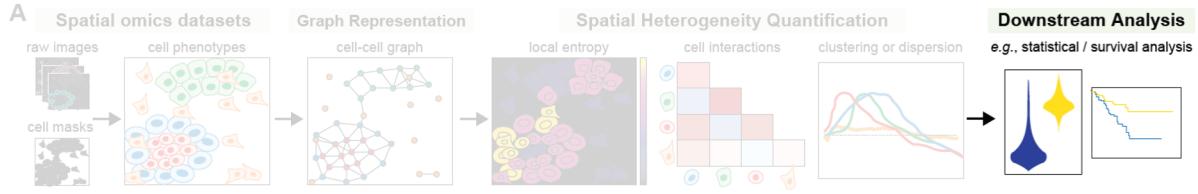
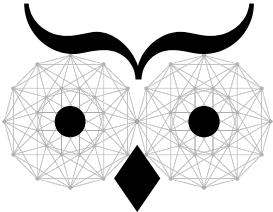




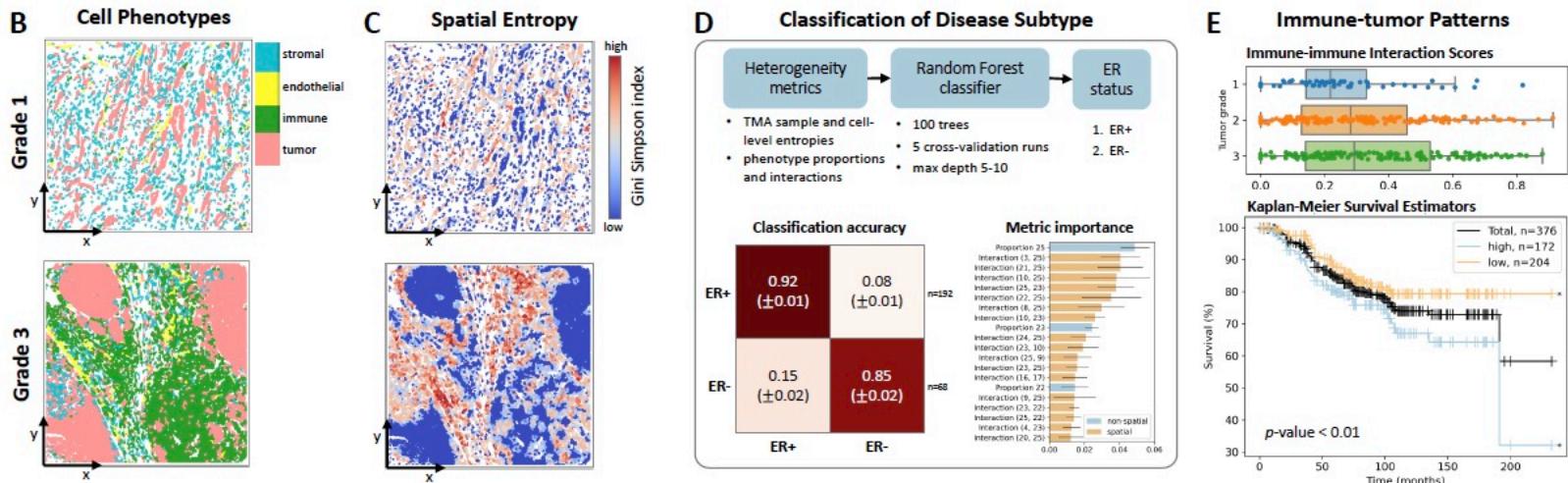
## Cell type interactions

### Neighborhood Analysis

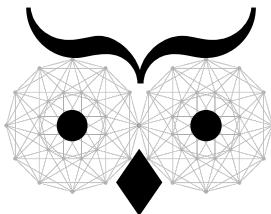




- Predict patient features based on heterogeneity (e.g., survival time, ER status, grade)
- Compare different graph structures and evaluate spatial feature importance



Poster presented at American Medical Informatics Association (AMIA) 2021 Annual Symposium (*distinguished poster award*)



# ATHENA

Analysis of Tumor Heterogeneity from Spatial Omics Measurements

## SpatialOmics Data Structure

**.images** dict  
multiplexed images  
{sample: numpy arrays}

**.G** nested dict  
cell-cell graphs  
{sample: {graph\_type: networkx graph}}

**.spl** dataframe  
sample annotations

**.var** dict  
feature annotations  
{sample: pandas dataframe}

**.masks** nested dict  
segmentation masks  
{sample: {mask\_type: numpy array}}

**.X** dict  
single-cell measurements  
{sample: pandas dataframe}

**.obs** dict  
single-cell annotations  
{sample: pandas dataframe}

**.uns** dict  
unstructured data



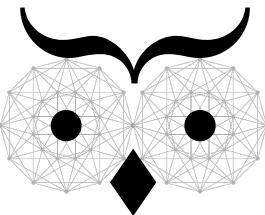
Implemented in Python



[github.com/histocartography/athena](https://github.com/histocartography/athena)

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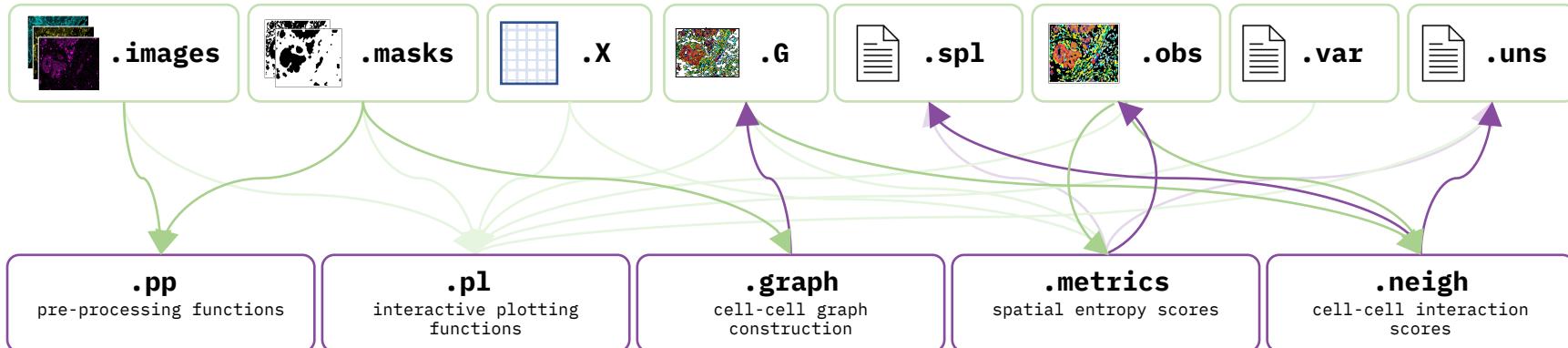
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# ATHENA

Analysis of Tumor Heterogeneity from Spatial Omics Measurements

## SpatialOmics Data Structure



## SpatialHeterogeneity



Implemented in Python

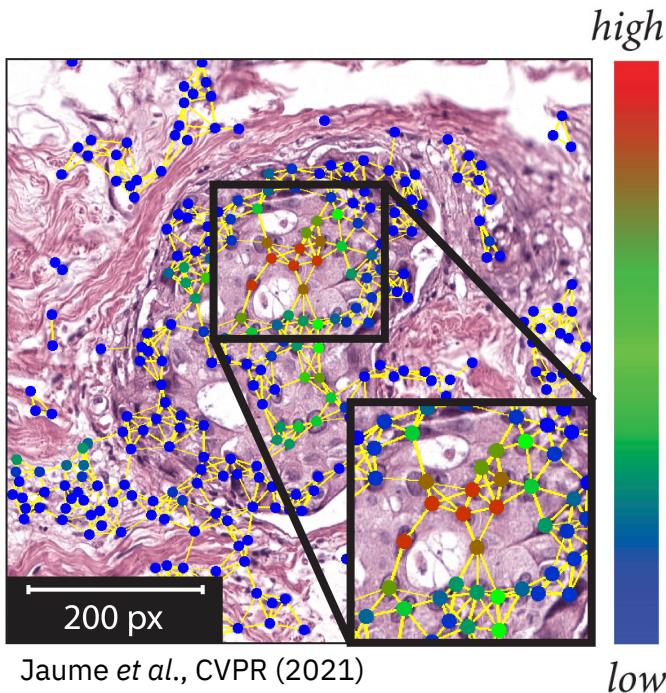


[github.com/histocartography/athena](https://github.com/histocartography/athena)

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# Next steps and extensions



- WSI instead of TMAs
- Test for additional spatial omics technologies (IMC, MIBI, mIHC/IF, Visium, merFISH, etc.)
- Incorporate additional metrics
- Benchmark GNNs for metadata prediction
- Interpretability of spatial features