Integrative analysis of breast cancer survival based on spatial features

Presented by
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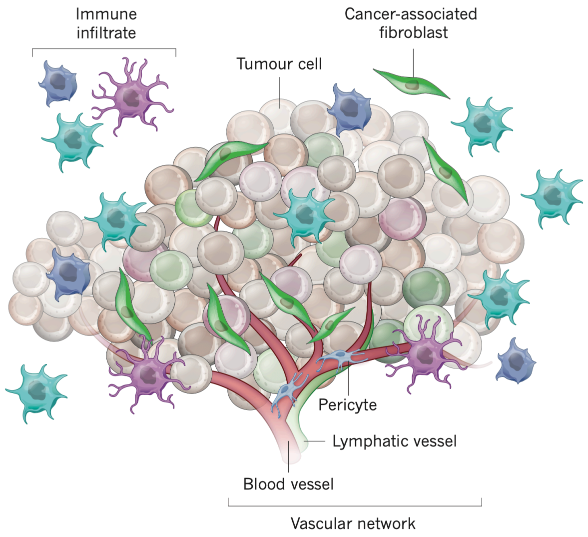
Motivation

Tumour microenvironment



Clinical features

Grade

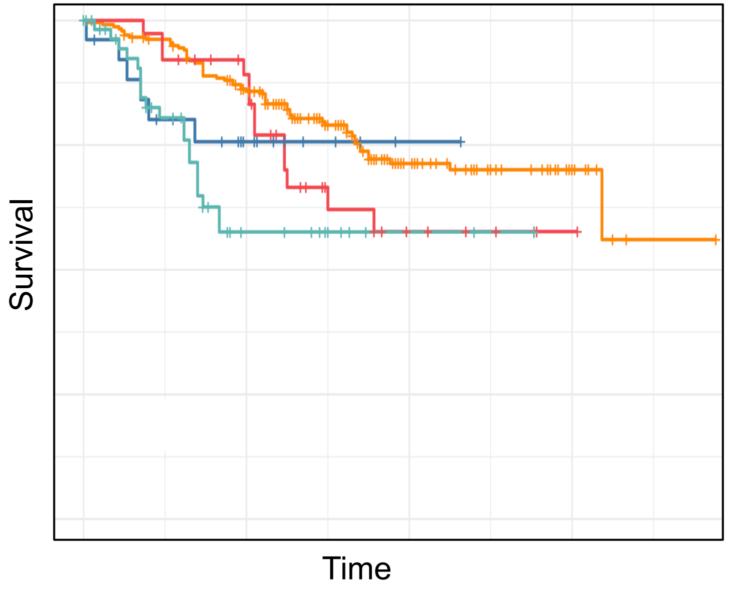
Stage

Tumour infiltration score

Clinical type

Age

Patient survival



Non-spatial features

Cell type composition

Marker

Cell state

Spatial features

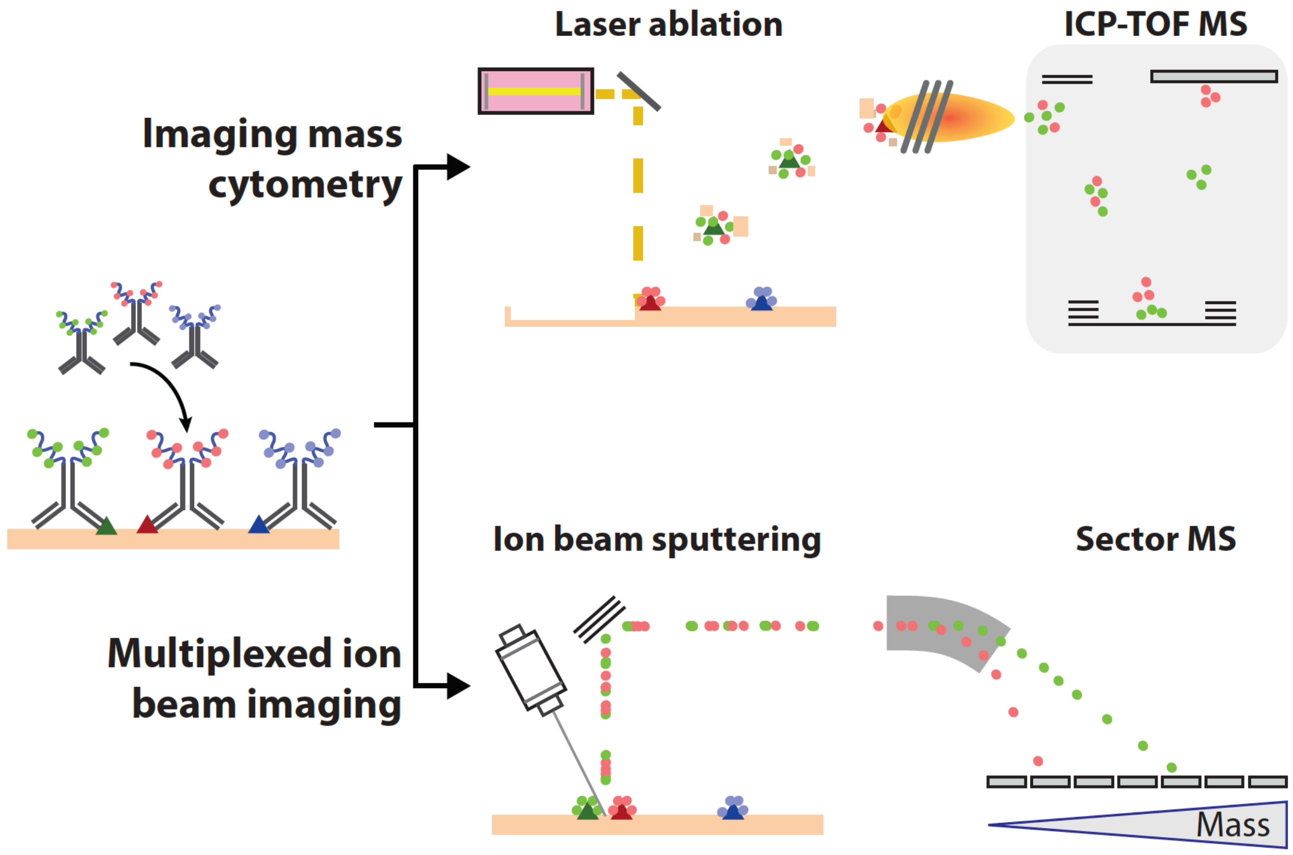
Cell type interaction

Marker spatial association

Cell localisation

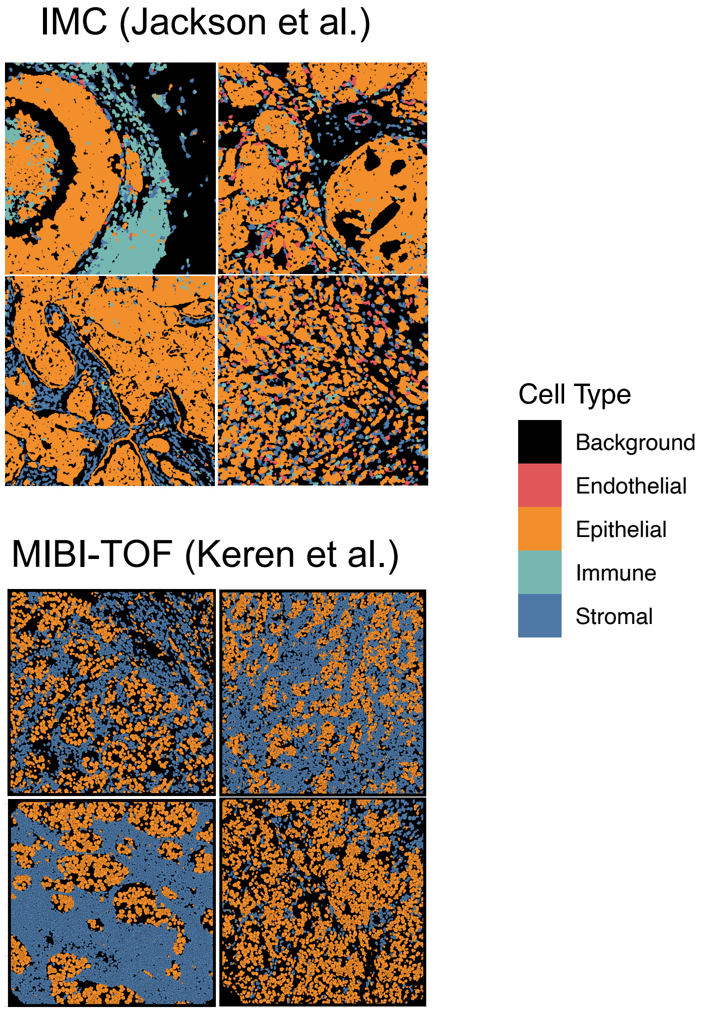
Junttila, M. R., & de Sauvage, F. J. (2013). Influence of tumour micro-environment heterogeneity on therapeutic response. *Nature*, *501*(7467), 346-354.

Data: Two Mass Cytometry Imaging data in breast cancer

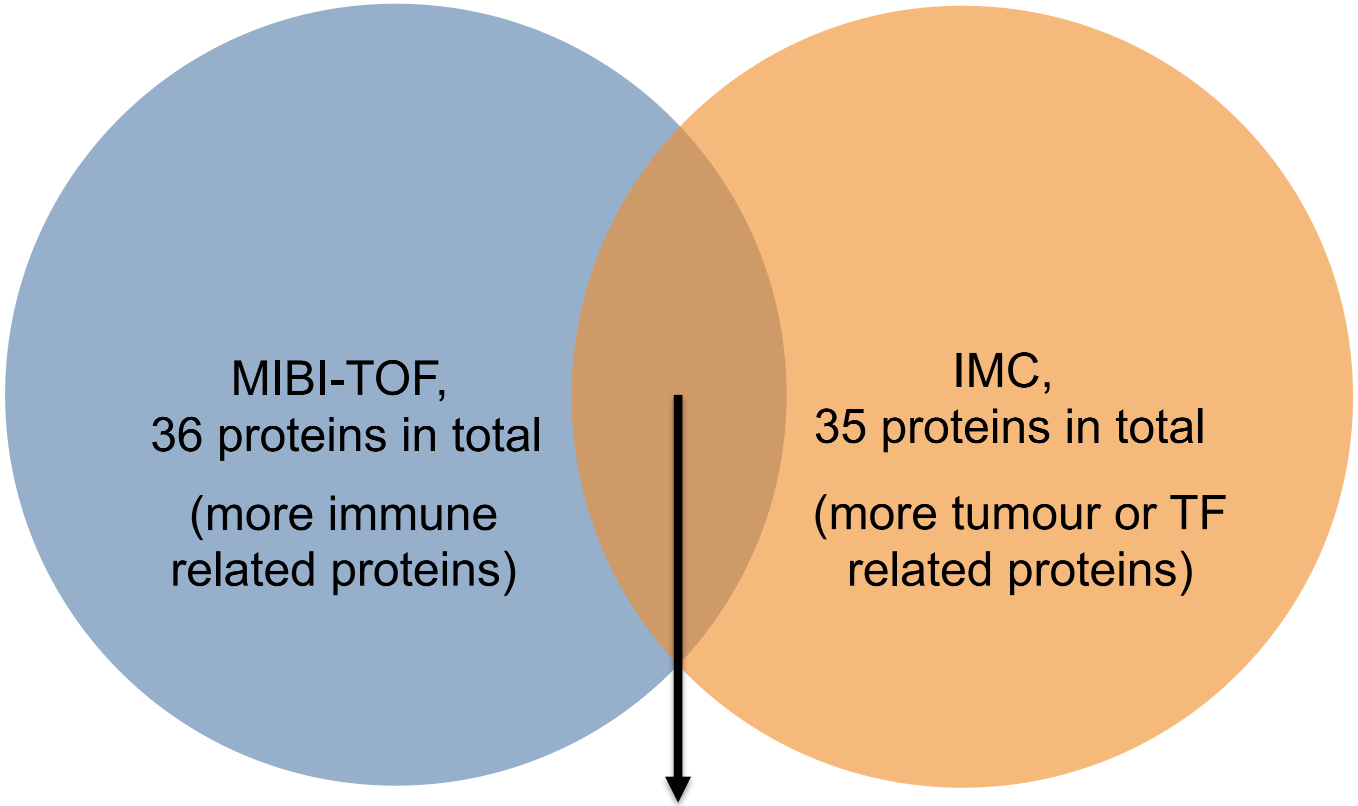


Bodenmiller, B. (2016). Multiplexed epitope-based tissue imaging for discovery and healthcare applications. *Cell systems*, 2(4), 225-238.

High dimensional images



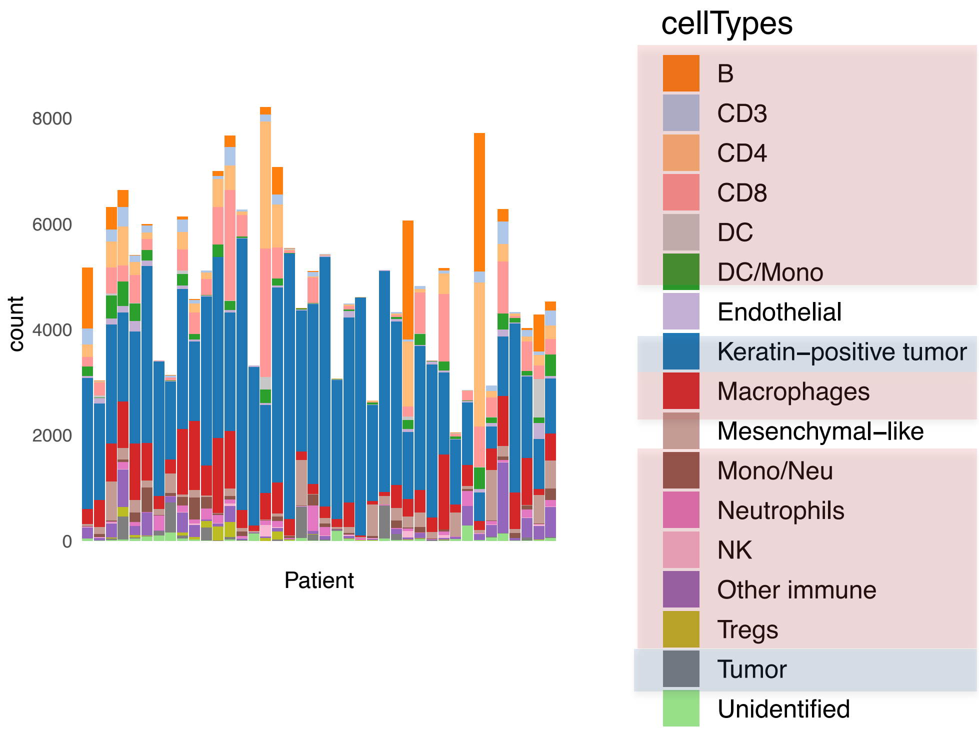
Integrative analysis challenge 1: Limited overlapped proteins



13 Common proteins:
EGFR, Ki67, SMA, Vimentin, p53, panCK, CD20, vWF, H3K27me3, CD45, CD68, CD3, pS6

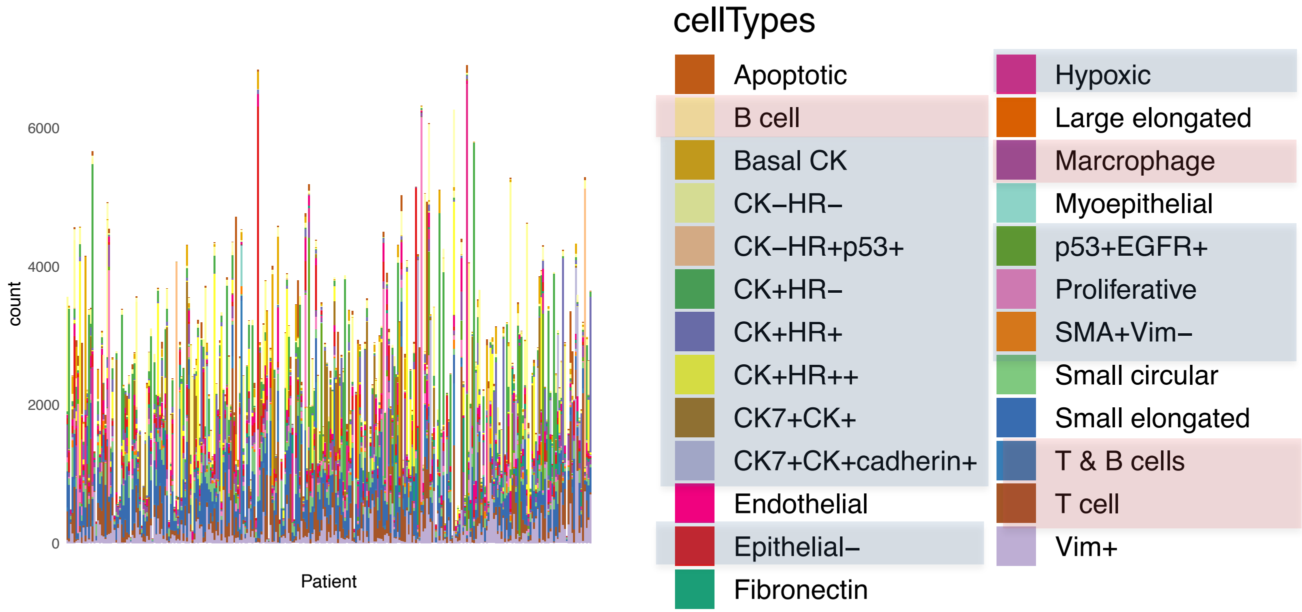
Integrative analysis challenge 2: Very different cell type annotation resolution

MIBI-TOF (Keren et al.)



Immune cell types

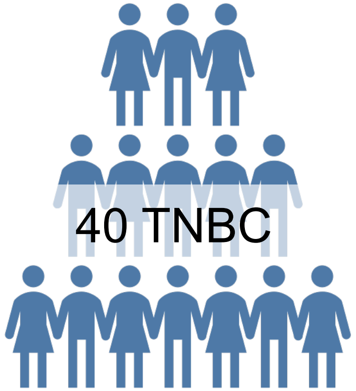
IMC (Jackson et al.)



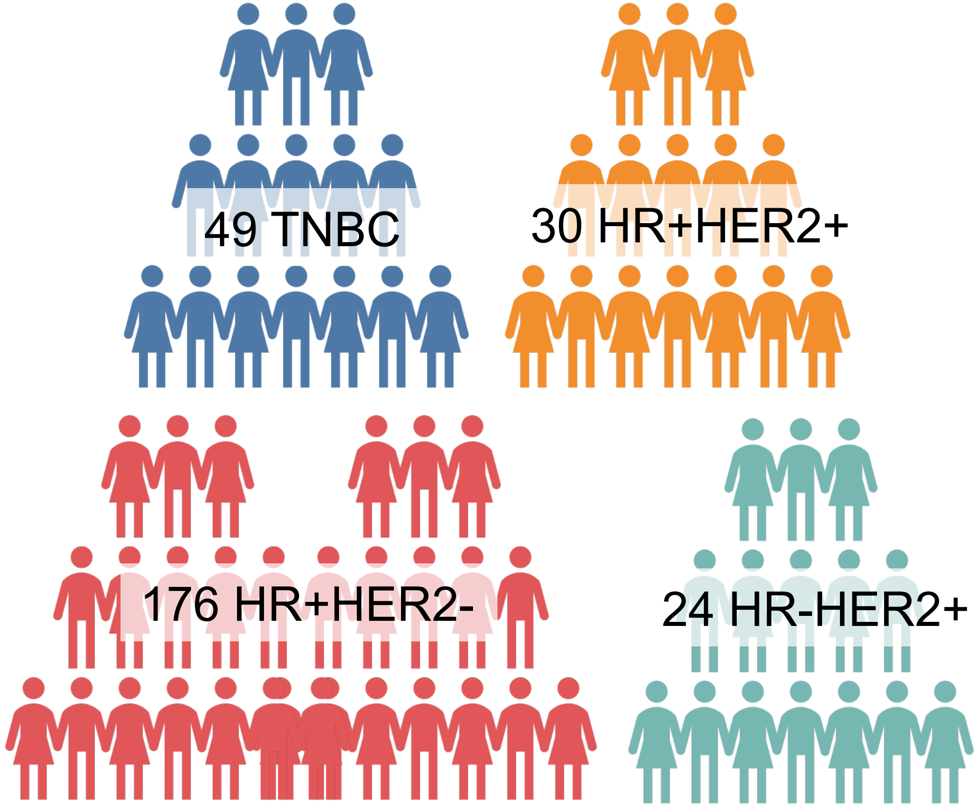
Epithelial cell types

Integrative analysis challenge 3: Partially overlapped of clinical types between these datasets

MIBI-TOF

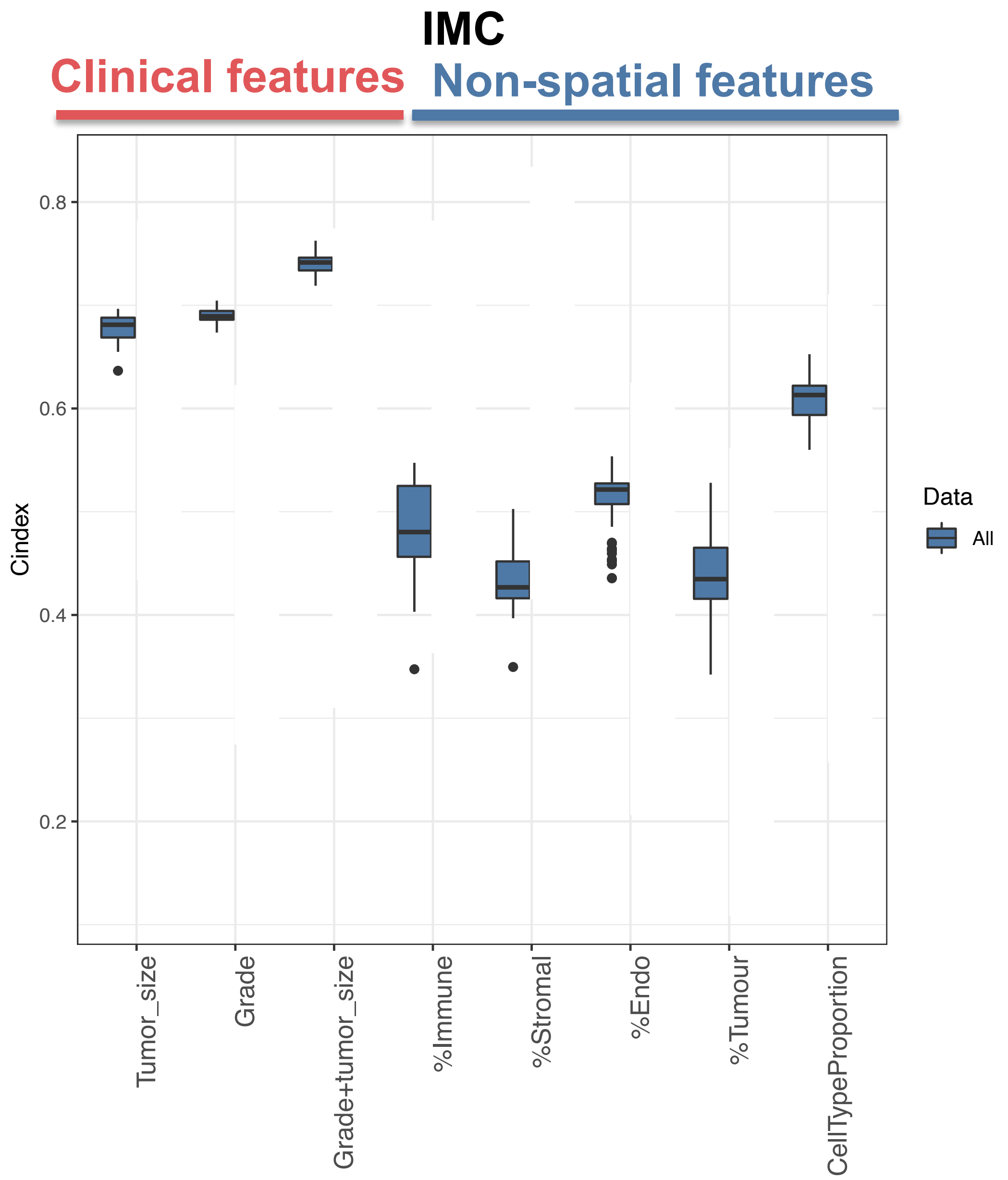


IMC



TNBC: Triple Negative Breast Cancer

Integrative analysis challenge 4: cohort heterogeneity



- Clinical features are more predictive than features like cell type proportion
- Clinical features perform poorly in triple negative breast cancer

Challenges and Questions

LIMITED OVERLAPPED PROTEIN

DIVERSE CELL TYPE ANNOTATION

PARTIALLY OVERLAPPED CLINICAL TYPE

HETEROGENEOUS COHORT

Spatial features

- Are the spatial features extracted from the images predictive in patient's survival?

Integrative analysis

- While integrating the two imaging data in the matrix level is challenging, are there common predictive spatial features shared between the two datasets?

Imputation

- Will other type of single-cell data information further improve the prediction in patient’s survival?

Challenges and Questions

Spatial features	• Are the spatial features extracted from the images predictive in patient's survival?
Integrative analysis	• While integrating the two imaging data in the matrix level is challenging, are there common predictive spatial features shared between the two datasets?
Imputation	• Will other type of single-cell data information further improve the prediction in patient's survival?

Spatial discriminative features

Survival analysis

Integration with CyTOF

Spatial features

Spatial discriminative features

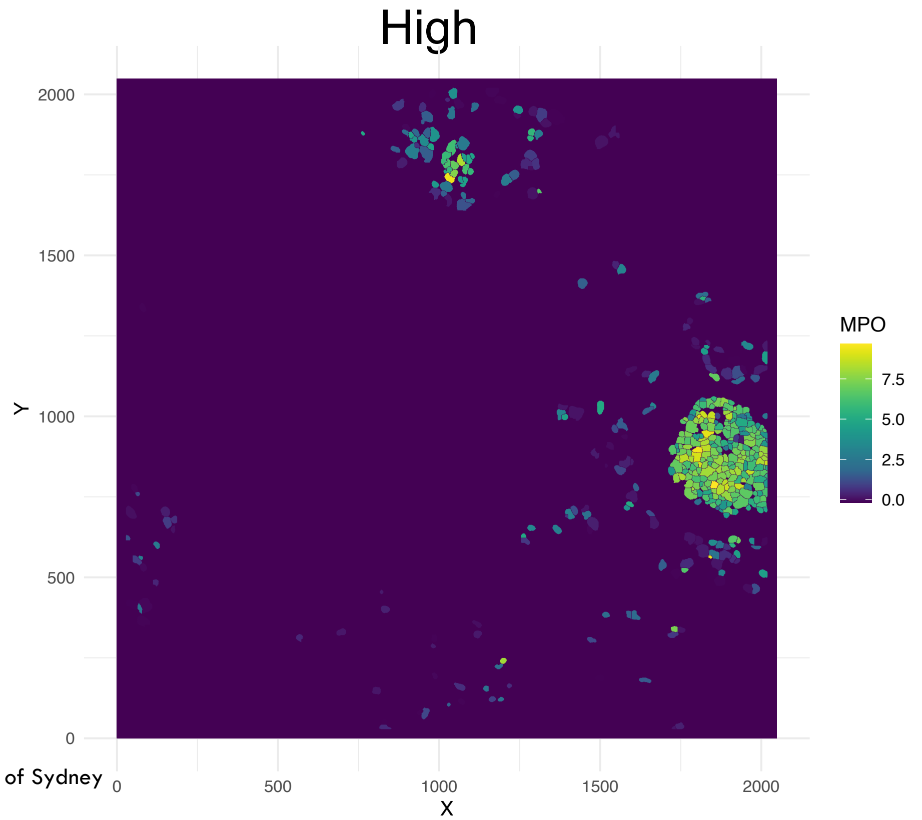
I. Moran's I	II. Nearest neighbour correlation	III. Cell type interaction composition	IV. L function

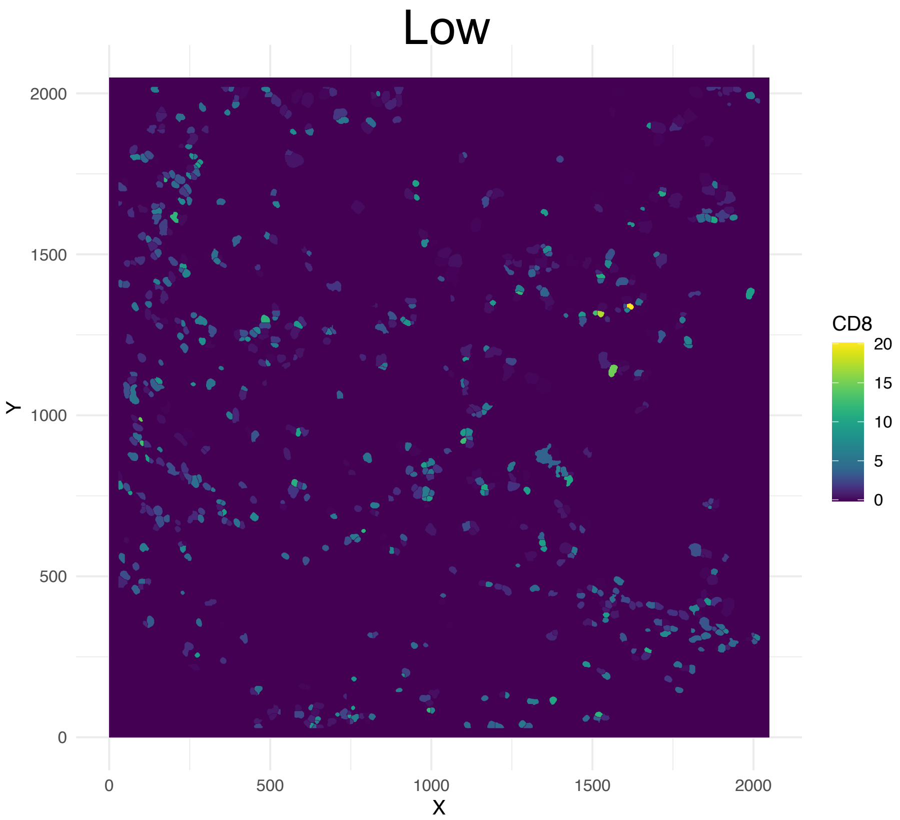
Spatial metrics I: Spatial autocorrelation - Moran's I

Moran's I measures spatial autocorrelation based on both feature locations and values simultaneously:

$$I = \frac{N}{\sum_{ij} w_{ij}} \frac{\sum_i \sum_j w_{ij}(x_i - \bar{x})(x_j - \bar{x})}{\sum_i (x_i - \bar{x})^2}$$

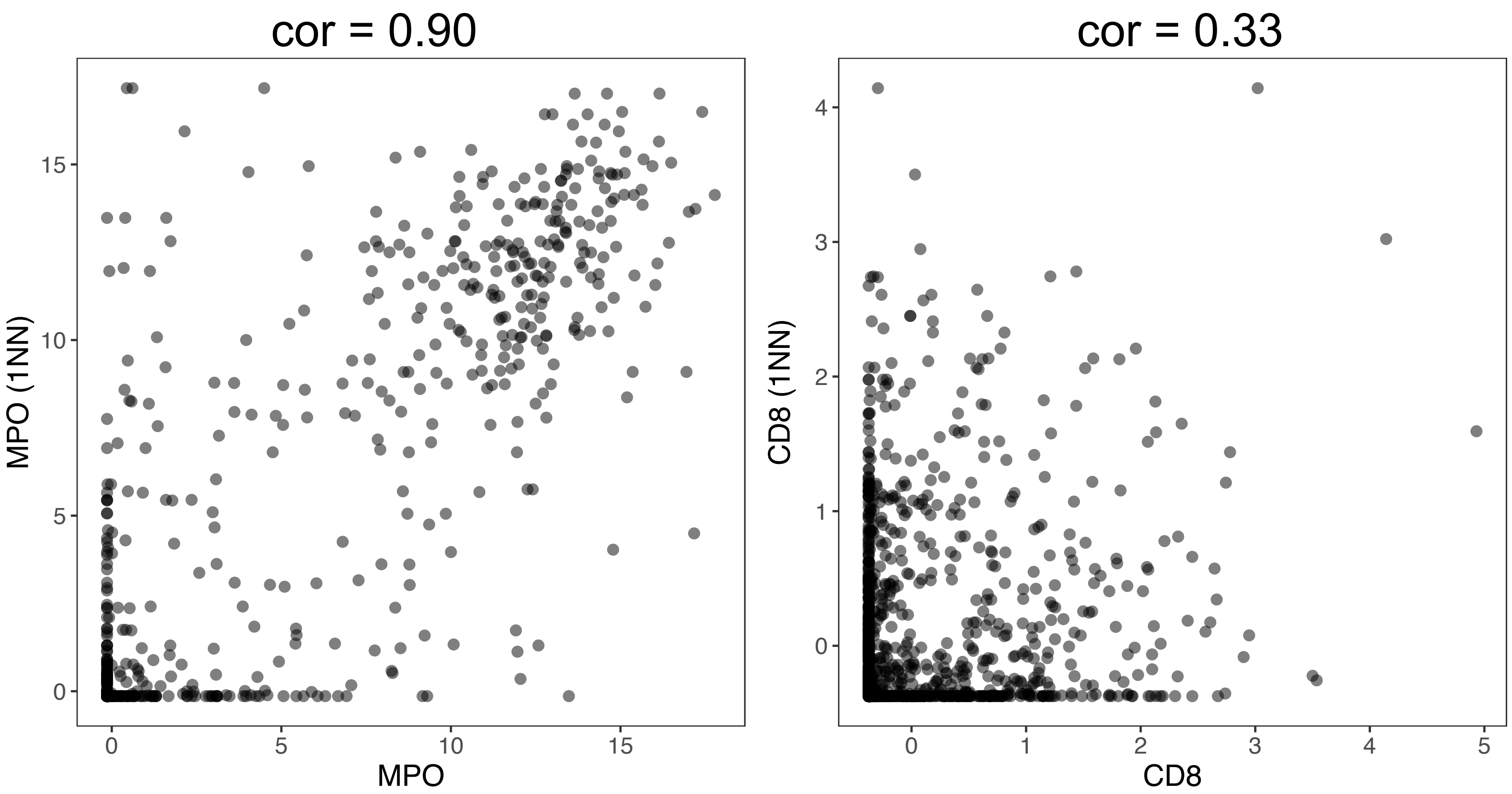
where N is the total number of cells indexed by i and j;
x is one epitope expression;
w_{ij} is a matrix of spatial weights





Spatial metrics II: Nearest Neighbour Correlation

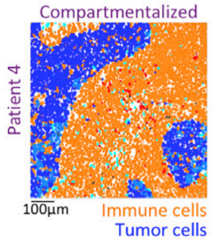
Nearest Neighbour Correlation: Correlation of protein expression between of cells with their nearest neighbours

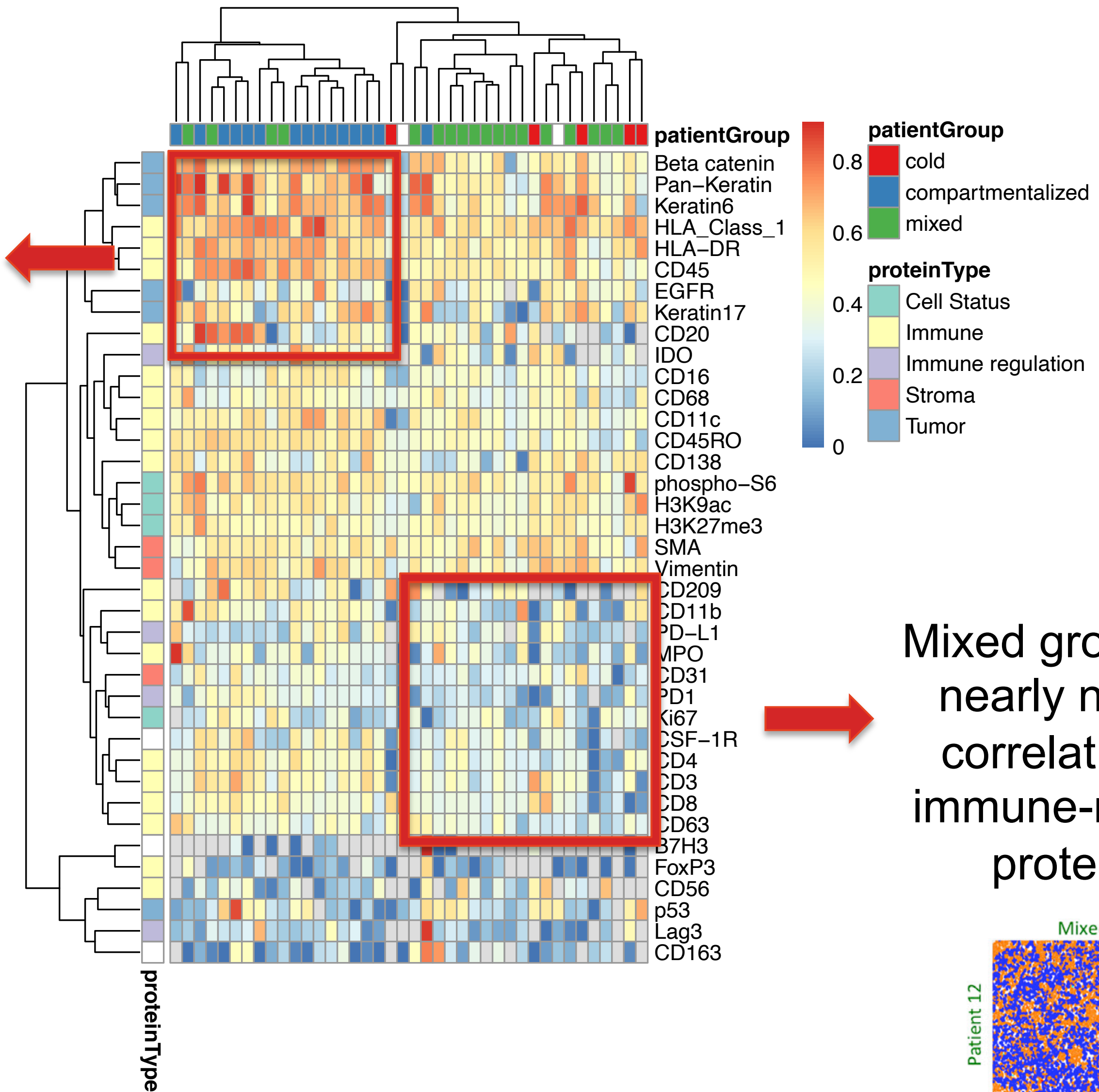


Spatial metrics II: Nearest Neighbour Correlation

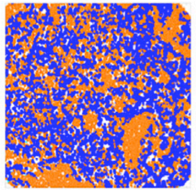
MIBI-TOF (Keren et al.)

Compartmentalized group has high NN correlation in tumor and immune related proteins



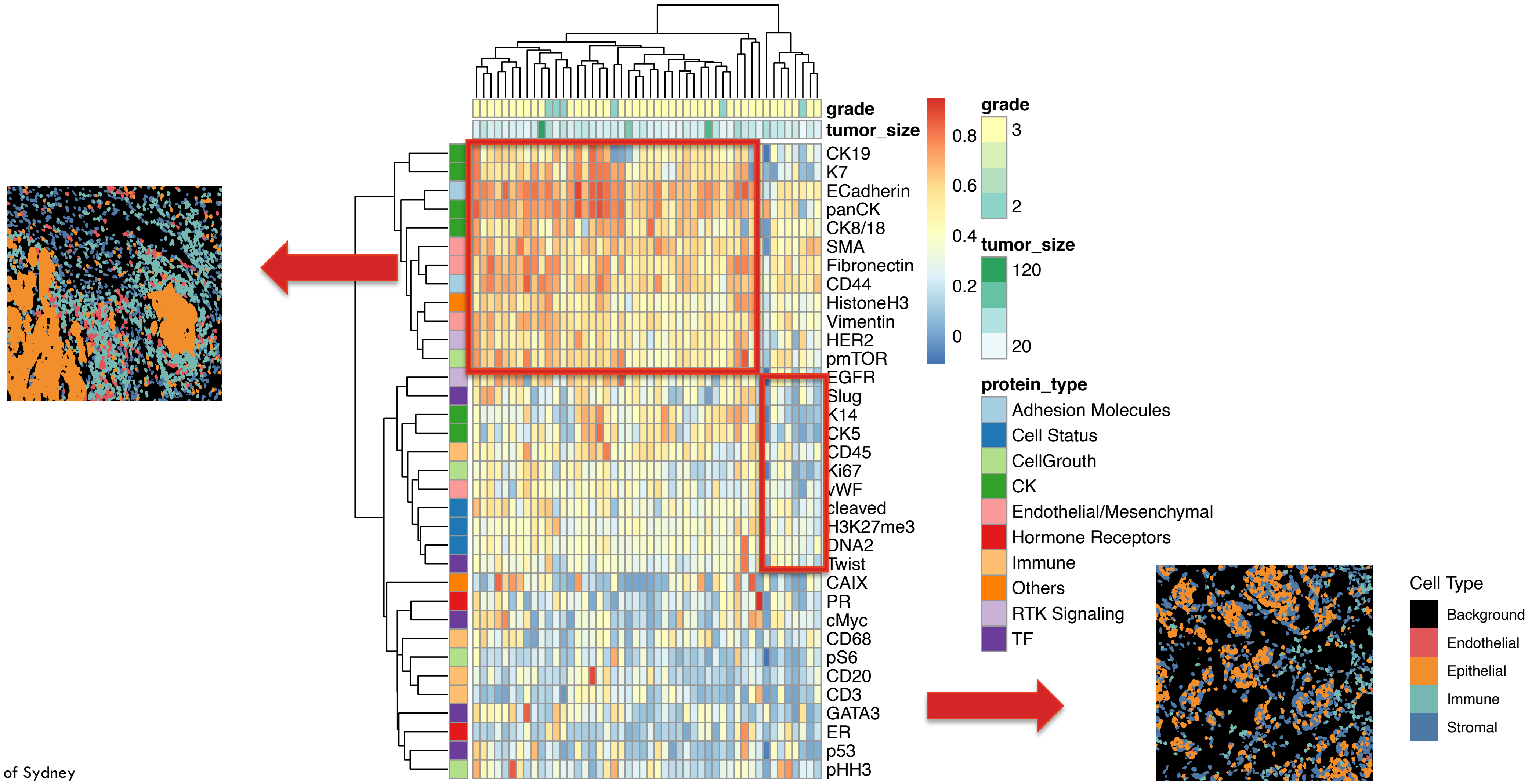


Mixed group has nearly no NN correlation in immune-related proteins

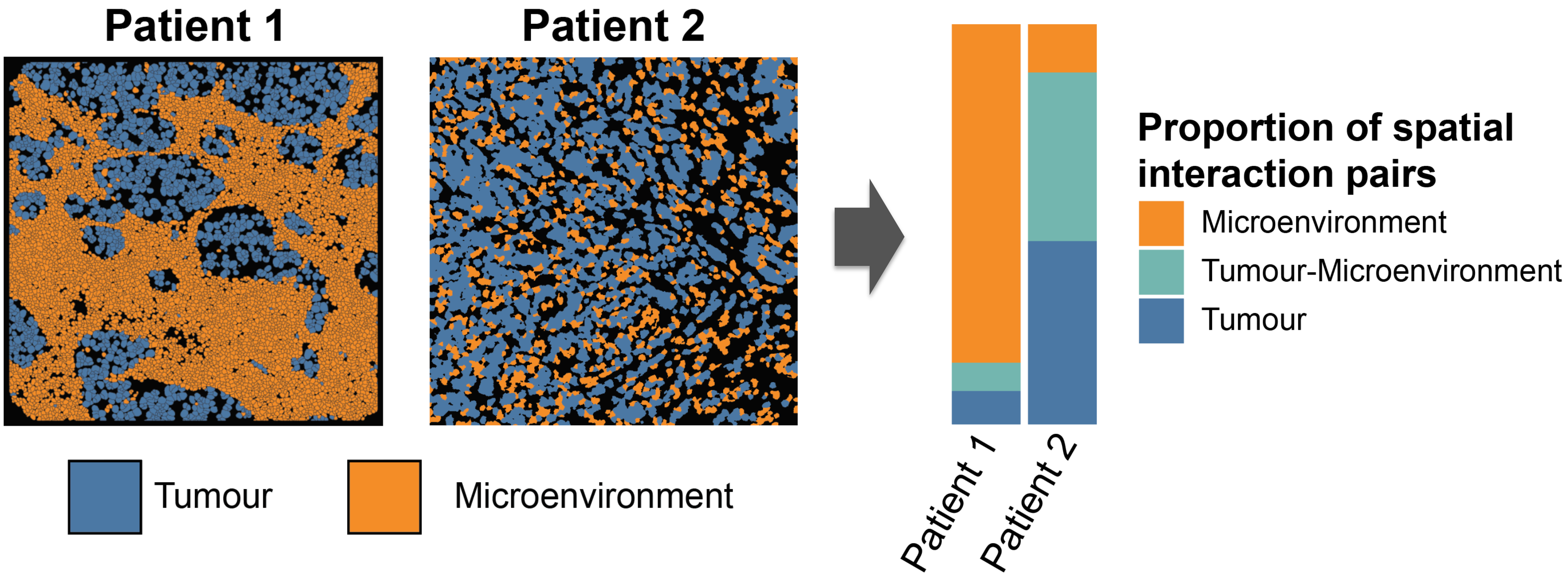


Spatial metrics II: Nearest Neighbour Correlation

IMC (Jackson et al.)

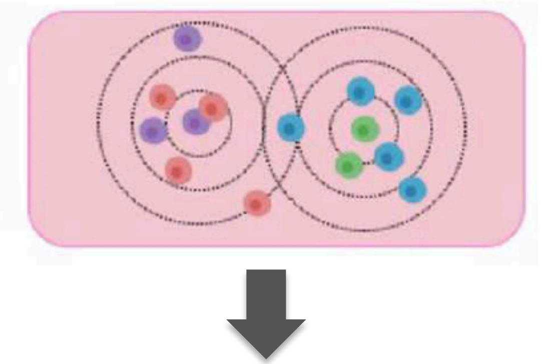


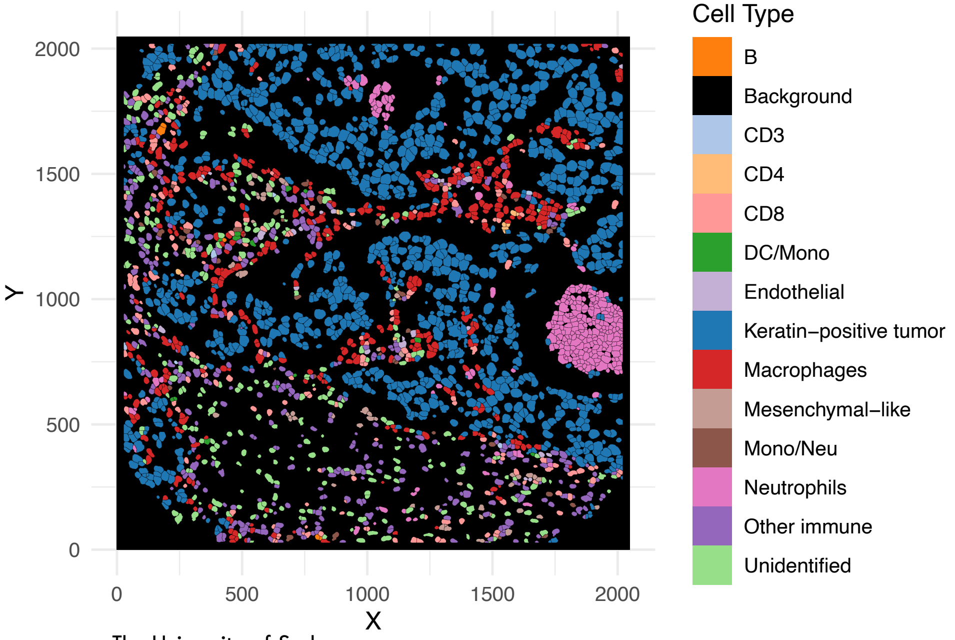
Spatial metrics III: Cell type interaction composition

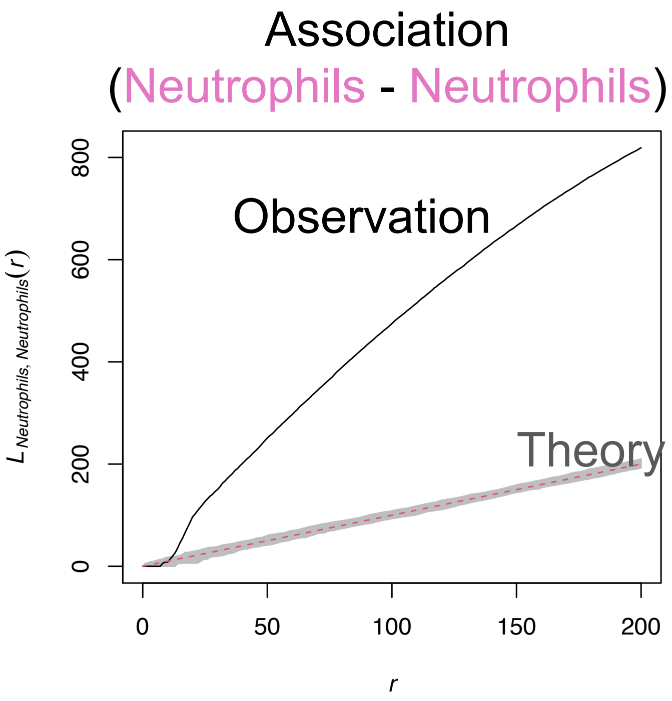


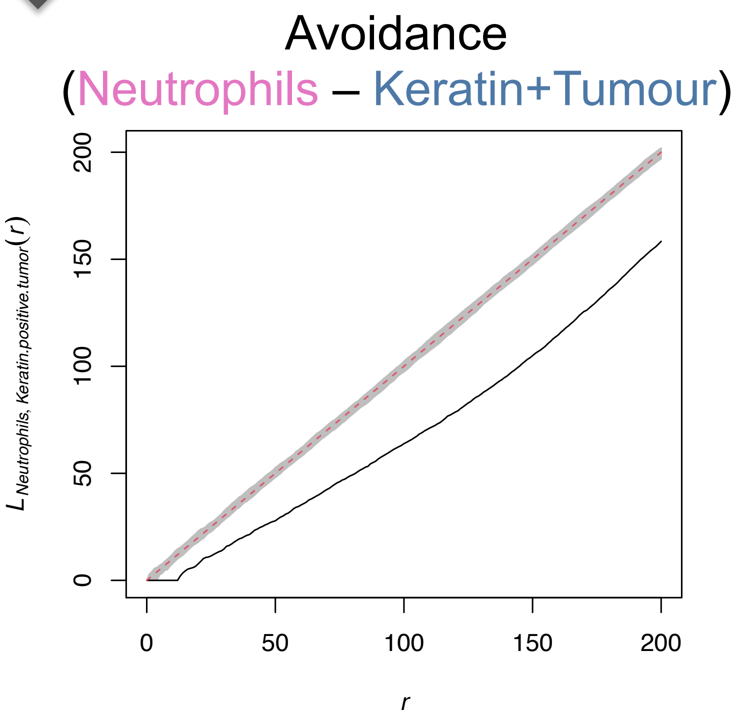
Spatial metrics IV: L functions

L functions: to assess the significance of cell-cell interactions









Baharlou, H., Canete, N. P., Cunningham, A. L., Harman, A. N., & Patrick, E. (2019). Mass Cytometry Imaging for the Study of Human Diseases—Applications and Data Analysis Strategies. *Frontiers in Immunology*, *10*.

Survival analysis using spatial features

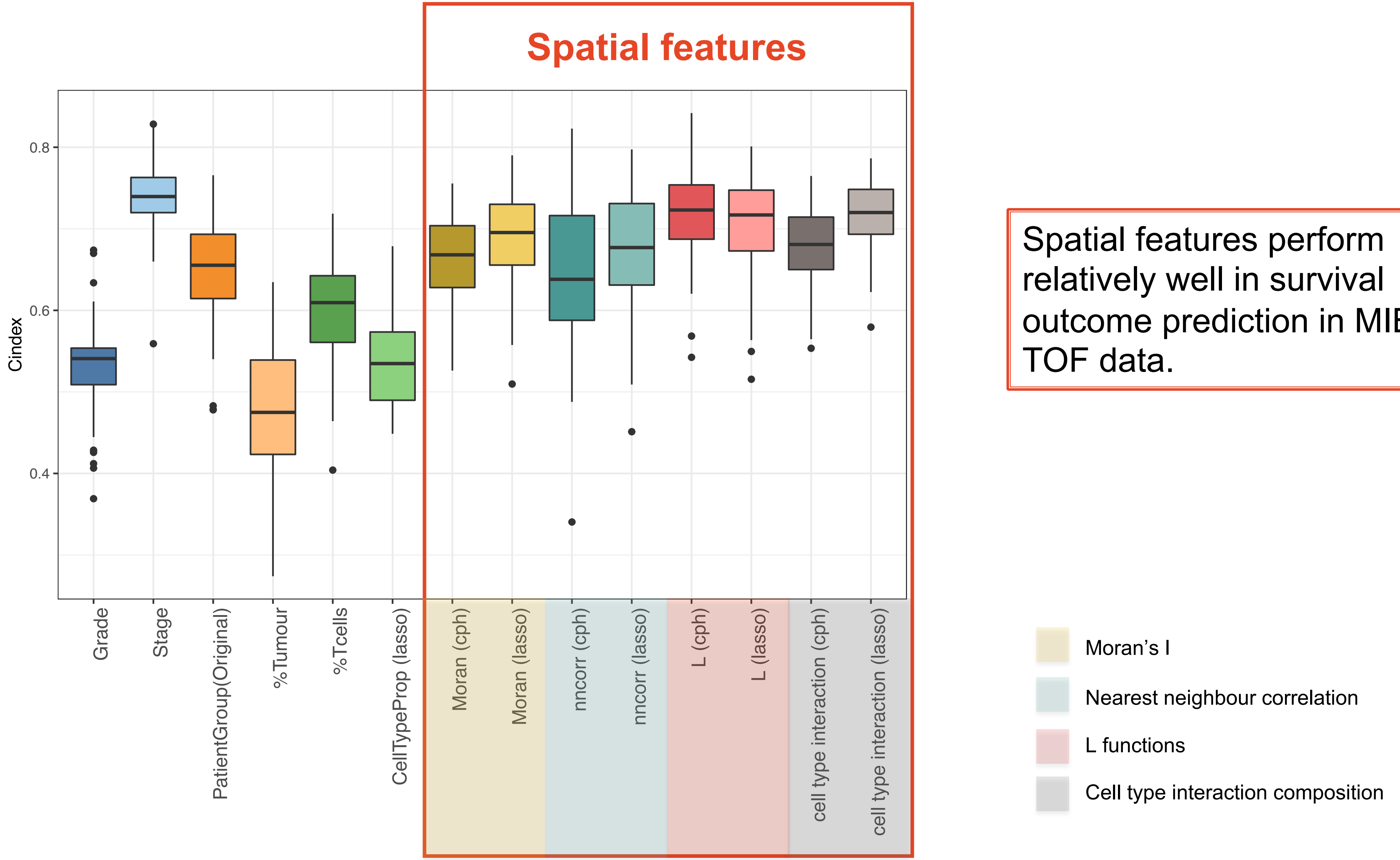
Spatial discriminative features

- I. Moran's I
- II. Nearest Neighbour correlation
- III. Cell type interaction composition
- IV. L function

Survival analysis

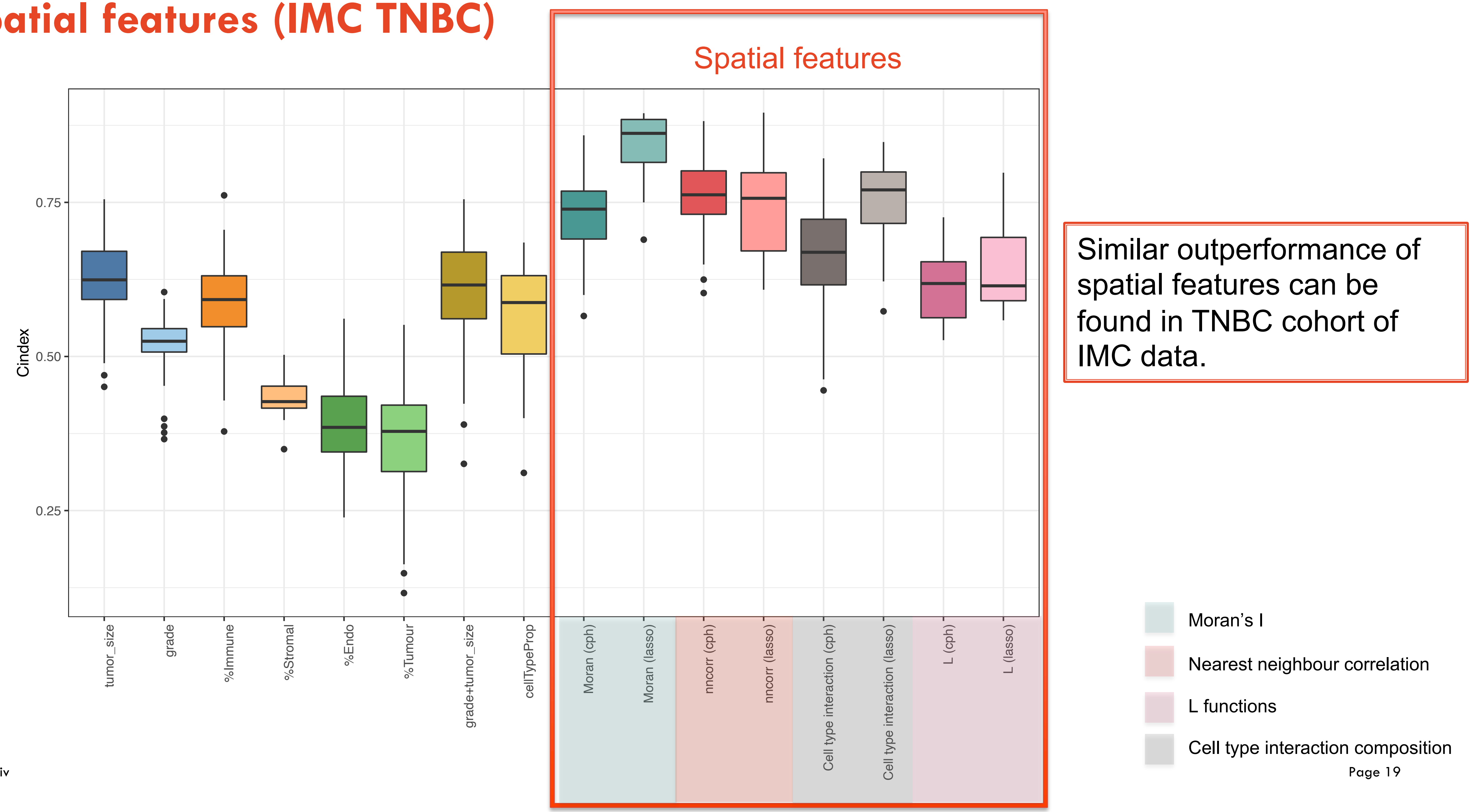
- Select features based on univariate cox model
- Fitting the multivariate cox model (coxph, lasso)
- Evaluating survival model using c-index via cross validation

Survival analysis (MIBI-TOF)



Spatial features perform relatively well in survival outcome prediction in MIBI-TOF data.

Spatial features (IMC TNBC)



Similar outperformance of spatial features can be found in TNBC cohort of IMC data.

Moran's I

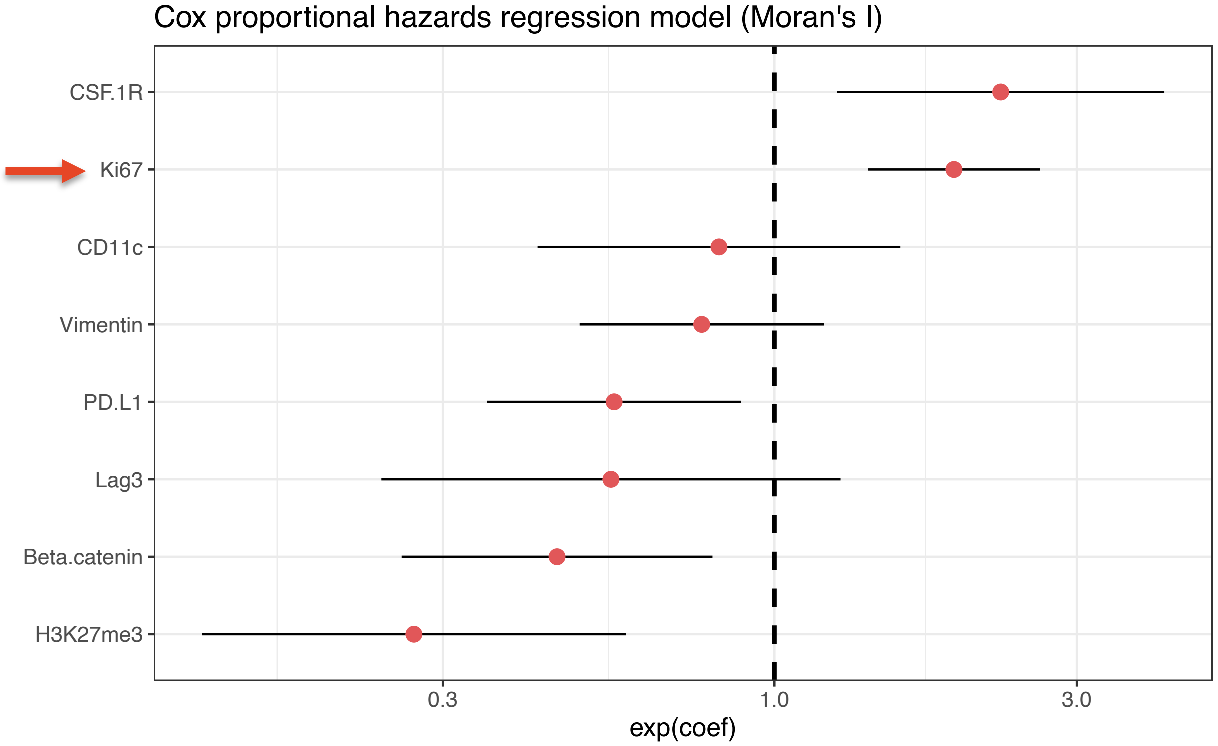
Mesenchymal markers
Immune markers
Cell status markers
Tumour markers
Immune regulation markers

MIBI-TOF | **IMC**

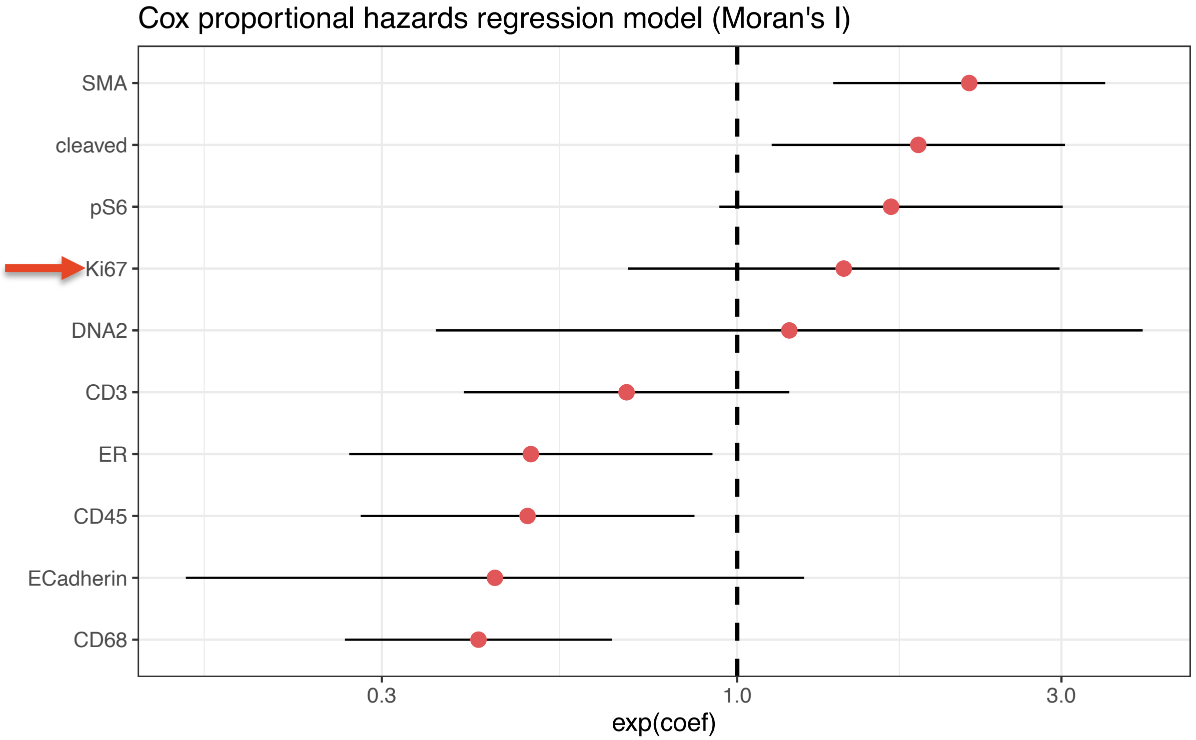
Top features are from diverse marker categories.

Moran’s I

MIBI-TOF



IMC



Only one common selected top features (Ki67, a cell proliferating marker) in two models

Optimal transport to impute imaging data using CyTOF data

Spatial discriminative features

I. Moran's I	II. Nearest Neighbour correlation	III. Cell type interaction composition	IV. L function

Survival analysis

Select features based on univariate cox model	Fitting the multivariate cox model (coxph, lasso)	Evaluating survival model using c-index

Integration with CyTOF

Optimal transport to predict additional protein expression

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Optimal transport

Optimal transport problem setting

$$\arg\min_{\gamma} < \gamma, M >_F + \lambda \sum_{i,j} \gamma_{ij} \log(\gamma_{ij})$$

s.t.

$$\sum_i \gamma_{ij} = a_j$$

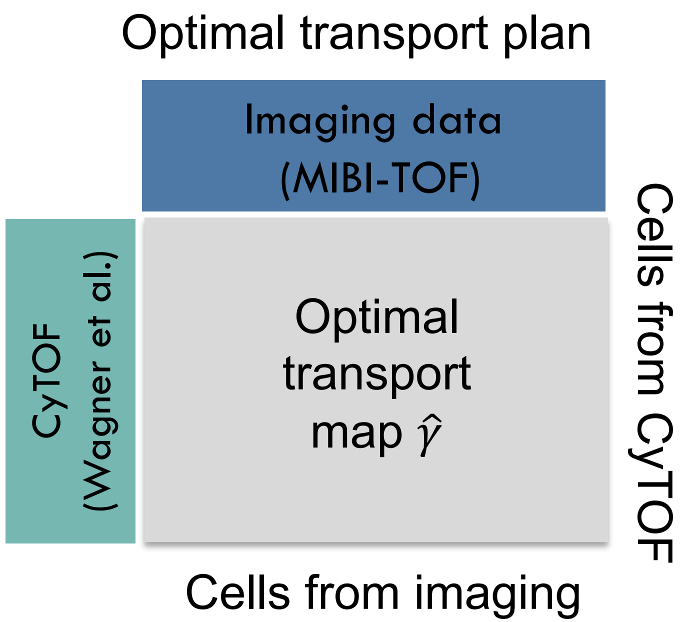
$$\sum_j \gamma_{ij} = b_i$$

$$\gamma \geq 0$$

where M is the cost matrix for the dissimilarity of cells between CyTOF and imaging data;
a_j is the weight for cell j in imaging data; and b_i is the weight for cell i in CyTOF data.

The prediction of a protein expression at position j in imaging using the CyTOF protein expression $g \in R^n$ is

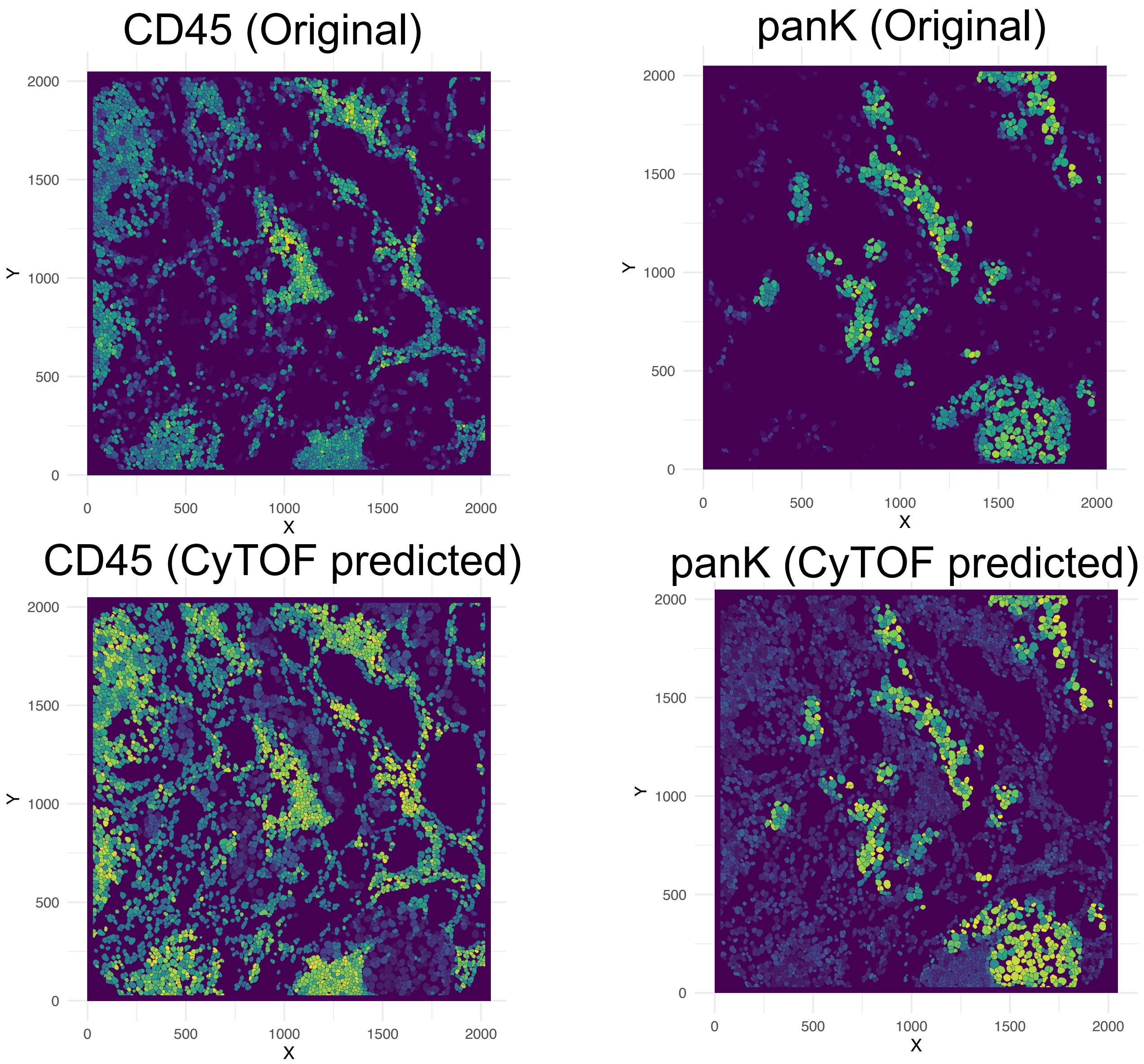
$$\frac{\sum_i \hat{\gamma}_{ij} \times g_i}{\sum_i \hat{\gamma}_{ij}}$$



Challenges:
- Wagner et al. CyTOF data only has ~14 proteins common with MIBI-TOF data

Cang et al. (2020) Nature Communication

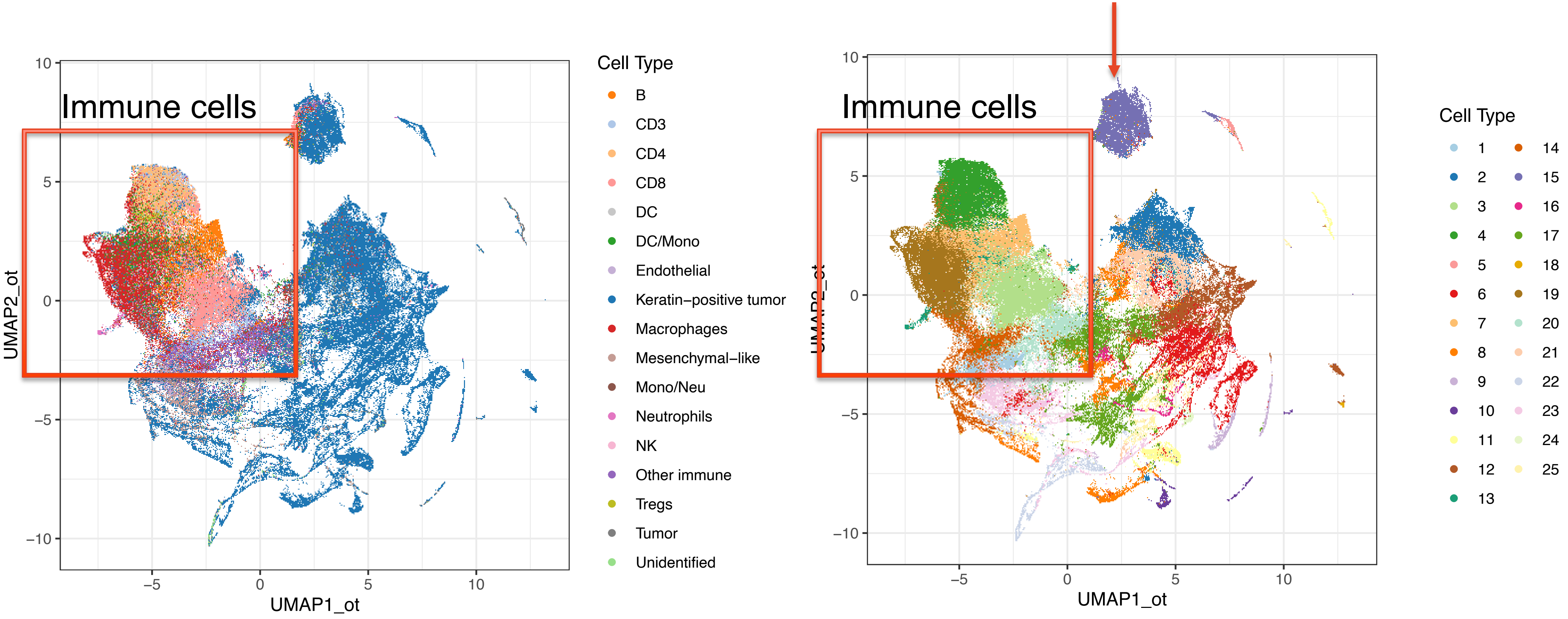
Protein prediction



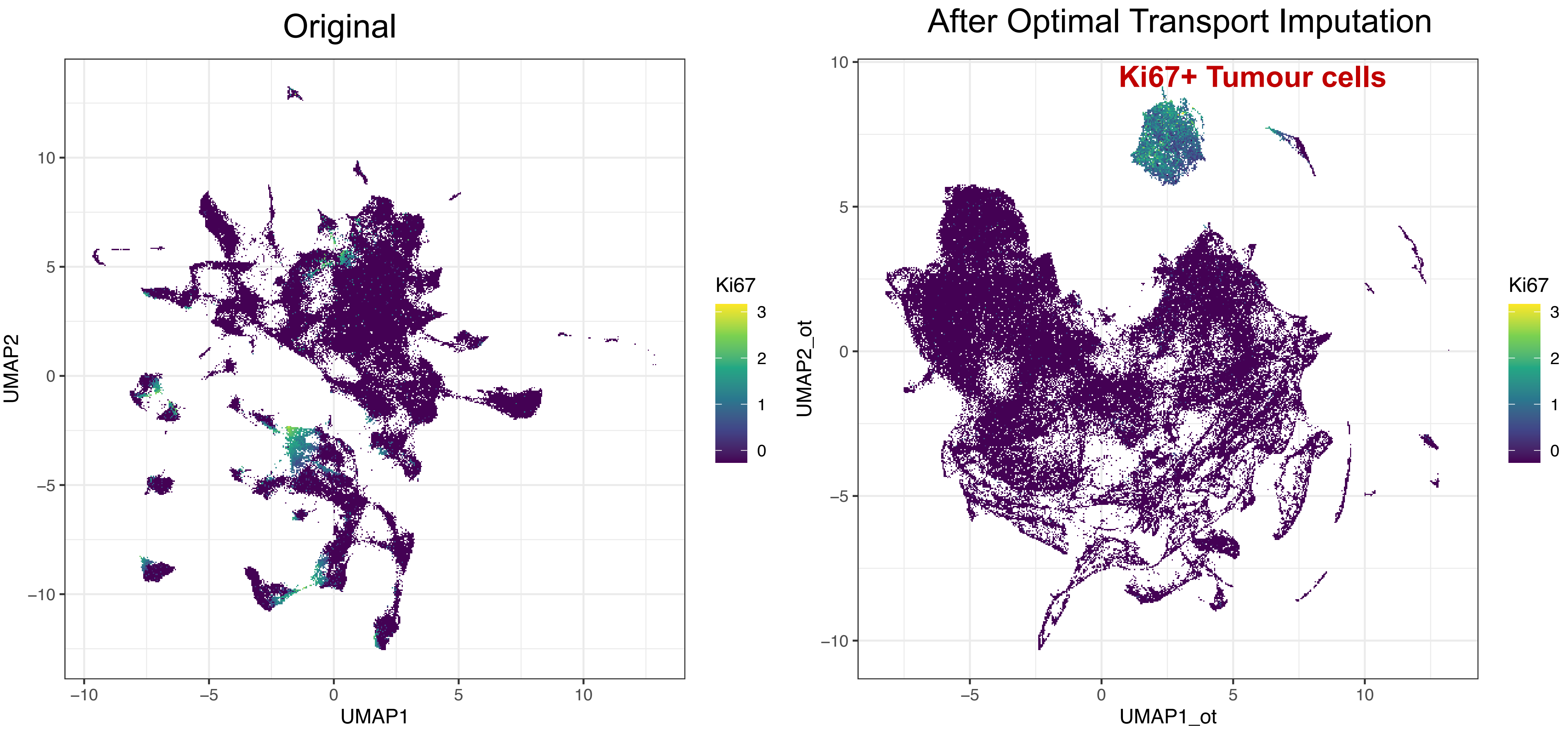
cor = 0.85

cor = 0.94

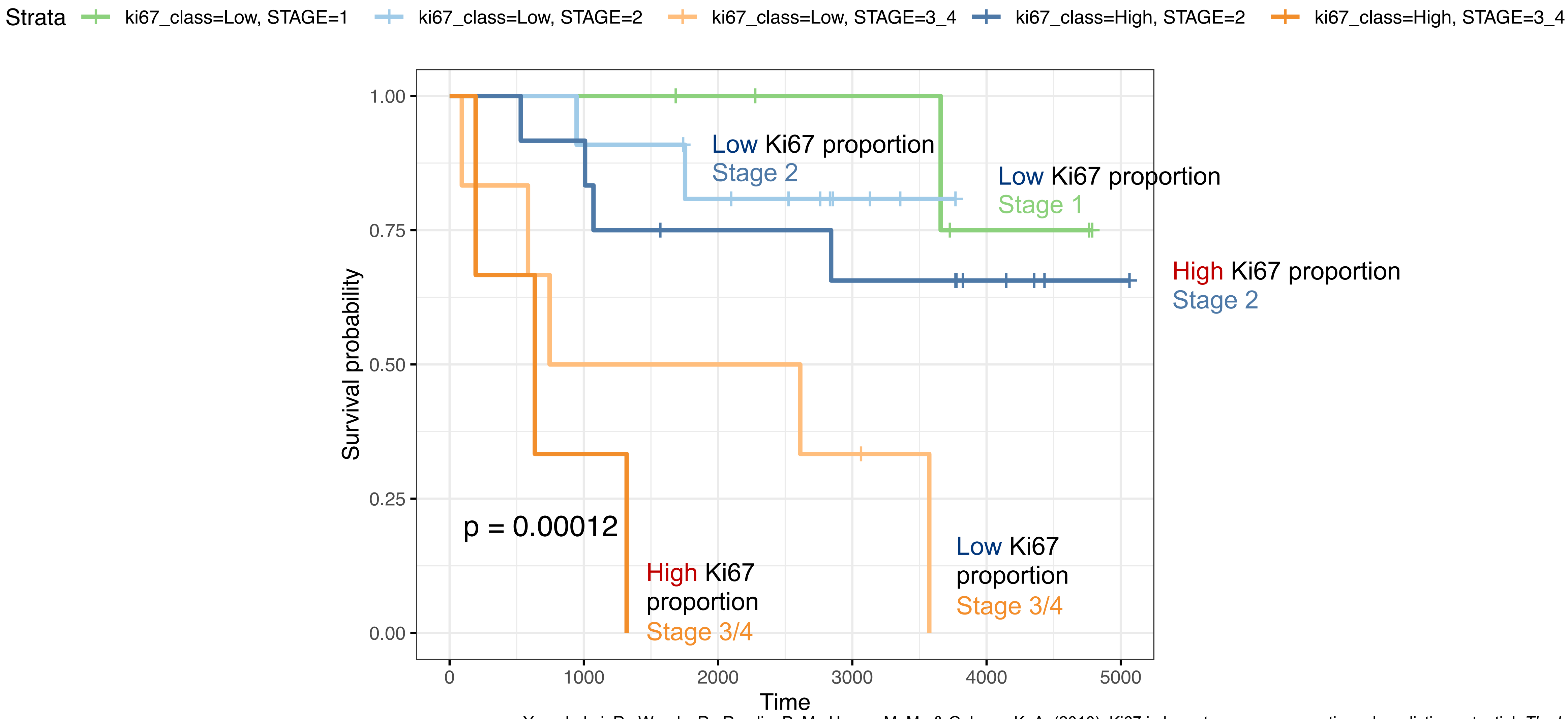
Identification of new sub cell type



Identification of new sub cell type



Survival analysis based on new annotations



Yerushalmi, R., Woods, R., Ravdin, P. M., Hayes, M. M., & Gelmon, K. A. (2010). Ki67 in breast cancer: prognostic and predictive potential. *The lancet oncology*, *11*(2), 174-183.

Inwald, E. C., Klinkhammer-Schalke, M., Hofstädter, F., Zeman, F., Koller, M., Gerstenhauer, M., & Ortmann, O. (2013). Ki-67 is a prognostic parameter in breast cancer patients: results of a large population-based cohort of a cancer registry. *Breast cancer research and treatment*, *139*(2), 539-552.

Conclusion

- Spatial features especially spatial association of the protein expression improve the survival prediction in both imaging datasets.
- Limited common feature is found between the survival models due to the limited common proteins measured in two datasets.
- Imputation of additional protein expression improved the cell type identification, and have potentials to increase the commonality between two datasets and further improve the survival prediction.

Acknowledgment

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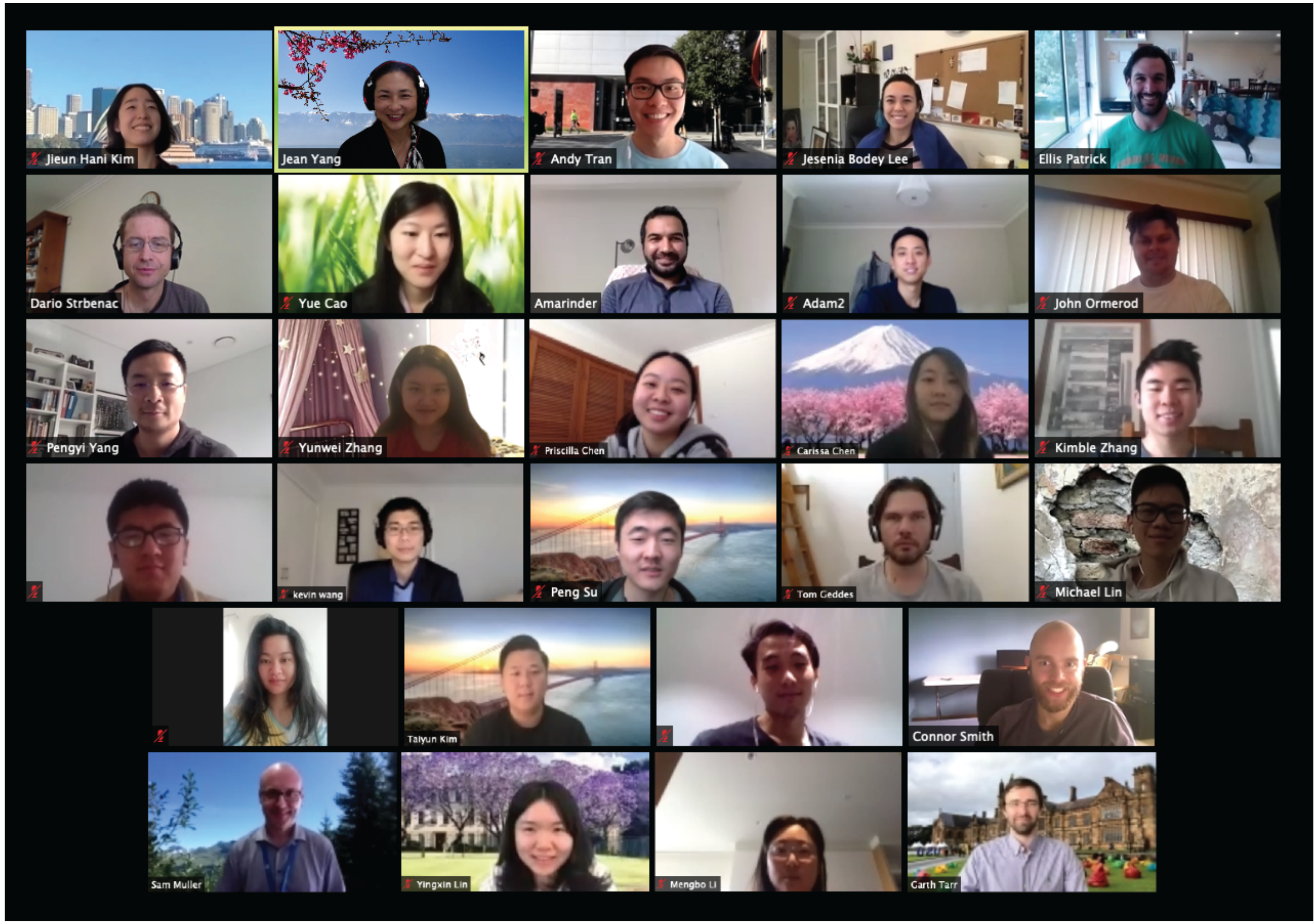

Lauren Hsu and Aedin Culhane for providing the processed MIBI-TOF and CyTOF data