

# A Tale of Two Spaces

## $\Phi$ -Space for the continuous phenotyping of spatial transcriptomics

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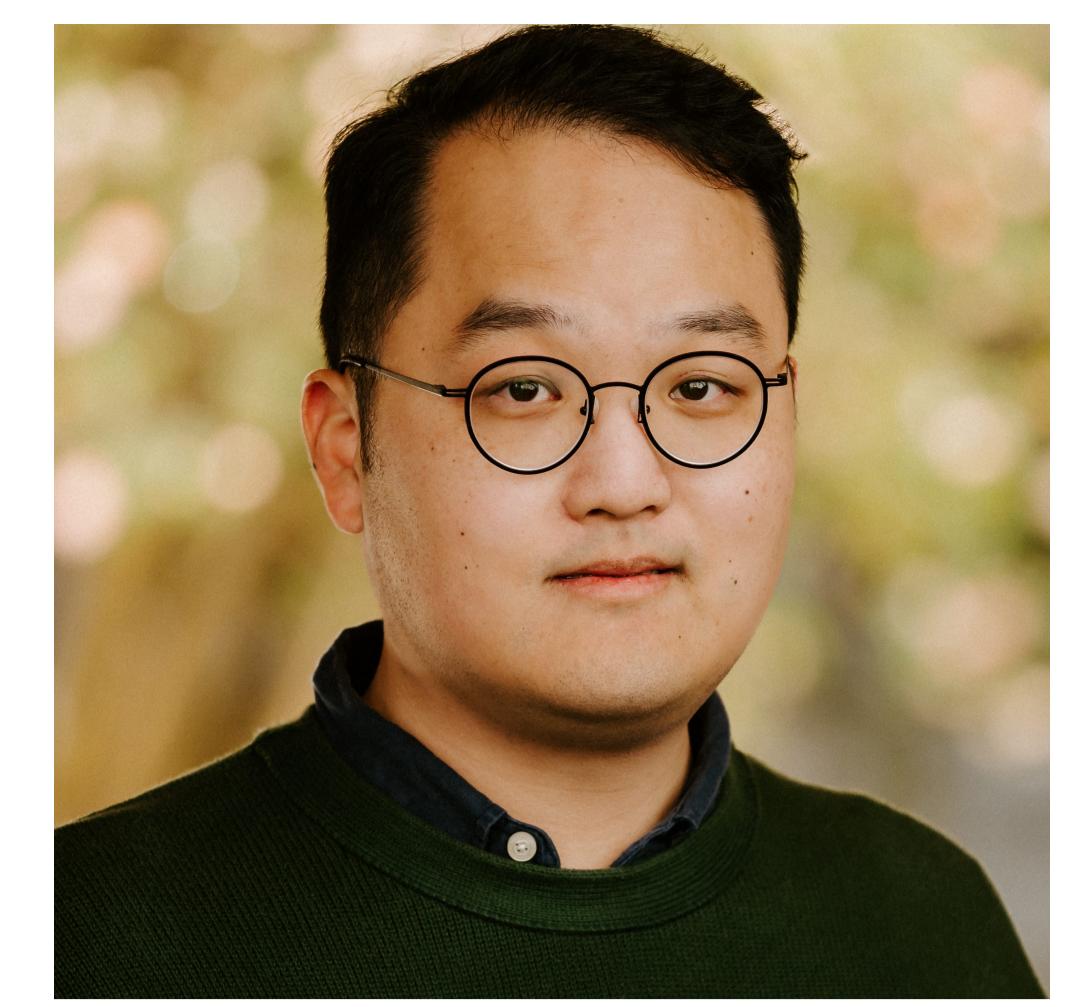
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<https://github.com/jiadongm>



### Highlights

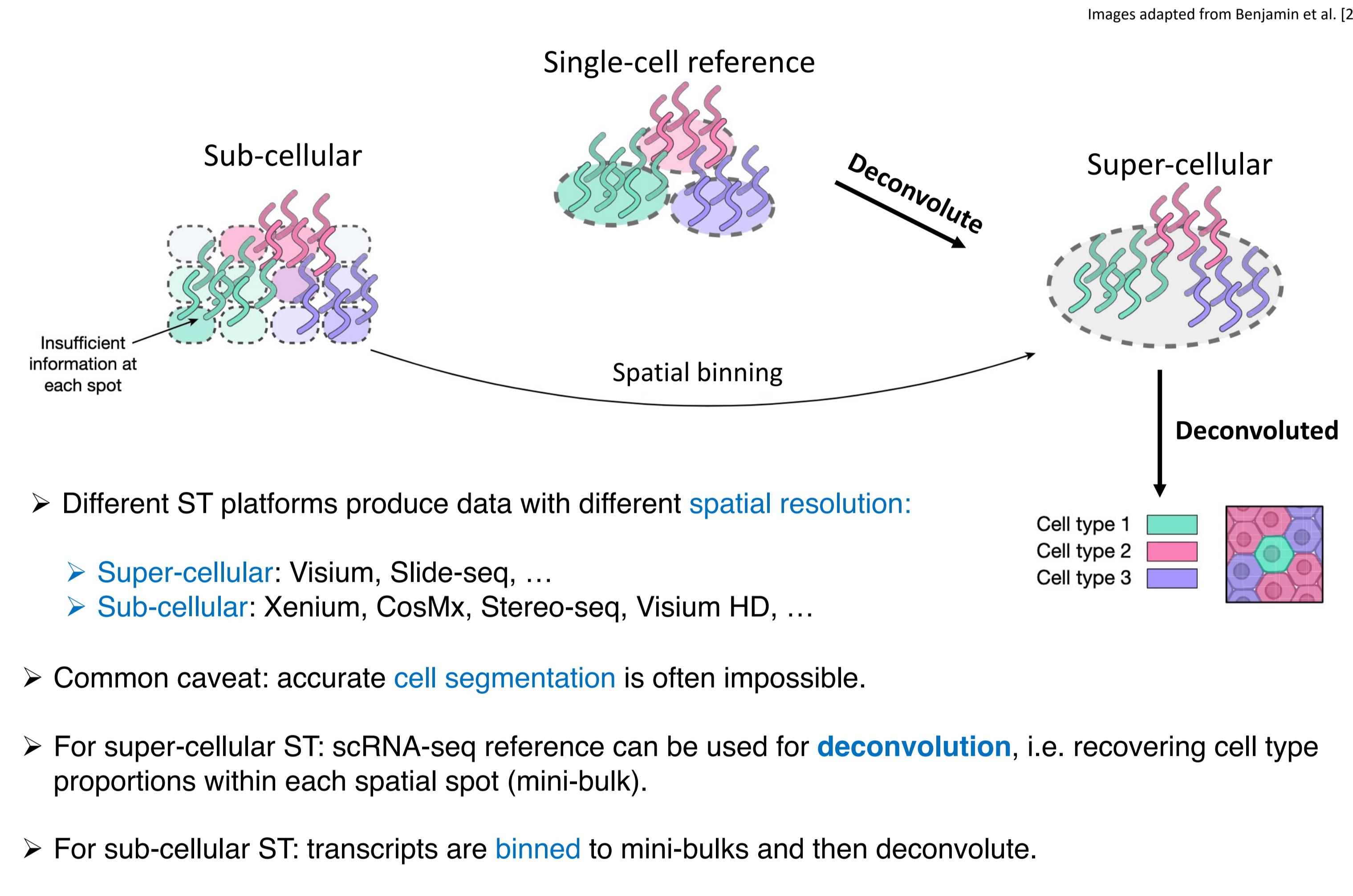
Can you use an atlas of healthy lung samples to annotate cancerous lung cells? You could. But how would you interpret a tumour cell being annotated as an alveolar cell?

- $\Phi$ -Space provides highly interpretable continuous phenotyping results, helping you better utilise existing bulk and scRNA-seq references to identify out-of-reference cell states.
- Previously we illustrated  $\Phi$ -Space's power to uncover complex biology in scRNA-seq, CITE-seq and scATAC-seq data, in the presence of strong batch effects [1].
- Here we apply  $\Phi$ -Space to uncovering spatial phenotypic patterns in spatial transcriptomics (ST) samples from NSCLC and AML patients.
- The datasets we used were generated from both super-cellular and sub-cellular ST platforms, demonstrating  $\Phi$ -Space's potential for a unified framework for processing ST samples.
- The  $\Phi$ -Space R package is freely available on GitHub, and manuscript on bioRxiv:

```
devtools::install_github('jiadongm/PhiSpace/pkg')
```

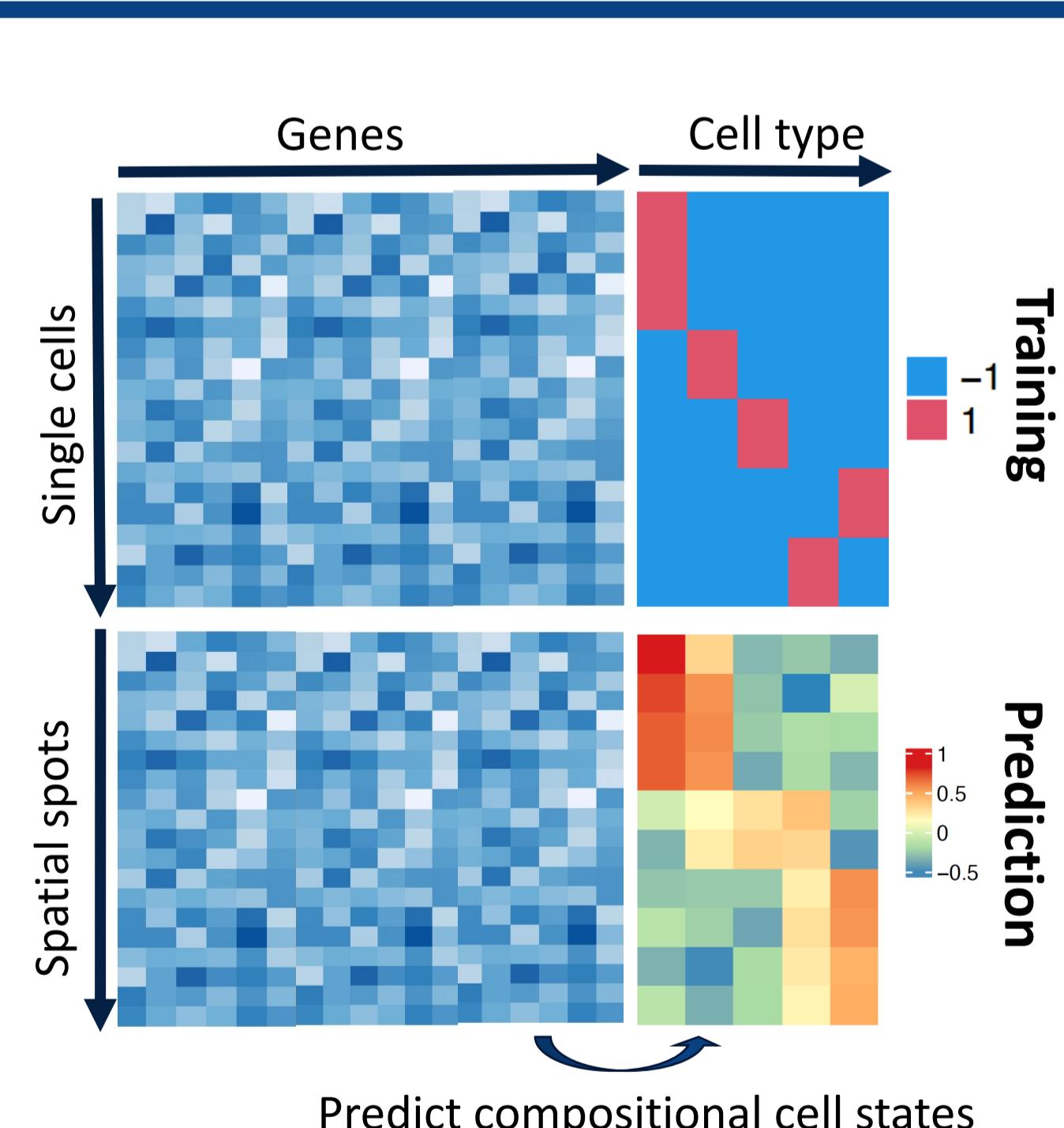


### Background

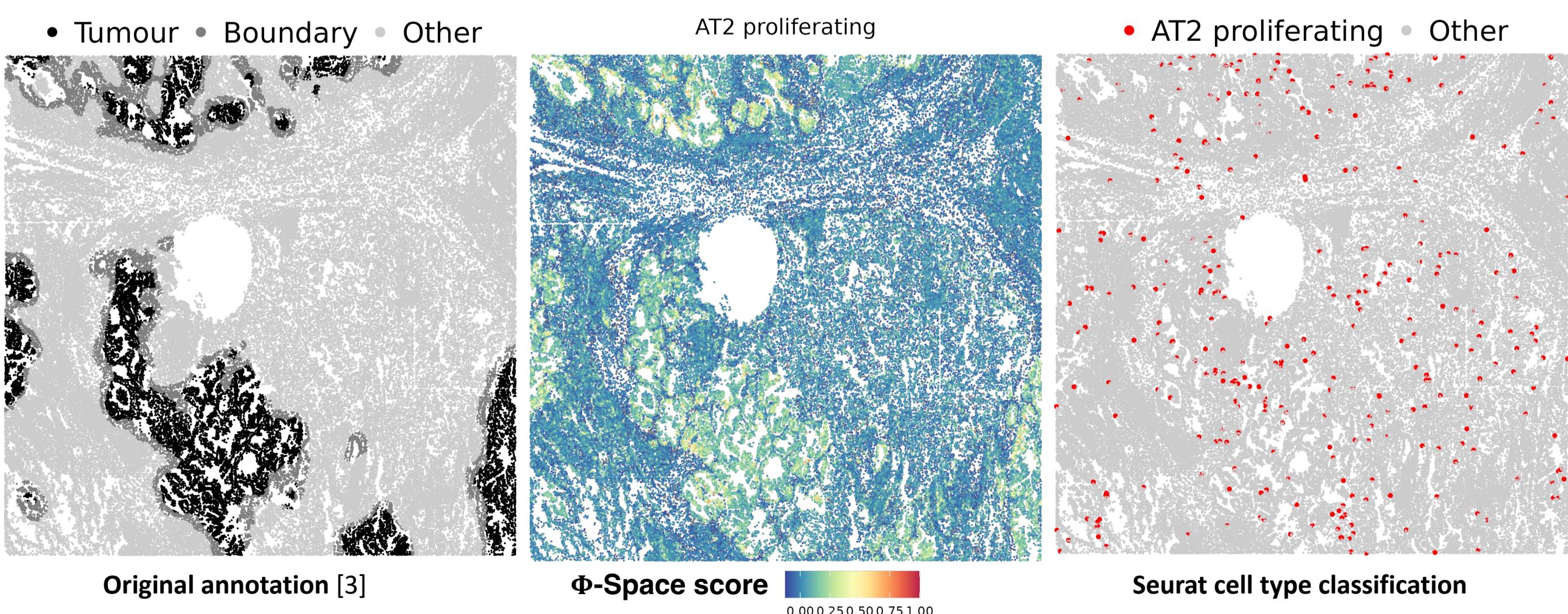


### Methods

- The core of  $\Phi$ -Space is partial least squares (PLS) regression.
- Using regression rather than a classification enables more flexible prediction of compositional cell states.
- We first train a PLS model using a scRNA-seq reference, and then use this PLS model to phenotype spatial spots on a continuum.
- Each spatial spot is characterised by a vector of continuous cell type scores, which we refer to as the spatial spot's phenotype space embedding.
- $\Phi$ -Space is very robust against batch effects in the reference, and it can pick up cell type signals neglected by conventional cell type classification methods.



### NSCLC CosMx



As a proof of concept, we show the benefits of continuous instead of discrete phenotyping.

- Reference: Azimuth human lung atlas [4];
- Query: CosMx LUAD sample with good quality cell segmentation.
- According to  $\Phi$ -Space, tumour region has slightly higher proliferating AT2 identity than non-tumour regions.
- This is not captured by a standard single-cell cell type classification via Seurat.
- What if cell segmentation is not available?

### Discussion

Based on  $\Phi$ -Space, we provided a unified framework for analysing cancerous ST tissues using healthy scRNA-seq references:

- When cell segmentation is reliable,  $\Phi$ -Space uncovers spatial patterns that are missed by conventional cell typing methods.
- When ST is super-cellular,  $\Phi$ -Space provides competitive deconvolution performances.
- When ST is sub-cellular,  $\Phi$ -Space deconvolves binned transcripts.
- $\Phi$ -Space revealed phenotypic heterogeneity of cancer clones.

### References

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Acknowledgement:  
ARC DP DP200102903



We thank Mark Dawson's Lab for providing processed version of the mouse spleen Stereo-seq data, and for their helpful suggestions for data analysis.