Plan of the course

1. ToMATo for colocalizing cell types

[Bae et al. - 2022 - *STopover captures spatial colocalization and interaction in the tumor microenvironment using topological analysis in spatial transcriptomics data*]

2. Rips persistence for marker gene correlations

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3. Multi-persistence for immune cell arrangements

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4. Future research directions

3. Multi-persistence for immune cell arrangements

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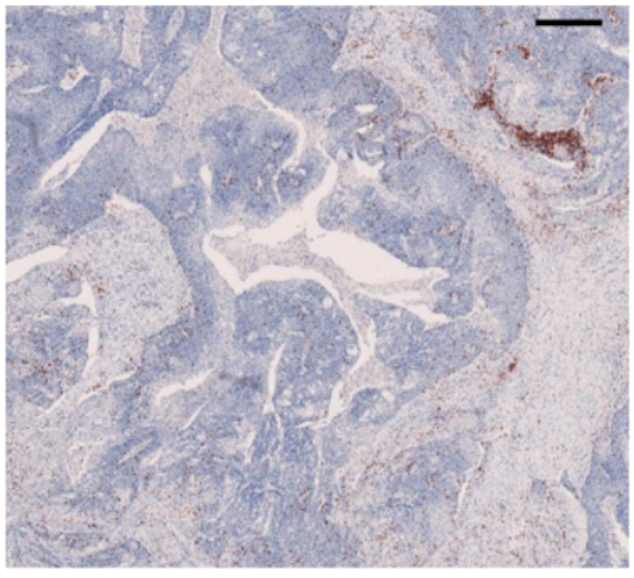
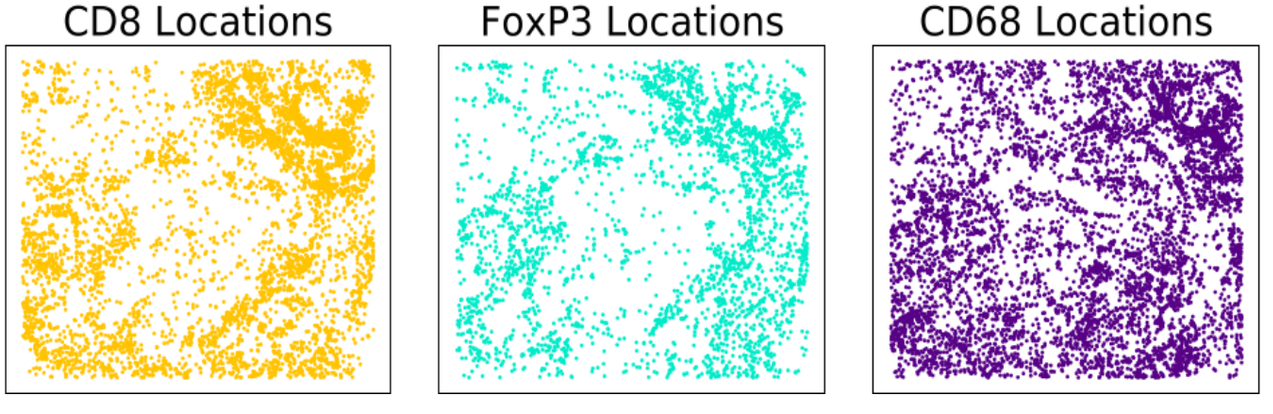
Q: How can one characterize the *geometric arrangement* of cells *of a given cell type* in a way that is robust to *cell type misclassifications*?

Indeed, cell types are often obtained by integration with scRNA-seq and prone to errors...





3. Multi-persistence for immune cell arrangements

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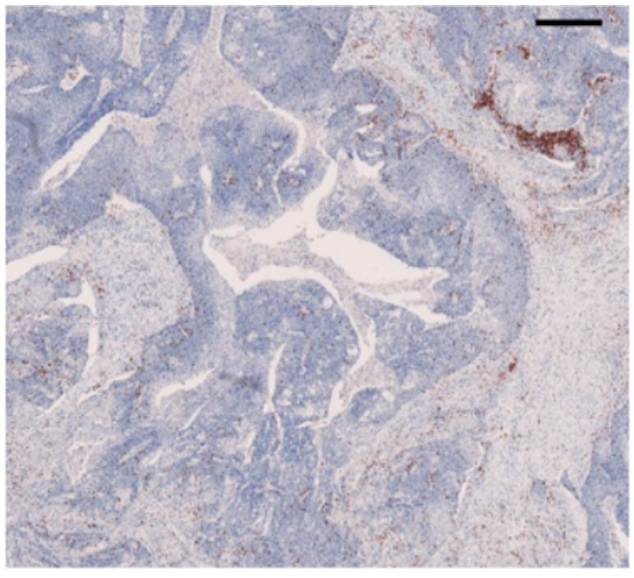
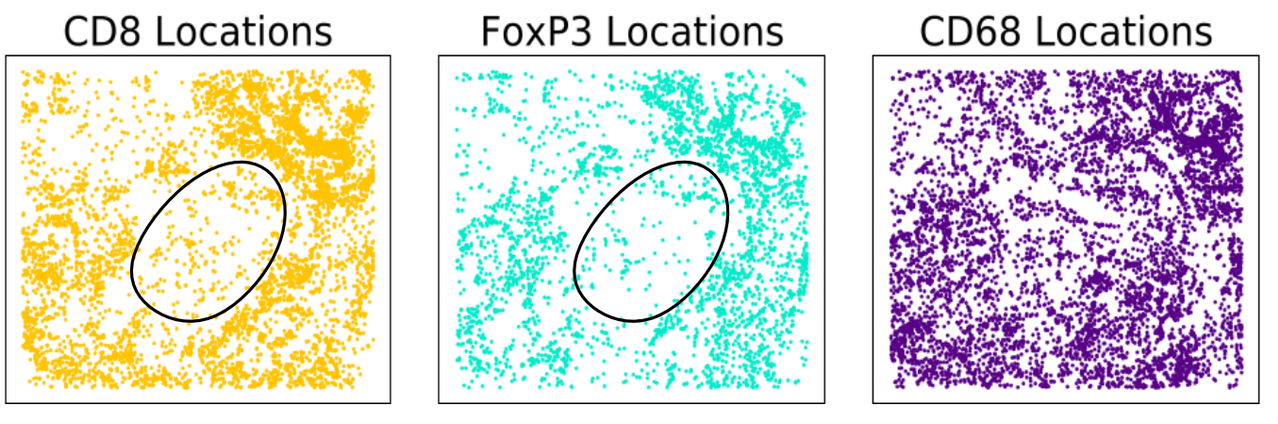


Loop structure



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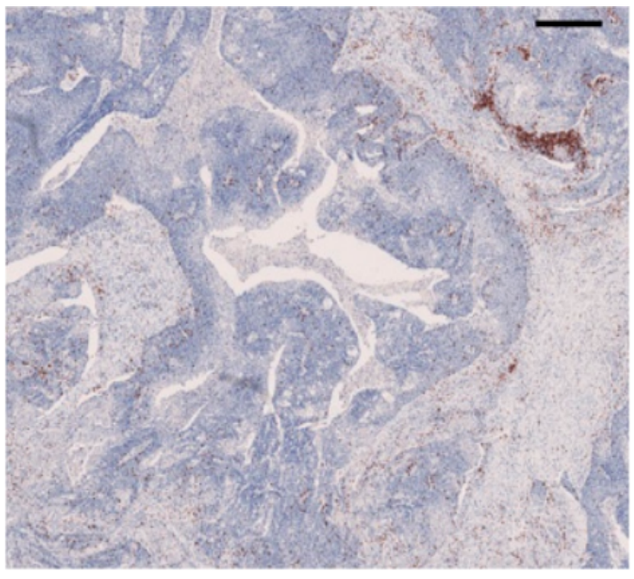

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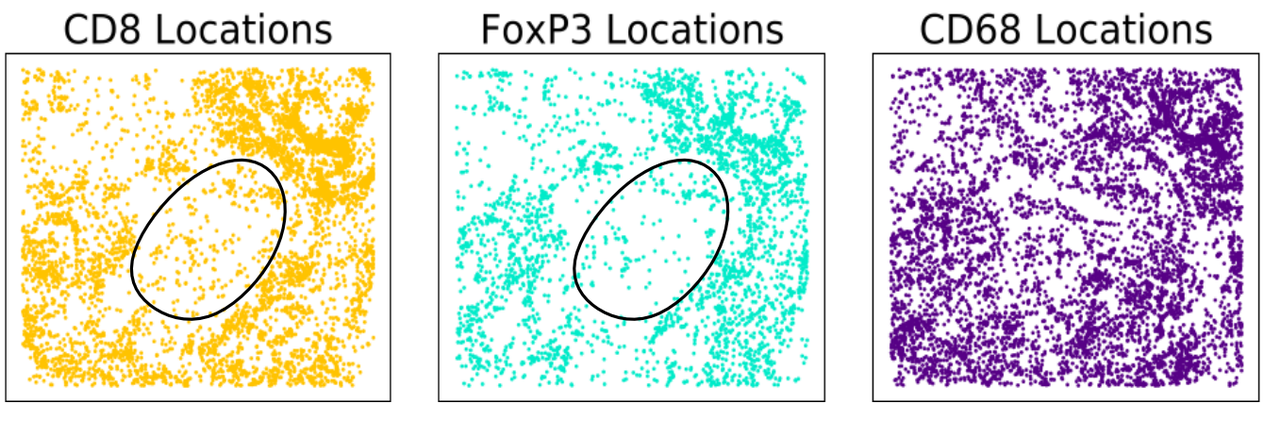

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A: Combine *Rips filtration* with *density estimation* to create an outlier-robust analogue of persistence diagrams with 2-parameter PH.

Instability of Rips persistence

Rips persistence diagrams are known to be sensitive to outliers.

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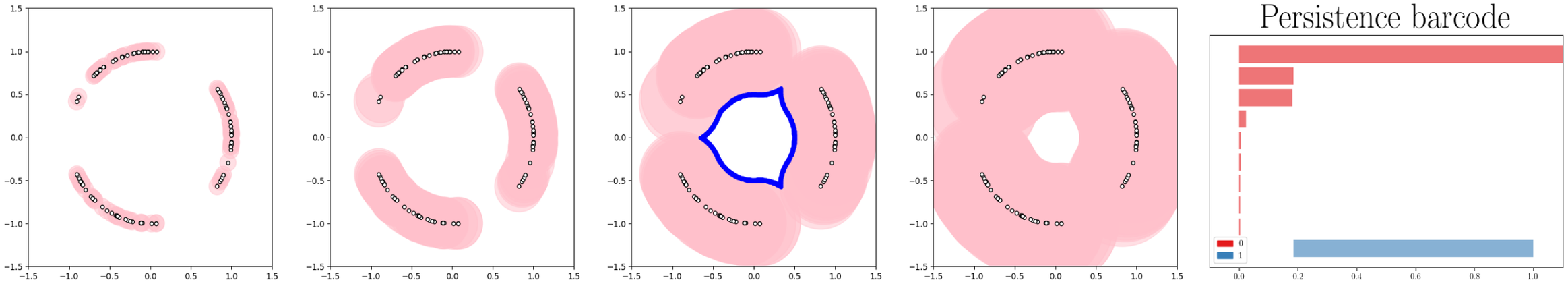

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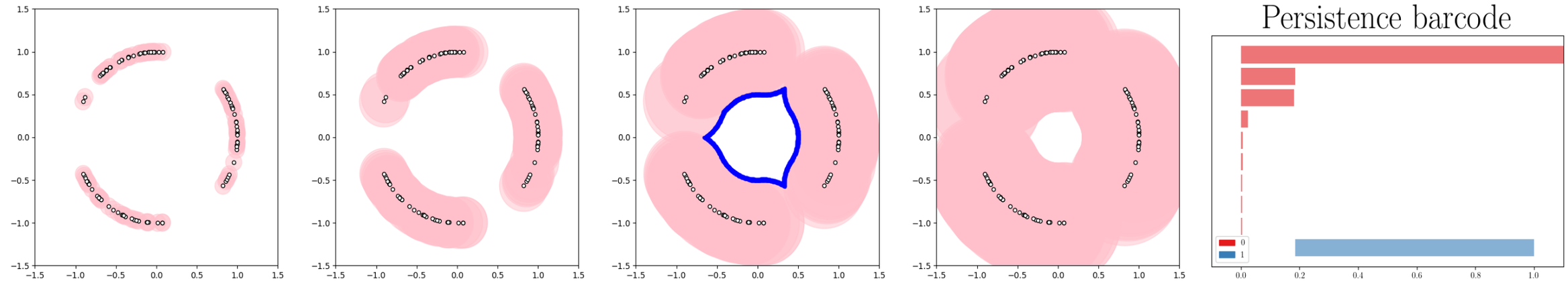

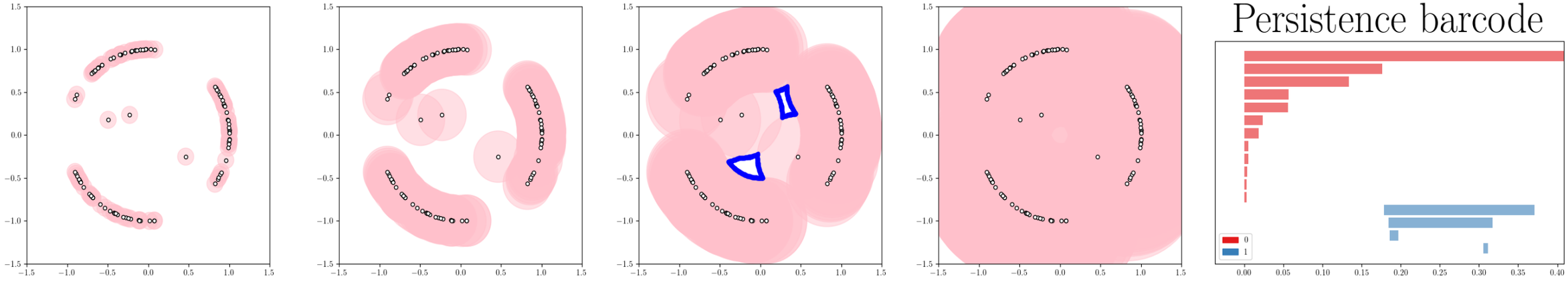

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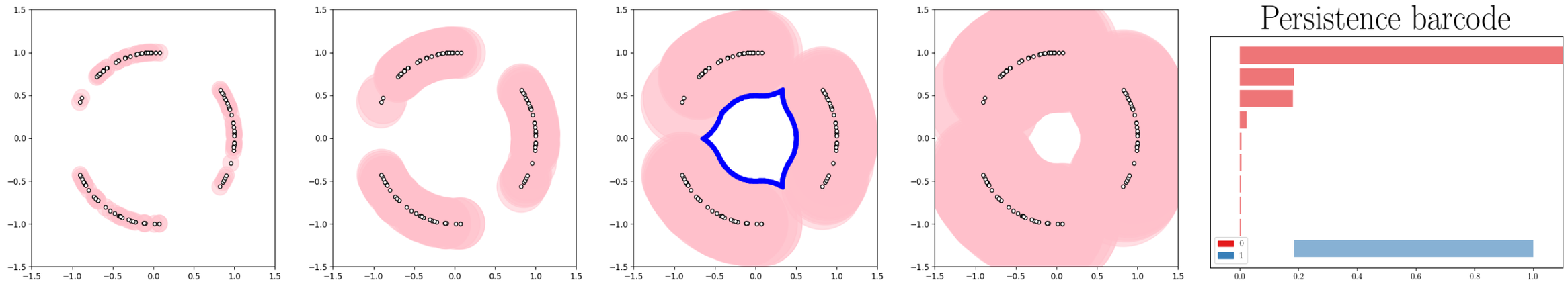
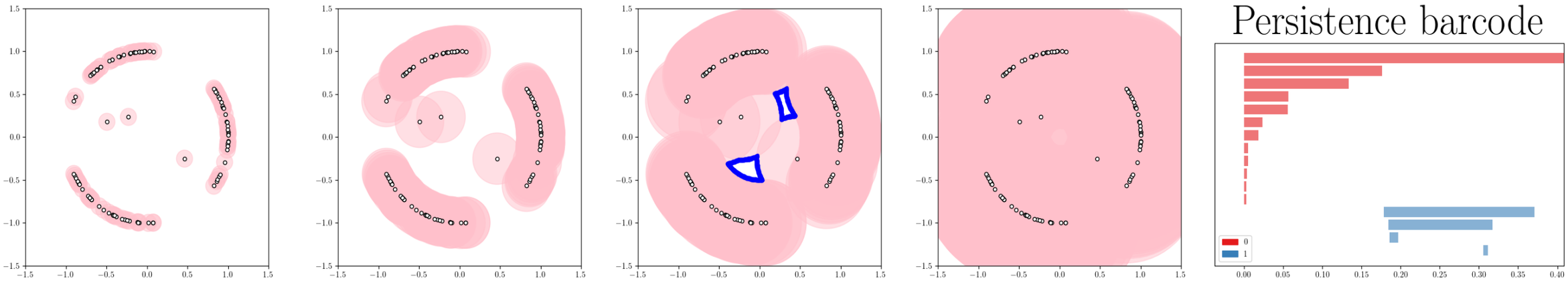
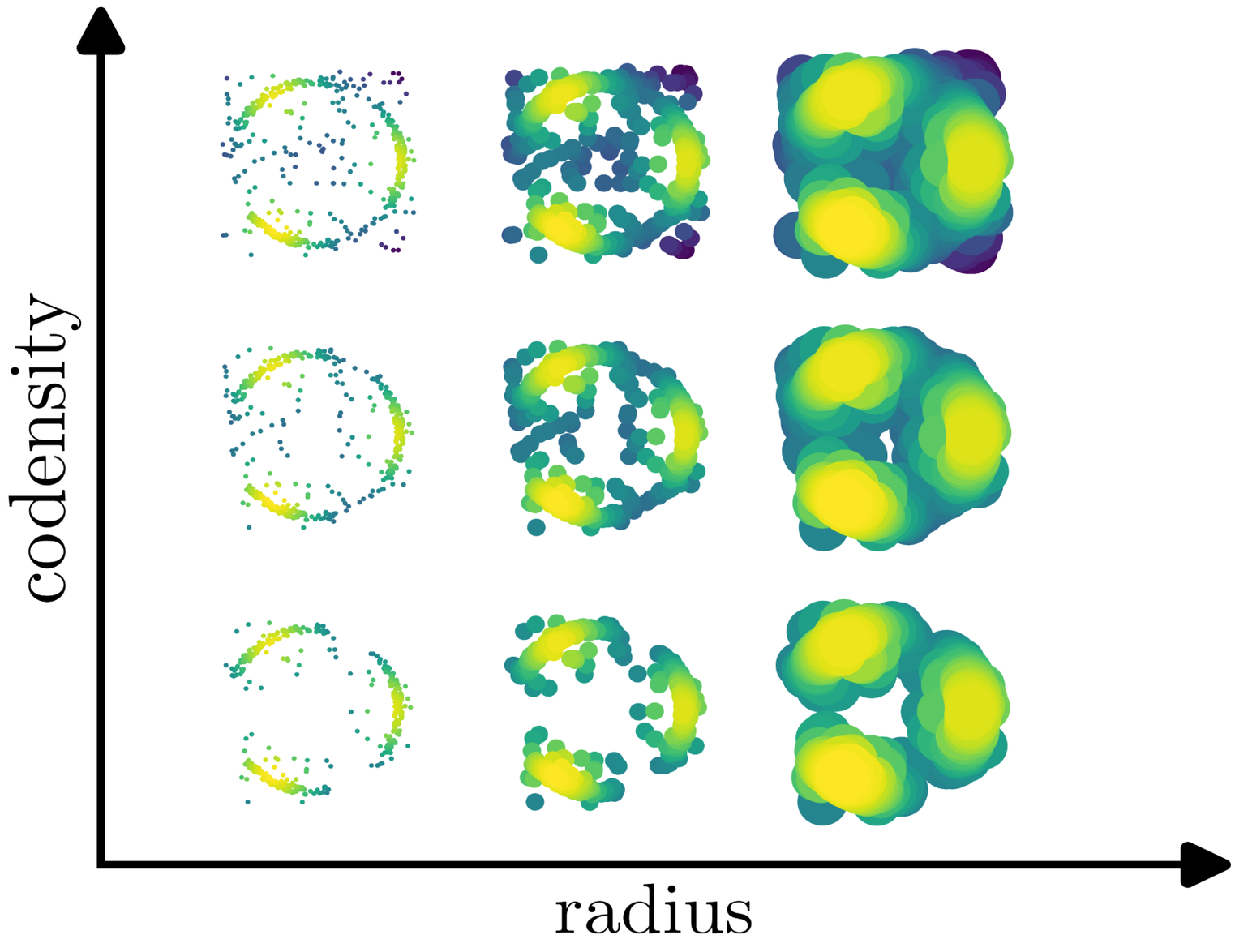




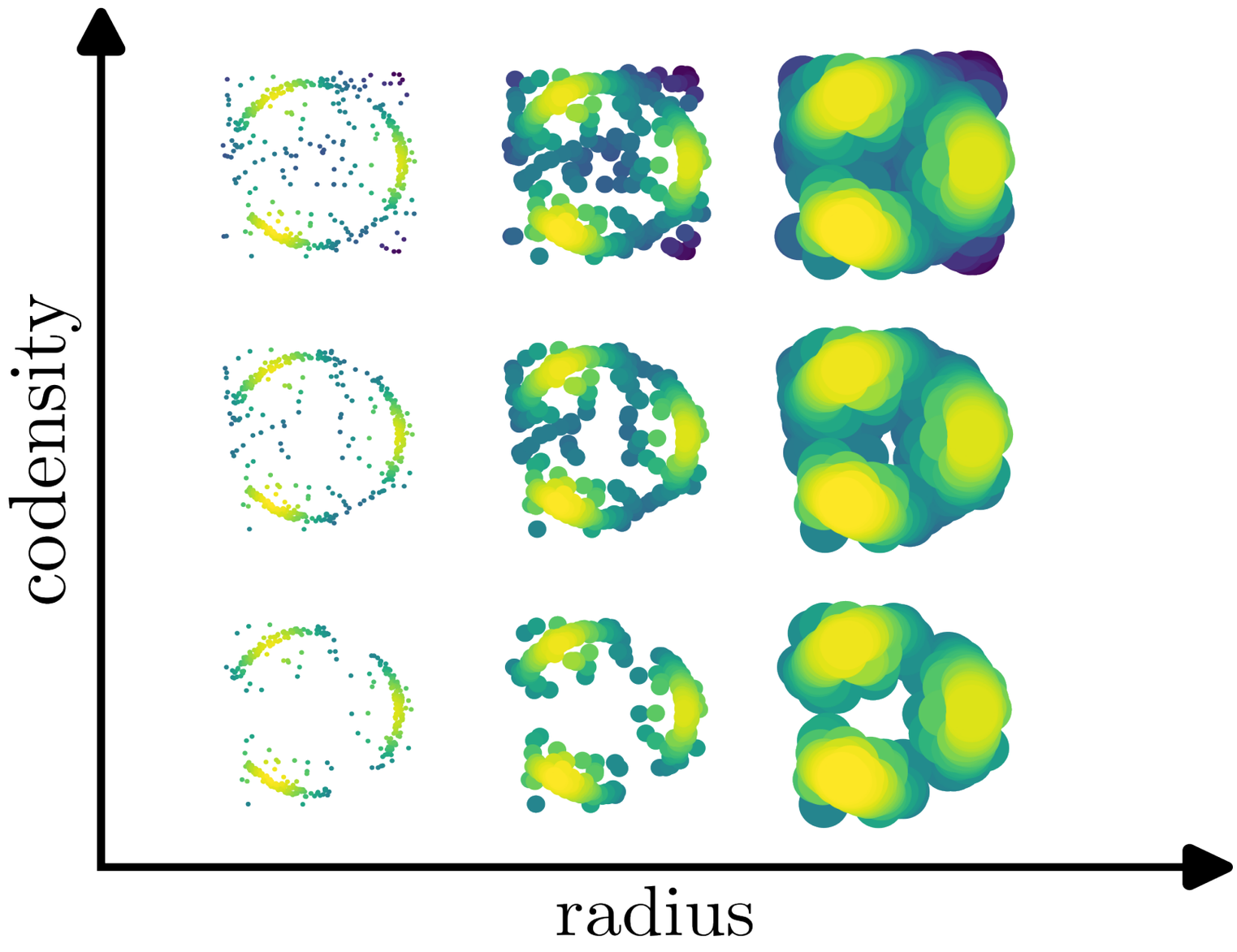
Hence, it seems natural to use density functions to prevent outliers from destroying topological structures.

2-parameter Persistent Homology



2-parameter Persistent Homology

Pb: persistence diagrams are not well-defined for more than 1 parameter.
(no decomposition theorem)



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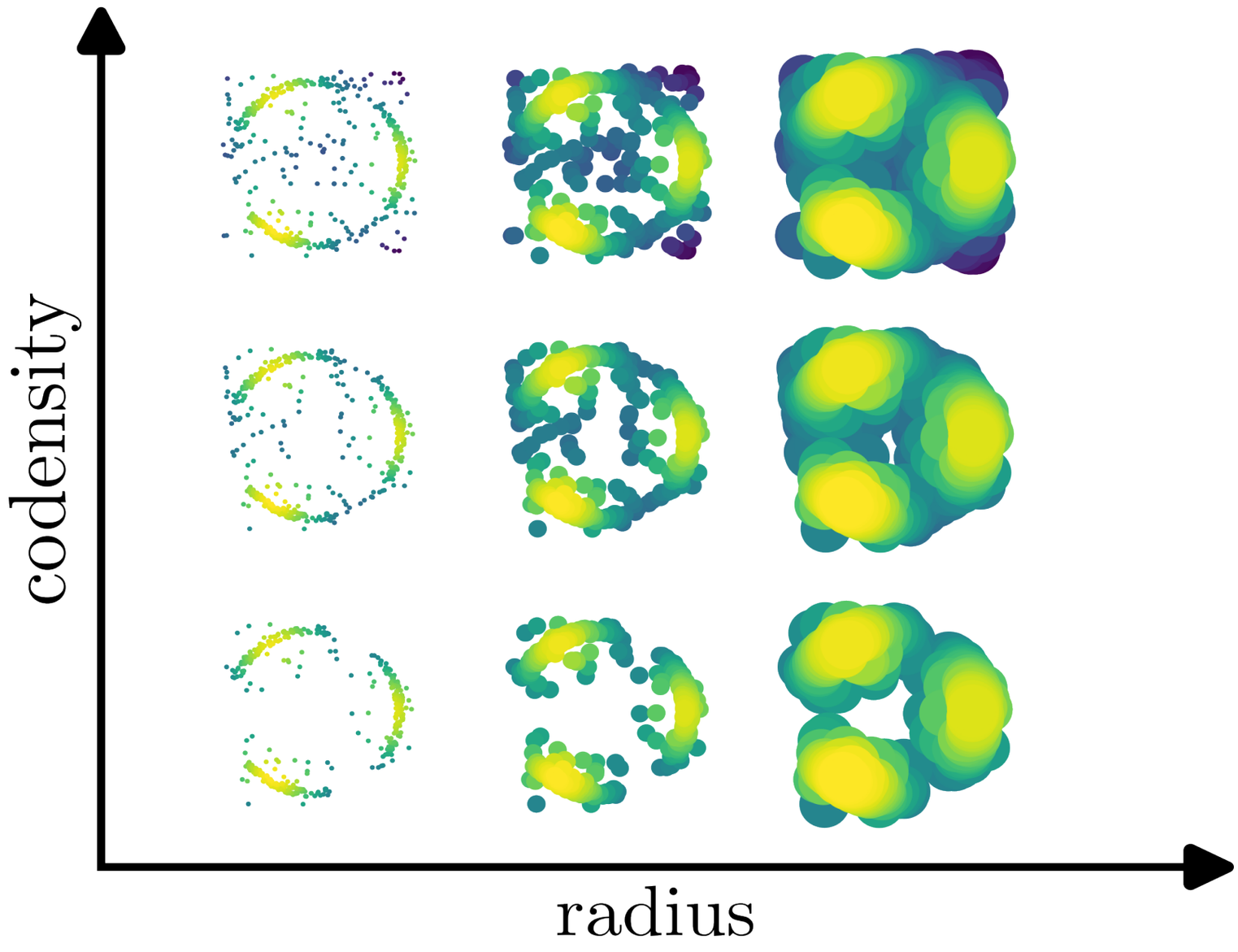

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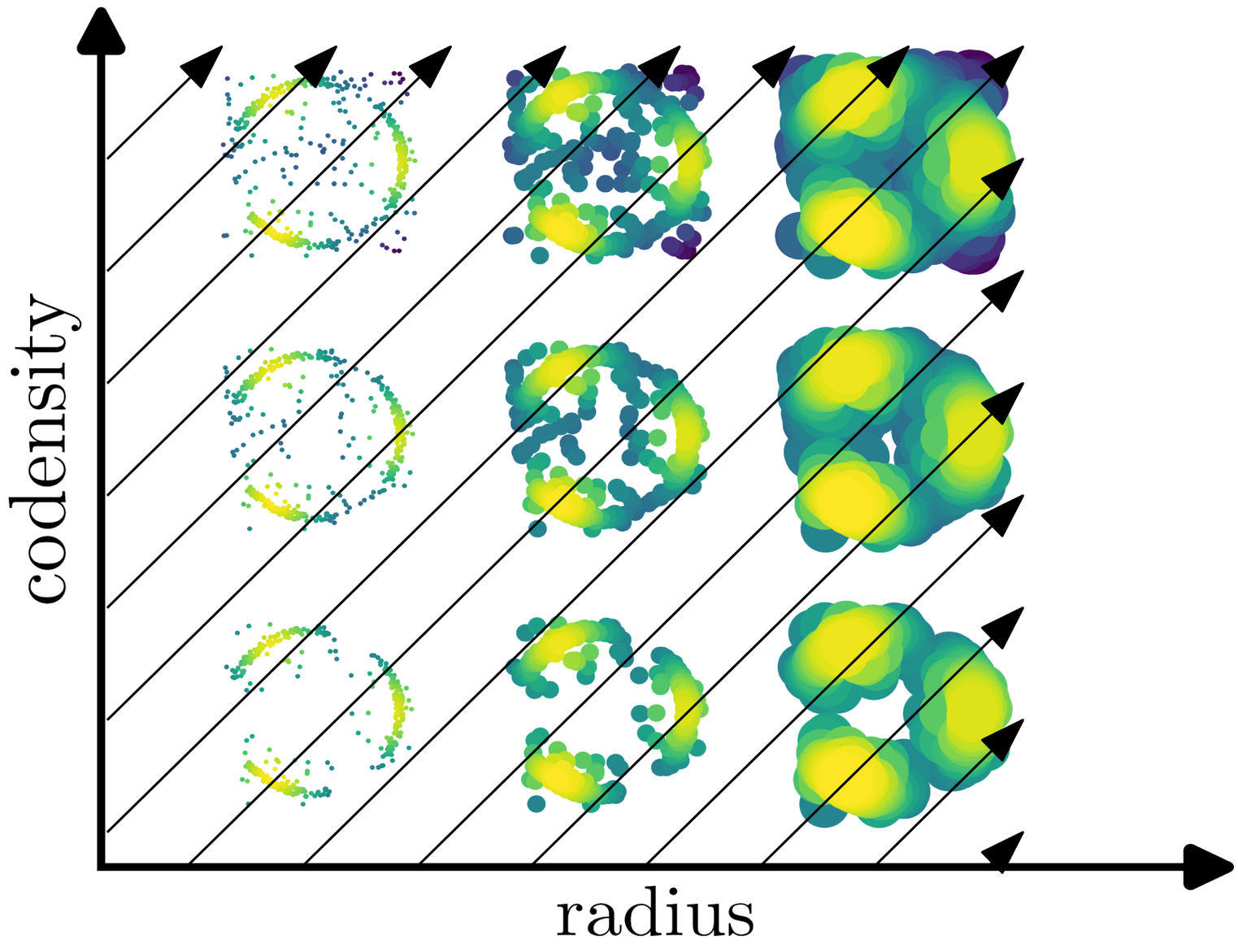

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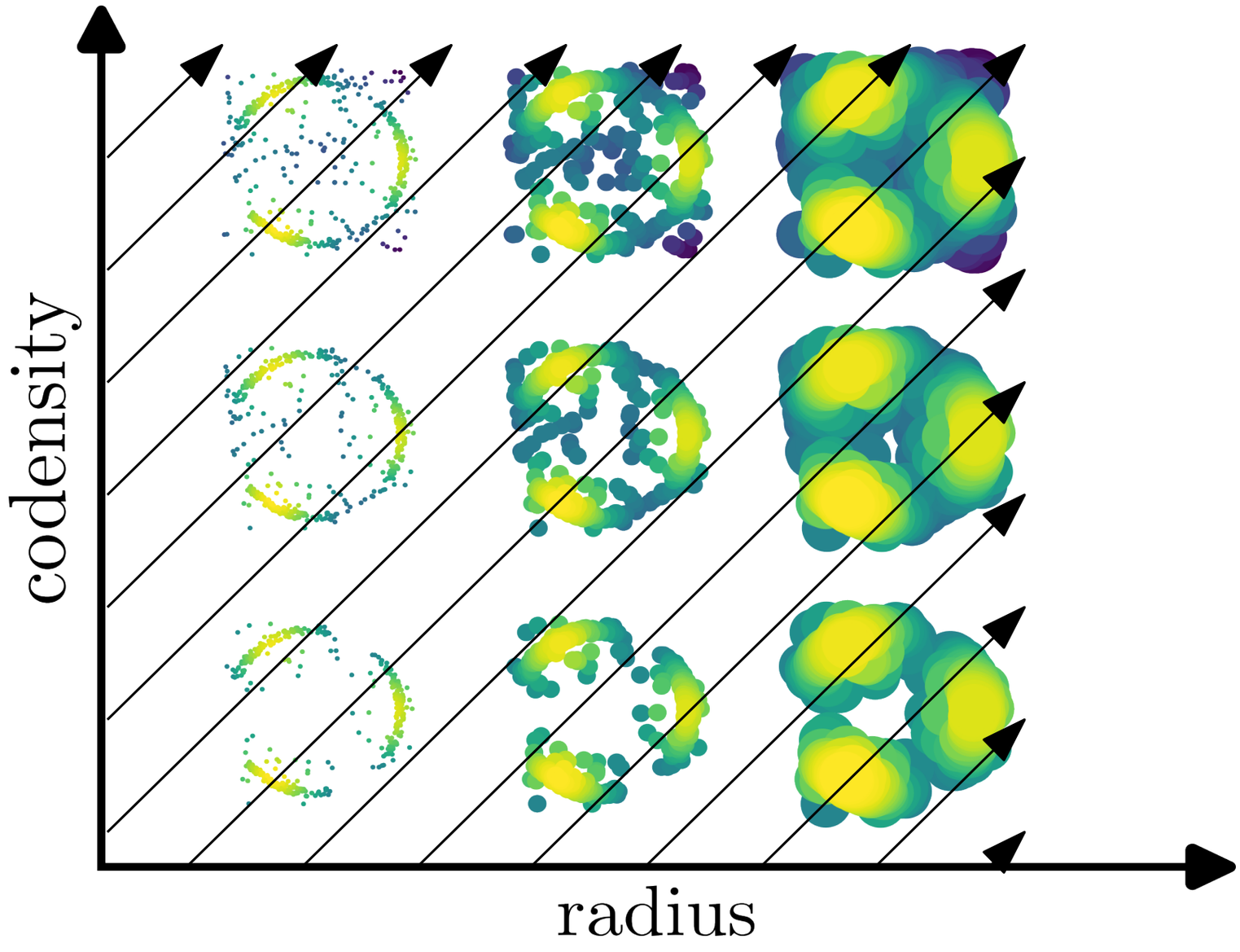

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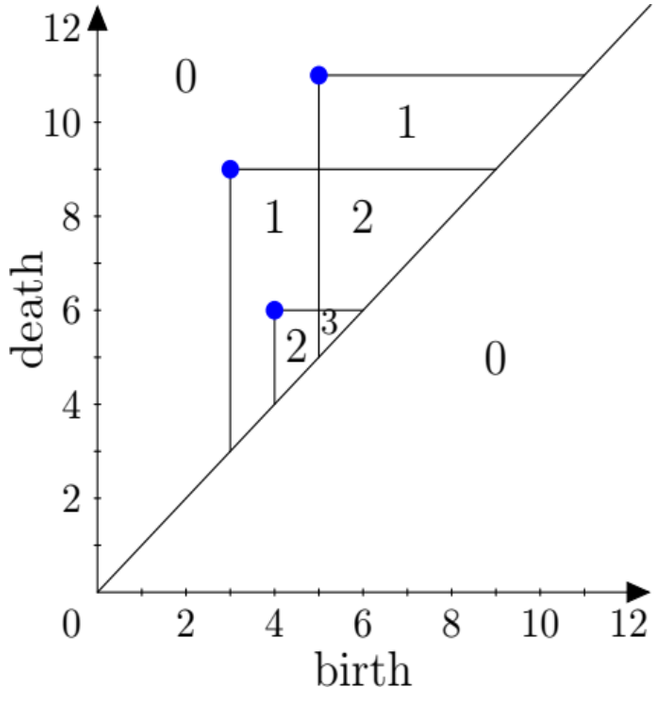

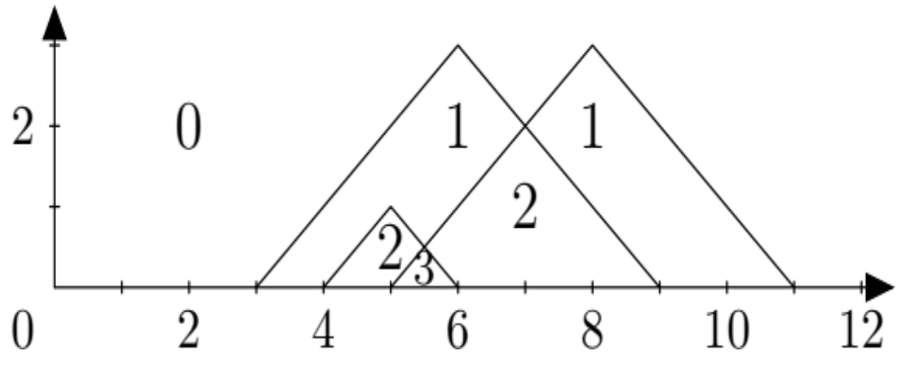

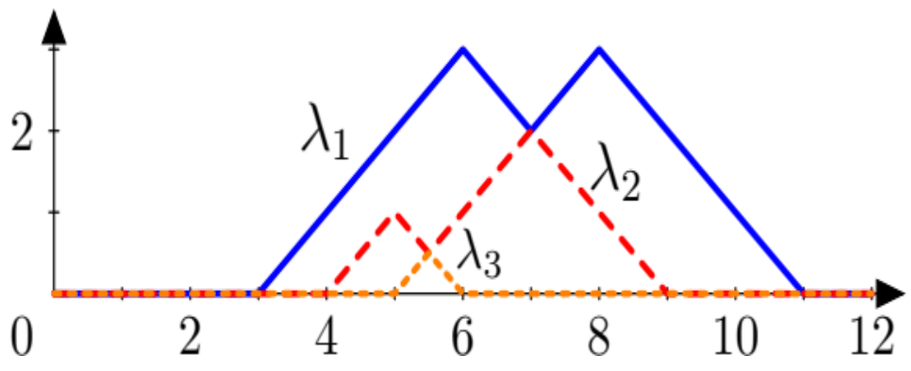

Rotate PD
Compute rank function

Use boundaries of rank function

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Ex: Multiparameter Persistence Landscapes.

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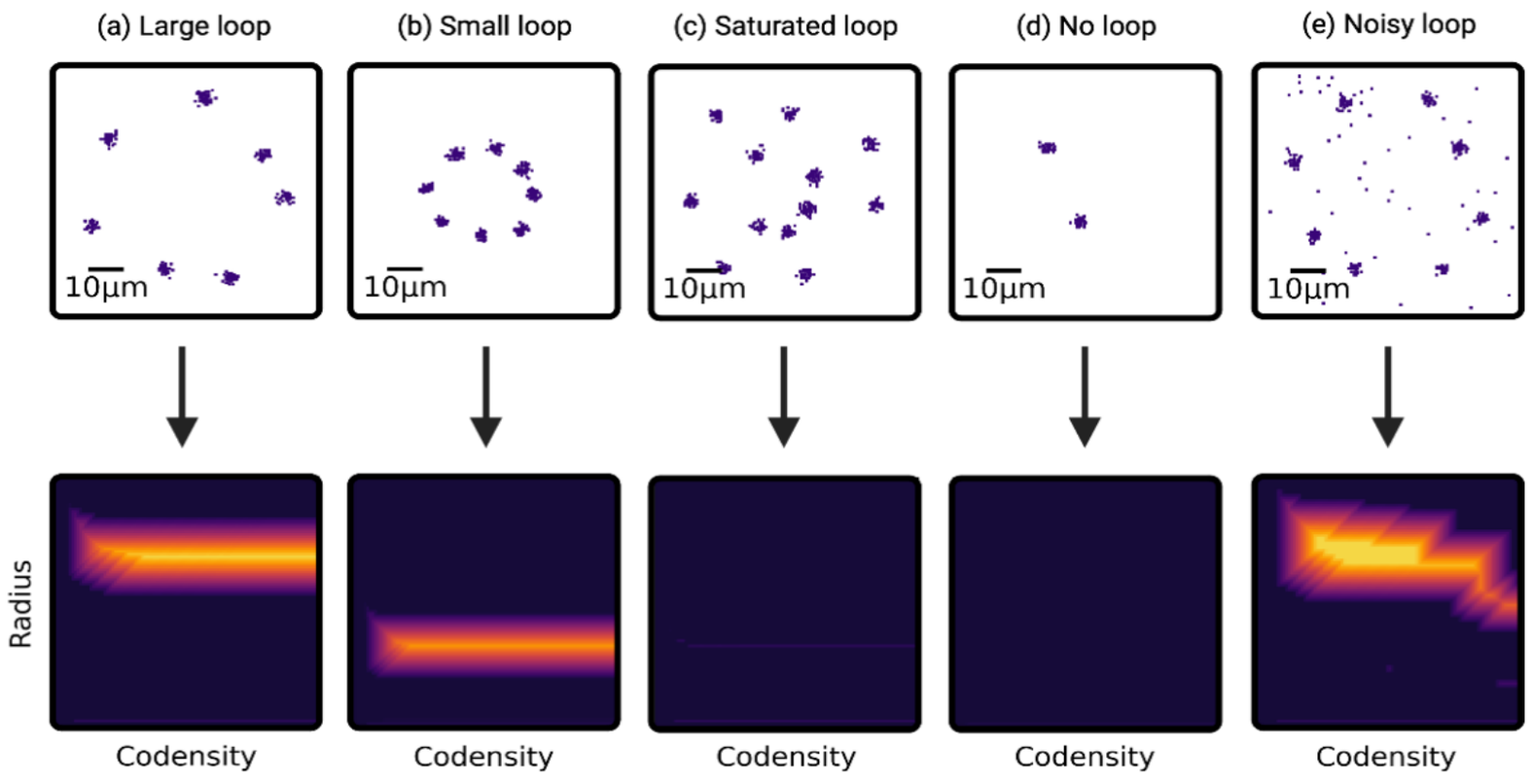

n-parameter Persistent Homology

[Loiseaux et al. - 2022 - *Fast, stable and efficient approximation of multi-parameter persistence modules with MMA*]

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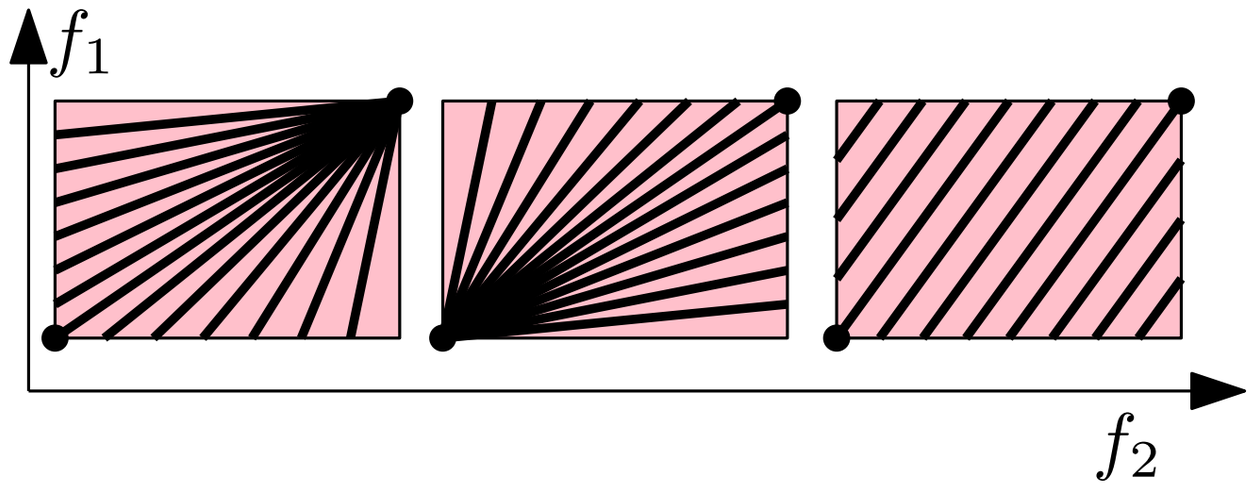

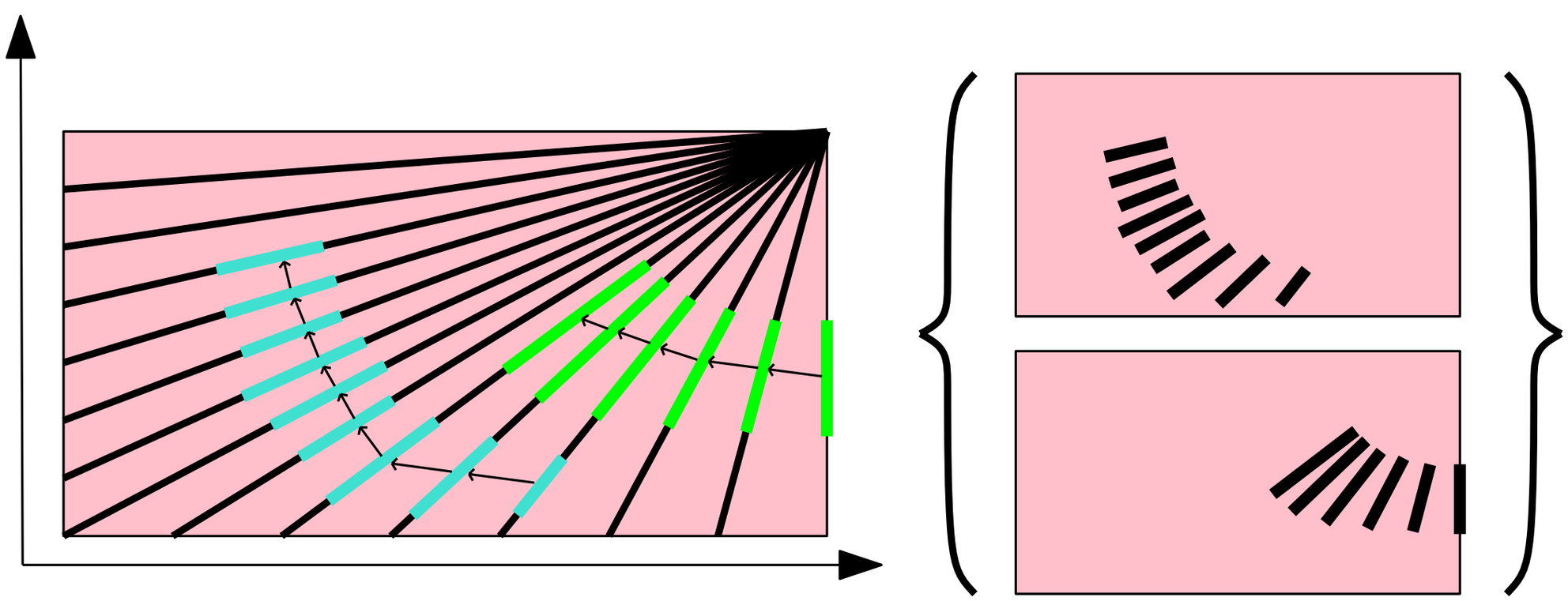

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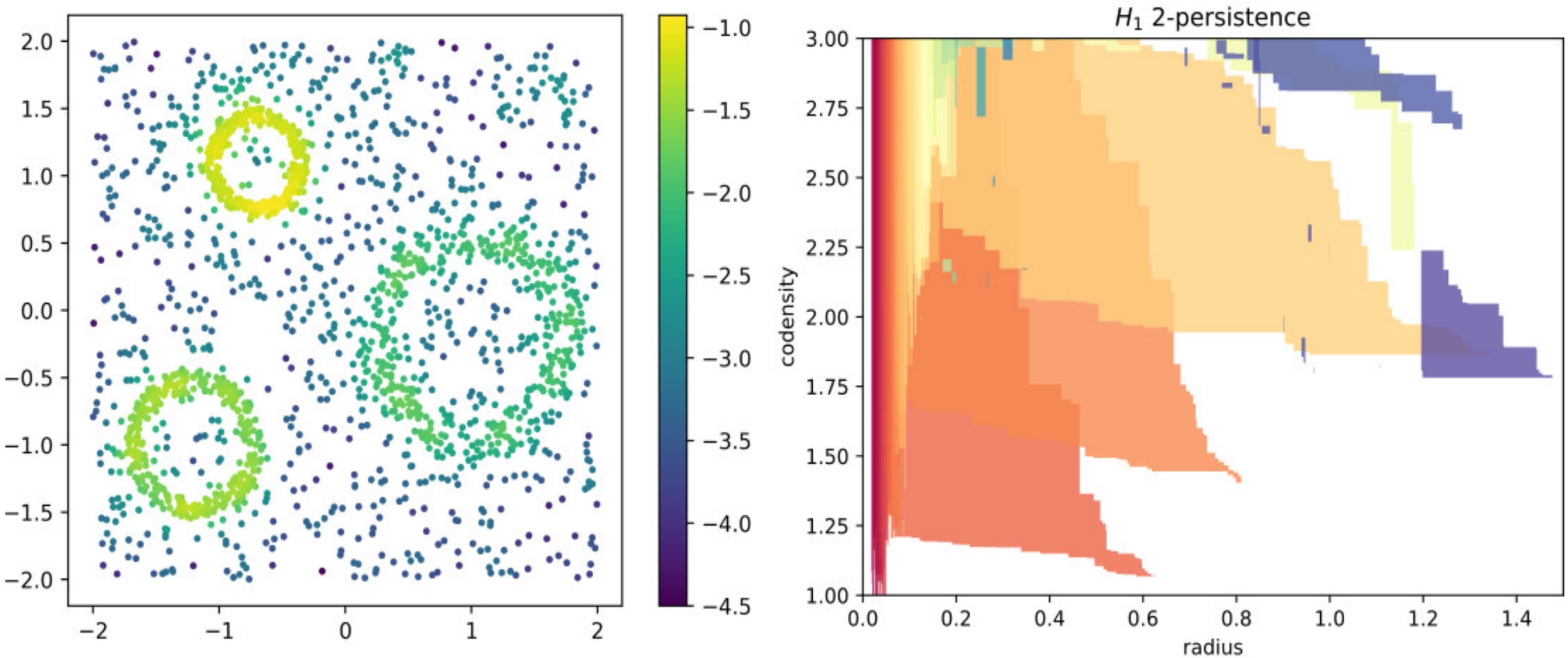
Approximate persistence module



Thm: Let M be an *interval decomposable* multiparameter persistence module, and $\tilde{M}$ be its approximation with a family of lines at distance δ. Then:

$$d_I(M, \tilde{M}) \leq \delta/2$$

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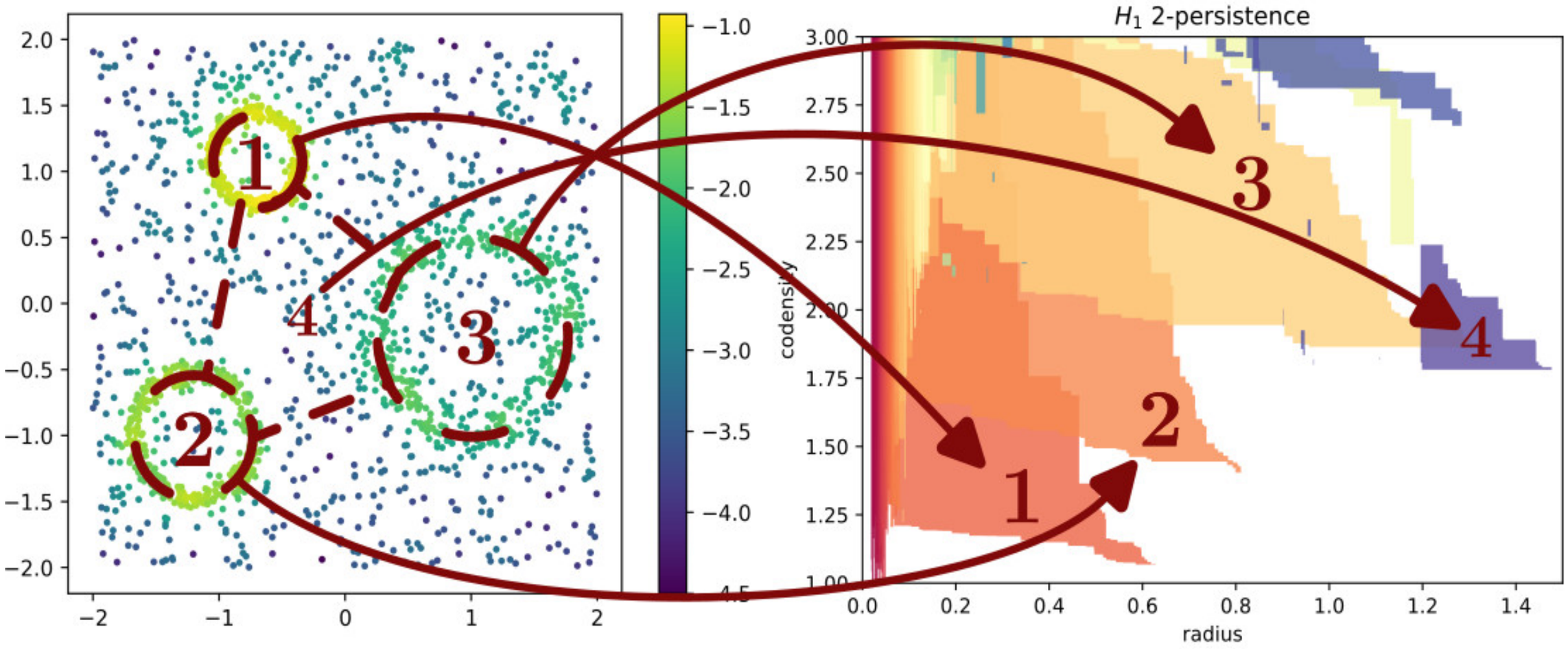

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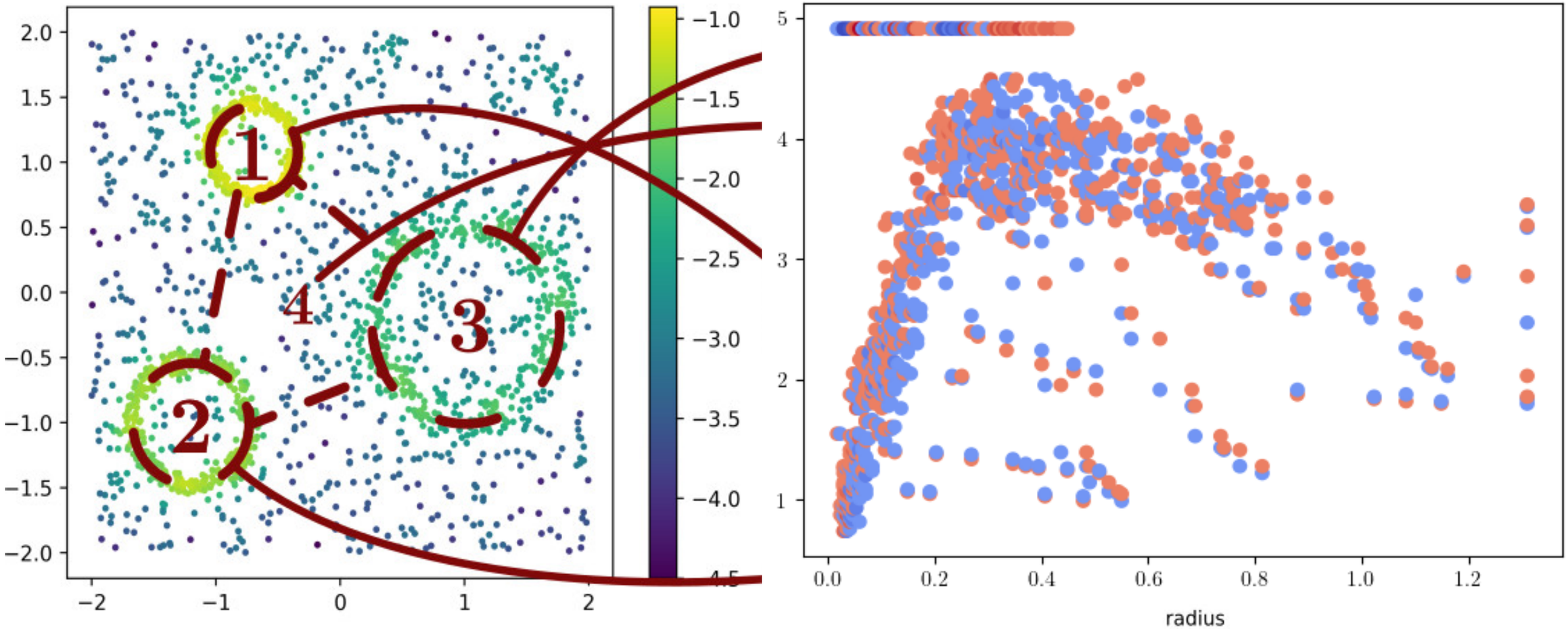
Representation with measure (of mass 0)



[Loiseaux et al. - 2023 - *Stable vectorization of multiparameter persistent homology using signed barcodes as measures*]

Thm: $\|\mu_f - \mu_g\|_1^K \leq \|f - g\|_1$

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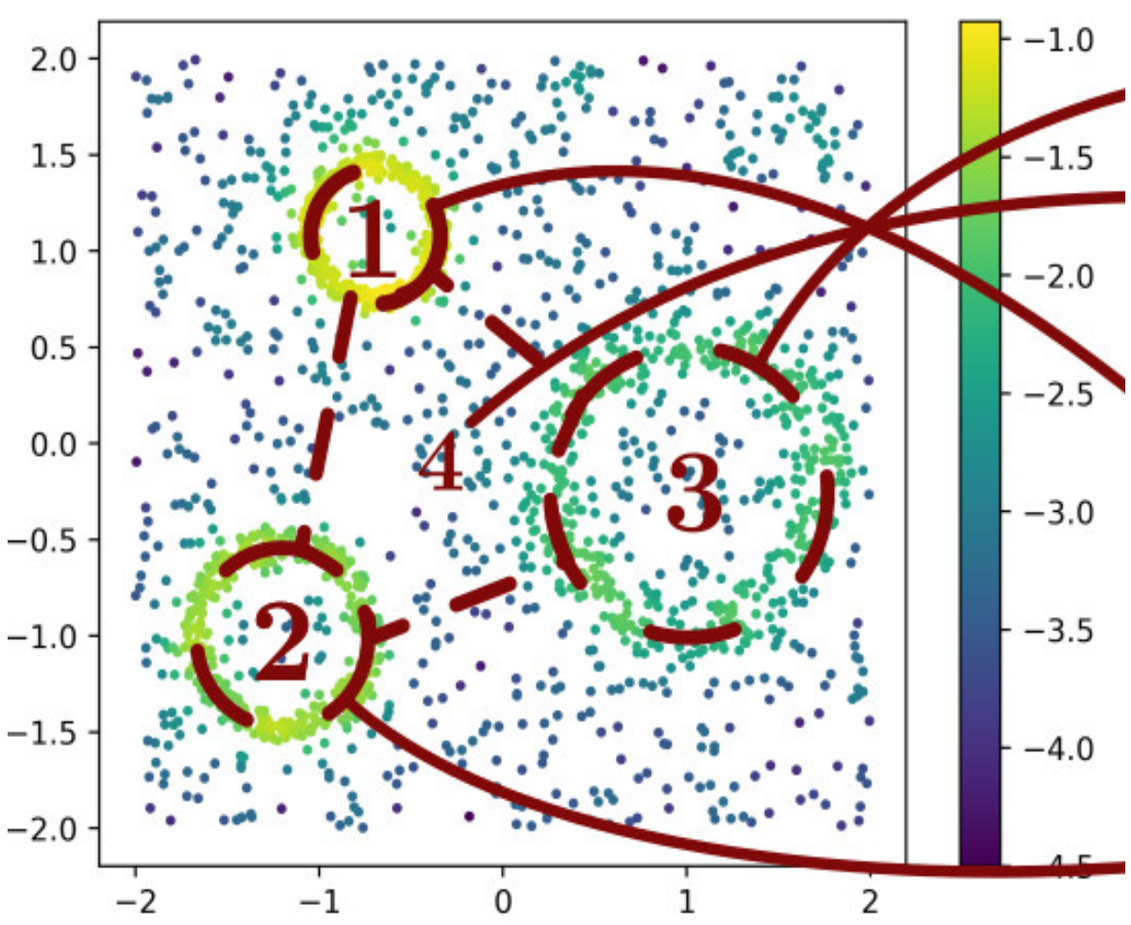

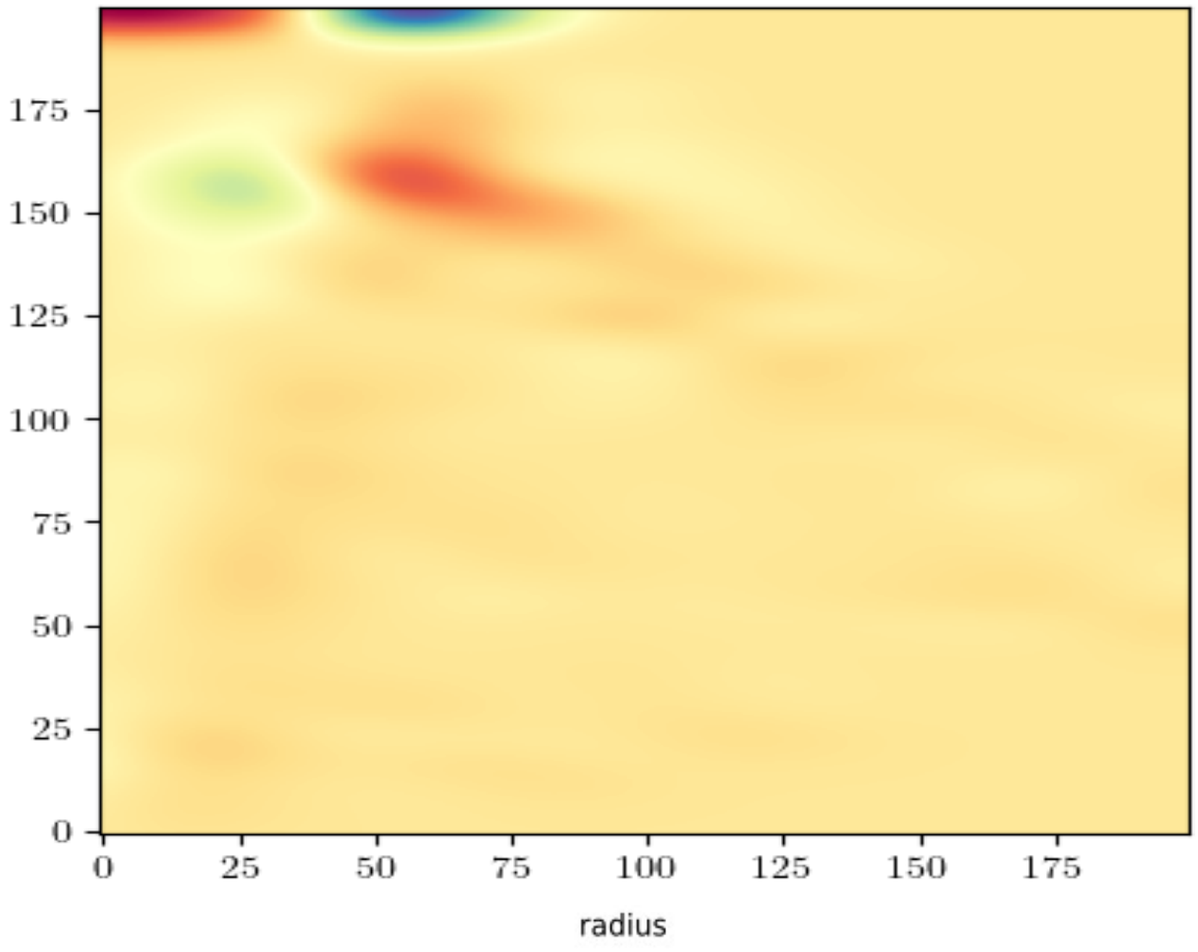

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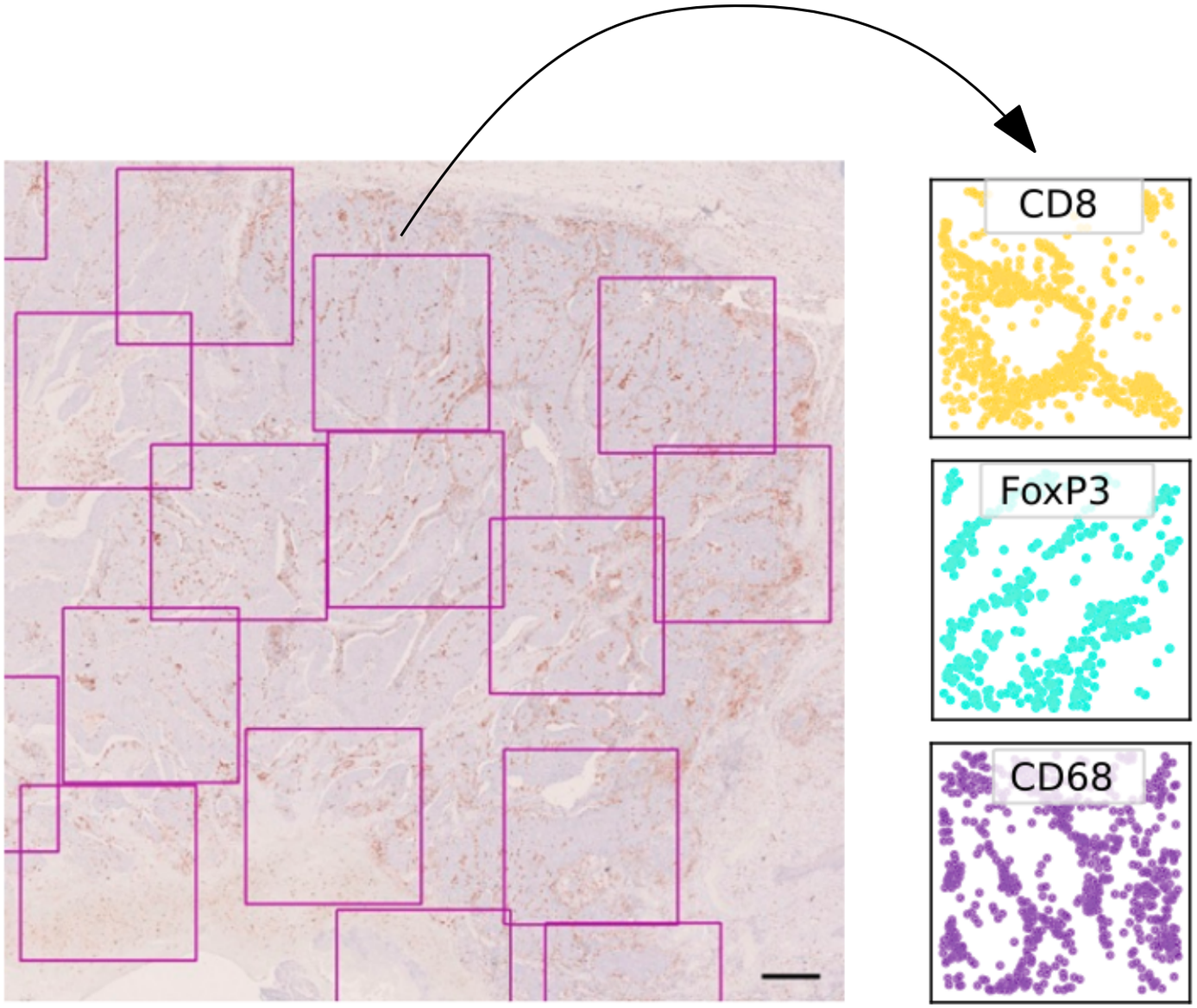
Application to cell arrangements

Method:

1. Extract local point clouds and cell types corresponding to several measurement spots.



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1. Extract local point clouds and cell types corresponding to several measurement spots.
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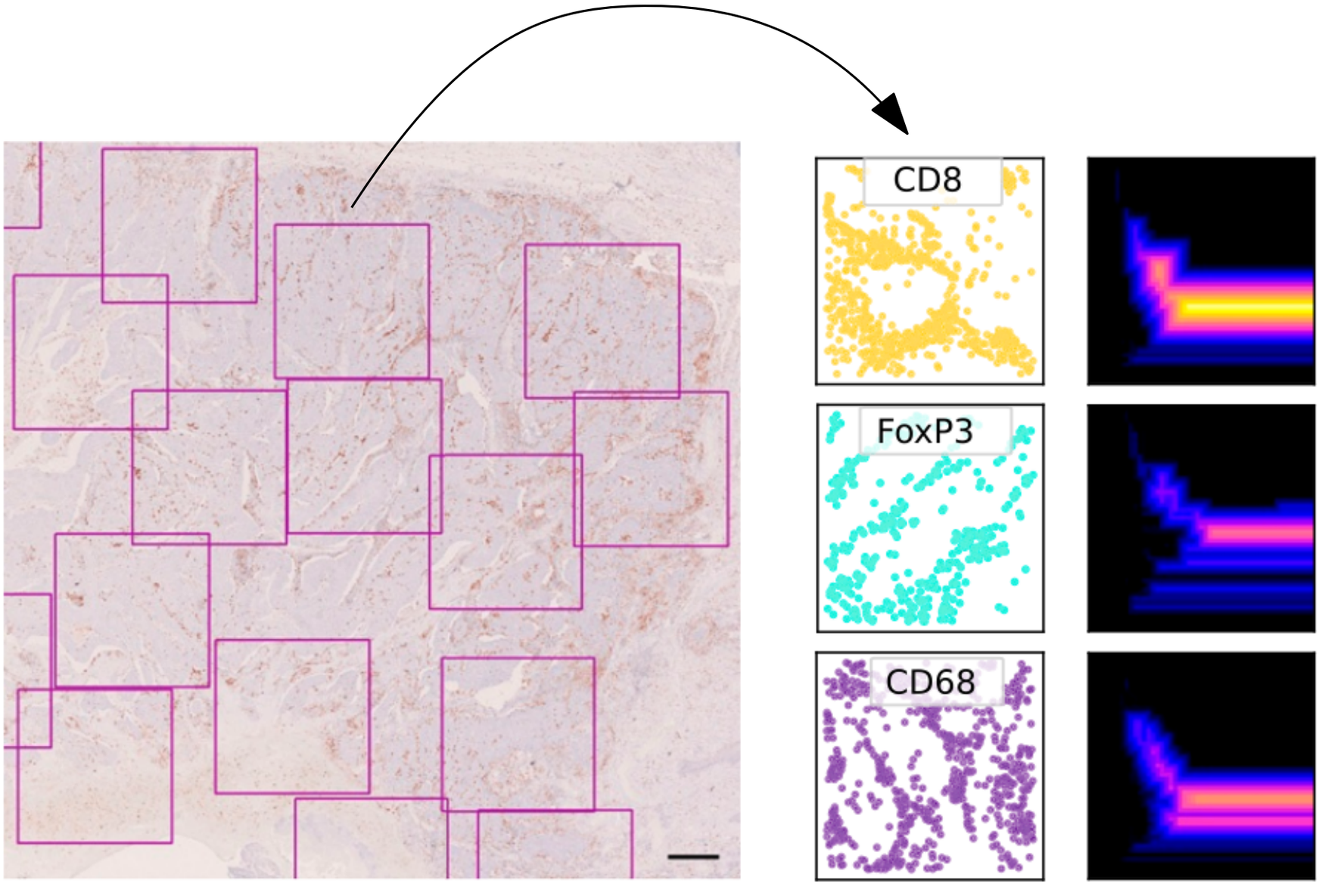

Application to cell arrangements

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1. Extract local point clouds and cell types corresponding to several measurement spots.
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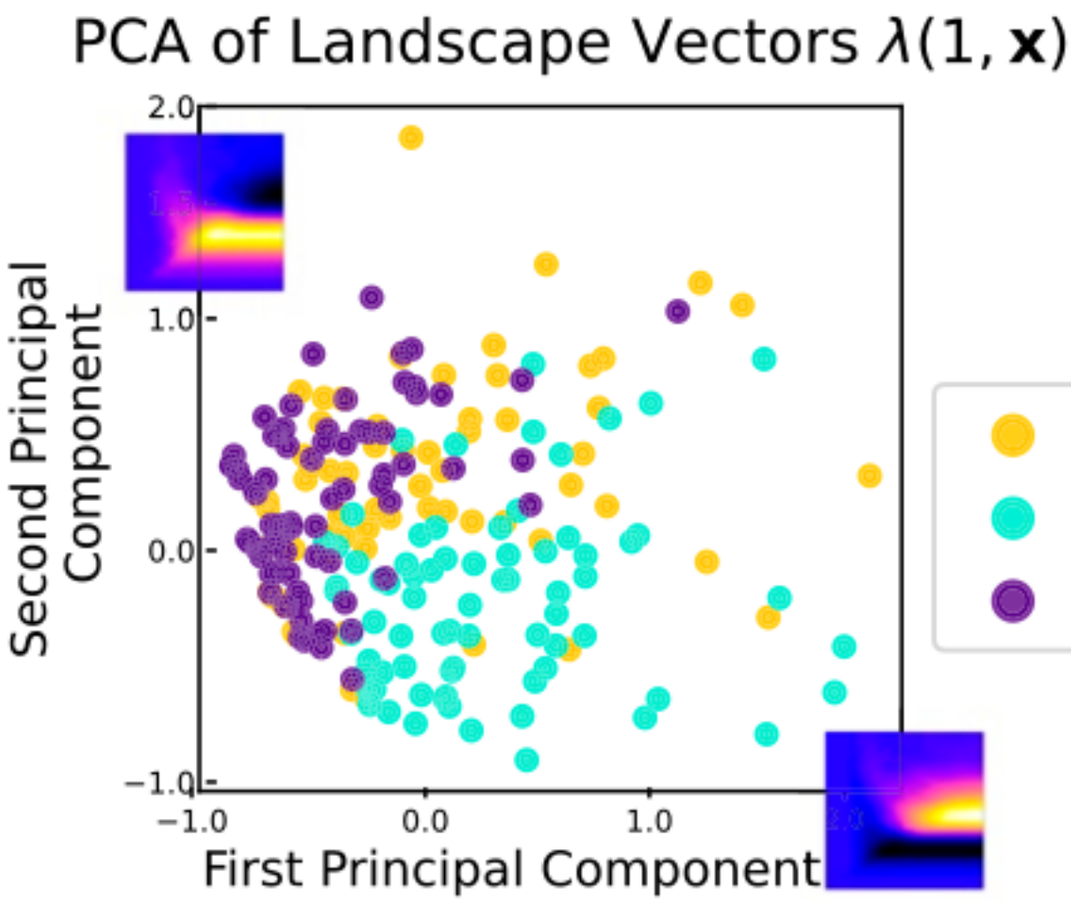
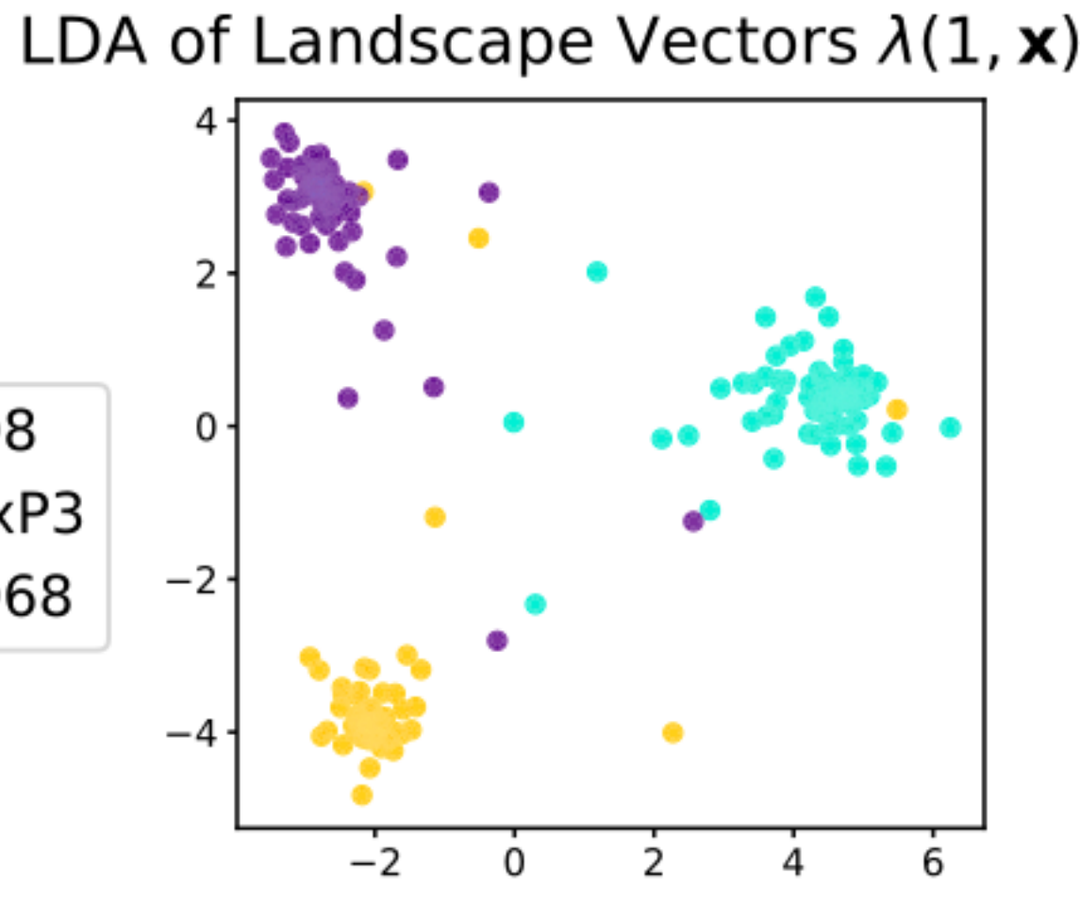
3. Visualize and predict cell types with MPLs.





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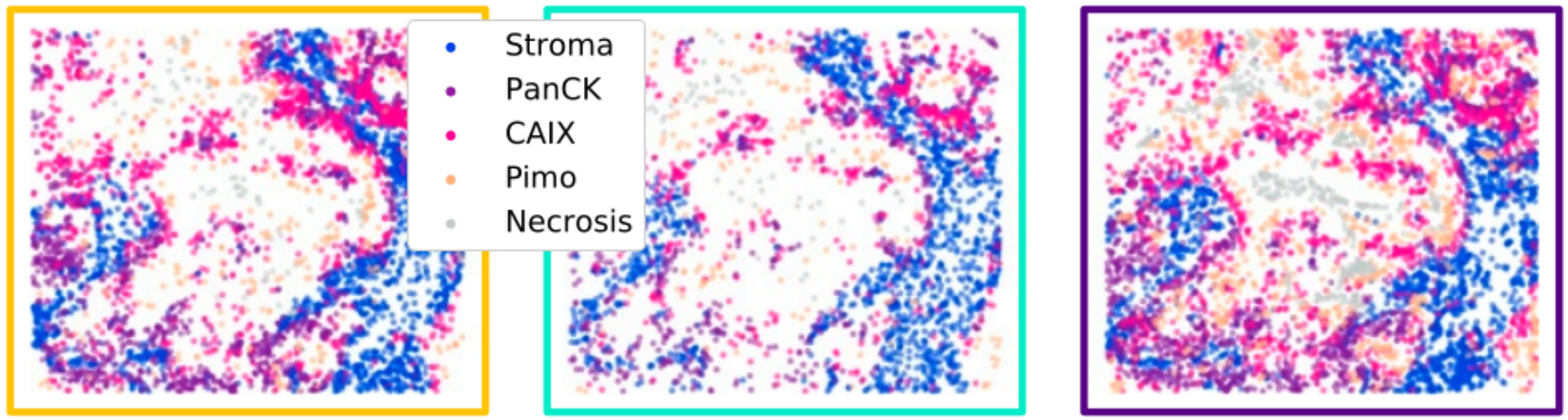
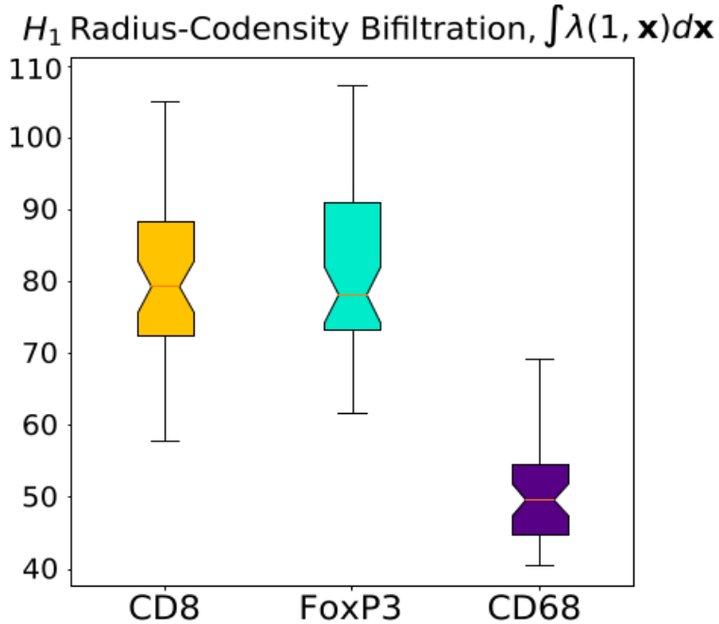
4. Perform biological inference from additional cell annotations.



The fact that the norm of CD68 MPL is smaller than the others means that CD68 cells have a bigger tendancy to infiltrate necrosis cells.



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MPLs were also used recently for studying immune responses in kidney glomeruli from mice with renal disease: a high MPL norm (in dimension 1) was shown to indicate high immune activity, exhibiting ring structures as spatial patterns.

[Benjamin et al. - 2022 - *Multiscale topology classifies and quantifies cell types in subcellular spatial transcriptomics*]

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Limitation: too many marker genes for running multi-persistence, which forces to pick (combinations of) maker genes *a priori*

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Limitation: 2-parameter PH is robust to outliers, but
(a) Outliers are less and less likely to happen due to progress in integration techniques, thus density could end up *removing accurate cells*.
(b) What about cells for which integration method is unsure (low confidence in the predicted cell types)? This could even happen systematically in some regions with high density.

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[Benjamin et al. - 2022 - *Multiscale topology classifies and quantifies cell types in subcellular spatial transcriptomics*]

Process (Spot in $\mathbb{R}^2$, Cell Type) pairs

To handle these, one could use the integration method confidence to process (Spot in $\mathbb{R}^2$, Cell Type **Probabilities**) pairs with TDA!

4. Future research directions

Summary of what we have seen:

TDA + Raw Spatial Transcriptomics

[Bae et al. - 2022 - *STopover captures spatial colocalization and interaction in the tumor microenvironment using topological analysis in spatial transcriptomics data*]

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Process (Spot in $\mathbb{R}^2$, Expression vector) pairs

[Alsaleh et al. - 2022 - *Spatial transcriptomic analysis reveals associations between genes and cellular topology in breast and prostate cancers*]

Process (Local point cloud $\subset \mathbb{R}^2$, Expression vector) pairs

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$\longrightarrow$ no need to cherry pick gene combinations

$\longrightarrow$ robust to outliers *and* integration methods

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Moreover, descriptors from n-parameter PH (approximate decompositions of persistence modules, signed barcodes, multivariate Mappers) could be used.

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Other recent (August 2023) directions on synthetic data:

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→ Characterize interactions between cell types with PH of *Dowker and Witness complexes*

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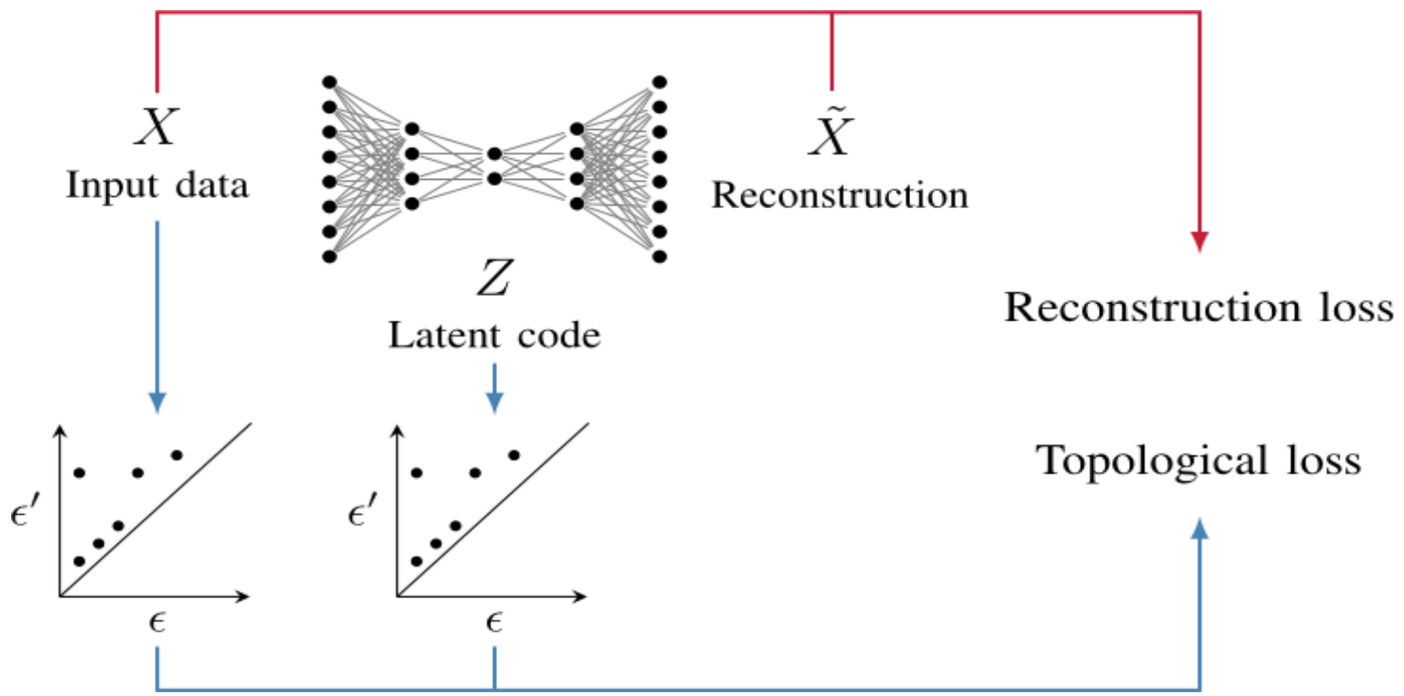
→ Characterize *time-dependent* spatial transcriptomics with *Zigzag and Vineyard* Rips PH

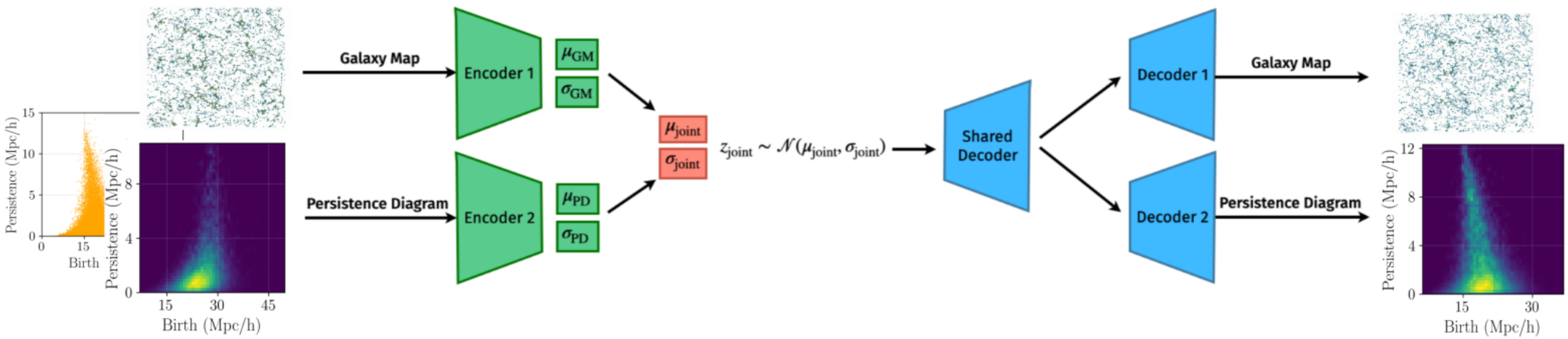
Other Topics: Differentiating PDs

Define gradient of persistence with

$$\forall p = (f(x_+), f(x_-)),\ \nabla p = [\nabla f(x_+), \nabla f(x_-)]$$

`https://github.com/GUDHI/TDA-tutorial/blob/master/Tuto-GUDHI-optimization.ipynb`

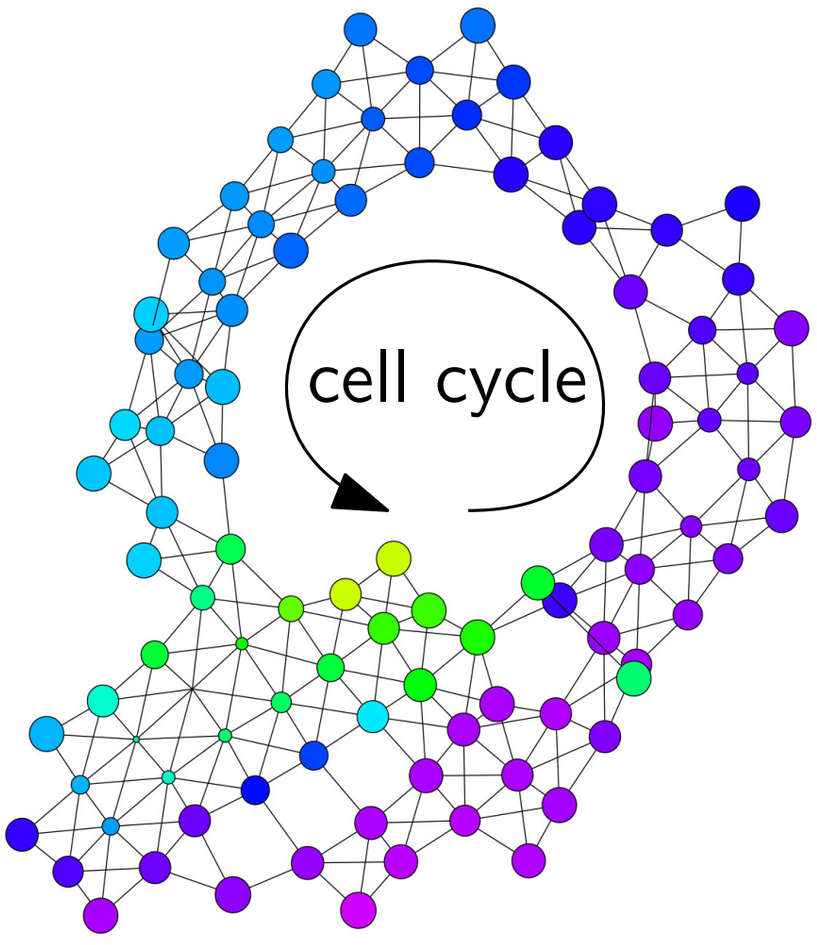




Other Topics: Exploratory Data Analysis with Mapper

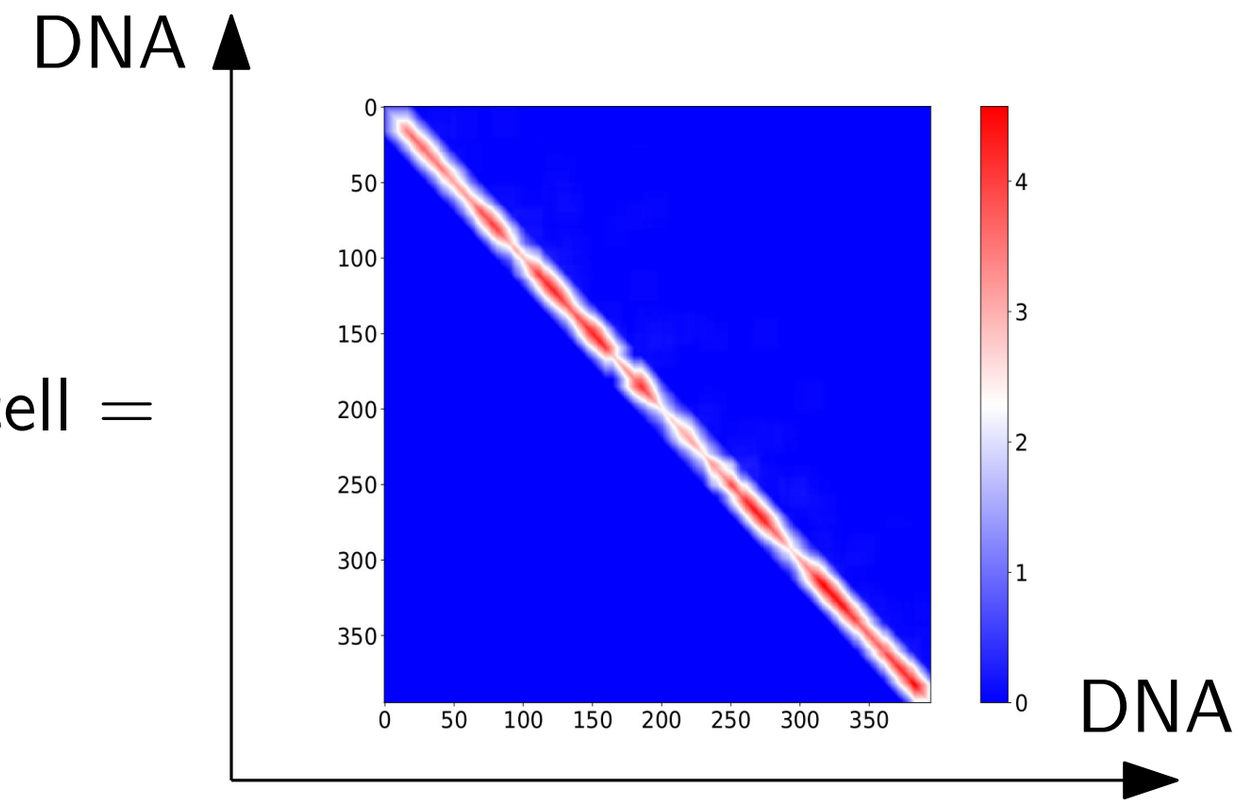
Mapper (and other cover complexes) allow to
represent and visualize datasets

`https://github.com/GUDHI/TDA-tutorial/blob/master/Tuto-GUDHI-cover-complex.ipynb`



Hi-C datasets =
Count matrices of *physically close* DNA fragments

cell =



Thank you!