

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

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

3. Multi-persistence for immune cell arrangements

[Vipond et al. - 2021 - *Multiparameter persistent homology landscapes identify immune cell spatial patterns in tumors*]

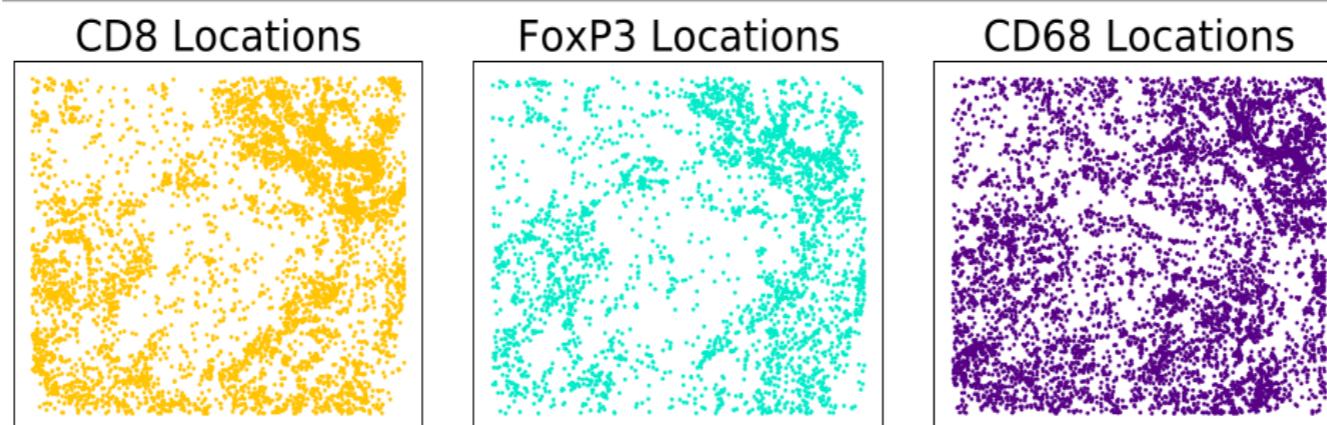
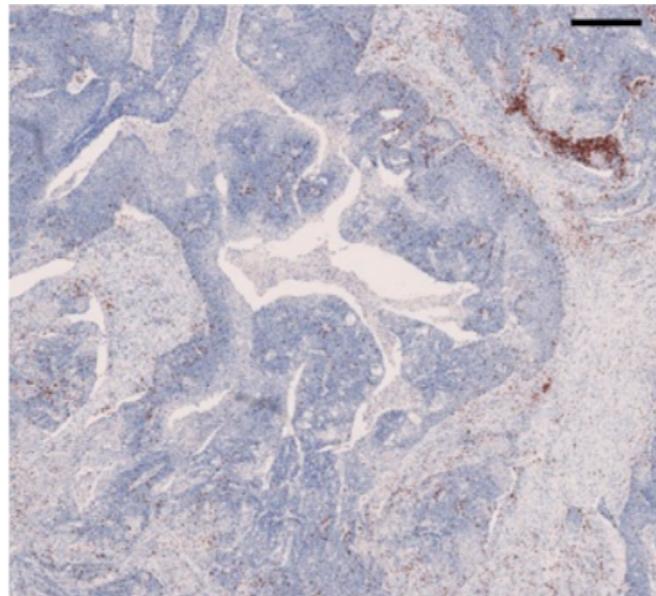
4. Future research directions

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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*?

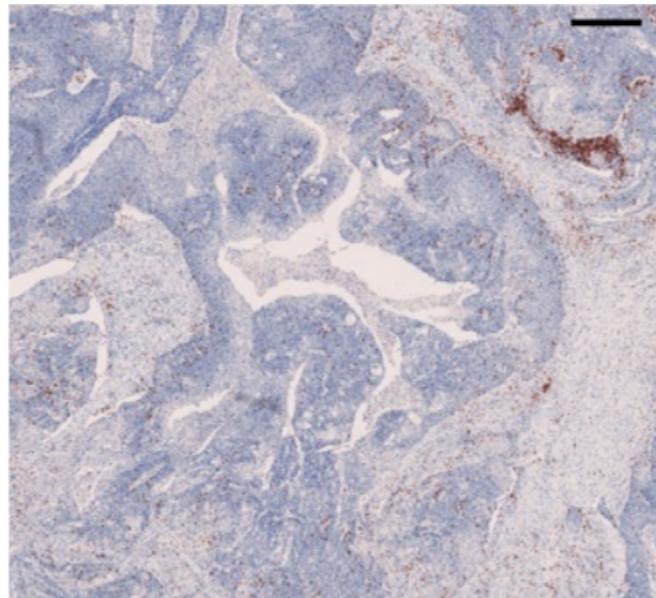
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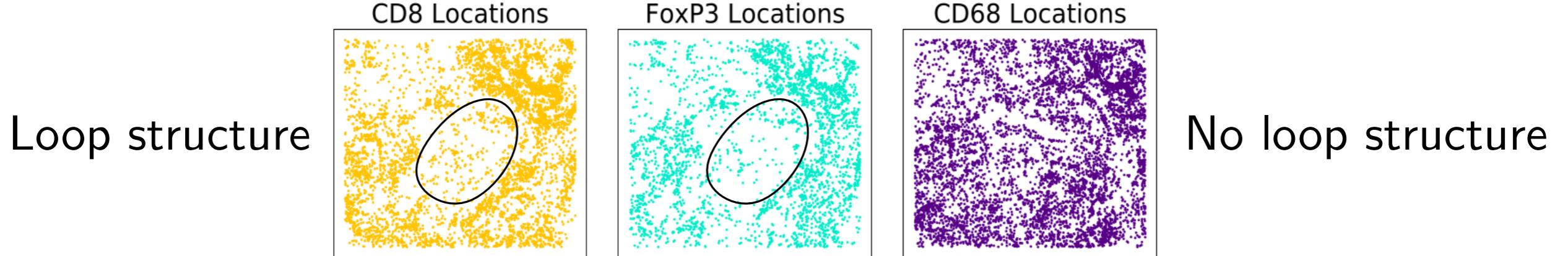
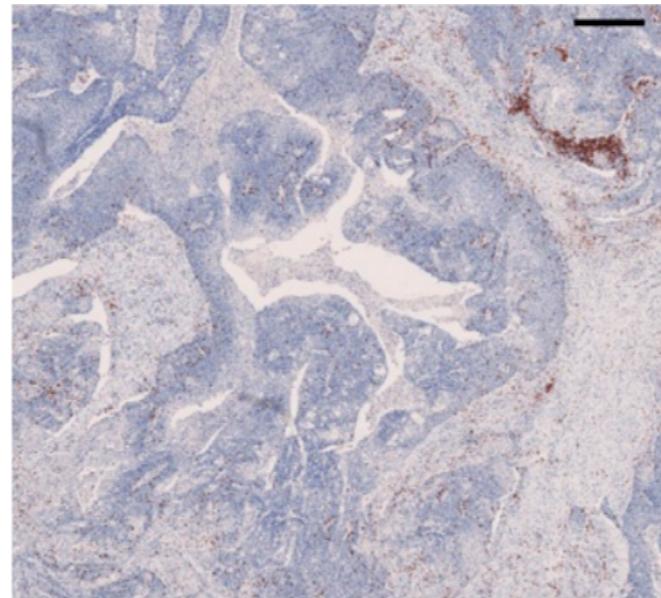
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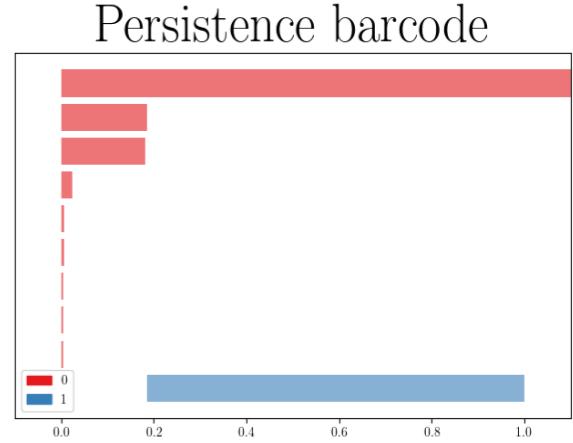
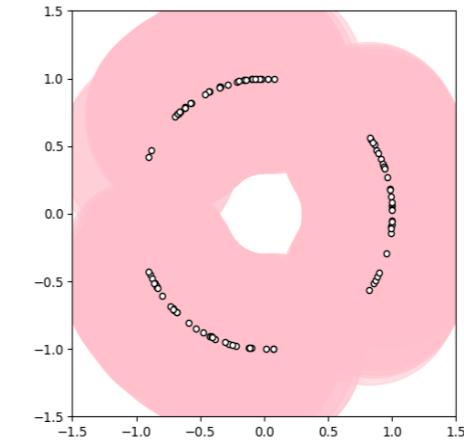
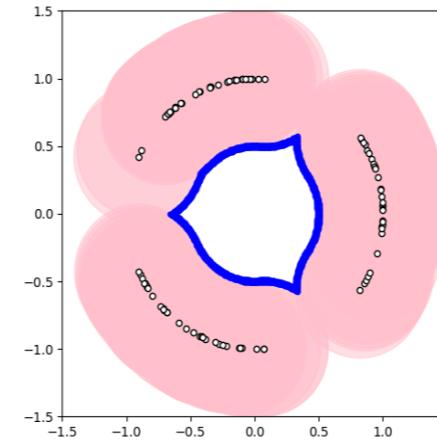
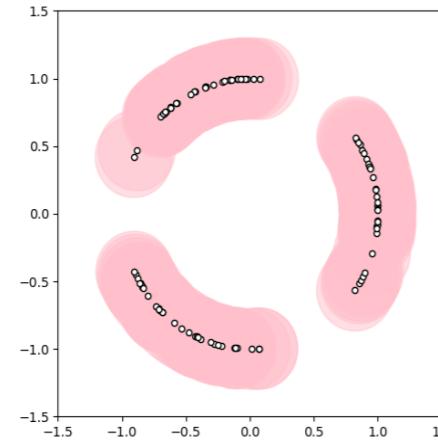
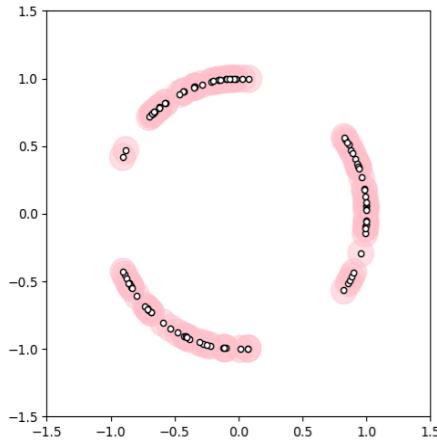
A: Combine Rips filtration with density estimation to create an outlier-robust analogue of persistence diagrams with 2-parameter PH.

Instability of Rips persistence

Rips persistence diagrams are known to be sensitive to outliers.

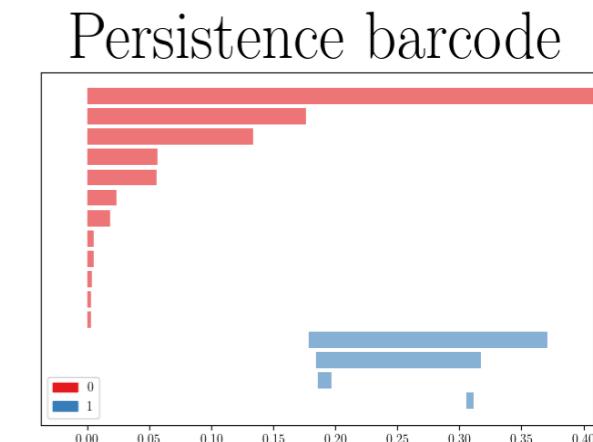
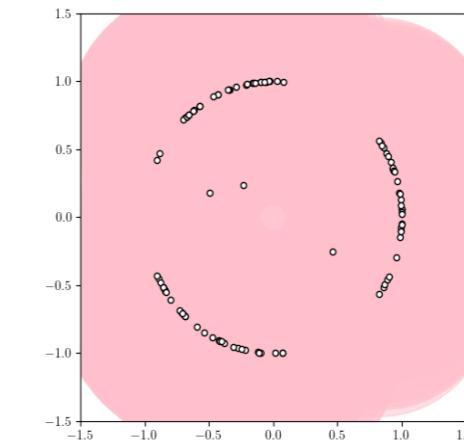
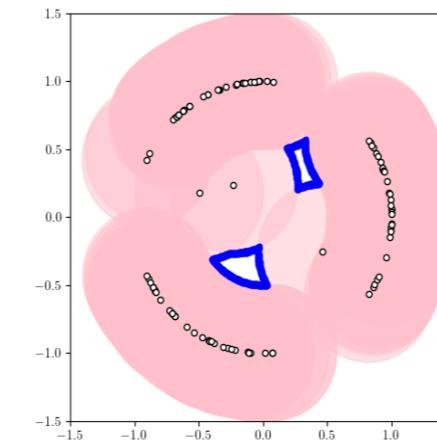
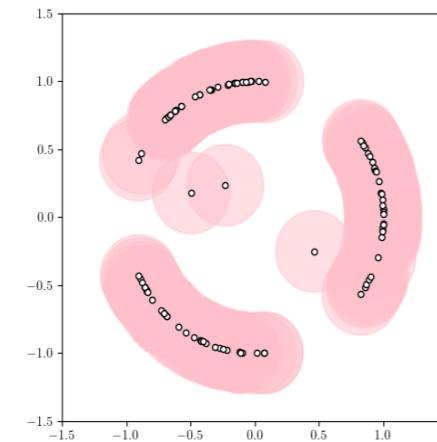
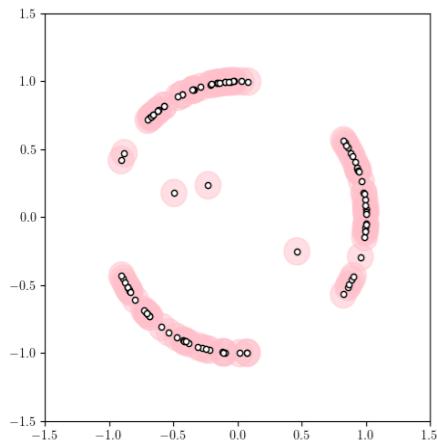
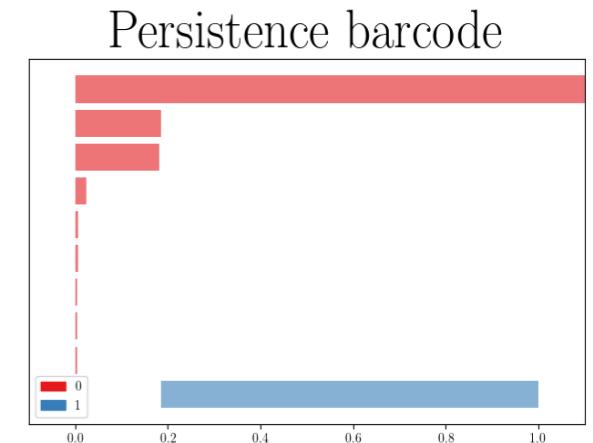
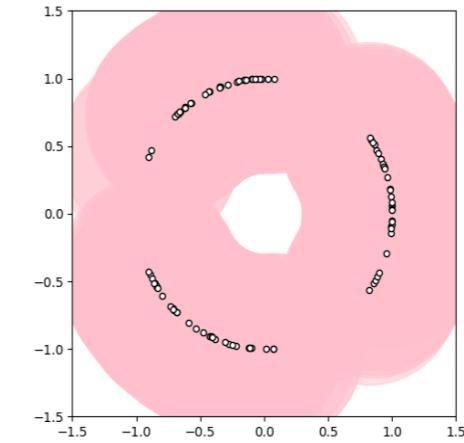
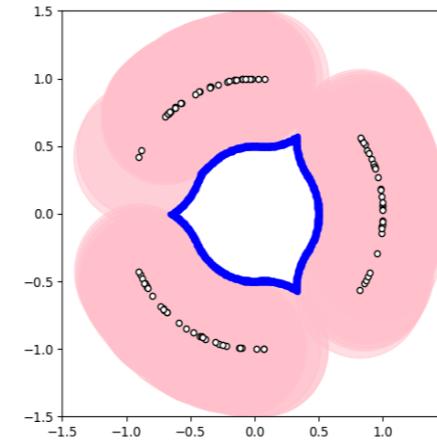
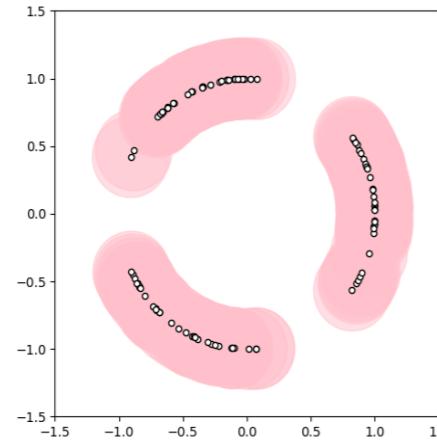
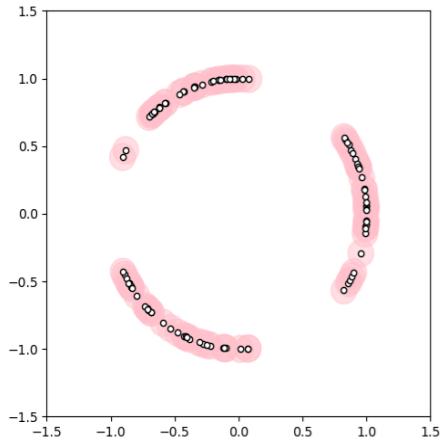
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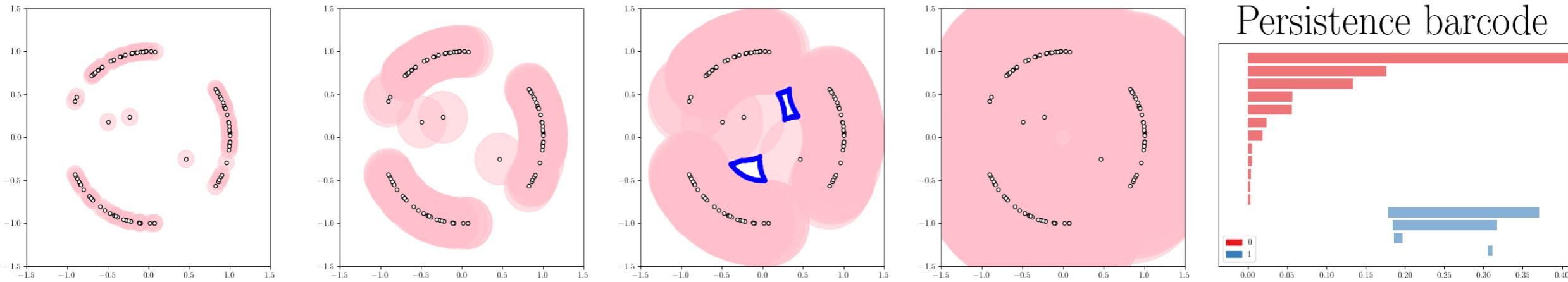
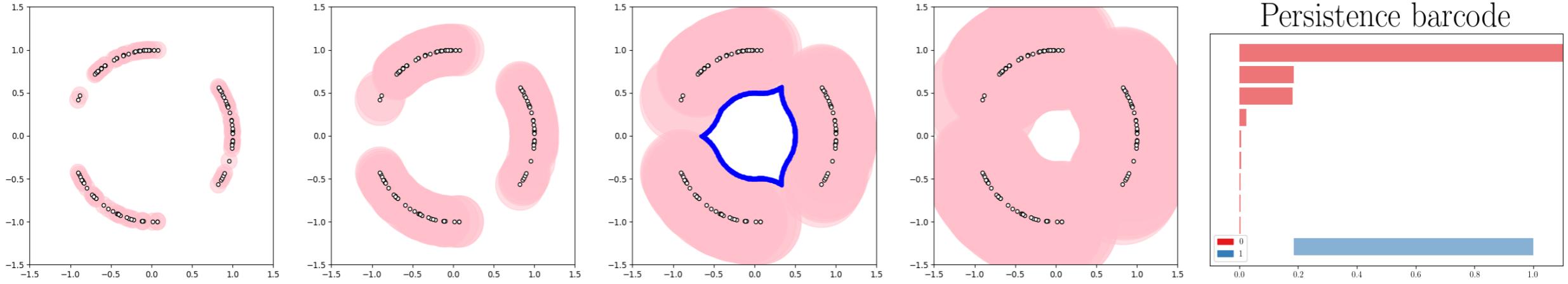
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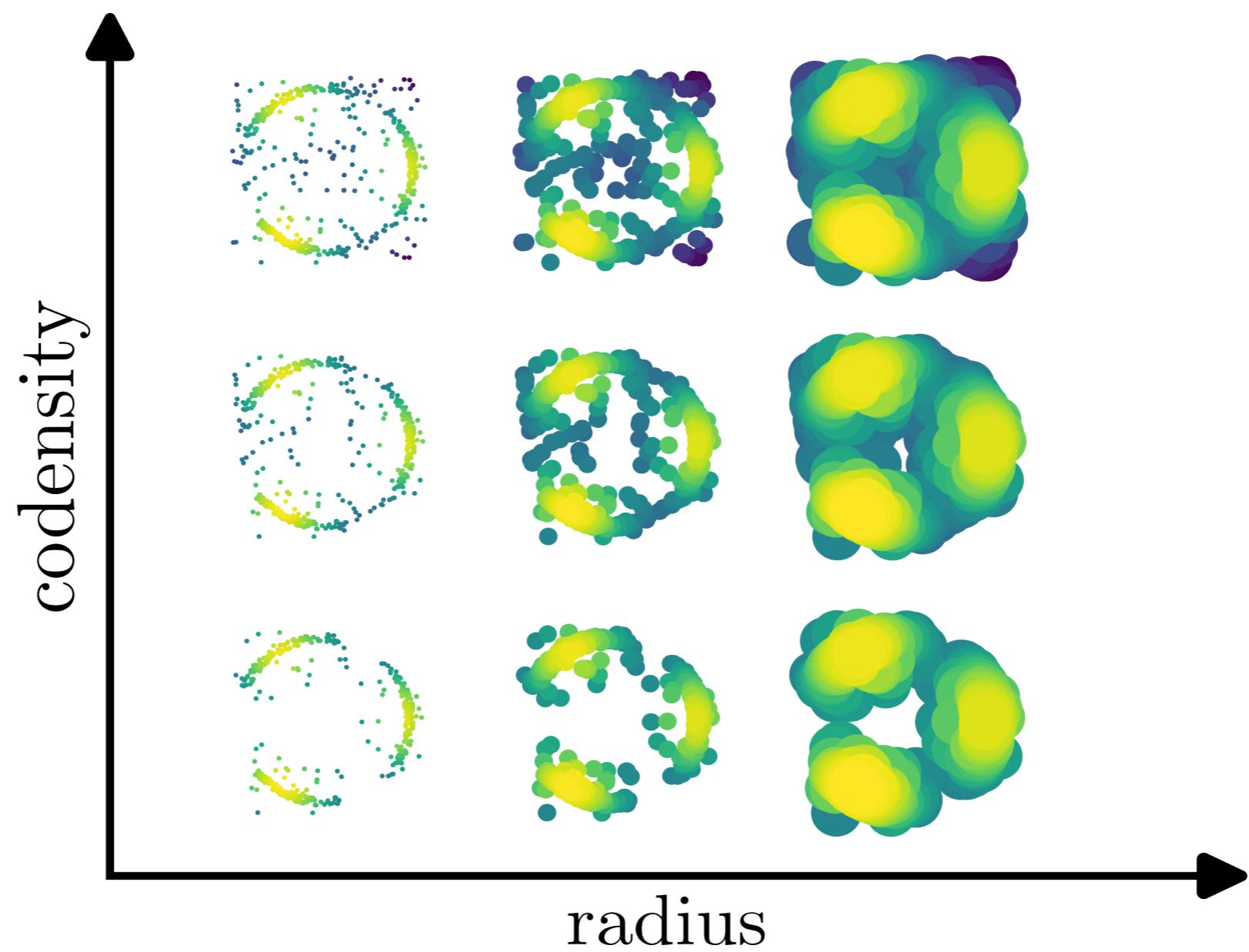
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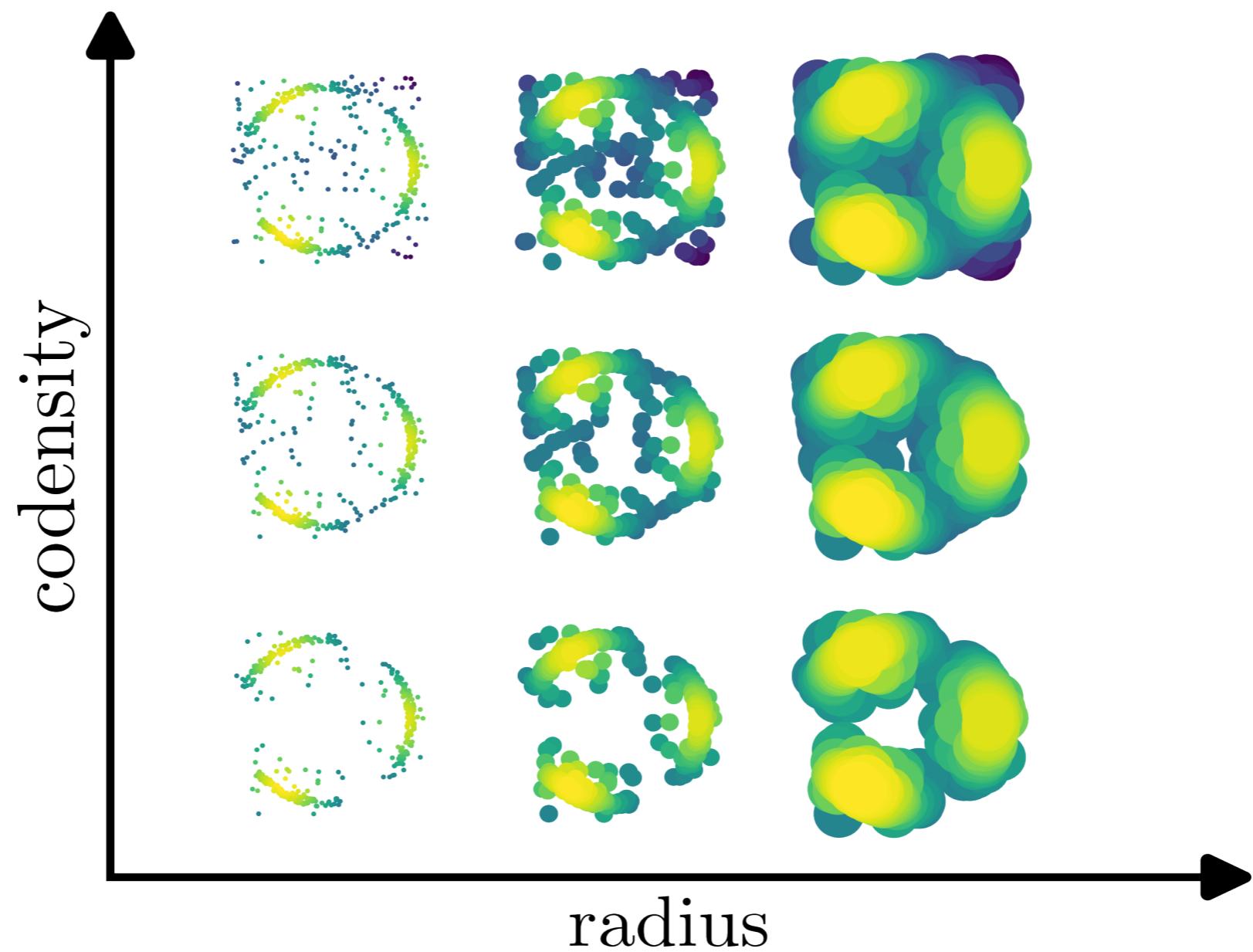
Hence, it seems natural to use density functions to prevent outliers from destroying topological structures.

2-parameter Persistent Homology



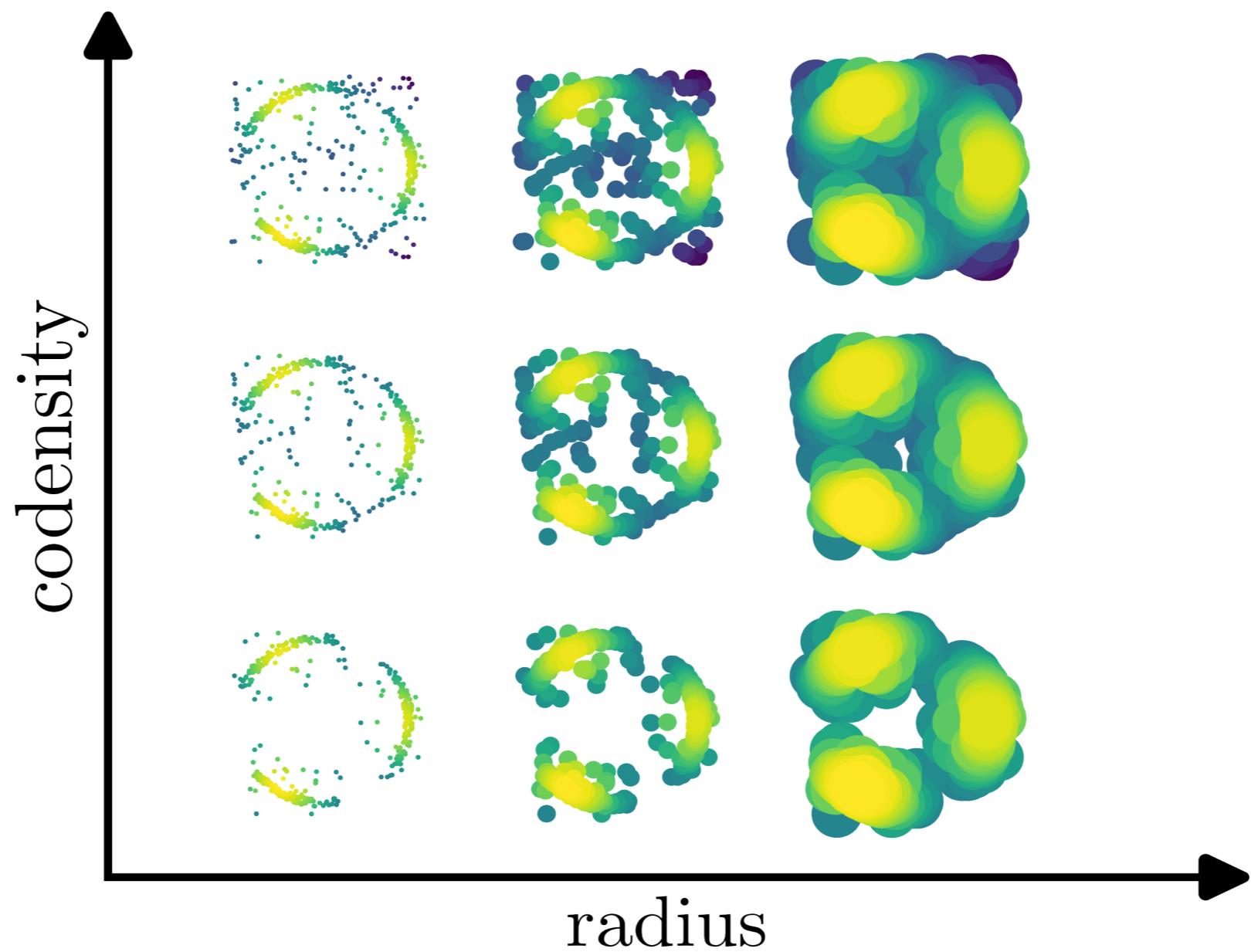
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Pb: persistence diagrams are not well-defined for more than 1 parameter.
(no decomposition theorem)



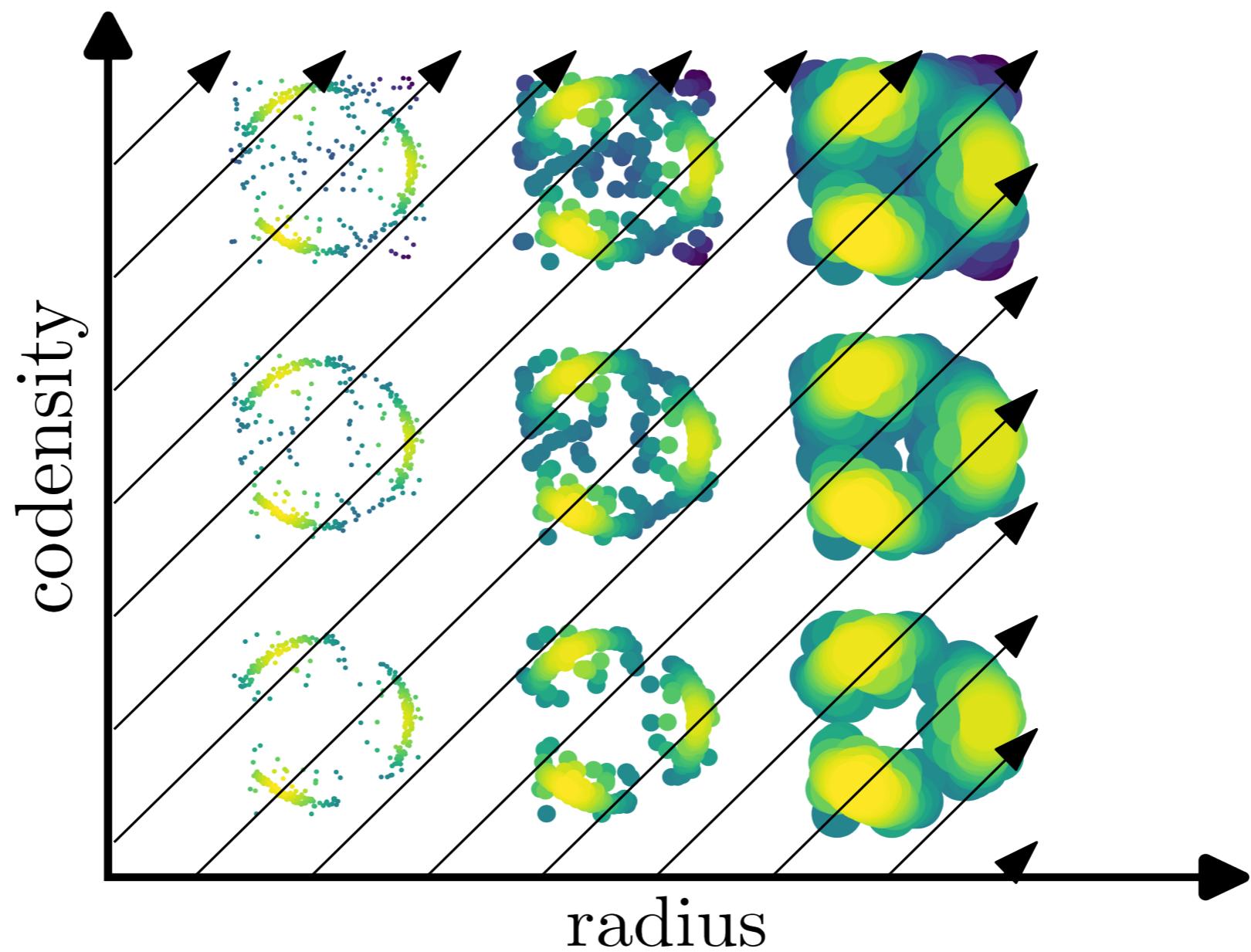
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A: Get back to the 1-parameter case by **slicing**.



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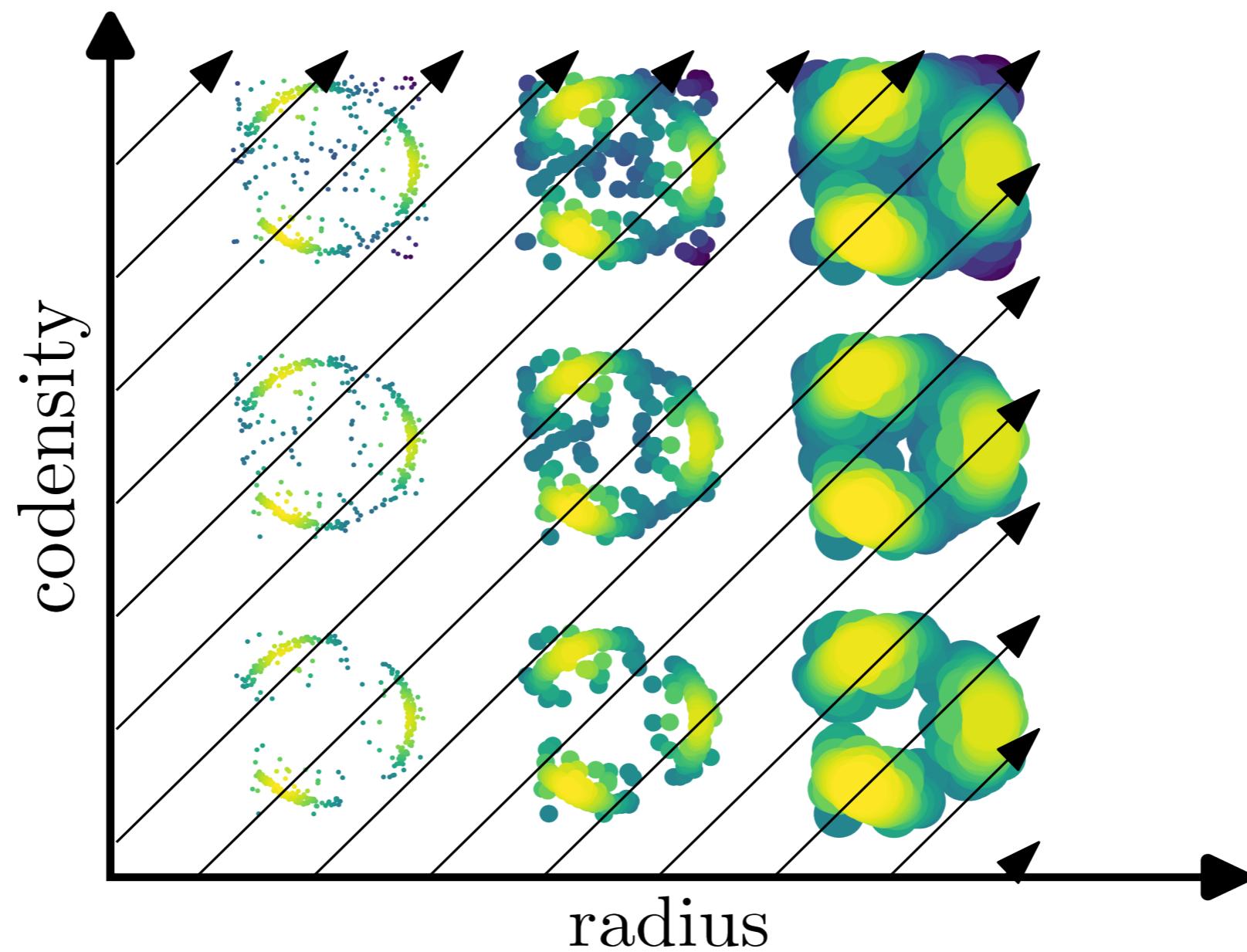
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Each line is a 1-parameter filtration obtained by linear combination, and has an associated persistence diagram. Hence one can represent 2-parameter PH by stacking the representations of the PDs from all lines.



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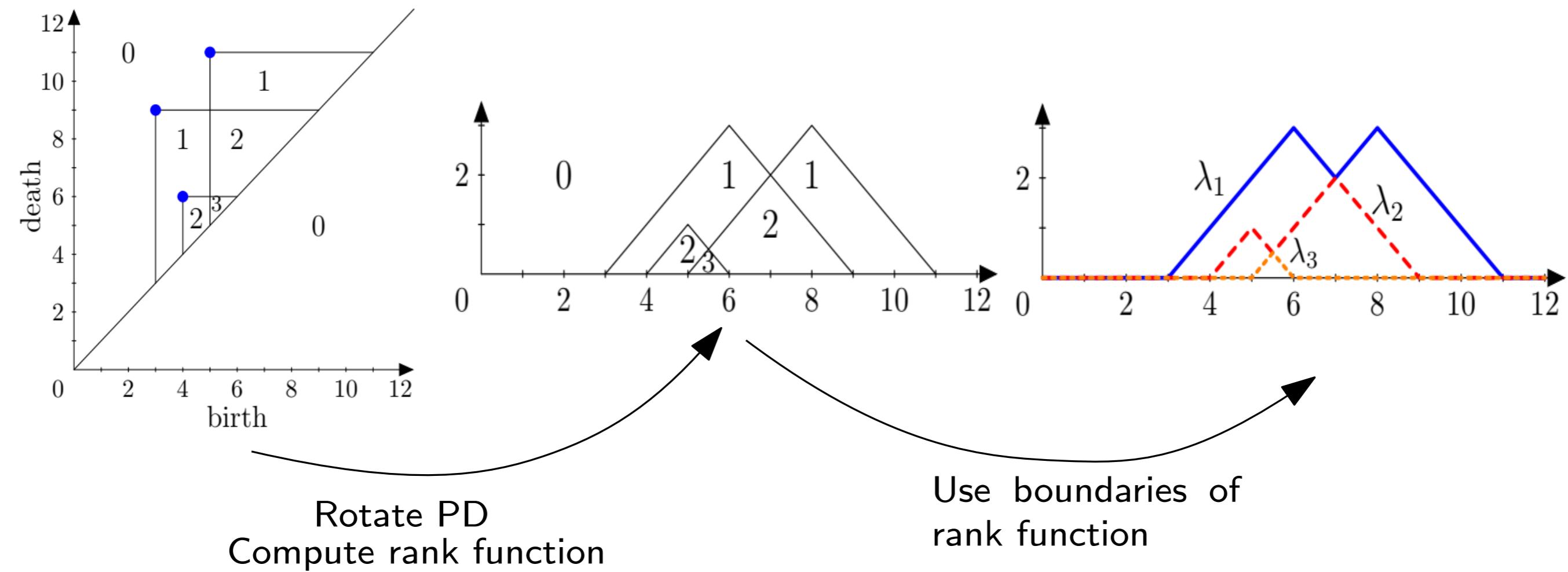
Ex: Persistence Landscapes.

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Ex: Multiparameter Persistence Landscapes.

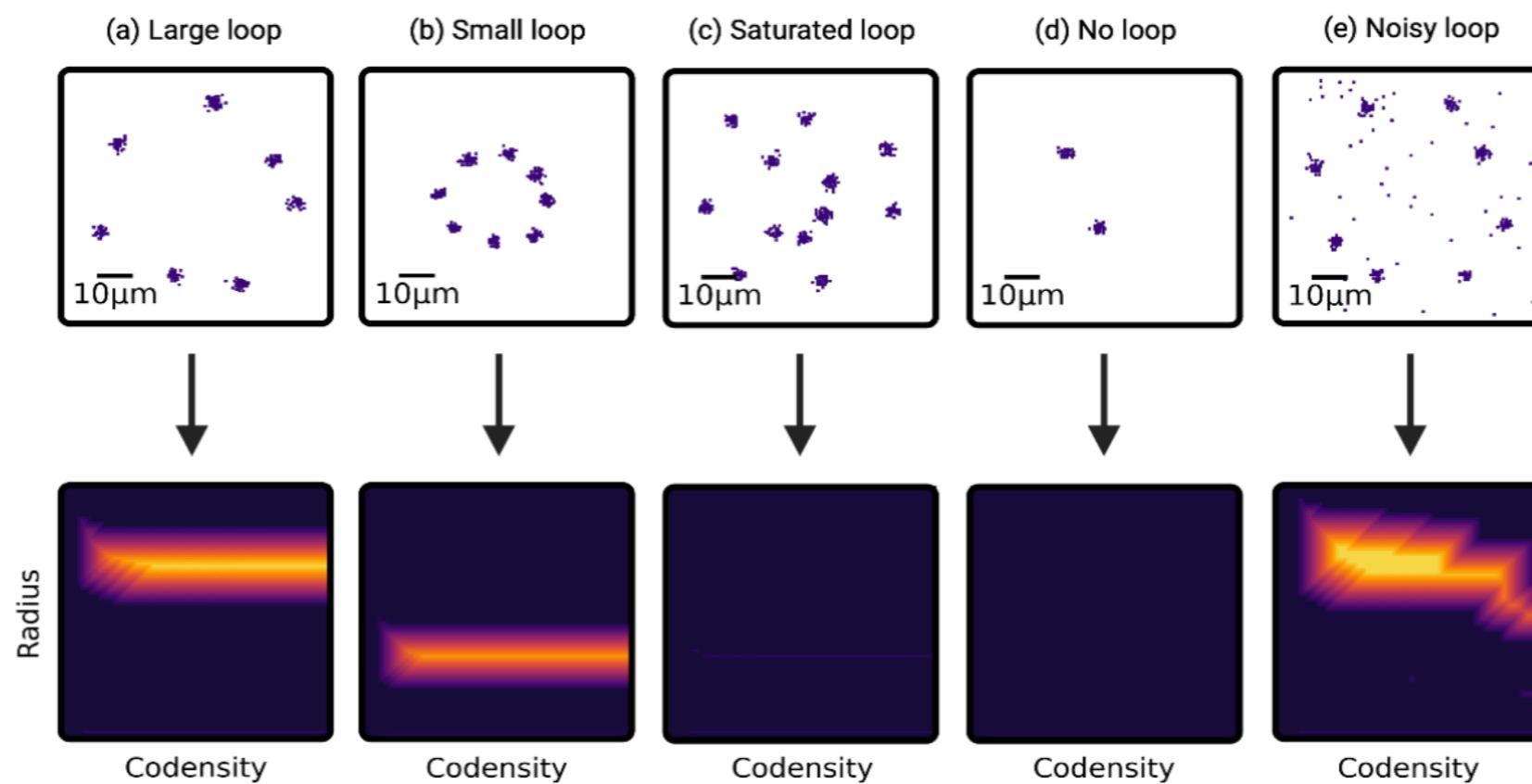
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n -parameter Persistent Homology

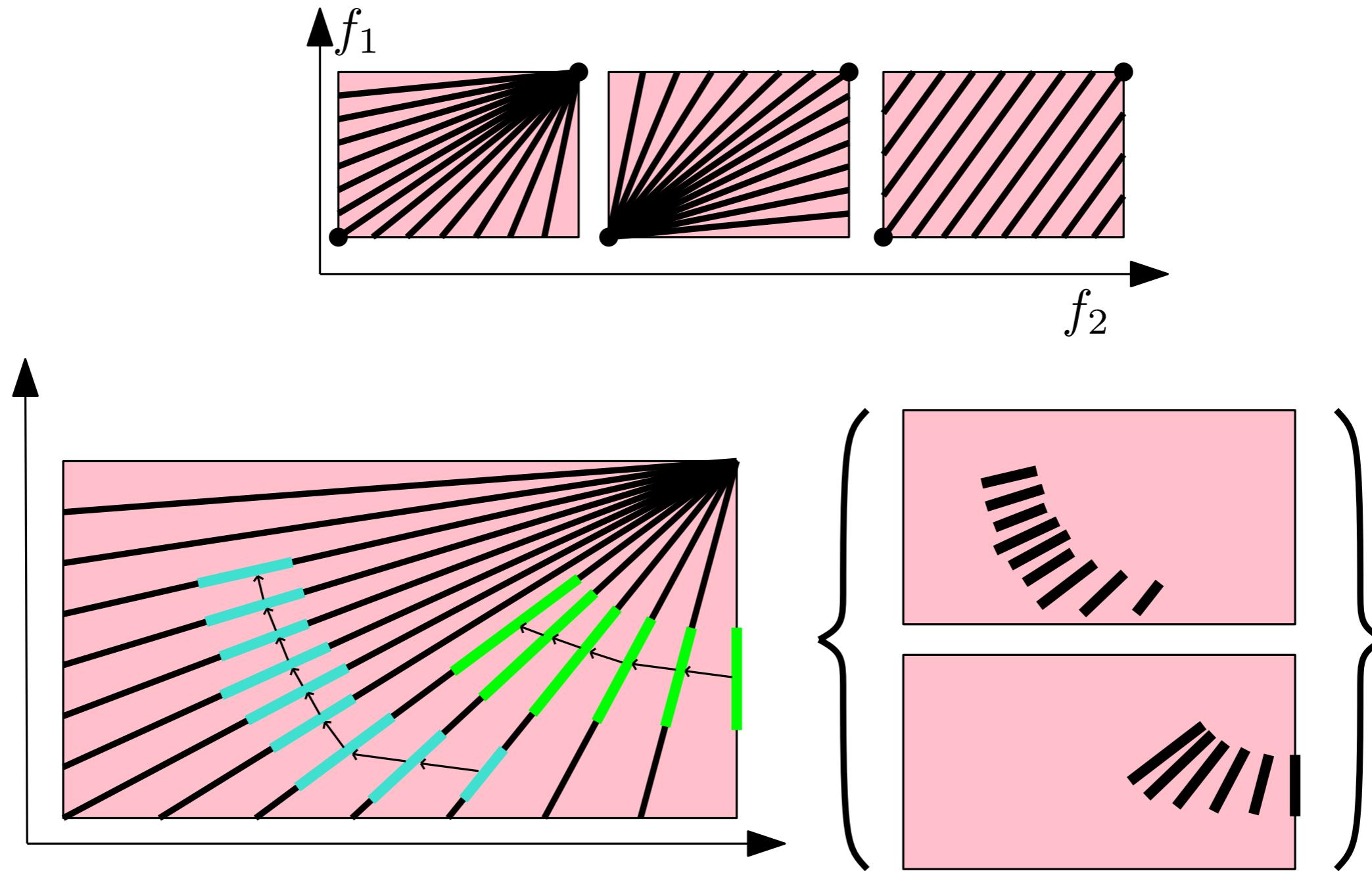
[Loiseaux et al. - 2022 - *Fast, stable and efficient approximation of multi-parameter persistence modules with MMA*]

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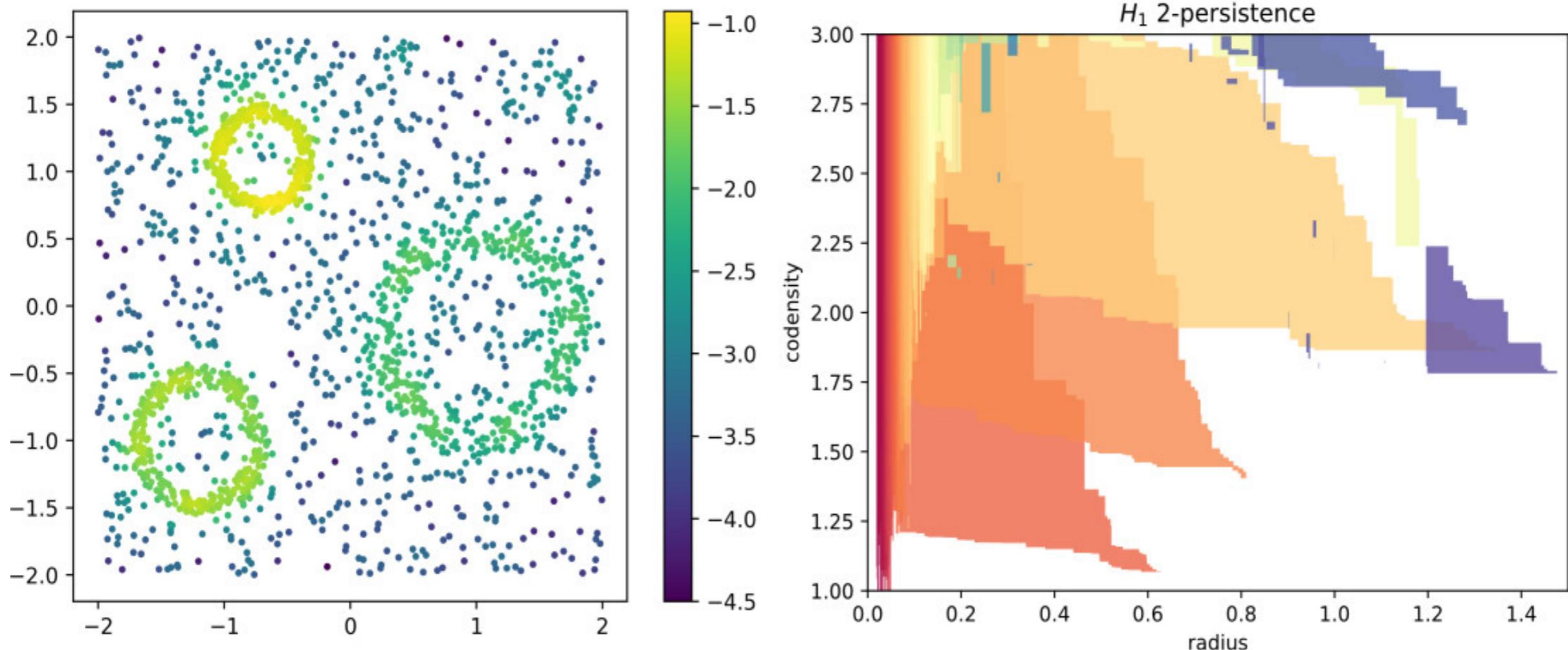


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Approximate persistence module



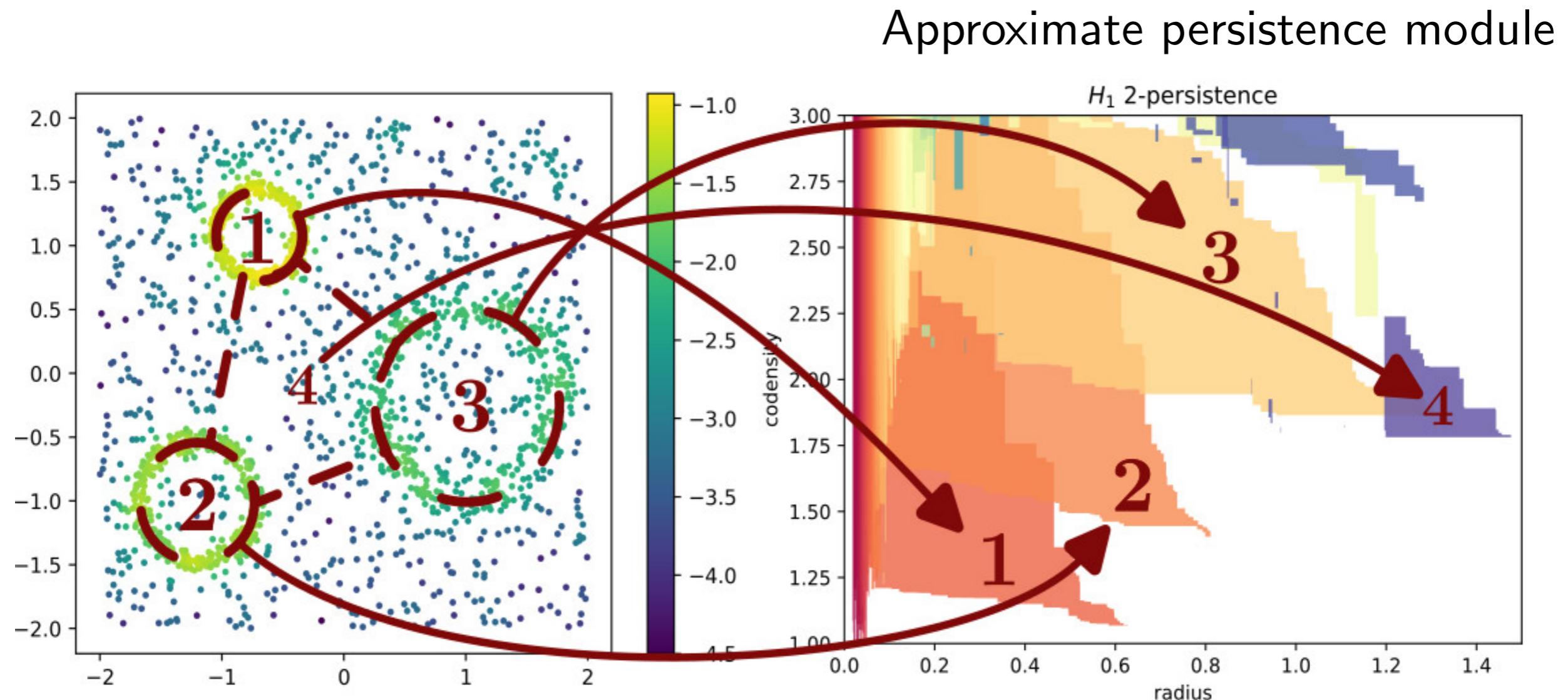
Thm: Let M be an *interval decomposable* multiparameter persistence module, and \tilde{M} be its approximation with a family of lines at distance δ . Then:

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

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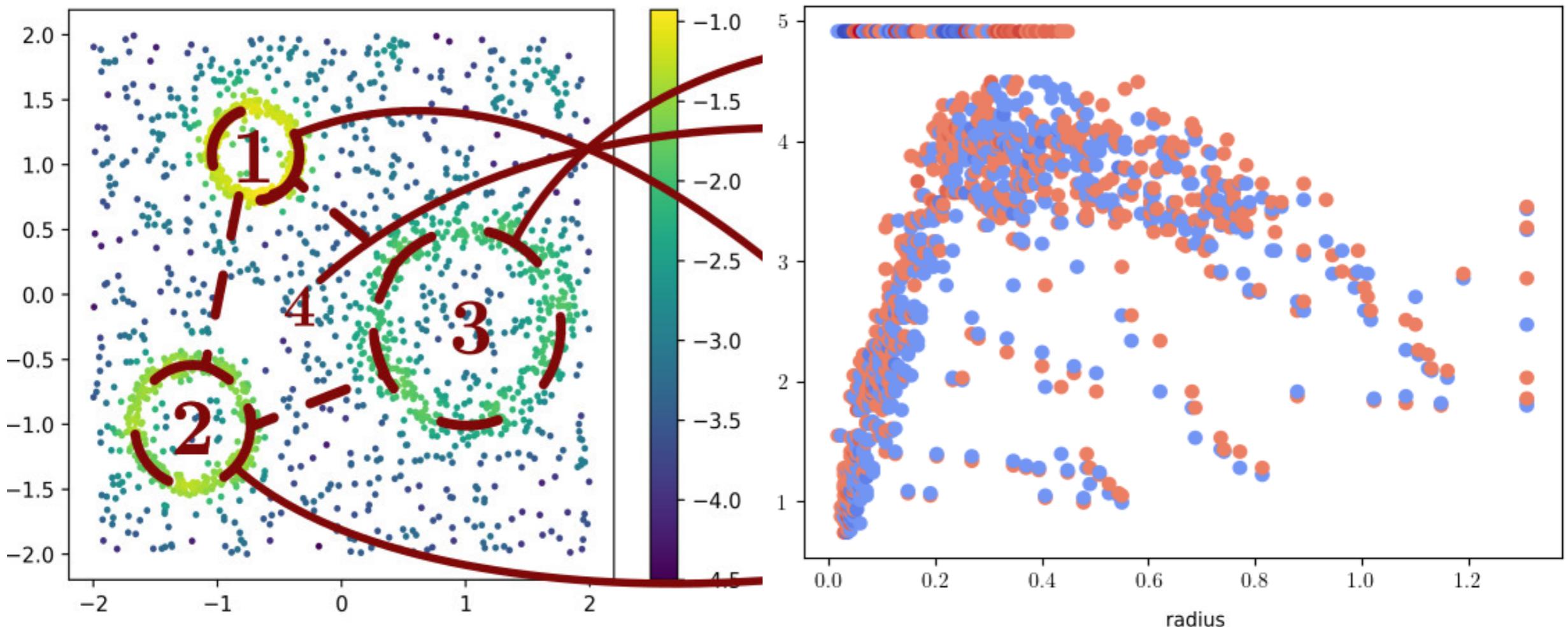
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Representation with measure (of mass 0)



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

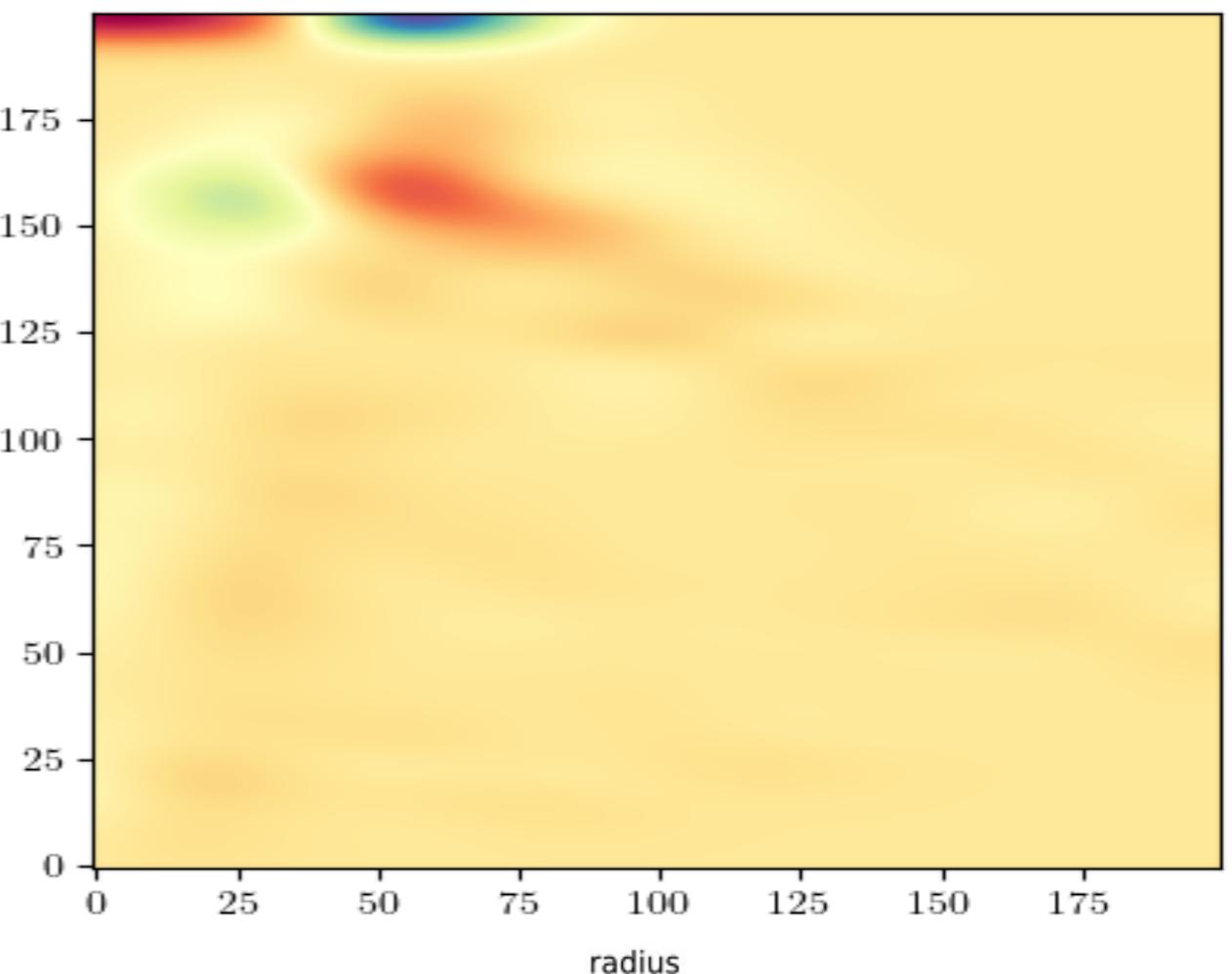
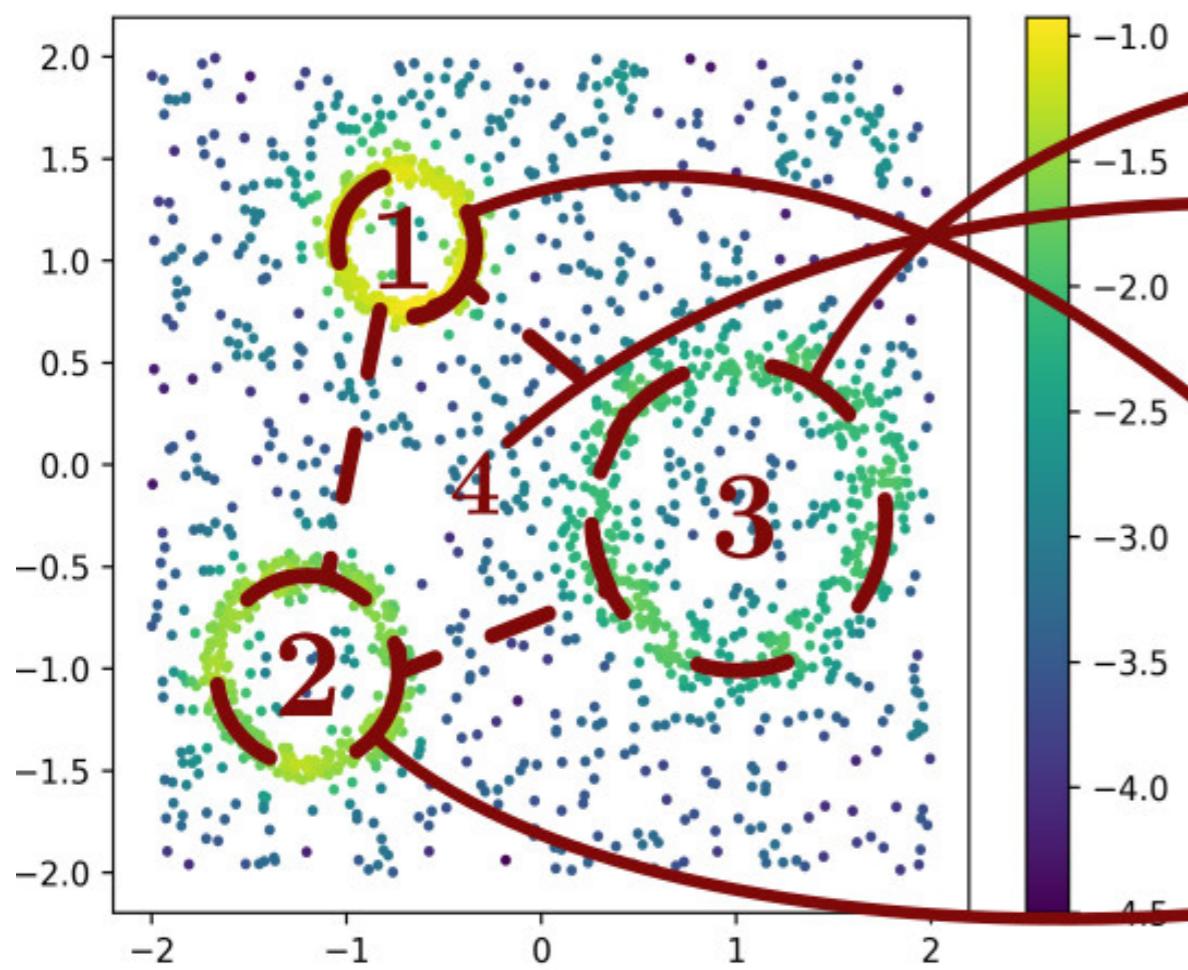
$$\text{Thm: } \|\mu_f - \mu_g\|_1^K \leq \|f - g\|_1$$

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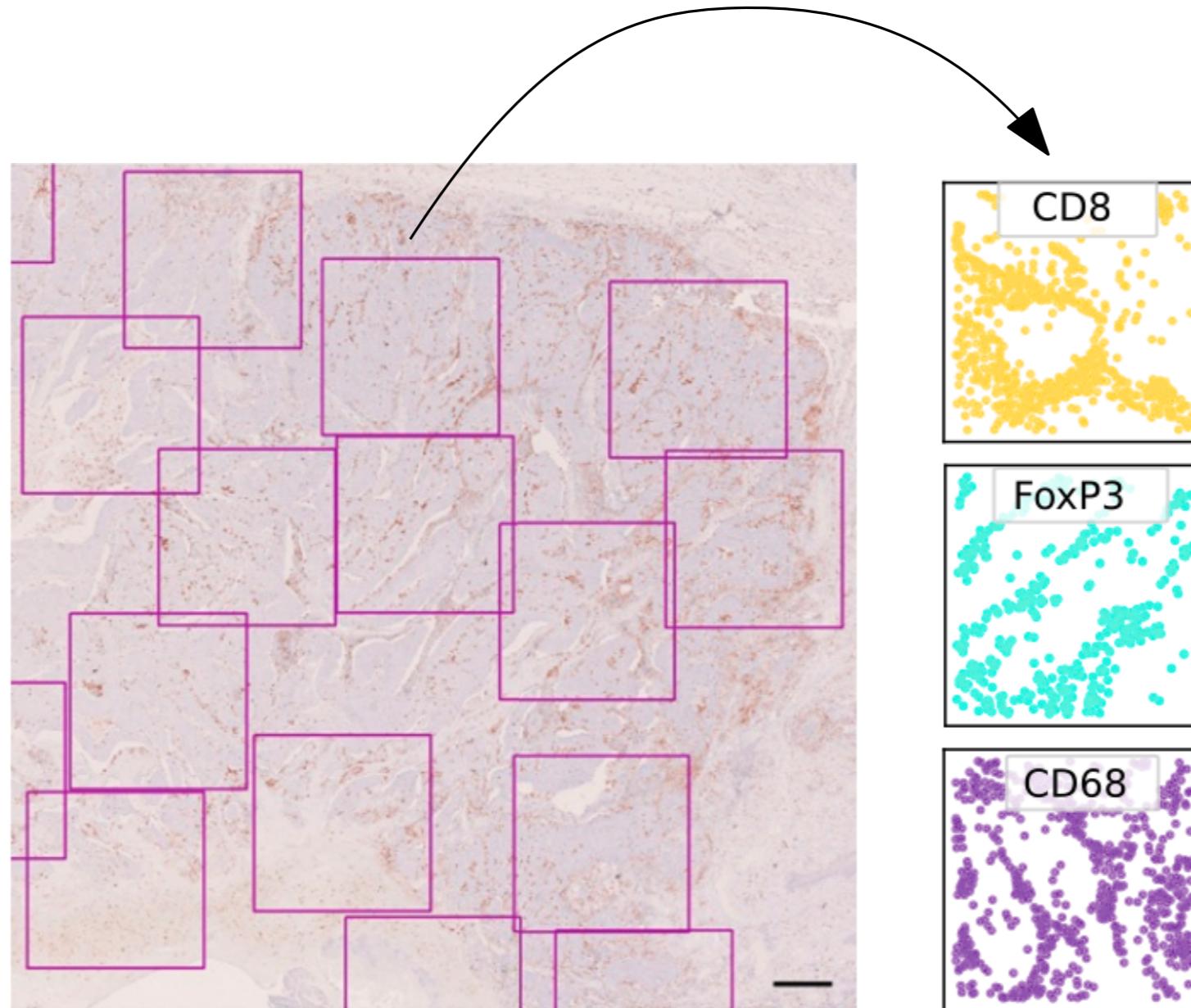
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$$\text{Thm: } \|K * \mu_f - K * \mu_g\|_2 \leq \|\mu_f - \mu_g\|_2^K$$

Application to cell arrangements

Method:

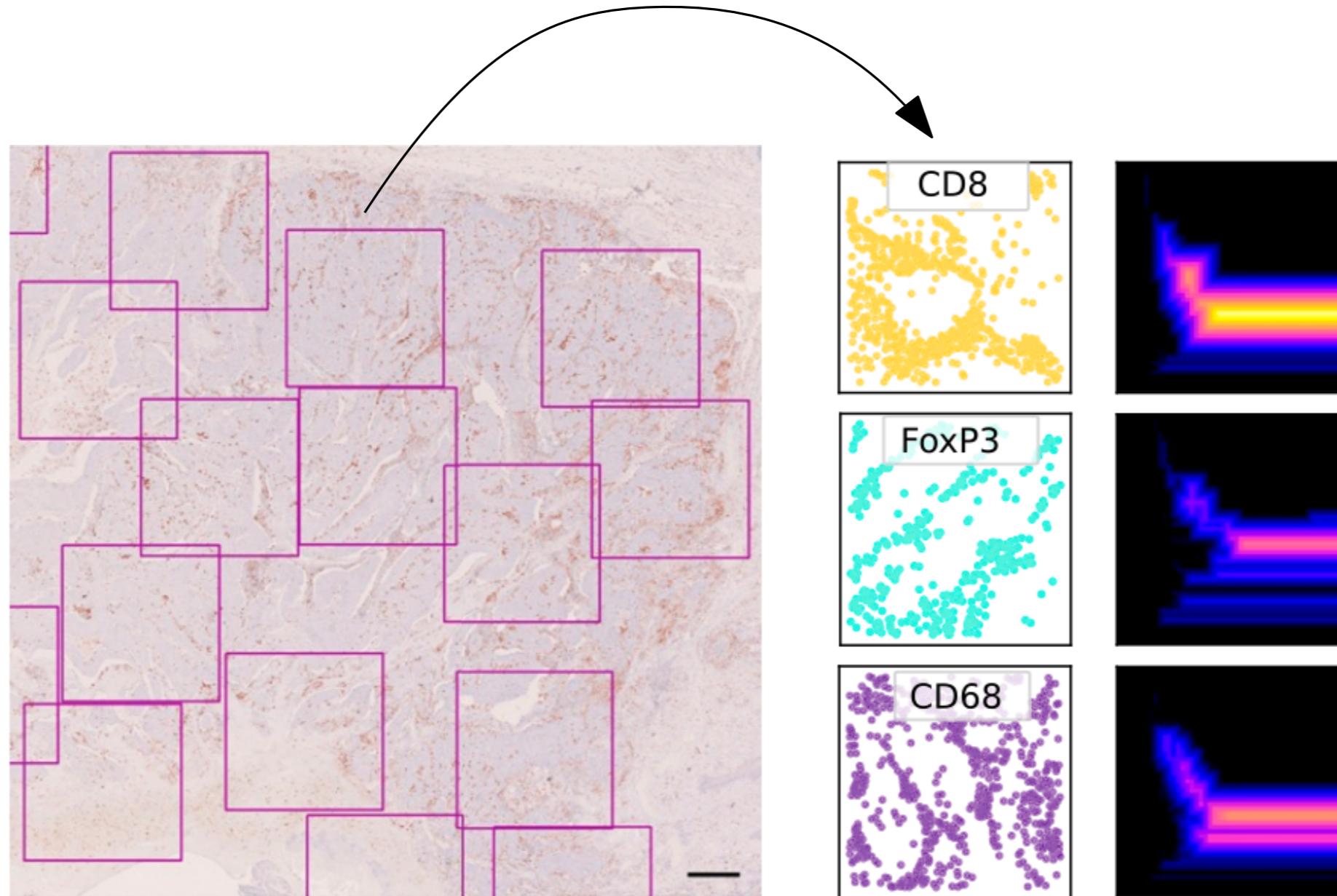
1. Extract local point clouds and cell types corresponding to several measurement spots.



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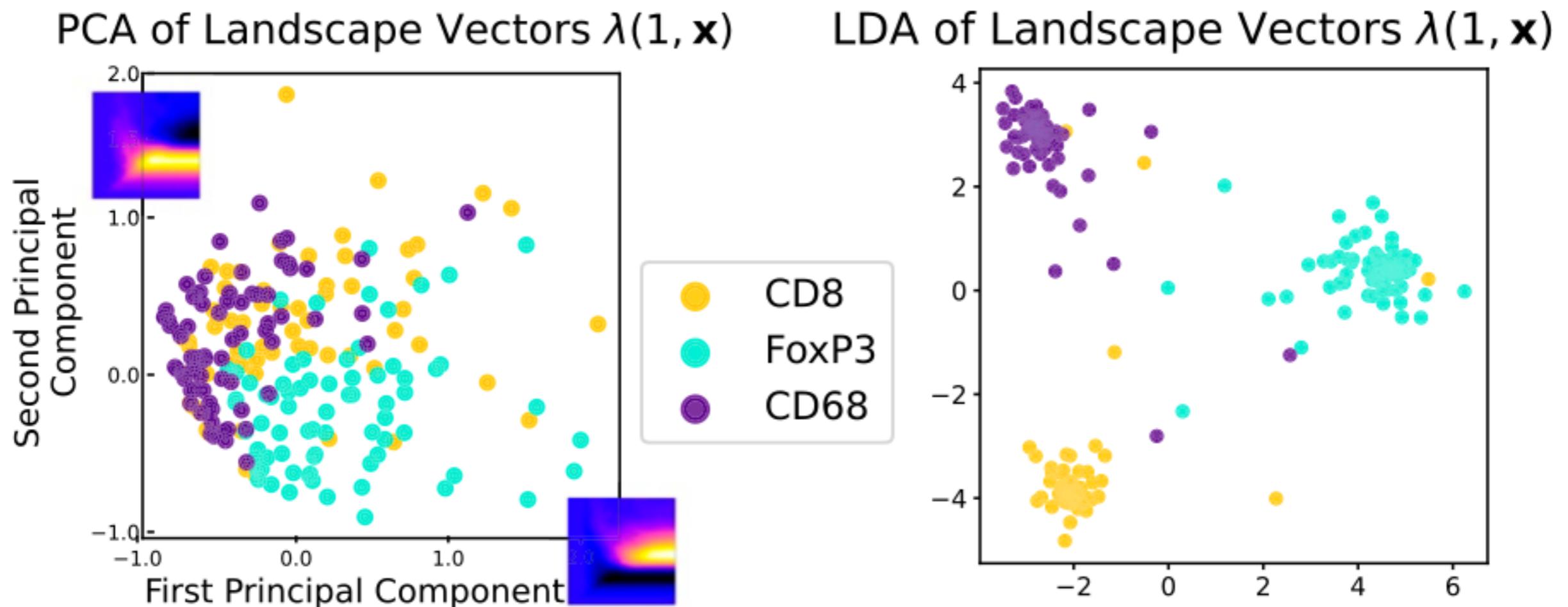
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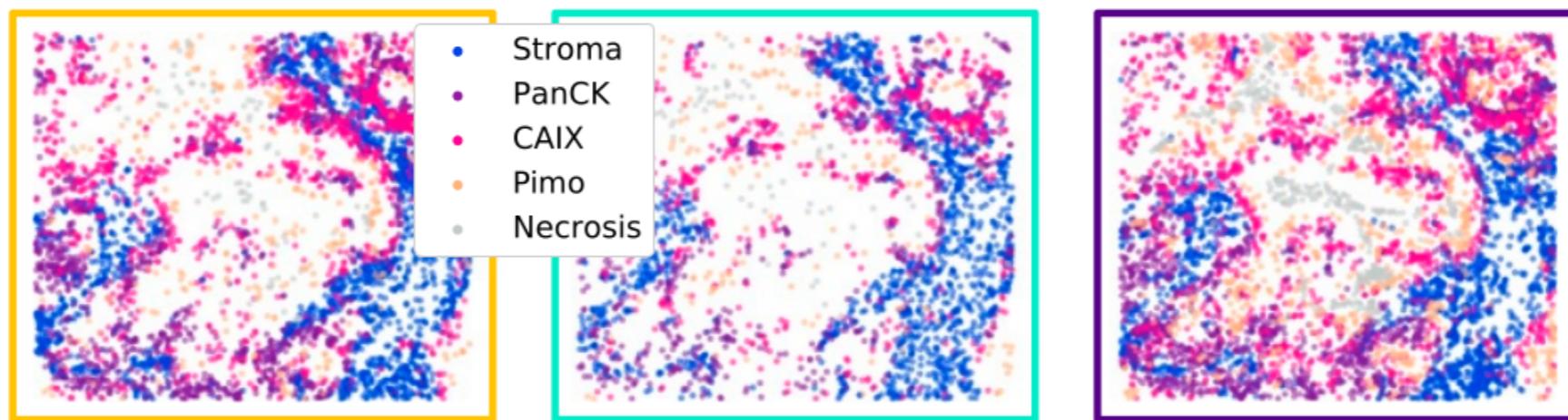
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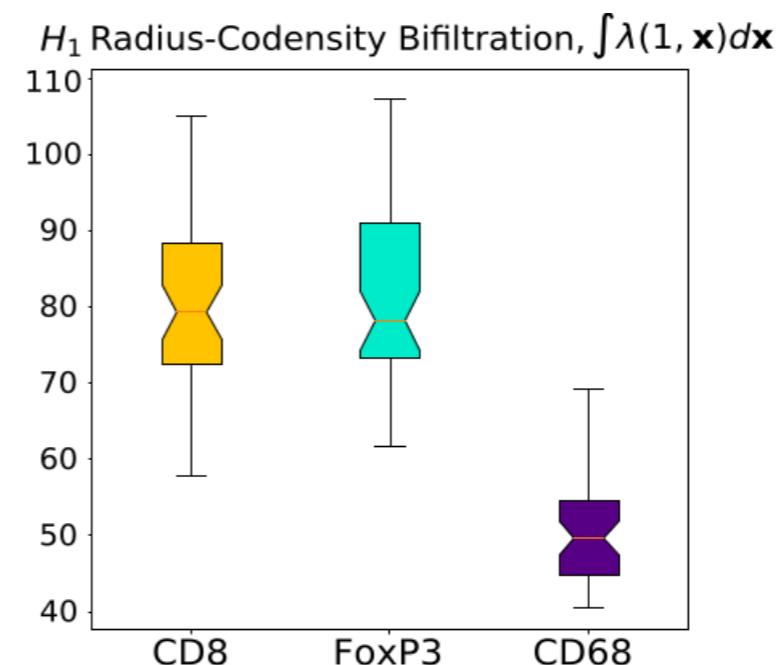
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4. Perform biological inference from additional cell annotations.



The fact that the norm of CD68 MPL is smaller than the others means that CD68 cells have a bigger tendency 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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Process (Spot in \mathbb{R}^2 , Expression vector) pairs

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[Aukerman et al. - 2022 - *Persistent homology-based characterization of the breast cancer immune microenvironment: a feasibility study*]

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Limitation: too many marker genes for running multi-persistence, which forces to pick (combinations of) marker 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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- no need to cherry pick gene combinations
- 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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Process (Local point cloud $\subset \mathbb{R}^2$, Expression vector) pairs

TDA + Integrated (w/ scRNA-seq) Spatial Transcriptomics

[Vipond et al. - 2021 - *Multiparameter persistent homology landscapes identify immune cell spatial patterns in tumors*]

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

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

Other recent (August 2023) directions on synthetic data:

[Stolz et al. - 2023 - *Relational persistent homology for multi-species data with application to the tumor microenvironment*]

[Yang et al. - 2023 - *Topological classification of tumour-immune interactions and dynamics*]



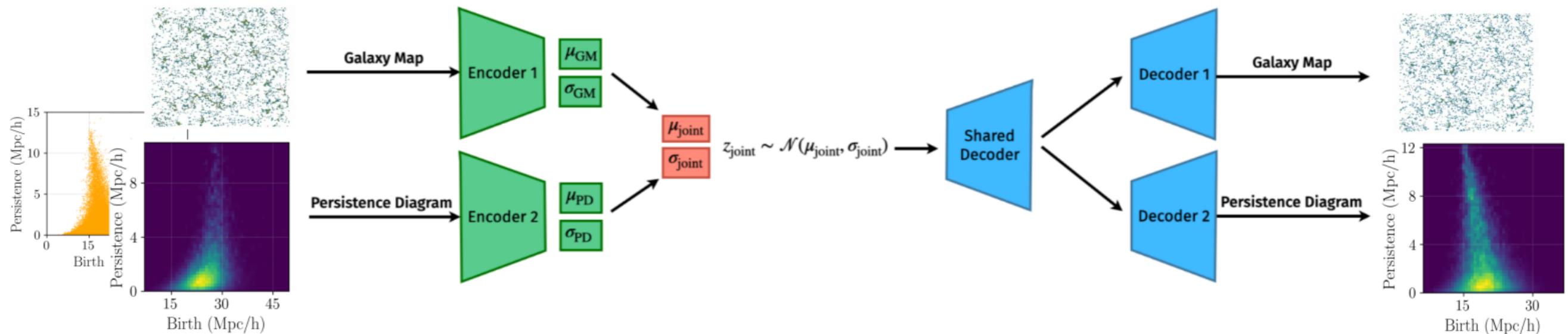
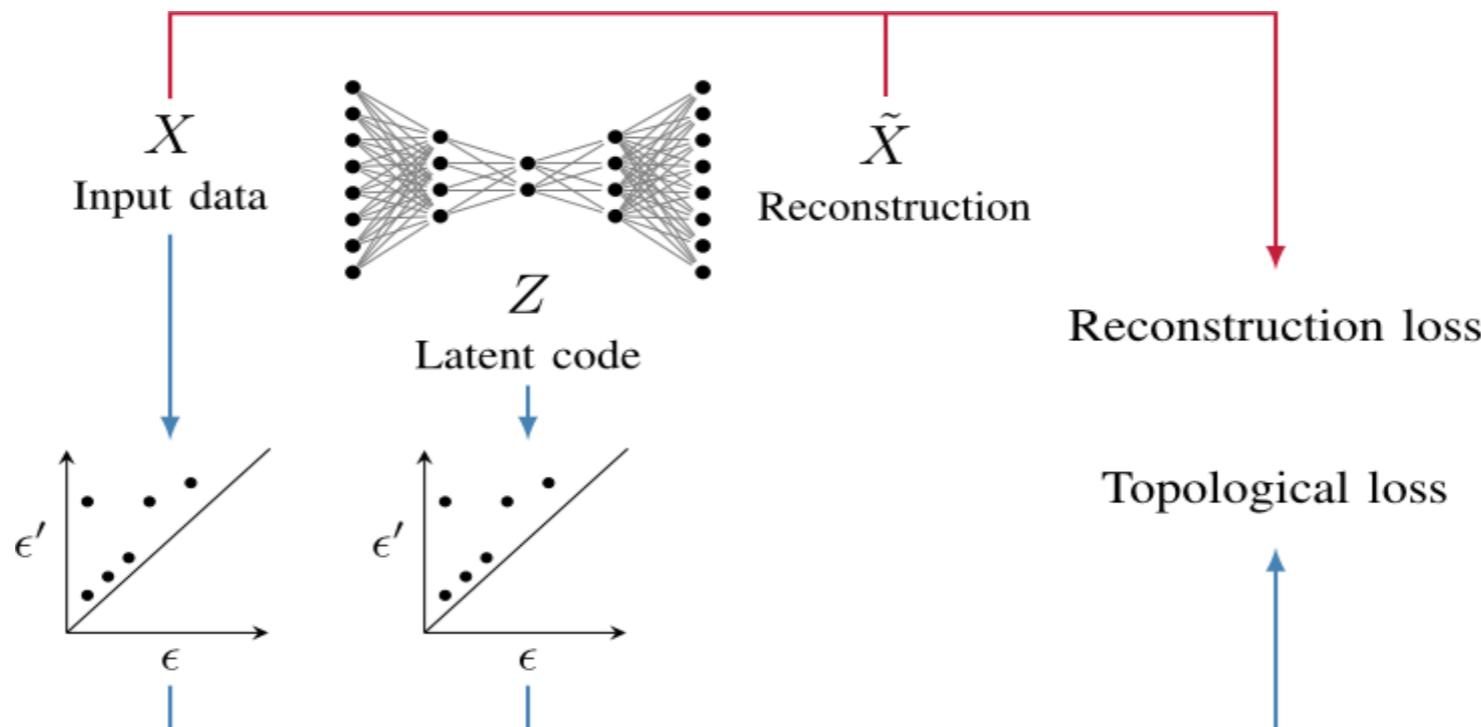
Characterize *time-dependent* spatial transcriptomics with Zigzag and Vineyard Rips PH

Other Topics: Differentiating PDs

Define gradient of persistence with

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

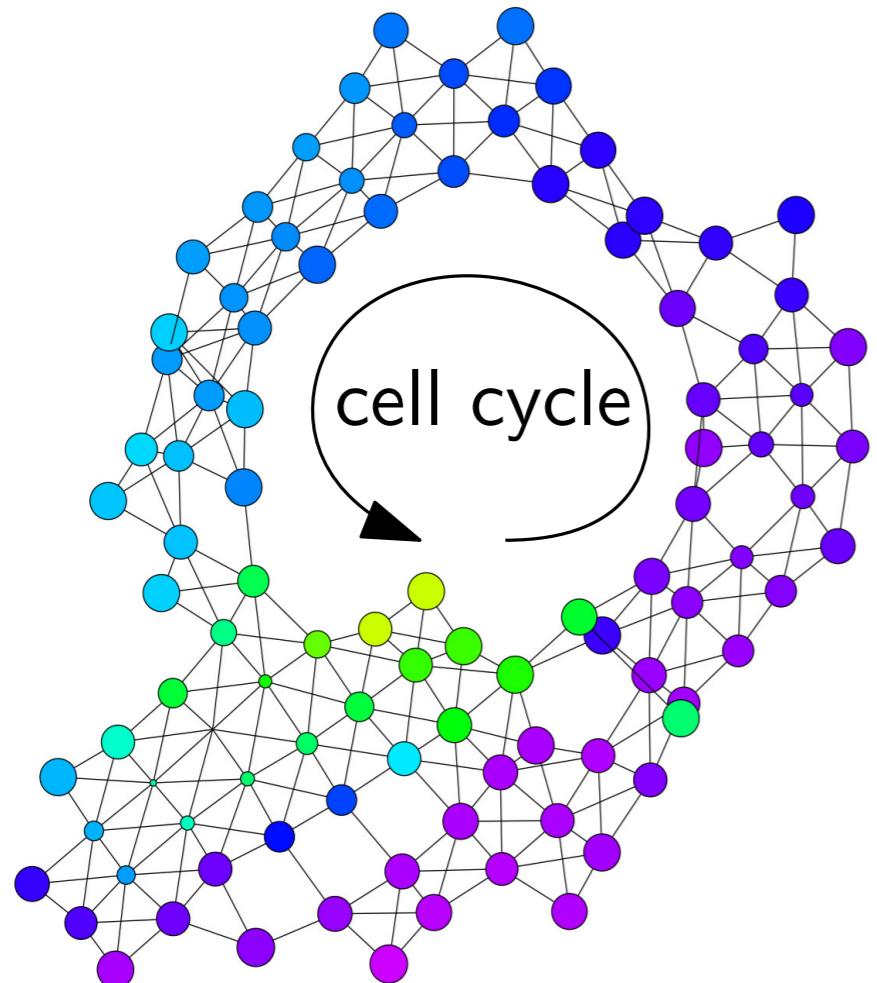
<https://github.com/GUDHI/TDA-tutorial/blob/master/Tuto-GUDHI-optimization.ipynb>



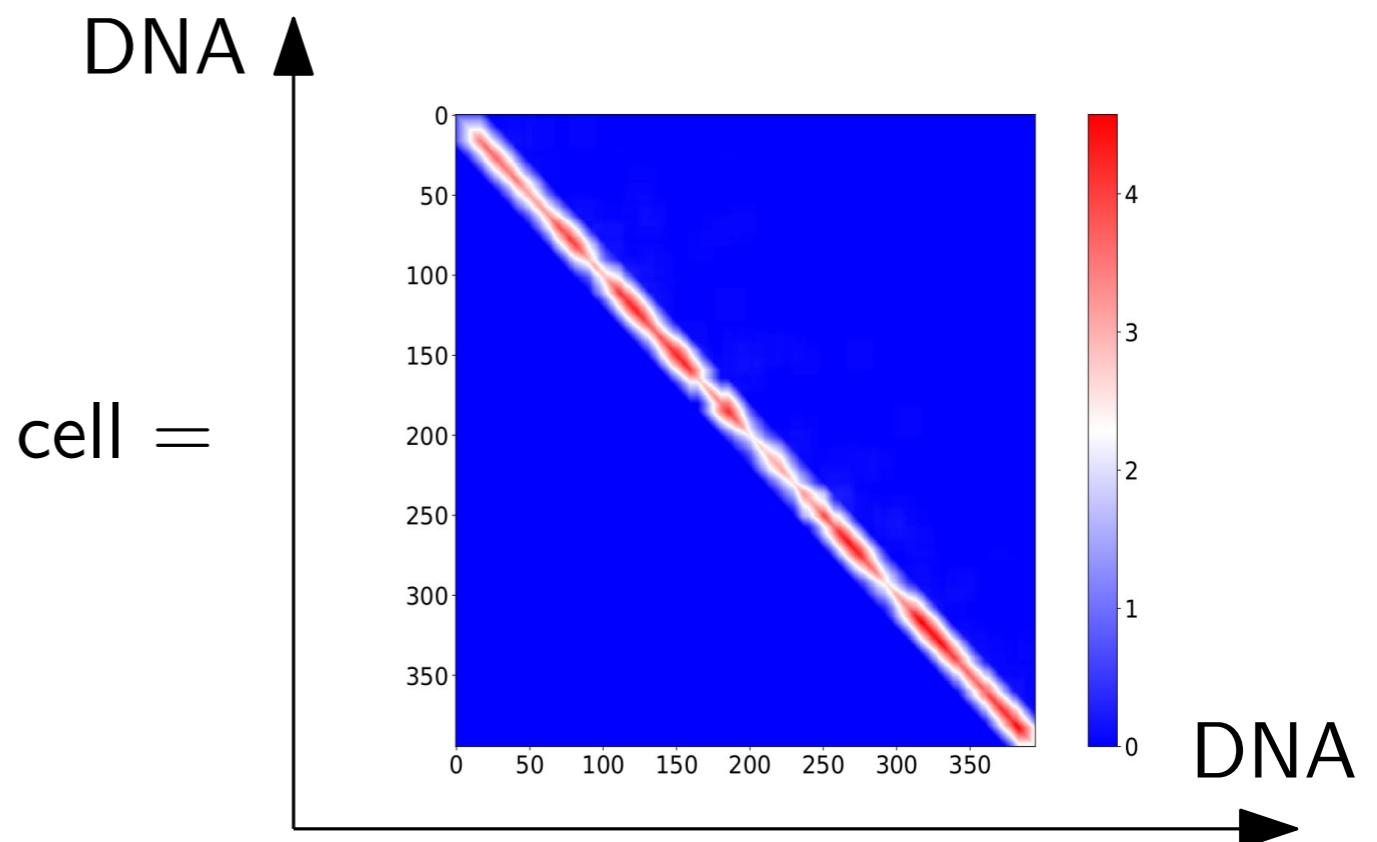
Other Topics: Exploratory Data Analysis with Mapper

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



Thank you!