

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*]

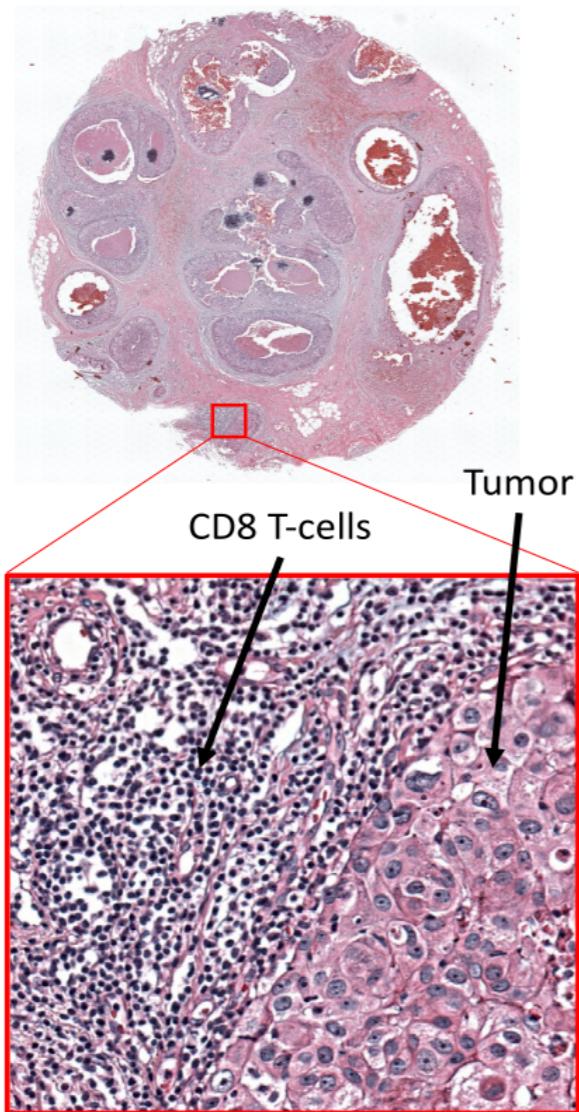
[Benjamin et al. - 2022 - *Multiscale topology classifies and quantifies cell types in subcellular spatial transcriptomics*]

4. Future research directions

2. Rips persistence for marker gene correlations

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Q: What are the relations and correlations between *spatial features* and *marker genes*? Can one influence the other?

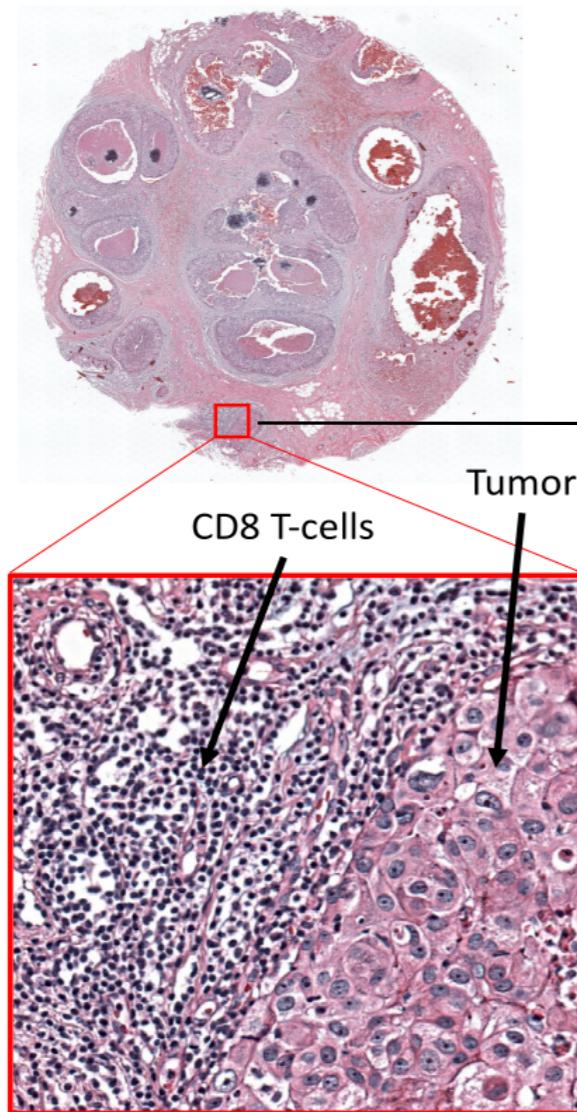


Local point cloud

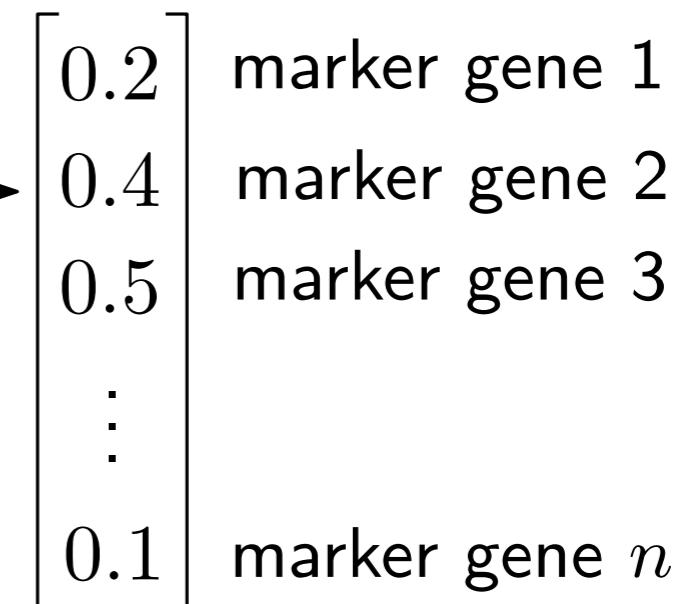
$$P = \{p_1, \dots, p_m\} \subset \mathbb{R}^2$$

2. Rips persistence for marker gene correlations

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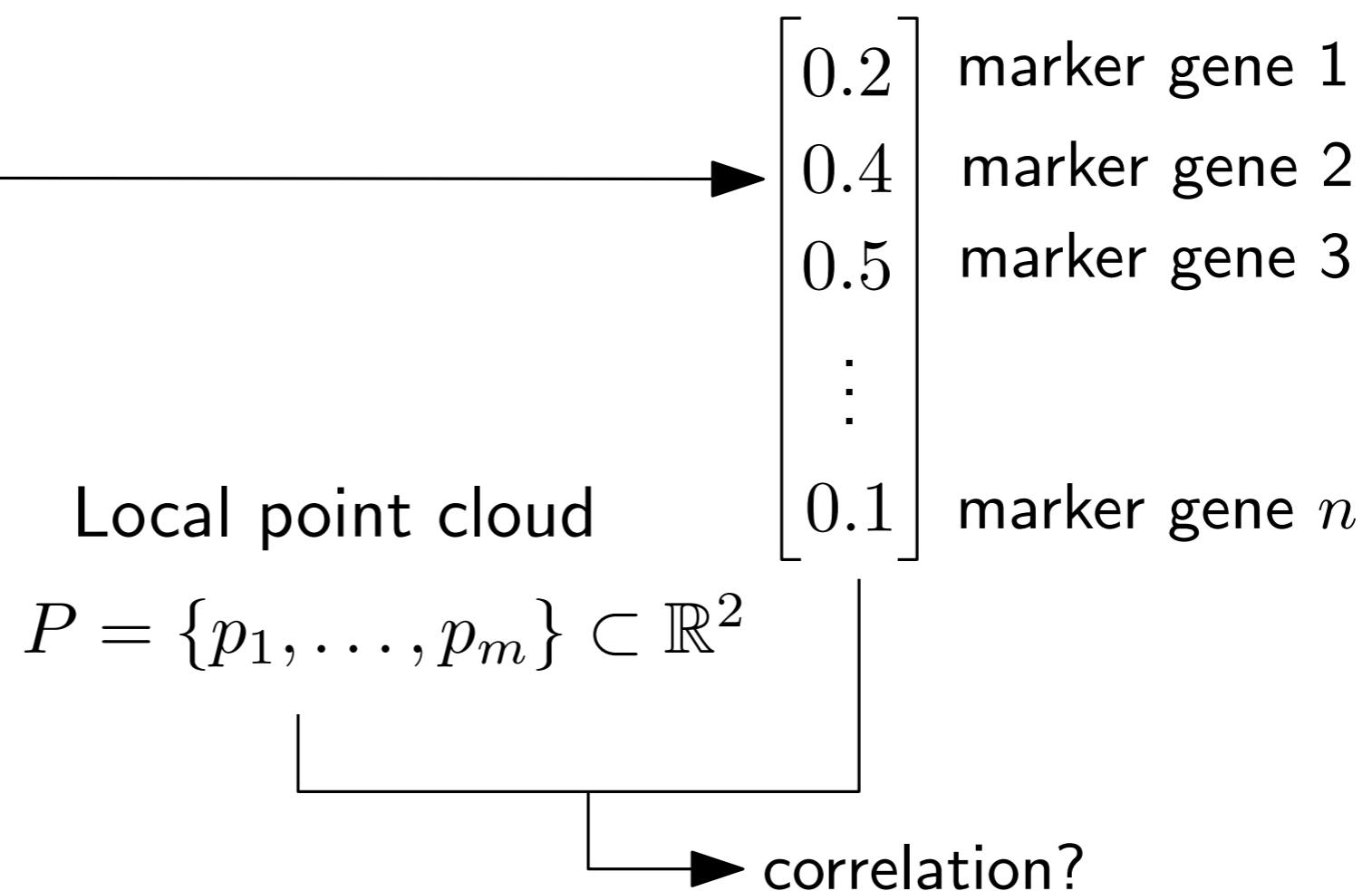
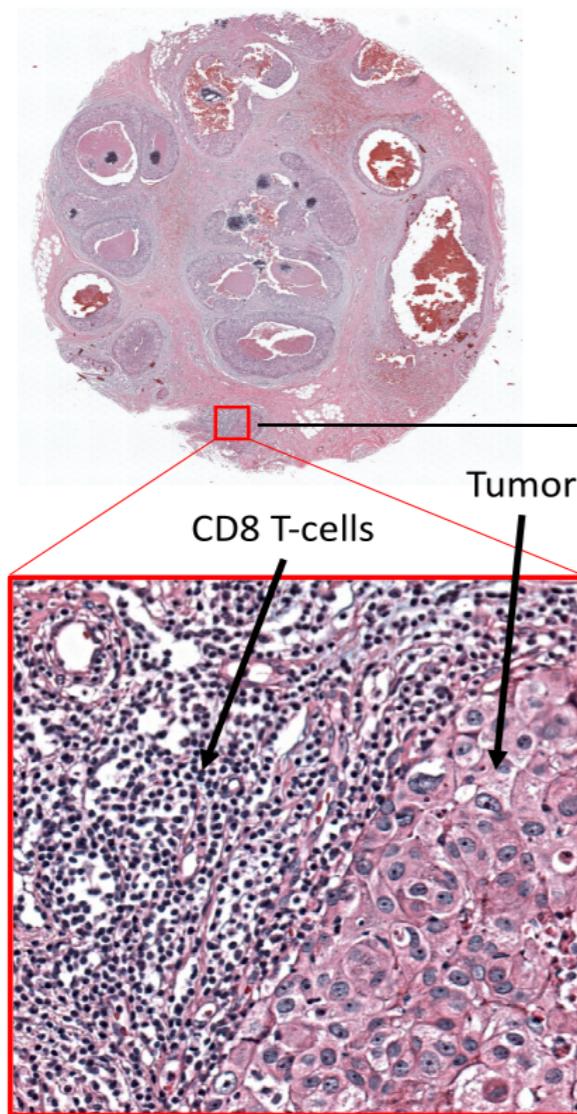
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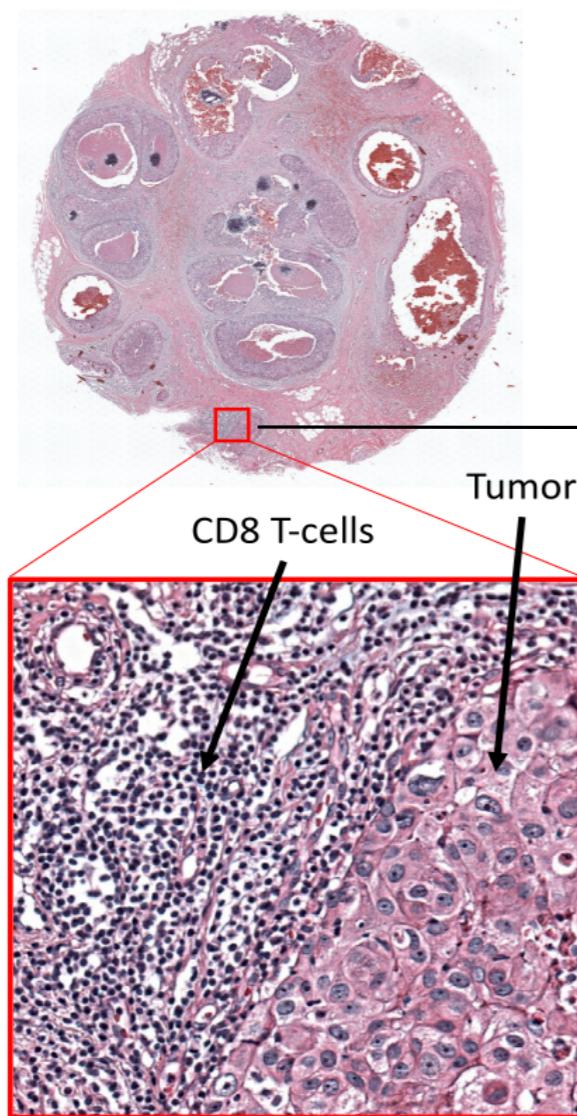
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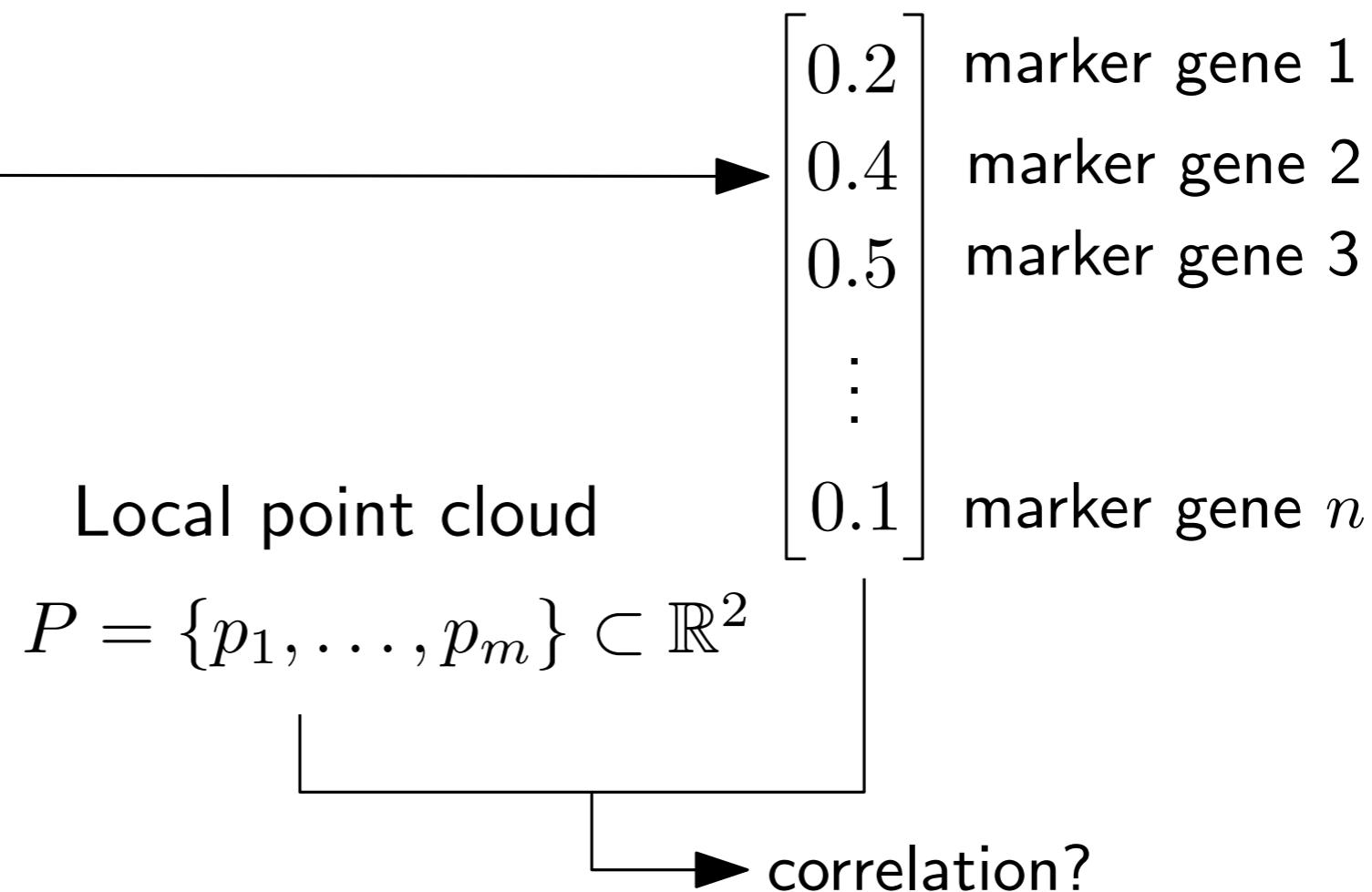


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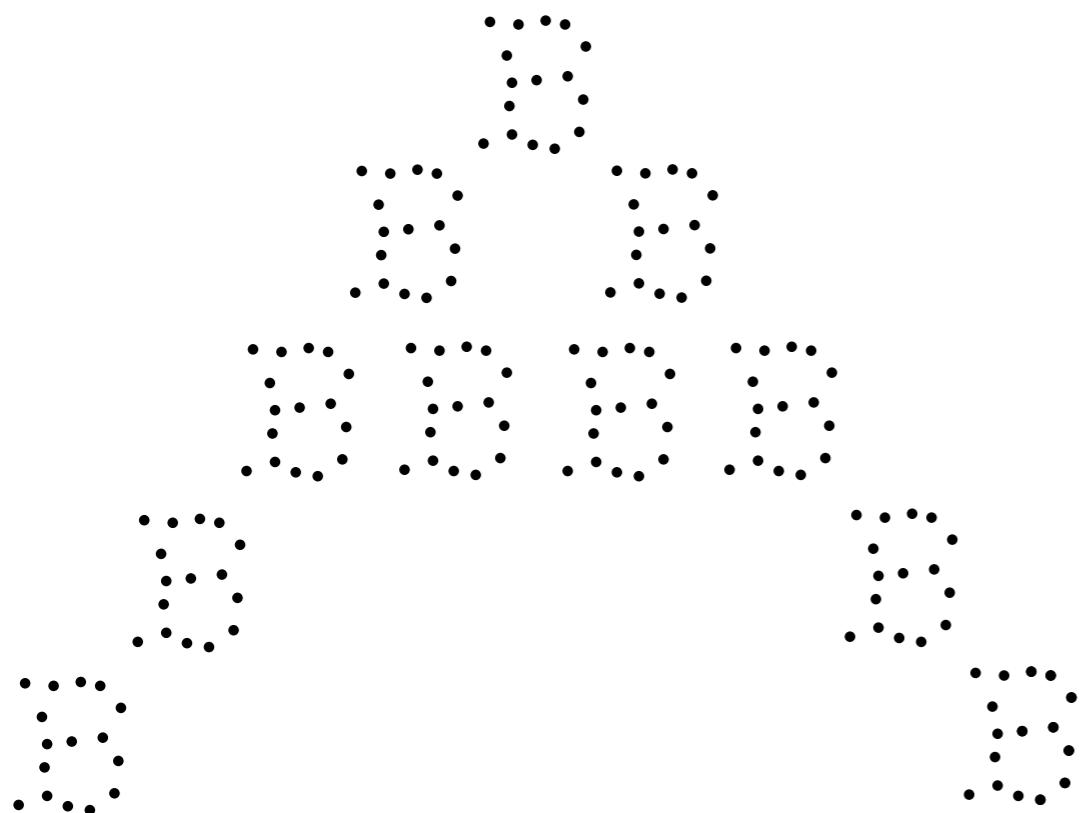


A: Use *Pearson correlation* between marker gene expression and **Rips persistence** of local point clouds.



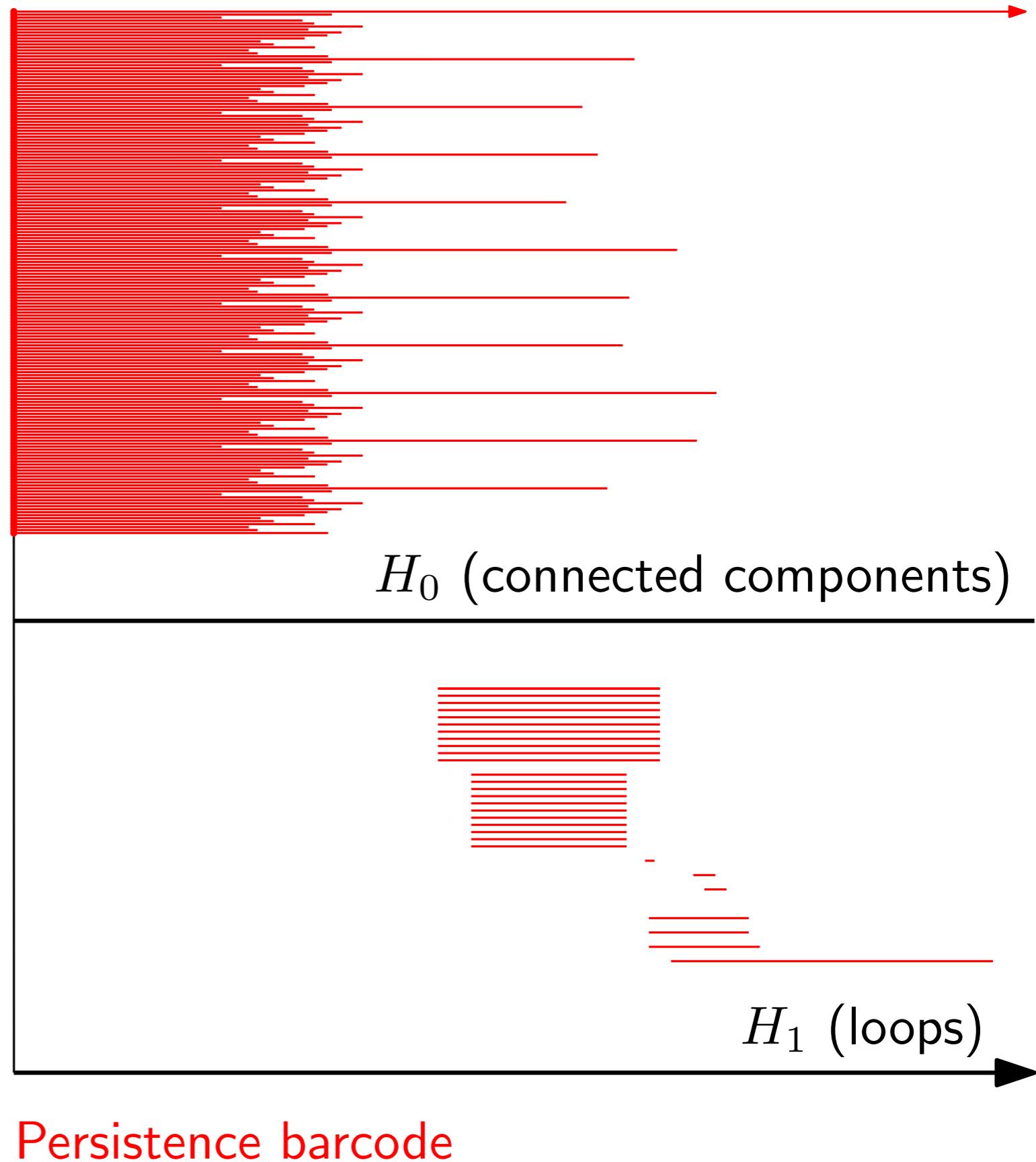
0- and 1-dimensional PH of Čech complexes

$$X = \mathbb{R}^2$$



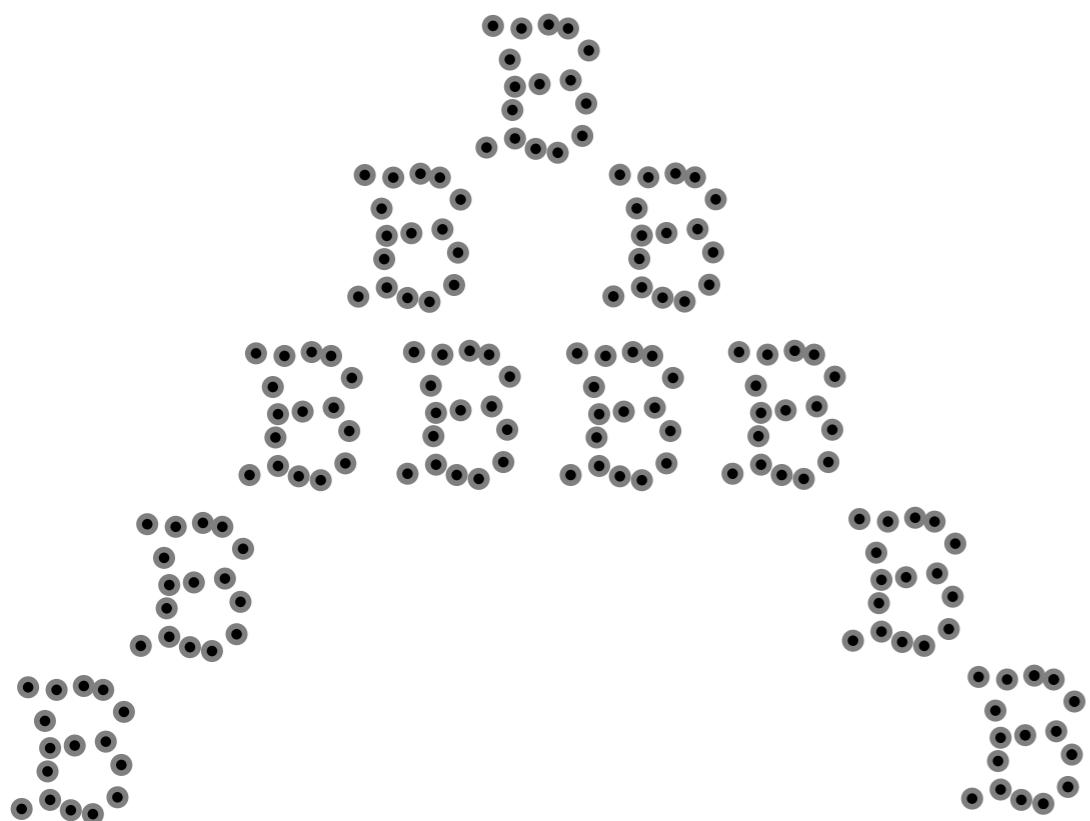
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a (pre-defined) point cloud P*

$$f(x) := \min_{p \in P} \|x - p\|$$



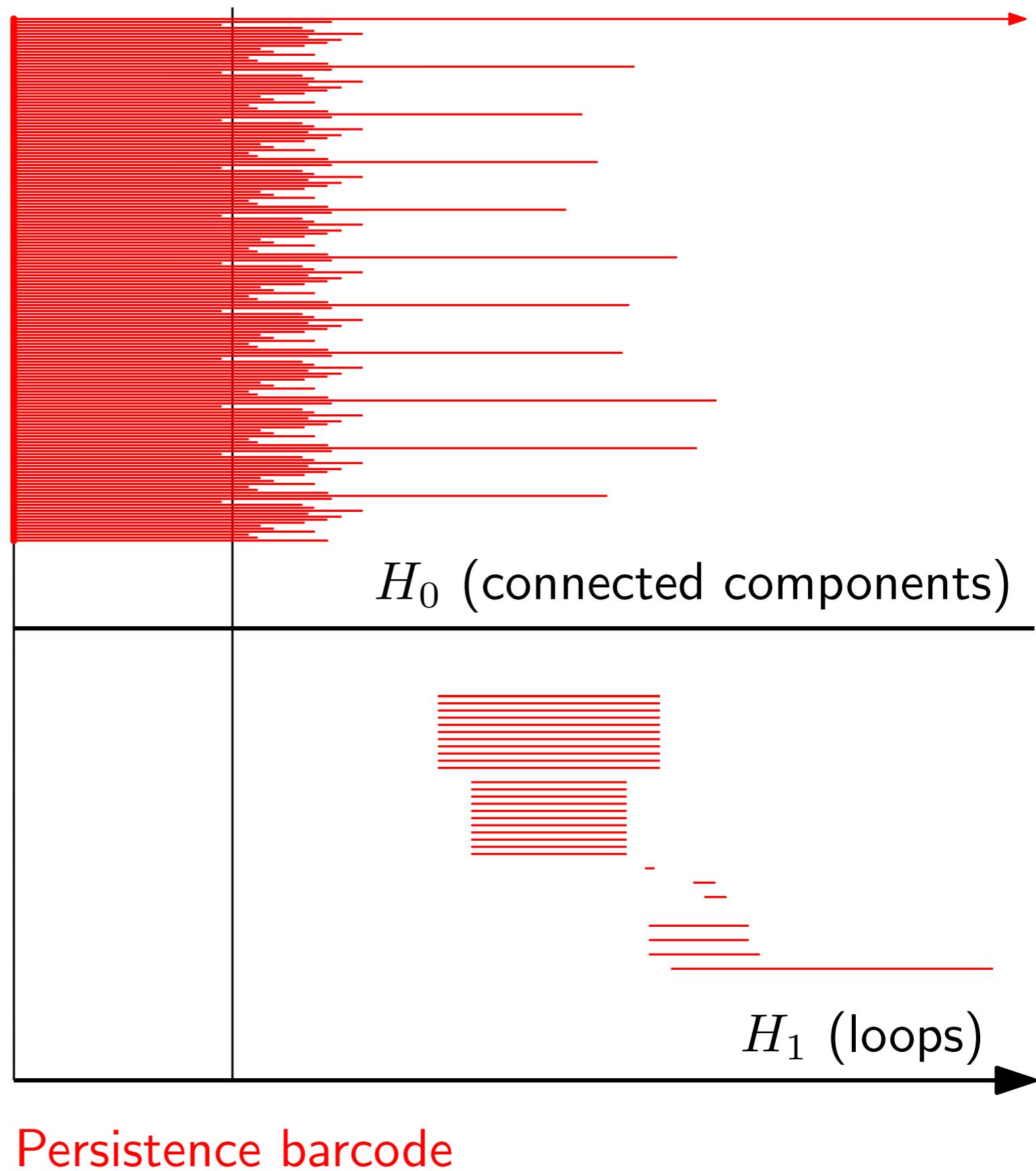
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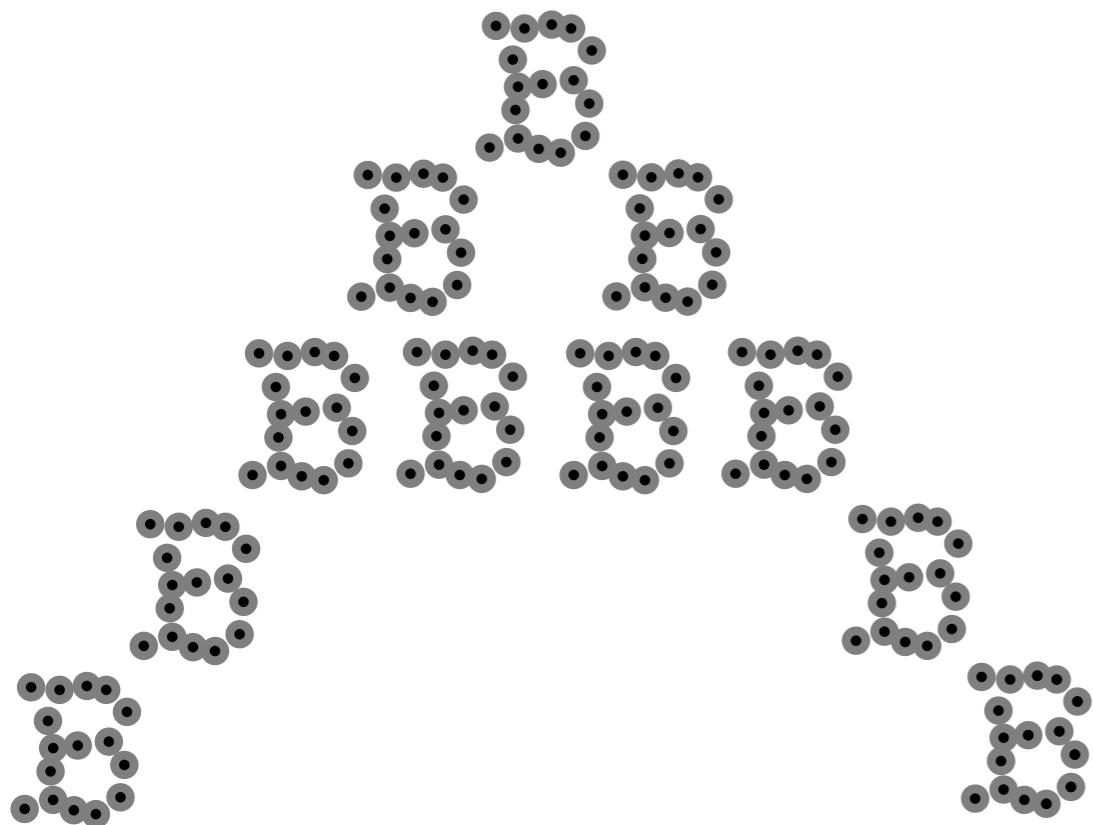
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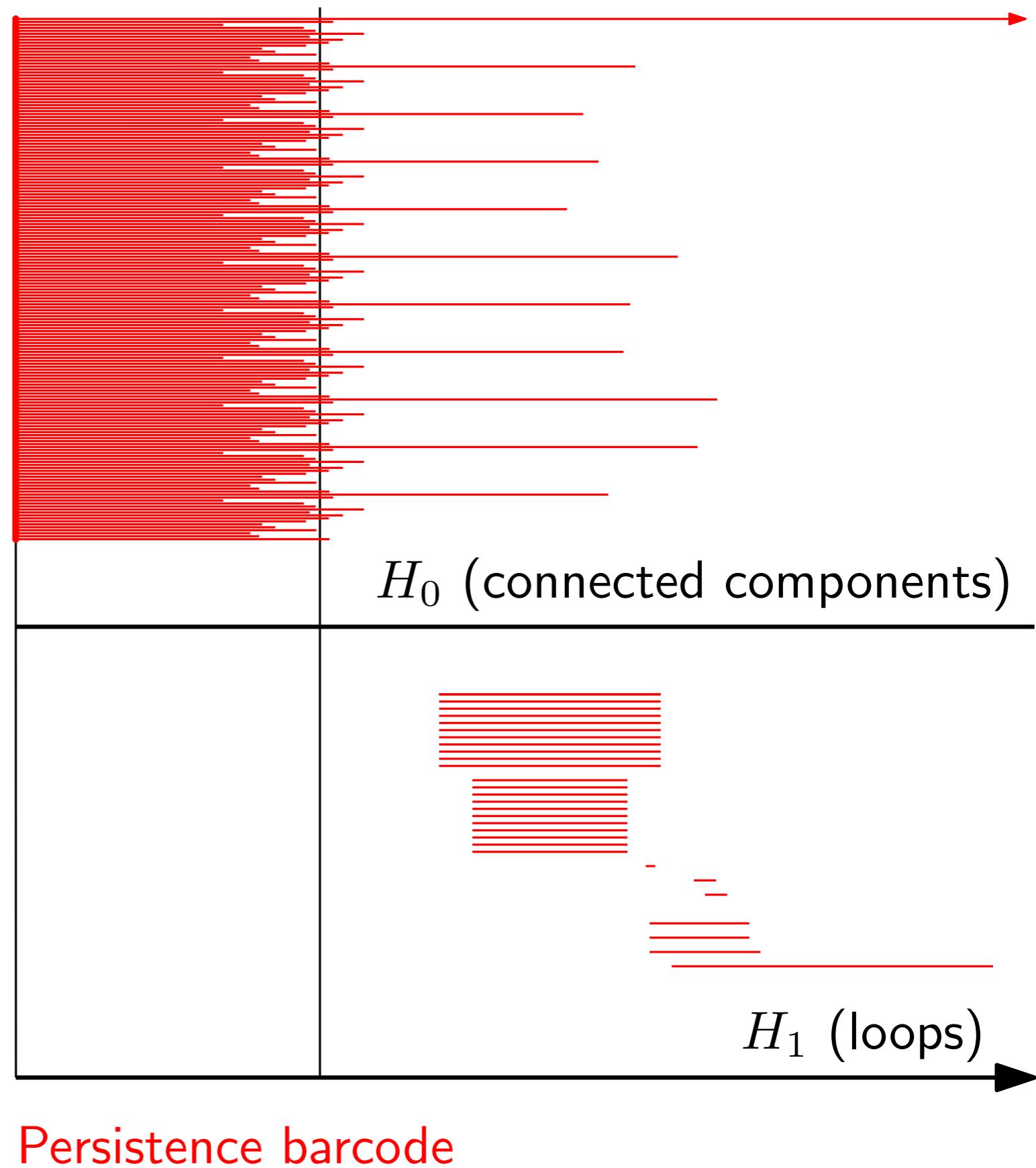
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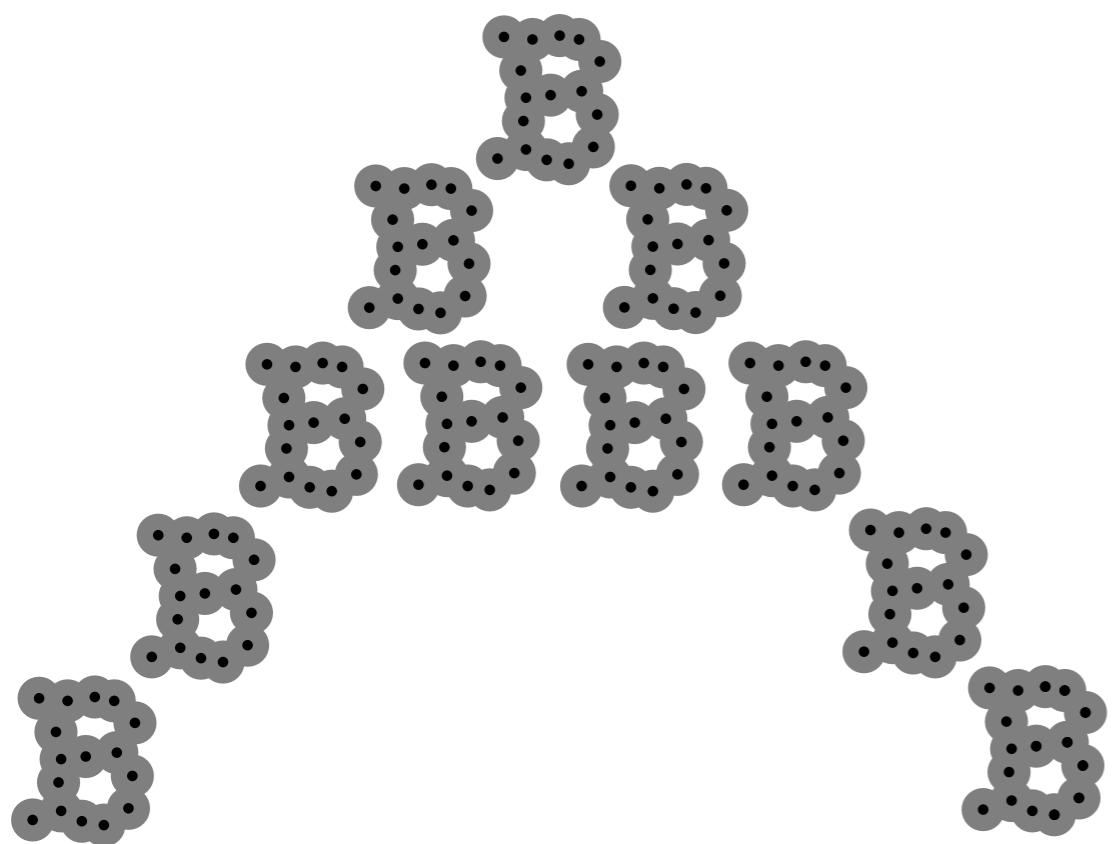
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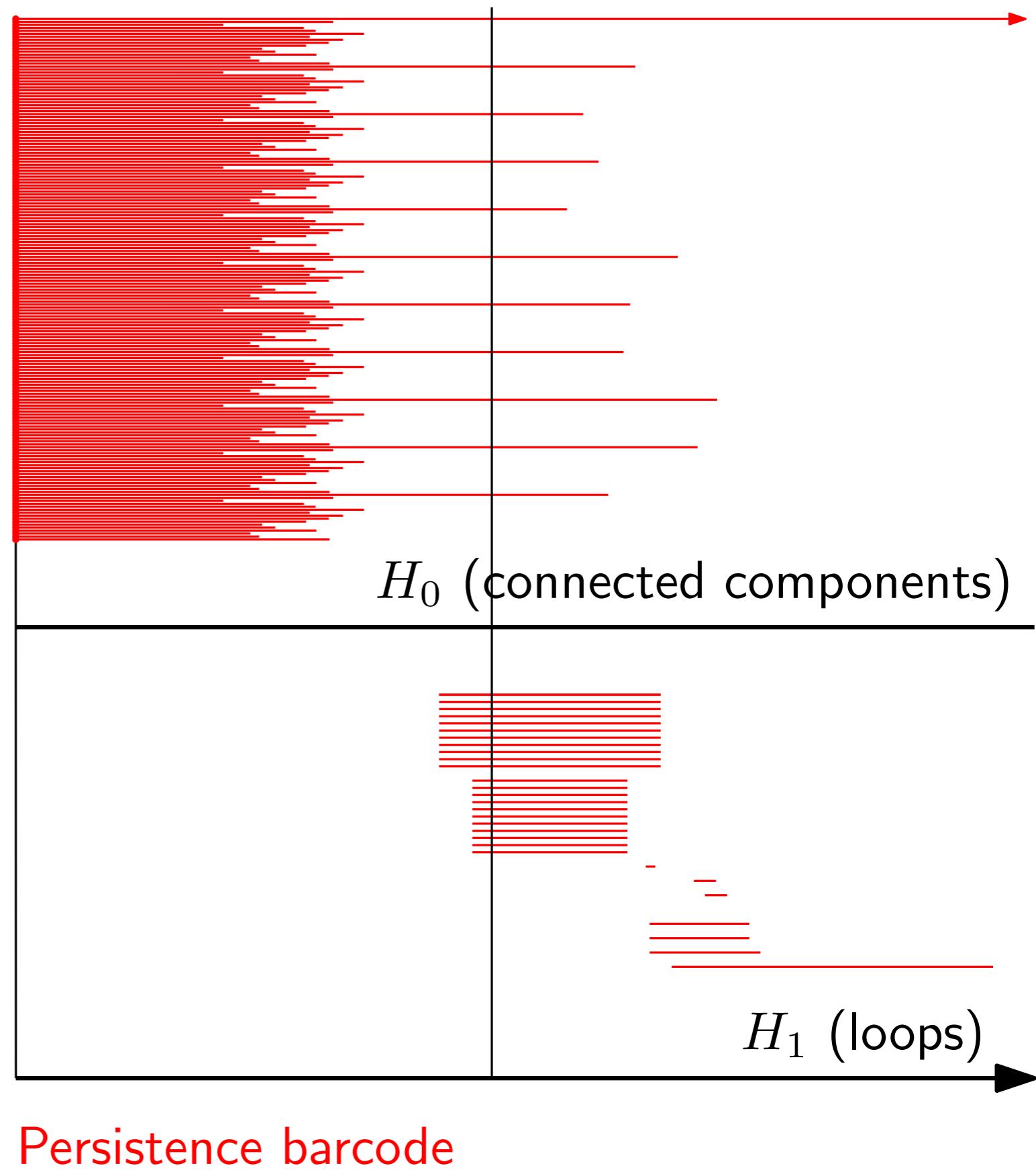
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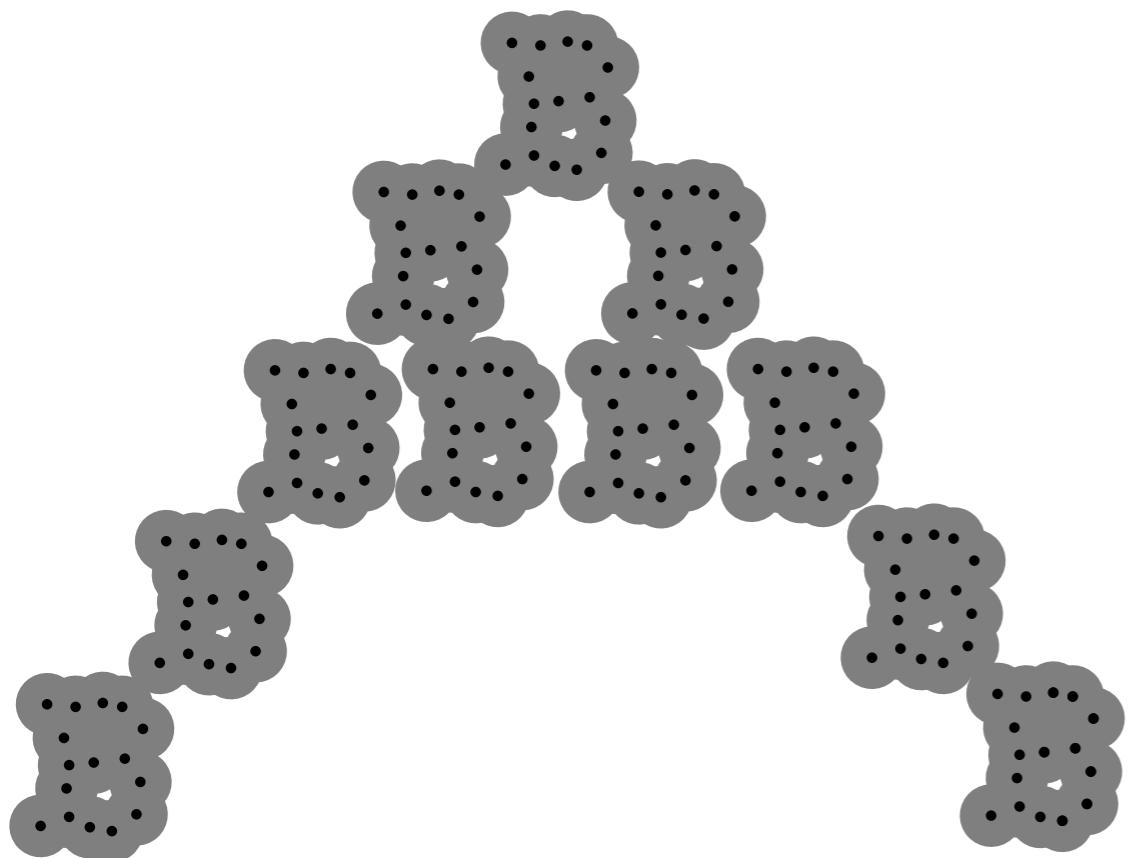
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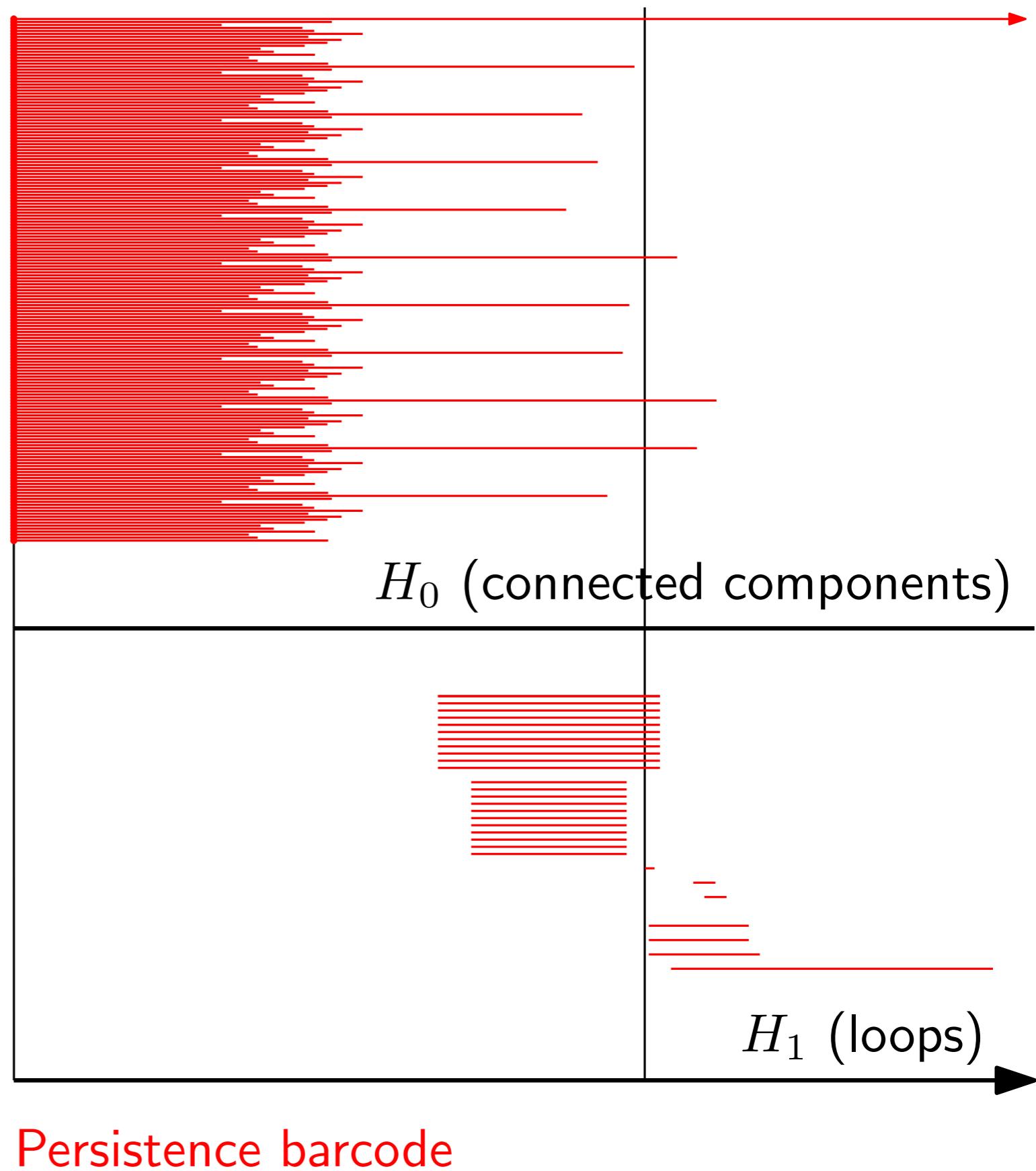
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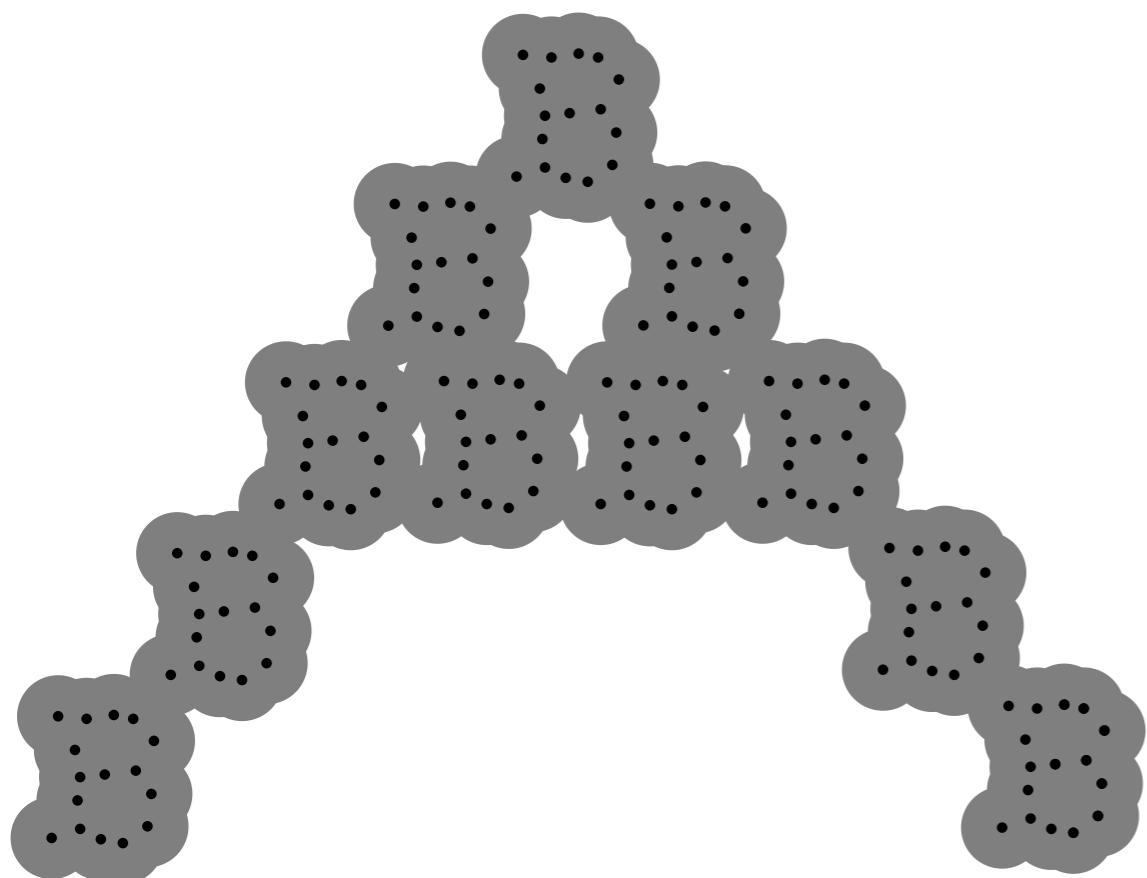
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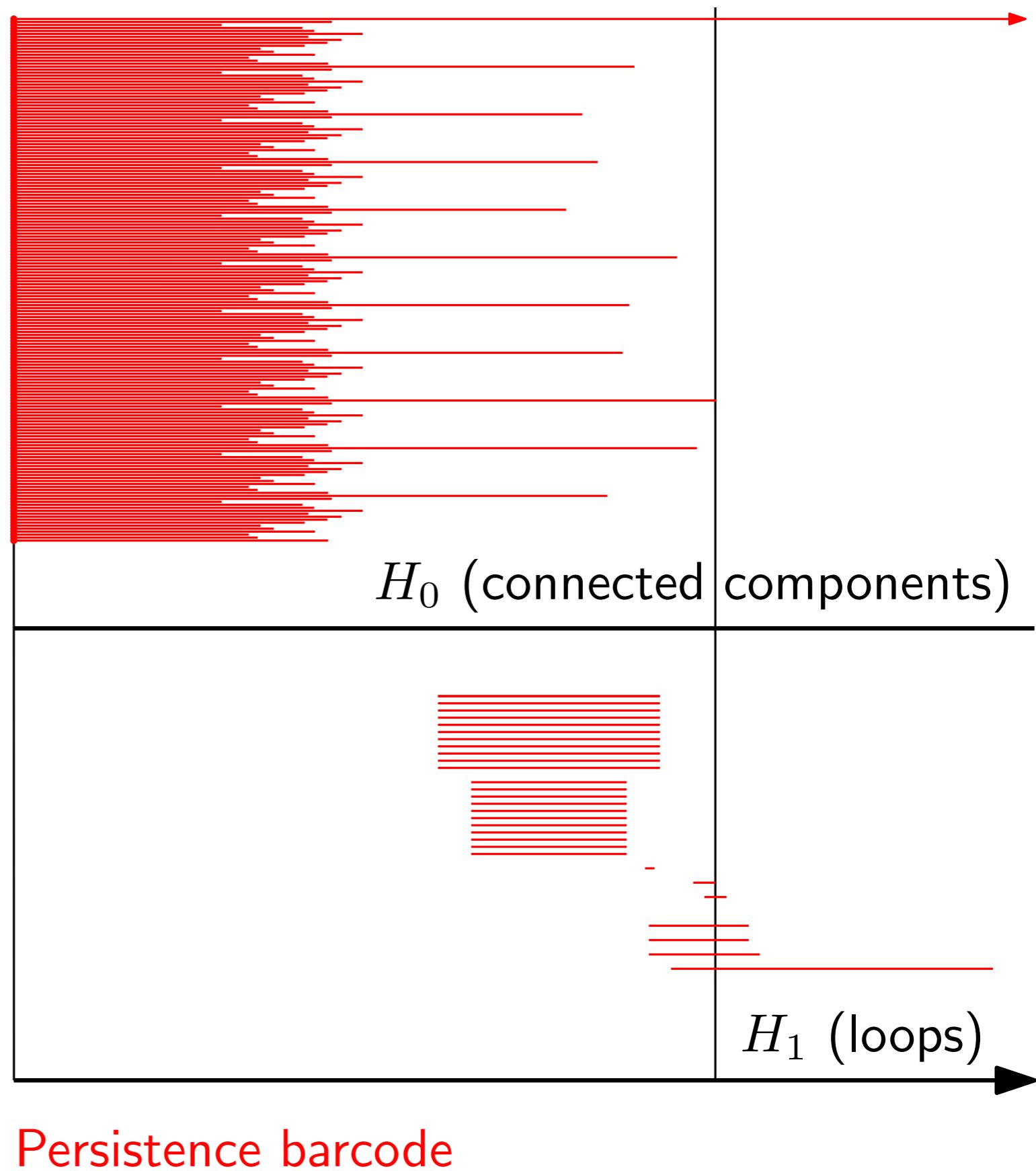
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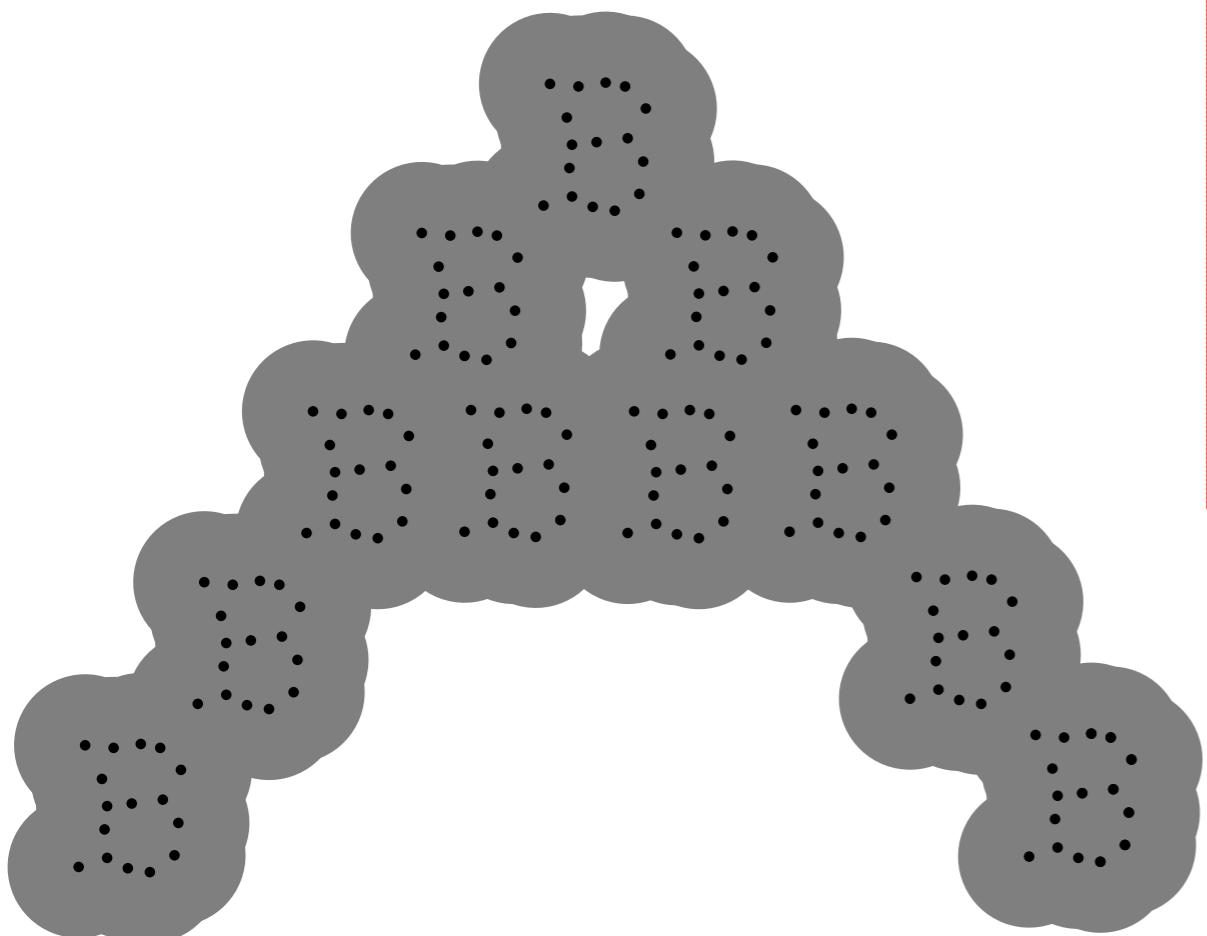
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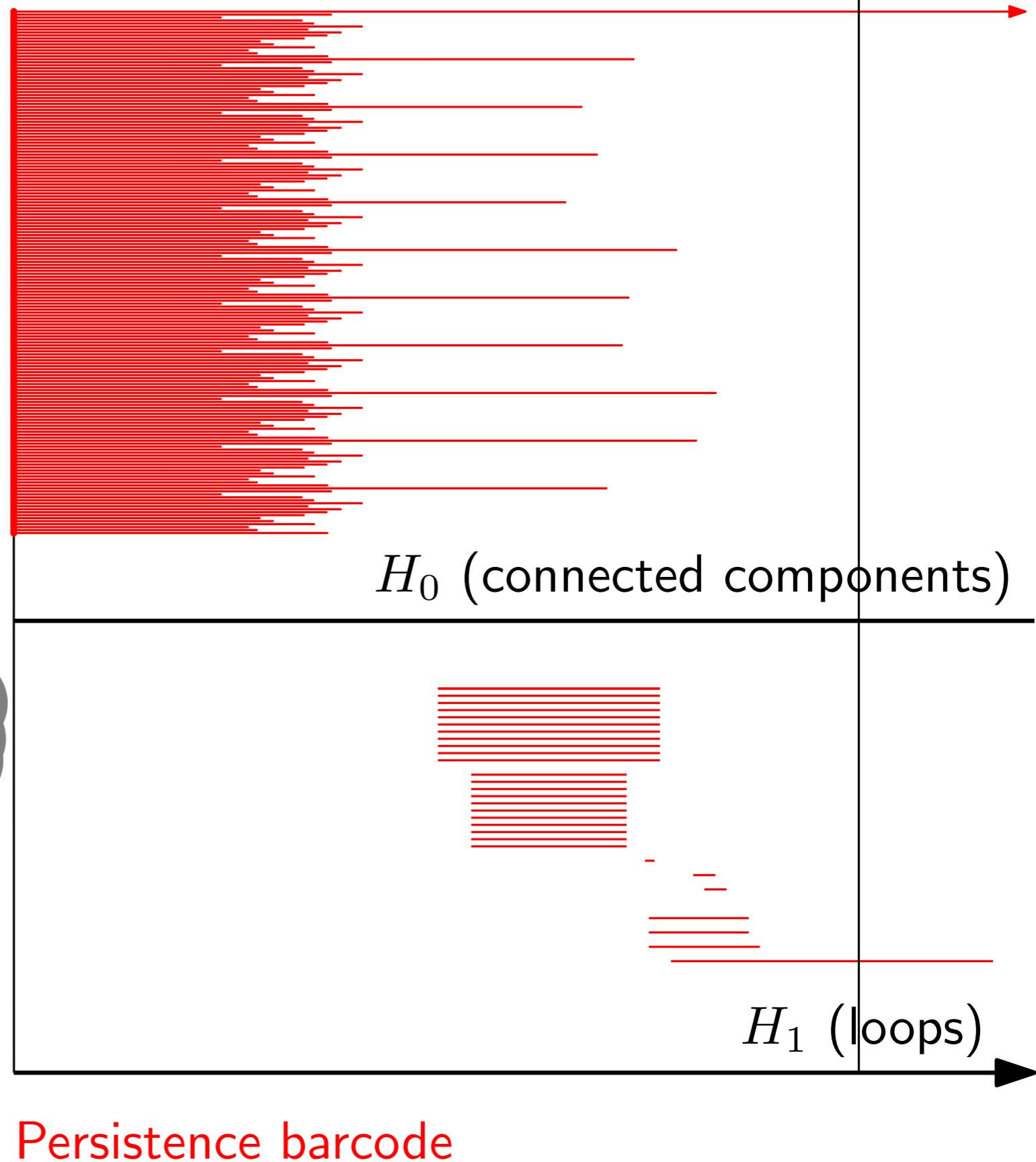
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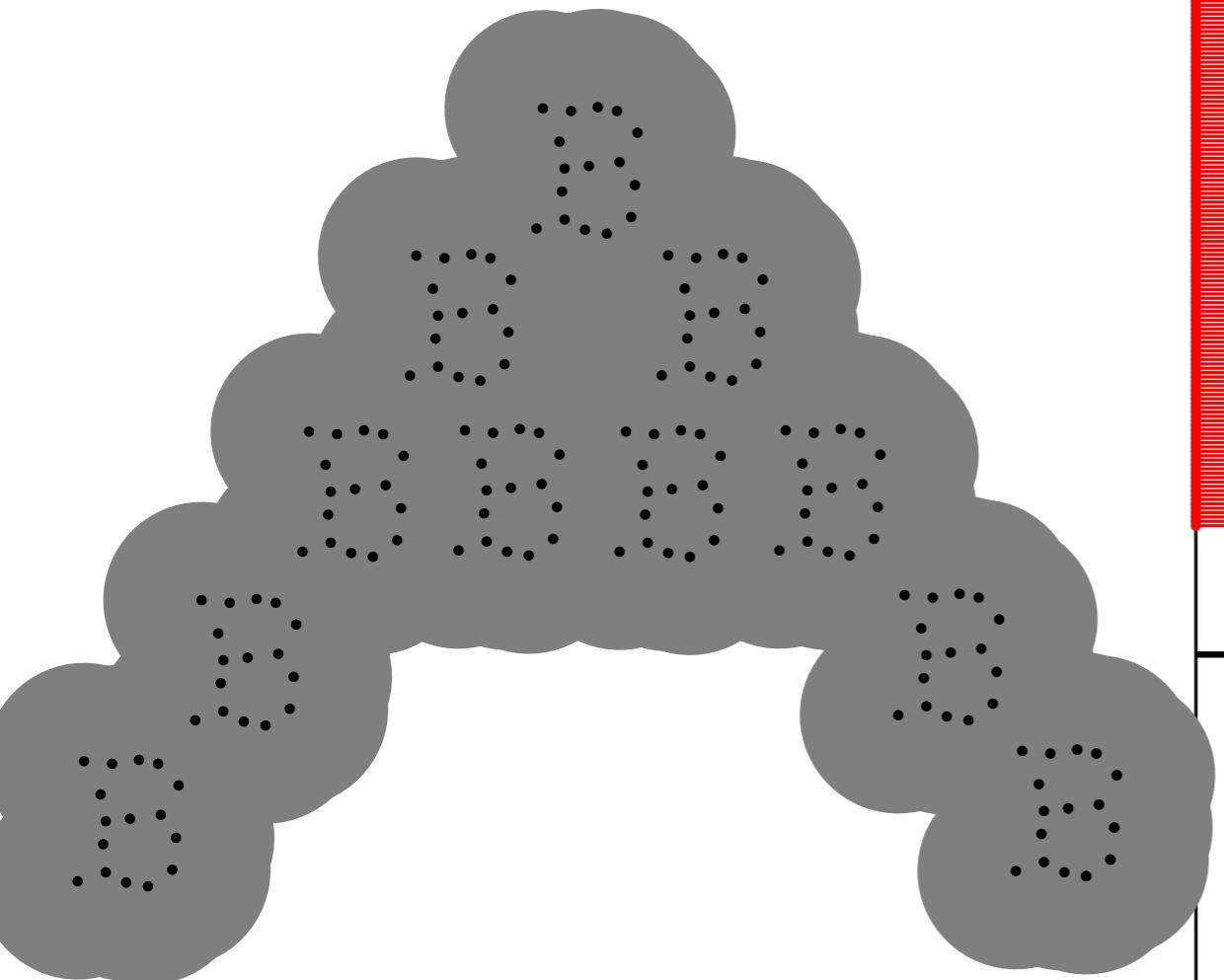
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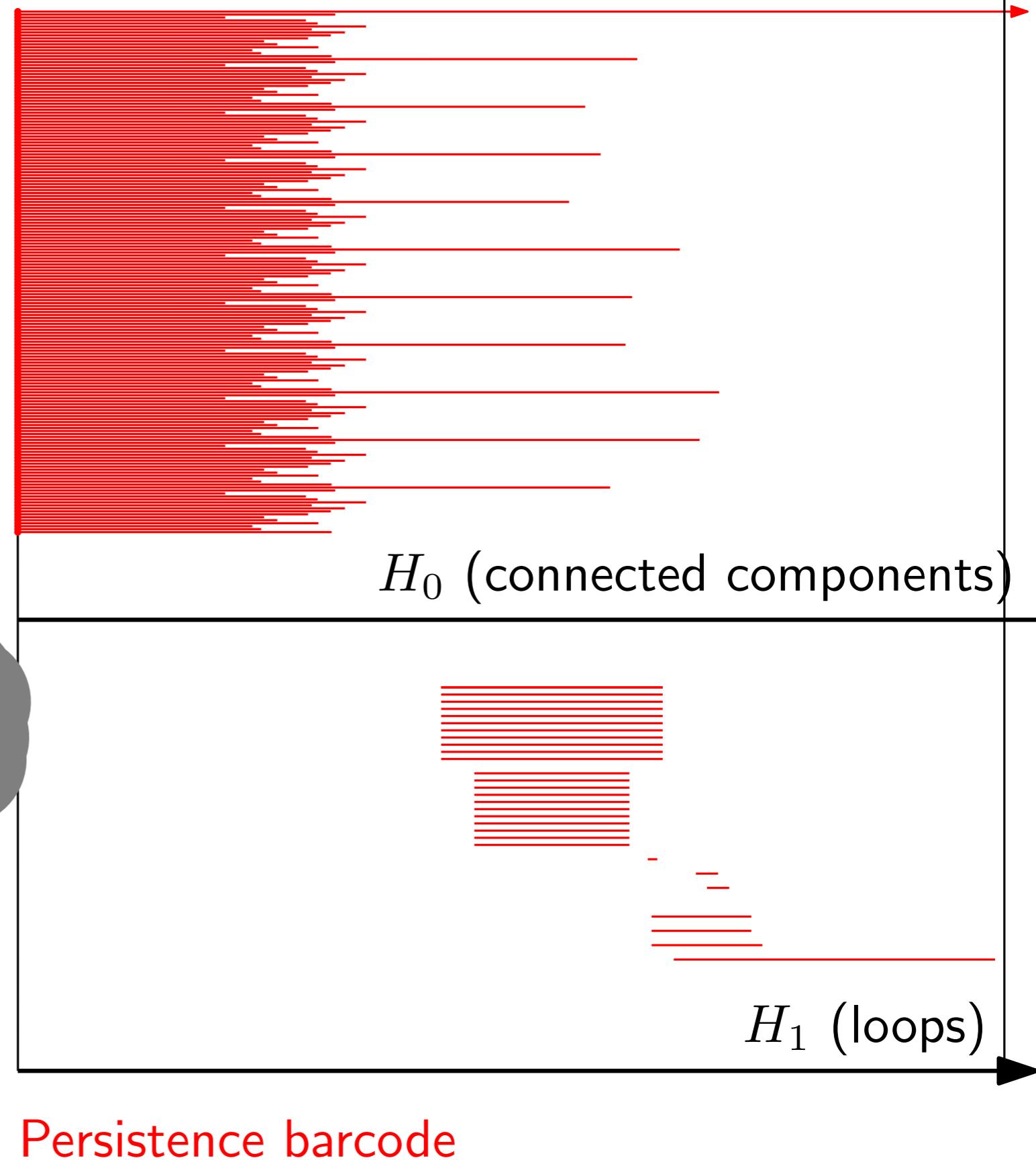
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$\check{\text{C}}$ ech and (Vietoris)-Rips complexes

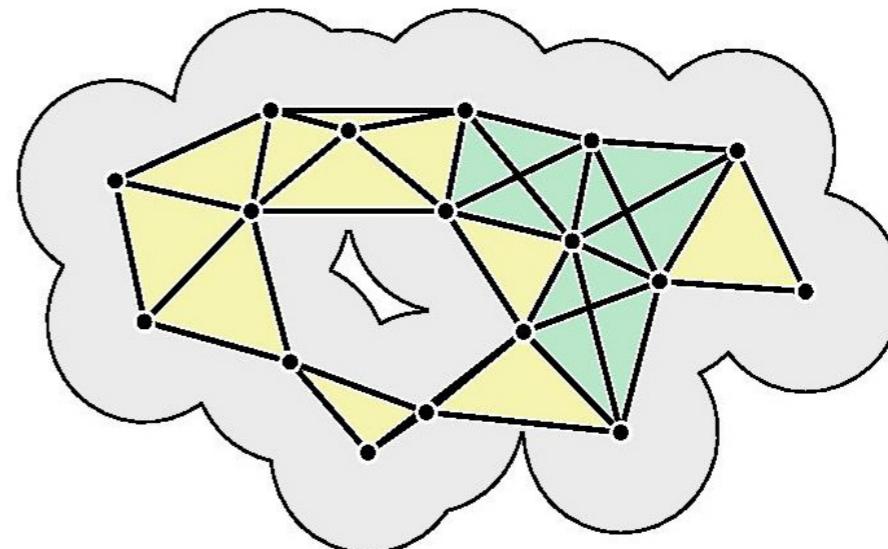
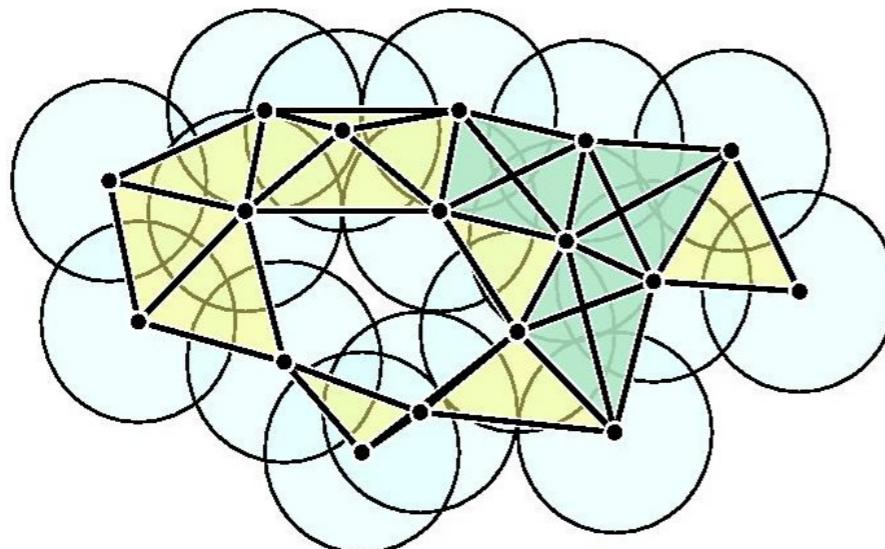
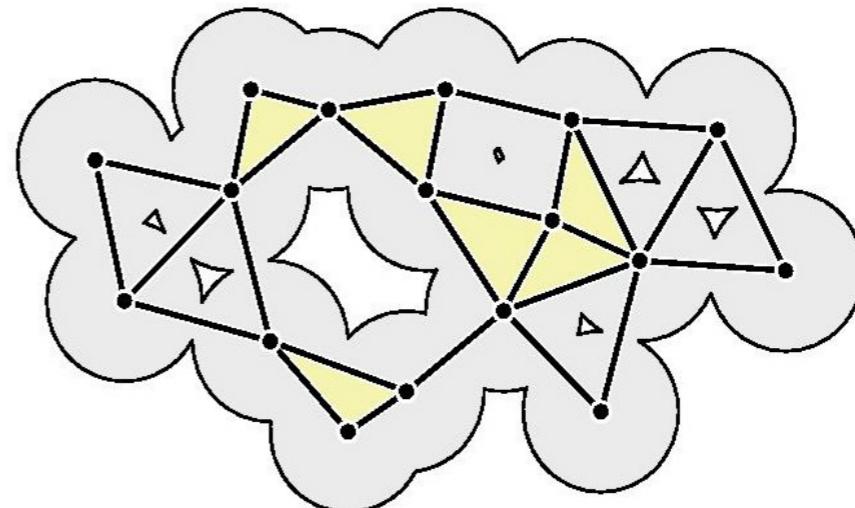
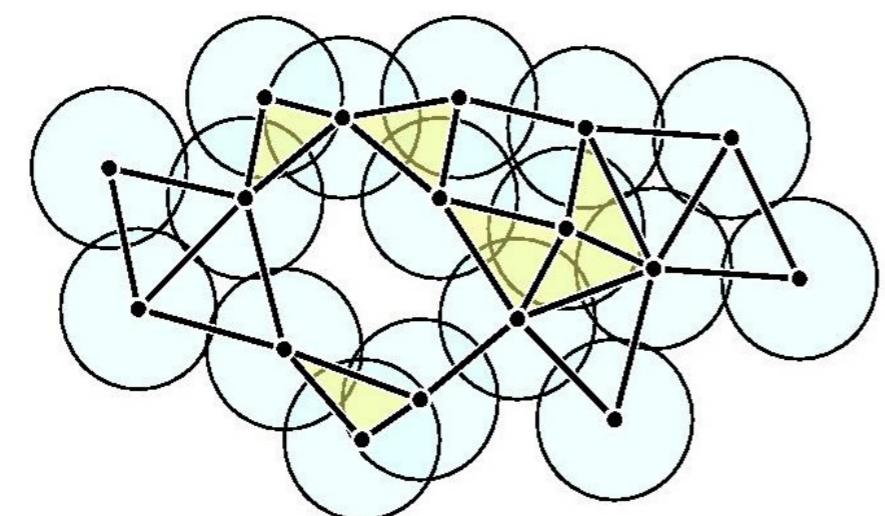
Def: Given a point cloud $P = \{P_1, \dots, P_n\} \subset \mathbb{R}^d$, its $\check{\text{C}}$ ech complex of radius $r > 0$ is the abstract simplicial complex $C(P, r)$ s.t. $\text{vert}(C(P, r)) = P$ and

$$\sigma = [P_{i_0}, P_{i_1}, \dots, P_{i_k}] \in C(P, r) \quad \text{iif} \quad \cap_{j=0}^k B(P_{i_j}, r) \neq \emptyset.$$

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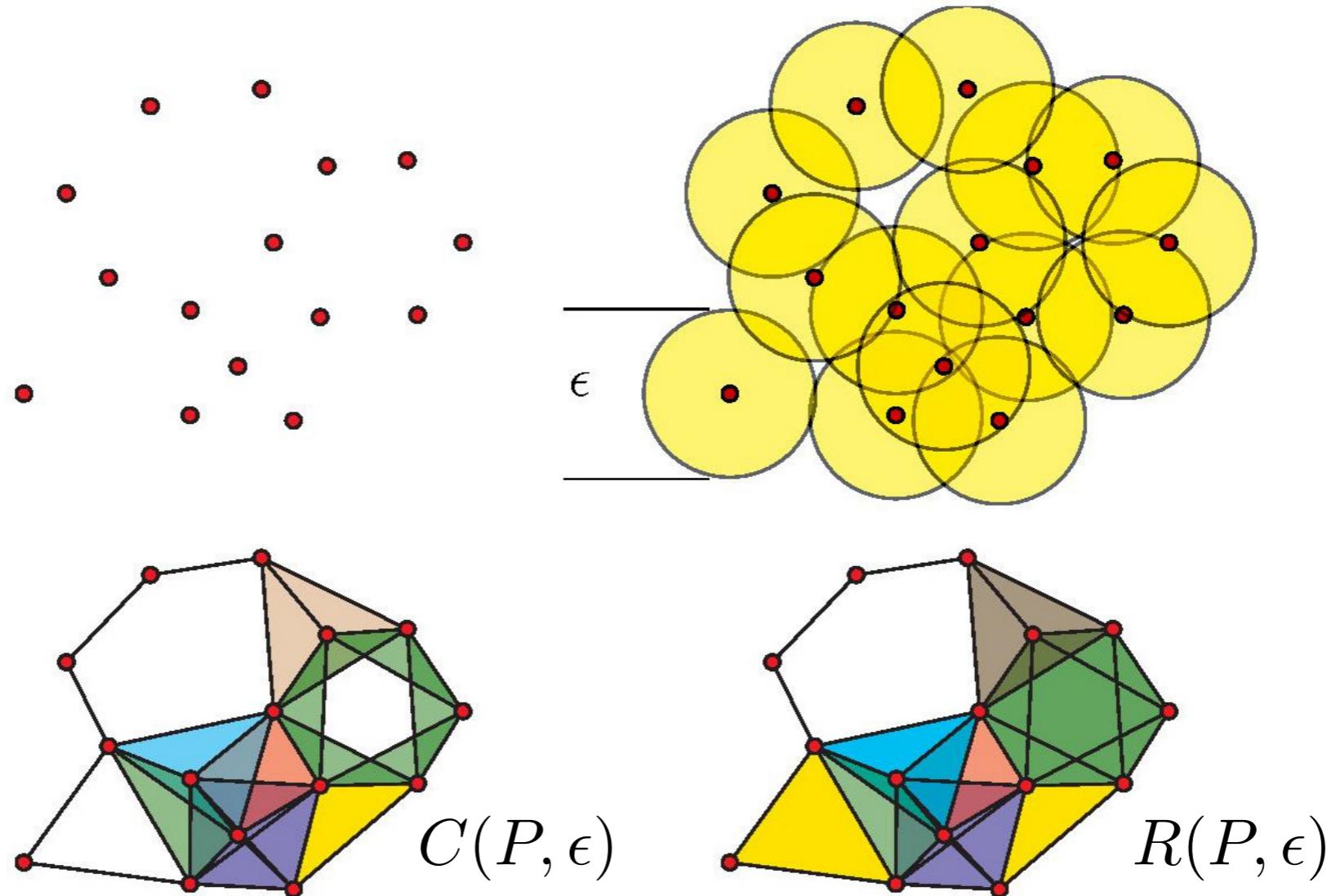
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Remark: The 1-skeleton $\text{Skel}_1(R(P, r))$ of a Rips complex of radius r is also called the r -neighborhood graph of P .

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Good news is that Rips and $\check{\text{C}}$ ech complexes are related:

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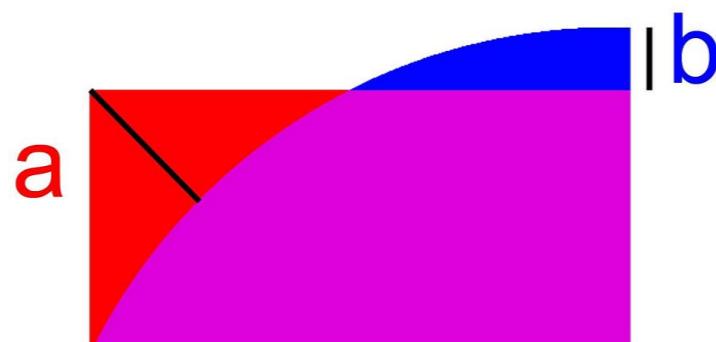
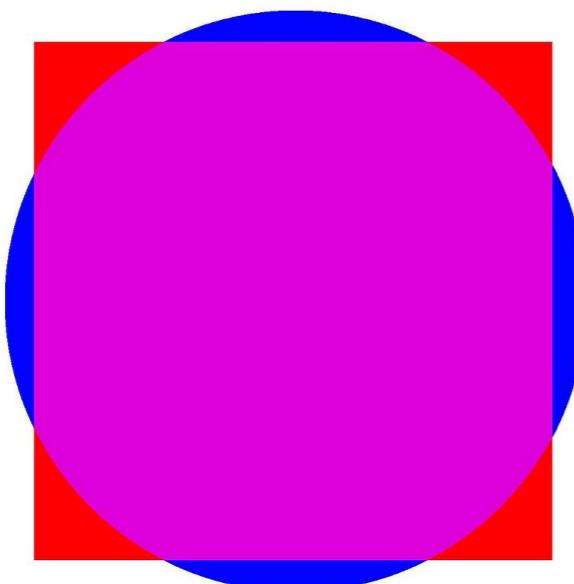
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Prop: $R(P, r/2) \subseteq C(P, r) \subseteq R(P, r)$.

Stability properties for point clouds

Def: The **Hausdorff distance** between two subspaces X, Y of a common metric space (Z, d) is:

$$\begin{aligned} d_H(X, Y) &= \max\{\sup_{y \in Y} d(y, X), \sup_{x \in X} d(x, Y)\} \\ &= \max\{\sup_{y \in Y} \inf_{x \in X} d(y, x), \sup_{x \in X} \inf_{y \in Y} d(x, y)\} \end{aligned}$$



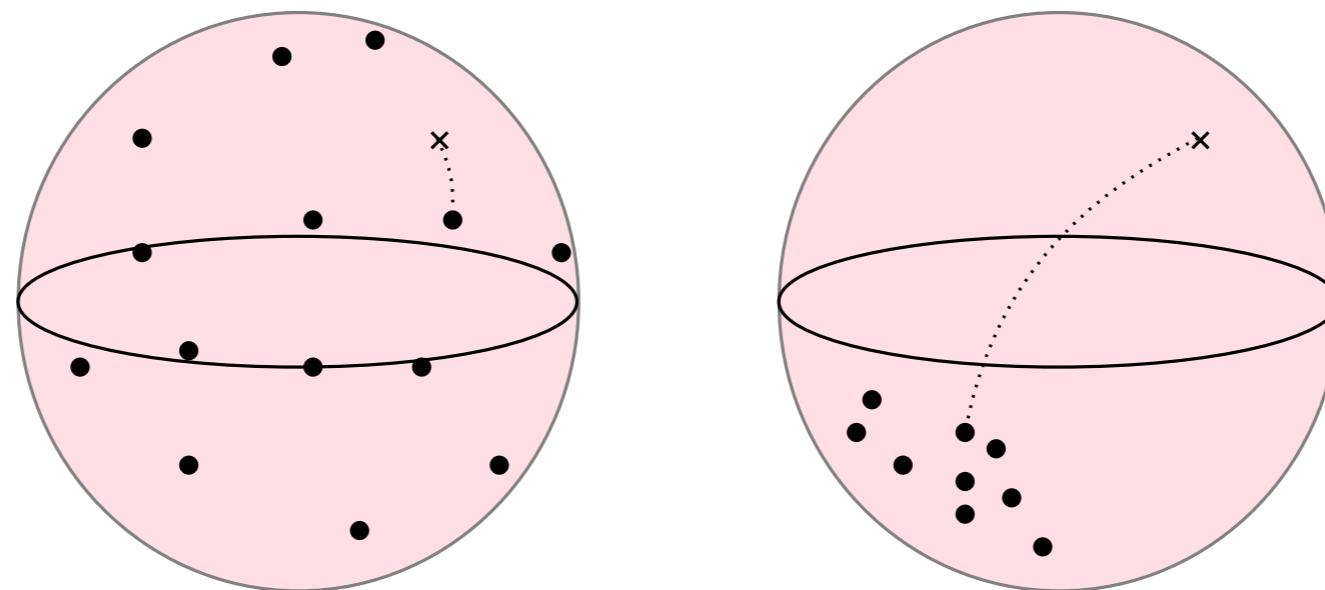
$$d_H(X, Y) = \max\{a, b\}$$

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Ex: Given a sampling $\hat{X}_n \subseteq X$, $d_H(\hat{X}_n, X)$ is a measure of sampling quality.



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Def: The **Gromov-Hausdorff distance** between metric spaces $(X, d_X), (Y, d_Y)$ is the Hausdorff distance of the best common isometric embedding:

$$d_{GH}((X, d_X), (Y, d_Y)) = \inf_{\gamma} d_H(\gamma(X), \gamma(Y)),$$

where $d(\gamma(x), \gamma(x')) = d_X(x, x')$ and $d(\gamma(y), \gamma(y')) = d_X(y, y')$.

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where $\mathcal{C} \subseteq X \times Y$ s.t. $\forall x, \exists y_x \in Y$ s.t. $(x, y_x) \in \mathcal{C}$ (and vice-versa).

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Thm: If X and Y are common subspaces of a common metric space (Z, d) , then

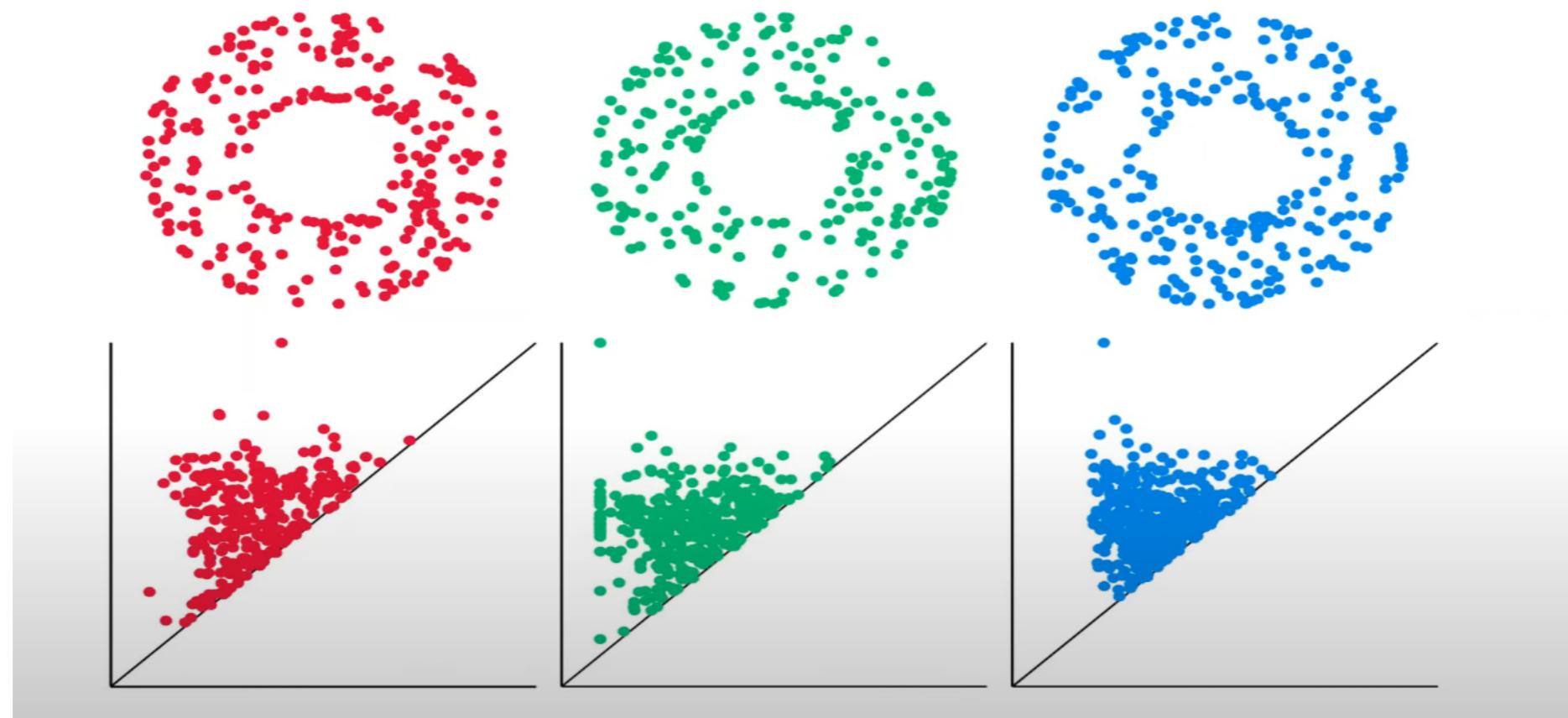
$$d_b(D_{\text{Cech}}(X), D_{\text{Cech}}(Y)) \leq d_H(X, Y).$$

Stability properties for point clouds

[*Persistence stability for geometric complexes*, Chazal, de Silva, Oudot, Geom. Dedicata, 2013].

Thm: If X and Y are pre-compact metric spaces, then

$$d_b(D_{\text{Rips}}(X), D_{\text{Rips}}(Y)) \leq d_{GH}(X, Y).$$



Rem: This result also holds for Čech and other families of filtrations (particular case of a more general theorem).

Representations of Persistence Diagrams

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Q: Persistence diagrams are **not** Euclidean vectors? How can one compute Pearson correlation between marker gene expression and persistence diagrams?

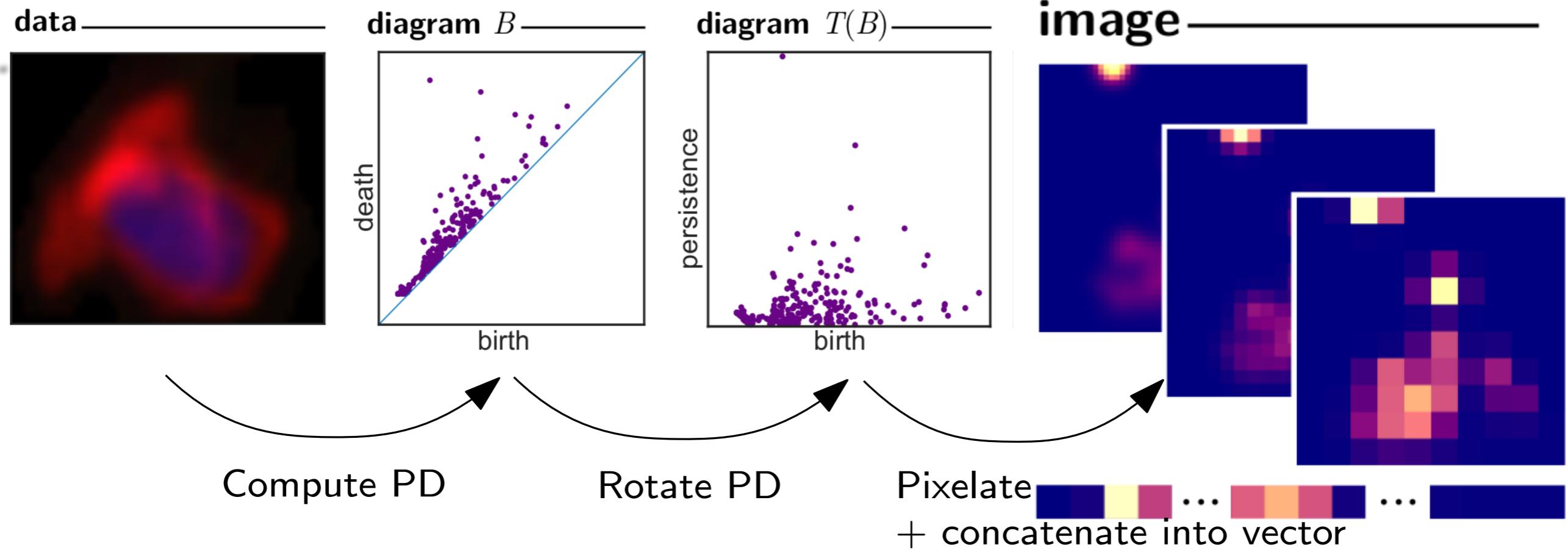
Representations of Persistence Diagrams

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A: Use **representations**, which are mappings $\Phi : \mathcal{D} \rightarrow \mathcal{H}$ from the space of persistence diagrams to Hilbert spaces.

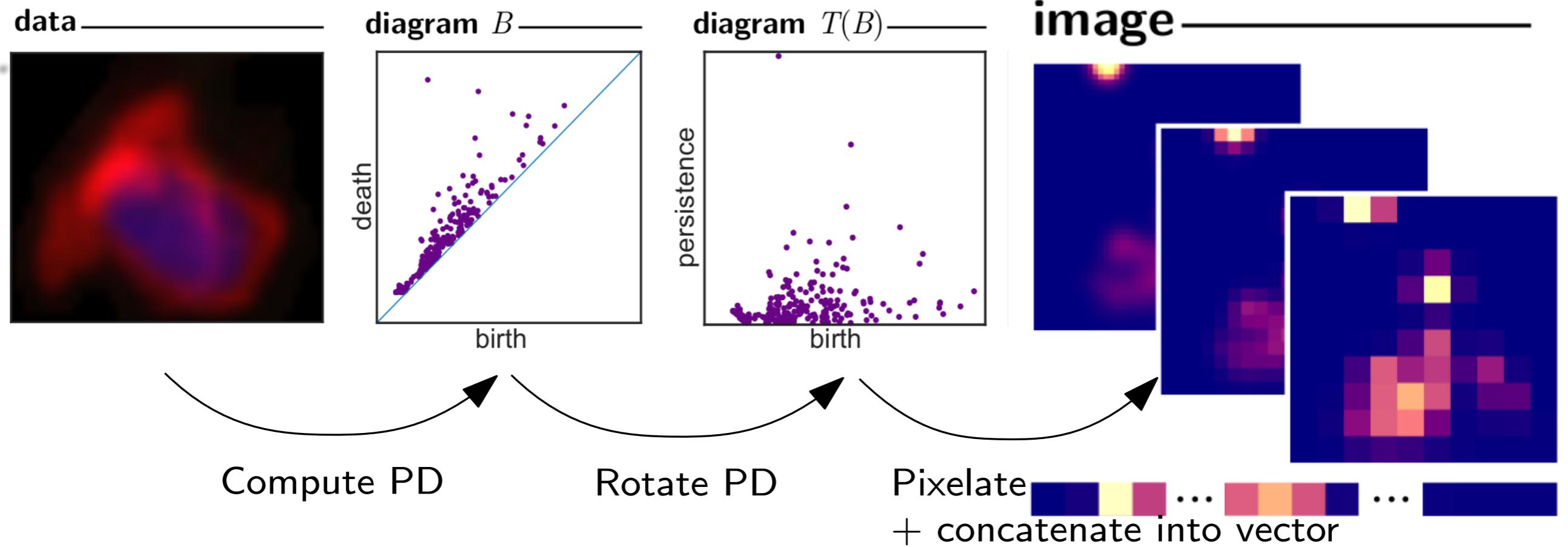
Persistence image

[*Persistence Images: A Stable Vector Representation of Persistent Homology*, Adams et al., JMLR, 2017]

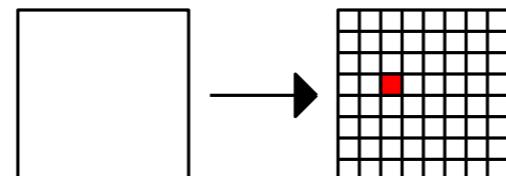


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Discretize plane into a grid:



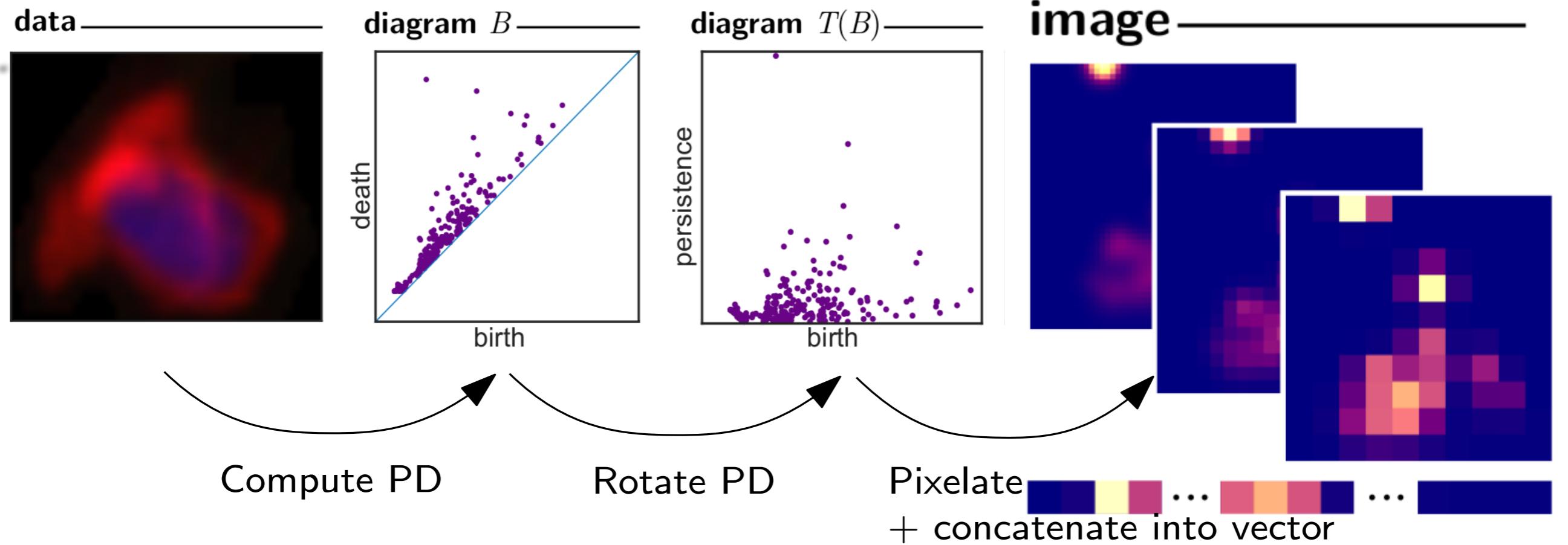
For each grid pixel P , compute $I(P) = \sum_{p \in D} \int \int_P w(p) \cdot \phi_p$.

Concatenate all $I(P)$ into a single vector $\text{PI}(D)$.

Ex: $\phi_p = \mathcal{N}(p, \sigma)$.

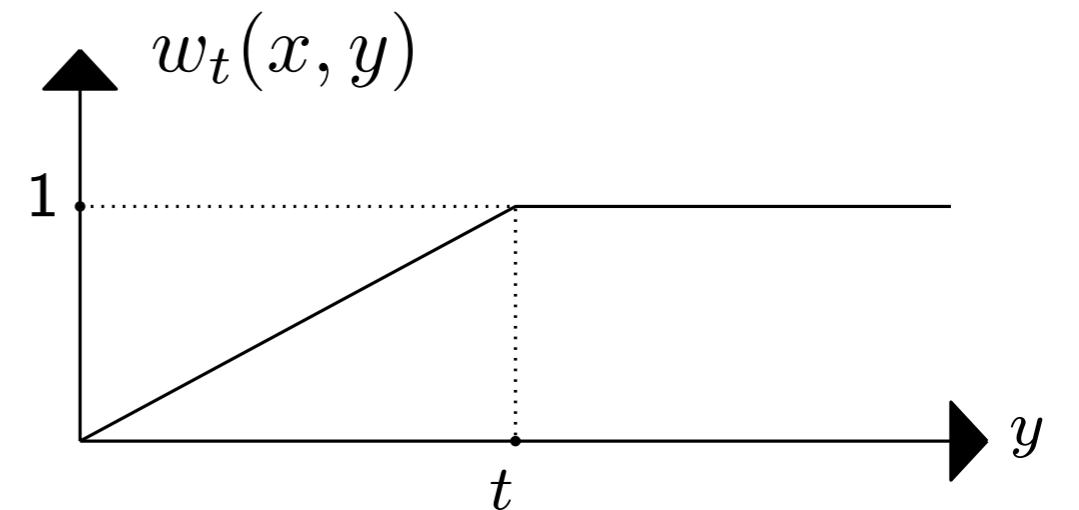
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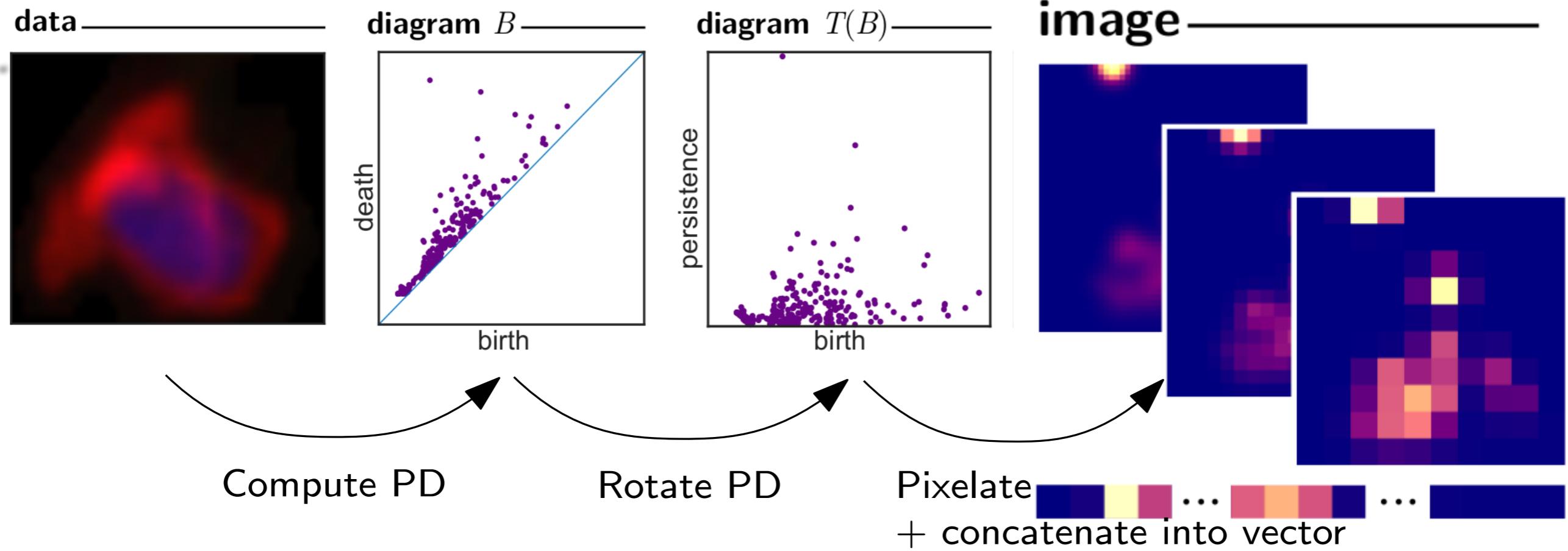
Weight functions that preserve stability must satisfy $w(p) \rightarrow 0$ when $d(p, \Delta) \rightarrow 0$.

[*Understanding the topology and the geometry of the persistence diagram space via optimal partial transport*, Divol, Lacombe, JACT, 2020]



Persistence image

[*Persistence Images: A Stable Vector Representation of Persistent Homology*, Adams et al., JMLR, 2017]

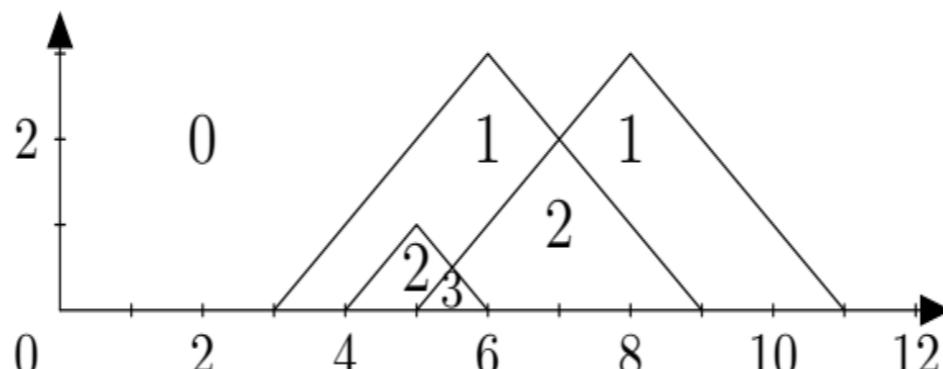
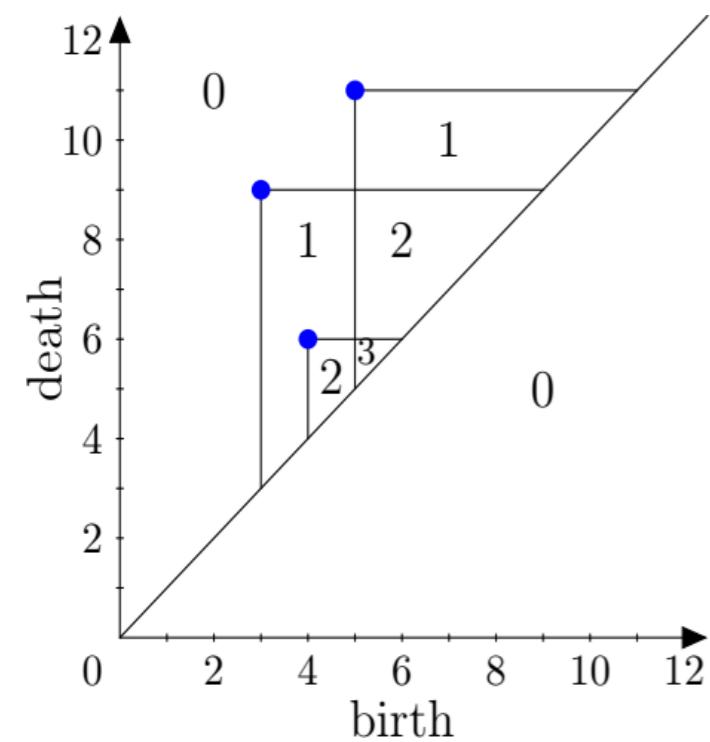


Prop: The following inequalities hold:

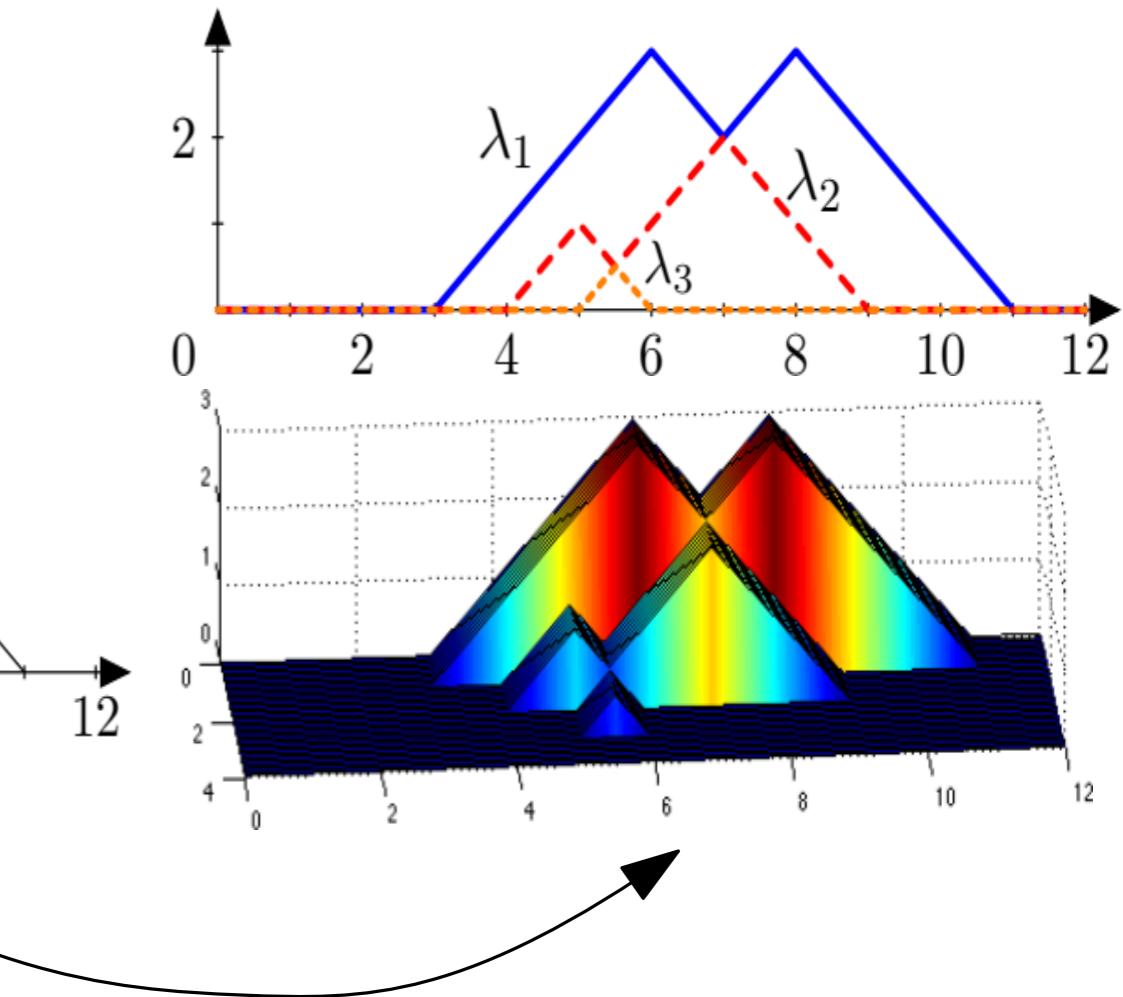
- $\|\text{PI}(D) - \text{PI}(D')\|_\infty \leq C(w, \phi_p) d_1(D, D').$
- $\|\text{PI}(D) - \text{PI}(D')\|_2 \leq \sqrt{d} \cdot C(w, \phi_p) d_1(D, D').$

Persistence landscape

[Statistical Topological Data Analysis using Persistence Landscapes, Bubenik, JMLR, 2015]



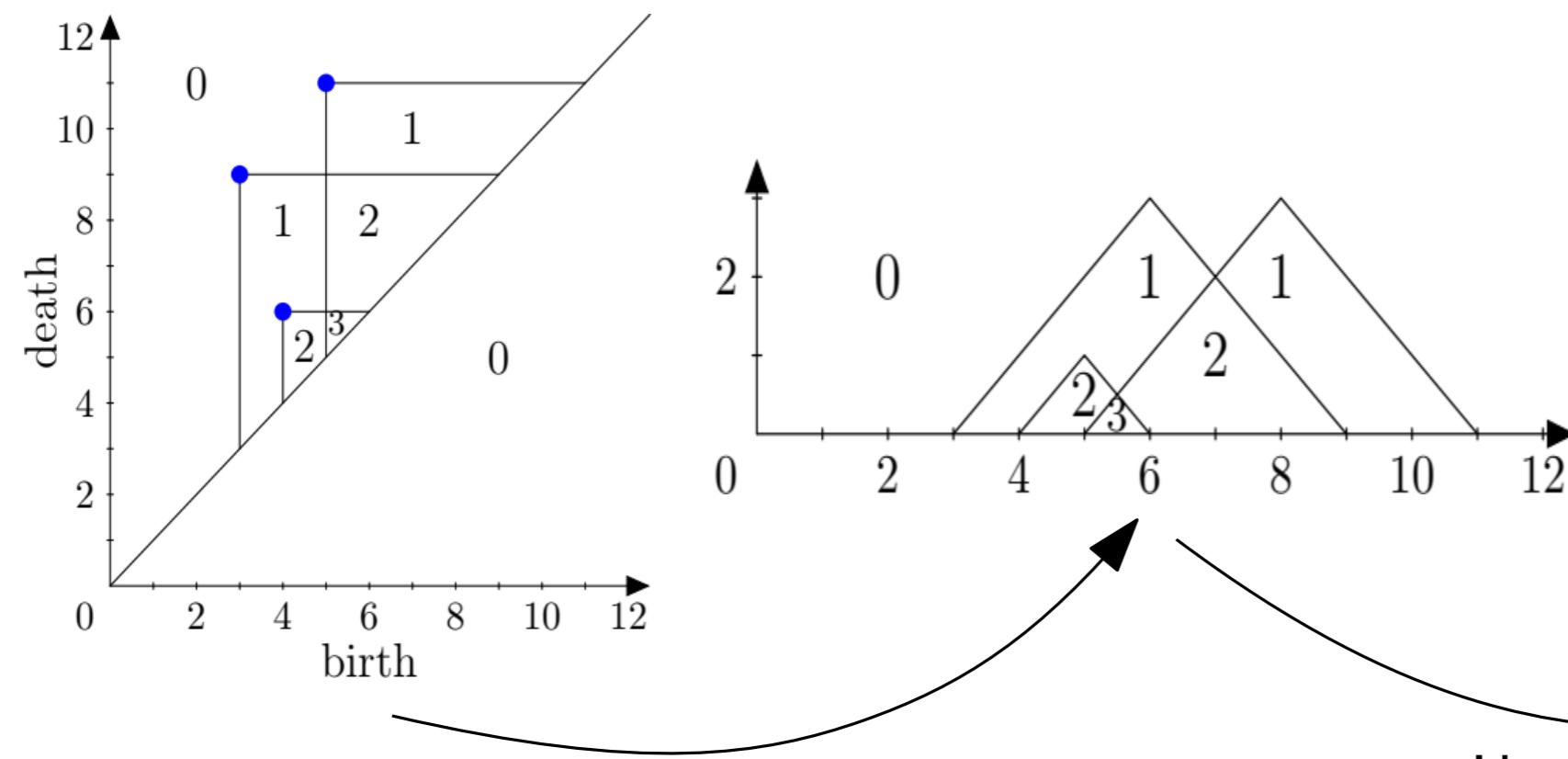
Rotate PD
Compute rank function



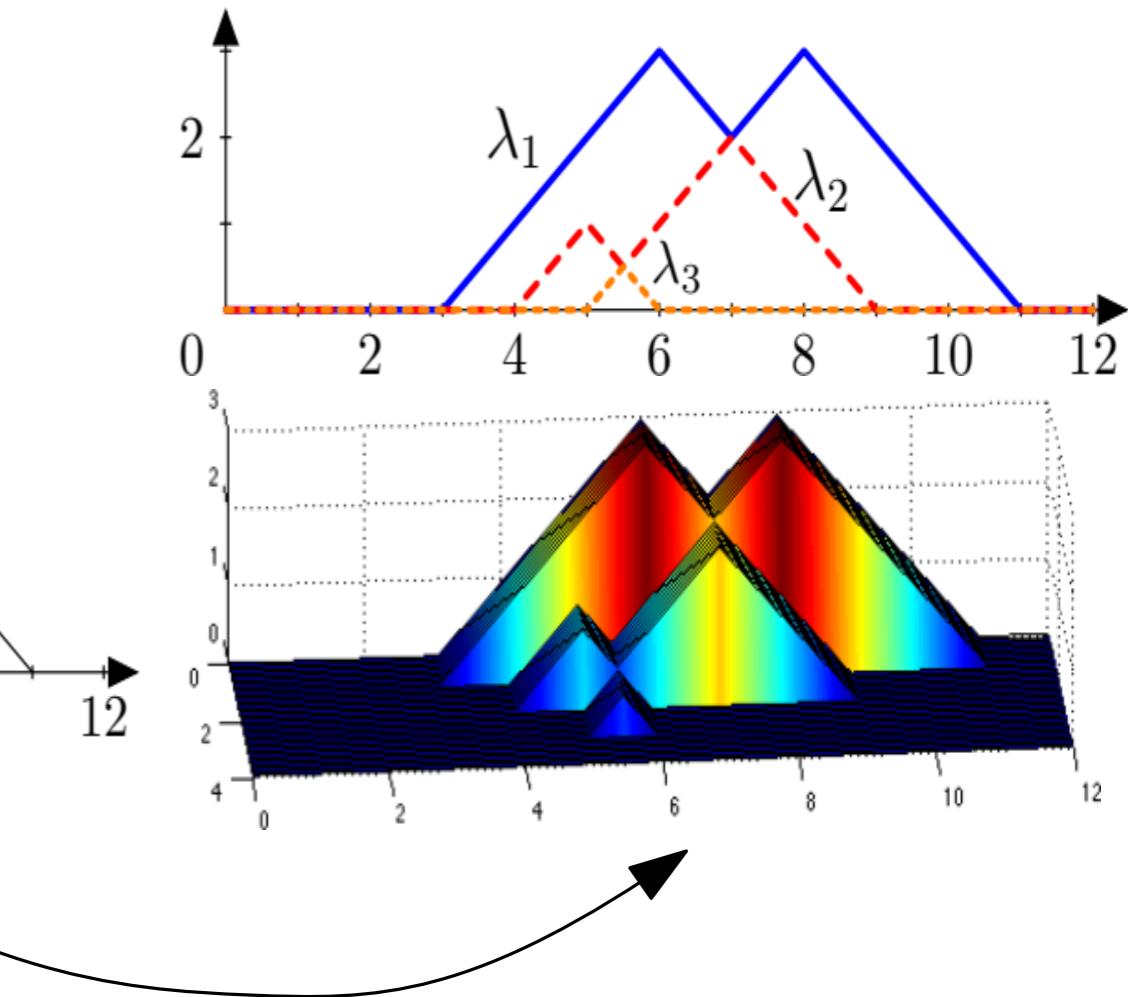
Use boundaries of
rank function

Persistence landscape

[Statistical Topological Data Analysis using Persistence Landscapes, Bubenik, JMLR, 2015]



Rotate PD
Compute rank function



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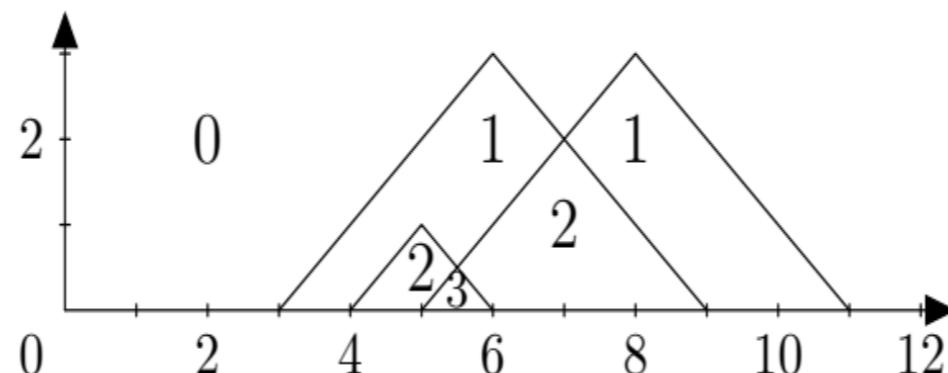
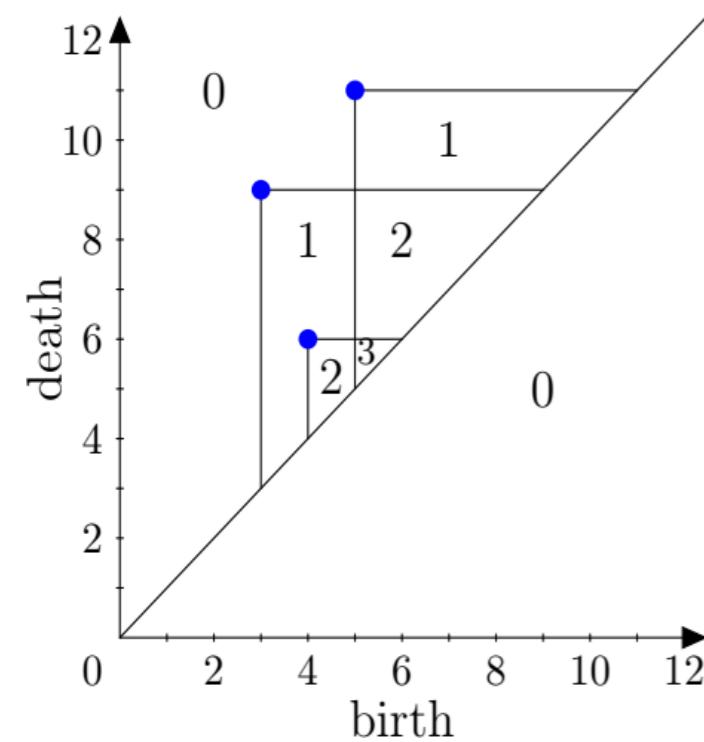
$$x \leq y \implies f^{-1}(-\infty, x) \subseteq f^{-1}(-\infty, y)$$

$\iota_x^y : H(f^{-1}(-\infty, x)) \rightarrow H(f^{-1}(-\infty, y))$ induced linear map

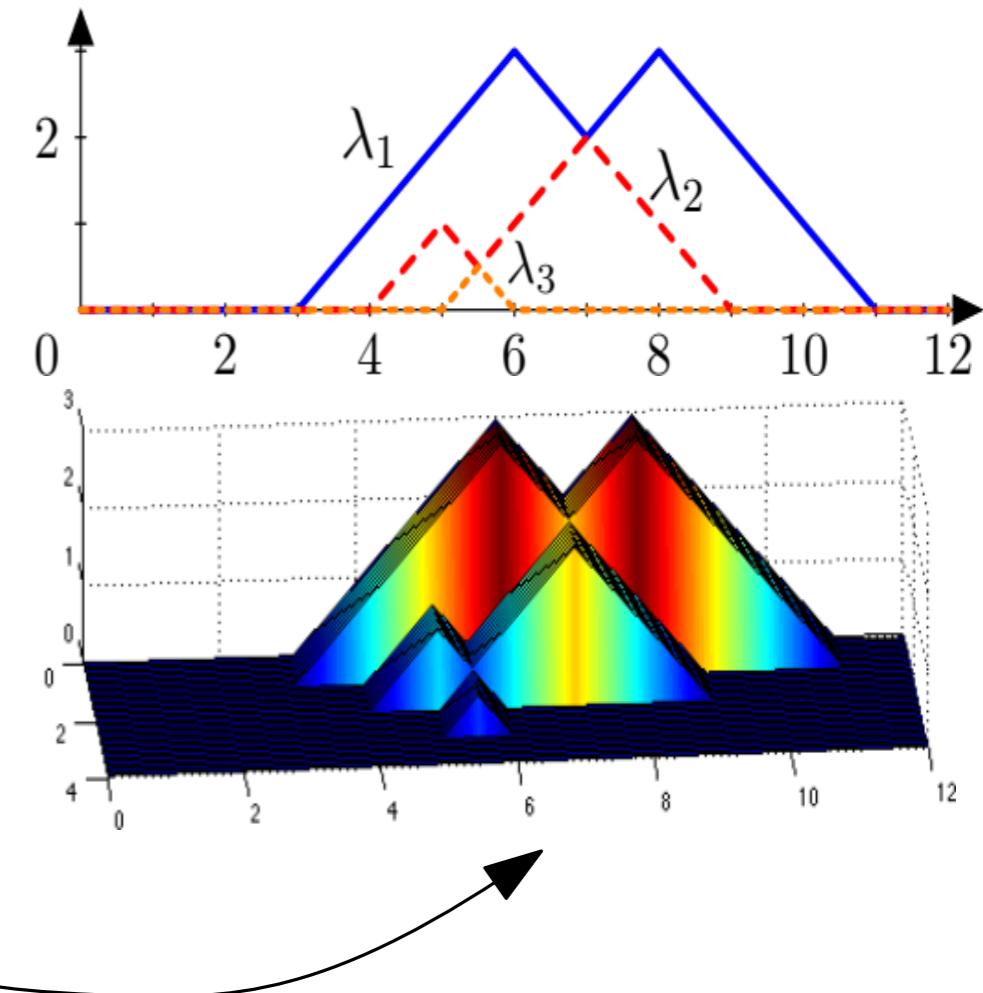
Rank function is defined as $\lambda(x, y) = \text{rank } \iota_x^y$

Persistence landscape

[Statistical Topological Data Analysis using Persistence Landscapes, Bubenik, JMLR, 2015]



Rotate PD
Compute rank function



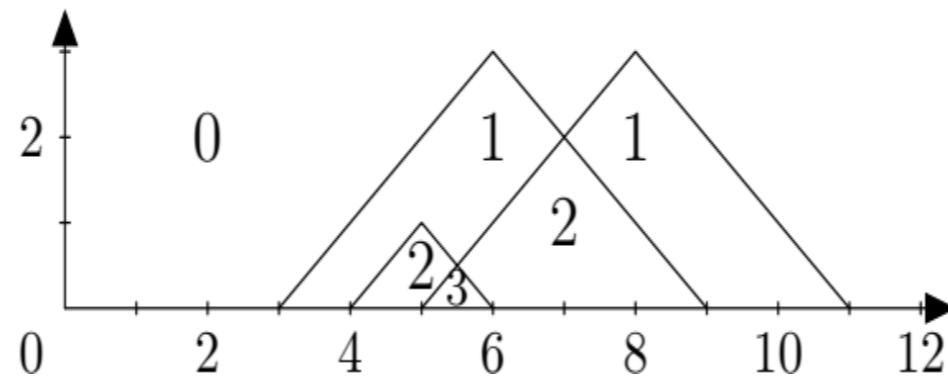
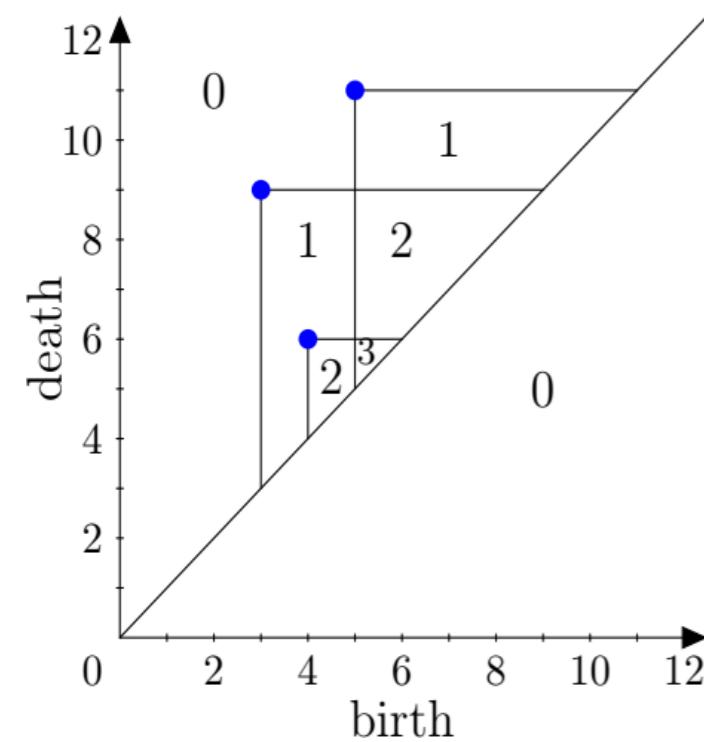
Boundaries of rank function: $\lambda_i(t) = \sup\{s \geq 0 : \lambda(t-s, t+s) \geq i\}$

Landscape $\Lambda : \mathbb{R}^2 \rightarrow \mathbb{R}$ is defined as: $\Lambda(i, t) = \lambda_{[i]}(t)$

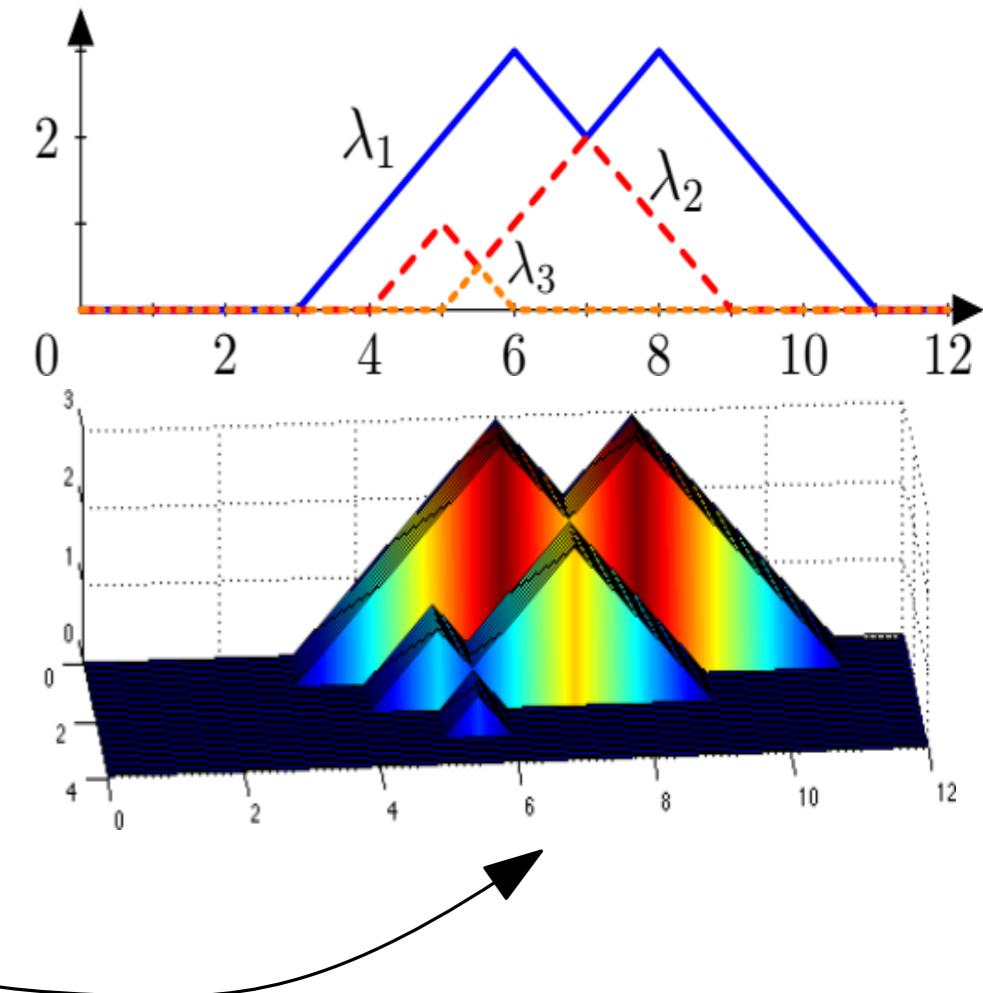
They can equivalently be defined as: $\Lambda(i, t) = i\text{-th } \max\{\lambda_j(t)\}$

Persistence landscape

[Statistical Topological Data Analysis using Persistence Landscapes, Bubenik, JMLR, 2015]



Rotate PD
Compute rank function



Use boundaries of
rank function

Prop: The following inequalities hold:

- $\|\Lambda(D) - \Lambda(D')\|_\infty \leq d_b(D, D').$
- $\min\{1, C(D, D')\} \|\Lambda(D) - \Lambda(D')\|_2 \leq d_2(D, D').$

The Deep Set architecture

[*Deep Sets*, Zaheer, Kottur, Ravanbakhsh, Poczos, Salakhutdinov, Smola, NeurIPS, 2017]

Deep Set is a novel neural net architecture that is able to handle sets instead of finite dimensional vectors

Input: $\{x_1, \dots, x_n\} \subset \mathbb{R}^d$ instead of $x \in \mathbb{R}^d$

The Deep Set architecture

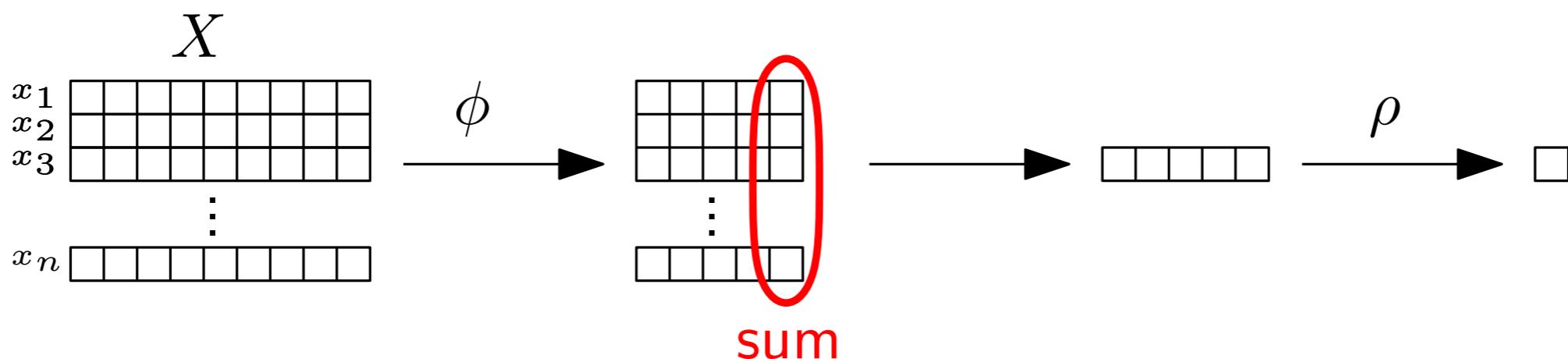
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Deep Set is a novel neural net architecture that is able to handle sets instead of finite dimensional vectors

Input: $\{x_1, \dots, x_n\} \subset \mathbb{R}^d$ instead of $x \in \mathbb{R}^d$

Network is *permutation invariant*: $F(X) = \rho(\sum_i \phi(x_i))$

$$\Rightarrow F(\{x_1, \dots, x_n\}) = F(\{x_{\sigma(1)}, \dots, x_{\sigma(n)}\}), \forall \sigma$$



In practice: $\phi(x_i) = W \cdot x_i + b$

The Deep Set architecture

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Universality theorem

Thm: A function f is permutation invariant iif $f(X) = \rho(\sum_i \phi(x_i))$ for some ρ and ϕ , whenever X is included in a *countable* space.

Application to PDs

Application to PDs

Permutation invariant layers generalize several TDA approaches

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Permutation invariant layers generalize several TDA approaches

→ persistence images

Application to PDs

Permutation invariant layers generalize several TDA approaches

→ persistence images → landscapes

Application to PDs

Permutation invariant layers generalize several TDA approaches

→ persistence images → landscapes → Betti curves

[*Time Series Classification via Topological Data Analysis*, Umeda, Trans. Jap. Soc. for AI, 2017]

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But not all of them since \mathbb{R}^2 is not countable

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Using any permutation invariant operation (such as max, min, k th largest value) allows to generalize other TDA approaches

Application to PDs

[*PersLay: A Neural Network Layer for Persistence Diagrams and New Graph Topological Signatures*, C., Chazal, Ike, Lacombe, Royer, Umeda, AISTATS, 2019]

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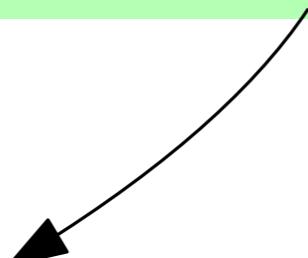
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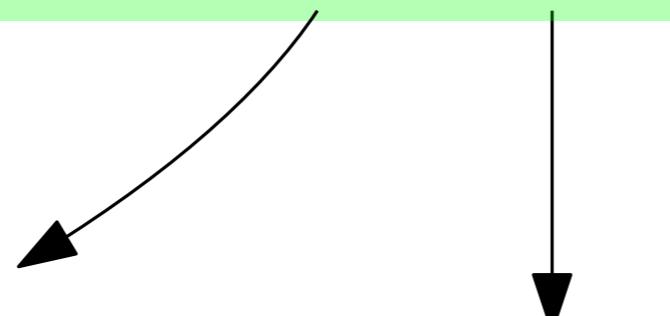
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Weight function

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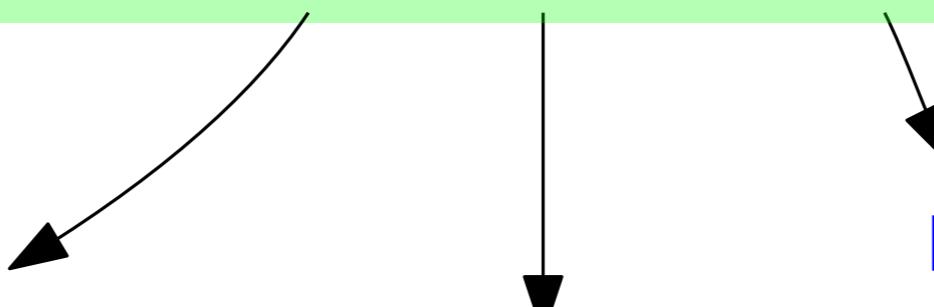
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Permutation-invariant
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Weight function

Point transformation

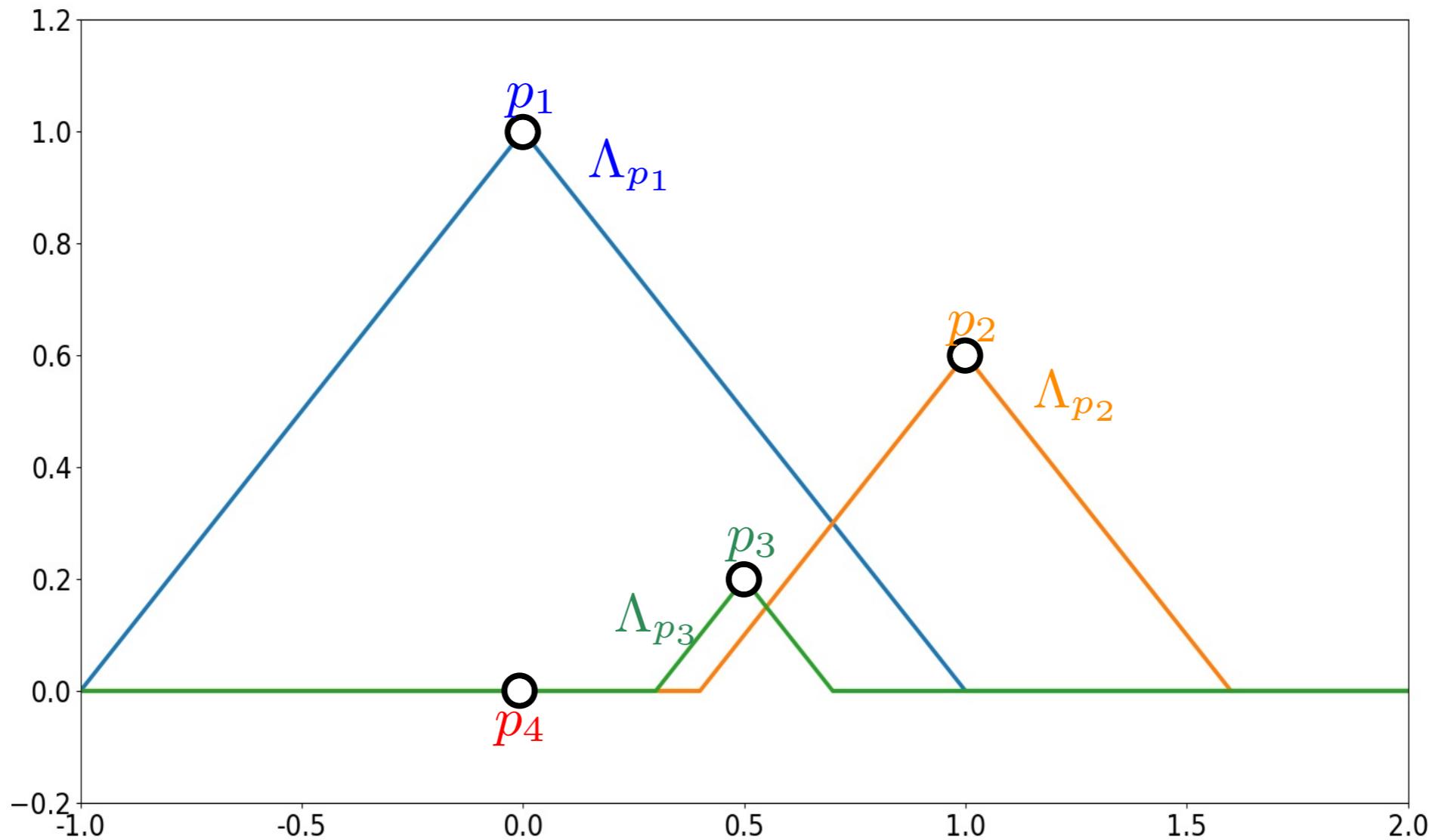
Application to PDs

[*PersLay: A Neural Network Layer for Persistence Diagrams and New Graph Topological Signatures*, C., Chazal, Ike, Lacombe, Royer, Umeda, AISTATS, 2019]

Parameters $t_1, \dots, t_q \in \mathbb{R}$

$$w(p) = 1$$

$$\phi_{\Lambda} : p \mapsto \begin{bmatrix} \Lambda_p(t_1) \\ \Lambda_p(t_2) \\ \vdots \\ \Lambda_p(t_q) \end{bmatrix} \quad \text{op} = \text{top-}k$$



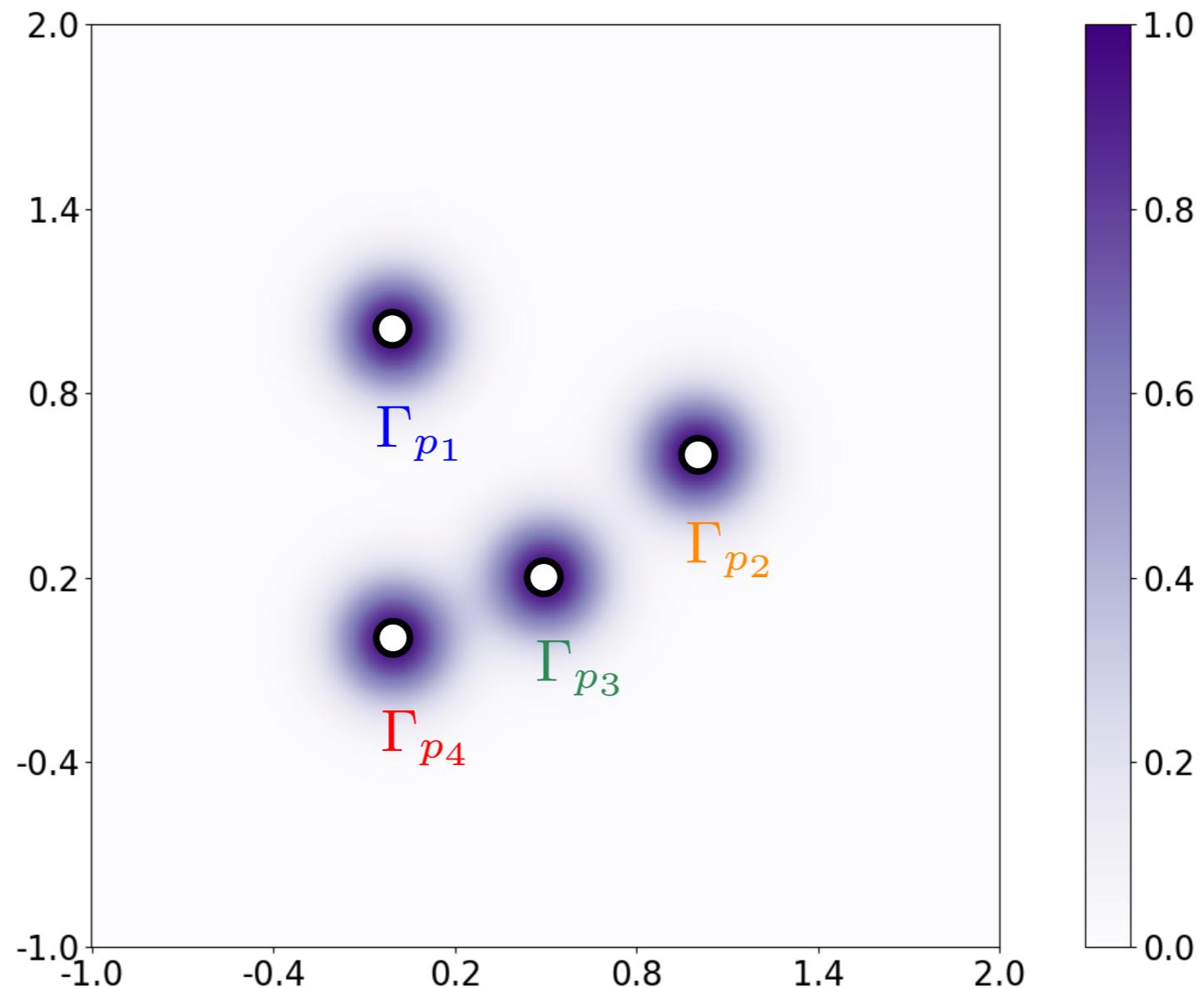
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Parameters $t_1, \dots, t_q \in \mathbb{R}^2$

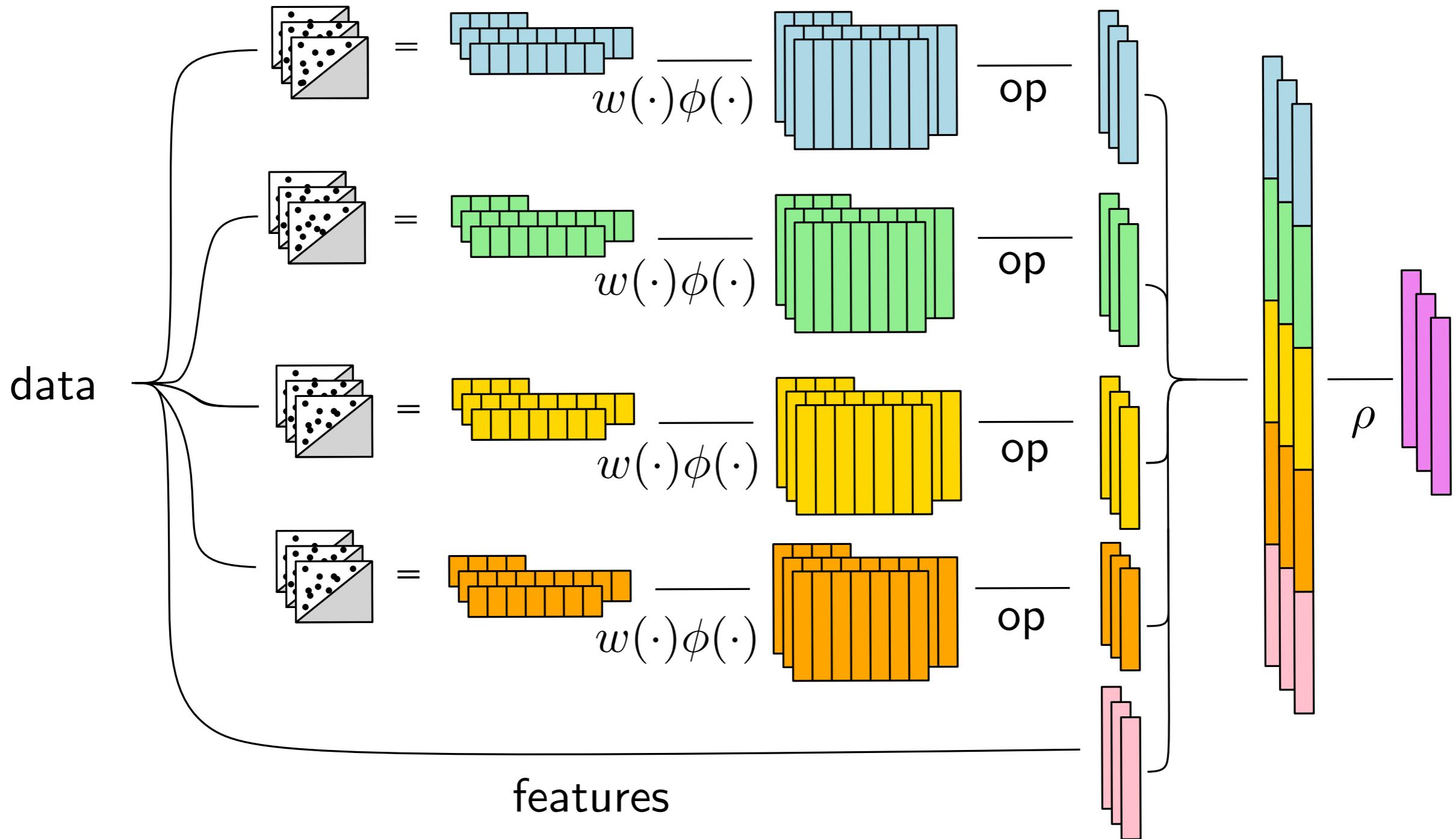
$$w(p) = w_t((x, y))$$

$$\phi_{\Gamma} : p \mapsto \begin{bmatrix} \Gamma_p(t_1) \\ \Gamma_p(t_2) \\ \vdots \\ \Gamma_p(t_q) \end{bmatrix} \quad \text{op} = \text{sum}$$



Application to PDs

[*PersLay: A Neural Network Layer for Persistence Diagrams and New Graph Topological Signatures*, C., Chazal, Ike, Lacombe, Royer, Umeda, AISTATS, 2019]



Application to graph classification

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Let $G = (V, E)$ be a graph, A its adjacency matrix

D its degree matrix

and $L_w(G) = I - D^{-1/2}AD^{-1/2}$ its normalized Laplacian.

Application to graph classification

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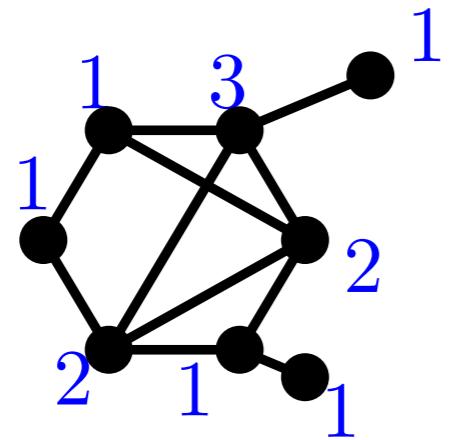
with eigenvalues $0 \leq \lambda_1 \leq \dots \leq \lambda_n \leq 2$

Def: Let $t \geq 0$, and define the *Heat Kernel Signature* of param t :

$$\text{hks}_{G,t} : v \mapsto \sum_{k=1}^n \exp(-\lambda_k t) \phi_k(v)^2$$

Application to graph classification

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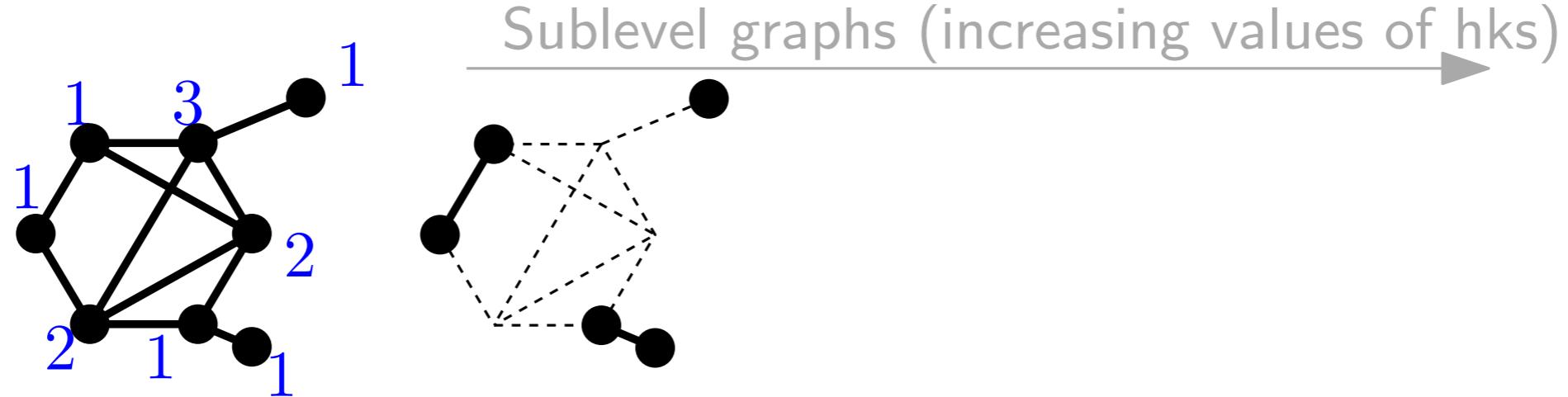


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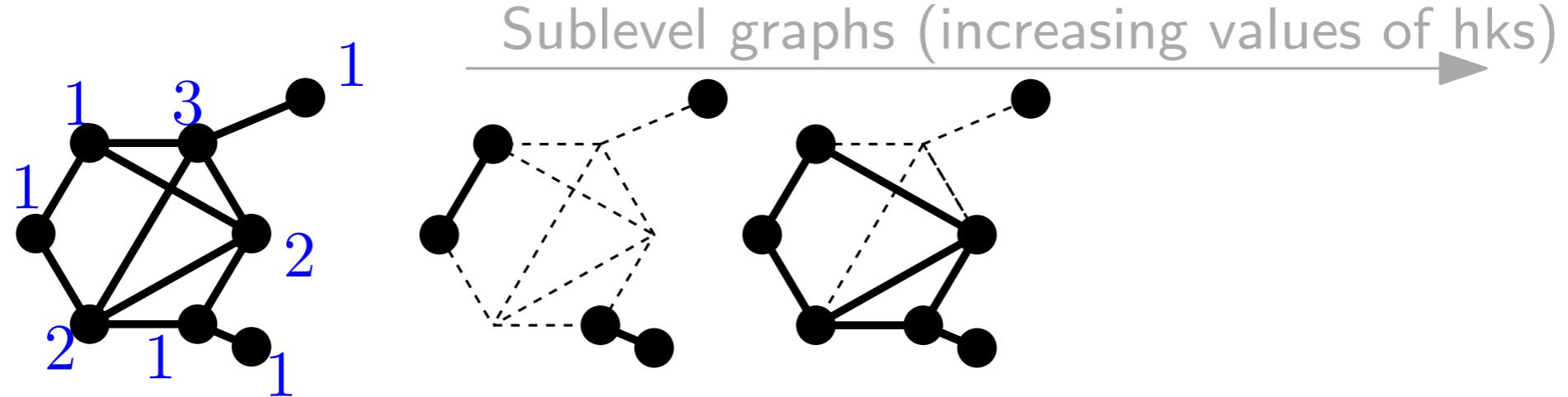


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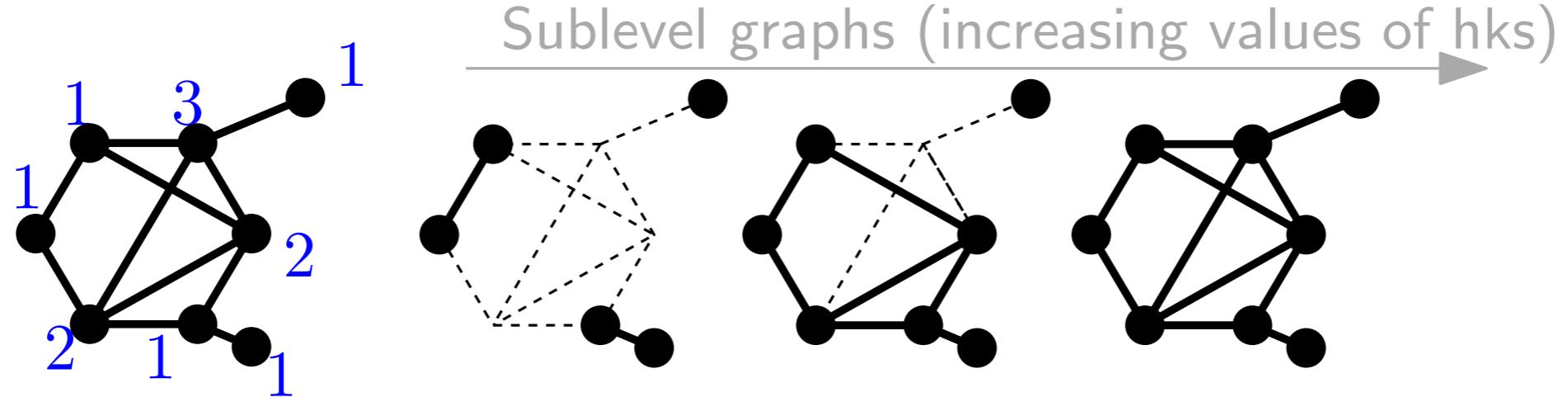


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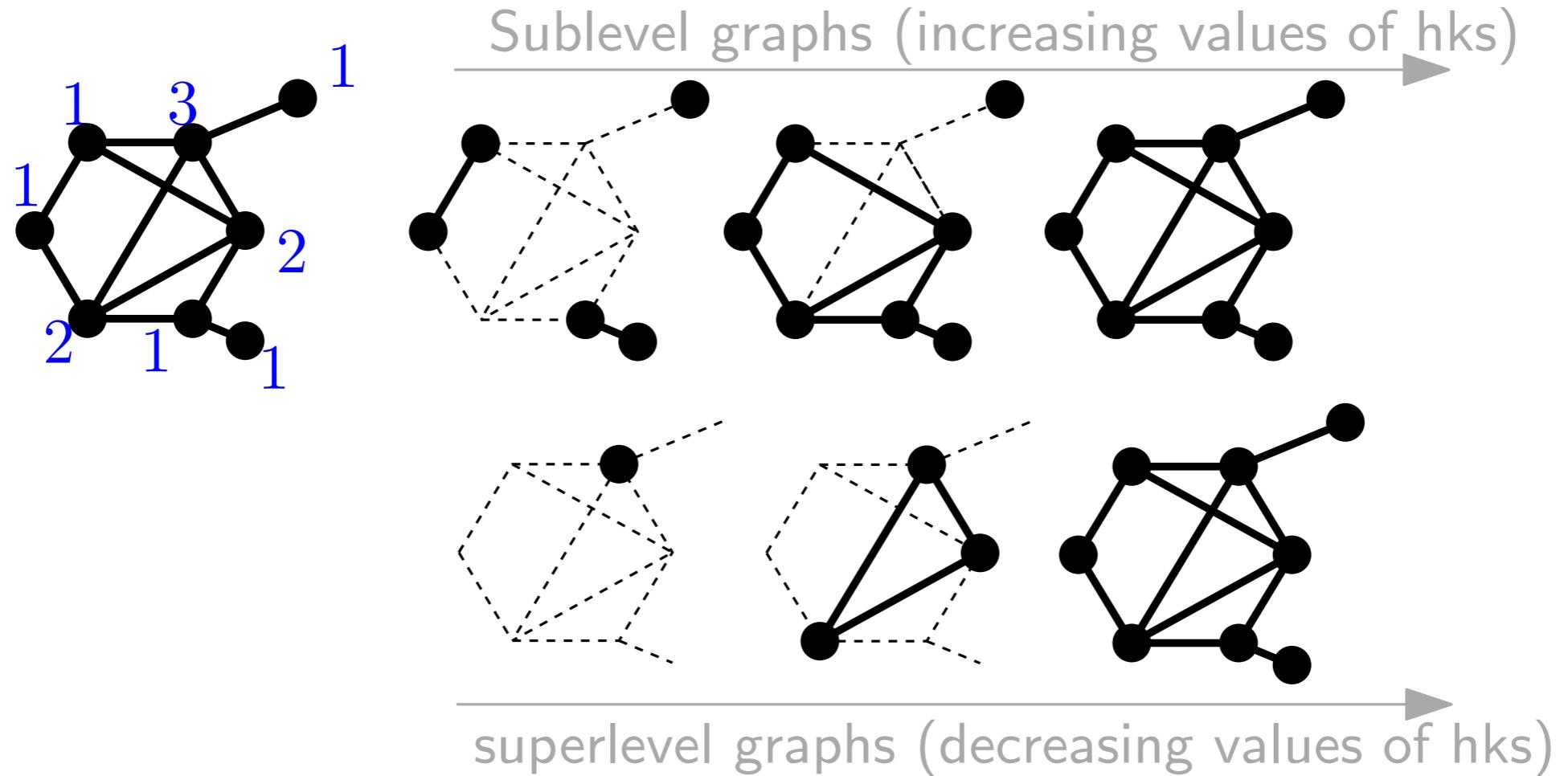


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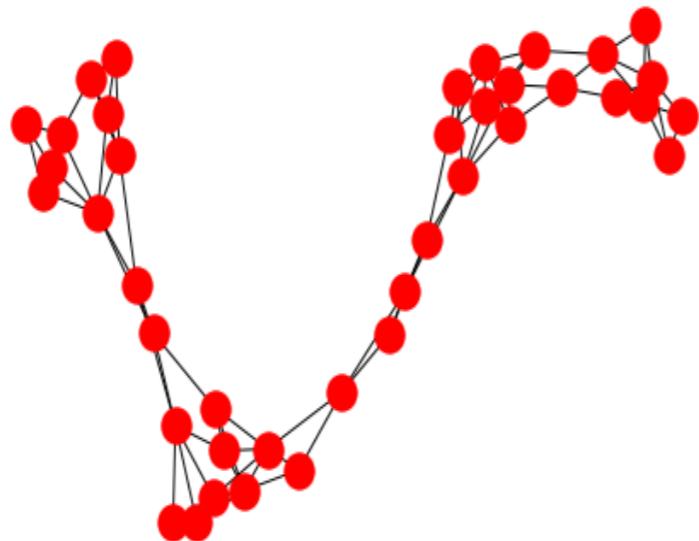
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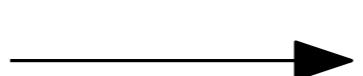
Application to graph classification

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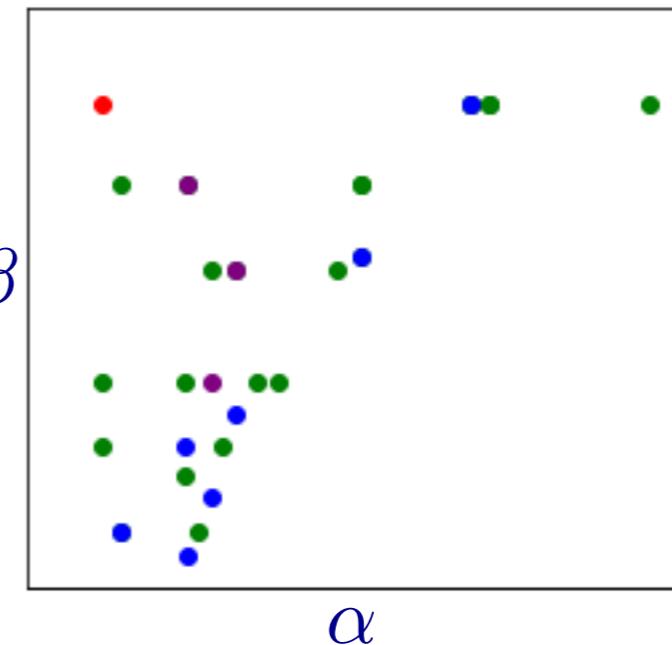
Graph from the PROTEINS dataset



Corresponding persistence diagram

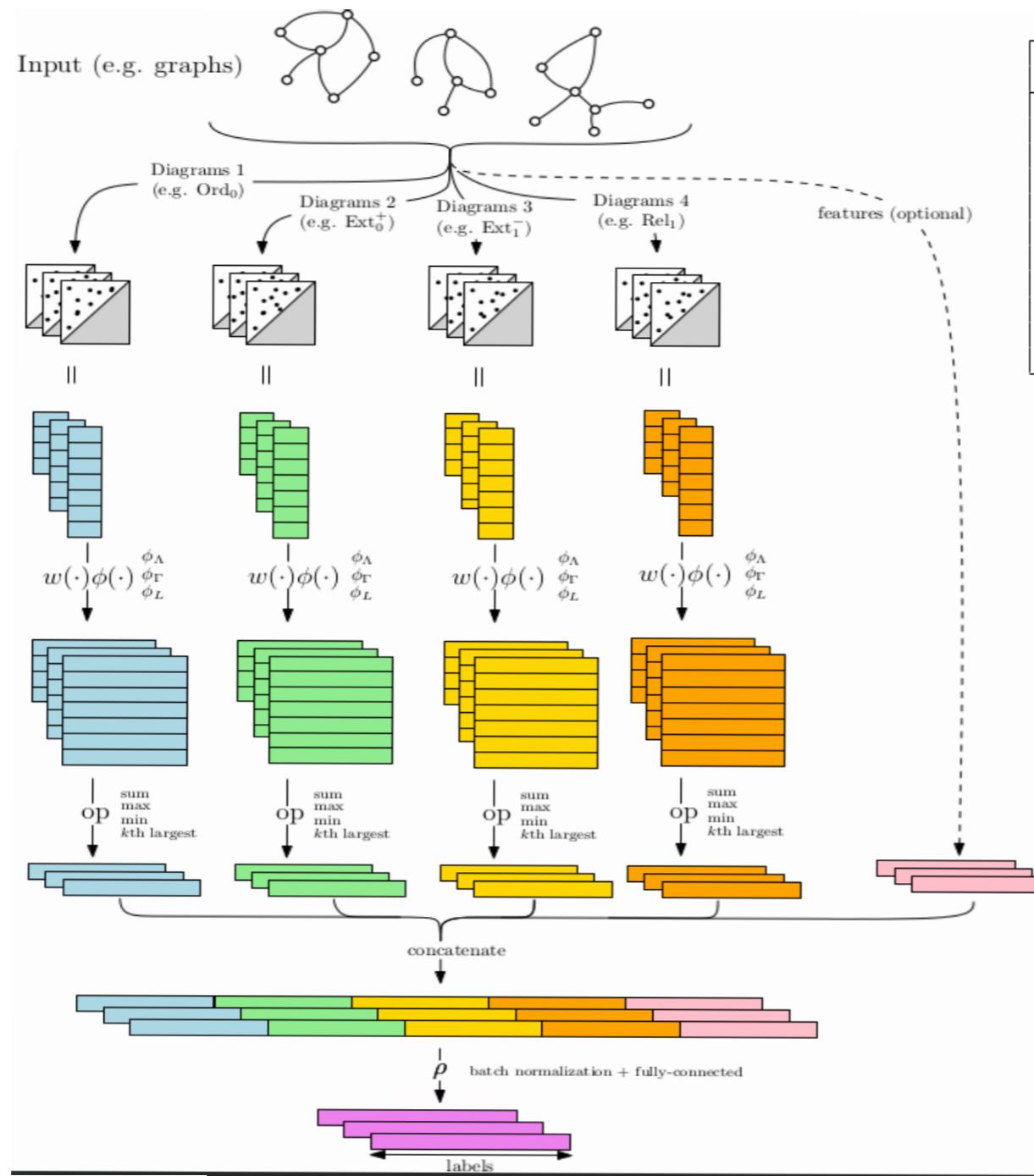


β



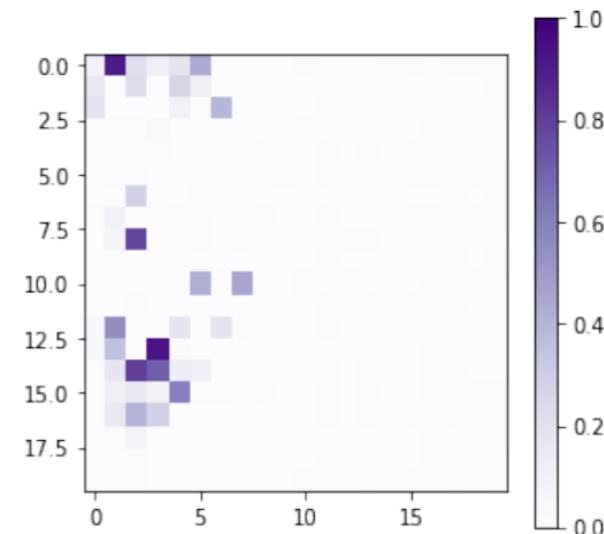
Application to graph classification

[*PersLayer: A Neural Network Layer for Persistence Diagrams and New Graph Topological Signatures*, C., Chazal, Ike, Lacombe, Royer, Umeda, AISTATS, 2019]



Dataset	SV ¹	RetGK* ²	FGSD ³	GCNN ⁴	GIN ⁵	PERSLAY Mean	PERSLAY Max
REDDIT5K	—	56.1	47.8	52.9	57.0	55.6	56.5
REDDIT12K	—	48.7	—	46.6	—	47.7	49.1
COLLAB	—	81.0	80.0	79.6	80.1	76.4	78.0
IMDB-B	72.9	71.9	73.6	73.1	74.3	71.2	72.6
IMDB-M	50.3	47.7	52.4	50.3	52.1	48.8	52.2
COX2*	78.4	80.1	—	—	—	80.9	81.6
DHFR*	78.4	81.5	—	—	—	80.3	80.9
MUTAG*	88.3	90.3	92.1	86.7	89.0	89.8	91.5
PROTEINS*	72.6	75.8	73.4	76.3	75.9	74.8	75.9
NCI1*	71.6	84.5	79.8	78.4	82.7	73.5	74.0
NCI109*	70.5	—	78.8	—	—	69.5	70.1

Weight function learnt



(after training on the
MUTAG dataset)

Application to Pearson correlation

Method:

1. Extract local point clouds corresponding to several measurement spots.

Application to Pearson correlation

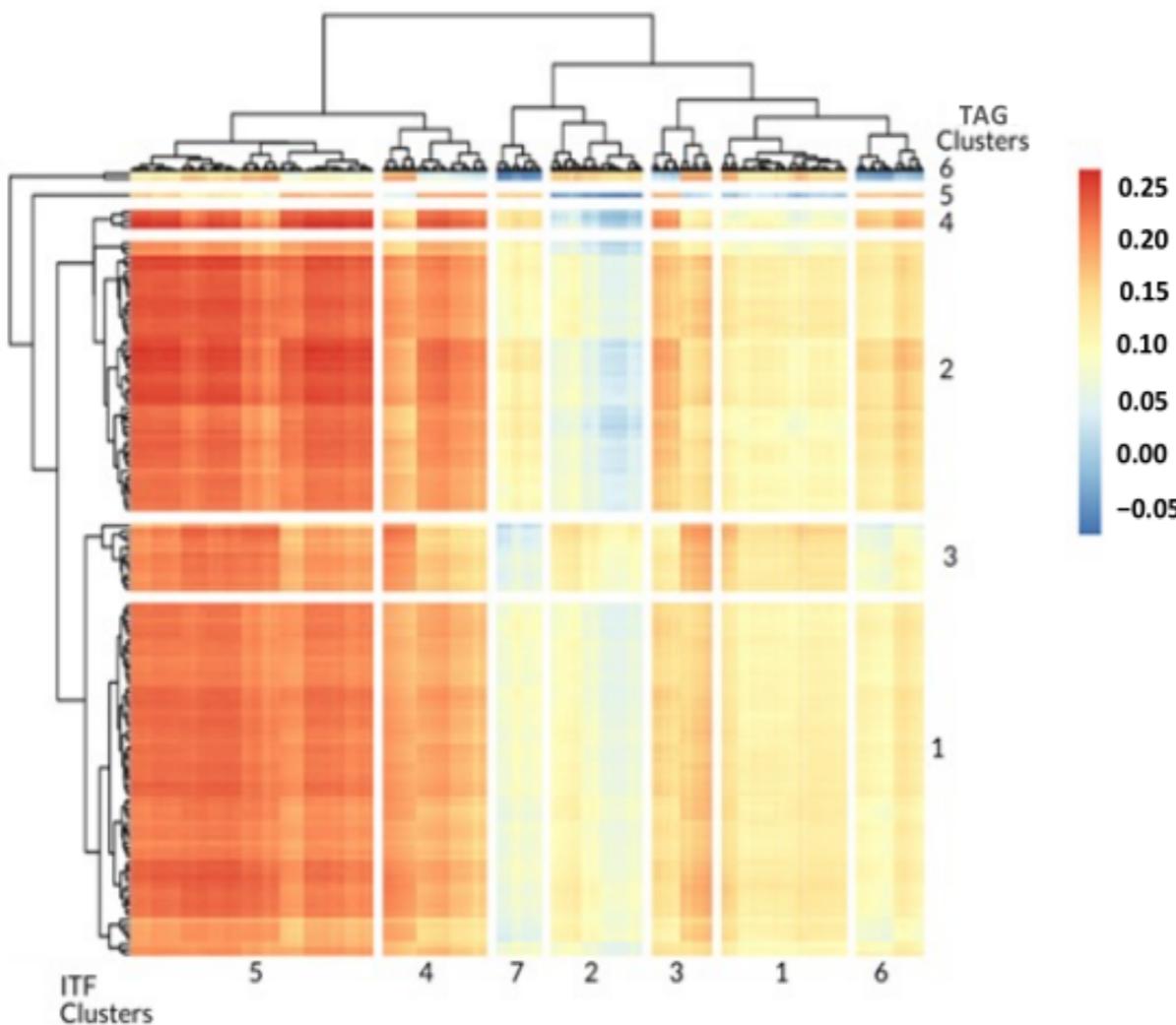
Method:

1. Extract local point clouds corresponding to several measurement spots.
2. Compute persistence images (PIMs) associated to Rips PDs of local point clouds.

Application to Pearson correlation

Method:

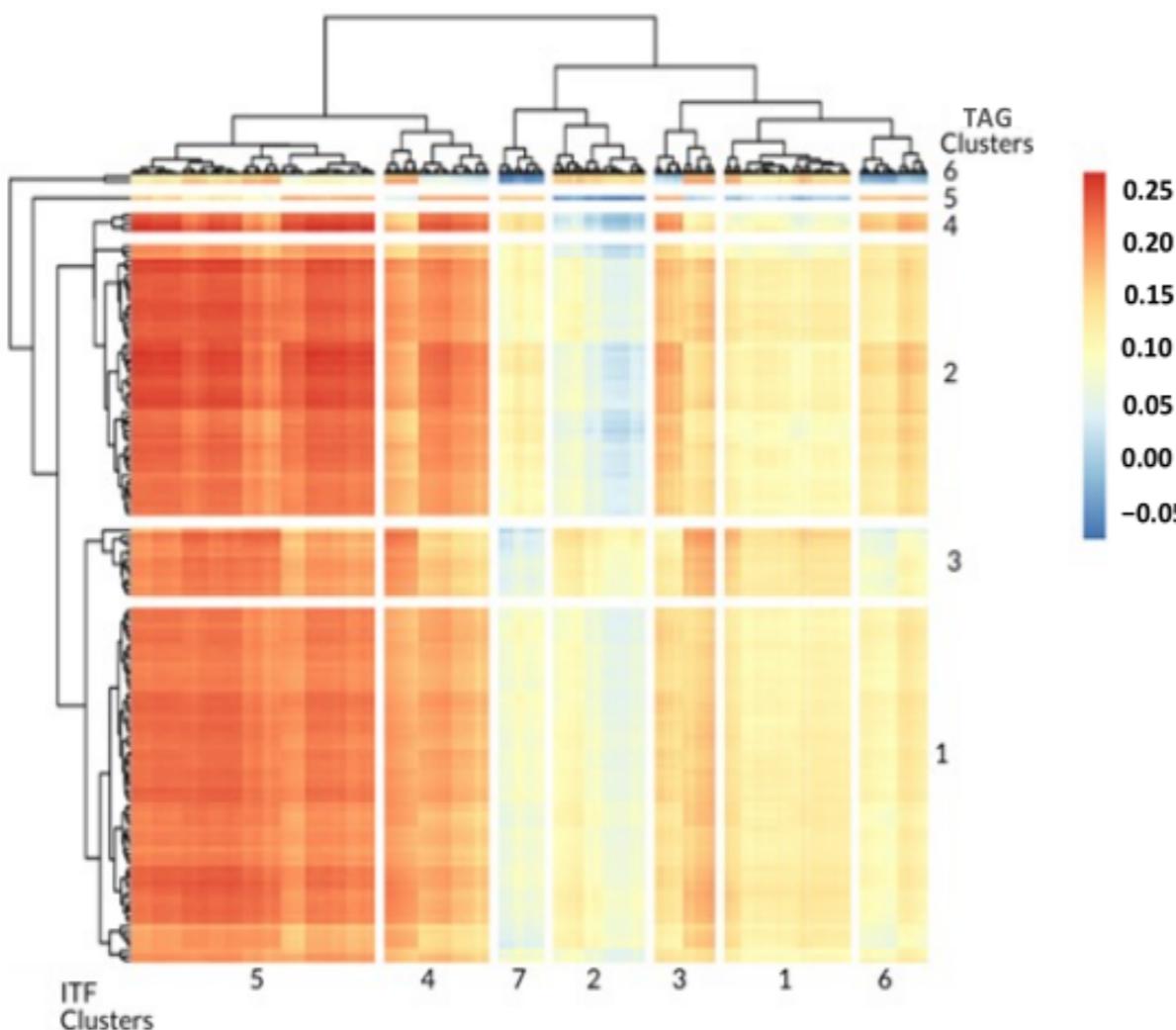
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4. Retrieve marker genes with highest correlations and match these *topologically associated genes* (TAGs) against gene ontology.



Term ID	Term name	Adjusted p-value
GO:0005615	Extracellular space	5.57×10^{-5}
GO:0070062	Extracellular exosome	1.27×10^{-3}
GO:1903561	Extracellular vesicle	1.41×10^{-3}
GO:0043230	Extracellular organelle	1.41×10^{-3}

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5. Predict TAG expression from ITFs only.

