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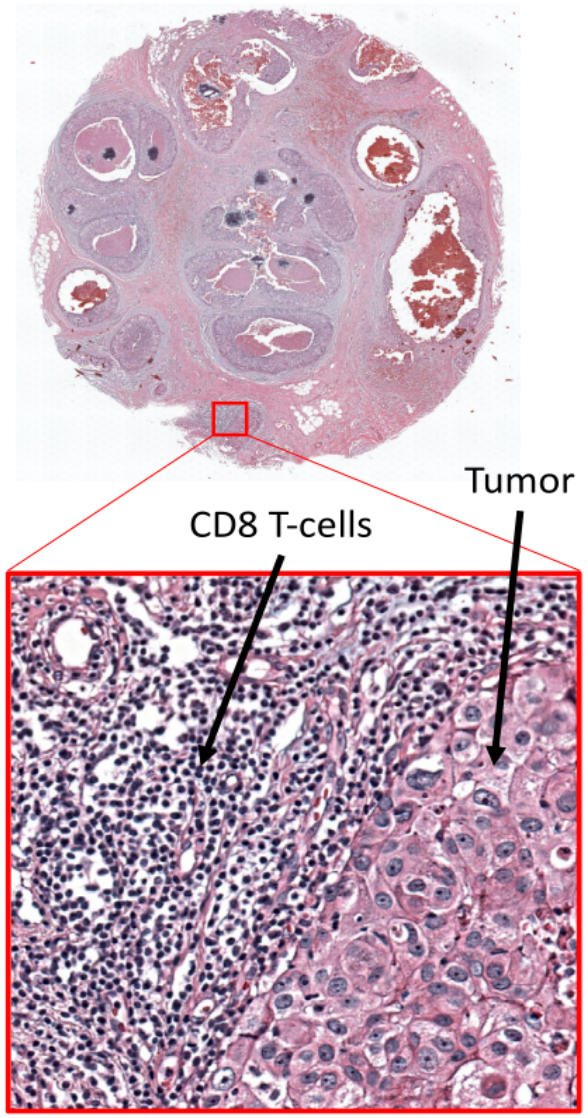
Q: What are the relations and correlations between *spatial features* and *marker genes*? Can one influence the other?



Local point cloud

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

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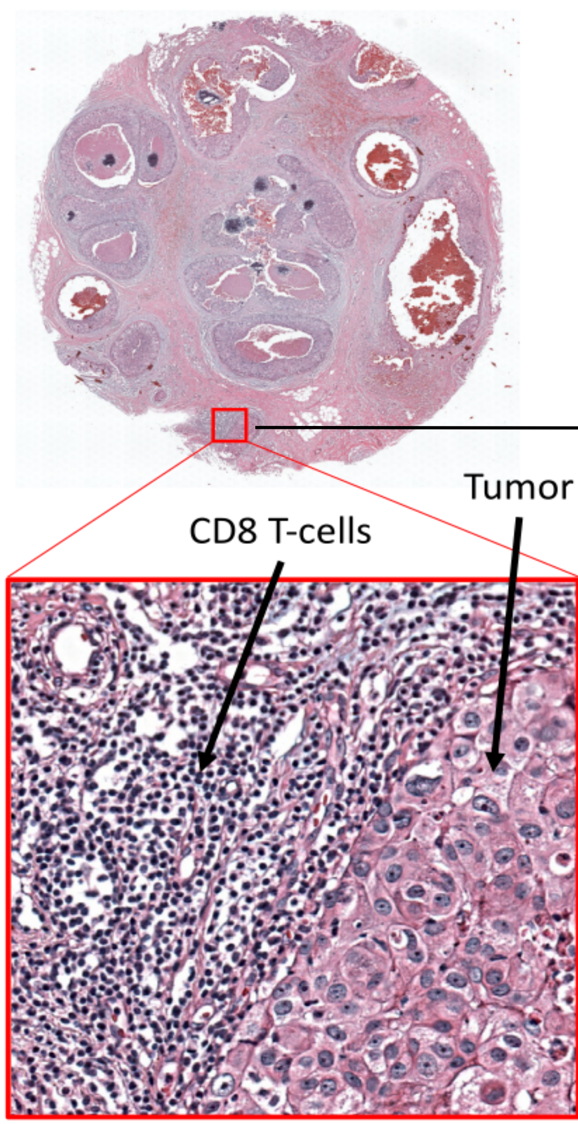

$$\begin{array}{cl} \begin{bmatrix} 0.2 \\ 0.4 \\ 0.5 \\ \vdots \\ 0.1 \end{bmatrix} & \begin{array}{l} \text{marker gene 1} \\ \text{marker gene 2} \\ \text{marker gene 3} \\ \\ \text{marker gene } n \end{array} \end{array}$$

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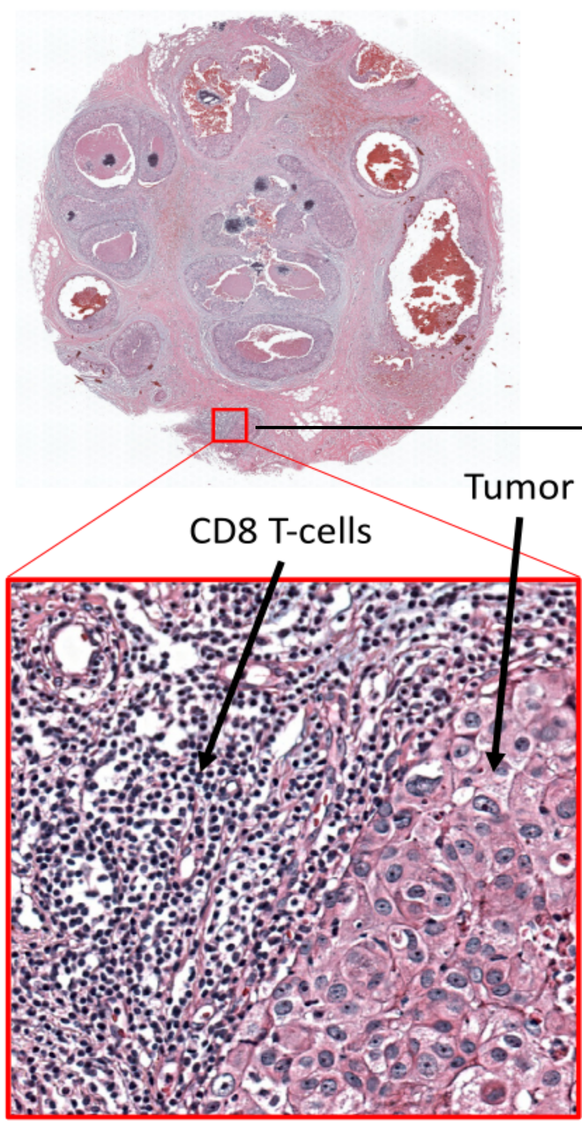

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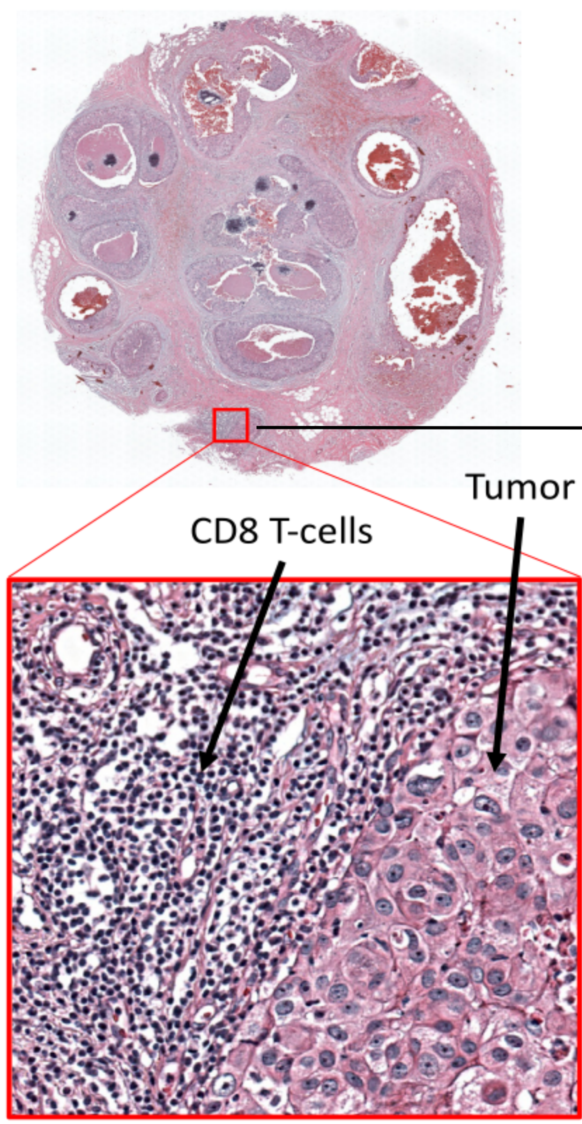
correlation?

2. Rips persistence for marker gene correlations

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

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



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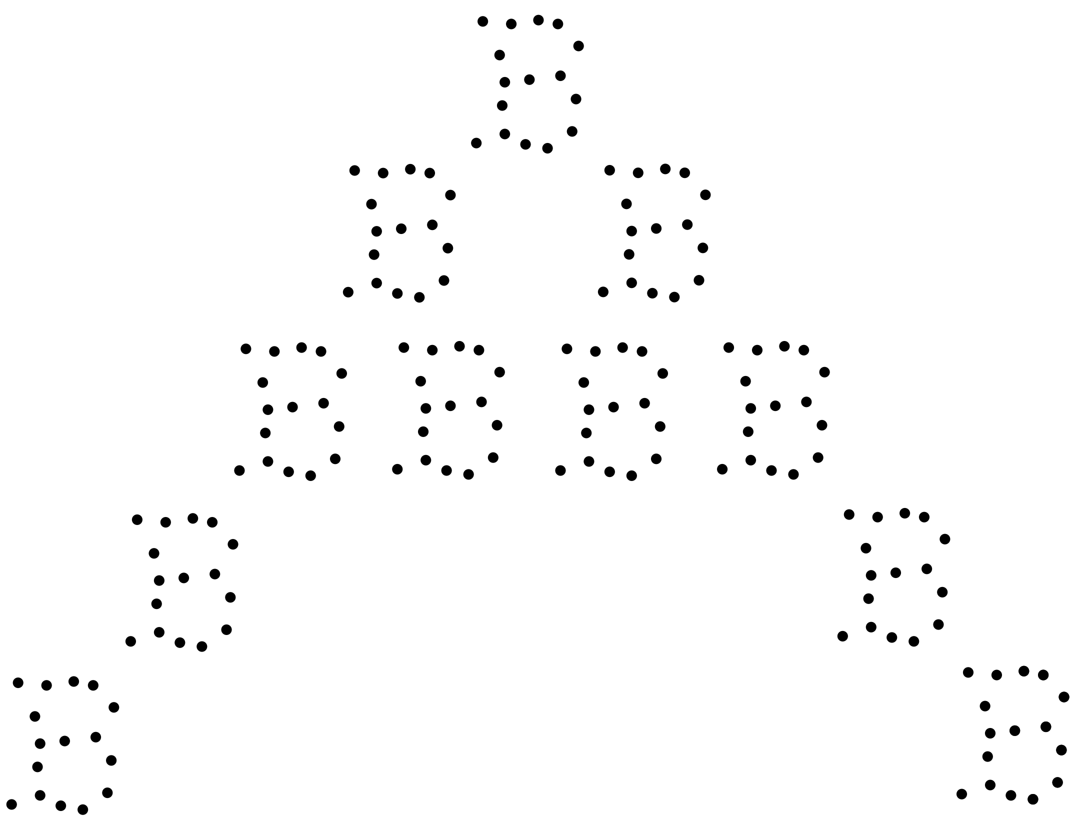
correlation?

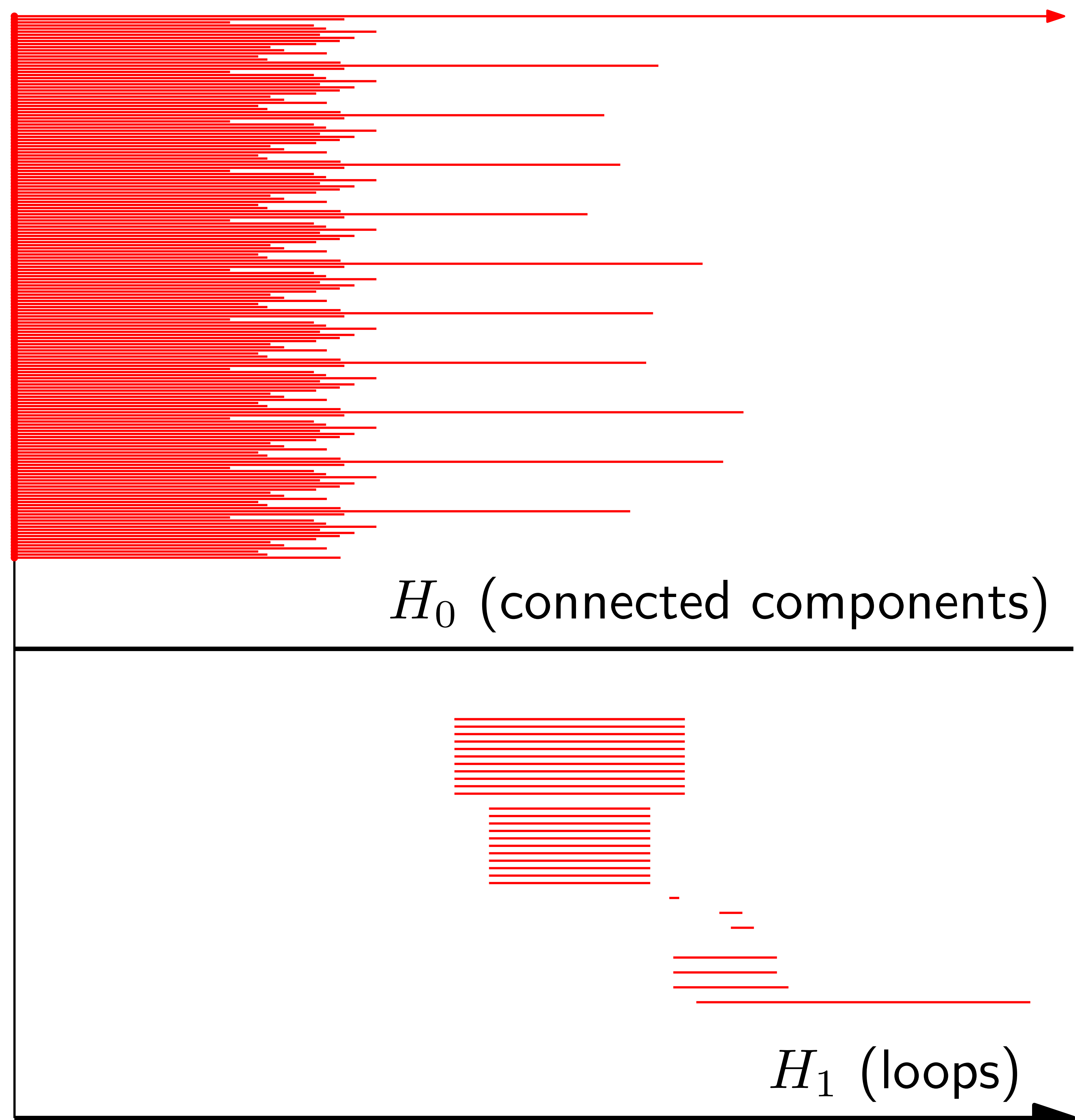
0- and 1-dimensional PH of Čech complexes

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



sublevel sets of $f =$ distance to a (pre-defined) point cloud P

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



Persistence barcode

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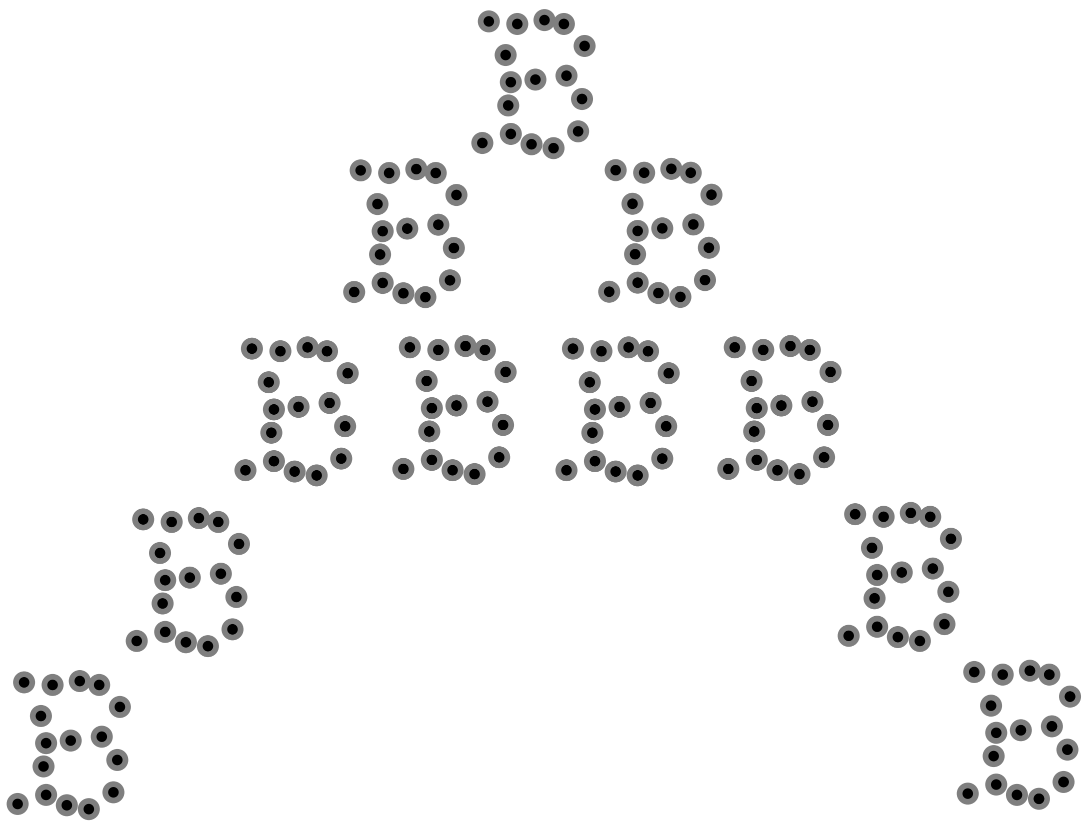

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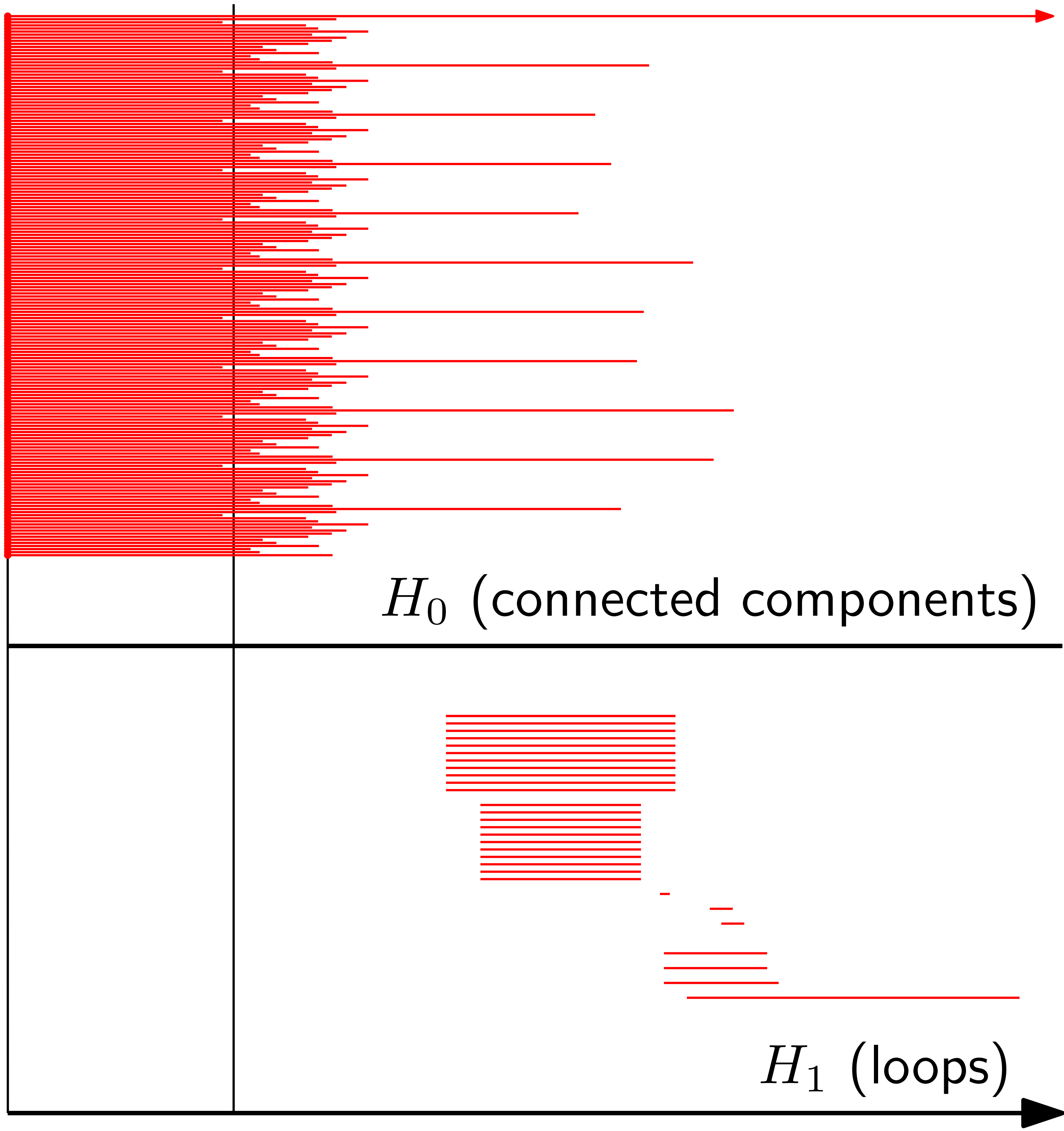

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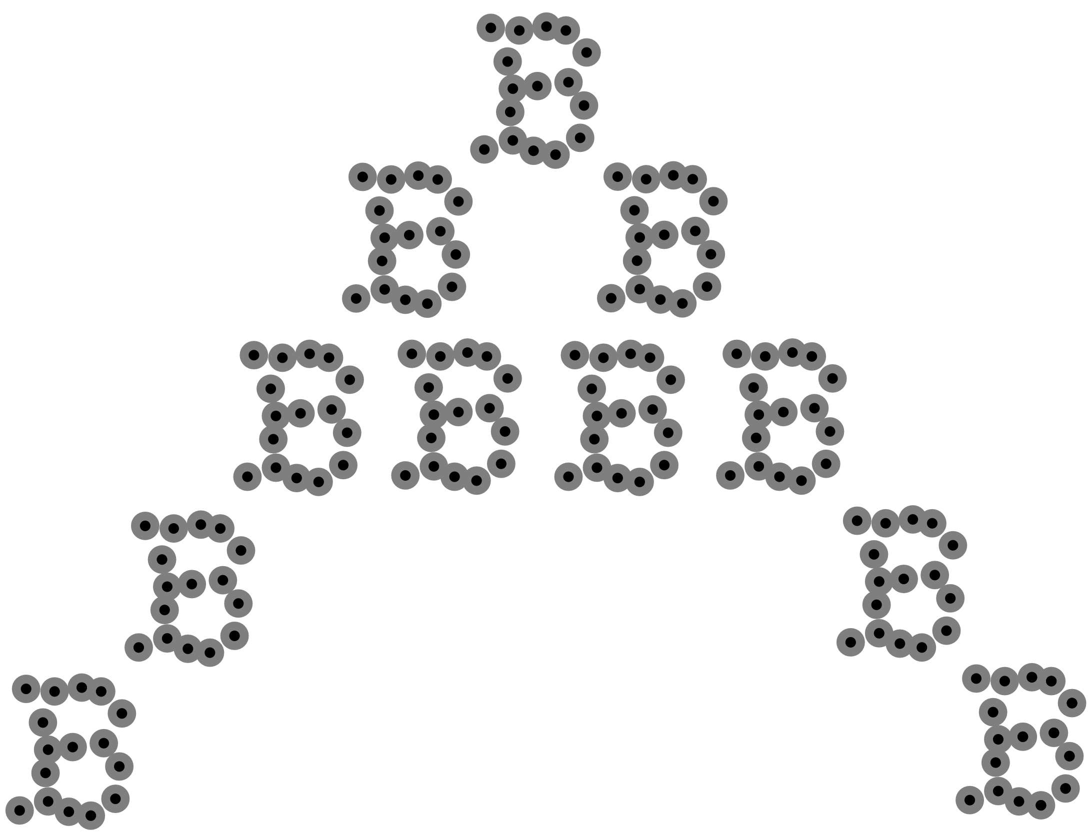

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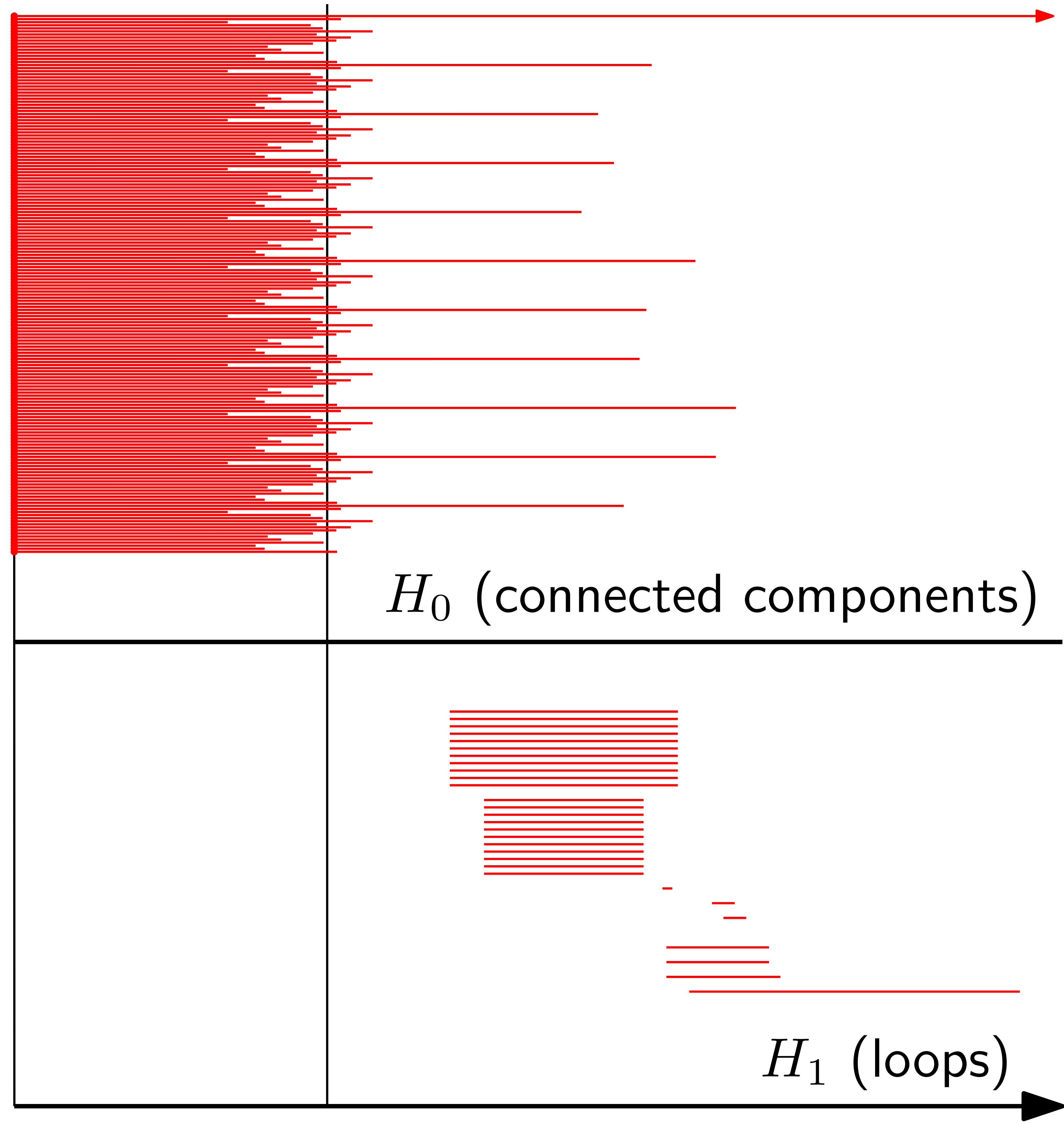

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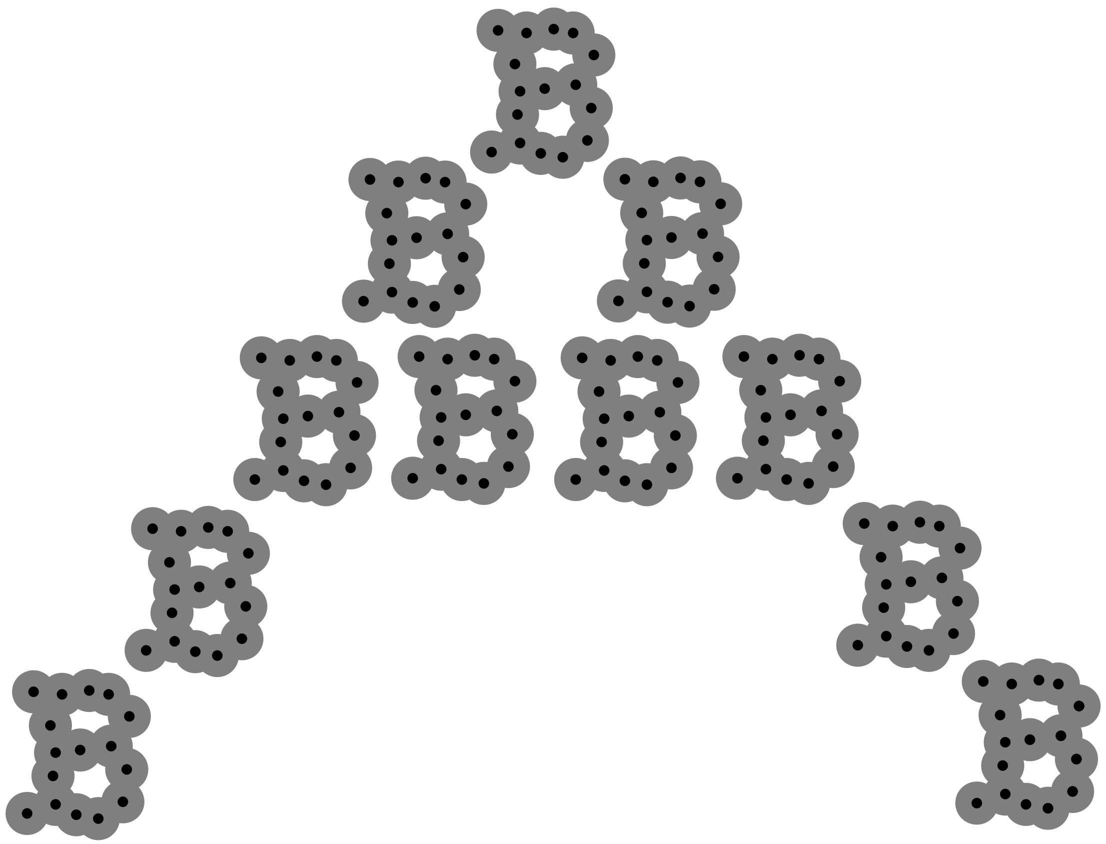

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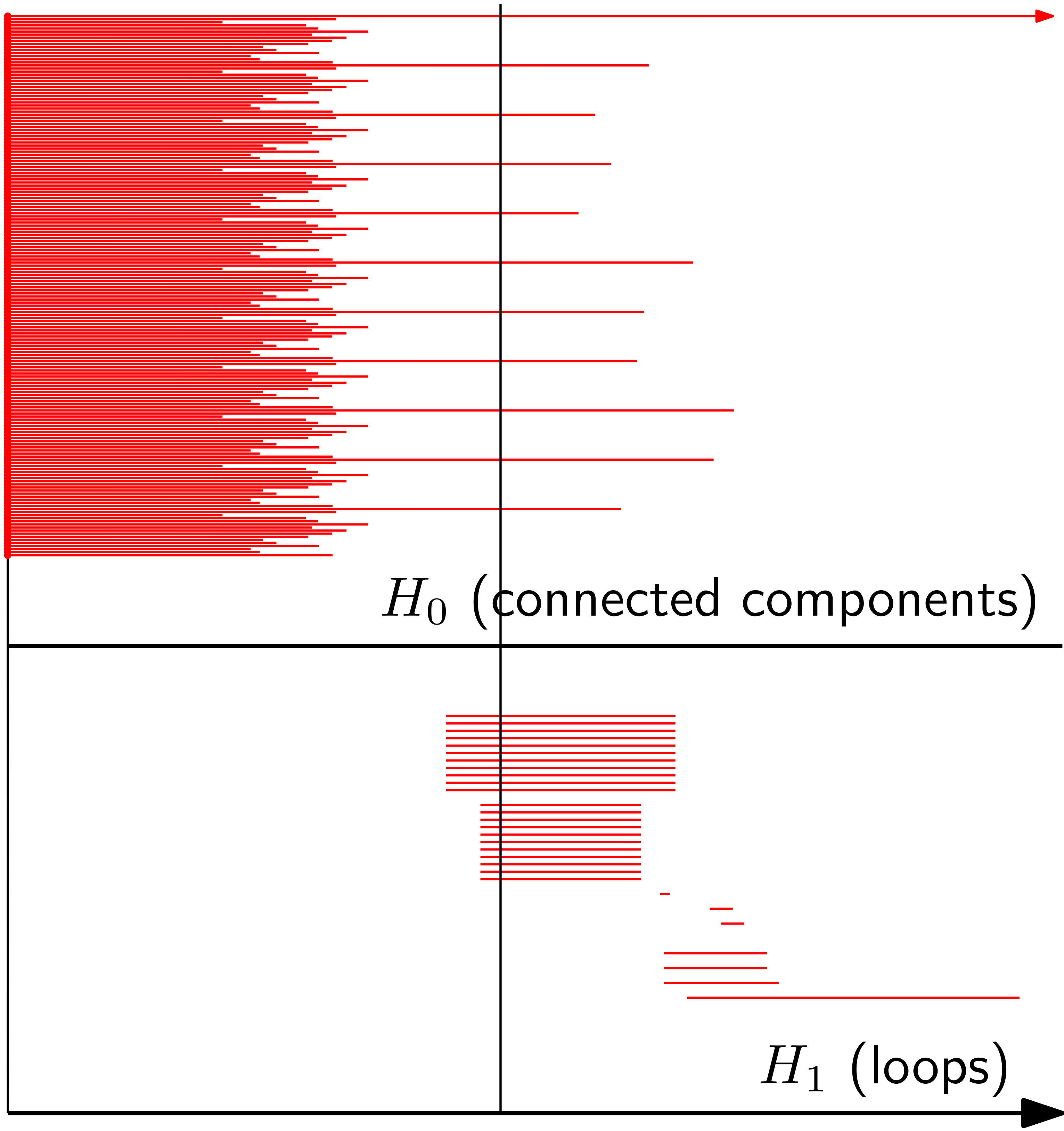

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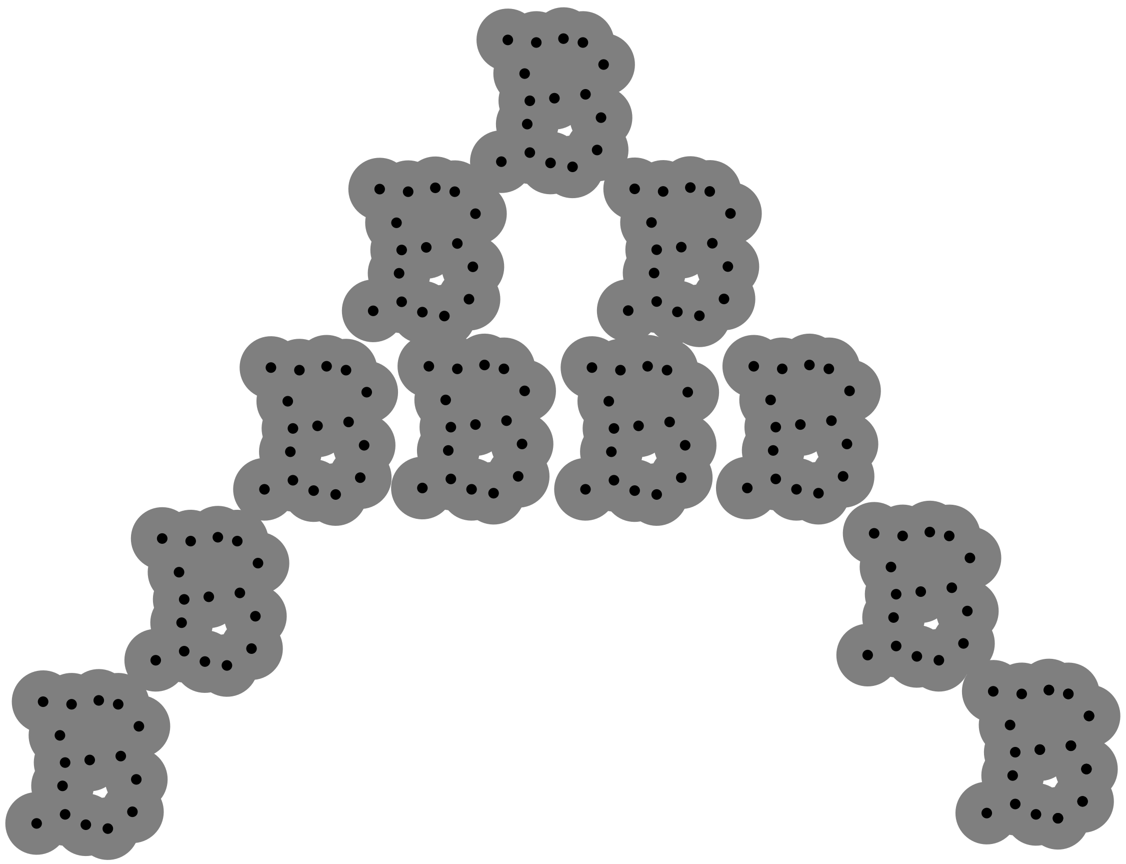

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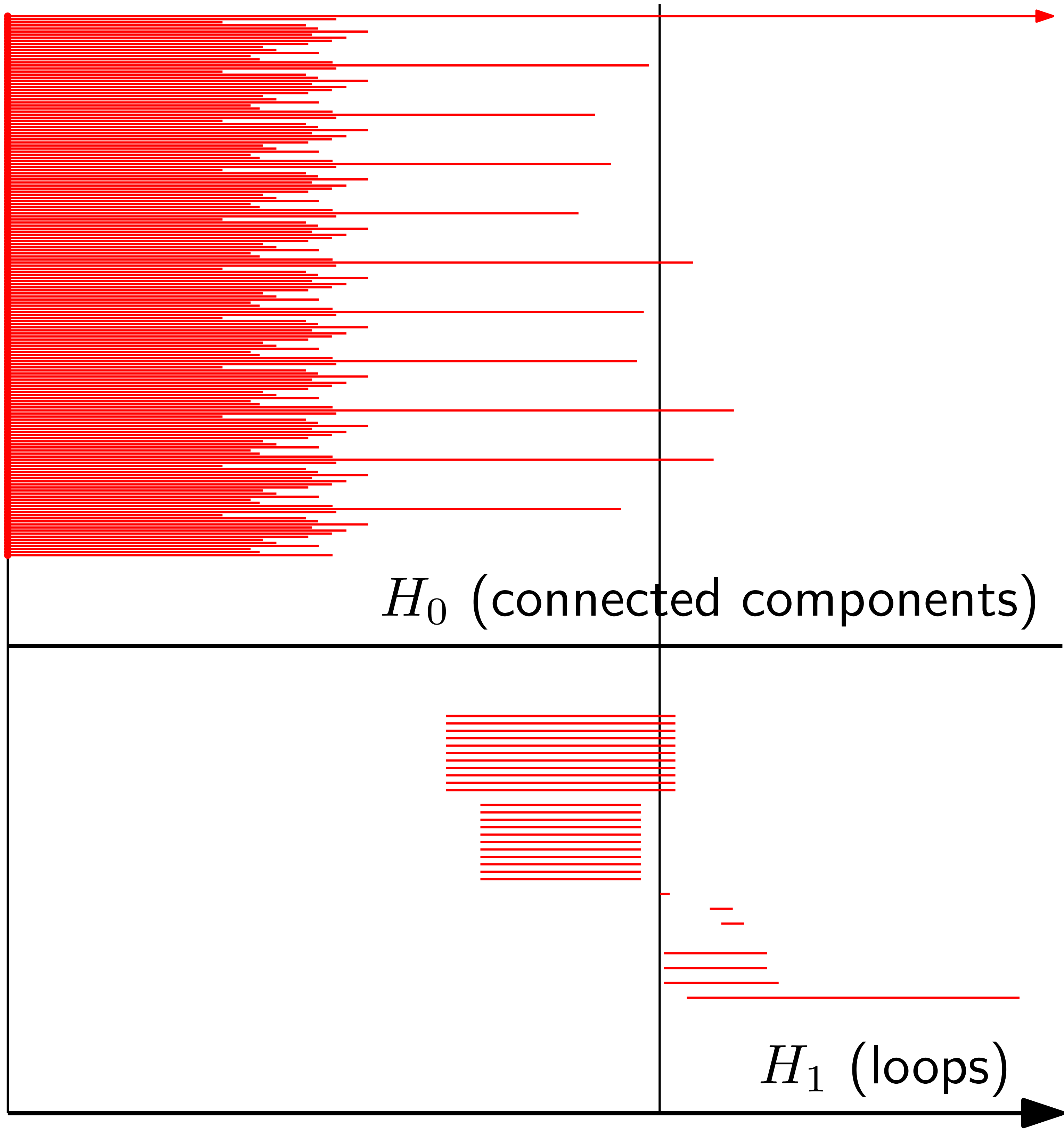

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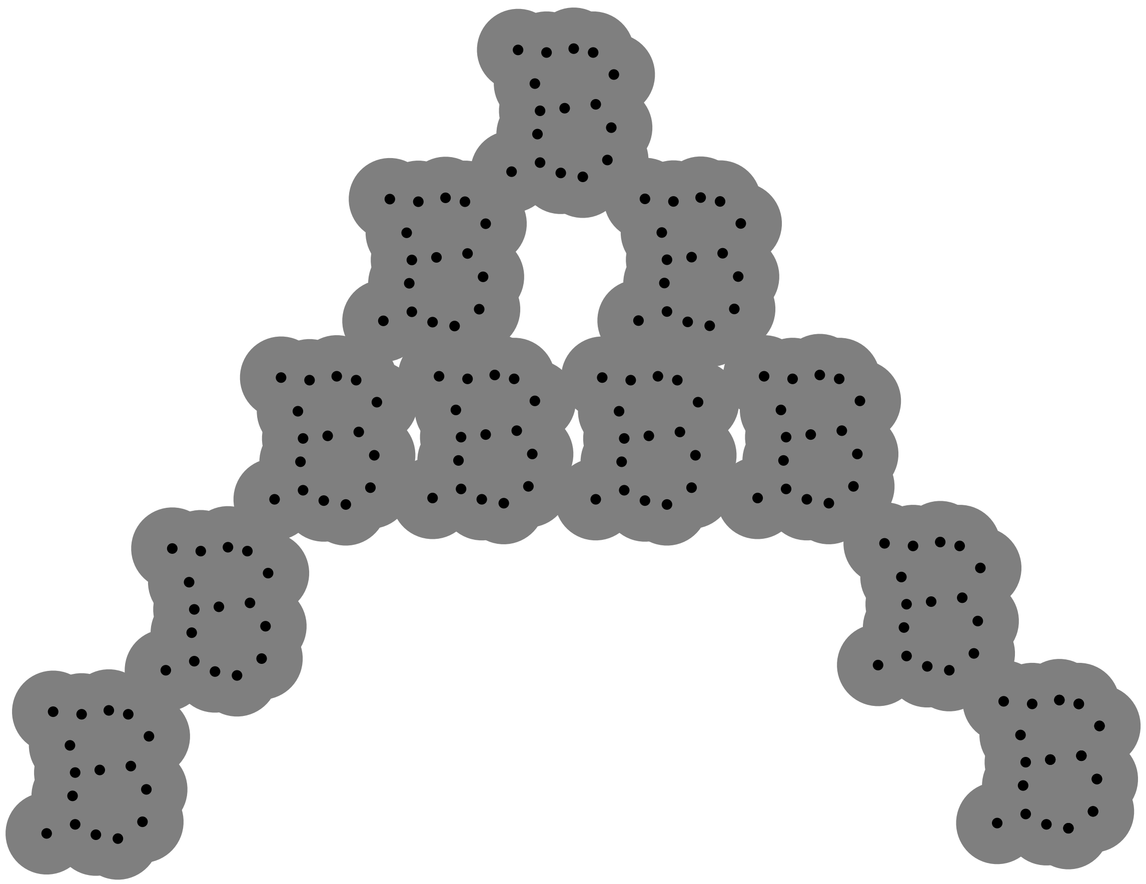

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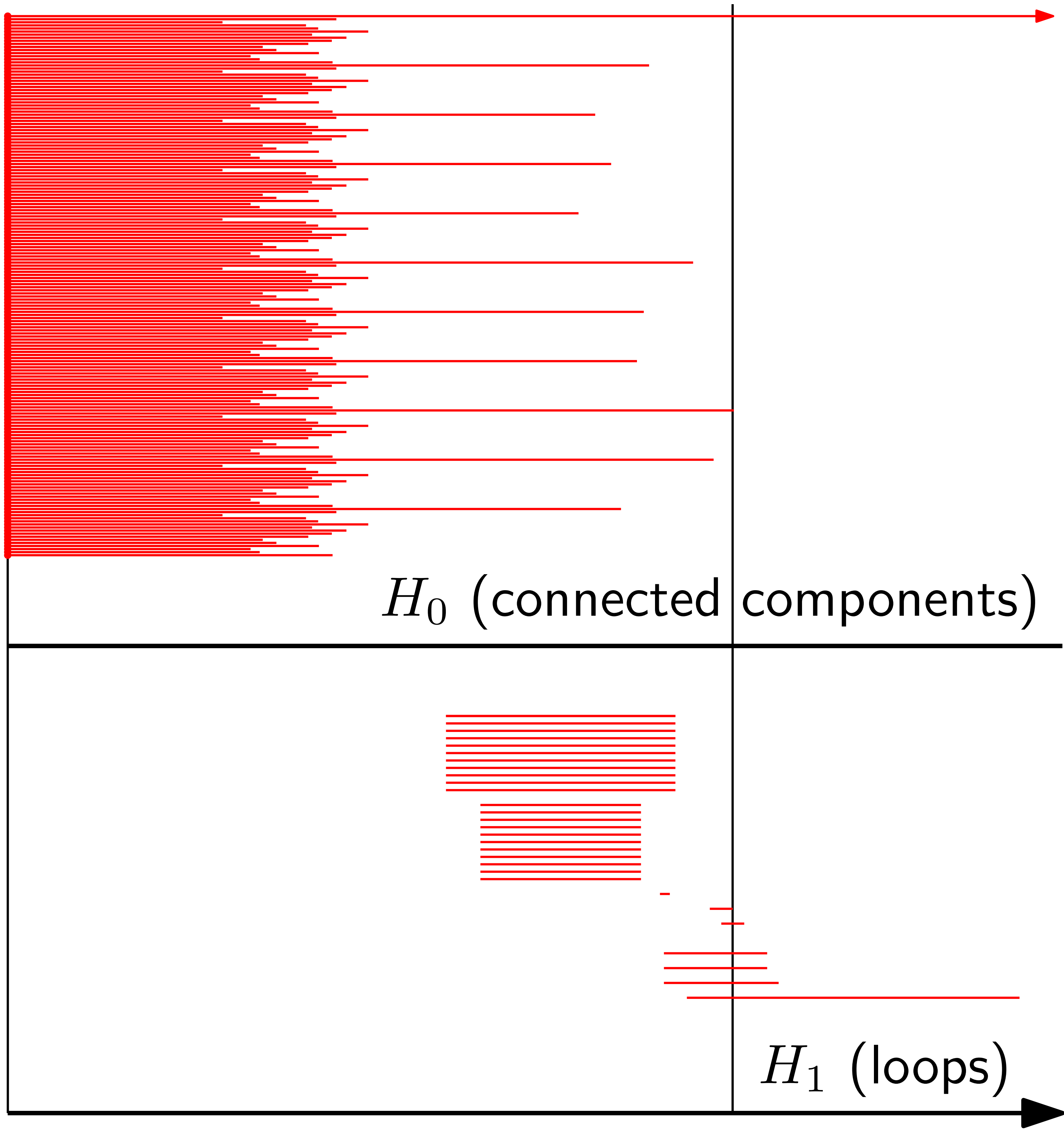

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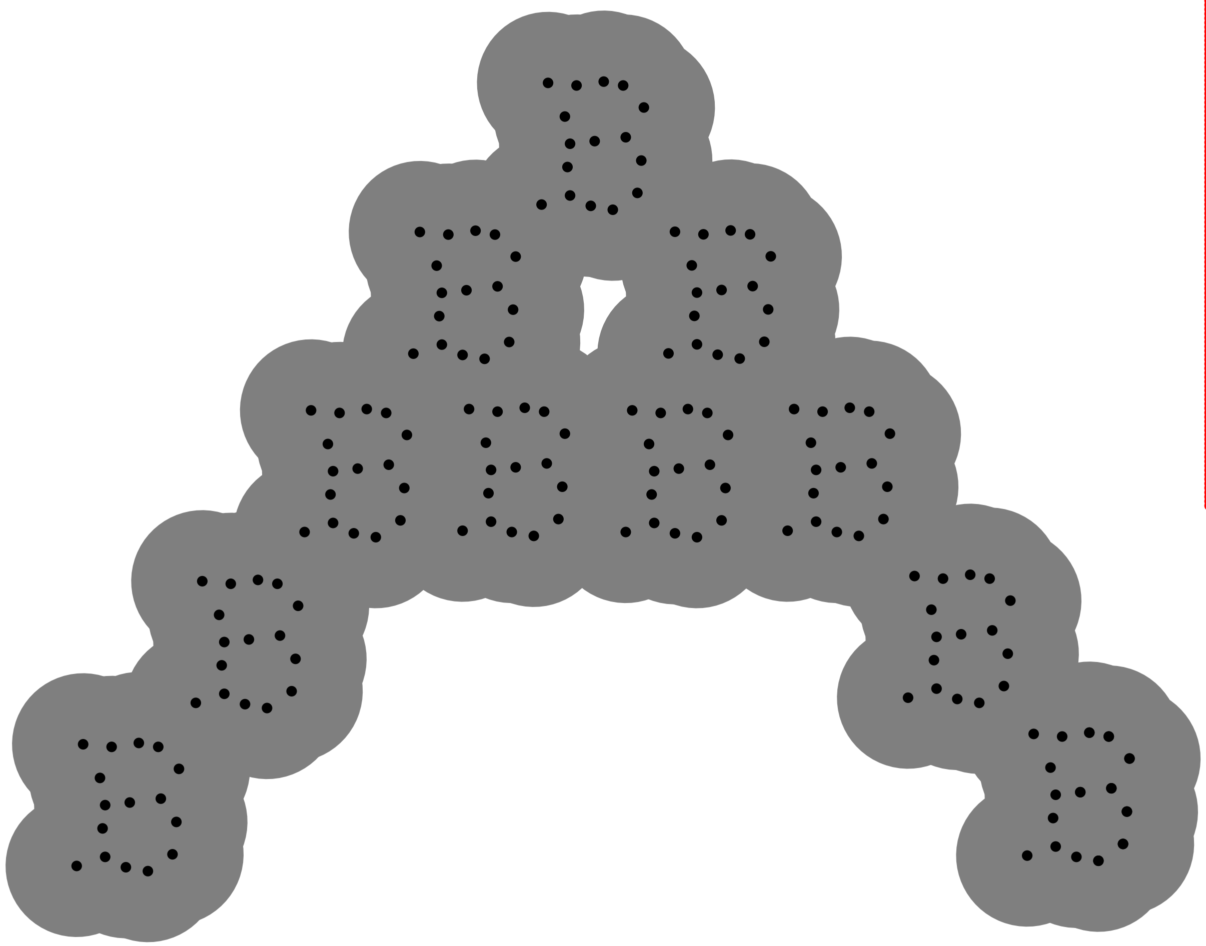

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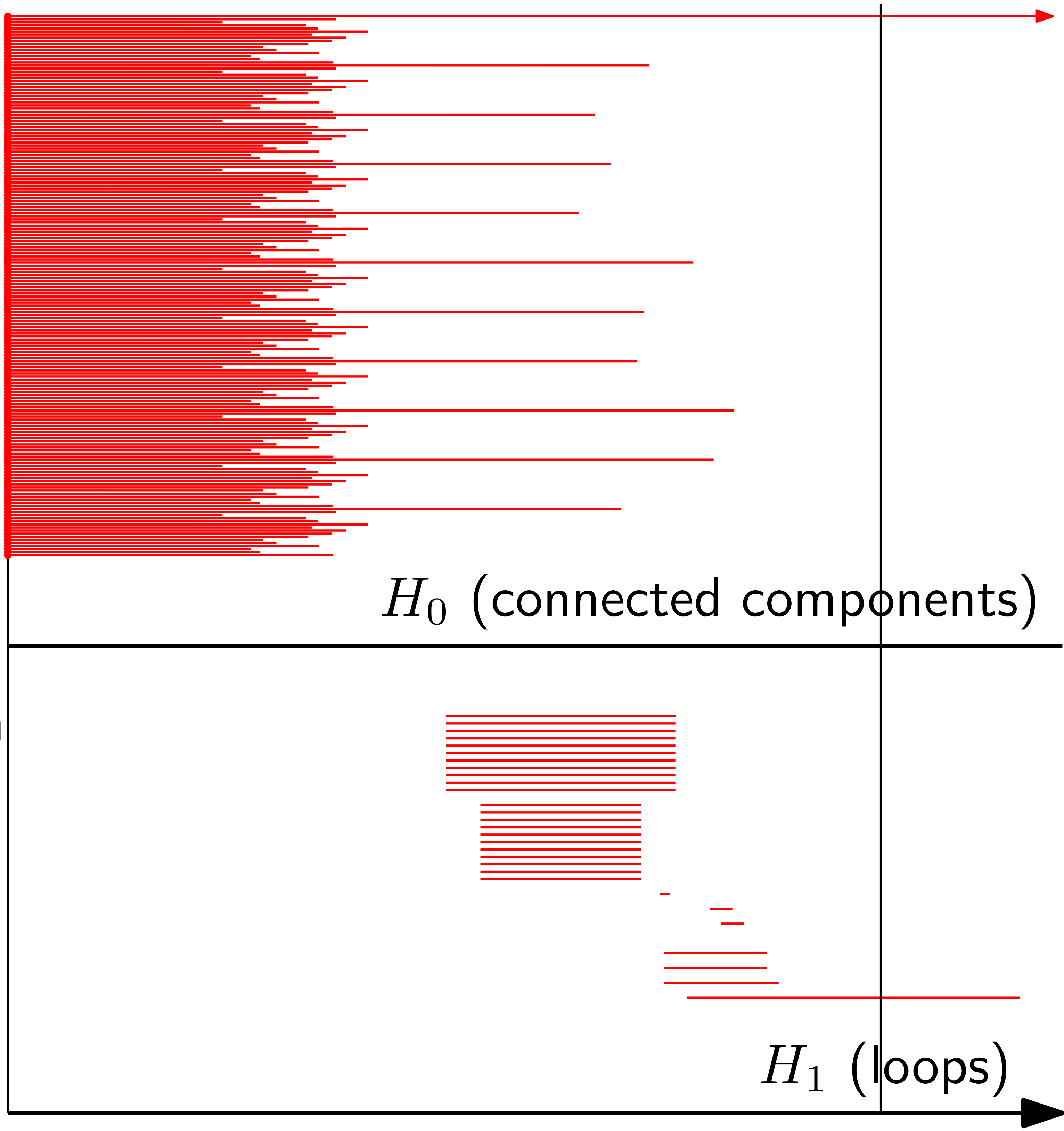

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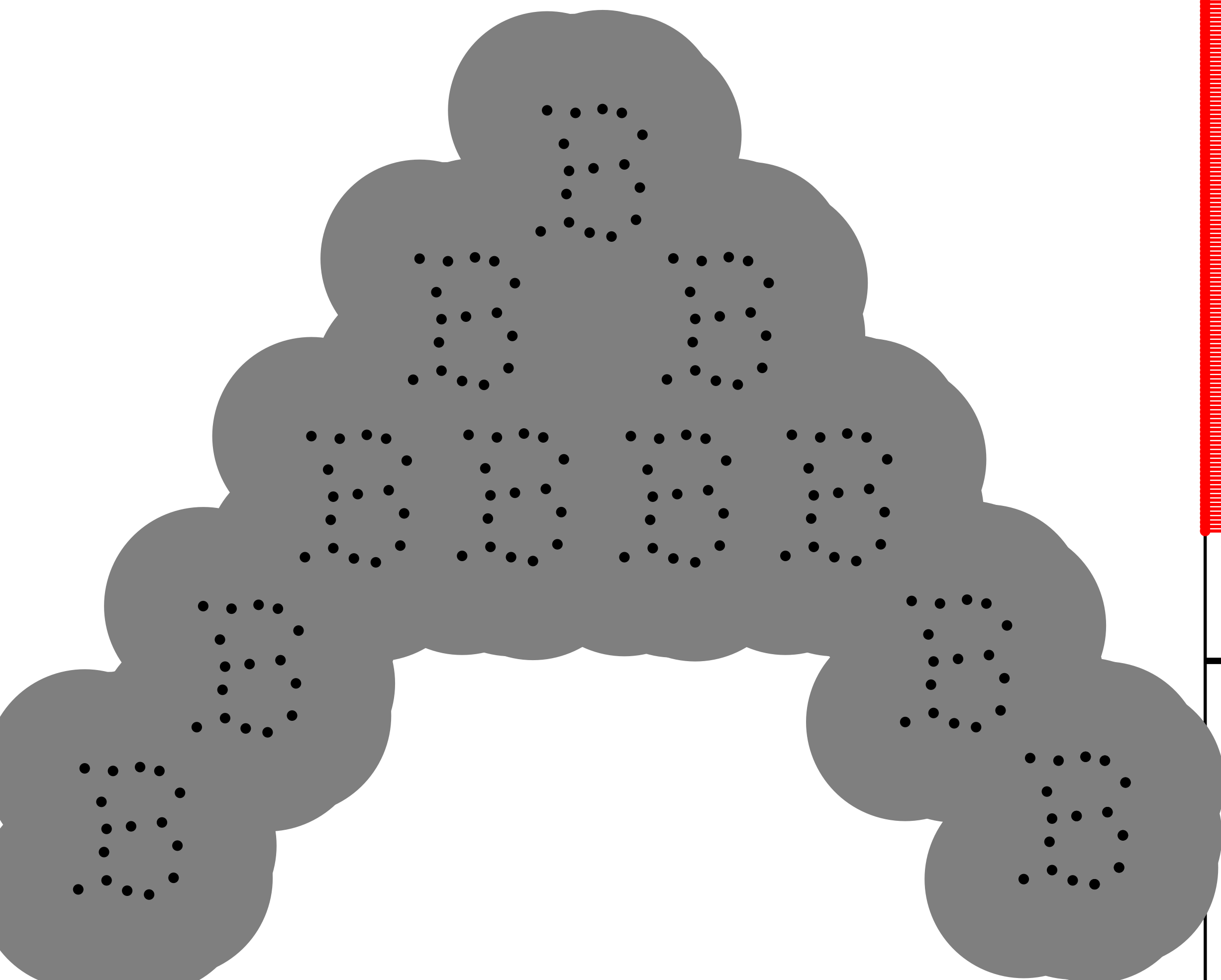

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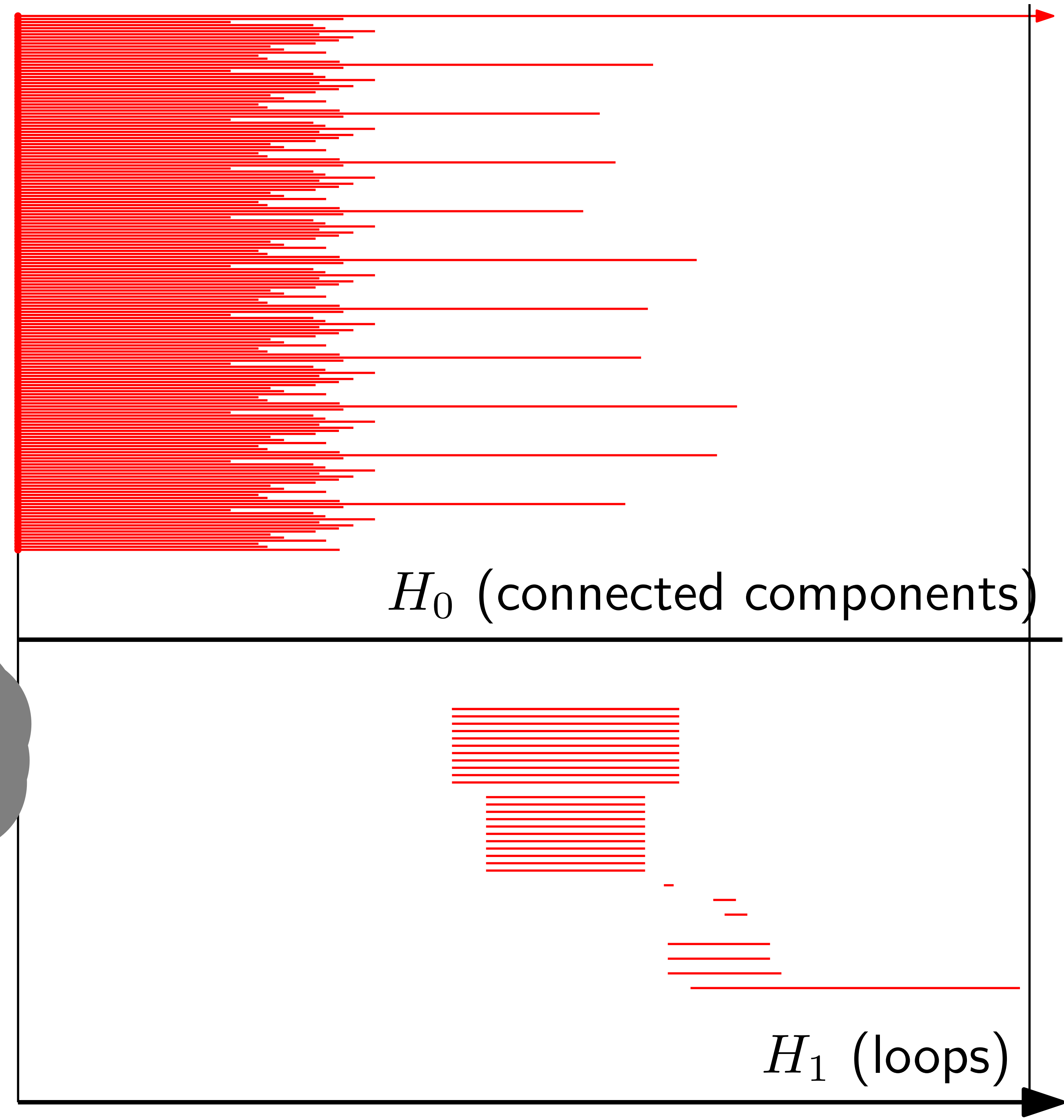

Persistence barcode

Čech and (Vietoris)-Rips complexes

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

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

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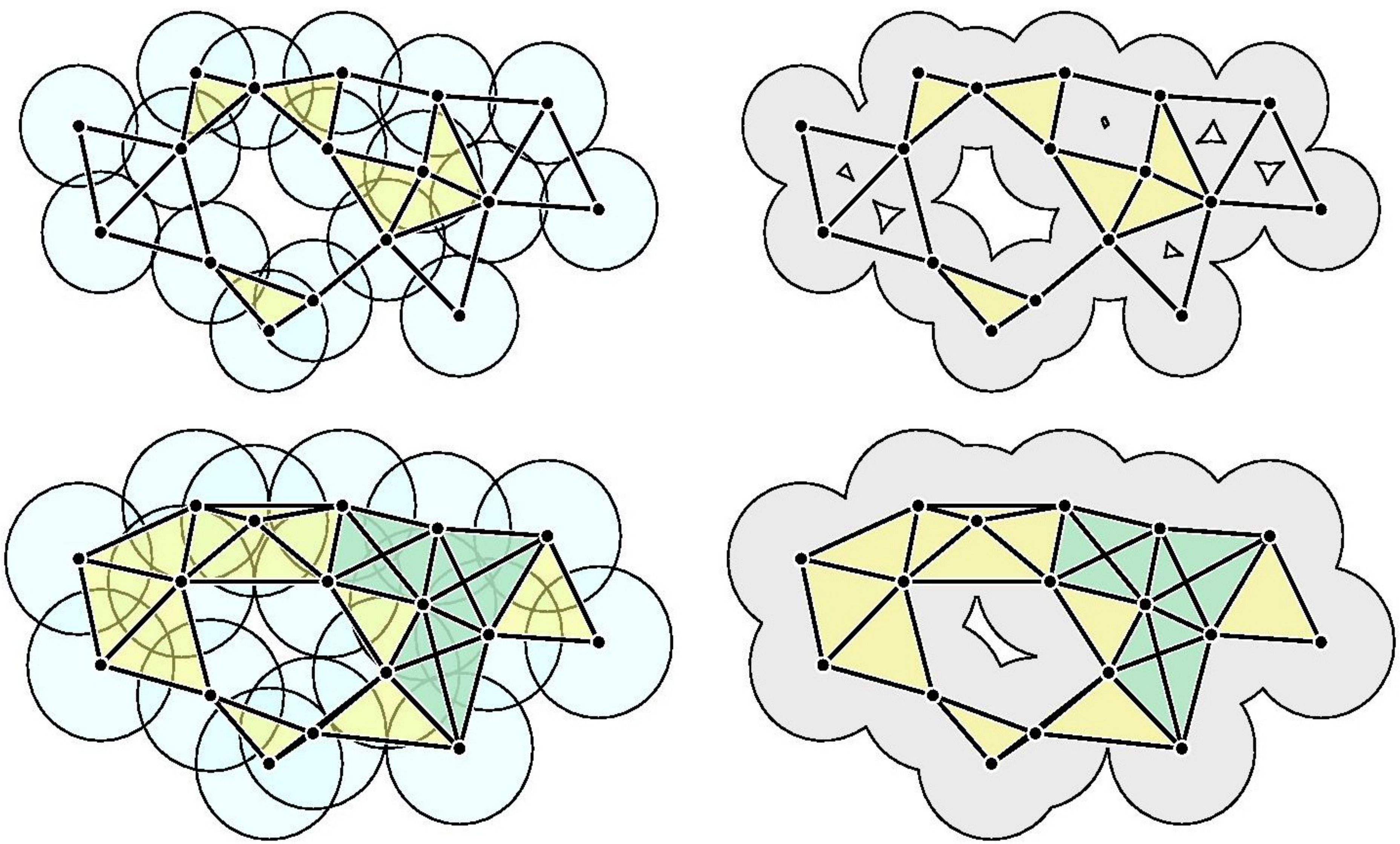

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Remark: The 1-skeleton $\mathrm{Skel}_1(R(P, r))$ of a Rips complex of radius r is also called the r-*neighborhood graph* of P.

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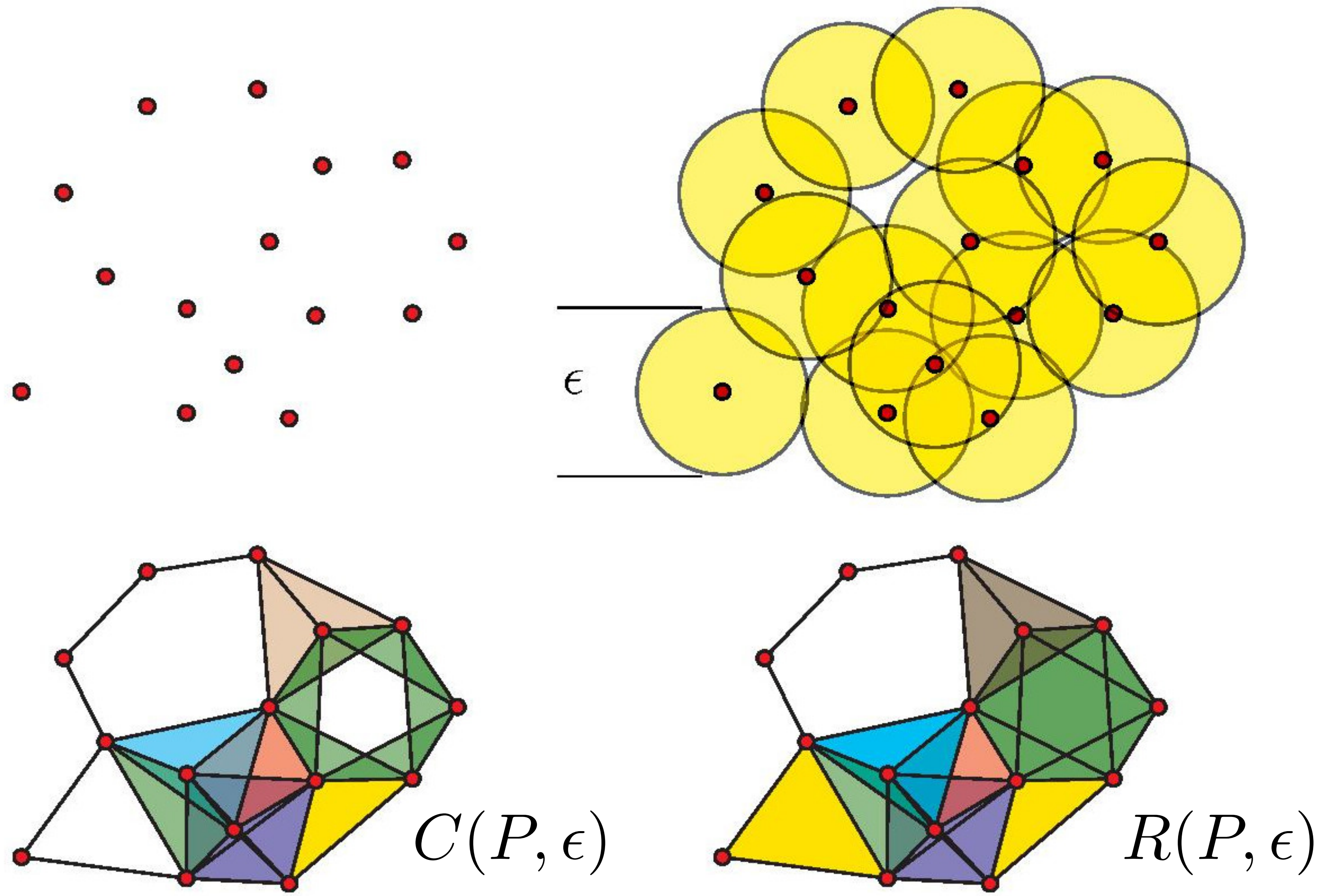

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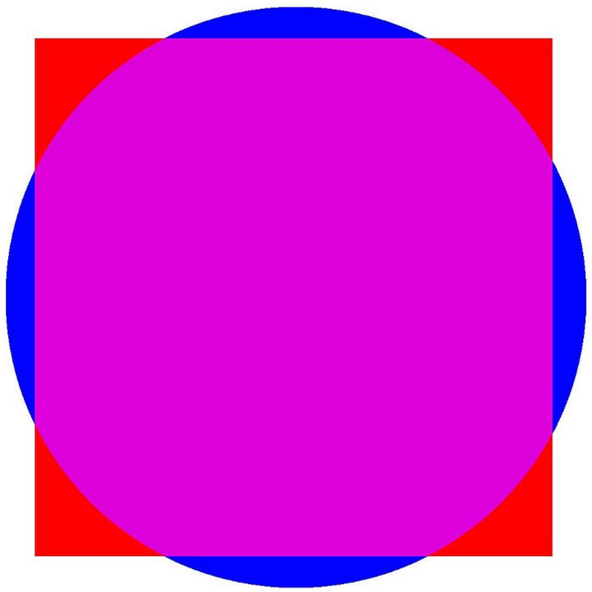
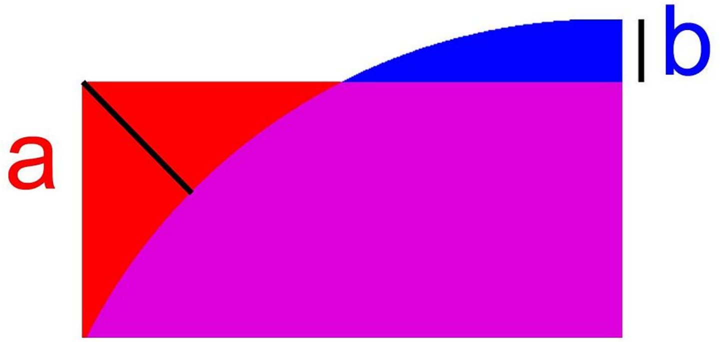
Prop: $R(P, r/2) \subseteq C(P, r) \subseteq R(P, r)$.

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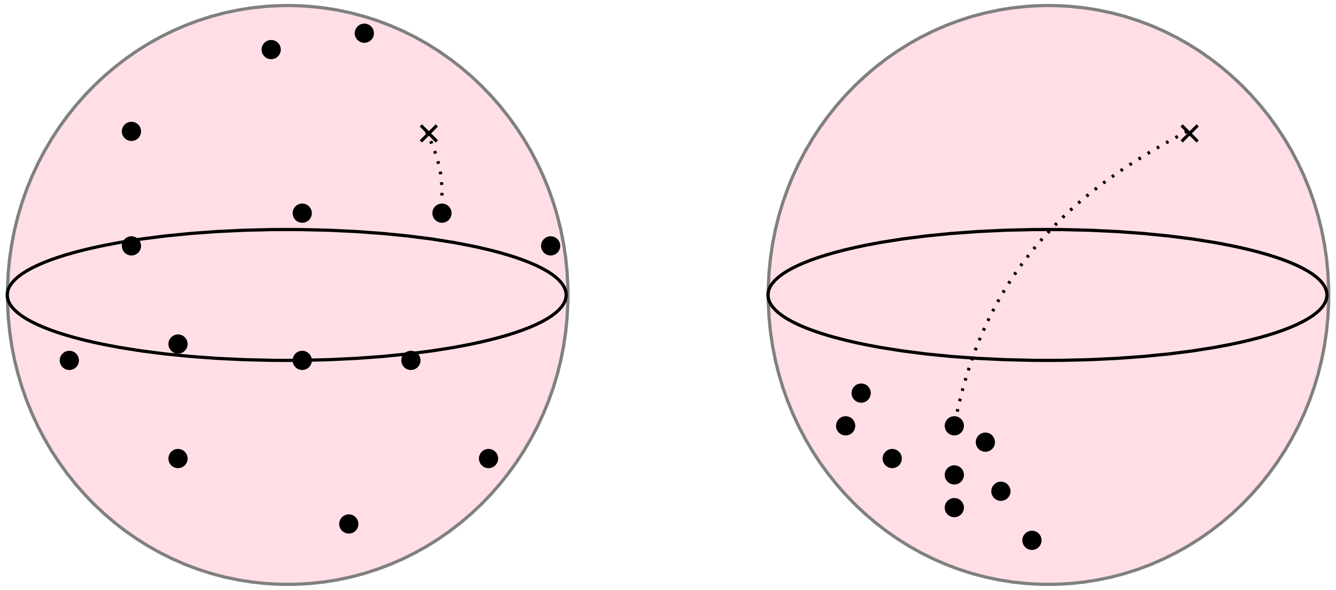
Ex: Given a sampling $\hat{X}_n \subseteq X$, $d_H(\hat{X}_n, X)$ is a measure of sampling quality.



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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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$$d_{GH}((X,d_X),(Y,d_Y)) = \inf_{\mathcal{C}} \sup_{(x,y),(x',y')\in\mathcal{C}} |d_X(x,x') - d_Y(y,y')|,$$

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

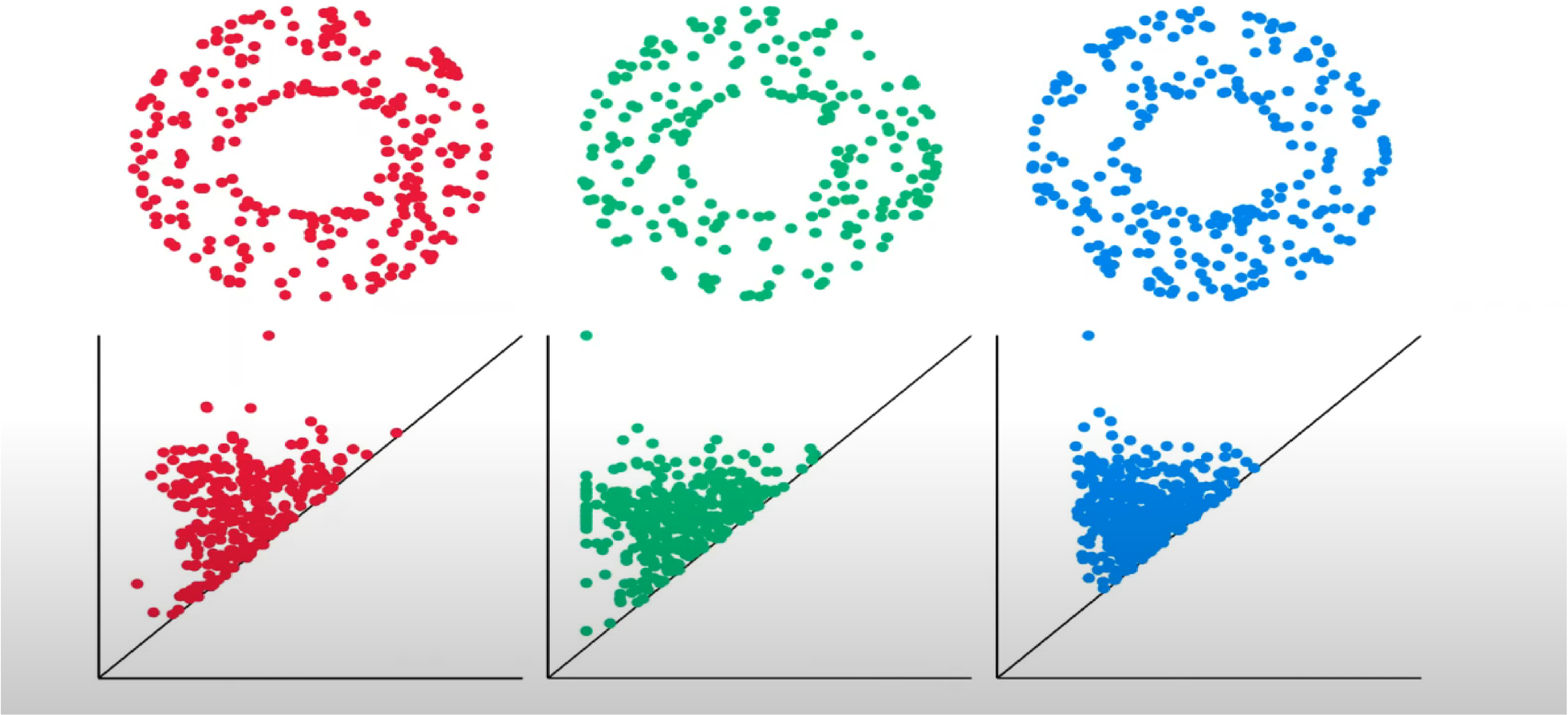
$$d_b(D_{\text{Cech}}(X), D_{\text{Cech}}(Y)) \leq d_H(X,Y).$$

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

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



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?

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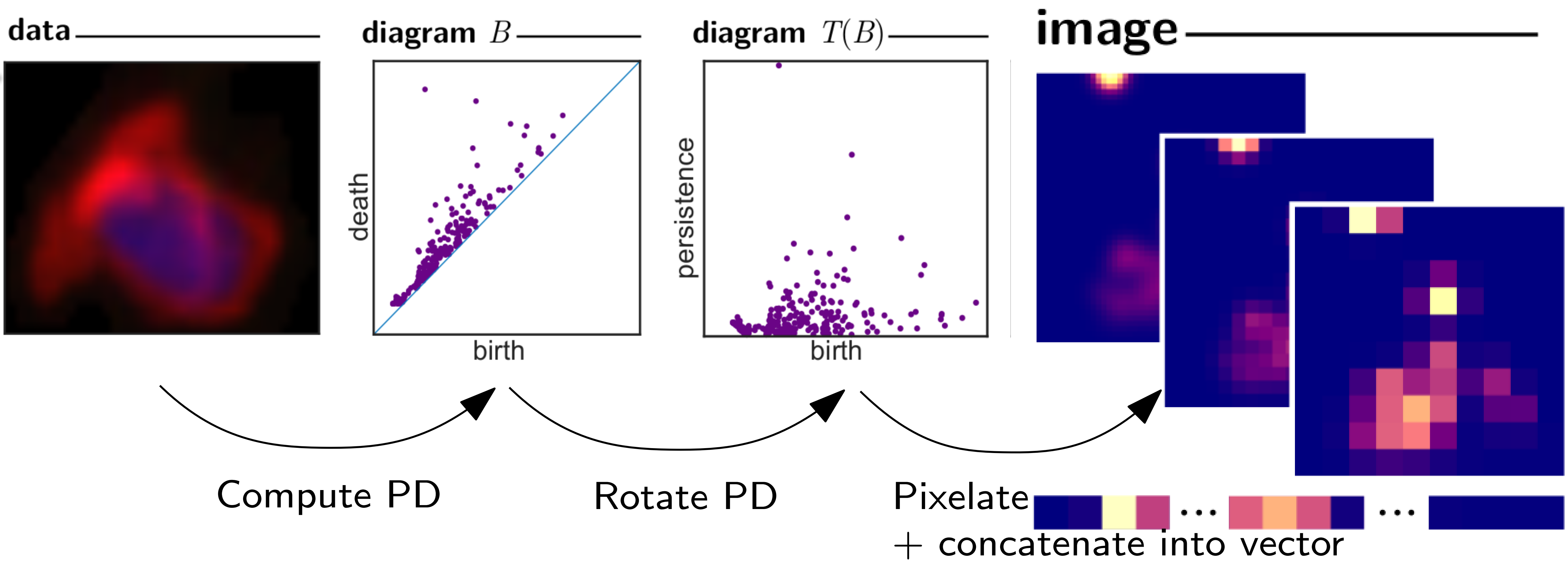
A: Use **representations**, which are mappings $\Phi : \mathcal{D} \to \mathcal{H}$ from the space of persistence diagrams to Hilbert spaces.

Persistence image

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



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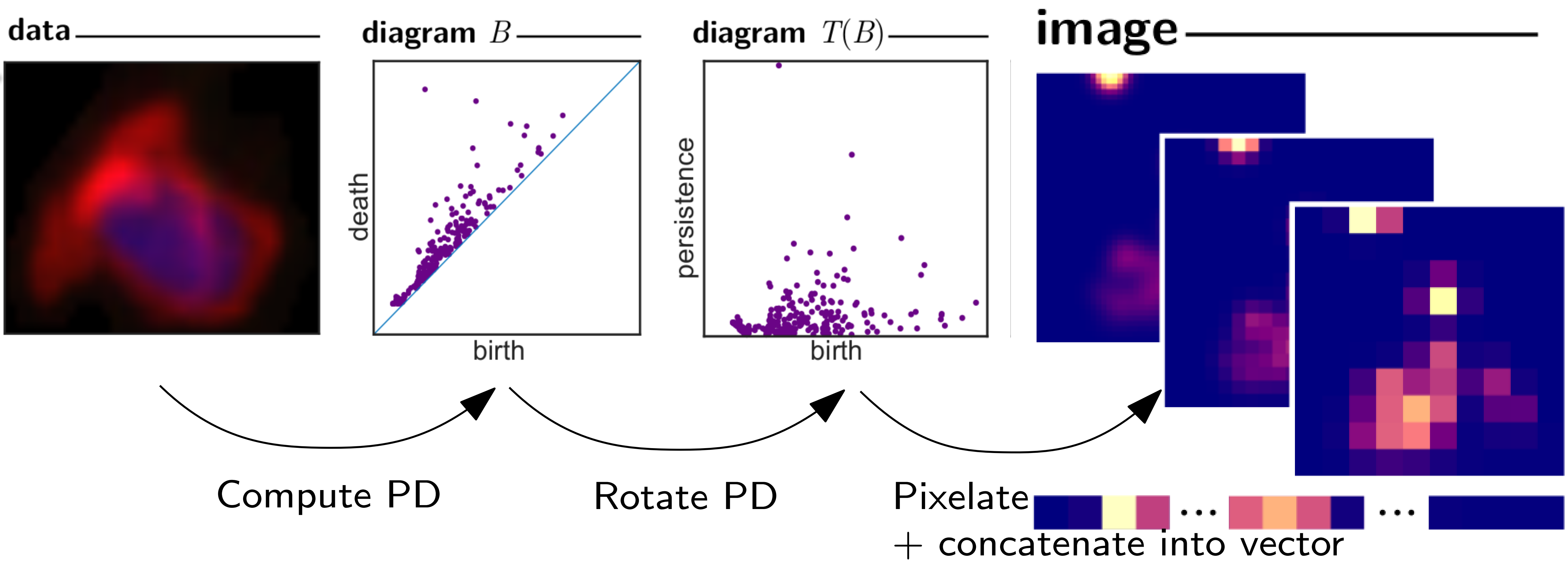
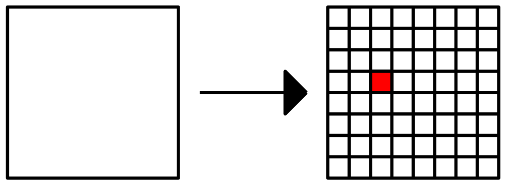


Discretize plane into a grid:



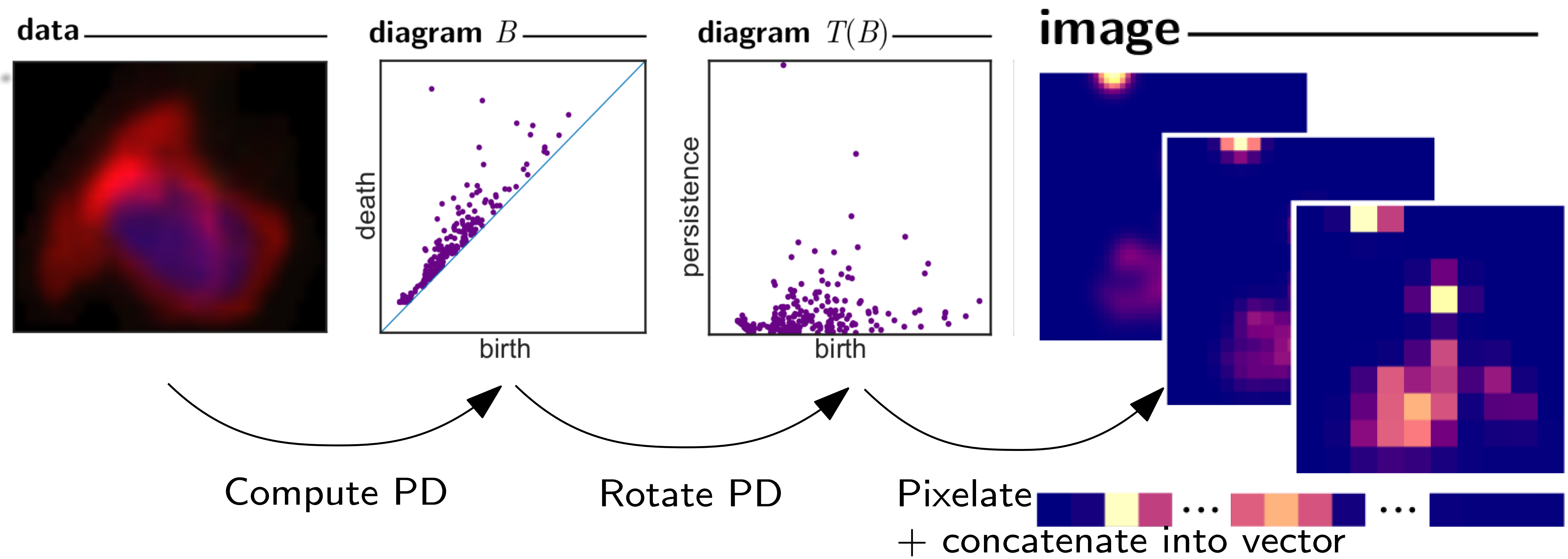
For each grid pixel P, compute $I(P) = \sum_{p\in D} \int\int_P w(p)\cdot\phi_p$.

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

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

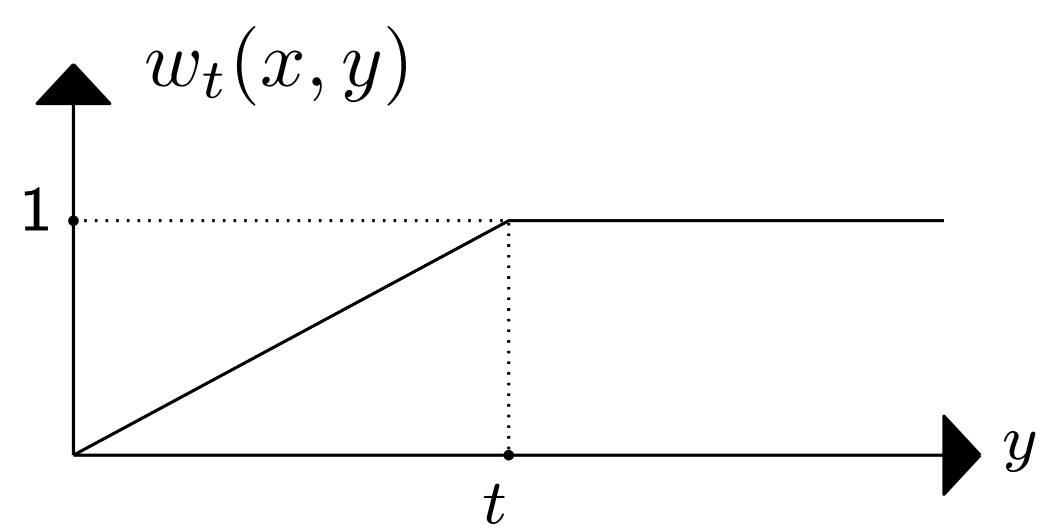
Persistence image

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



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

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



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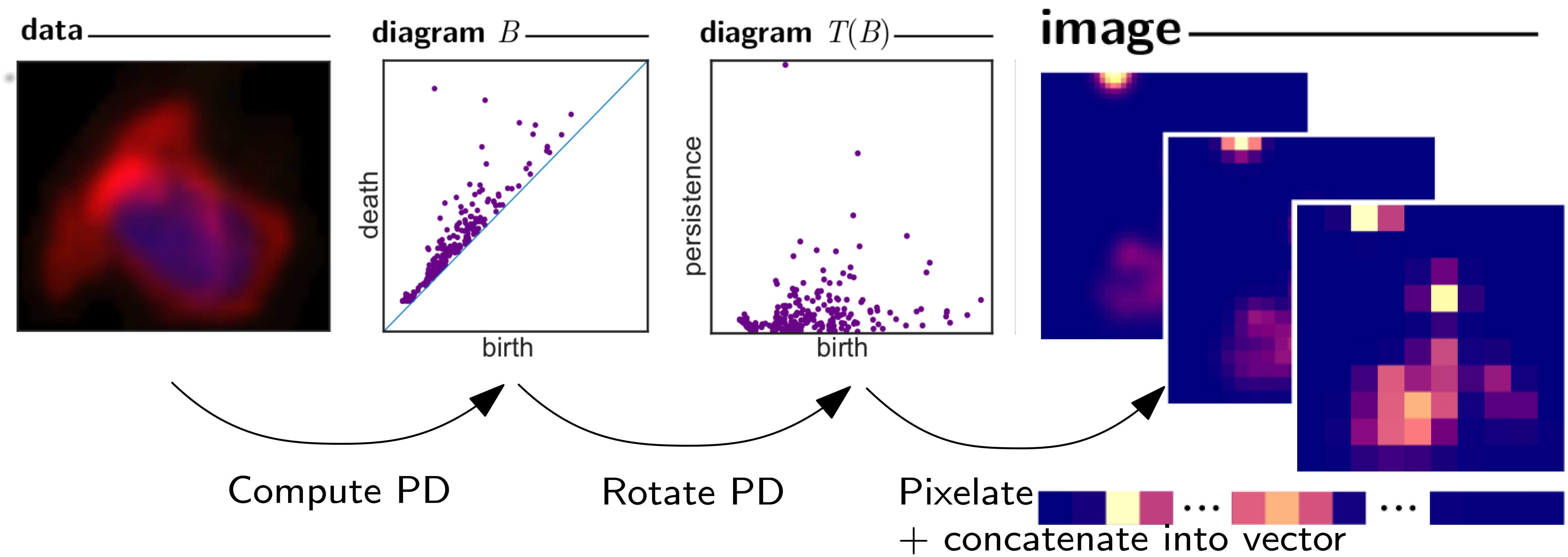
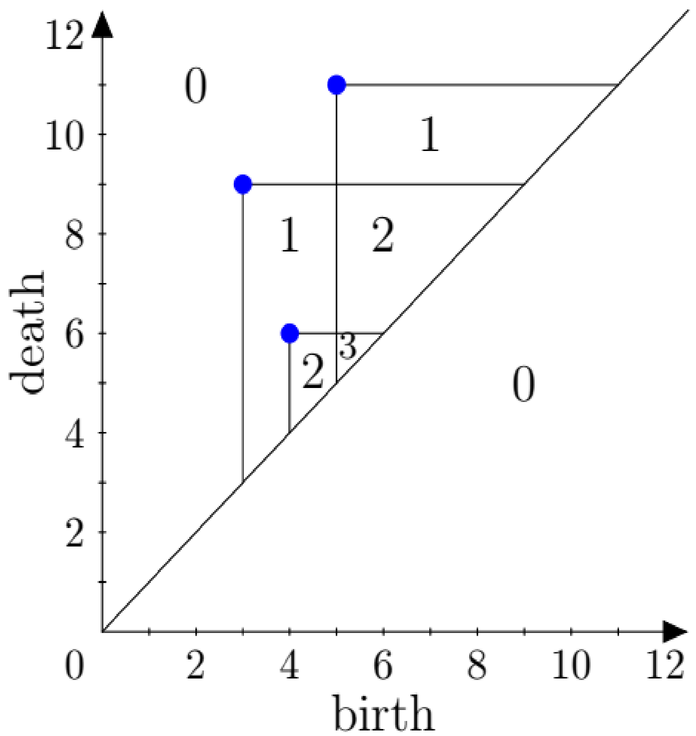


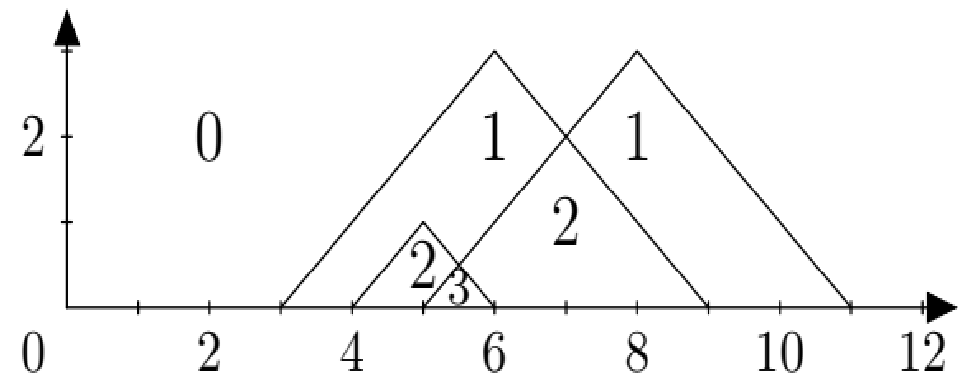
Prop: The following inequalities hold:

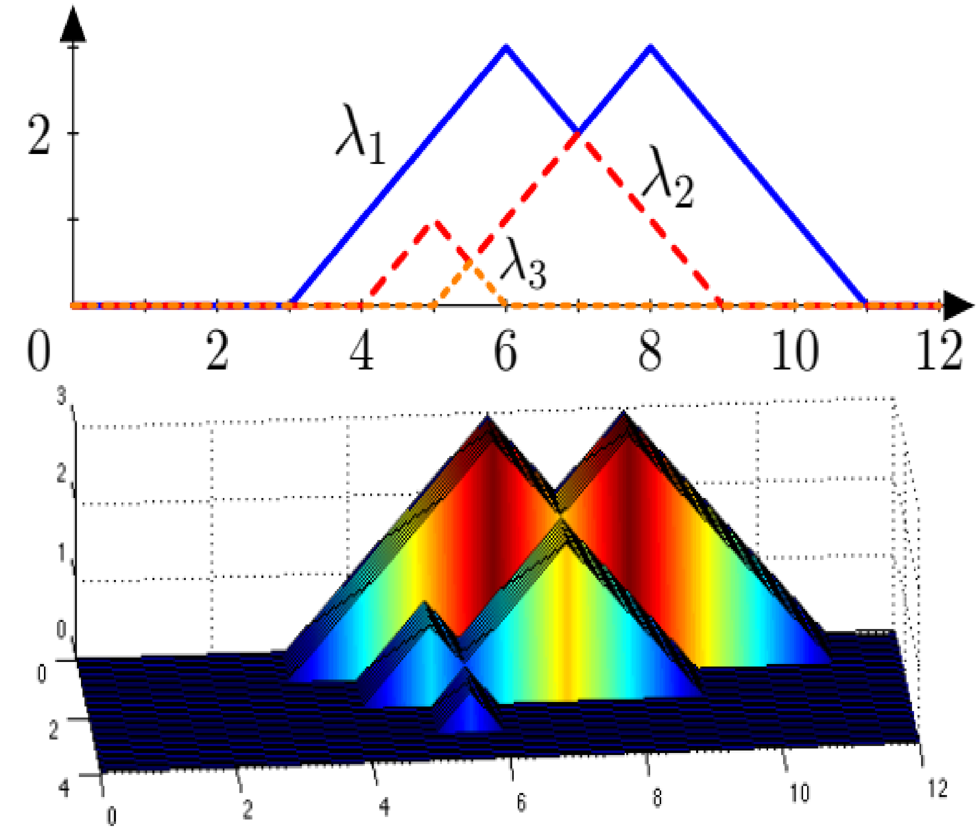
- $\|\mathrm{PI}(D) - \mathrm{PI}(D')\|_\infty \leq C(w, \phi_p)\, d_1(D, D')$.
- $\|\mathrm{PI}(D) - \mathrm{PI}(D')\|_2 \leq \sqrt{d} \cdot C(w, \phi_p)\, d_1(D, D')$.

Persistence landscape

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





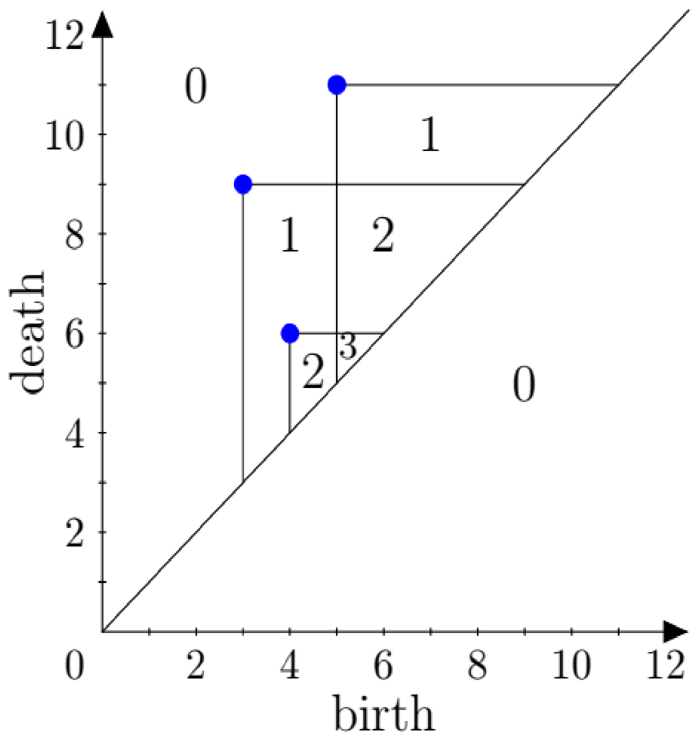


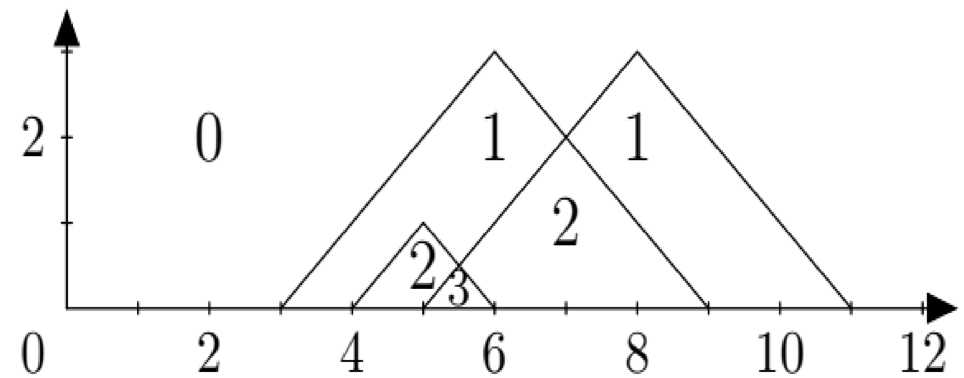
Rotate PD
Compute rank function

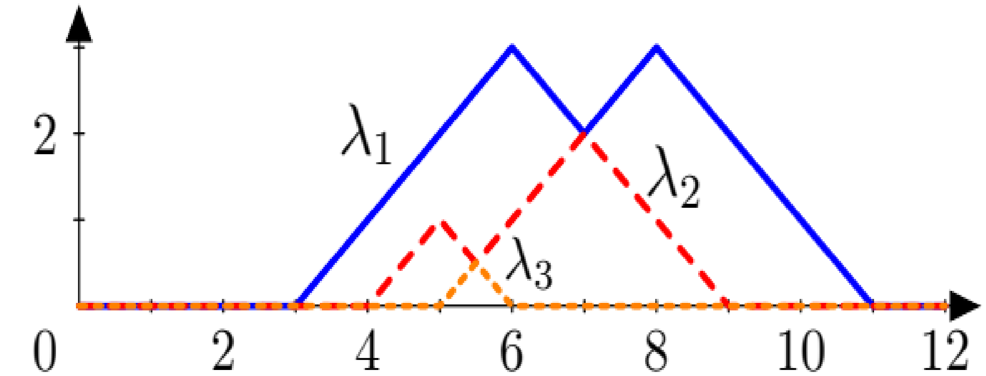
Use boundaries of
rank function

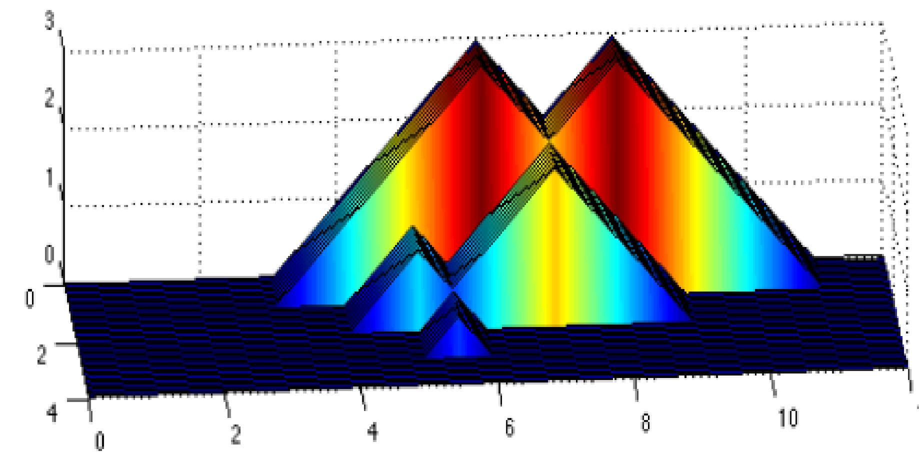
Persistence landscape

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









Rotate PD
Compute rank function

Use boundaries of rank function

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

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

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

Persistence landscape

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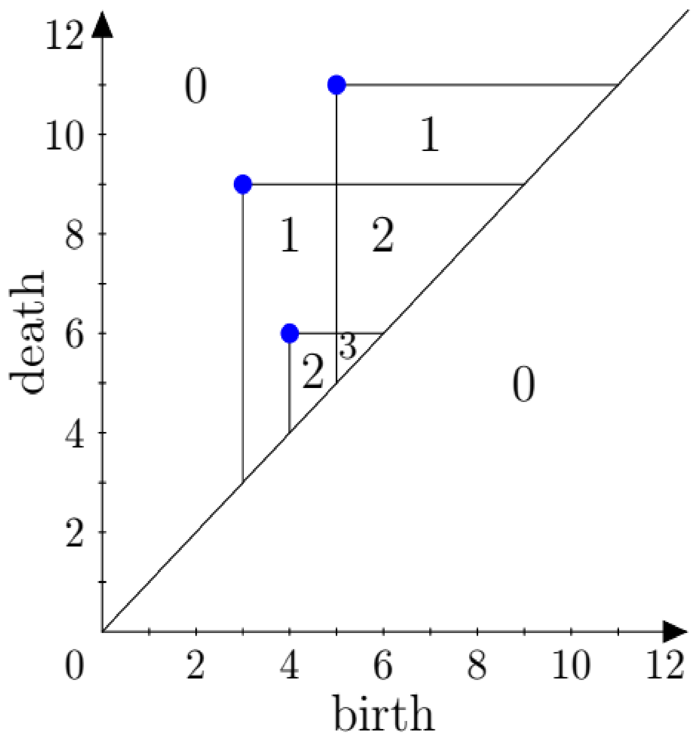

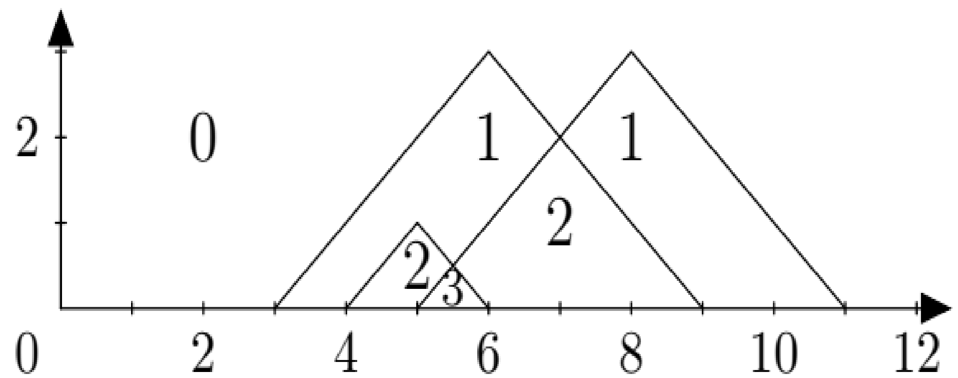

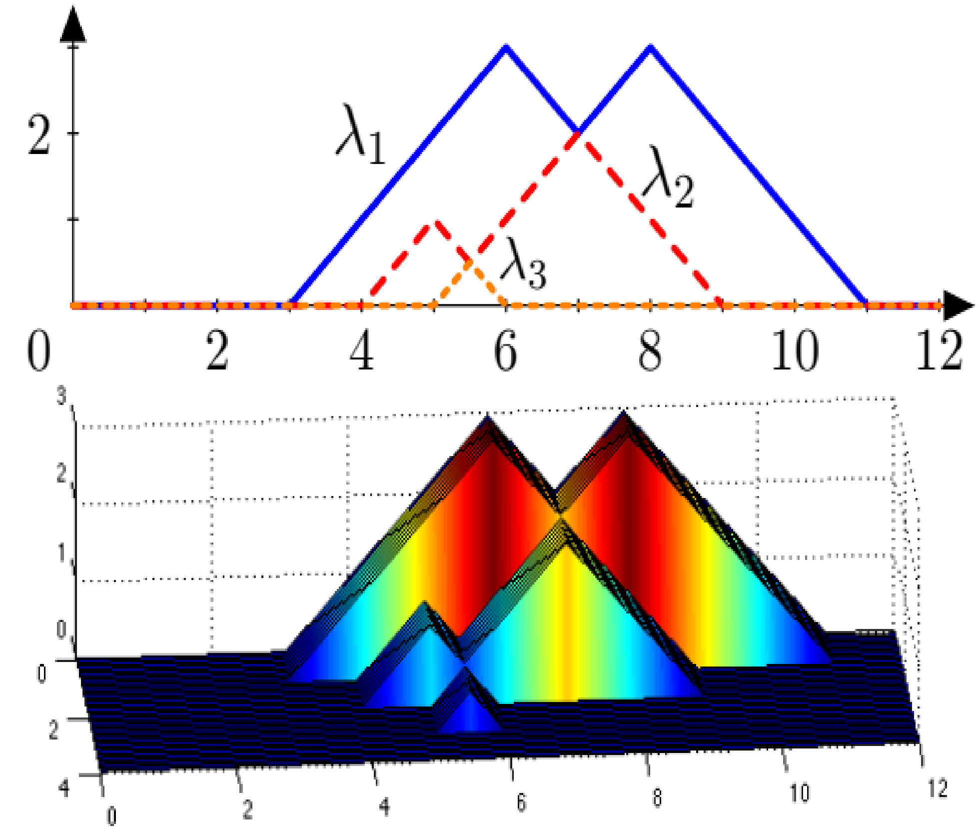

Rotate PD
Compute rank function

Use boundaries of rank function

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

Landscape $\Lambda : \mathbb{R}^2 \to \mathbb{R}$ is defined as: $\Lambda(i,t) = \lambda_{\lfloor i \rfloor}(t)$

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

Persistence landscape

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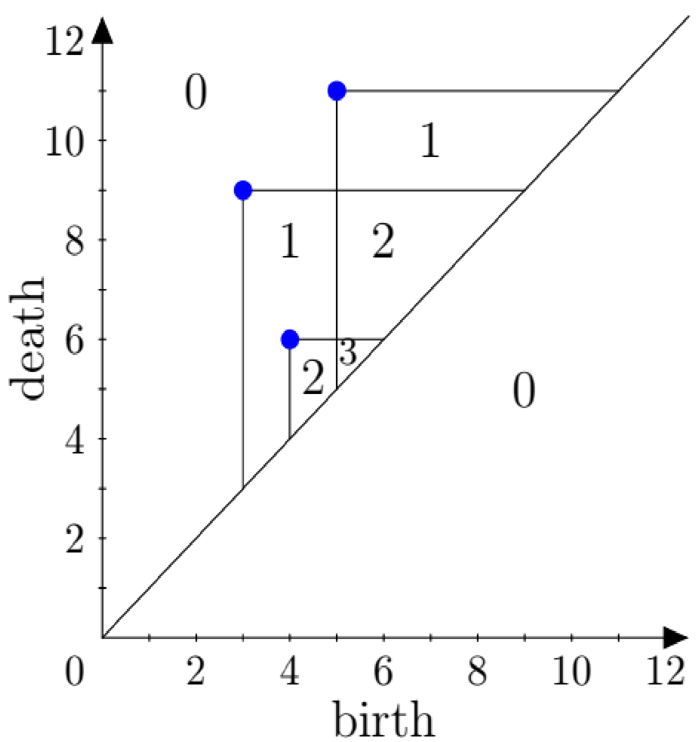

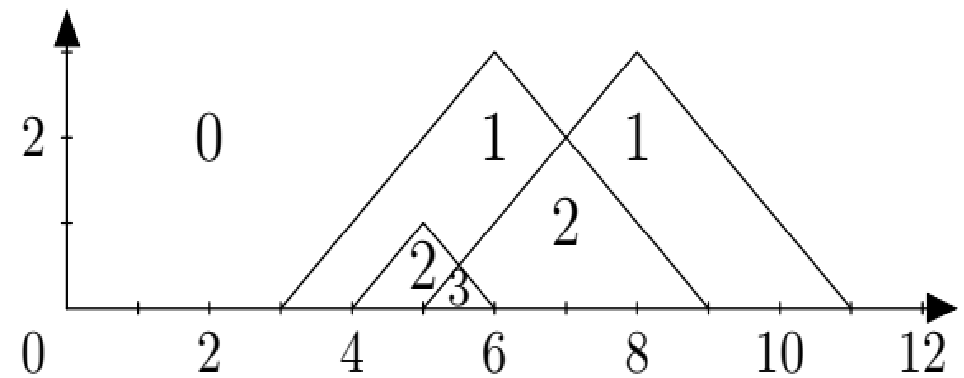

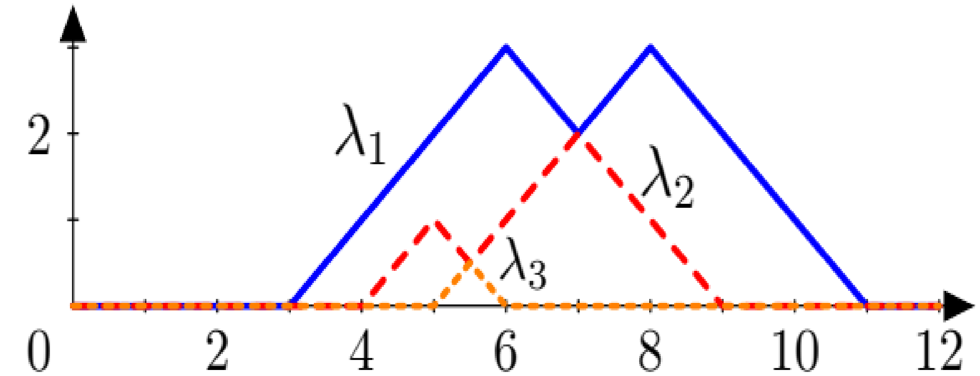

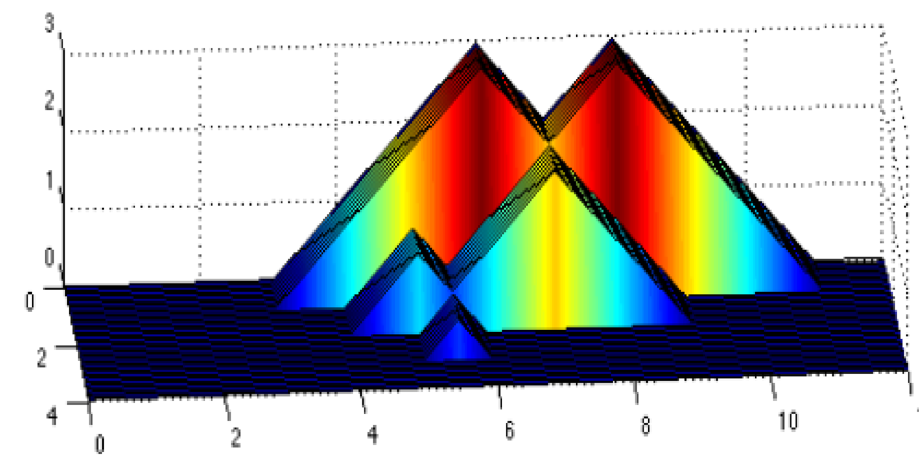

Rotate PD
Compute rank function

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

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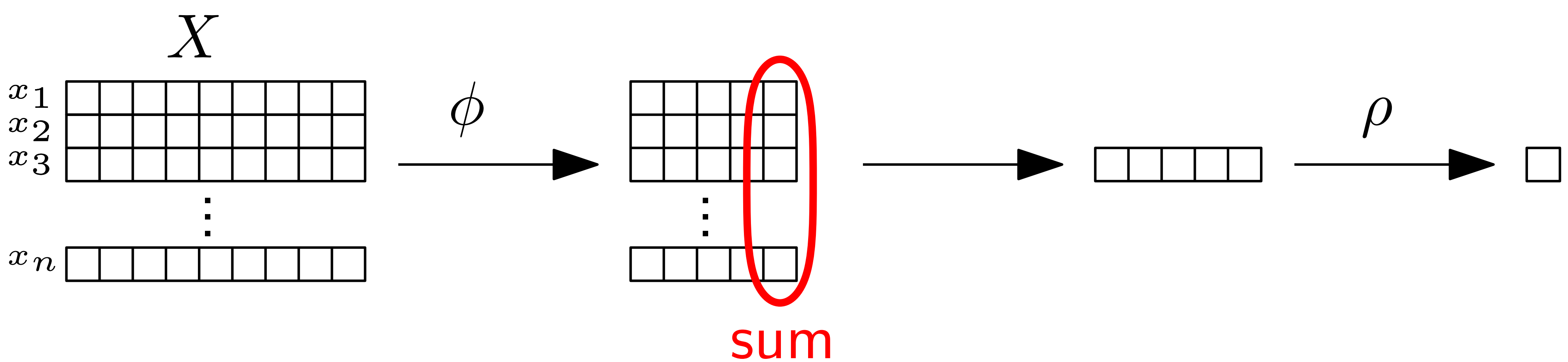
Input: $\{x_1, ..., x_n\} \subset \mathbb{R}^d$ instead of $x \in \mathbb{R}^d$

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

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



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

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Universality theorem

Thm: A function f is permutation invariant iif $f(X) = \rho\left(\sum_i \phi(x_i)\right)$ 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

Application to PDs

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$\longrightarrow$ persistence images

Application to PDs

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$\rightarrow$ persistence images $\quad$ $\rightarrow$ landscapes

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$\rightarrow$ persistence images $\rightarrow$ landscapes $\rightarrow$ 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, kth largest value) allows to generalize other TDA approaches

Application to PDs

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$$\mathrm{PersLay}(D) = \rho\left(\mathsf{op}\{w(p) \cdot \phi(p)\}_{p \in D}\right)$$

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Point transformation

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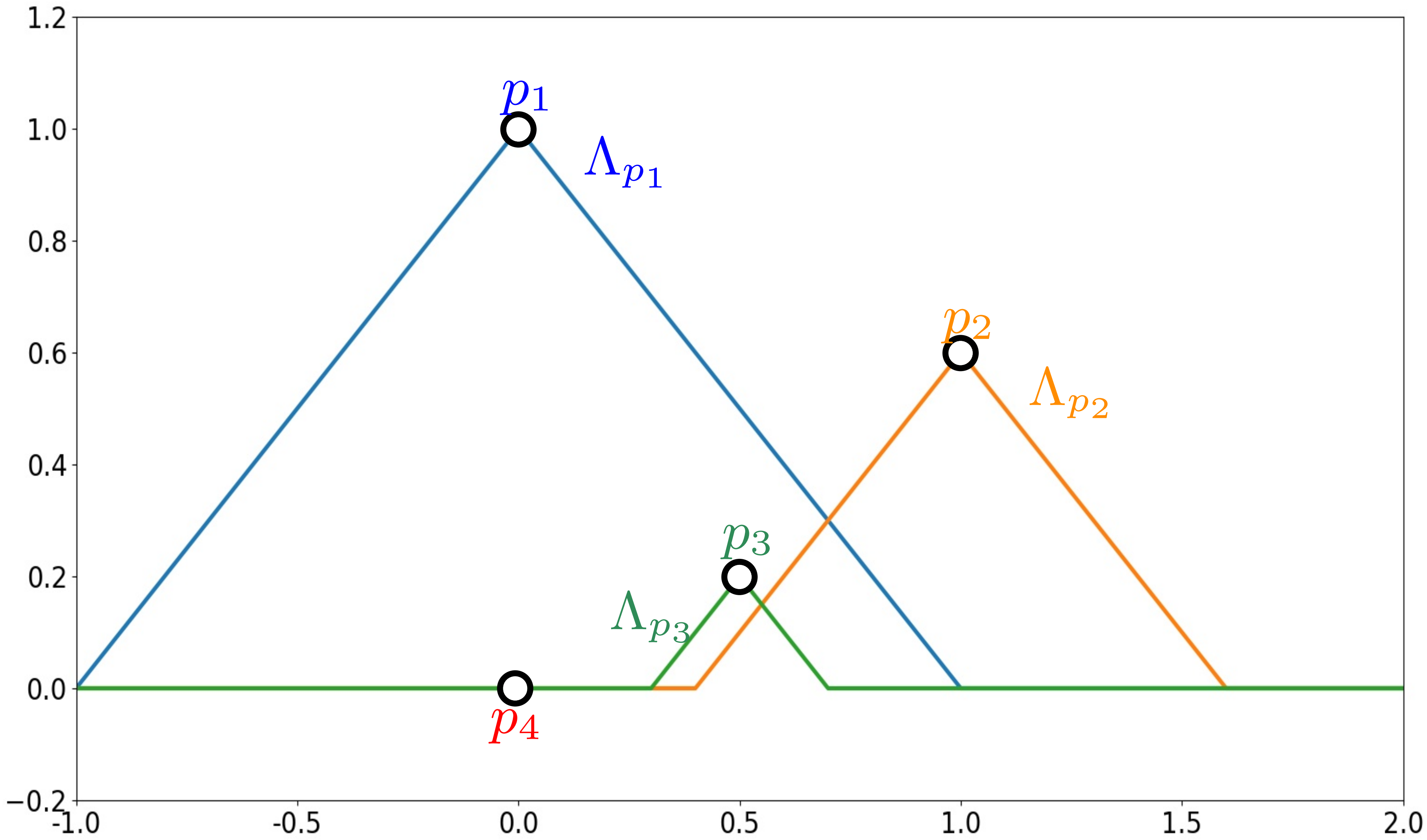
Parameters $t_1, \cdots, t_q \in \mathbb{R}$

$$w(p) = 1 \qquad \phi_\Lambda : p \mapsto \begin{bmatrix} \Lambda_p(t_1) \\ \Lambda_p(t_2) \\ \vdots \\ \Lambda_p(t_q) \end{bmatrix} \qquad \text{op} = \text{top-}k$$



Application to PDs

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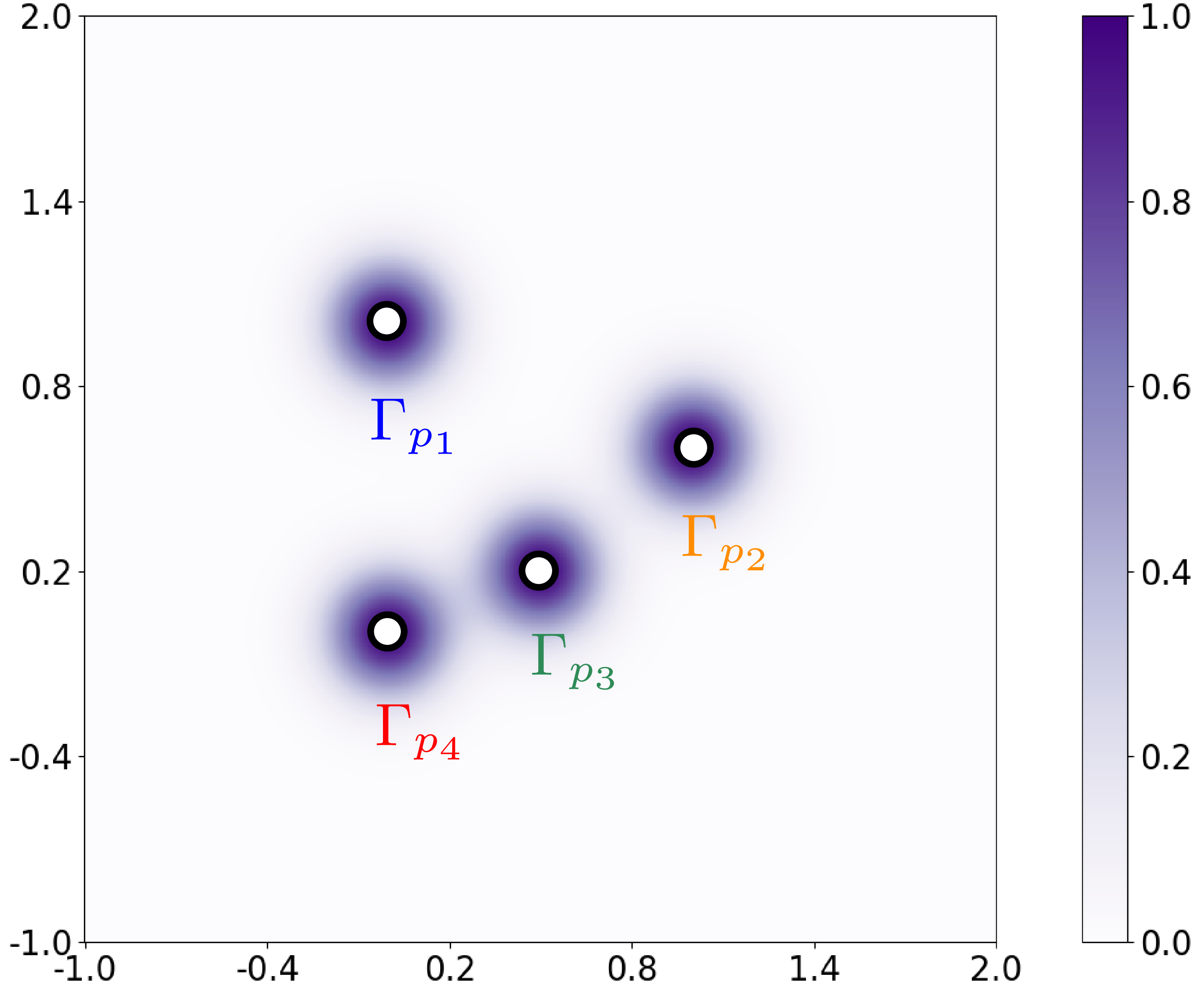
Parameters $t_1, \cdots, t_q \in \mathbb{R}^2$

$$w(p) = w_t((x, y)) \qquad \phi_\Gamma : p \mapsto \begin{bmatrix} \Gamma_p(t_1) \\ \Gamma_p(t_2) \\ \vdots \\ \Gamma_p(t_q) \end{bmatrix}$$

op = sum



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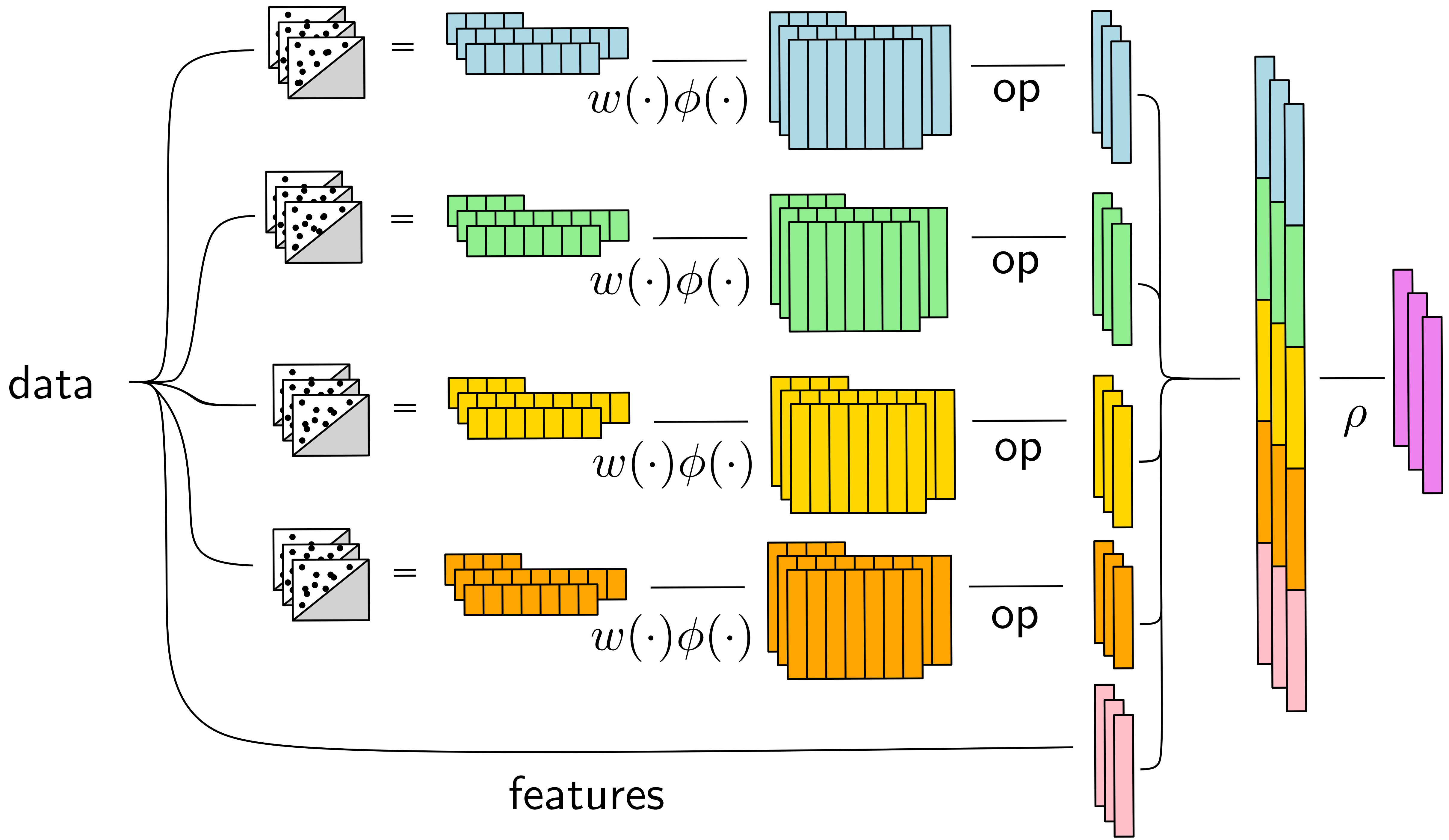

Application to graph classification

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

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 $0 \le \lambda_1 \le \cdots \le \lambda_n \le 2$

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

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

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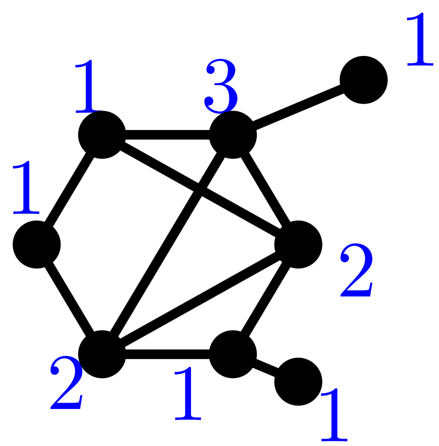

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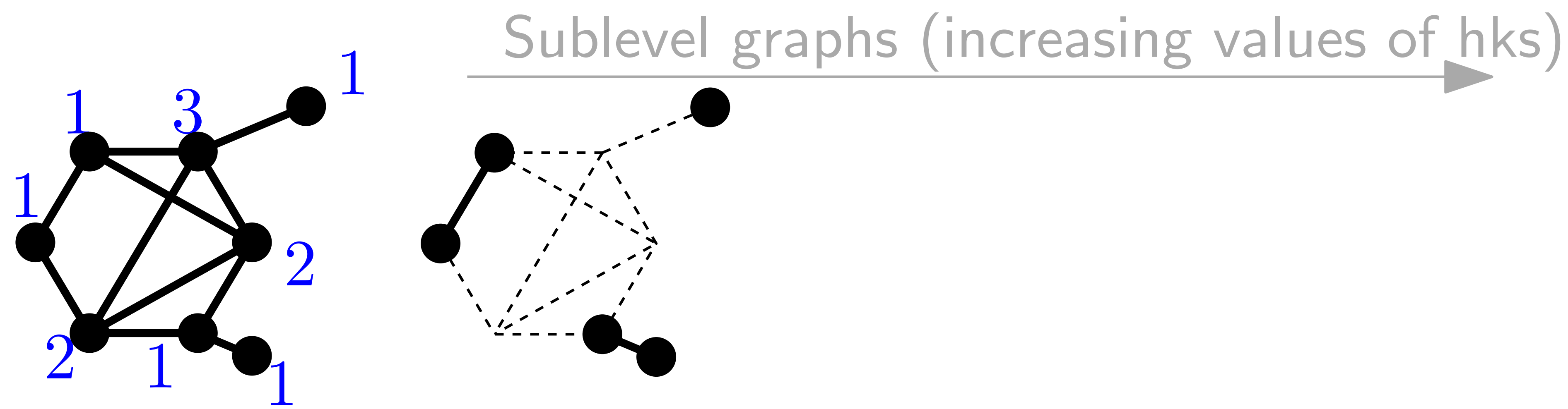

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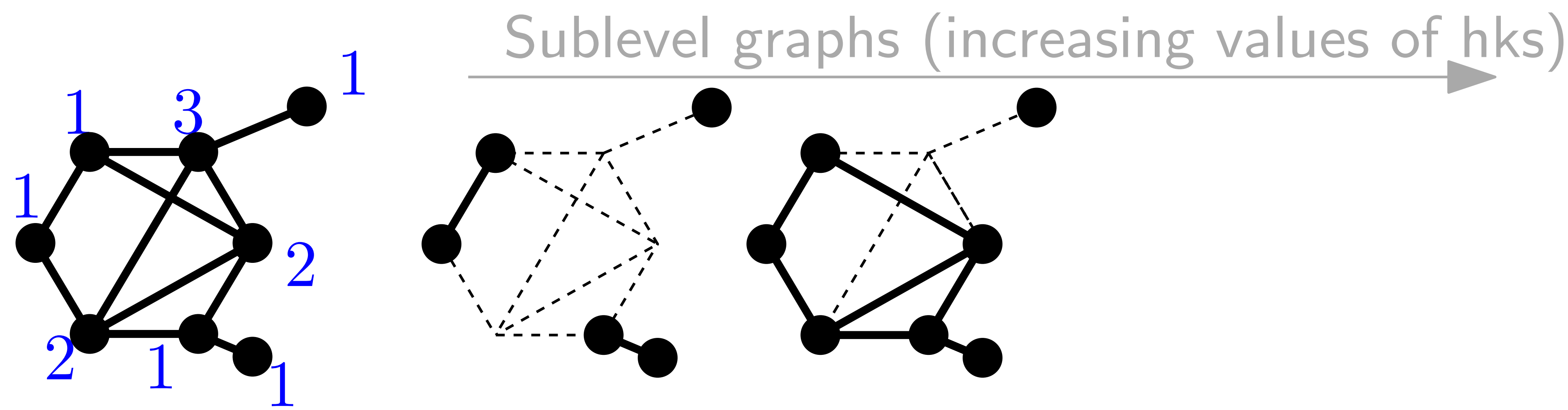

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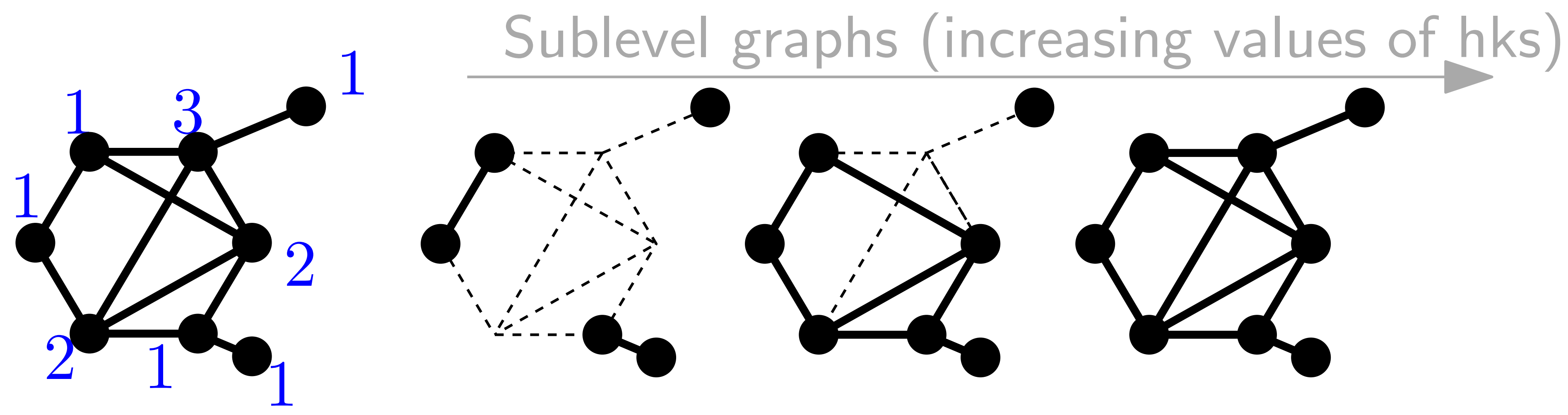

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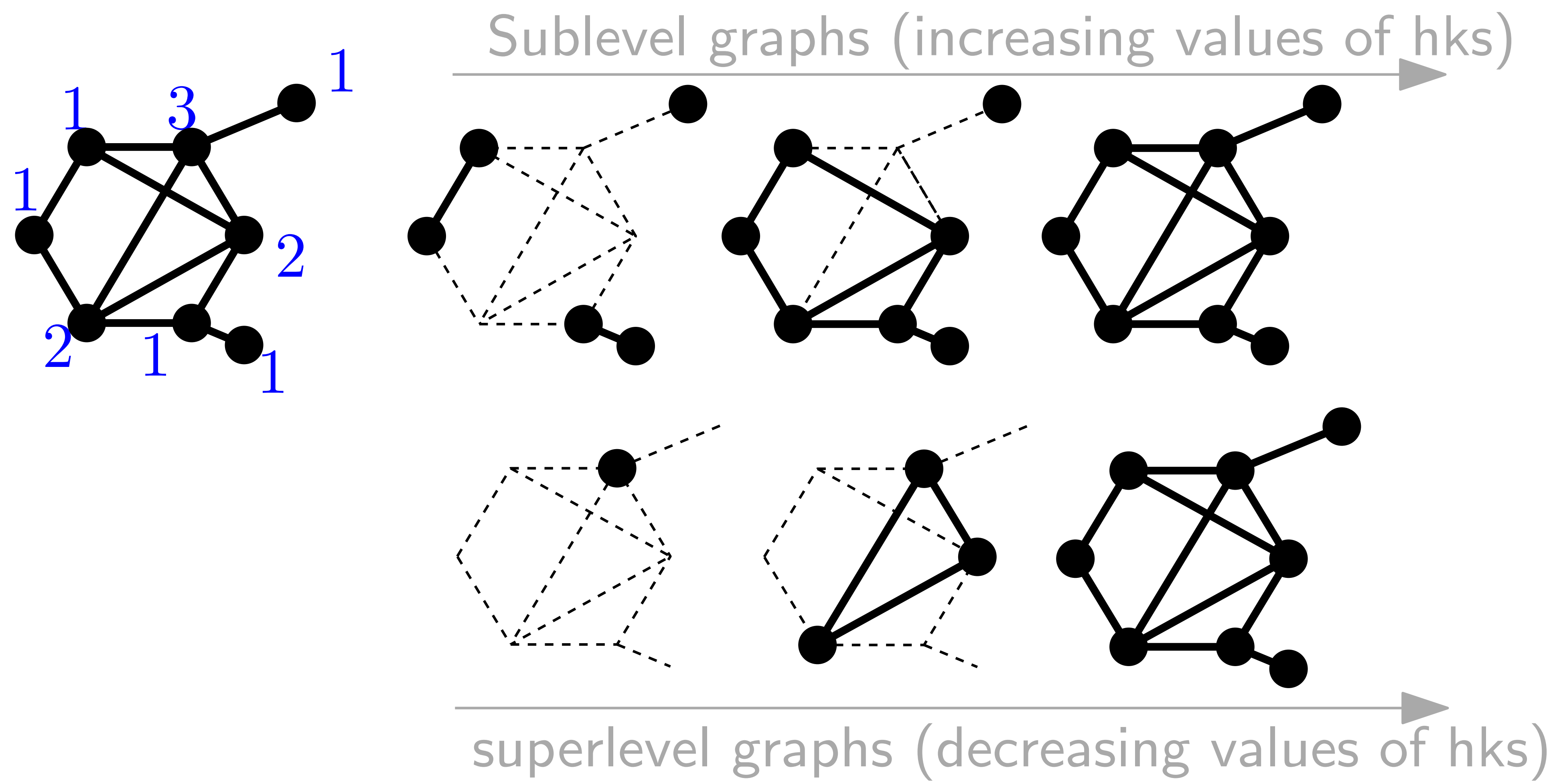

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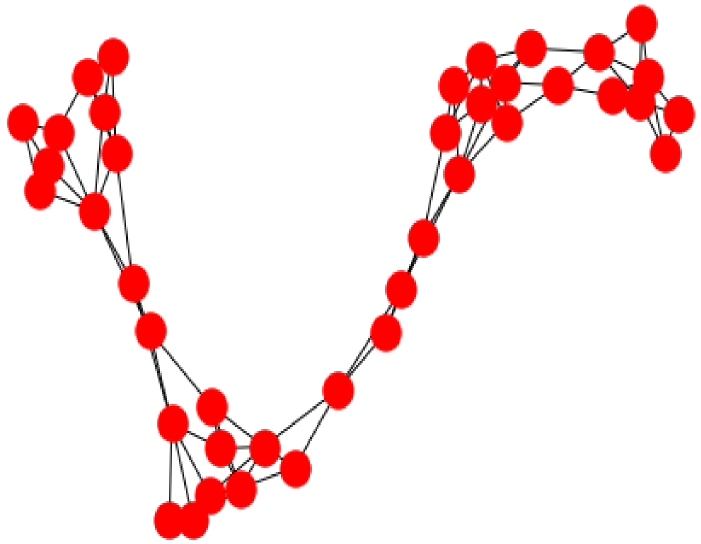
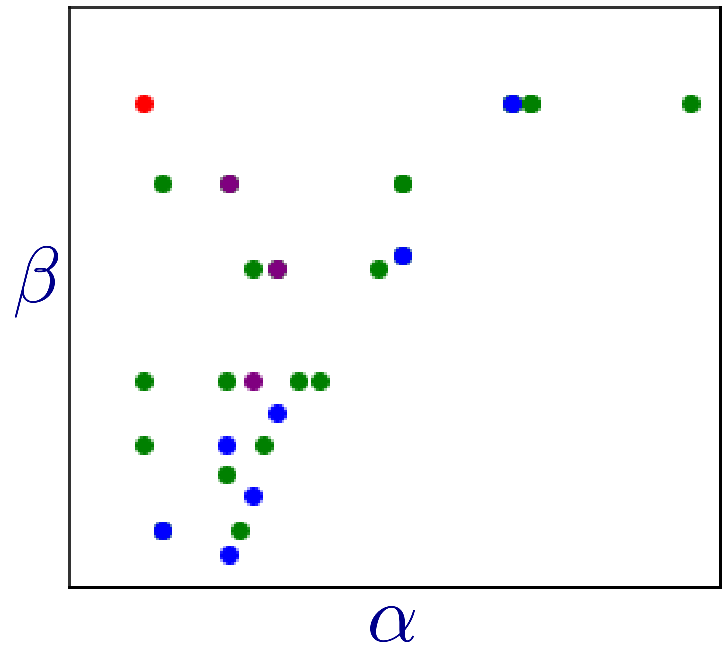
Graph from the `PROTEINS` dataset



Corresponding persistence diagram



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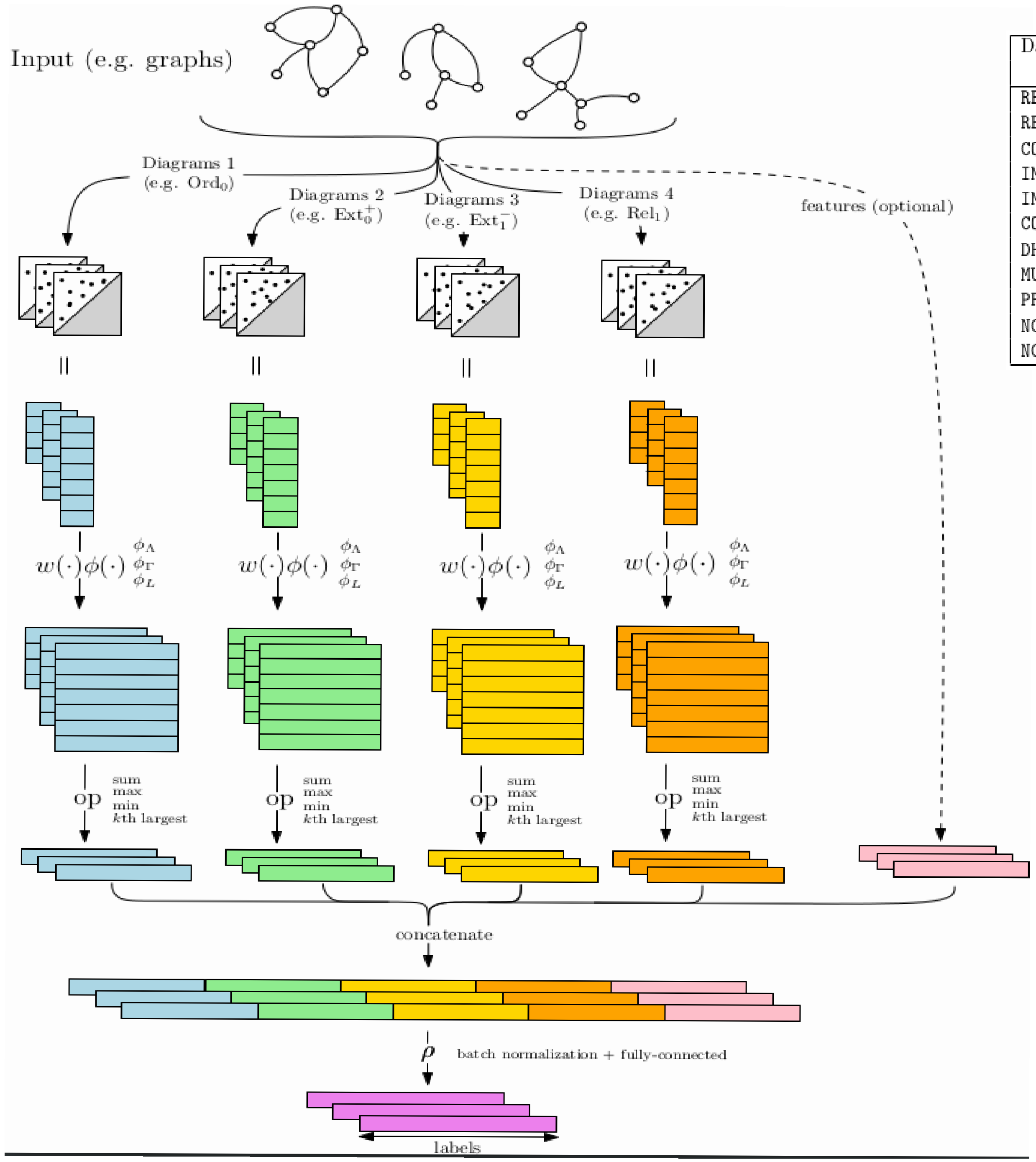
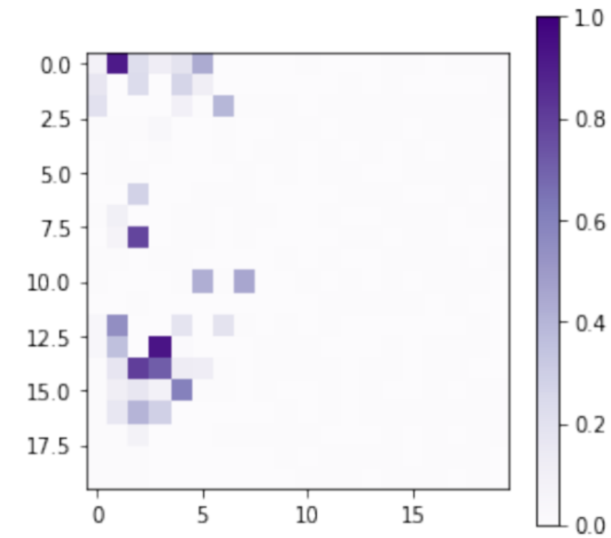


Dataset	SV[1]	RetGK* [2]	FGSD [3]	GCNN [4]	GIN [5]	PersLay	
						Mean	Max
REDDIT5K	—	56.1	47.8	52.9	57.0	55.6	56.5
REDDIT12K	—	48.7	—	46.6	—	47.7	49.1
COLLAB	—	81.0	80.0	79.6	80.1	76.4	78.0
IMDB-B	72.9	71.9	73.6	73.1	74.3	71.2	72.6
IMDB-M	50.3	47.7	52.4	50.3	52.1	48.8	52.2
COX2*	78.4	80.1	—	—	—	80.9	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

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2. Compute persistence images (PIMs) associated to Rips PDs of local point clouds.

Application to Pearson correlation

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1. Extract local point clouds corresponding to several measurement spots.
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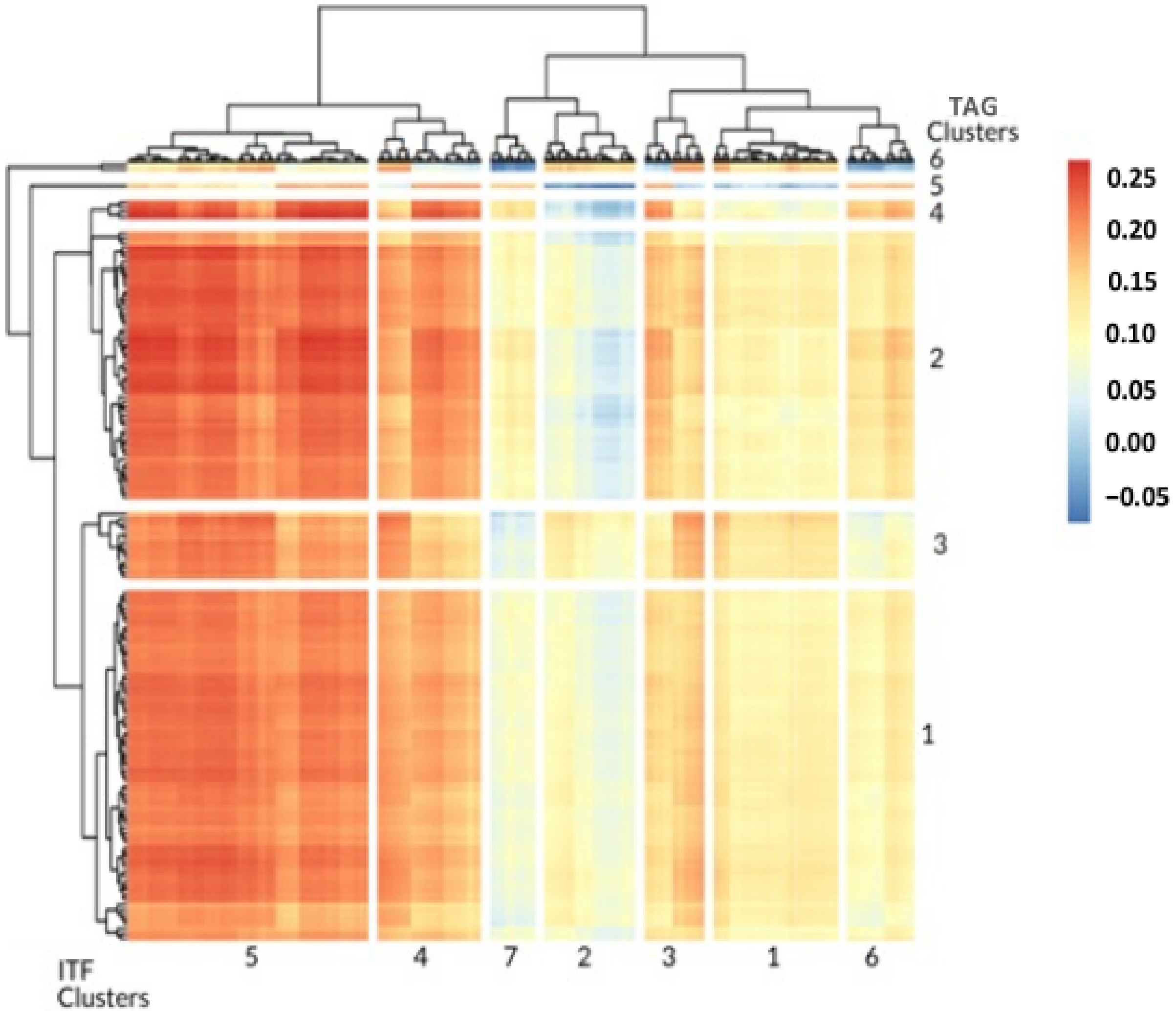
3. Cluster Image Topological Features (ITFs), i.e., PIM pixels, and marker genes, and compute all pairwise correlations.



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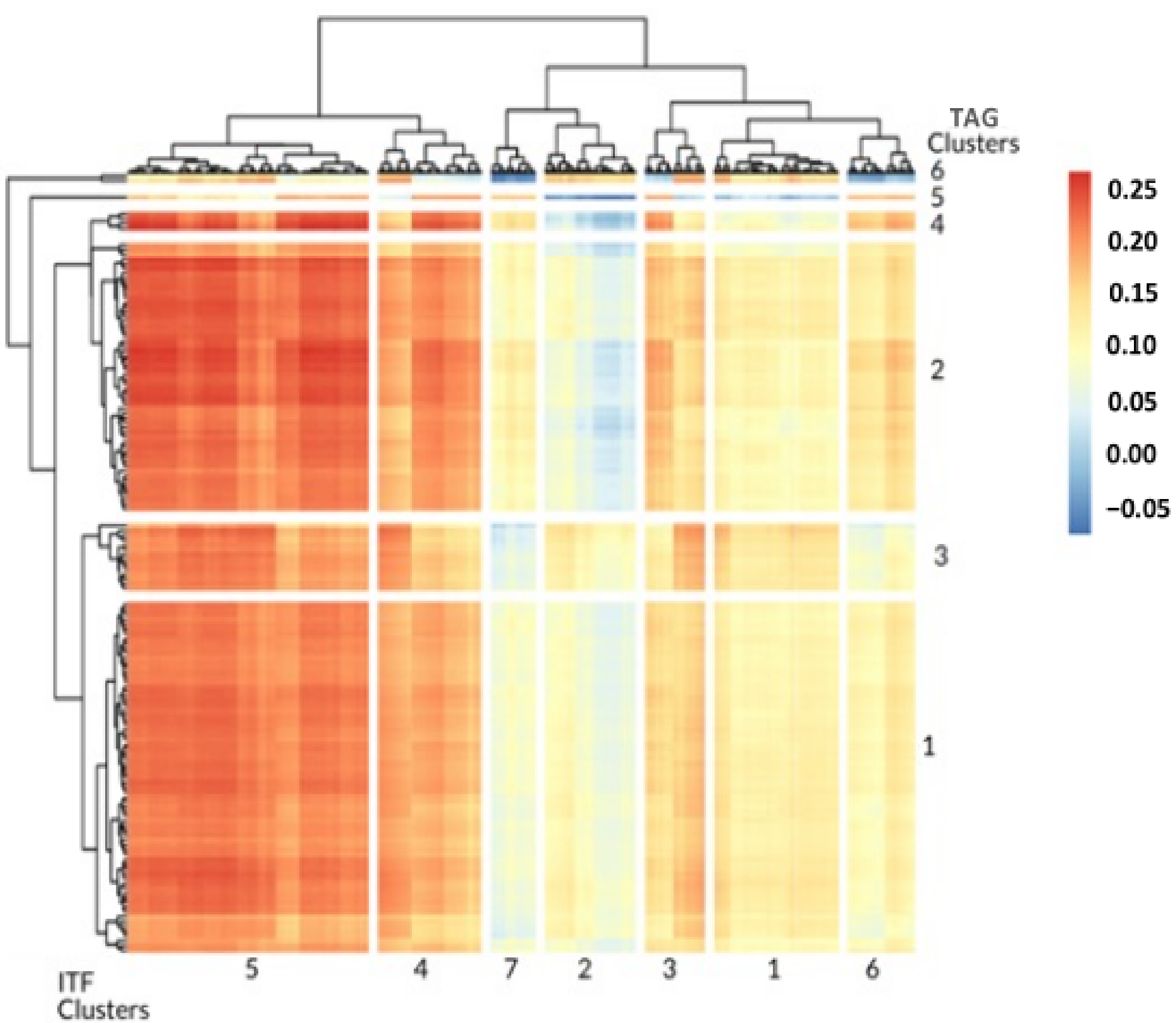
4. Retrieve marker genes with highest correlations and match these *topologically associated genes* (TAGs) against gene ontology.



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 vescicle	1.41×10^{-3}
GO:0043230	Extracellular organelle	1.41×10^{-3}

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5. Predict TAG expression from ITFs only.