

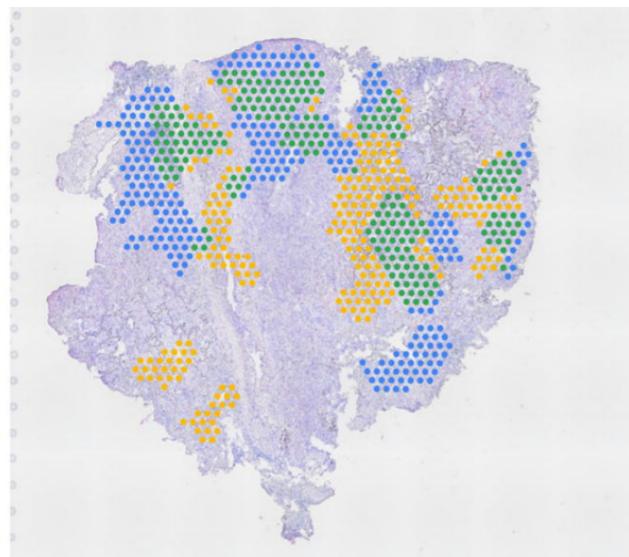
# Topological Data Analysis and Spatial Transcriptomics

**Instructor:**

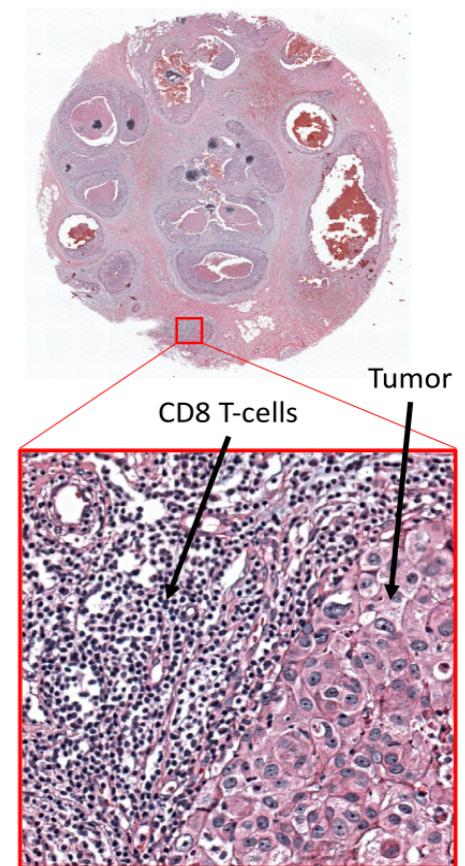
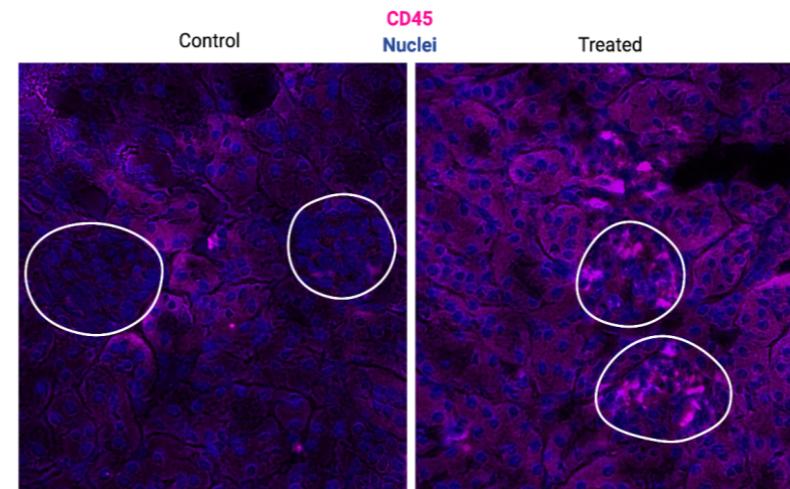
Mathieu Carrière

Centre Inria d'Université Côte d'Azur

[firstname.lastname@inria.fr](mailto:firstname.lastname@inria.fr)

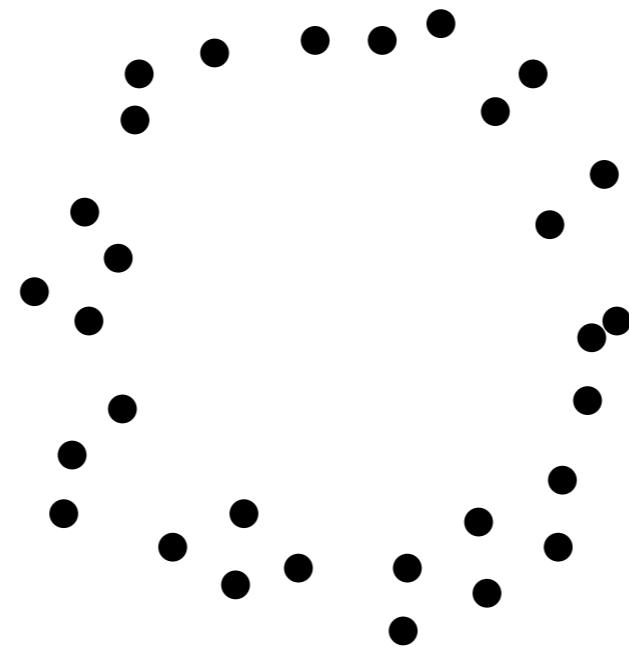


● B2M  
● TFRC  
● Overlap



# Introduction: what is TDA?

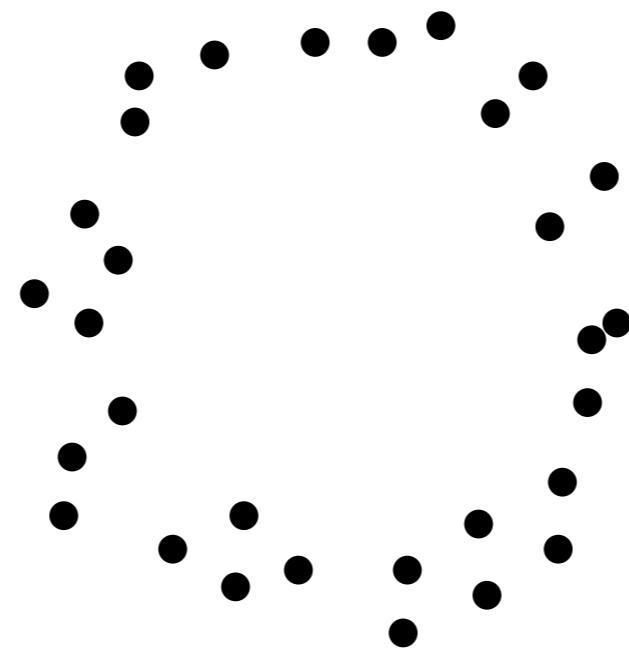
Roughly speaking, TDA allows to build features and descriptors from data sets using **topology** (i.e., the presence of holes in arbitrary dimensions)...



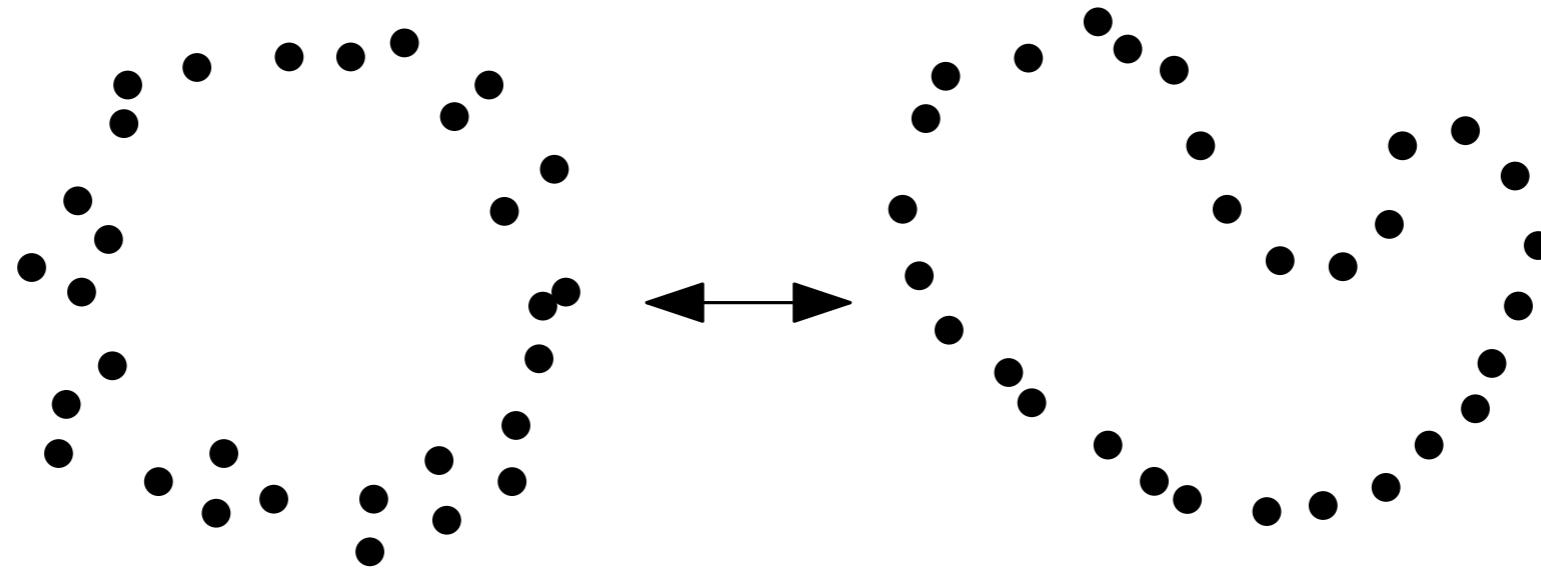
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...but why is that interesting?

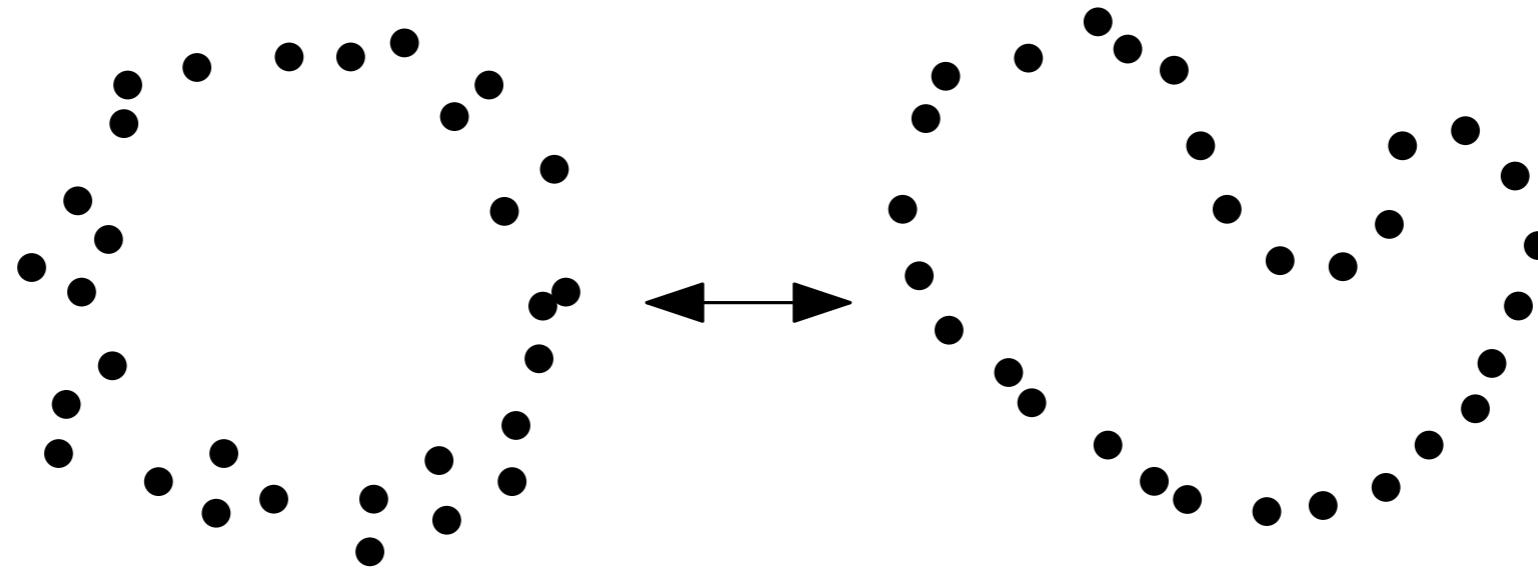


# Introduction: what is TDA?



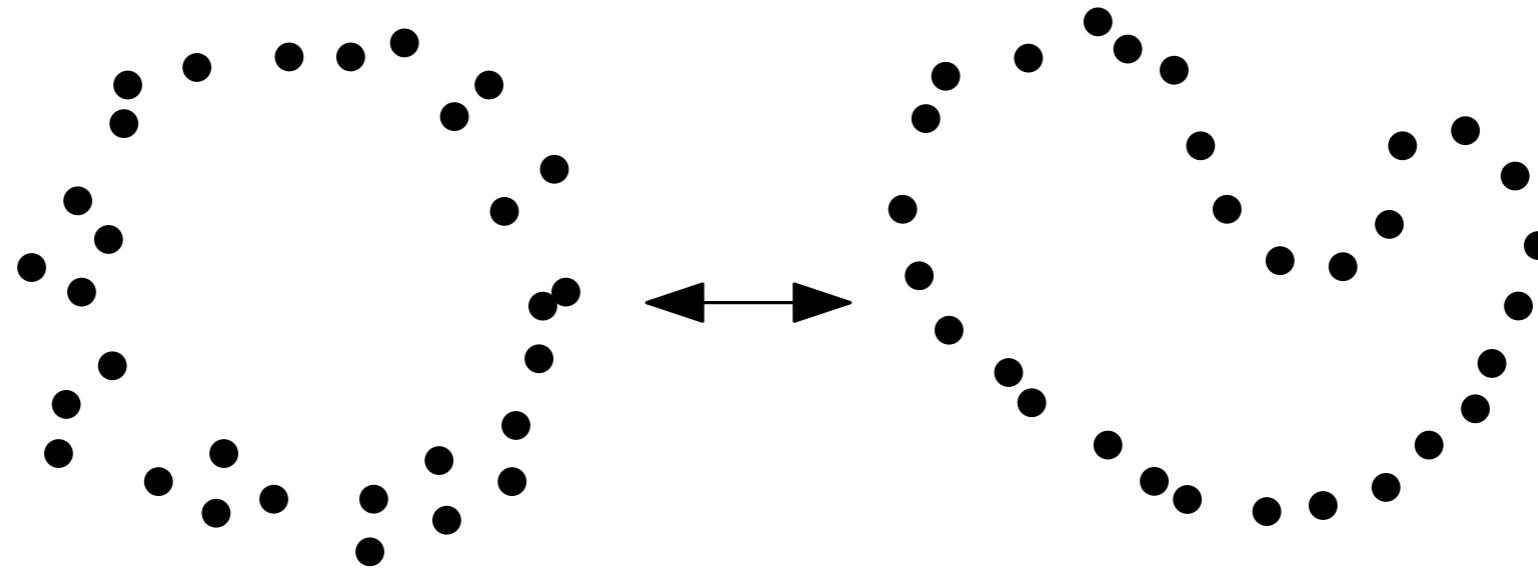
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- **Deformation invariance:** topological features are invariant under homeomorphism and reparameterization.

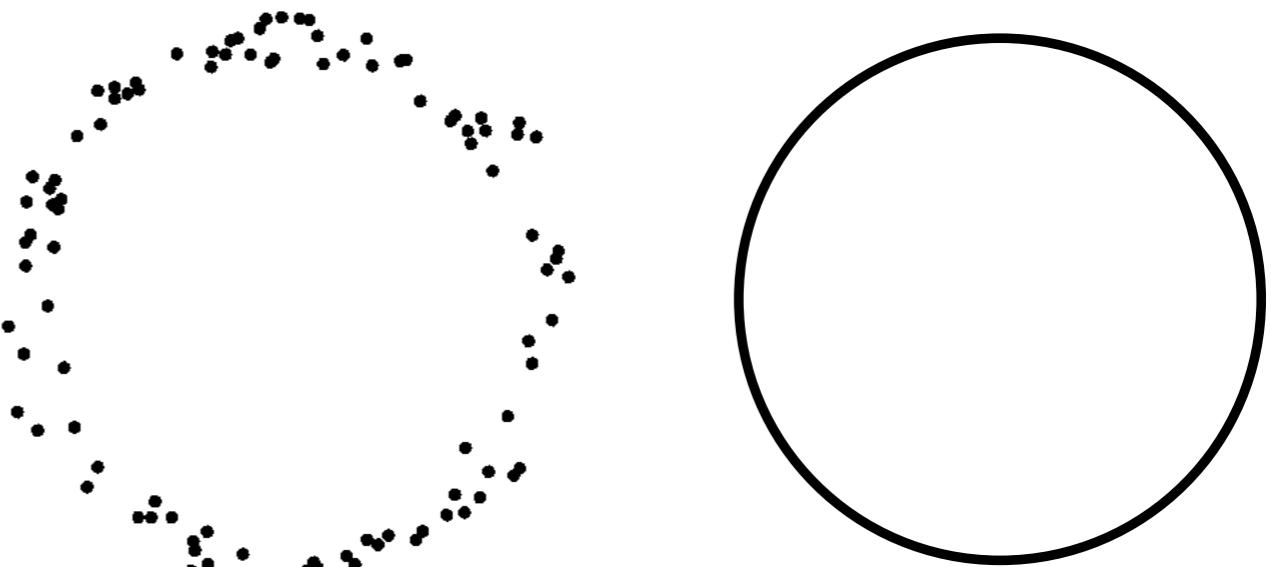
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- **Deformation invariance:** topological features are invariant under homeomorphism and reparameterization.
- **Compressed representation:** topology offers a set of tools to summarize the data in compact ways while preserving its topological structure.

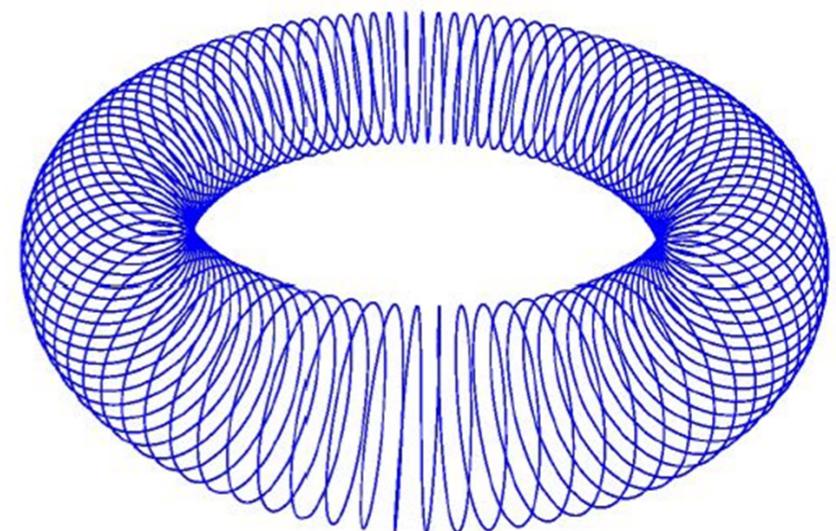
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**Problem:** how to define the *topology* of a data set?



**Cons of topology:**

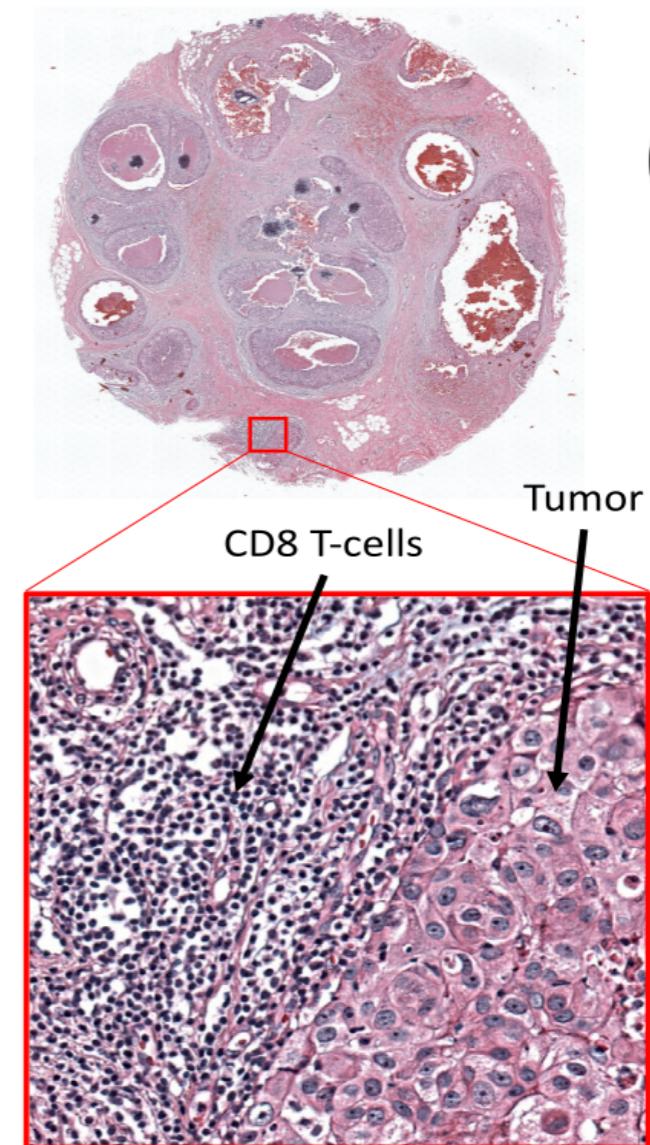
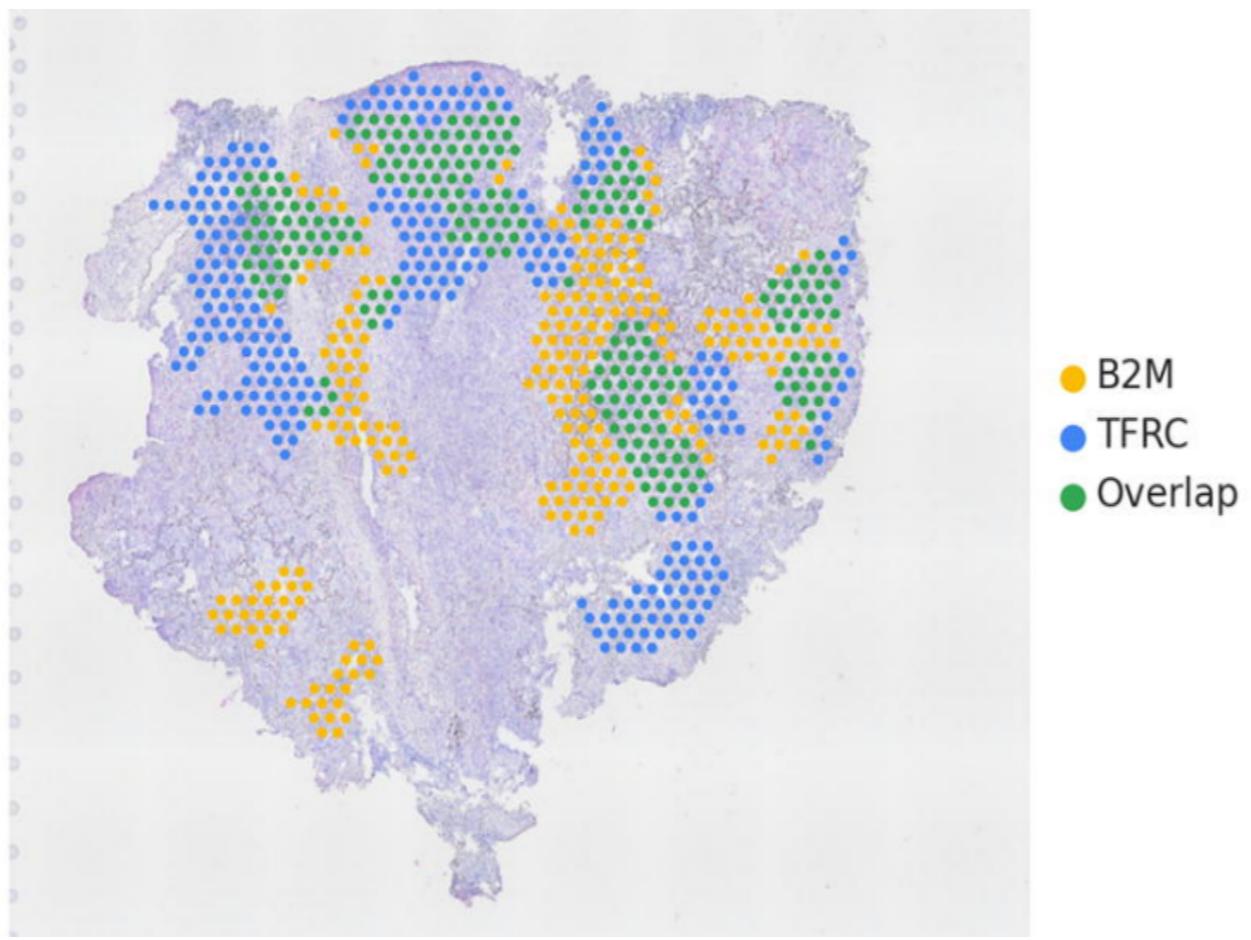
- No direct access to topological/geometric information: need of intermediate constructions built on top of the data.
- Distinguish topological “signal” from noise.
- Topological information may be multiscale.
- Statistical analysis of topological information.



# Introduction: spatial transcriptomics data

Spatial transcriptomics data measures two things:

- the **position** ( $x$  and  $y$  coordinates) of each cell in a tissue,
- the **expression** of every gene of each cell in a tissue.



# Plan of the course

1. ToMATo for colocalizing cell types
2. Rips persistence for marker gene correlations
3. Multi-persistence for immune cell arrangements
4. Future research directions

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[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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# 1. ToMATo for colocalizing cell types

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A: Compute the *Jaccard similarity* between **stable spatial clusters** computed from **marker gene expression** as a *colocalization quantifier*.

→ 0-dimensional persistent homology with **ToMATo**

# Motivation: the (in)stability of dendograms

**Input:** A set  $X_n = \{x_1, \dots, x_n\}$  in a metric space  $(X, d)$  (or just a matrix of pairwise dissimilarities  $((d_{i,j}))_{i,j}$ ).

Given two clusters  $C, C' \subseteq X_n$  let  $d(C, C') = \inf_{x \in C, x' \in C'} d(x, x')$ .

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sup: complete linkage

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$\frac{1}{|C| \cdot |C'|} \sum$ : average linkage

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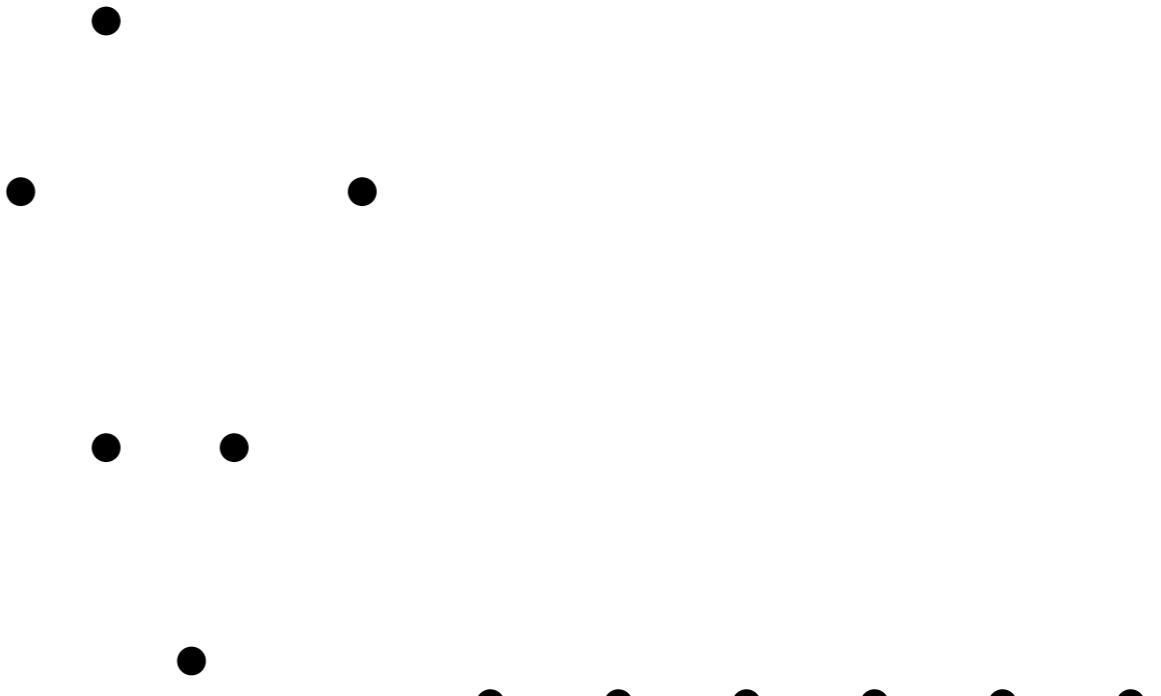
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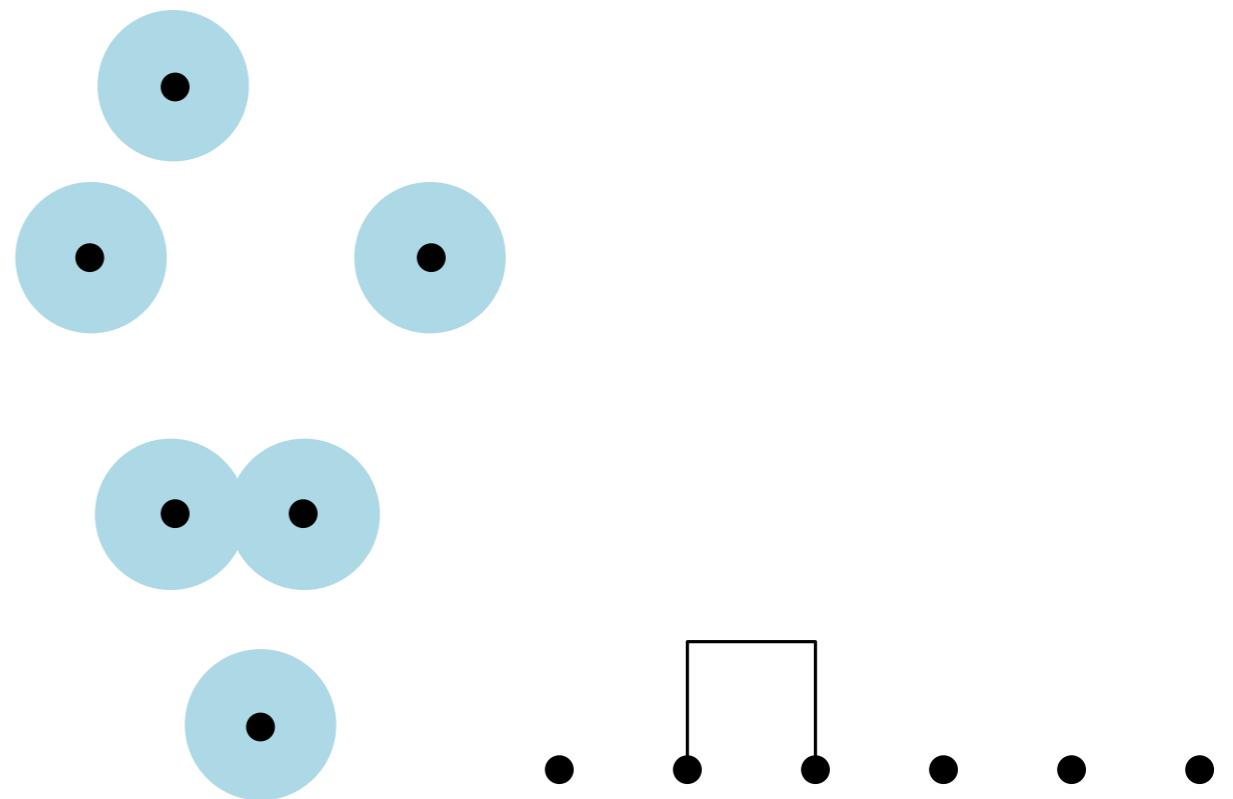
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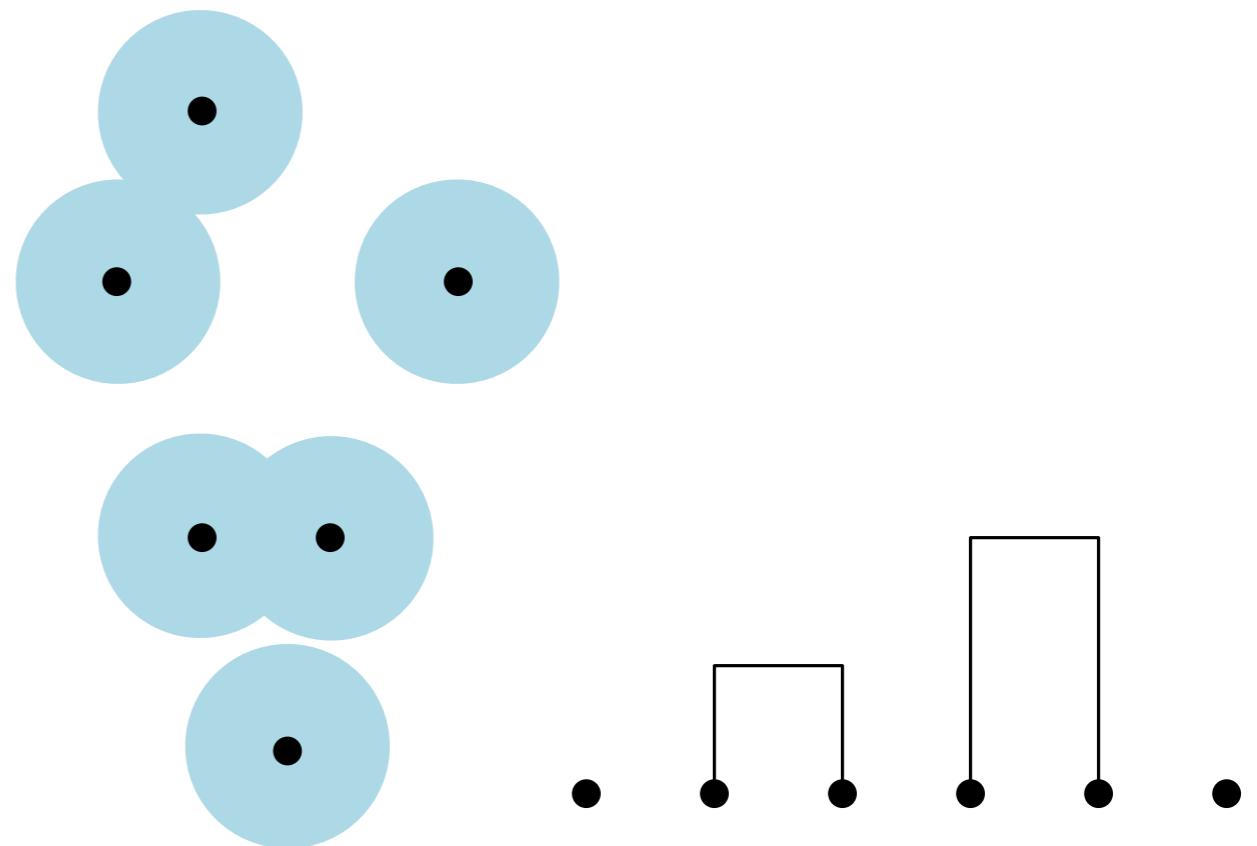
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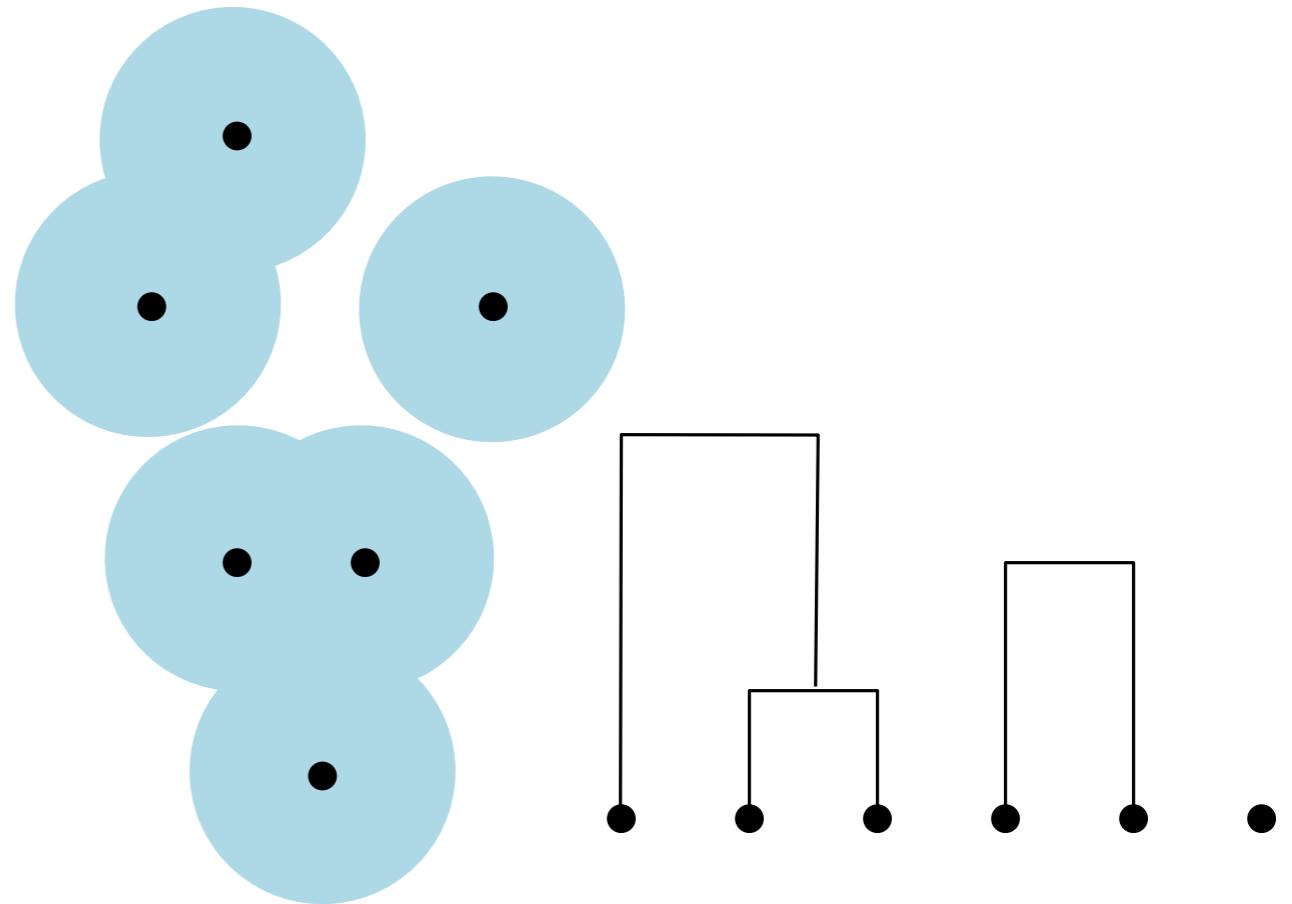
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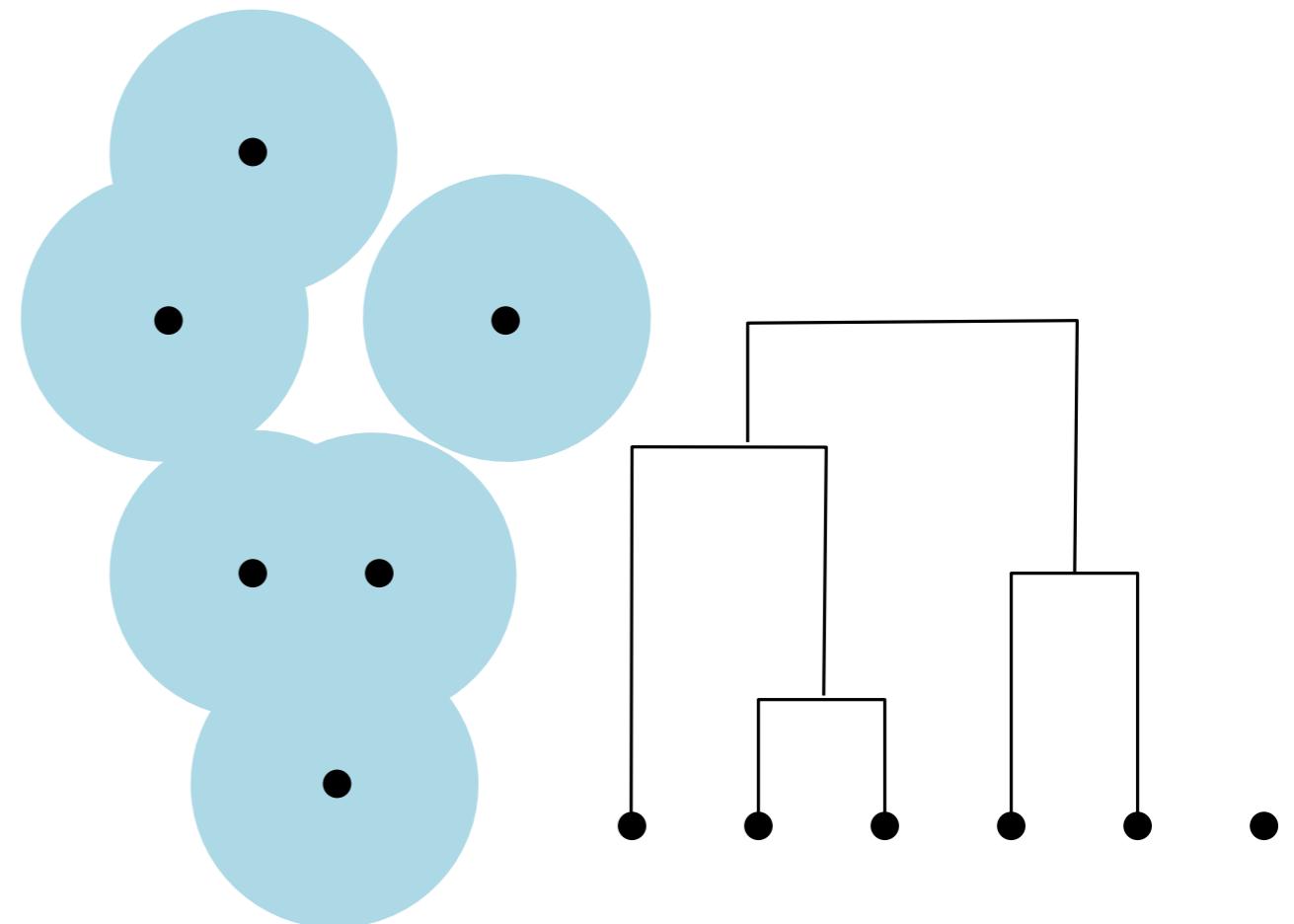
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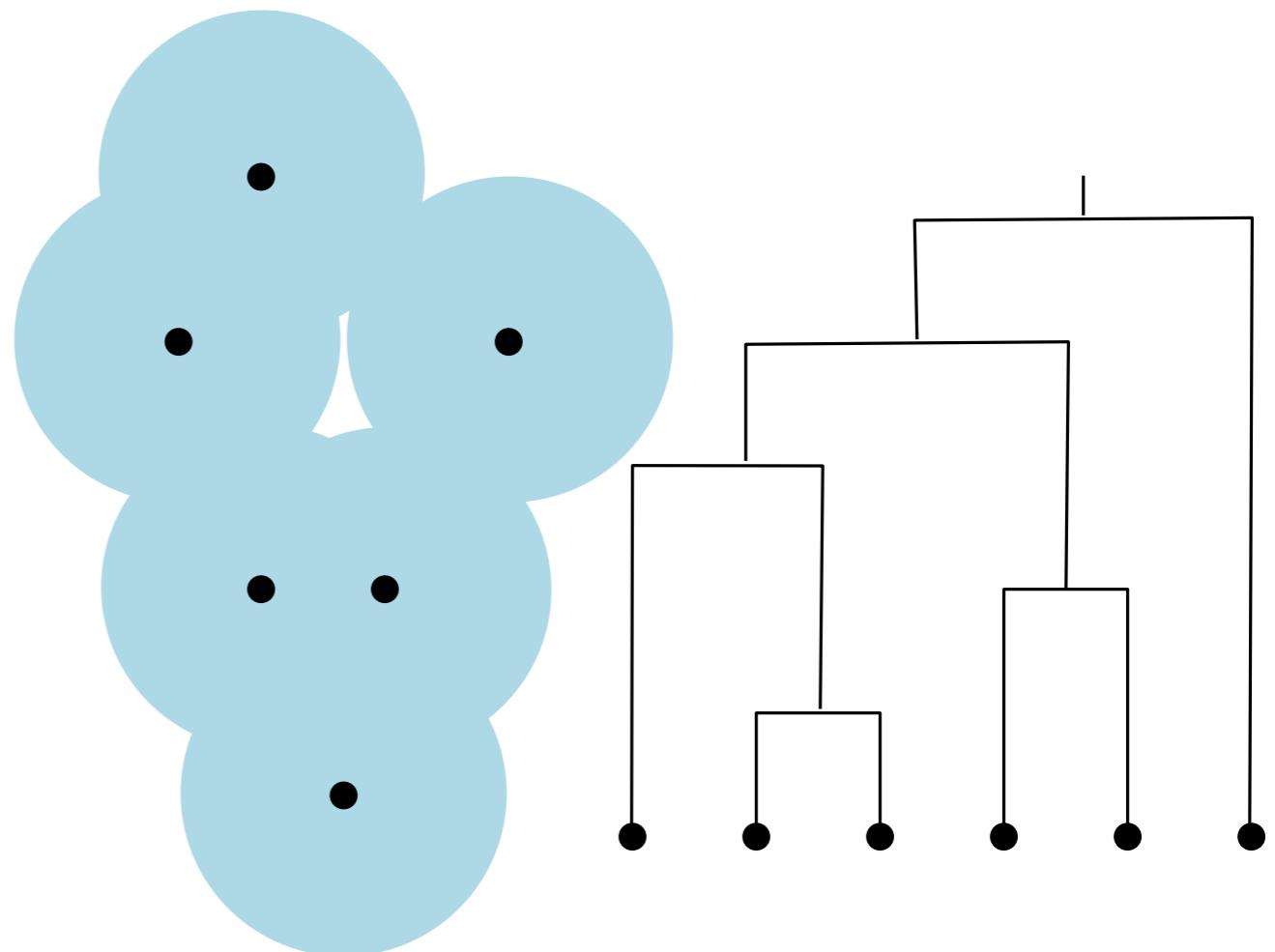
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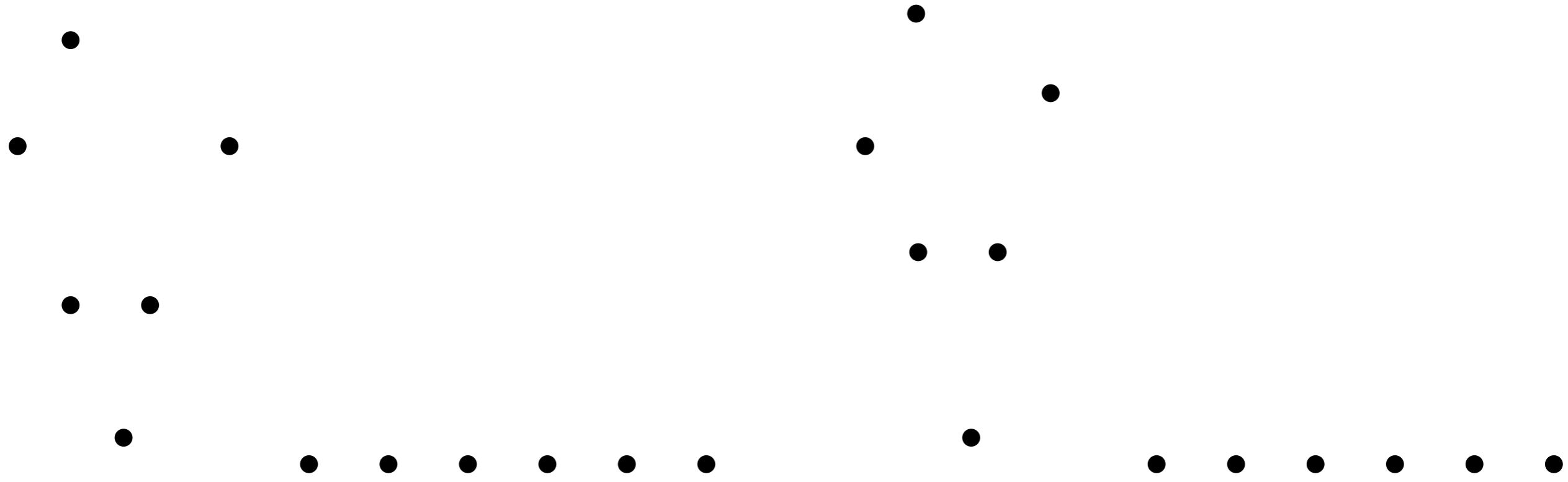
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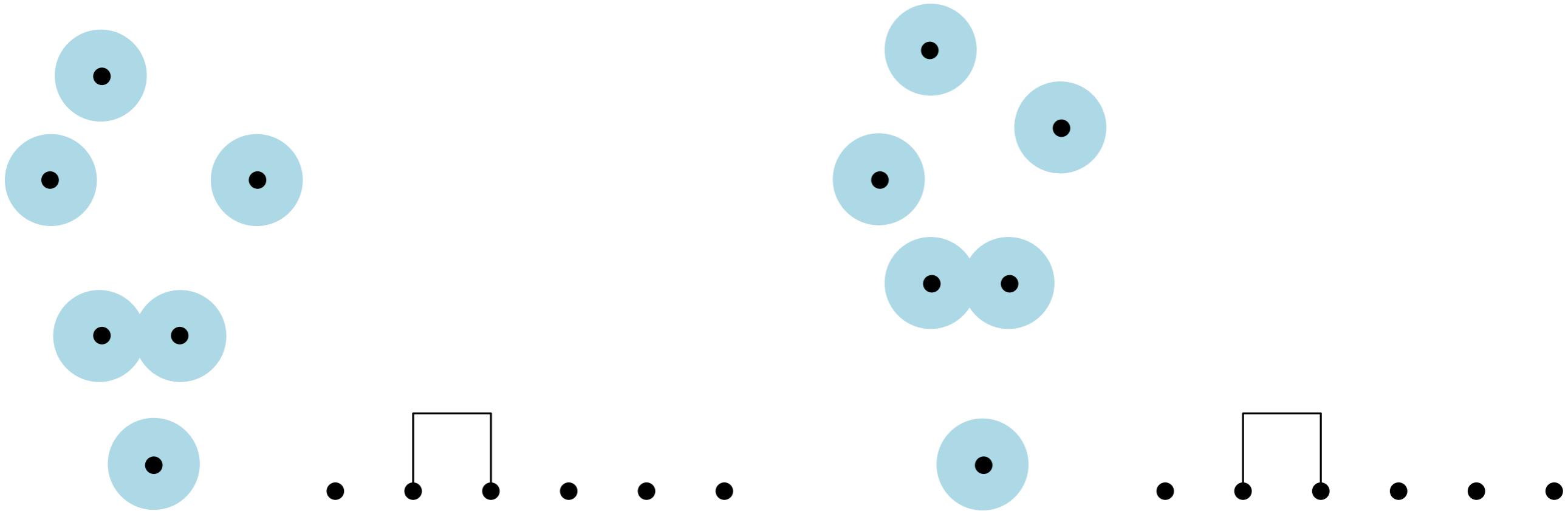
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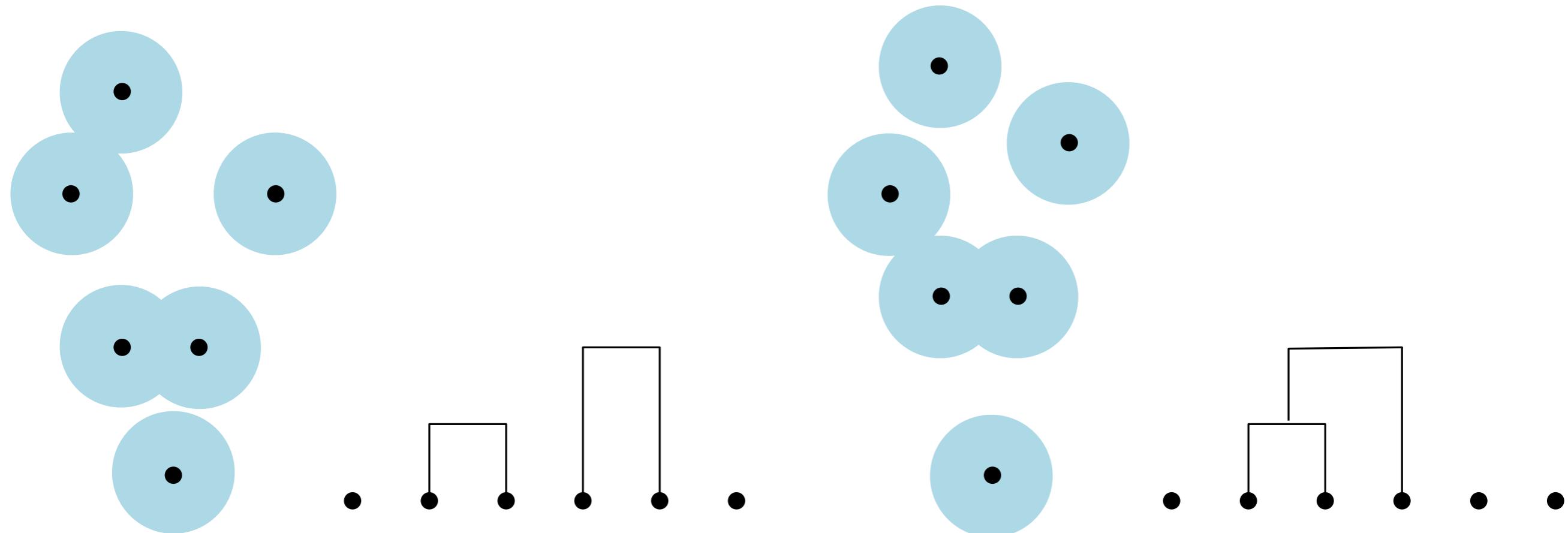
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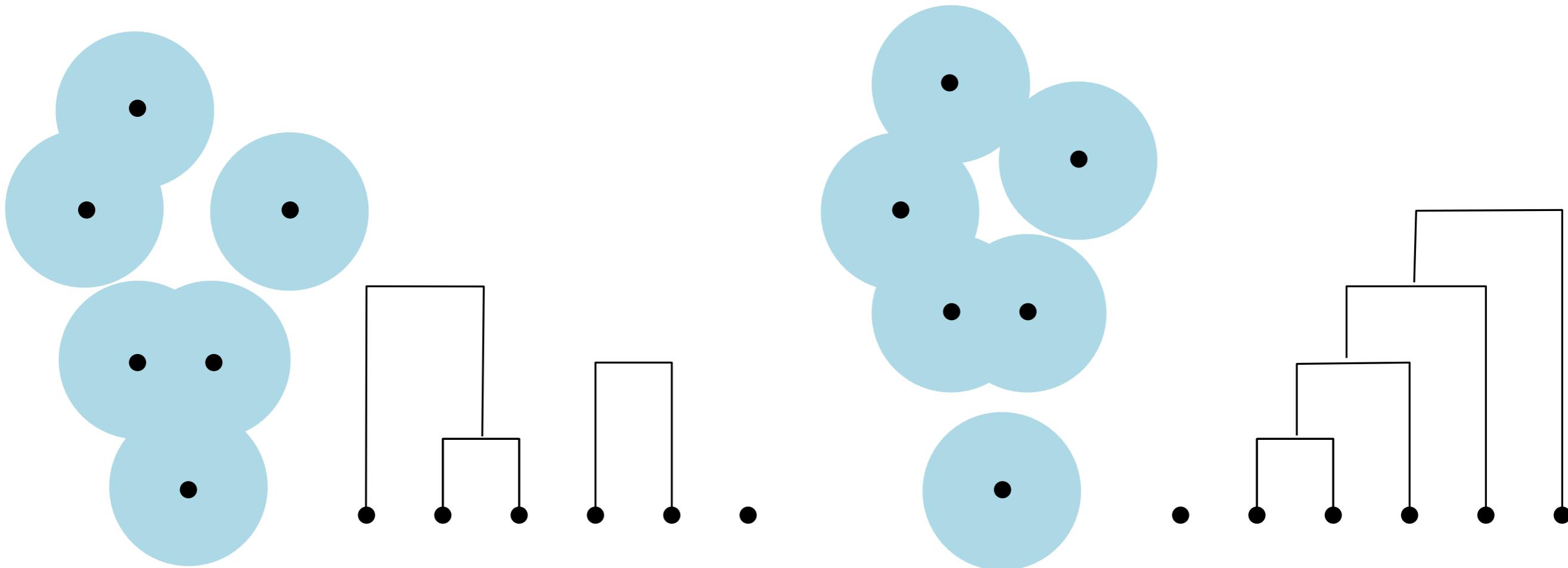
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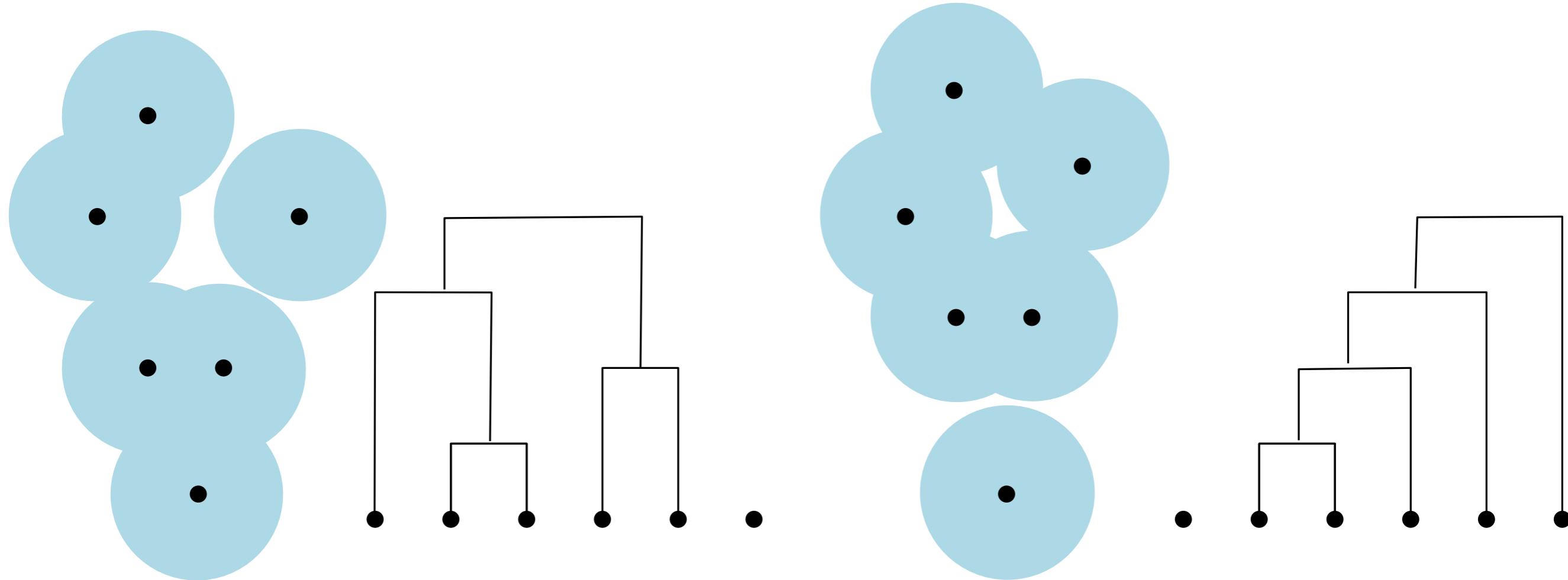
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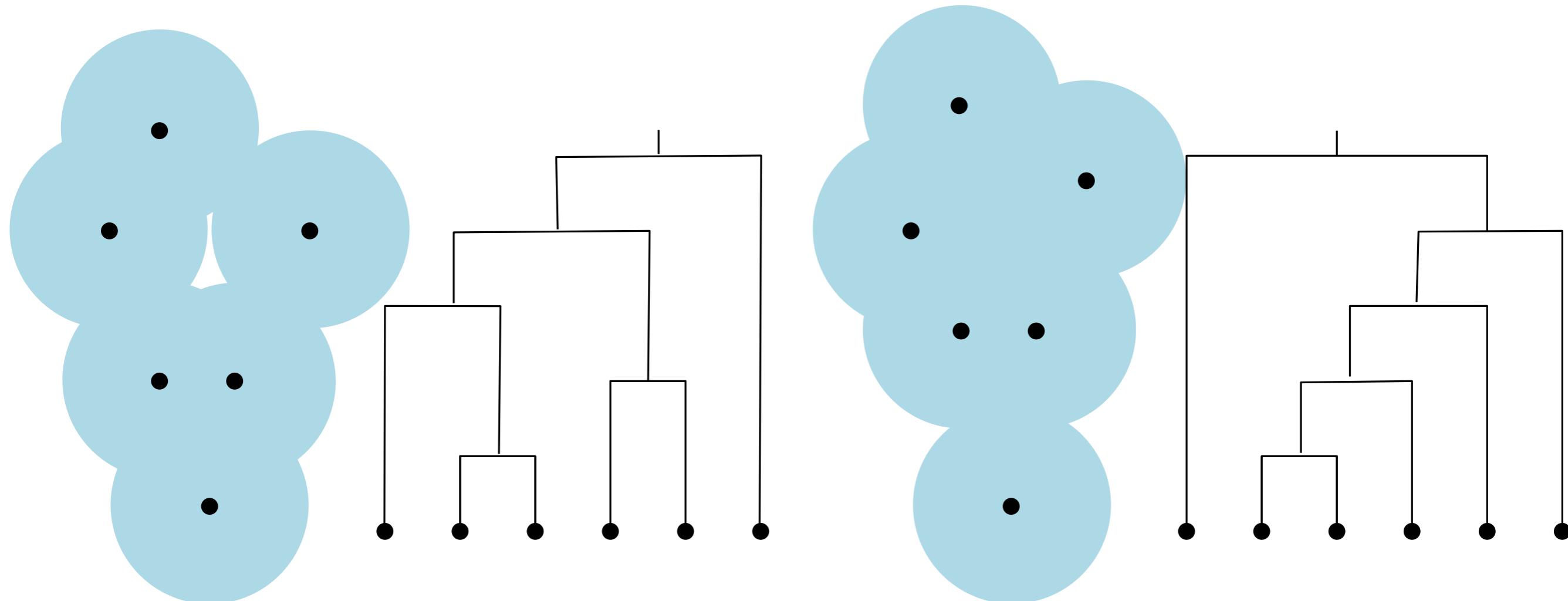
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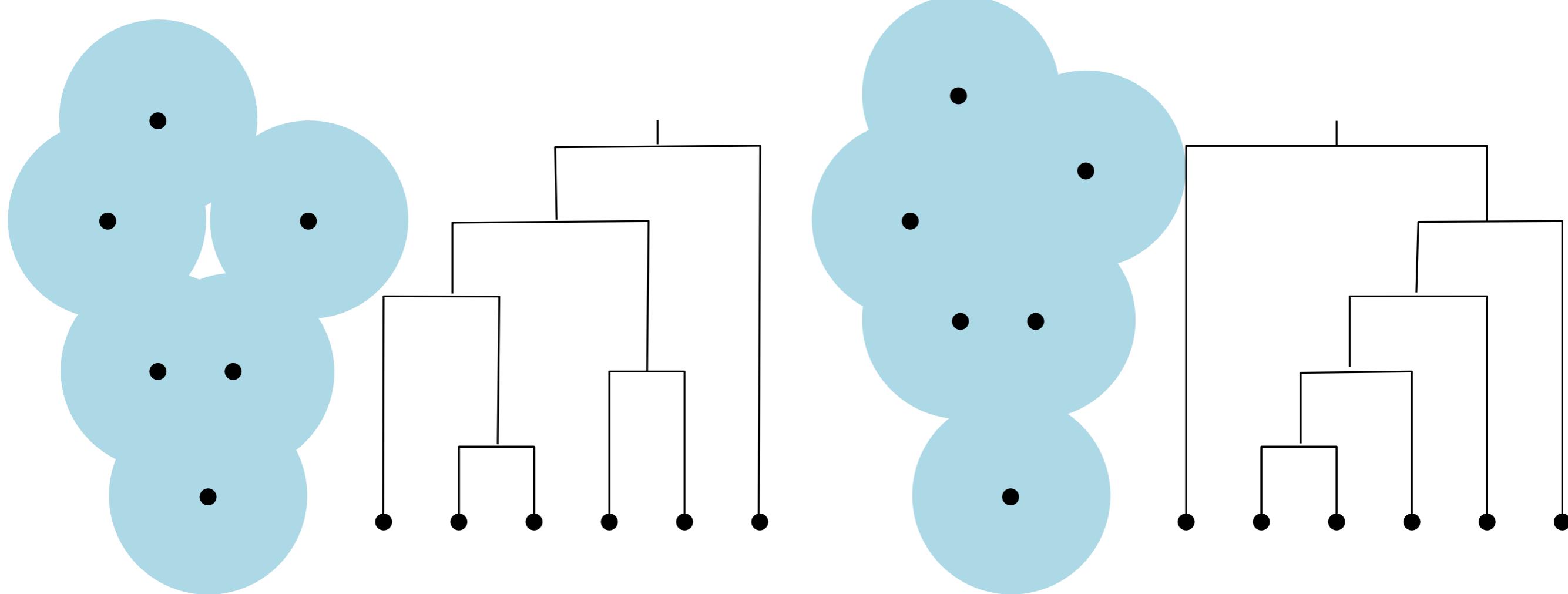
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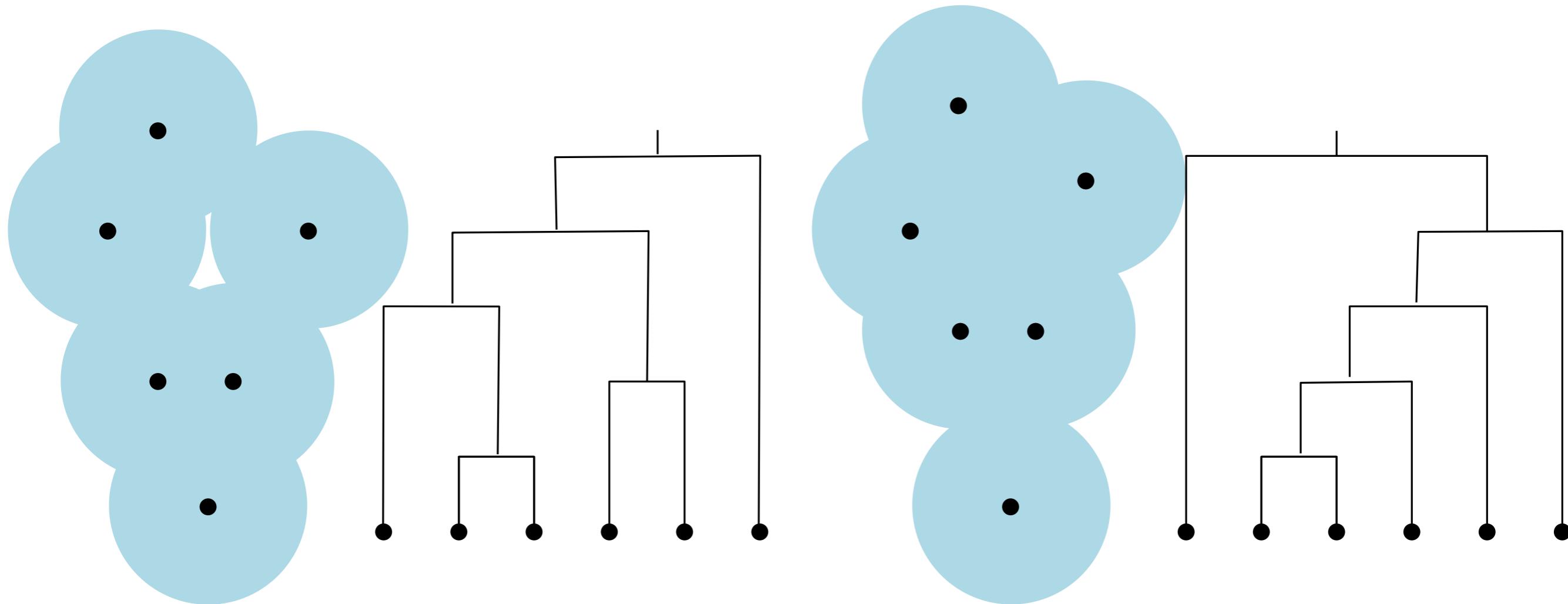


# Motivation: the (in)stability of dendrograms



Small perturbations on the input data can induce wide changes in the structure of the output dendograms. However, the merging times (height of dendrogram nodes) remain stable.

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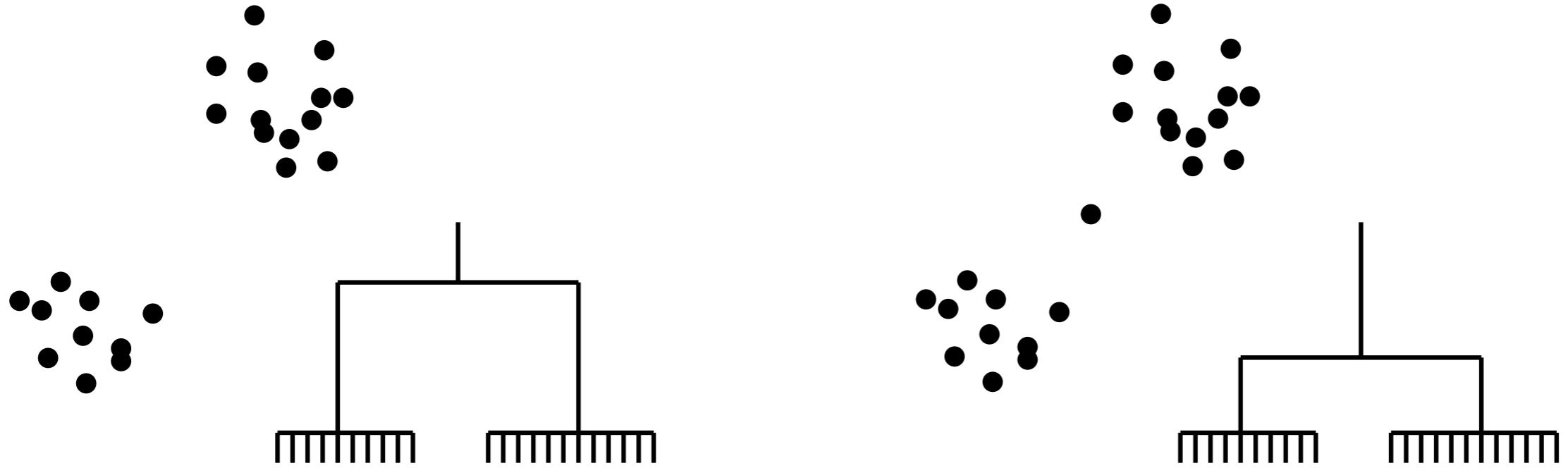
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Moreover, single linkage clustering keeps track of the evolution of the connected components of the distance function to the data (for Euclidean data).

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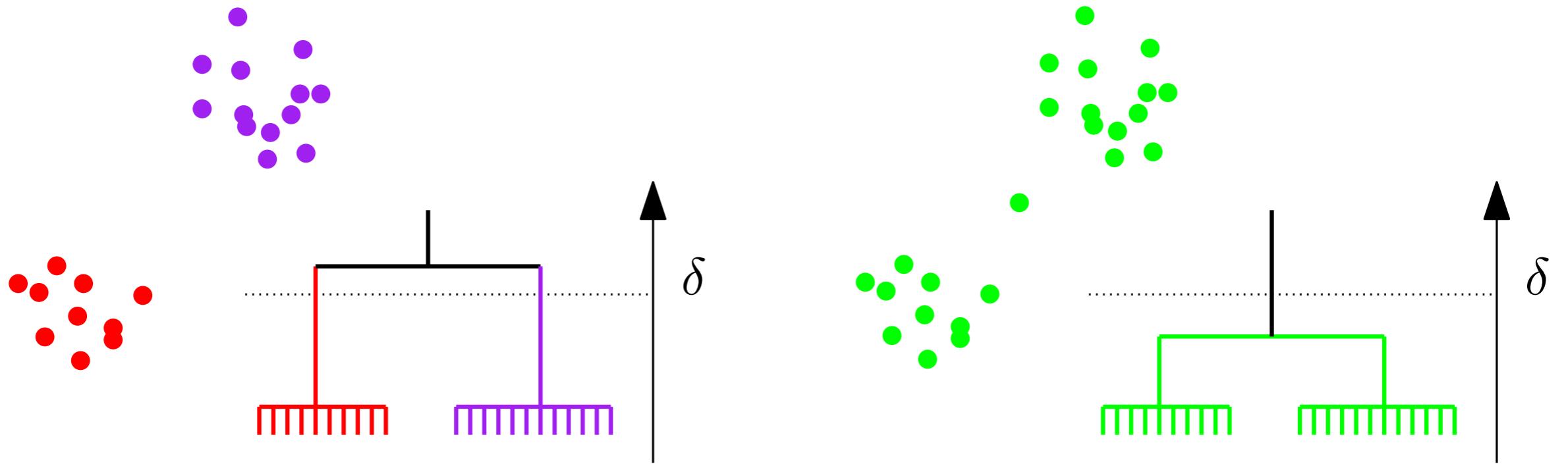
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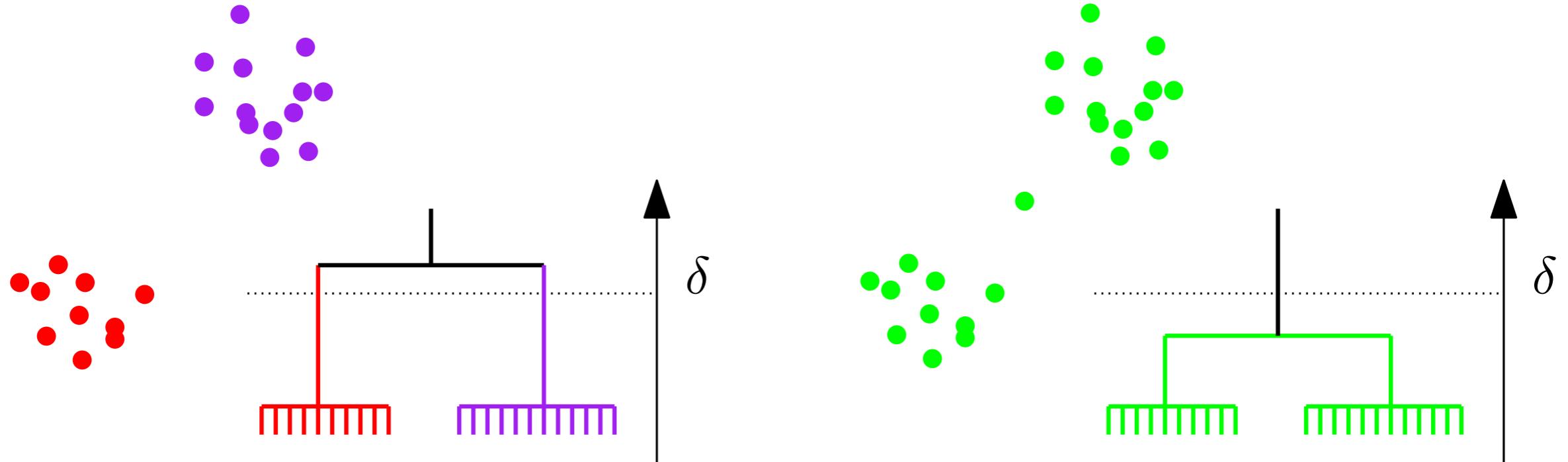
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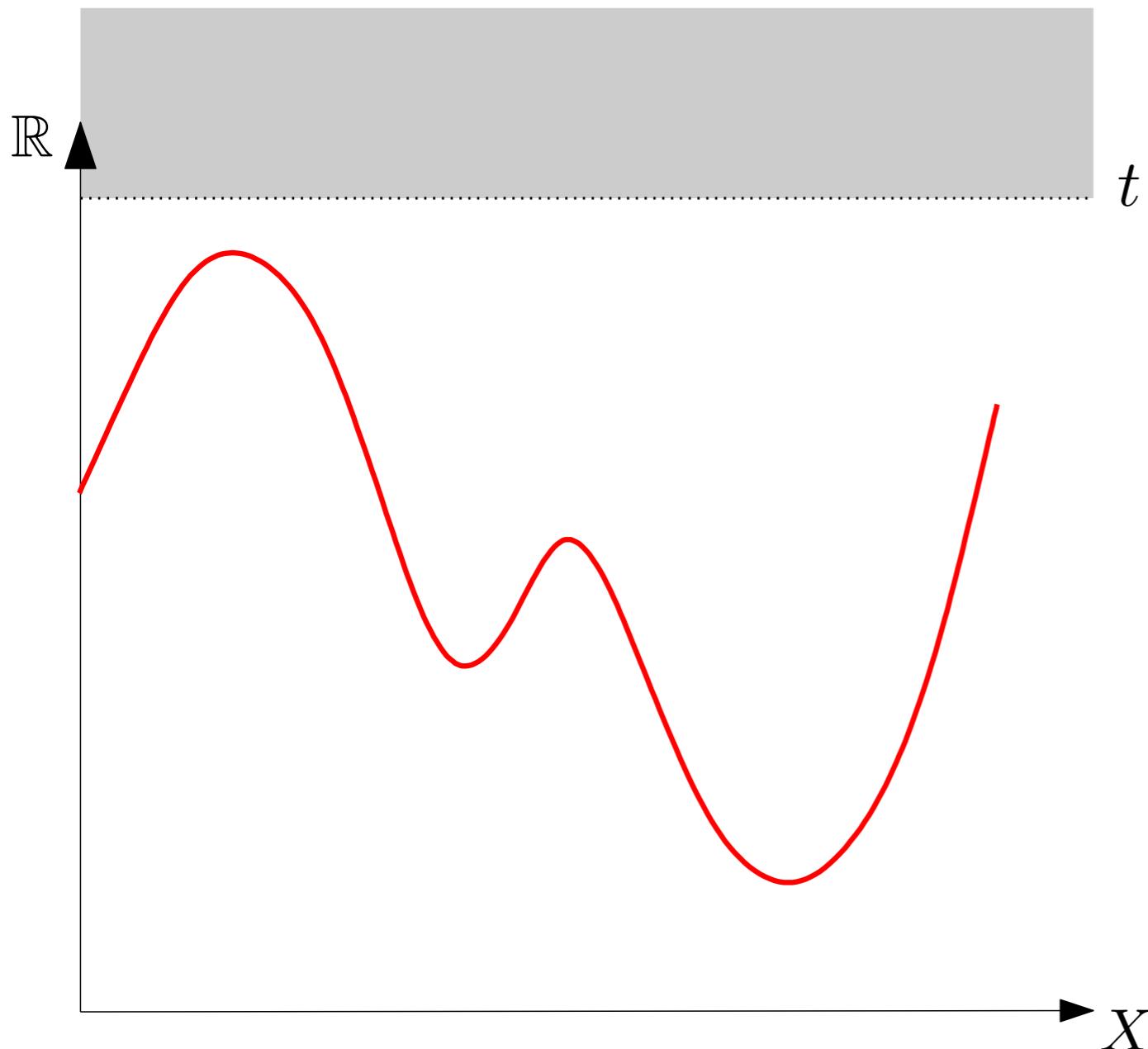


However, building a hierarchy based on spatial proximity is still not a great idea when there are outliers, since there is no stability of merging times anymore.

Another way to build a hierarchy is with the sublevel sets of a **filter function**. For instance, using density as filter is at the core of mode-seeking algorithms.

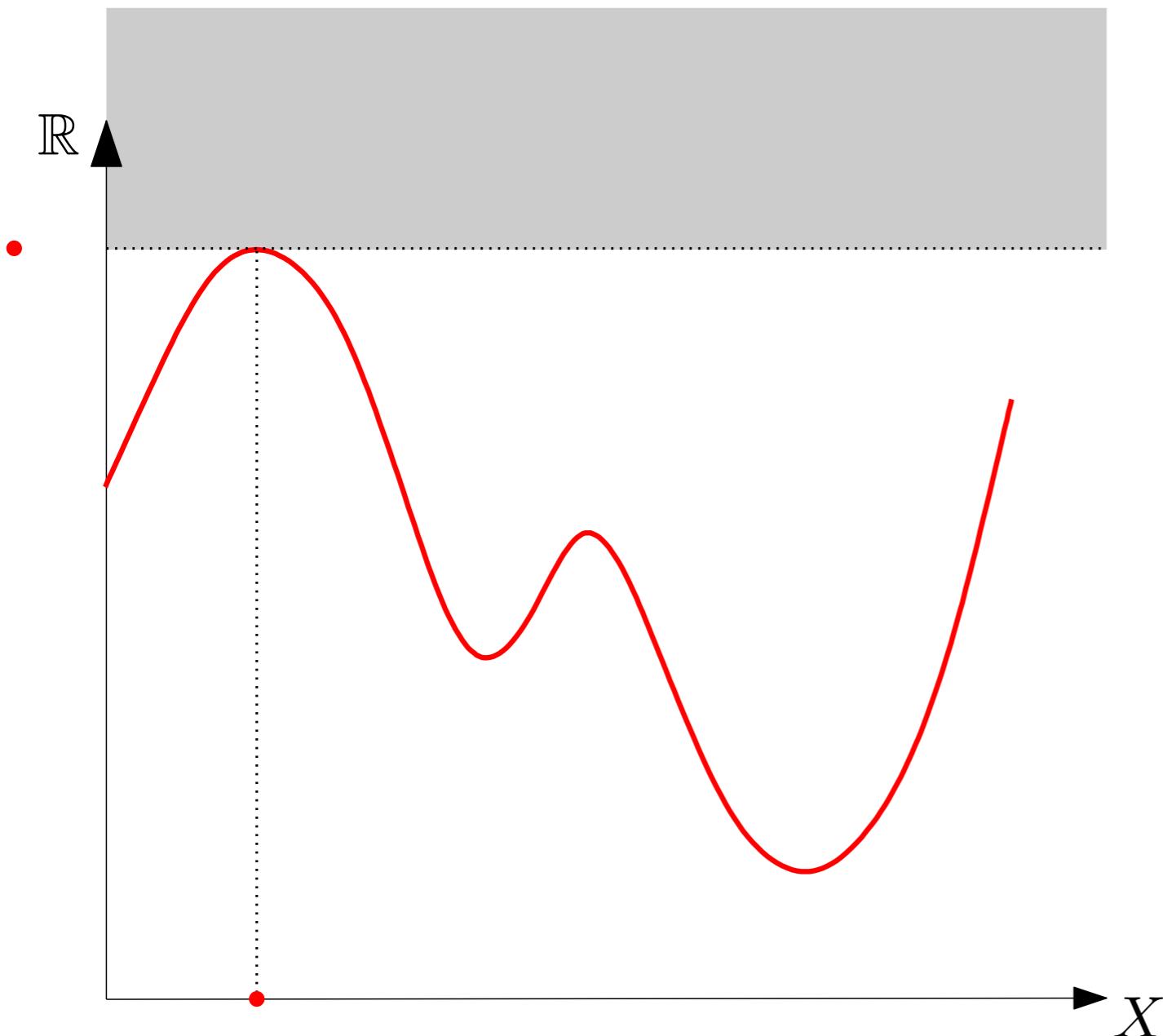
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Given a continuous function  $f : X \rightarrow \mathbb{R}$ , we will consider the *superlevel-set filtration*  $f^{-1}([t, +\infty))$  for  $t$  from  $+\infty$  to  $-\infty$ , and track the **appearance** and **merging** of connected components / clusters in the process.



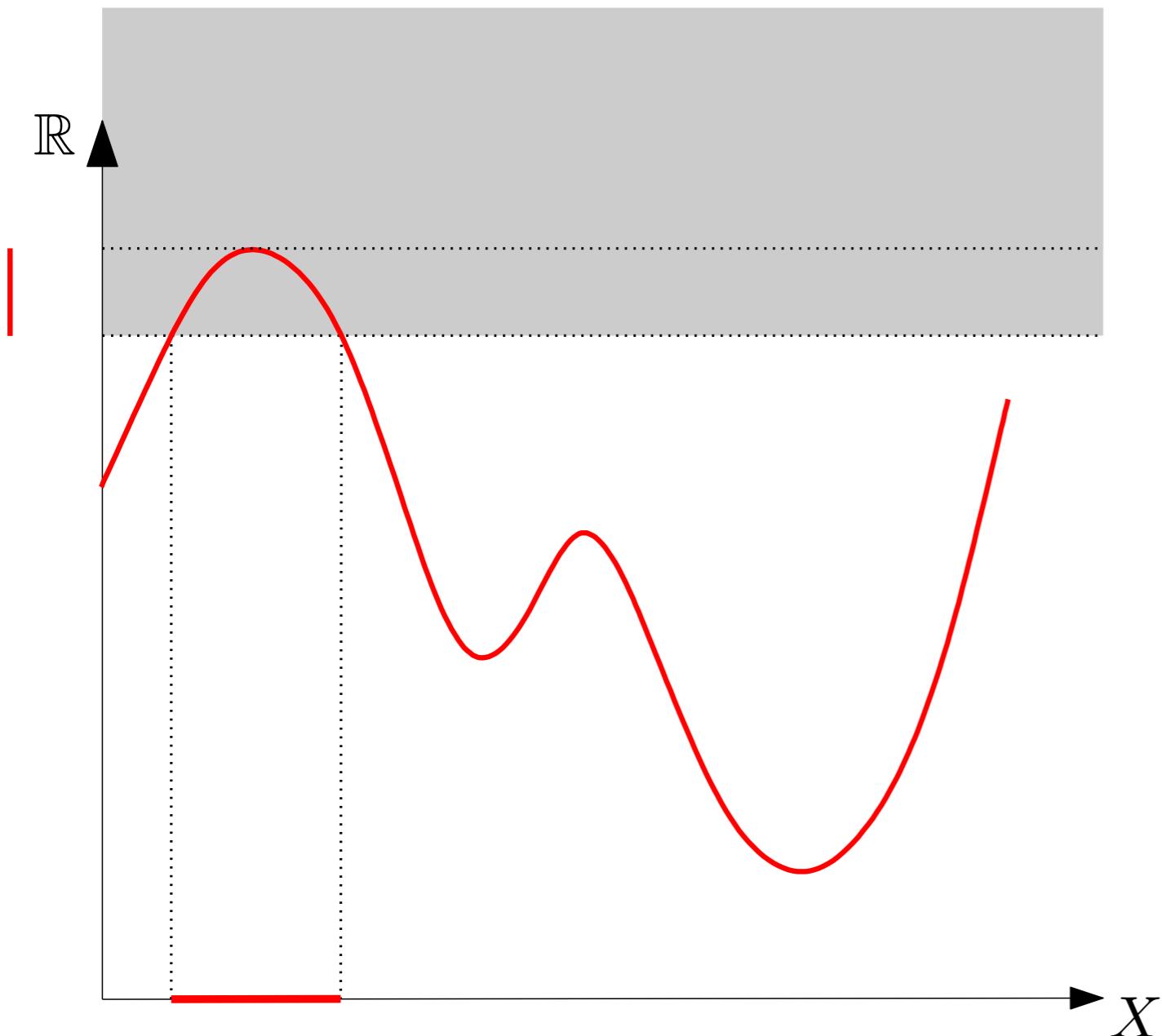
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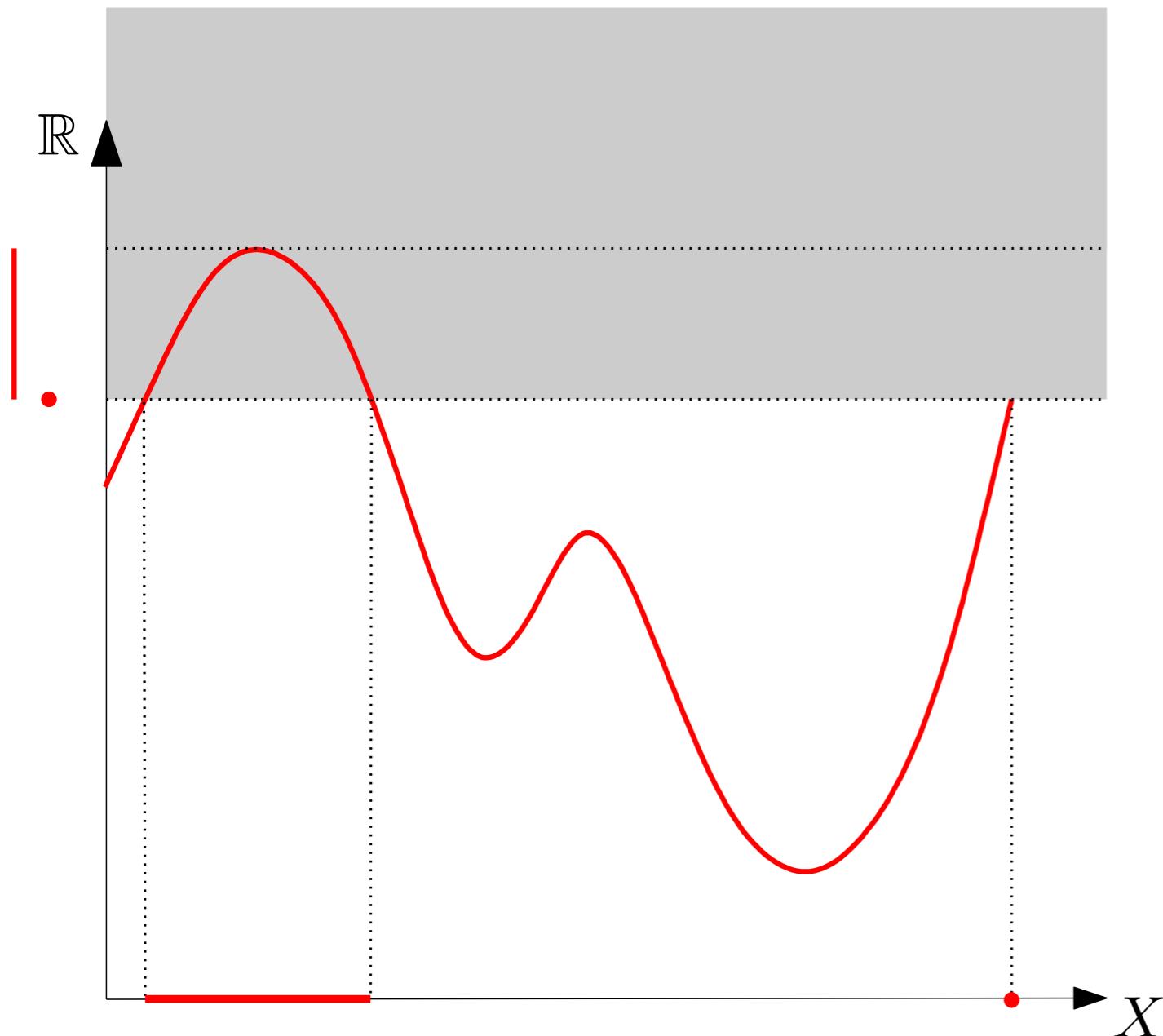
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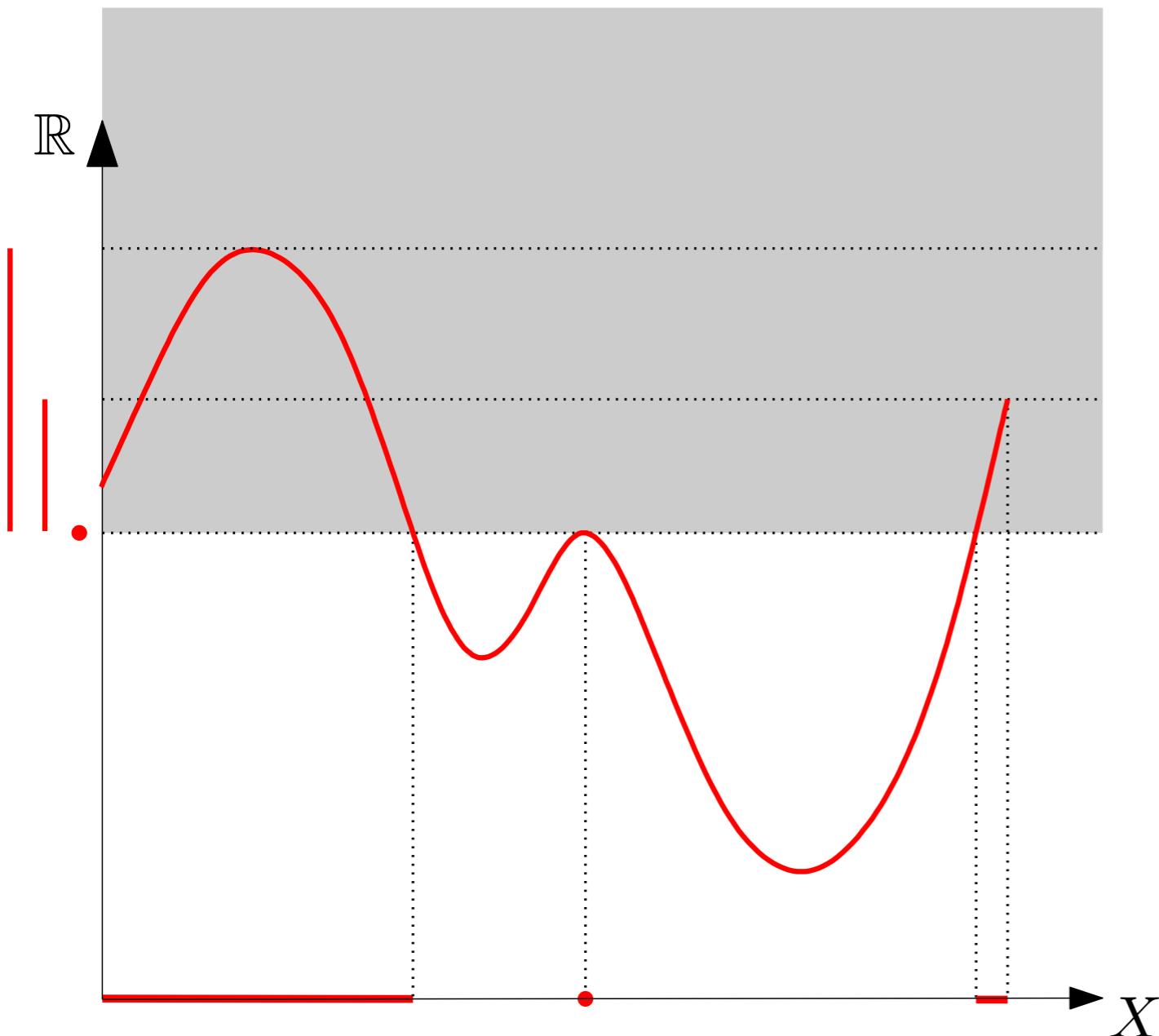
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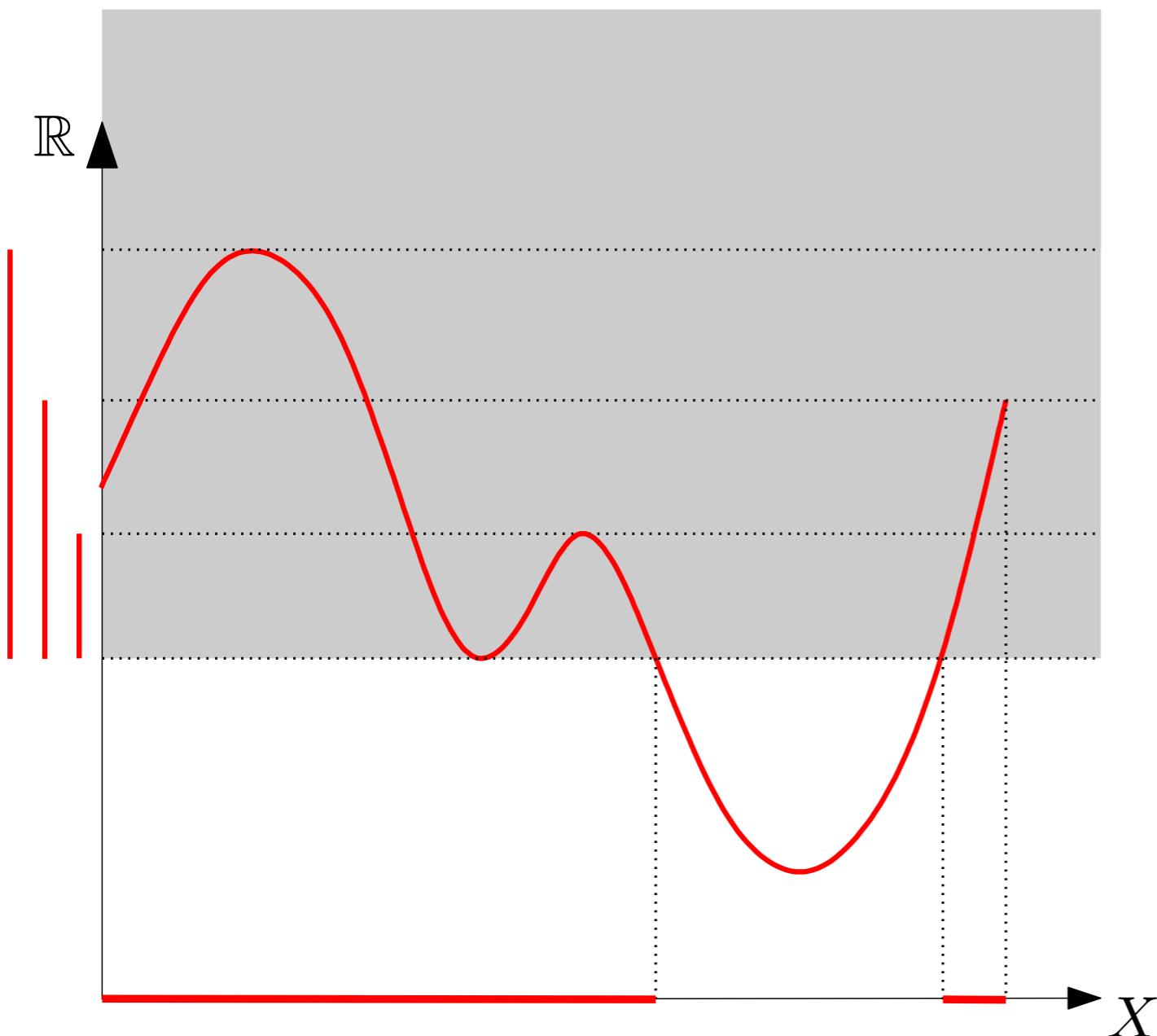
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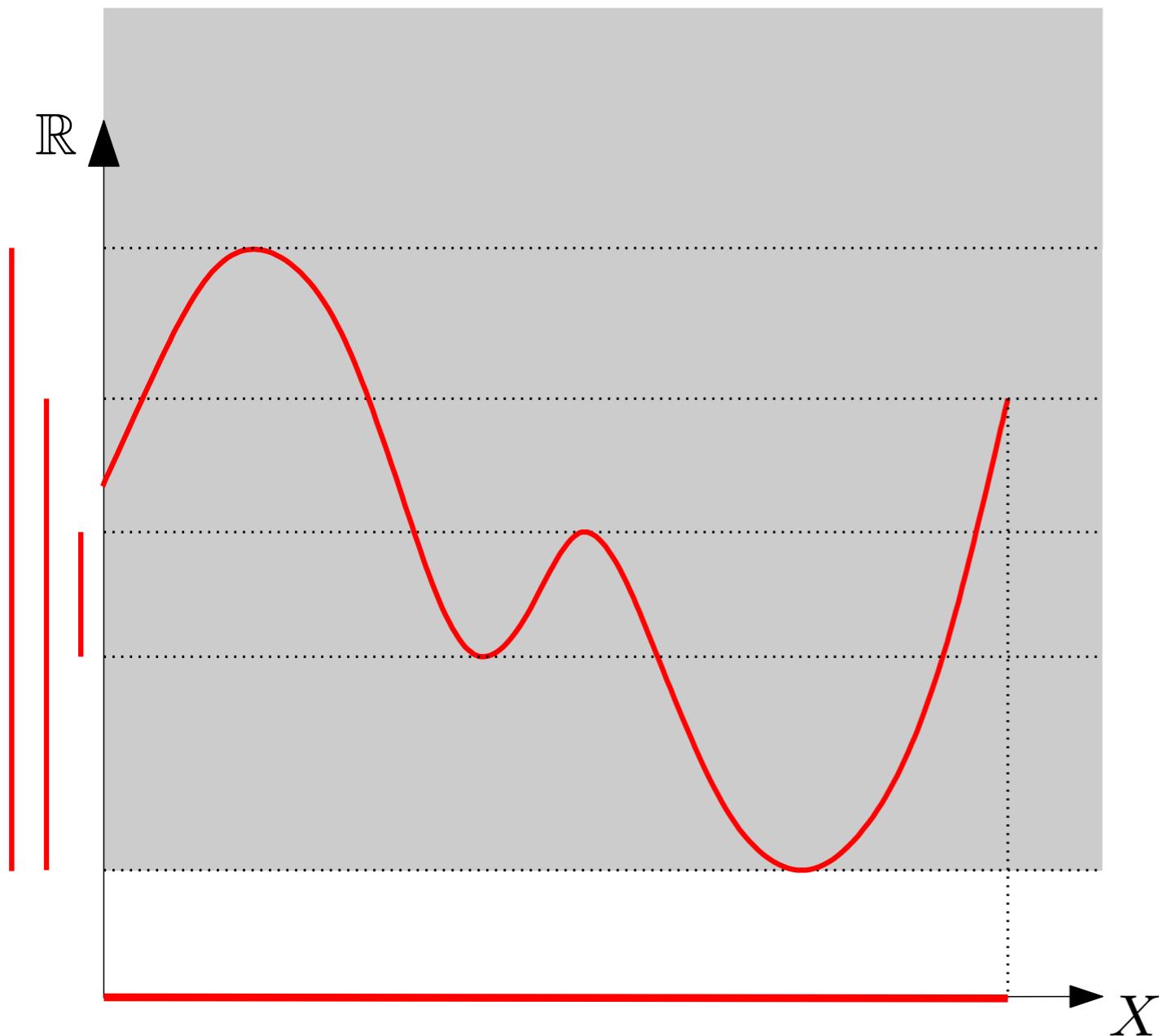
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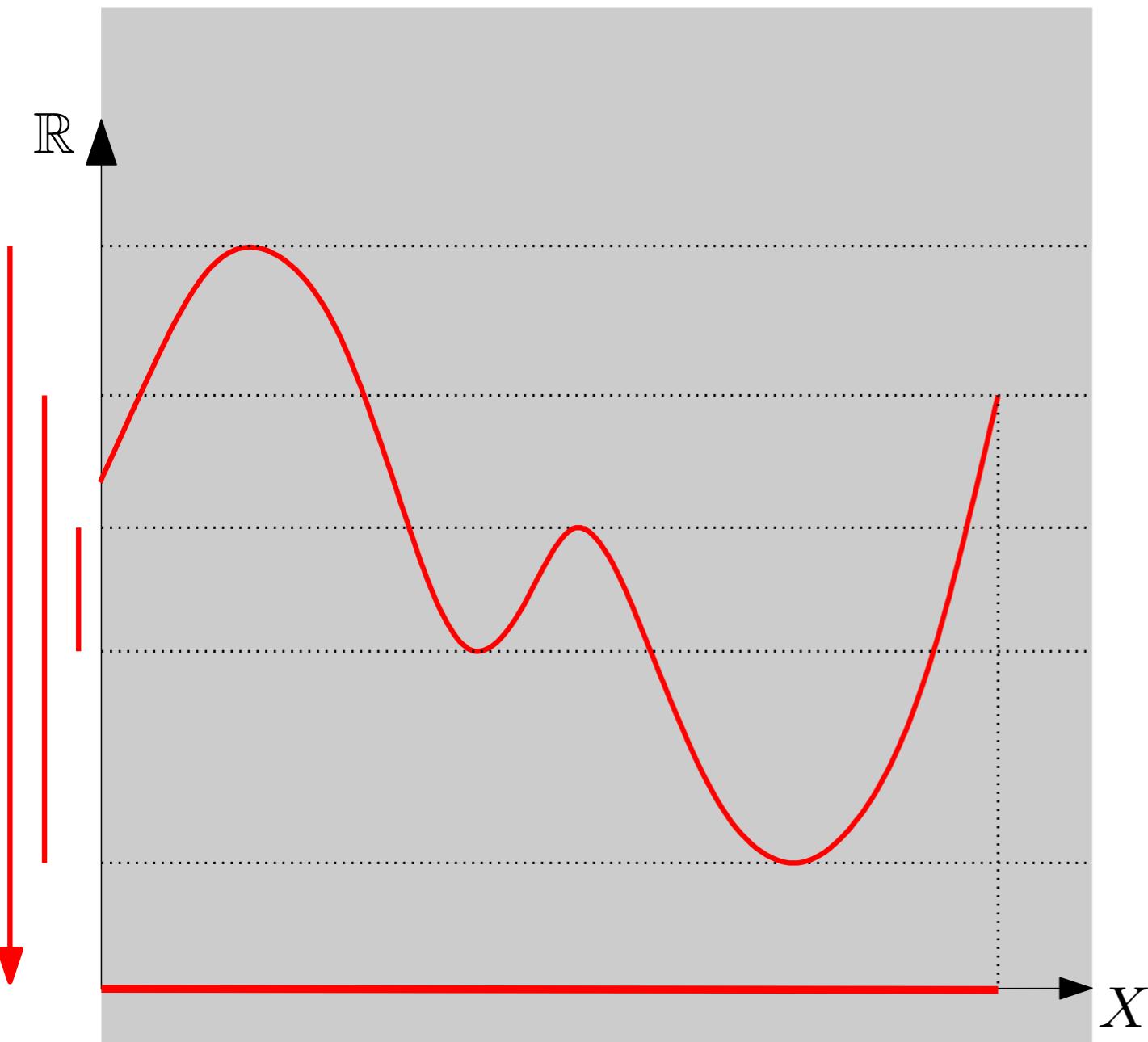
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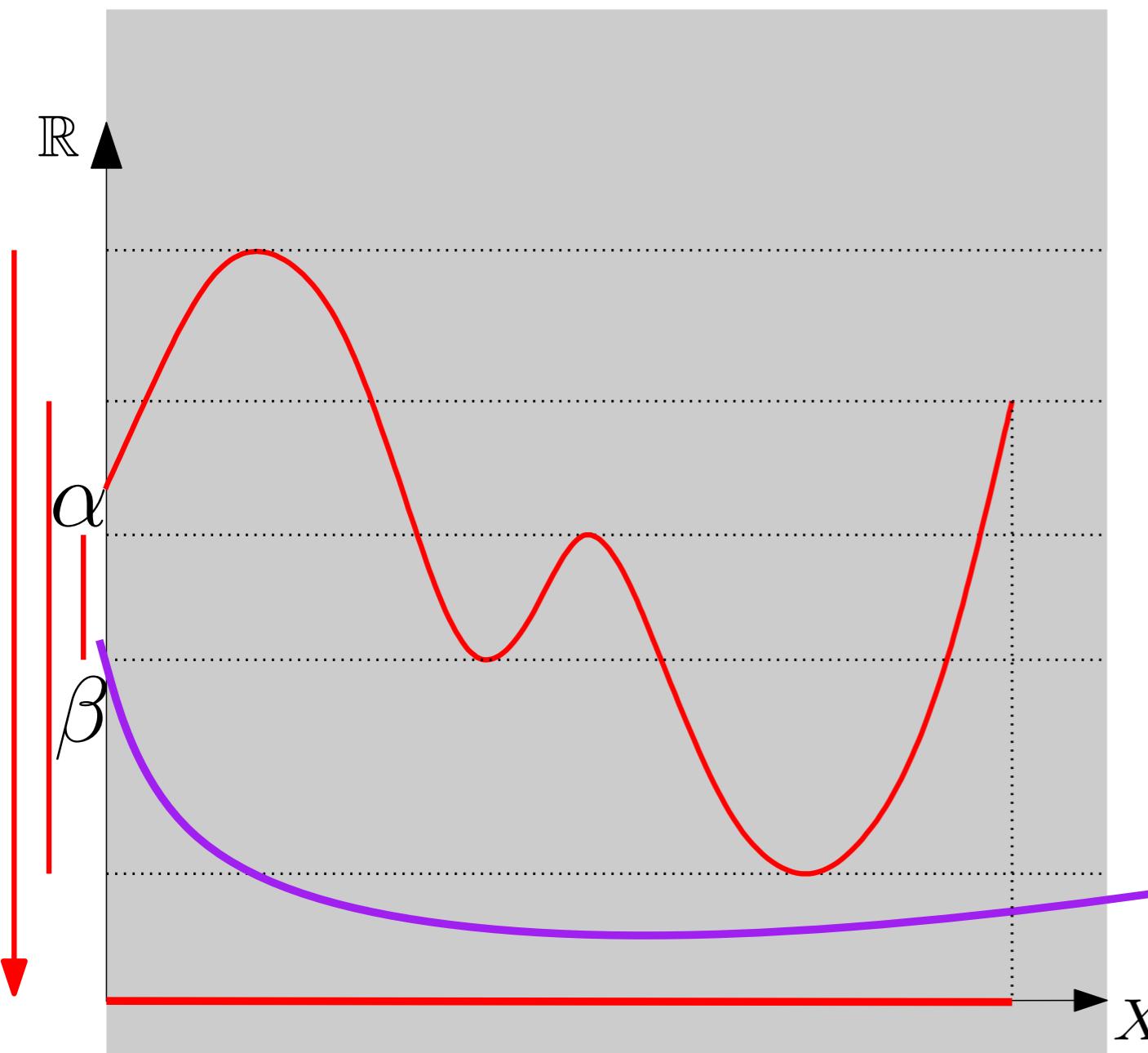
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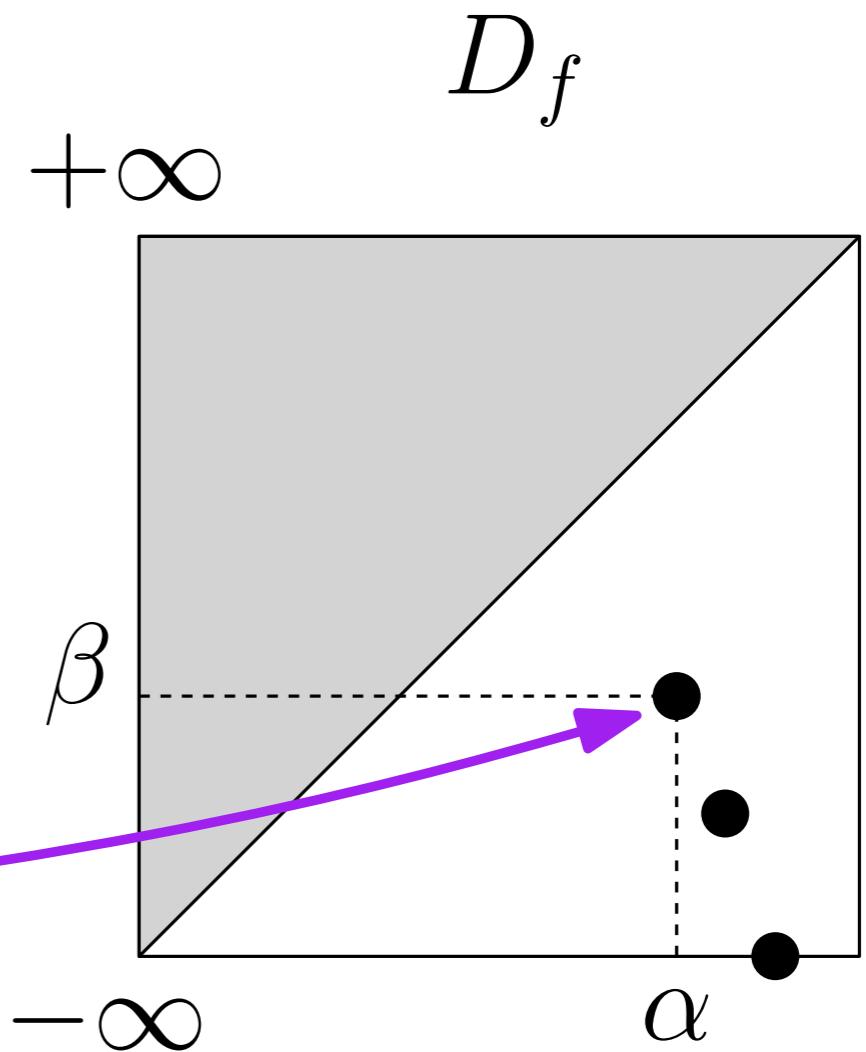
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Persistence barcode



Persistence diagram



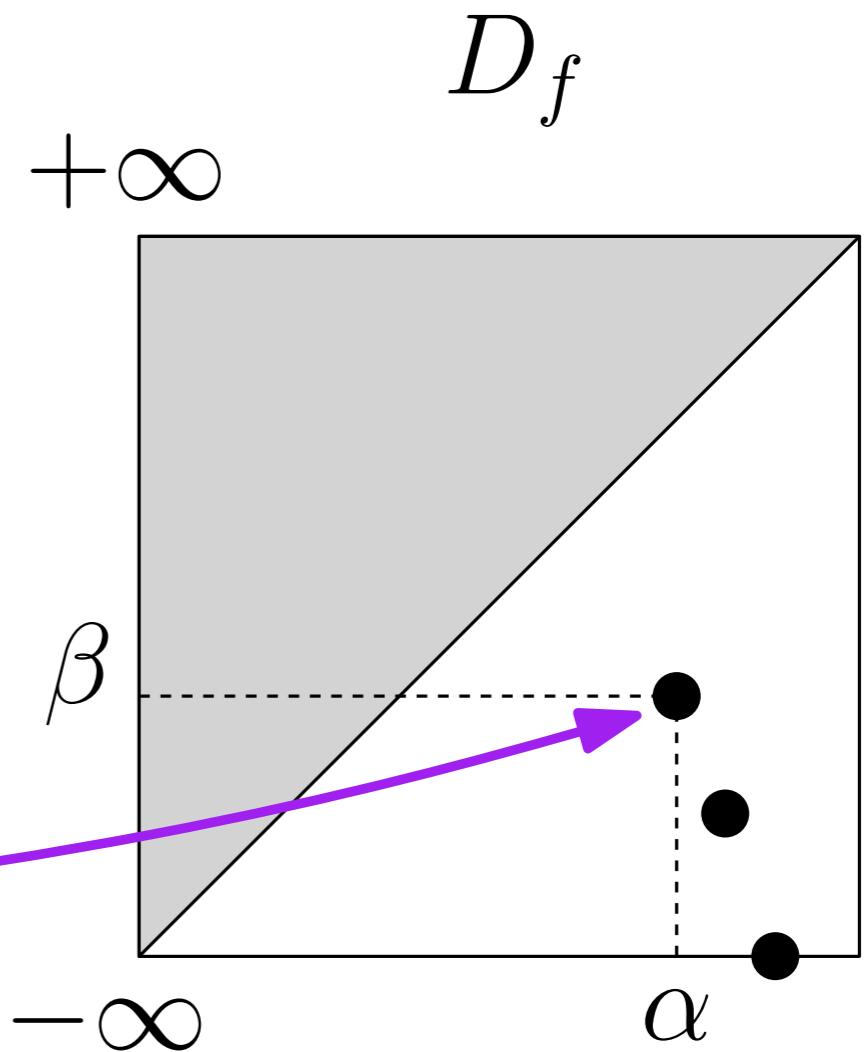
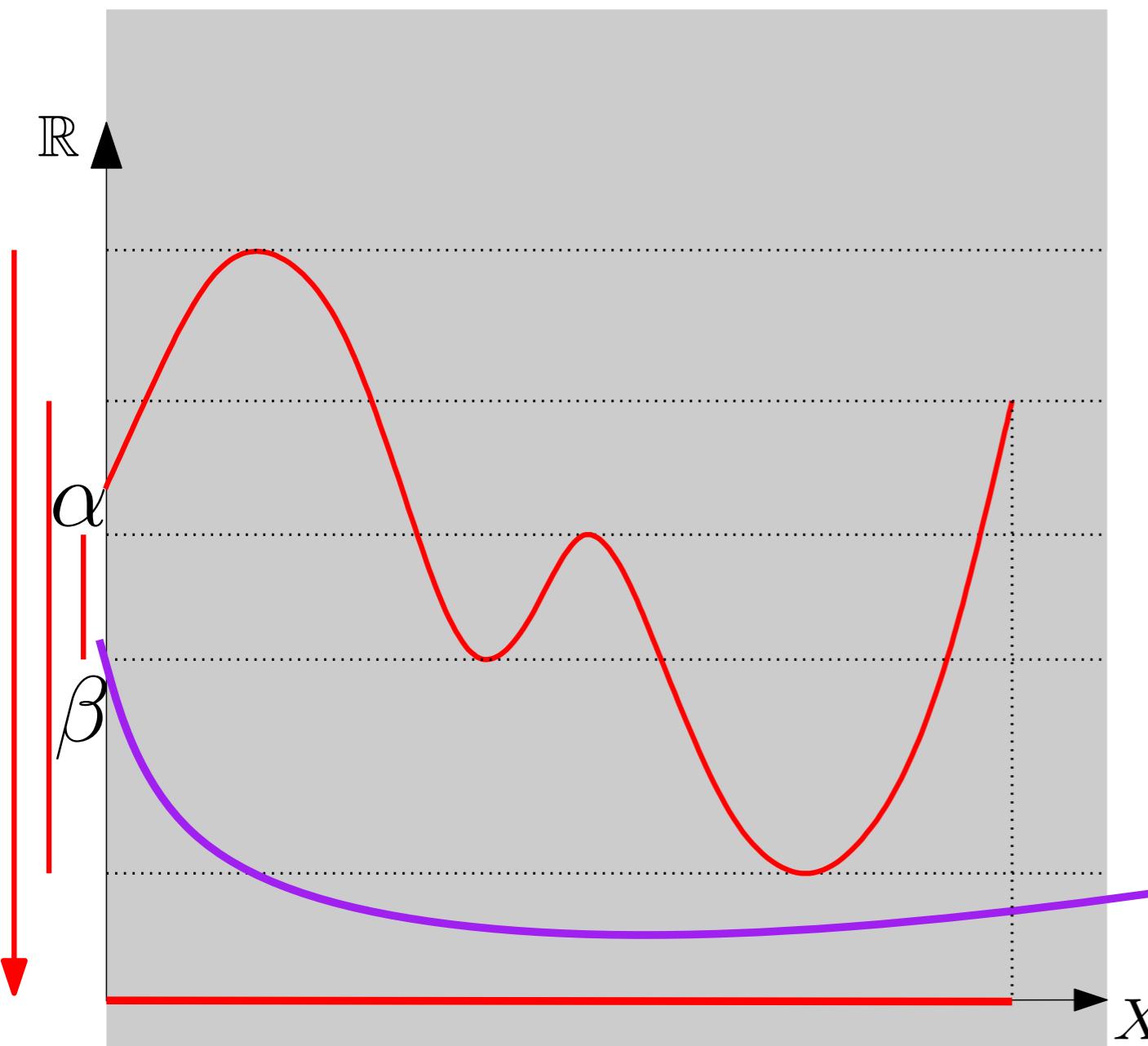
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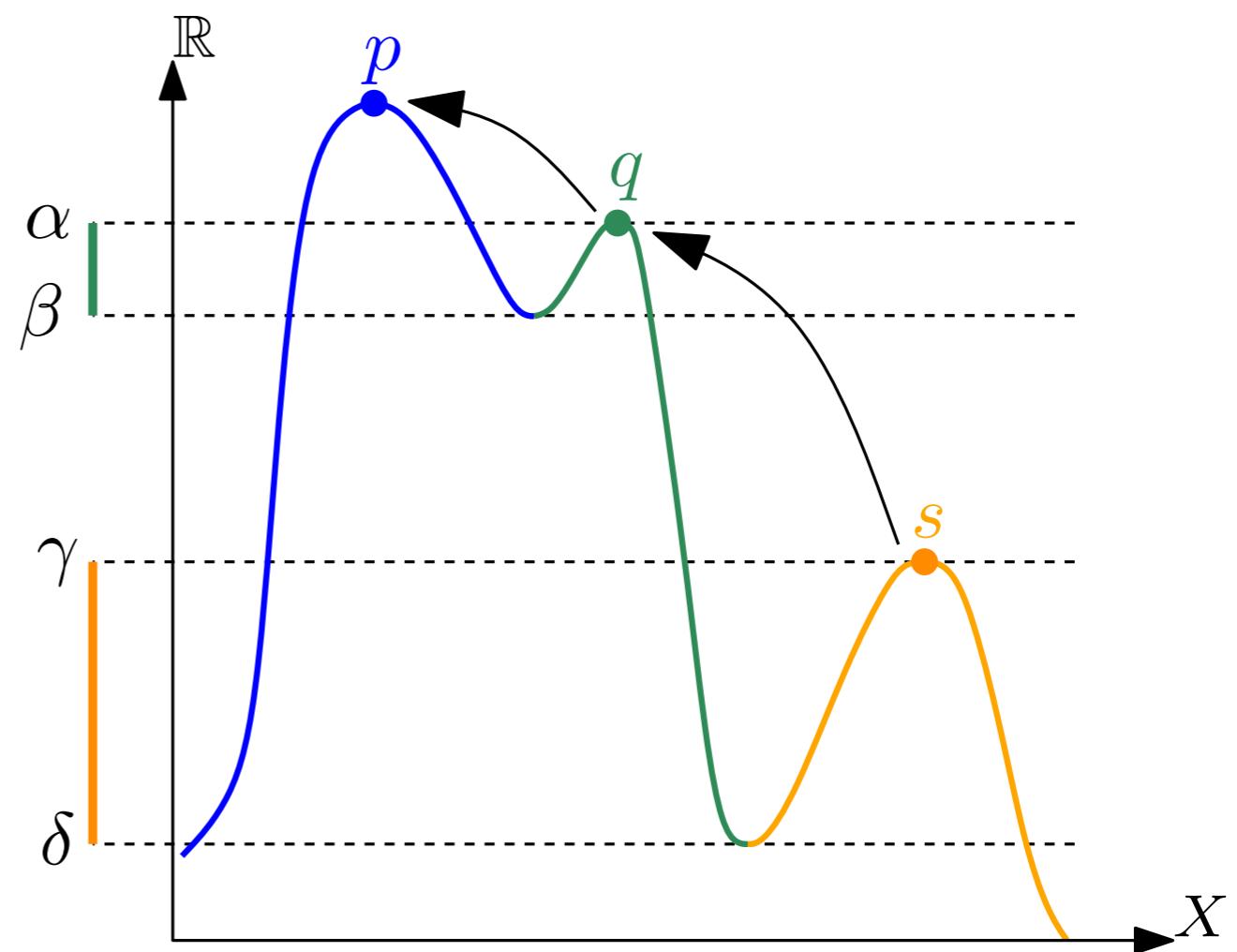
requires some sort of **connectivity**,  
e.g., neighborhood graph

Persistence diagram



# Building a hierarchy of clusters

Moreover, 0-dimensional PH also remembers the connected components / clusters that were merged together during the filtration process and builds a hierarchy out of this information.



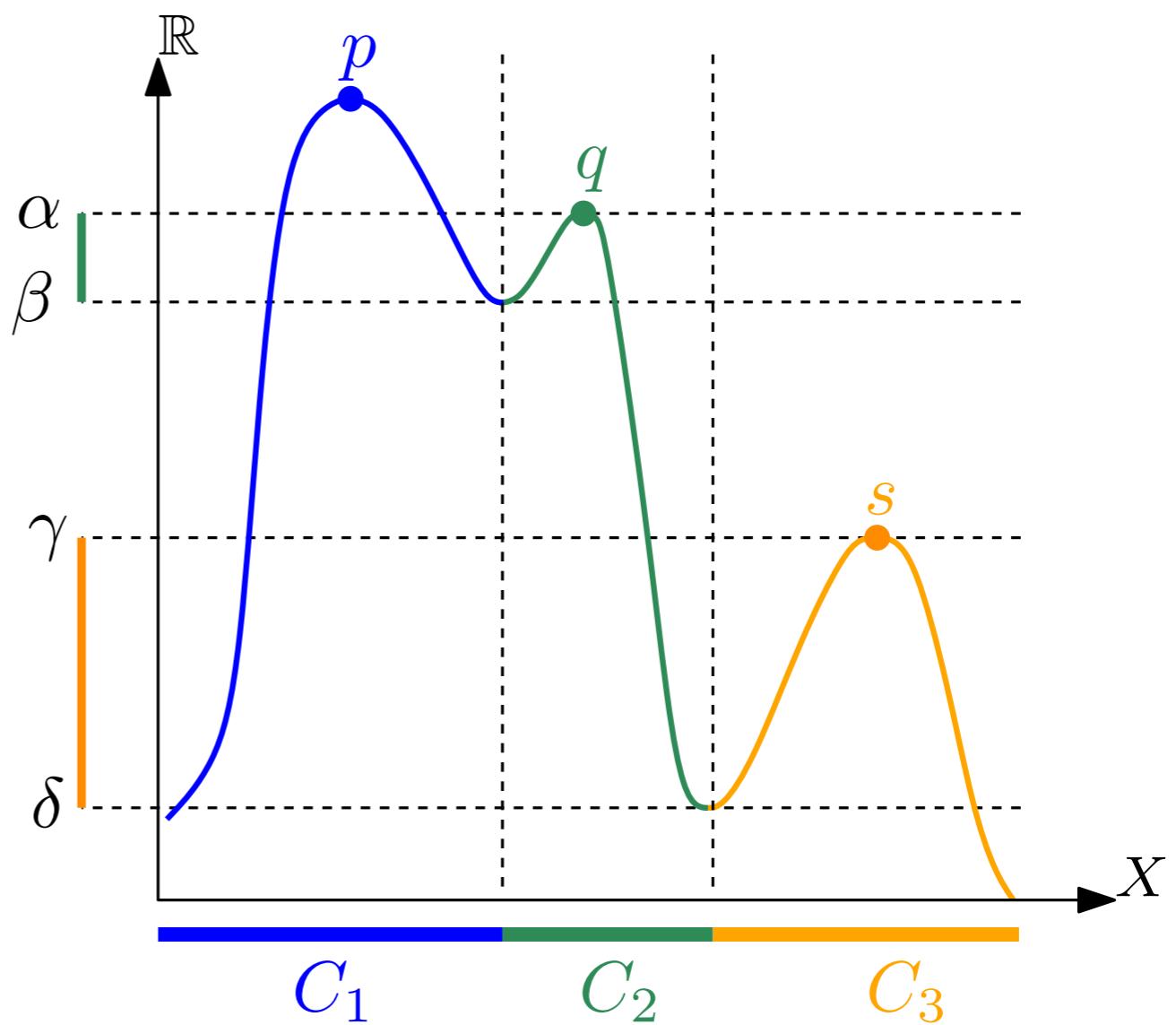
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This means that, given a fixed threshold  $\tau \geq 0$ , one can even retrieve the connected components / clusters associated to all the bars of length  $> \tau$ !

## Topological Mode Analysis Tool

$$0 \leq \tau \leq \alpha - \beta$$



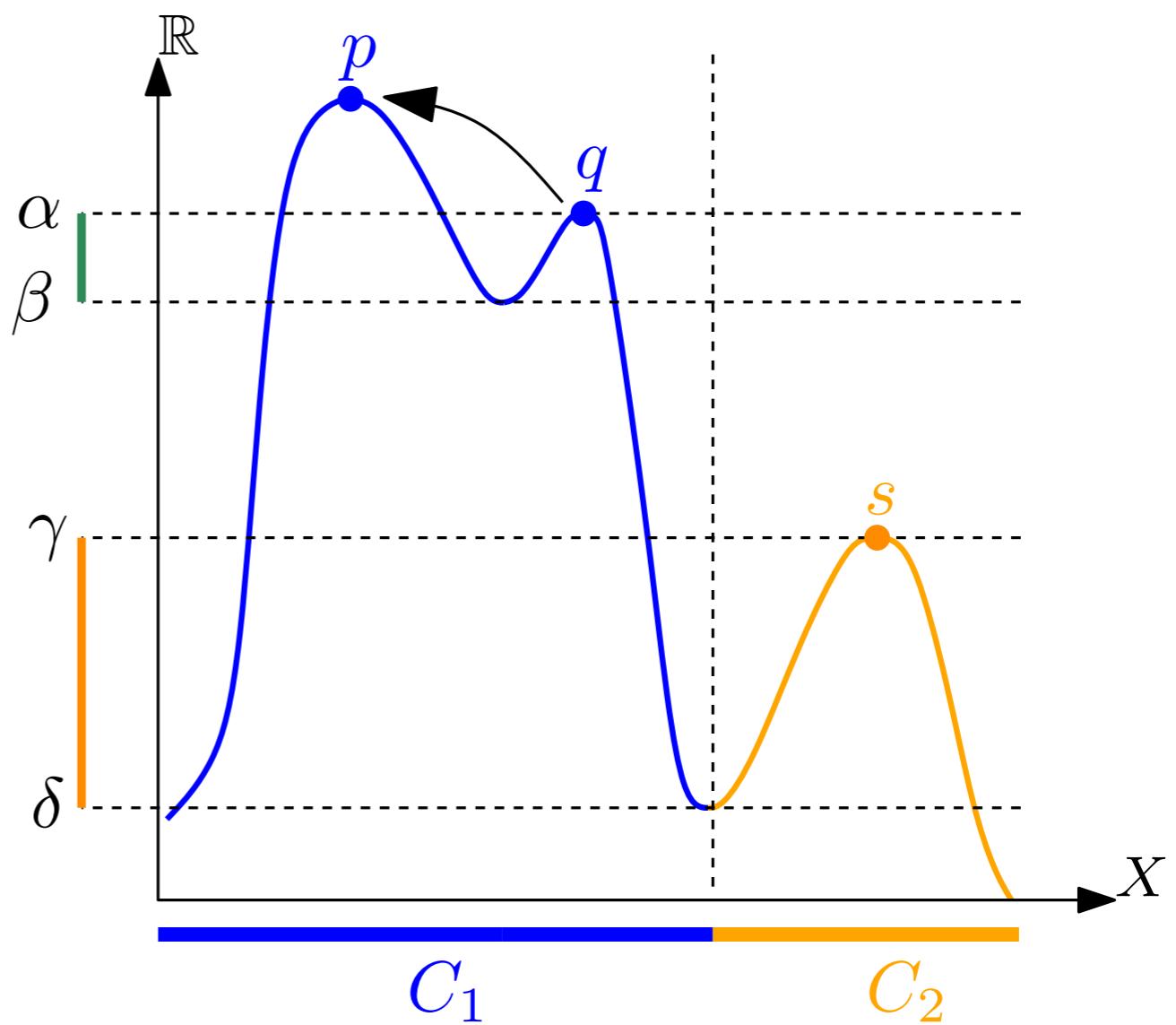
# Building a hierarchy of clusters

Moreover, 0-dimensional PH also remembers the connected components / clusters that were merged together during the filtration process and builds a hierarchy out of this information.

This means that, given a fixed threshold  $\tau \geq 0$ , one can even retrieve the connected components / clusters associated to all the bars of length  $> \tau$ !

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$$\alpha - \beta < \tau \leq \gamma - \delta$$



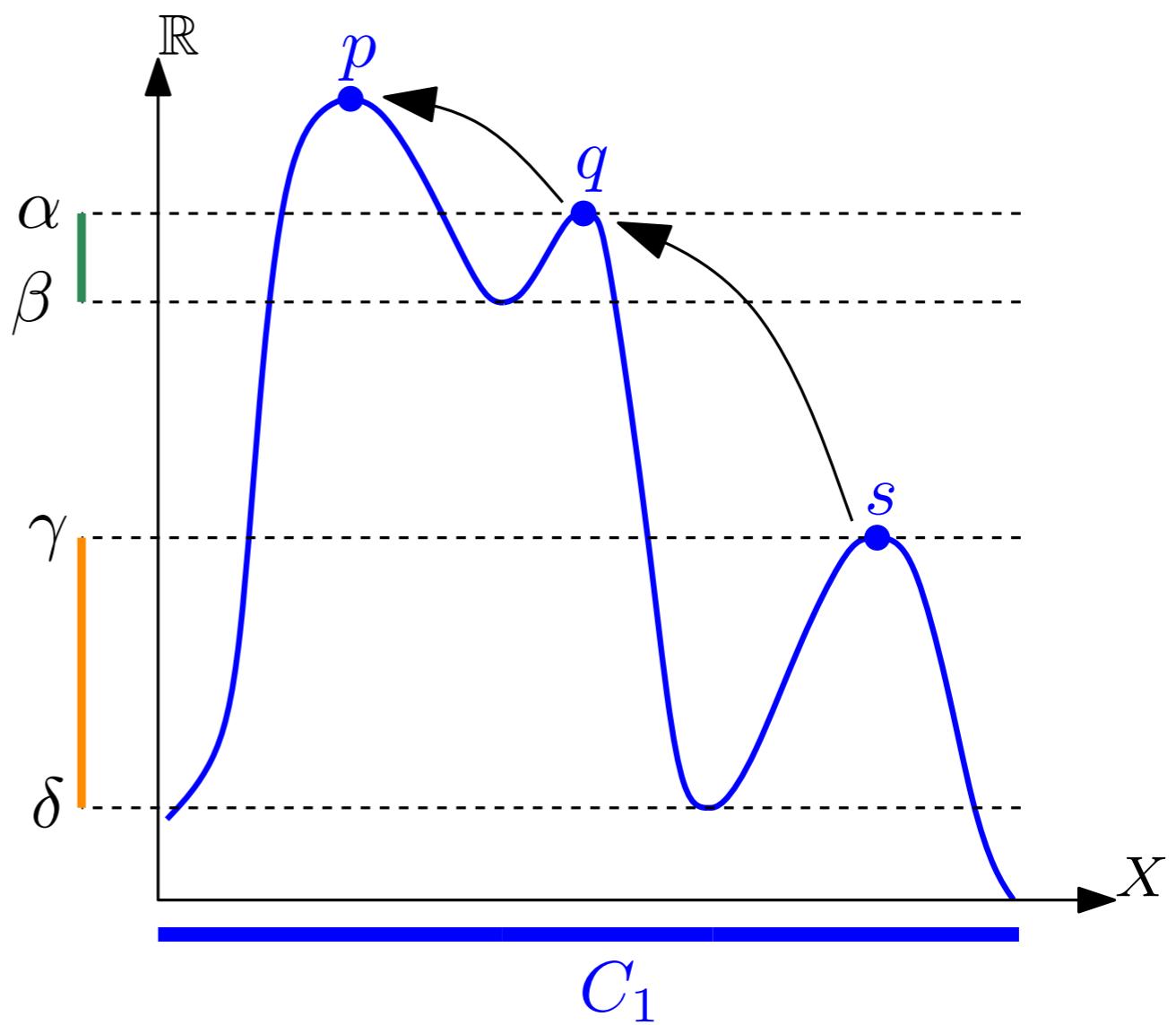
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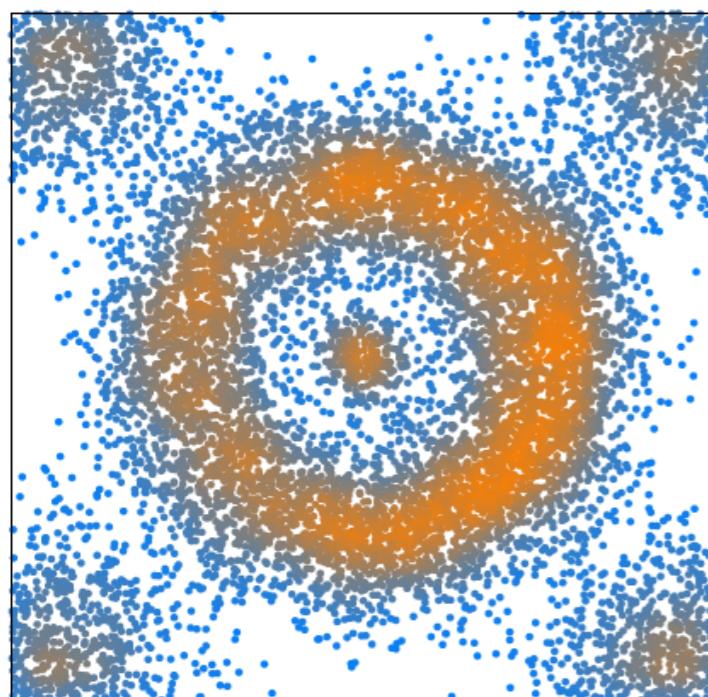
$$\gamma - \delta < \tau \leq +\infty$$



# ToMATo: Topological Mode Analysis Tool

[*Persistence-Based Clustering in Riemannian Manifolds*, Chazal, Oudot, Skraba, Guibas, J. ACM, 2013]

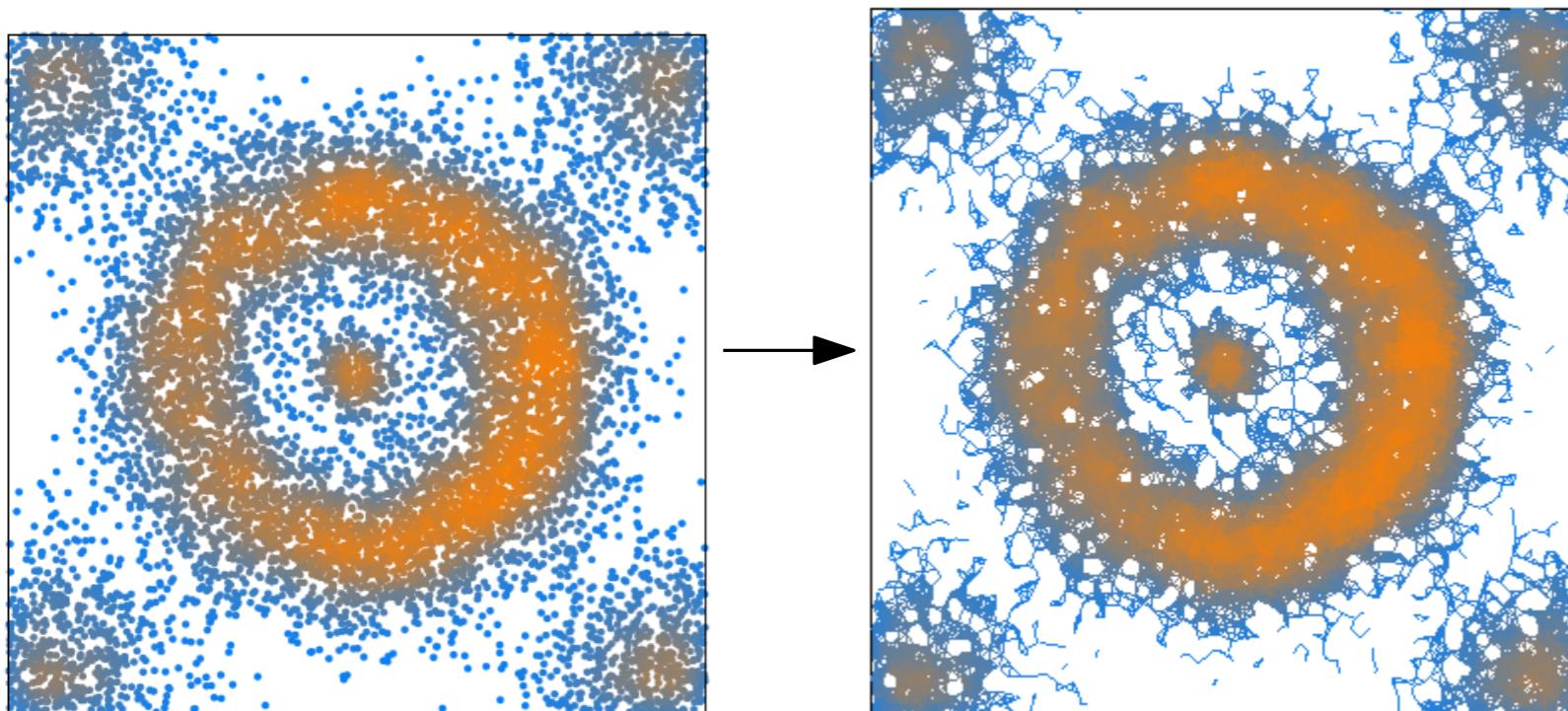
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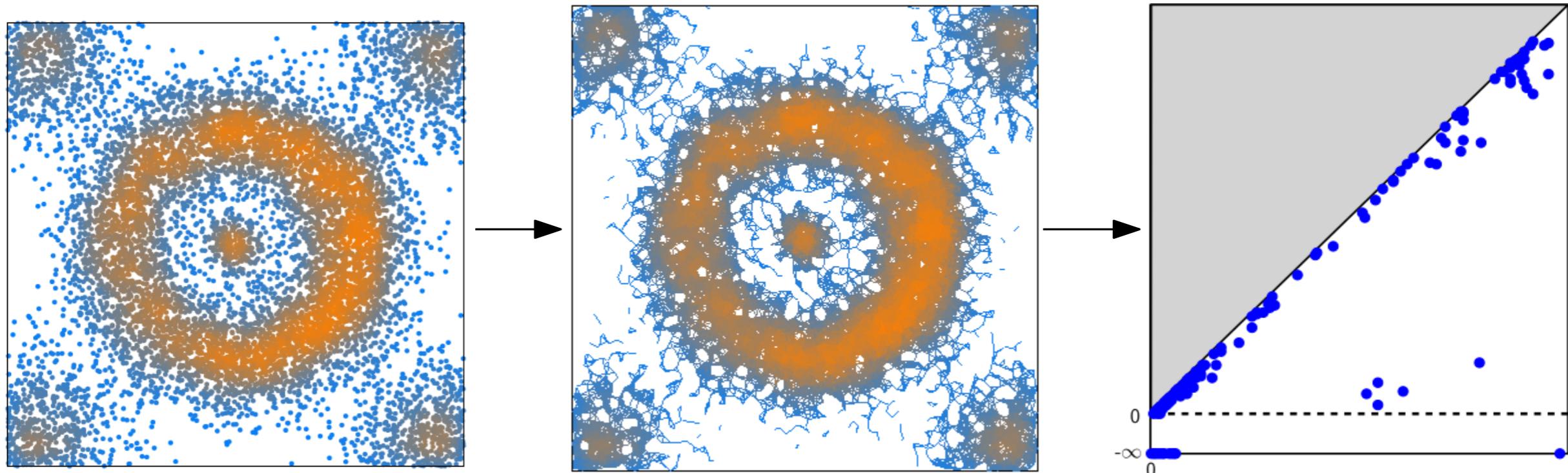
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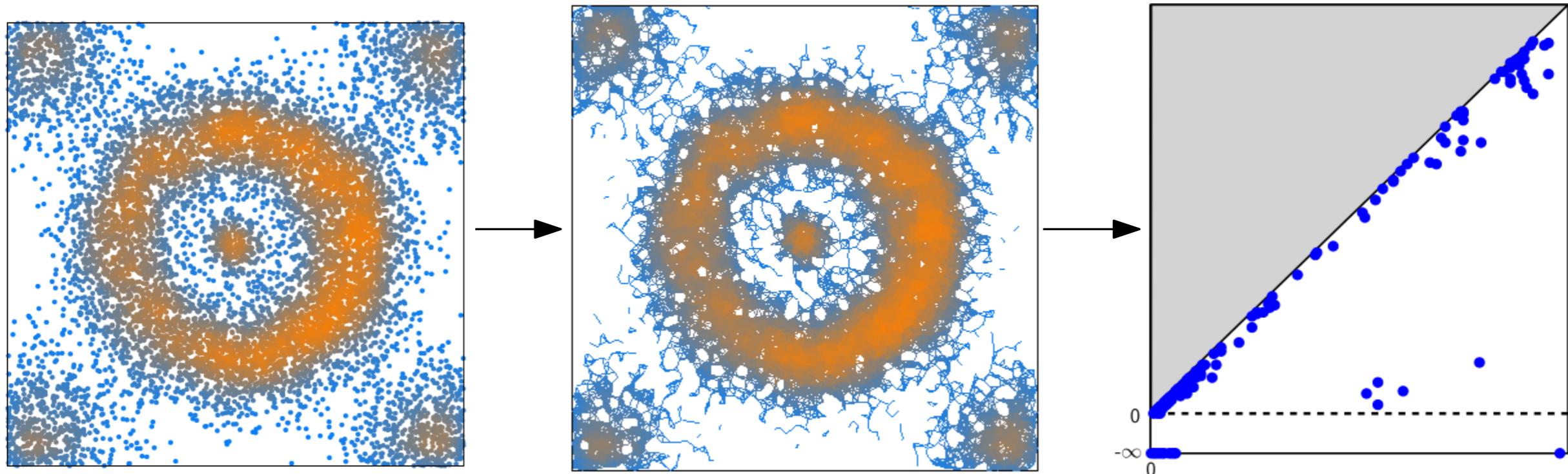
# ToMATo: Topological Mode Analysis Tool

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Given a neighborhood graph with  $n$  vertices and  $m$  edges:

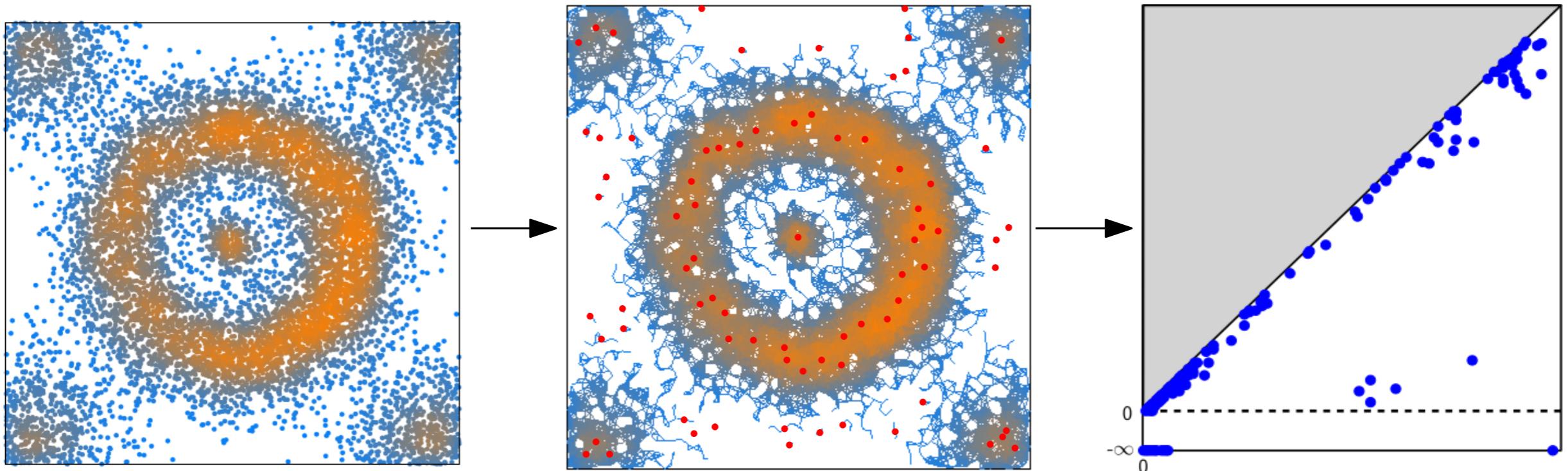
1. the algorithm sorts the vertices by decreasing density values,
2. and then makes a single pass through the vertex set, merging clusters on the fly using a union-find data structure.

→ Running time:  $O(n \log n + (n + m)\alpha(n))$   
→ Space complexity:  $O(n + m)$   
→ Main memory usage:  $O(n)$



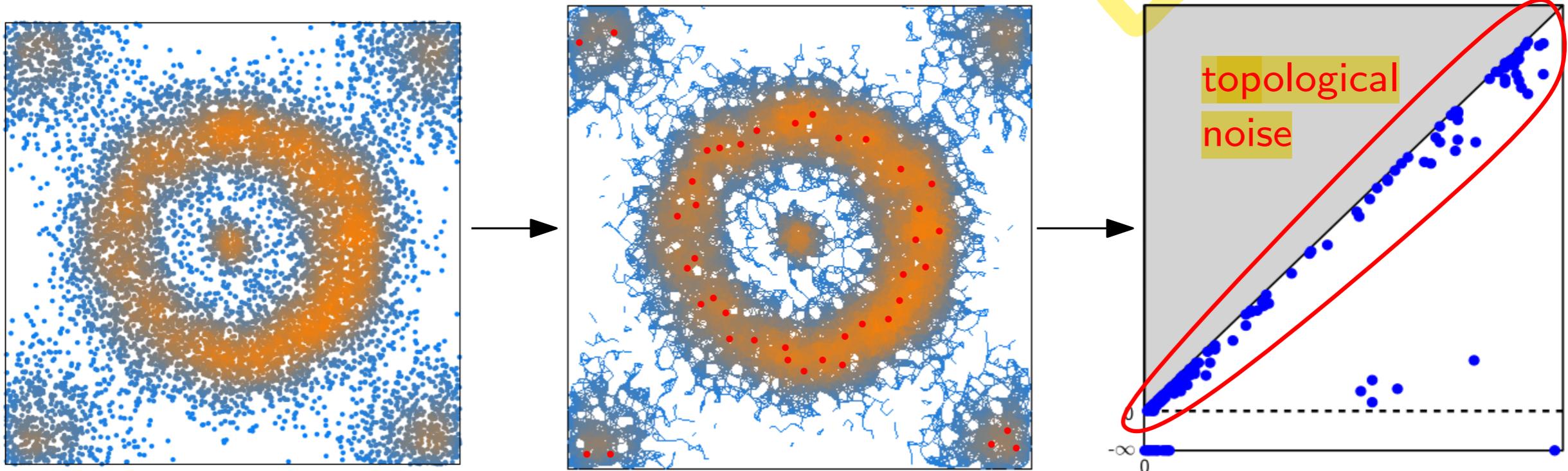
# Estimating the correct number of clusters

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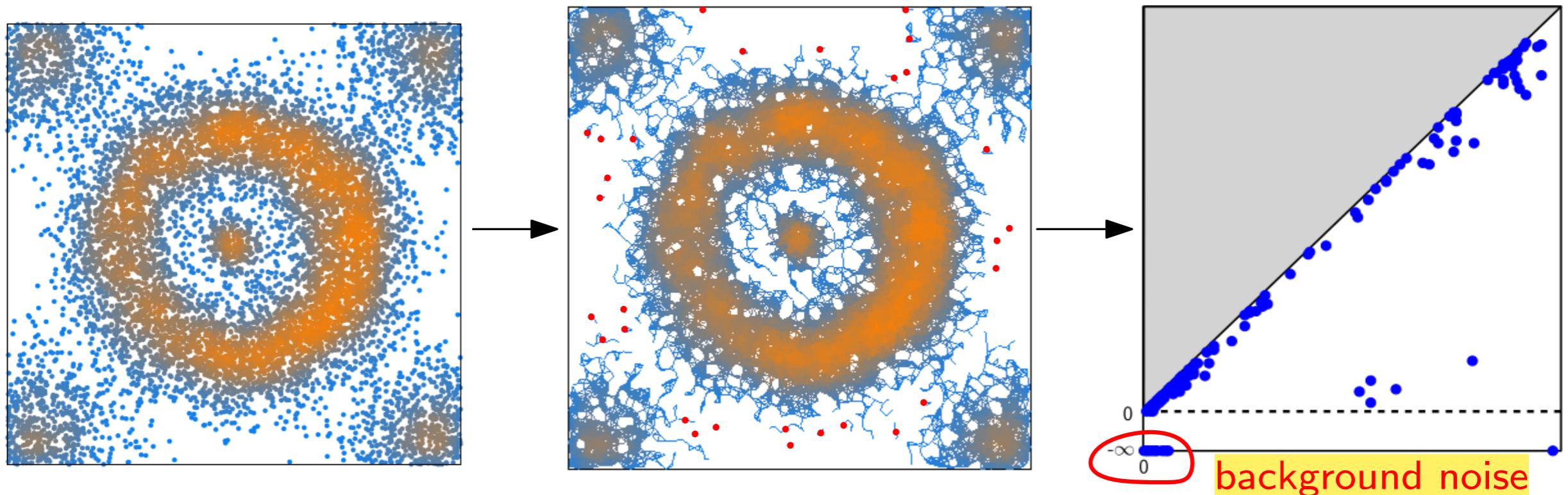
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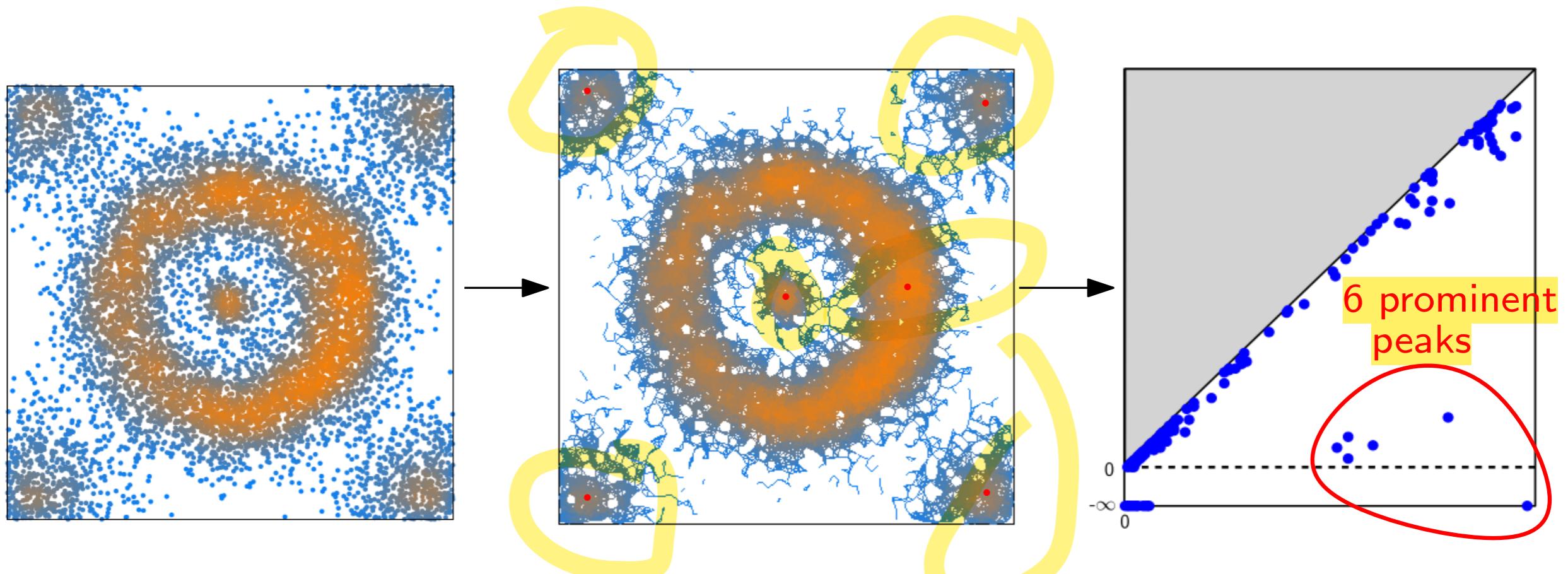
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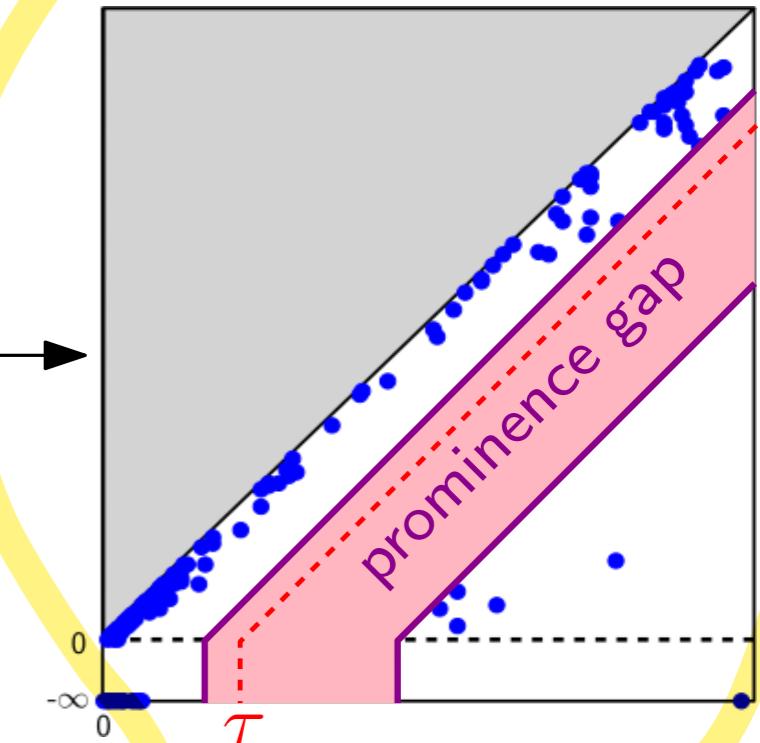
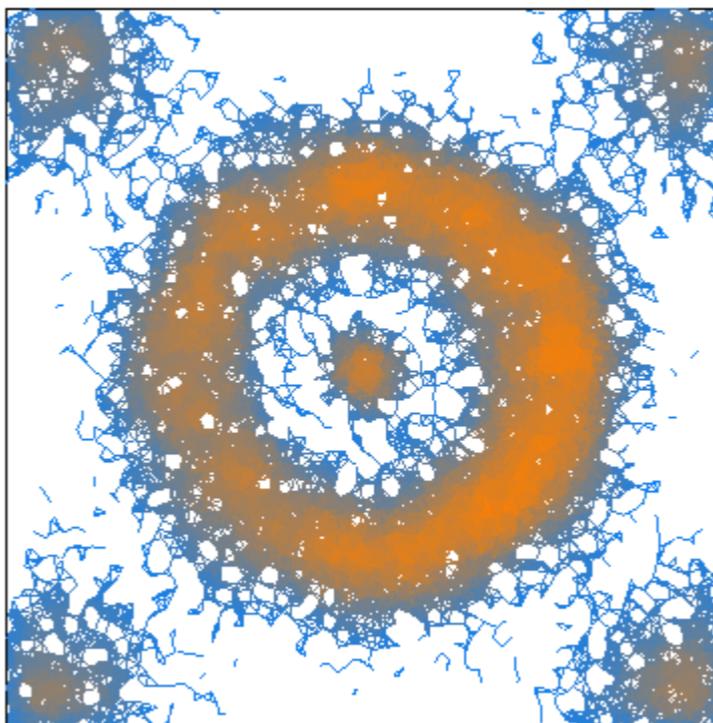
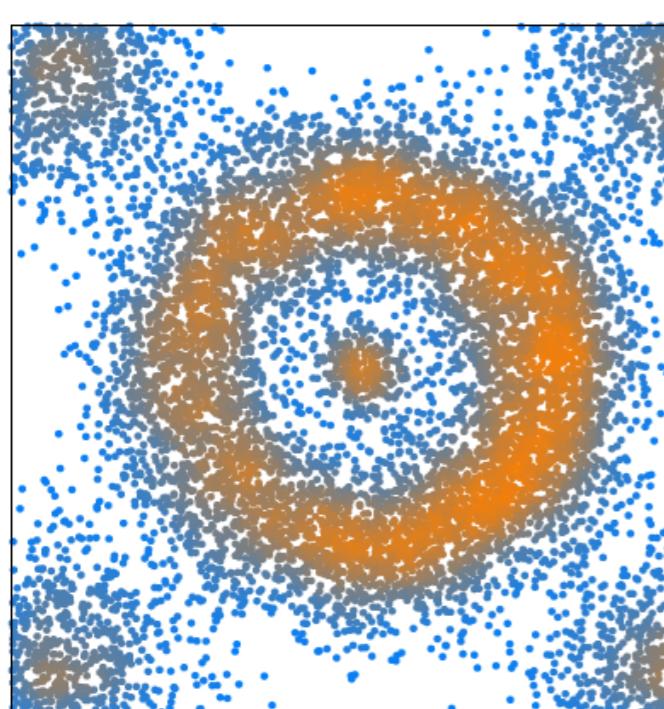
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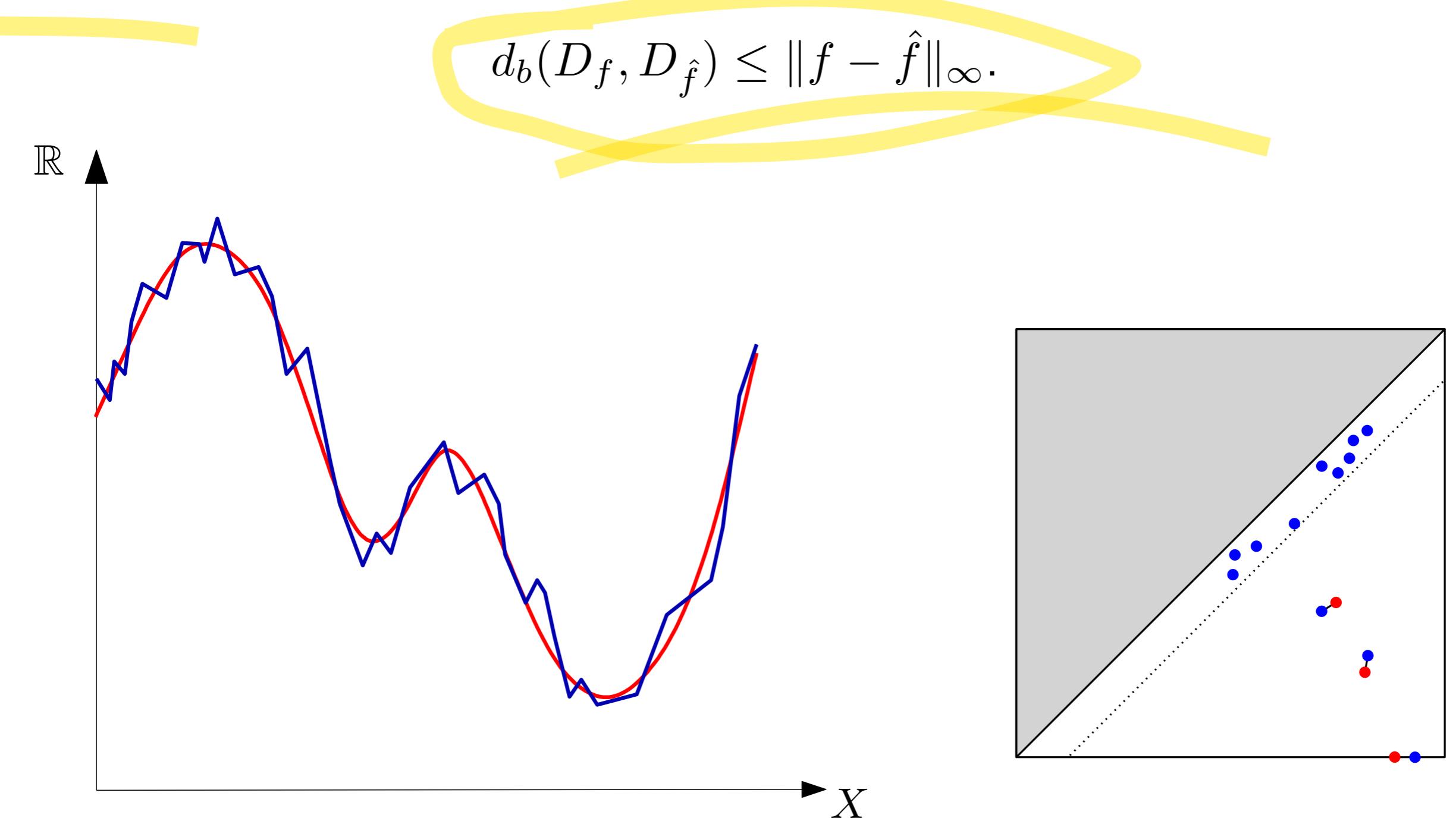
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# The Stability Theorem

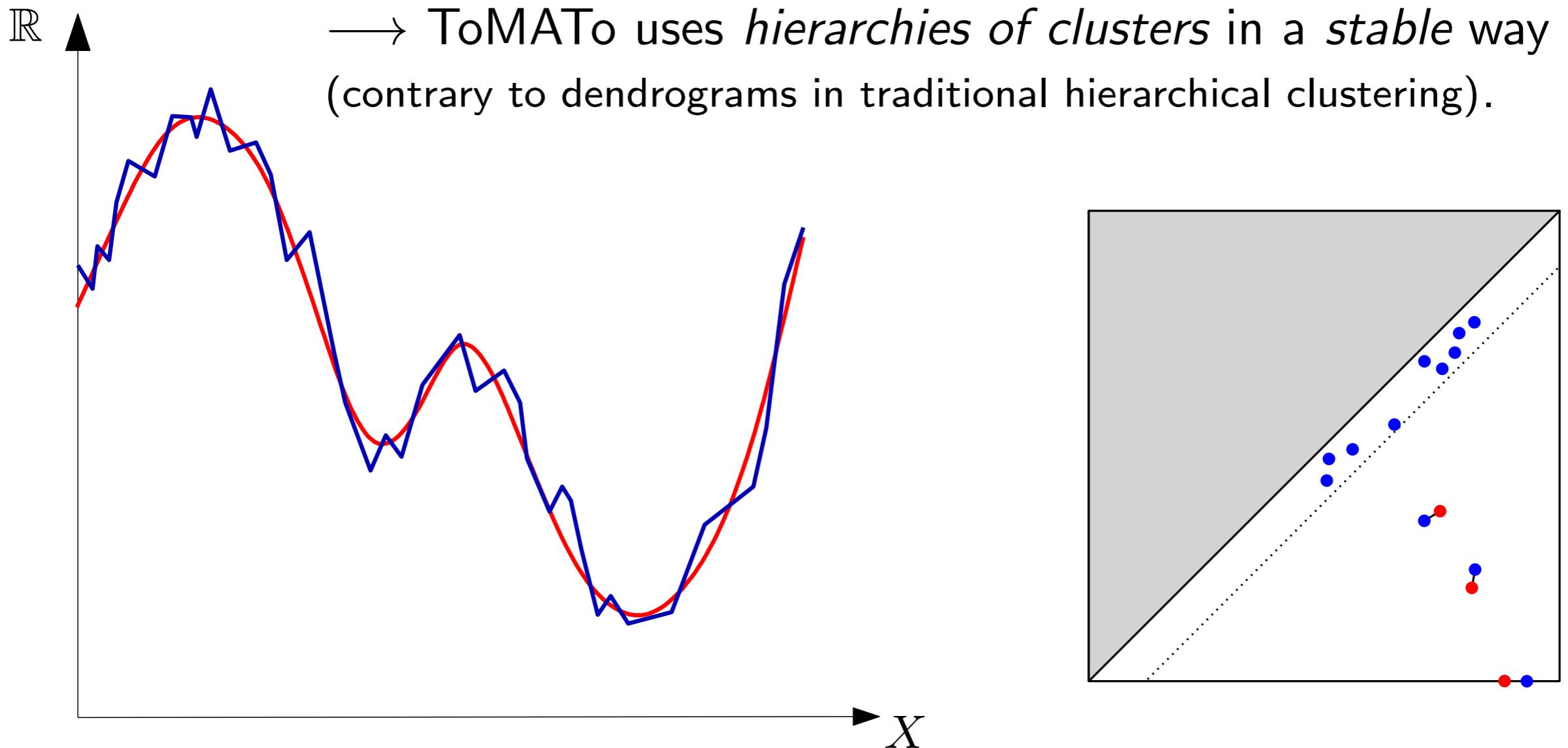
This seminal TDA result ensures that, given an underlying ground-truth function  $f : X \rightarrow \mathbb{R}$ , and an estimator  $\hat{f} : X \rightarrow \mathbb{R}$  of it, one has:



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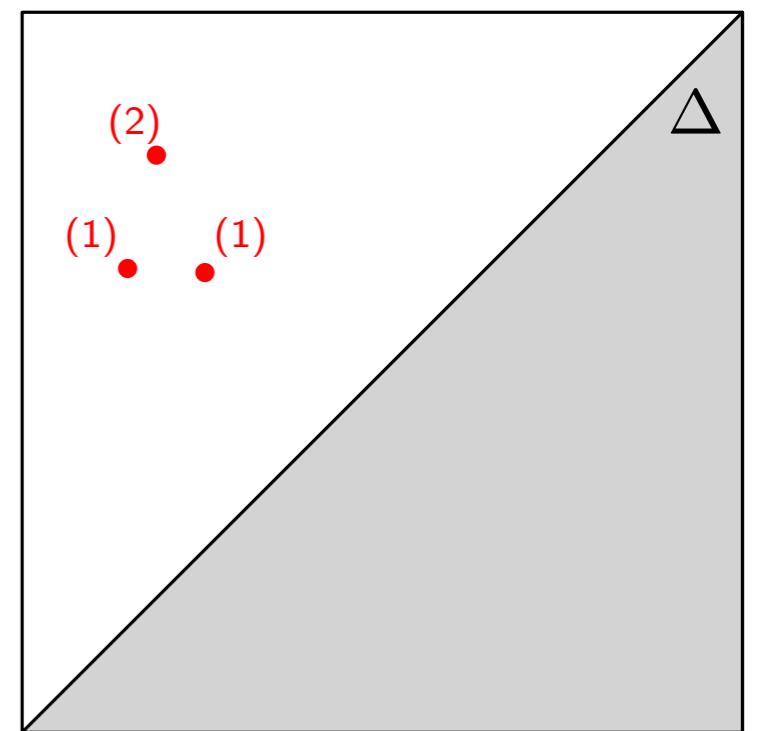
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$$d_b(D_f, D_{\hat{f}}) \leq \|f - \hat{f}\|_\infty.$$



# Distance between persistence diagrams

Persistence diagram  $\equiv$  **finite multiset** in the open half-plane  $\Delta \times \mathbb{R}_{>0}$ .



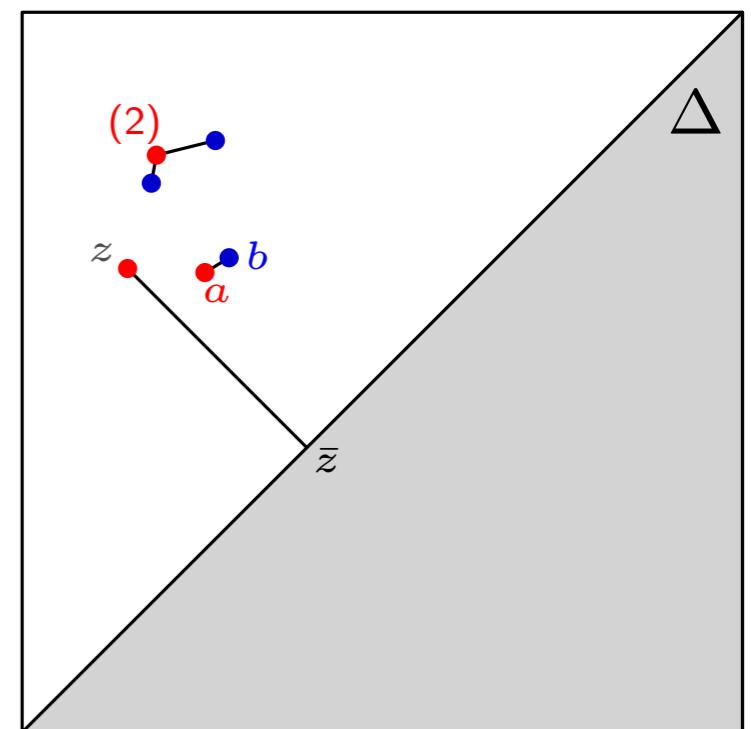
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Given a **partial matching**  $M : D \leftrightarrow D'$ :

- cost of a matched pair  $(a, b) \in M$ :  $c_p(a, b) := \|a - b\|_\infty^p$ ,
- cost of an unmatched point  $c \in D \sqcup D'$ :  $c_p(c) := \|c - \bar{c}\|_\infty^p$ ,
- **cost of  $M$** :

$$c_p(M) := \left( \sum_{(a, b) \text{ matched}} c_p(a, b) + \sum_{c \text{ unmatched}} c_p(c) \right)^{1/p}$$



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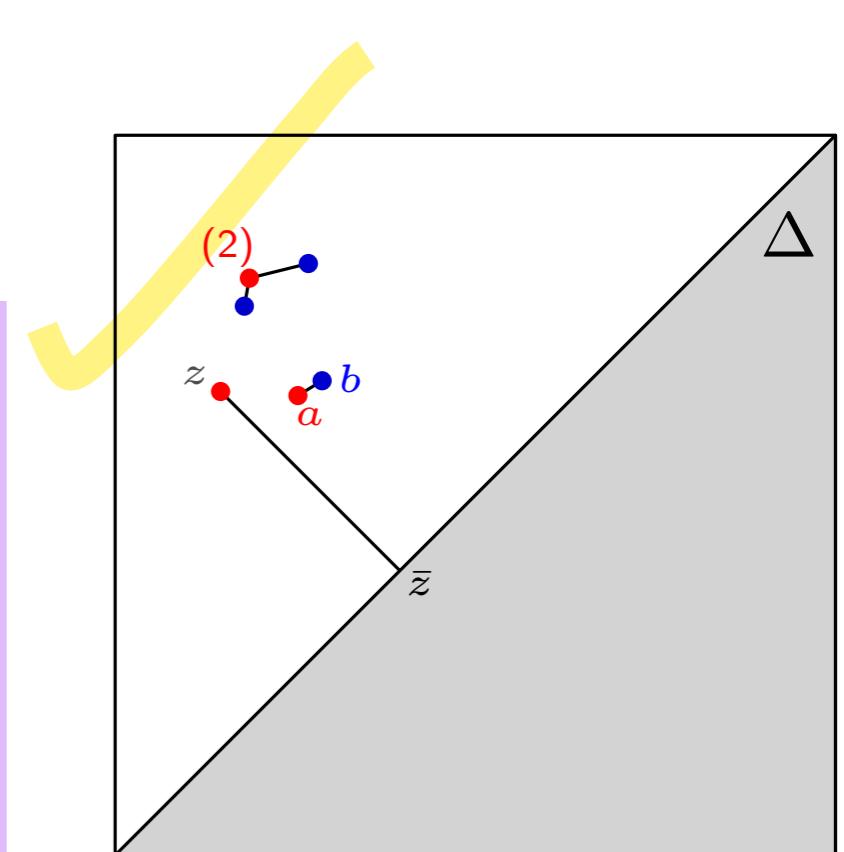
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**Def:**  $p$ -th diagram distance (extended metric):

$$d_p(D, D') := \inf_{M: D \leftrightarrow D'} c_p(M)$$

**Def:** **bottleneck distance:**

$$d_b(D, D') = d_\infty(D, D') := \lim_{p \rightarrow \infty} d_p(D, D')$$

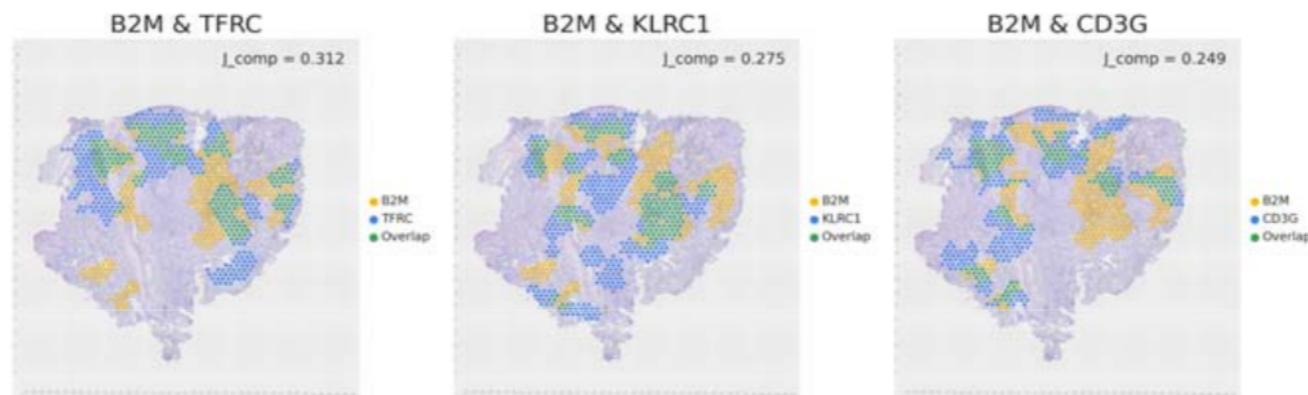


# Application to colocalization

## Method:

1. Compute clusters associated to several gene markers with ToMATo and compute pairwise Jaccard similarities:

$$0 \leq J(C, C') := \frac{\#\{C \cap C'\}}{\#\{C \cup C'\}} \leq 1$$



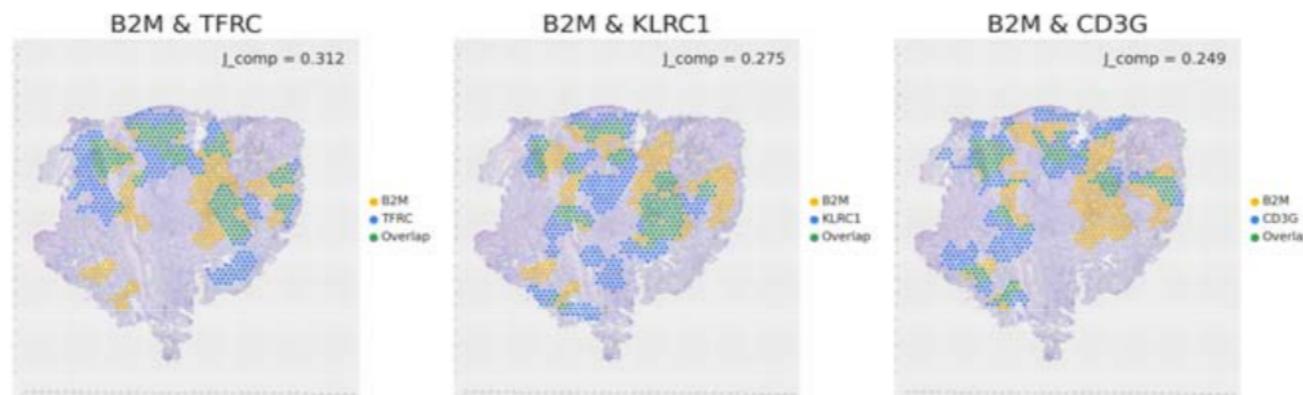
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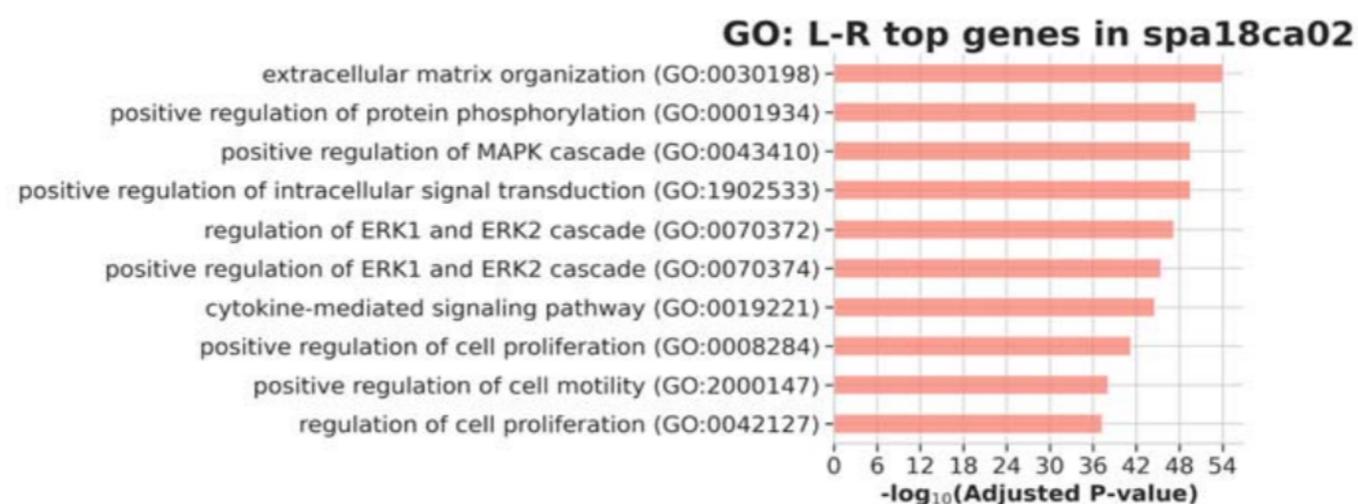
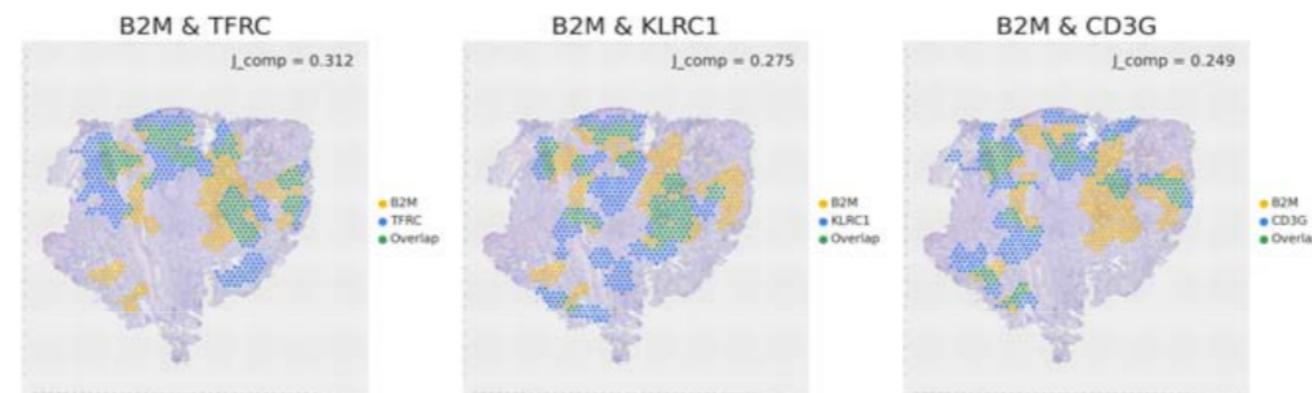
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One can also play the same game by using *higher-dimensional* homology, and then predict phenotypes solely from the corresponding persistence diagrams.

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