

Data thinning to overcome double dipping

Anna Neufeld

Final Exam

May 9, 2023

What is double dipping?

Classical statistical methods assume that we only ever test pre-specified hypotheses about pre-specified models.

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In reality, we explore our data, fit several models, evaluate these models, select our favorite model, then test hypotheses about this model.

Double Dipping: Using the same data for two tasks, such as:

1. Generating and testing a null hypothesis.
2. Fitting and evaluating a model.

Approach 1: develop specialized procedures that account for double dipping

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Project 1

Journal of Machine Learning Research 23 (2022) 1-43

Submitted 6/21; Revised 10/22; Published 11/22

Tree-Values: Selective Inference for Regression Trees

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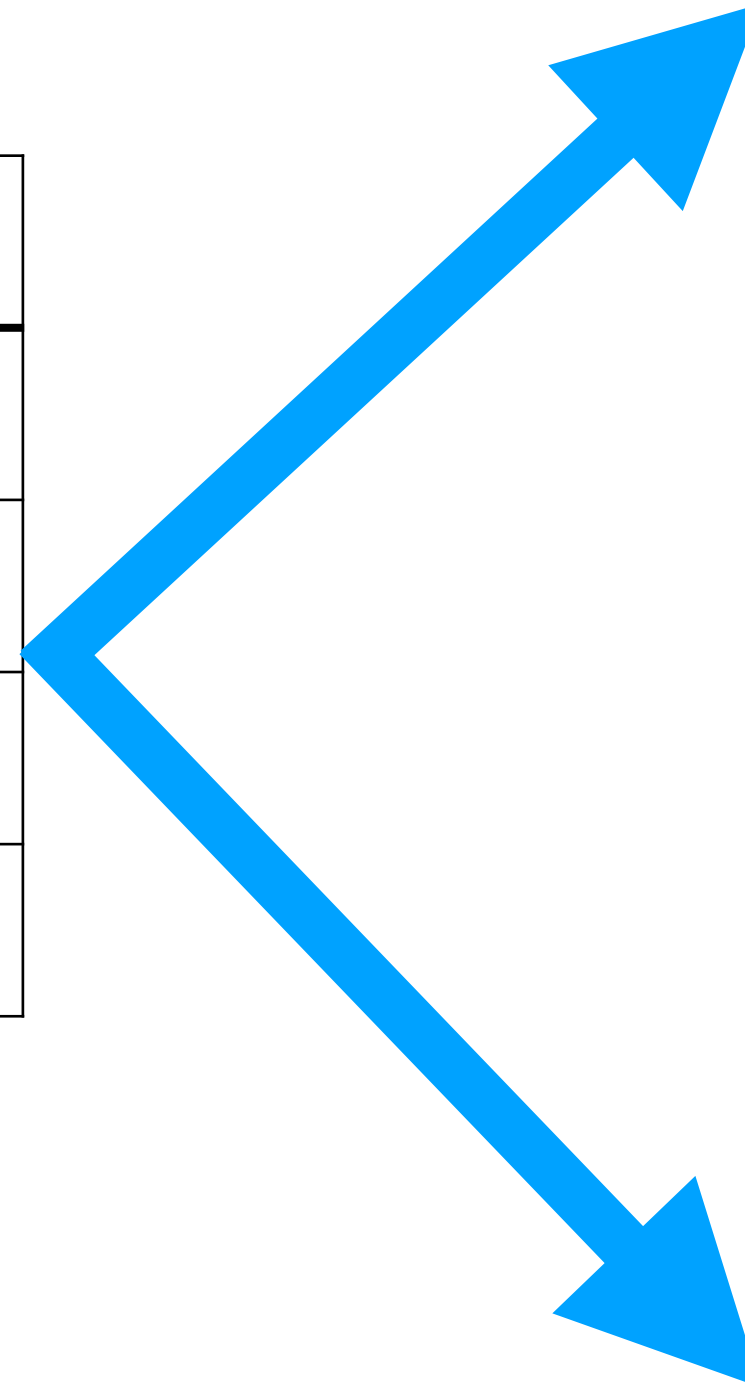
R package and tutorials: <https://anna-neufeld.github.io/treevalues/>

Approach 2: avoid double dipping entirely via sample splitting

	Feature 1	Feature 2
Obs. 1	12	6
Obs. 2	31	8
Obs. 3	11	31
Obs. 4	22	34

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	Feature 1	Feature 2
Obs. 1	12	6
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Train

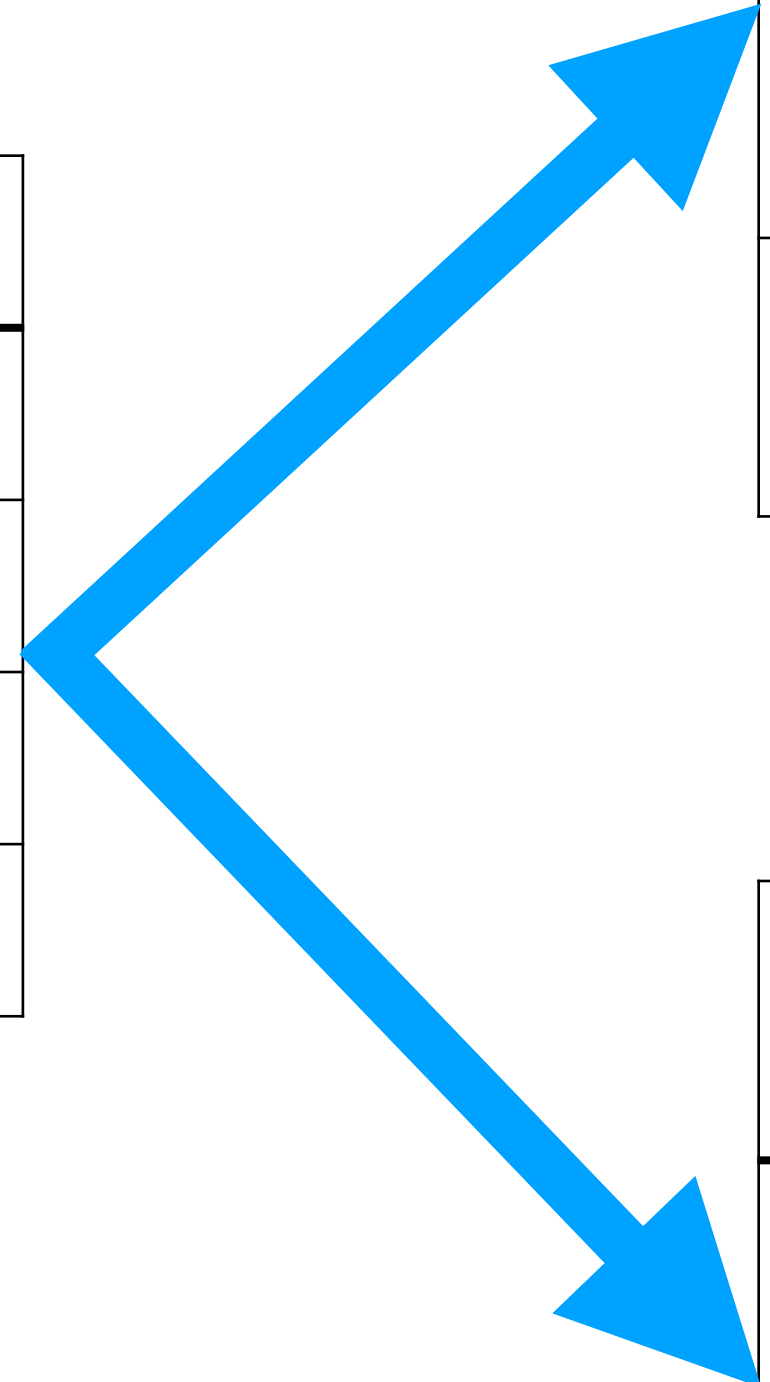
	Feature 1	Feature 2
Obs. 1	12	6
Obs. 2	31	8

Test

	Feature 1	Feature 2
Obs. 3	11	31
Obs. 4	22	34

Approach 2: avoid double dipping entirely via sample splitting

	Feature 1	Feature 2
Obs. 1	12	6
Obs. 2	31	8
Obs. 3	11	31
Obs. 4	22	34



Train

	Feature 1	Feature 2
Obs. 1	12	6
Obs. 2	31	8

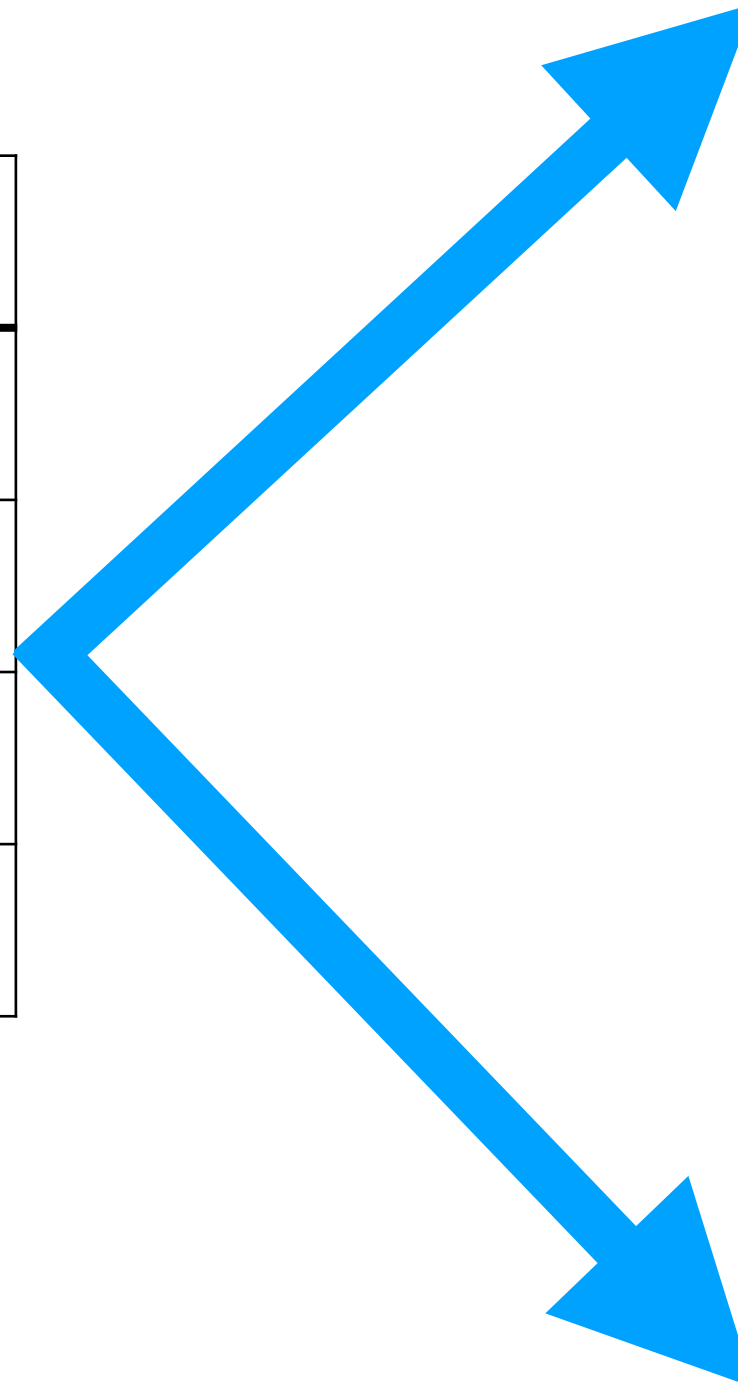
Test

	Feature 1	Feature 2
Obs. 3	11	31
Obs. 4	22	34

Select hypothesis.

Approach 2: avoid double dipping entirely via sample splitting

	Feature 1	Feature 2
Obs. 1	12	6
Obs. 2	31	8
Obs. 3	11	31
Obs. 4	22	34



Train

	Feature 1	Feature 2
Obs. 1	12	6
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Select hypothesis.

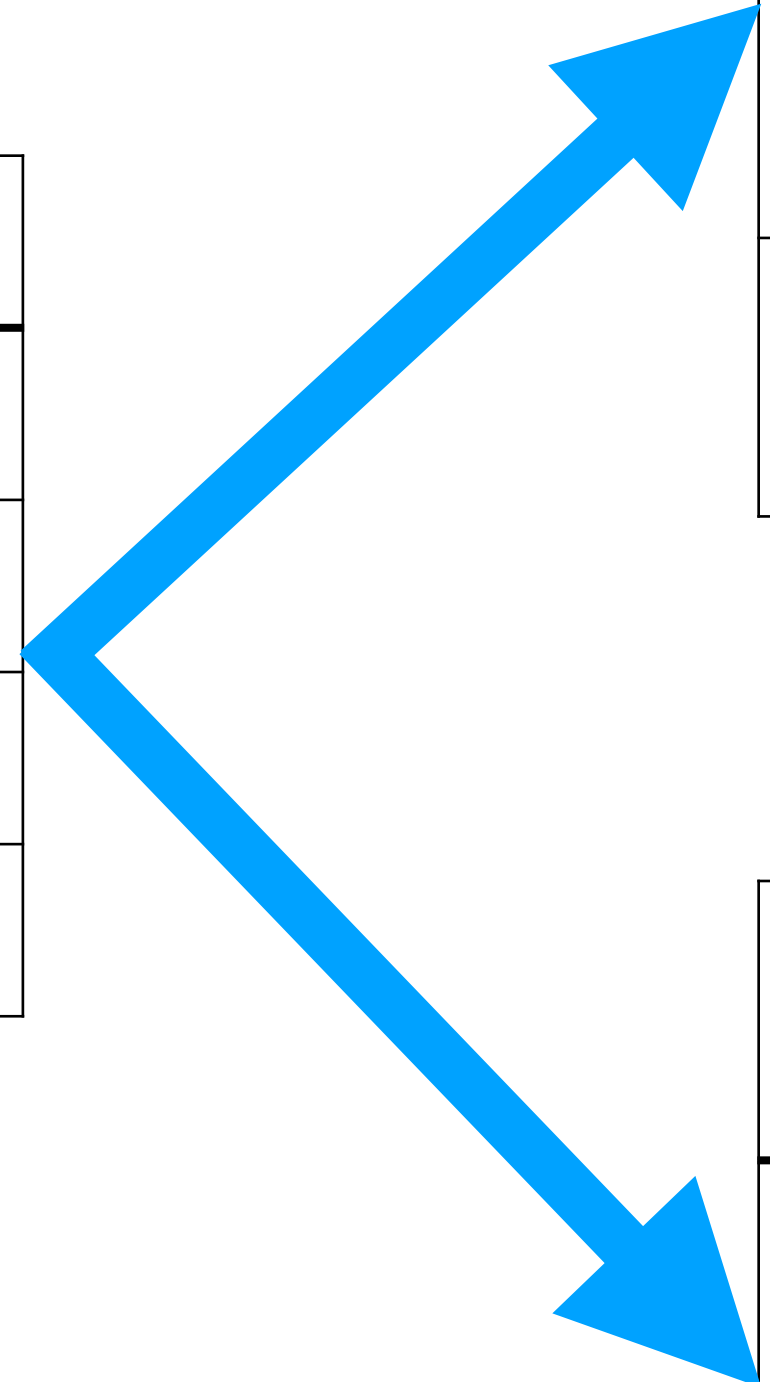
Test

	Feature 1	Feature 2
Obs. 3	11	31
Obs. 4	22	34

Test hypothesis.

Approach 2: avoid double dipping entirely via sample splitting

	Feature 1	Feature 2
Obs. 1	12	6
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Train

	Feature 1	Feature 2
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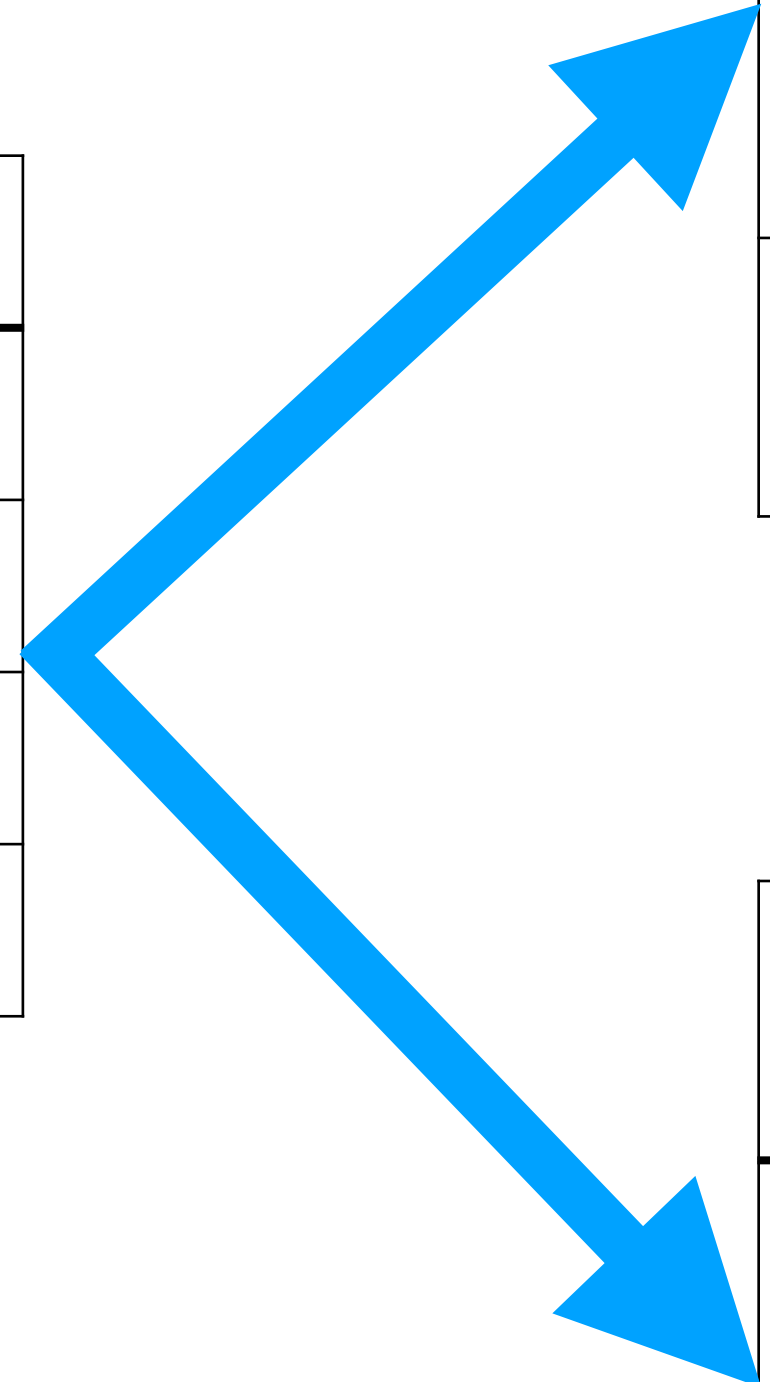
Fit model.

Test

	Feature 1	Feature 2
Obs. 3	11	31
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	Feature 1	Feature 2
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Train

	Feature 1	Feature 2
Obs. 1	12	6
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Fit model.

Test

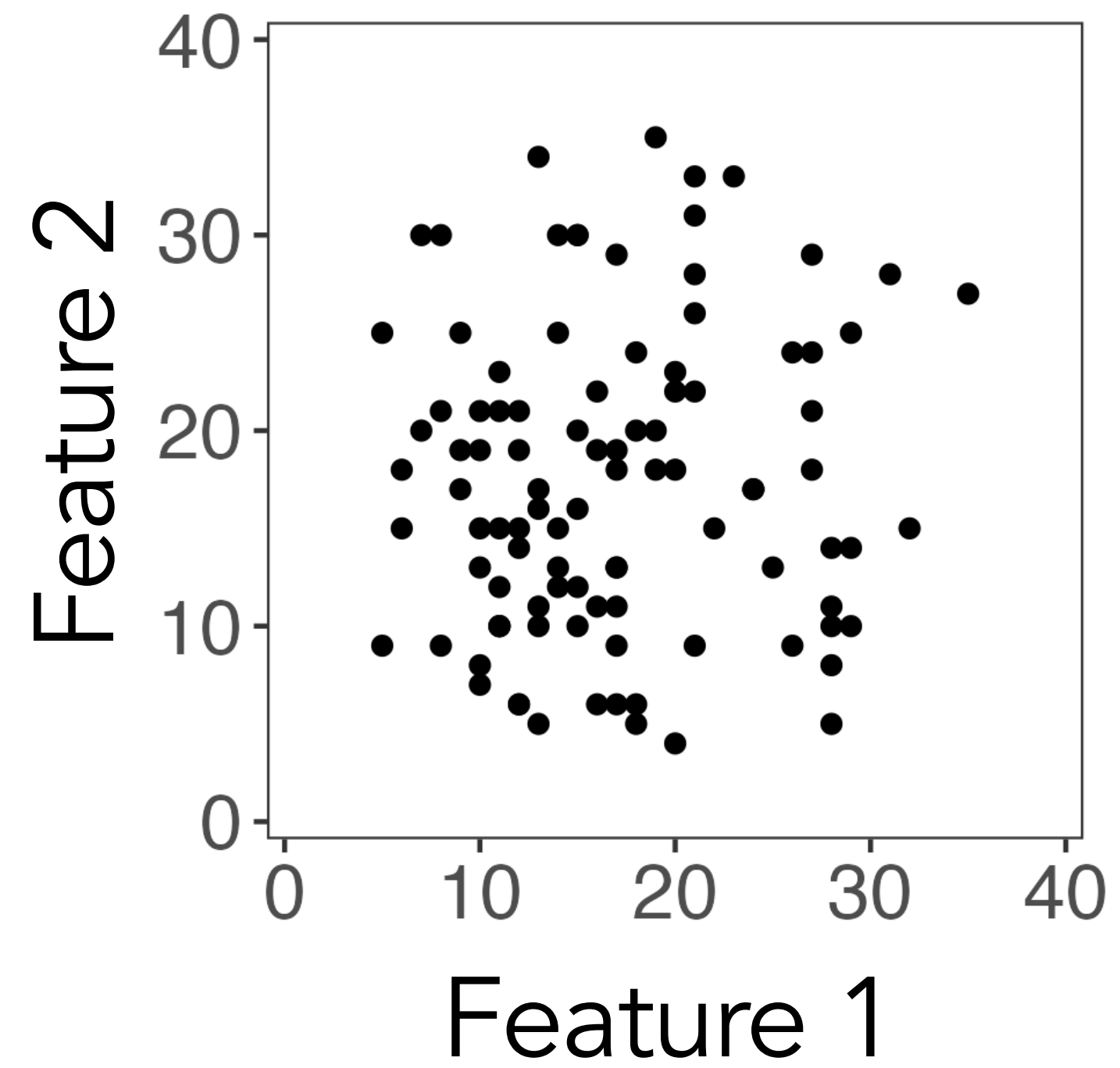
	Feature 1	Feature 2
Obs. 3	11	31
Obs. 4	22	34

Evaluate model.

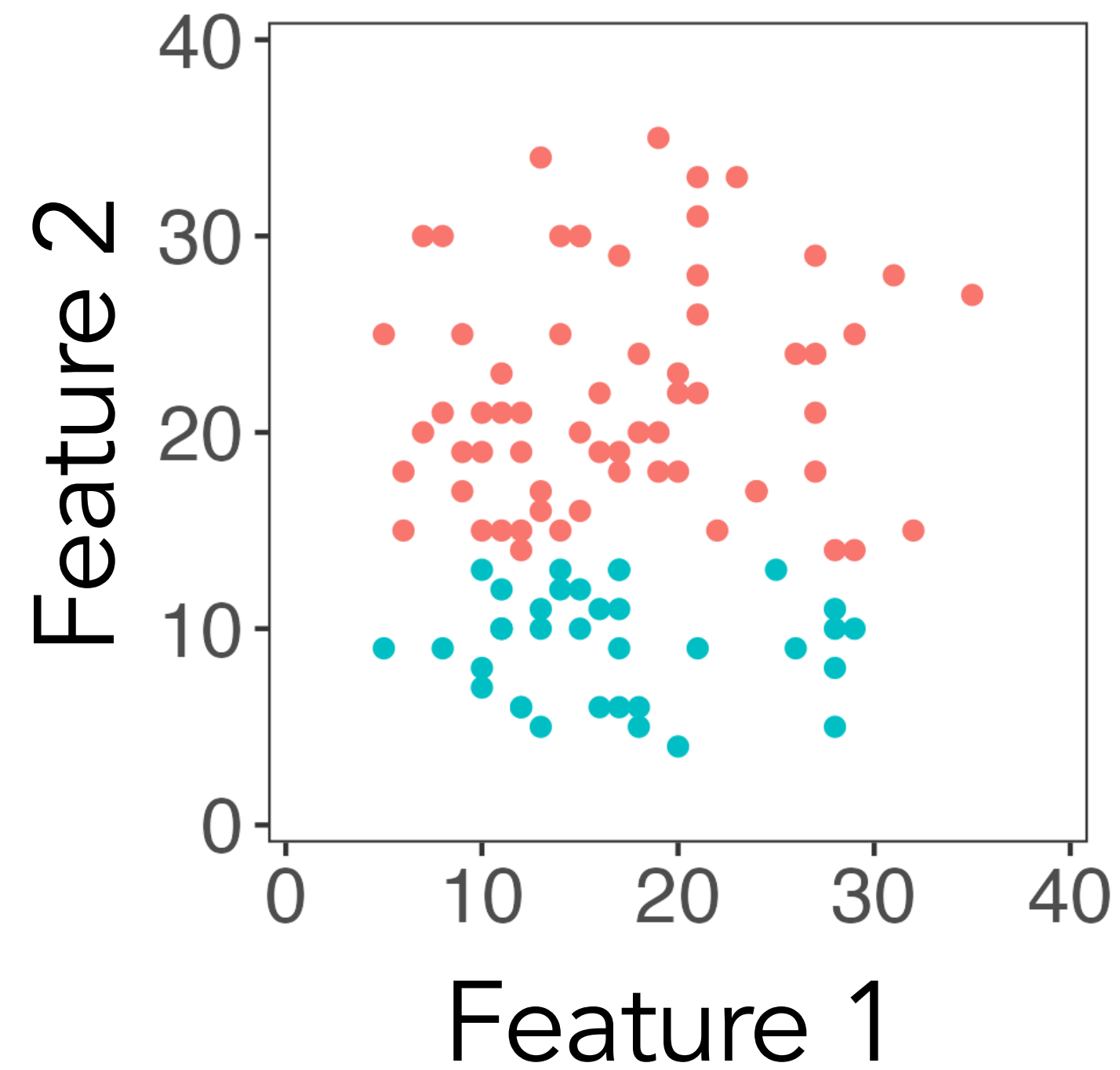
Outline

1. **Motivation: settings where sample splitting doesn't work**
2. Poisson thinning
3. Data thinning
4. Application to single-cell RNA sequencing data
5. Ongoing work

Example 1: using the same data to generate and test a hypothesis

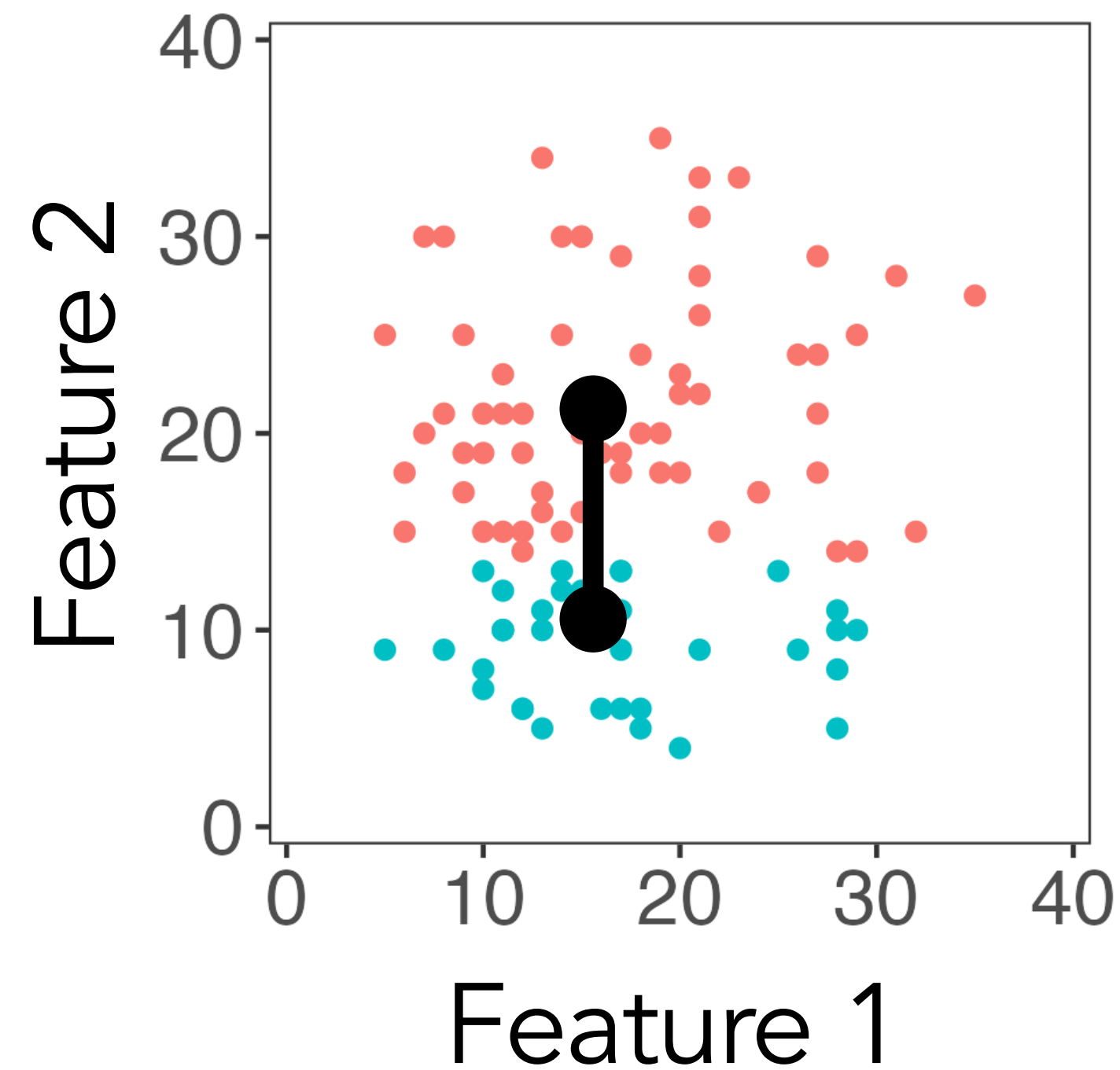


Example 1: using the same data to generate and test a hypothesis



Step 1: cluster the observations.

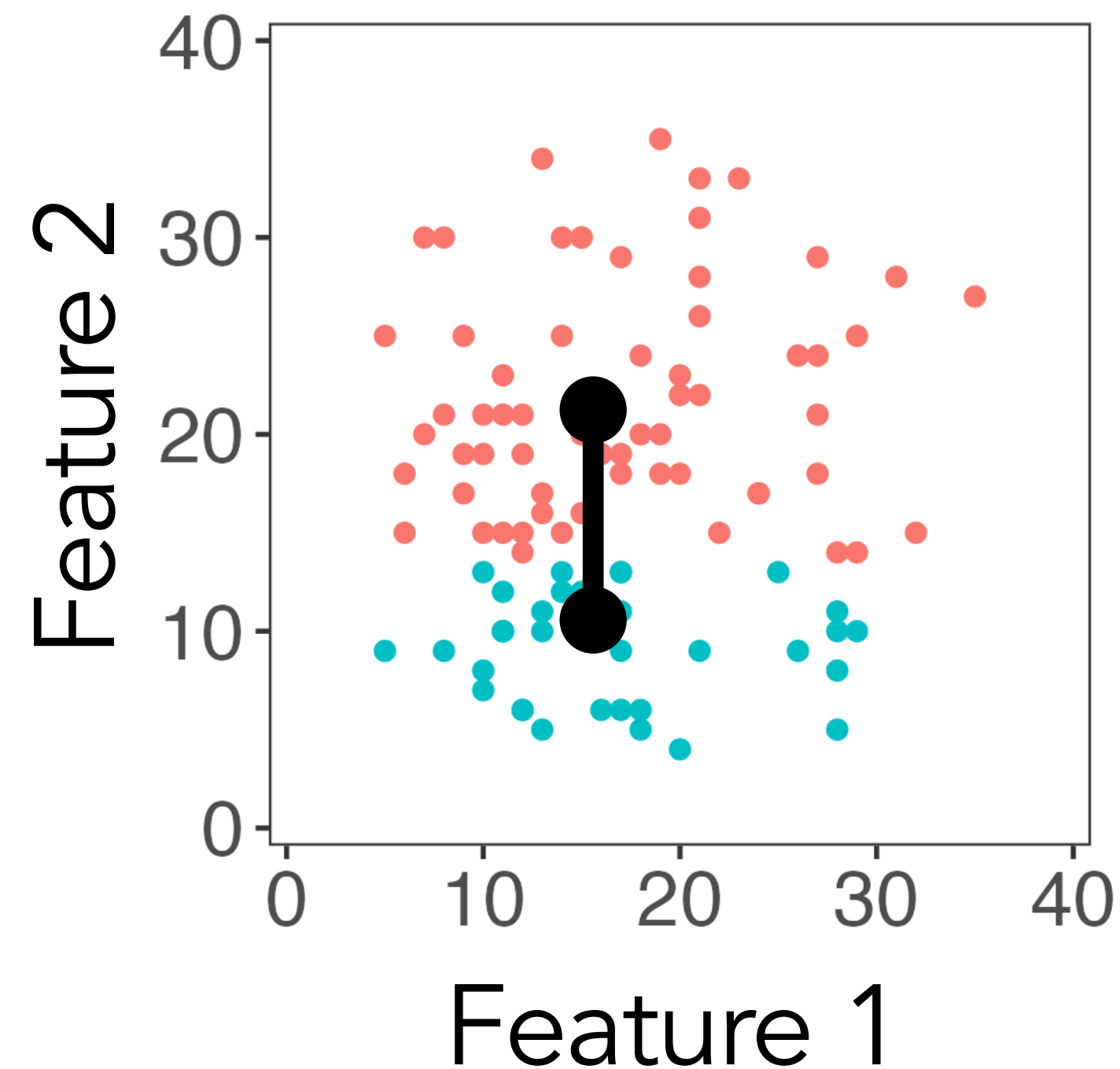
Example 1: using the same data to generate and test a hypothesis



Step 1: cluster the observations.

Generate H_0 : "the expected value of Feature 2 is the same between red observations and the blue observations."

Example 1: using the same data to generate and test a hypothesis



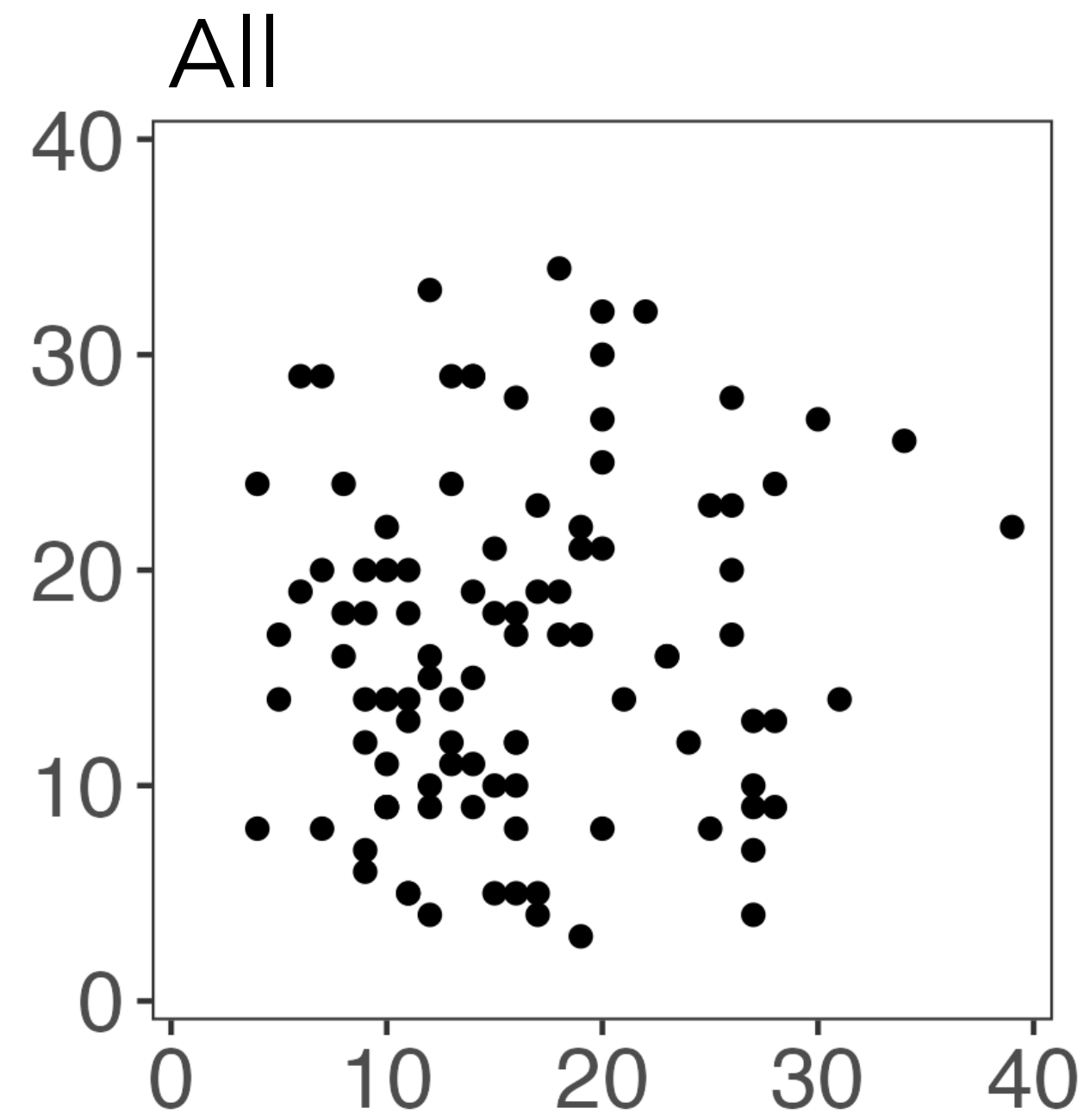
$p < 10^{-10}$ 🤯

Step 1: cluster the observations.

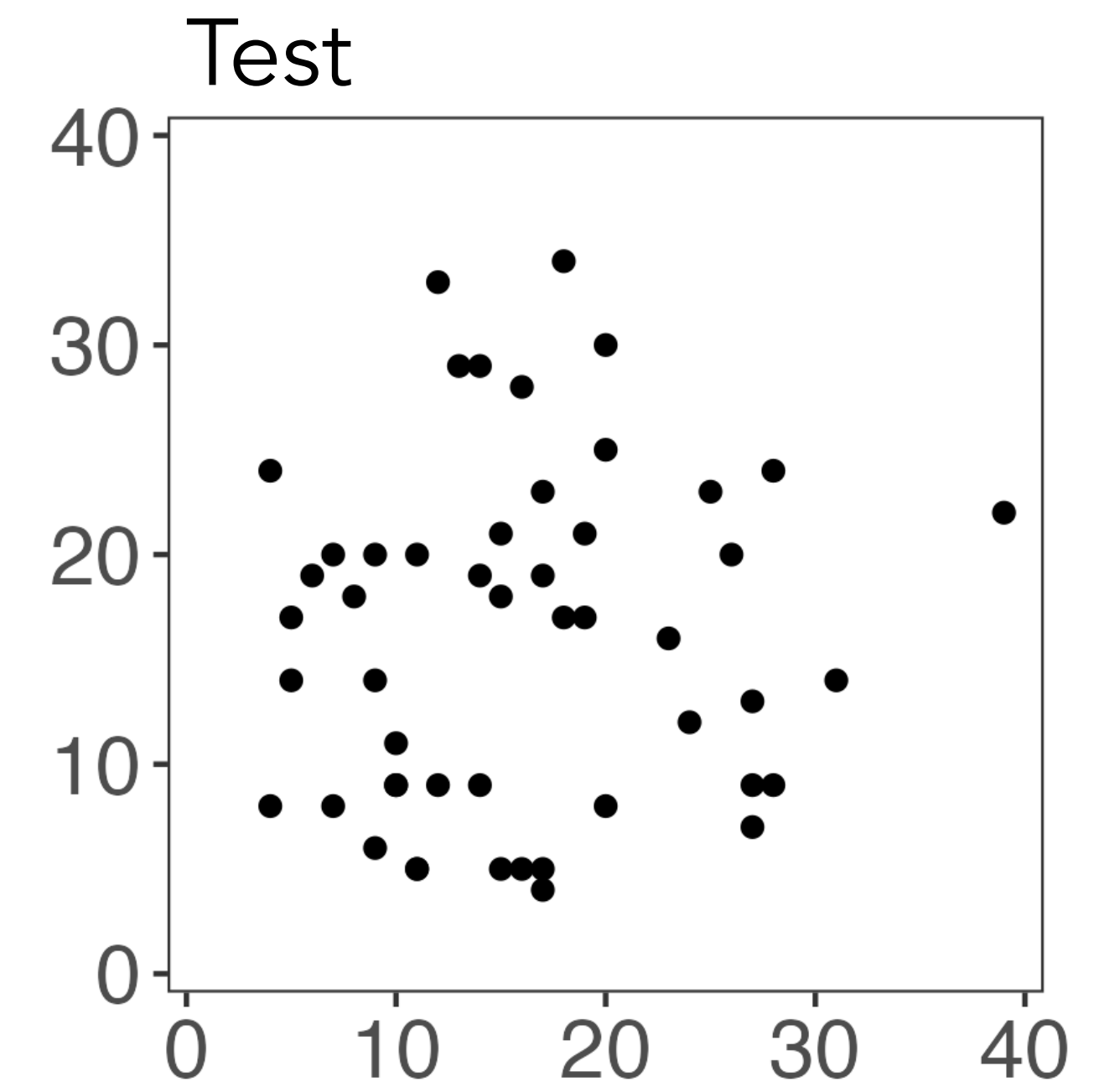
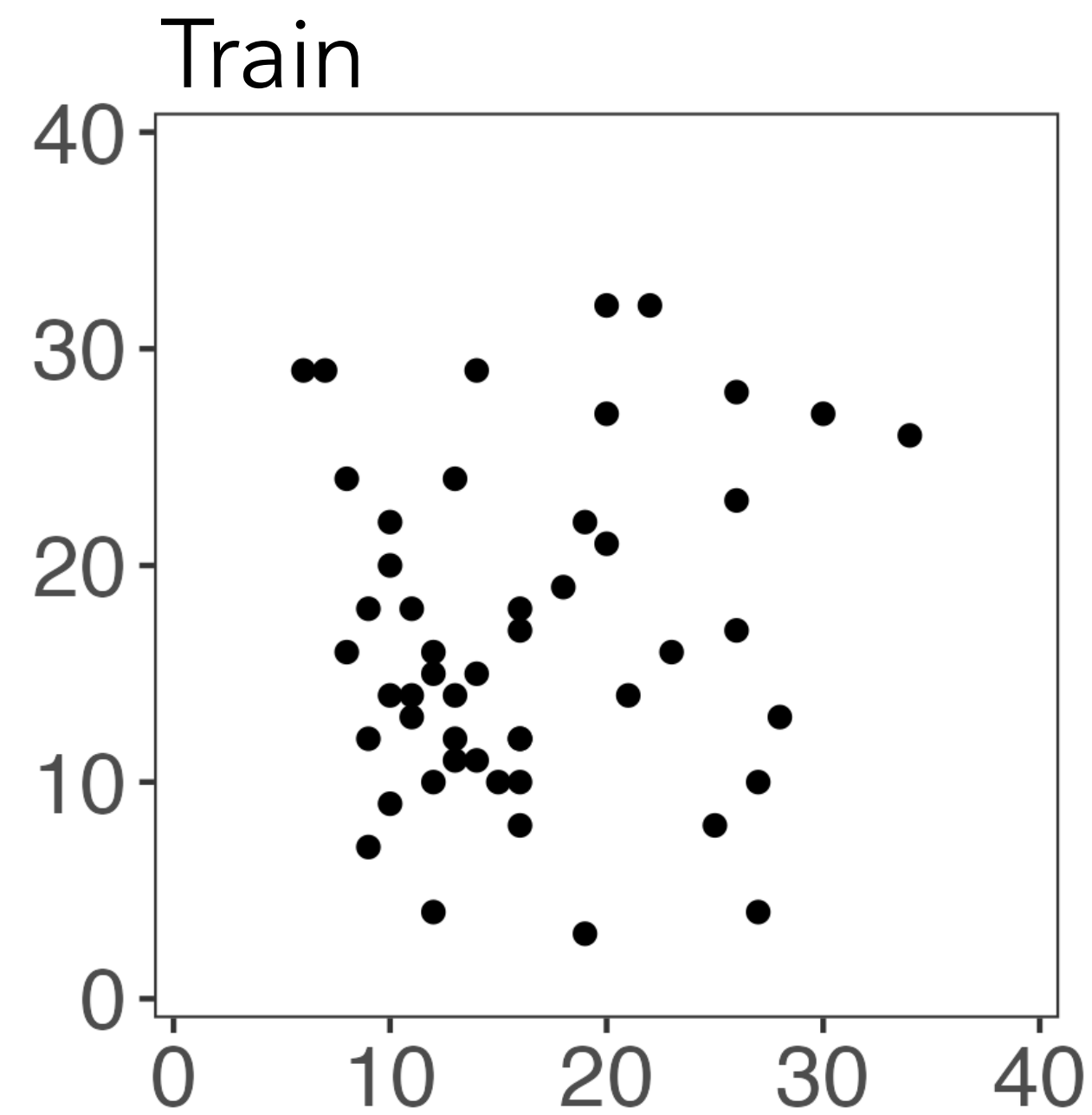
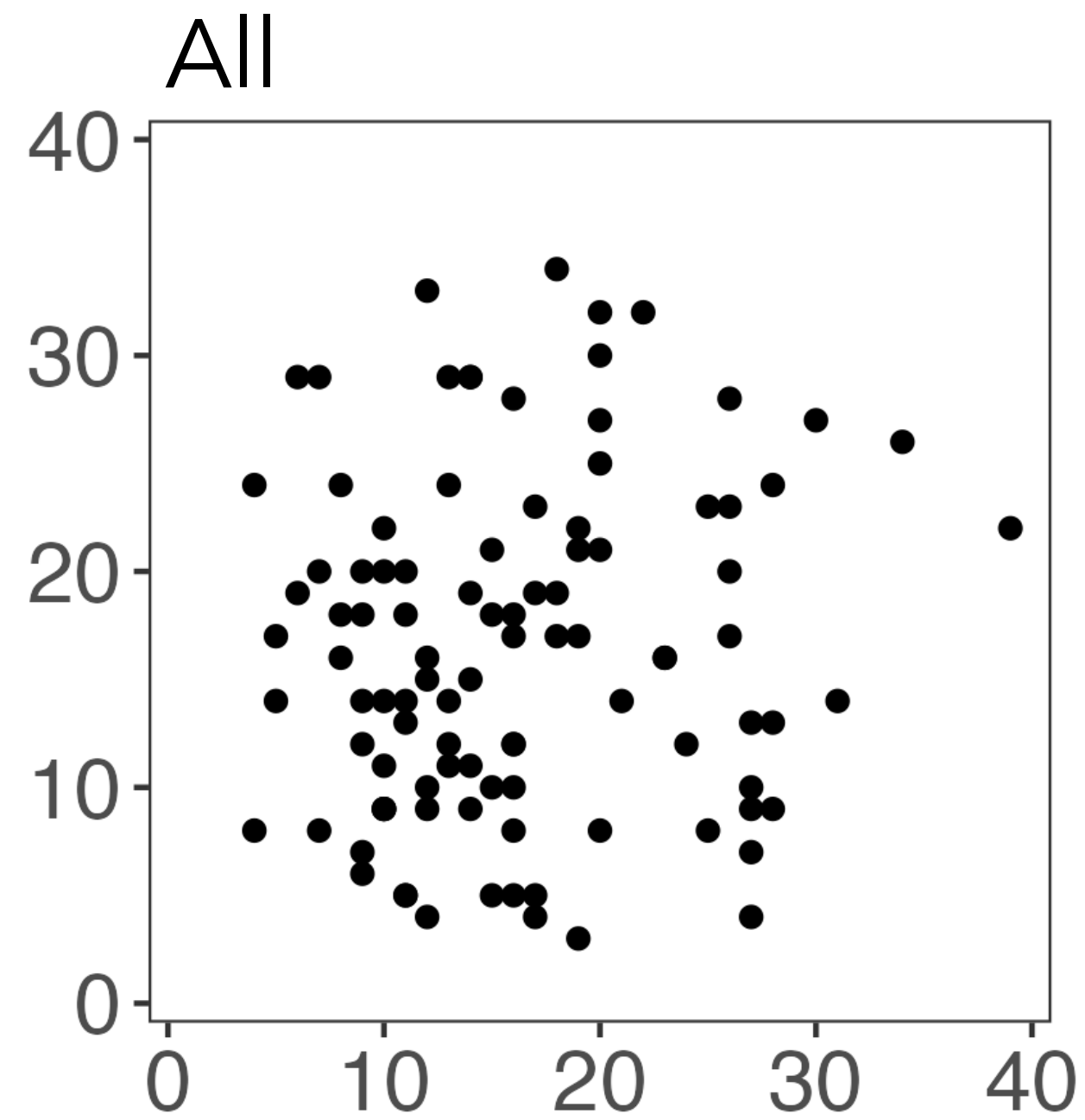
Generate H_0 : "the expected value of Feature 2 is the same between red observations and the blue observations."

Step 2: test H_0 with a t-test.

Sample splitting cannot be used for example 1

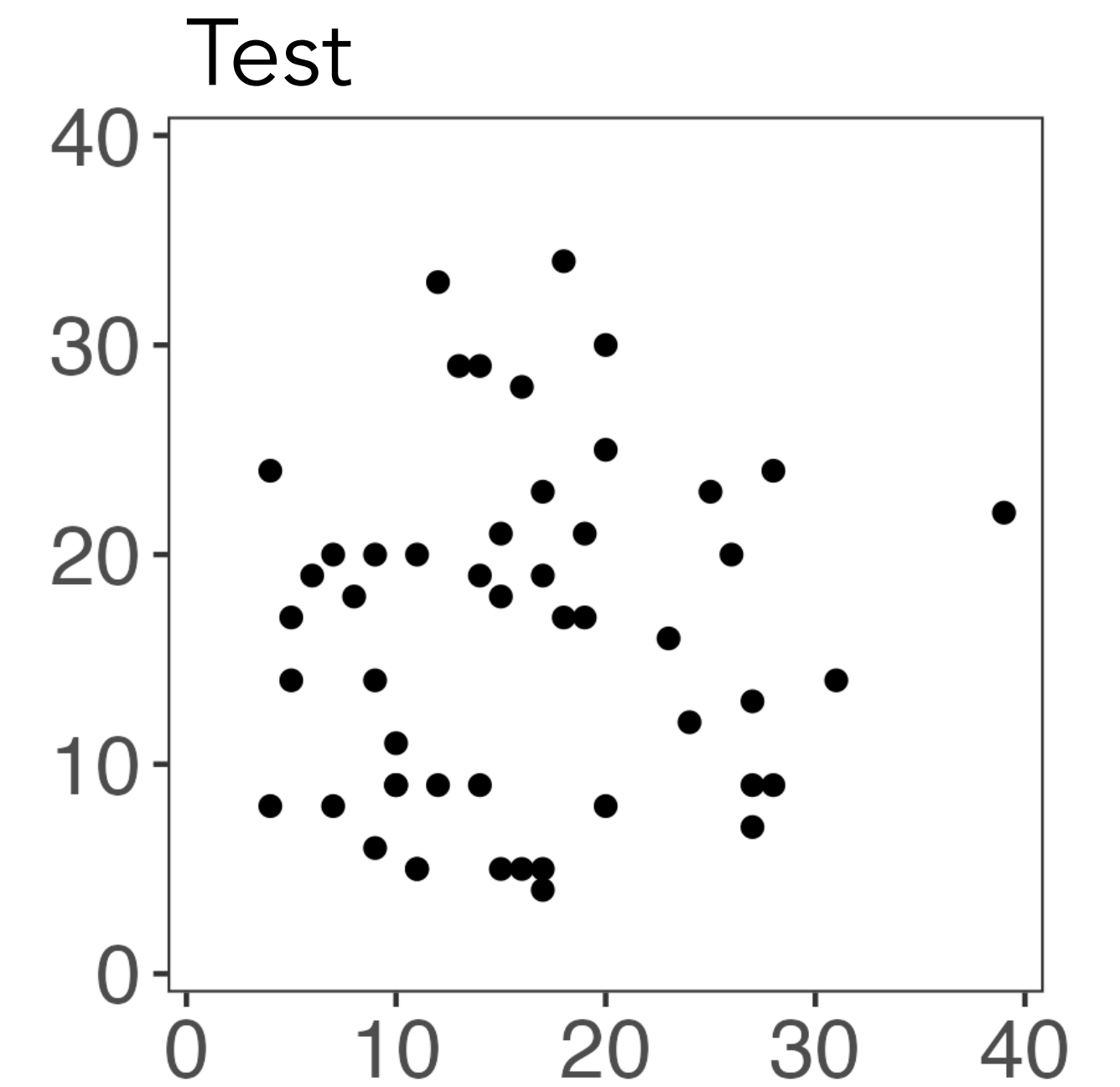
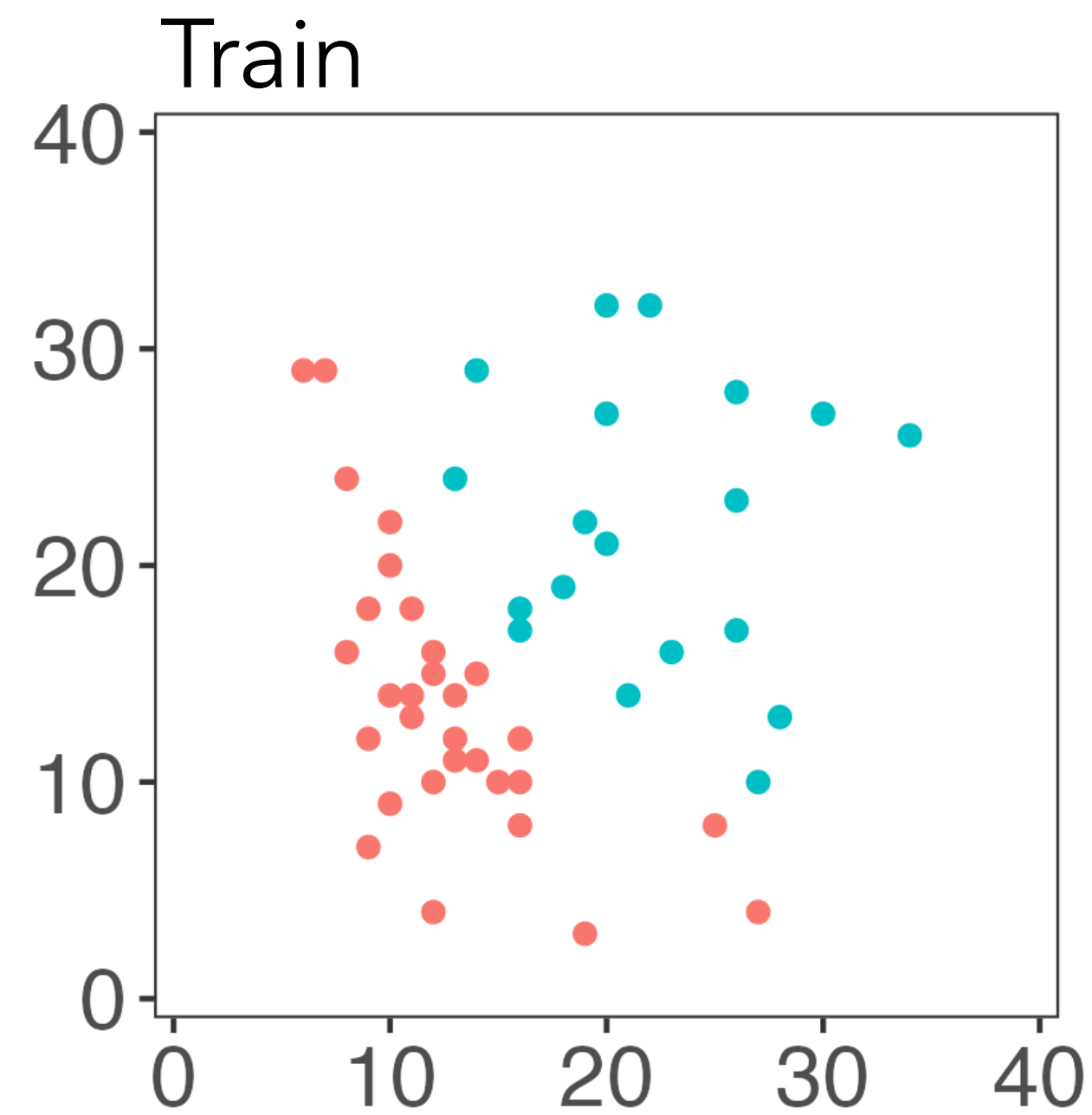
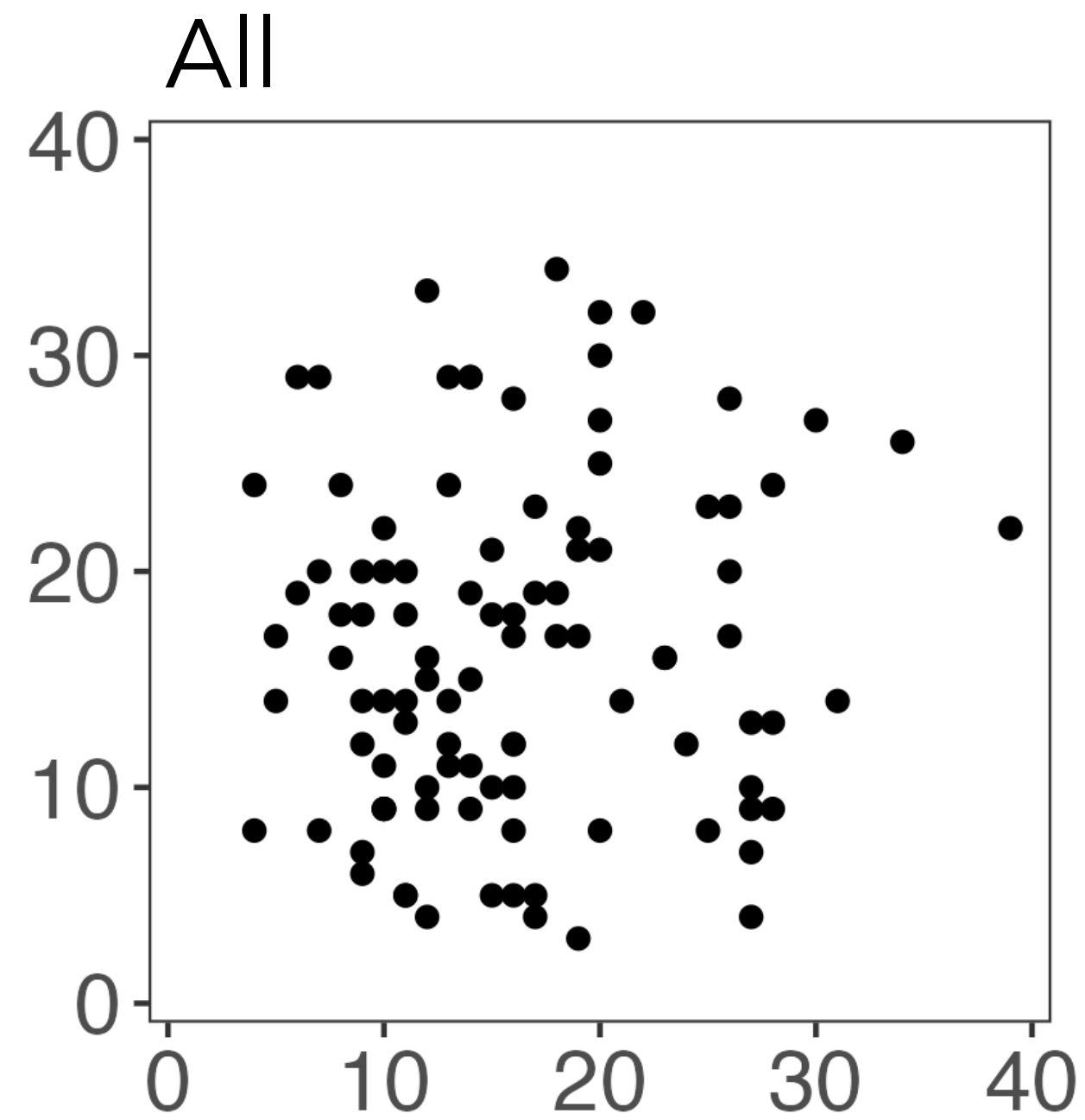


Sample splitting cannot be used for example 1



Step 1: split observations into train/test.

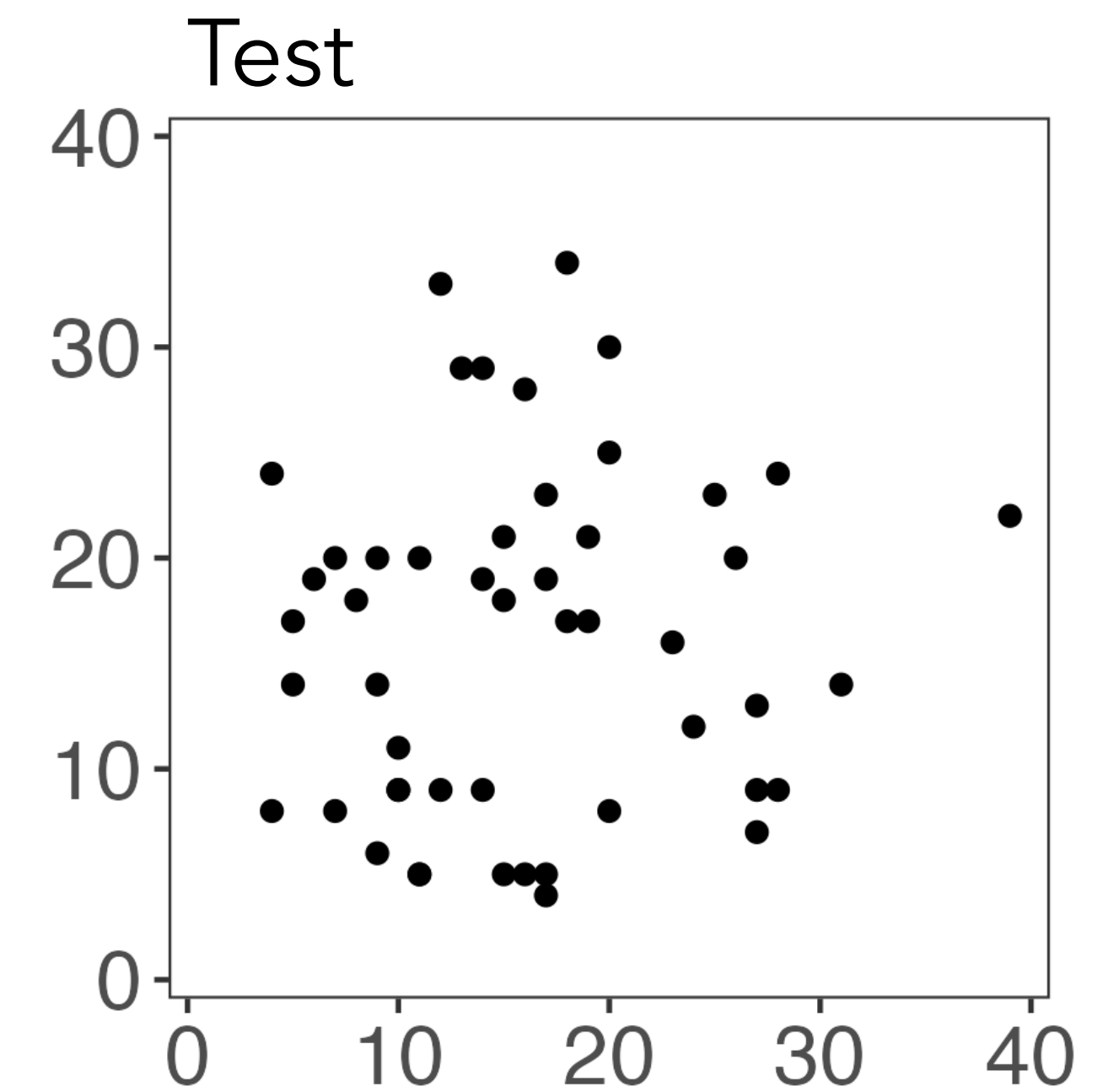
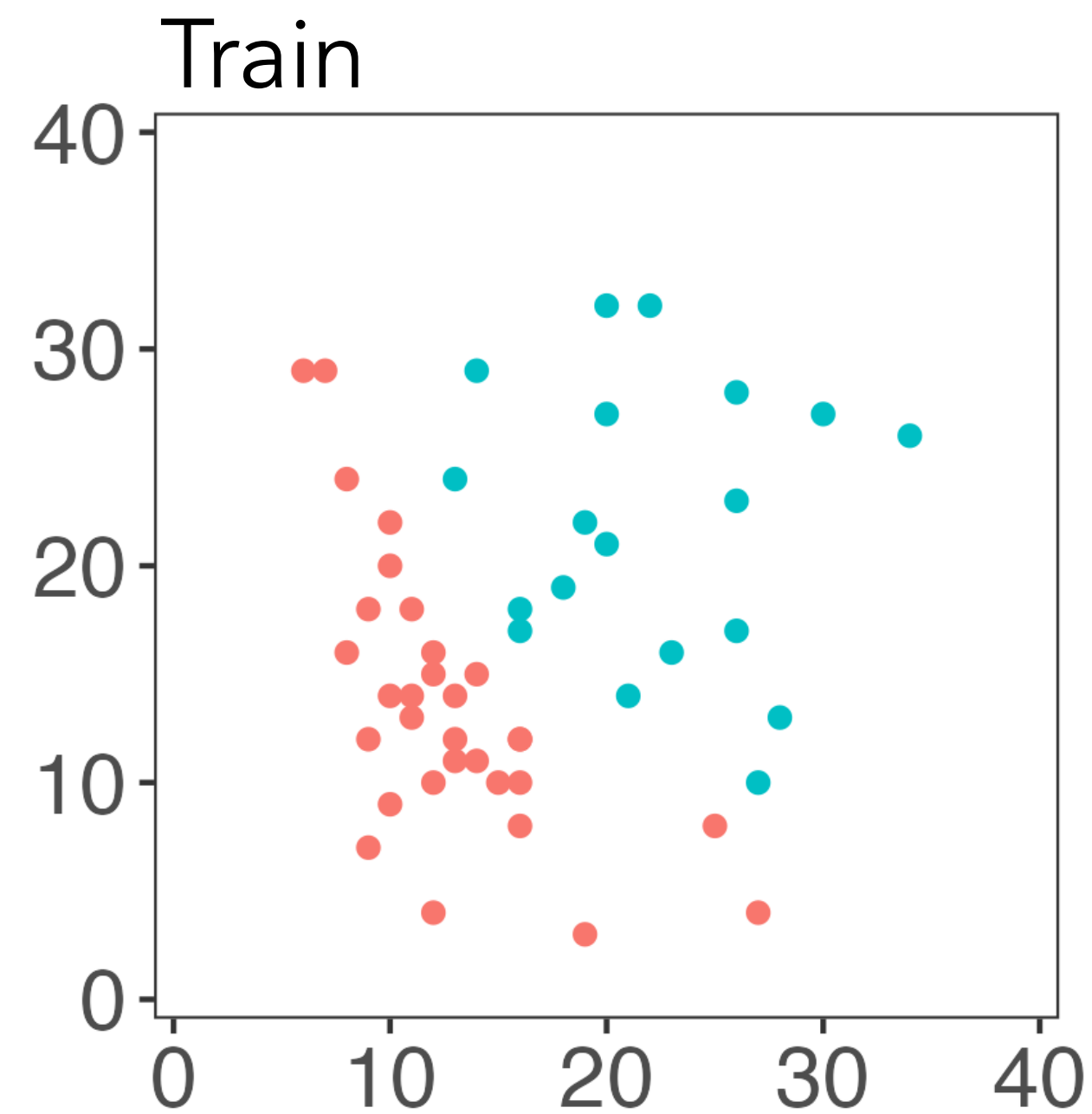
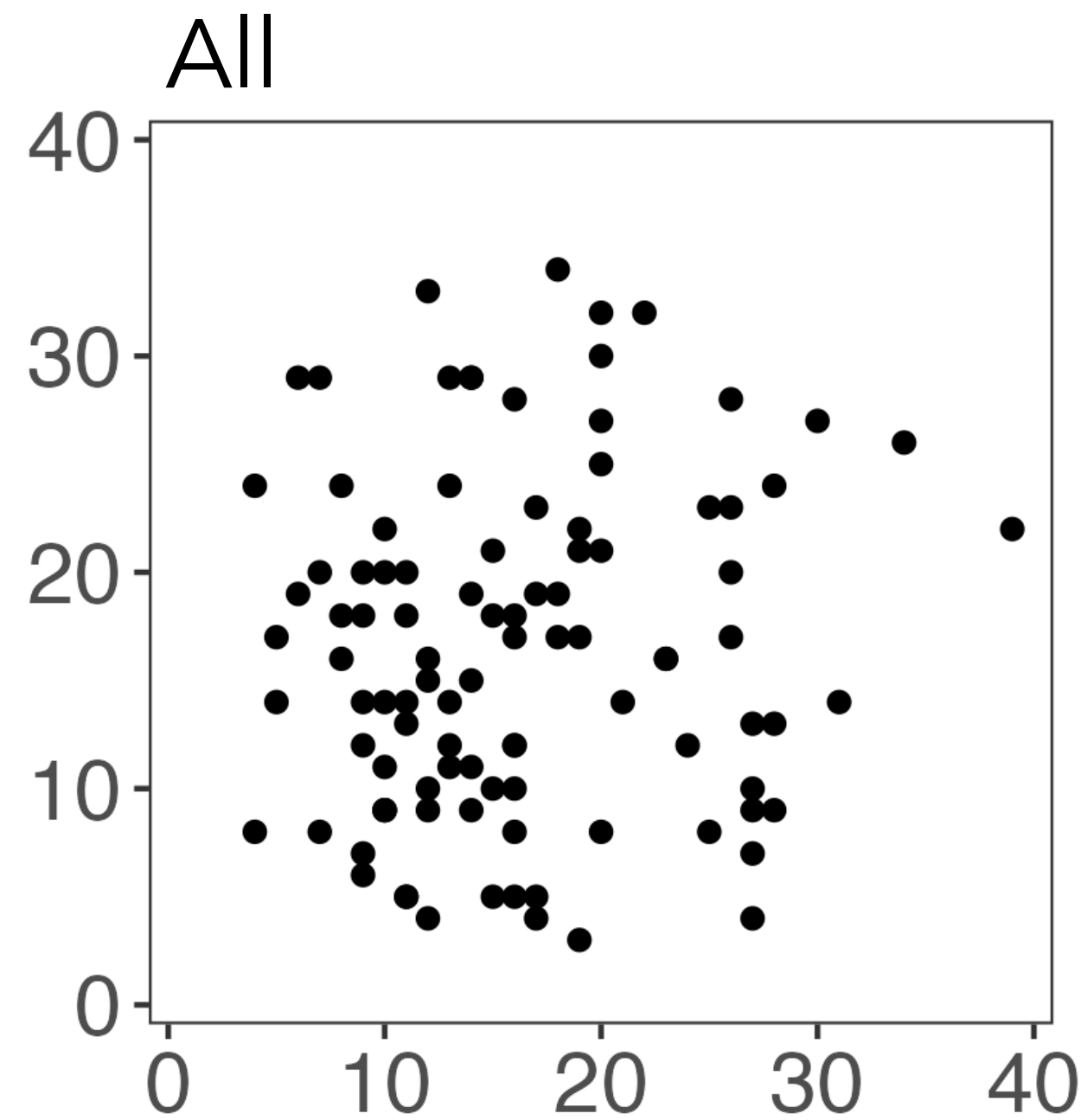
Sample splitting cannot be used for example 1



Step 1: split observations into train/test.

Step 2: cluster the training set.

Sample splitting cannot be used for example 1

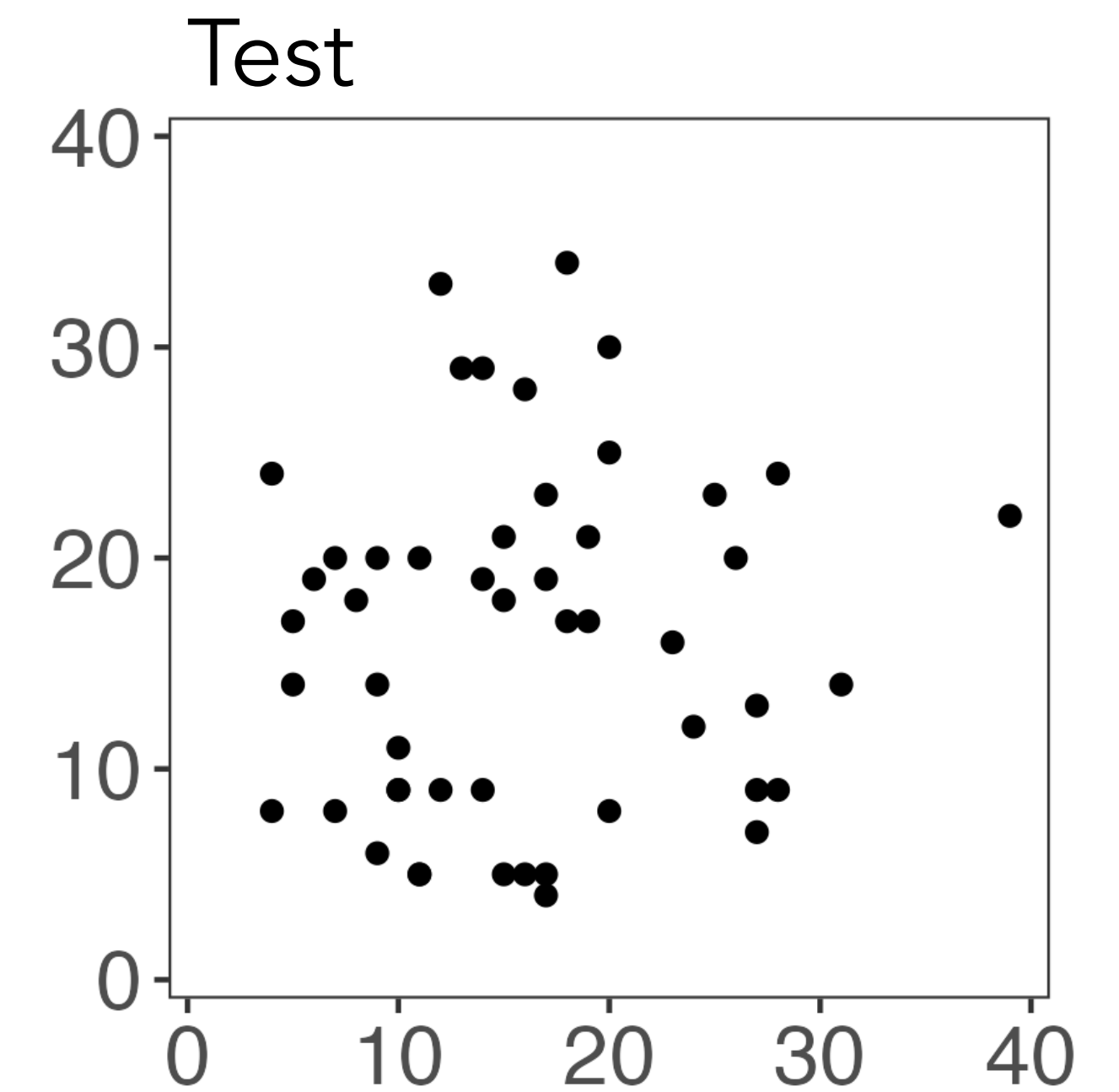
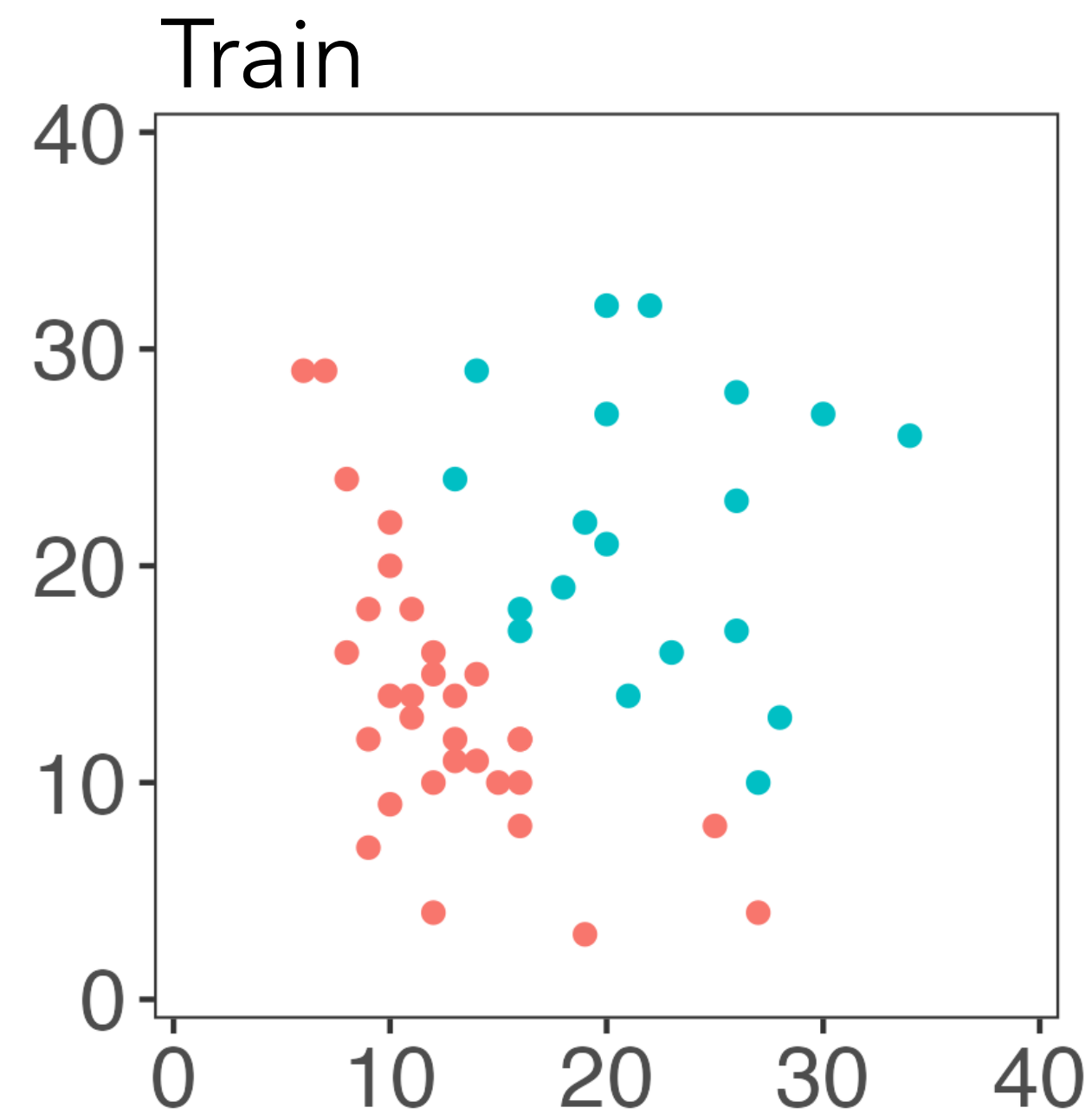
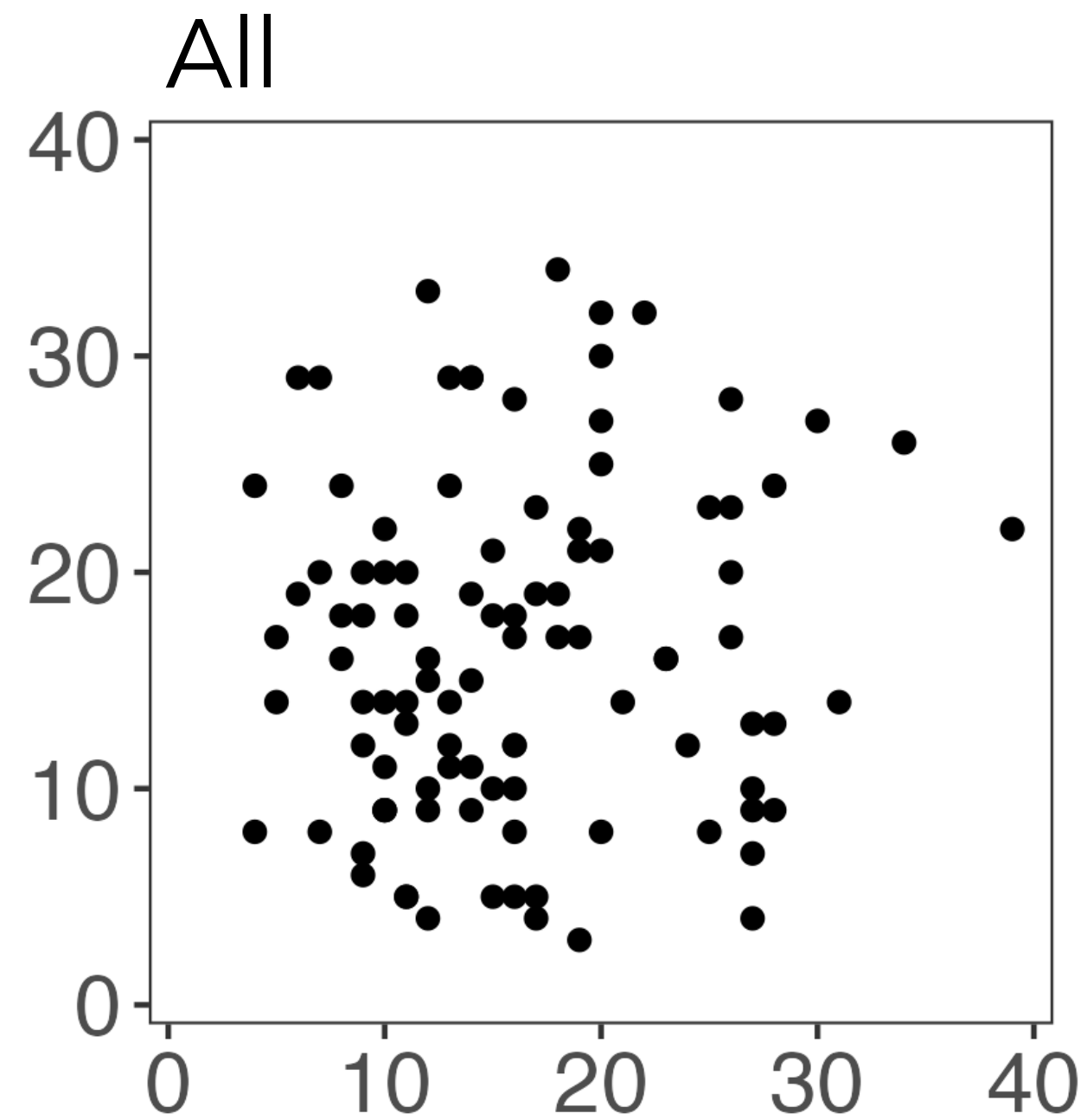


Step 1: split observations into train/test.

Step 2: cluster the training set.

Step 3: test for difference in means using test set.

Sample splitting cannot be used for example 1



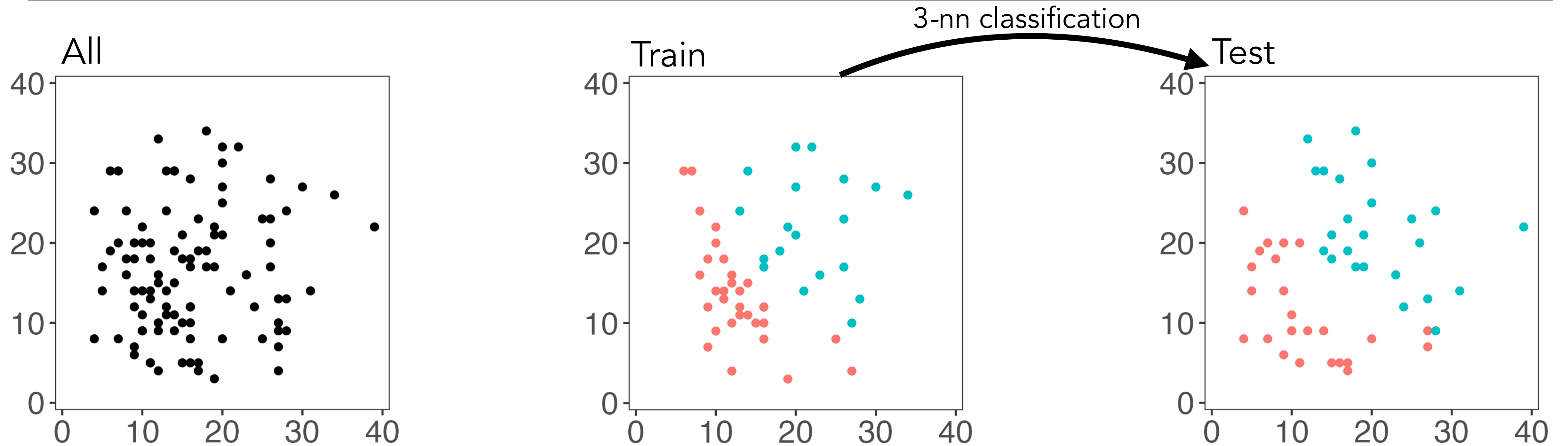
Step 1: split observations into train/test.

Step 2: cluster the training set.

Step 2.5: assign labels to observations in test set.

Step 3: test for difference in means using test set.

Sample splitting cannot be used for example 1



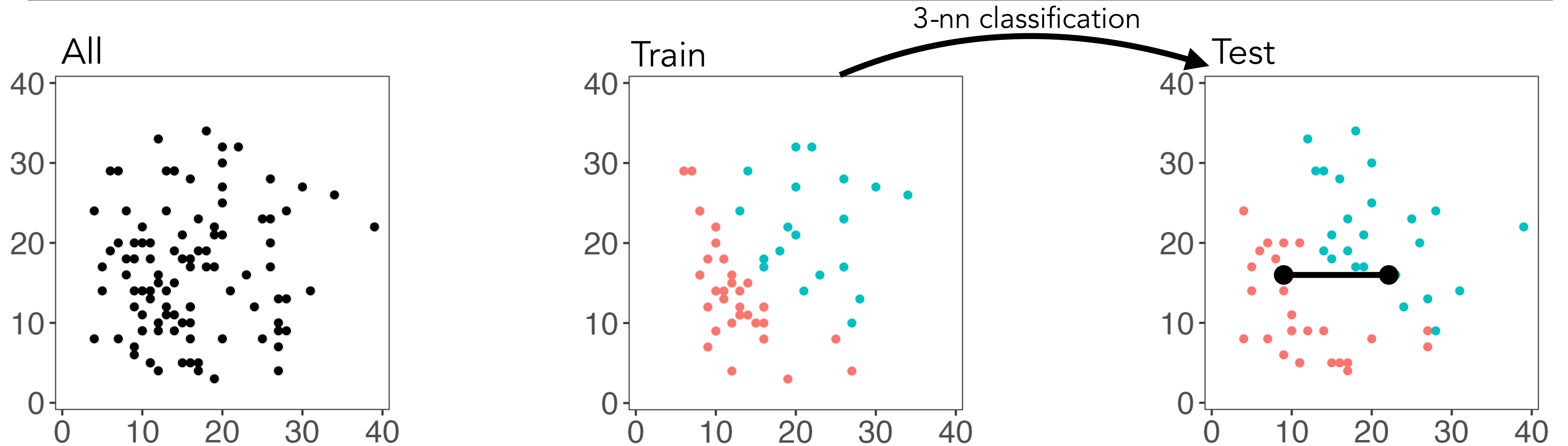
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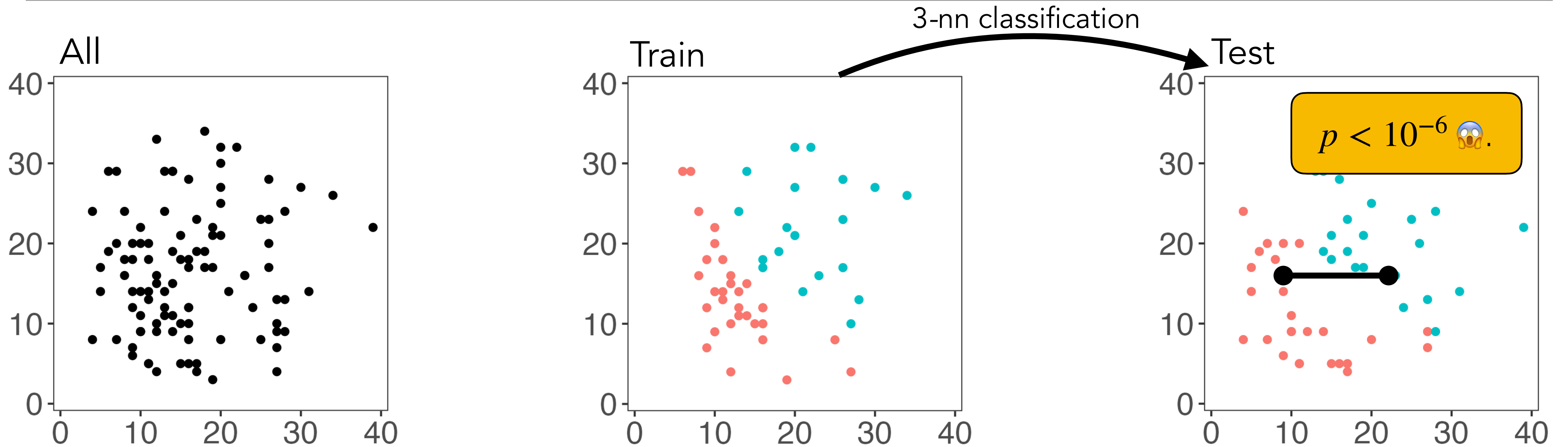
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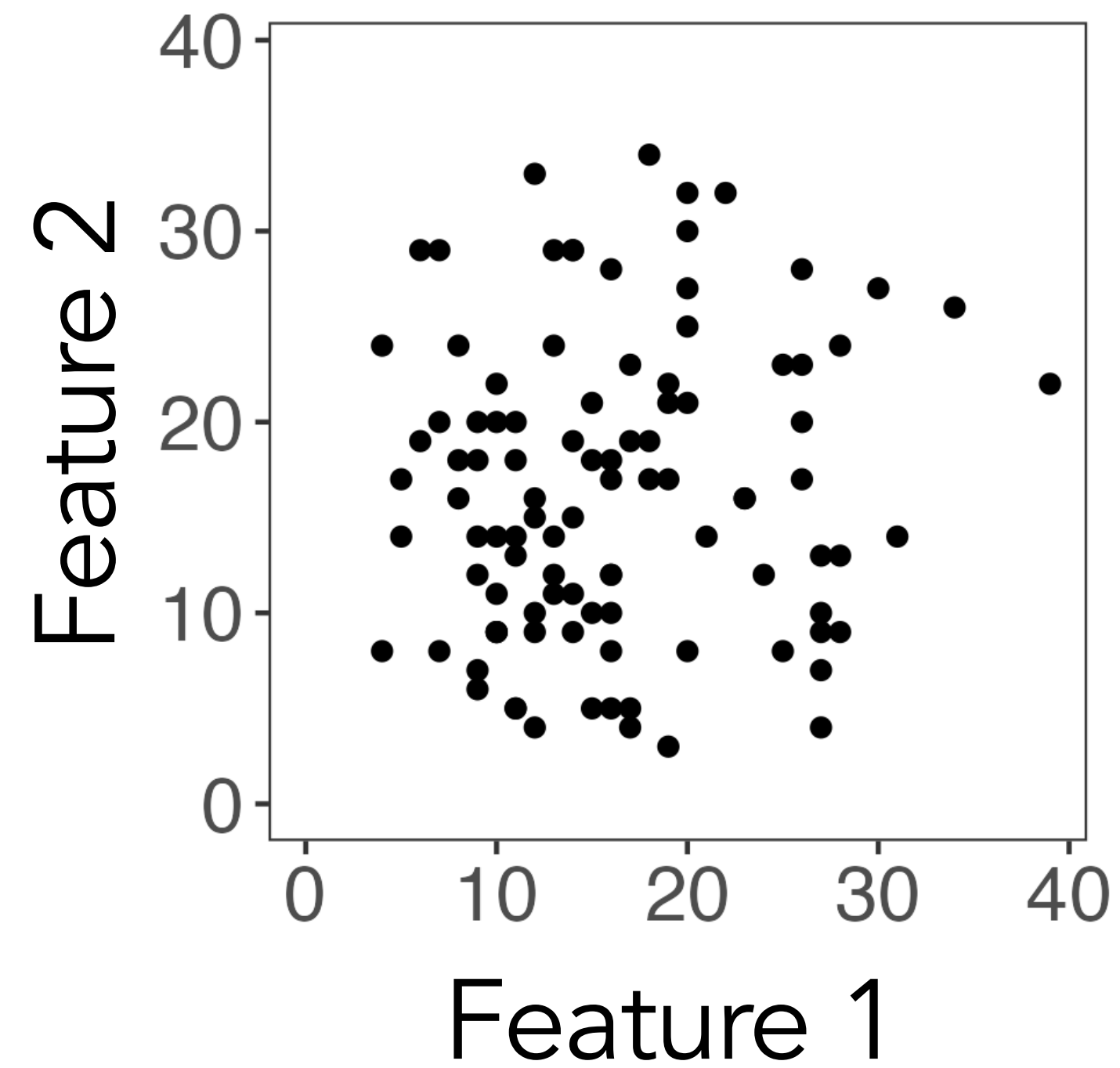
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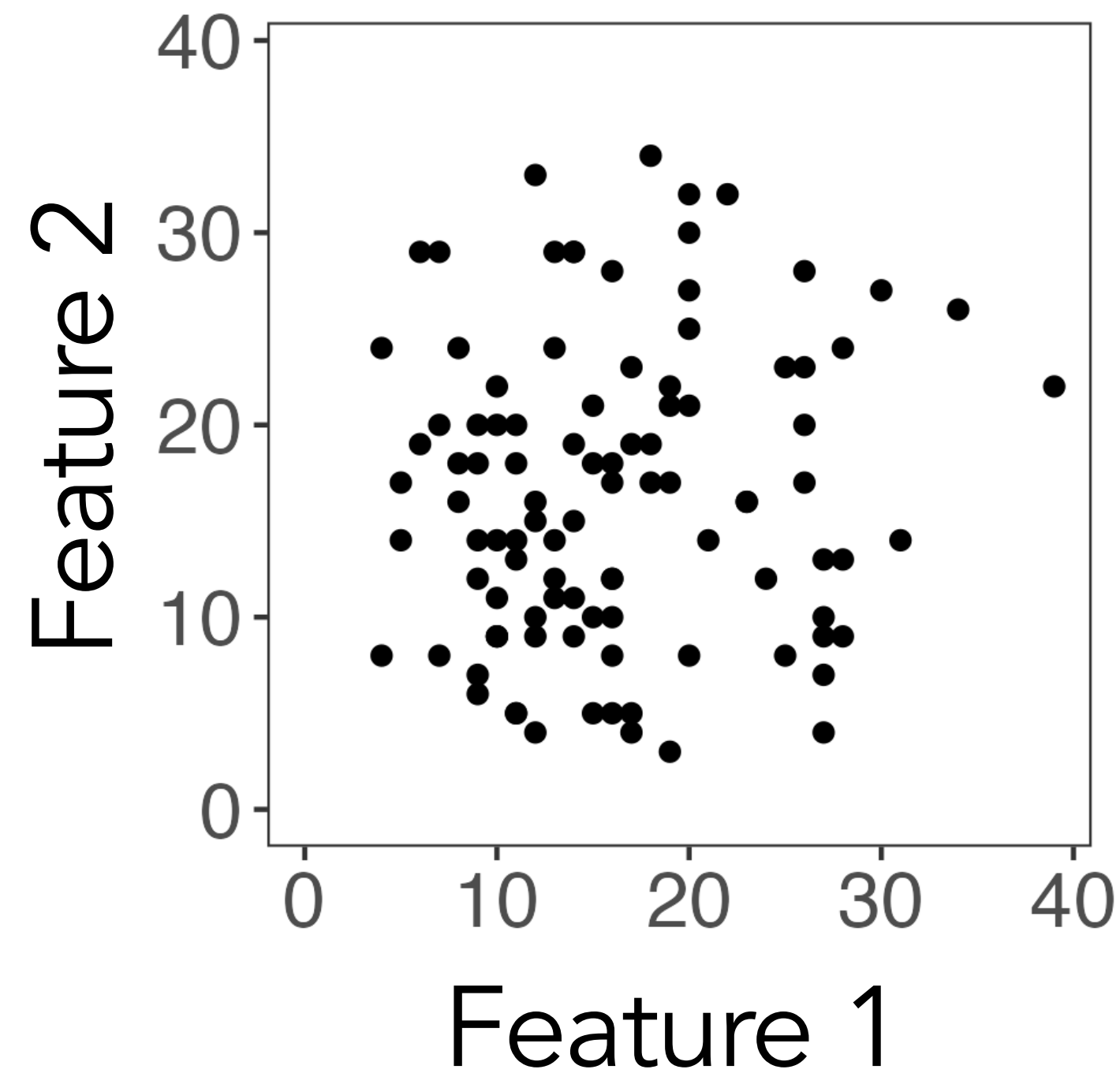
Step 2.5: assign labels to observations in test set.

Step 3: test for difference in means using test set.

Example 2: using the same data to fit and evaluate a model

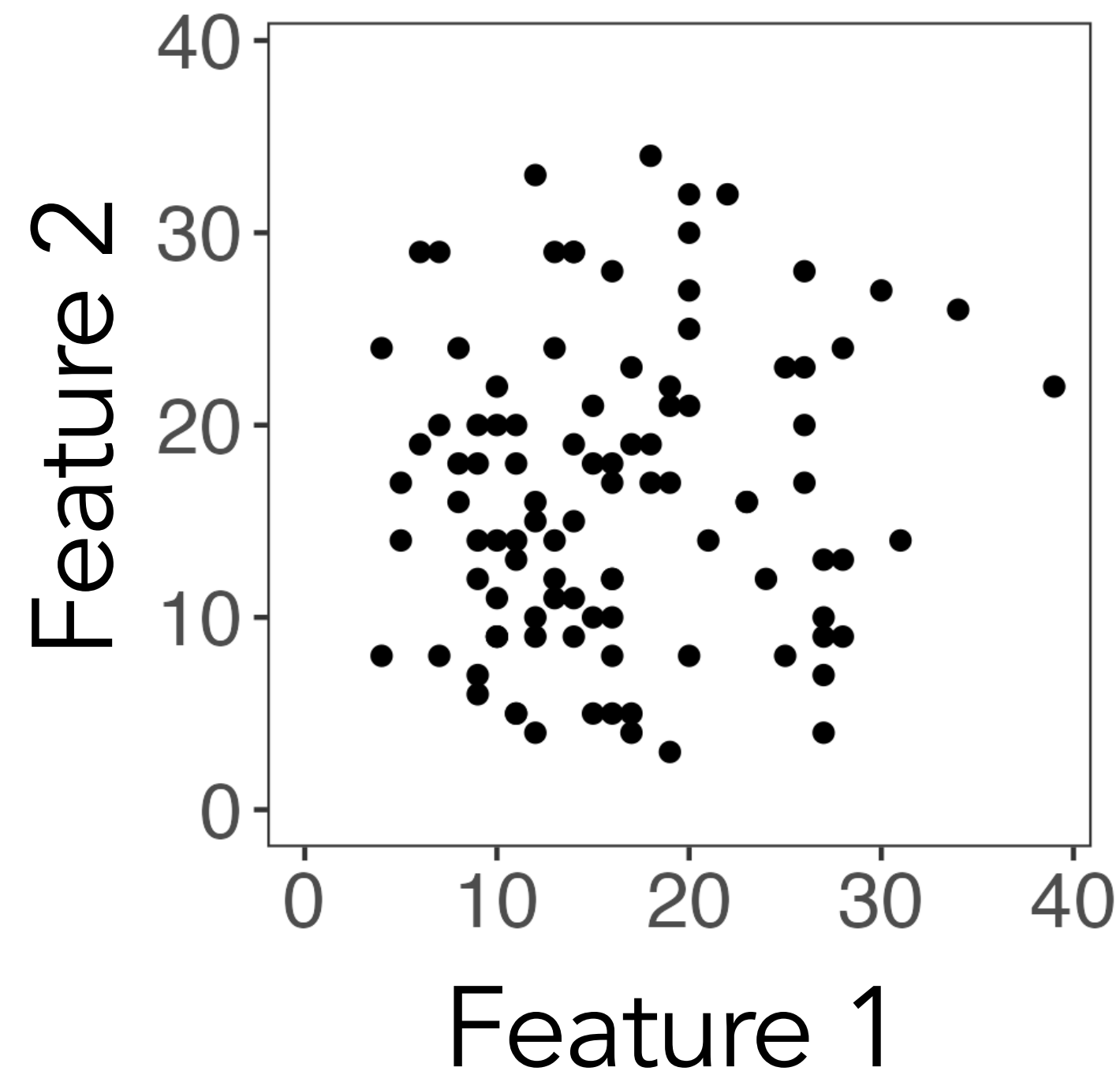


Example 2: using the same data to fit and evaluate a model



Goal: how many clusters are in this data?

Example 2: using the same data to fit and evaluate a model



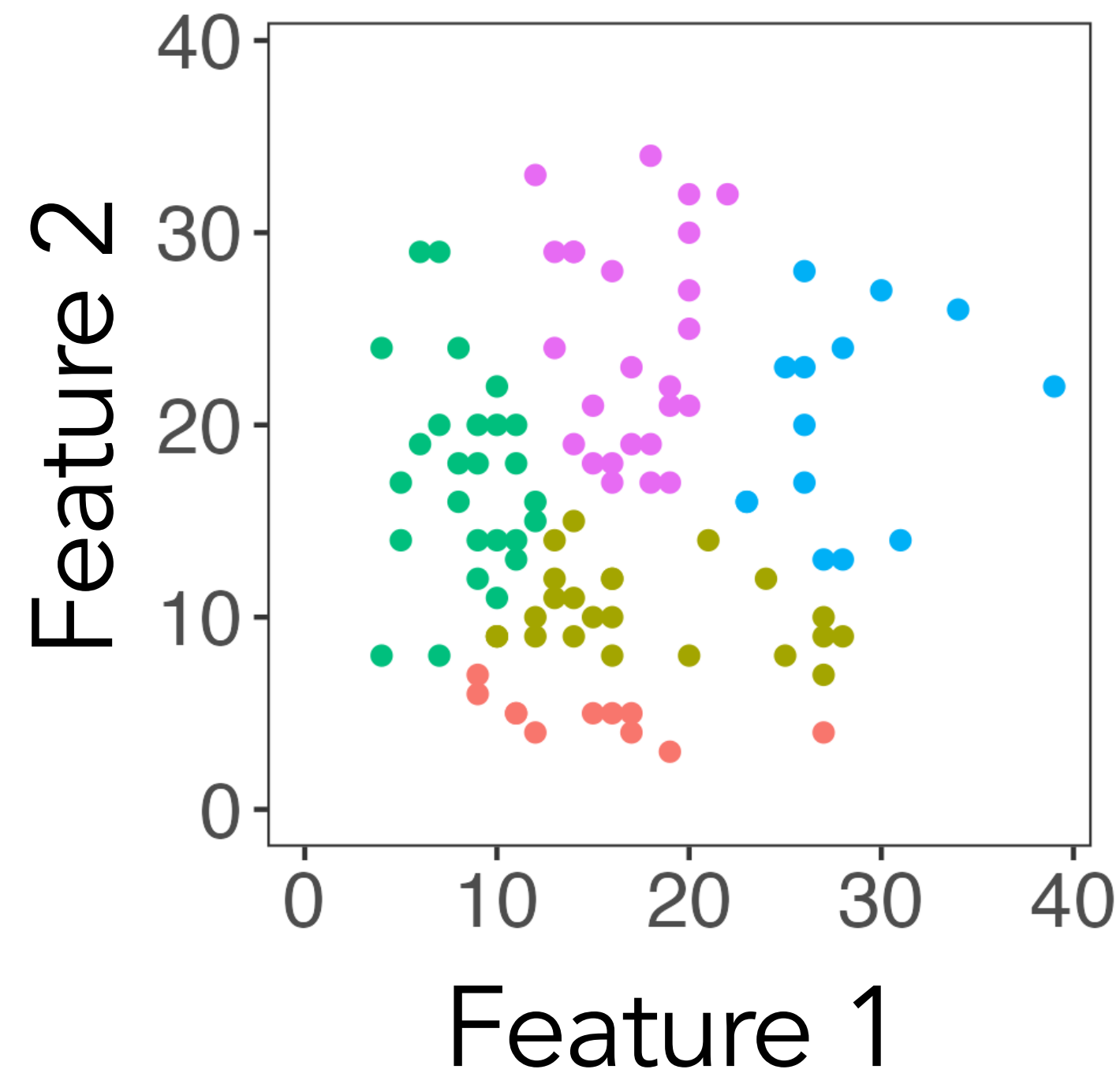
Goal: how many clusters are in this data?

For several values of k :

Step 1: fit a model with k clusters.

Step 2: evaluate model using a loss function.

Example 2: using the same data to fit and evaluate a model



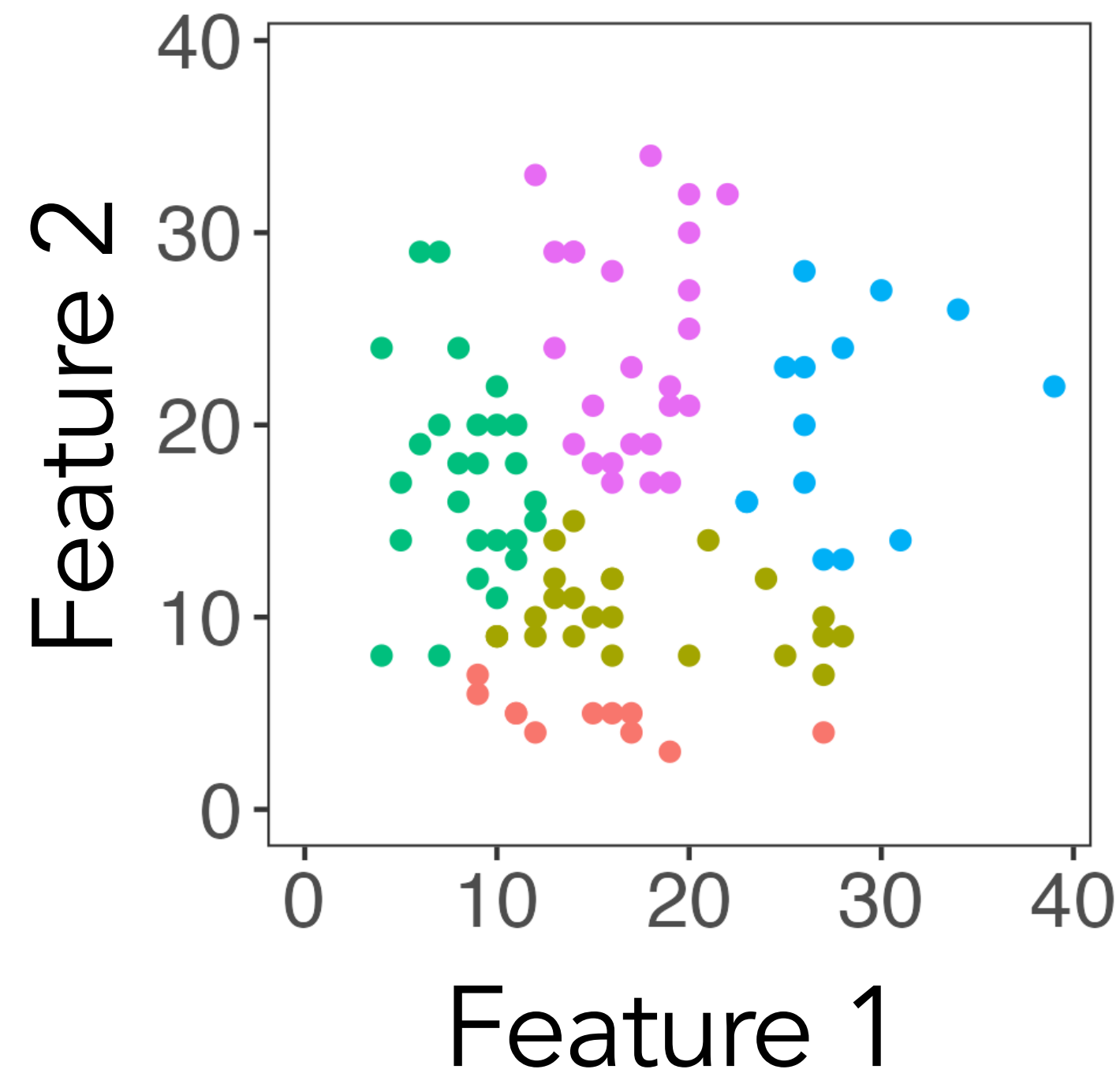
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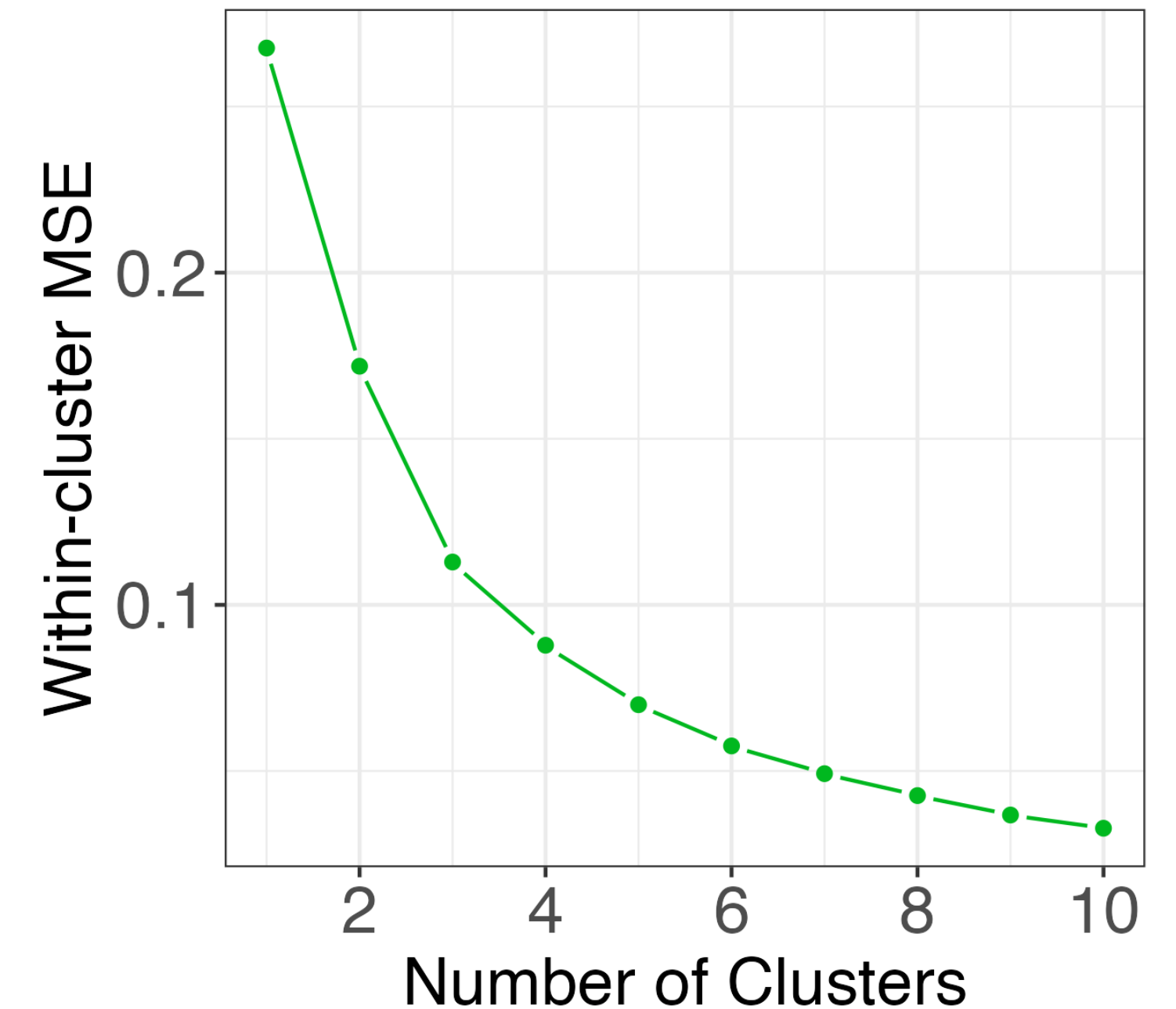


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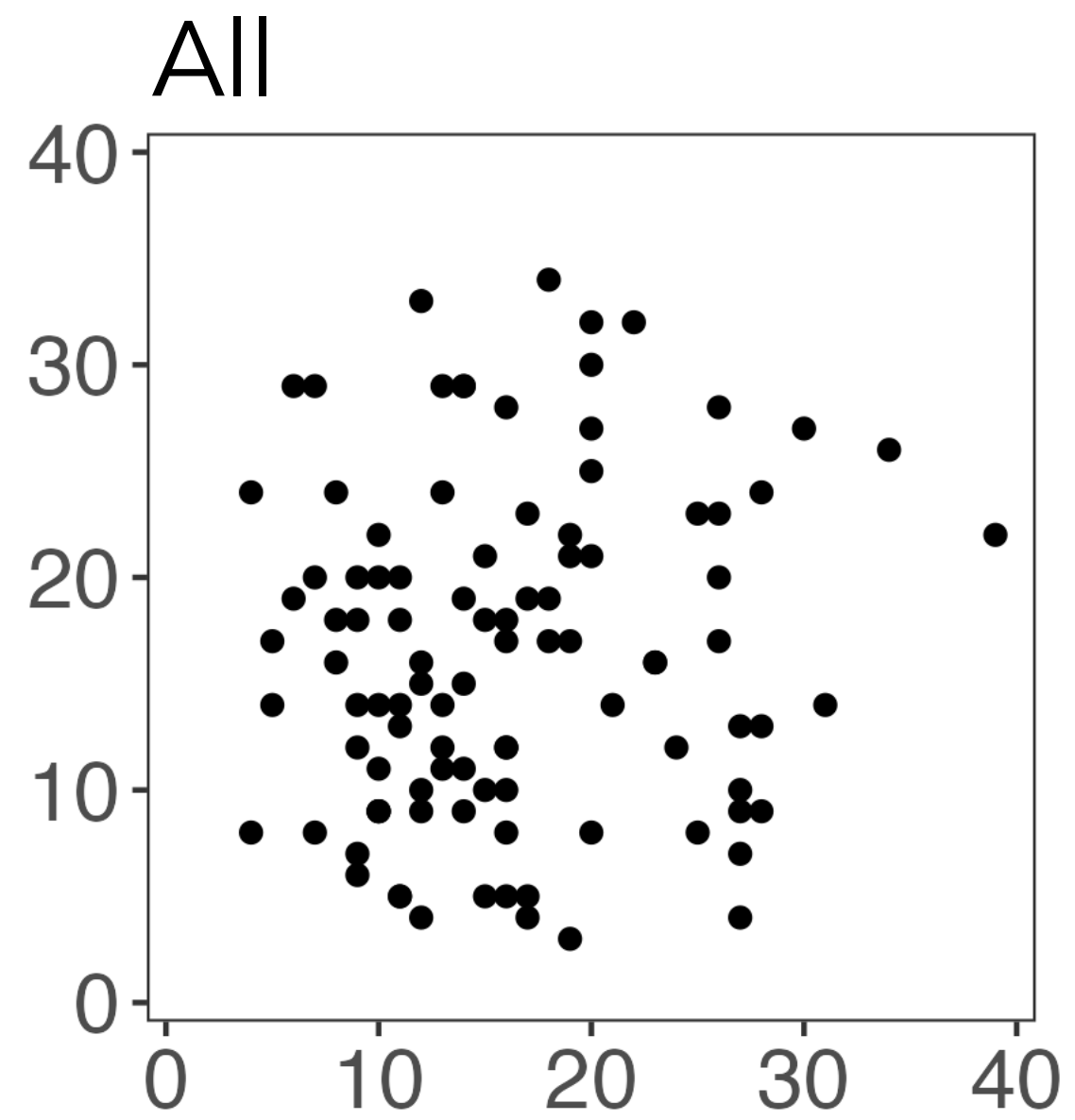
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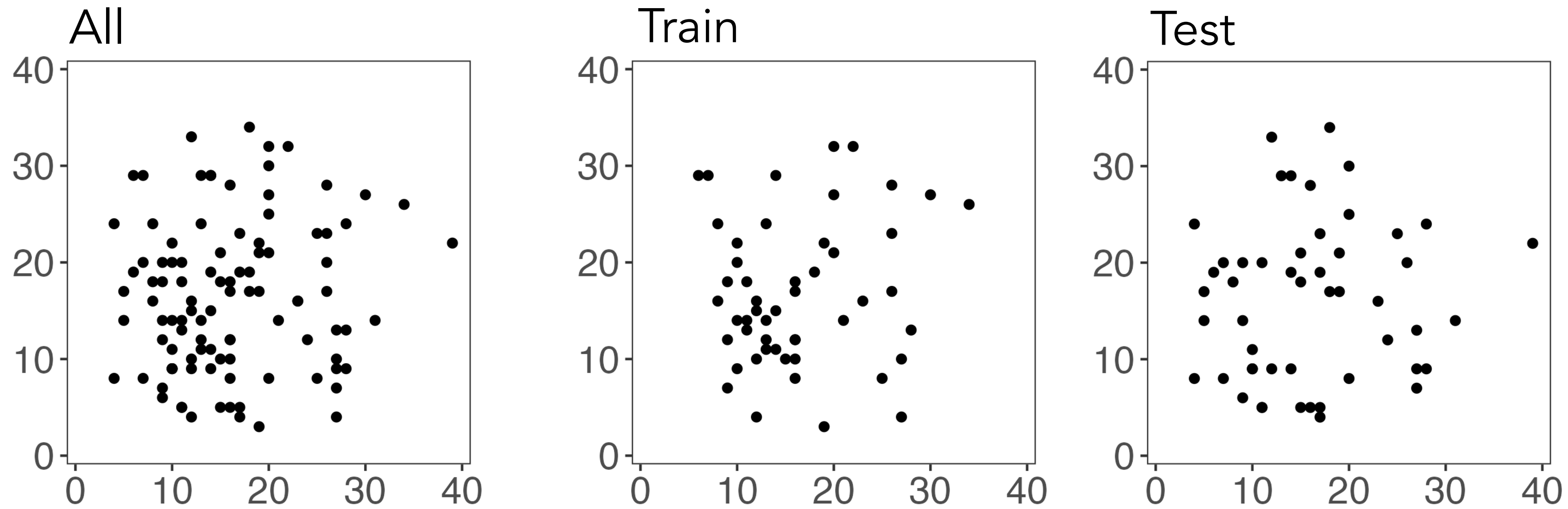
Step 2: evaluate model using a loss function.



Sample splitting cannot be used for example 2

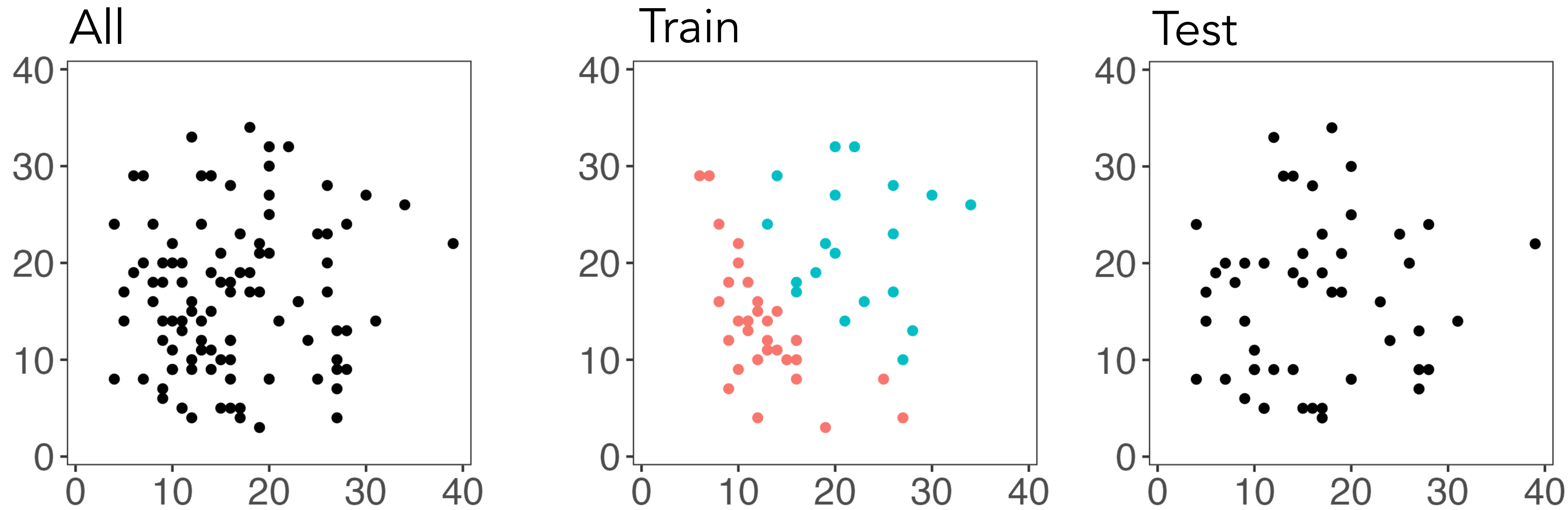


Sample splitting cannot be used for example 2



Step 1: split observations into train/test.

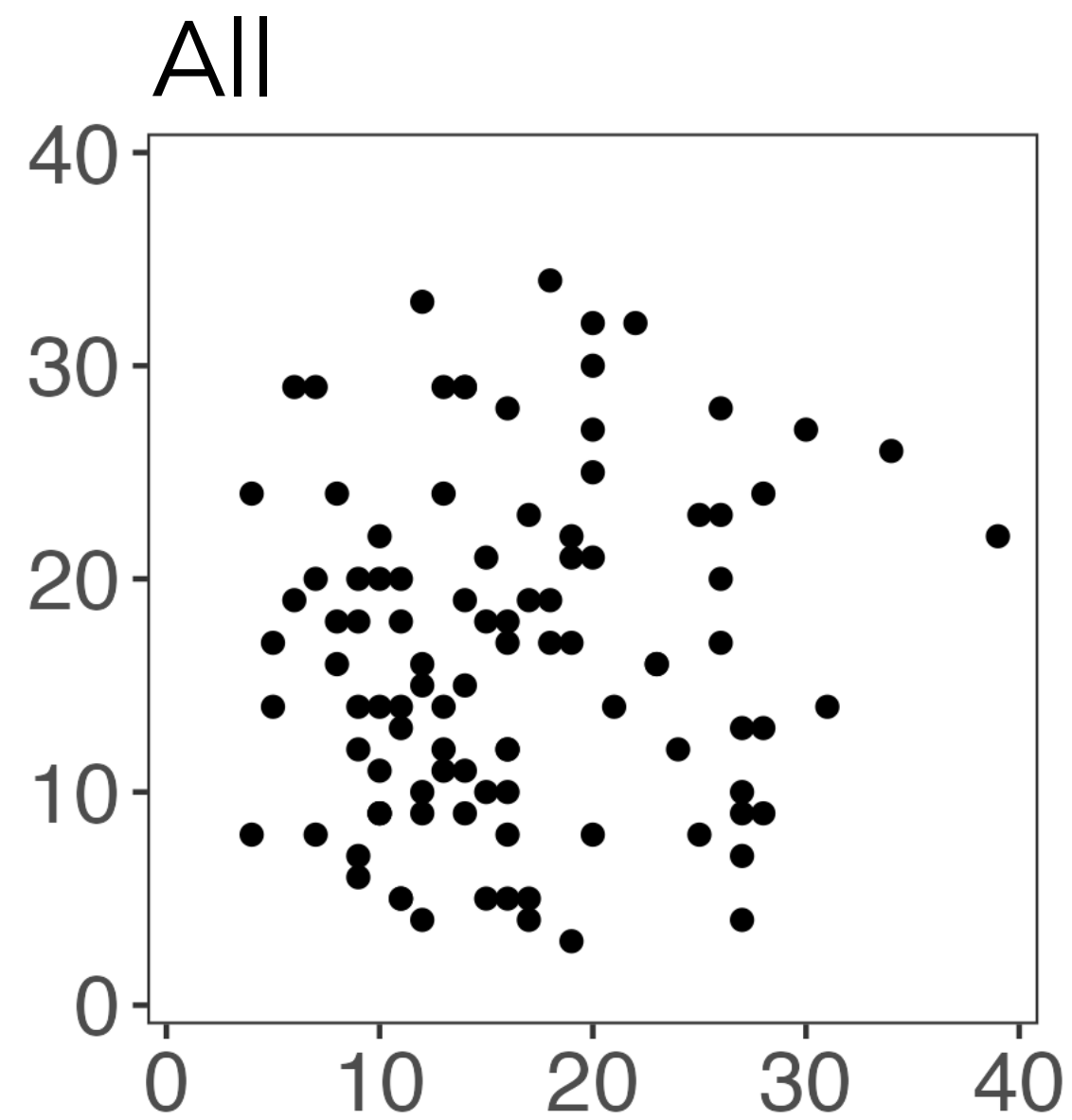
Sample splitting cannot be used for example 2



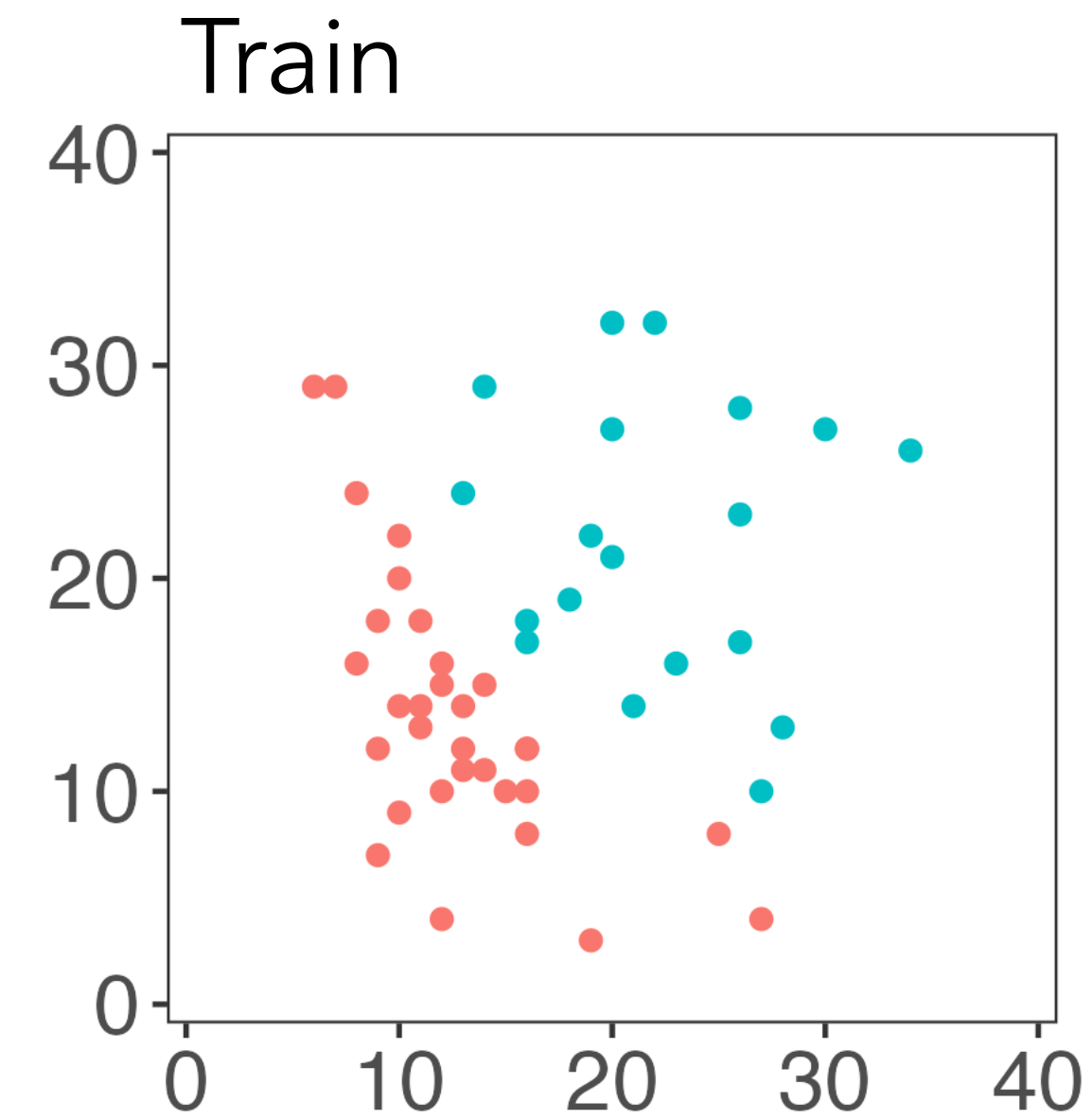
Step 1: split observations into train/test.

Step 2: cluster the training set.

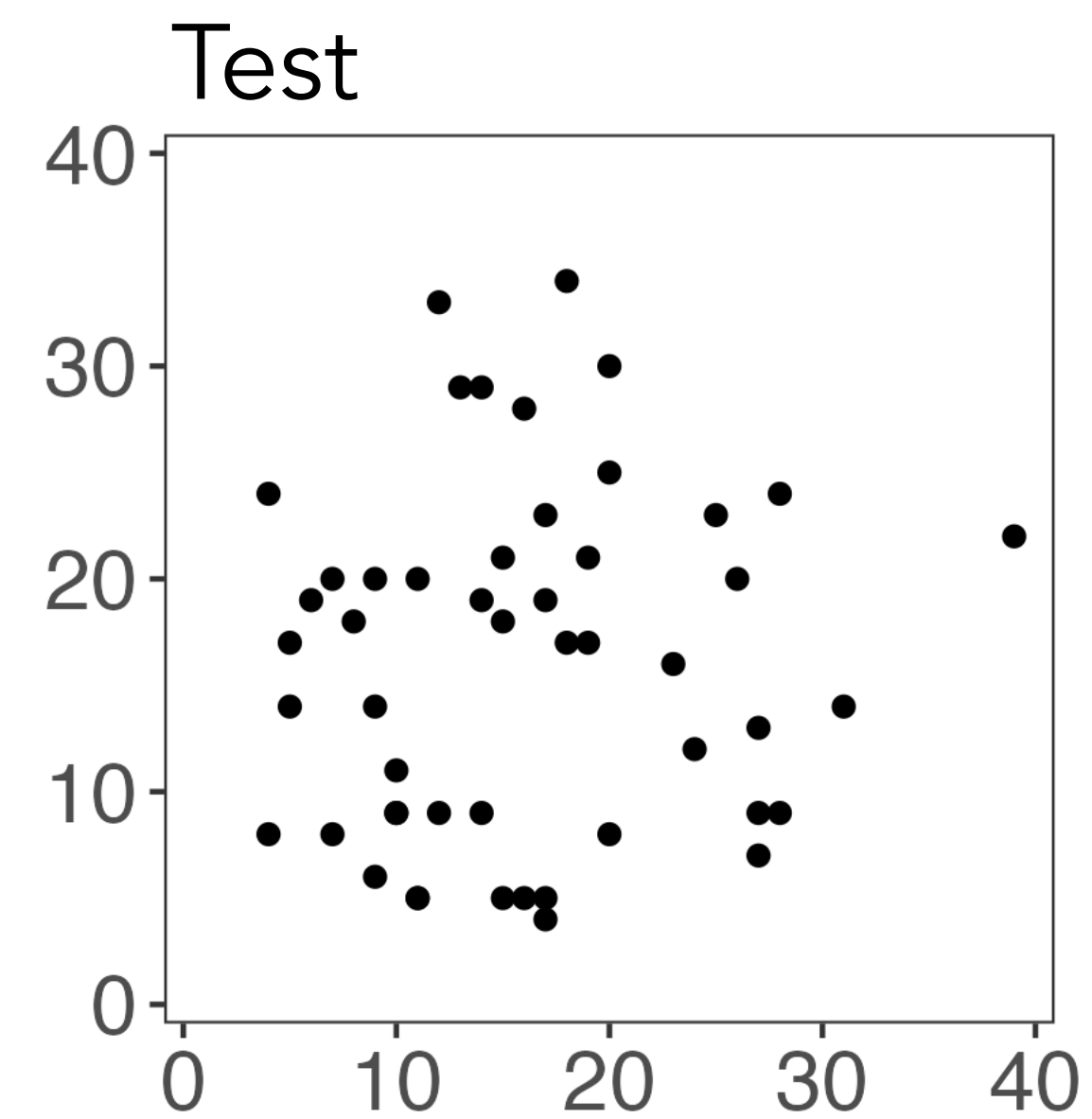
Sample splitting cannot be used for example 2



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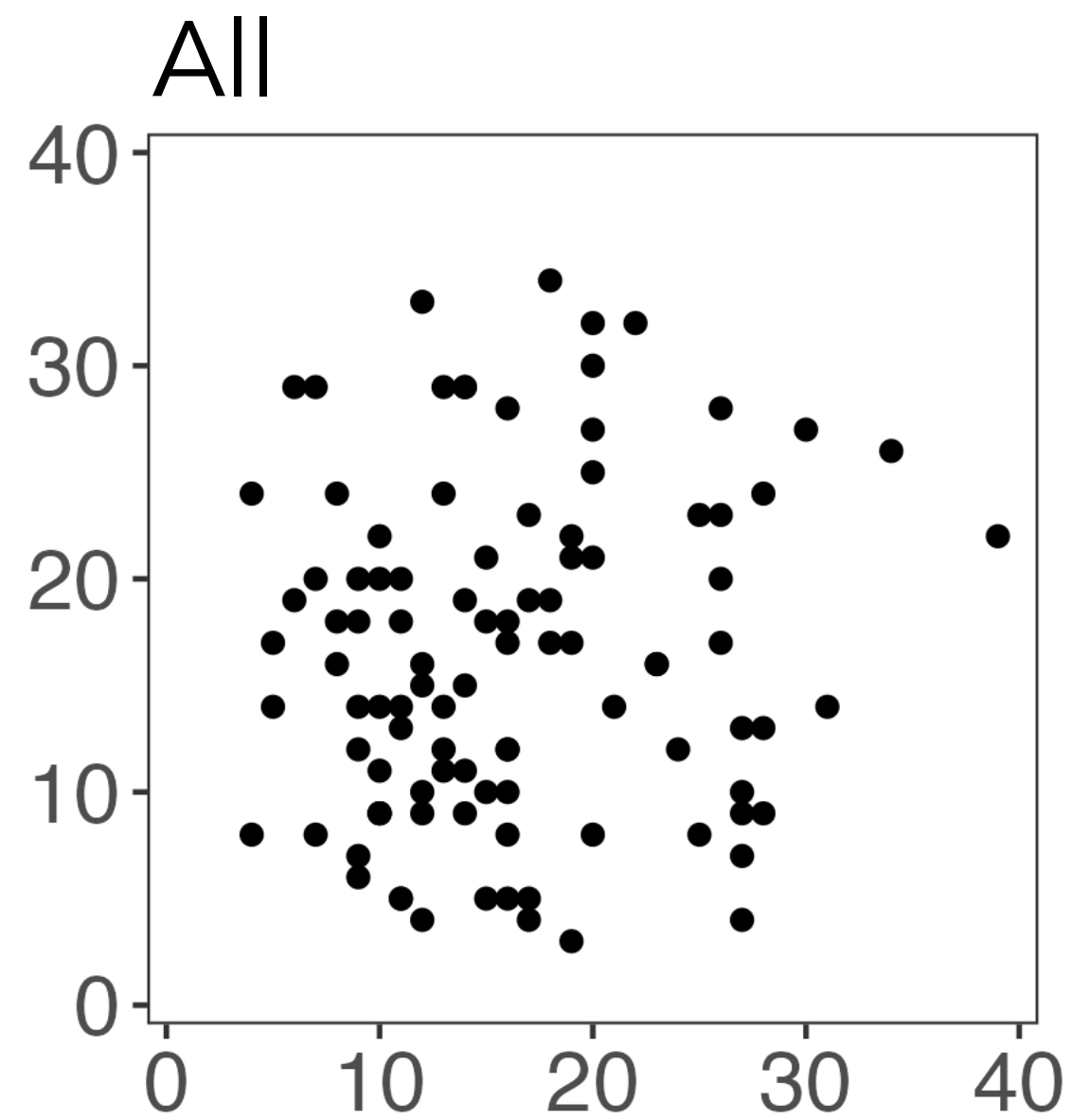


Step 2: cluster the training set.

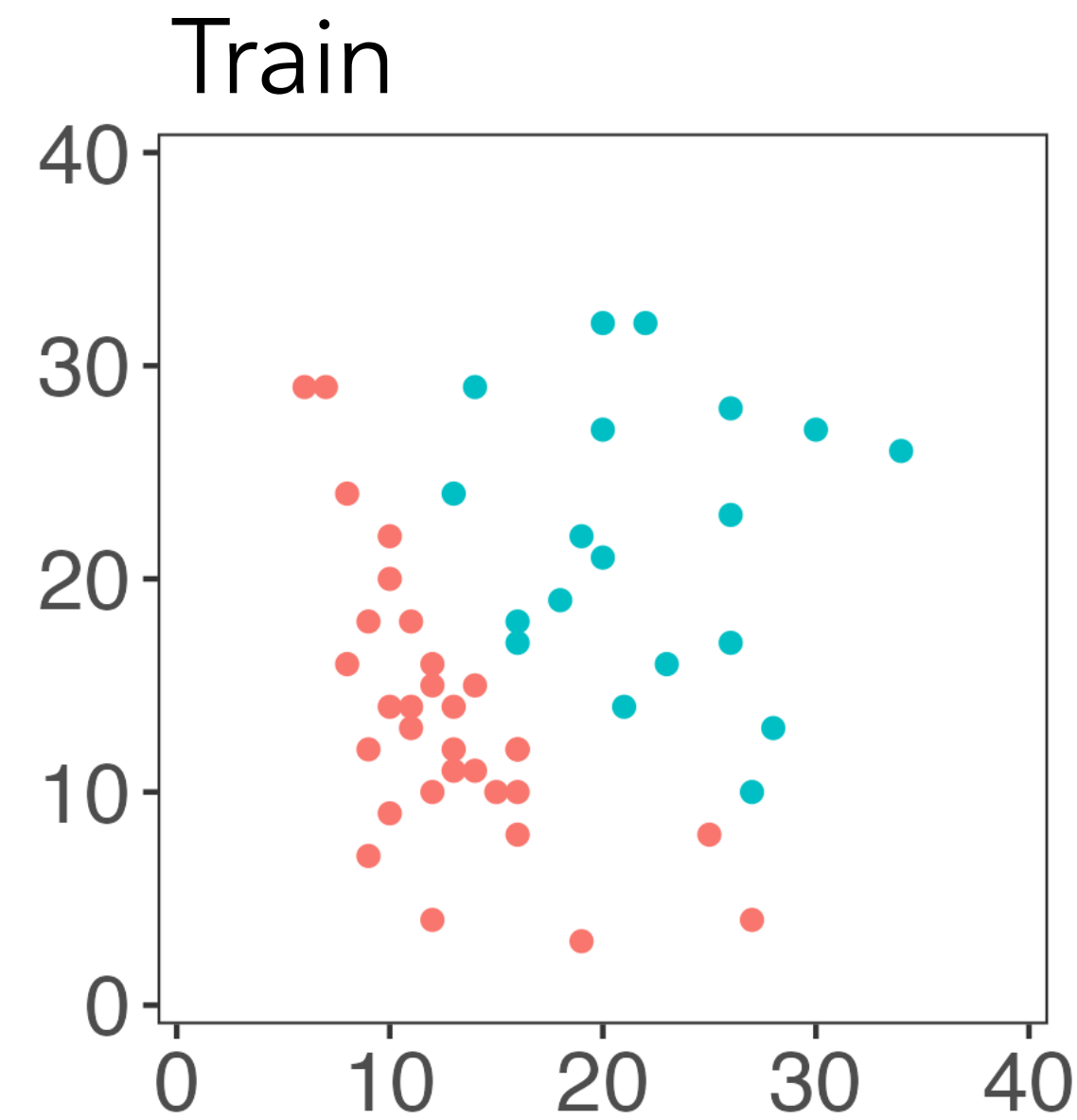


Step 3: evaluate clusters using test set.

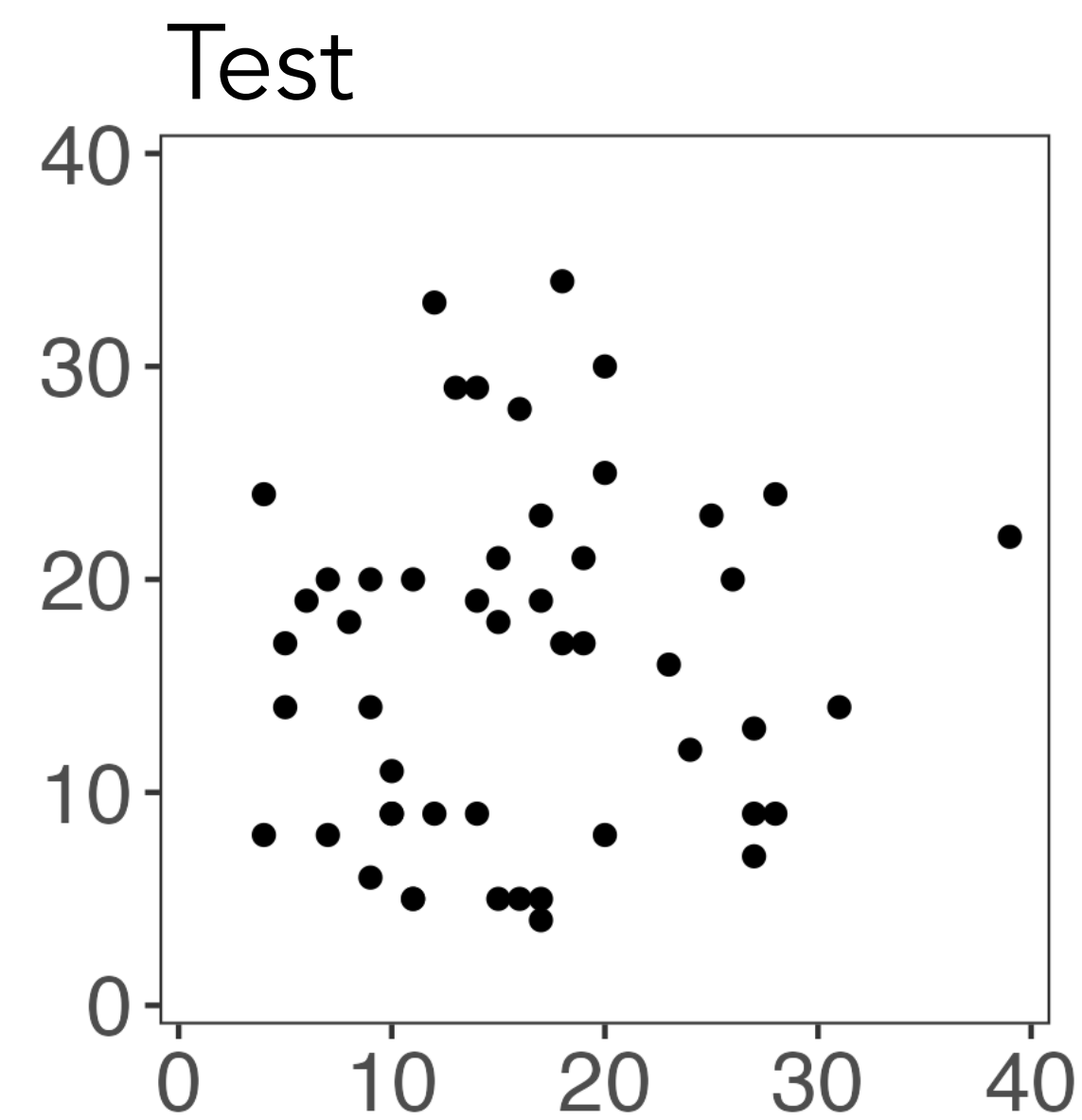
Sample splitting cannot be used for example 2



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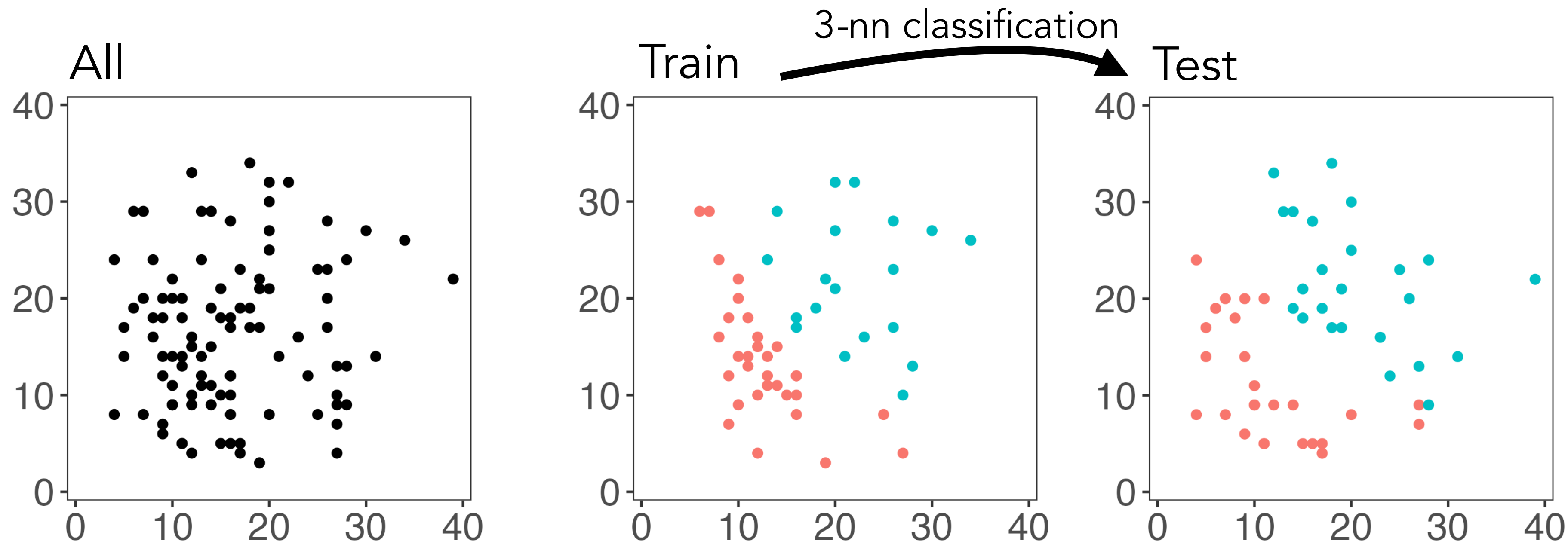
Step 2: cluster the training set.



Step 2.5: assign labels to observations in test set.

Step 3: evaluate clusters using test set.

Sample splitting cannot be used for example 2



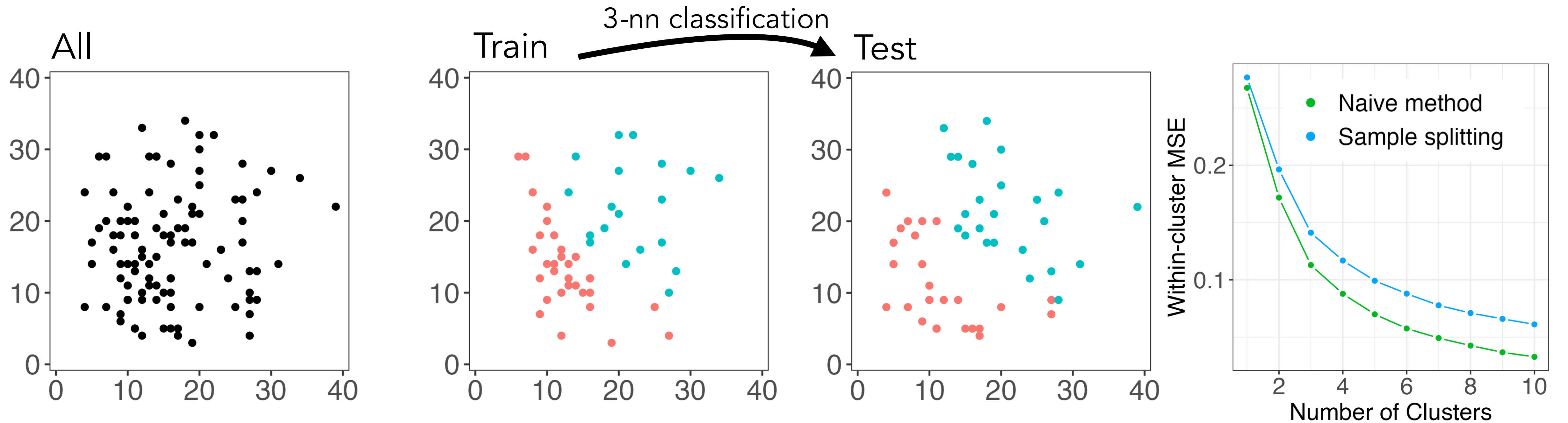
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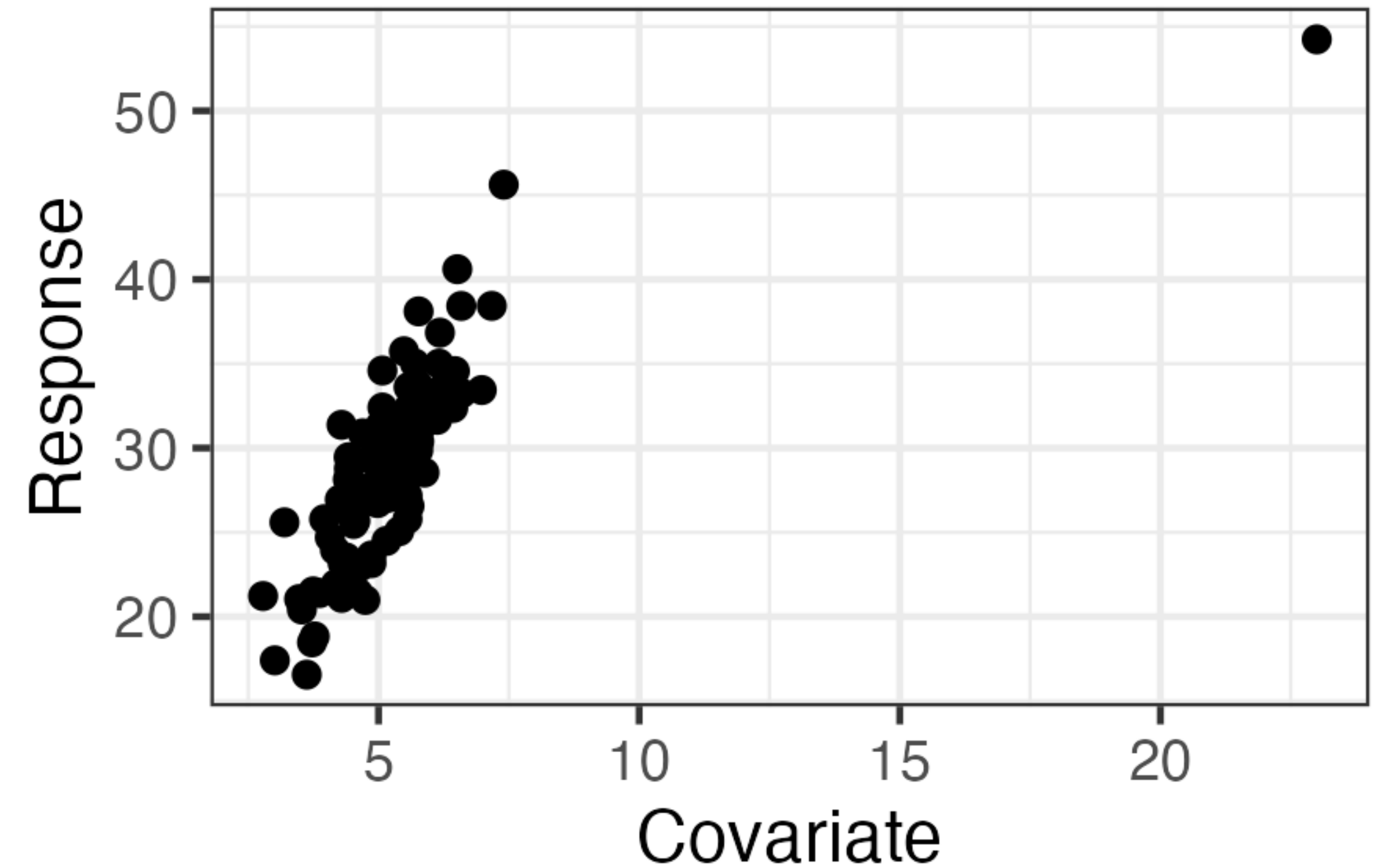
Step 2: cluster the training set.

Step 2.5: assign labels to observations in test set.

Step 3: evaluate clusters using test set.

Other situations in which sample splitting is not a good option

1. Fixed-X regression settings.
2. Non-IID data.
3. Data with outliers or influential points.



Outline

1. Motivation: settings where sample splitting doesn't work
- 2. Poisson thinning**
3. Data thinning
4. Application to single-cell RNA sequencing data
5. Ongoing work

Poisson thinning

X

	Feature 1	Feature 2
Obs. 1	18	6
Obs. 2	31	8
Obs. 3	11	31
Obs. 4	22	34

Poisson thinning

X

	Feature 1	Feature 2
Obs. 1	18	6
Obs. 2	31	8
Obs. 3	11	31
Obs. 4	22	34

$X^{(1)}$

	Feature 1	Feature 2
Obs. 1	14	1
Obs. 2	10	6
Obs. 3	5	17
Obs. 4	6	25

$X^{(2)}$

	Feature 1	Feature 2
Obs. 1	4	5
Obs. 2	21	2
Obs. 3	6	14
Obs. 4	16	9

Poisson thinning

X

	Feature 1	Feature 2
Obs. 1	18	6
Obs. 2	31	8
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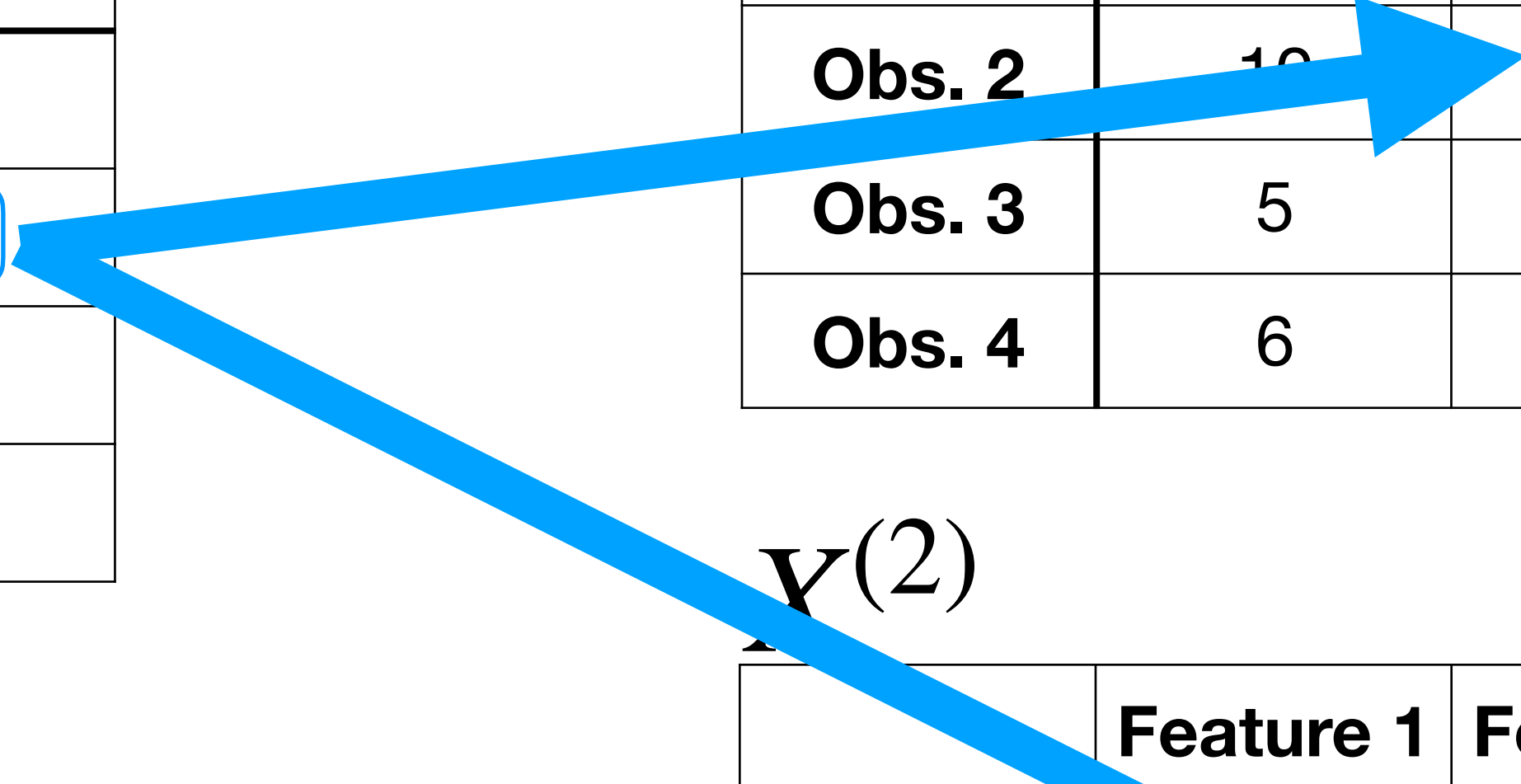
$X^{(1)}$

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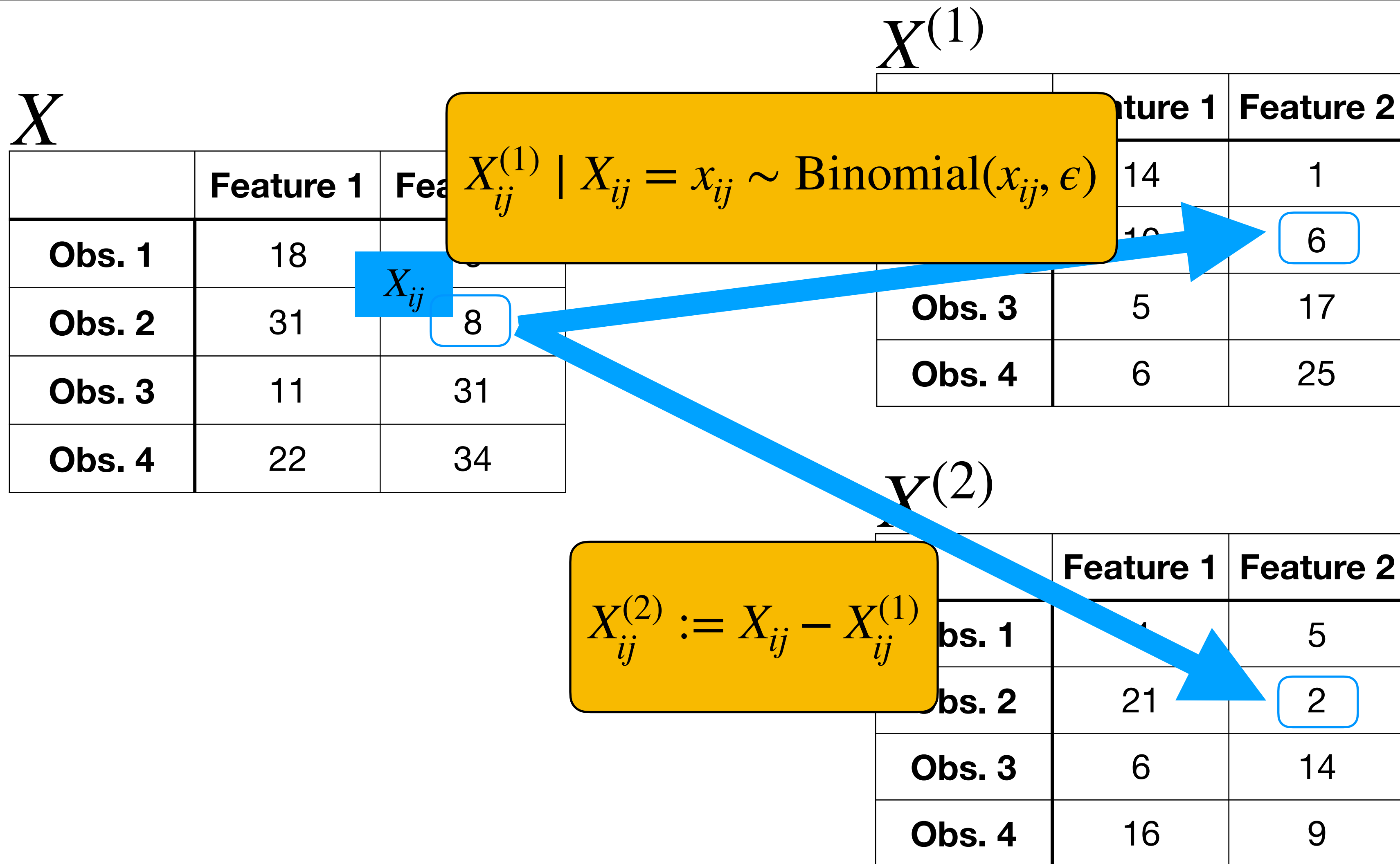
$Y^{(2)}$

	Feature 1	Feature 2
Obs. 1	4	5
Obs. 2	21	2
Obs. 3	6	14
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X_{ij}



Poisson thinning



Poisson thinning

X			$X^{(1)}$		
	Feature 1	Feature 2		Feature 1	Feature 2
Obs. 1	18	10	Obs. 1	14	1
Obs. 2	31	8	Obs. 2	19	6
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Obs. 4	22	34	Obs. 4	6	25

$$X_{ij}^{(1)} \mid X_{ij} = x_{ij} \sim \text{Binomial}(x_{ij}, \epsilon)$$

X_{ij}

- If $X_{ij} \sim \text{Poisson}(\Lambda_{ij})$, then:
- $X_{ij}^{(1)} \sim \text{Poisson}(\epsilon\Lambda_{ij})$
 - $X_{ij}^{(2)} \sim \text{Poisson}((1 - \epsilon)\Lambda_{ij})$
 - $X_{ij}^{(1)} \perp\!\!\!\perp X_{ij}^{(2)}$

$$X_{ij}^{(2)} := X_{ij} - X_{ij}^{(1)}$$

$X^{(2)}$			X		
	Feature 1	Feature 2		Feature 1	Feature 2
Obs. 1	4	5	Obs. 1	18	10
Obs. 2	21	2	Obs. 2	31	8
Obs. 3	6	14	Obs. 3	11	31
Obs. 4	16	9	Obs. 4	22	34

A very well-known result.

Poisson thinning

X			$X^{(1)}$		
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Obs. 4					

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Select hypothesis.

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$X^{(2)}$		
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Test hypothesis.

A very well-known result.

Poisson thinning

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Obs. 1	31	8	19	6	
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Fit model.

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$X^{(2)}$			Feature 1	Feature 2
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Poisson thinning

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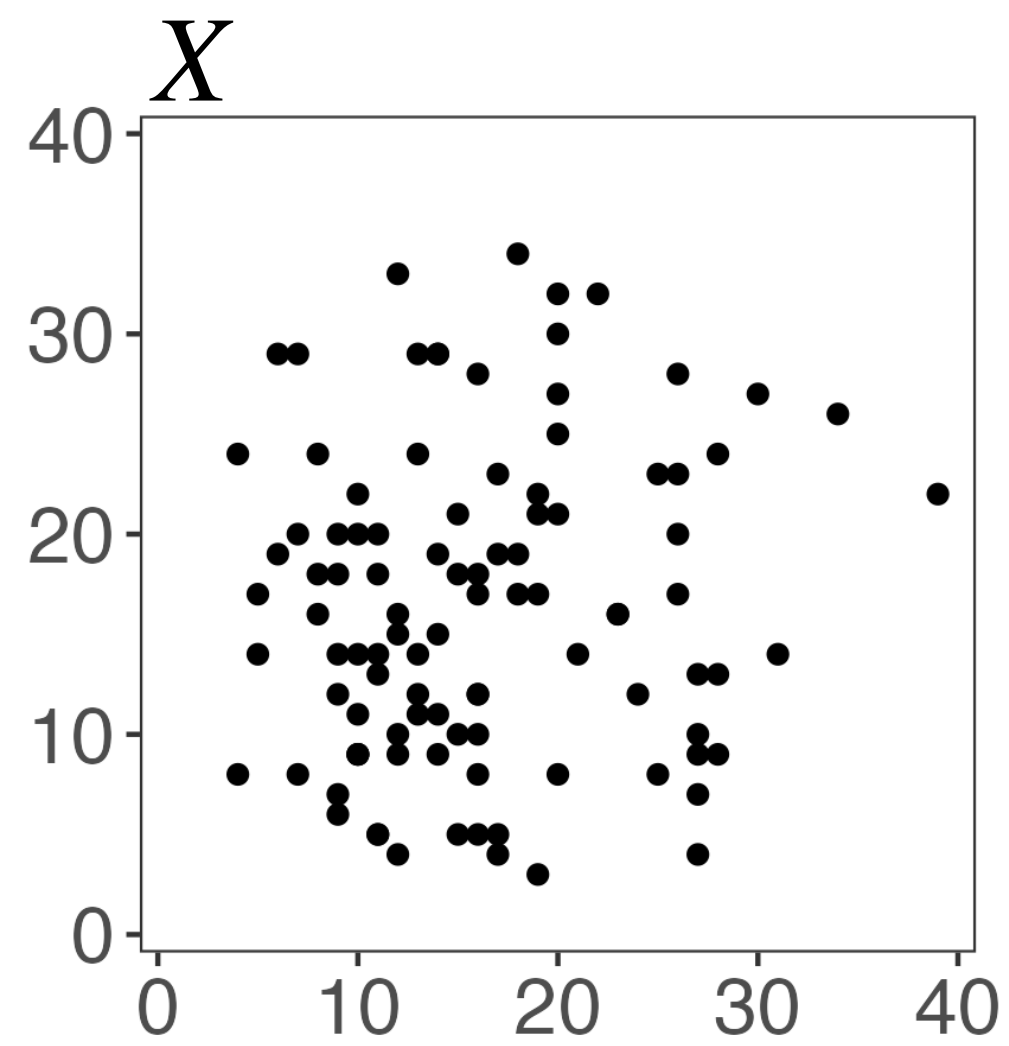
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$X^{(2)}$			X		
	Feature 1	Feature 2	Feature 1	Feature 2	
Obs. 1	4	5	18	10	
Obs. 2	21	2	31	8	
Obs. 3	6	14	11	31	
Obs. 4	16	9	22	34	

Evaluate model.

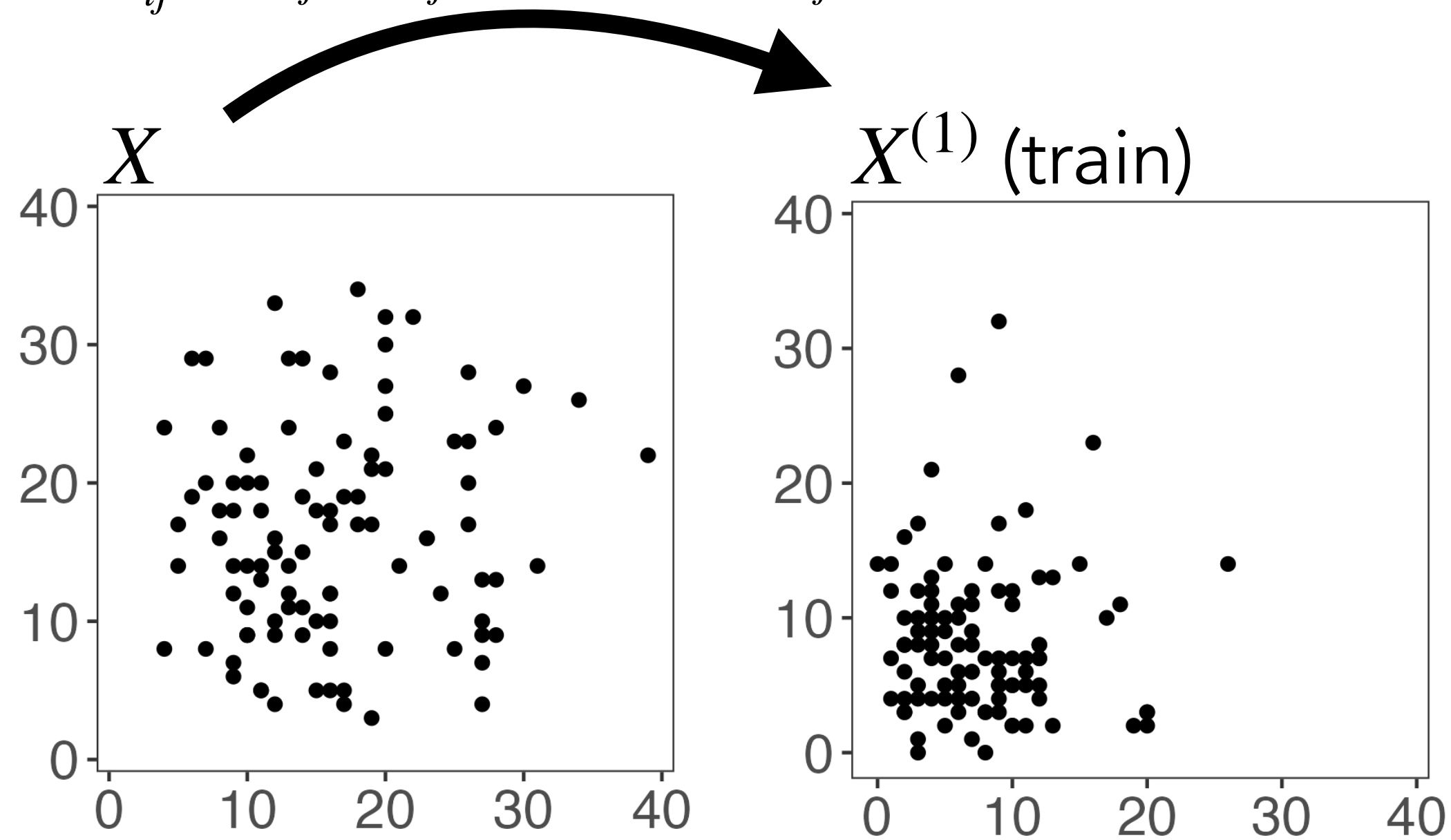
A very well-known result.

Thinning avoids the pitfall of sample splitting on our motivating examples



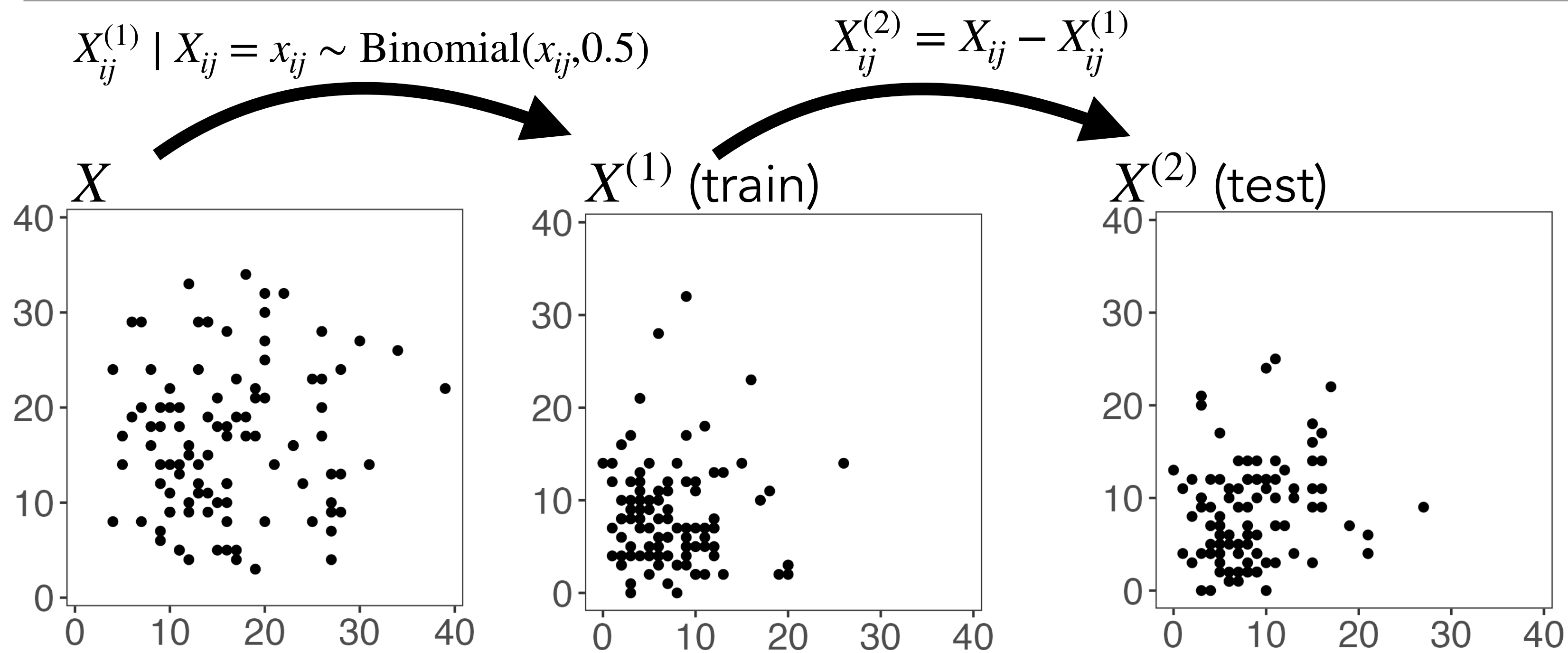
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$$X_{ij}^{(1)} \mid X_{ij} = x_{ij} \sim \text{Binomial}(x_{ij}, 0.5)$$



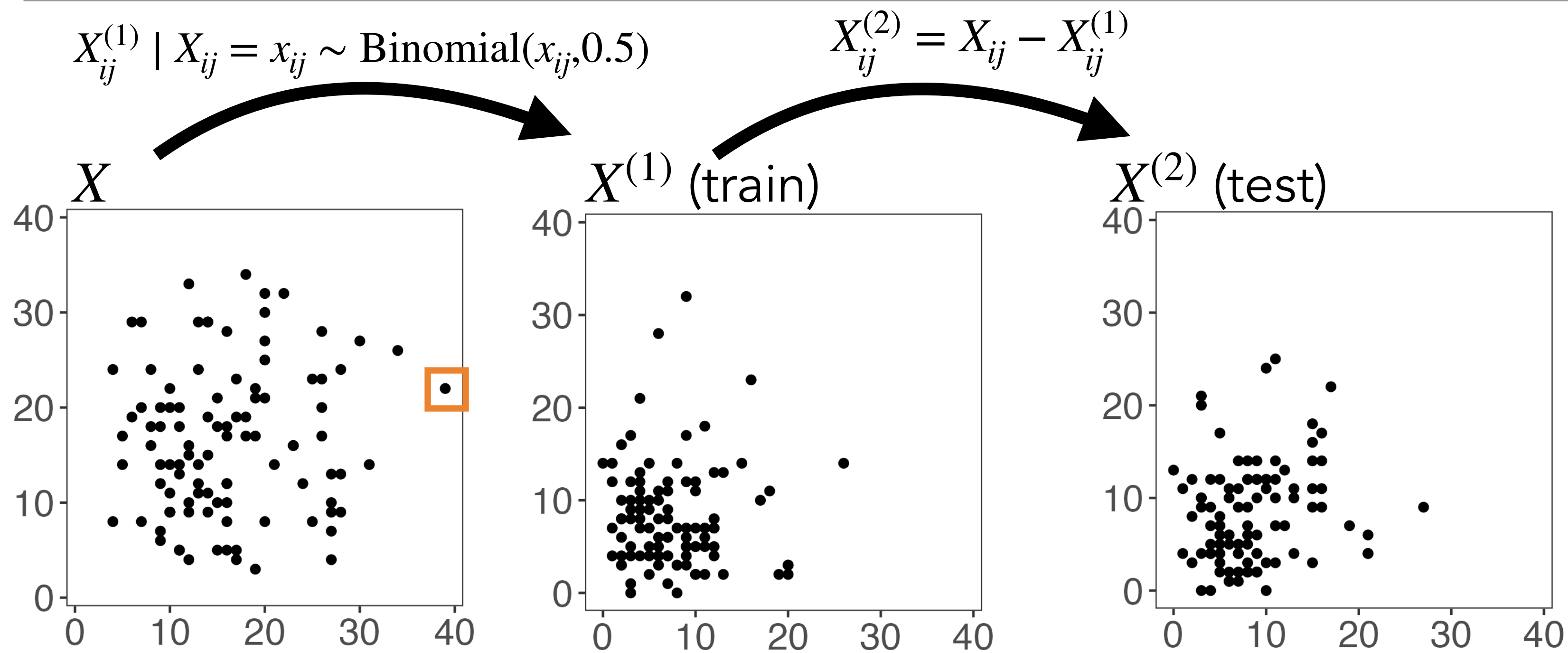
Step 1: thin observations into train/test.

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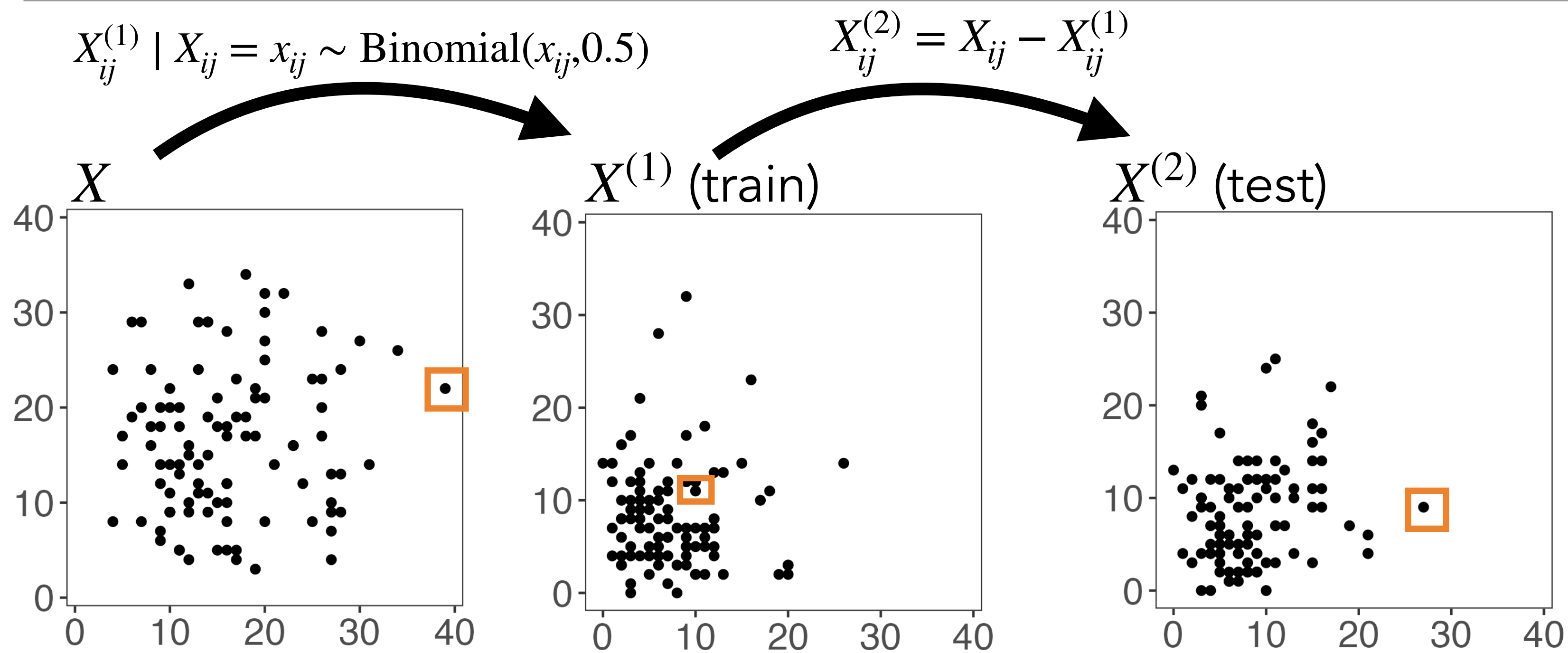
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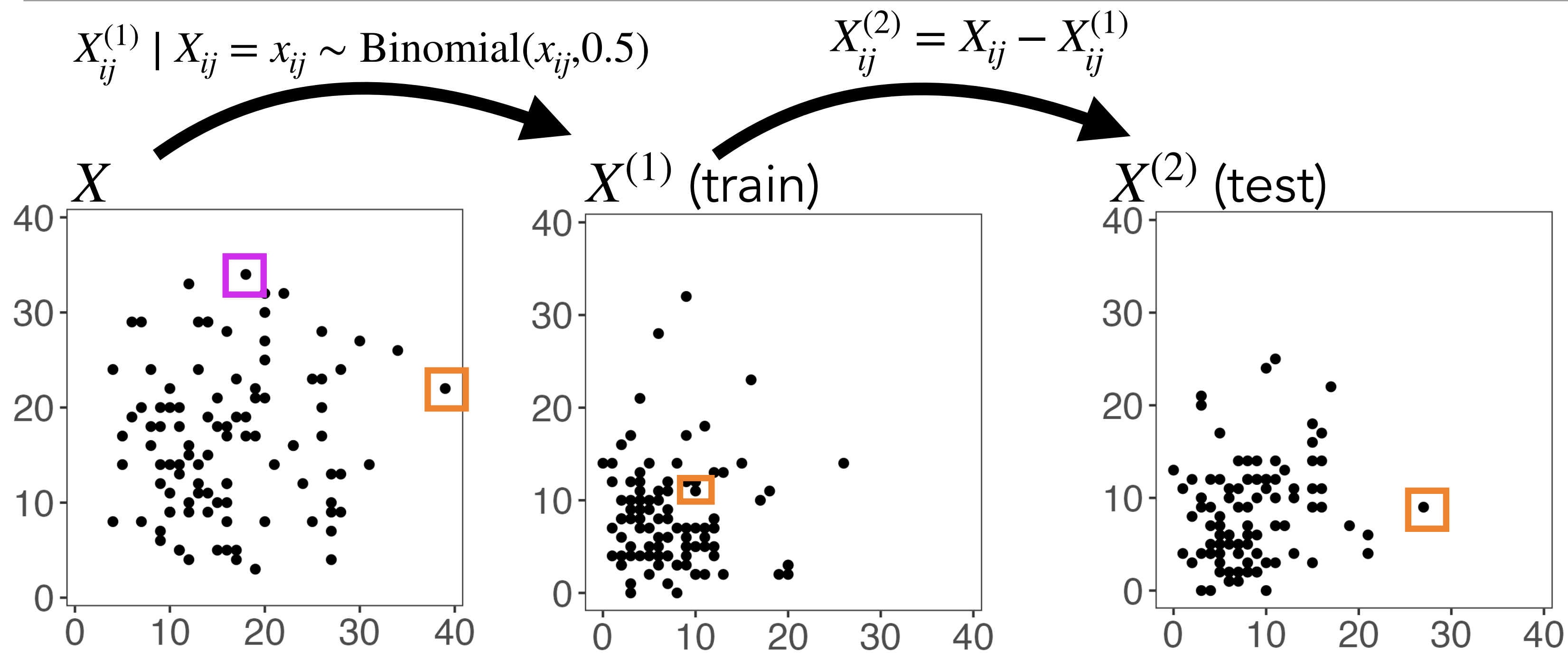
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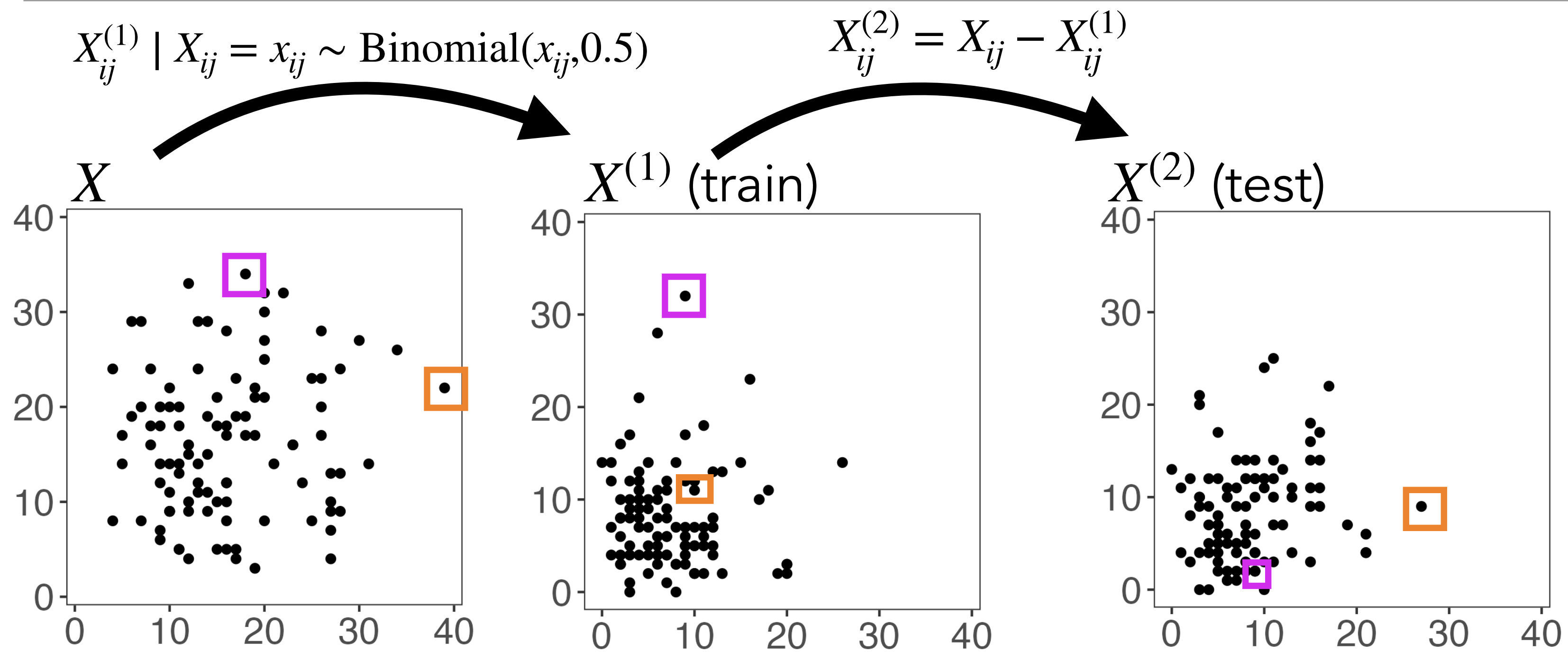
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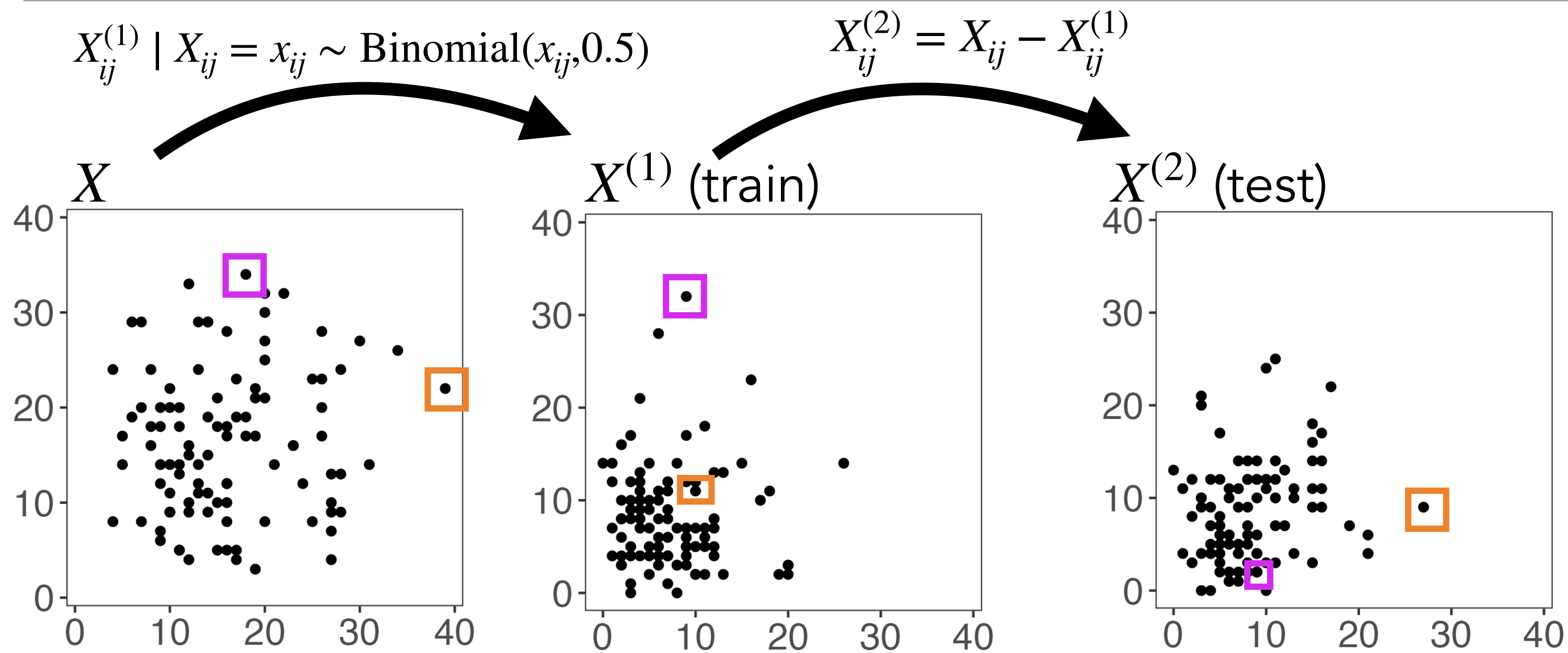
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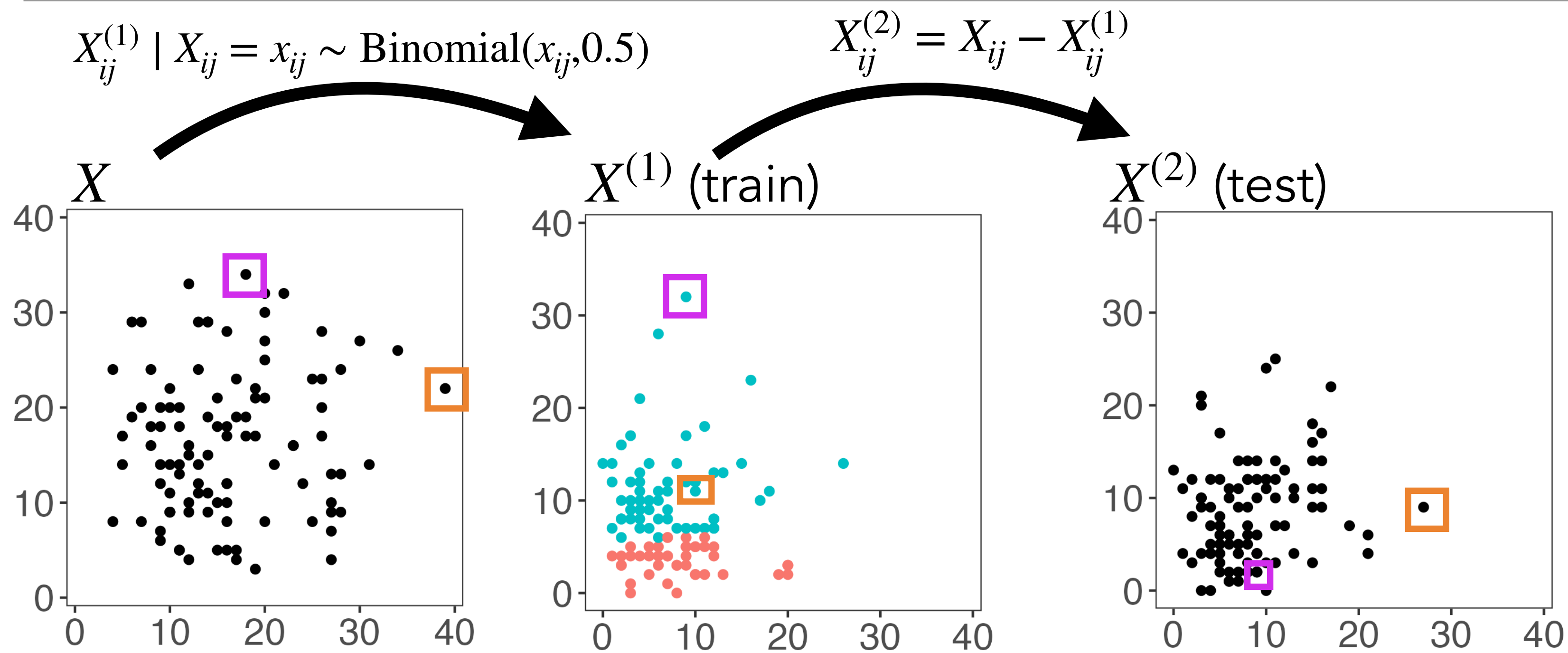
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Step 1: thin observations into train/test.

Step 2: cluster the training set.

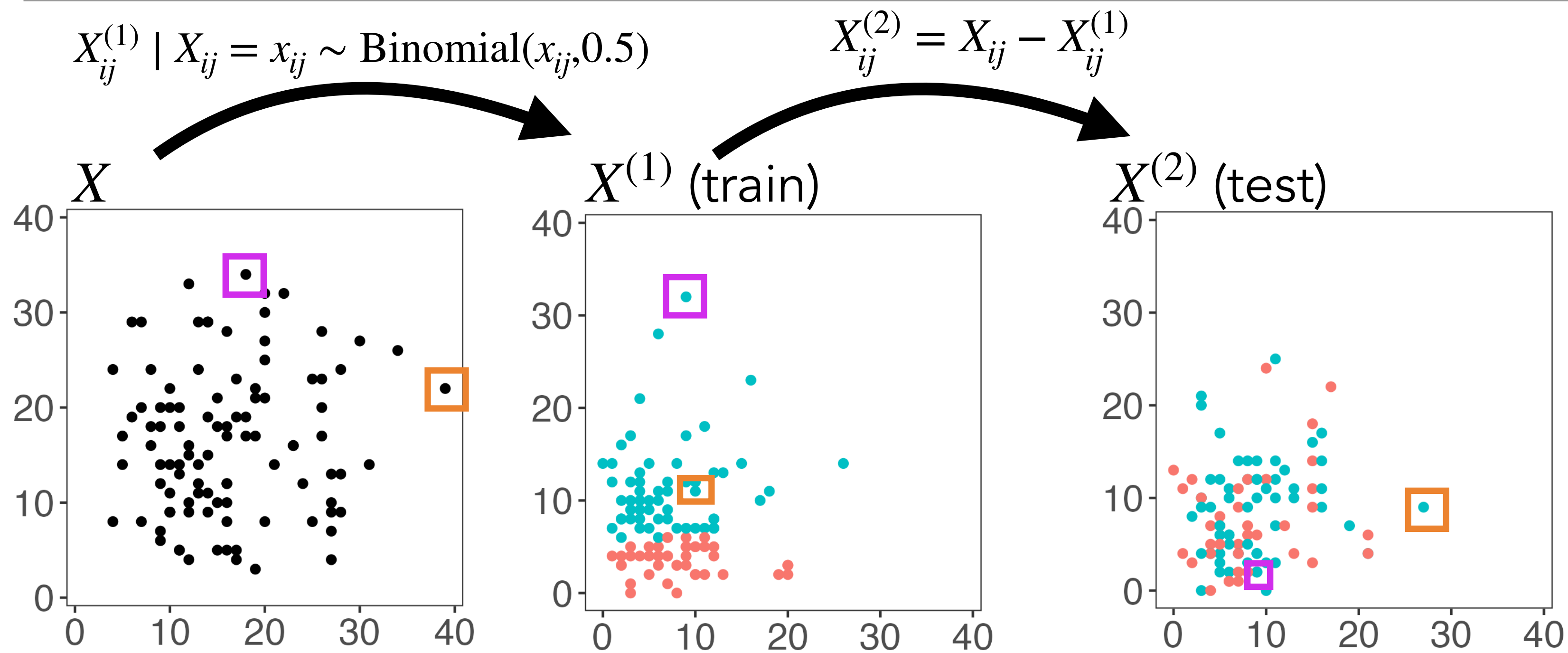
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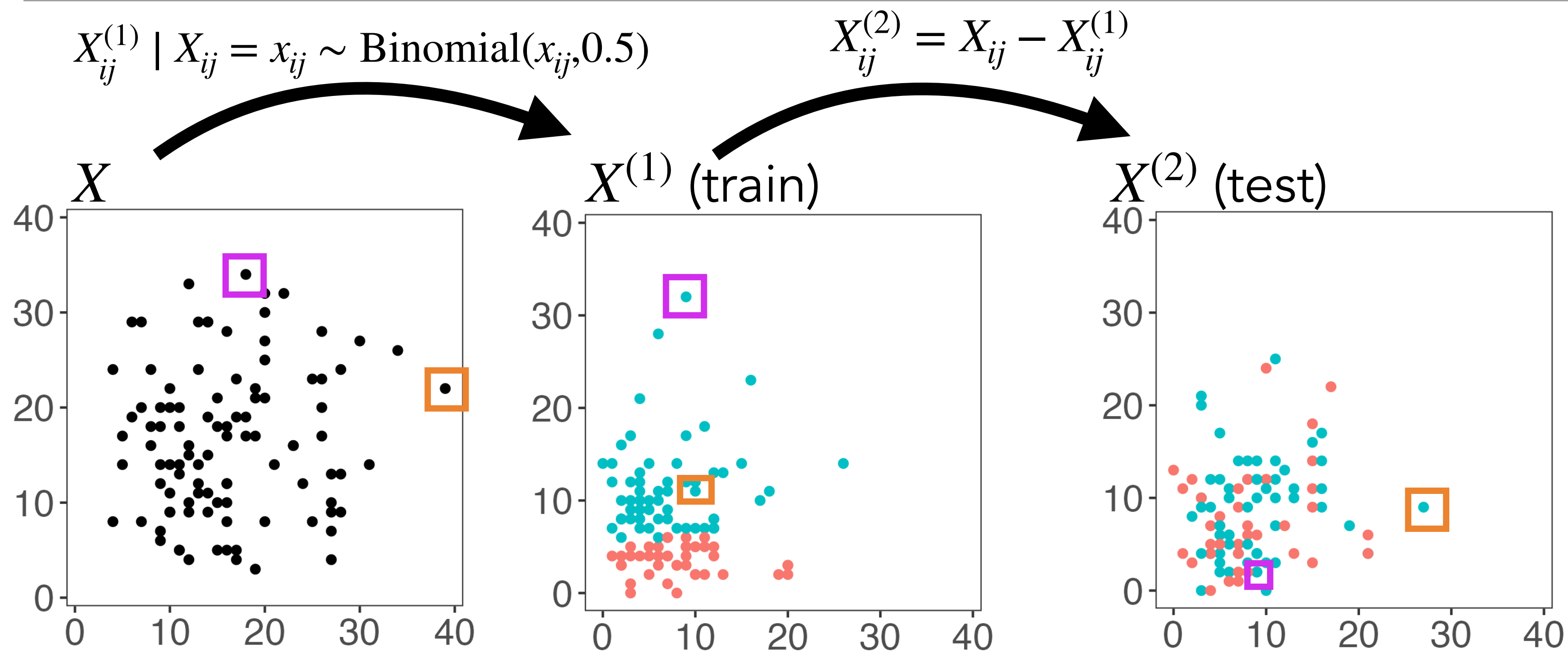
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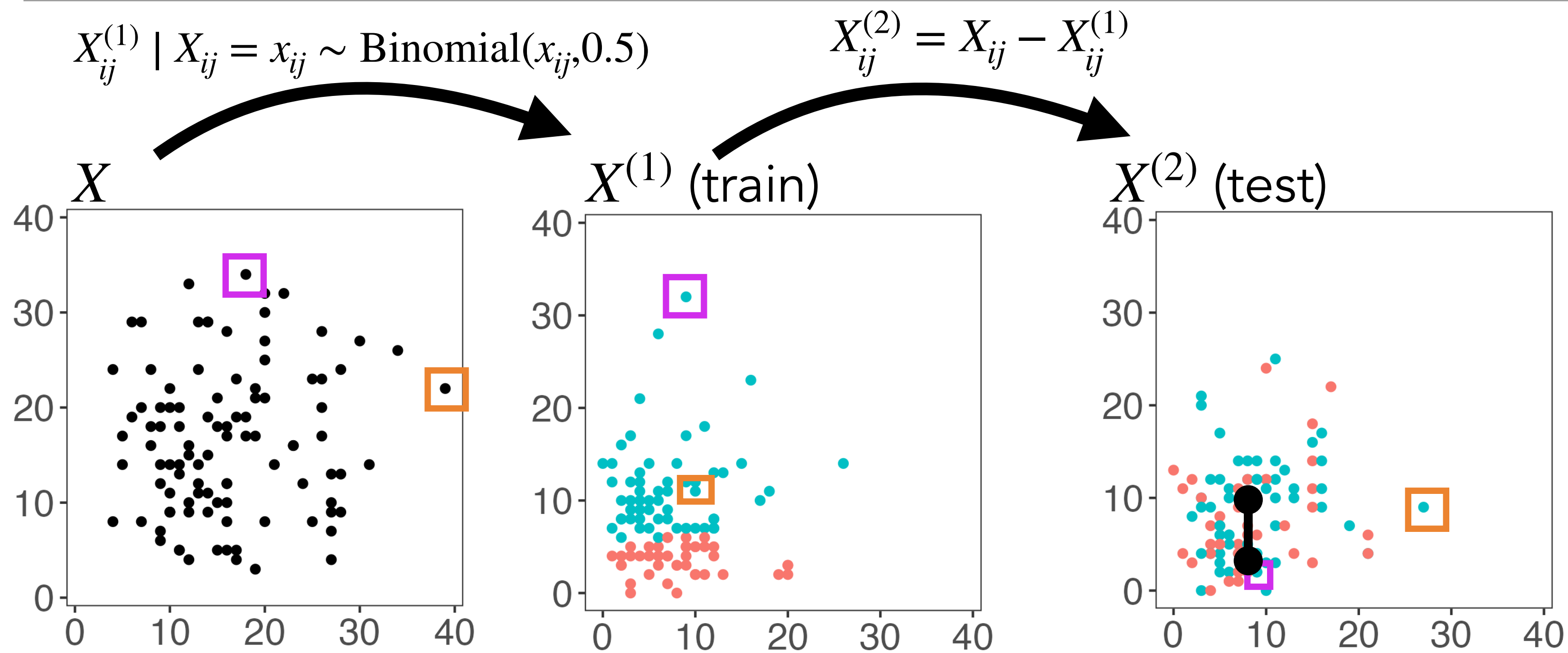


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Step 3: test for difference in means or evaluate clusters on test set.

Thinning avoids the pitfall of sample splitting on our motivating examples

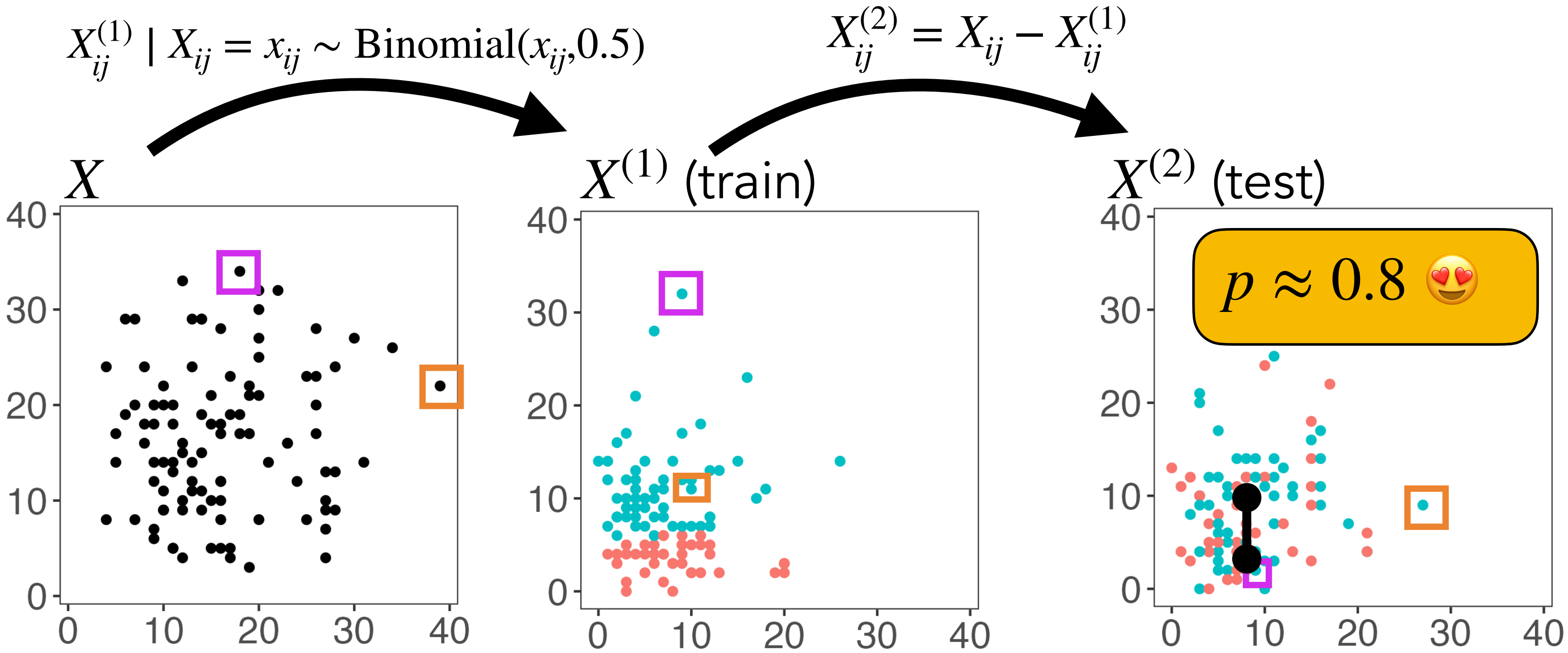


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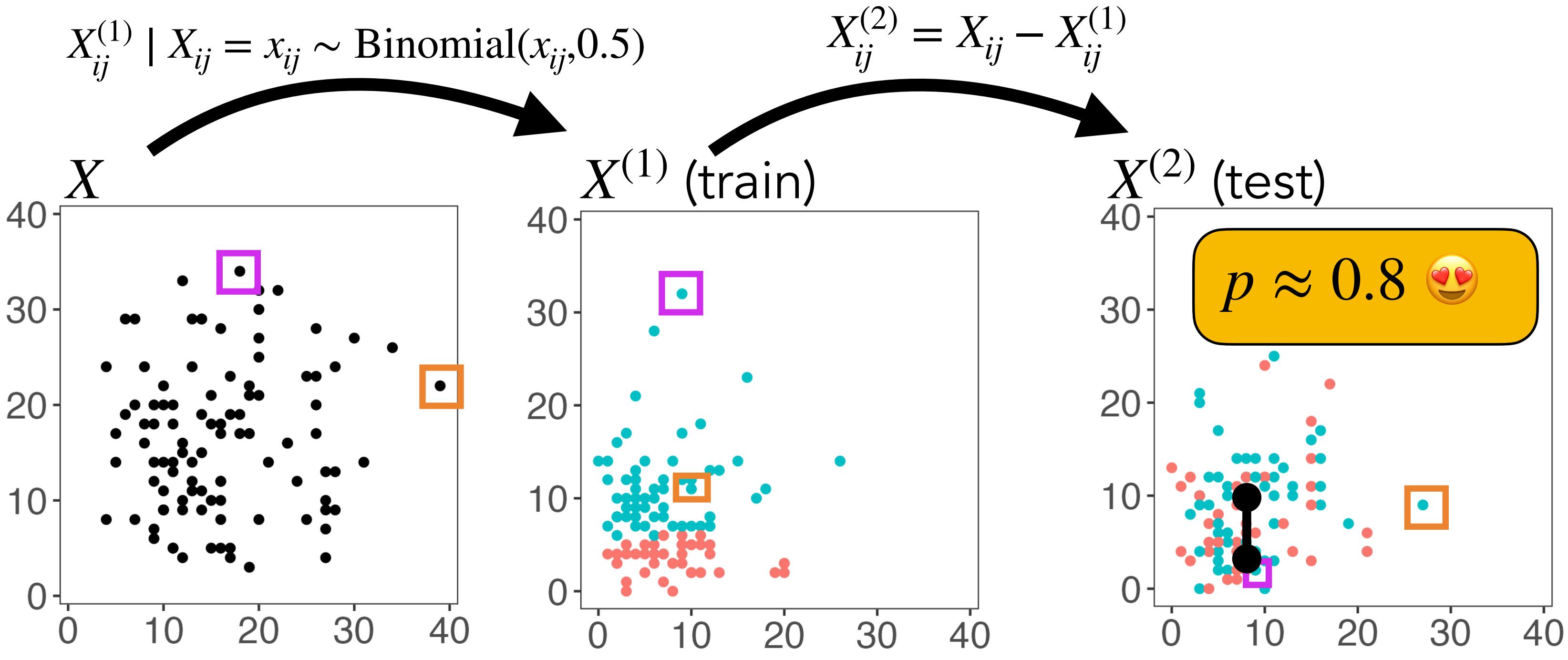


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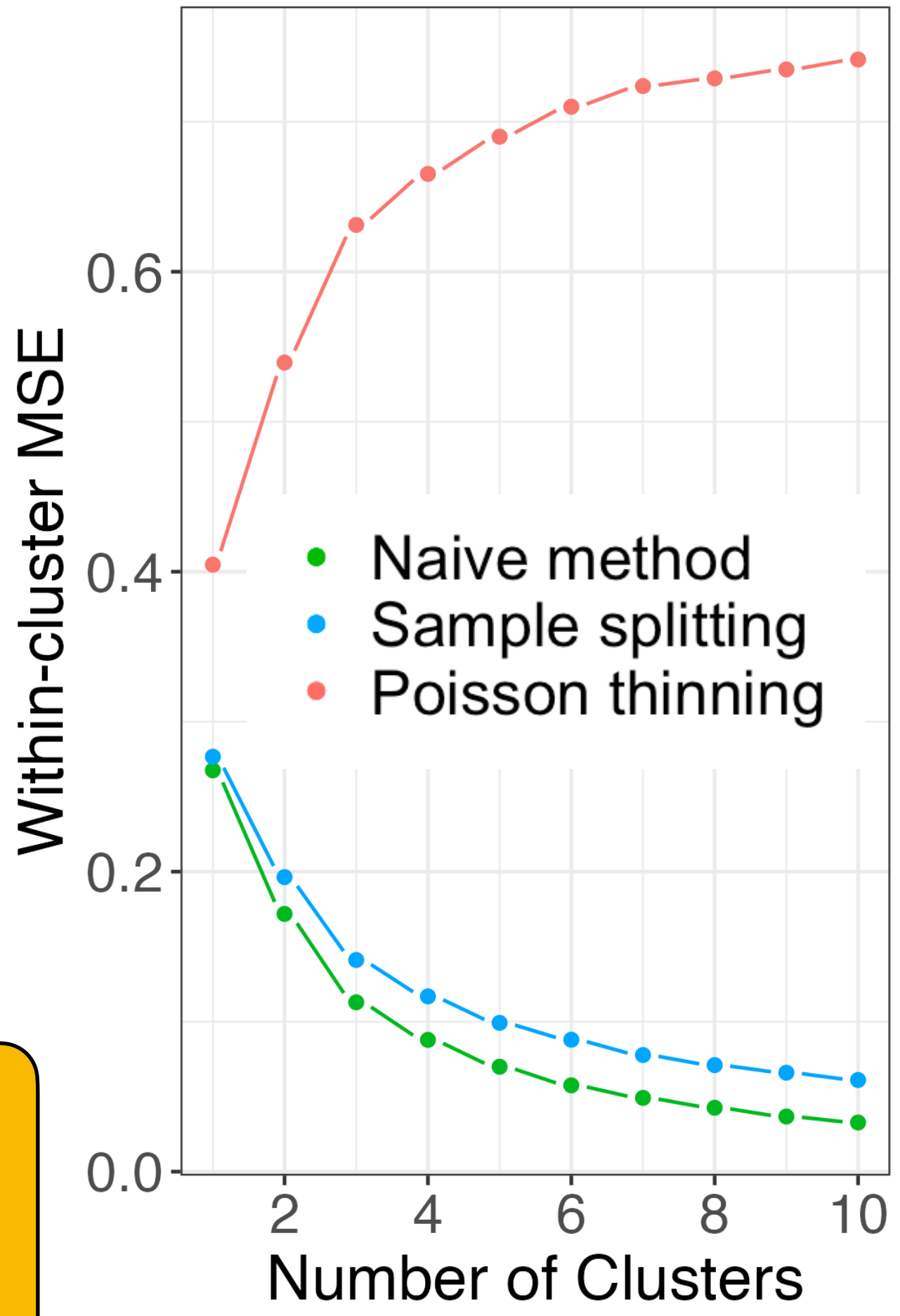
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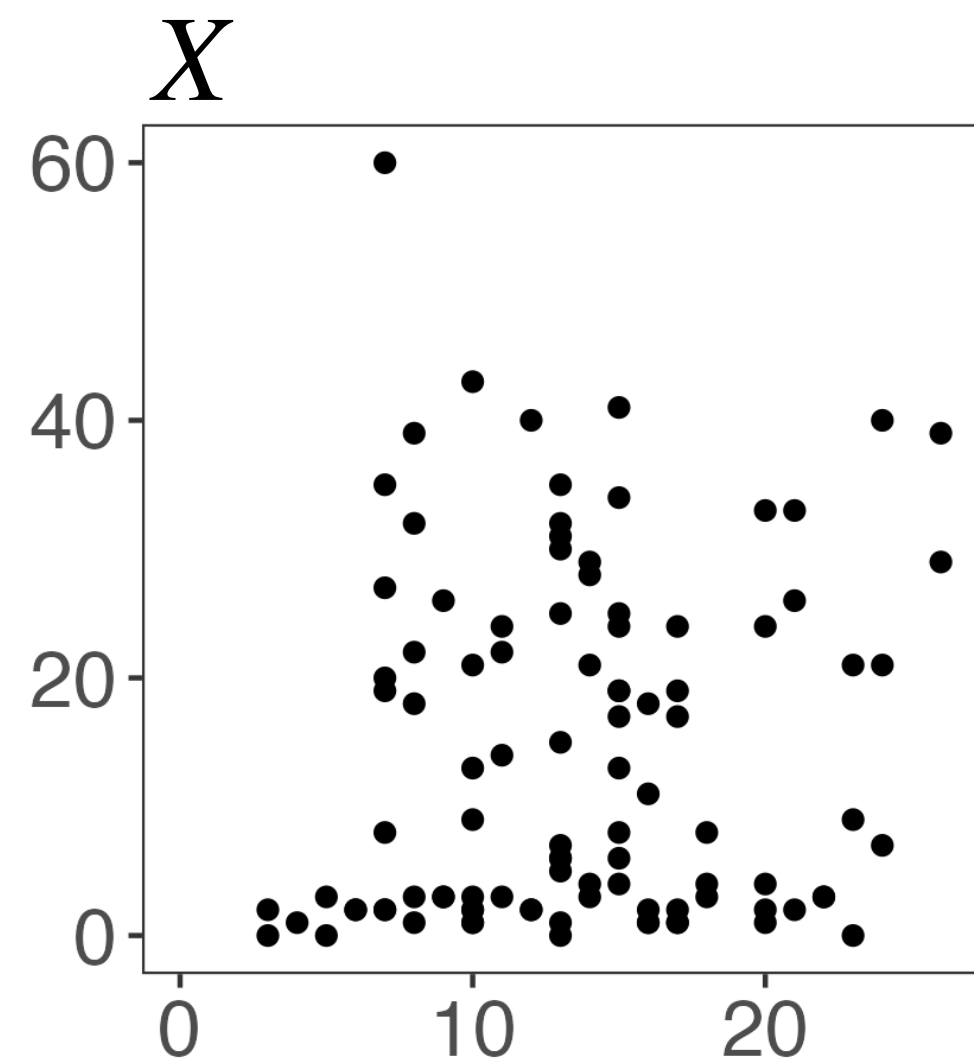
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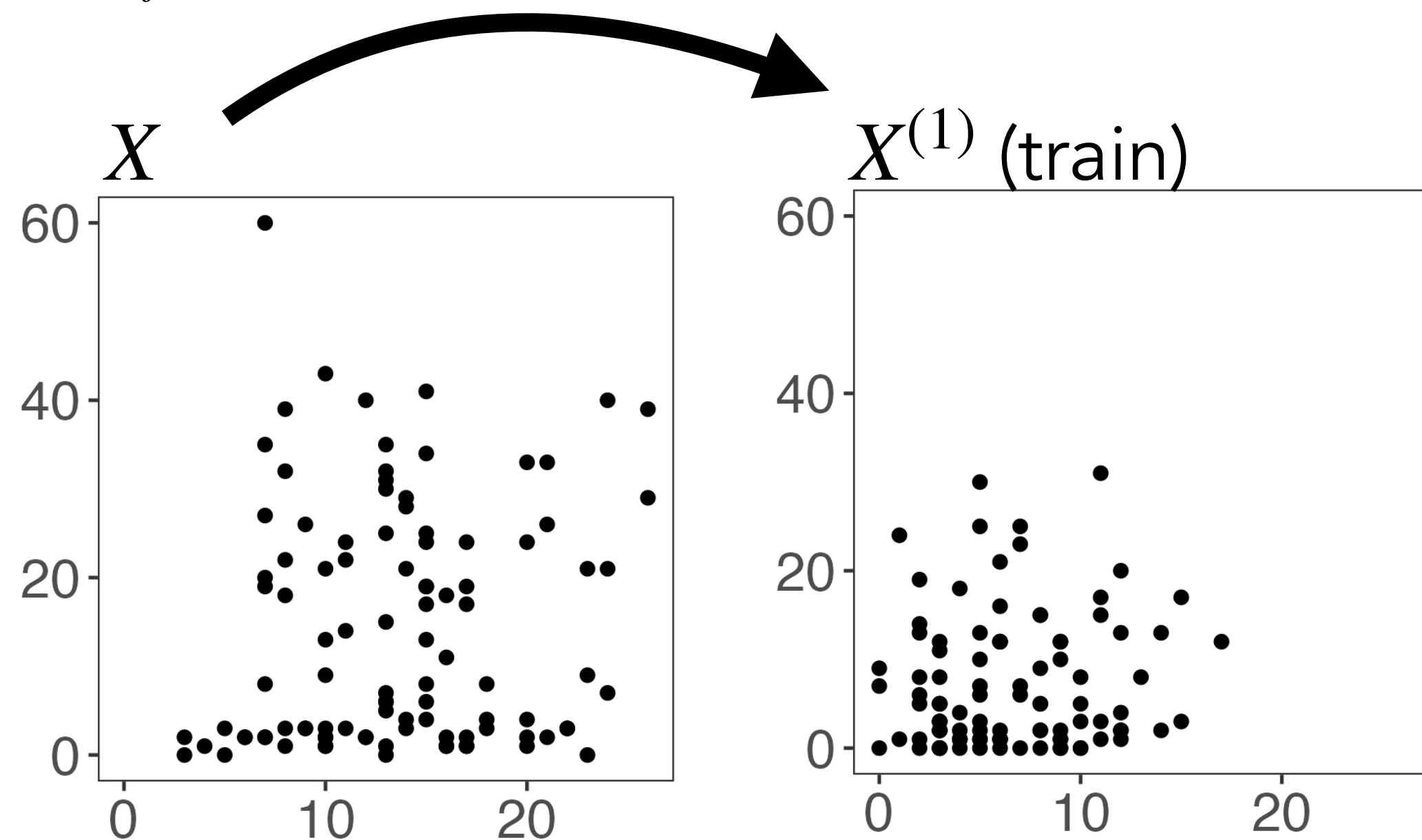
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$$X_{i2} \sim \begin{cases} \text{Poisson}(3) & \text{if } i \leq 50 \\ \text{Poisson}(25) & \text{if } i > 50 \end{cases}$$

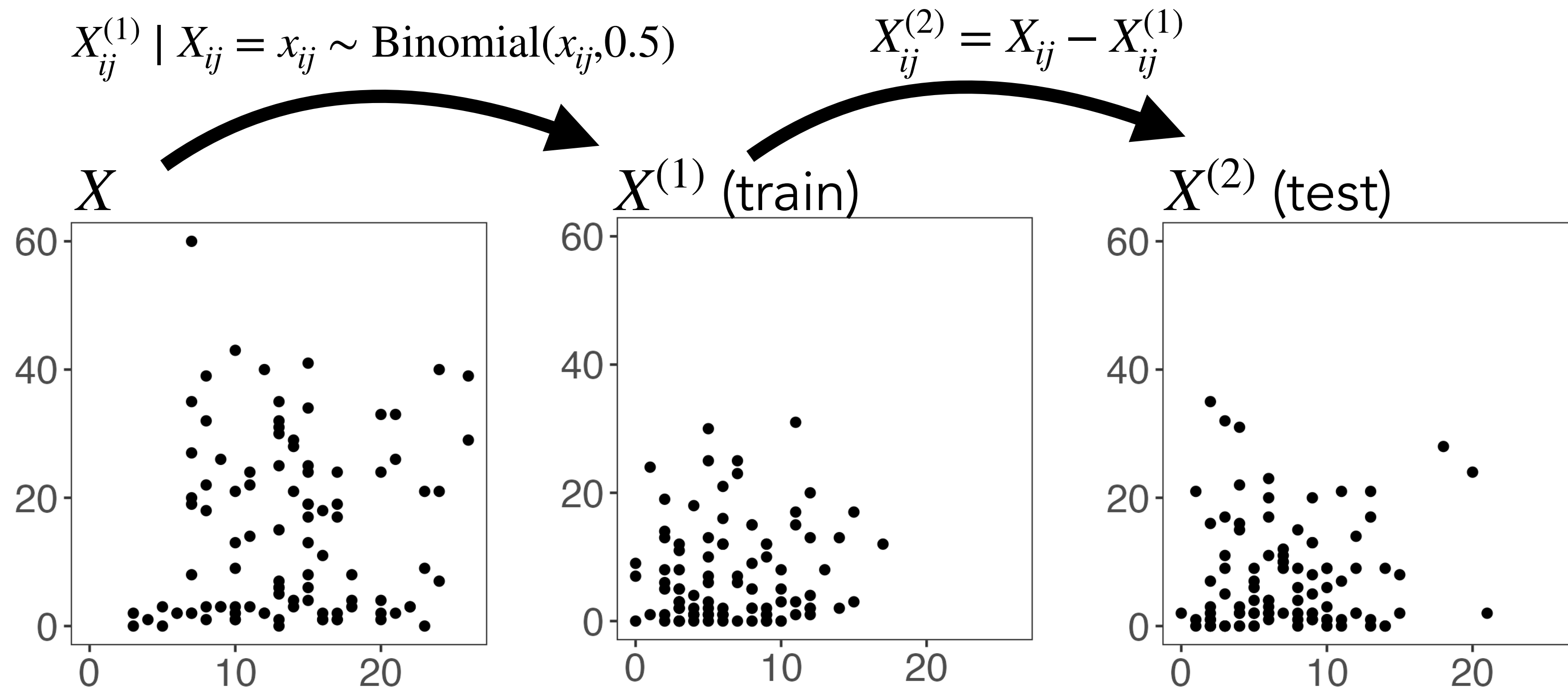
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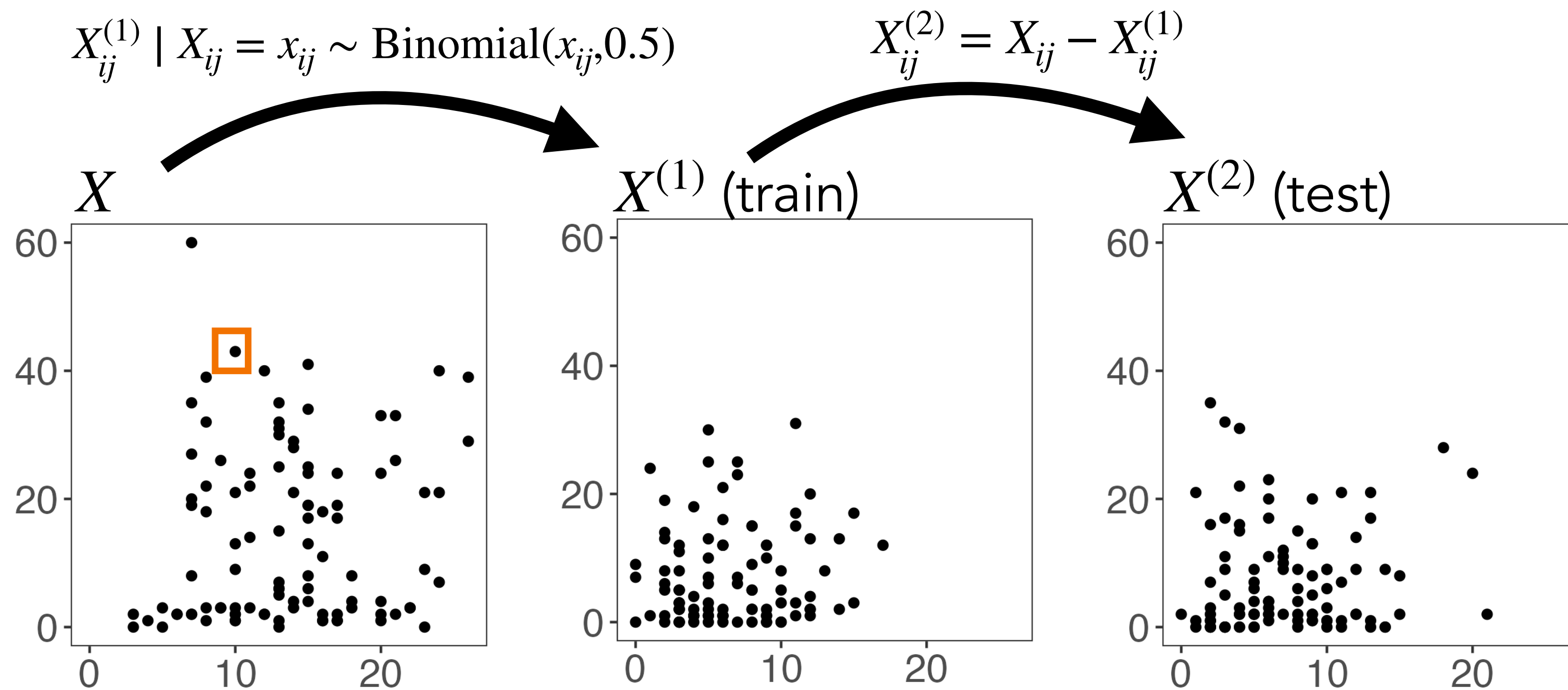
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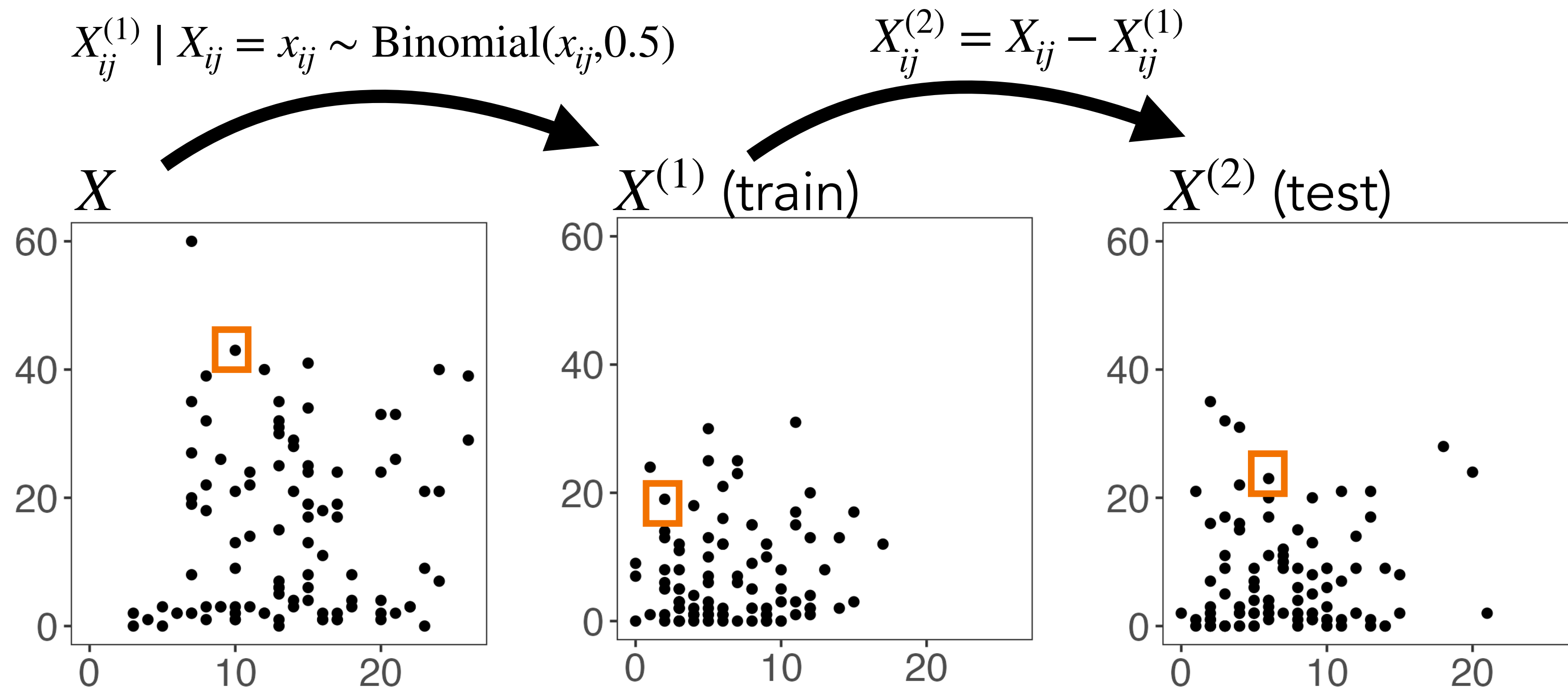
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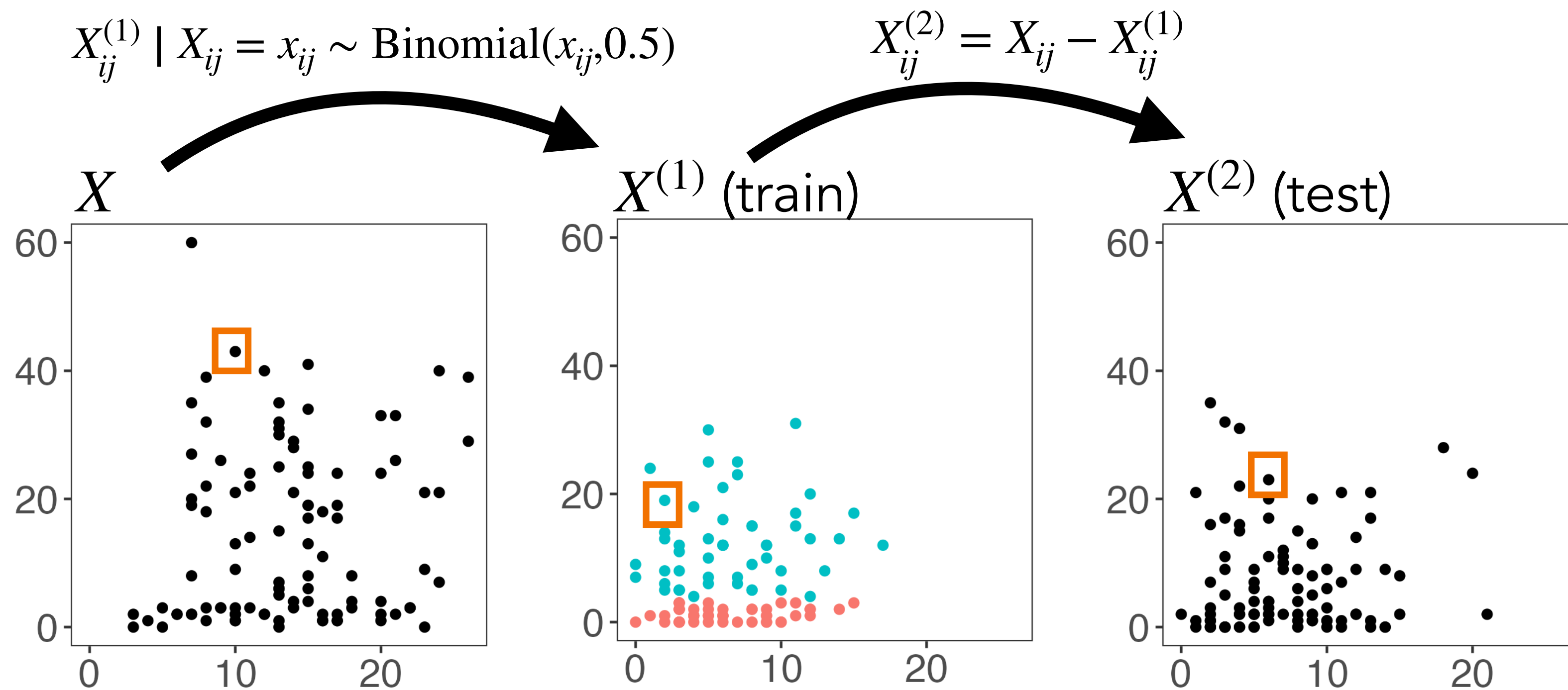
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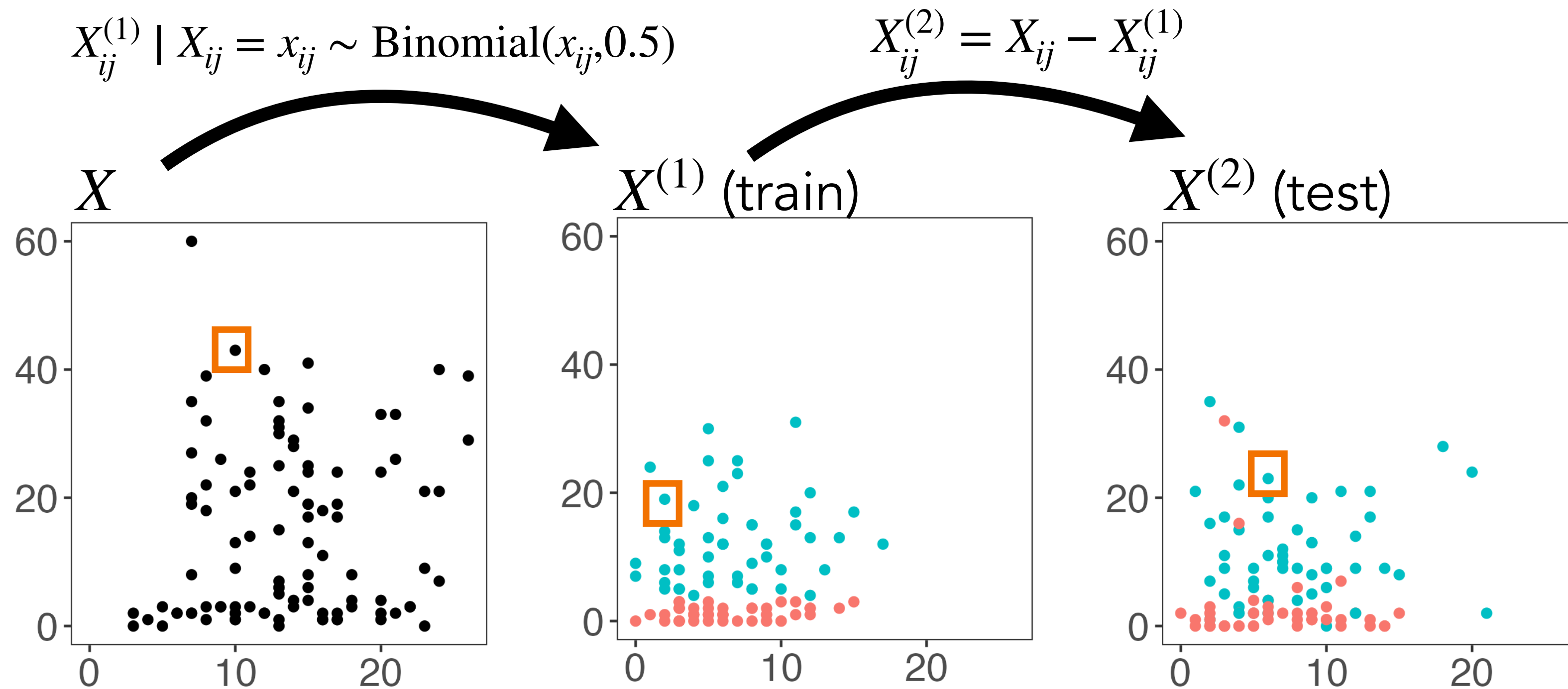
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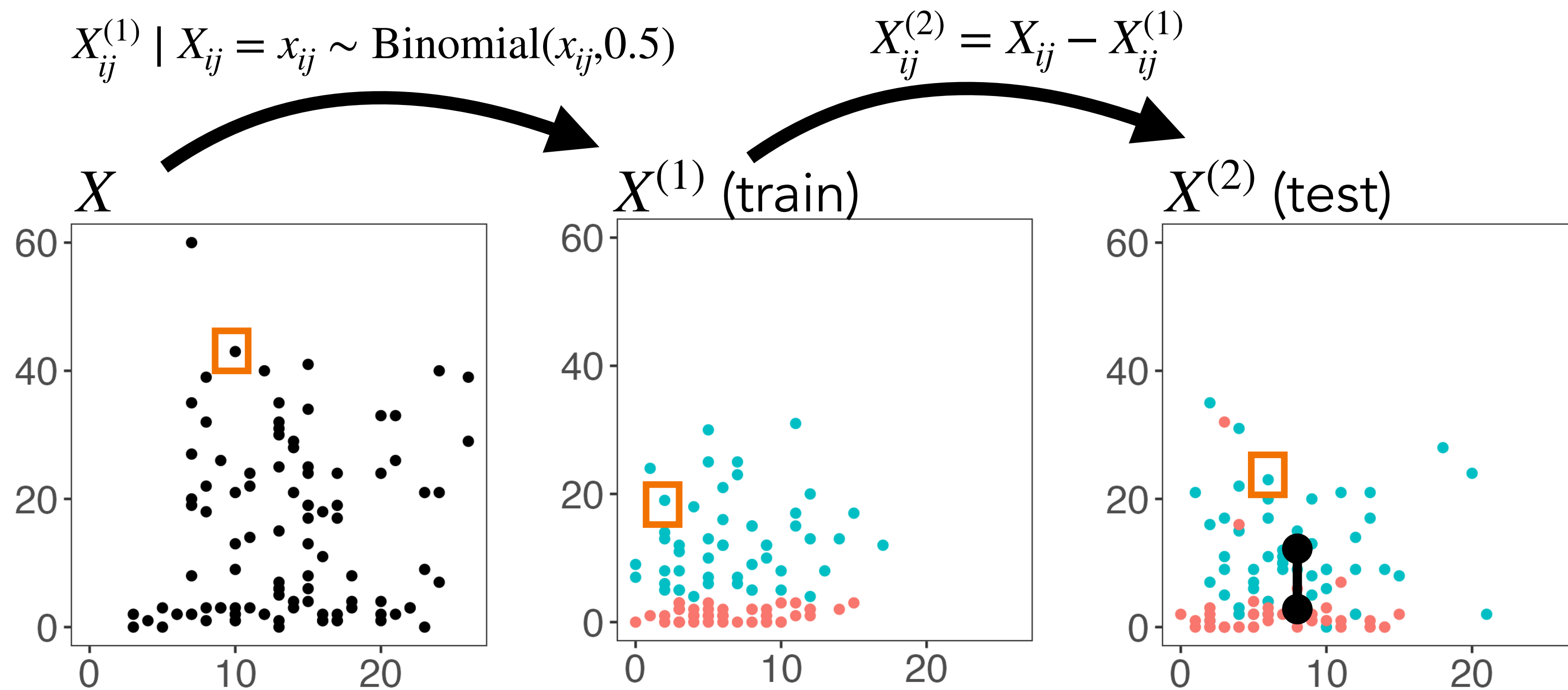
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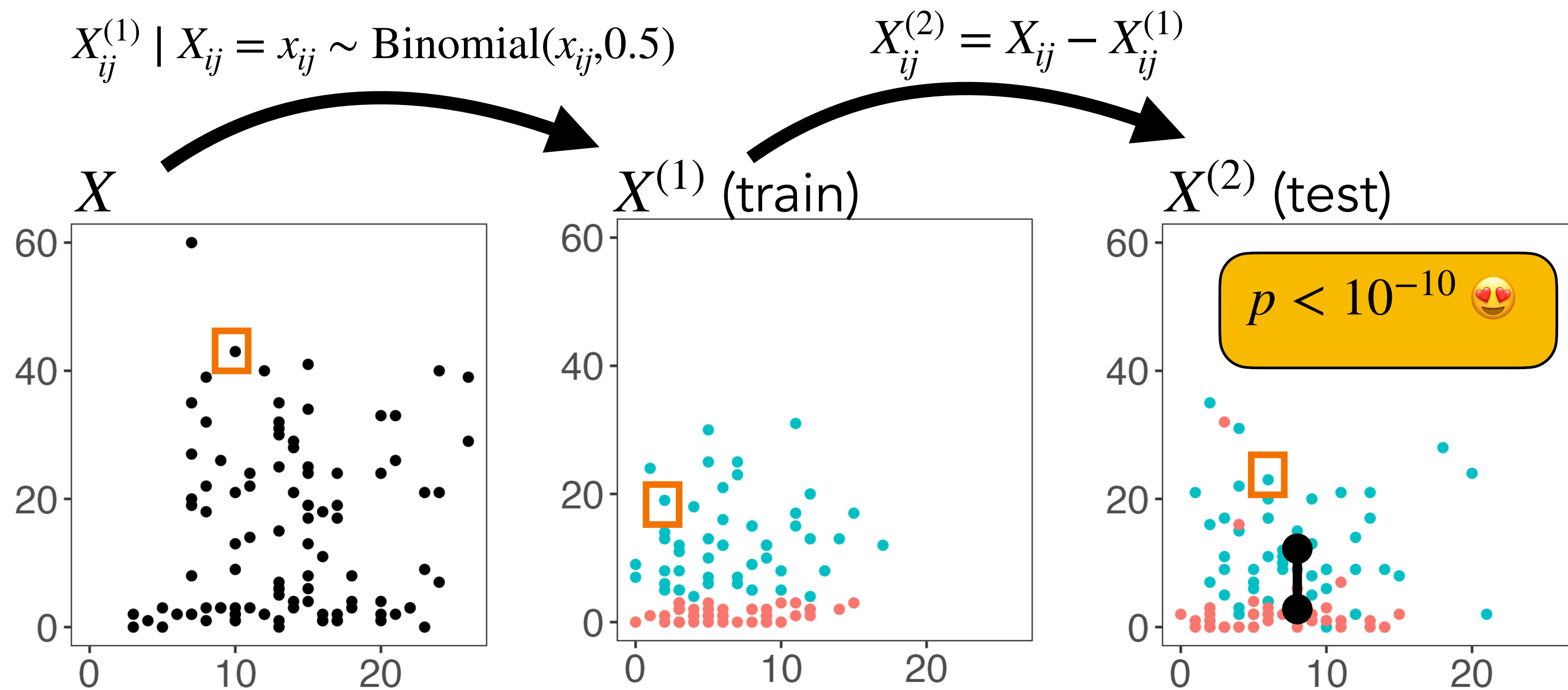
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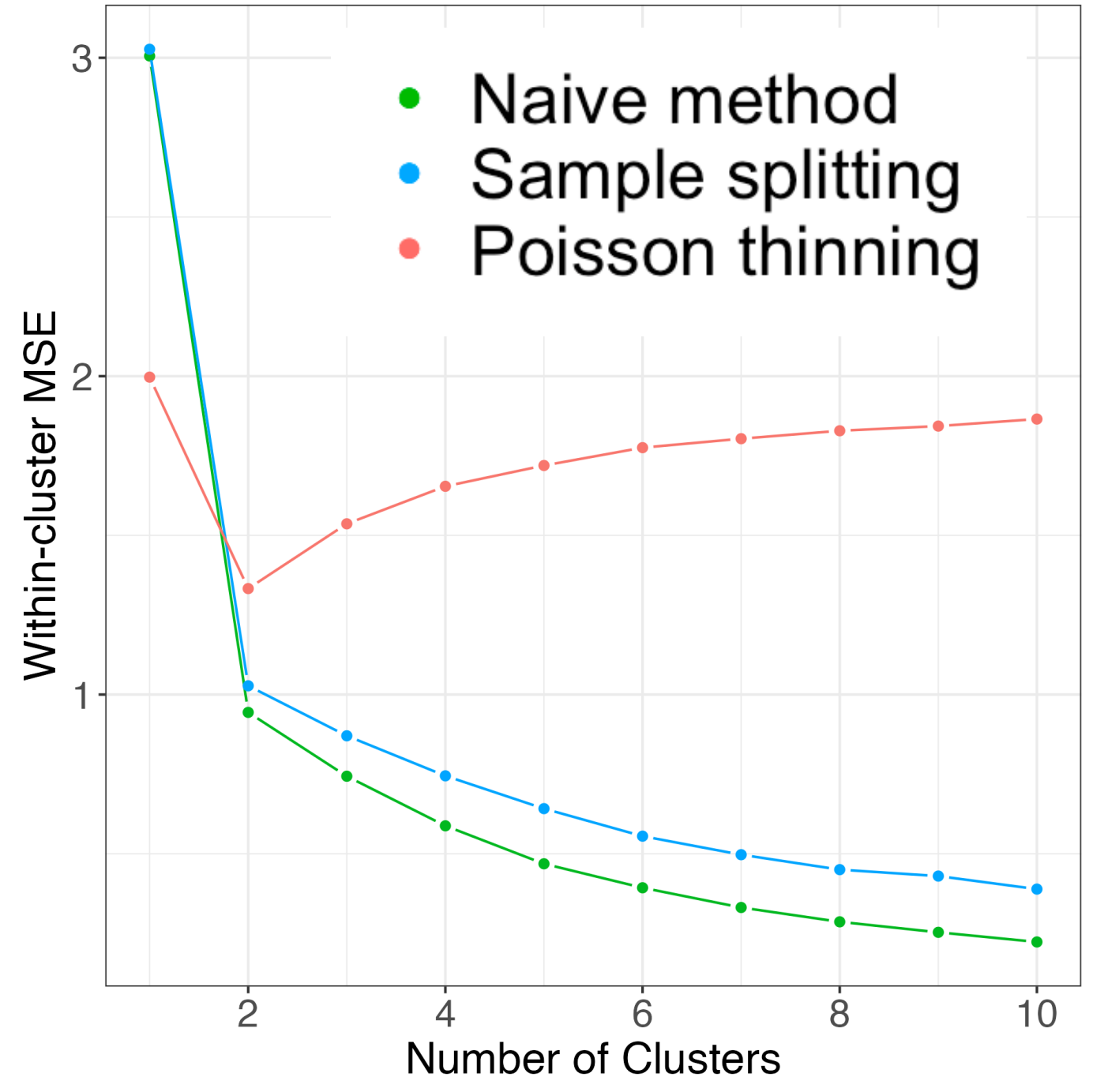
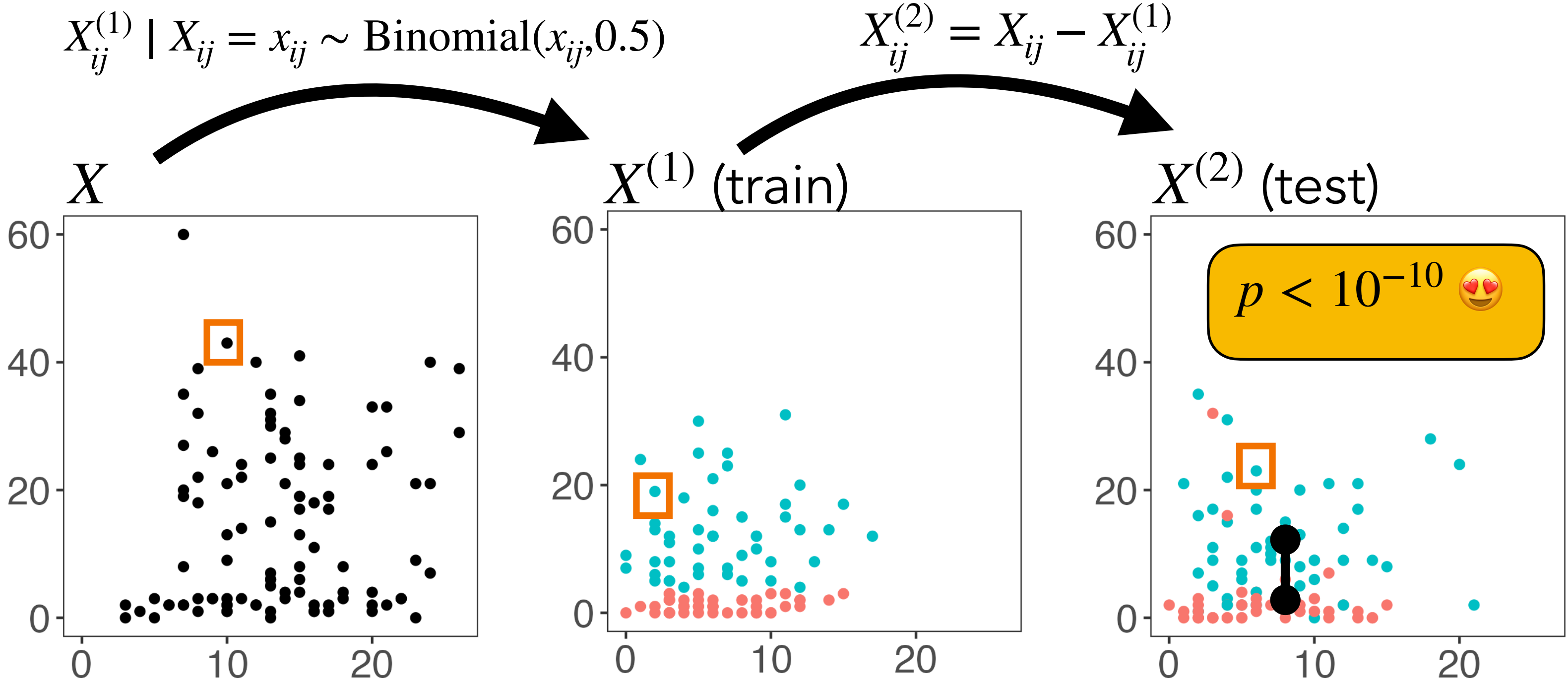
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Poisson thinning is useful in the analysis of single-cell RNA sequencing data

Lähnemann *et al. Genome Biology* (2020) 21:31
<https://doi.org/10.1186/s13059-020-1926-6>

Genome Biology

REVIEW

Open Access

Eleven grand challenges in single-cell data science



David Lähnemann^{1,2,3}, Johannes Köster^{1,4}, Ewa Szczurek⁵, Davis J. McCarthy^{6,7}, Stephanie C. Hicks⁸, Mark D. Robinson⁹ , Catalina A. Vallejos^{10,11}, Kieran R. Campbell^{12,13,14}, Niko Beerenwinkel^{15,16}, Ahmed Mahfouz^{17,18}, Luca Pinello^{19,20,21}, Pavel Skums²², Alexandros Stamatakis^{23,24}, Camille Stephan-Otto Attolini²⁵, Samuel Aparicio^{13,26}, Jasmijn Baaijens²⁷, Marleen Balvert^{27,28}, Buys de Barbanson^{29,30,31}, Antonio Cappuccio³², Giacomo Corleone³³, Bas E. Dutilh^{28,34}, Maria Florescu^{29,30,31}, Victor Gurtev³⁵, Rens Holmer³⁶, Katharina Jahn^{15,16}, Tamar Jessurun Lobo³⁵, Emma M. Keizer³⁷, Tzu-Hao Kuo³, Bouwe J. van der Valk³⁸, Tobias Marschall⁴⁷, Jeroen de Ridder²⁹, Fabian J. Theis⁵⁴, H. Scott Young⁵⁵, Sohrab P. Shah⁵⁹ and

Status

Currently, the vast majority of differential expression detection methods assume that the groups of cells to be compared are known in advance (e.g., experimental conditions or cell types). However, current analysis pipelines typically rely on clustering or cell type assignment to identify such groups, before downstream differential analysis is performed, without propagating the uncertainty in these assignments or accounting for the double use of data (clustering, differential testing between clusters).

Poisson thinning is useful in the analysis of single-cell RNA sequencing data

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REVIEW

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Project 2

Biostatistics (2022) 00, 00, pp. 1–18
<https://doi.org/10.1093/biostatistics/kxac047>



Inference after latent variable estimation for single-cell RNA sequencing data

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Department of Computer Science, Johns Hopkins University, Baltimore, MD 21218, USA

DANIELA WITTEN

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Biostatistics, University of Washington, Seattle, WA 98195, USA

R package and tutorials:
<https://anna-neufeld.github.io/countsplit/>

But generalizations of Poisson thinning are needed

Choudhary and Satija *Genome Biology* (2022) 23:27
<https://doi.org/10.1186/s13059-021-02584-9>


Genome Biology

RESEARCH

Open Access

Comparison and evaluation of statistical error models for scRNA-seq



Saket Choudhary¹ and Rahul Satija^{1,2*} 

Results: Here, we analyze 59 scRNA-seq datasets that span a wide range of technologies, systems, and sequencing depths in order to evaluate the performance of different error models. We find that while a Poisson error model appears appropriate for sparse datasets, we observe clear evidence of overdispersion for genes with sufficient sequencing depth in all biological systems, necessitating the use of a negative binomial model. Moreover, we find that the degree of overdispersion varies widely across datasets, systems, and gene abundances, and argues for a data-driven approach for parameter estimation.

Outline

1. Motivation: settings where sample splitting doesn't work
2. Poisson thinning
- 3. Data thinning**
4. Application to single-cell RNA sequencing data
5. Ongoing work

What did we like about Poisson thinning?

We split a single observation X into $X^{(1)}$ and $X^{(2)}$ such that:

- (1)** $X^{(1)}$ and $X^{(2)}$ have the same distribution as X , up to a parameter scaling.
- (2)** $X^{(1)} \perp\!\!\!\perp X^{(2)}$.

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Can we achieve these same properties when X is not Poisson?

Data thinning

Goal: split a single observation X into $X^{(1)}$ and $X^{(2)}$ such that:

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J. Appl. Prob. 33, 664–677 (1996)

Printed in Israel

© Applied Probability Trust 1996

**TIME SERIES MODELS WITH UNIVARIATE MARGINS
IN THE CONVOLUTION-CLOSED INFINITELY DIVISIBLE CLASS**

HARRY JOE,* *University of British Columbia*

Convolution-closed distributions

A family of distributions F_λ is "convolution-closed" in parameter λ if

- $X' \sim F_{\lambda_1}$
- $X'' \sim F_{\lambda_2}$
- $X' \perp\!\!\!\perp X''$

together imply that

$$X' + X'' \sim F_{\lambda_1 + \lambda_2}.$$

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together imply that $X' + X'' \sim F_{\lambda_1 + \lambda_2}$.

Distribution	Convolution-closed in:
$X \sim \text{Poisson}(\lambda)$	λ
$X \sim \text{N}(\mu, \sigma^2)$	(μ, σ^2)
$X \sim \text{NegativeBinomial}(\mu, b)$	(μ, b)
$X \sim \text{Gamma}(\alpha, \beta)$	α , if β is fixed
$X \sim \text{Binomial}(r, p)$	r , if p is fixed
$X \sim \text{N}_k(\mu, \Sigma)$.	(μ, Σ) .
$X \sim \text{Multinomial}_k(r, p)$	r , if p is fixed
$X \sim \text{Wishart}_p(n, \Sigma)$	n , if p and Σ are fixed.

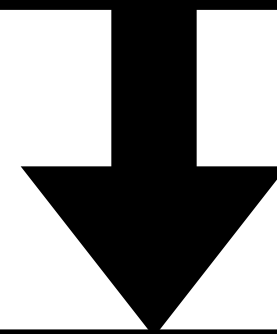
Data thinning for convolution-closed distributions

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We observe realization x from $X \sim F_\lambda$.

Data thinning for convolution-closed distributions

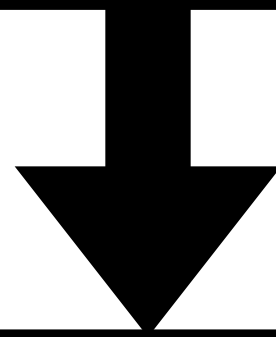
We know x could have arisen as $x' + x''$, where
 $X' \sim F_{\epsilon\lambda}$, $X'' \sim F_{(1-\epsilon)\lambda}$, $X' \perp\!\!\!\perp X''$.



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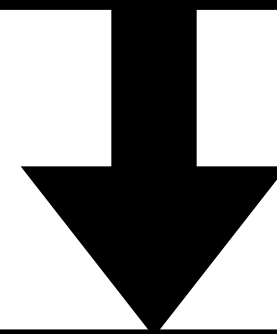


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If we had observed x' and x'' , we would have satisfied our goal of data thinning!

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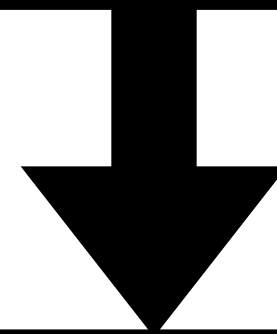
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Can we work backwards to recover x' and x'' ?

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Draw $X^{(1)}$ from $G_{\epsilon,x}$. Let $X^{(2)} := X - X^{(1)}$.

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Theorem:

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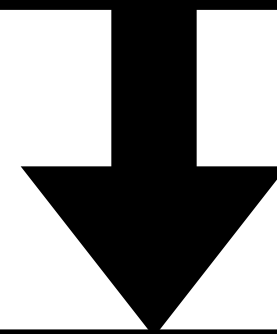
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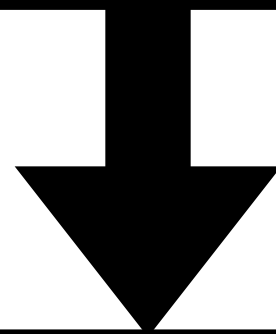
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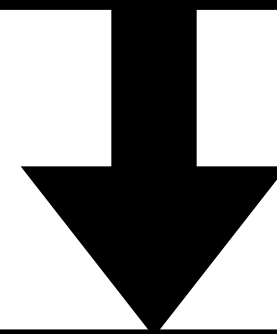


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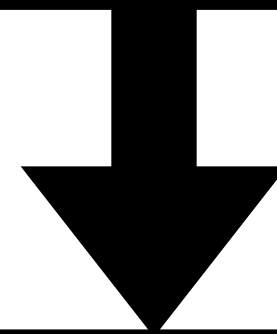
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Draw $X^{(1)}$ from $\text{Binomial}(x, \epsilon)$. Let $X^{(2)} := X - X^{(1)}$.

Theorem:

$X^{(1)} \sim \text{Pois}(\epsilon\lambda)$, $X^{(2)} \sim \text{Pois}((1 - \epsilon)\lambda)$, $X^{(1)} \perp\!\!\!\perp X^{(2)}$.

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Can we work backwards to recover x' and x'' ?

The conditional distribution of $X' \mid X = x$ is $\text{Binomial}(x, \epsilon)$.

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We have recovered Poisson thinning!

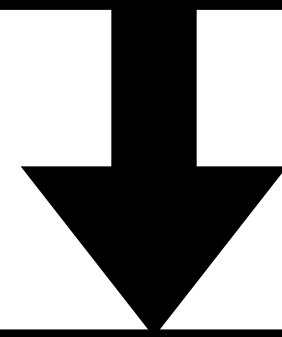
Data thinning for the Gaussian distribution

Data thinning for the Gaussian distribution

We observe realization x from $X \sim N(\mu, \sigma^2)$.

Data thinning for the Gaussian distribution

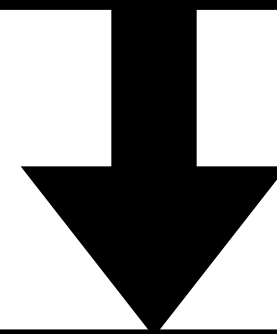
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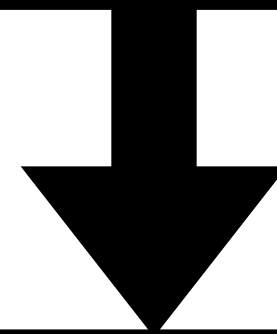


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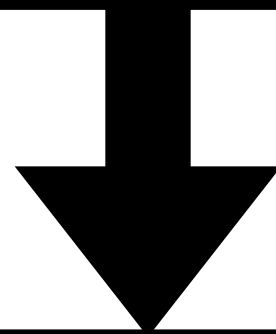
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This is (similar to) a well-known result!

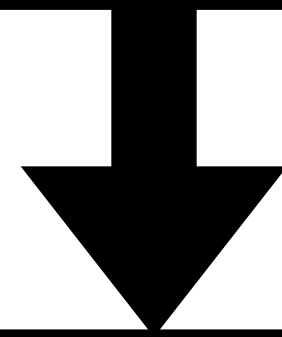
Data thinning recipe for the negative binomial distribution

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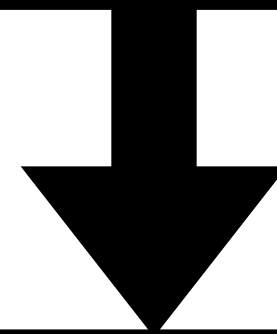
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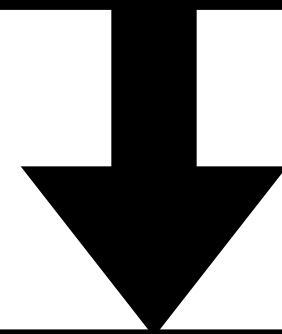


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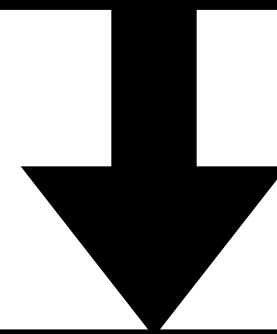
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This is a new result!

For many common distributions, the distribution $G_{\epsilon, x}$ has a simple form

Distribution of X :	Draw $X^{(1)} \mid X = x$ from $G_{\epsilon, x}$, where $G_{\epsilon, x}$ is:	Distribution of $X^{(1)}$:	Distribution of $X^{(2)}$, where $X^{(2)} = X - X^{(1)}$:
Poisson(λ)	Binomial(x, ϵ)	Poisson($\epsilon\lambda$)	Poisson($(1 - \epsilon)\lambda$)

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Related work on Poisson thinning:

- Sarkar and Stephens, 2021, Nature Genetics.
- Chen et al., 2021, arXiv:2108.03336
- Leiner et al., 2021, arXiv:2112.11079.
- Neufeld et al., 2022, Biostatistics.
- Oliveira, Lei, and Tibshirani, 2022, arXiv:2212.01943.

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Related work on Gaussian thinning:

- Tian and Taylor, 2018, Annals of Statistics.
- Tian, 2020, Annals of Statistics.
- Rasines and Young, 2022, Biometrika.
- Leiner et al., 2022, arXiv:2112.11079.
- Oliveira, Lei, and Tibshirani, 2022, arXiv:2111.09447.

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NegativeBinomial(μ, b)	BetaBinomial($x, \epsilon b, (1 - \epsilon)b$).	NegativeBinomial($\epsilon\mu, \epsilon b$)	NegativeBinomial($(1 - \epsilon)\mu, (1 - \epsilon)b$)

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Binomial(r, p)	Hypergeometric($\epsilon r, (1 - \epsilon)r, x$).	Binomial($\epsilon r, p$)	Binomial($(1 - \epsilon)r, p$)
Gamma(α, β)	$x \cdot \text{Beta}(\epsilon\alpha, (1 - \epsilon)\alpha)$.	Gamma($\epsilon\alpha, \beta$)	Gamma($(1 - \epsilon)\alpha, \beta$)
Exponential(λ)	$x \cdot \text{Beta}(\epsilon, (1 - \epsilon))$.	Gamma(ϵ, λ)	Gamma($1 - \epsilon, \lambda$)
$N_k(\mu, \Sigma)$	$N(\epsilon x, \epsilon(1 - \epsilon)\Sigma)$.	$N_k(\epsilon\mu, \epsilon\Sigma)$	$N_k((1 - \epsilon)\mu, (1 - \epsilon)\Sigma)$
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What if we get a nuisance parameter wrong?

Negative binomial thinning algorithm

Suppose $X \sim \text{NegBin}(\mu, b)$.

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$X^{(1)} \sim \text{BetaBinomial}(x, \epsilon b, (1 - \epsilon)b)$,

$X^{(2)} = X - X^{(1)}$, then:

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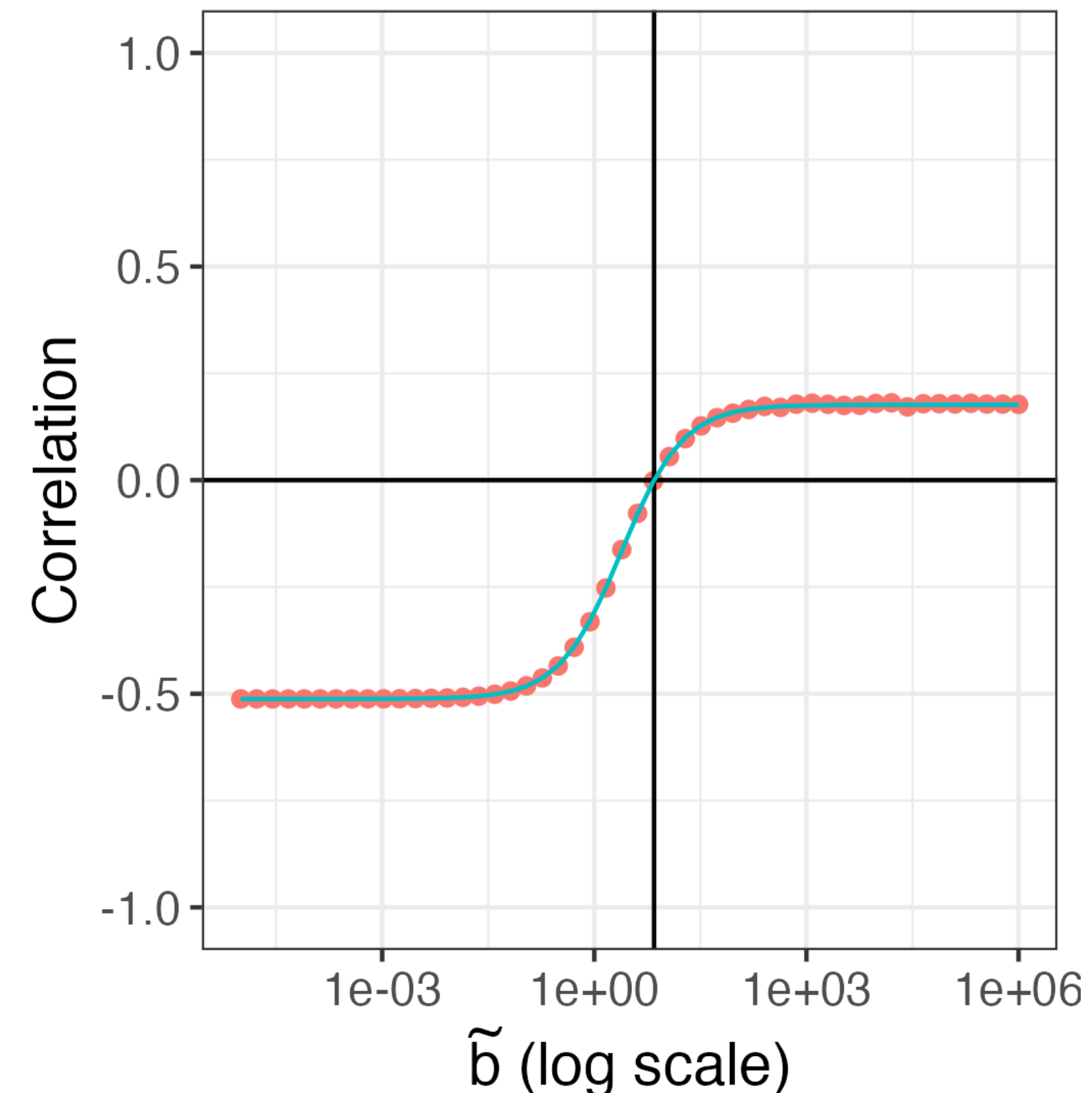
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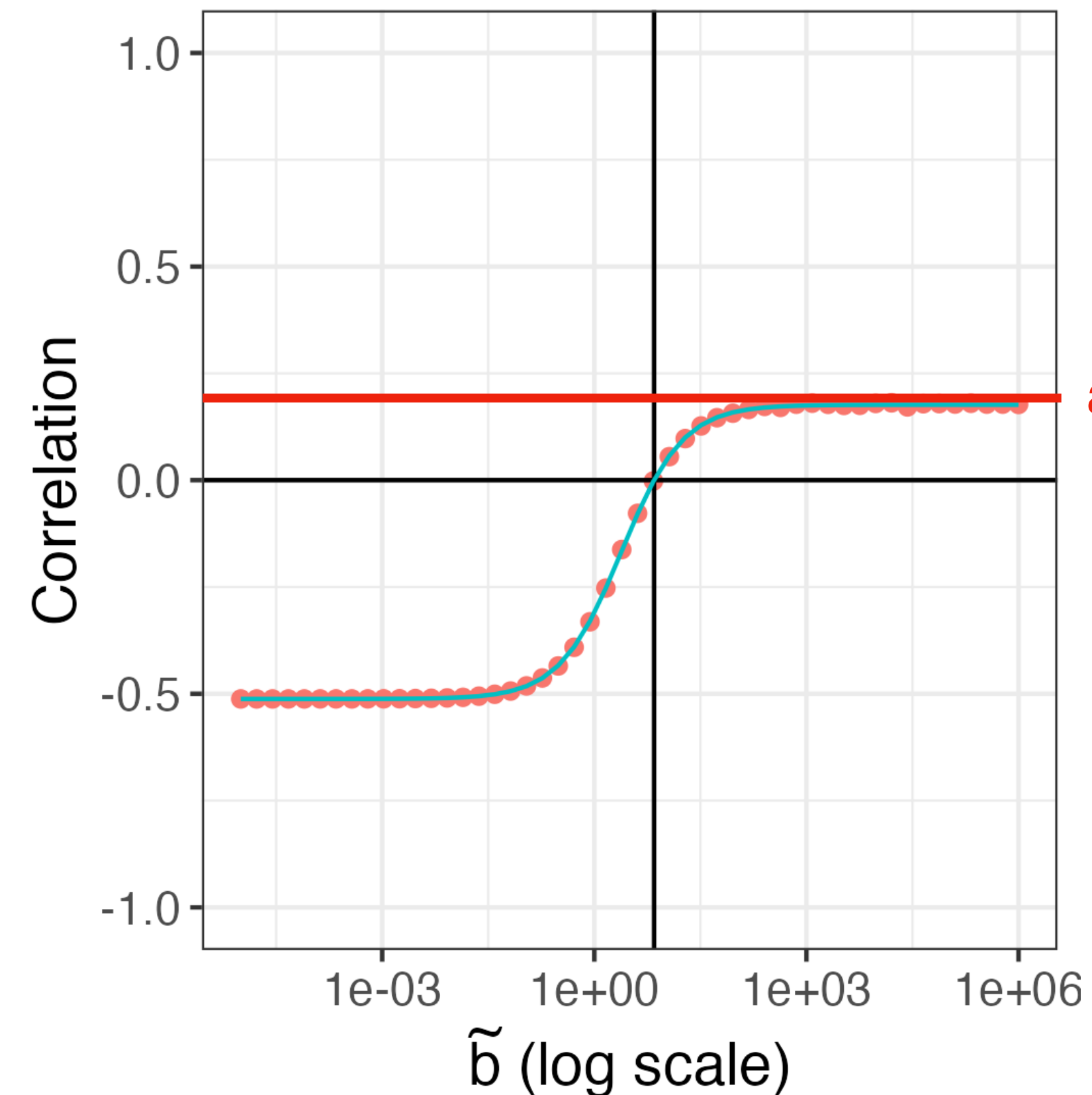
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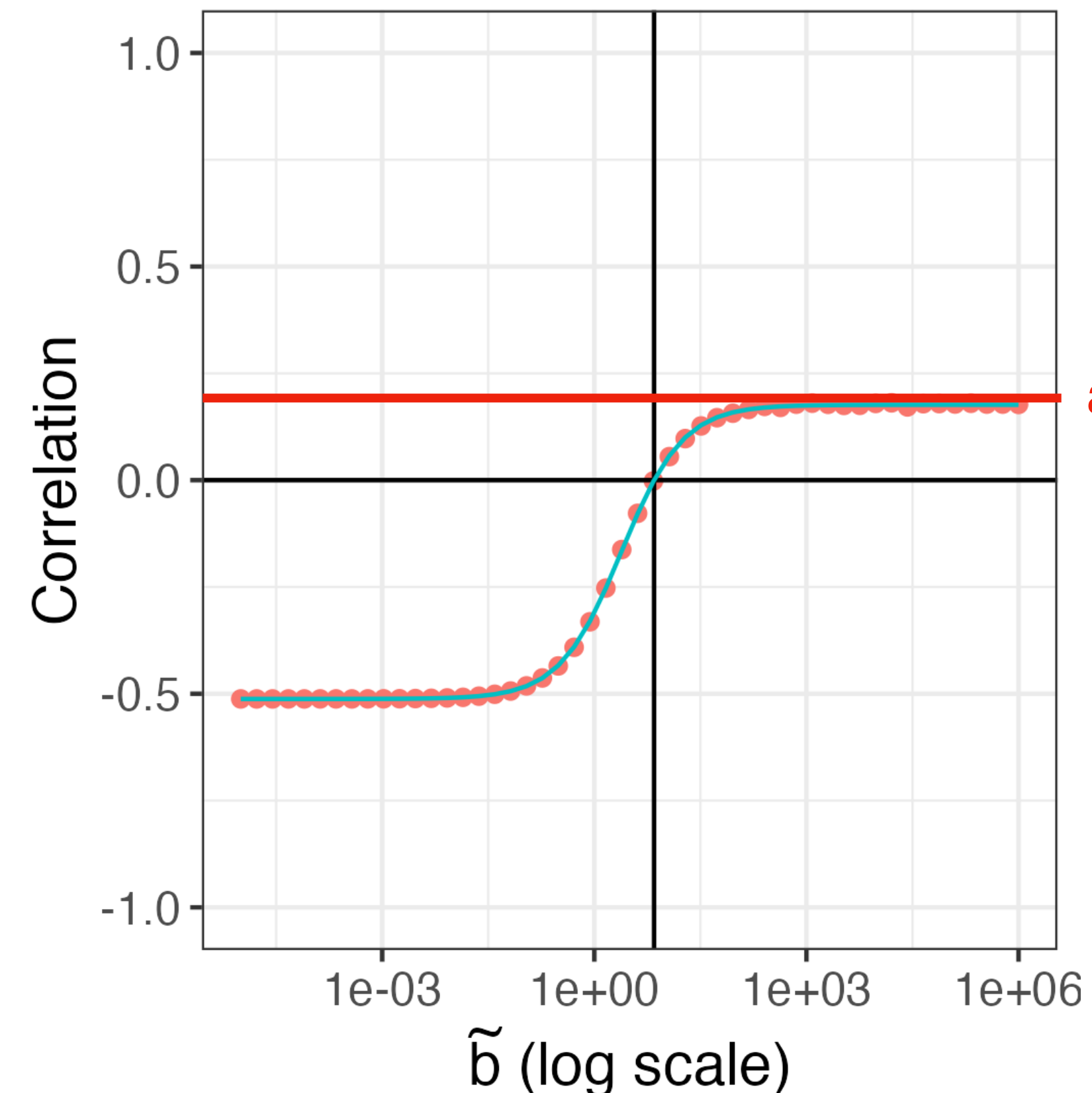
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Similar results can be derived for other decompositions.

The parameter ϵ governs an information tradeoff

Gaussian thinning algorithm

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Poisson(λ)	Multinomial($x, \epsilon_1, \dots, \epsilon_M$)	Poisson($\epsilon_m \lambda$)
$N(\mu, \sigma^2)$	$N_M(\epsilon \mu, \sigma^2 \text{diag}(\epsilon) - \sigma^2 \epsilon \epsilon^T)$.	$N(\epsilon_m \mu, \epsilon_m \sigma^2)$

Our recipe extends naturally to splitting into $M > 2$ folds

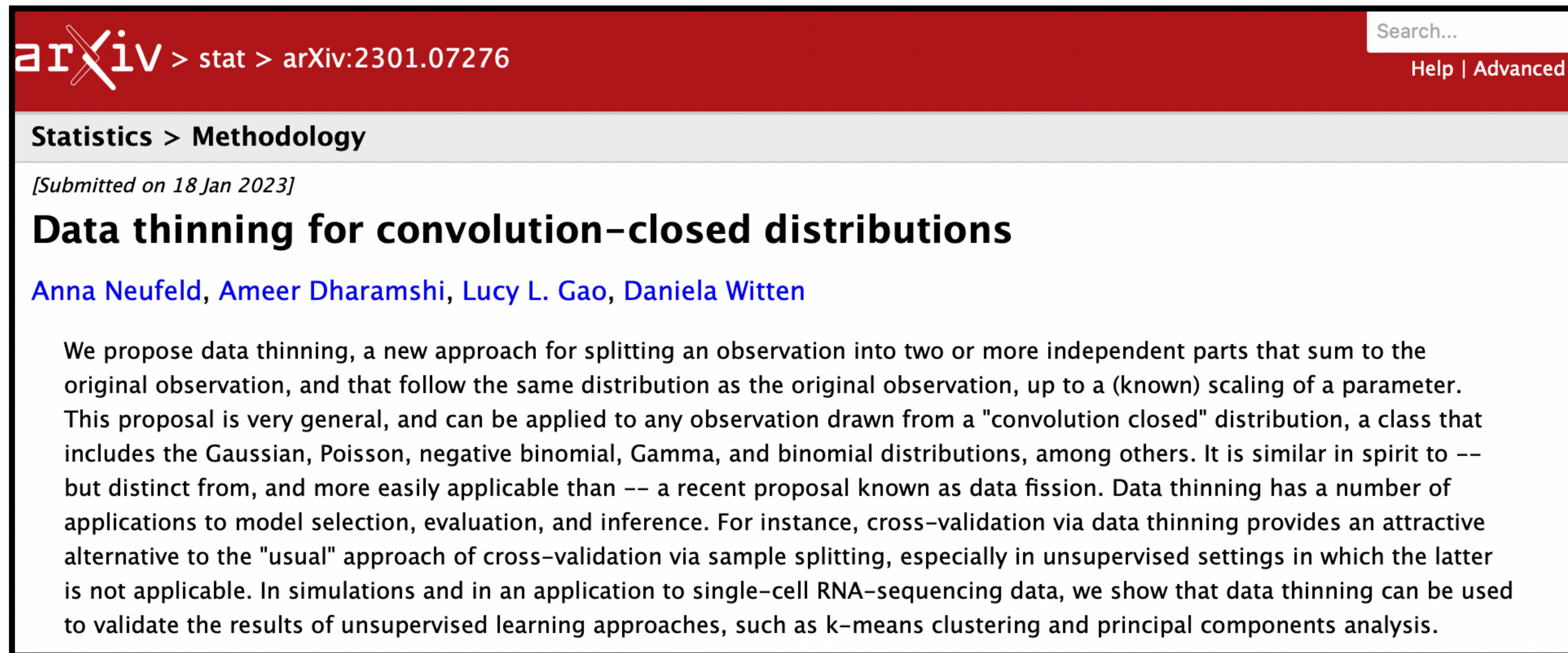
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NegativeBinomial(μ, b)	DirichletMultinomial($x, \epsilon_1 b, \dots, \epsilon_M b$).	NegativeBinomial($\epsilon_m \mu, \epsilon_m b$)

Our recipe extends naturally to splitting into $M > 2$ folds

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NegativeBinomial(μ, b)	DirichletMultinomial($x, \epsilon_1 b, \dots, \epsilon_M b$).	NegativeBinomial($\epsilon_m \mu, \epsilon_m b$)
Gamma(α, β)	$x \cdot \text{Dirichlet}(\epsilon_1 \alpha, \dots, \epsilon_M \alpha)$	Gamma($\epsilon_m \alpha, \beta$)
Exponential(λ)	$x \cdot \text{Dirichlet}(\epsilon_1, \dots, \epsilon_M)$	Gamma(ϵ_m, λ)
Binomial(r, p)	MultivariateHypergeometric($\epsilon_1 r, \dots, \epsilon_M r, x$).	Binomial($\epsilon_m r, p$)

Data thinning is a simple alternative to sample splitting that can be used in a variety of settings

Project 3



The screenshot shows the arXiv website interface. At the top left is the arXiv logo, followed by the breadcrumb 'stat > arXiv:2301.07276'. On the top right, there is a search bar and links for 'Help' and 'Advanced'. Below the breadcrumb is a category bar for 'Statistics > Methodology'. The main content area shows the submission date '[Submitted on 18 Jan 2023]', the title 'Data thinning for convolution-closed distributions', and the authors 'Anna Neufeld, Ameer Dharamshi, Lucy L. Gao, Daniela Witten'. The abstract text follows, describing the proposed data thinning method and its applications.

arXiv > stat > arXiv:2301.07276 Search... Help | Advanced

Statistics > Methodology

[Submitted on 18 Jan 2023]

Data thinning for convolution-closed distributions

Anna Neufeld, Ameer Dharamshi, Lucy L. Gao, Daniela Witten

We propose data thinning, a new approach for splitting an observation into two or more independent parts that sum to the original observation, and that follow the same distribution as the original observation, up to a (known) scaling of a parameter. This proposal is very general, and can be applied to any observation drawn from a "convolution closed" distribution, a class that includes the Gaussian, Poisson, negative binomial, Gamma, and binomial distributions, among others. It is similar in spirit to -- but distinct from, and more easily applicable than -- a recent proposal known as data fission. Data thinning has a number of applications to model selection, evaluation, and inference. For instance, cross-validation via data thinning provides an attractive alternative to the "usual" approach of cross-validation via sample splitting, especially in unsupervised settings in which the latter is not applicable. In simulations and in an application to single-cell RNA-sequencing data, we show that data thinning can be used to validate the results of unsupervised learning approaches, such as k-means clustering and principal components analysis.

R package and tutorials: <https://anna-neufeld.github.io/datathin/>

Outline

1. Motivation: settings where sample splitting doesn't work
2. Poisson thinning
3. Data thinning
- 4. Application to single-cell RNA sequencing data**
5. Ongoing work

How can we validate the results of clustering?

RESEARCH ARTICLE

HUMAN GENOMICS

A human cell atlas of fetal gene expression

Junyue Cao^{1*}, Diana R. O'Day², Hannah A. Pliner³, Paul D. Kingsley⁴, Mei Deng², Riza M. Daza¹, Michael A. Zager^{3,5}, Kimberly A. Aldinger^{2,6}, Ronnie Blecher-Gonen¹, Fan Zhang⁷, Malte Spielmann^{8,9}, James Palis⁴, Dan Doherty^{2,3,6}, Frank J. Steemers⁷, Ian A. Glass^{2,3,6}, Cole Trapnell^{1,3,10†}, Jay Shendure^{1,3,10,11†}

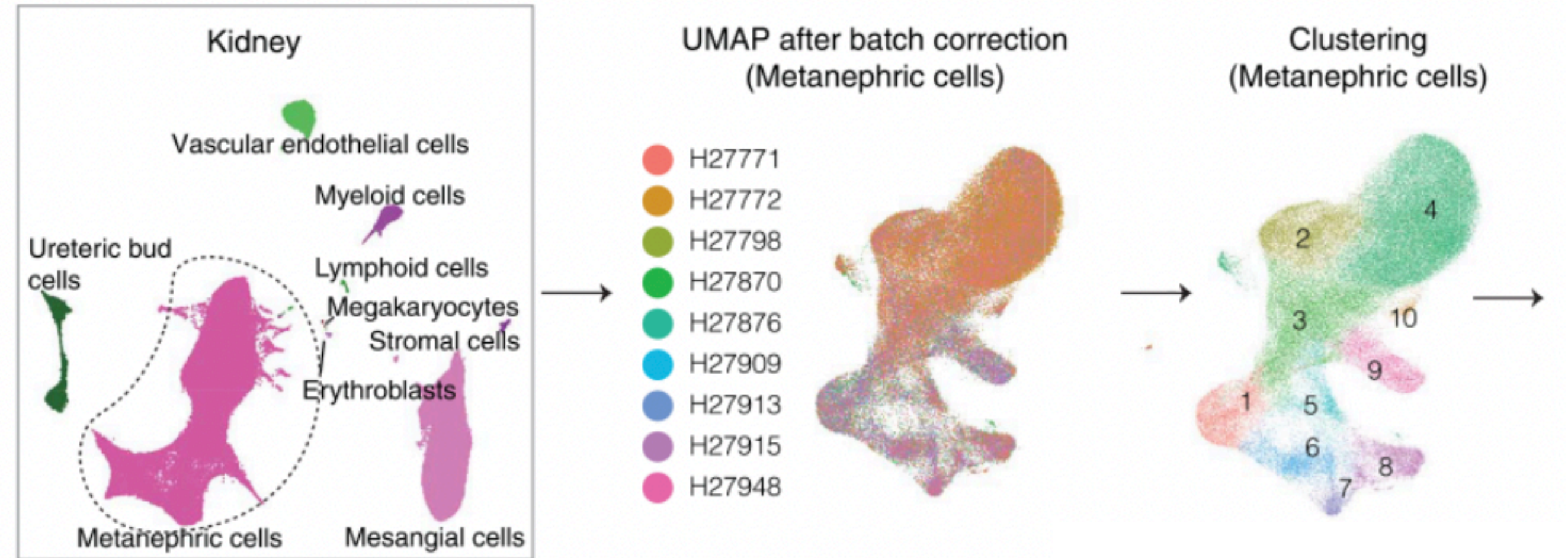
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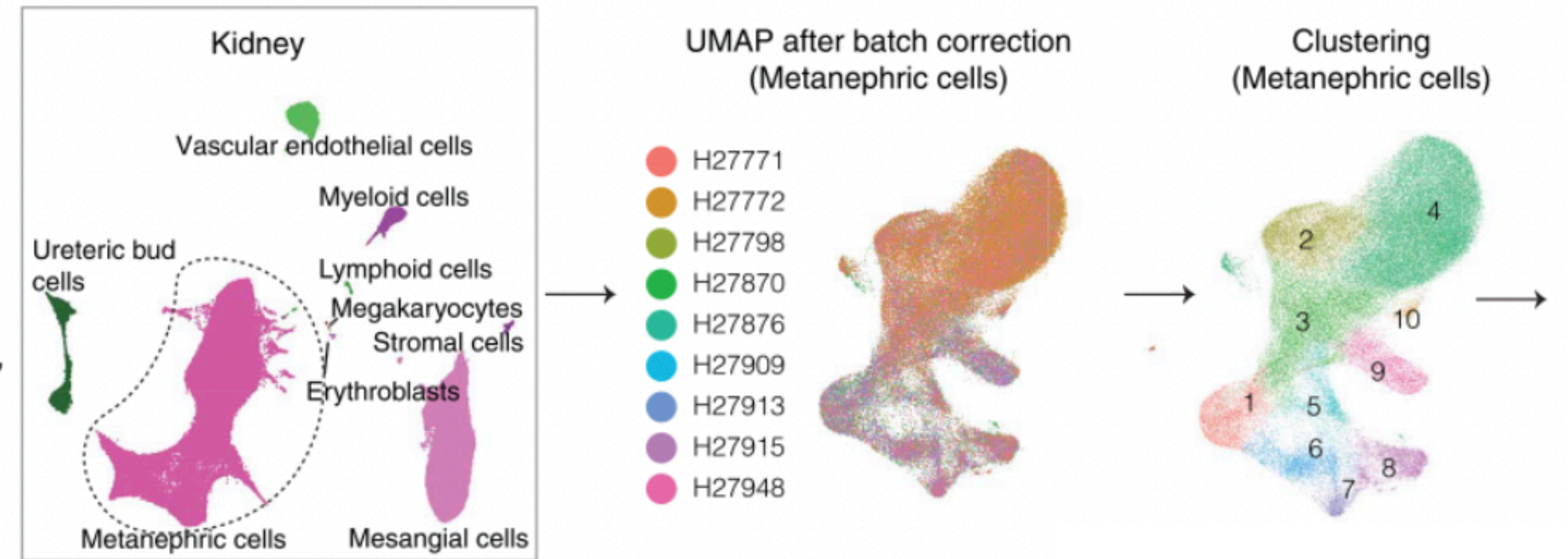
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●Step 1: Cluster cells.



How can we validate the results of clustering?

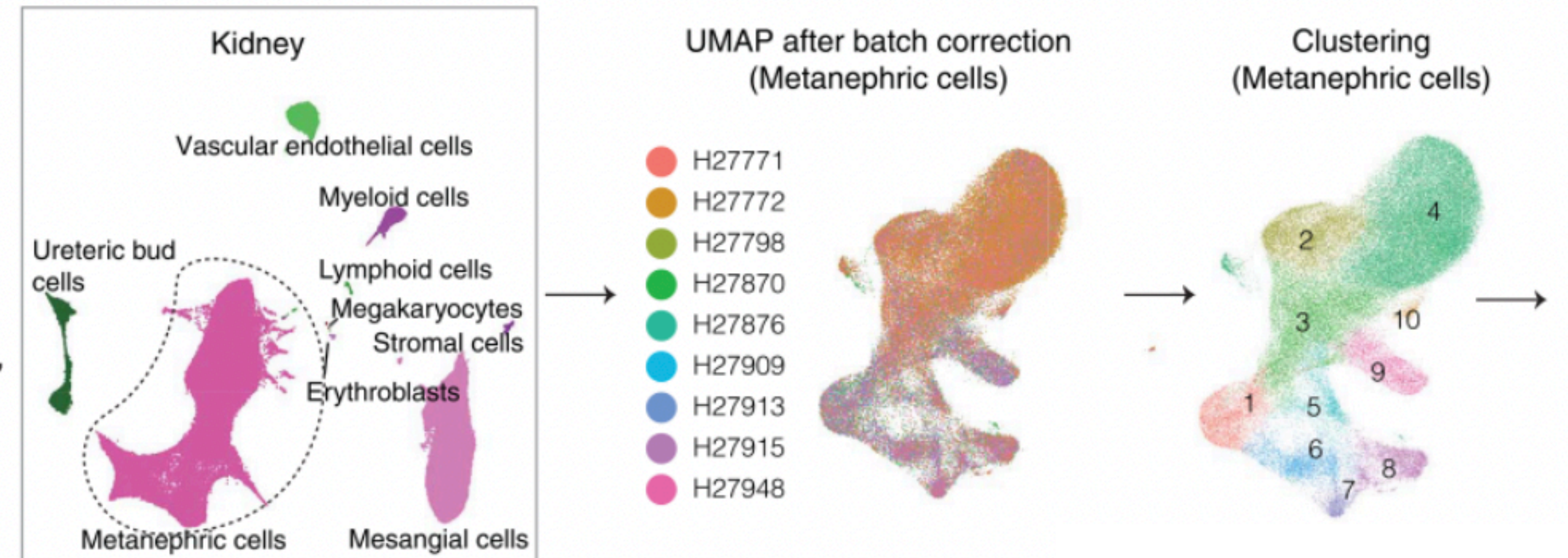
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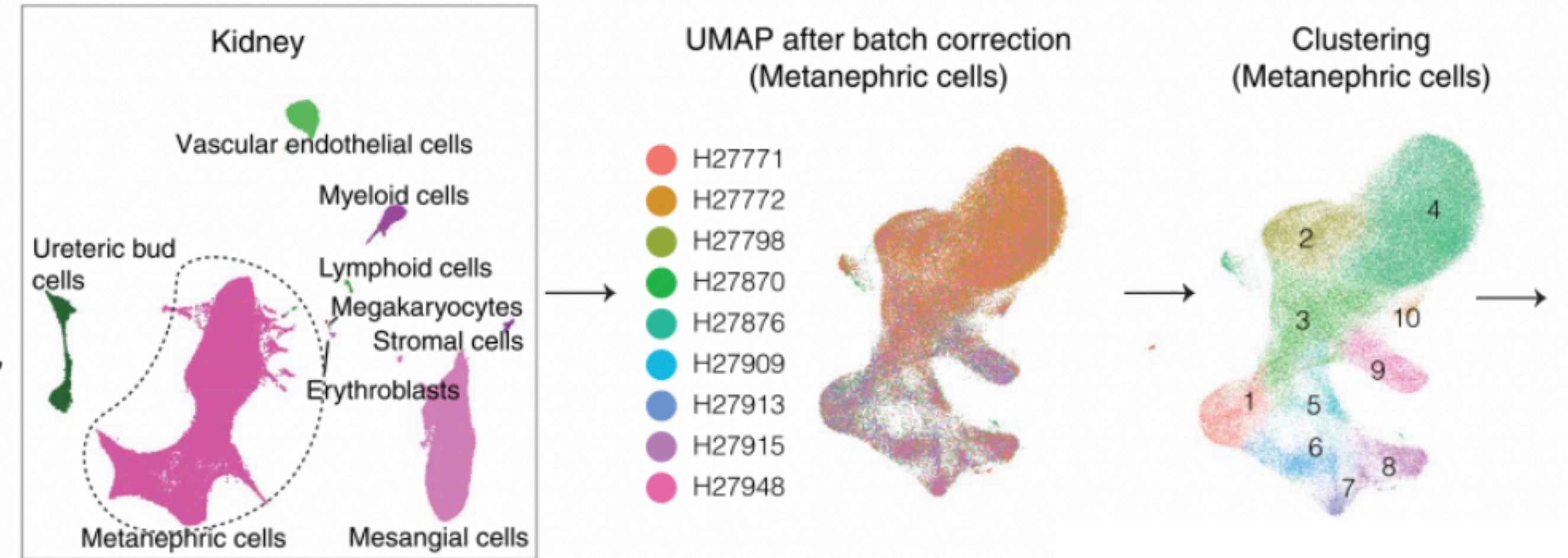
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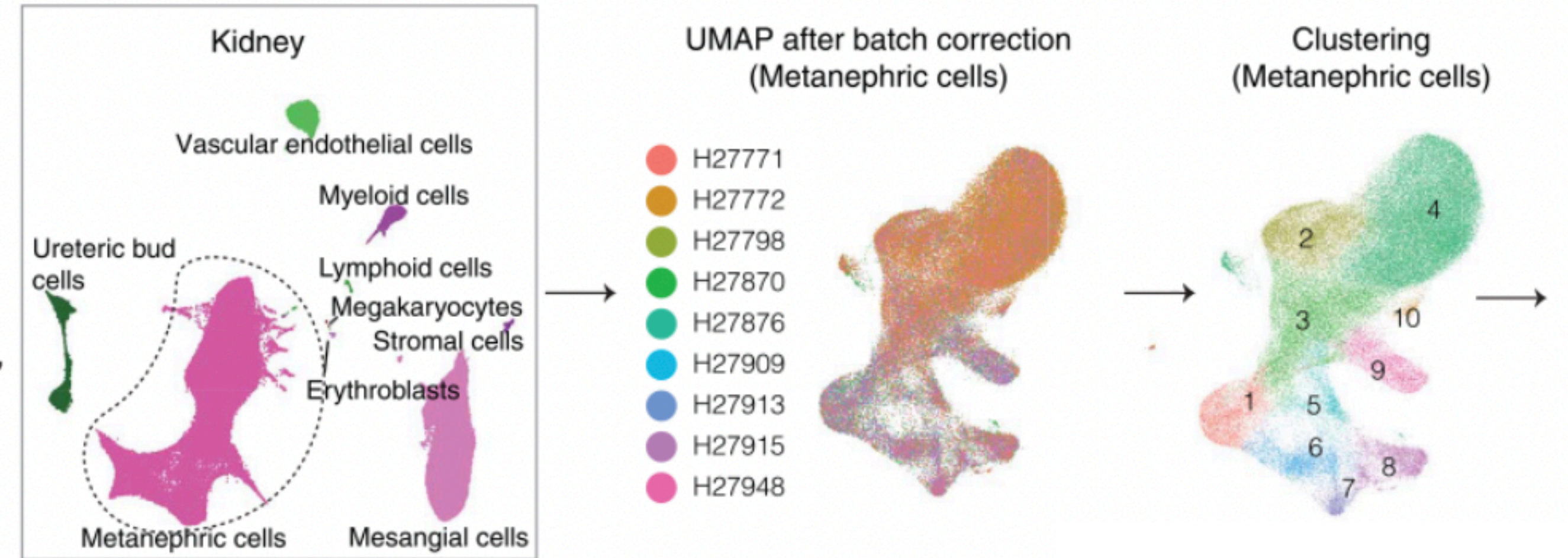
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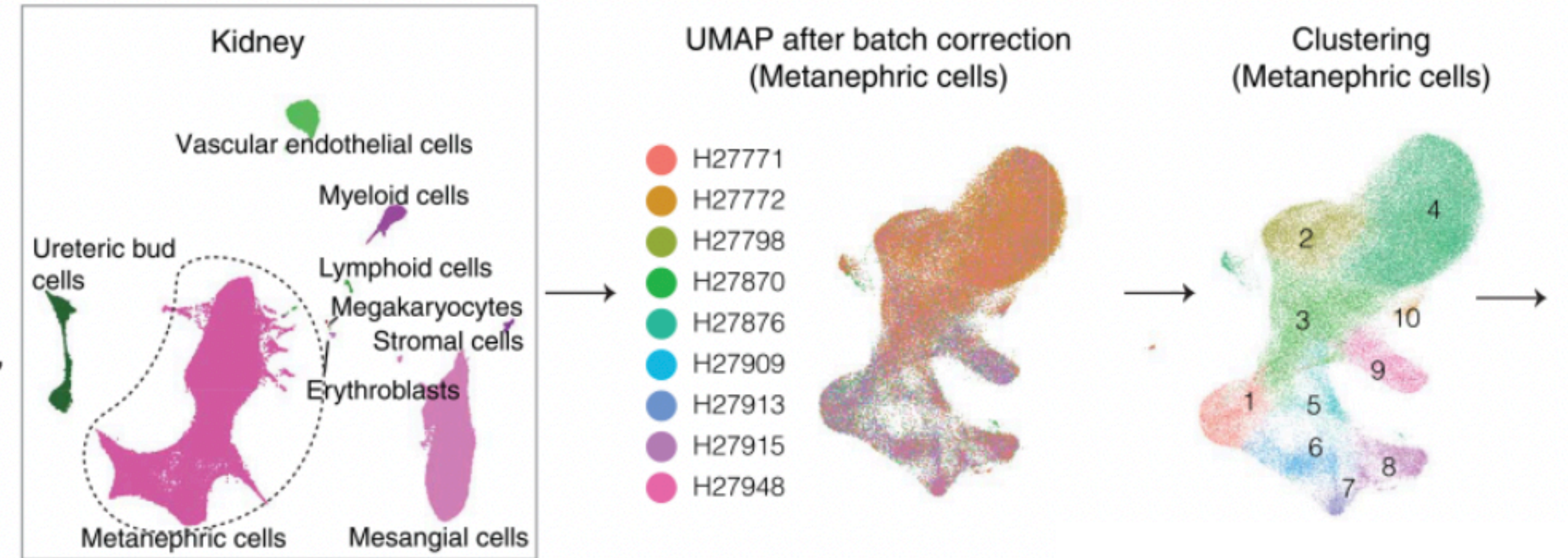
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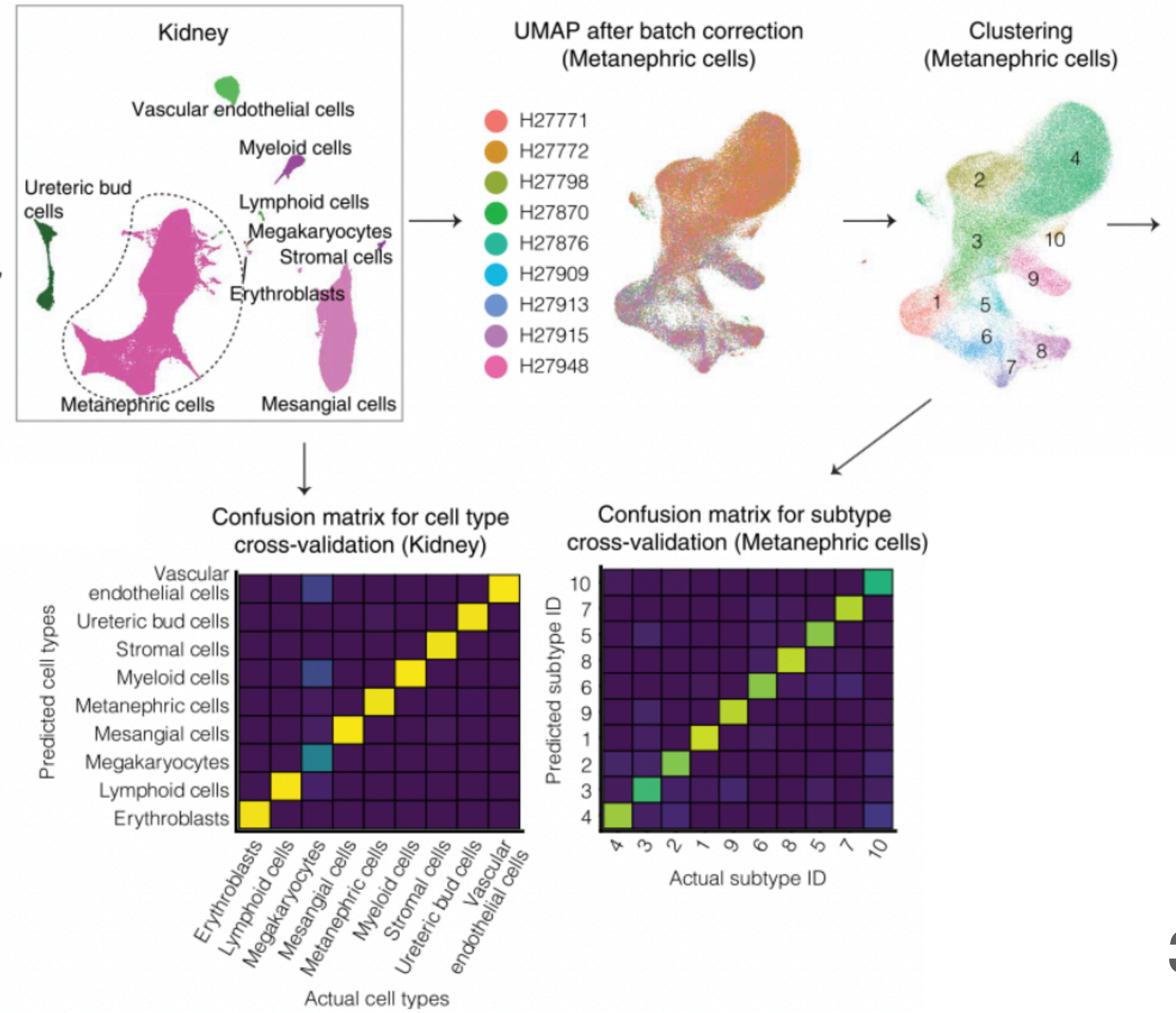
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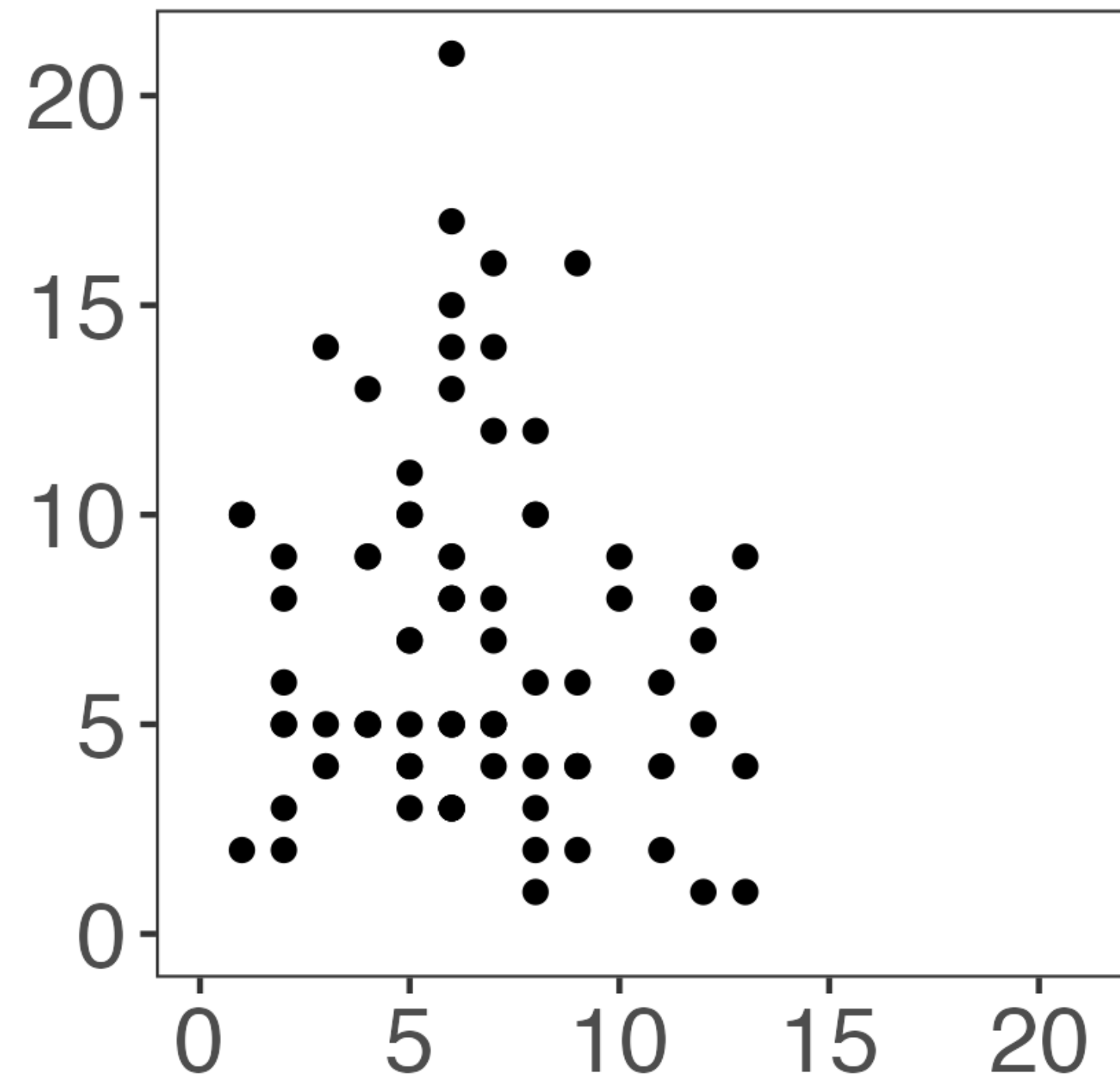
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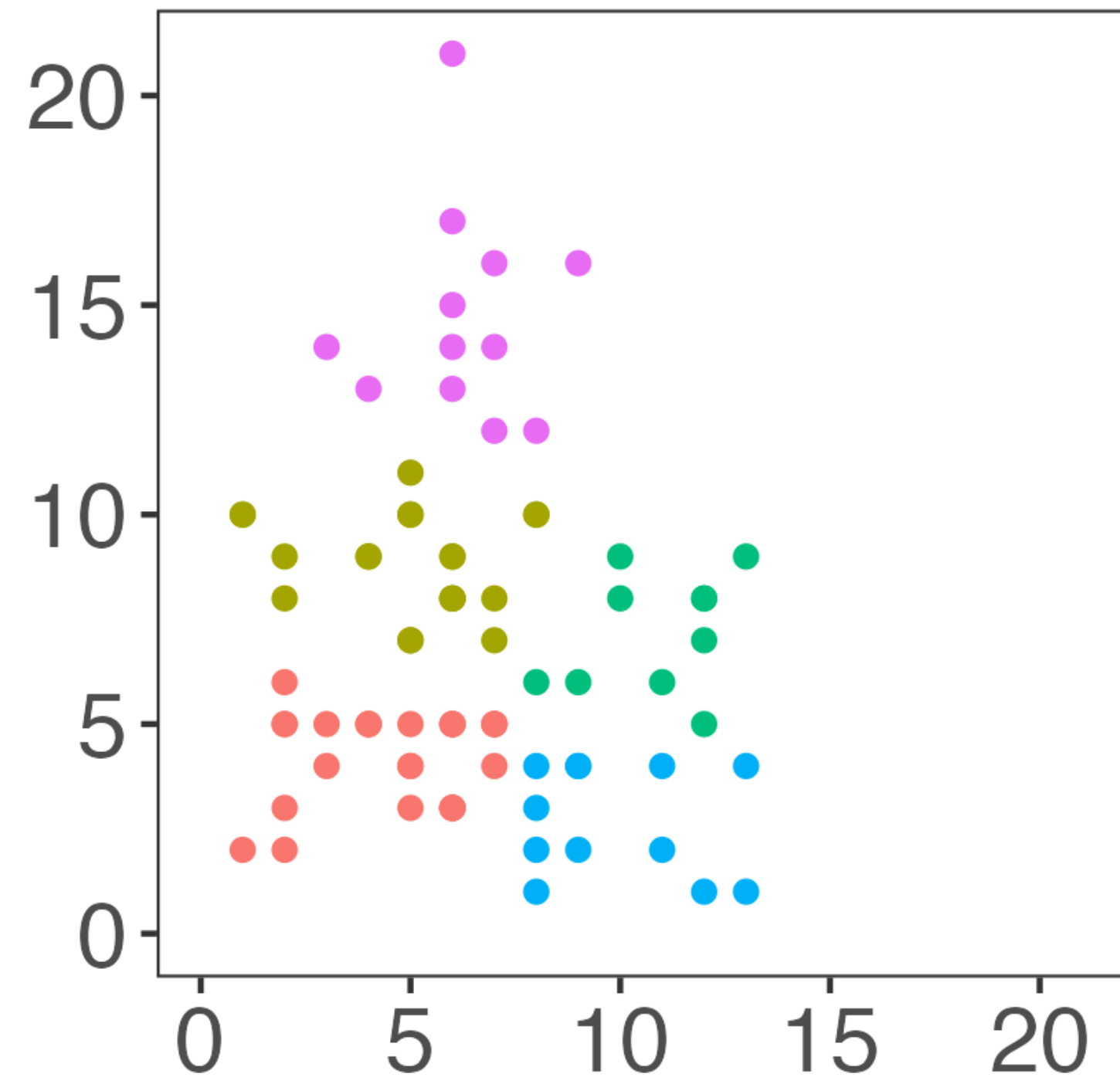
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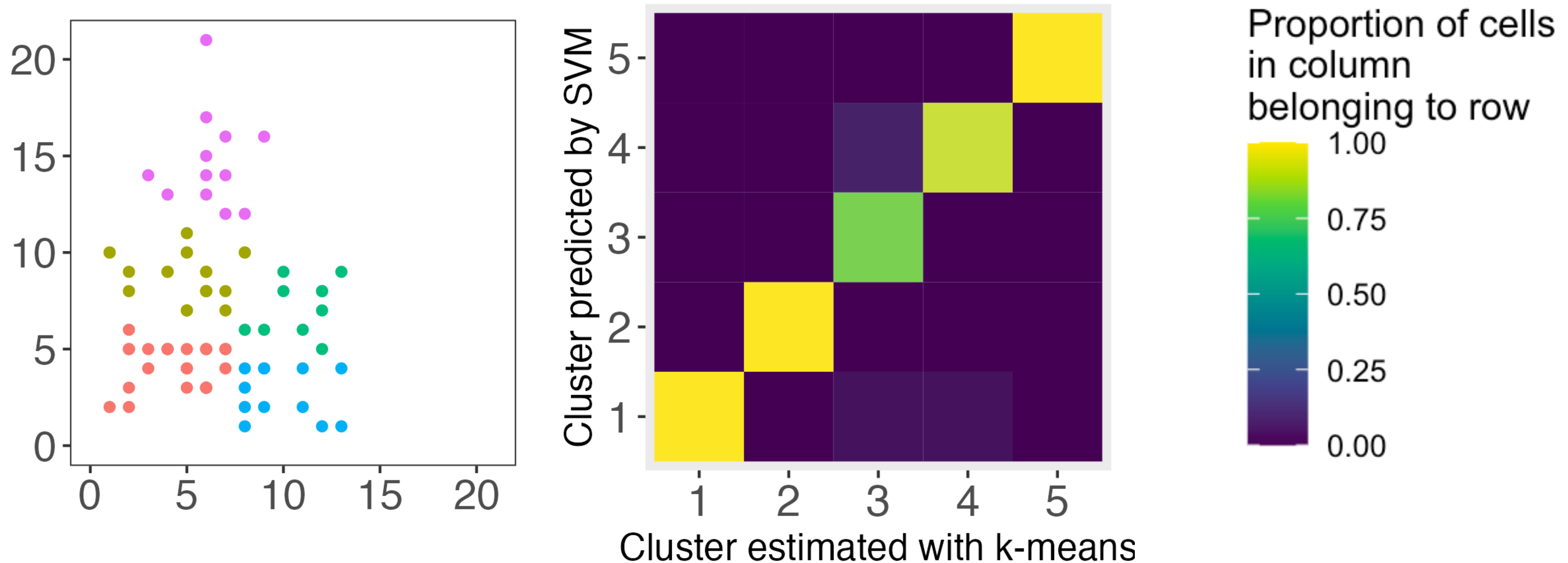
This cross validation procedure double dips



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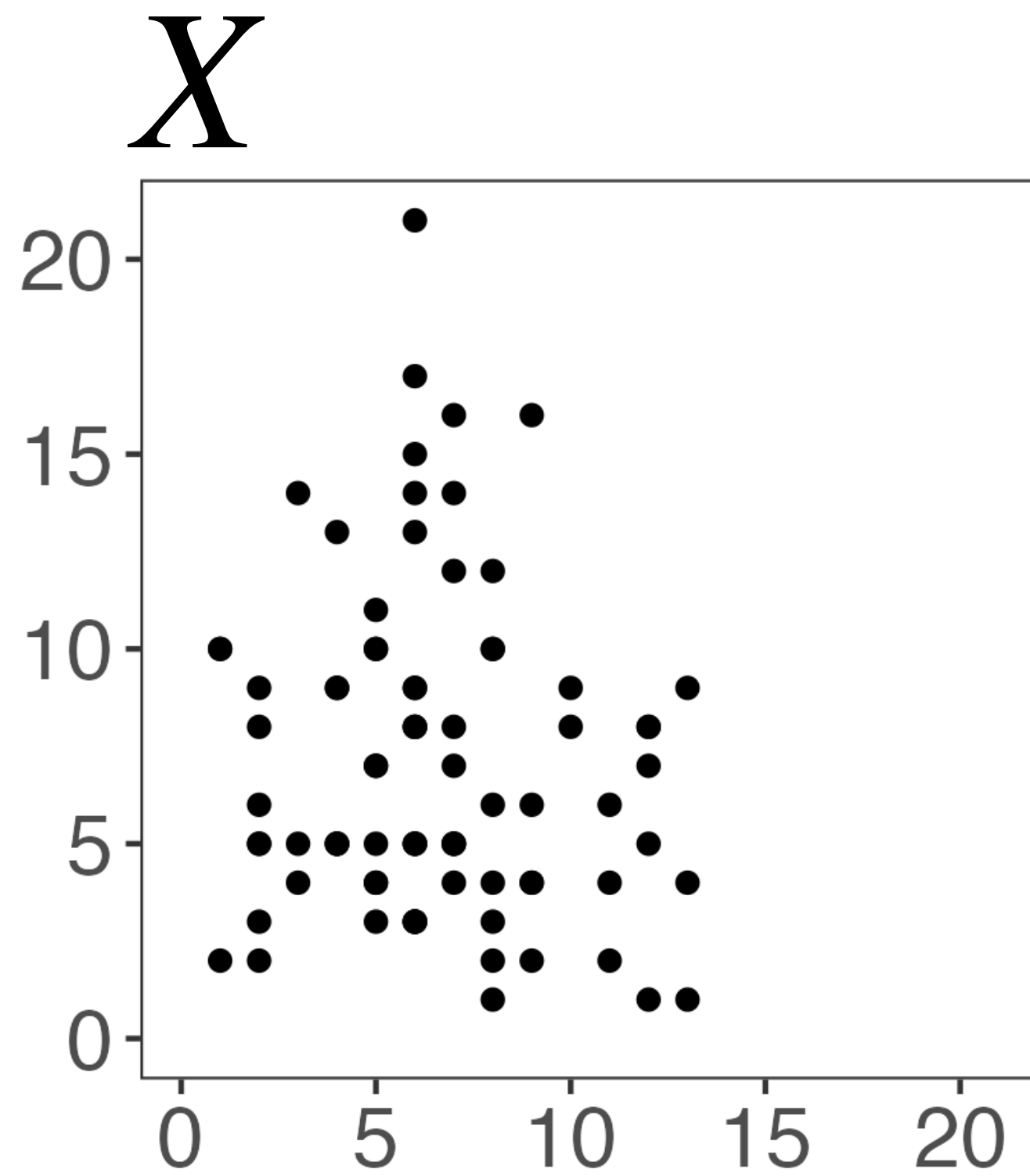


This cross validation procedure double dips



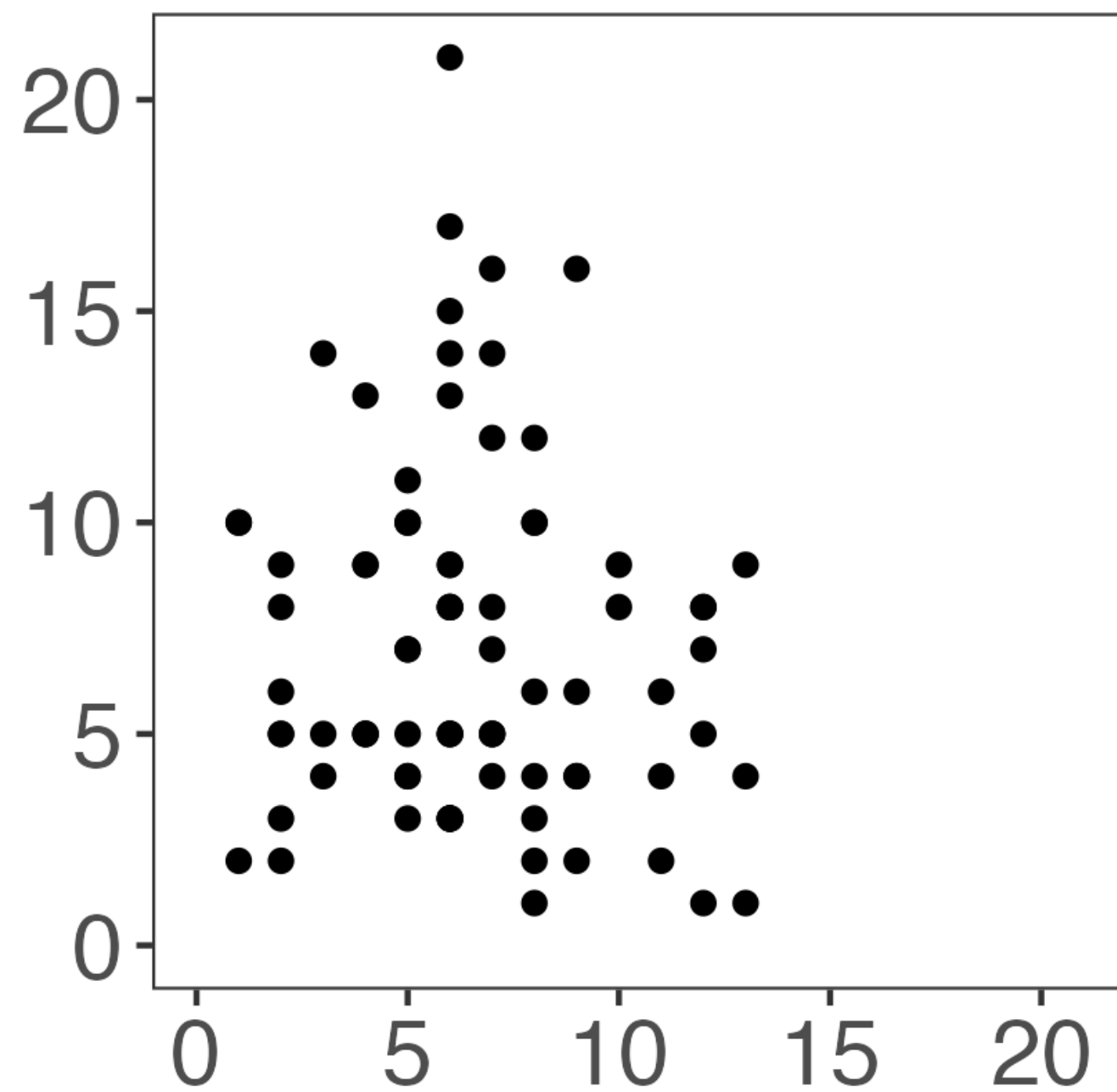
SVM gets 96% accuracy on test set, despite the fact that clusters are not "real".

Data thinning provides a simple alternative

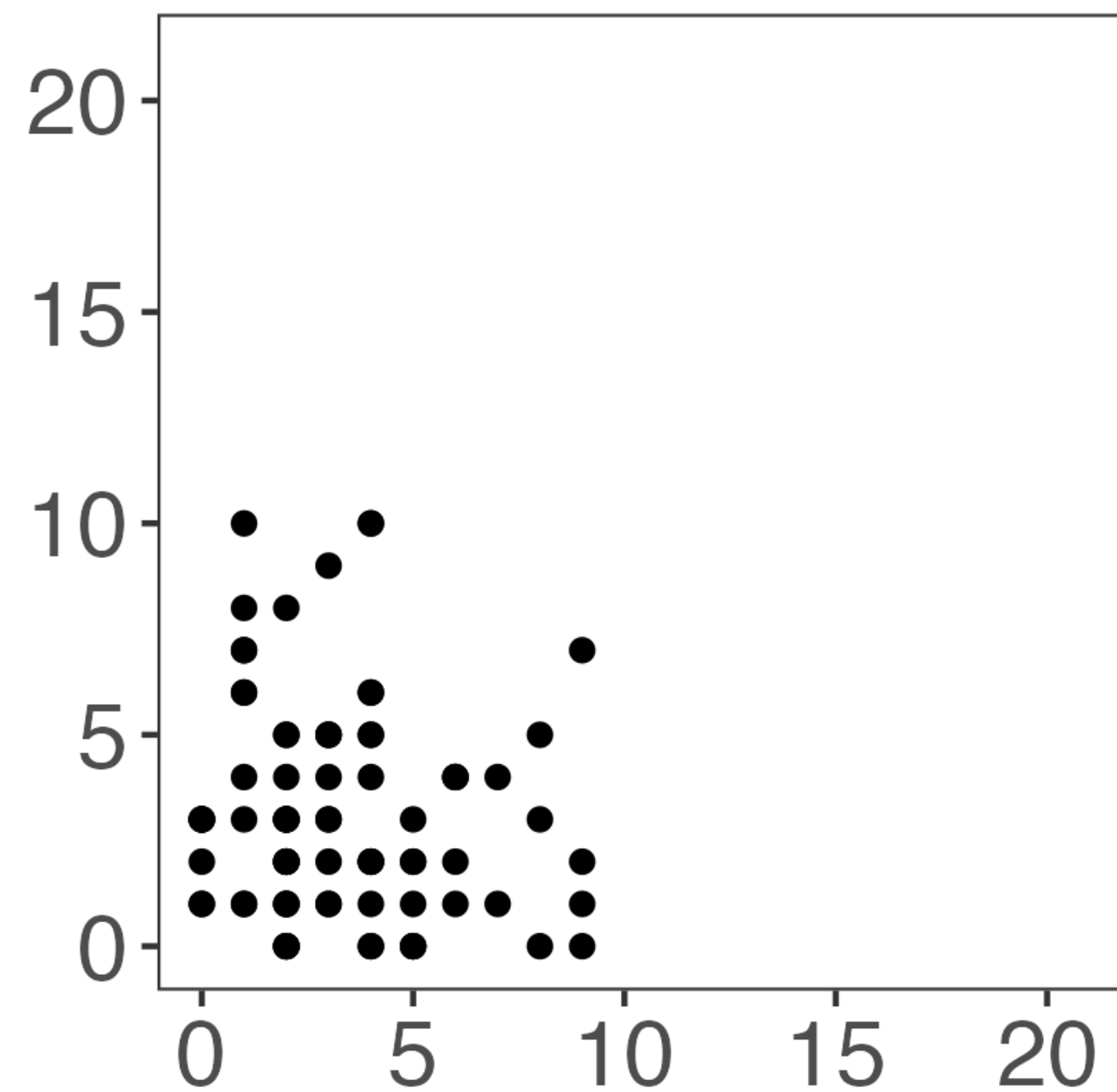


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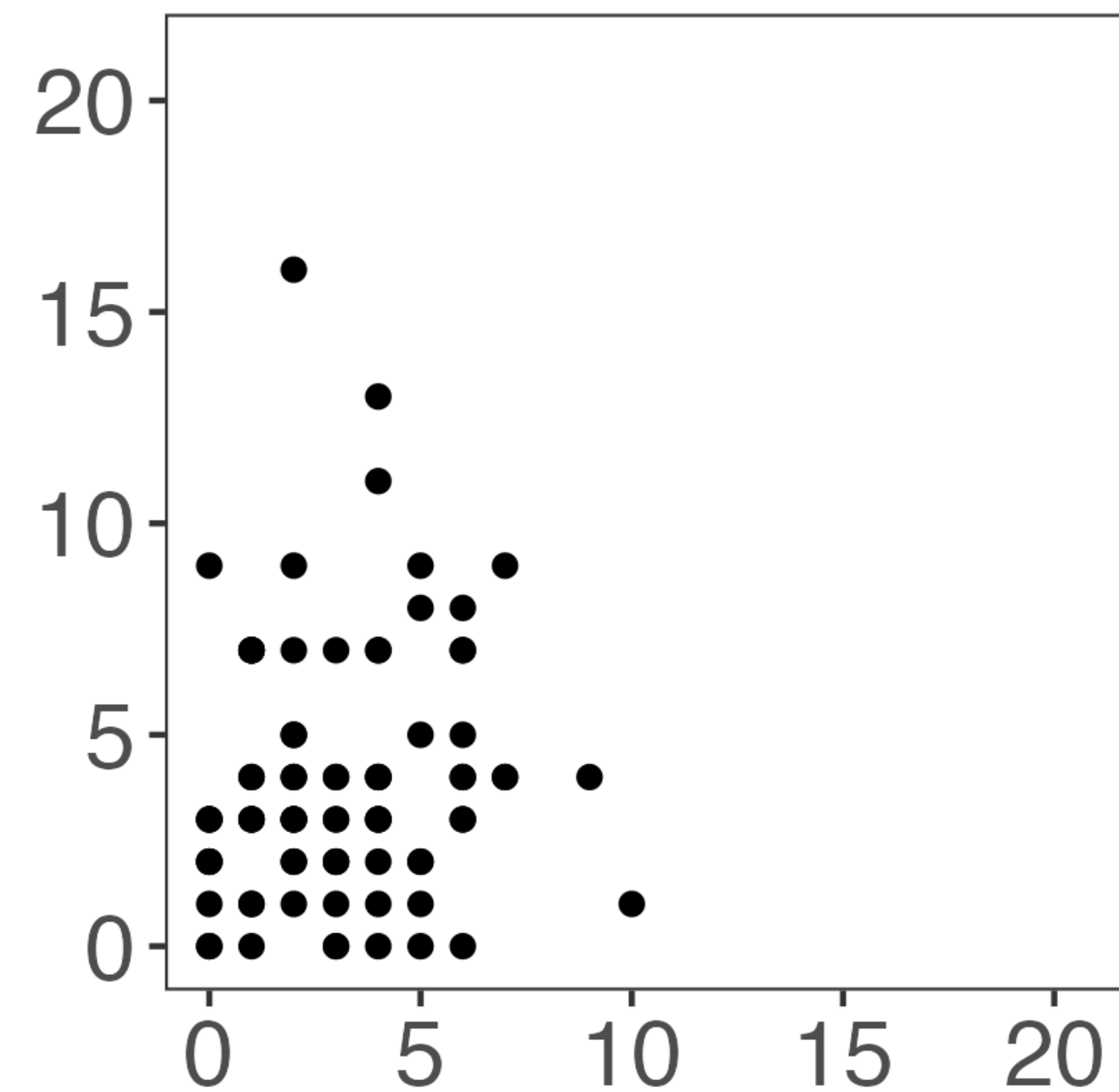
X



$X^{(1)}$

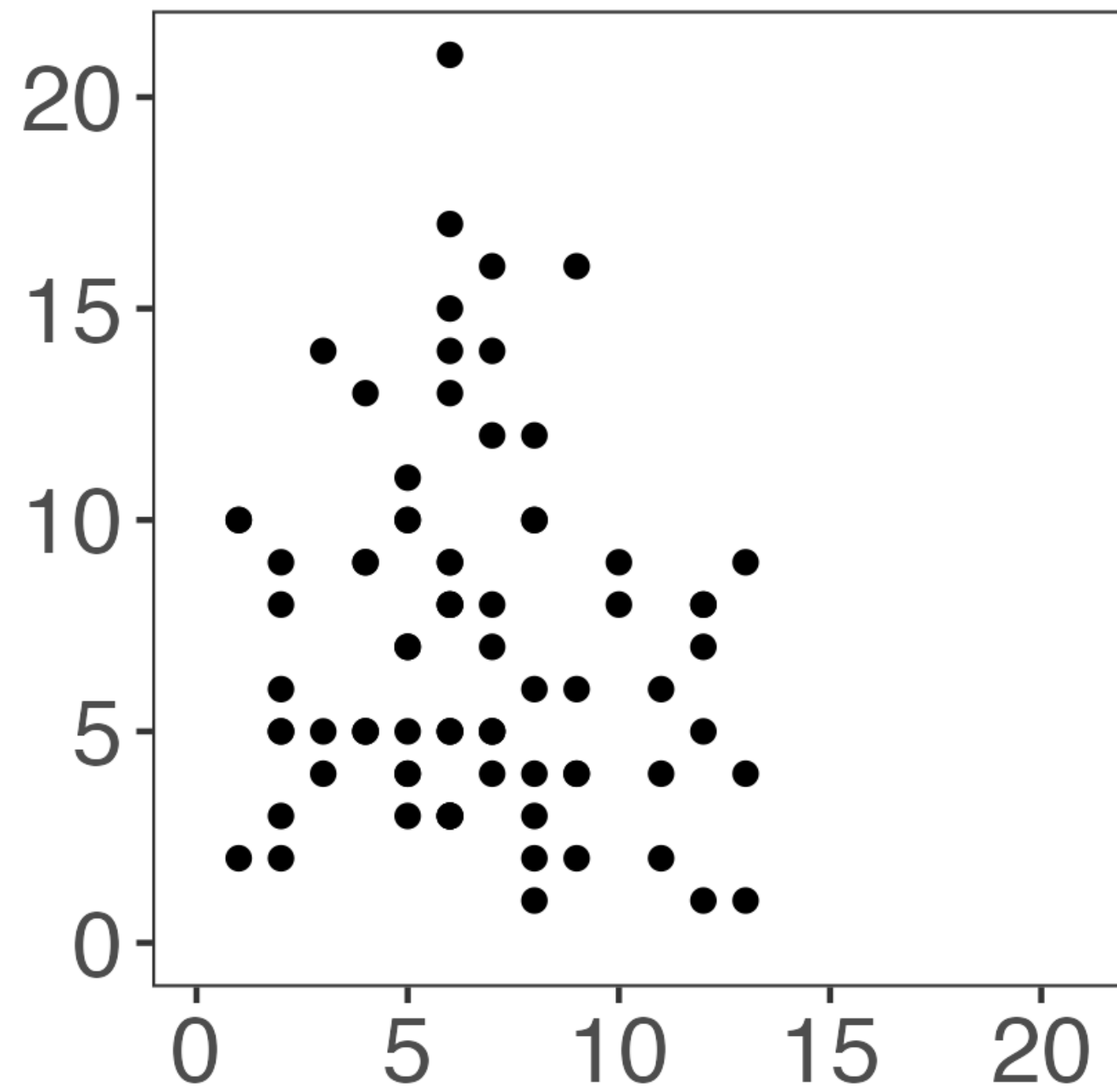


$X^{(2)}$

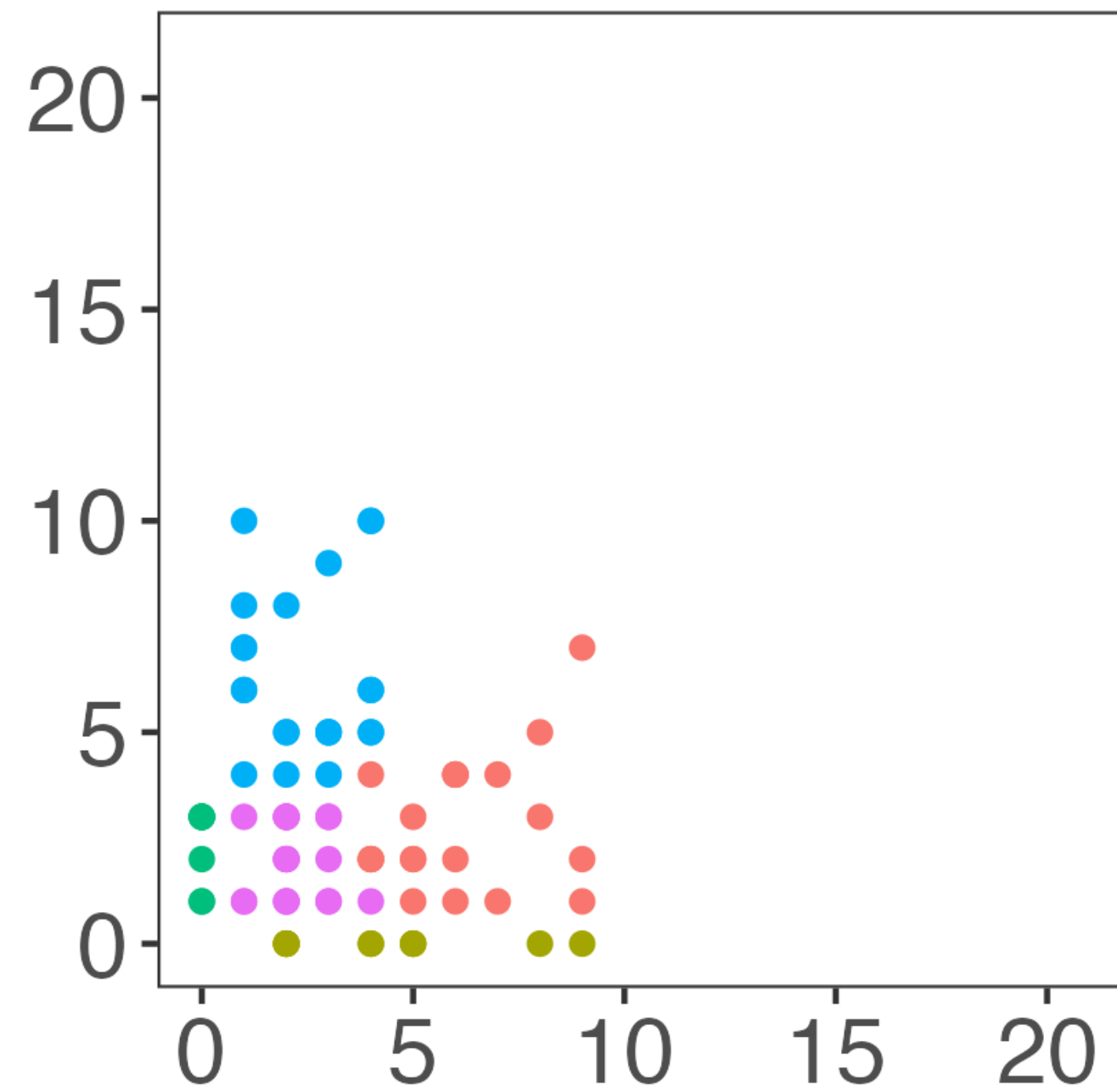


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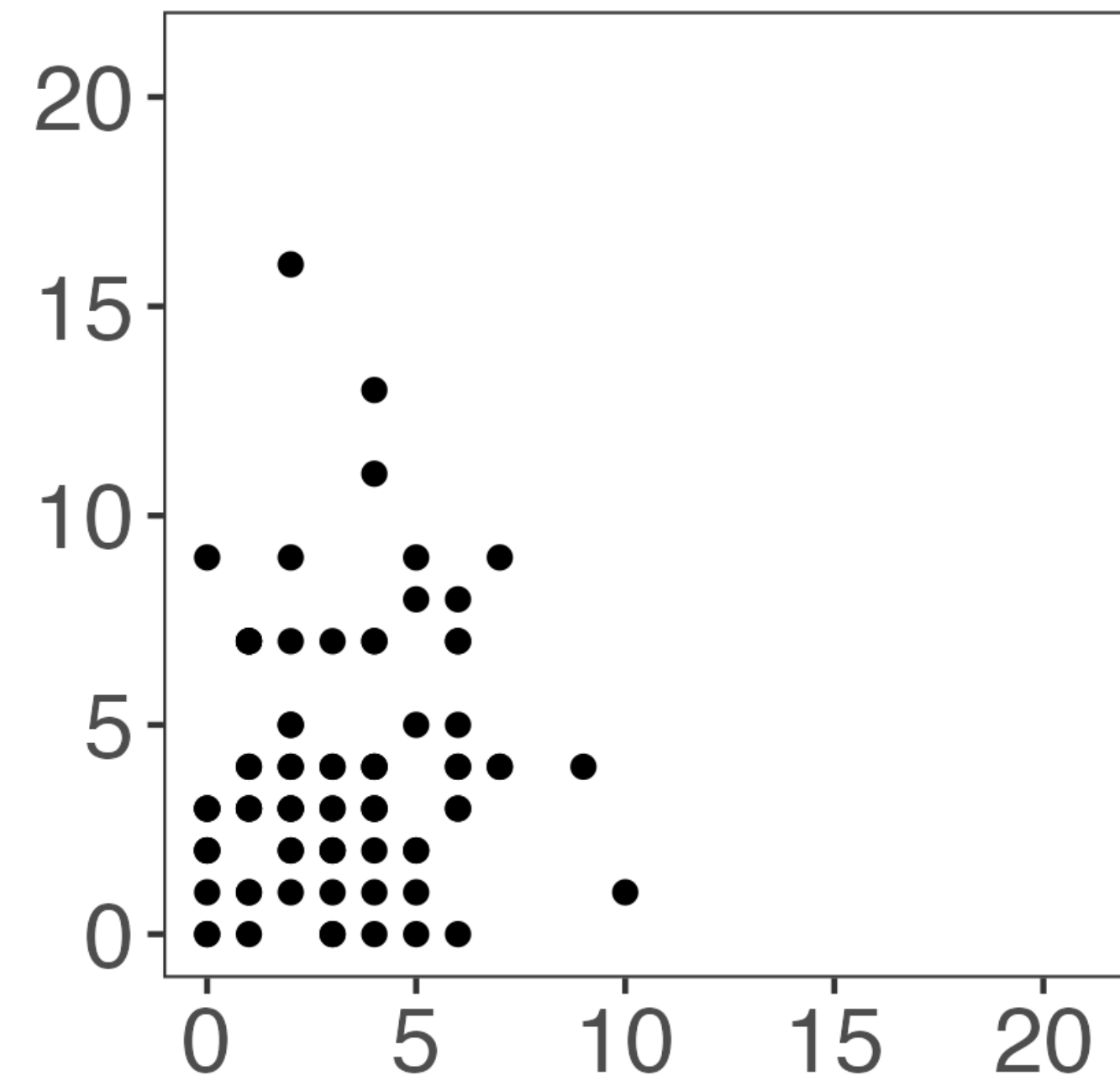
X



$X^{(1)}$

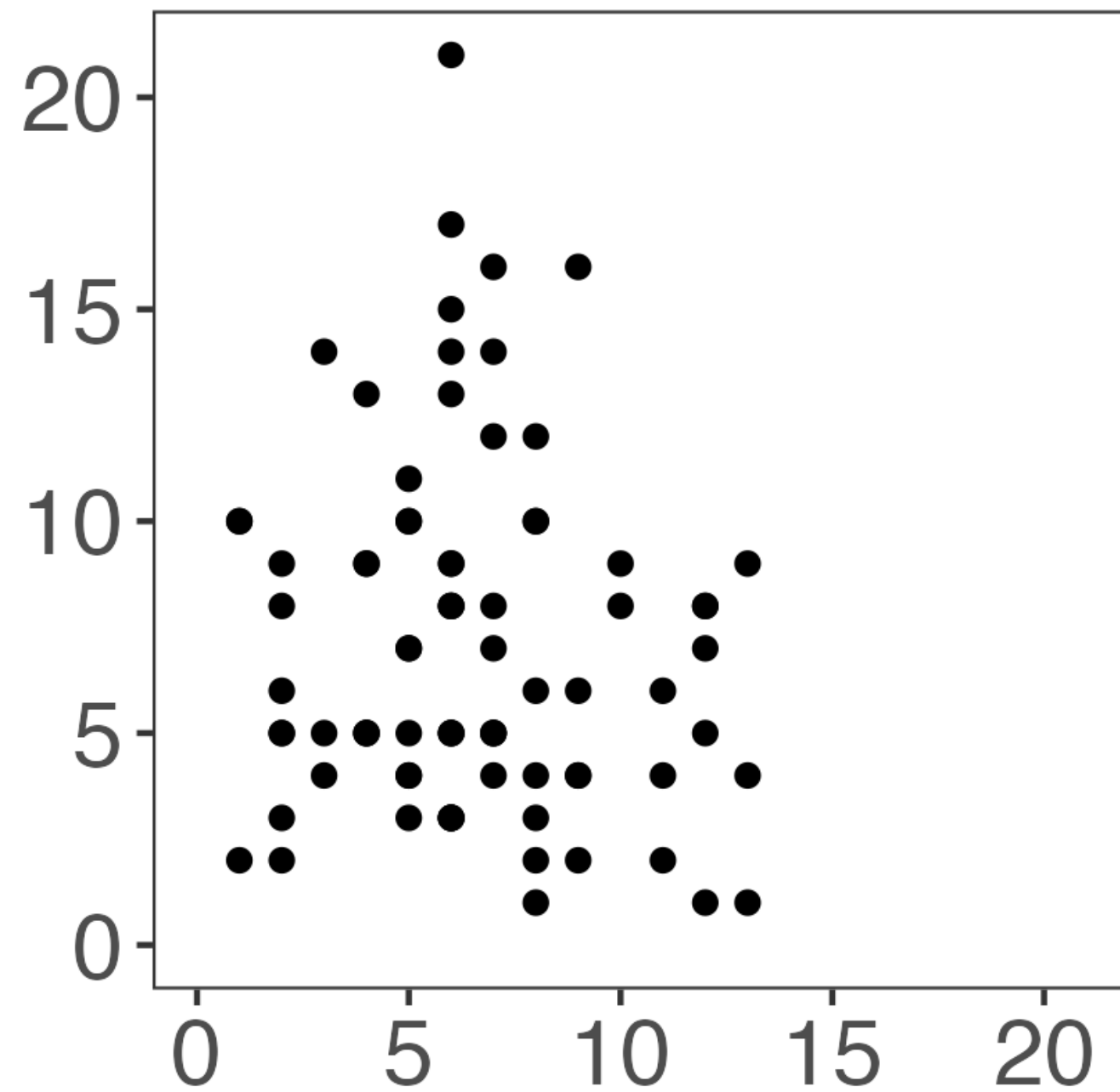


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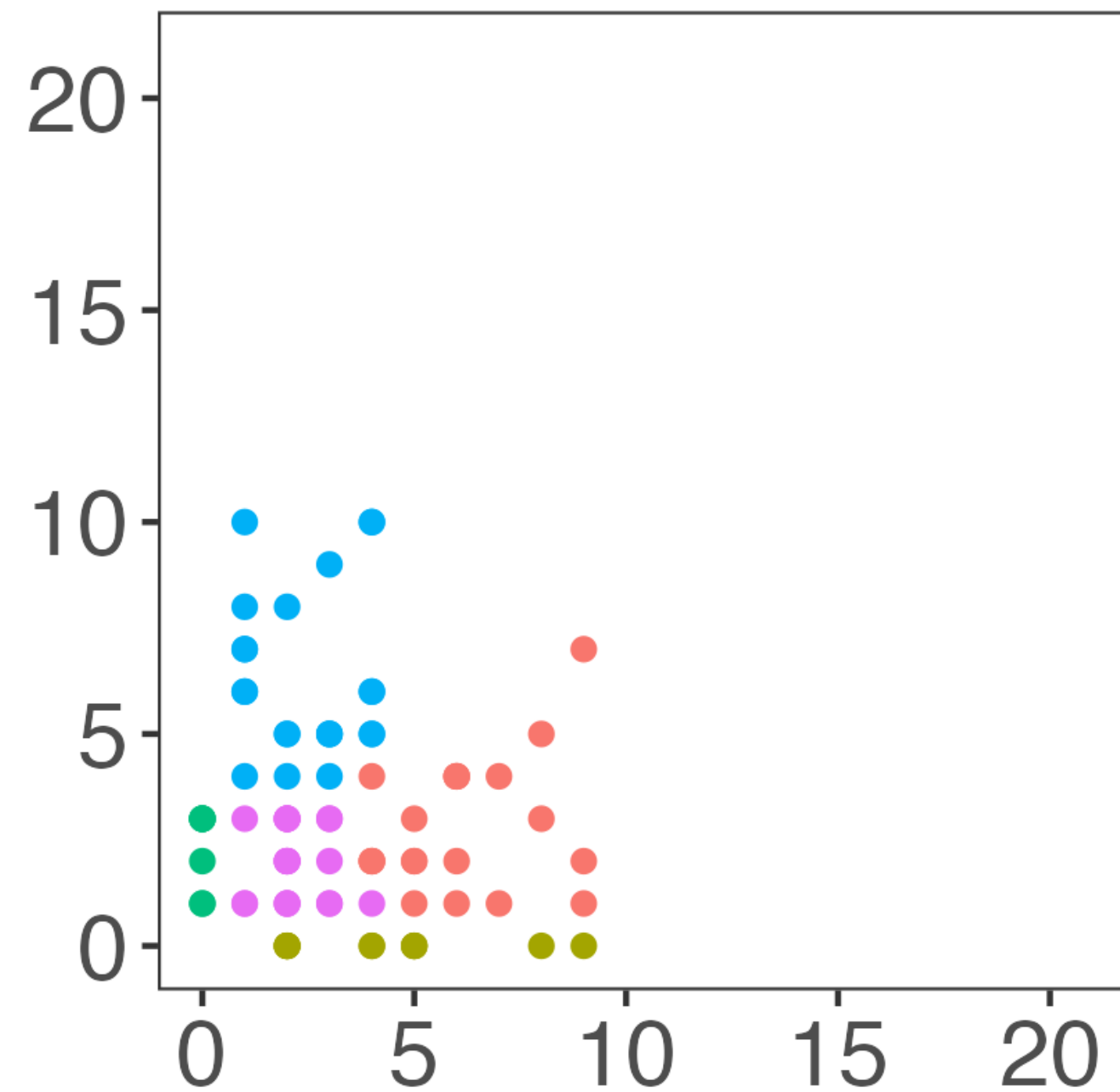


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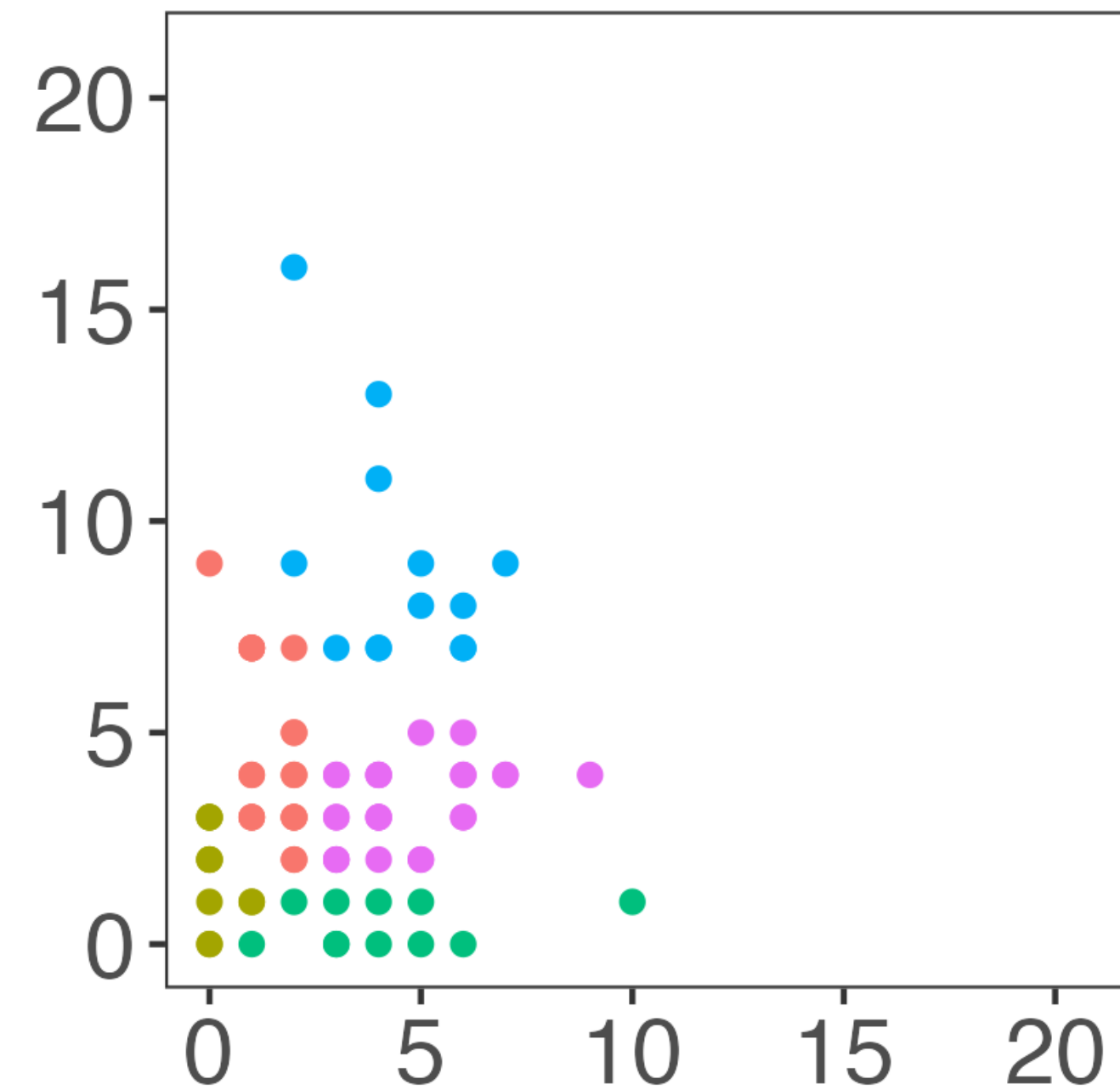
X



$X^{(1)}$

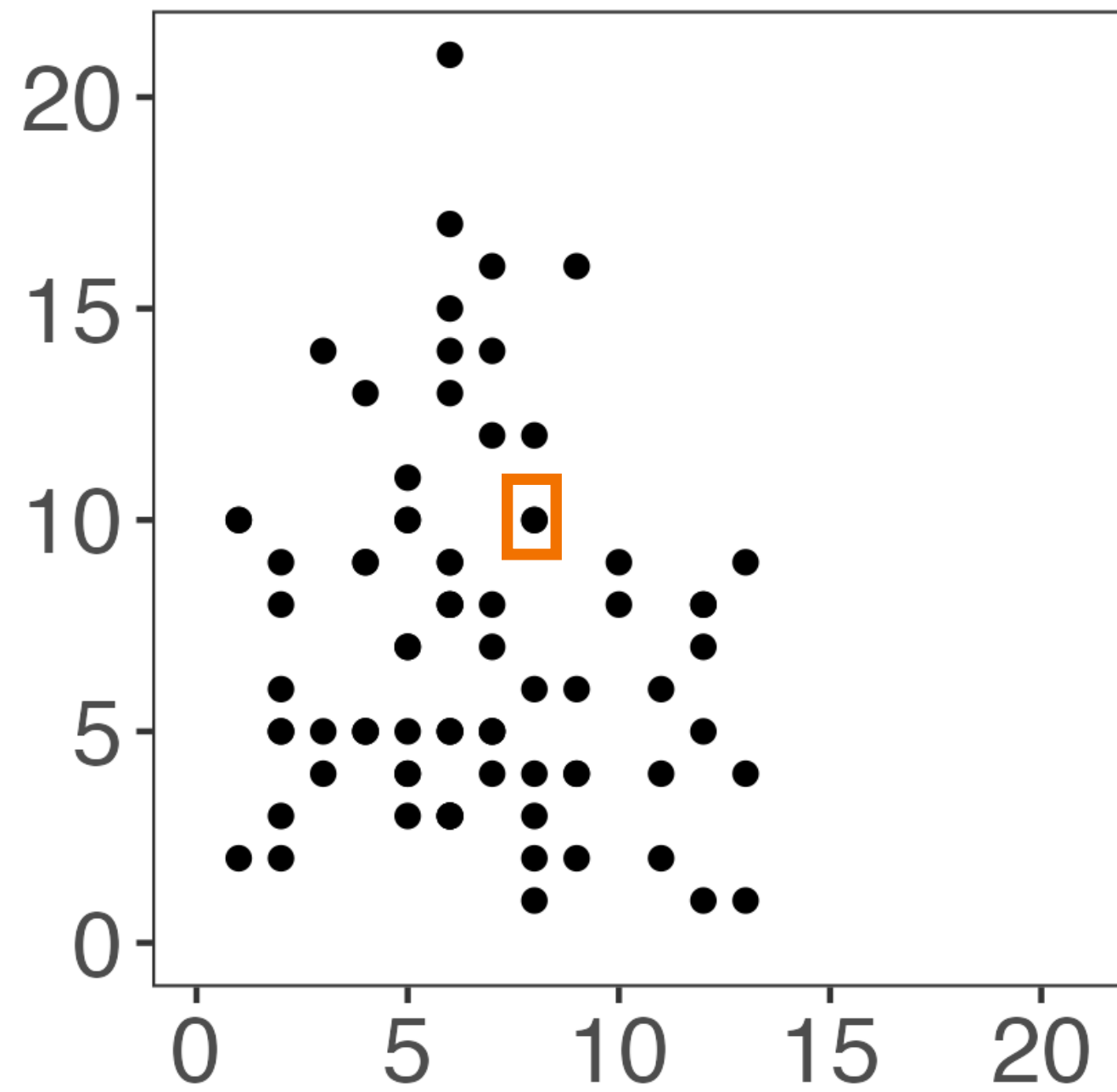


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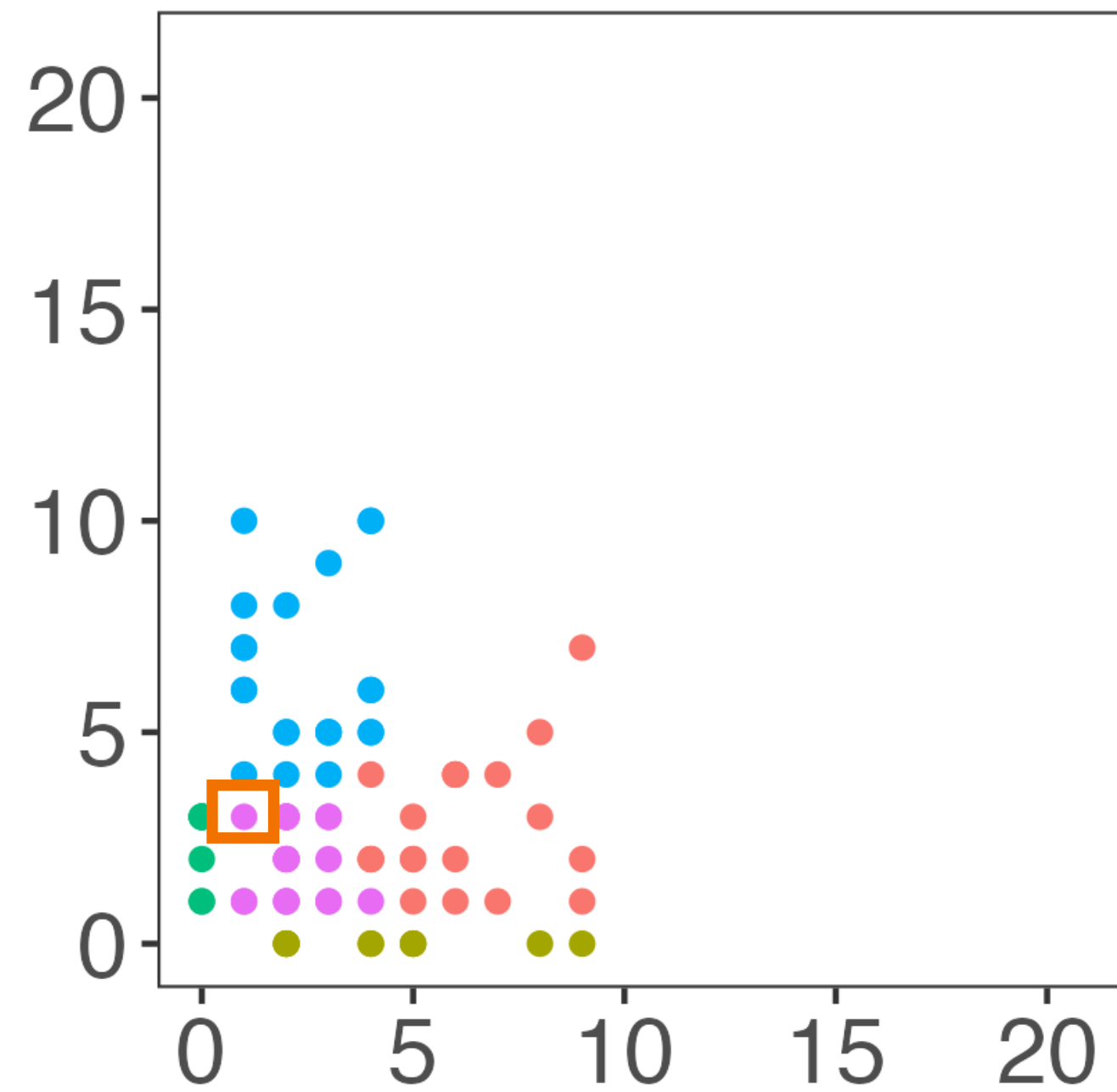


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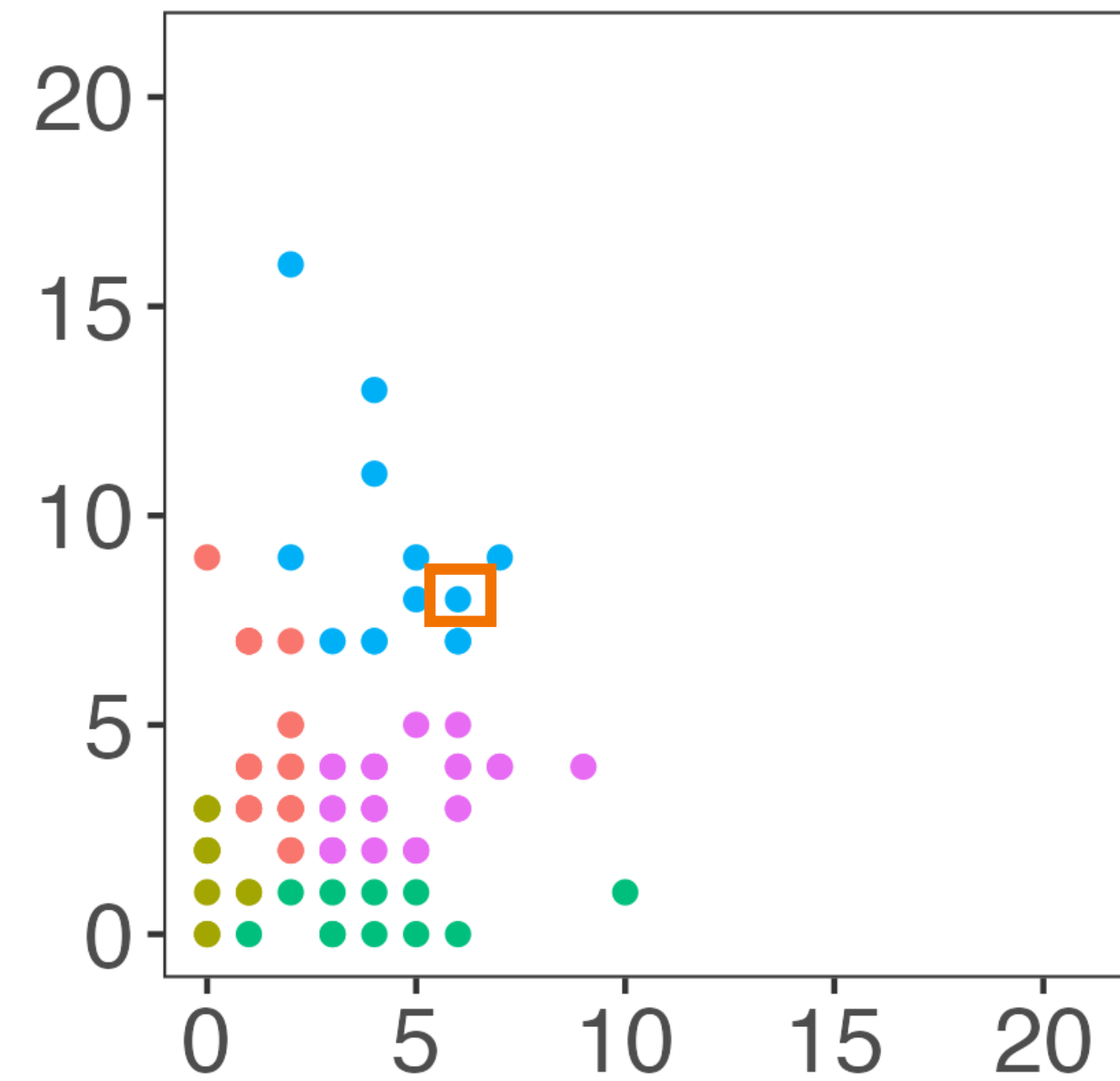
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$X^{(1)}$

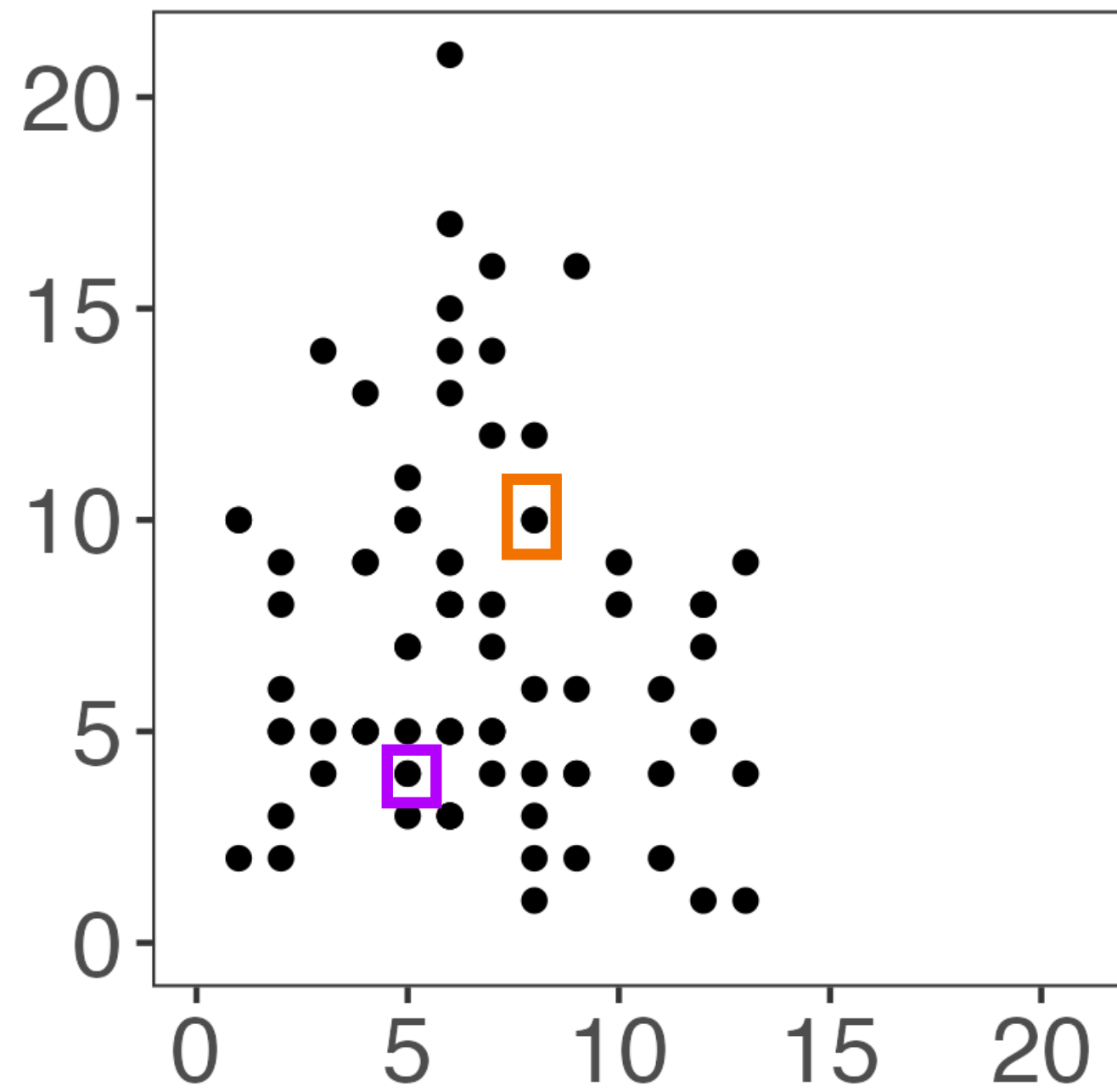


$X^{(2)}$

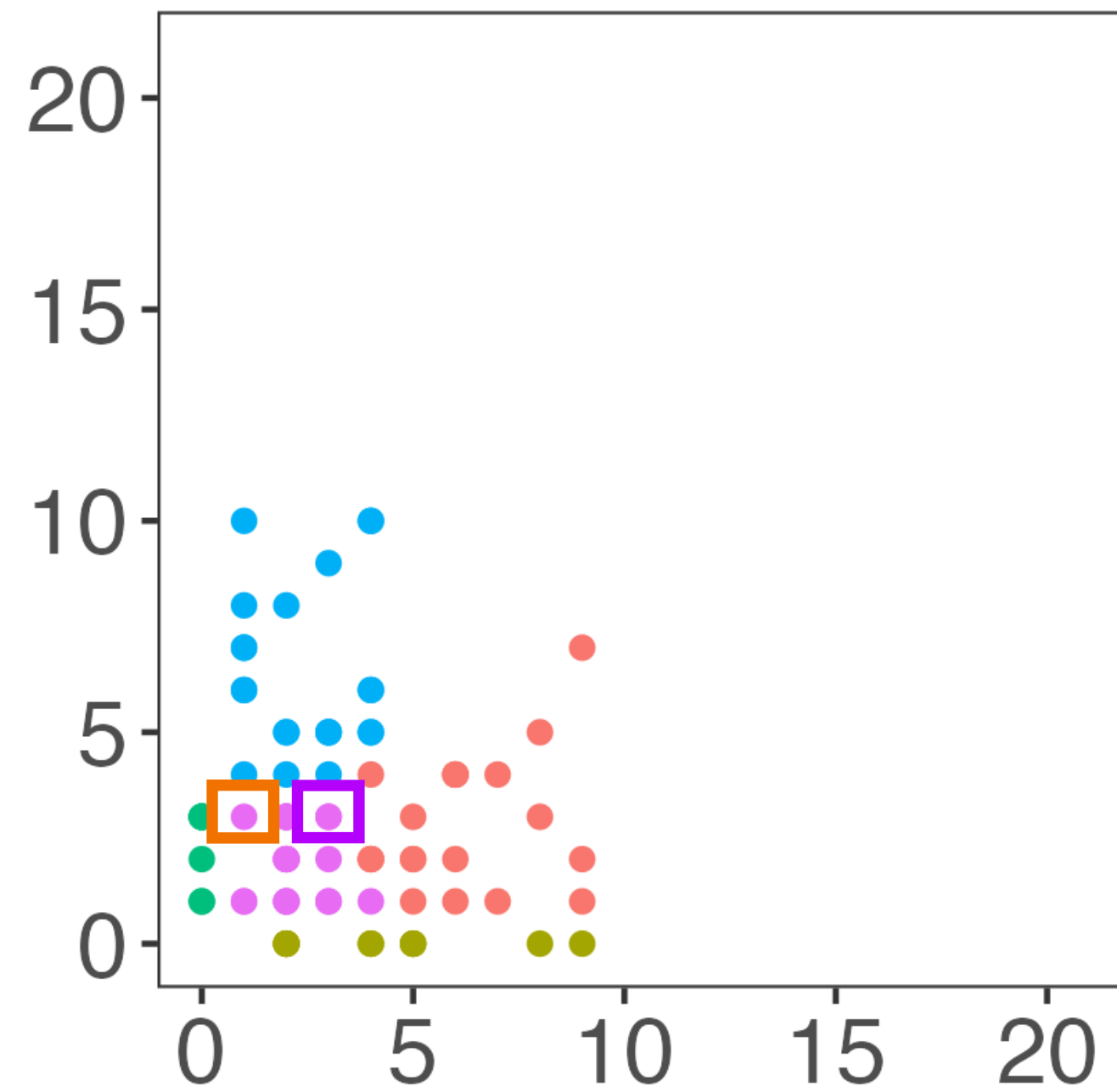


Data thinning provides a simple alternative

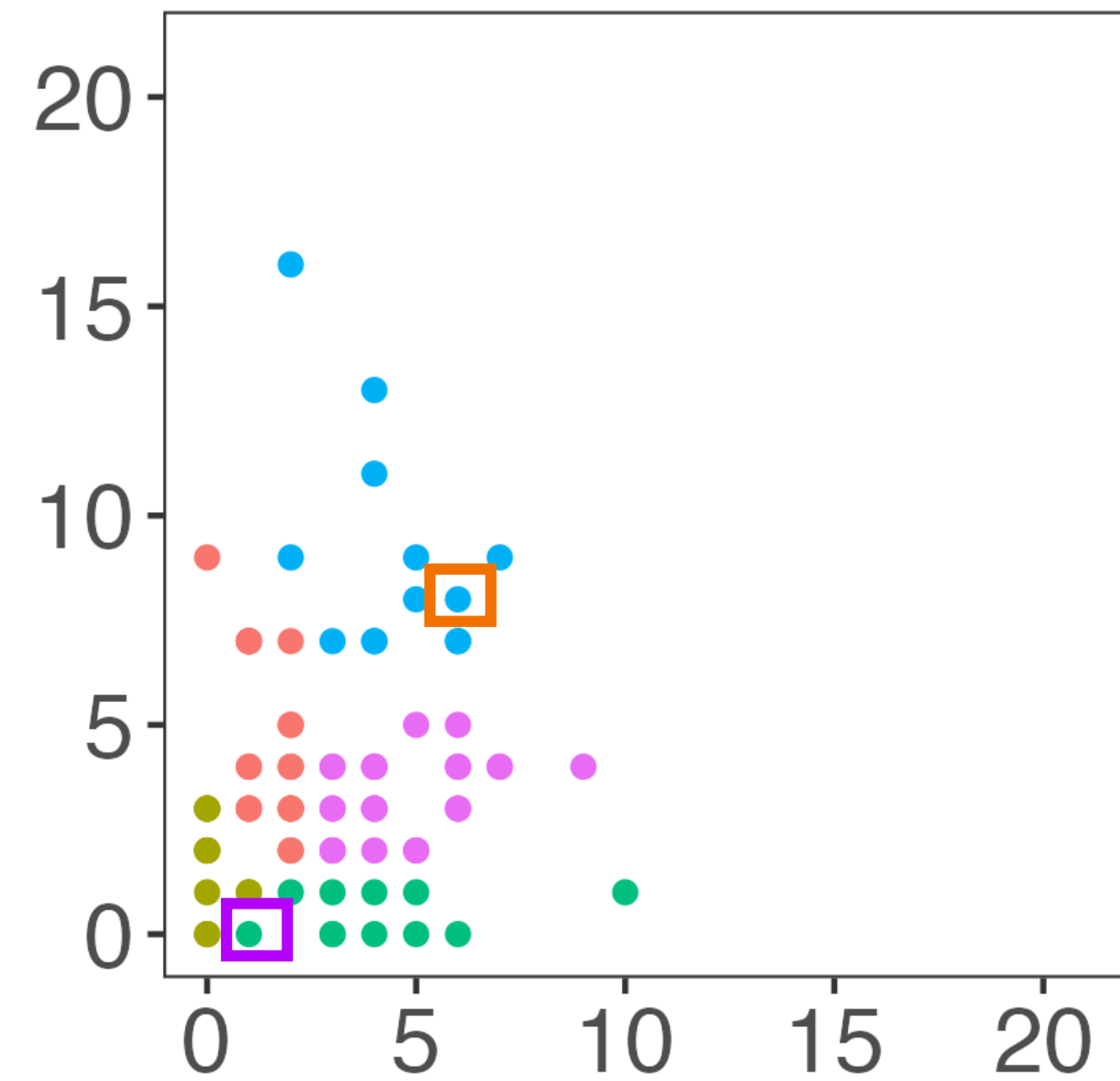
X



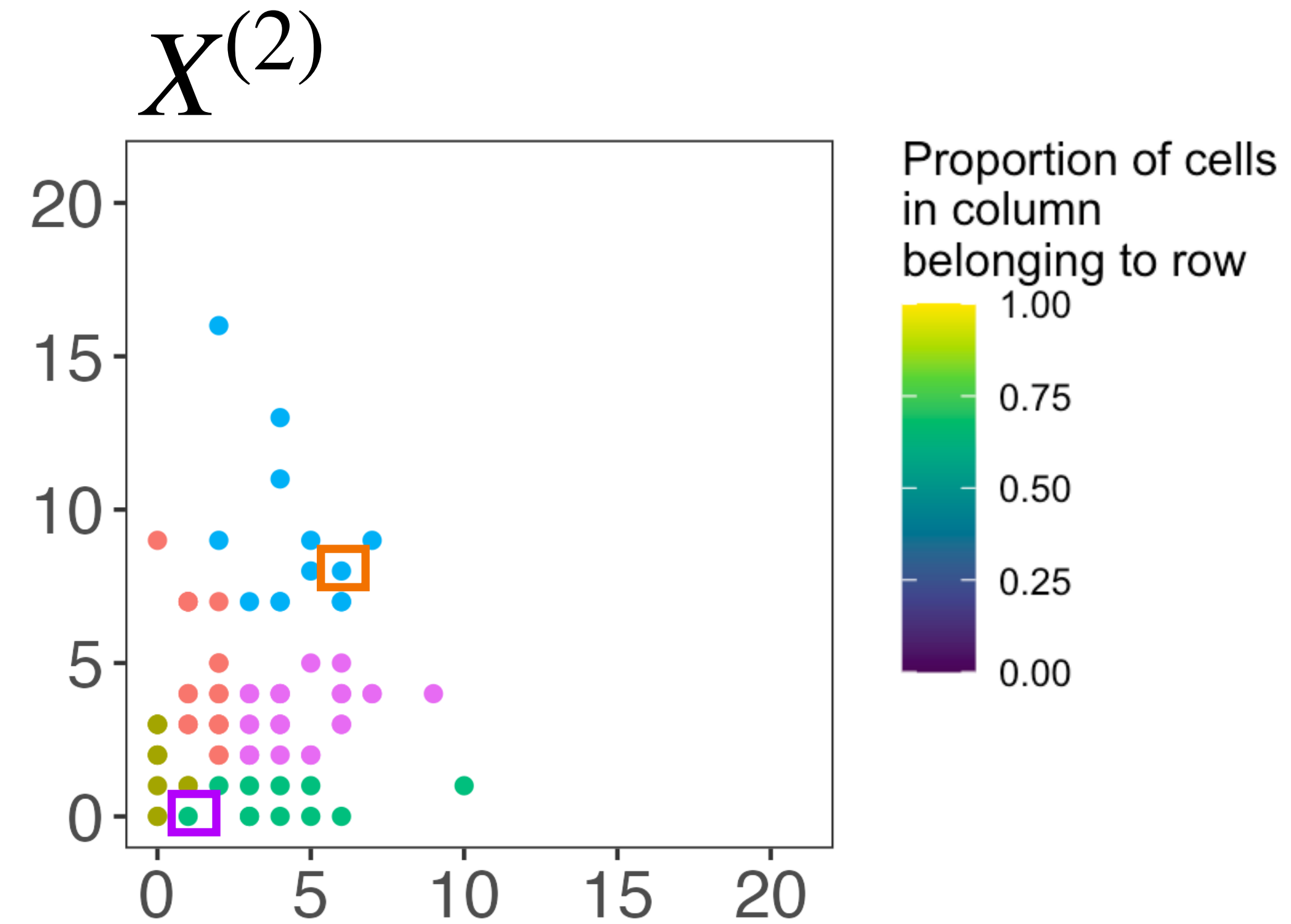
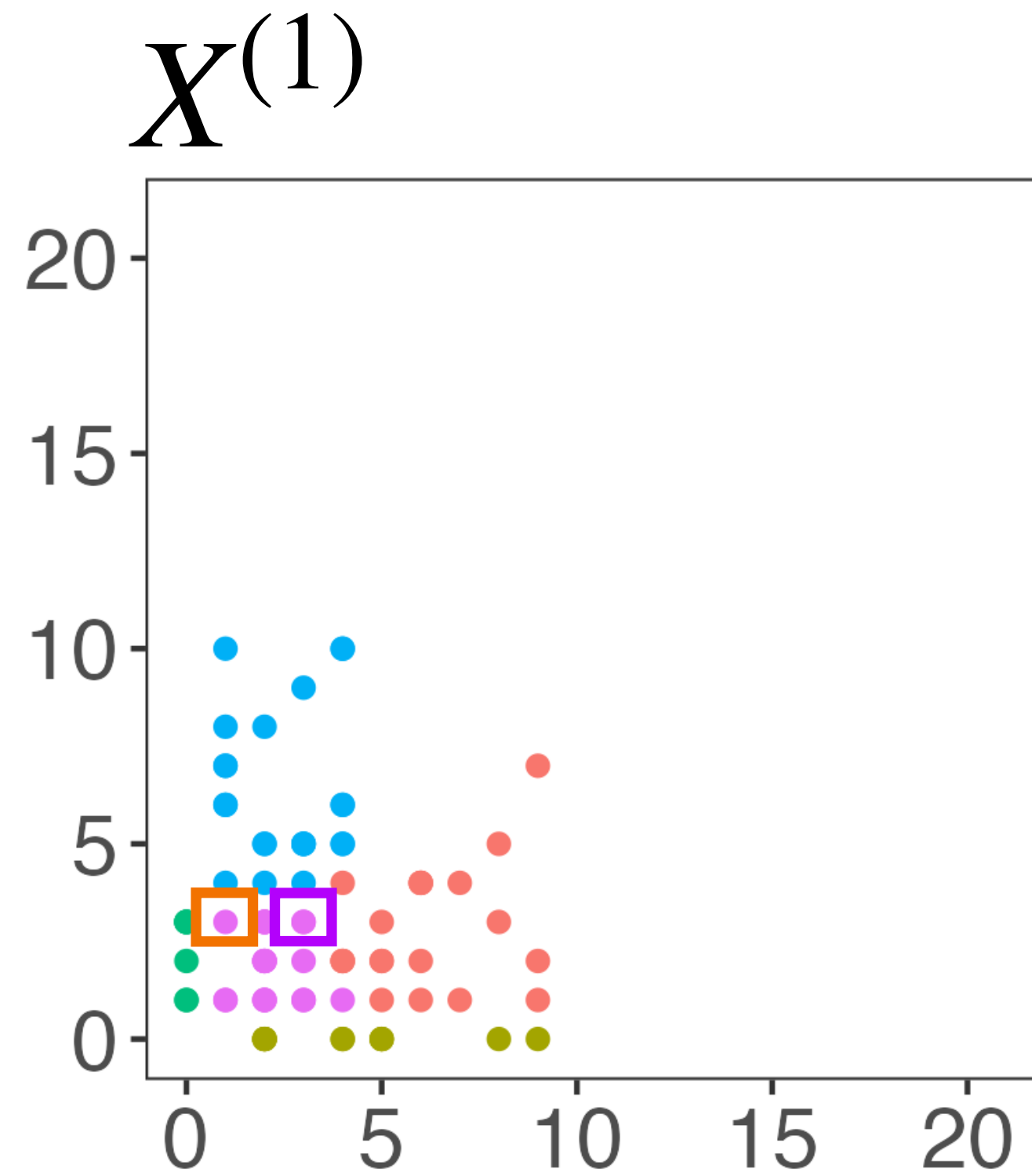
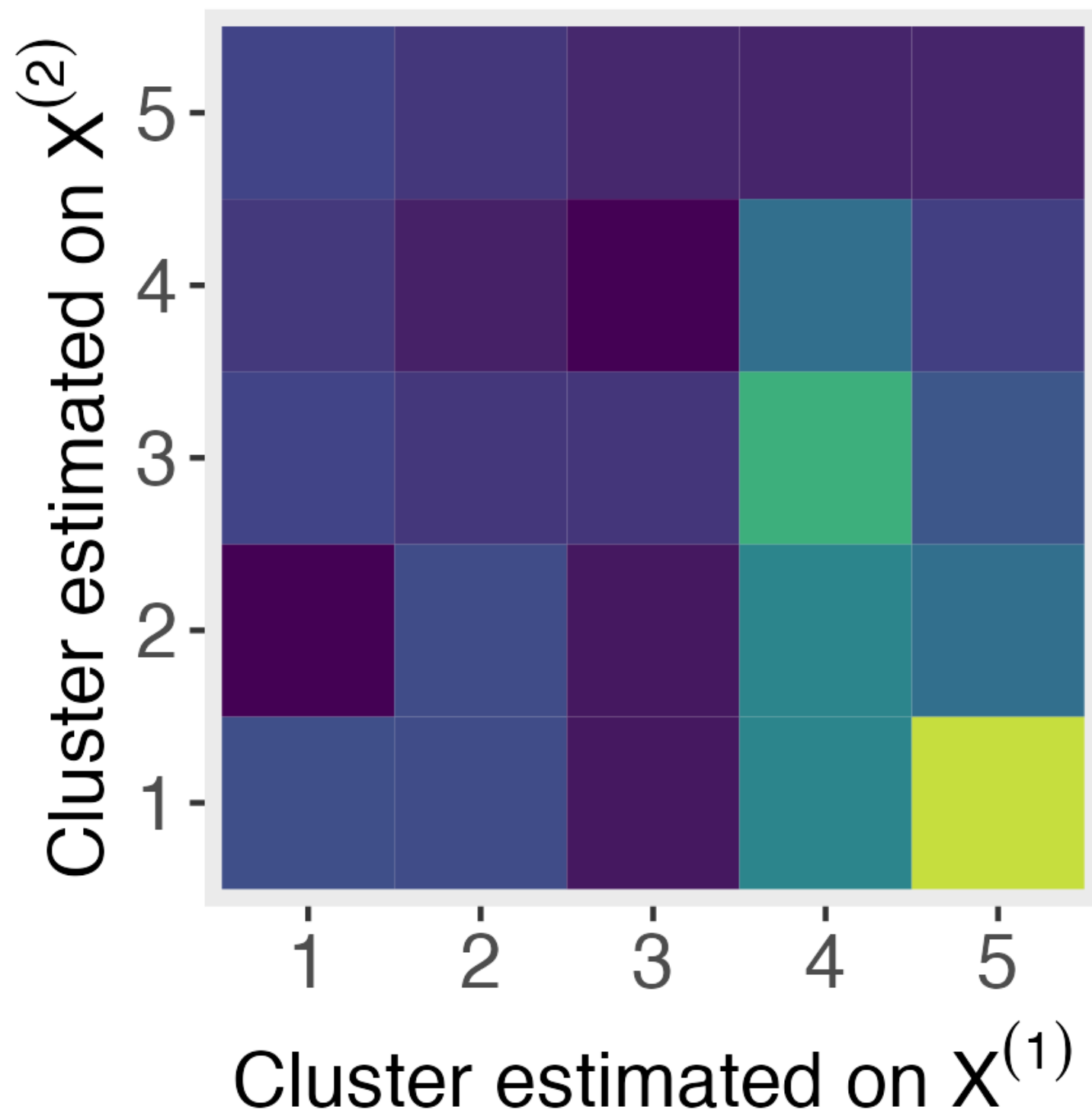
$X^{(1)}$



$X^{(2)}$



Data thinning provides a simple alternative

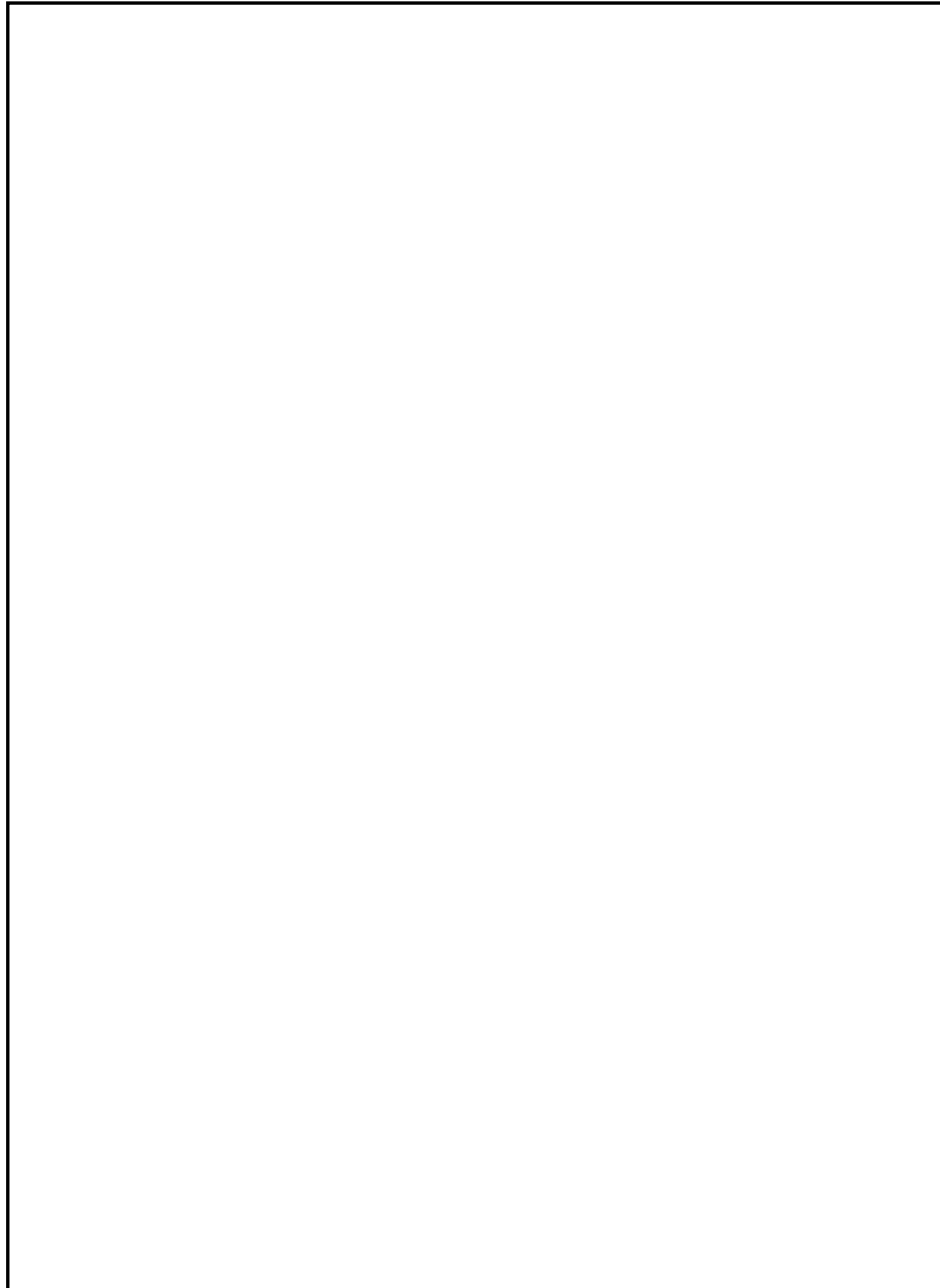


Adjusted Rand Index ≈ 0.01

Re-analysis of Kidney cell data from fetal cell atlas

Re-analysis of Kidney cell data from fetal cell atlas

Intradataset cross validation



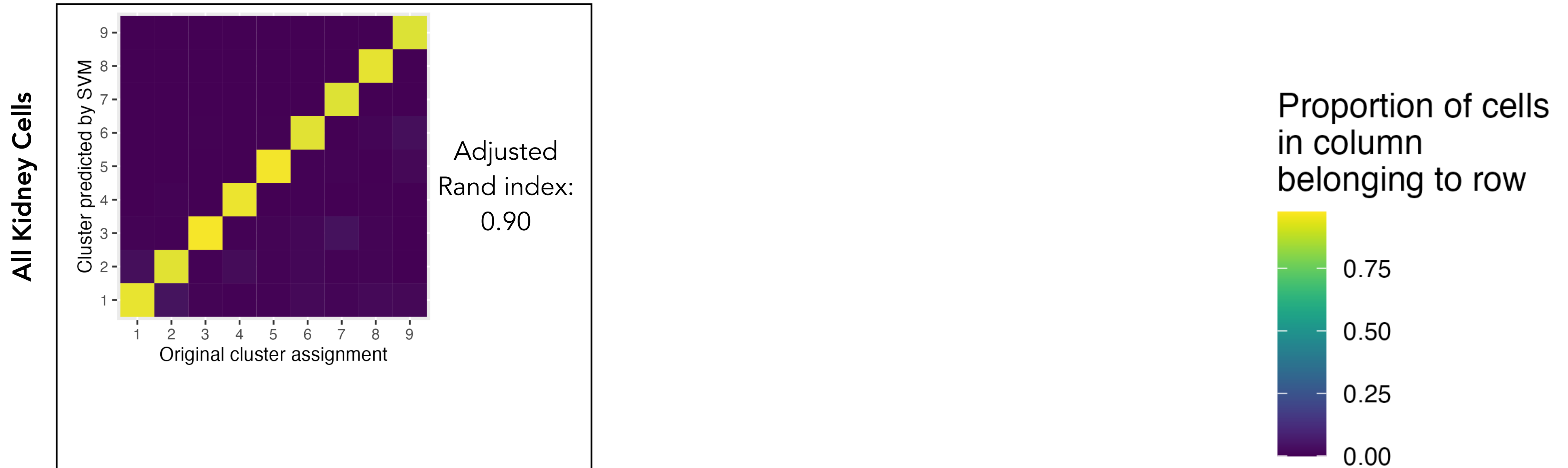
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Intradataset cross validation



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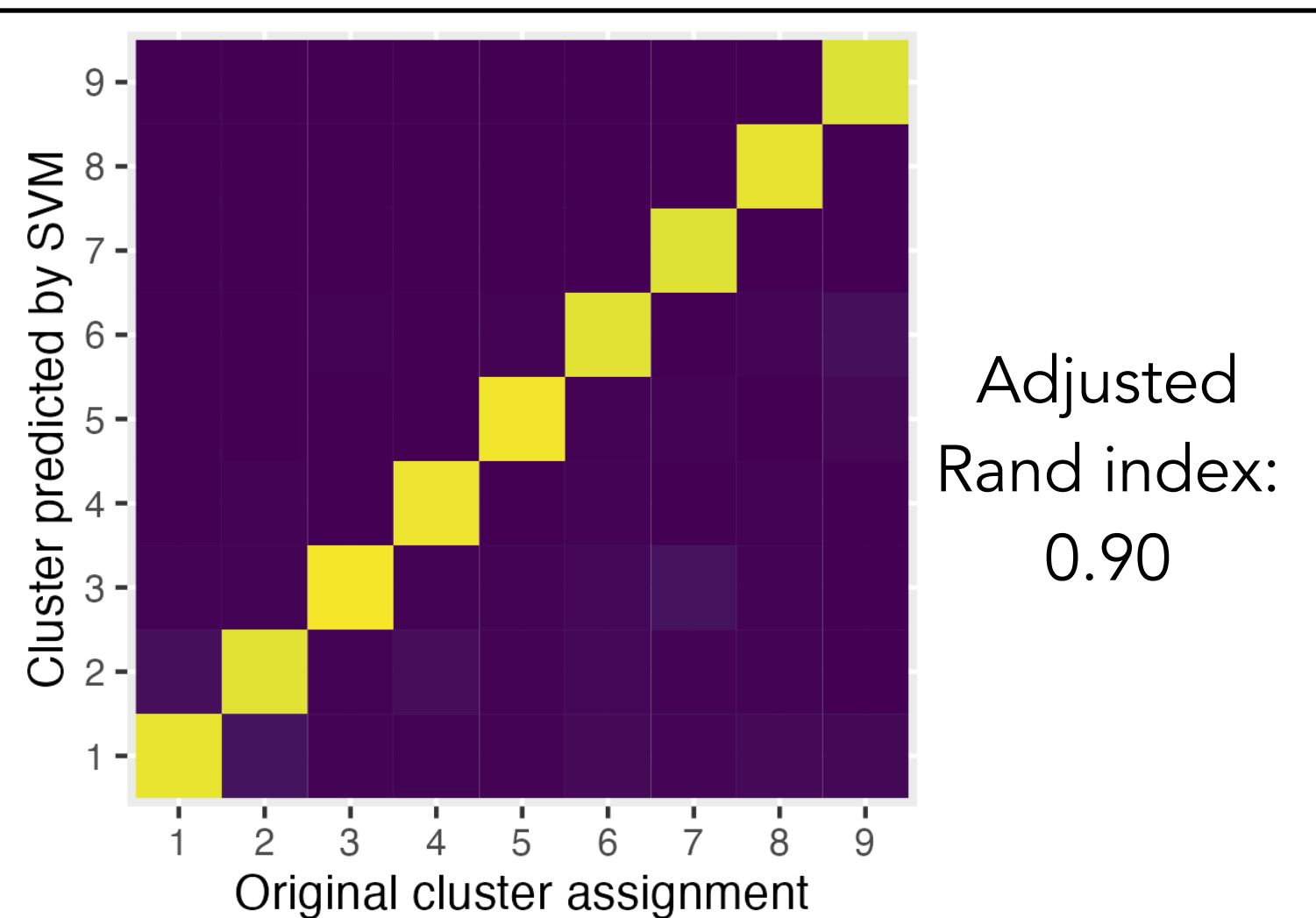
Intradataset cross validation



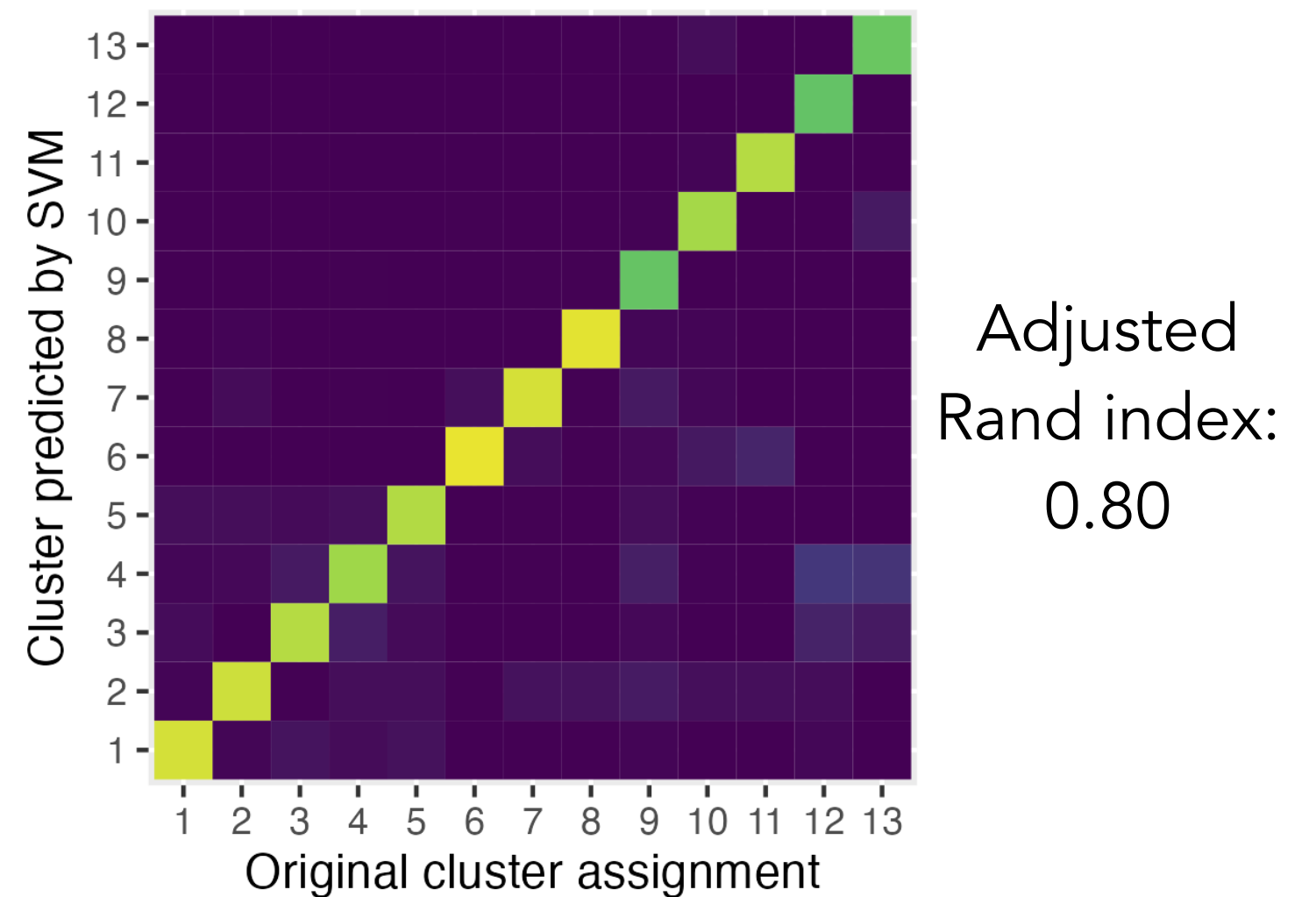
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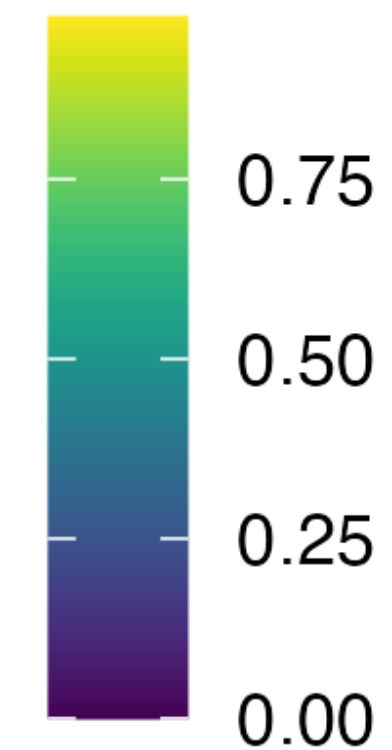
All Kidney Cells



Metanephric Cells



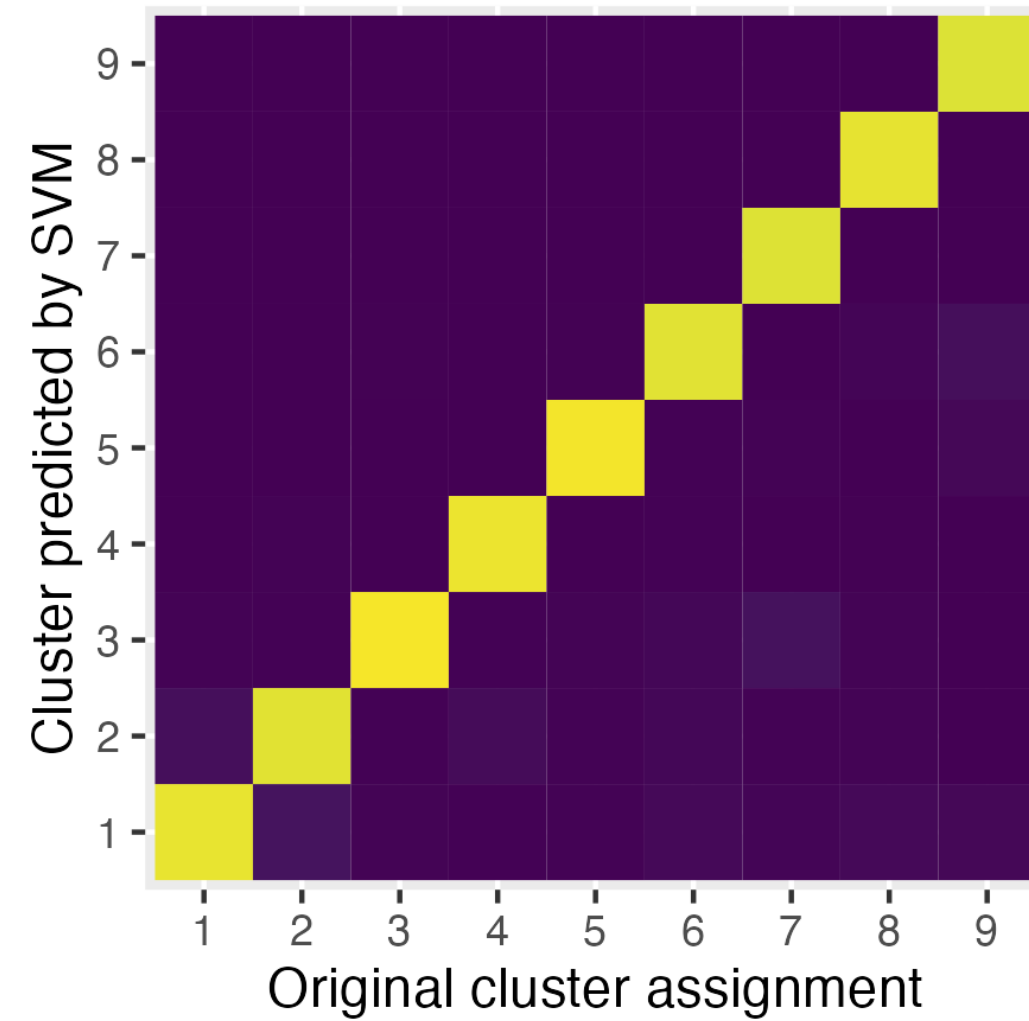
Proportion of cells in column belonging to row



Re-analysis of Kidney cell data from fetal cell atlas

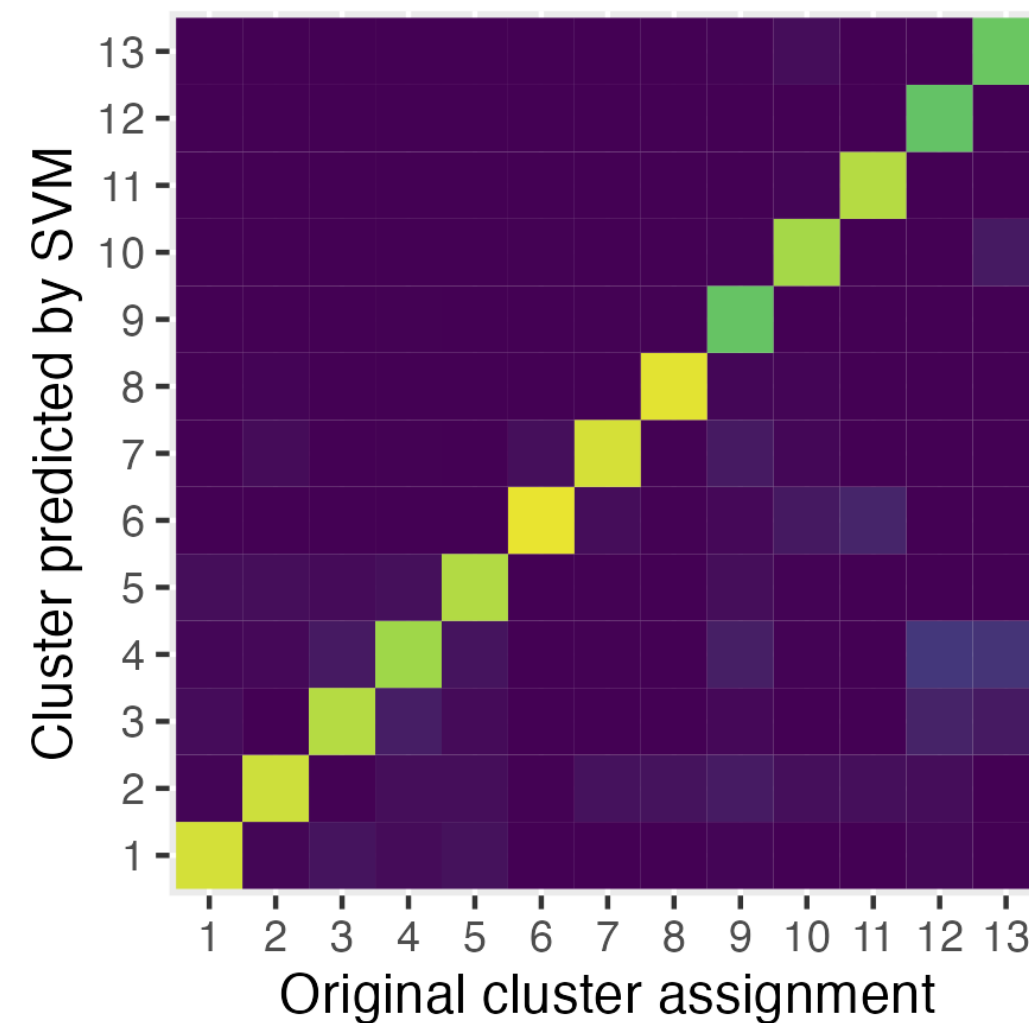
Intradataset cross validation

All Kidney Cells



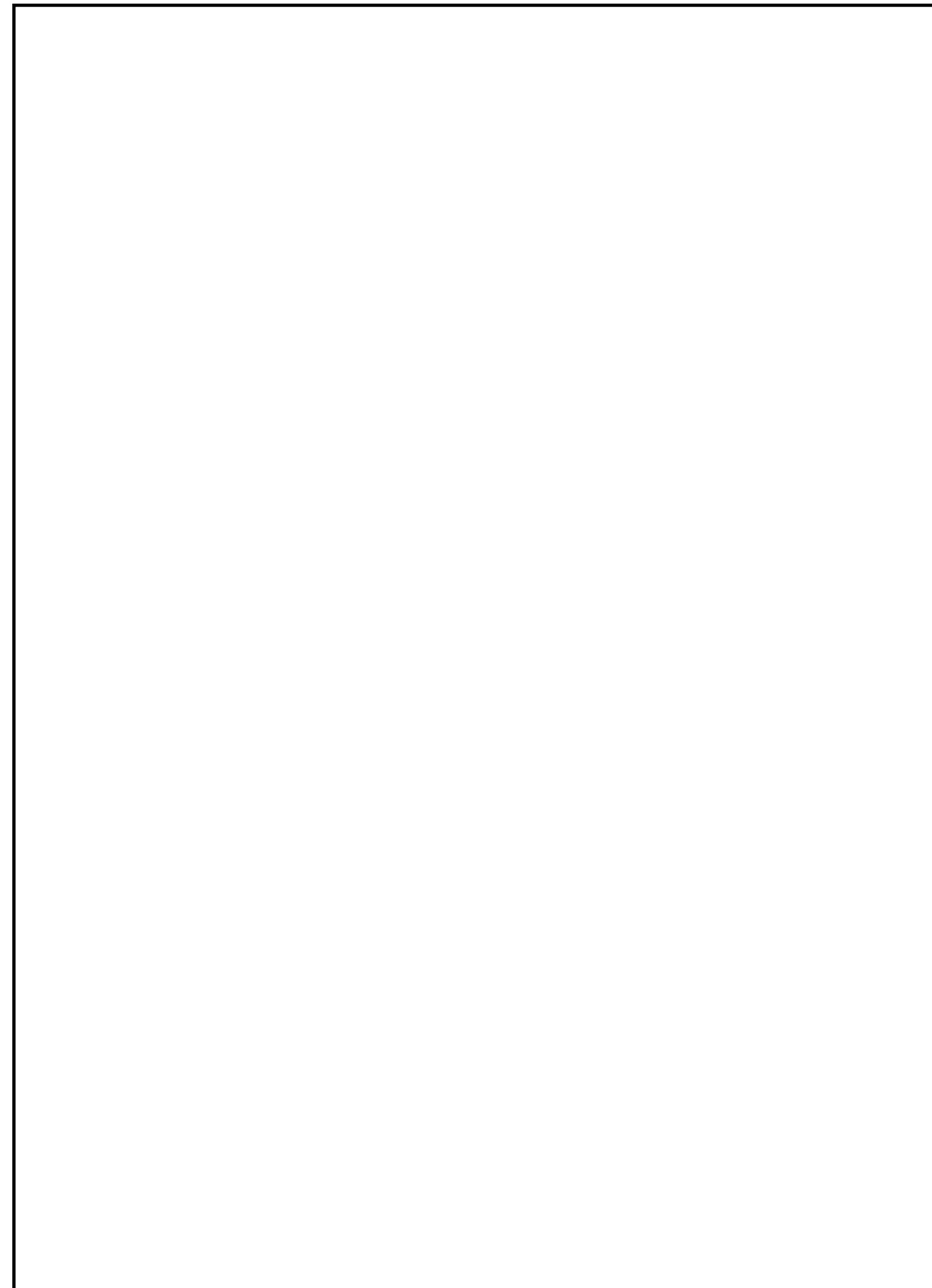
Adjusted Rand index: 0.90

Metanephric Cells

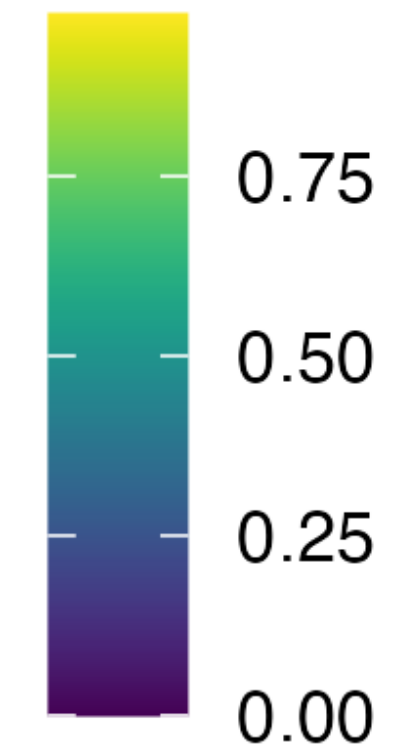


Adjusted Rand index: 0.80

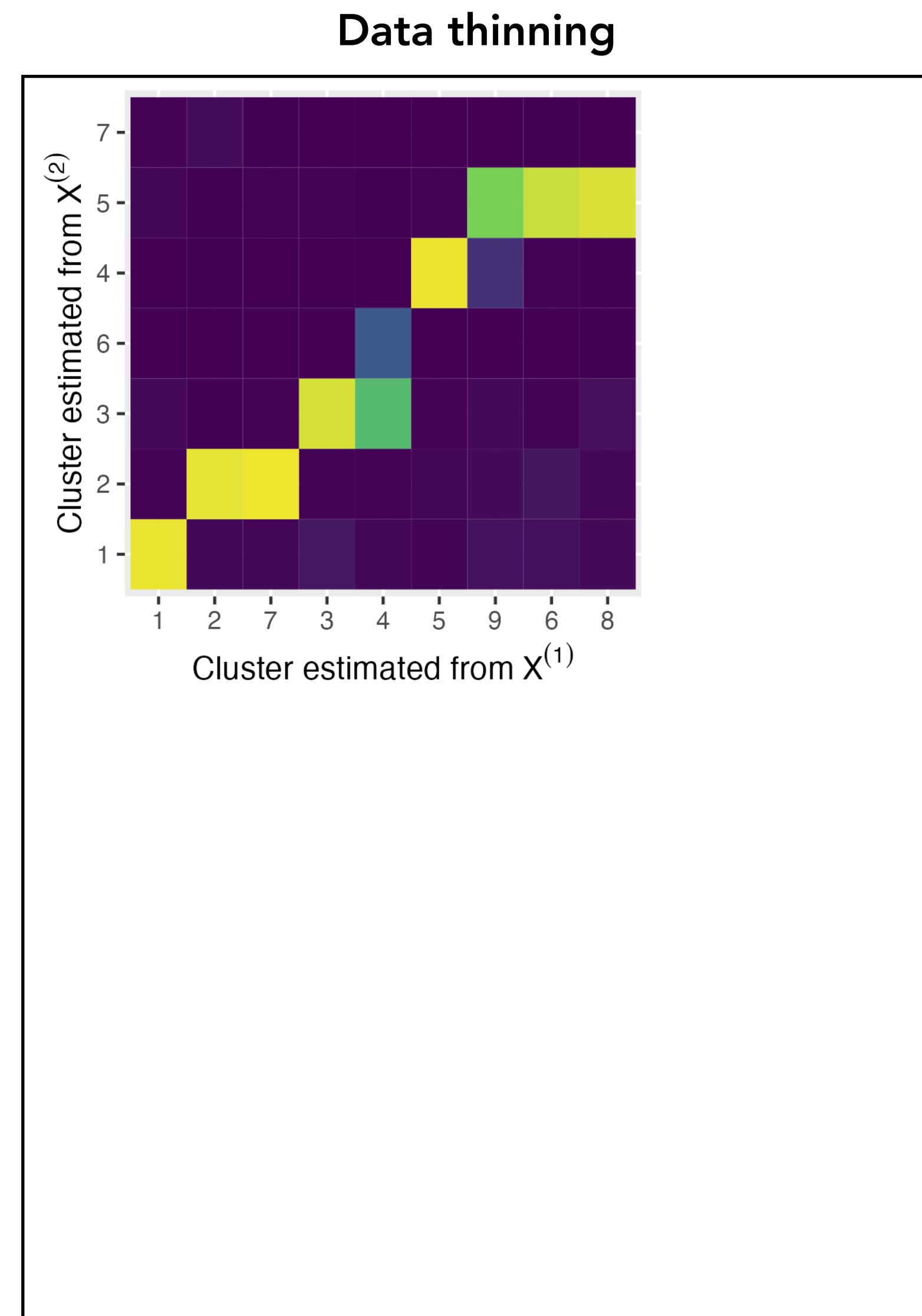
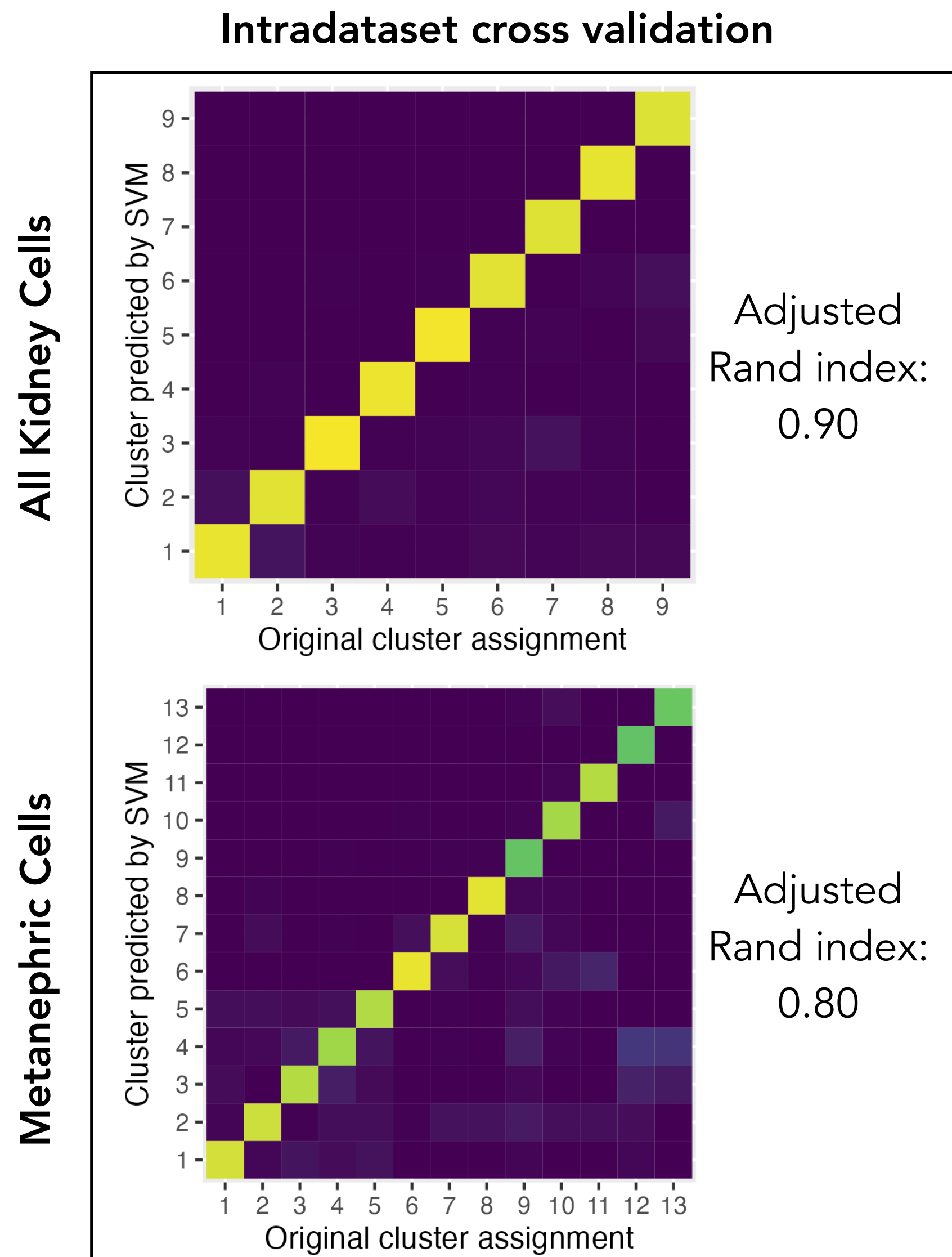
Data thinning



Proportion of cells in column belonging to row



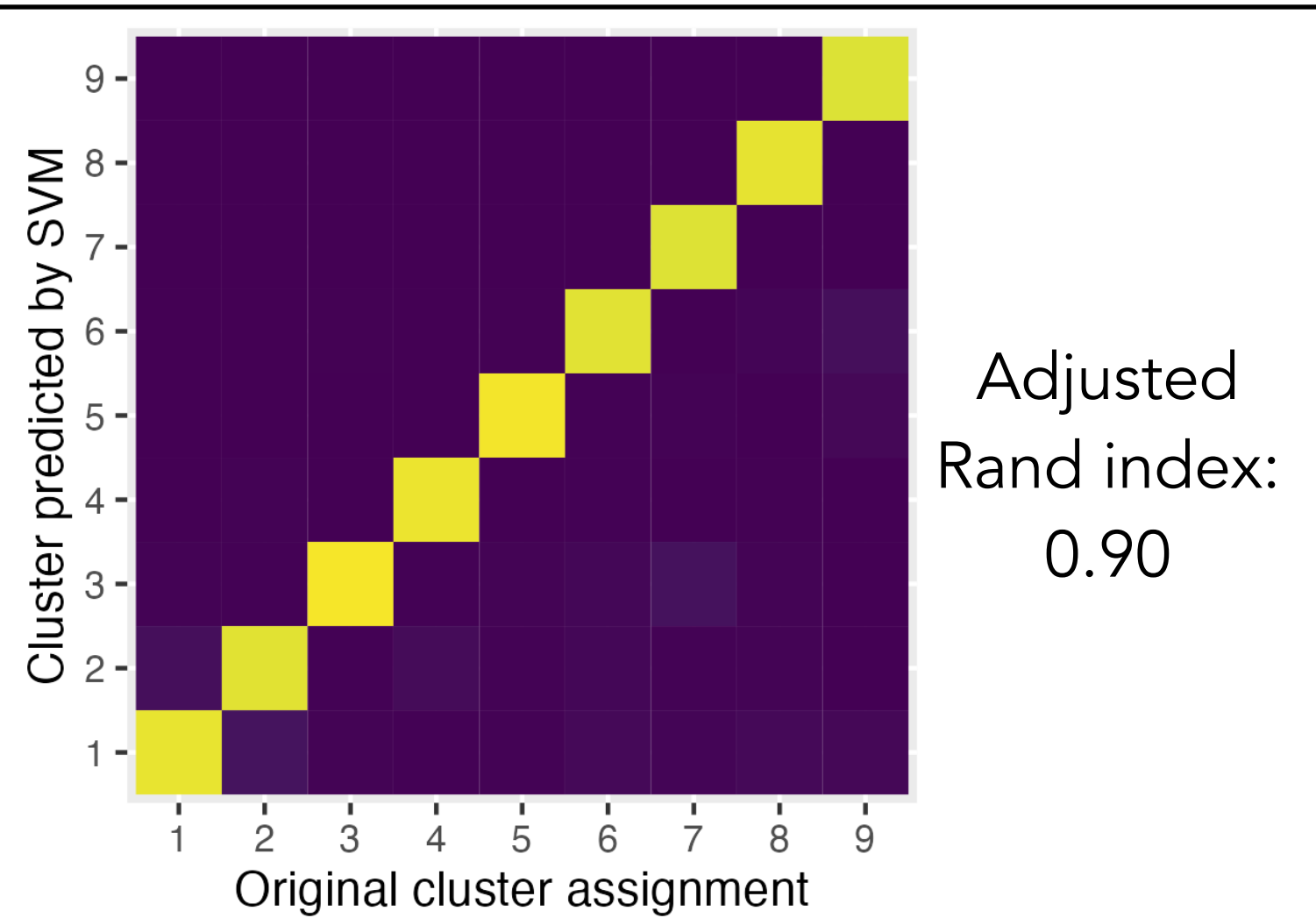
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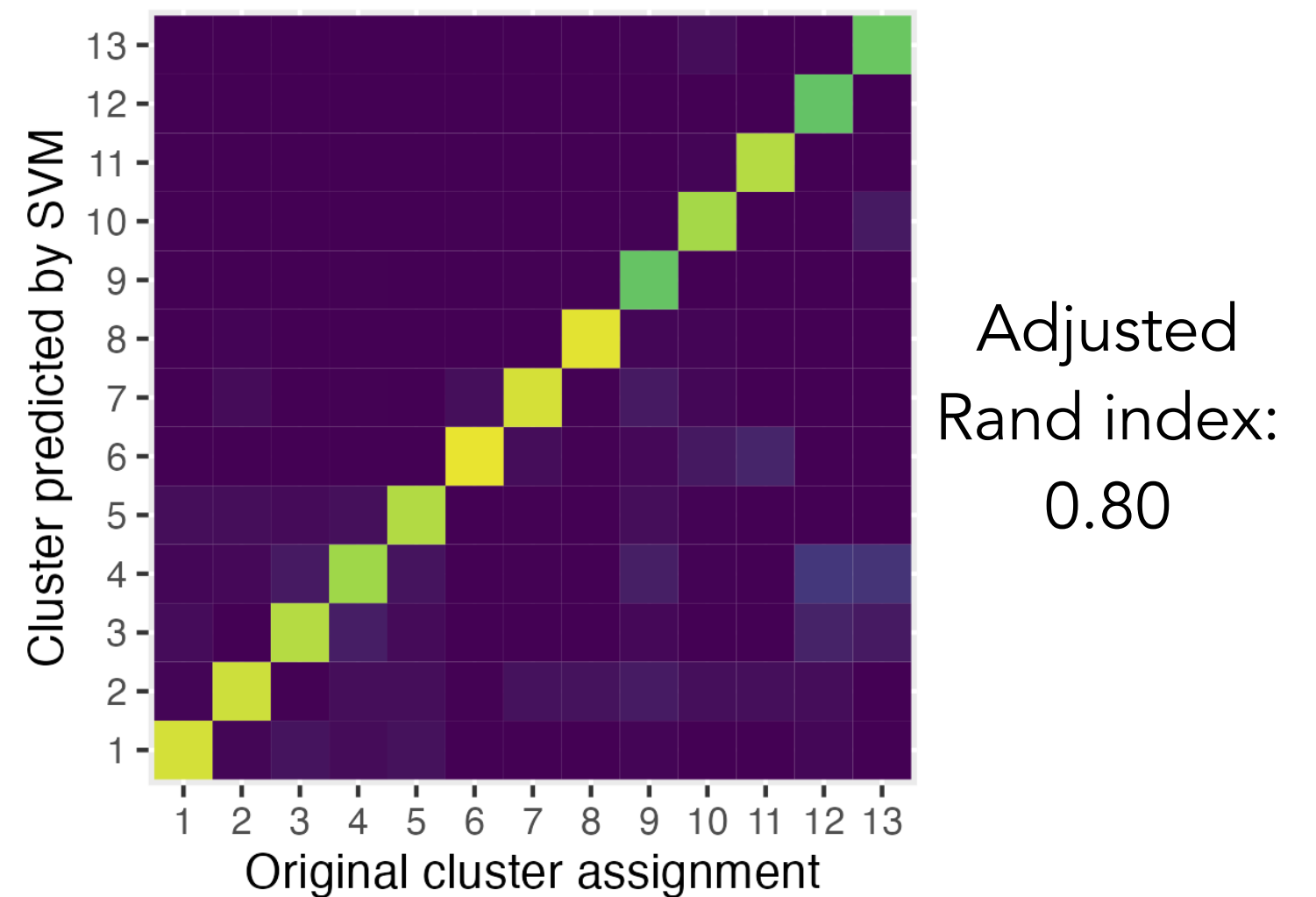
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All Kidney Cells

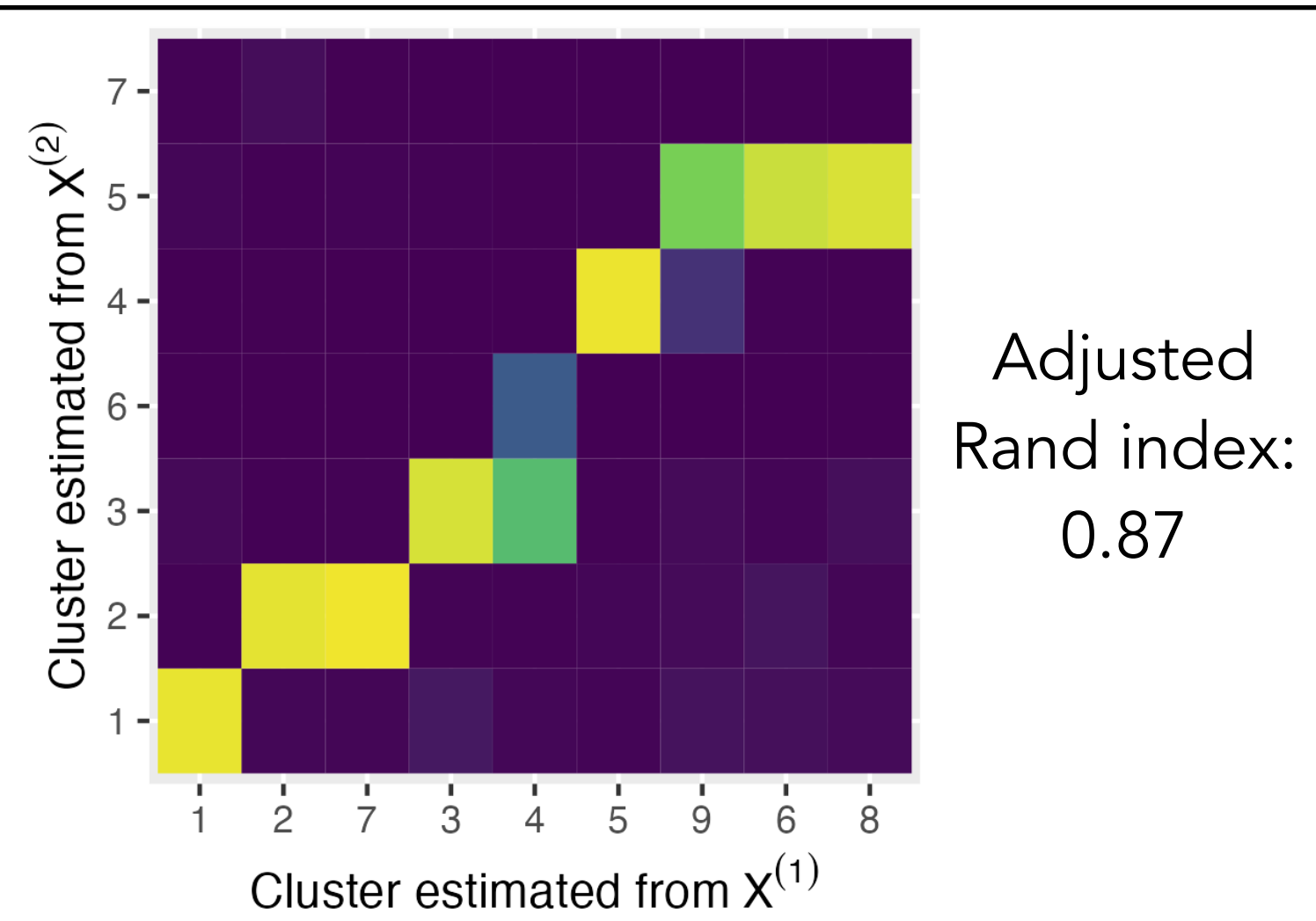
Intradataset cross validation



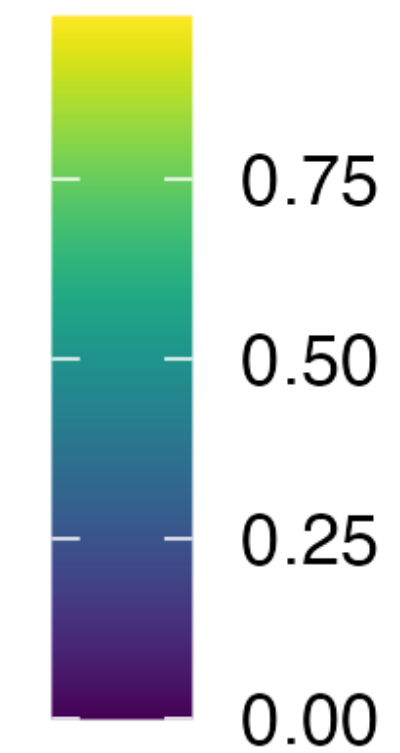
Metanephric Cells



Data thinning



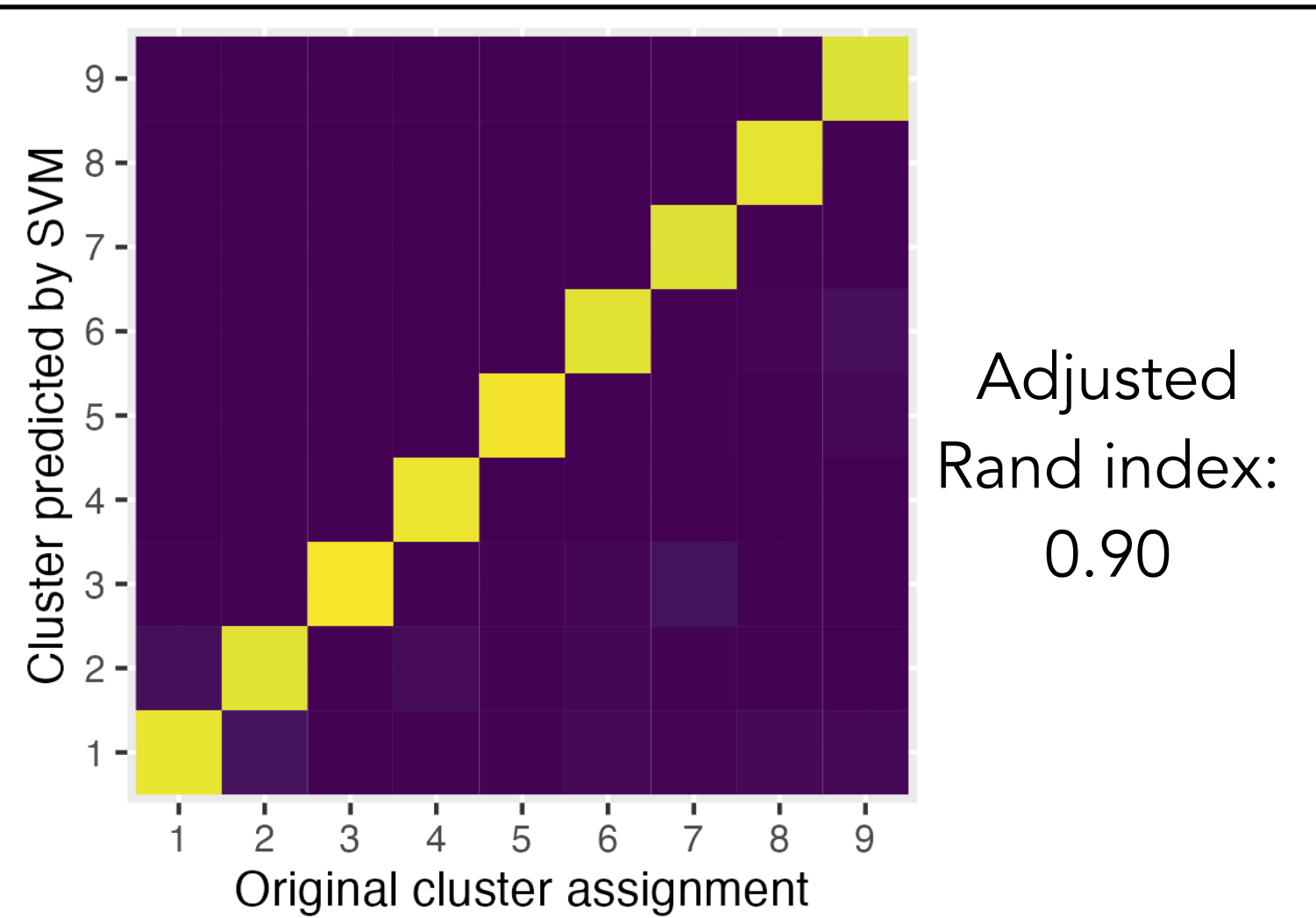
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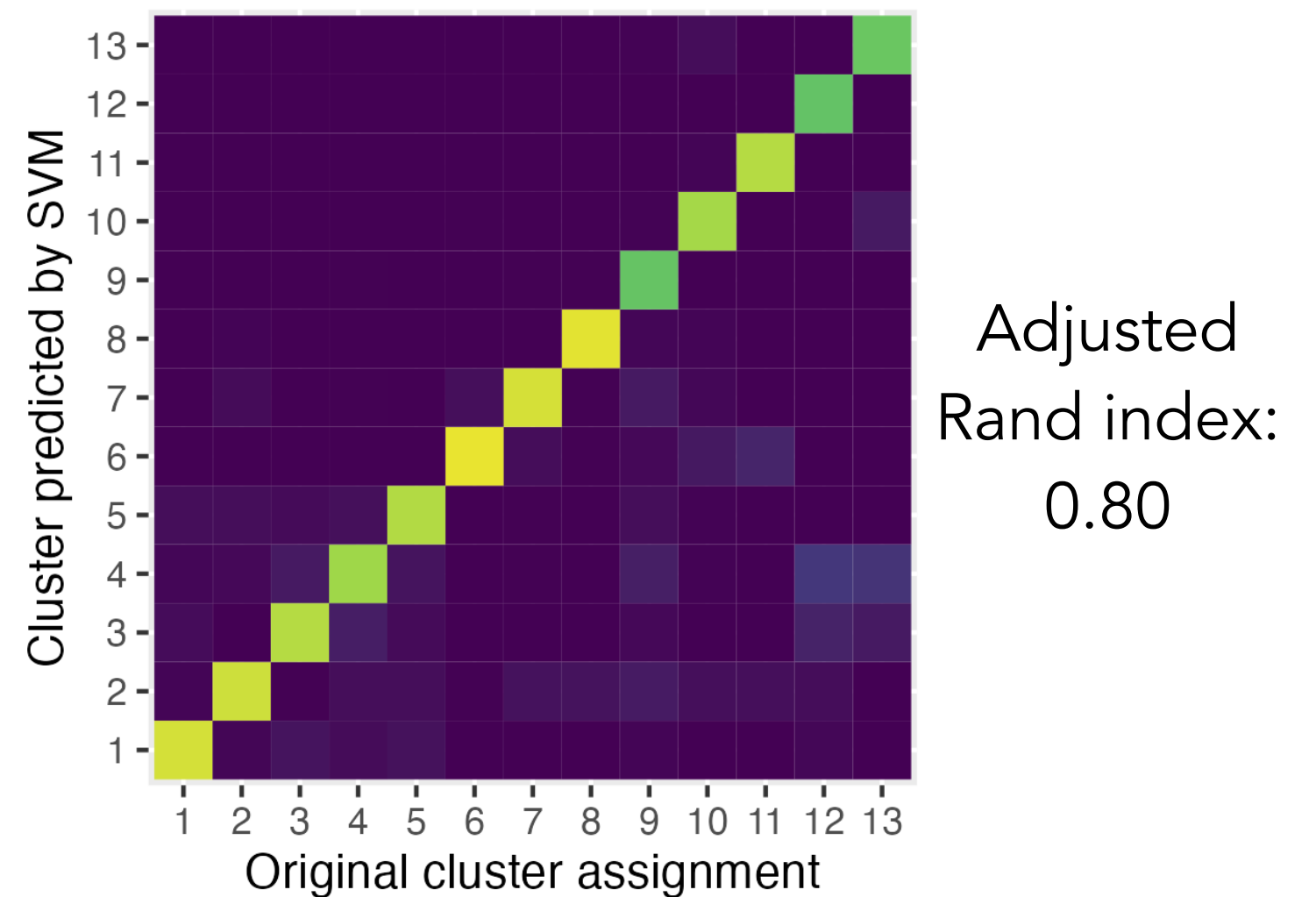
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All Kidney Cells

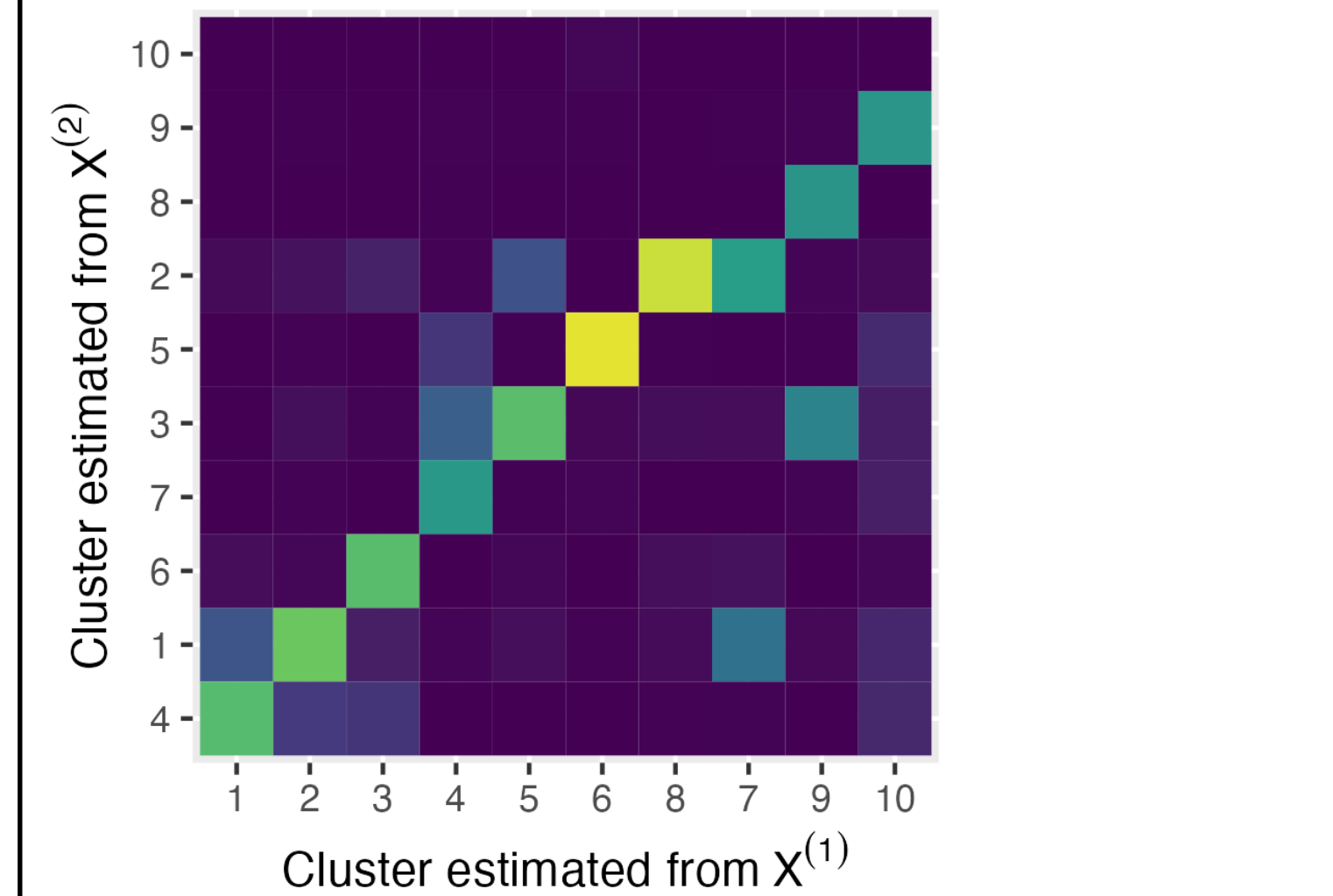
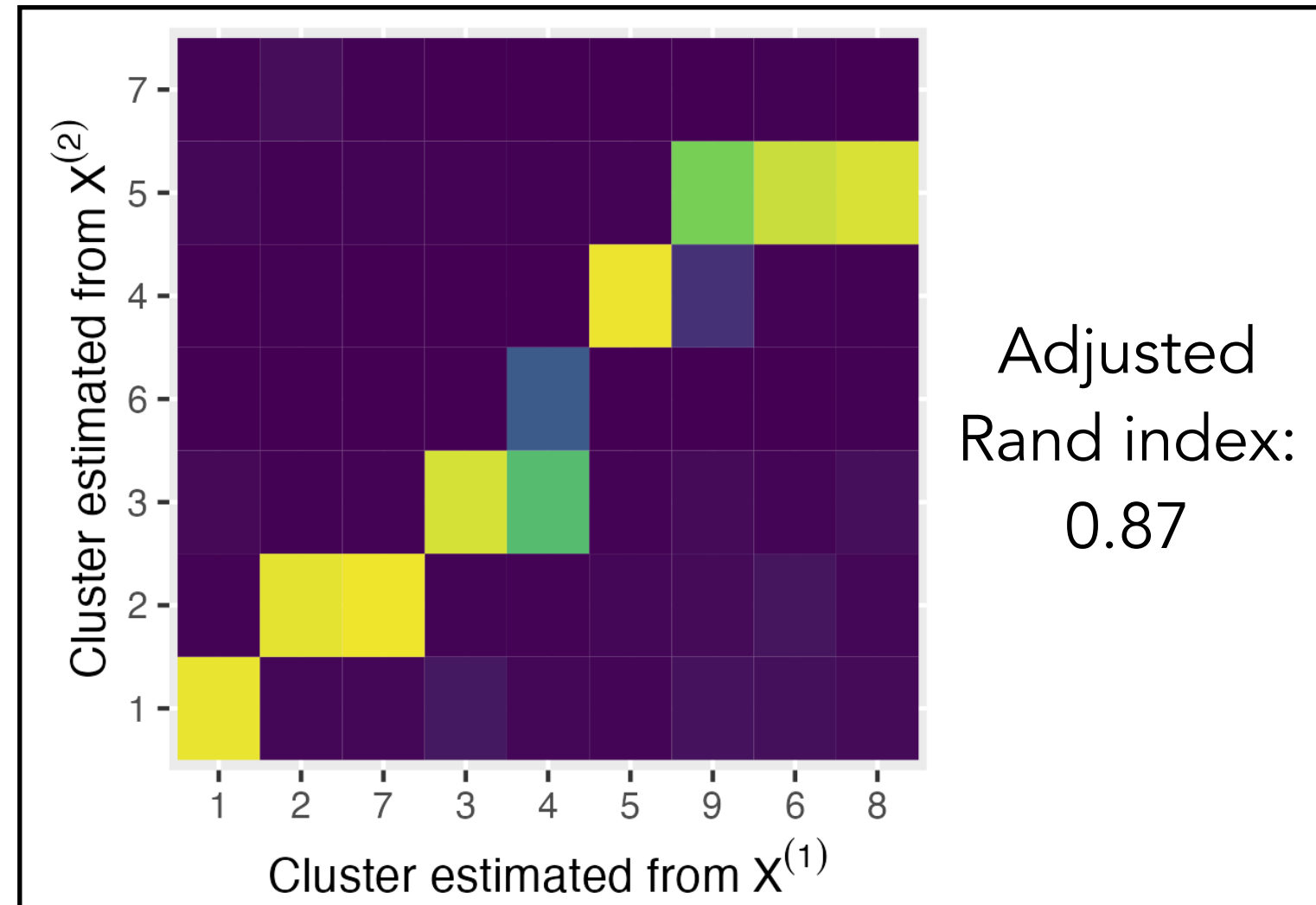
Intradataset cross validation



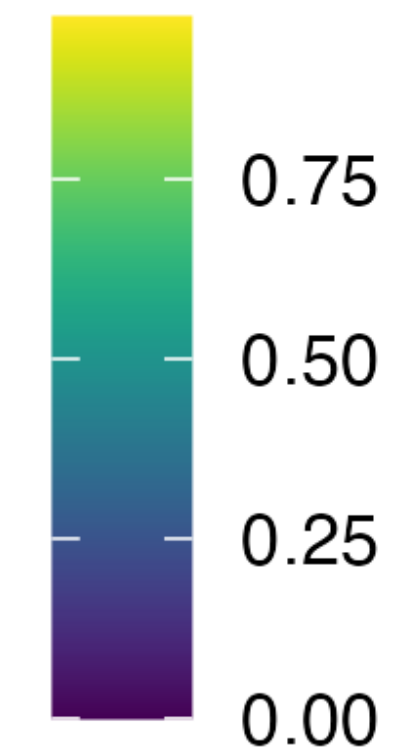
Metanephric Cells



Data thinning



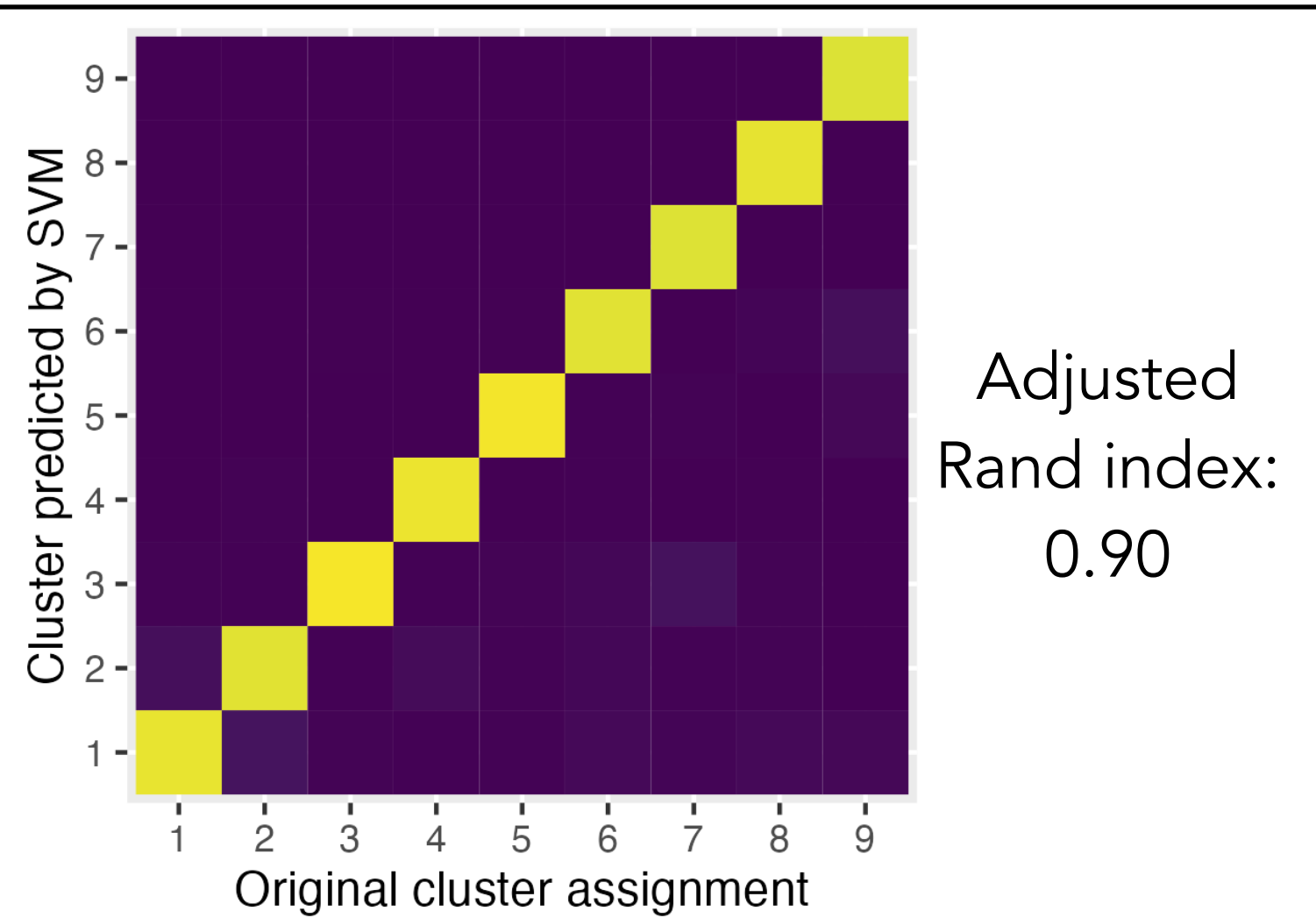
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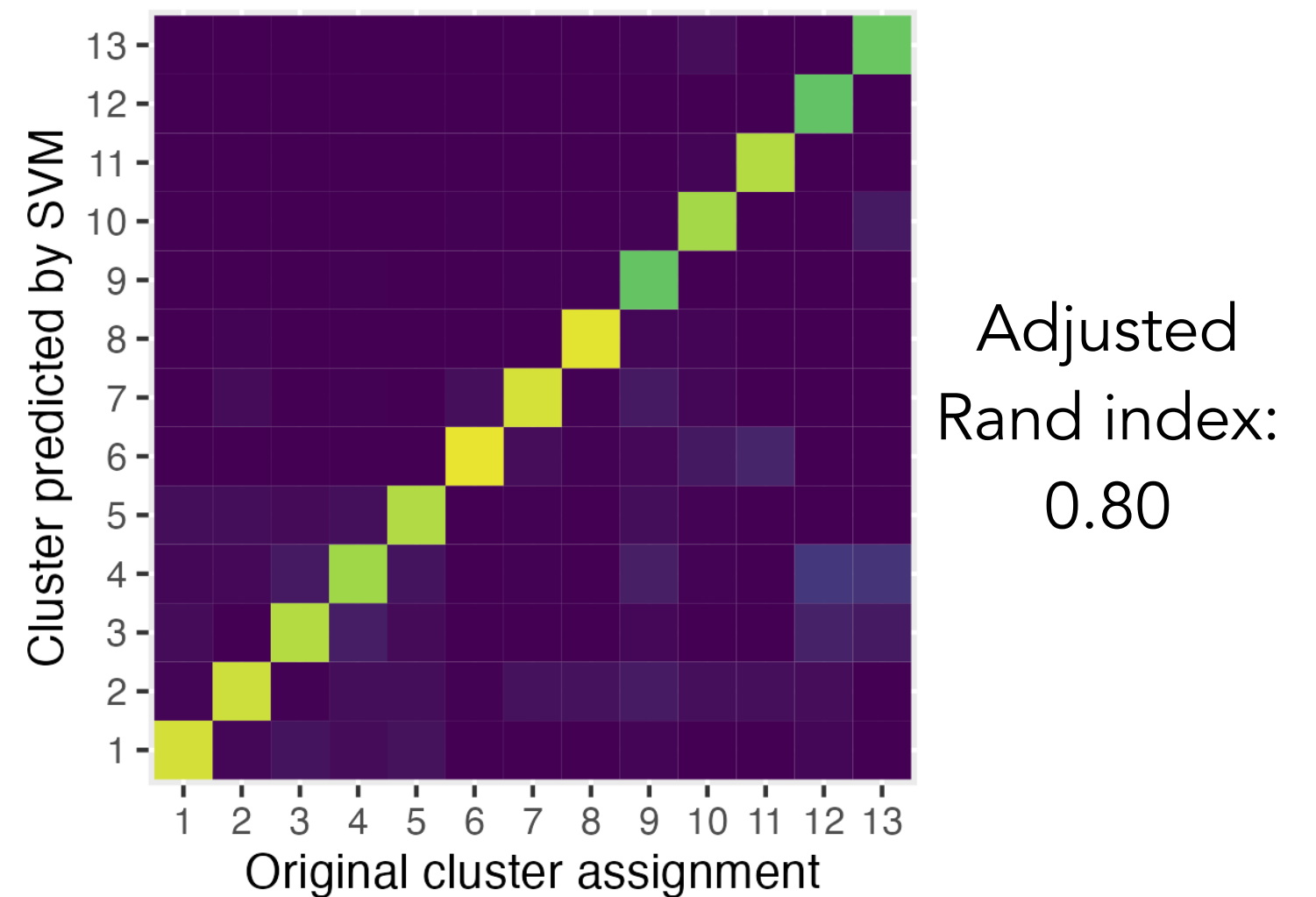
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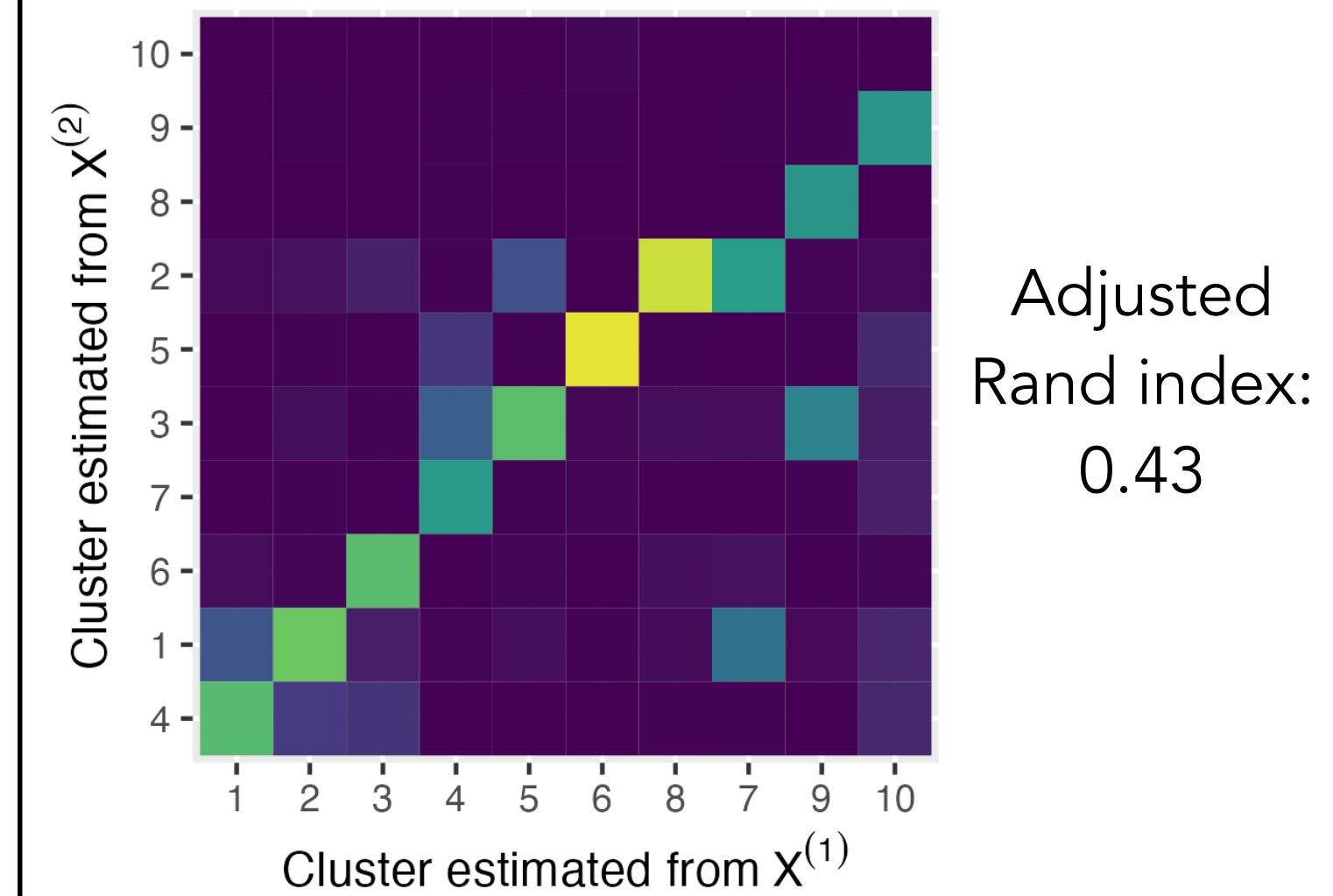
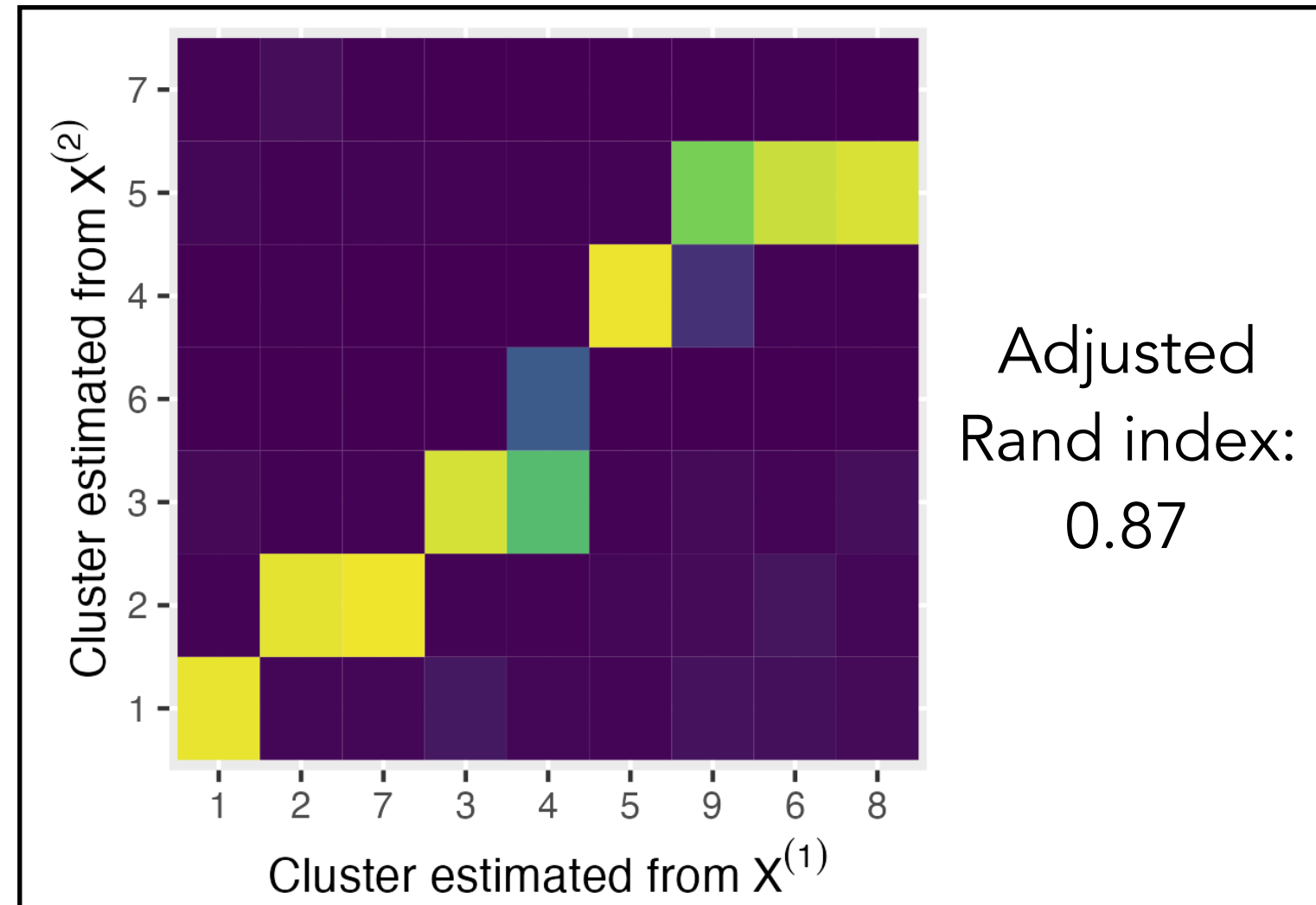
Intradataset cross validation



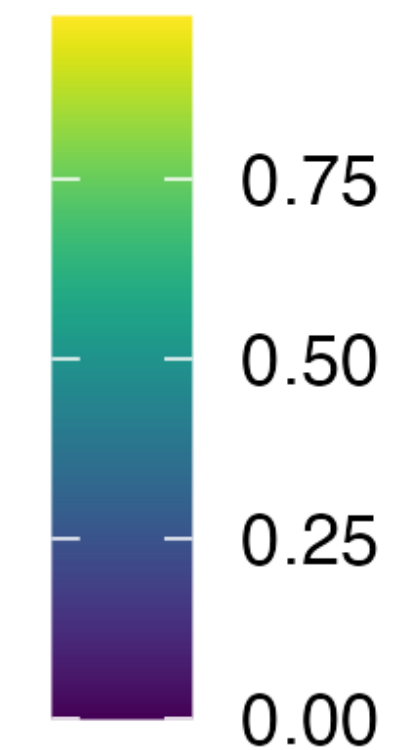
Metanephric Cells



Data thinning



Proportion of cells in column belonging to row



Negative binomial data thinning is useful in the analysis of single-cell RNA sequencing data

Project 4

Negative binomial count splitting
for single cell RNA sequencing data

Anna Neufeld, Lucy Gao, Josh Popp, Alexis Battle, Daniela Witten

Arxiv preprint will be posted soon!

Outline

1. Motivation: settings where sample splitting doesn't work
2. Poisson thinning
3. Data thinning
4. Application to single-cell RNA sequencing data
5. **Ongoing work**

Three ways to avoid double dipping

1. Specialized methods, such as selective inference.
2. Sample splitting.
3. Data thinning.

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Limited to convolution-closed distributions?

Revisiting the goals of data thinning

Goal: split a single observation X into $X^{(1)}$ and $X^{(2)}$ such that:

- (1) $X^{(1)}$ and $X^{(2)}$ have the same distribution as X , up to a parameter scaling.
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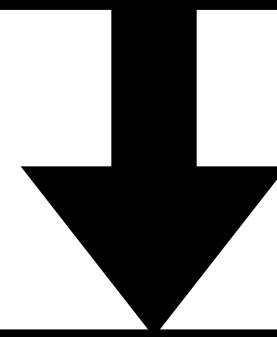
Generalized thinning with non-additive decompositions

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We observe realization x from $X \sim P_\theta$.

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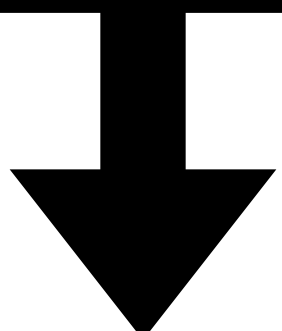
We know x could have arisen as $T(x', x'')$, where
 $X' \sim Q_\theta^1$, $X'' \sim Q_\theta^2$, $X' \perp\!\!\!\perp X''$.



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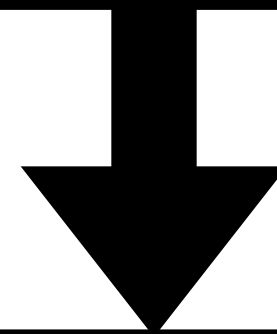


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Theorem:

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Key idea: If $X = T(X', X'')$ is sufficient for θ
in the joint of (X', X'') , then $G_{x,\theta}$ does not
depend on θ .

The list of distributions we can thin is extensive

Family	Distribution P_θ , where $X \sim P_\theta$.	Distribution $Q_\theta^{(k)}$ where $X^{(k)} \stackrel{ind.}{\sim} Q_\theta^{(k)}$.	Sufficient statistic T (sufficient for θ)
Natural exponential family (in parameter θ)	$N(\theta, \sigma^2)$ Poisson(θ) NegBin(r, θ) Binomial(r, θ) Gamma(α, θ) $N_p(\boldsymbol{\theta}, \Sigma)$ Multinomial $_p(r, \boldsymbol{\theta})$	$N(\epsilon_k \theta, \epsilon_k \sigma^2)$ Poisson($\epsilon_k \theta$) NegBin($\epsilon_k r, \theta$) Binomial($\epsilon_k r, \theta$) Gamma($\epsilon_k \alpha, \theta$) $N_p(\epsilon_k \boldsymbol{\theta}, \epsilon_k \Sigma)$ Multinomial $_p(\epsilon_k r, \boldsymbol{\theta})$	$\sum_{k=1}^K X^{(k)}$
	Gamma($K/2, \theta$) Gamma(K, θ)	$N(0, \frac{1}{2\theta})$ Weibull($\theta^{-\frac{1}{\nu}}, \nu$)	$\sum_{k=1}^K (X^{(k)})^2$ $\sum_{k=1}^K (X^{(k)})^\nu$
General exponential family (in parameter θ)	Beta(θ, β) Beta(α, θ) Gamma(θ, β) Weibull(θ, ν) Pareto(ν, θ)	Beta($\frac{1}{K}\theta + \frac{k-1}{K}, \frac{1}{K}\beta$) Beta($\frac{1}{K}\alpha, \frac{1}{K}\theta + \frac{k-1}{K}$) Gamma($\frac{1}{K}\theta + \frac{k-1}{K}, \frac{1}{K}\beta$) Gamma($\frac{1}{K}, \theta^{-\nu}$) Gamma($\frac{1}{K}, \theta$)	$(\prod_{k=1}^K X^{(k)})^{1/K}$ $(\prod_{k=1}^K (1 - X^{(k)}))^{1/K}$ $(\prod_{k=1}^K X^{(k)})^{1/K}$ $(\sum_{k=1}^K X^{(k)})^{1/\nu}$ $\nu \times \text{Exp}(\sum_{k=1}^K X^{(k)})$
	$N(0, \theta)$ $N_K(\theta_1 \mathbf{1}_K, \theta_2 \mathbf{I}_K)$	Gamma($\frac{1}{2K}, \frac{1}{2\theta}$) $N(\theta_1, \theta_2)$	$X^2 = \sum_{k=1}^K X^{(k)}$ sample mean and variance
Truncated support family	Unif($0, \theta$) $\theta \cdot \text{Beta}(\alpha, 1)$	$\theta \cdot \text{Beta}(\frac{1}{K}, 1)$ $\theta \cdot \text{Beta}(\frac{\alpha}{K}, 1)$	$\max(X^{(1)}, \dots, X^{(K)})$
	$\theta + \text{Exp}(\lambda)$	$\theta + \text{Exp}(\lambda/K)$	$\min(X^{(1)}, \dots, X^{(K)})$
Non-parametric	F^n	F^{n_k}	sort($X^{(1)}, \dots, X^{(K)}$)

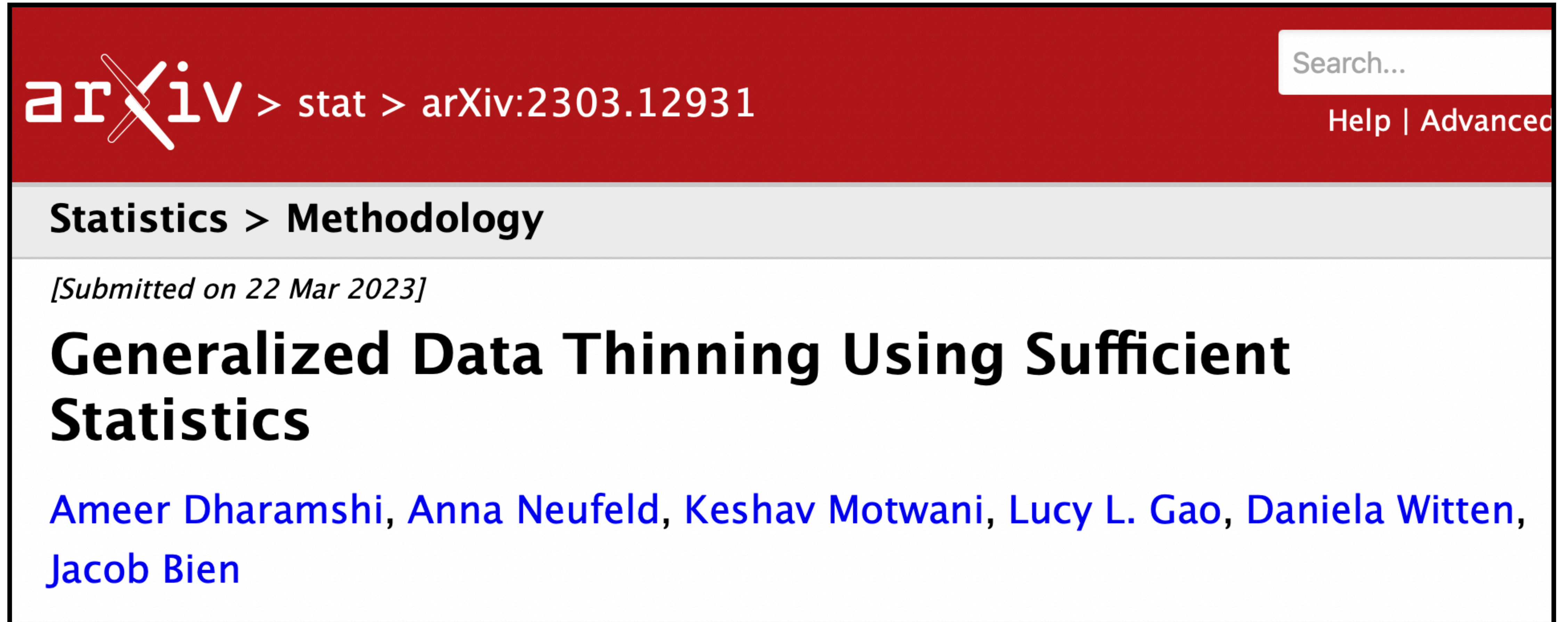
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Natural exponential family (in parameter θ)	$N(\theta, \sigma^2)$ $Poisson(\theta)$ $NegBin(r, \theta)$ $Binomial(r, \theta)$ $Gamma(\alpha, \theta)$ $N_p(\theta, \Sigma)$ $Multinomial_p(r, \theta)$	$N(\epsilon_k \theta, \epsilon_k \sigma^2)$ $Poisson(\epsilon_k \theta)$ $NegBin(\epsilon_k r, \theta)$ $Binomial(\epsilon_k r, \theta)$ $Gamma(\epsilon_k \alpha, \theta)$ $N_p(\epsilon_k \theta, \epsilon_k \Sigma)$ $Multinomial_p(\epsilon_k r, \theta)$	$\sum_{k=1}^K X^{(k)}$
	$Gamma(K/2, \theta)$ $Gamma(K, \theta)$	$N(0, \frac{1}{2\theta})$ $Weibull(\theta^{-\frac{1}{\nu}}, \nu)$	$\sum_{k=1}^K (X^{(k)})^2$ $\sum_{k=1}^K (X^{(k)})^\nu$
General exponential family (in parameter θ)	$Beta(\theta, \beta)$ $Beta(\alpha, \theta)$ $Gamma(\theta, \beta)$ $Weibull(\theta, \nu)$ $Pareto(\nu, \theta)$	$Beta\left(\frac{1}{K}\theta + \frac{k-1}{K}, \frac{1}{K}\beta\right)$ $Beta\left(\frac{1}{K}\alpha, \frac{1}{K}\theta + \frac{k-1}{K}\right)$ $Gamma\left(\frac{1}{K}\theta + \frac{k-1}{K}, \frac{1}{K}\beta\right)$ $Gamma\left(\frac{1}{K}, \theta^{-\nu}\right)$ $Gamma\left(\frac{1}{K}, \theta\right)$	$(\prod_{k=1}^K X^{(k)})^{1/K}$ $(\prod_{k=1}^K (1 - X^{(k)}))^{1/K}$ $(\prod_{k=1}^K X^{(k)})^{1/K}$ $(\sum_{k=1}^K X^{(k)})^{1/\nu}$ $\nu \times \text{Exp}\left(\sum_{k=1}^K X^{(k)}\right)$
	$N(0, \theta)$ $N_K(\theta_1 1_K, \theta_2 I_K)$	$Gamma\left(\frac{1}{2K}, \frac{1}{2\theta}\right)$ $N(\theta_1, \theta_2)$	$X^2 = \sum_{k=1}^K X^{(k)}$ sample mean and variance
Truncated support family	$Unif(0, \theta)$ $\theta \cdot Beta(\alpha, 1)$ $\theta + \text{Exp}(\lambda)$	$\theta \cdot Beta\left(\frac{1}{K}, 1\right)$ $\theta \cdot Beta\left(\frac{\alpha}{K}, 1\right)$ $\theta + \text{Exp}(\lambda/K)$	$\max(X^{(1)}, \dots, X^{(K)})$ $\min(X^{(1)}, \dots, X^{(K)})$
Non-parametric	F^n	F^{n_k}	$\text{sort}(X^{(1)}, \dots, X^{(K)})$

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Natural exponential family (in parameter θ)	$N(\theta, \sigma^2)$	$N(\epsilon_k \theta, \epsilon_k \sigma^2)$	$\sum_{k=1}^K X^{(k)}$	
	Poisson(θ)	Poisson($\epsilon_k \theta$)		
General exponential family (in parameter θ)	NegBin(r, θ)	NegBin($\epsilon_k r, \theta$)	$(\prod_{k=1}^K X^{(k)})^{1/K}$ $(\prod_{k=1}^K (1 - X^{(k)}))^{1/K}$	
	Binomial(r, θ)	Binomial($\epsilon_k r, \theta$)		
	Gamma(α, θ)	Gamma($\epsilon_k \alpha, \theta$)		
	$N_p(\boldsymbol{\theta}, \Sigma)$	$N_p(\epsilon_k \boldsymbol{\theta}, \epsilon_k \Sigma)$		
	Multinomial $_p(r, \boldsymbol{\theta})$	Multinomial $_p(\epsilon_k r, \boldsymbol{\theta})$		
	Gamma($K/2, \theta$)	$N(0, \frac{1}{2\theta})$		$\sum_{k=1}^K (X^{(k)})^2$
	Gamma(K, θ)	Weibull($\theta^{-\frac{1}{\nu}}, \nu$)		$\sum_{k=1}^K (X^{(k)})^\nu$
	Beta(θ, β)	Beta($\frac{1}{K}\theta + \frac{k-1}{K}, \frac{1}{K}\beta$)		$(\prod_{k=1}^K X^{(k)})^{1/K}$
	Beta(α, θ)	Beta($\frac{1}{K}\alpha, \frac{1}{K}\theta + \frac{k-1}{K}$)		$(\prod_{k=1}^K (1 - X^{(k)}))^{1/K}$
	Gamma(θ, β)	Gamma($\frac{1}{K}\theta + \frac{k-1}{K}, \frac{1}{K}\beta$)		$(\prod_{k=1}^K X^{(k)})^{1/K}$
Weibull(θ, ν)	Gamma($\frac{1}{K}, \theta^{-\nu}$)	$(\sum_{k=1}^K X^{(k)})^{1/\nu}$		
Pareto(ν, θ)	Gamma($\frac{1}{K}, \theta$)	$\nu \times \text{Exp}(\sum_{k=1}^K X^{(k)})$		
Truncated support family	$N(0, \theta)$	Gamma($\frac{1}{2K}, \frac{1}{2\theta}$)	$X^2 = \sum_{k=1}^K X^{(k)}$	
	$N_K(\theta_1 \mathbf{1}_K, \theta_2 \mathbf{I}_K)$	$N(\theta_1, \theta_2)$	sample mean and variance	
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	$\theta \cdot \text{Beta}(\alpha, 1)$	$\theta \cdot \text{Beta}(\frac{\alpha}{K}, 1)$		
	$\theta + \text{Exp}(\lambda)$	$\theta + \text{Exp}(\lambda/K)$	$\min(X^{(1)}, \dots, X^{(K)})$	
Non-parametric	F^n	F^{n_k}	sort($X^{(1)}, \dots, X^{(K)}$)	

We are working on additional extensions to Project 3



The image is a screenshot of an arXiv preprint page. At the top left is the arXiv logo, followed by the breadcrumb path 'stat > arXiv:2303.12931'. On the top right, there is a search bar with the text 'Search...' and links for 'Help | Advanced'. Below the breadcrumb path is a grey bar with the text 'Statistics > Methodology'. Underneath this is the submission date '[Submitted on 22 Mar 2023]'. The main title of the preprint is 'Generalized Data Thinning Using Sufficient Statistics' in a large, bold, black font. Below the title, the authors are listed in blue text: 'Ameer Dharamshi, Anna Neufeld, Keshav Motwani, Lucy L. Gao, Daniela Witten, Jacob Bien'.

arXiv > stat > arXiv:2303.12931

Search...
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Statistics > Methodology

[Submitted on 22 Mar 2023]

Generalized Data Thinning Using Sufficient Statistics

Ameer Dharamshi, Anna Neufeld, Keshav Motwani, Lucy L. Gao, Daniela Witten, Jacob Bien

Acknowledgements

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Questions?
