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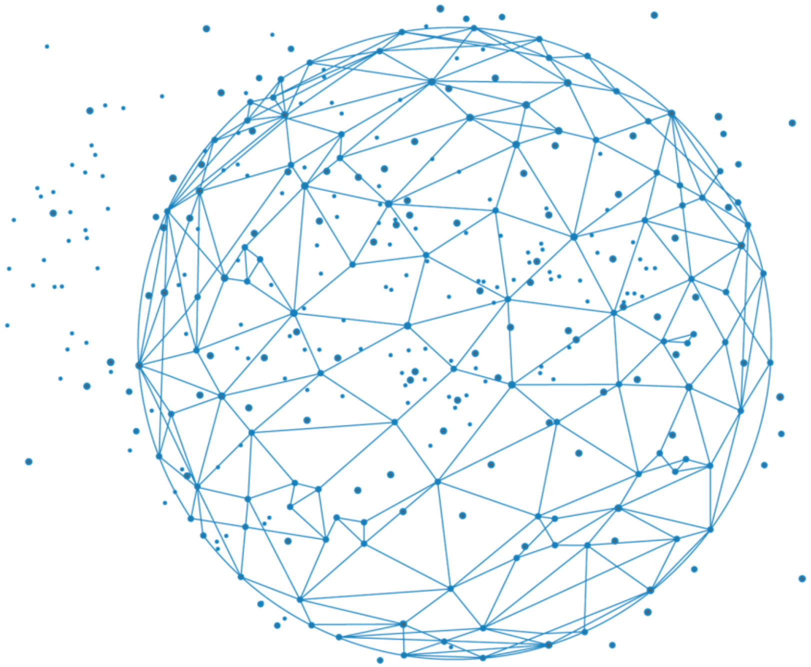
ÉCOLE THÉMATIQUE ETBII BIOINFORMATIQUE INTÉGRATIVE IFB



Regularized Generalized Canonical Correlation Analysis (RGCCA)

Jimmy Vandel (Plateforme Lilloise en Biologie & Santé)
Arnaud Gloaguen (CNRGH - CEA)
Vincent Guillemot (Institut Pasteur)

DOI version final

INSTITUT FRANÇAIS DE BIOINFORMATIQUE

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1. Introduction of the case study

2. **Unsupervised analysis with one-block:** Principal Component Analysis (PCA)

3. **Unsupervised analysis with two-blocks:**
   Partial Least Squares (PLS) and Canonical Correlation Analysis (CCA)

4. **Unsupervised analysis with $\boldsymbol{L}$-blocks:**
   Regularized Generalized Canonical Correlation Analysis (RGCCA)

5. **Supervised analysis with RGCCA**

6. **Variable selection in RGCCA:**
   Sparse Generalized Canonical Correlation Analysis (SGCCA)

7. **The flexible Optimization Framework of RGCCA**

   - The general principal
   - Extension to multi-way analysis
   - From Sequential to Global

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4. **Unsupervised analysis with L-blocks:**
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Sparse Generalized Canonical Correlation Analysis (SGCCA)

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    - Extension to multi-way analysis
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Case Study: Major Depressive Disorder (MDD)

Data from this case study comes from Amazigh et. al 2024 **Sex-specific and multiomic integration enhance accuracy of peripheral blood biomarkers of major depressive disorder**.

a

Cohort Description

Sex	n .max	Group	mean.Age	mean.BMI	mean.HDRS	n (mRNA)	n (miRNA)	n (DNAm)
Female	55	Control	45	23.97	1.44	55 (100%)	51 (92.7%)	50 (90.9%)
	50	Patient	42	24	23.16	50 (100%)	39 (78%)	39 (78%)
Male	34	Control	45	24.02	1.18	34 (100%)	34 (100%)	31 (91.1%)
	30	Patient	43	25.51	23.47	30 (100%)	30 (100%)	28 (93.3%)
Total	**169**							

b

Data Collection

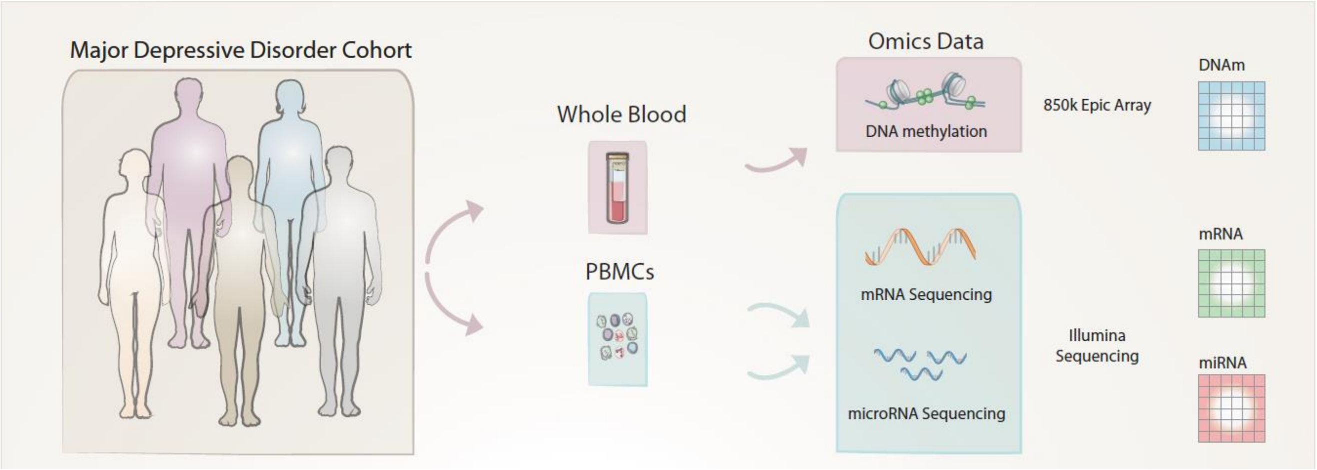

Figure taken from Amazigh Mokhtari’s PhD manuscript.

Case Study: Covariates

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> summary(DNAm_covariates_explored_female)
  Sample_Group          BMI              BMI.bin           Age             Age.bin       Age_bin       Array                    Slide    
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                                                                 >70   : 1             (Other): 8    (Other)     :73  
      CD4                 CD8                  MO                   B                   NK                  GR        
 Min.   :0.08709    Min.   :0.02919    Min.   :0.04979    Min.   :0.00000    Min.   :0.00000    Min.   :0.3883  
 1st Qu.:0.15202    1st Qu.:0.08095    1st Qu.:0.07906    1st Qu.:0.01484    1st Qu.:0.03505    1st Qu.:0.5122  
 Median :0.19110    Median :0.10843    Median :0.08997    Median :0.02433    Median :0.05053    Median :0.5982  
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 3rd Qu.:0.21439    3rd Qu.:0.12263    3rd Qu.:0.10495    3rd Qu.:0.03967    3rd Qu.:0.07699    3rd Qu.:0.6446  
 Max.   :0.30672    Max.   :0.19381    Max.   :0.14454    Max.   :0.13657    Max.   :0.14684    Max.   :0.7691  
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Case Study: Covariates

Low (≤ 25), High (≥ 30).

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Relative to blood cell composition (T cells subsets, monocytes, B cells, NK cells and granulocytes) inferred from DNAm.

Case Study: Pre-processing

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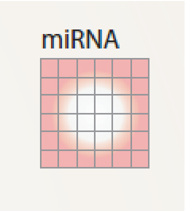

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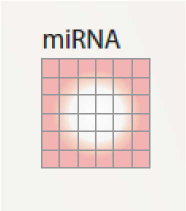

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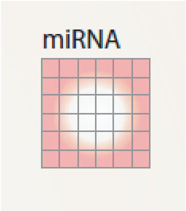

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2. Log Counts Per Million (logCPM) normalization.

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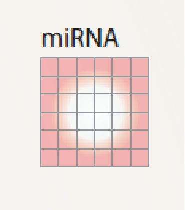

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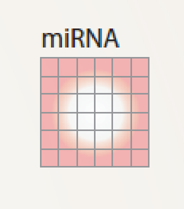

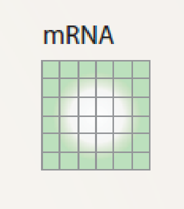

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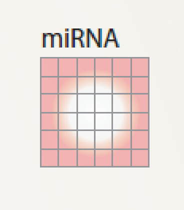

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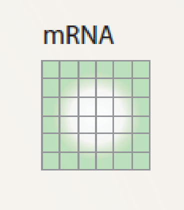

1. Normalization with Variance Stabilizing Transformations (VST; package DESeq2).

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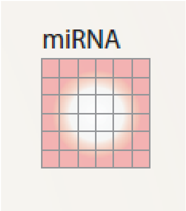

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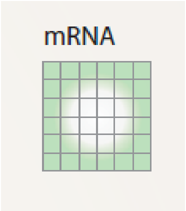

1. Normalization with Variance Stabilizing Transformations (VST; package DESeq2).
2. Keep only genes both present in males and females.

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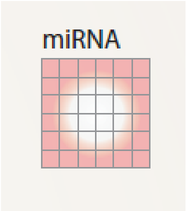

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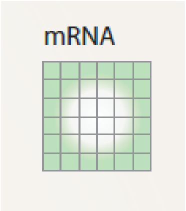

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$MAD = median(|x_i - median(\mathbf{x})|)$, it is a robust estimation of the standard deviation.

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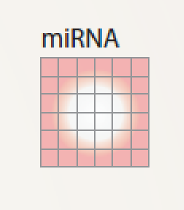

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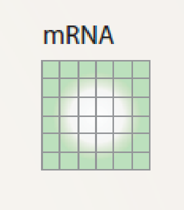

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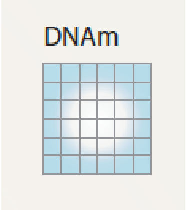

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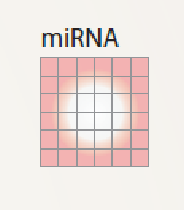

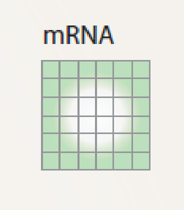

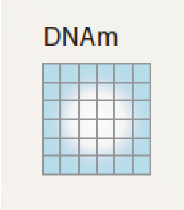

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1. Normalization with Variance Stabilizing Transformations (VST; package DESeq2).
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1. Normalization with Beta-MIxture Quantile (BMIQ) Normalization method (package ChAMP).

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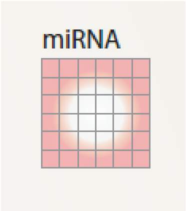

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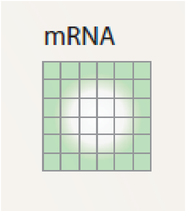

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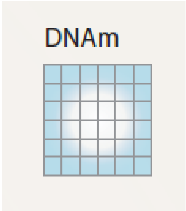

1. Normalization with Beta-MIxture Quantile (BMIQ) Normalization method (package ChAMP).
2. Remove duplicated samples.

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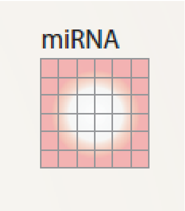

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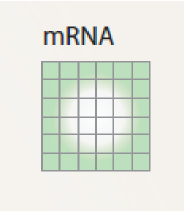

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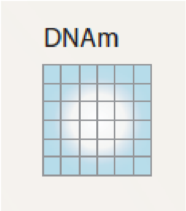

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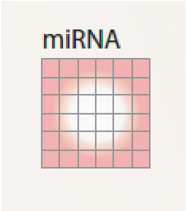

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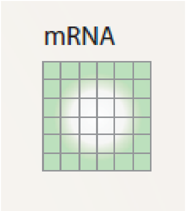

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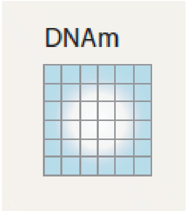

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Finally: individuals common to ALL omics data are kept.

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6. **Variable selection in RGCCA:**
   Sparse Generalized Canonical Correlation Analysis (SGCCA)

7. **The flexible Optimization Framework of RGCCA**

   - The general principal
   - Extension to multi-way analysis
   - From Sequential to Global

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$$F = \frac{(RSS_0 - RSS_1)}{1} \times \frac{(n-2)}{RSS_1} = \frac{\left(\sum_i (y_i - \beta_0)^2 - \sum_i (y_i - \beta_0 - \beta_1 x_i)^2\right)}{1} \times \frac{(n-2)}{\sum_i (y_i - \beta_0 - \beta_1 x_i)^2}$$

It is possible to show that F follows an F-distribution of 1 and $n - 2$ degrees of freedom.

If the variables are strongly linked ➔ $RSS_0 \gg RSS_1$ ➔ $F \sim \frac{RSS_0}{RSS_1} \times (n-2) \gg n - 2$ ➔ The test is likely to be rejected.

If the variables are NOT strongly linked

ChAMP's representation: F-test

In order to evaluate the link between two continuous variables y_i and x_i, the following model is used:

$$y_i = \beta_0 + \beta_1 x_i + \epsilon_i$$

Where β_0 is the intercept, β_1 is the coefficient associated with x_i and $\epsilon_i \sim \mathcal{N}(0, \sigma^2)$.

The following test is used: $\begin{cases} \mathrm{H}_0: \beta_1 = 0, \\ \mathrm{H}_1: \beta_1 \neq 0 \end{cases}$

With the statistic:

$$F = \frac{(RSS_0 - RSS_1)}{1} \times \frac{(n-2)}{RSS_1} = \frac{(\sum_i (y_i - \beta_0)^2 - \sum_i (y_i - \beta_0 - \beta_1 x_i)^2)}{1} \times \frac{(n-2)}{\sum_i (y_i - \beta_0 - \beta_1 x_i)^2}$$

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If the variables are strongly linked ➔ $RSS_0 \gg RSS_1$ ➔ $F \sim \frac{RSS_0}{RSS_1} \times (n-2) \gg n-2$ ➔ The test is likely to be rejected.

If the variables are NOT strongly linked ➔ $RSS_0 \sim RSS_1$

ChAMP's representation: F-test

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If the variables are strongly linked ➔ $RSS_0 \gg RSS_1$ ➔ $F \sim \frac{RSS_0}{RSS_1} \times (n-2) \gg n-2$ ➔ The test is likely to be rejected.

If the variables are NOT strongly linked ➔ $RSS_0 \sim RSS_1$ ➔ $F \sim 0$

ChAMP's representation: F-test

In order to evaluate the link between two continuous variables y_i and x_i, the following model is used:

$$y_i = \beta_0 + \beta_1 x_i + \epsilon_i$$

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$$F = \frac{(RSS_0 - RSS_1)}{1} \times \frac{(n-2)}{RSS_1} = \frac{\left(\sum_i (y_i - \beta_0)^2 - \sum_i (y_i - \beta_0 - \beta_1 x_i)^2\right)}{1} \times \frac{(n-2)}{\sum_i (y_i - \beta_0 - \beta_1 x_i)^2}$$

It is possible to show that F follows an F-distribution of 1 and $n-2$ degrees of freedom.

If the variables are strongly linked ➔ $RSS_0 \gg RSS_1$ ➔ $F \sim \frac{RSS_0}{RSS_1} \times (n-2) \gg n-2$ ➔ The test is likely to be rejected.

If the variables are NOT strongly linked ➔ $RSS_0 \sim RSS_1$ ➔ $F \sim 0$ ➔ The test is likely to be accepted.

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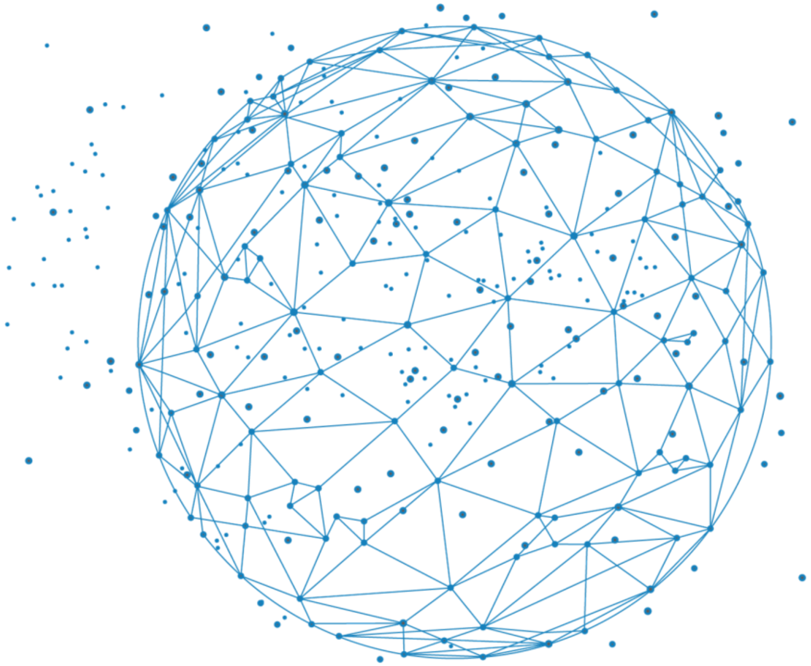
Now with this 2 tests, let us see what are the results of PCA on the MDD case study

➔ See section 1 on the Rmarkdown `MDD_case_study_RGCCA`



1. Introduction of the case study

2. **Unsupervised analysis with one-block:** Principal Component Analysis (PCA)

3. **Unsupervised analysis with two-blocks:**
   Partial Least Squares (PLS) and Canonical Correlation Analysis (CCA)

4. **Unsupervised analysis with L-blocks:**
   Regularized Generalized Canonical Correlation Analysis (RGCCA)

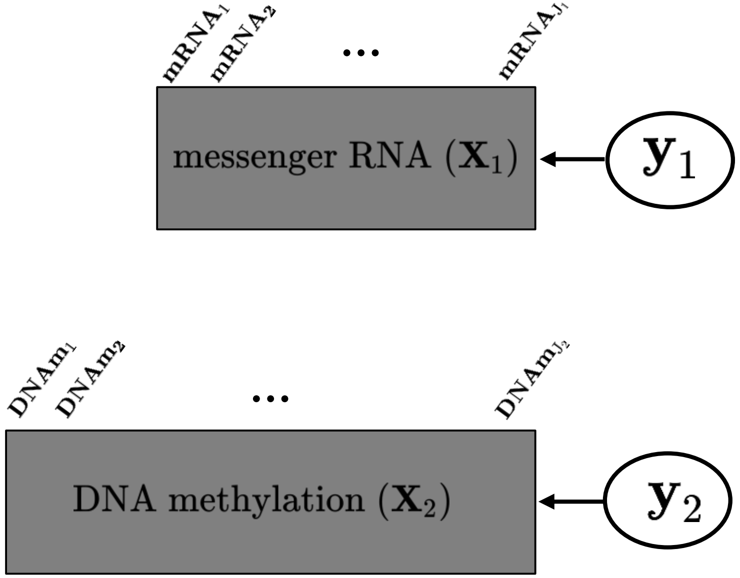
5. **Supervised analysis with RGCCA**

6. **Variable selection in RGCCA:**
   Sparse Generalized Canonical Correlation Analysis (SGCCA)

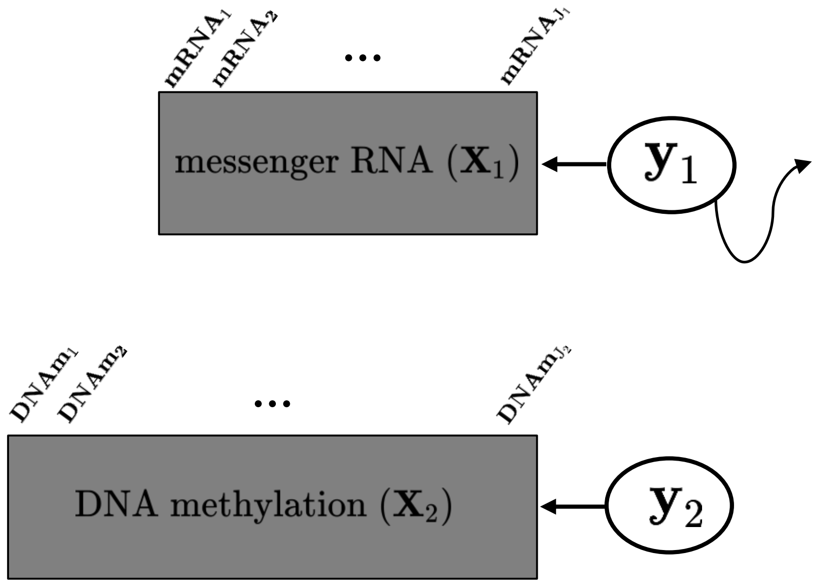
7. **The flexible Optimization Framework of RGCCA**

   - The general principal
   - Extension to multi-way analysis
   - From Sequential to Global

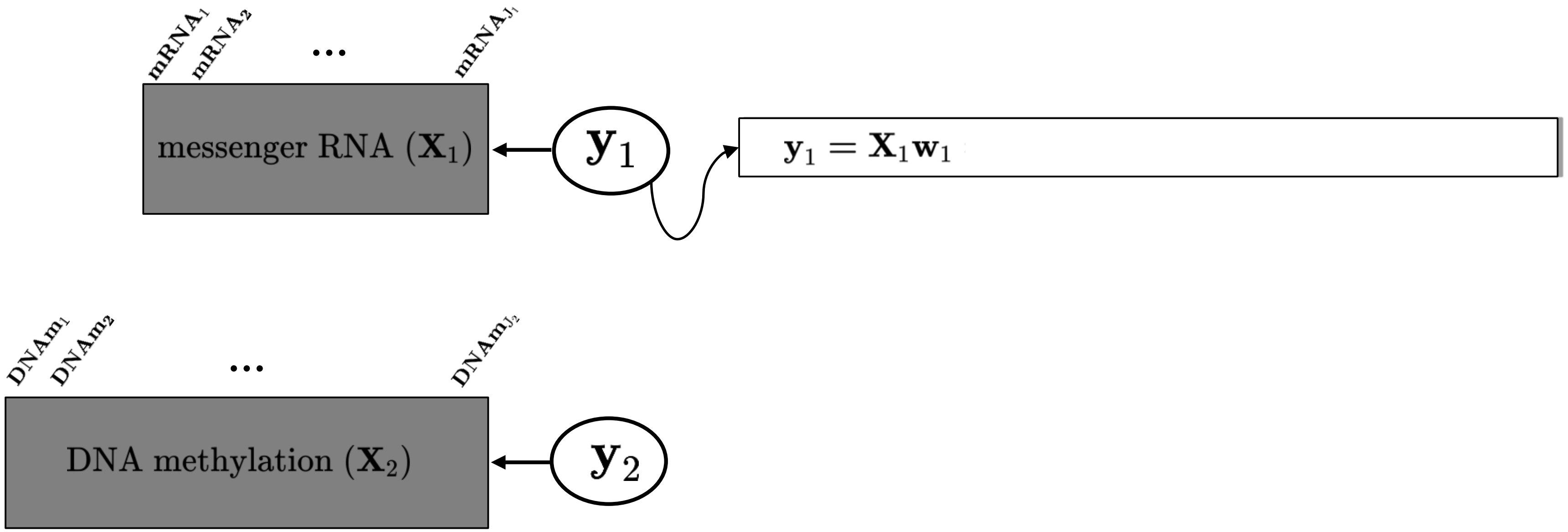
The philosophy of multiblock component methods



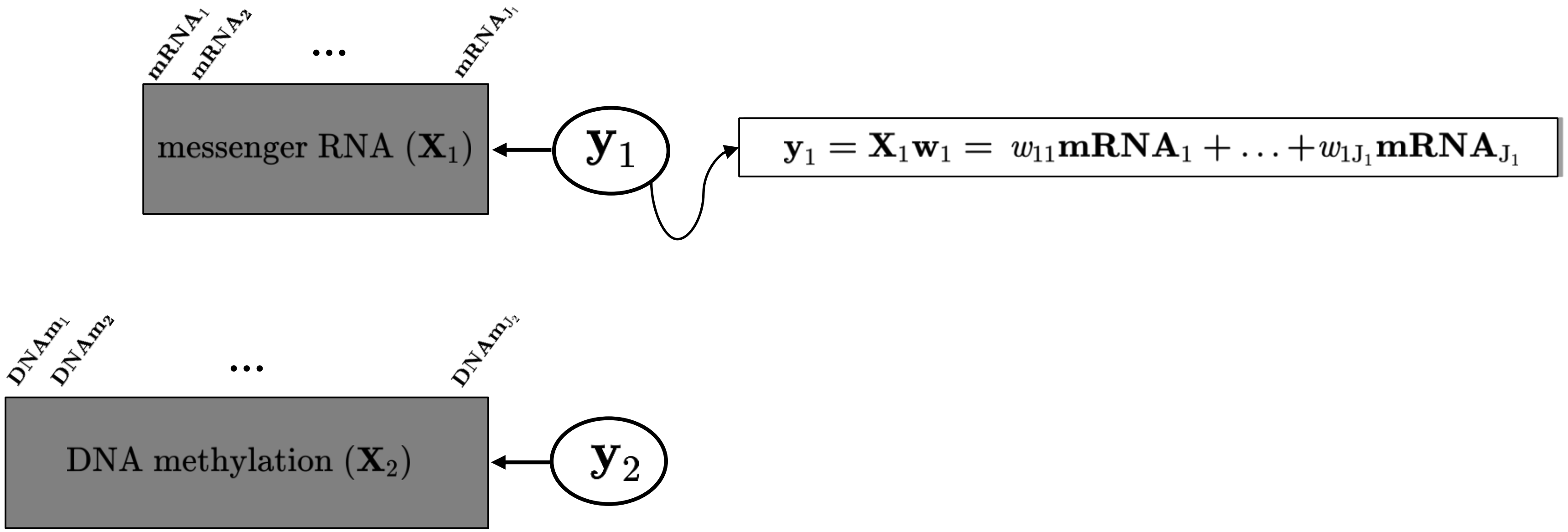
The philosophy of multiblock component methods



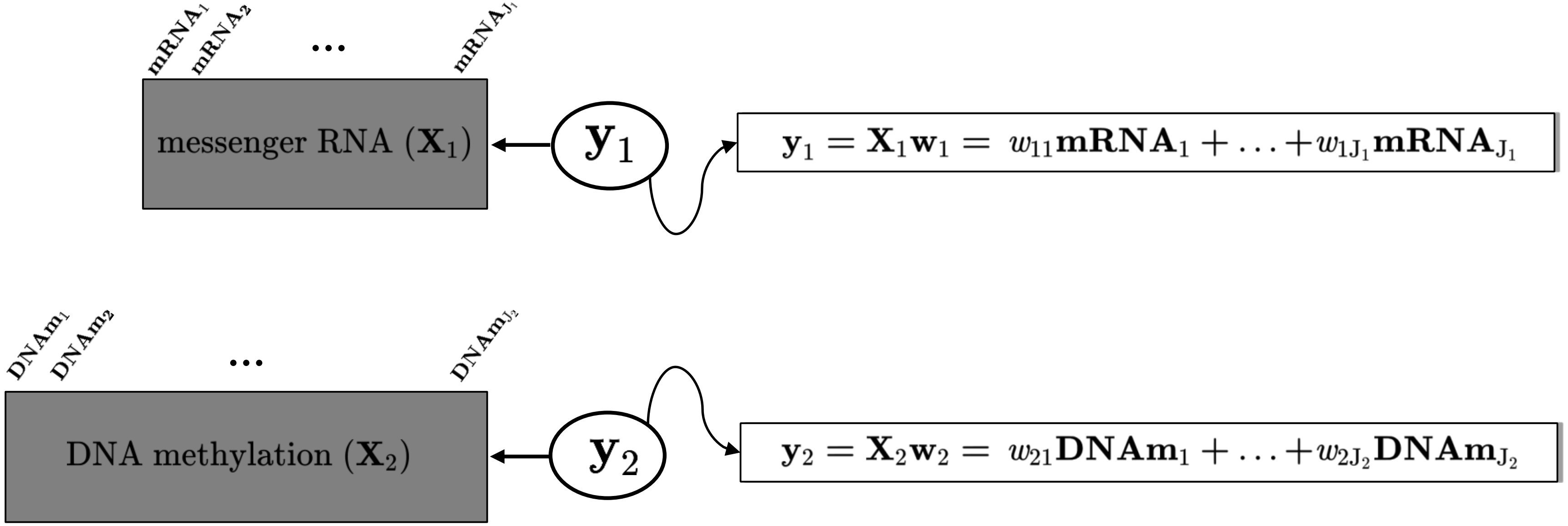
The philosophy of multiblock component methods



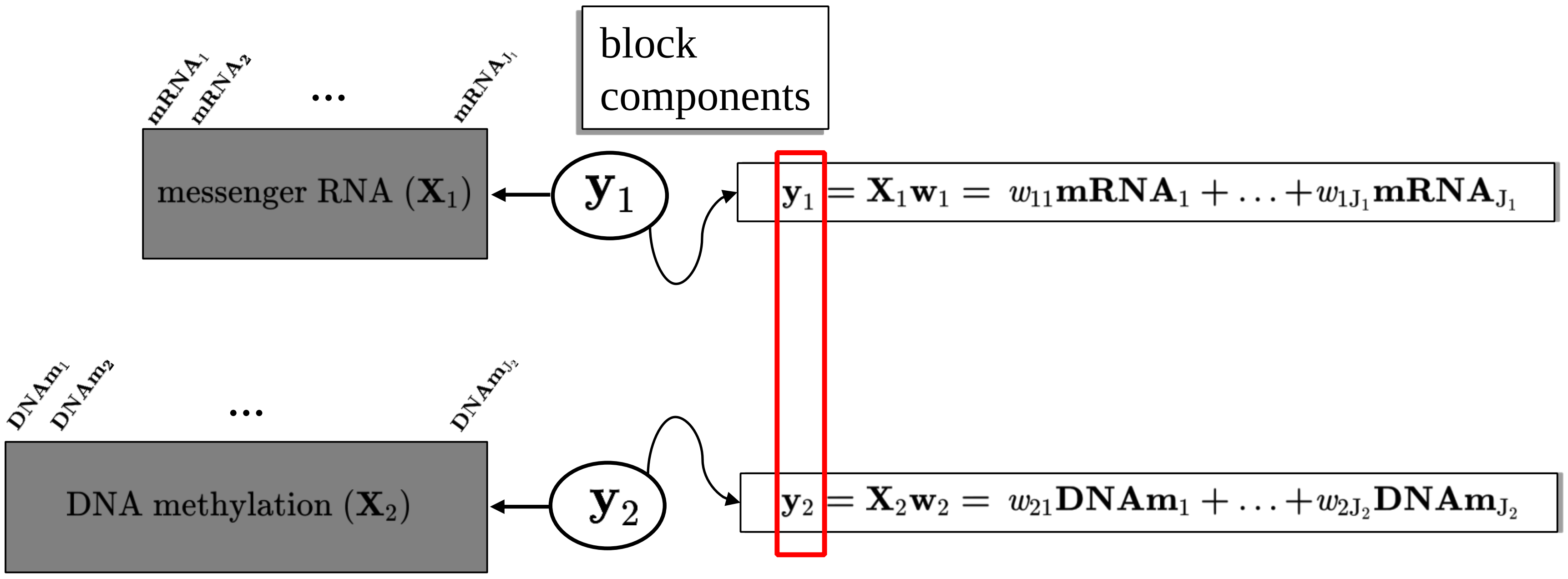
The philosophy of multiblock component methods



The philosophy of multiblock component methods



The philosophy of multiblock component methods



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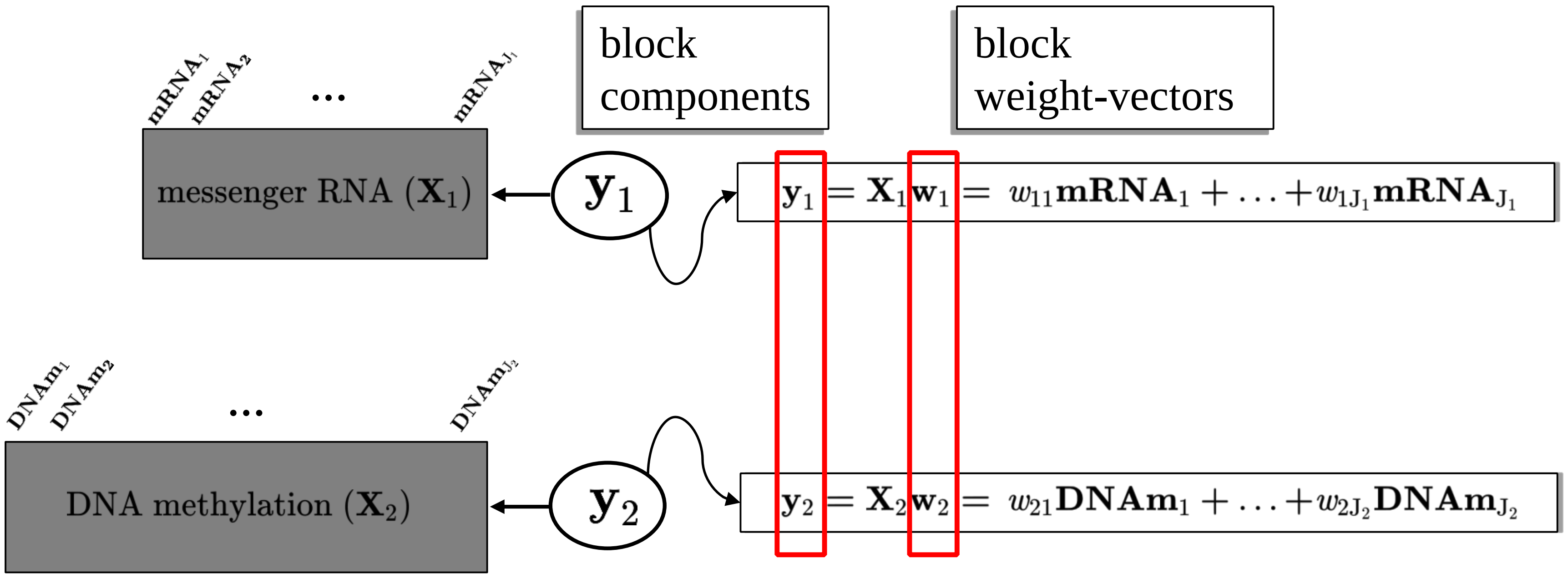
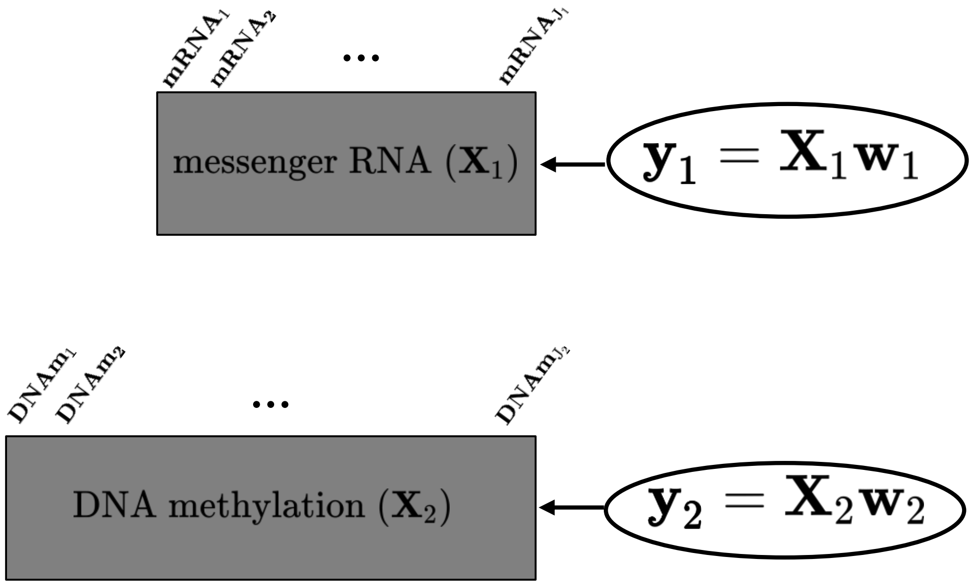


The philosophy of multiblock component methods

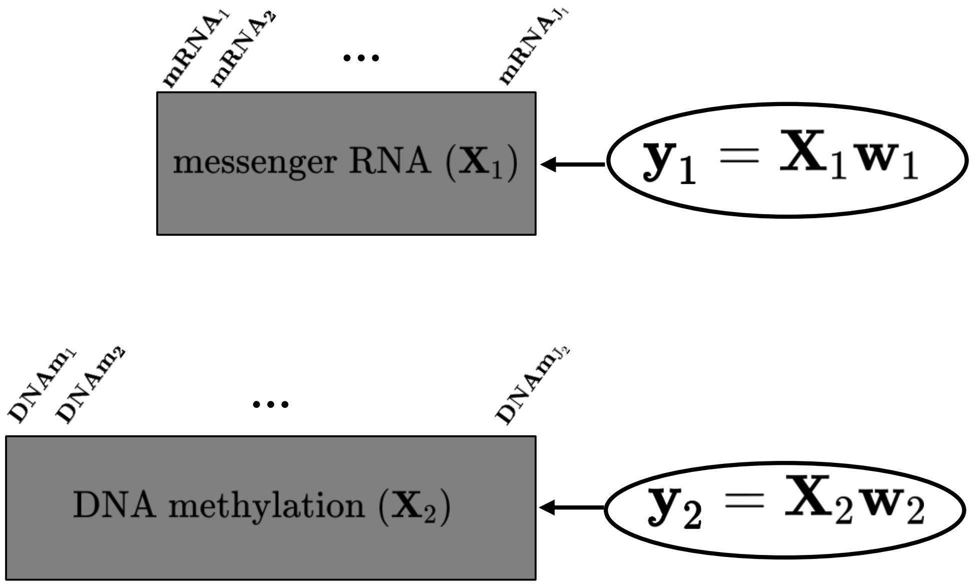


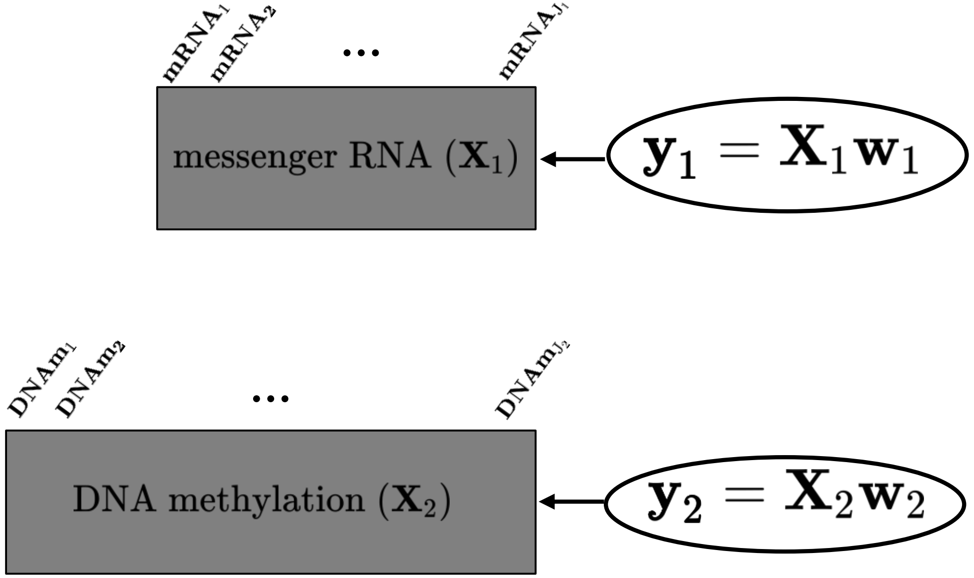
Block components should verified two properties at the same time:

1. Block components well explain their own block.

1. Block components are as correlated as possible for connected blocks.

The philosophy of multiblock component methods





Correlation based methods

Find block-weight vectors $\mathbf{w}_1, \ldots, \mathbf{w}_J$ maximizing a function of $\mathbf{\Phi} = \{\text{cor}(\mathbf{X}_j\mathbf{w}_j, \mathbf{X}_k\mathbf{w}_k)\}$.

Covariance based methods

Find block-weight vectors $\mathbf{w}_1, \ldots, \mathbf{w}_J$ maximizing a function of $\mathbf{\Psi} = \{\text{cov}(\mathbf{X}_j\mathbf{w}_j, \mathbf{X}_k\mathbf{w}_k)\}$.

Courtesy to Arthur Tenenhaus.

Principal Component Analysis (PCA)

$$\max_{\substack{\mathbf{w} \\ \|\mathbf{w}\|_2^2=1}} \ \mathrm{Var}(\mathbf{X}\mathbf{w})$$

From PCA to PLS/CCA

How can we "adapt" PCA for two-blocks analysis ?

$$\max_{\substack{\mathbf{w} \\ \|\mathbf{w}\|_2^2=1}} \ \mathrm{Var}(\mathbf{Xw})$$

From PCA to PLS/CCA

How can we "adapt" PCA for two-blocks analysis ?

$$\max_{\substack{\mathbf{w}_1,\mathbf{w}_2 \\ \|\mathbf{w}_\mathrm{i}\|_2^2 = 1}} \mathrm{Var}(\mathbf{X}_1\mathbf{w}_1)\,\mathrm{Var}(\mathbf{X}_2\mathbf{w}_2)$$

From PCA to PLS/CCA

How can we "adapt" PCA for two-blocks analysis ?

$$\max_{\substack{\mathbf{w}_1,\mathbf{w}_2 \\ \|\mathbf{w}_\mathrm{i}\|_2^2 = 1}} \quad \mathrm{Var}(\mathbf{X}_1\mathbf{w}_1) \qquad\qquad \mathrm{Var}(\mathbf{X}_2\mathbf{w}_2)$$

From PCA to PLS/CCA

How can we "adapt" PCA for two-blocks analysis ?

$$\max_{\substack{\mathbf{w}_1,\mathbf{w}_2 \\ \|\mathbf{w}_i\|_2^2 = 1}} \ \mathrm{Var}(\mathbf{X}_1\mathbf{w}_1)\,\mathrm{Cor}(\mathbf{X}_1\mathbf{w}_1, \mathbf{X}_2\mathbf{w}_2)\mathrm{Var}(\mathbf{X}_2\mathbf{w}_2)$$

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From PCA to PLS/CCA

How can we "adapt" PCA for two-blocks analysis ?

$$\max_{\substack{\mathbf{w}_1,\mathbf{w}_2 \\ \|\mathbf{w}_\mathrm{i}\|_2^2 = 1}} \sqrt{\mathrm{Var}(\mathbf{X}_1\mathbf{w}_1)}\,\mathrm{Cor}(\mathbf{X}_1\mathbf{w}_1, \mathbf{X}_2\mathbf{w}_2)\sqrt{\mathrm{Var}(\mathbf{X}_2\mathbf{w}_2)}$$

How can we "adapt" PCA for two-blocks analysis ?

$$\max_{\substack{\mathbf{w}_1,\mathbf{w}_2 \\ \|\mathbf{w}_\mathrm{i}\|_2^2 = 1}} \underbrace{\sqrt{\mathrm{Var}(\mathbf{X}_1\mathbf{w}_1)}\,\mathrm{Cor}(\mathbf{X}_1\mathbf{w}_1, \mathbf{X}_2\mathbf{w}_2)\sqrt{\mathrm{Var}(\mathbf{X}_2\mathbf{w}_2)}}_{\mathrm{Cov}(\mathbf{X}_1\mathbf{w}_1, \mathbf{X}_2\mathbf{w}_2)}$$

From PCA to PLS/CCA

<u>How can we “adapt” PCA for two-blocks analysis ?</u>

$$\max_{\substack{\mathbf{w}_1,\mathbf{w}_2 \\ \|\mathbf{w}_\mathrm{i}\|_2^2 = 1}} \quad \mathrm{Cov}(\mathbf{X}_1\mathbf{w}_1, \mathbf{X}_2\mathbf{w}_2)$$

From PCA to PLS/CCA

<u>How can we "adapt" PCA for two-blocks analysis ?</u>

$$\max_{\substack{\mathbf{w}_1,\mathbf{w}_2 \\ \mathrm{Var}(\mathbf{X}_i\mathbf{w}_i)=1}} \quad \mathrm{Cov}(\mathbf{X}_1\mathbf{w}_1, \mathbf{X}_2\mathbf{w}_2)$$

From PCA to PLS/CCA

How can we “adapt” PCA for two-blocks analysis ?

$$\max_{\substack{\mathbf{w}_1,\mathbf{w}_2 \\ \mathrm{Var}(\mathbf{X}_i\mathbf{w}_i)=1}} \mathrm{Cov}(\mathbf{X}_1\mathbf{w}_1, \mathbf{X}_2\mathbf{w}_2) = \max_{\substack{\mathbf{w}_1,\mathbf{w}_2 \\ \mathrm{Var}(\mathbf{X}_i\mathbf{w}_i)=1}} \mathrm{Cor}(\mathbf{X}_1\mathbf{w}_1, \mathbf{X}_2\mathbf{w}_2)$$

From PCA to PLS/CCA

From PCA to PLS/CCA

<u>Partial Least Squares</u> (PLS2)

$$\max_{\substack{\mathbf{w}_1,\mathbf{w}_2 \\ \|\mathbf{w}_i\|_2^2=1}} \quad \mathrm{Cov}(\mathbf{X}_1\mathbf{w}_1, \mathbf{X}_2\mathbf{w}_2)$$

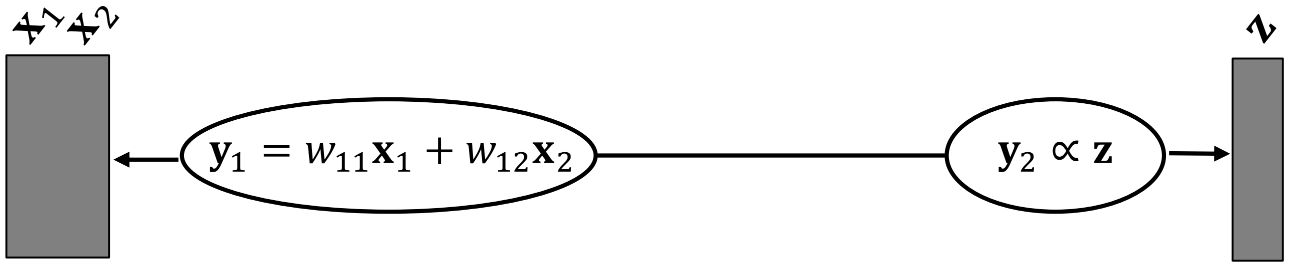
Canonical Correlation Analysis (CCA)

$$\max_{\substack{\mathbf{w}_1,\mathbf{w}_2 \\ \mathrm{Var}(\mathbf{X}_i\mathbf{w}_i)=1}} \mathrm{Cov}(\mathbf{X}_1\mathbf{w}_1, \mathbf{X}_2\mathbf{w}_2)$$

Partial Least Squares (PLS2)

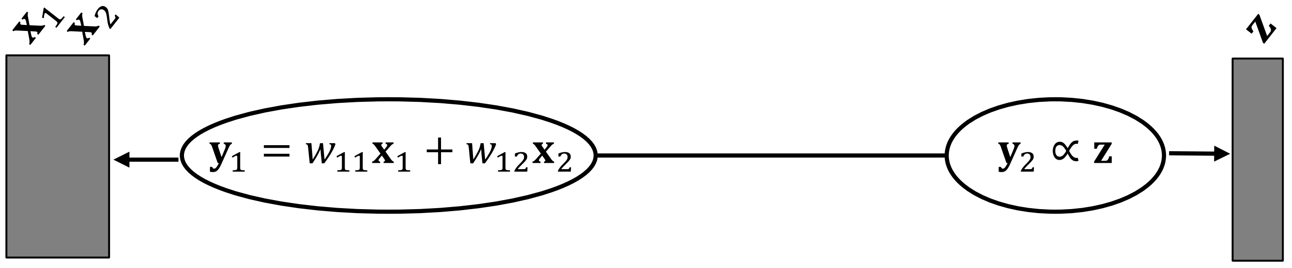
$$\max_{\substack{\mathbf{w}_1,\mathbf{w}_2 \\ \|\mathbf{w}_i\|_2^2=1}} \mathrm{Cov}(\mathbf{X}_1\mathbf{w}_1, \mathbf{X}_2\mathbf{w}_2)$$

PLS & CCA with a figure



PLS & CCA with a figure

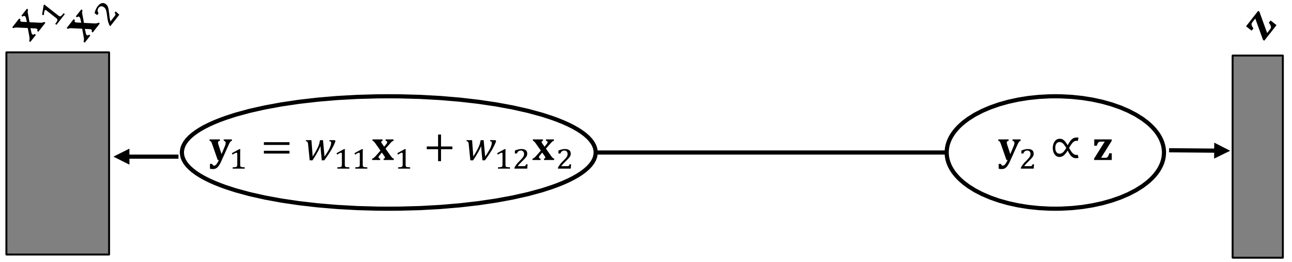
$$[\mathbf{x}_1\ \mathbf{x}_2] \sim \mathcal{N}\left((0,0), \begin{pmatrix} 1 & 0.5 \\ 0.5 & 1 \end{pmatrix}\right)$$



PLS & CCA with a figure

$$[\mathbf{x}_1\ \mathbf{x}_2] \sim \mathcal{N}\left((0,0), \begin{pmatrix} 1 & 0.5 \\ 0.5 & 1 \end{pmatrix}\right)$$

$$(\boldsymbol{z})_i = \begin{cases} 0 \text{ if } (\mathbf{x})_i < 0 \\ 1 \text{ otherwise} \end{cases}$$



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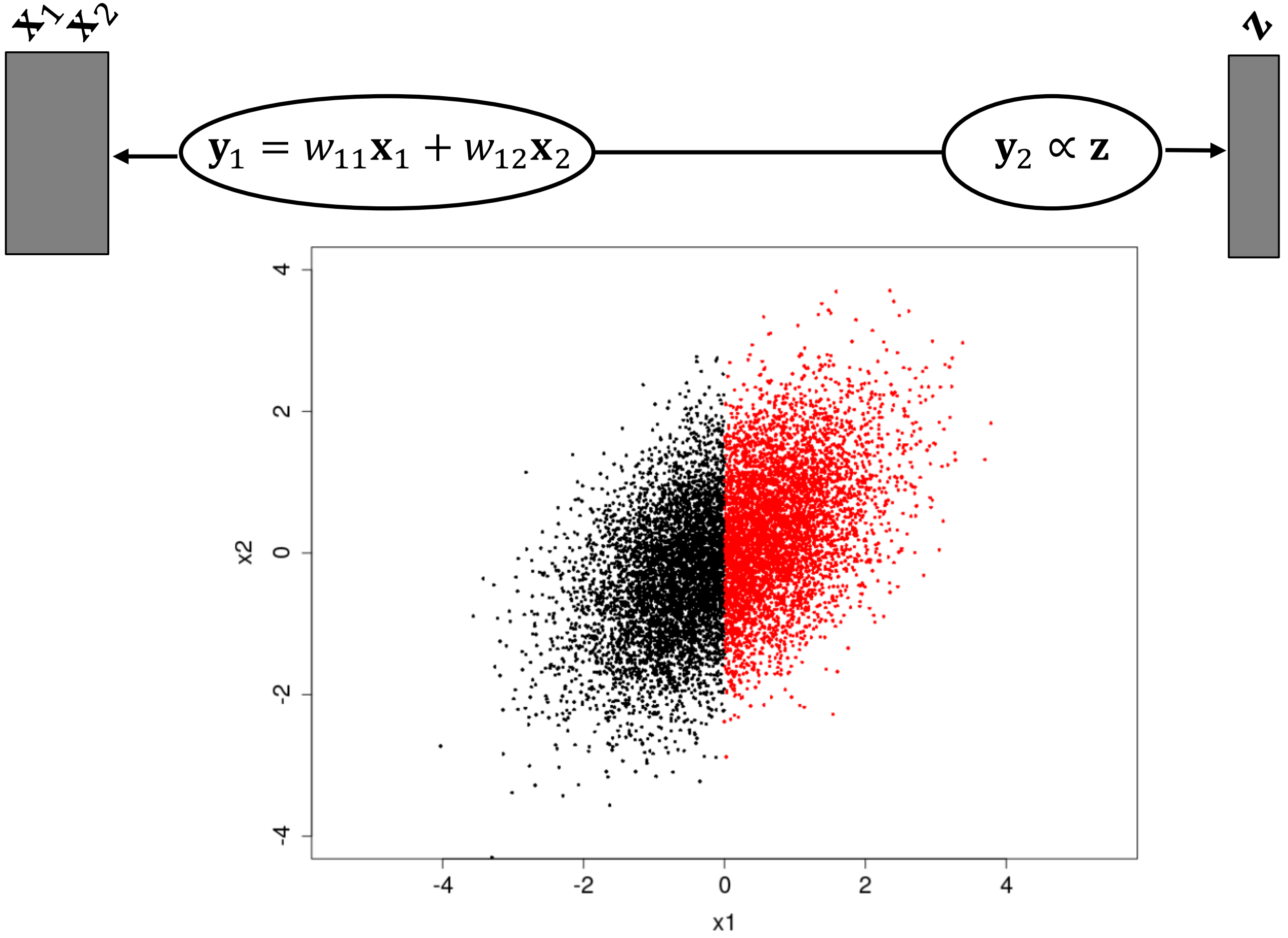

PLS & CCA with a figure

$$[\mathbf{x}_1\ \mathbf{x}_2] \sim \mathcal{N}\left((0,0), \begin{pmatrix} 1 & 0.5 \\ 0.5 & 1 \end{pmatrix}\right)$$

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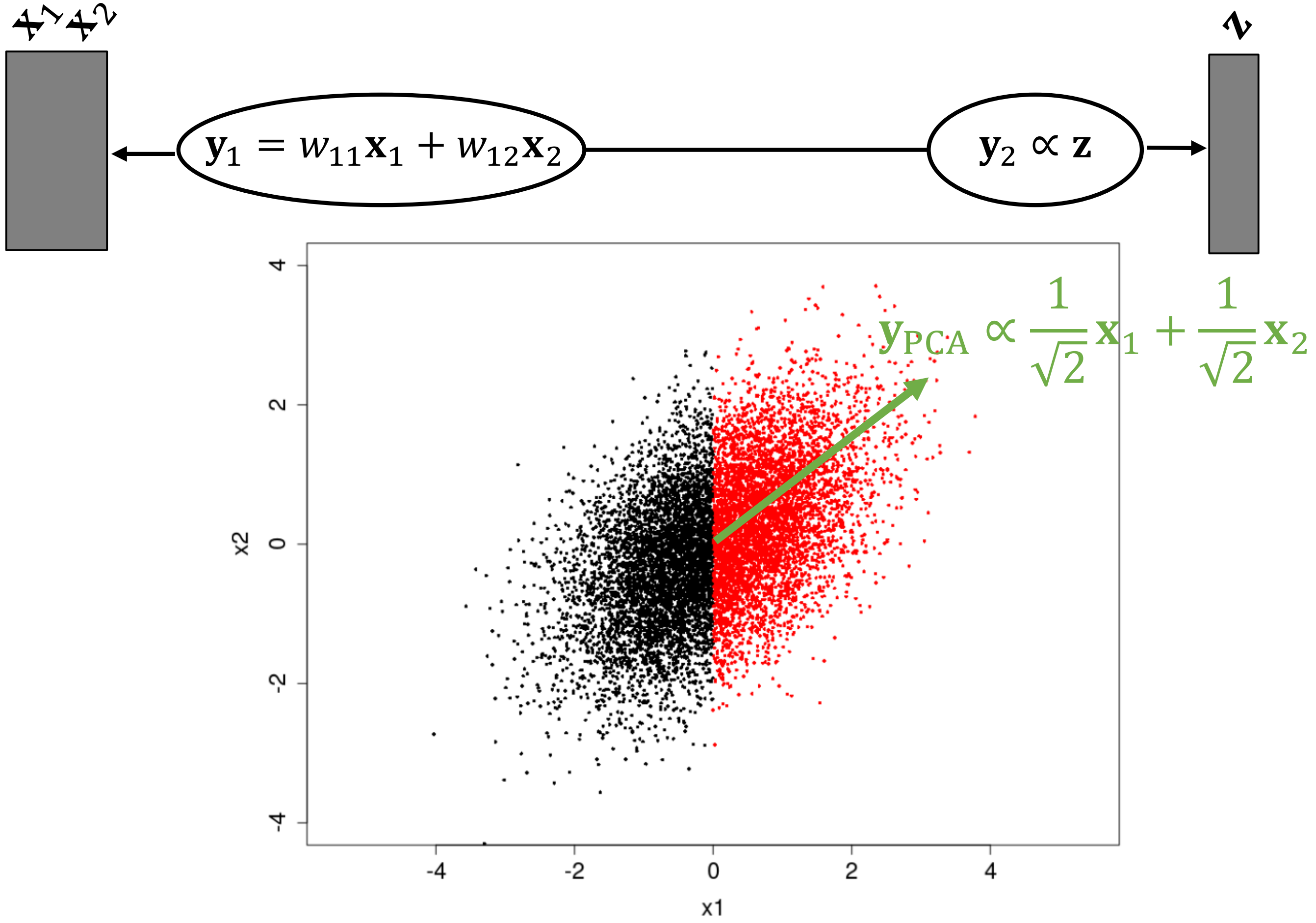

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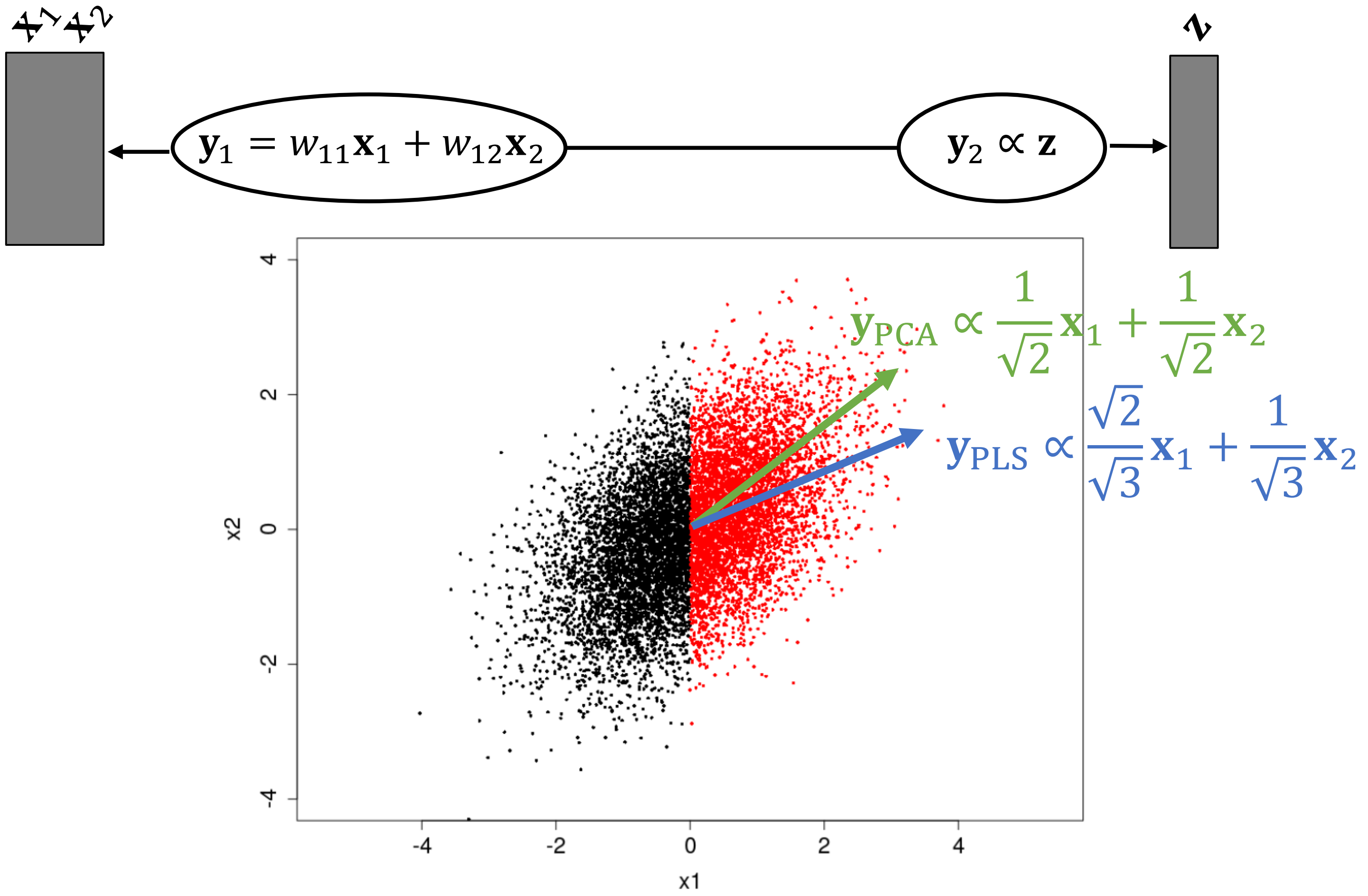

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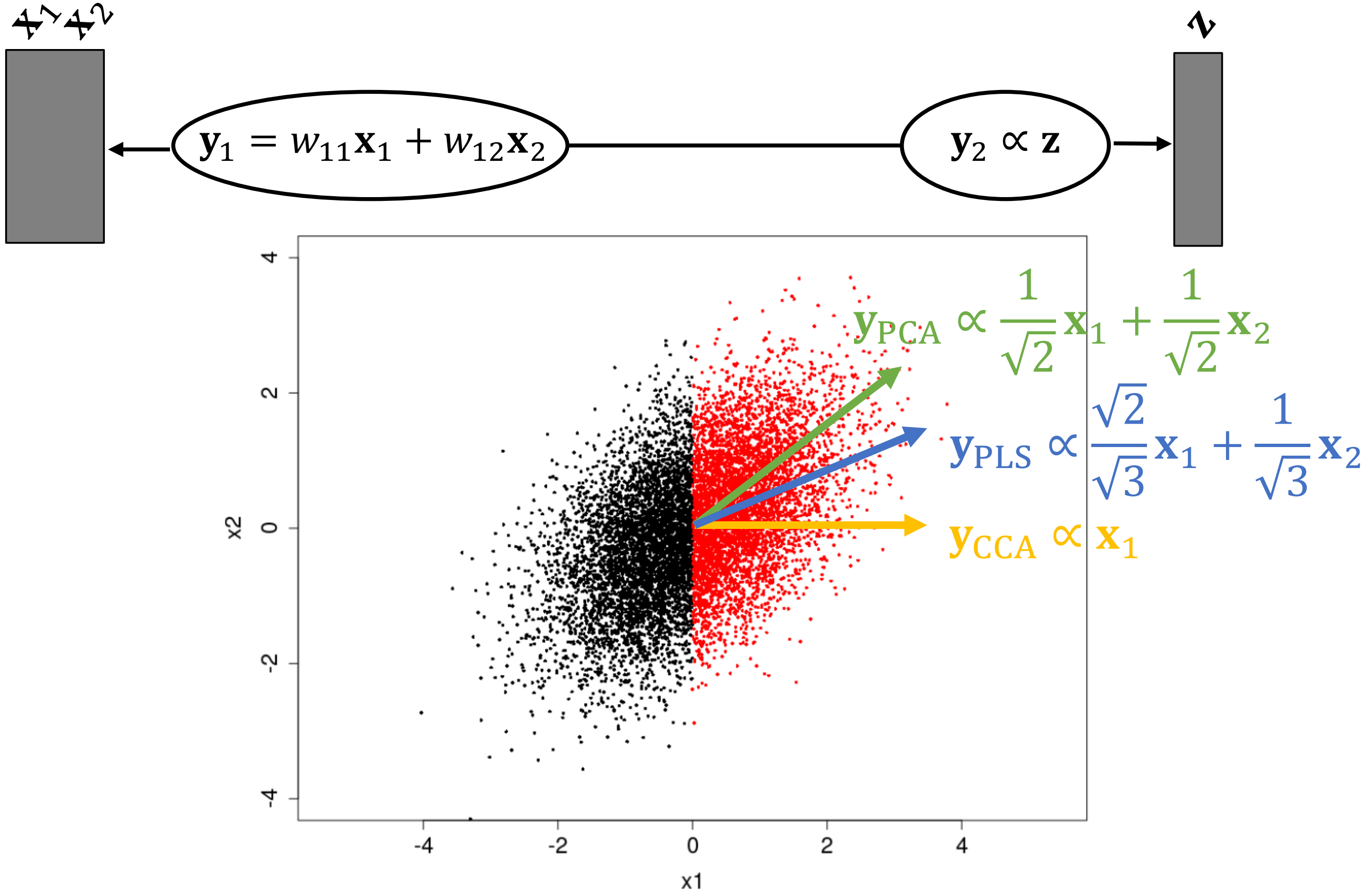

Let us see what are the results of PLS/CCA on the MDD case study

➔ See section 2.2 & 2.3 on the Rmarkdown `MDD_case_study_RGCCA`

Overfitting

Overfitting

	x_1	x_2	x_3	x_4	y
	Intercept	Age	Nb_sisters	Neighbor'weight (kg)	Subject's Height (cm)
Subj1	1	5	1	1	90
Subj2	1	10	2	50	125
Subj3	1	15	1	80	160
Subj4	1	20	2	90	180

Overfitting

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	Intercept	Age	Nb_sisters	Neighbor'weight (kg)	Subject's Height (cm)
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TEST: Subj1

TRAIN: Subj2–Subj4

Overfitting

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TEST (Subj1) / TRAIN (Subj2–Subj4)

We are looking for $\beta_1, \beta_2, \beta_3$ and β_4 that minimizes $J_{TRAIN} = \sum_{i=2}^{4}(y_i - \beta_1 x_{i1} - \beta_2 x_{i2} - \beta_3 x_{i3} - \beta_4 x_{i4})^2$.

Overfitting

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Similarly, we can define $J_{TEST} = (y_1 - \beta_1 x_{11} - \beta_2 x_{12} - \beta_3 x_{13} - \beta_4 x_{14})^2$.

Overfitting

	x_1	x_2	x_3	x_4	y
	Intercept	Age	Nb_sisters	Neighbor'weight (kg)	Subject's Height (cm)
Subj1	1	5	1	1	90
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TEST (Subj1)

TRAIN (Subj2–Subj4)

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Here, we are in "high-dimension" as $n < p$. The problem is ill-posed (more unknown parameters than equations).

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Overfitting

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➔ It is possible to find an infinite number of solutions:

Overfitting

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Here, we are in "high-dimension" as $n < p$. The problem is ill-posed (more unknown parameters than equations).

➔ It is possible to find an infinite number of solutions:

	β_1	β_2	β_3	β_4	J_{train}	J_{test}
Solution 1	43.75	0	1.375	6.25	8.4e-22	1491.891
Solution 2	-7456.25	-1000	251.375	2506.25	1.1e-19	95817179
⋮						

Overfitting

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	Intercept	Age	Nb_sisters	Neighbor'weight (kg)	Subject's Height (cm)
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TEST (Subj1)

TRAIN (Subj2–Subj4)

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⋮						

Go against the idea that age is the best explanatory variable.

Overfitting

	x_1	x_2	x_3	x_4	y
	Intercept	Age	Nb_sisters	Neighbor'weight (kg)	Subject's Height (cm)
Subj1	1	5	1	1	90
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Subj3	1	15	1	80	160
Subj4	1	20	2	90	180

TEST (Subj1) / TRAIN (Subj2–Subj4)

We are looking for $\beta_1, \beta_2, \beta_3$ and β_4 that minimizes $J_{TRAIN} = \sum_{i=2}^{4}(y_i - \beta_1 x_{i1} - \beta_2 x_{i2} - \beta_3 x_{i3} - \beta_4 x_{i4})^2$.

Similarly, we can define $J_{TEST} = (y_1 - \beta_1 x_{11} - \beta_2 x_{12} - \beta_3 x_{13} - \beta_4 x_{14})^2$.

Here, we are in "high-dimension" as $n < p$. The problem is ill-posed (more unknown parameters than equations).

➔ It is possible to find an infinite number of solutions:

	β_1	β_2	β_3	β_4	J_{train}	J_{test}
Solution 1	43.75	0	1.375	6.25	8.4e-22	1491.891
Solution 2	-7456.25	-1000	251.375	2506.25	1.1e-19	95817179
⋮						

OVERFITTING

Go against the idea that age is the best explanatory variable.

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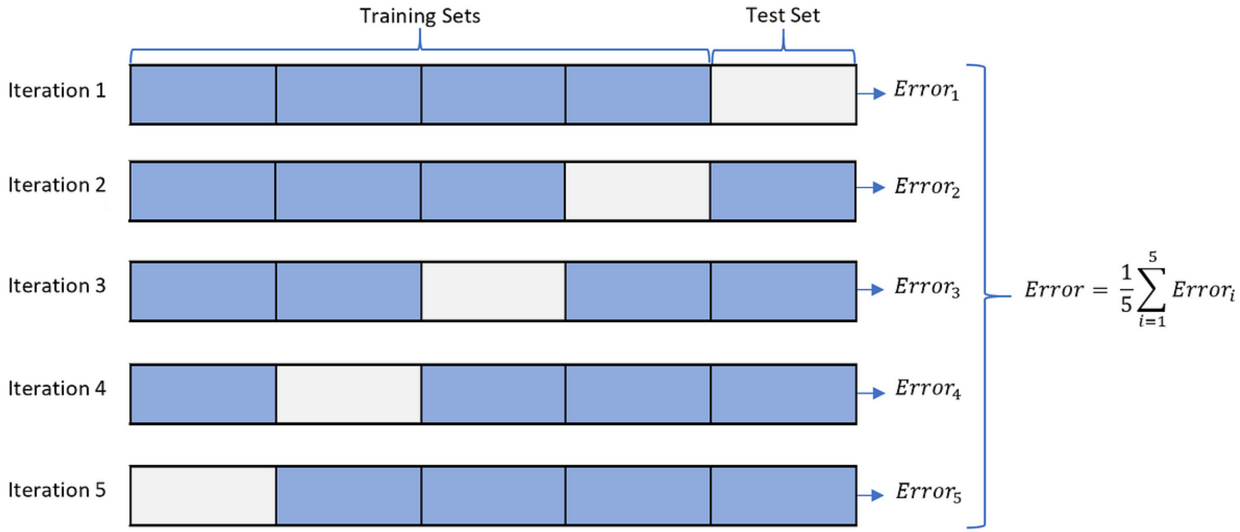

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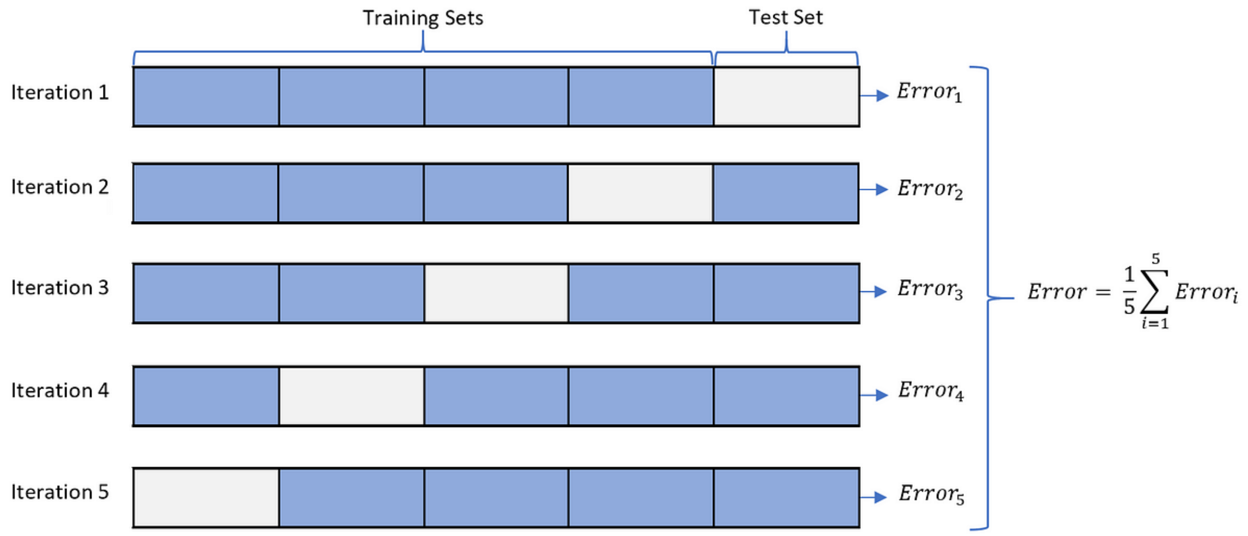

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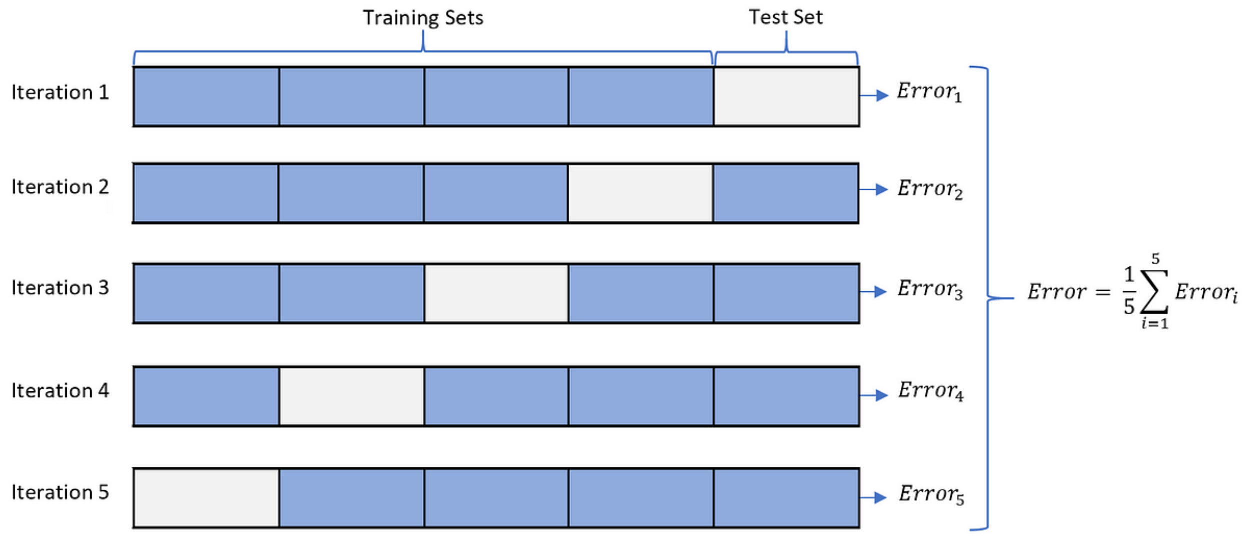

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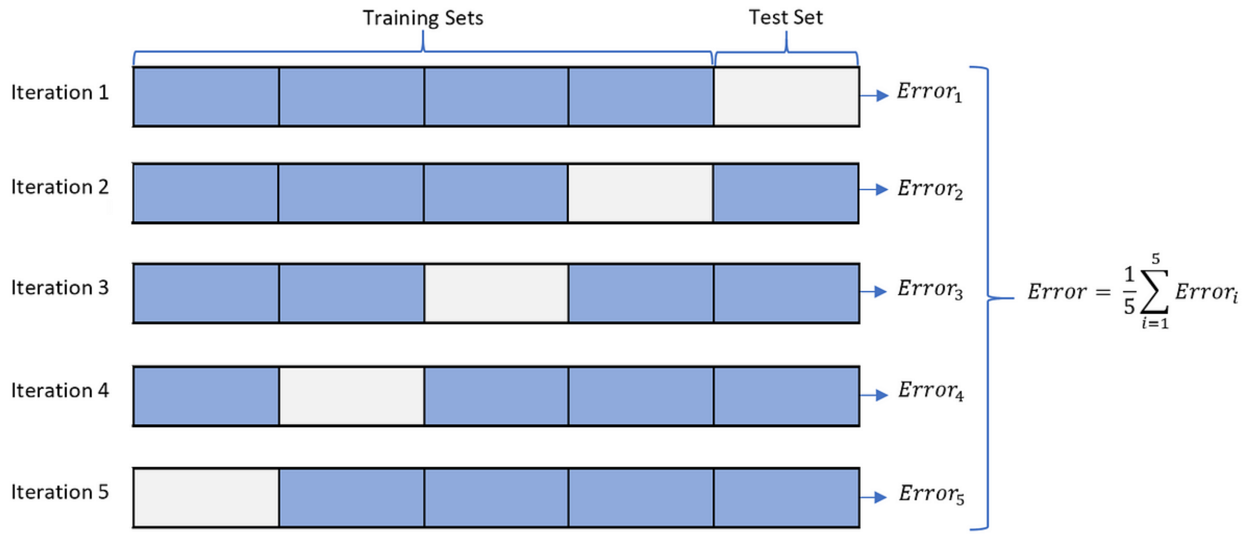

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Here, we choose to regularize the model by forcing it to have a low number of variables.

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(x_1, x_2)	3.750000e+01	100
(x_1, x_3)	2.403846e+01	959.8081
(x_1, x_4)	1.512500e+03	4900
(x_1, x_2, x_3)	1.831567e-22	203.0625
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CV was also used here so set an hyper-parameter: «the number of variables to keep in the model».

Here apparently, keeping only 2 variables leads to the best model with the variable «Age», which was expected.

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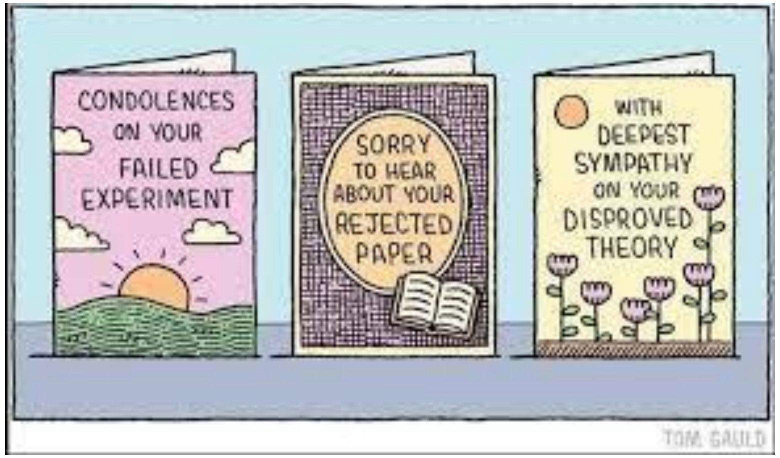

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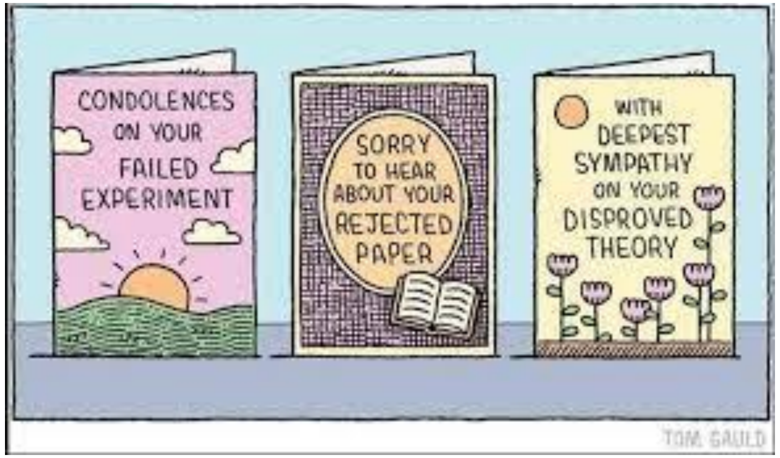

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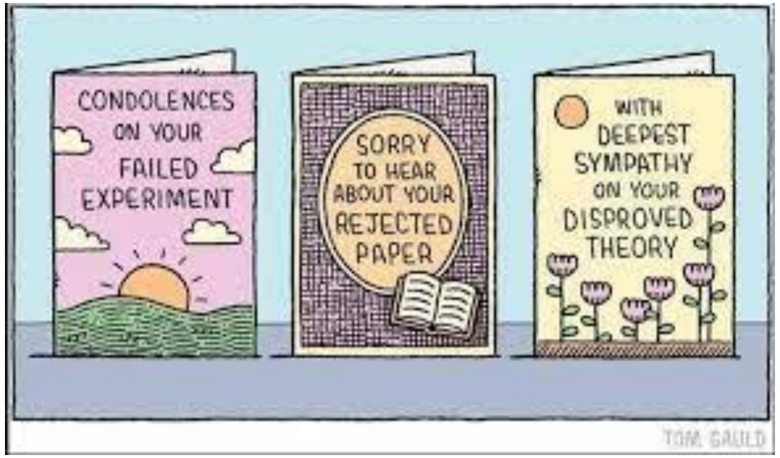

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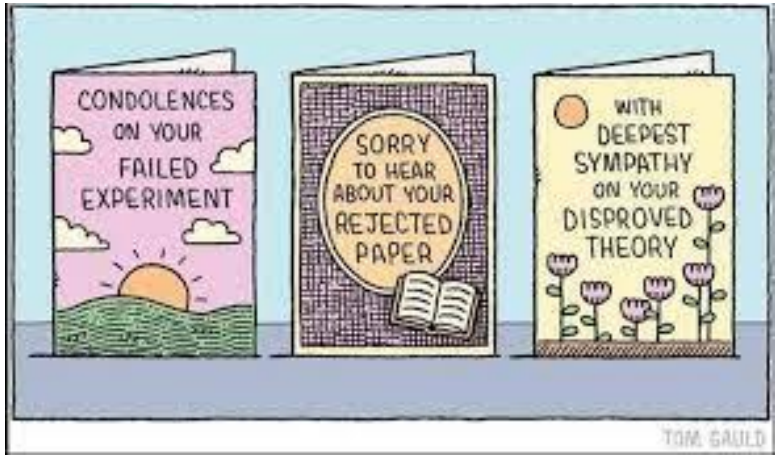

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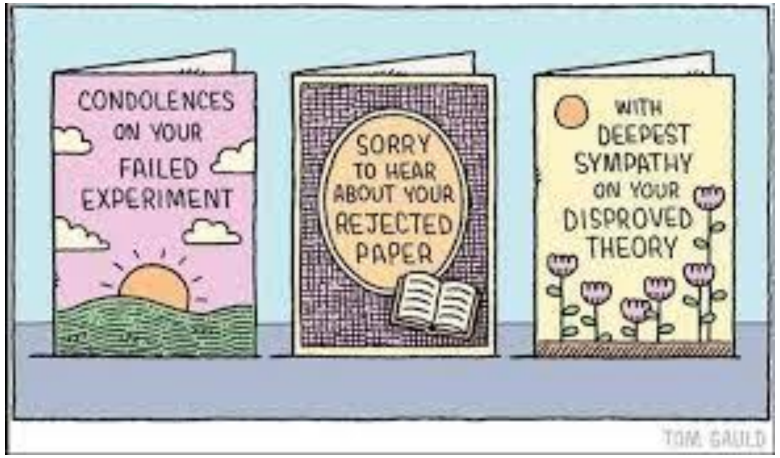

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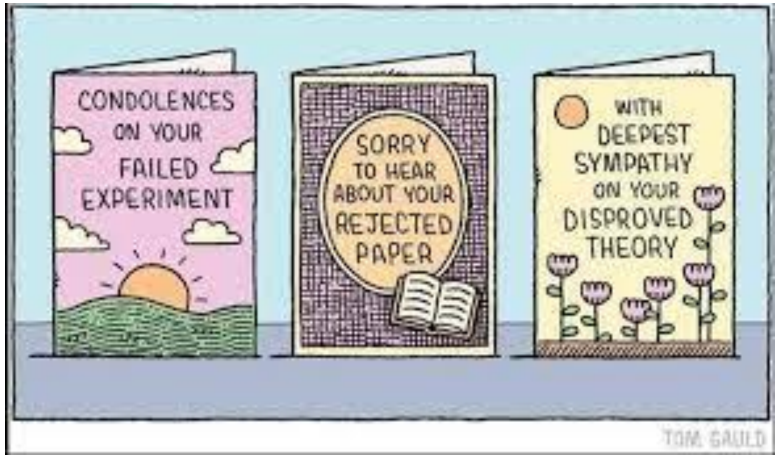

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1. Normalization accross subjects is performed on the whole data-set.
2. Variable selection is performed on the whole data-set (ex: differentially expressed genes)

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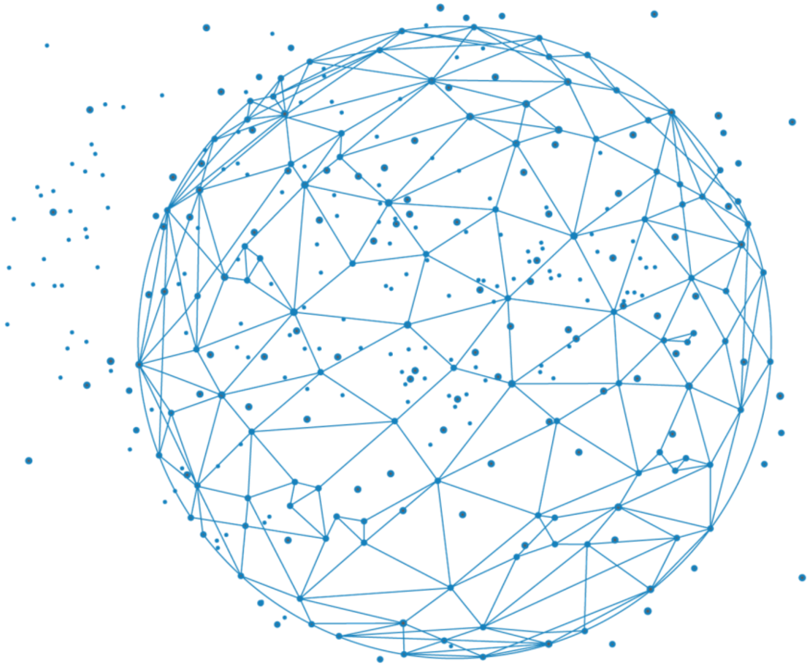
Figure taken from https://typeset.io/resources/top-reasons-for-research-paper-rejection/

How do we regularize CCA ?



Two-blocks special cases: PLS & CCA

Canonical Correlation Analysis (CCA)

$$\max_{\substack{\mathbf{w}_1,\mathbf{w}_2 \\ \mathrm{Var}(\mathbf{X}_i\mathbf{w}_i)=1}} \mathrm{Cov}(\mathbf{X}_1\mathbf{w}_1, \mathbf{X}_2\mathbf{w}_2)$$

Partial Least Squares (PLS2)

$$\max_{\substack{\mathbf{w}_1,\mathbf{w}_2 \\ \|\mathbf{w}_i\|_2^2=1}} \mathrm{Cov}(\mathbf{X}_1\mathbf{w}_1, \mathbf{X}_2\mathbf{w}_2)$$

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Regularized-CCA

$$\max_{\mathbf{w}_1,\mathbf{w}_2} \mathrm{Cov}(\mathbf{X}_1\mathbf{w}_1, \mathbf{X}_2\mathbf{w}_2)$$

$$\text{s.t. } (1-\tau_i)\mathrm{Var}(\mathbf{X}_i\mathbf{w}_i) + \tau_i\|\mathbf{w}_i\|_2^2 = 1.$$

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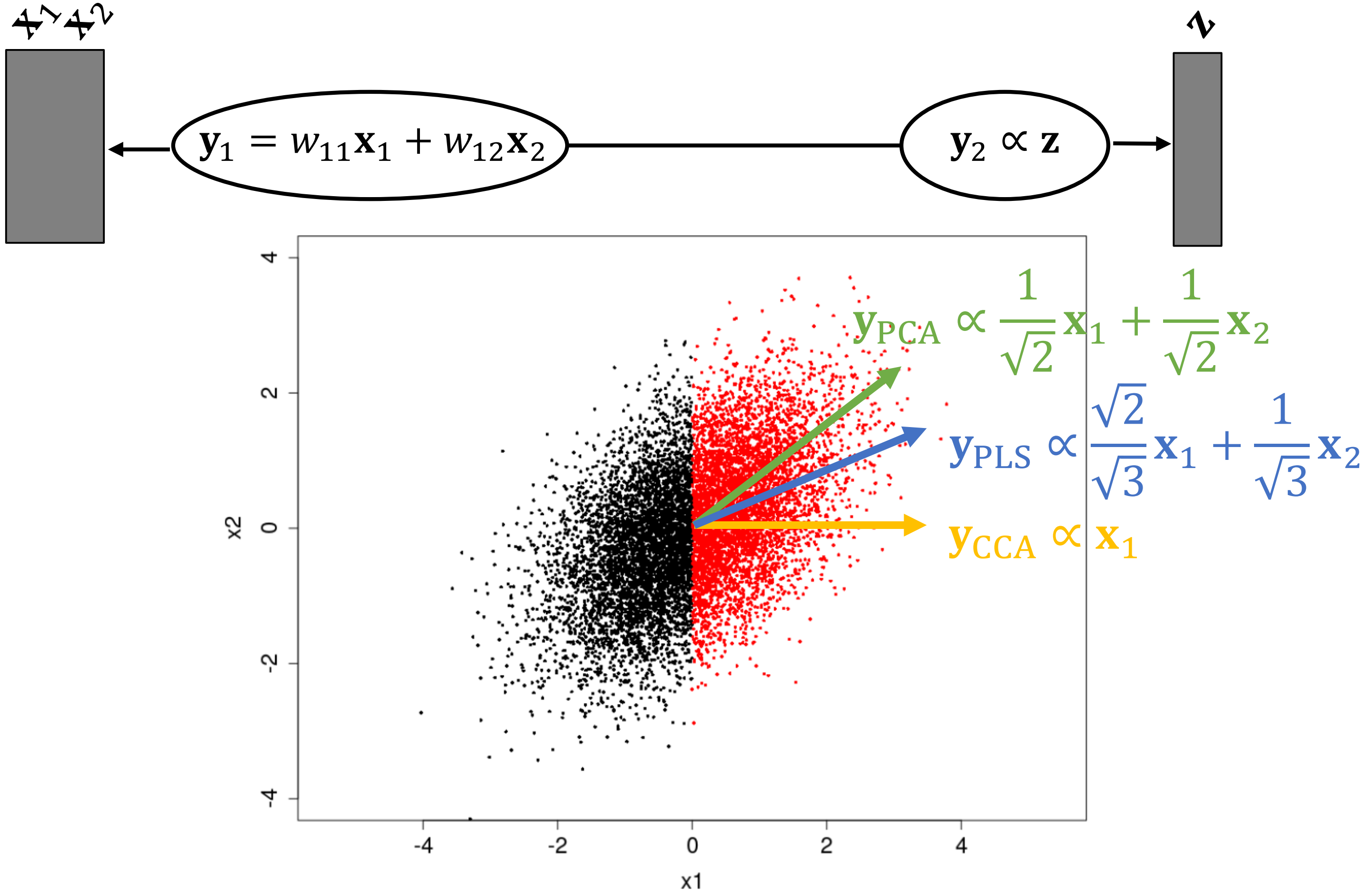
PLS & CCA with a figure

$$[\mathbf{x}_1\ \mathbf{x}_2] \sim \mathcal{N}\left((0,0), \begin{pmatrix} 1 & 0.5 \\ 0.5 & 1 \end{pmatrix}\right)$$

$$(\mathbf{z})_i = \begin{cases} 0 \text{ if } (\mathbf{x})_i < 0 \\ 1 \text{ otherwise} \end{cases}$$



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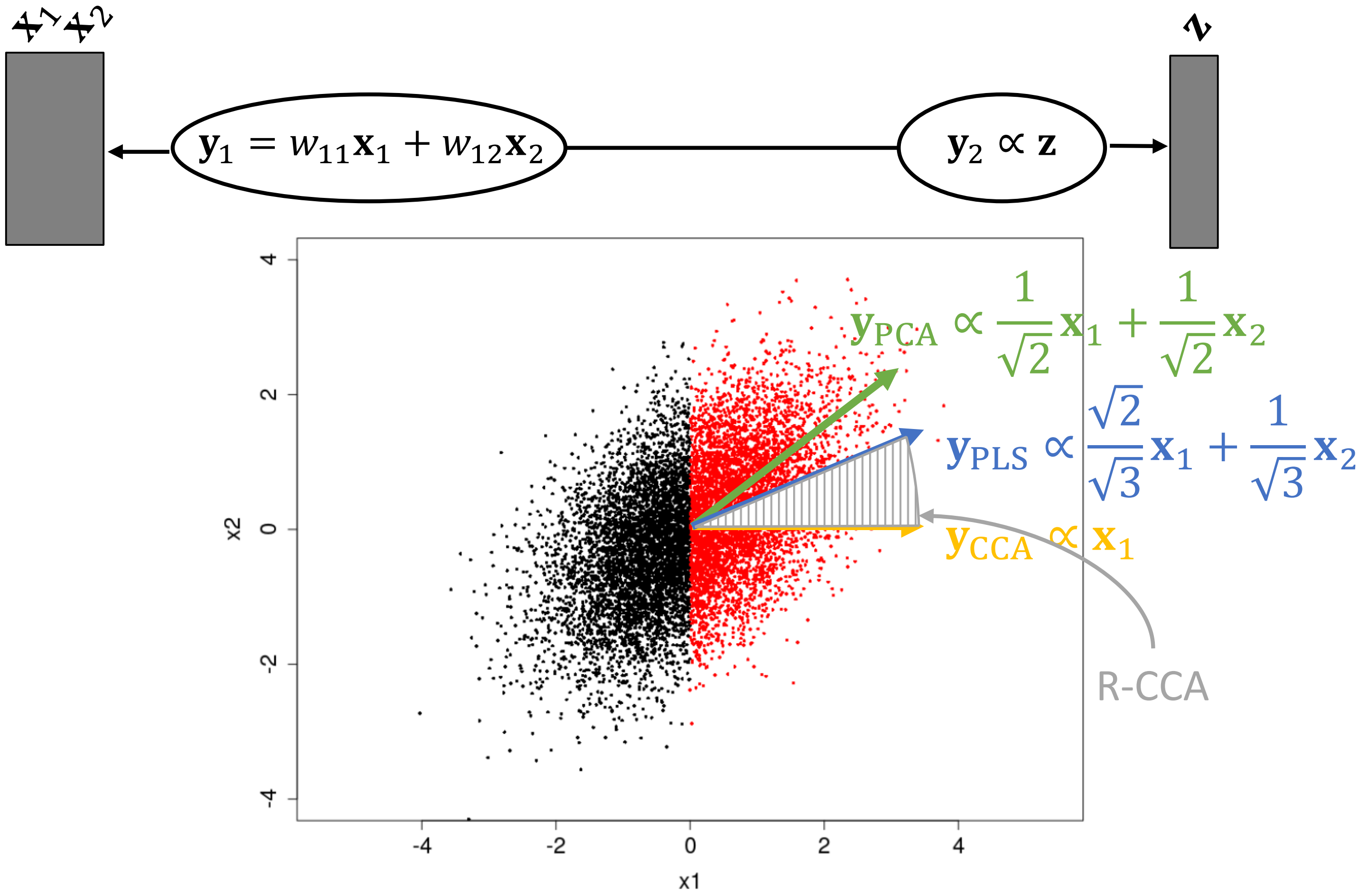
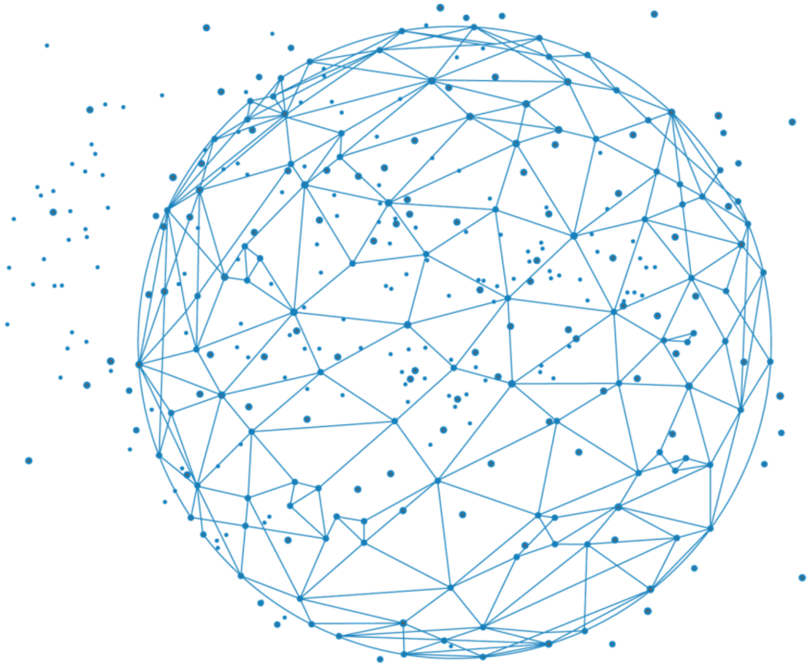


Let us see how Regularize CCA performs on the MDD case study

➔ See section 2.4 & 2.5 on the Rmarkdown `MDD_case_study_RGCCA`



1. Introduction of the case study

2. **Unsupervised analysis with one-block:** Principal Component Analysis (PCA)

3. **Unsupervised analysis with two-blocks:**
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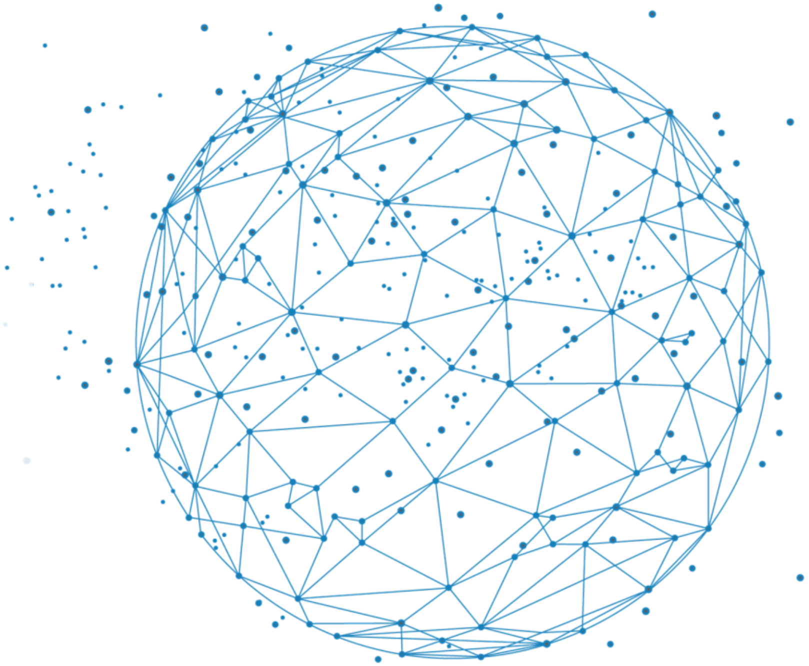
4. **Unsupervised analysis with L-blocks:**
   Regularized Generalized Canonical Correlation Analysis (RGCCA)

5. Supervised analysis with RGCCA

6. **Variable selection in RGCCA:**
   Sparse Generalized Canonical Correlation Analysis (SGCCA)

7. The flexible Optimization Framework of RGCCA

   - The general principal
   - Extension to multi-way analysis
   - From Sequential to Global



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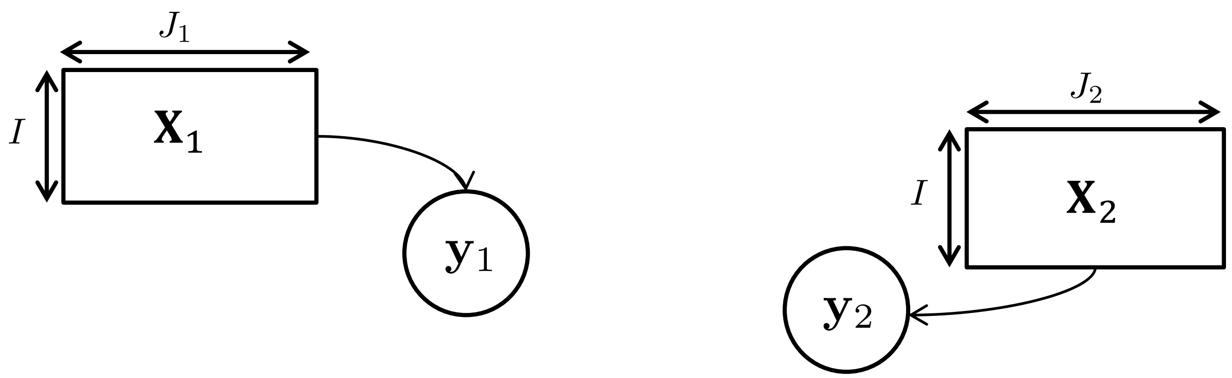

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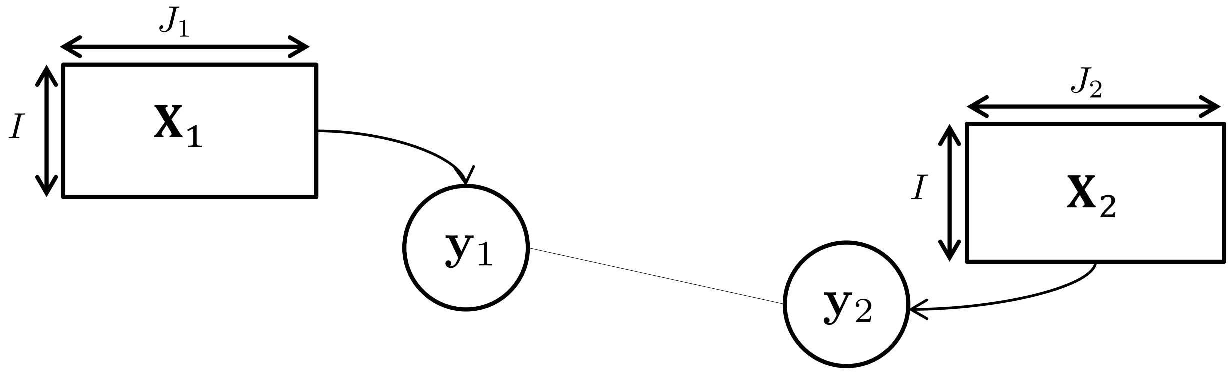

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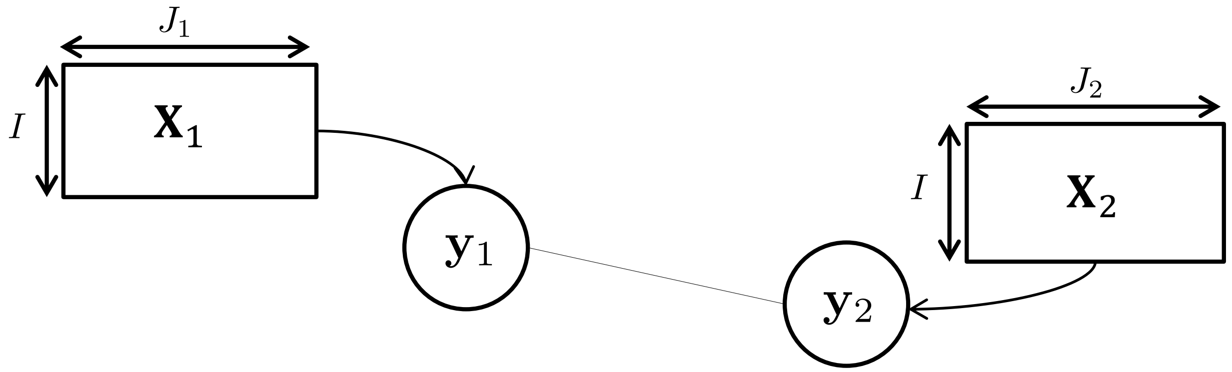

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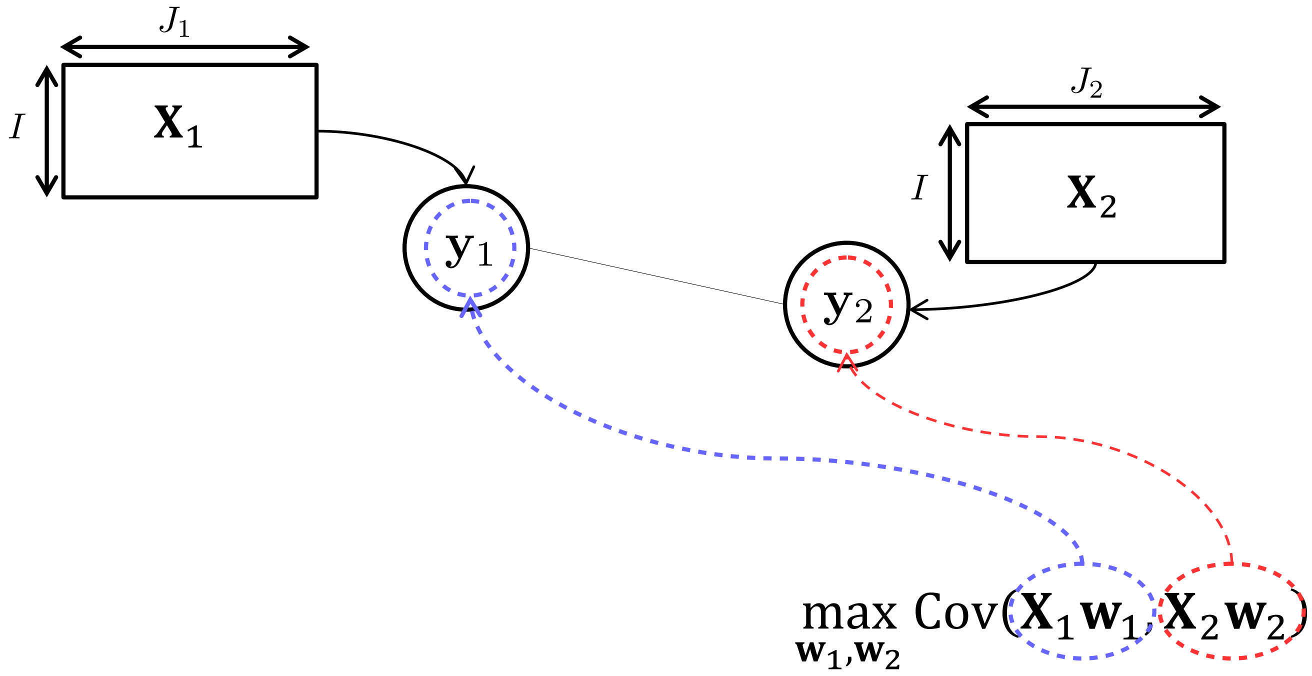

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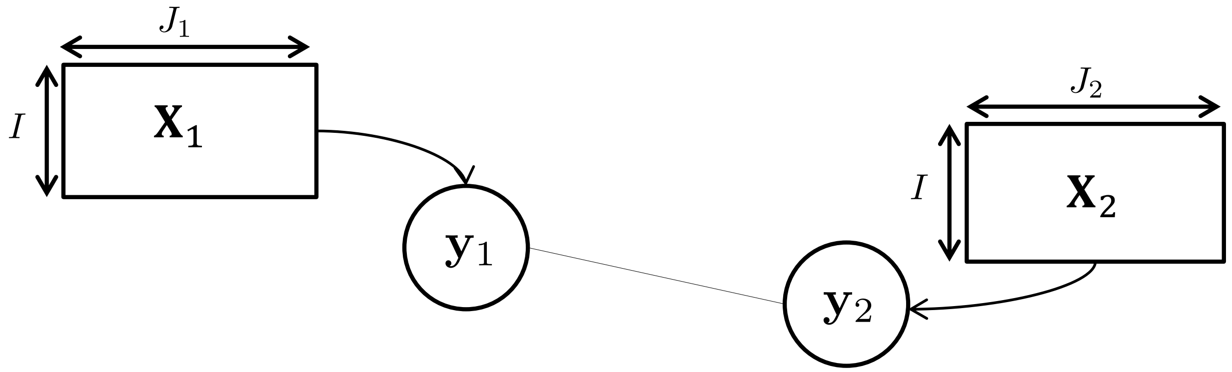

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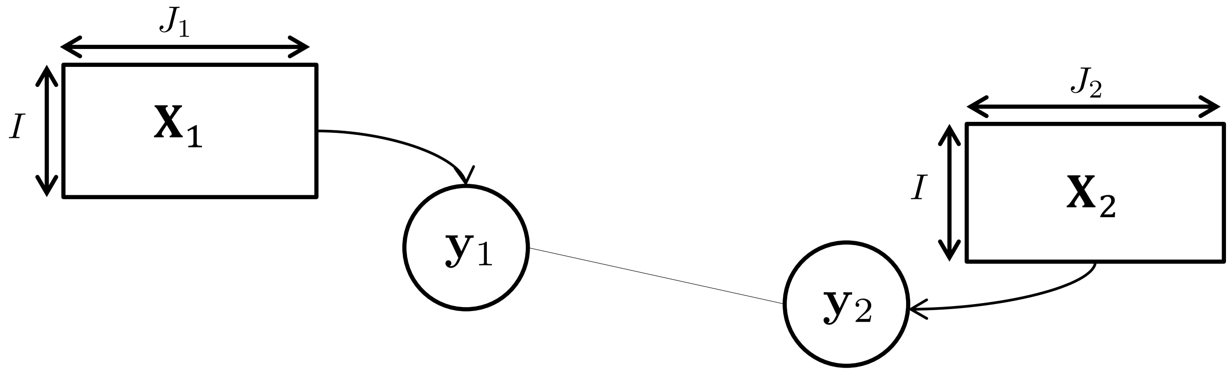

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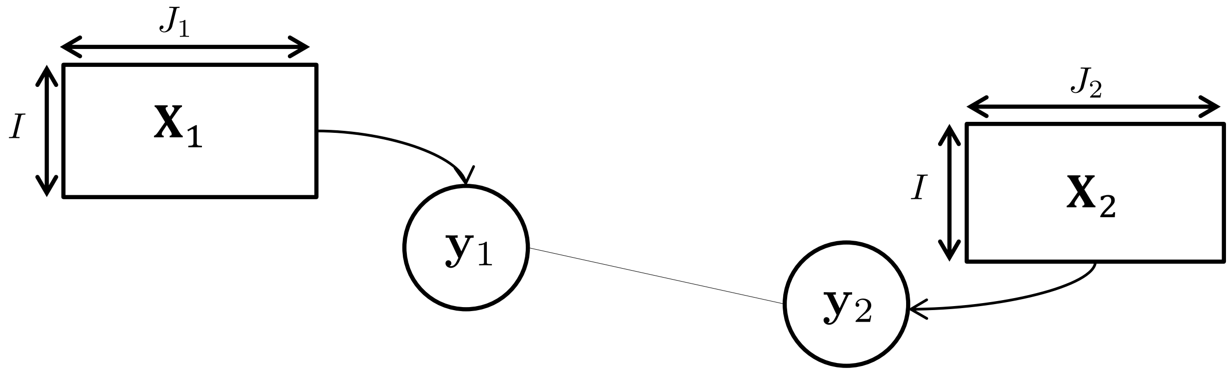

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➡ Canonical Correlation Analysis

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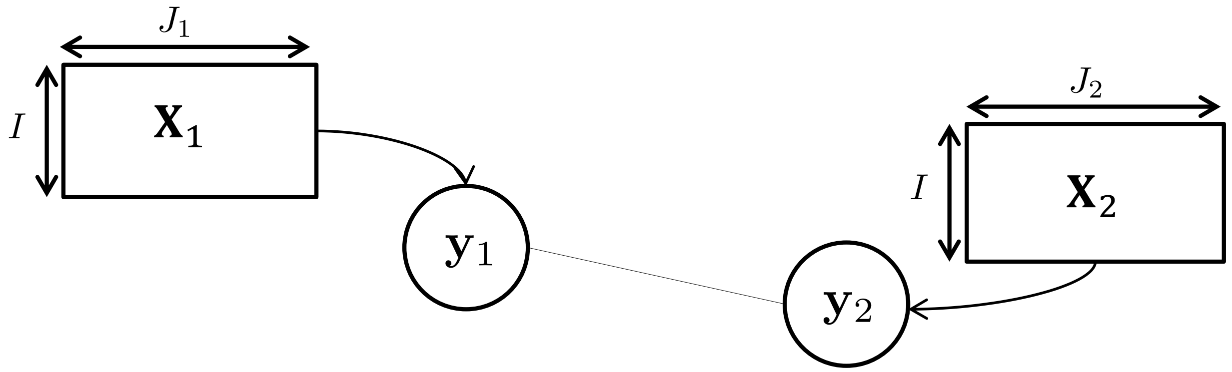

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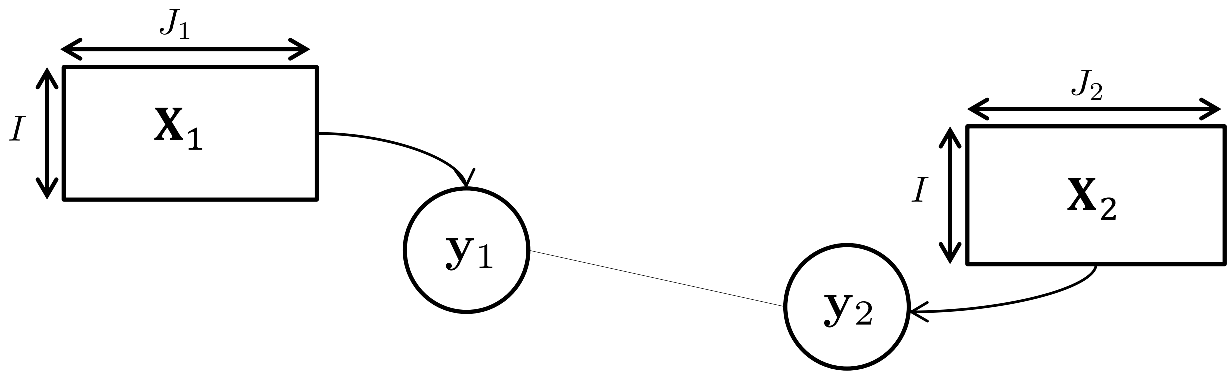

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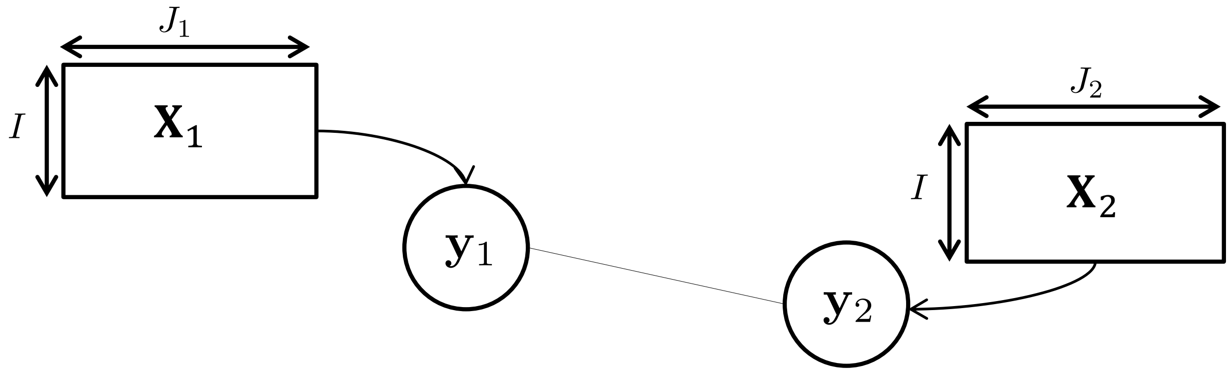

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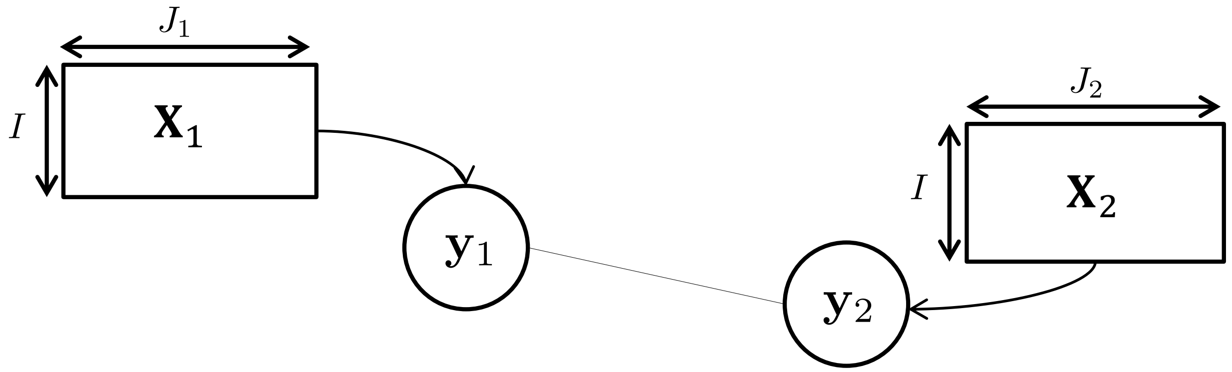
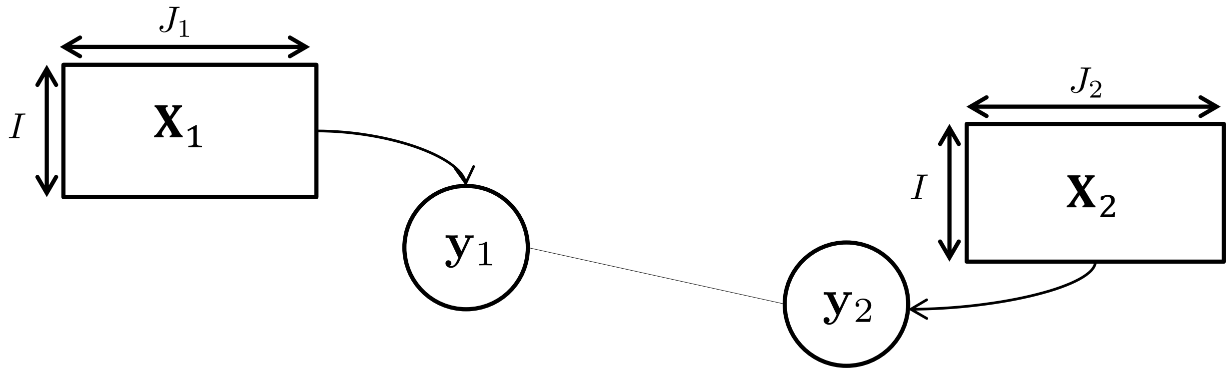
➡ Partial Least Squares 2

Regularized Generalized Canonical Correlation Analysis (RGCCA)



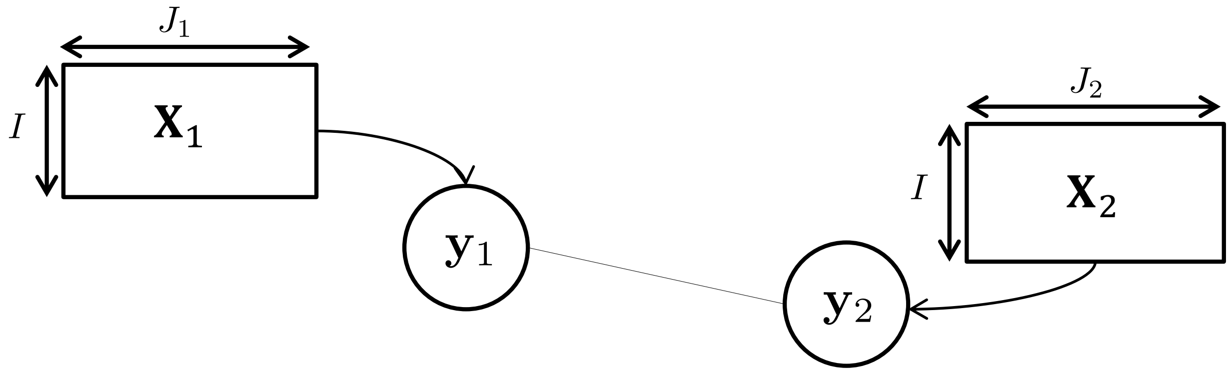
$$\max_{\mathbf{w}_1,\mathbf{w}_2} \mathrm{Cov}(\mathbf{X}_1\mathbf{w}_1, \mathbf{X}_2\mathbf{w}_2)$$

$$\text{s.t. } \|\mathbf{w}_l\|_2^2 = 1, \qquad l = 1, 2.$$



$$\max_{\mathbf{w}_1,\mathbf{w}_2} \mathrm{Cov}(\mathbf{X}_1\mathbf{w}_1, \mathbf{X}_2\mathbf{w}_2)$$

$$\text{s.t. } \mathbf{w}_l^\top \mathbf{M}_l \mathbf{w}_l = 1, \qquad l = 1, 2.$$



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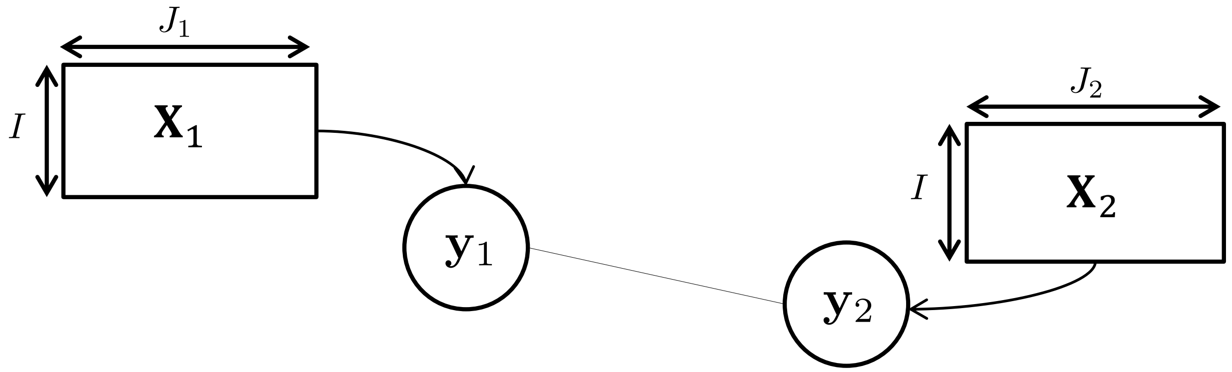
where $\mathbf{M}_l$ is any $J_l \times J_l$ positive definite matrix

Regularized Generalized Canonical Correlation Analysis (RGCCA)



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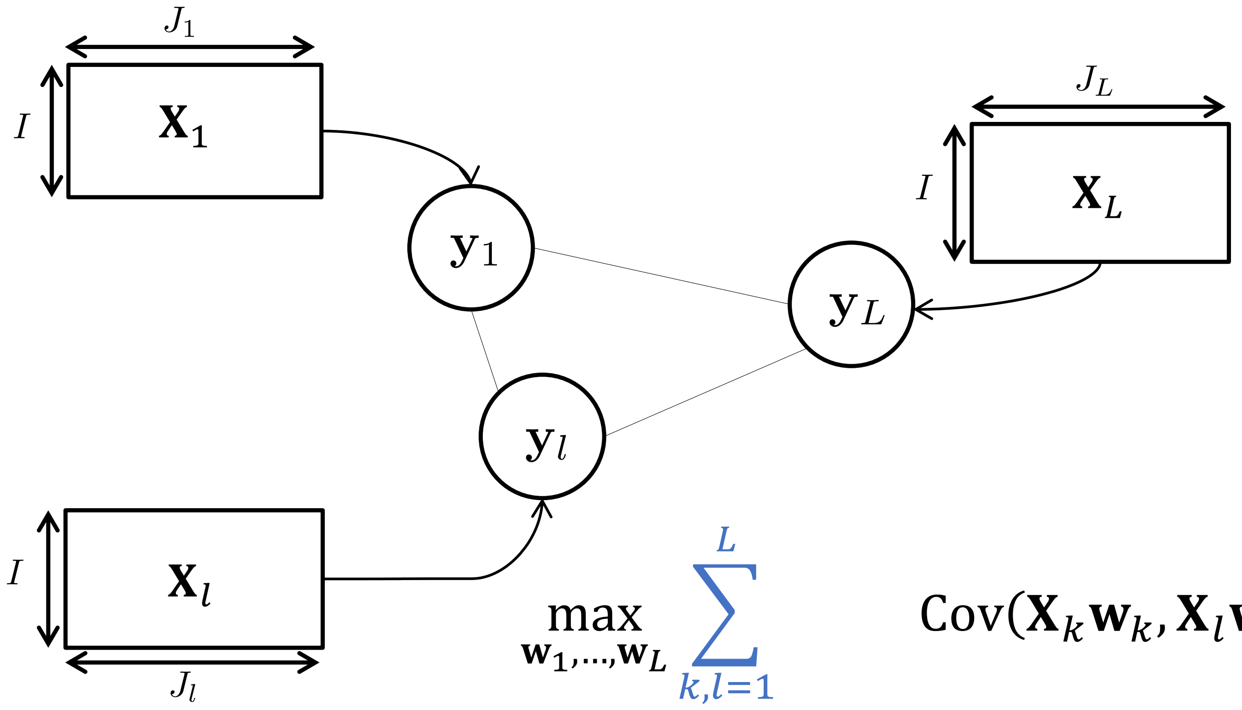

$$\max_{\mathbf{w}_1,\ldots,\mathbf{w}_L} \sum_{k,l=1}^{L} \operatorname{Cov}(\mathbf{X}_k\mathbf{w}_k, \mathbf{X}_l\mathbf{w}_l)$$

$$\text{s.t. } \mathbf{w}_l^\top \mathbf{M}_l \mathbf{w}_l = 1,\ l = 1, \ldots, L.$$

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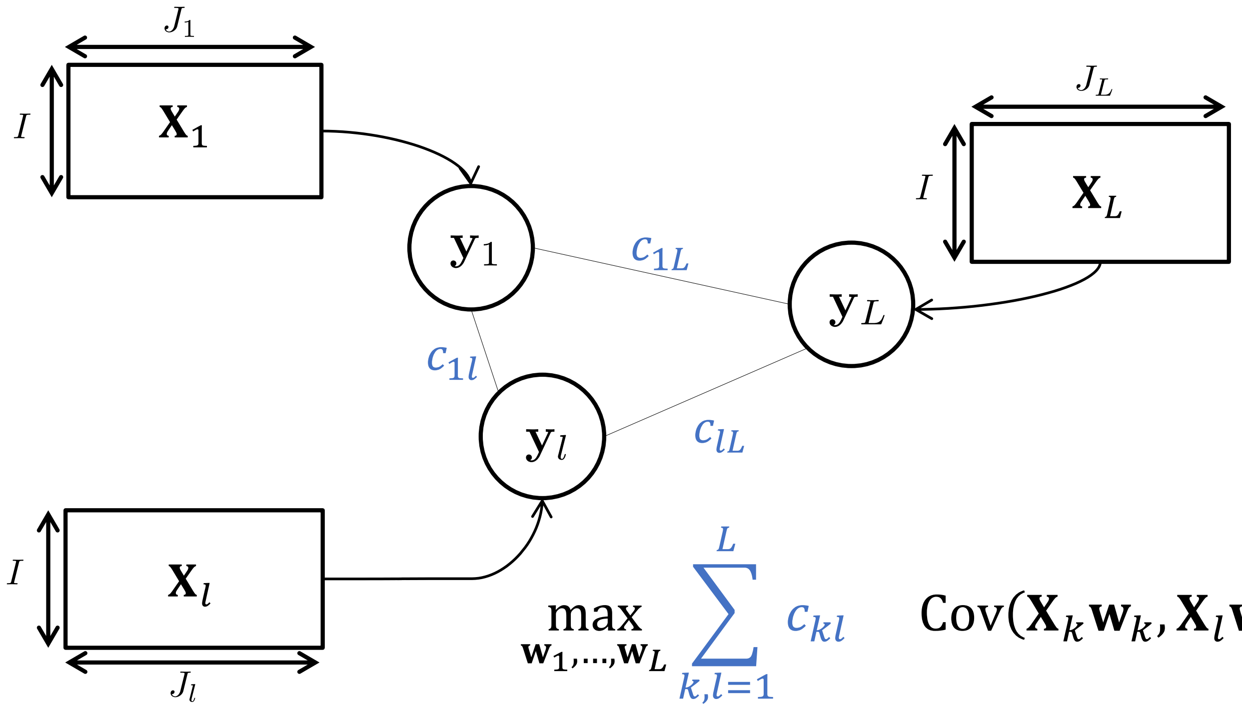

$$\max_{\mathbf{w}_1,\ldots,\mathbf{w}_L} \sum_{k,l=1}^{L} c_{kl} \quad \mathrm{Cov}(\mathbf{X}_k\mathbf{w}_k, \mathbf{X}_l\mathbf{w}_l)$$

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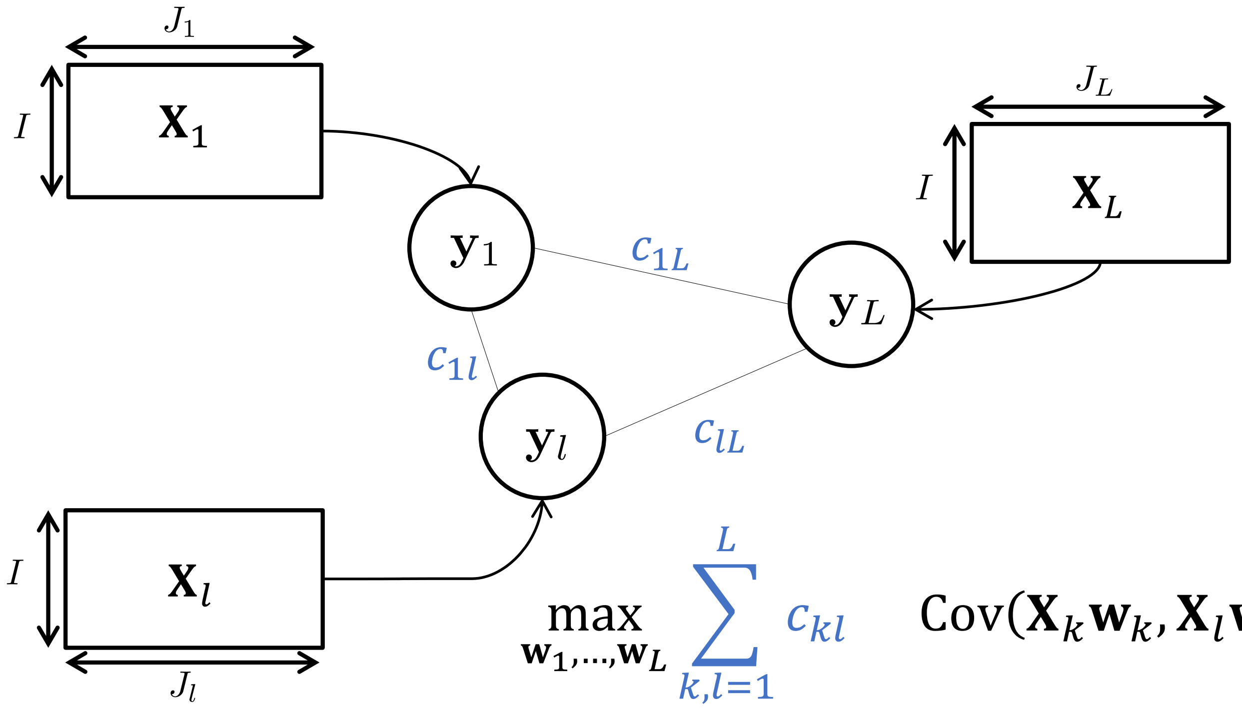

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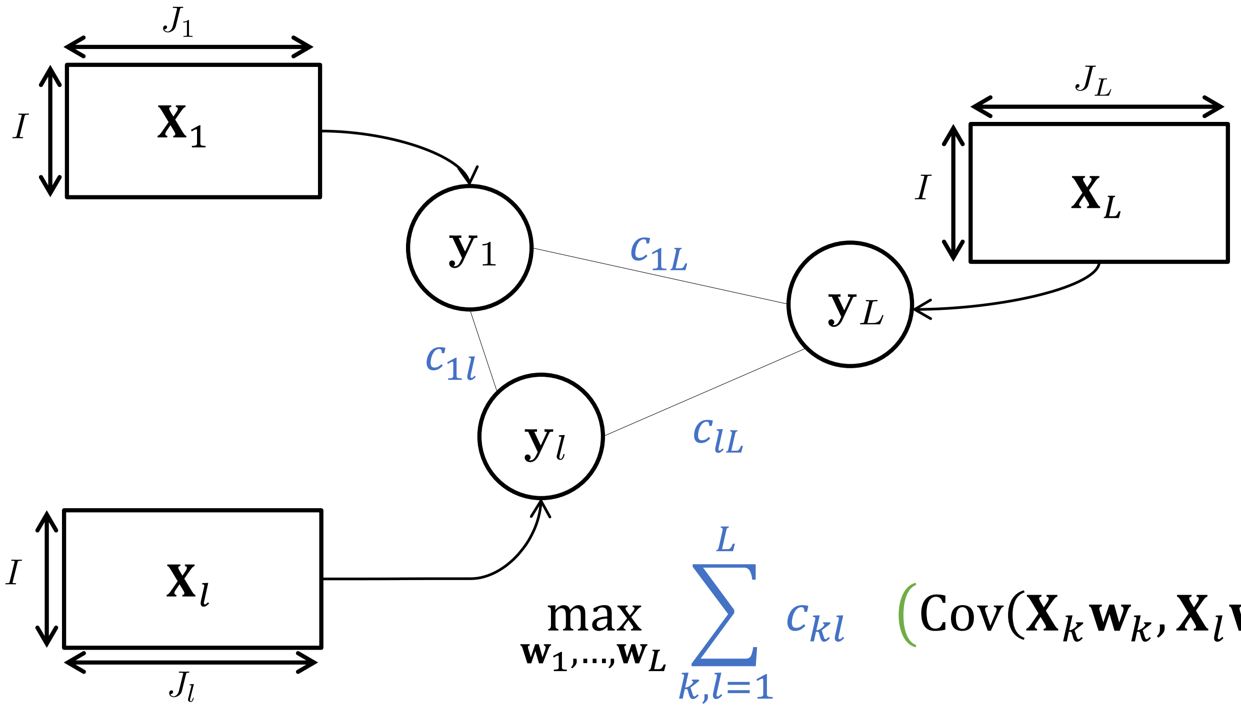
⇨ if all blocks are connected and $\mathbf{M}_l = \mathbf{I}_l$ ⇨ SUMCOV-2

Regularized Generalized Canonical Correlation Analysis (RGCCA)

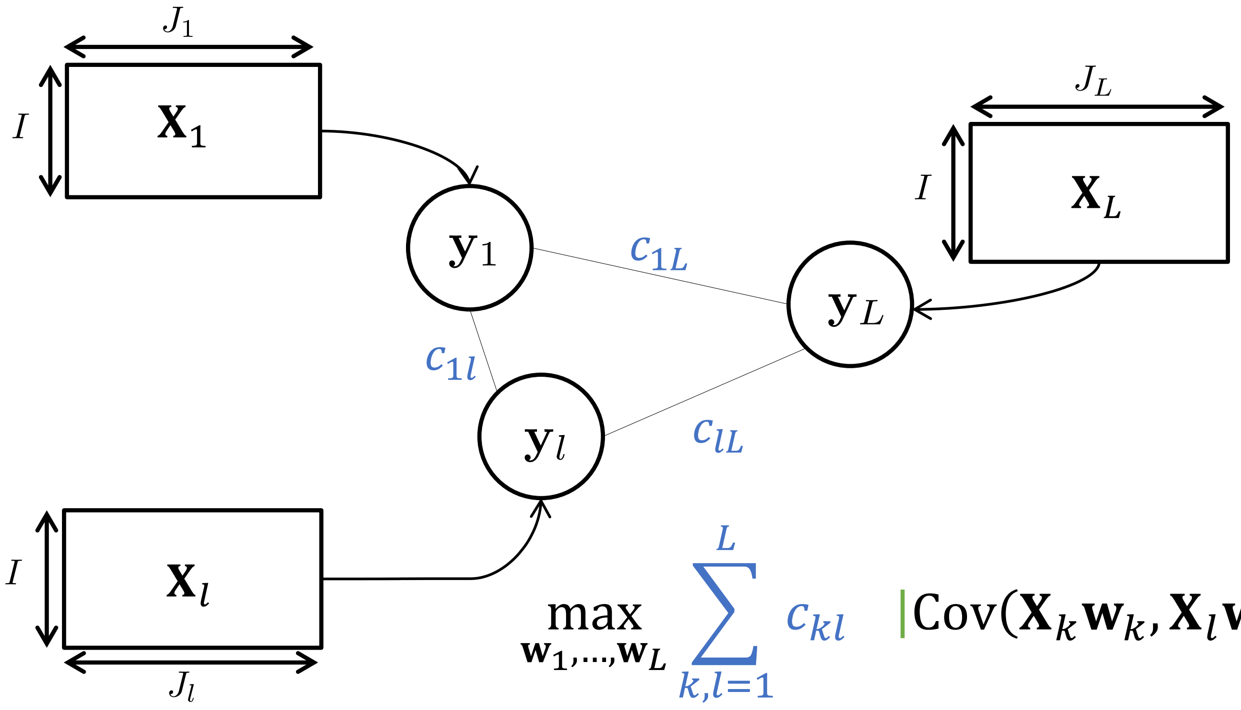


$$\max_{\mathbf{w}_1,\ldots,\mathbf{w}_L} \sum_{k,l=1}^{L} c_{kl} \left(\mathrm{Cov}(\mathbf{X}_k\mathbf{w}_k, \mathbf{X}_l\mathbf{w}_l)\right)^2$$

$$\text{s.t. } \mathbf{w}_l^\top \mathbf{M}_l \mathbf{w}_l = 1, \; l = 1, \ldots, L.$$

➡ if all blocks are connected and $\mathbf{M}_l = \mathbf{I}_l$ ➡ SSQCOV-2

Regularized Generalized Canonical Correlation Analysis (RGCCA)



$$\max_{\mathbf{w}_1,\ldots,\mathbf{w}_L} \sum_{k,l=1}^{L} c_{kl} \left|\mathrm{Cov}(\mathbf{X}_k\mathbf{w}_k, \mathbf{X}_l\mathbf{w}_l)\right|$$

$$\text{s.t. } \mathbf{w}_l^\top \mathbf{M}_l \mathbf{w}_l = 1, \; l = 1, \ldots, L.$$

if all blocks are connected and $\mathbf{M}_l = \mathbf{I}_l$ SABSCOV-2

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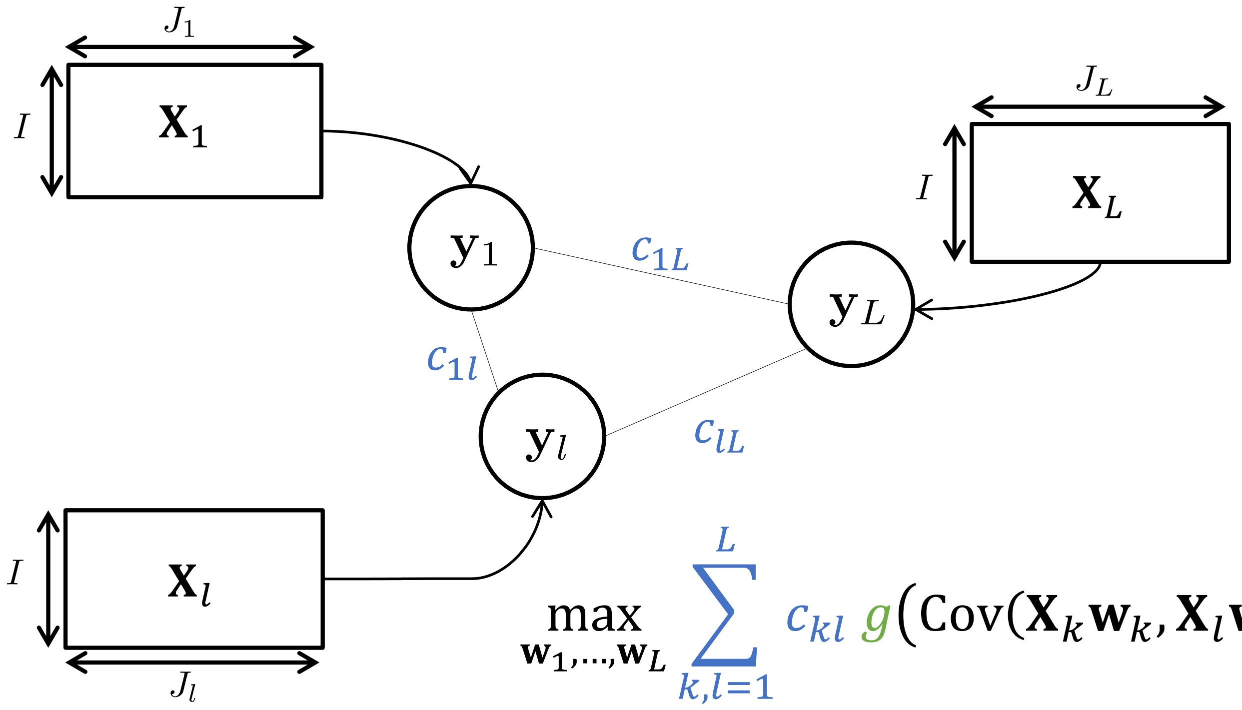

$$\max_{\mathbf{w}_1,\ldots,\mathbf{w}_L} \sum_{k,l=1}^{L} c_{kl}\, g\big(\mathrm{Cov}(\mathbf{X}_k\mathbf{w}_k, \mathbf{X}_l\mathbf{w}_l)\big)$$

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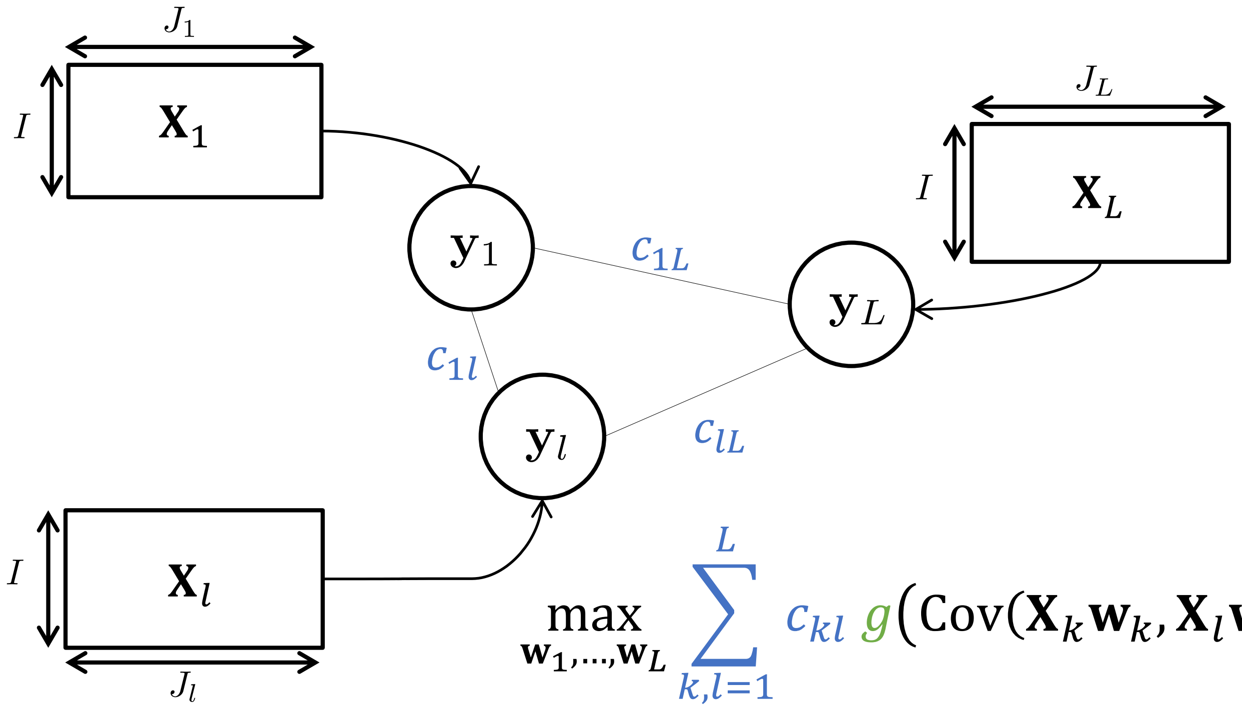

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➡ with g a continuous, convex and derivable function.

Summary of RGCCA

The Regularized Generalized Canonical Correlation Analysis (RGCCA) Optimization criterion :

$$\max_{\mathbf{w}_1,\ldots,\mathbf{w}_L} \sum_{k,l=1}^{L} c_{kl}\; g\big(\mathrm{Cov}(\mathbf{X}_k\mathbf{w}_k, \mathbf{X}_l\mathbf{w}_l)\big)$$

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Most of the time (this is the case today !) $\mathbf{M}_l$ is chosen such that:

$$\mathbf{w}_l^\top \mathbf{M}_l \mathbf{w}_l = \quad (1-\tau_l)\mathrm{Var}(\mathbf{X}_l\mathbf{w}_l) + \tau_l \|\mathbf{w}_l\|_2^2 \quad = 1.$$

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$$\max_{\mathbf{w}_1,\dots,\mathbf{w}_L} \sum_{k,l=1}^{L} c_{kl}\, g\big(\mathrm{Cov}(\mathbf{X}_k\mathbf{w}_k, \mathbf{X}_l\mathbf{w}_l)\big)$$

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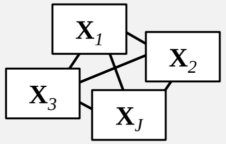
Regularized version of the sample covariance matrix

Overview of the Multi-Block litterature

ALL BLOCKS ARE INTERCONNECTED 	
SUMCOR (Horst, 1961)	$\max_{\mathbf{w}_j} \sum_{j,k} \text{cor}(\mathbf{X}_j\mathbf{w}_j, \mathbf{X}_k\mathbf{w}_k)$
SSQCOR (Kettenring, 1961)	$\max_{\mathbf{w}_j} \sum_{j,k} \text{cor}^2(\mathbf{X}_j\mathbf{w}_j, \mathbf{X}_k\mathbf{w}_k)$
SABSCOR (Wold, 1982)	$\max_{\mathbf{w}_j} \sum_{j,k} \lvert\text{cor}(\mathbf{X}_j\mathbf{w}_j, \mathbf{X}_k\mathbf{w}_k)\rvert$

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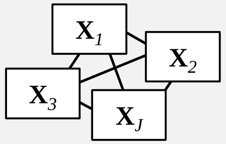
ALL BLOCKS ARE INTERCONNECTED	
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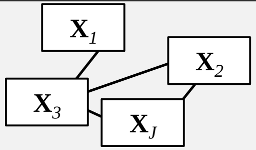
SABSCOR (Wold, 1982)	$\max_{\mathbf{w}_j} \sum_{j,k} \lvert\mathrm{cor}(\mathbf{X}_j\mathbf{w}_j, \mathbf{X}_k\mathbf{w}_k)\rvert$
SUMCOV (Van de Geer, 1984)	$\max_{\lVert\mathbf{w}_j\rVert=1} \sum_{j,k} \mathrm{cov}(\mathbf{X}_j\mathbf{w}_j, \mathbf{X}_k\mathbf{w}_k)$
SSQCOV (Hanafi & Kiers, 2006)	$\max_{\lVert\mathbf{w}_j\rVert=1} \sum_{j,k} \mathrm{cov}^2(\mathbf{X}_j\mathbf{w}_j, \mathbf{X}_k\mathbf{w}_k)$
SABSCOV (Krämer, 2007)	$\max_{\lVert\mathbf{w}_j\rVert=1} \sum_{j,k} \lvert\mathrm{cov}(\mathbf{X}_j\mathbf{w}_j, \mathbf{X}_k\mathbf{w}_k)\rvert$

Overview of the Multi-Block litterature

BLOCKS ARE PARTIALLY CONNECTED

$c_{jk} = 1$ if $\mathbf{X}_j \leftrightarrow \mathbf{X}_k$, 0 otherwise



SUMCOR	$\max_{\mathbf{w}_j} \sum_{j,k} c_{jk} \text{cor}(\mathbf{X}_j\mathbf{w}_j, \mathbf{X}_k\mathbf{w}_k)$
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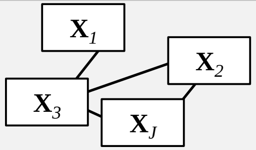
Overview of the Multi-Block litterature



BLOCKS ARE PARTIALLY CONNECTED $c_{jk} = 1$ if $\mathbf{X}_j \leftrightarrow \mathbf{X}_k$, 0 otherwise	
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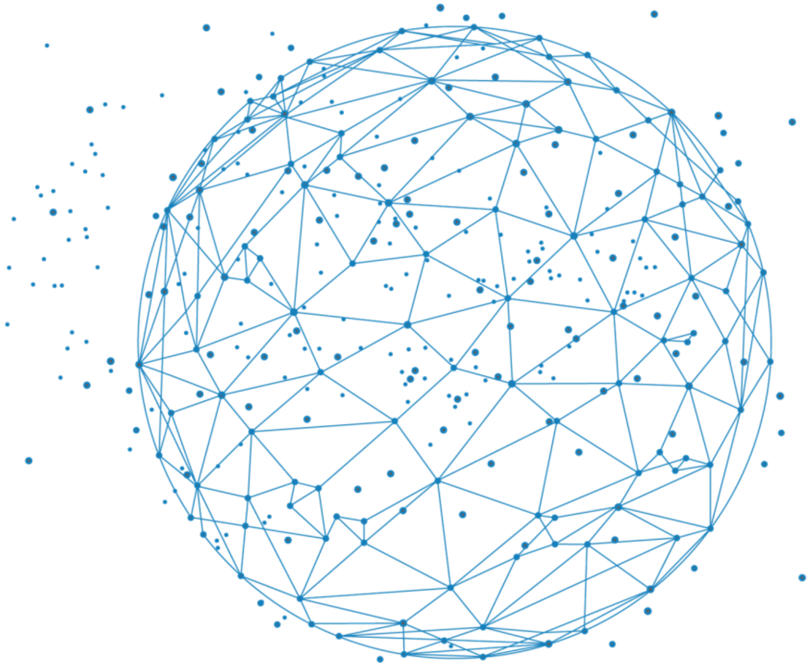
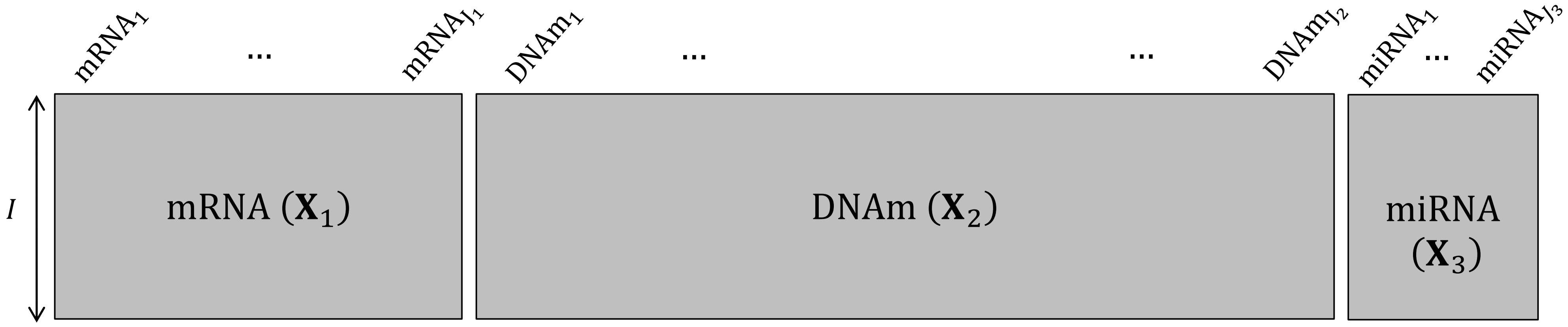
Courtesy to Arthur Tenenhaus.

Let us see how RGCCA performs on the MDD case study

➔ See section 3.2 on the Rmarkdown `MDD_case_study_RGCCA`



Tune parameters in an unsupervised setting



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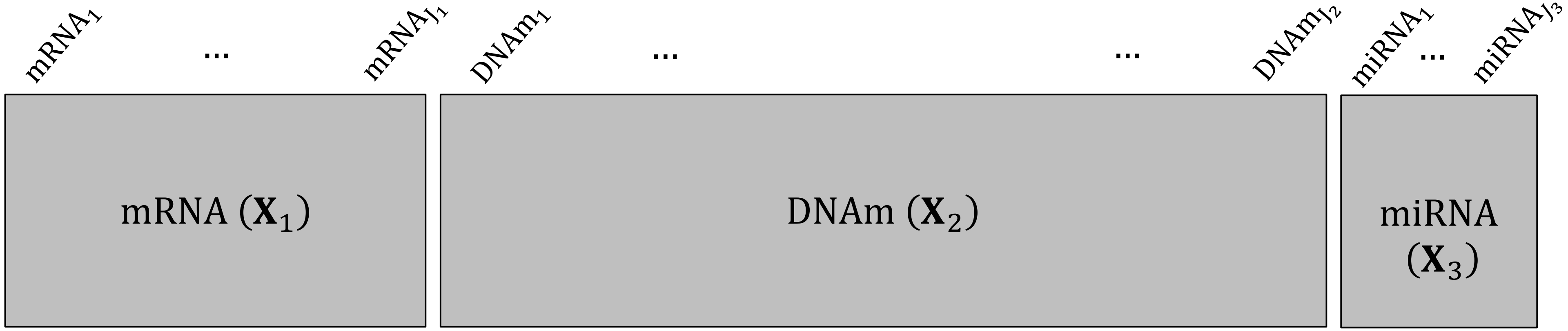

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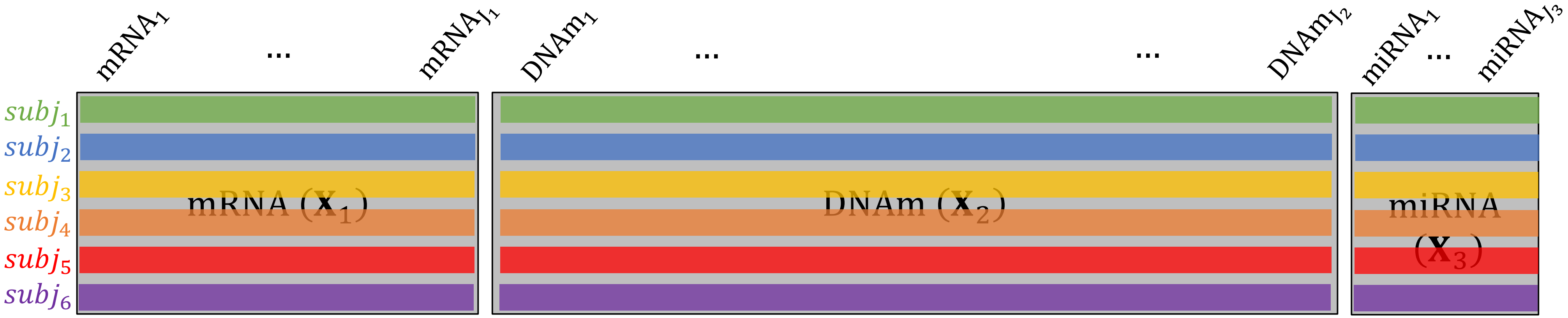
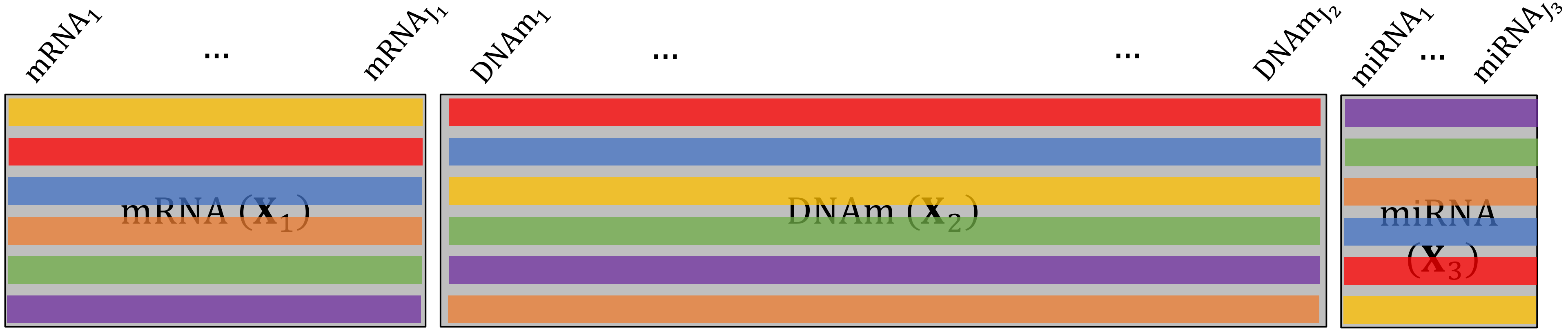


Tune parameters in an unsupervised setting

Permutation n°1

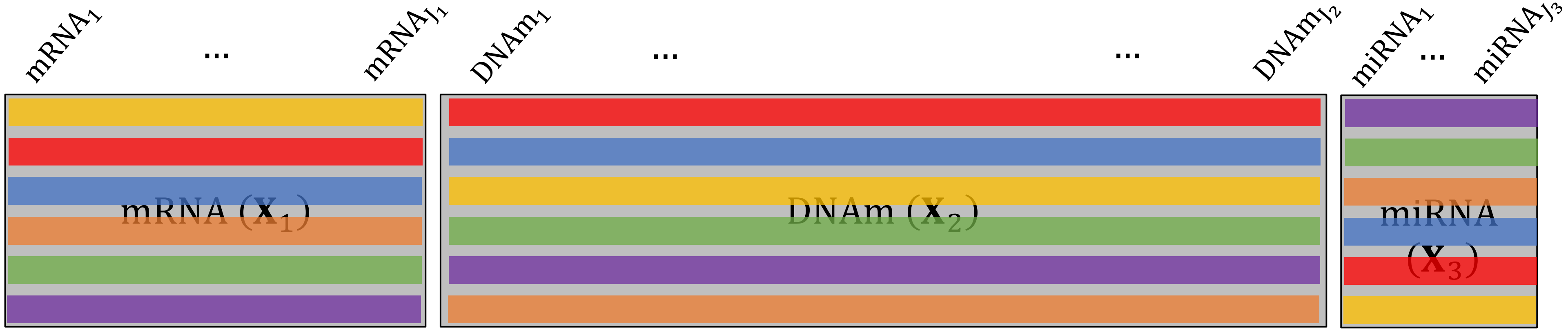
Tune parameters in an unsupervised setting



Permutation n°1

Parameter set n°1

Tune parameters in an unsupervised setting



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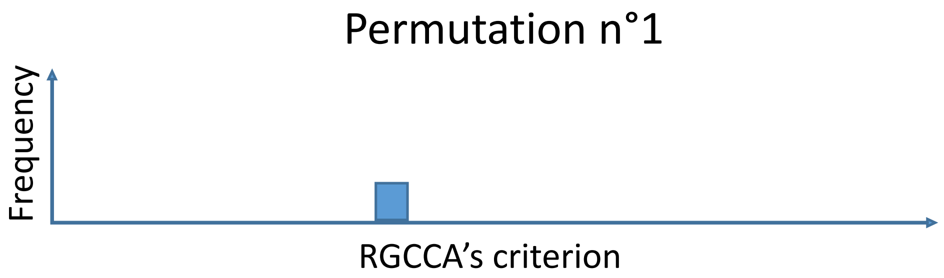
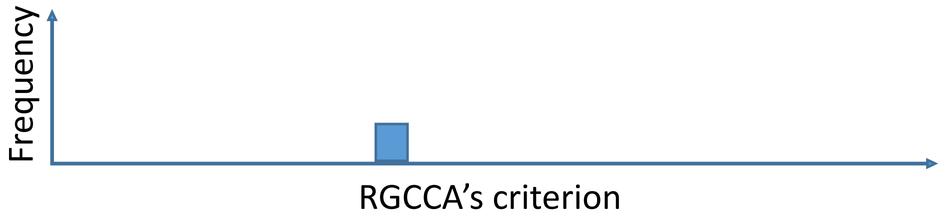


Tune parameters in an unsupervised setting

Permutation n°1

Parameter set n°1



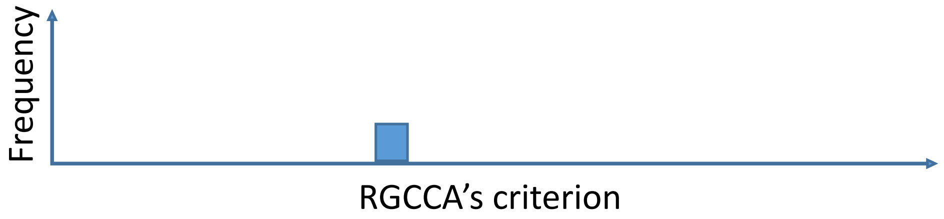
⋮

Parameter set n°K

Tune parameters in an unsupervised setting

Permutation n°1

Parameter set n°1



⋮

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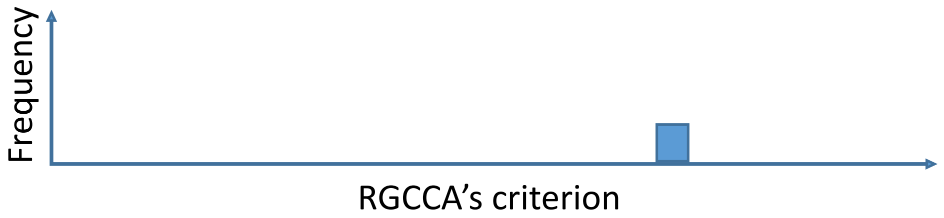
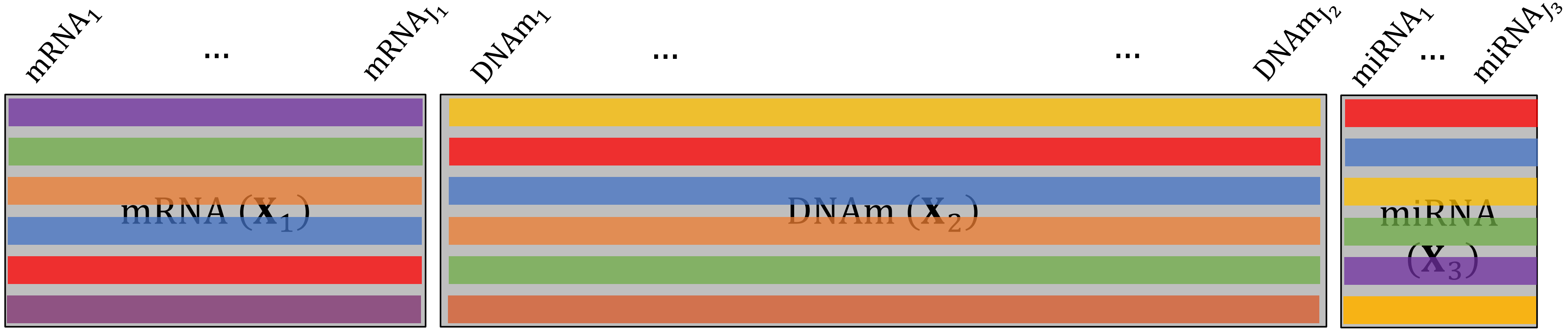
Parameter set n°K

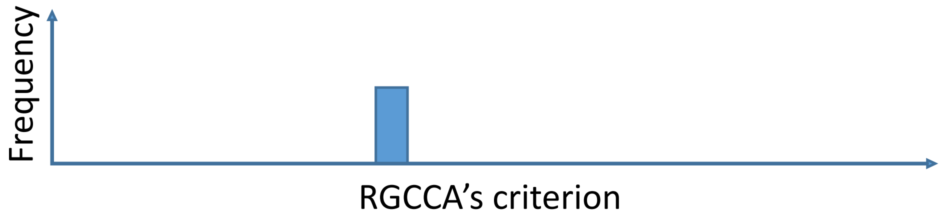


Tune parameters in an unsupervised setting



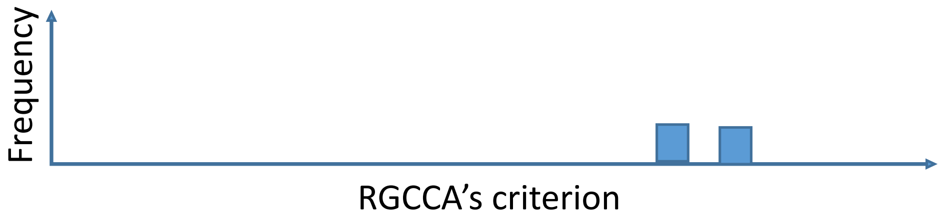
Permutation n°2

Parameter set n°1

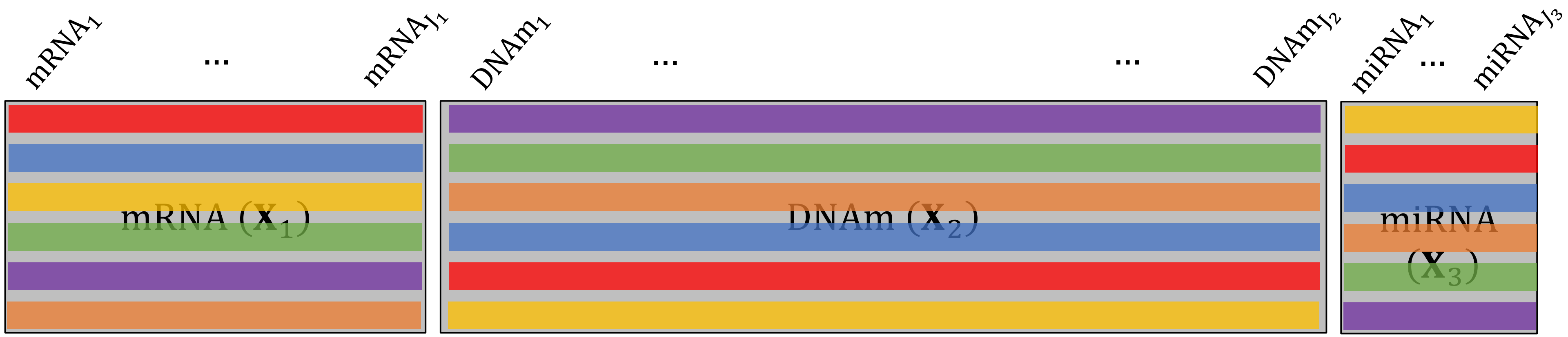


⋮ ⋮

Parameter set n°K

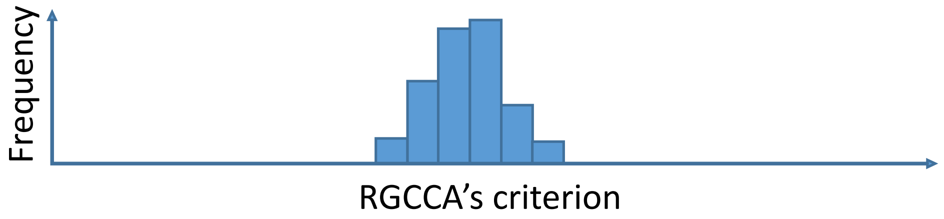


Tune parameters in an unsupervised setting



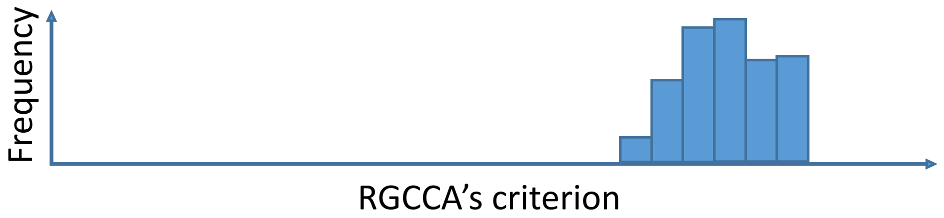
Permutation n°N

Parameter set n°1

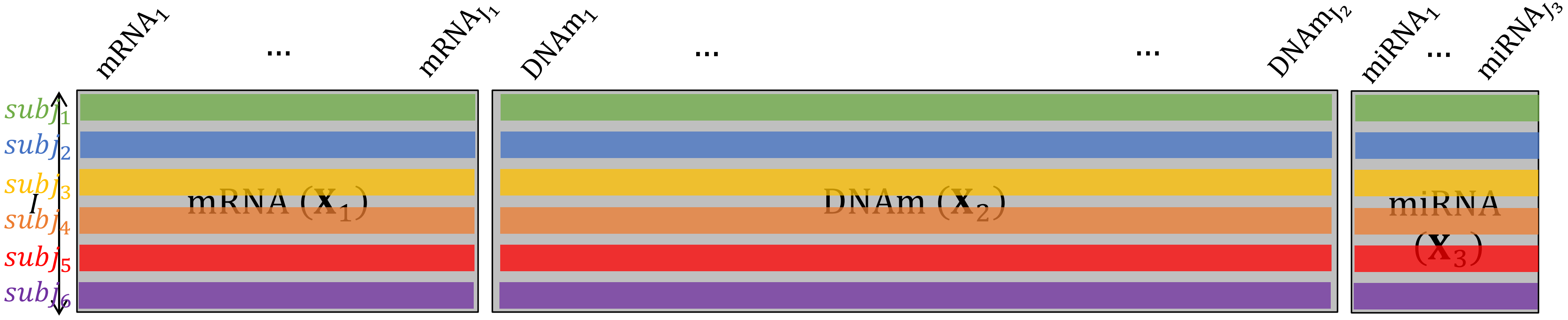


⋮ ⋮

Parameter set n°K

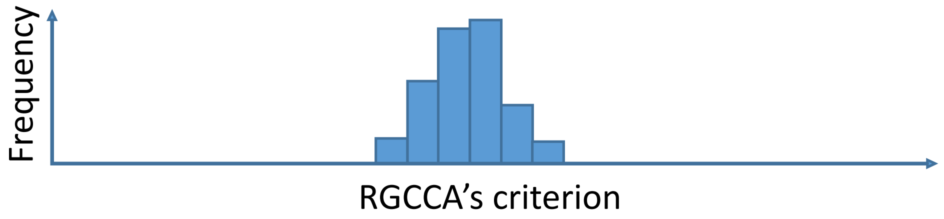


Tune parameters in an unsupervised setting



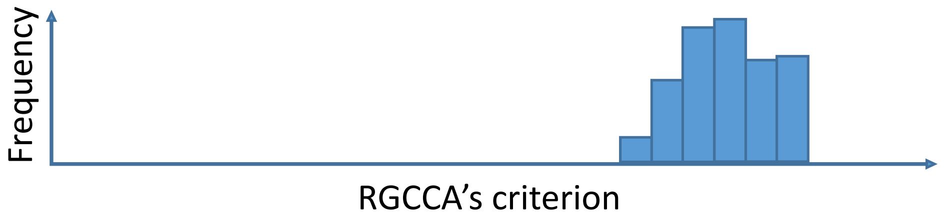
No Permutation

Parameter set n°1

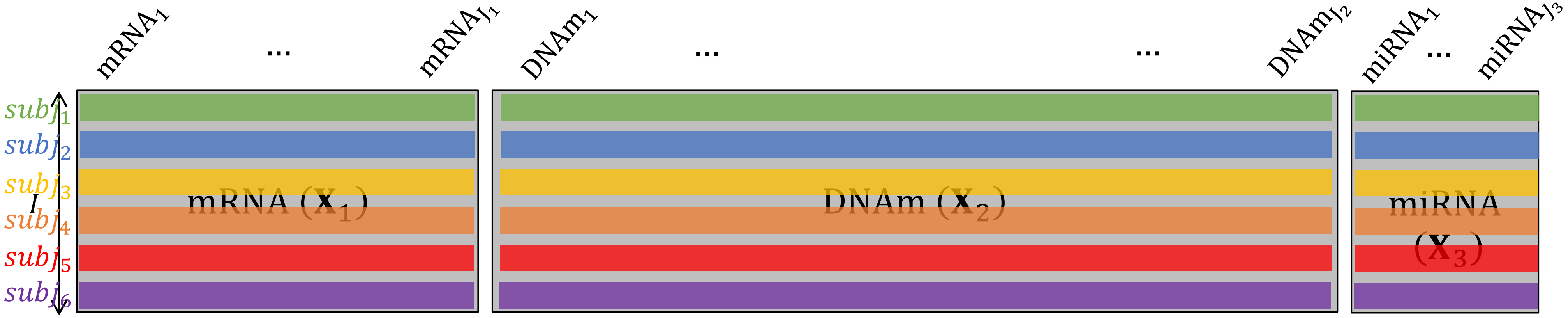


⋮

Parameter set n°K

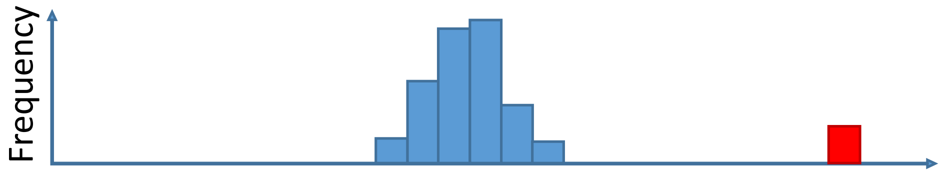


Tune parameters in an unsupervised setting



No Permutation

Parameter set n°1

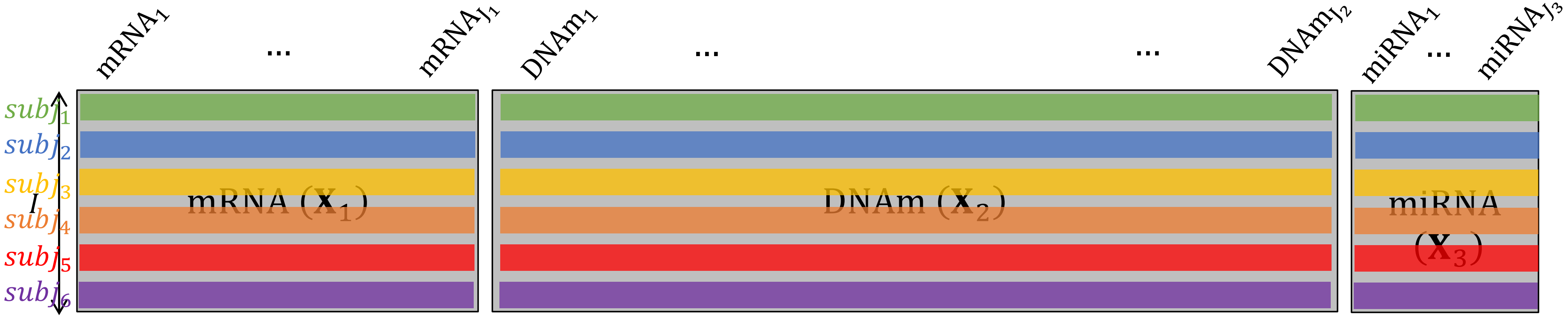


⋮

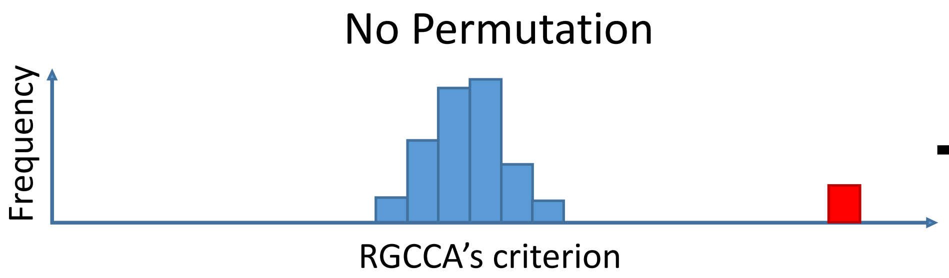
⋮

Parameter set n°K

Tune parameters in an unsupervised setting



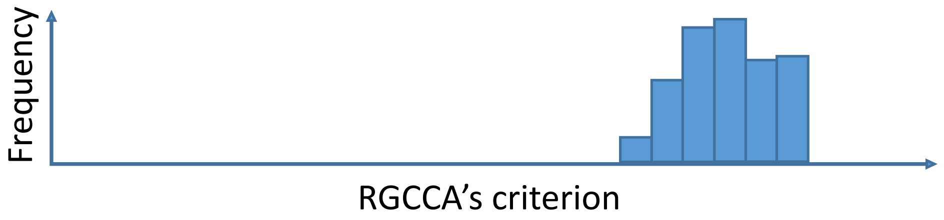
Parameter set n°1



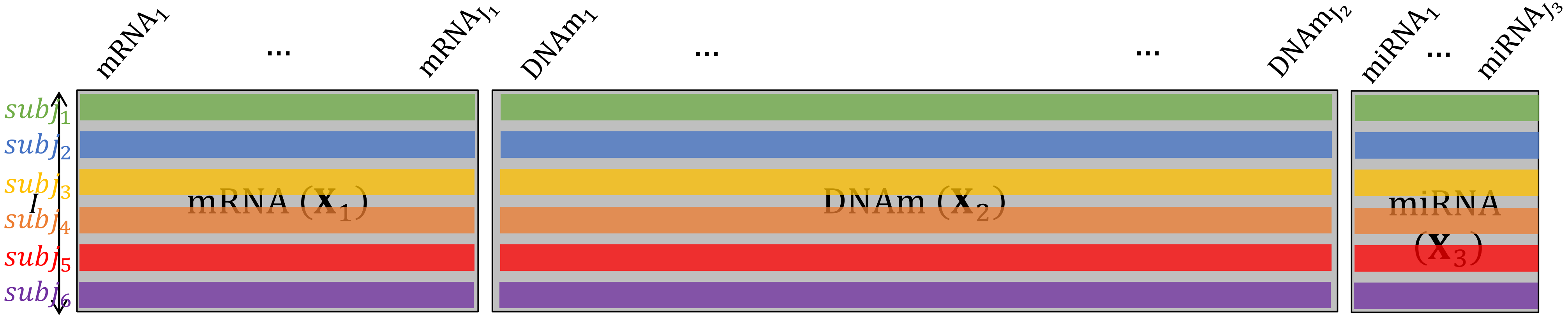
➔ The set of parameters is likely to be selected.

⋮

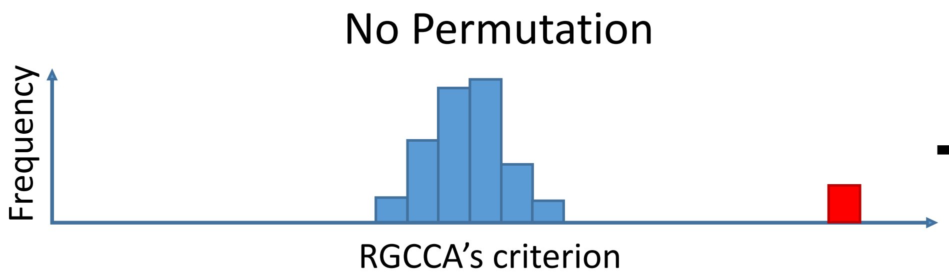
Parameter set n°K



Tune parameters in an unsupervised setting



Parameter set n°1



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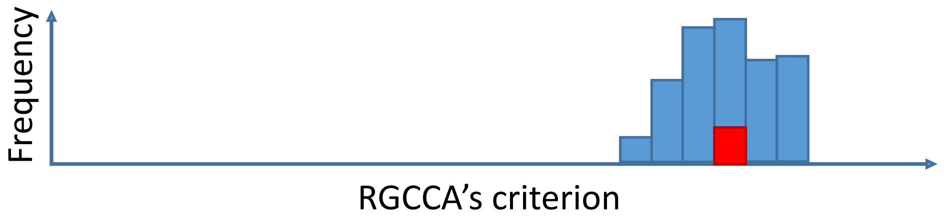
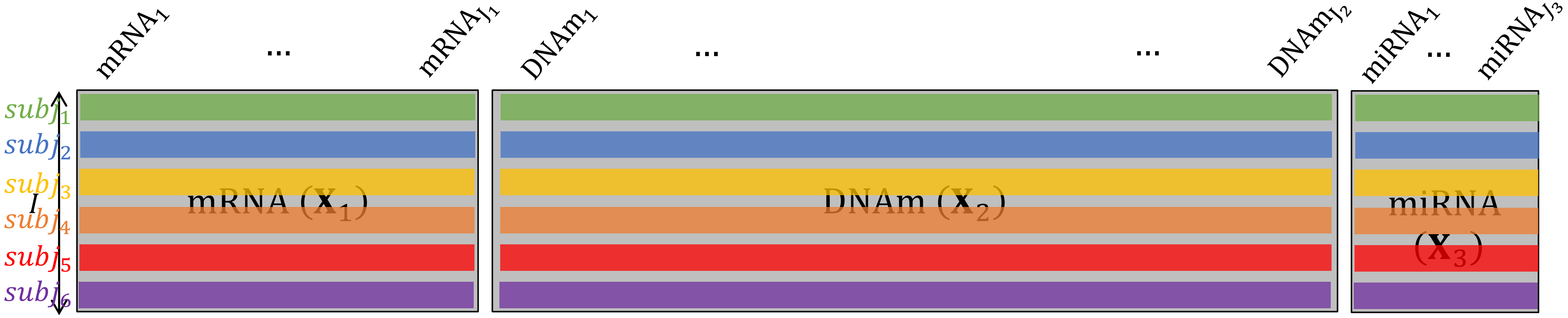
⋮

⋮

Parameter set n°K

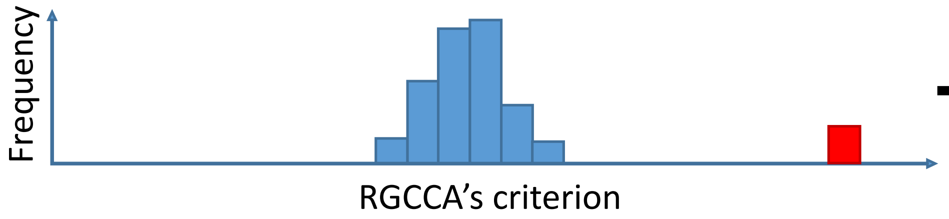


Tune parameters in an unsupervised setting



No Permutation

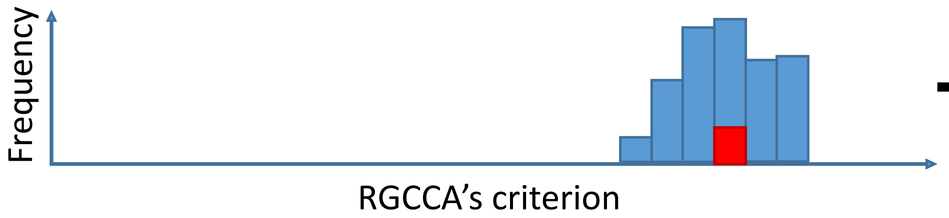
Parameter set n°1



➔ The set of parameters is likely to be selected.

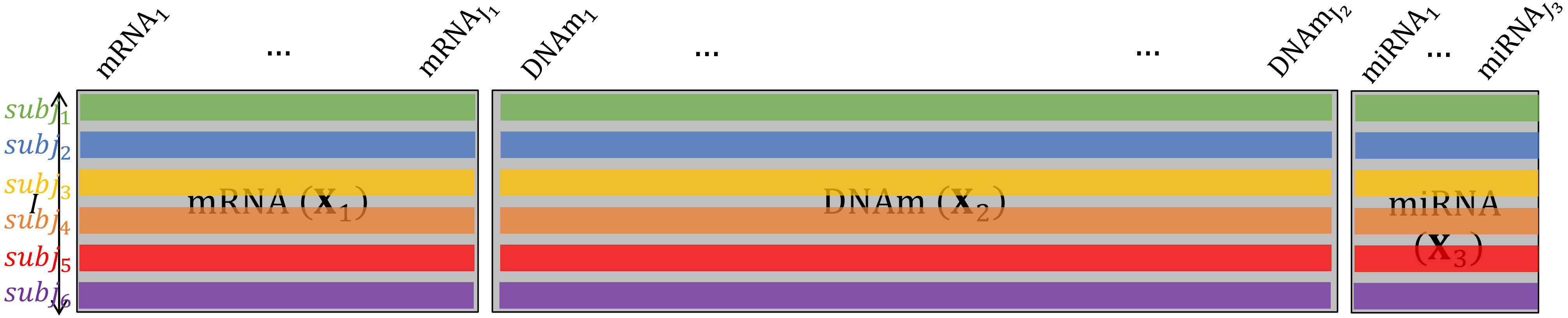
⋮ ⋮

Parameter set n°K

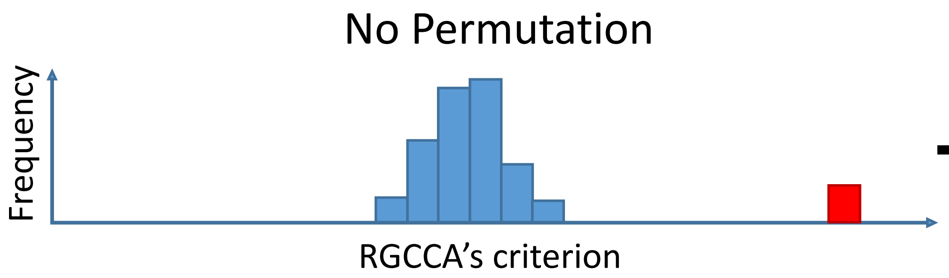


➔ The set of parameters is unlikely to be selected.

Tune parameters in an unsupervised setting



Parameter set n°1



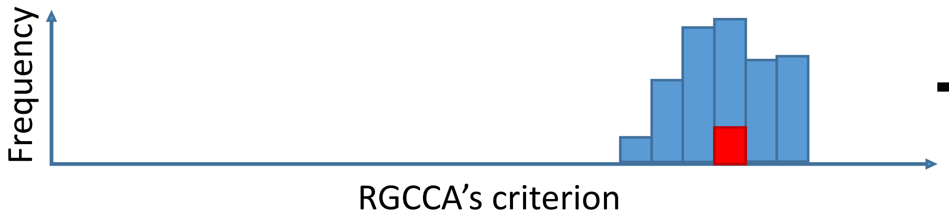
➔ The set of parameters is likely to be selected.

⋮

RGCCA choose the best set of parameters as the one with the highest value of $Z_k = \frac{(crit_{unperm} - \mu_{crit}^{perm})}{\sigma_{crit}^{perm}}$

⋮

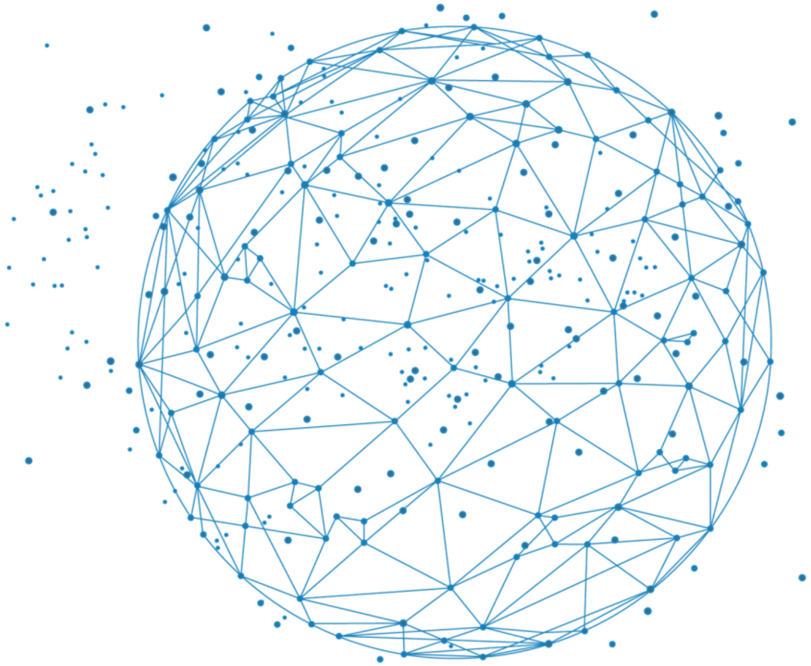
Parameter set n°K



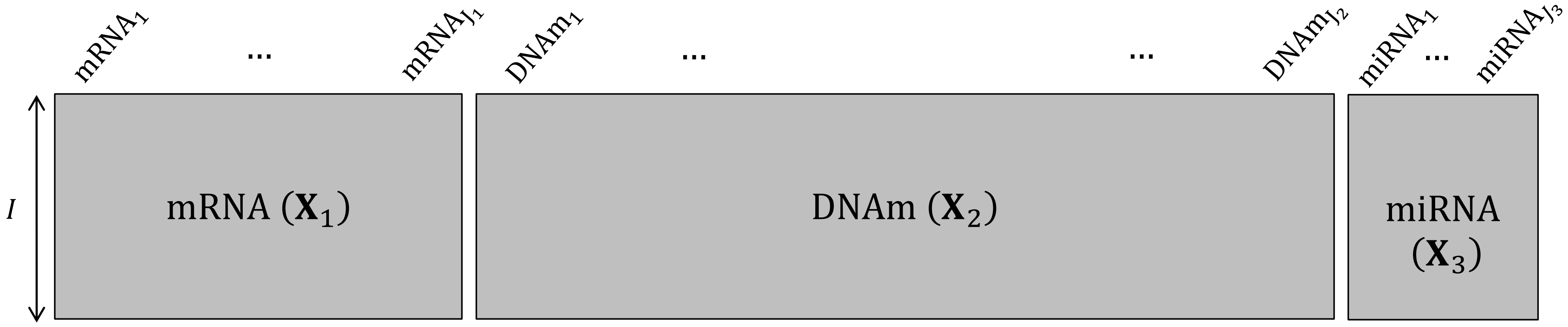
➔ The set of parameters is unlikely to be selected.

Let us apply this permutation procedure on the MDD case study

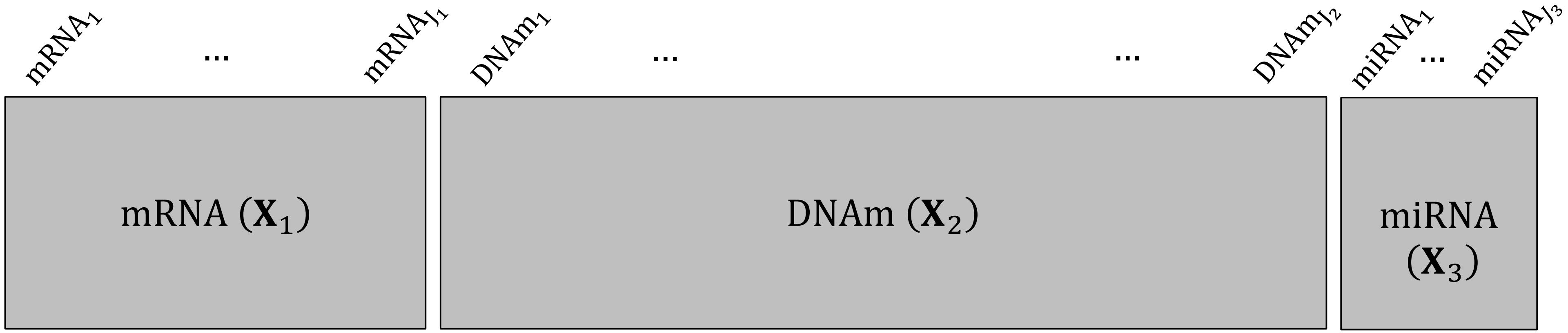
➔ See section 3.3 on the Rmarkdown `MDD_case_study_RGCCA`



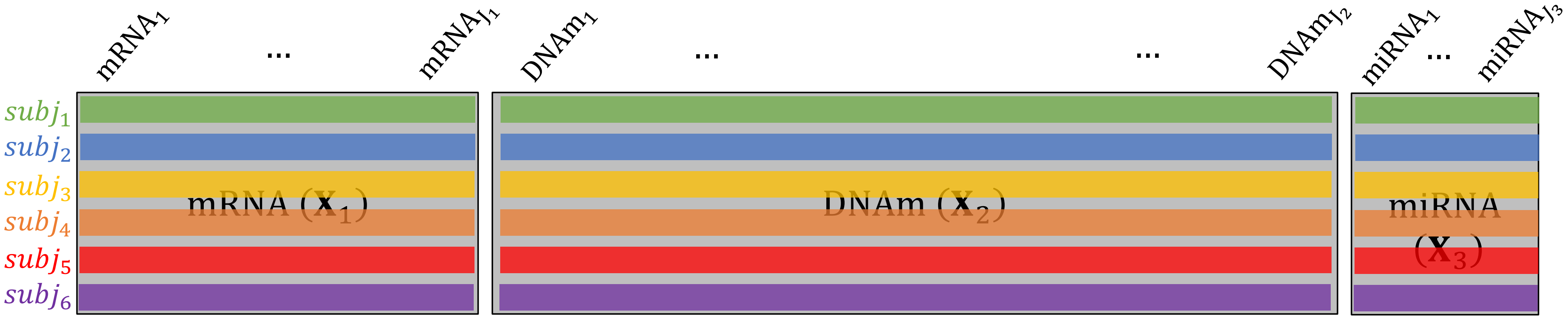
Evaluate the robustness of the model by bootstrapping.



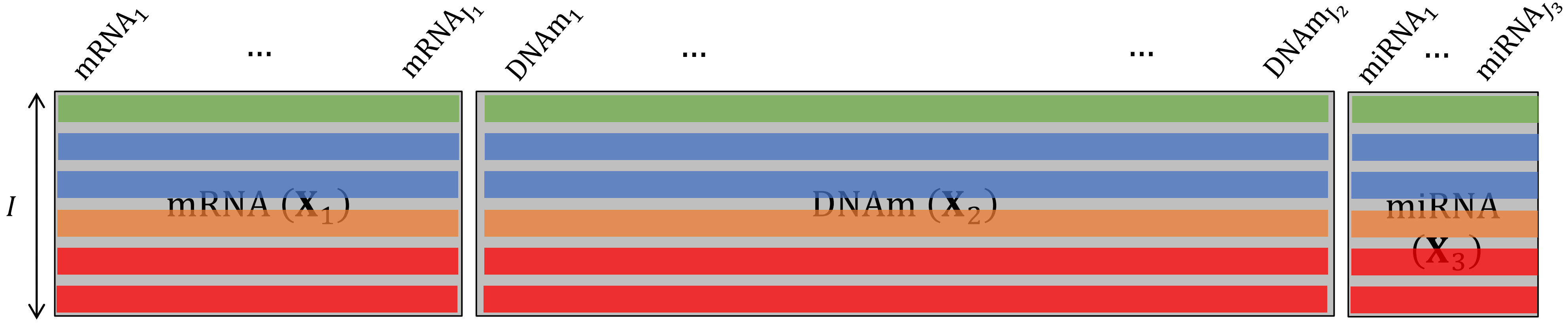
Evaluate the robustness of the model by bootstrapping.



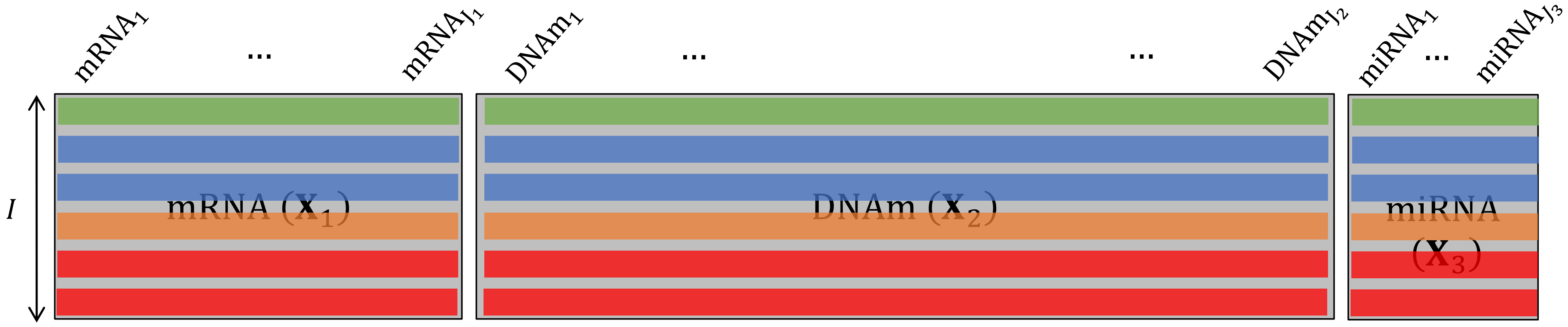
Evaluate the robustness of the model by bootstrapping.



Evaluate the robustness of the model by bootstrapping.

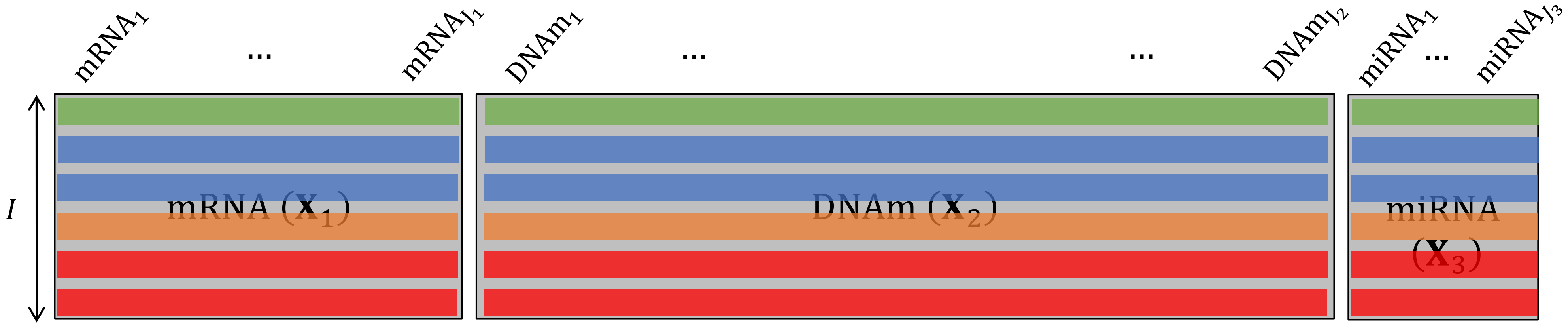


Evaluate the robustness of the model by bootstrapping.



Bootstrap sample n°1

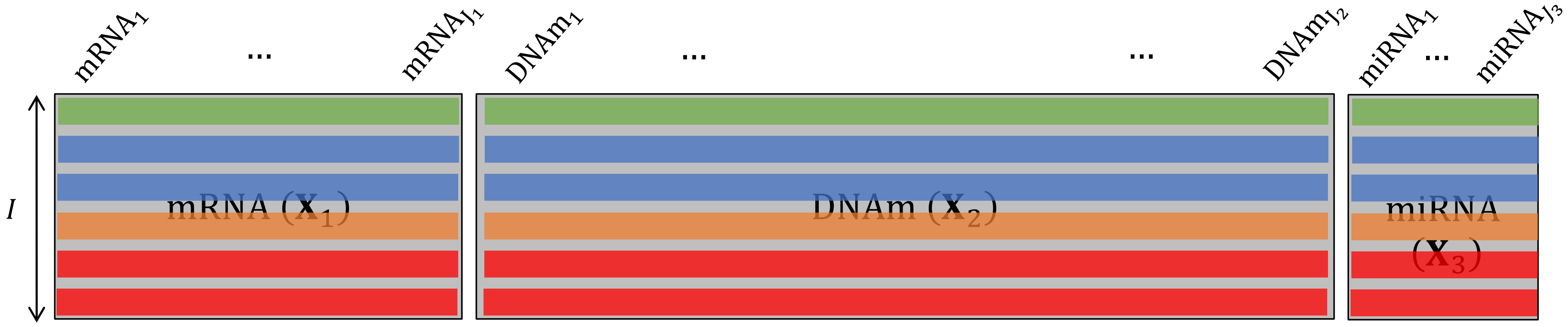
Evaluate the robustness of the model by bootstrapping.



Bootstrap sample n°1

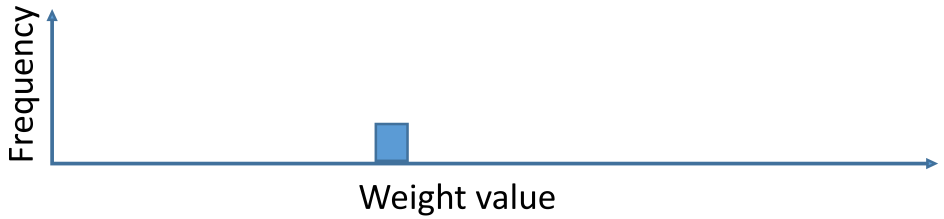
Weight for mRNA_1

Evaluate the robustness of the model by bootstrapping.

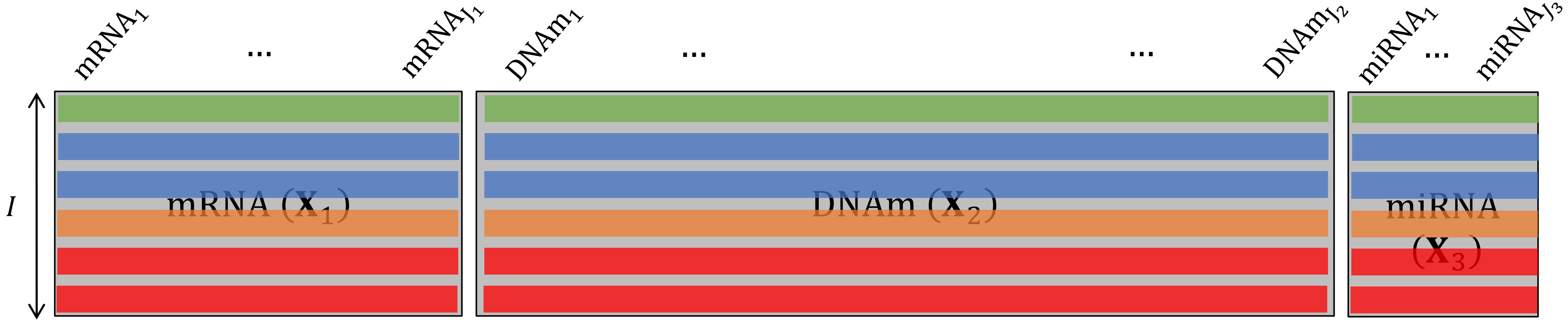


Bootstrap sample n°1

Weight for mRNA_1

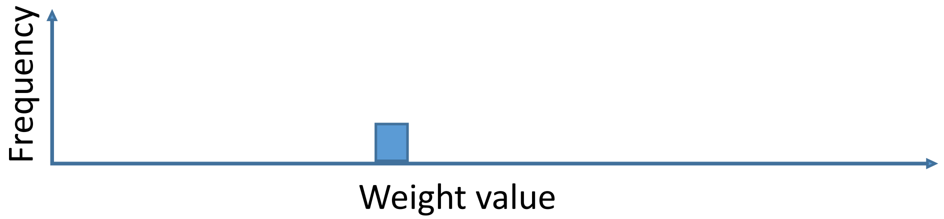


Evaluate the robustness of the model by bootstrapping.



Bootstrap sample n°1

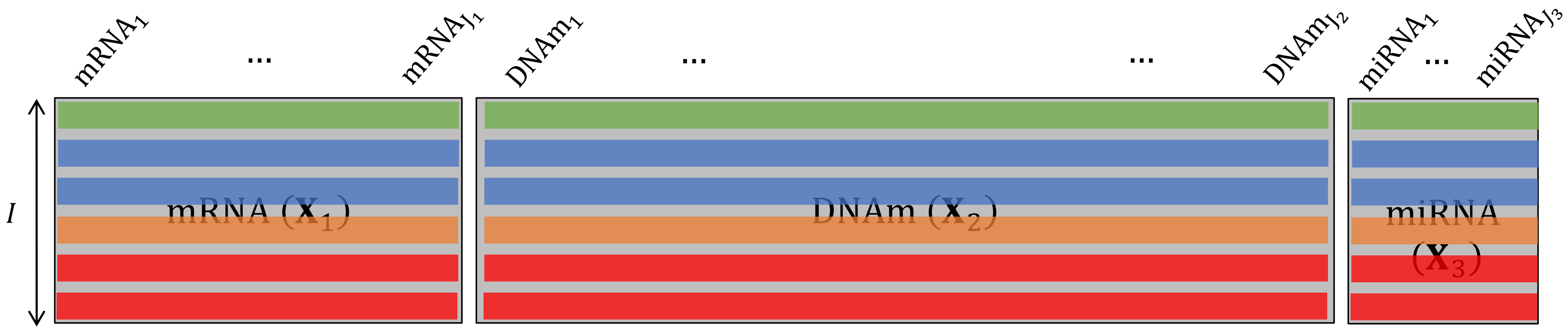
Weight for $mRNA_1$



⋮

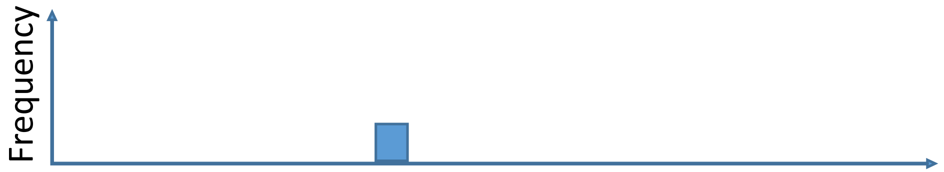
Weight for $miRNA_{J_3}$

Evaluate the robustness of the model by bootstrapping.



Bootstrap sample n°1

Weight for $mRNA_1$

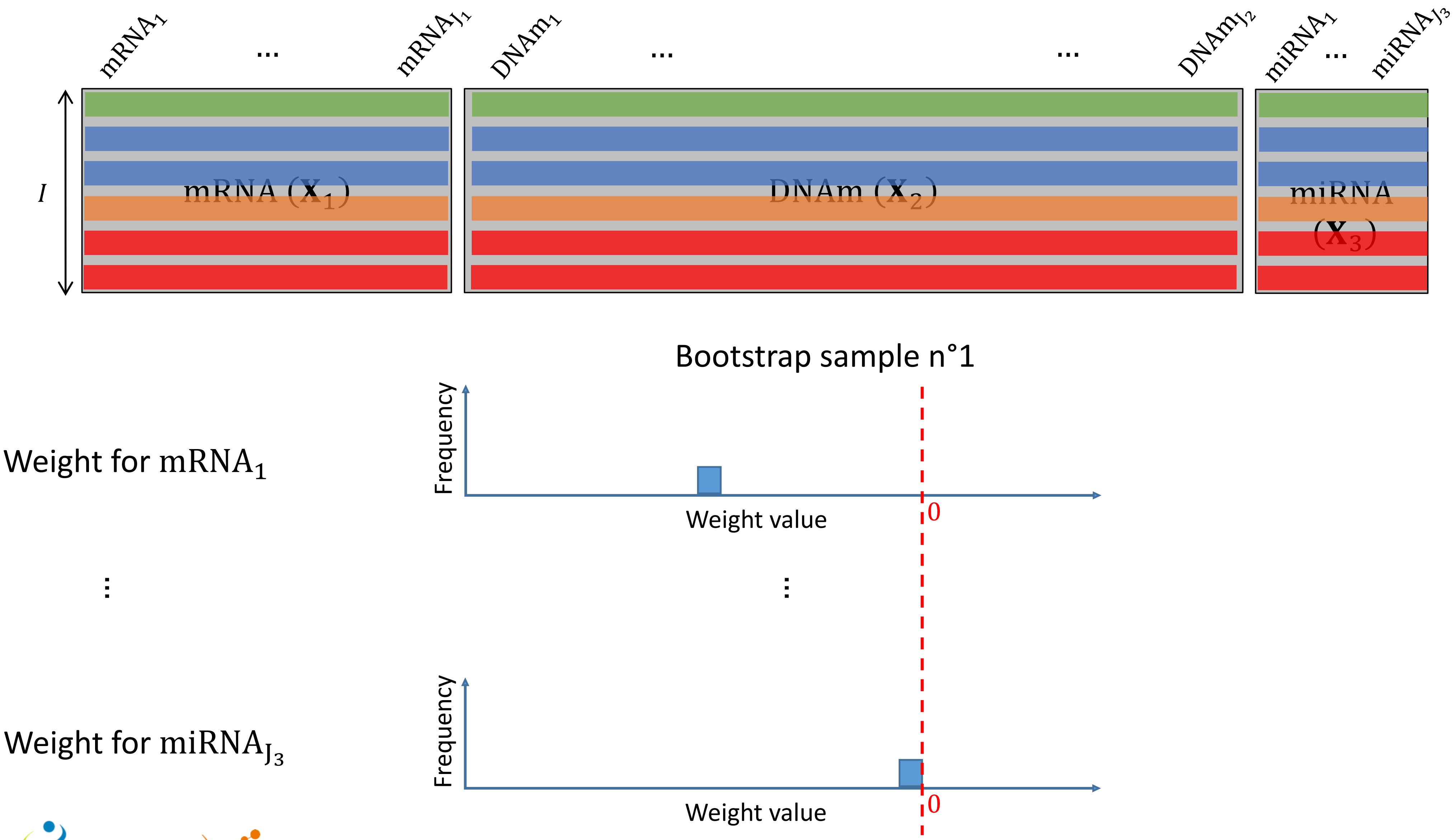


⋮

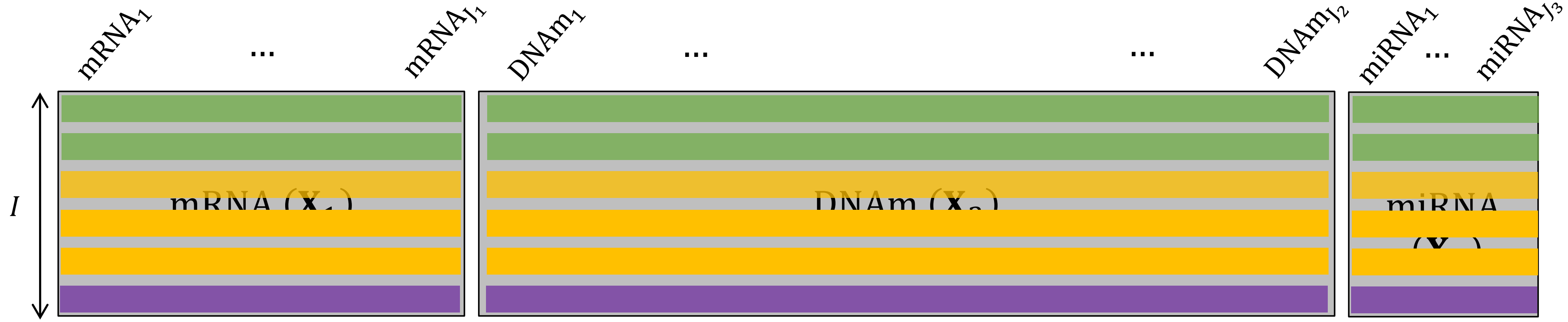
⋮

Weight for $miRNA_{J_3}$

Evaluate the robustness of the model by bootstrapping.



Evaluate the robustness of the model by bootstrapping.

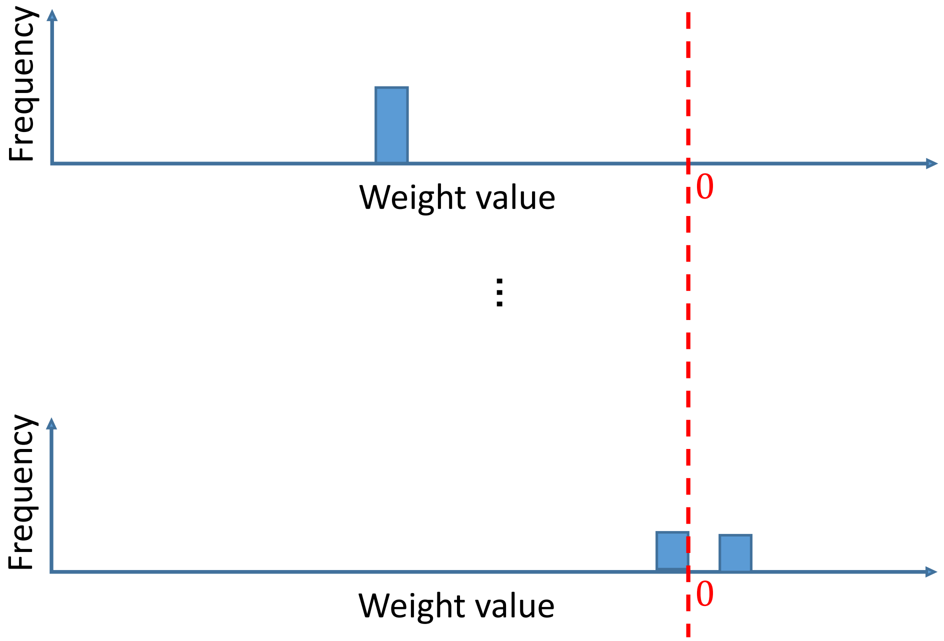


Bootstrap sample n°2

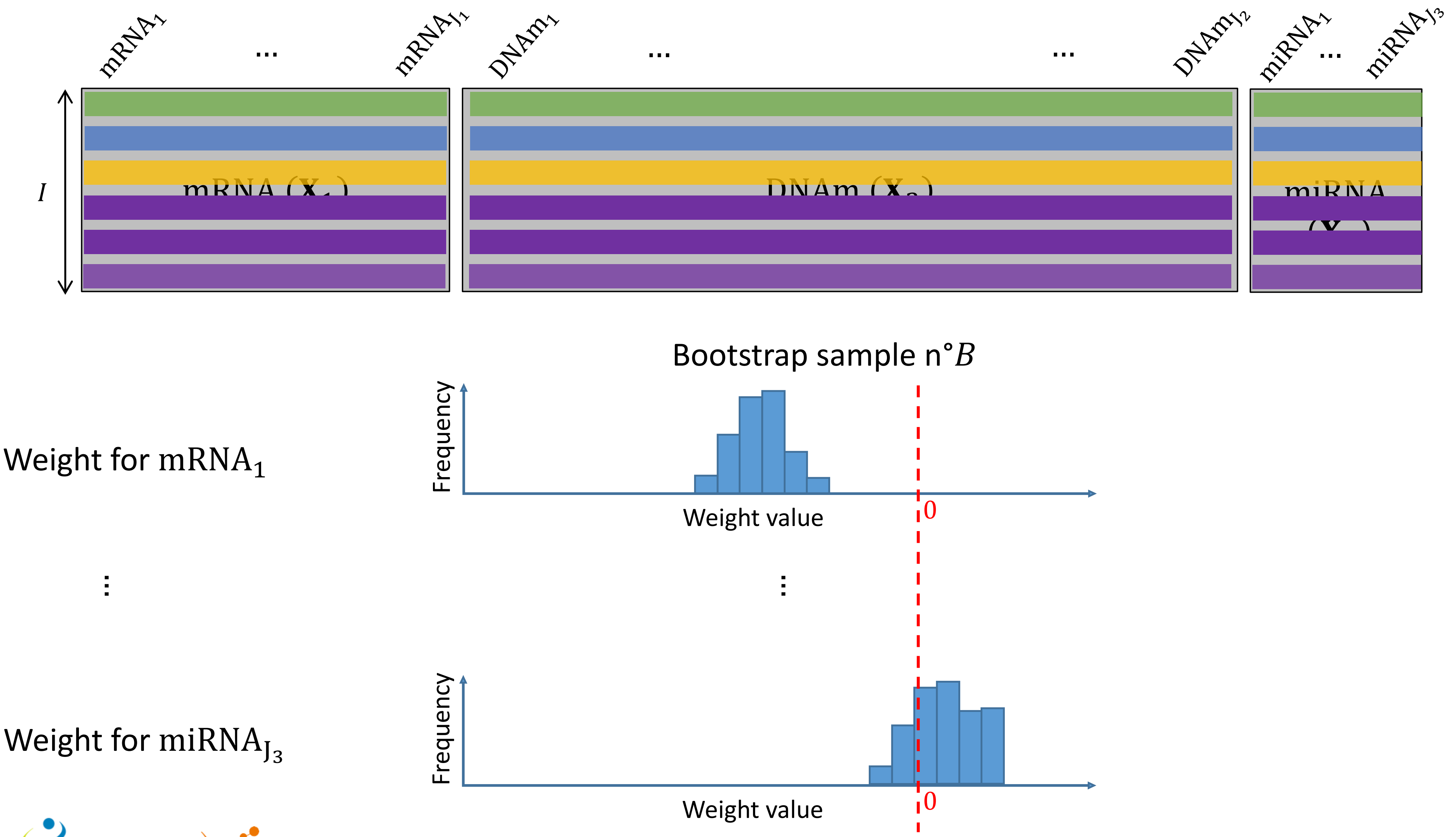
Weight for $mRNA_1$

⋮

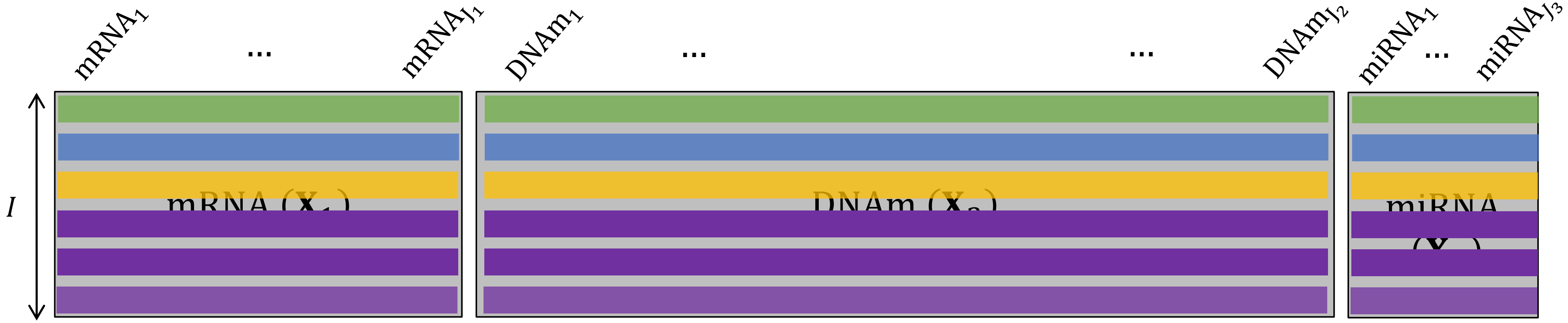
Weight for $miRNA_{J_3}$



Evaluate the robustness of the model by bootstrapping.



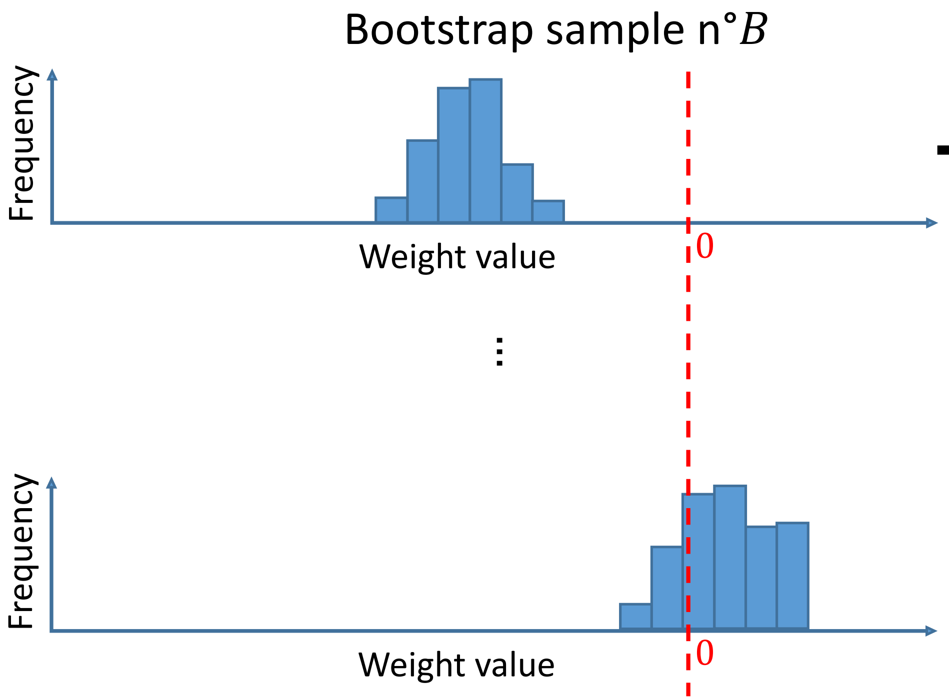
Evaluate the robustness of the model by bootstrapping.



Weight for mRNA_1

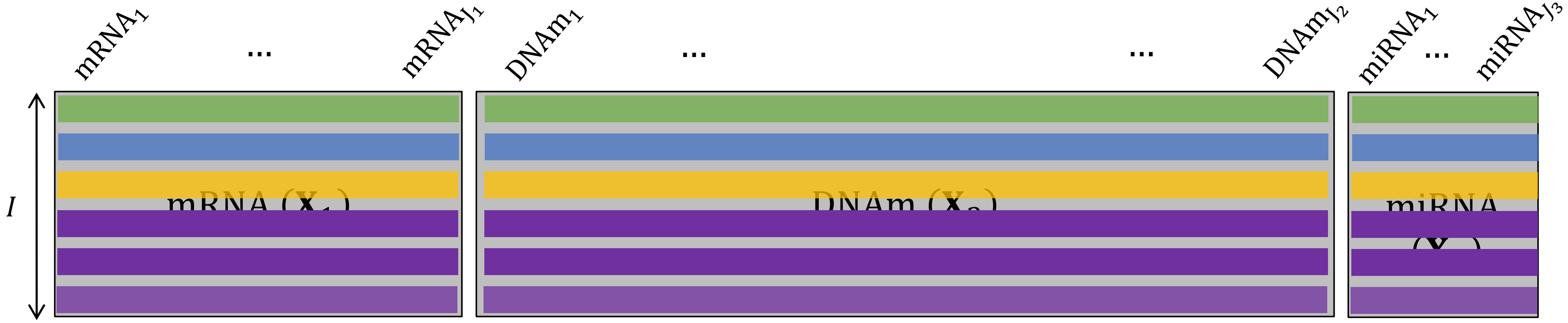
⋮

Weight for miRNA_{J_3}



➔ The weight is likely to be considered as It is significantly different from 0.

Evaluate the robustness of the model by bootstrapping.

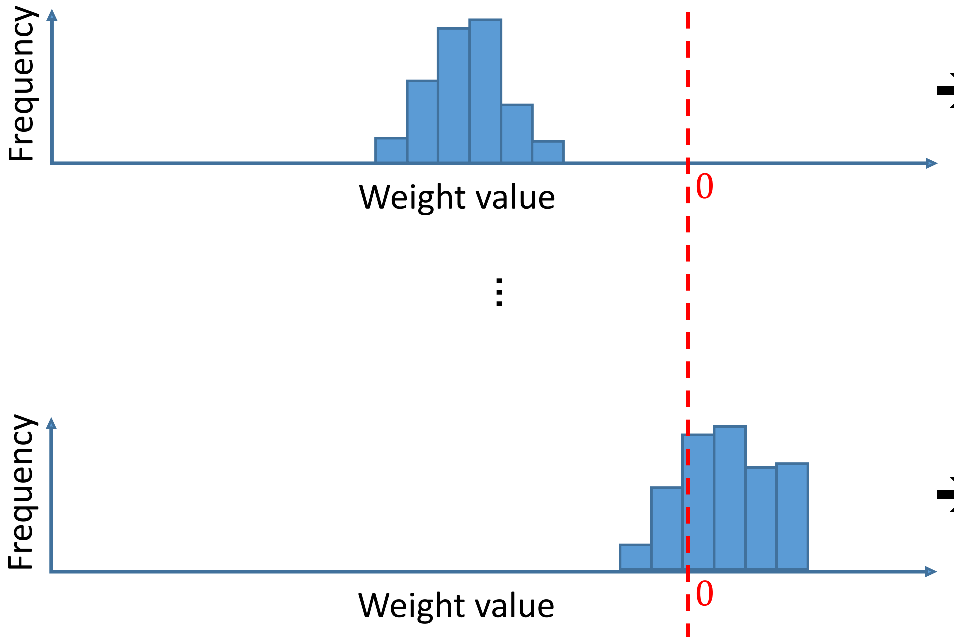


Bootstrap sample n°B

Weight for $mRNA_1$

⋮

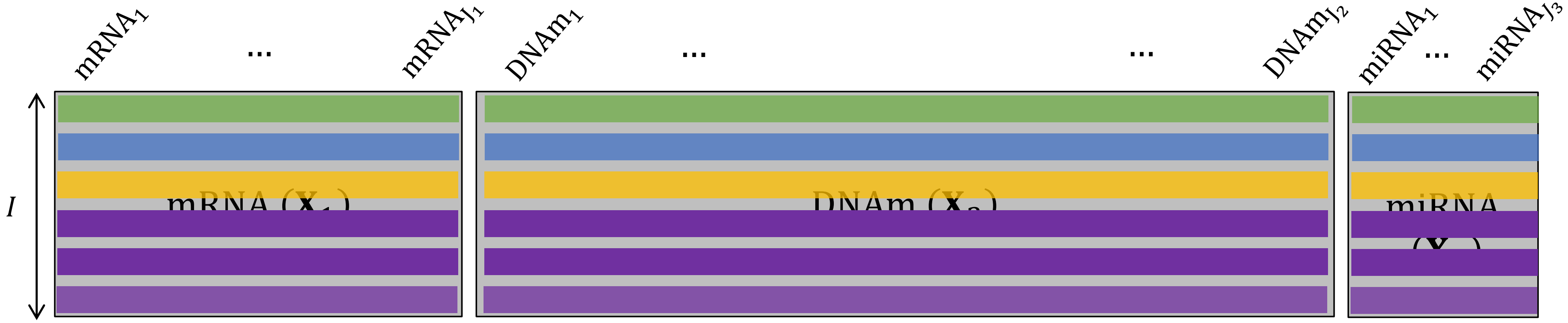
Weight for $miRNA_{J_3}$



➔ The weight is likely to be considered as
It is significantly different from 0.

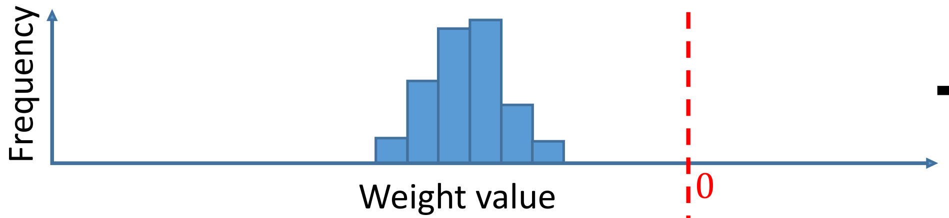
➔ The weight is unlikely to be considered as
It is not significantly different from 0.

Evaluate the robustness of the model by bootstrapping.



Bootstrap sample n°B

Weight for $mRNA_1$



➔ The weight is likely to be considered as It is significantly different from 0.

⋮

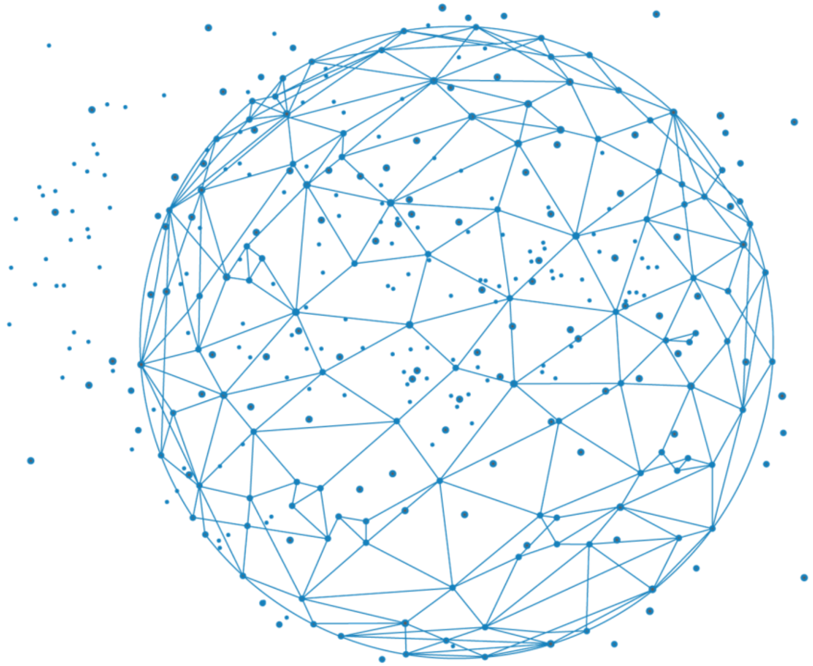
Out of these distributions, RGCCA non-parametrically estimates confidence intervals $([q_{0.025}, q_{0.975}])$ and p-values $\left(min(Nb_{\geq 0}, Nb_{\leq 0})/max(Nb_{\geq 0}, Nb_{\leq 0})\right)$.

Weight for $miRNA_{J_3}$

➔ The weight is unlikely to be considered as It is not significantly different from 0.

Let us apply this permutation procedure on the MDD case study

➔ See section 3.4 on the Rmarkdown `MDD_case_study_RGCCA`



1. Introduction of the case study
2. **Unsupervised analysis with one-block:** Principal Component Analysis (PCA)
3. **Unsupervised analysis with two-blocks:**
   Partial Least Squares (PLS) and Canonical Correlation Analysis (CCA)
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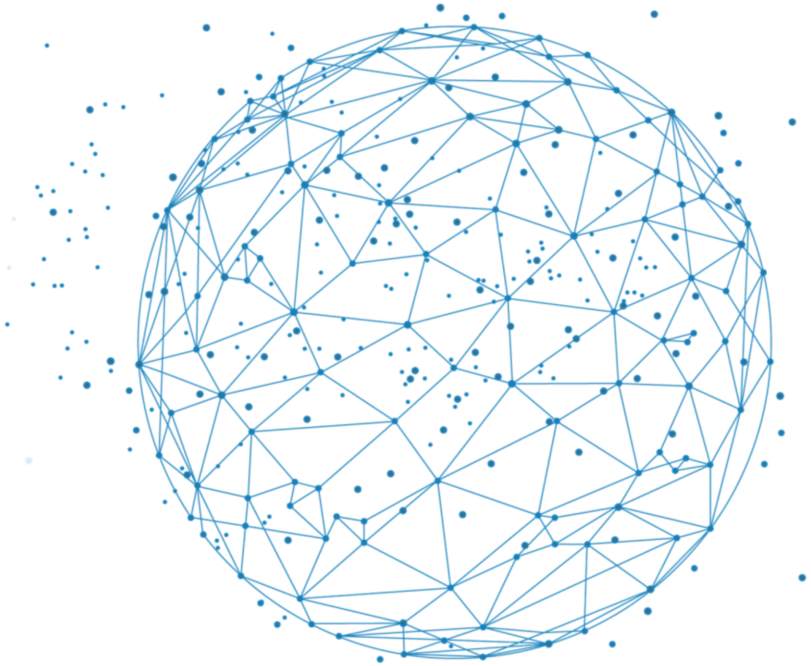
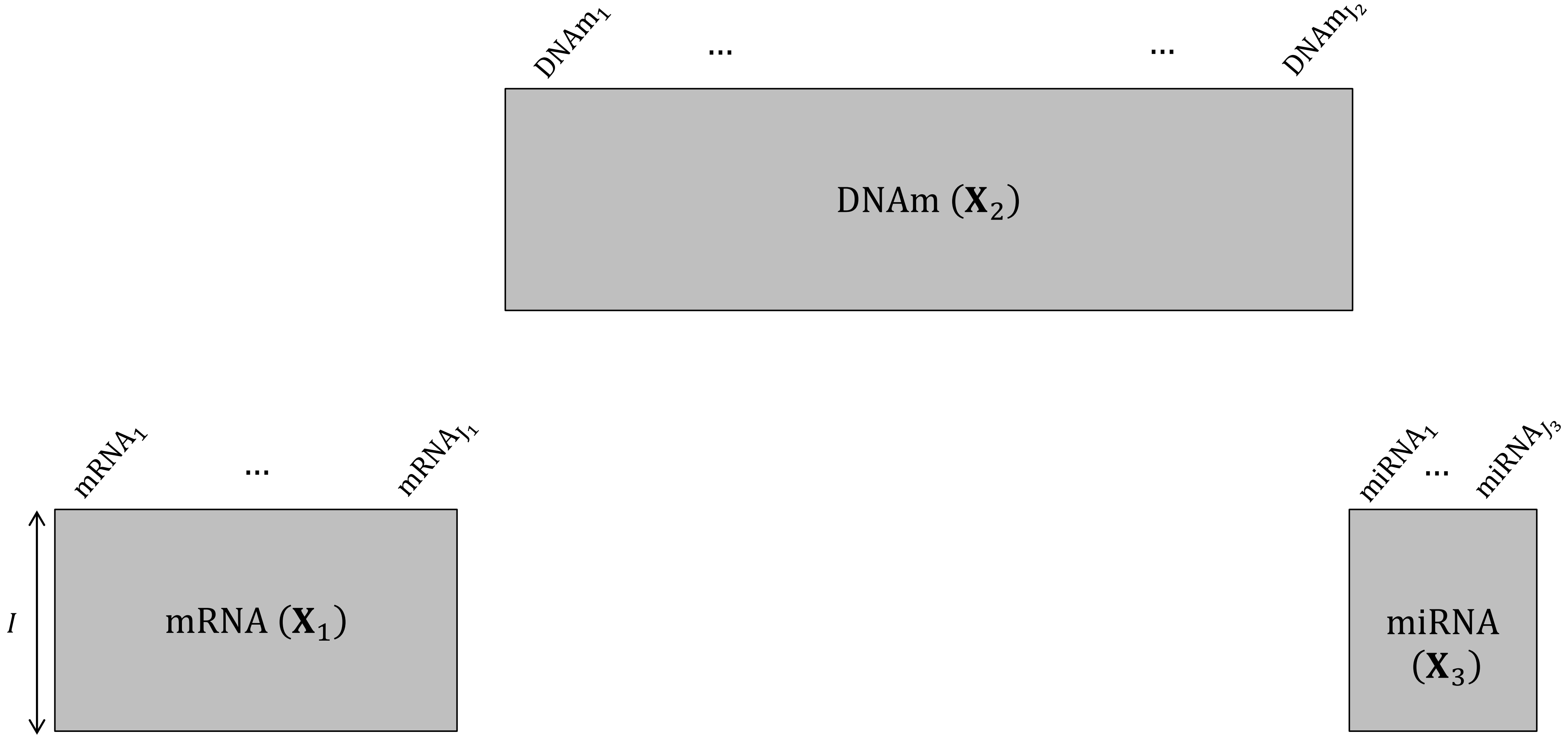
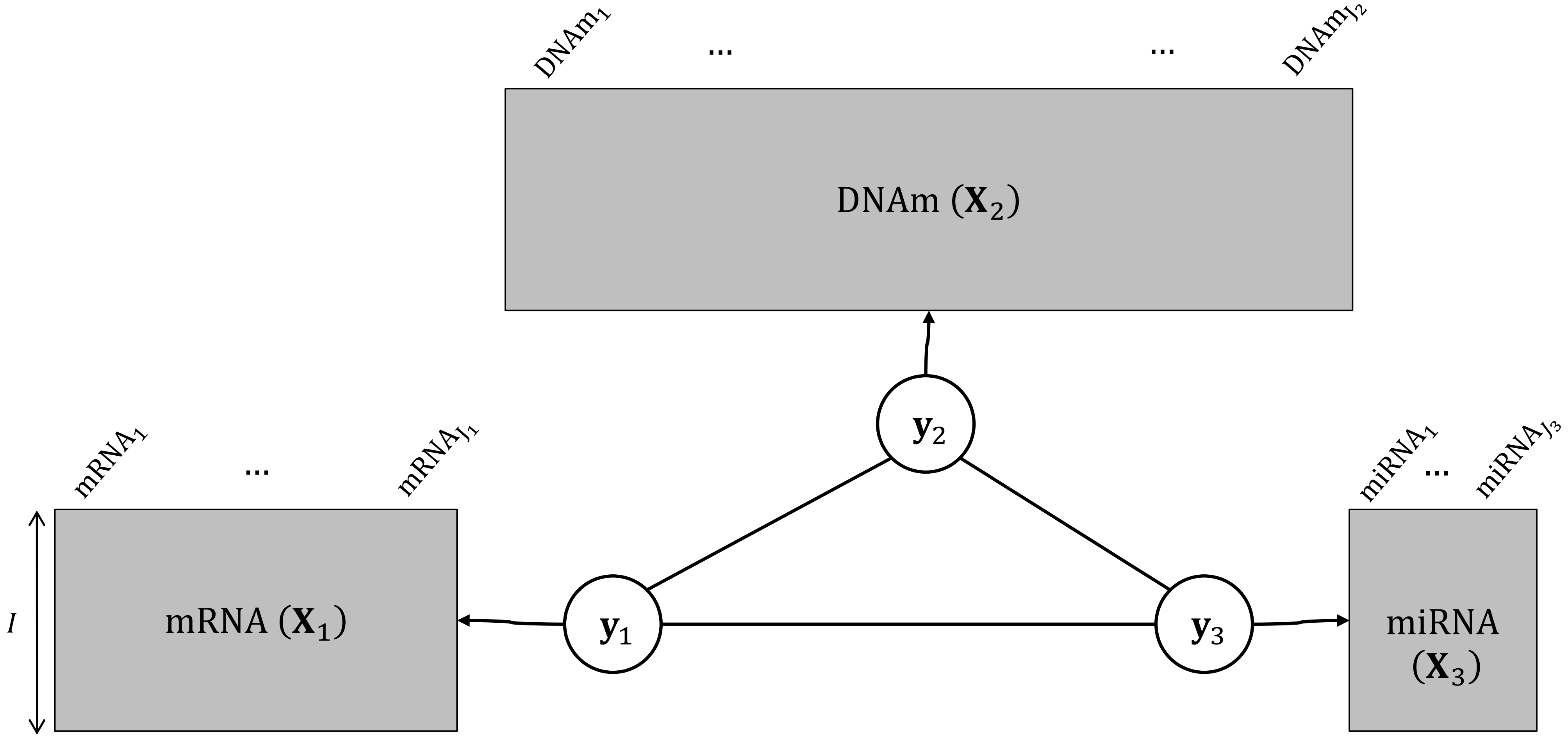
7. **The flexible Optimization Framework of RGCCA**
   - The general principal
   - Extension to multi-way analysis
   - From Sequential to Global



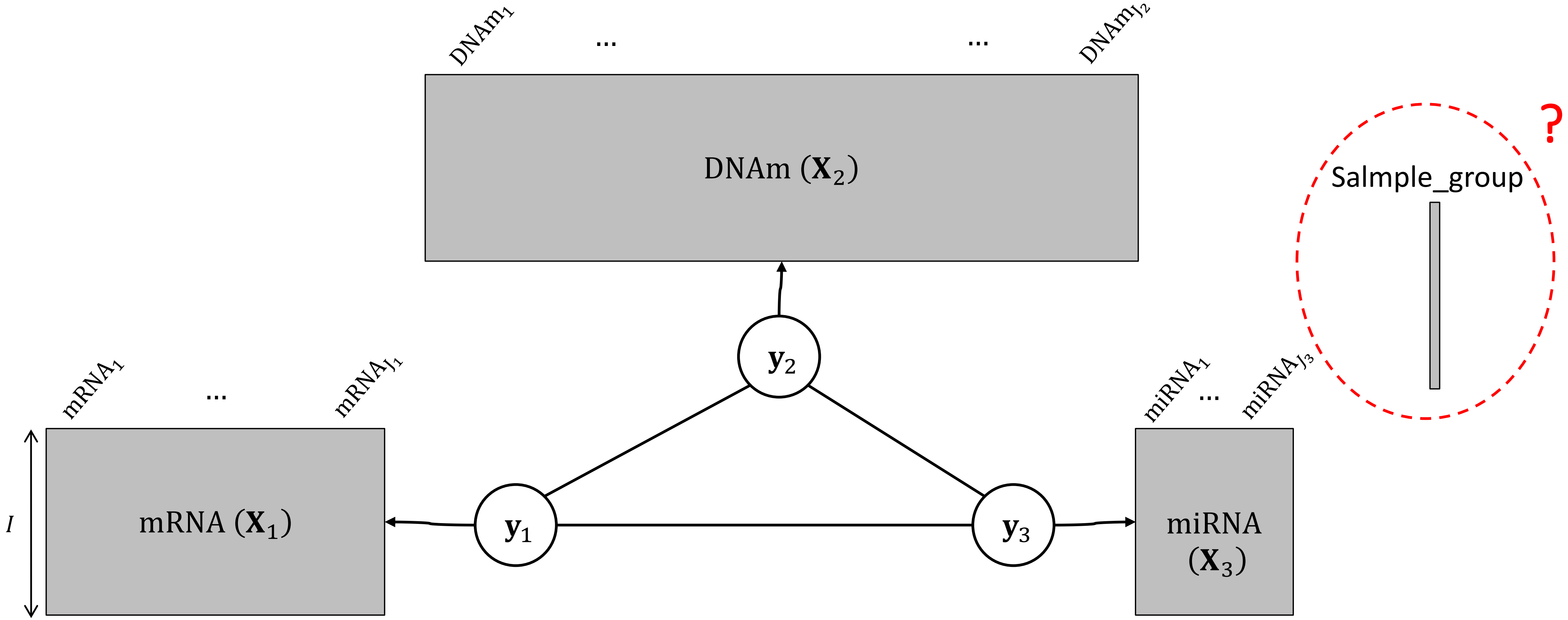
Supervising with RGCCA



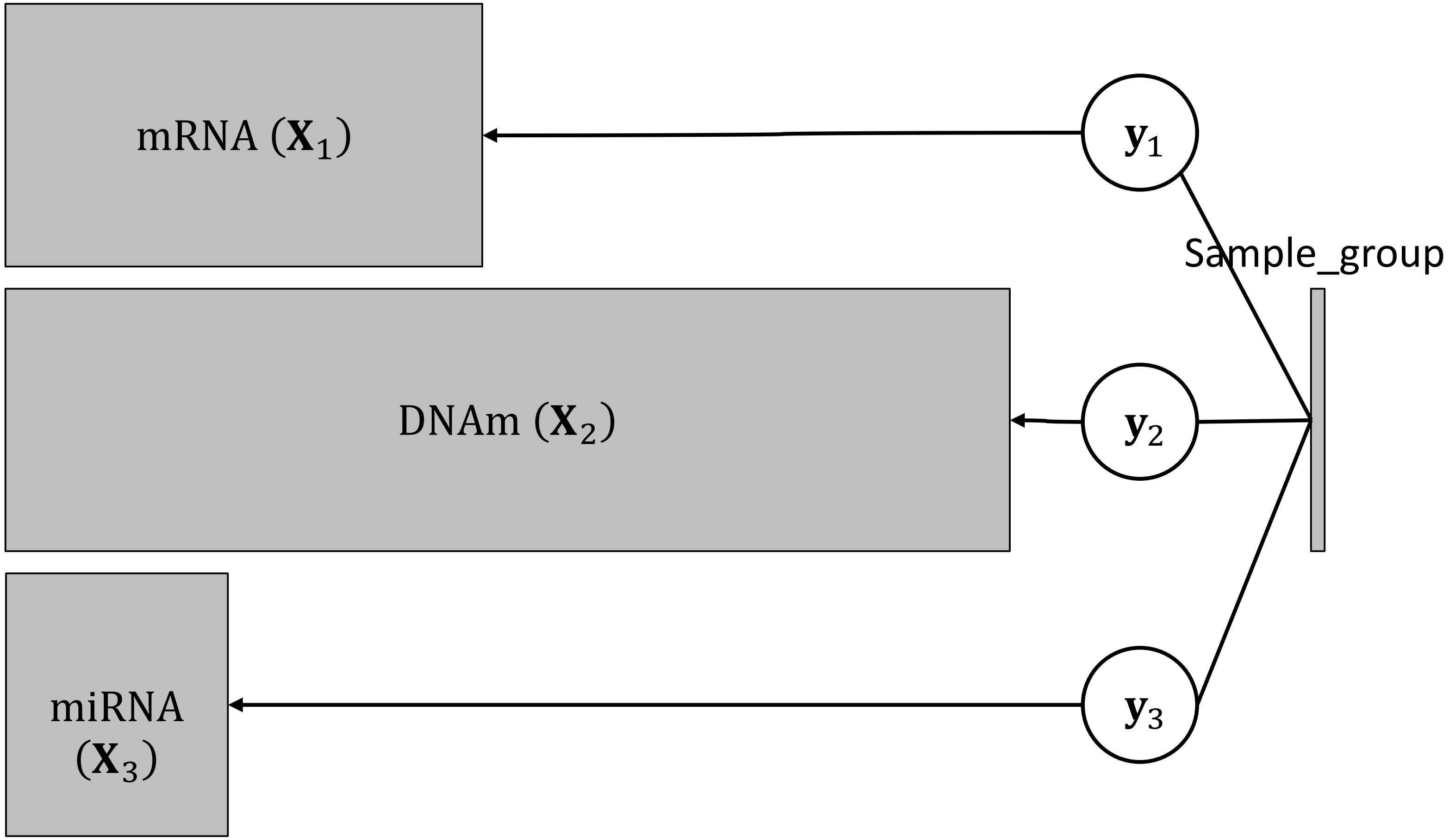
Supervising with RGCCA



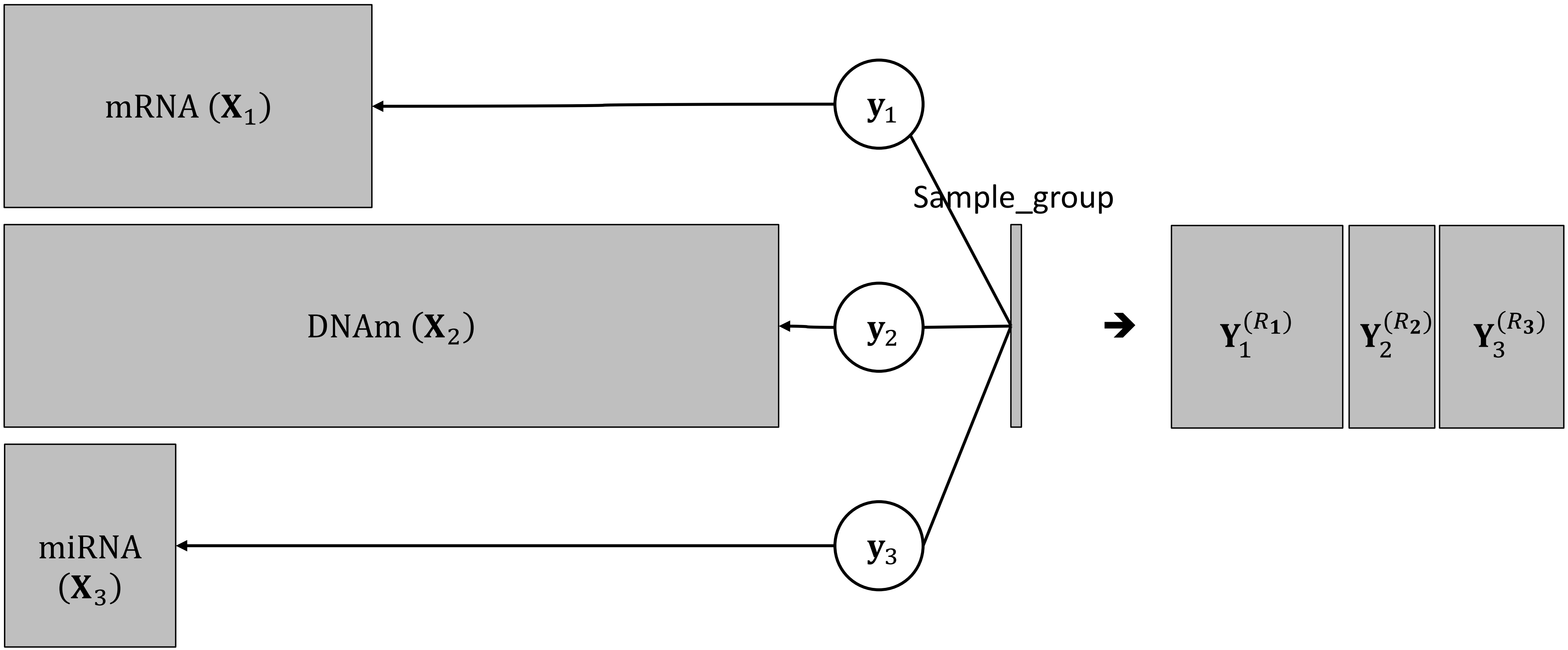
Supervising with RGCCA



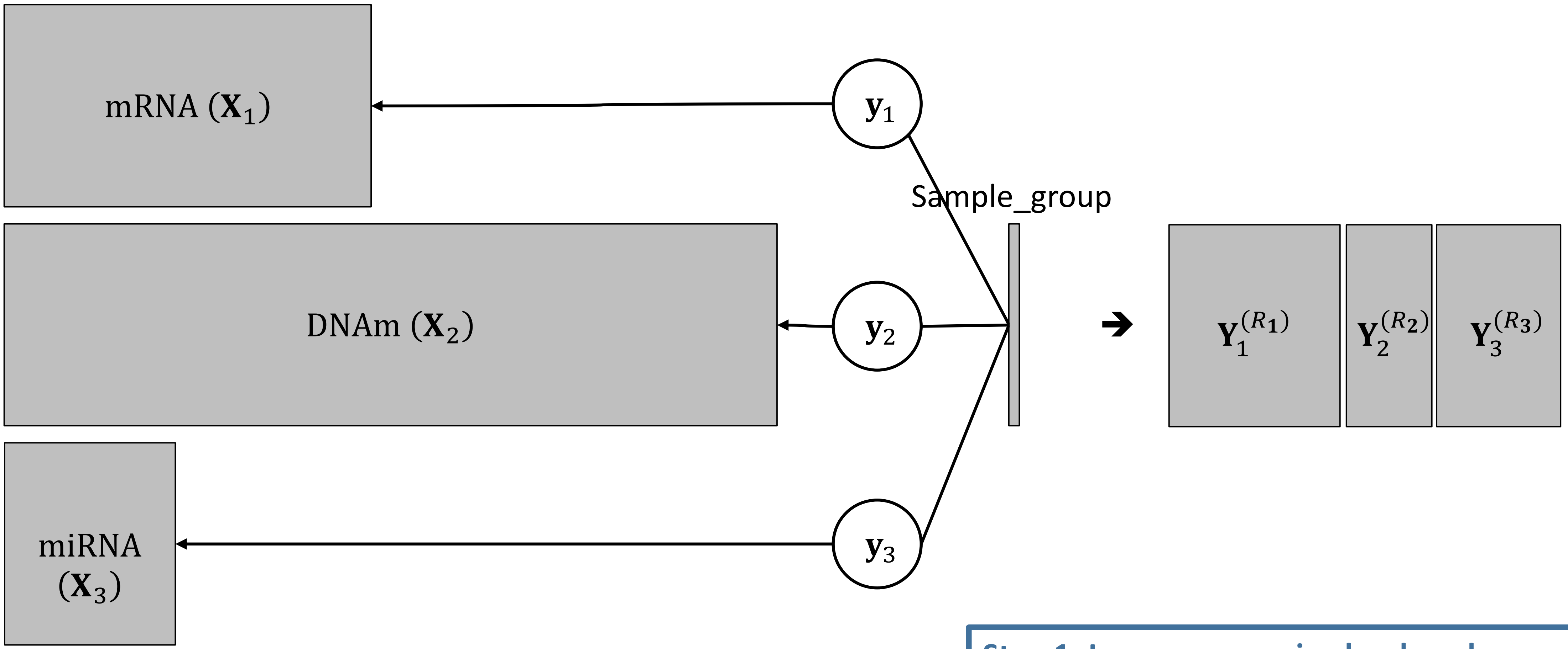
Supervising with RGCCA



Supervising with RGCCA

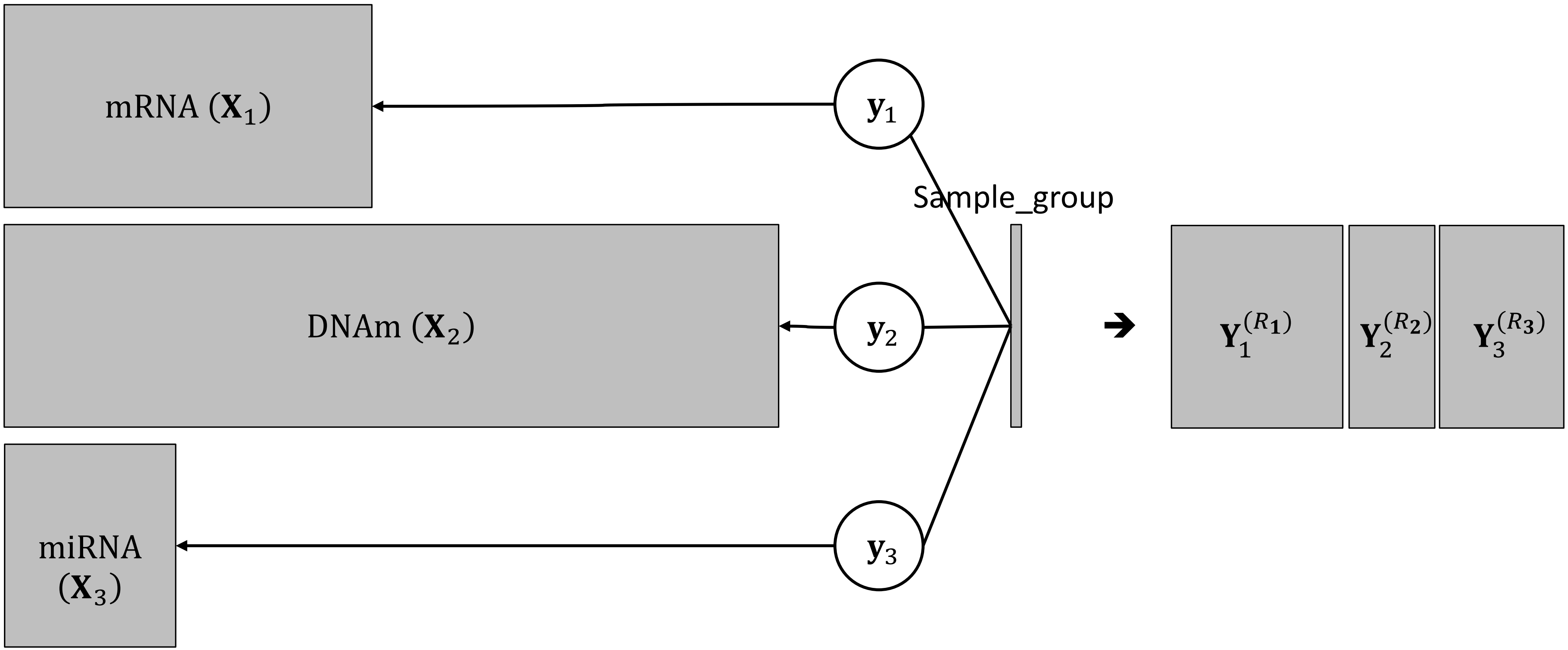


Supervising with RGCCA

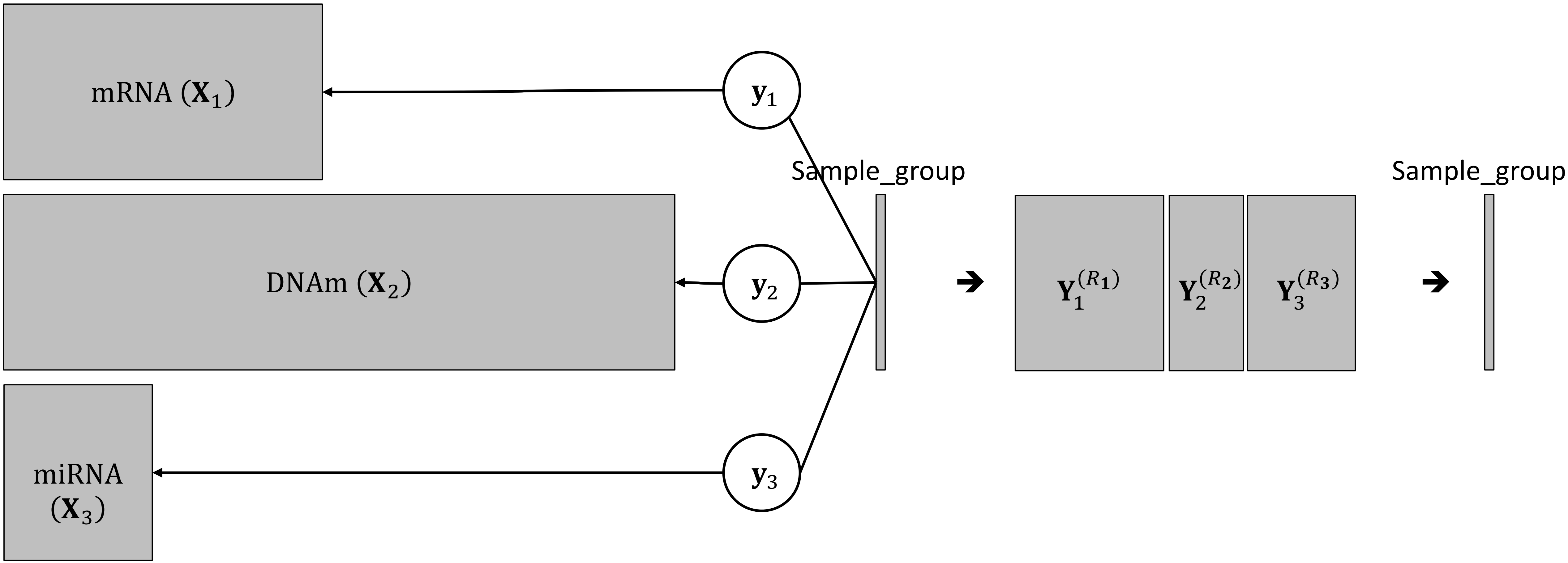


Step 1: Learn a supervised reduced space

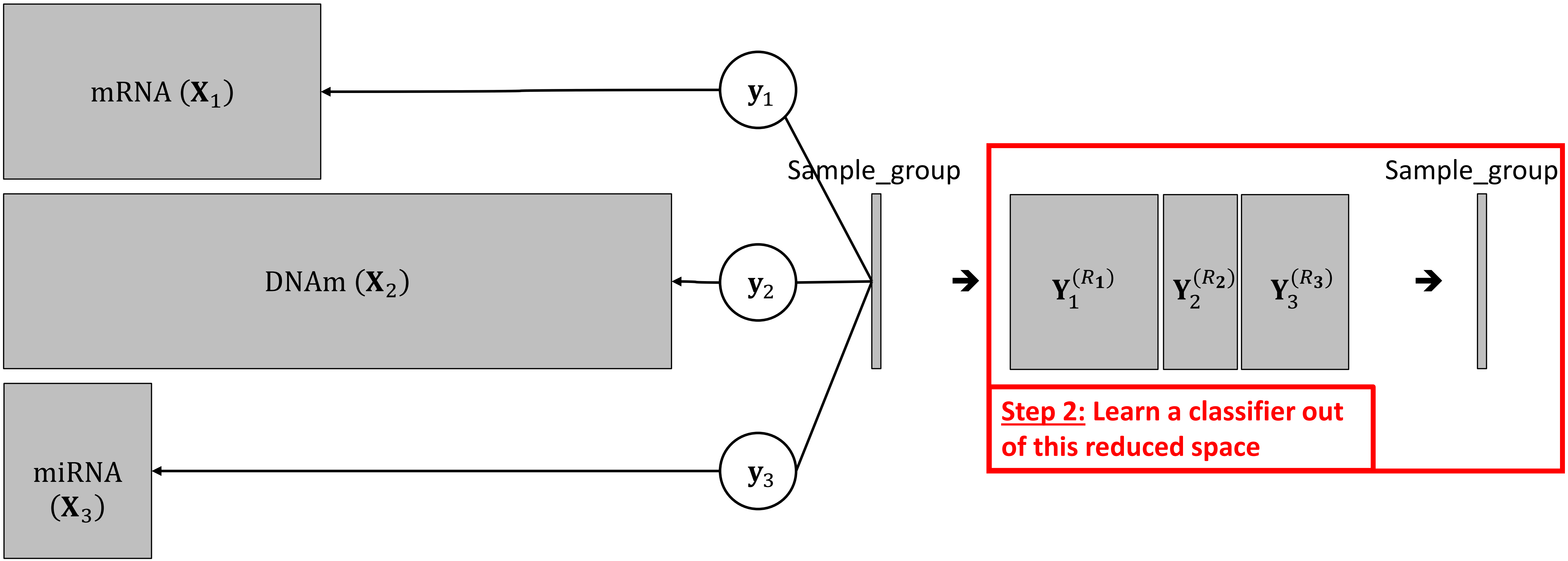
Supervising with RGCCA



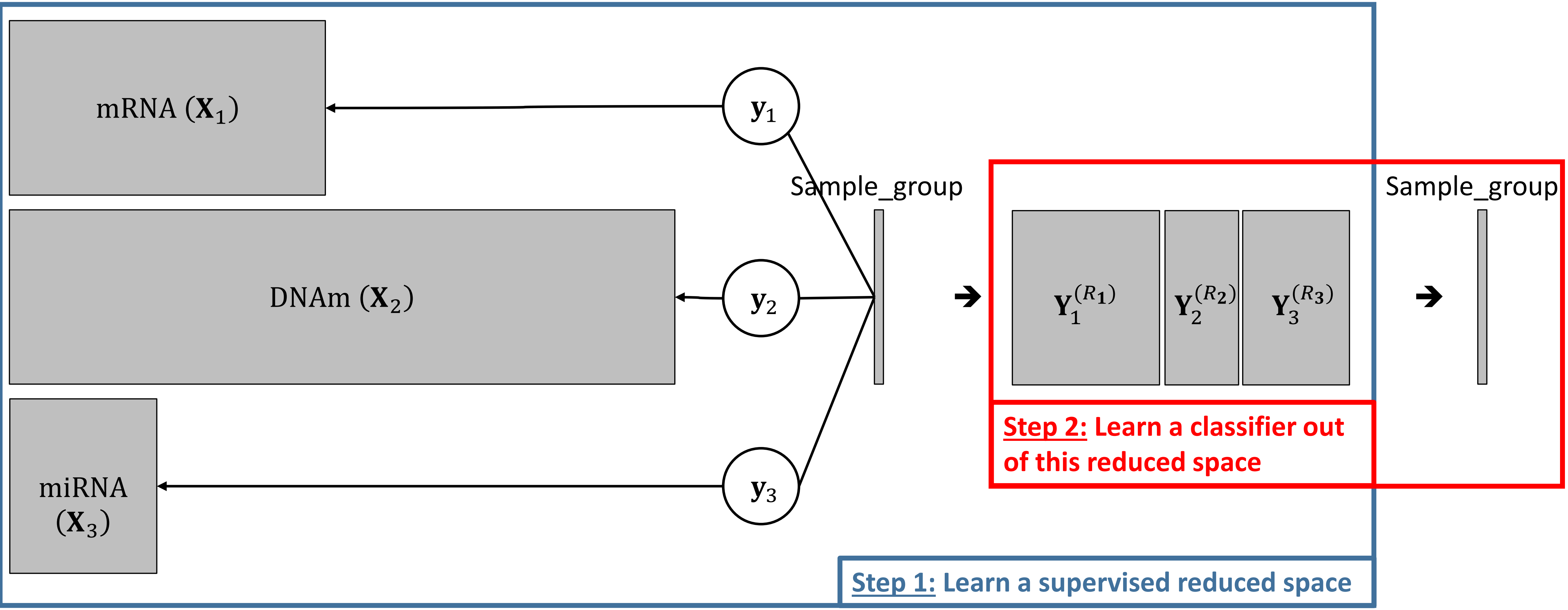
Supervising with RGCCA



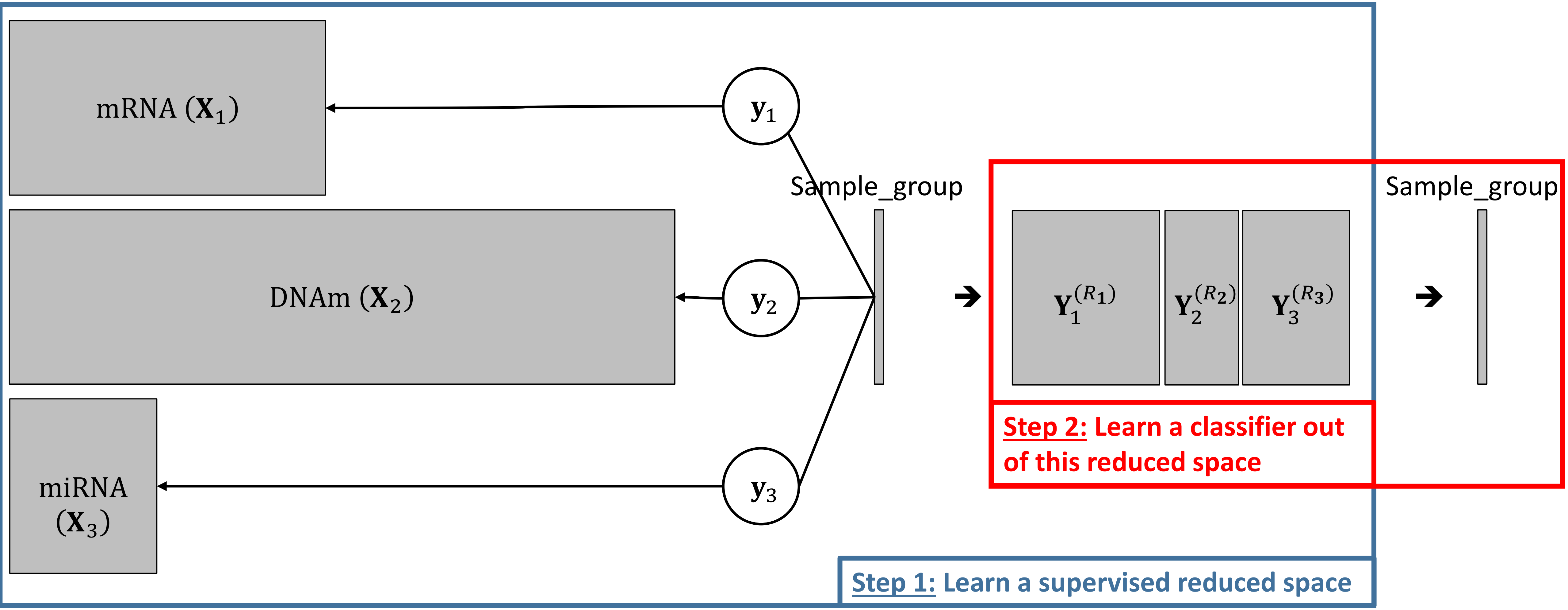
Supervising with RGCCA



Supervising with RGCCA

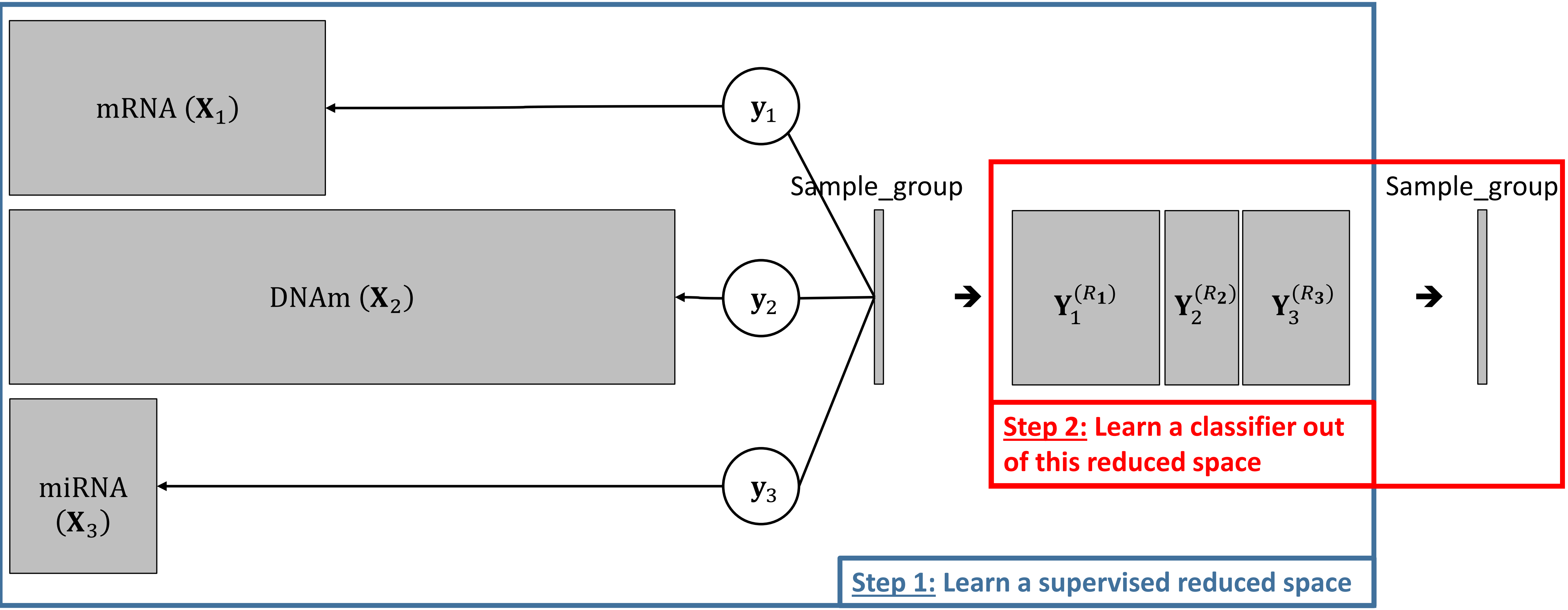


Supervising with RGCCA



The model sequentially learn block-weight vectors to compute components and a classifier.

Supervising with RGCCA



The model sequentially learn block-weight vectors to compute components and a classifier.

Standard Cross-Validation can be performed.

F1-score

F1-score

Confusion Matrix:

		True labels	
		Positive	Negative
Predicted labels	Positive	True Positive (TP)	False Positive (FP)
	Negative	False Negative (FN)	True Negative (TN)

F1-score

Confusion Matrix:

		True labels	
		Positive	Negative
Predicted labels	Positive	True Positive (TP)	False Positive (FP)
	Negative	False Negative (FN)	True Negative (TN)

$$precision = \frac{TP}{TP + FP}$$

➔ How many positive predicted labels are true ?

F1-score

Confusion Matrix:

		True labels	
		Positive	Negative
Predicted labels	Positive	True Positive (TP)	False Positive (FP)
	Negative	False Negative (FN)	True Negative (TN)

$$precision = \frac{TP}{TP + FP}$$

➔ How many positive predicted labels are true ?

$$recall = \frac{TP}{TP + FN}$$

➔ How many true positive labels are retrieved ?

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F1-score

Confusion Matrix:

		True labels	
		Positive	Negative
Predicted labels	Positive	True Positive (TP)	False Positive (FP)
	Negative	False Negative (FN)	True Negative (TN)

$$precision = \frac{TP}{TP + FP}$$

➔ How many positive predicted labels are true ?

$$recall = \frac{TP}{TP + FN}$$

➔ How many true positive labels are retrieved ?

$$F = \frac{2}{\frac{1}{recall} + \frac{1}{precision}} = \frac{2precision.recall}{recall + precision}$$

Let us apply a supervised version of RGCCA on the MDD case study

➔ See section 4 on the Rmarkdown `MDD_case_study_RGCCA`

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   - The general principal
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   - From Sequential to Global

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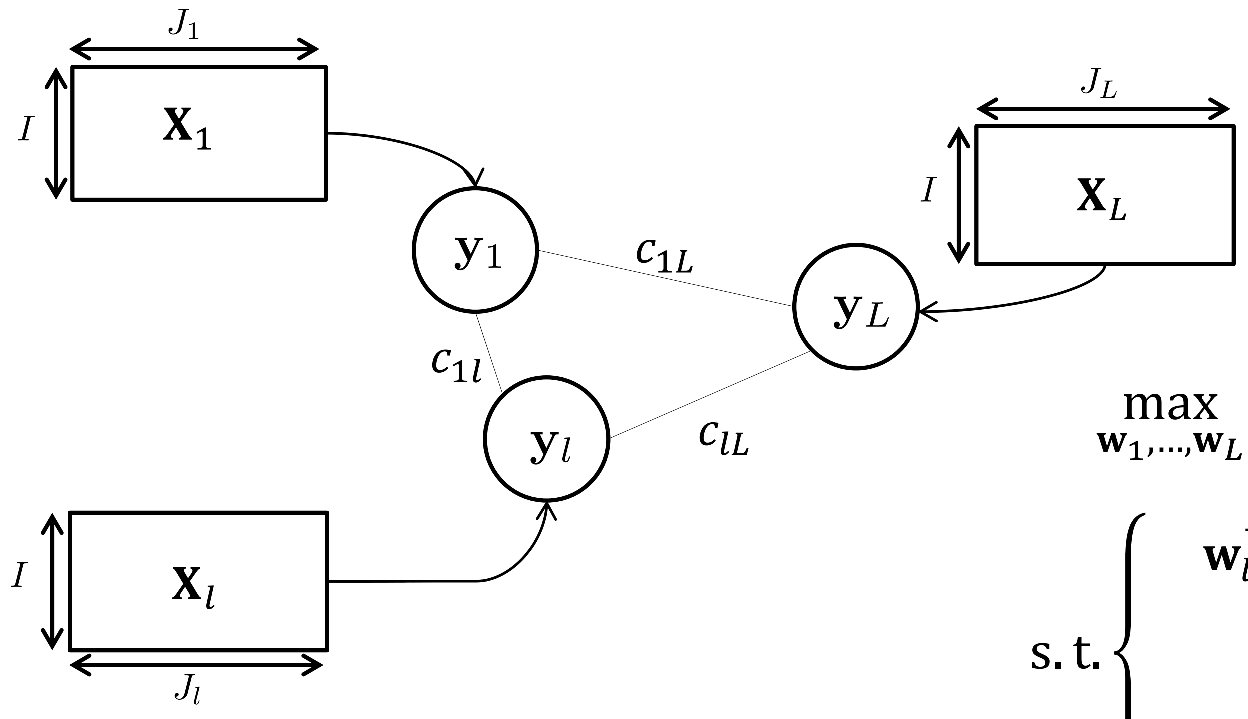
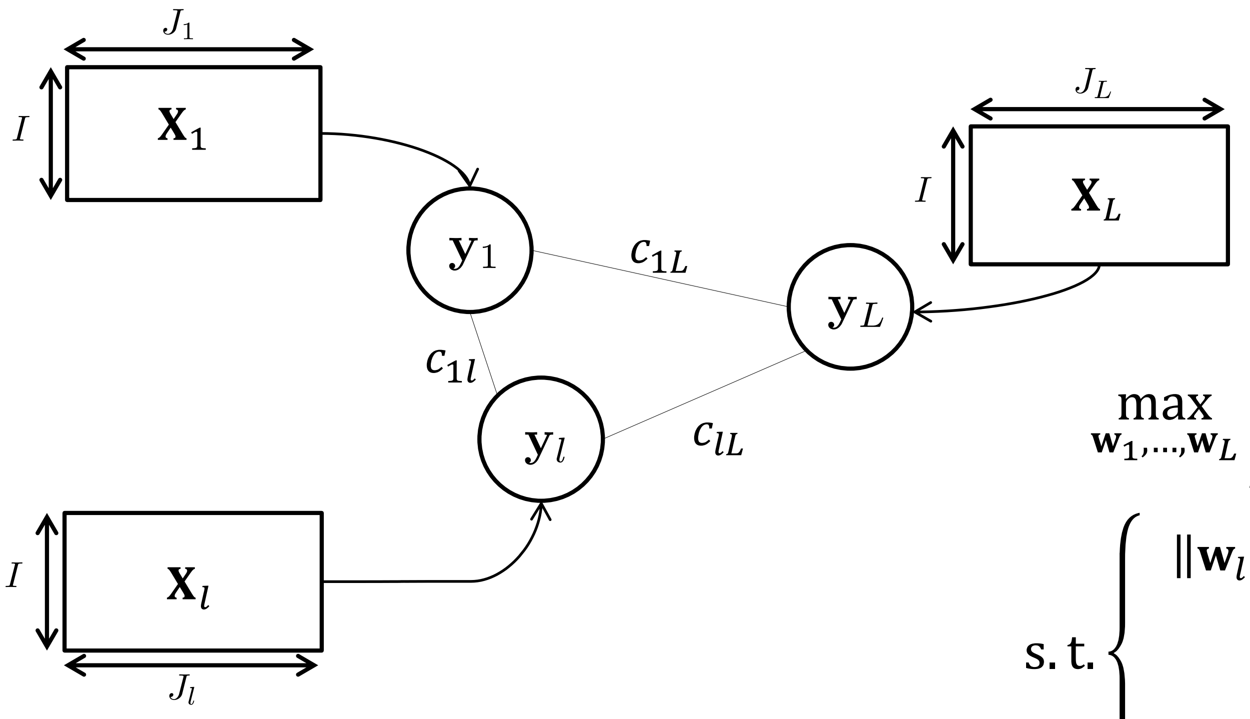
Sparse Generalized Canonical Correlation Analysis (SGCCA)



$$\max_{\mathbf{w}_1,\ldots,\mathbf{w}_L} \sum_{k,l=1}^{L} c_{kl}\, g\big(\mathrm{Cov}(\mathbf{X}_k\mathbf{w}_k, \mathbf{X}_l\mathbf{w}_l)\big)$$

$$\text{s.t.} \begin{cases} \mathbf{w}_l^\top \mathbf{M}_l \mathbf{w}_l = 1 \\ \qquad\qquad\qquad\qquad , l = 1, \ldots, L. \\ \end{cases}$$

Sparse Generalized Canonical Correlation Analysis (SGCCA)



$$\max_{\mathbf{w}_1,\ldots,\mathbf{w}_L} \sum_{k,l=1}^{L} c_{kl}\, g\big(\mathrm{Cov}(\mathbf{X}_k\mathbf{w}_k, \mathbf{X}_l\mathbf{w}_l)\big)$$

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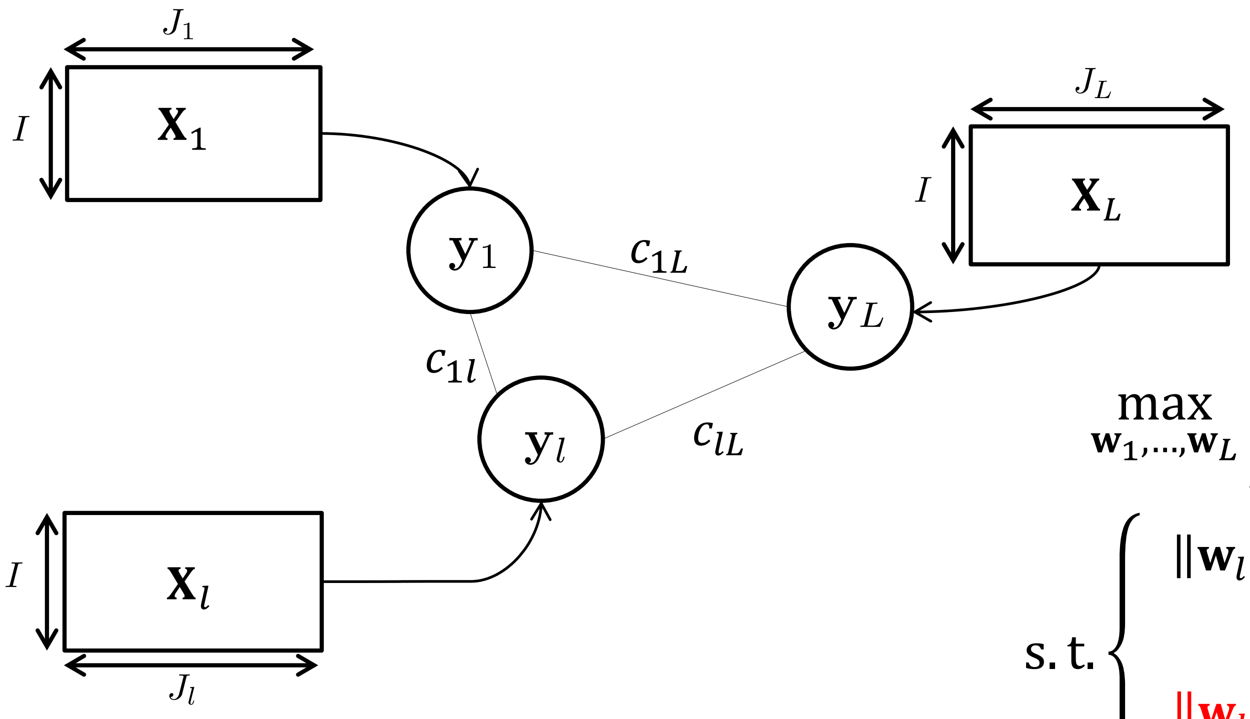

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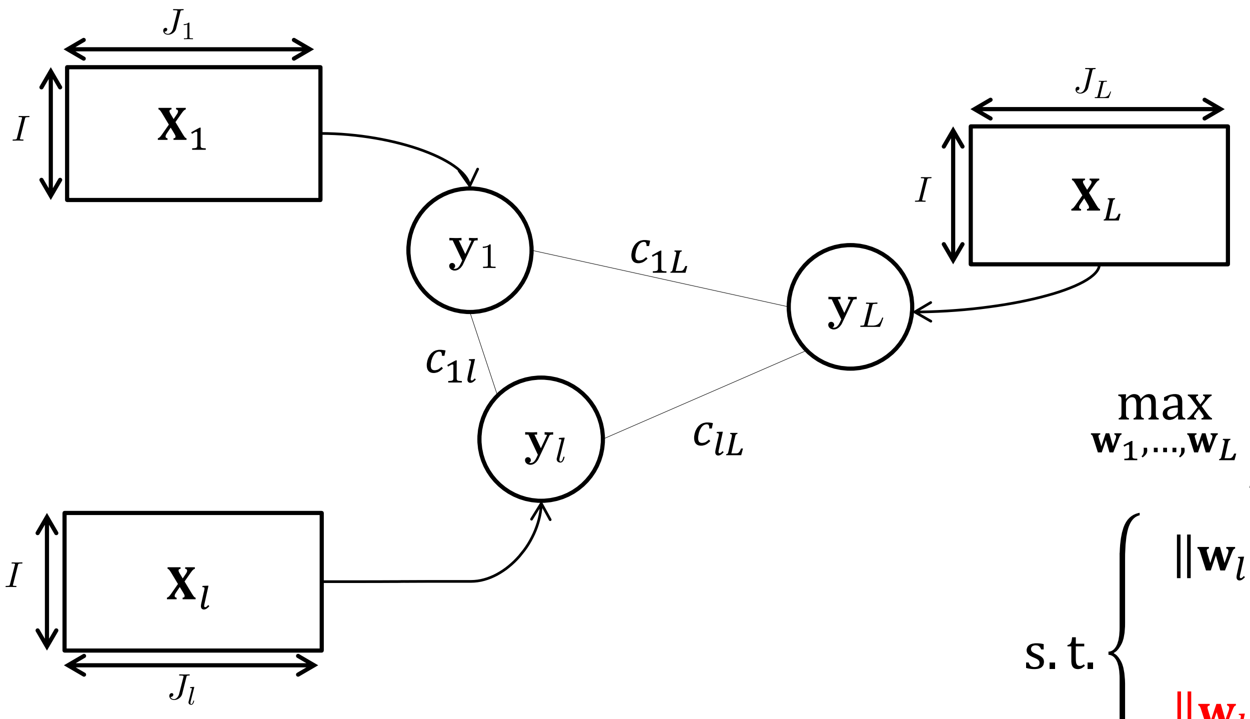

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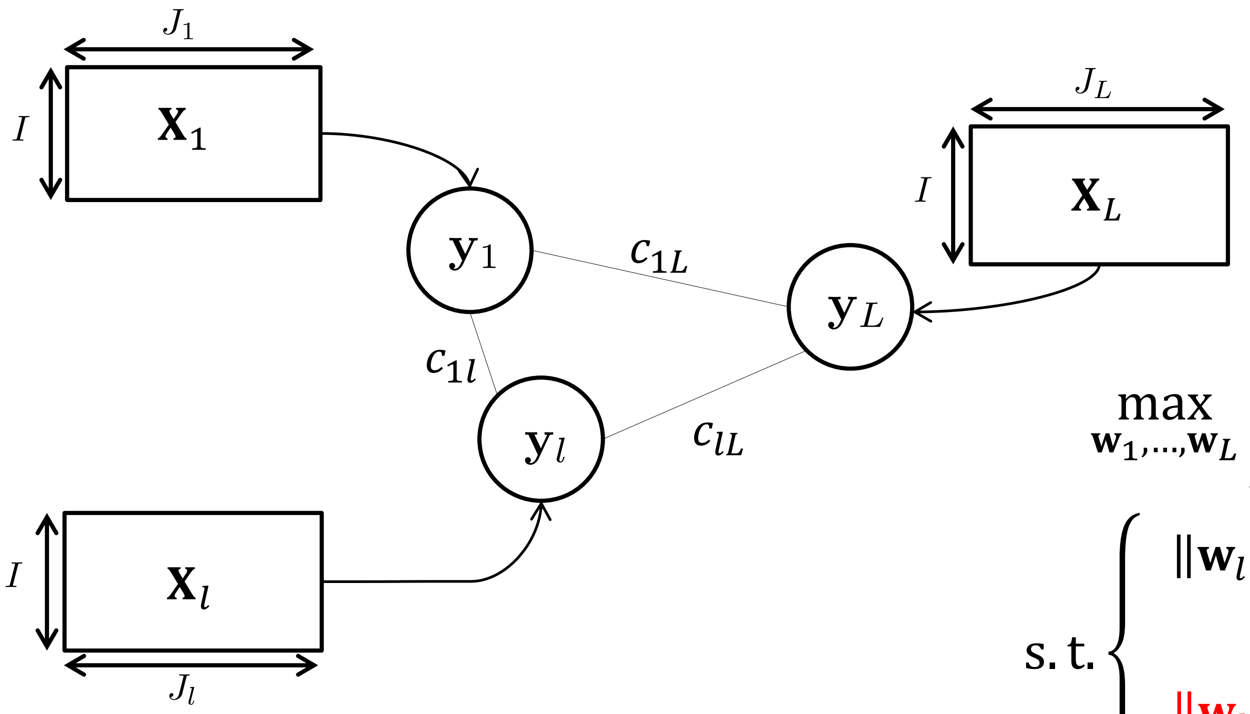

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Controls the level of sparsity (has to be tuned).

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The Variable Importance in Projection (VIP) score

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The Variable Importance in Projection (VIP) score

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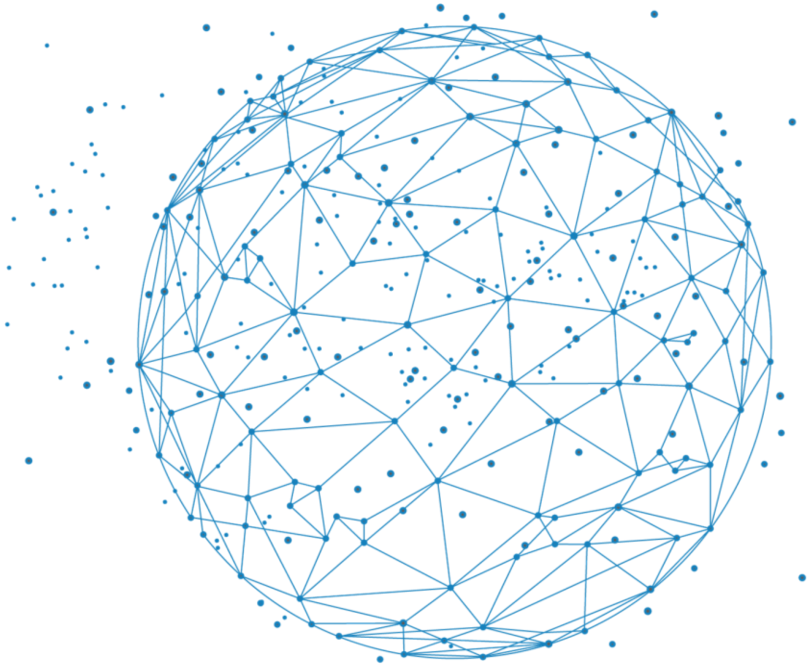
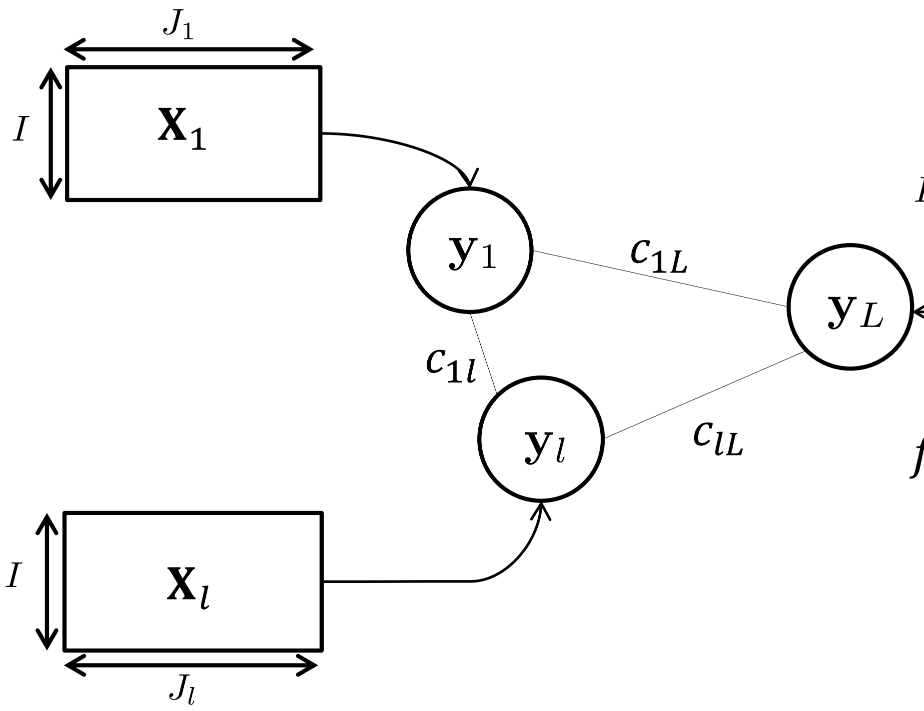
Let us apply both an unsupervised/supervised version of SGCCA on the MDD case study

➔ See section 5 & 6 on the Rmarkdown `MDD_case_study_RGCCA`



1. Introduction of the case study
2. Unsupervised analysis with one-block: Principal Component Analysis (PCA)
3. Unsupervised analysis with two-blocks:
   Partial Least Squares (PLS) and Canonical Correlation Analysis (CCA)
4. Unsupervised analysis with L-blocks:
   Regularized Generalized Canonical Correlation Analysis (RGCCA)
5. Supervised analysis with RGCCA
6. Variable selection in RGCCA:
   Sparse Generalized Canonical Correlation Analysis (SGCCA)
7. **The flexible Optimization Framework of RGCCA**
   - **The general principal**
   - Extension to multi-way analysis
   - From Sequential to Global

Principle of the RGCCA Optimization Algorithm



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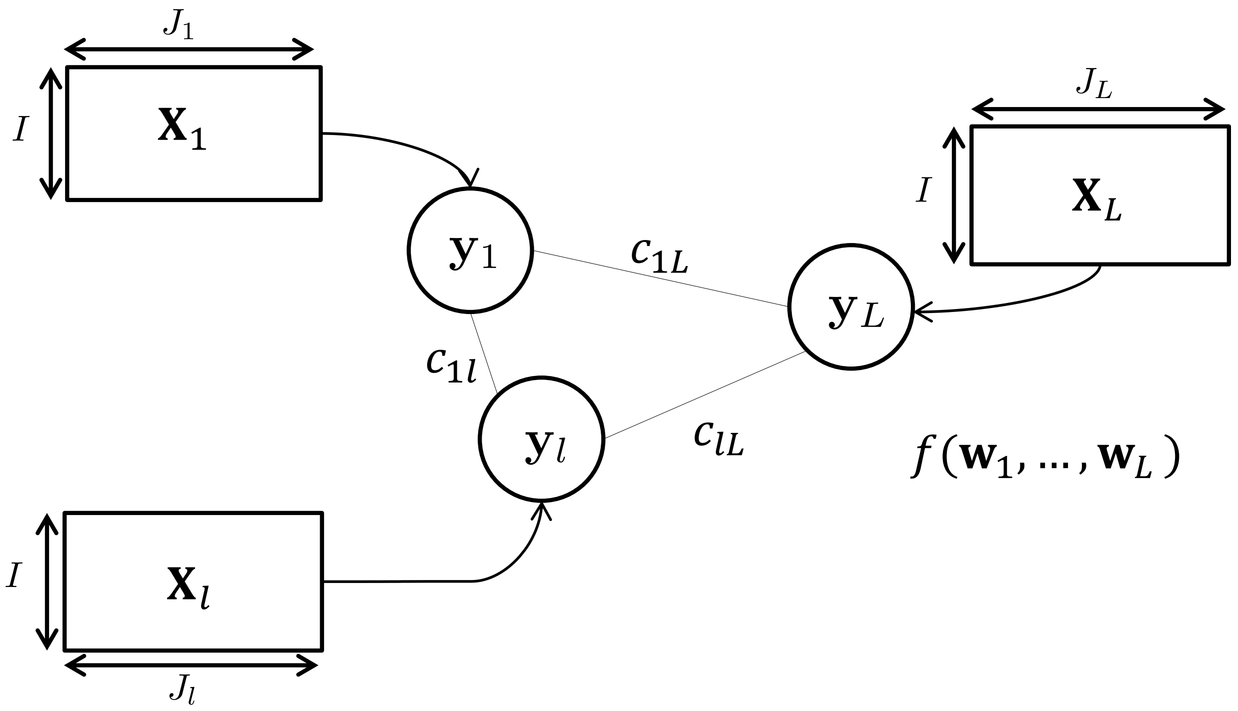

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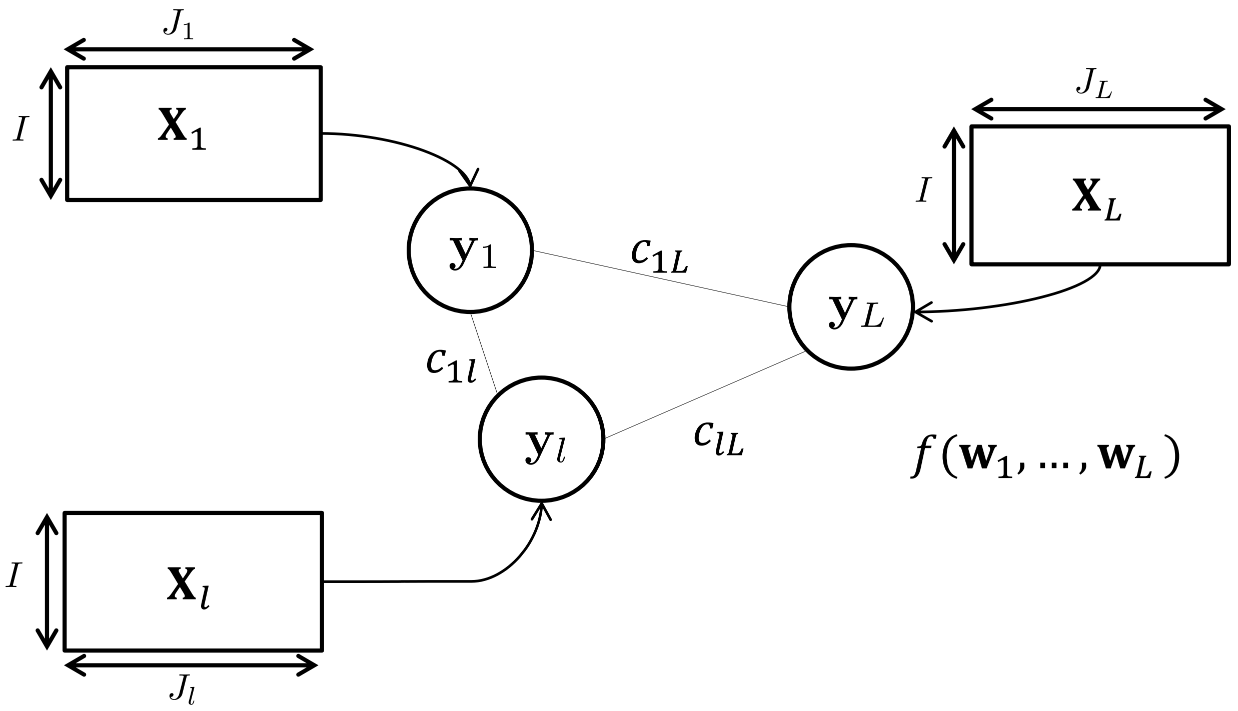

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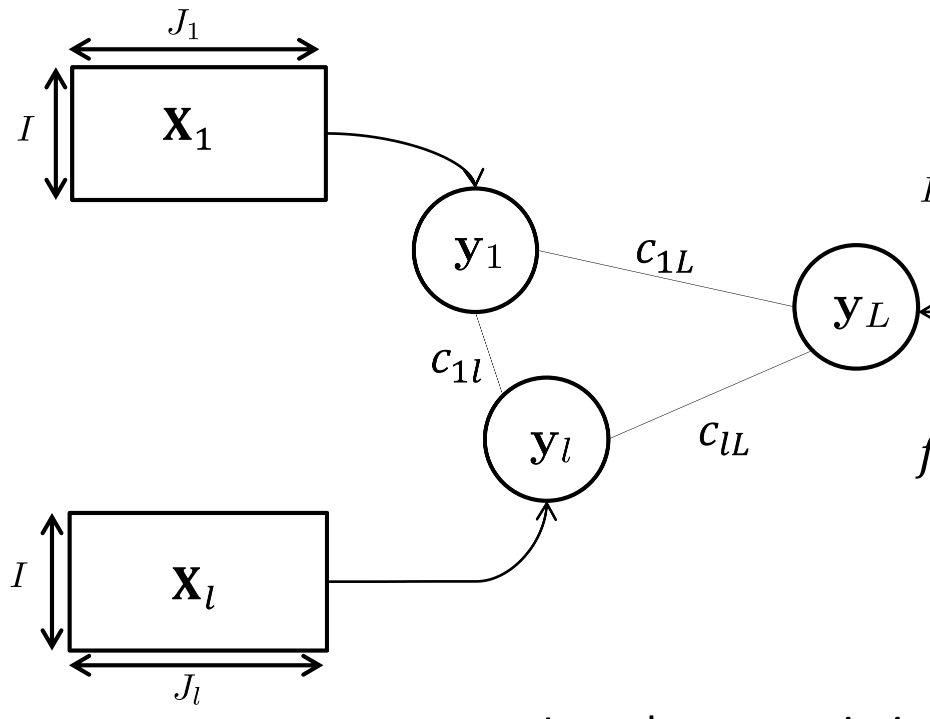

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two key ingredients are used:

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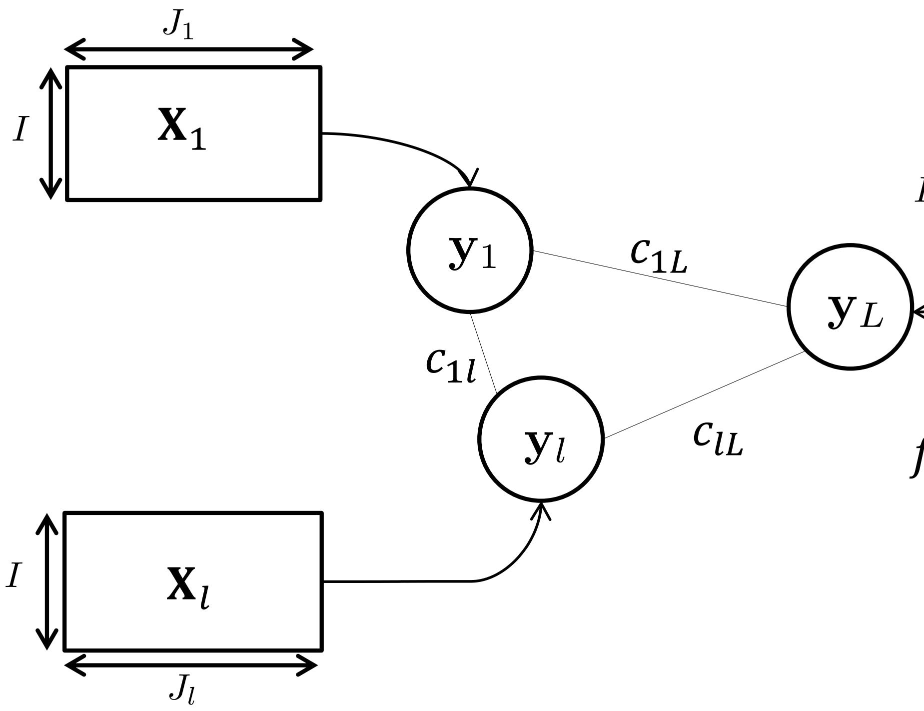

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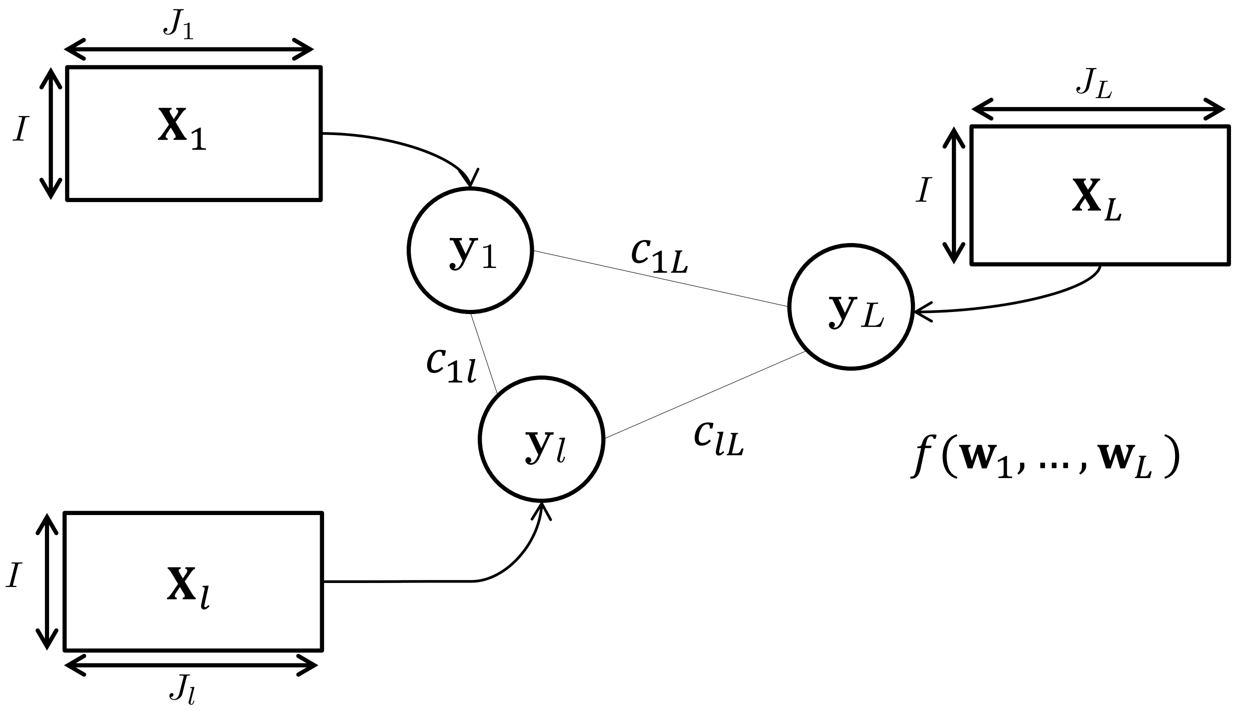

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- Block Coordinate Ascent (BCA).
- Minorize-Maximize (MM) principle.

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$$\underset{\mathbf{w}_2, \mathbf{w}_2^\top \mathbf{M}_2 \mathbf{w}_2 = 1}{\operatorname{argmax}} f(\mathbf{w}_1^{s+1}, \mathbf{w}_2, \dots, \mathbf{w}_L^s)$$

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$$\mathbf{w}^{s+1} = (\mathbf{w}_1^{s+1}, \mathbf{w}_2^{s+1}, \dots, \mathbf{w}_L^{s+1})$$

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Minorize-Maximize (MM) principle

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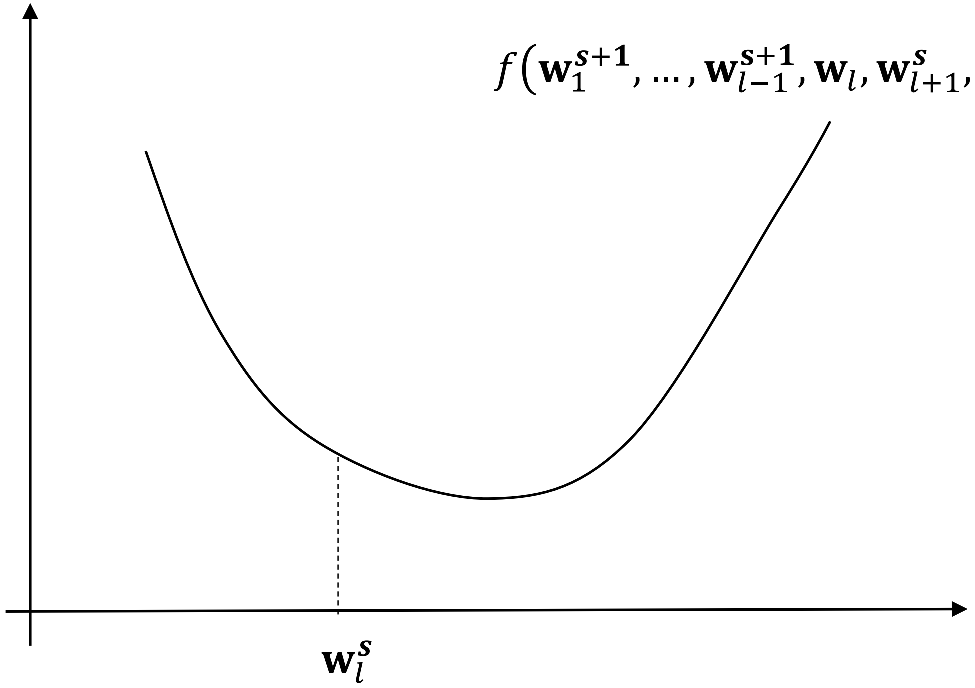

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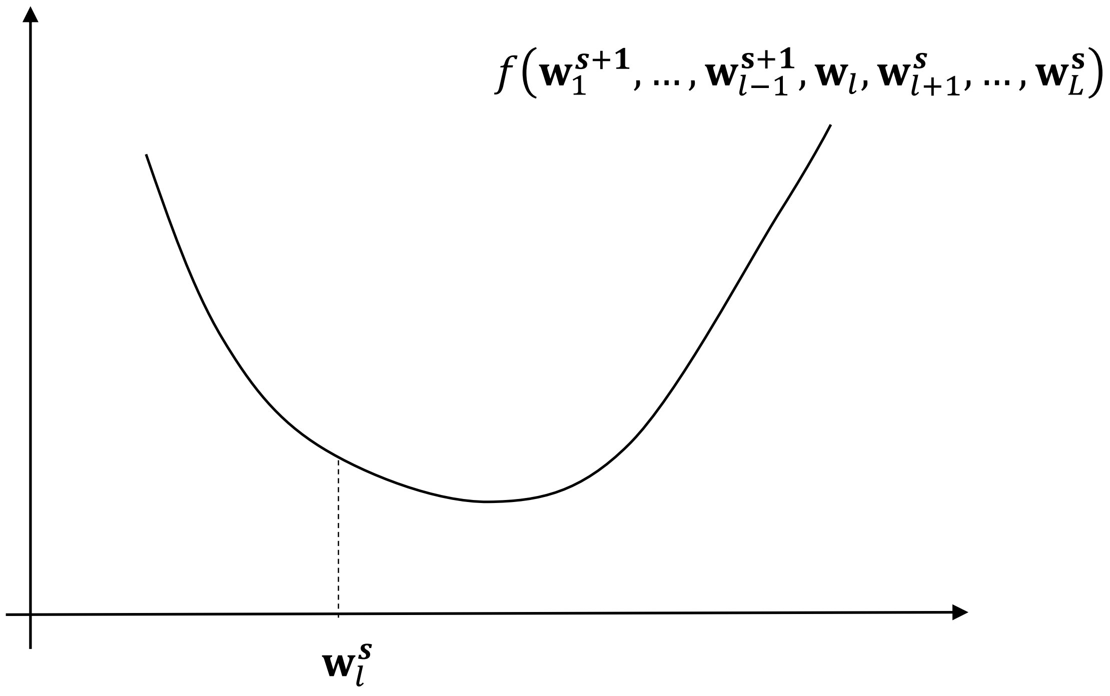
Let us introduce: $\mathbf{w}^{\mathbf{s},\mathbf{l}\rightarrow\mathbf{L}} = \left(\mathbf{w}_1^{s+1}, \dots, \mathbf{w}_{l-1}^{\mathbf{s+1}}, \mathbf{w}_l^{s}, \mathbf{w}_{l+1}^{s}, \dots, \mathbf{w}_L^{\mathbf{s}}\right)$



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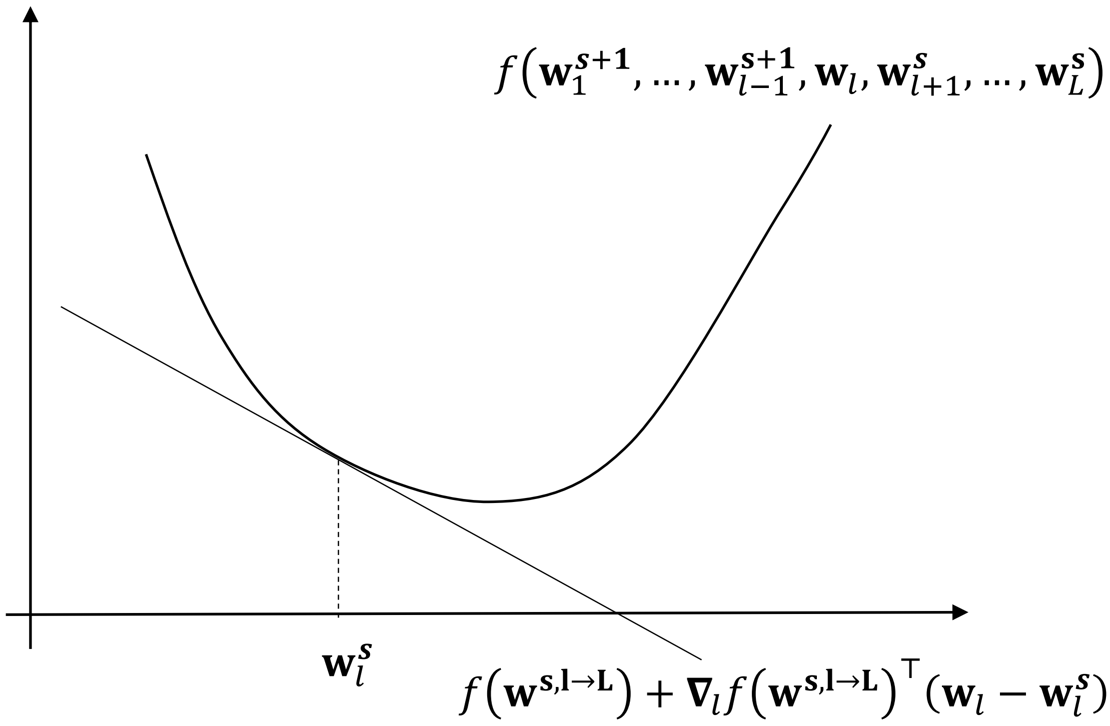

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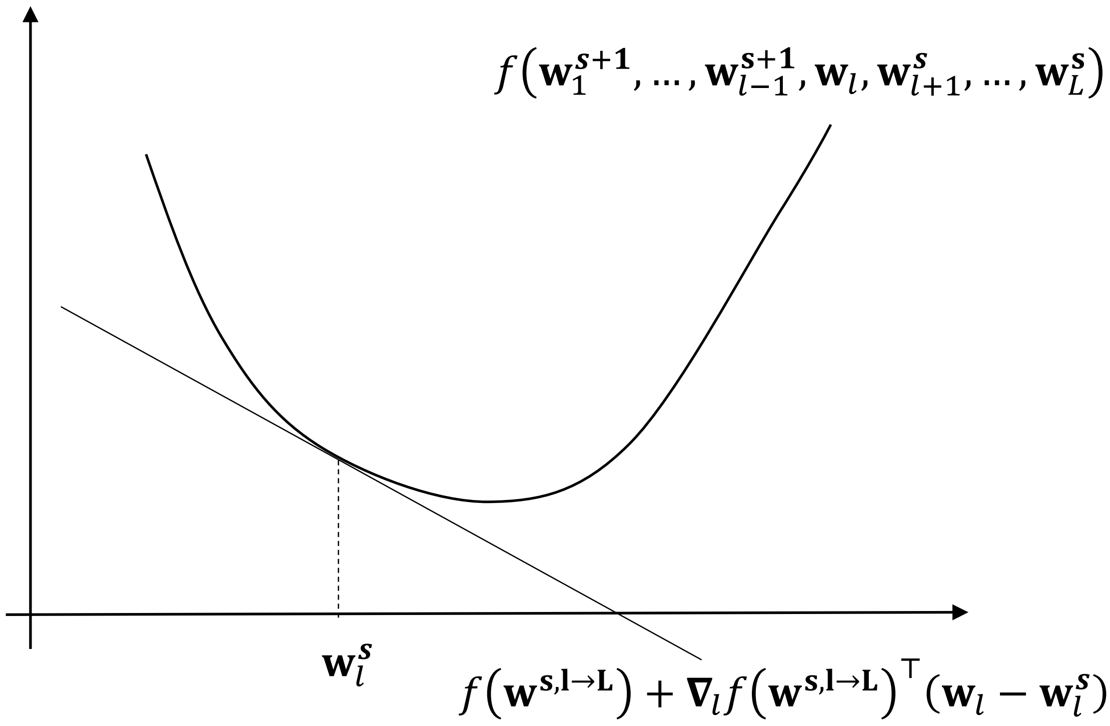

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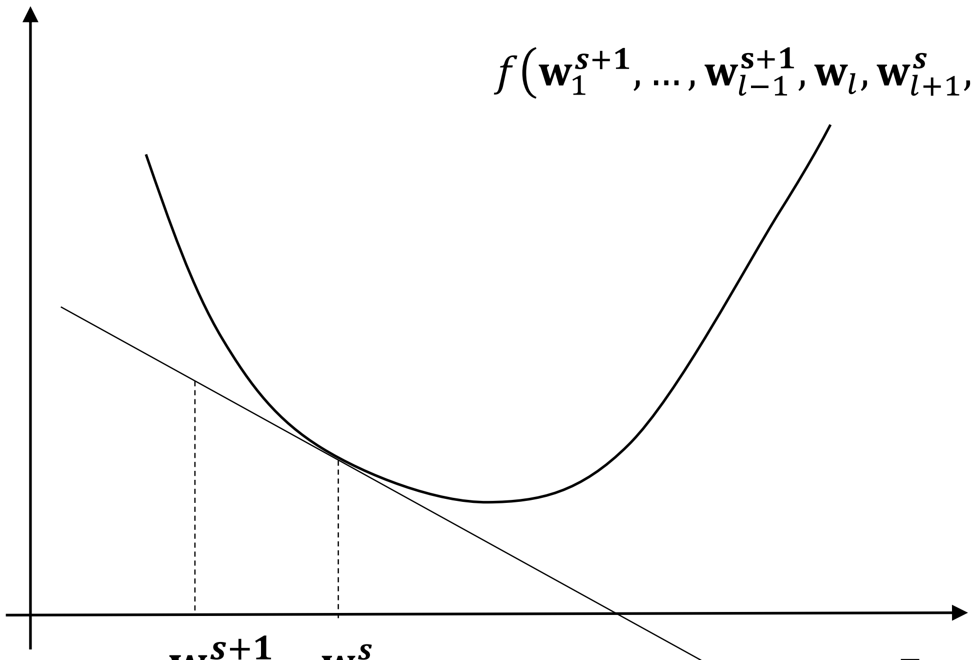

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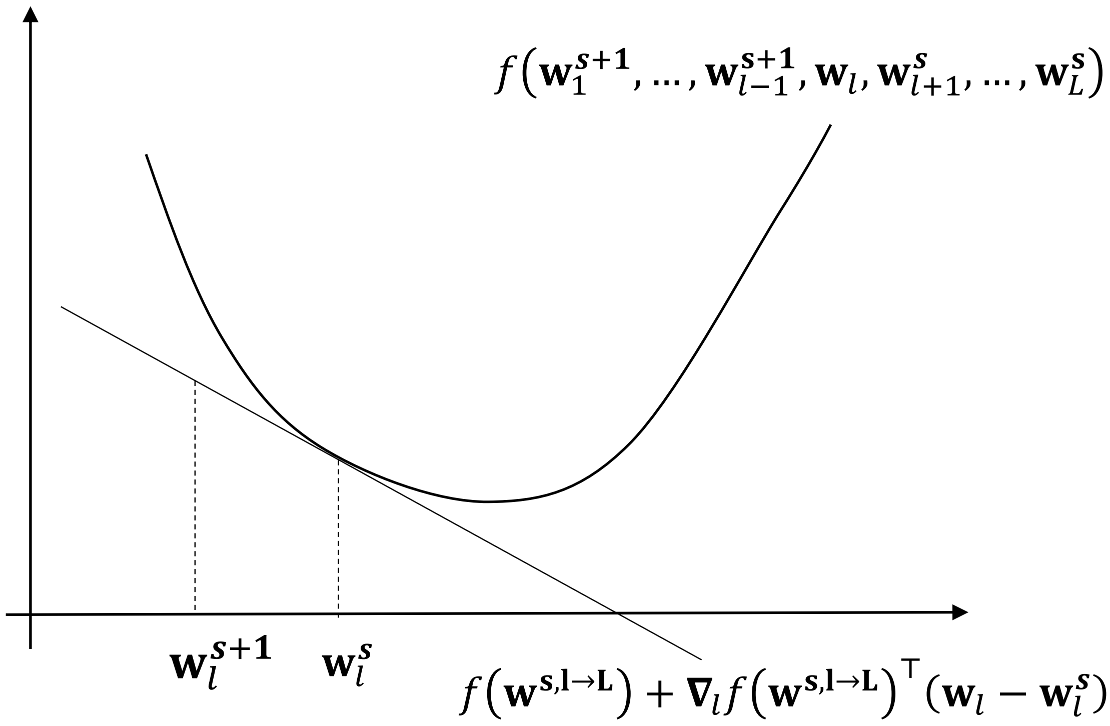

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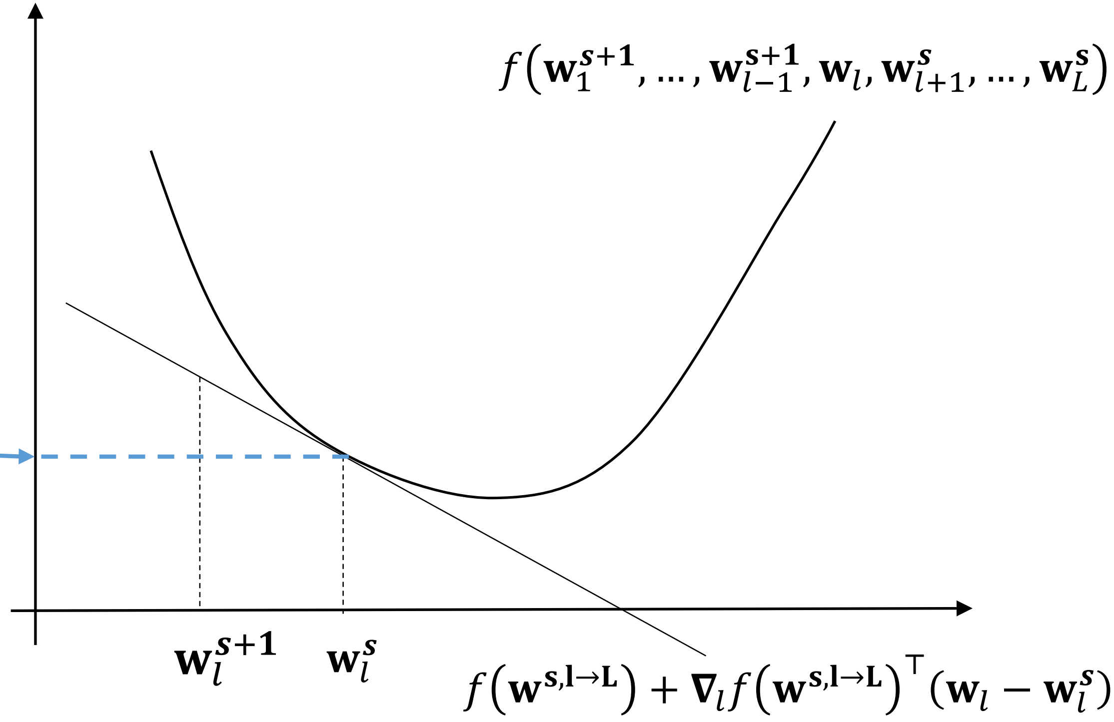

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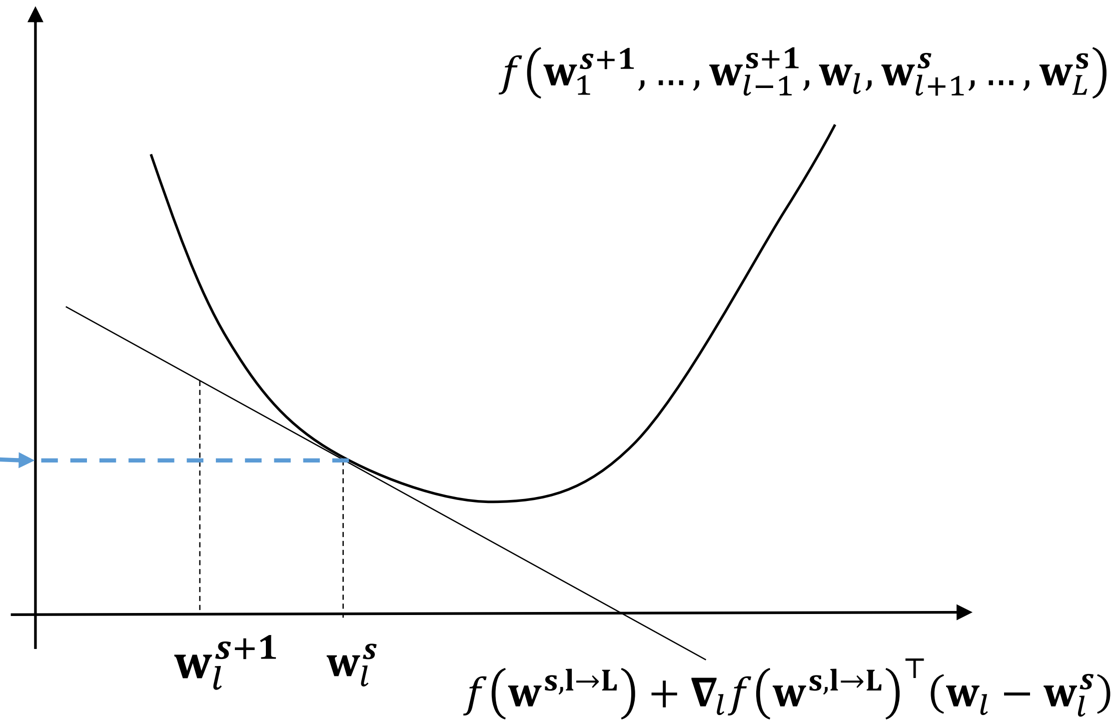

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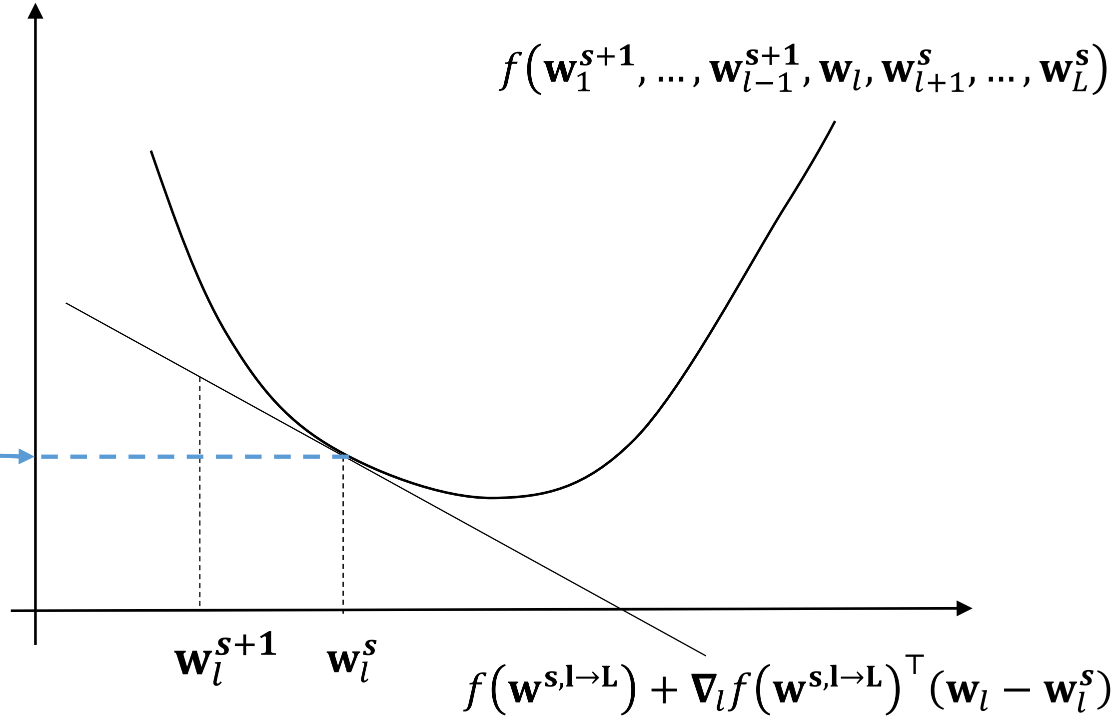

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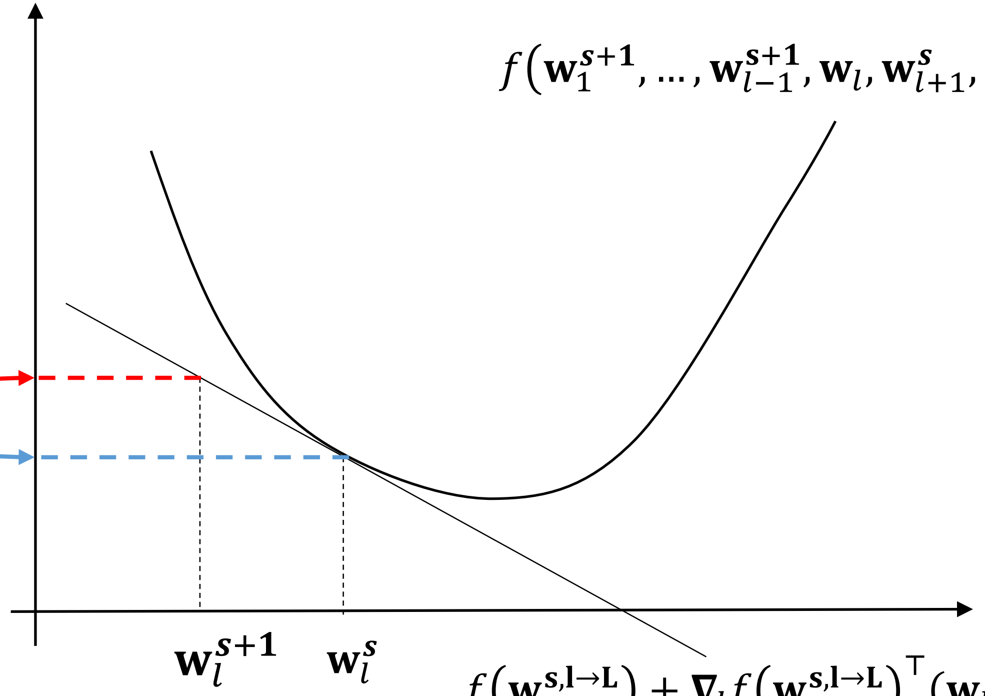

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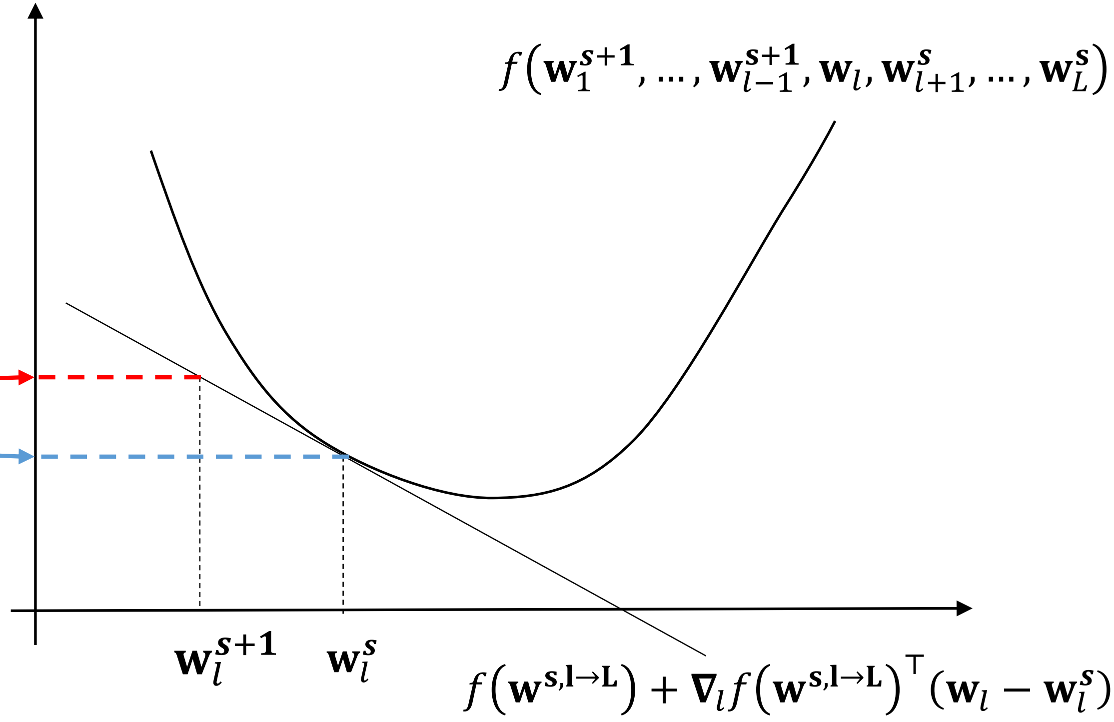

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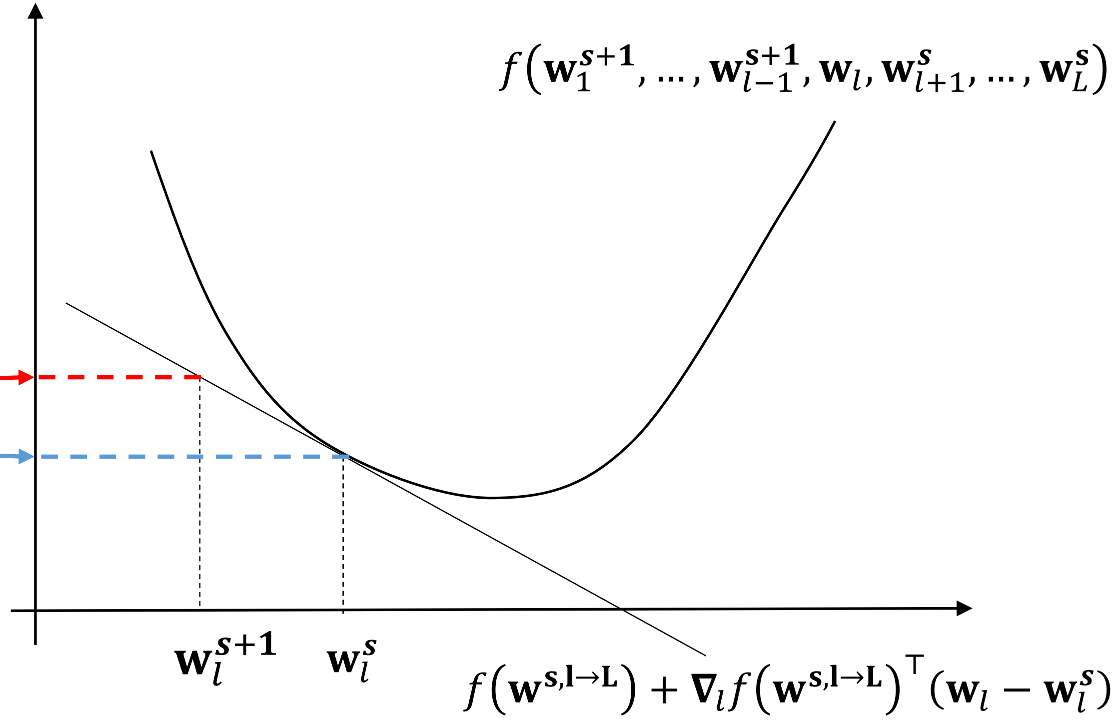

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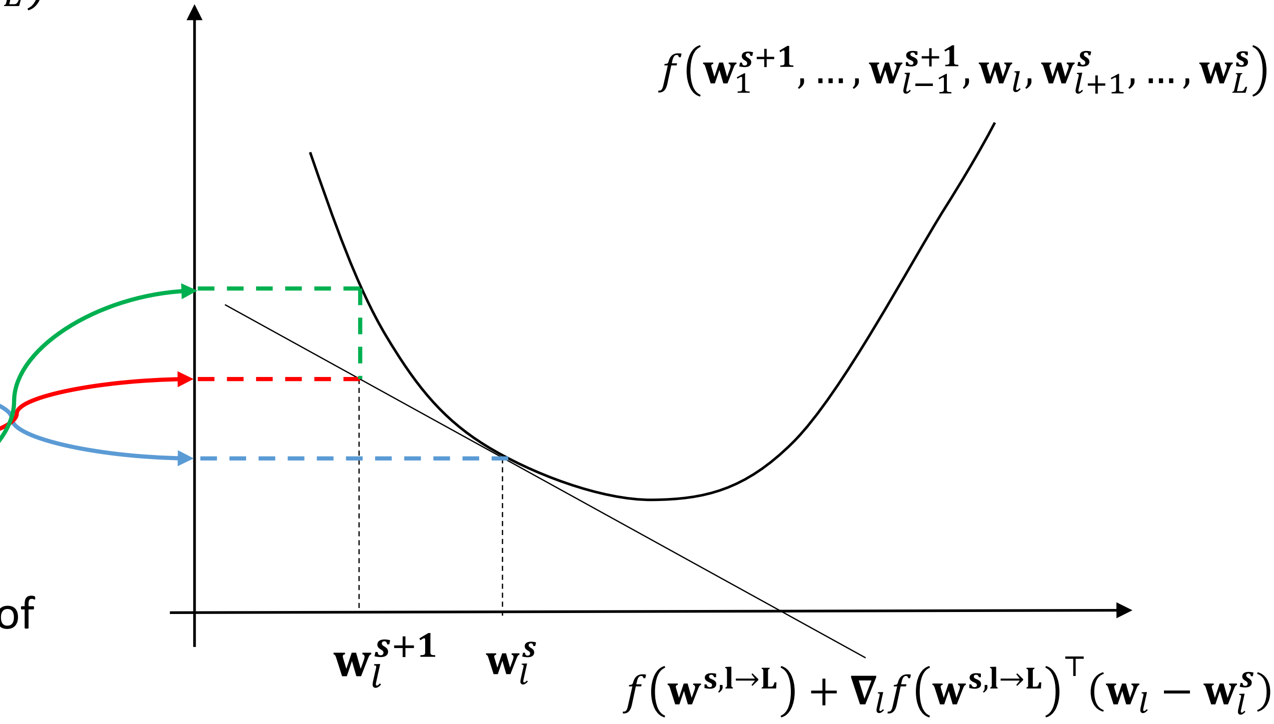

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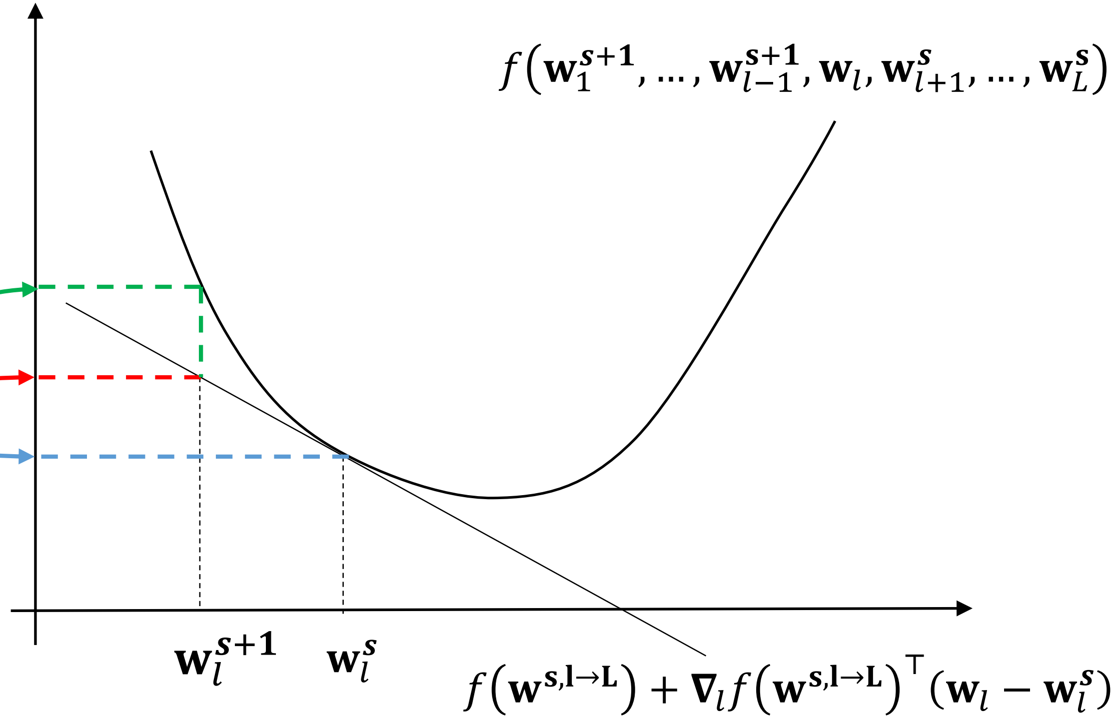

In the end $f\left(\mathbf{w}_1^{s+1}, \dots, \mathbf{w}_{l-1}^{s+1}, \mathbf{w}_l^{s}, \mathbf{w}_{l+1}^{s}, \dots, \mathbf{w}_L^{s}\right) \leq f\left(\mathbf{w}_1^{s+1}, \dots, \mathbf{w}_{l-1}^{s+1}, \mathbf{w}_l^{s+1}, \mathbf{w}_{l+1}^{s}, \dots, \mathbf{w}_L^{s}\right)$

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RGCCA framework - State of the Art of the **package**

Core Optimization Problem

Constraints

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Core Optimization Problem	
$\max \boldsymbol{\nabla}_l f(\mathbf{w^s})^\top \mathbf{w}_l$	

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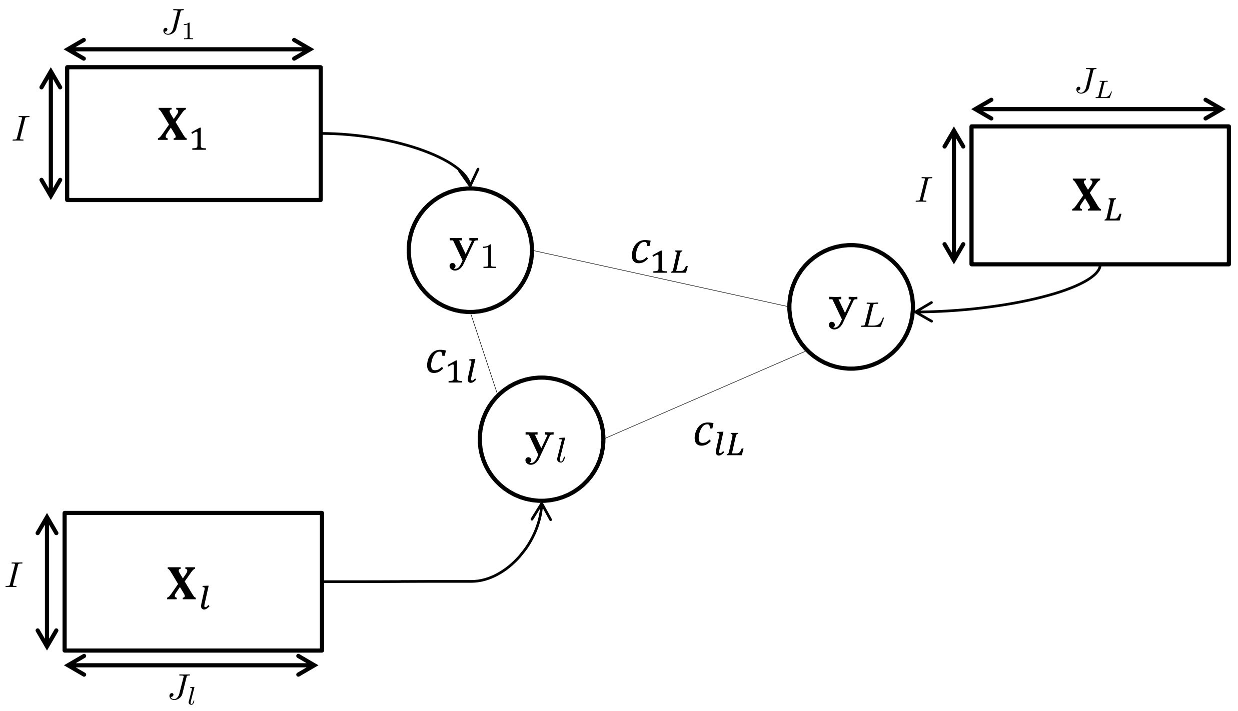
1. Introduction of the case study
2. **Unsupervised analysis with one-block:** Principal Component Analysis (PCA)
3. **Unsupervised analysis with two-blocks:**
   Partial Least Squares (PLS) and Canonical Correlation Analysis (CCA)
4. **Unsupervised analysis with L-blocks:**
   Regularized Generalized Canonical Correlation Analysis (RGCCA)
5. Supervised analysis with RGCCA
6. **Variable selection in RGCCA:**
   Sparse Generalized Canonical Correlation Analysis (SGCCA)
7. **The flexible Optimization Framework of RGCCA**
   - The general principal
   - Extension to multi-way analysis
   - From Sequential to Global

From RGCCA to Multiway GCCA



$$\max_{\mathbf{w}_1,\ldots,\mathbf{w}_L} \sum_{k,l=1}^{L} c_{kl}\, g\big(\mathrm{Cov}(\mathbf{X}_k\mathbf{w}_k, \mathbf{X}_l\mathbf{w}_l)\big)$$

$$\text{s.t.} \begin{cases} \mathbf{w}_l^\top \mathbf{M}_l \mathbf{w}_l = 1 \\ \qquad\qquad\qquad\qquad , l = 1, \ldots, L. \\ \end{cases}$$

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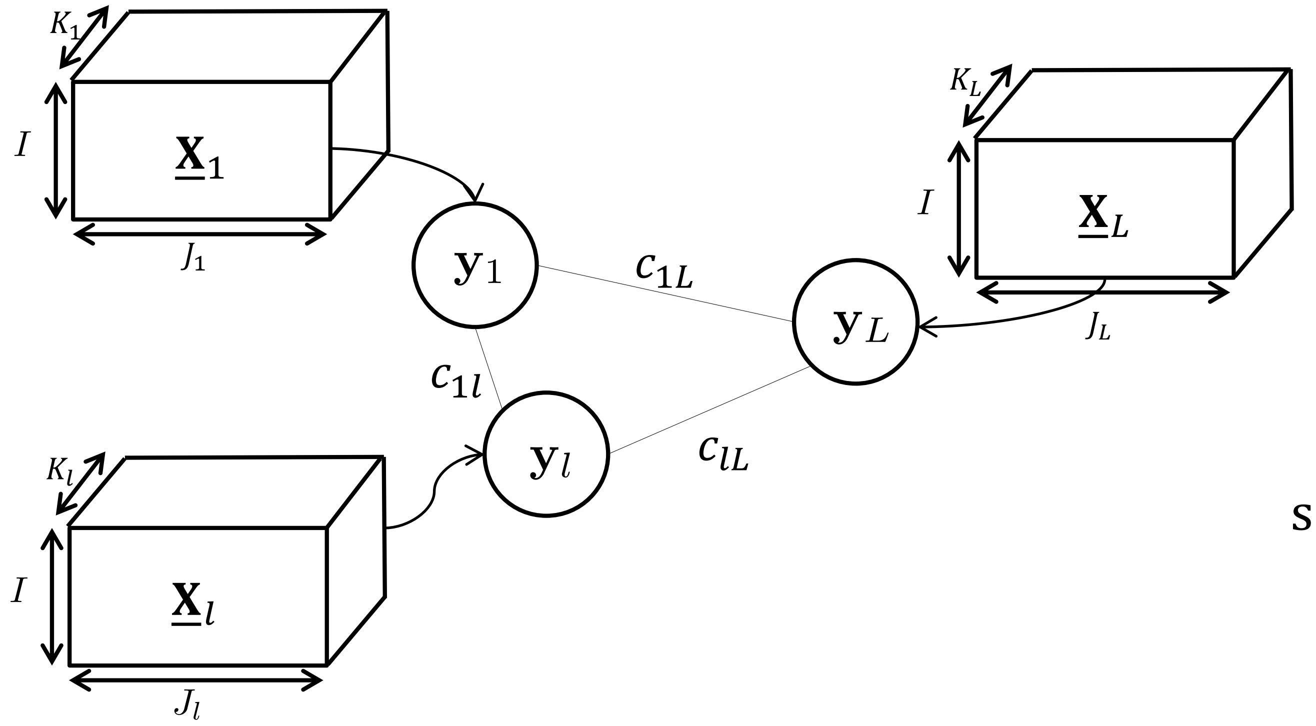

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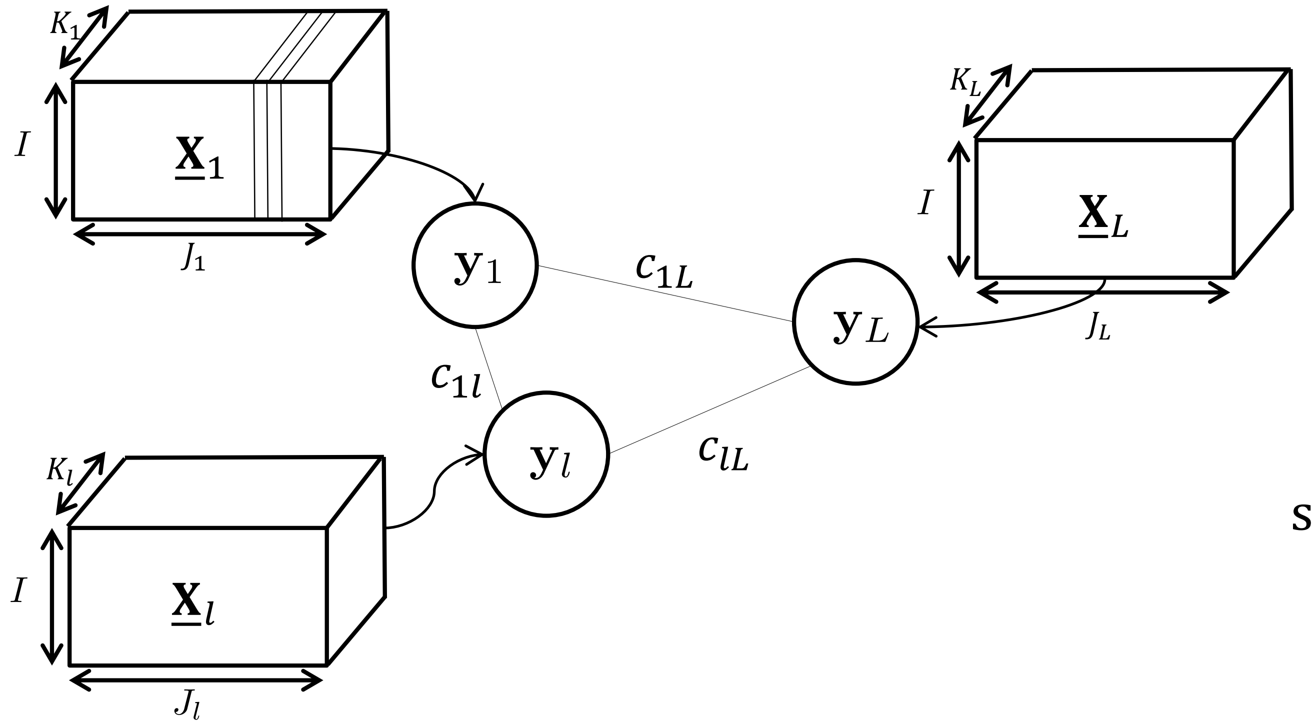

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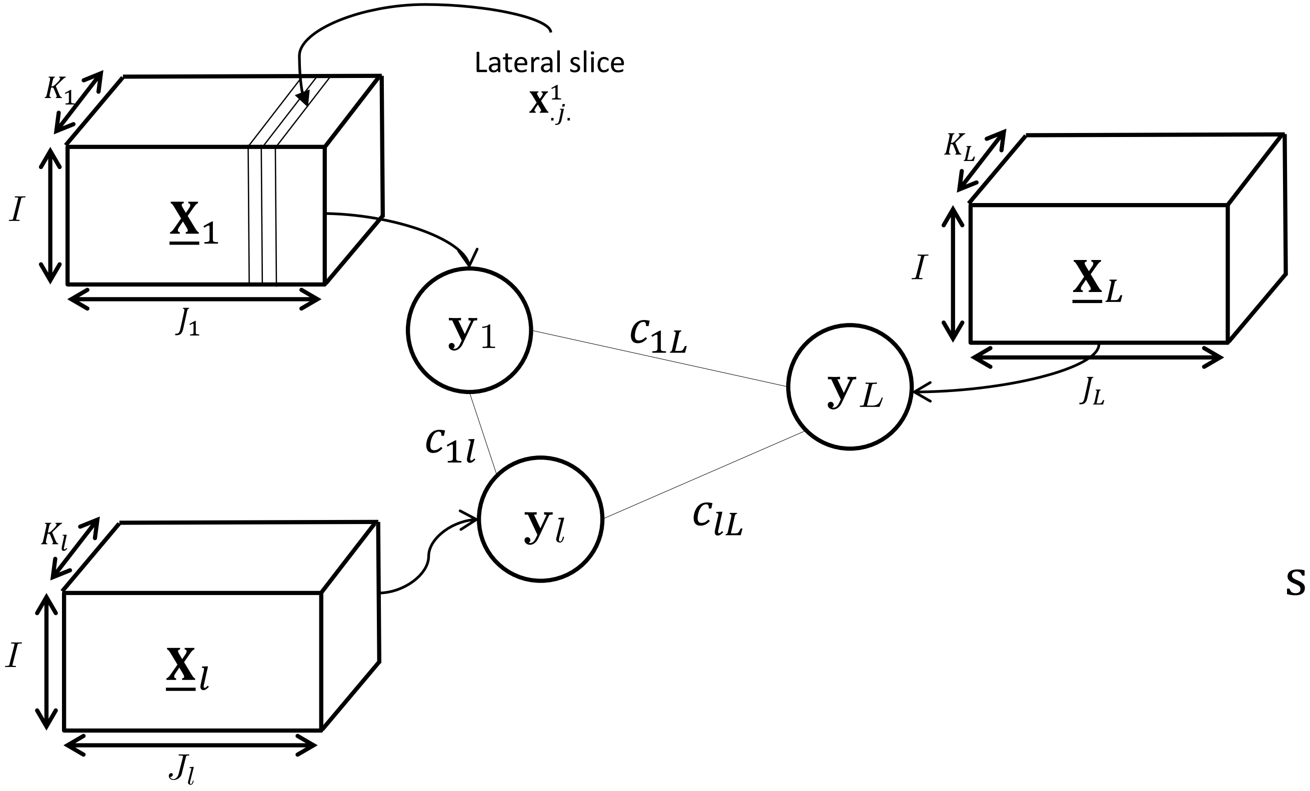

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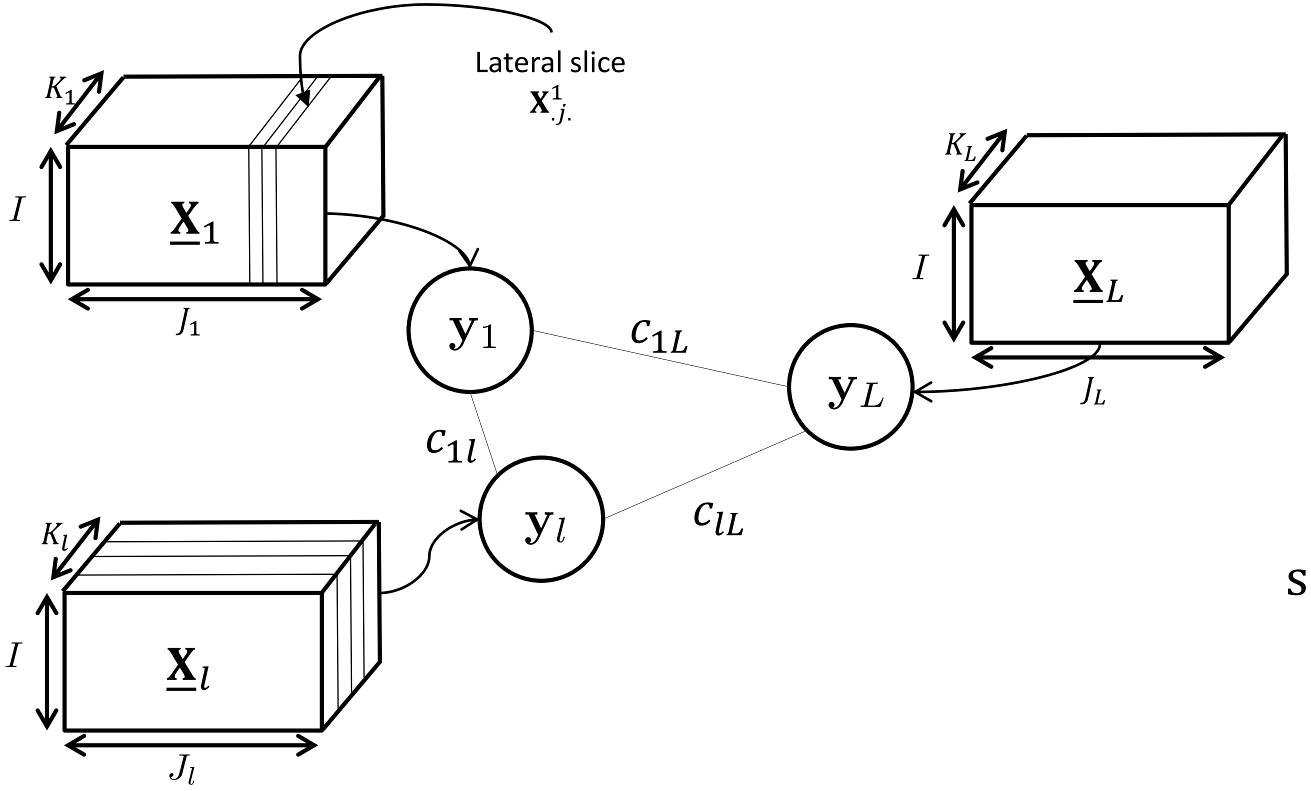

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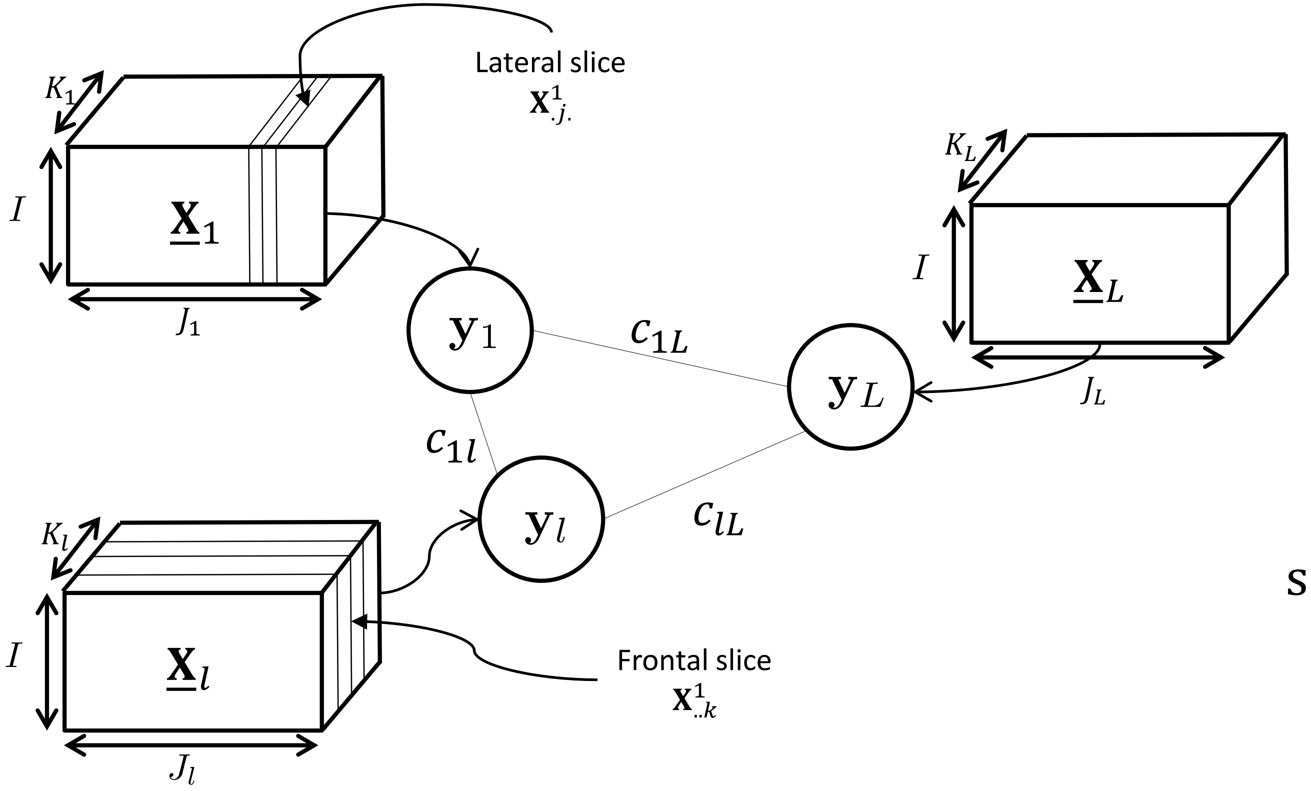

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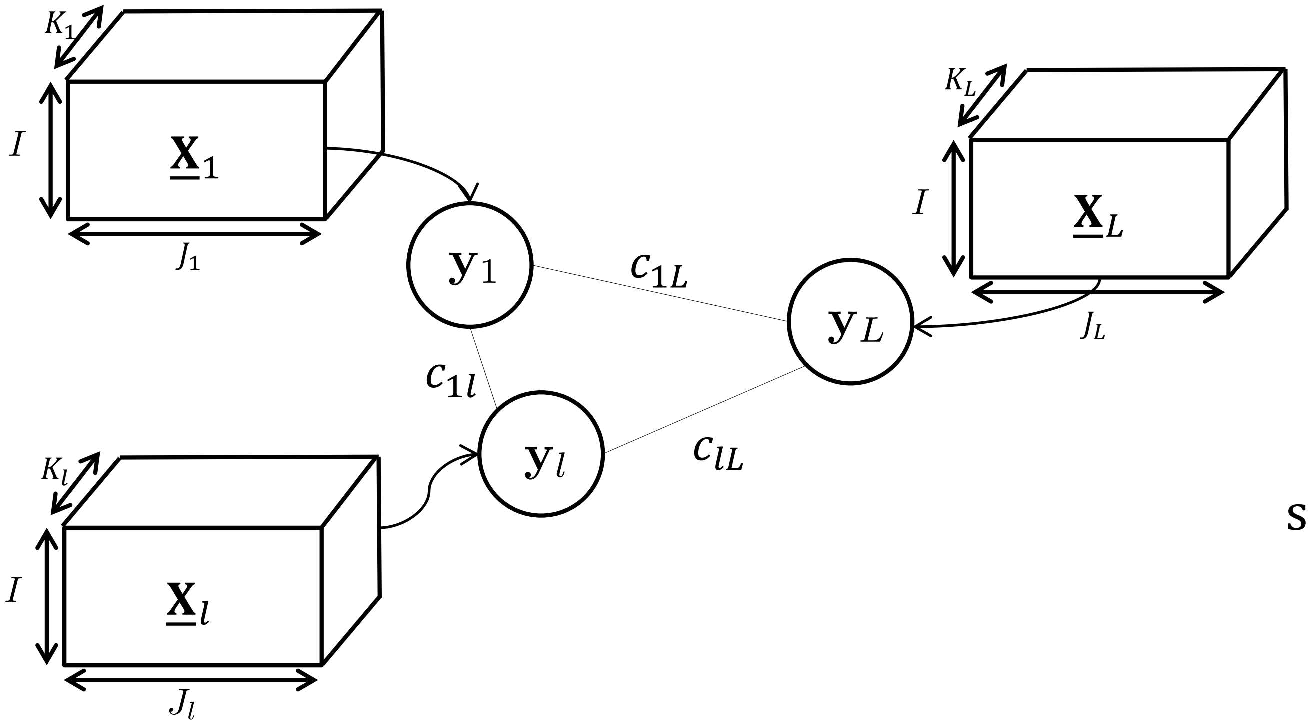

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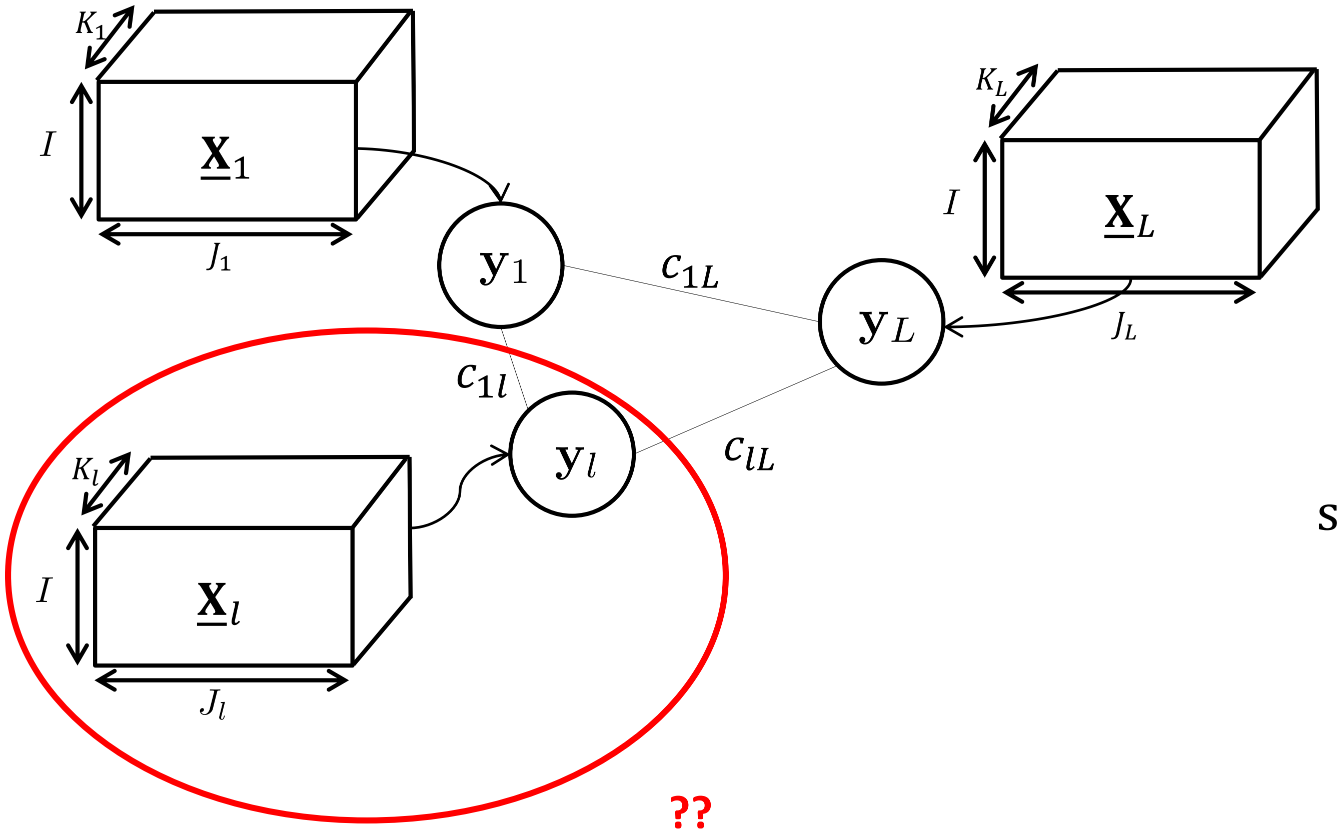

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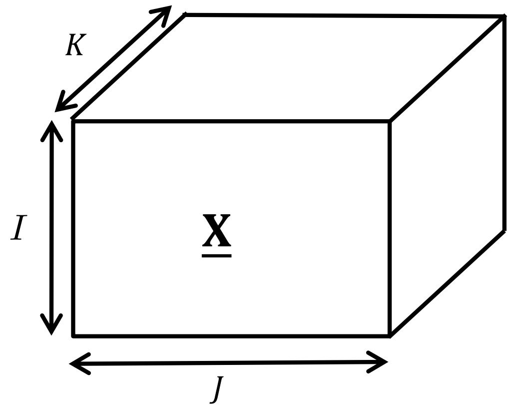

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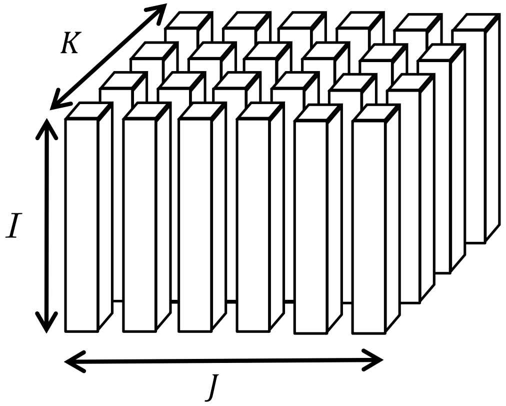

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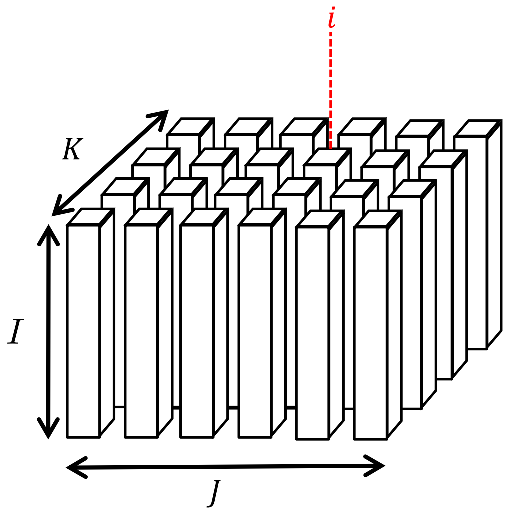

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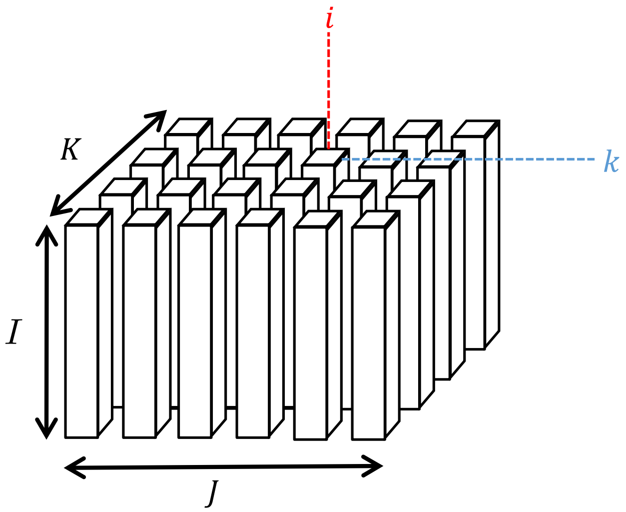

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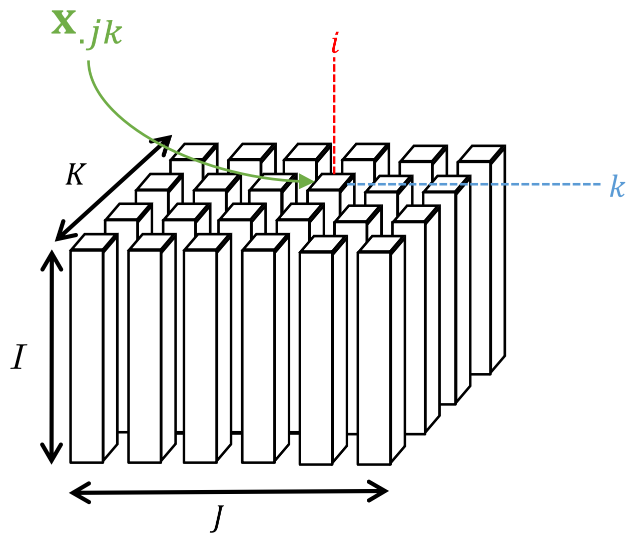

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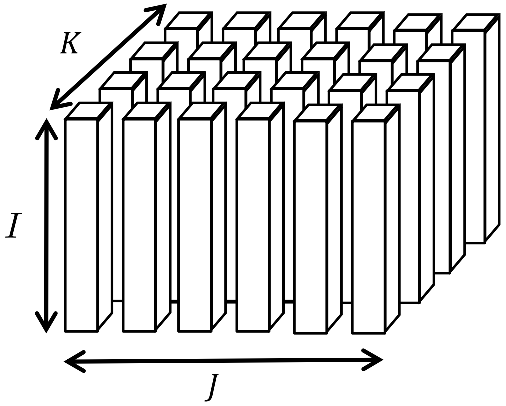

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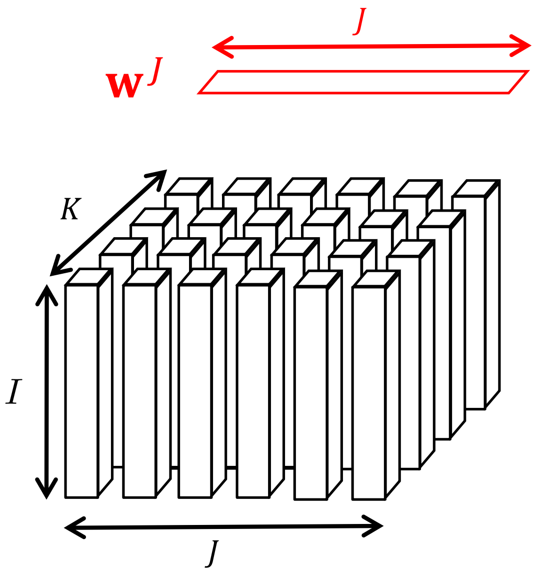

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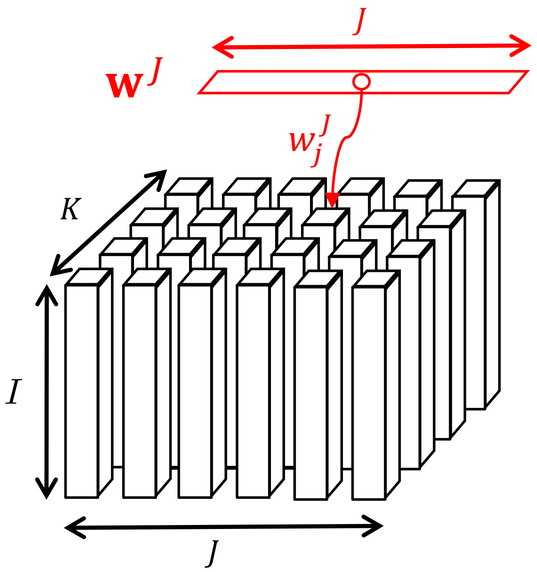

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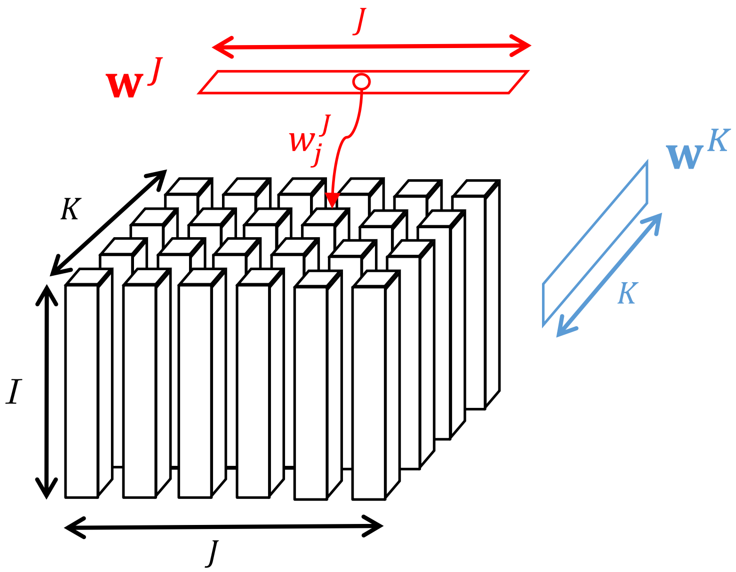

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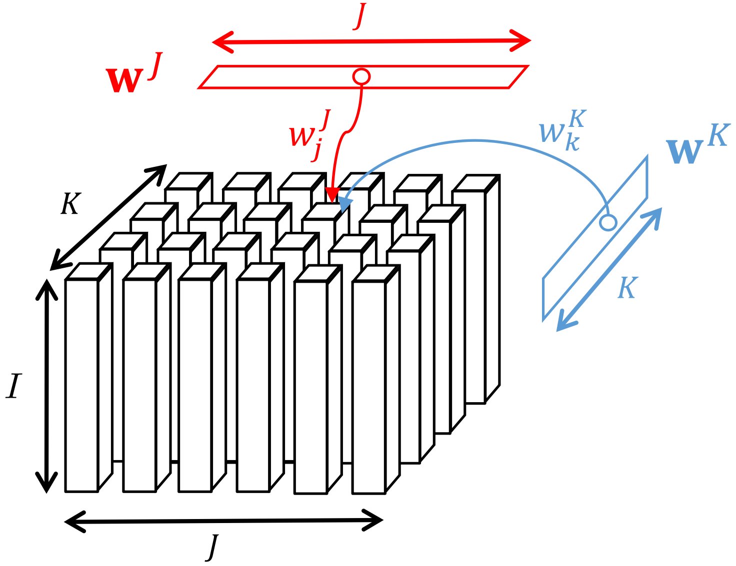

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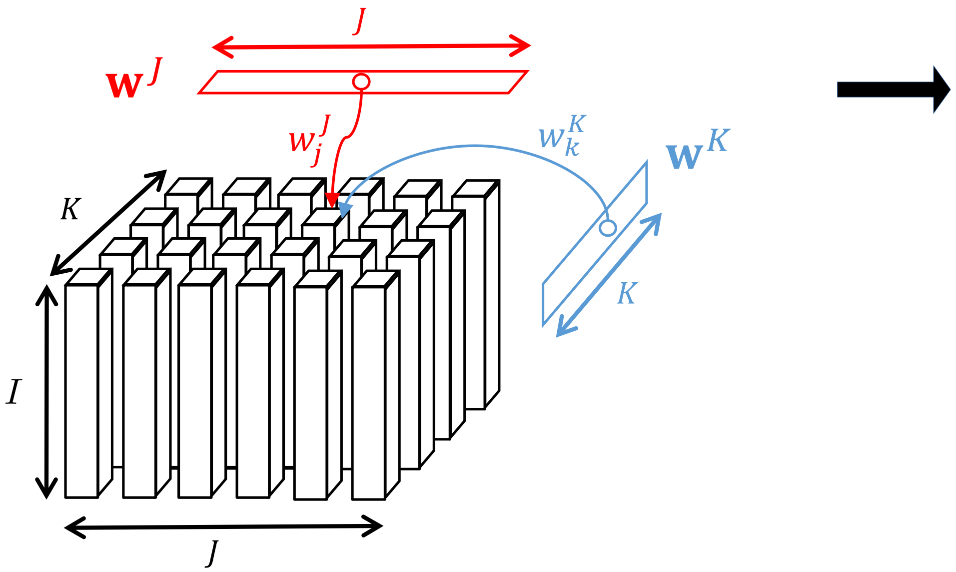

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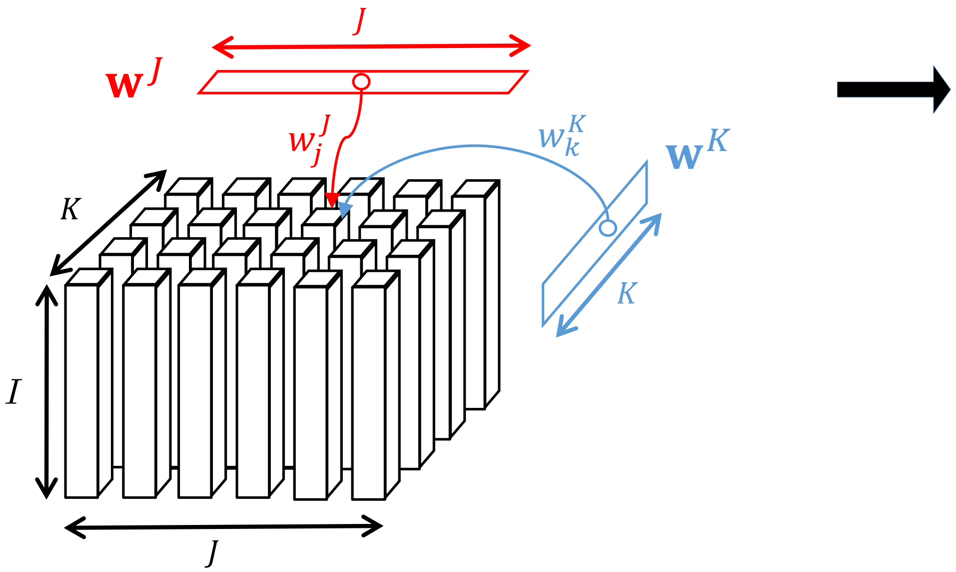

$$\mathbf{y} = \sum_{j=1}^{J} \sum_{k=1}^{K} w_k^K w_j^J \mathbf{x}_{.jk}$$

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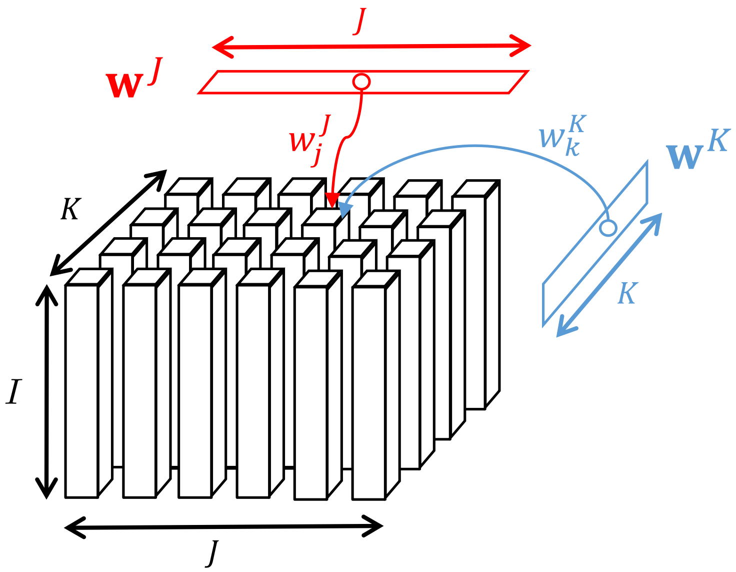

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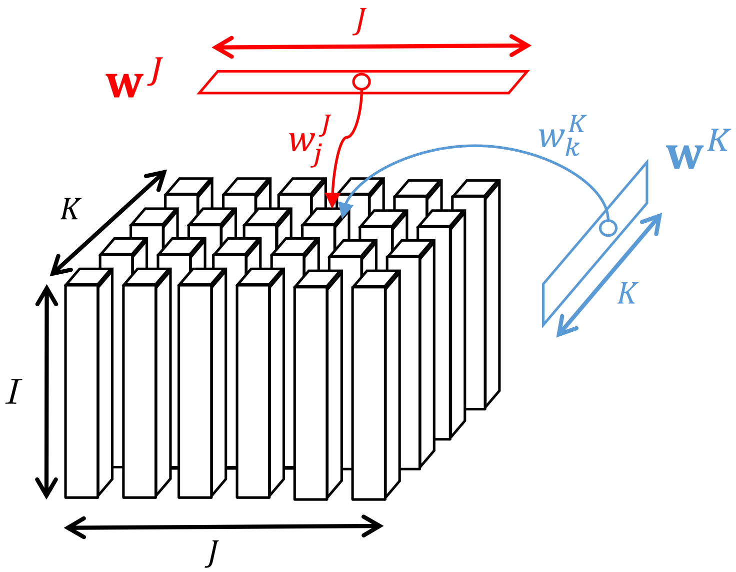

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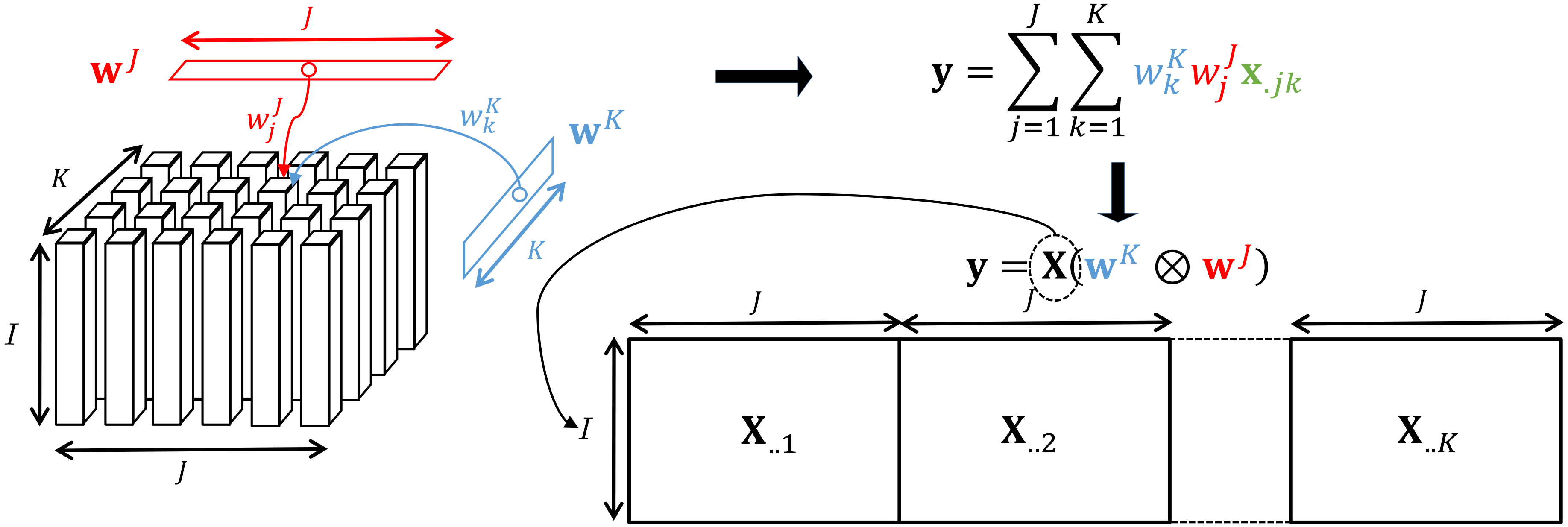

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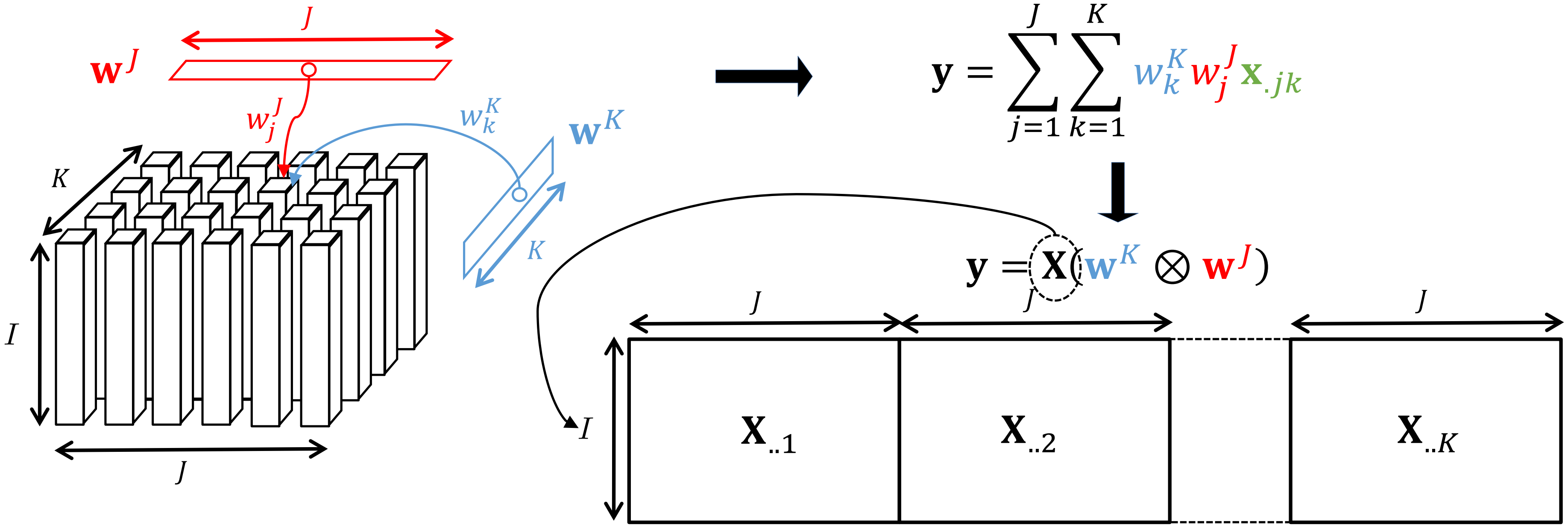

Interest in taking into account 3-way structure with the Kronecker product:

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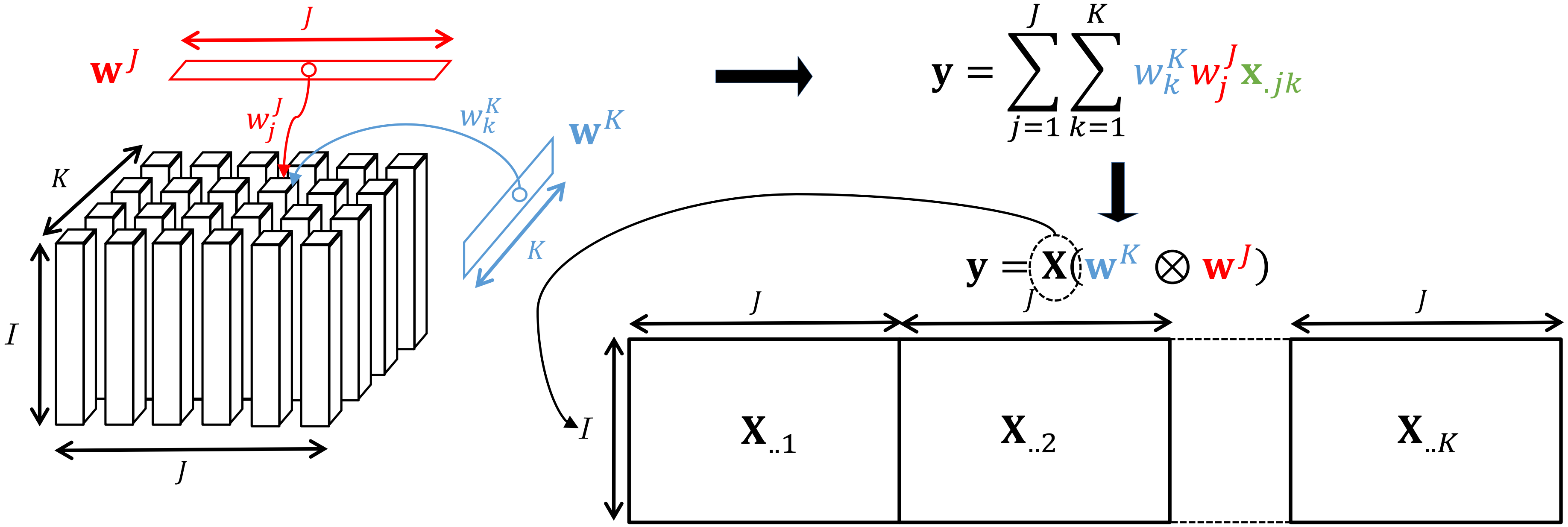

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❖ Gain in interpretability thanks to vector weights specific to each dimension.

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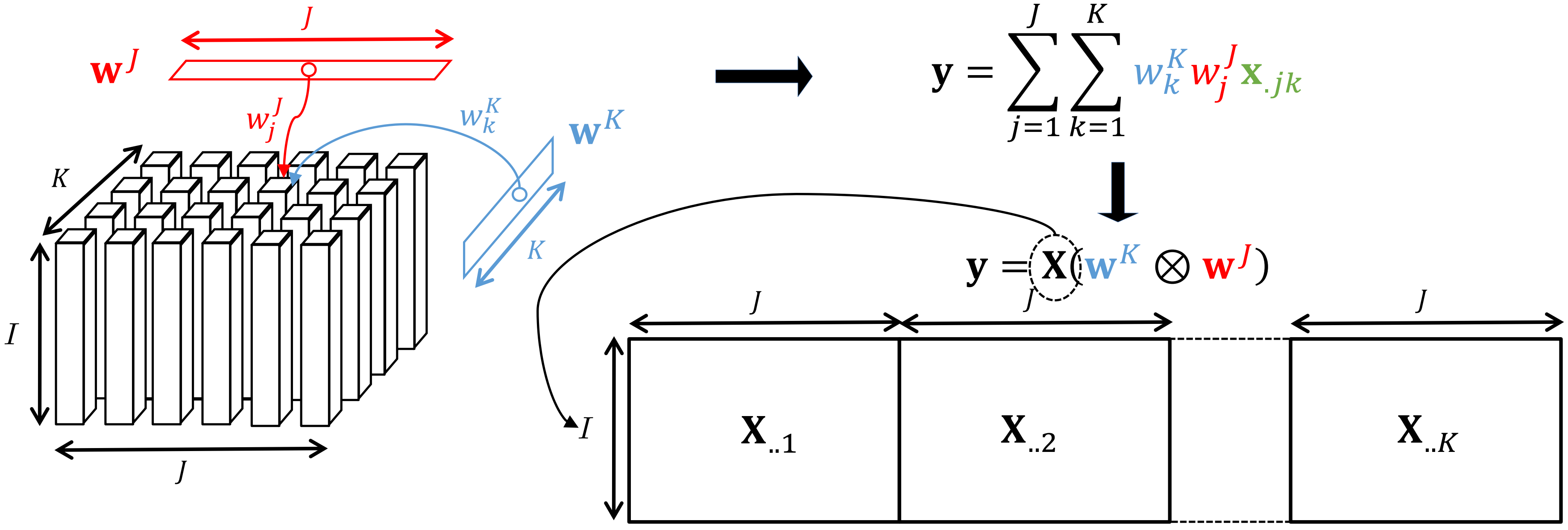

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- ❖ Less weights to estimate: from $J \times K$ to $J + K$.

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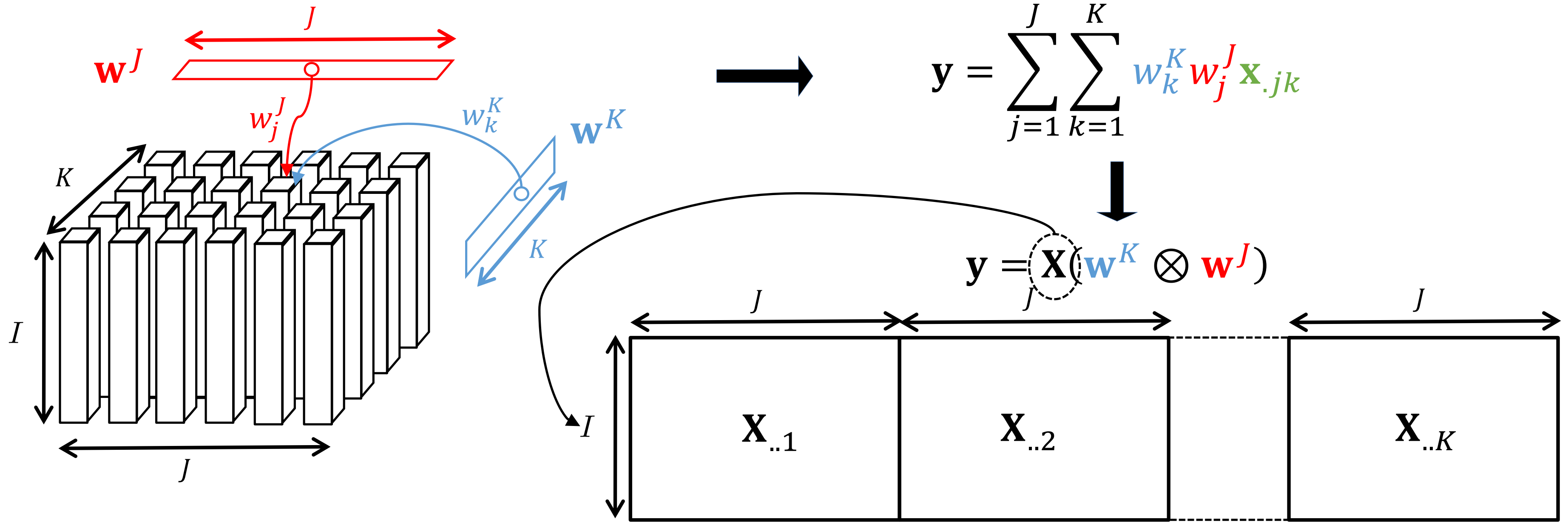

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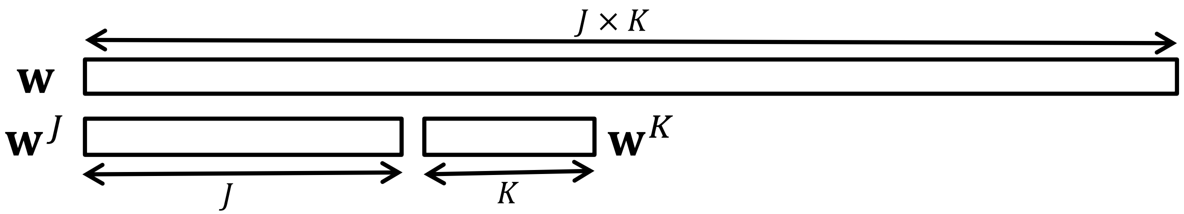

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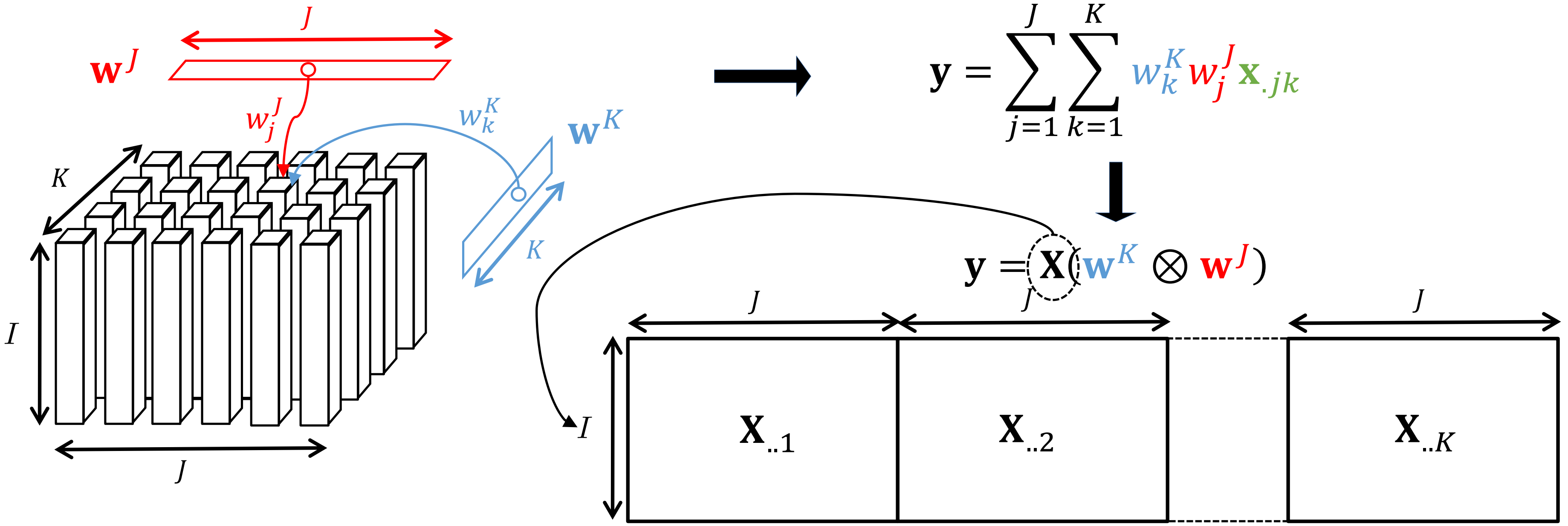

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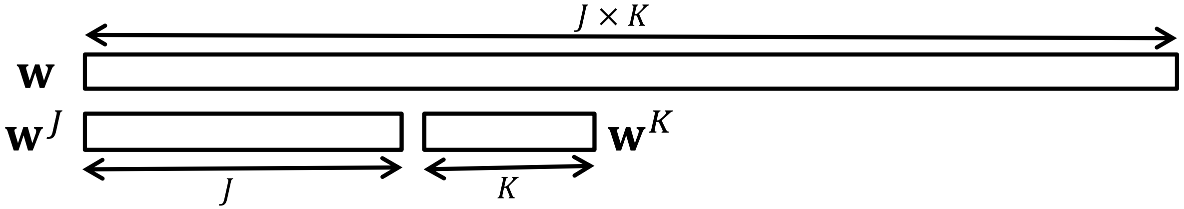
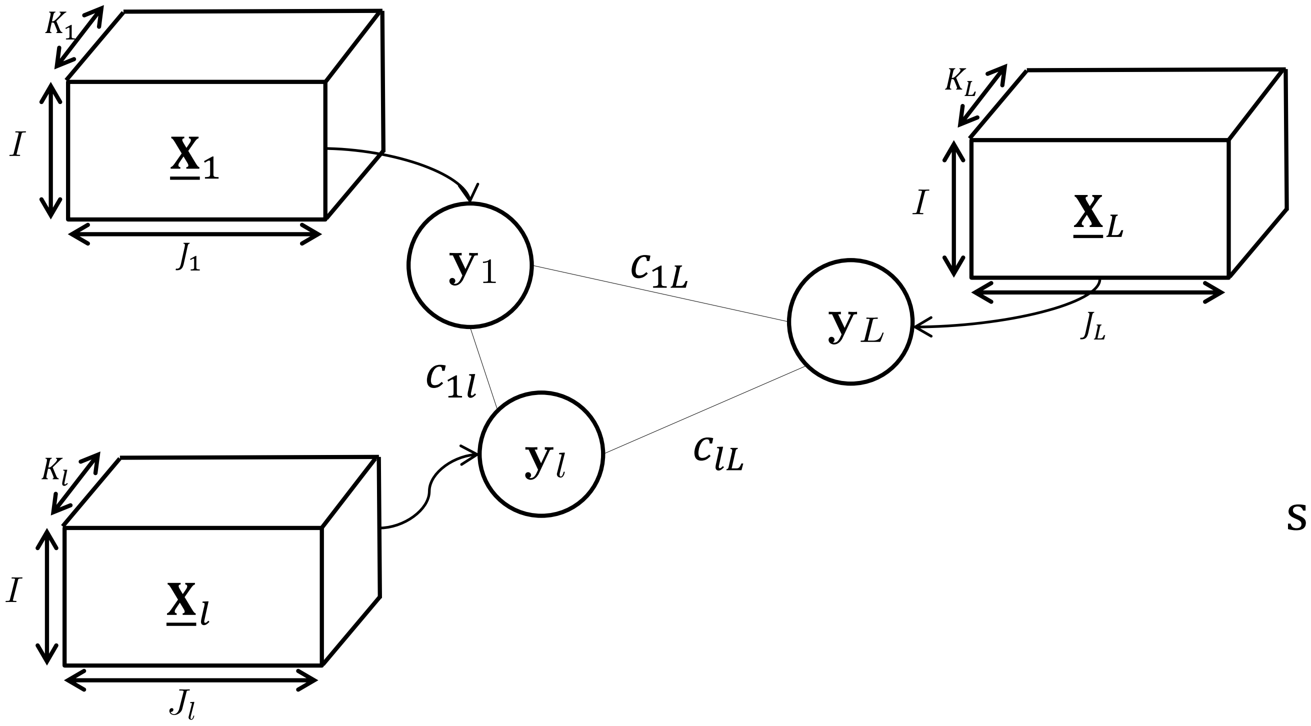


$J \times K$ Vs $J + K$

Multiway Generalized Canonical Correlation Analysis (MGCCA)



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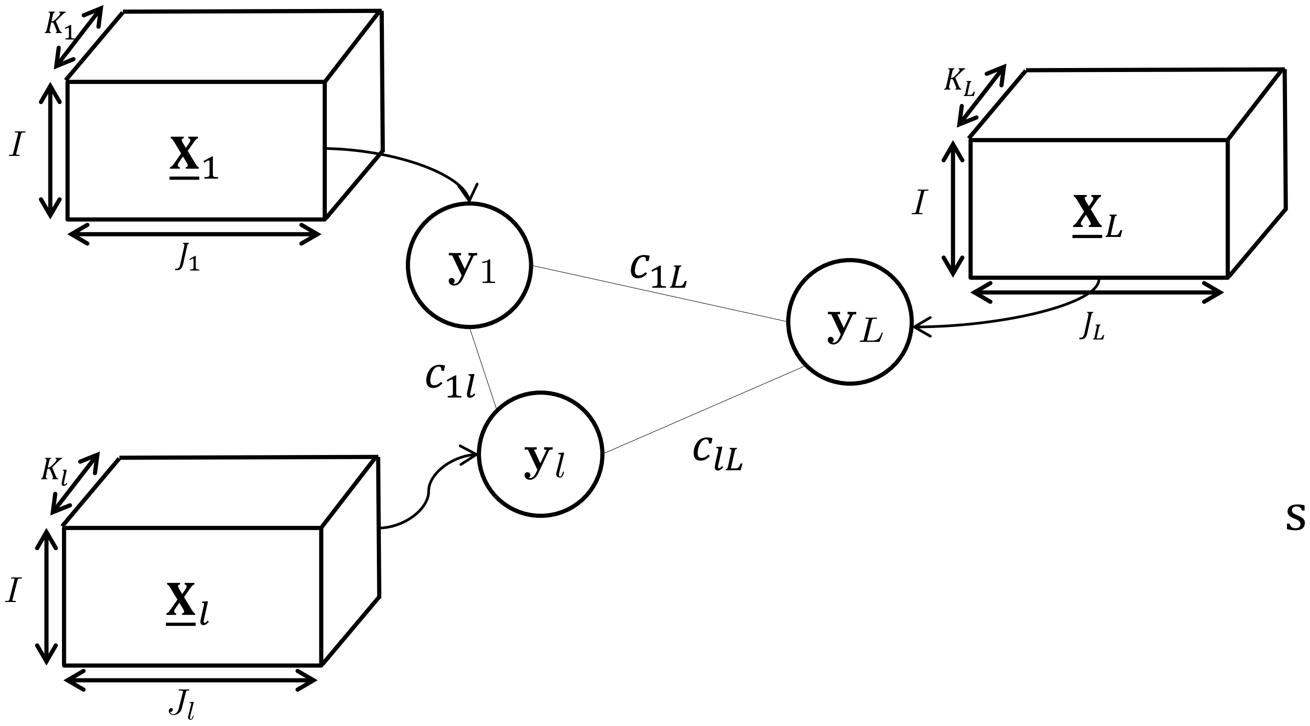

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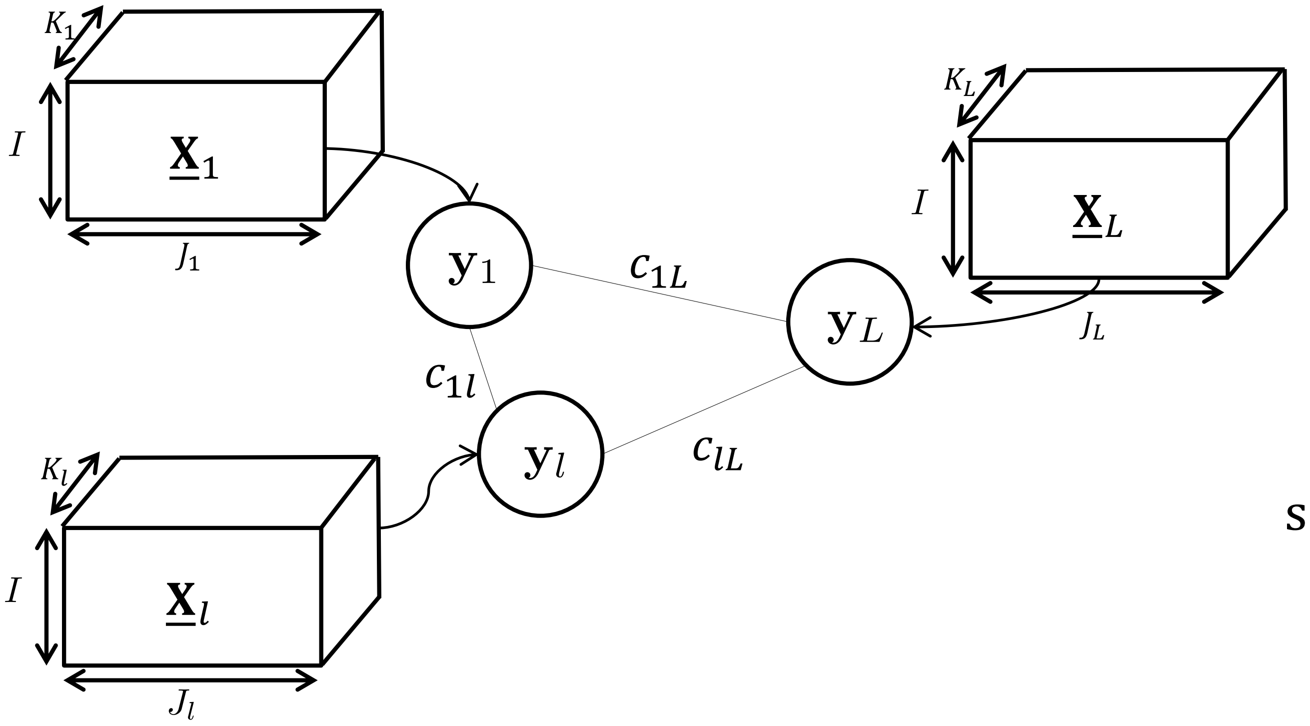

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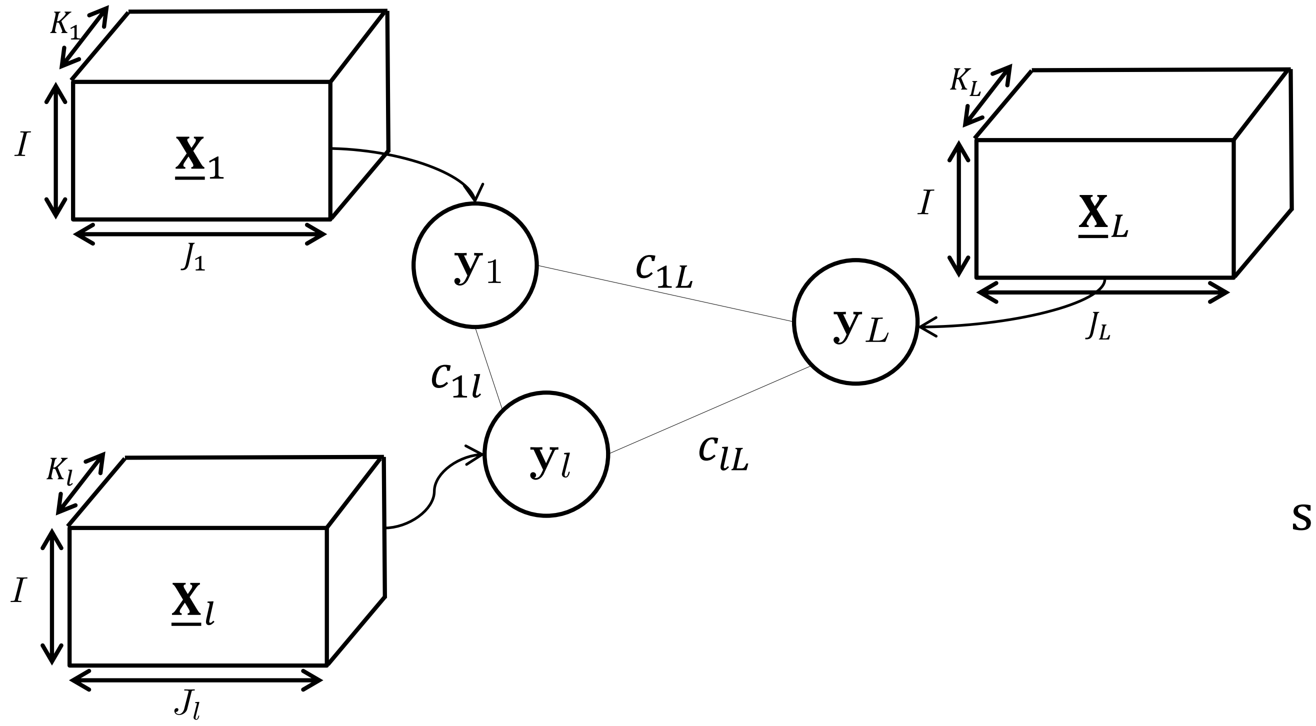

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Example of such data: Electro-EncephaloGrams.

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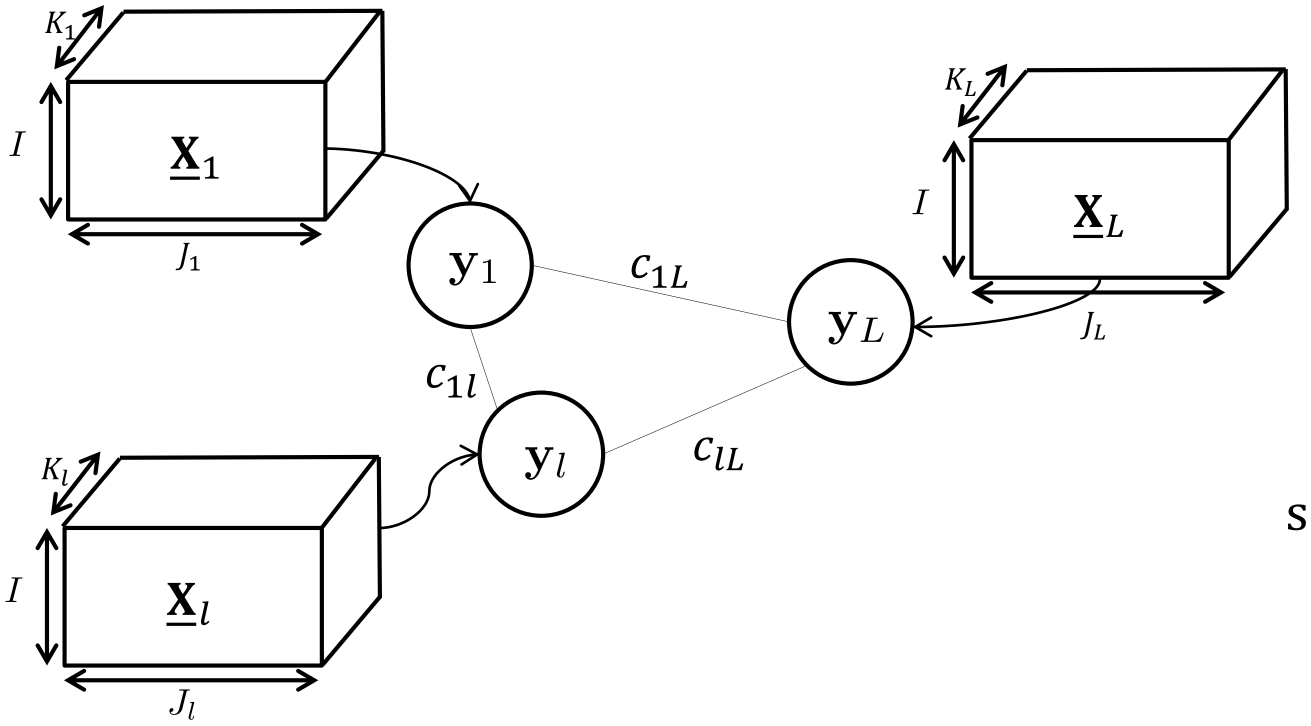

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Idea of the Algorithm:

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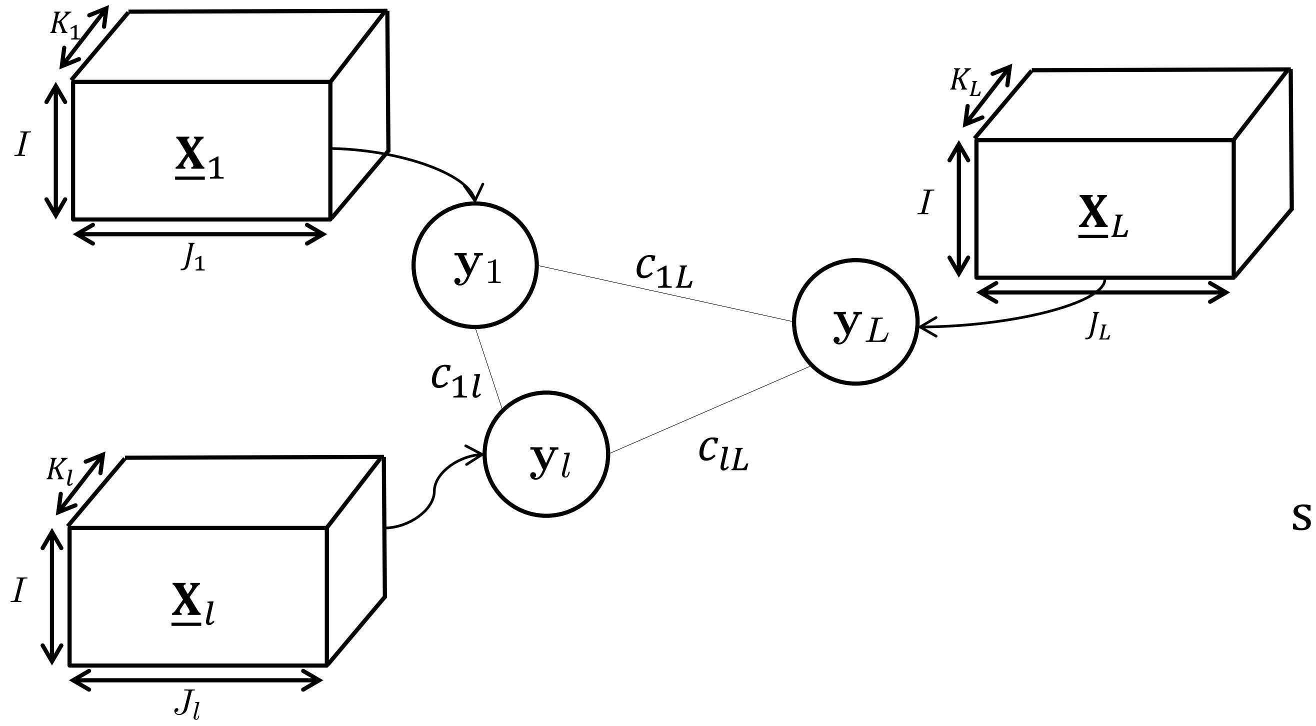

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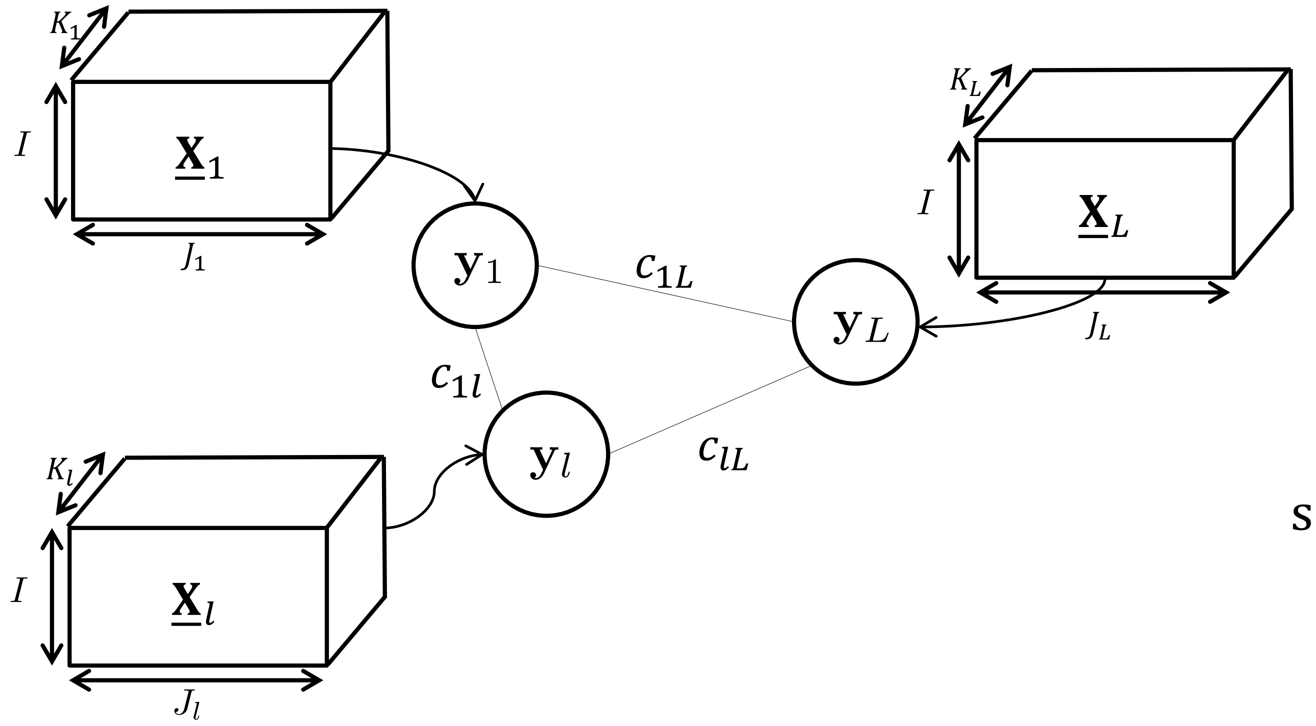

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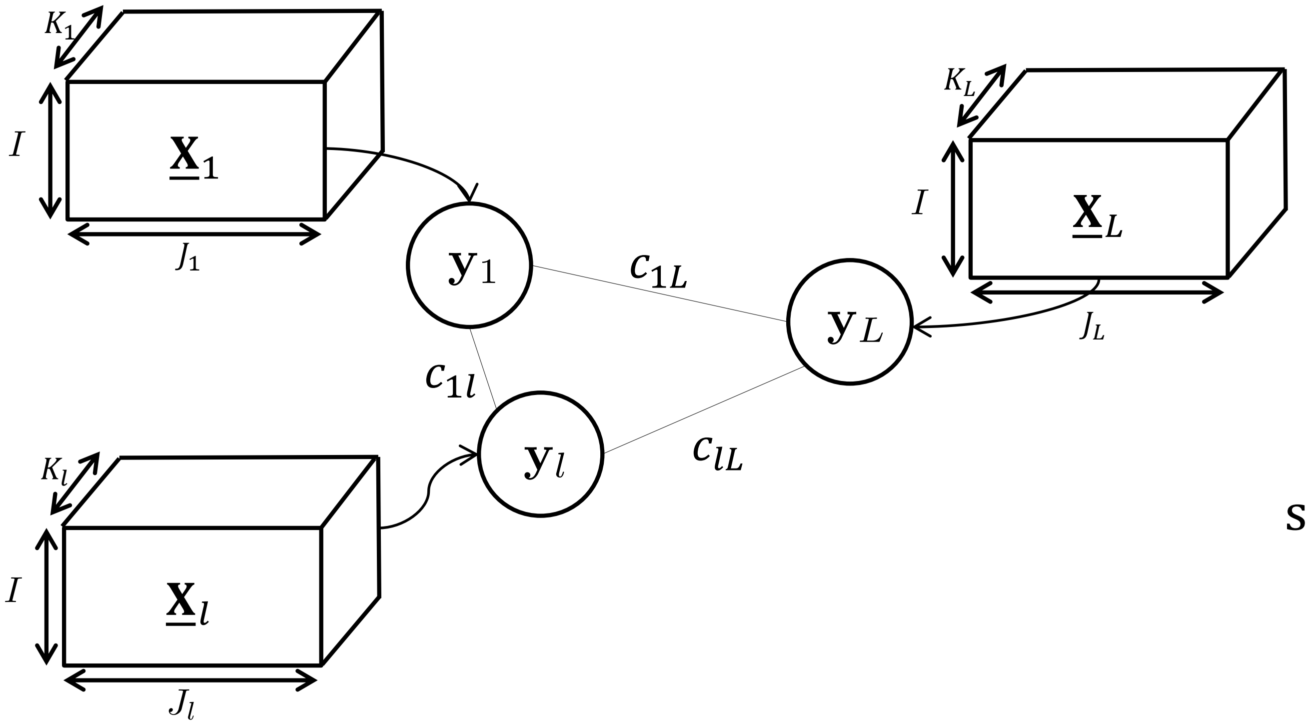

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Global convergence of this algorithm was shown.

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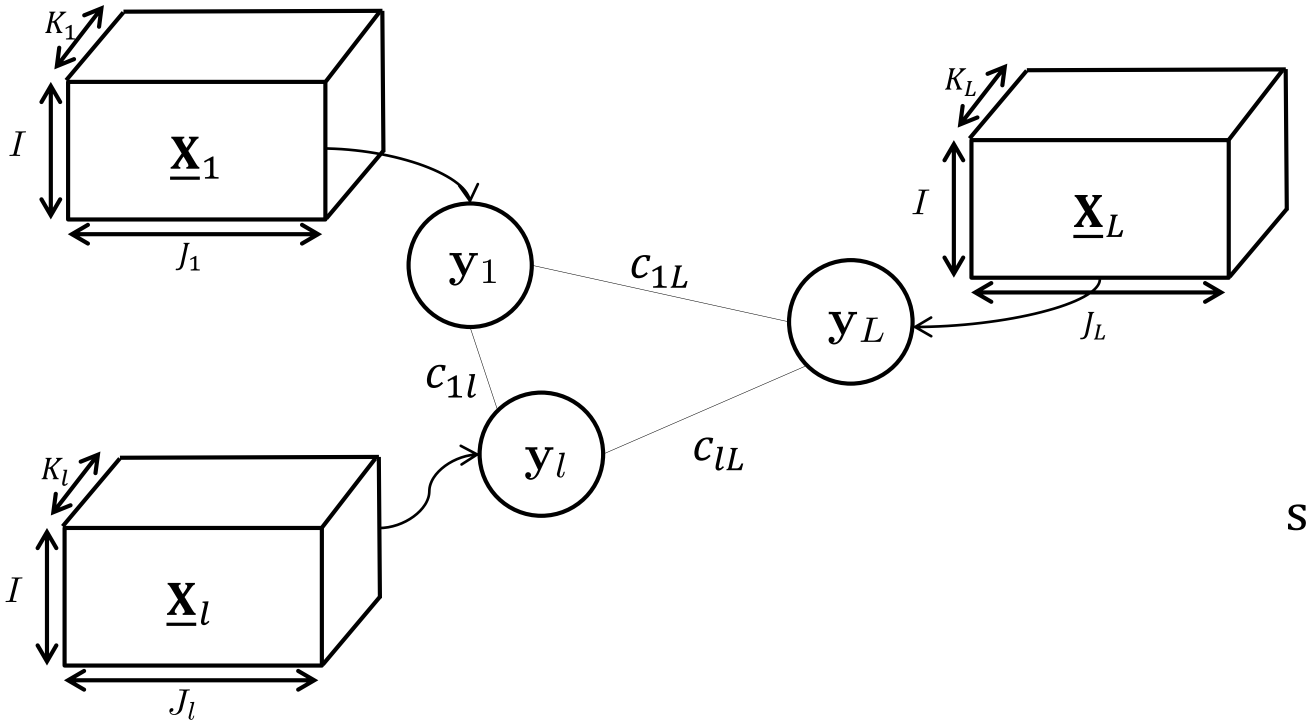

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New extension with Tensor GCCA

Global convergence of this algorithm was shown.

		Core Optimization Problem			
		$\max \boldsymbol{\nabla}_l f(\mathbf{w}^{\mathbf{s}})^\top \mathbf{w}_l$			
Constraints	$\mathbf{w}_l \in \omega_l$	RGCCA[1,2]			Constraints
	$\begin{cases} \|\mathbf{w}_l\|_2^2 = 1 \\ \|\mathbf{w}_l\|_1 \leq s_l \end{cases}$	SGCCA[3]			

$$\omega_l = \left\{\mathbf{w}_l \in \mathbb{R}^{J_l};\ \mathbf{w}_l^\top \mathbf{M}_l \mathbf{w}_l = 1\right\}$$

1. (Tenenhaus and Tenenhaus, 2011) 2. (Tenenhaus, Tenenhaus and Groenen, 2017) 3. (Tenenhaus et al., 2014)

RGCCA framework - State of the Art

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		$\max \boldsymbol{\nabla}_l f(\mathbf{w^s})^\top \mathbf{w}_l$			
Constraints	$\mathbf{w}_l \in \omega_l$	RGCCA[1,2]			Constraints
	$\begin{cases} \|\mathbf{w}_l\|_2^2 = 1 \\ \|\mathbf{w}_l\|_1 \leq s_l \end{cases}$	SGCCA[3]			
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		$\max \boldsymbol{\nabla}_l f(\mathbf{w^s})^\top \mathbf{w}_l$			
Constraints	$\mathbf{w}_l \in \omega_l$	RGCCA[1,2]			Constraints
	$\begin{cases} \lVert \mathbf{w}_l \rVert_2^2 = 1 \\ \lVert \mathbf{w}_l \rVert_1 \leq s_l \end{cases}$	SGCCA[3]			
	$\begin{cases} \mathbf{w}_l = \mathbf{w}_l^K \otimes \mathbf{w}_l^J \\ \mathbf{w}_l \in \omega_l \end{cases}$	MGCCA[4]/TGCCA[5]			

$$\omega_l = \{\mathbf{w}_l \in \mathbb{R}^{J_l};\ \mathbf{w}_l^\top \mathbf{M}_l \mathbf{w}_l = 1\}$$

1. (Tenenhaus and Tenenhaus, 2011) 2. (Tenenhaus, Tenenhaus and Groenen, 2017) 3. (Tenenhaus et al., 2014) 4. (Gloaguen et al., 2022)

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1. Introduction of the case study
2. **Unsupervised analysis with one-block:** Principal Component Analysis (PCA)
3. **Unsupervised analysis with two-blocks:**
   Partial Least Squares (PLS) and Canonical Correlation Analysis (CCA)
4. **Unsupervised analysis with L-blocks:**
   Regularized Generalized Canonical Correlation Analysis (RGCCA)
5. **Supervised analysis with RGCCA**
6. **Variable selection in RGCCA:**
   Sparse Generalized Canonical Correlation Analysis (SGCCA)
7. **The flexible Optimization Framework of RGCCA**
   - The general principal
   - Extension to multi-way analysis
   - From Sequential to Global

Optimization criterion: From Sequential to Global

$$\underset{\mathbf{w}_1, \ldots, \mathbf{w}_L}{\text{argmax}} \sum_{k,l=1}^{L} c_{kl} \, g\left(\text{Cov}\left(\mathbf{X}_k \mathbf{w}_k, \mathbf{X}_l \mathbf{w}_l\right)\right)$$

$$\text{s.t.} \begin{cases} \mathbf{w}_l^\top \mathbf{M}_l \mathbf{w}_l = 1 \end{cases}, l = 1, \ldots, L.$$

Where:

- $\mathbf{w}_l \in \mathbb{R}^{J_l}$ is a block-weight vector.

Optimization criterion: From Sequential to Global

$$\underset{\mathbf{w}_1^{(1)},\ldots,\mathbf{w}_L^{(1)}}{\text{argmax}} \sum_{k,l=1}^{L} c_{kl} \quad g\left(\text{Cov}\left(\mathbf{X}_k\mathbf{w}_k^{(1)}, \mathbf{X}_l\mathbf{w}_l^{(1)}\right)\right)$$

$$\text{s.t.} \begin{cases} {\mathbf{w}_l^{(1)}}^\top \mathbf{M}_l \mathbf{w}_l^{(1)} = 1 \\ \end{cases} \quad , l = 1, \ldots, L.$$

Where:

- ❖ $\mathbf{w}_l^{(1)} \in \mathbb{R}^{J_l}$ is a the first block-weight vector.

Optimization criterion: From Sequential to Global

$$\underset{\mathbf{w}_1^{(2)},\ldots,\mathbf{w}_L^{(2)}}{\text{argmax}} \sum_{k,l=1}^{L} c_{kl} \quad g\left(\text{Cov}\left(\mathbf{X}_k\mathbf{w}_k^{(2)}, \mathbf{X}_l\mathbf{w}_l^{(2)}\right)\right)$$

$$\text{s.t.} \begin{cases} {\mathbf{w}_l^{(2)}}^\top \mathbf{M}_l \mathbf{w}_l^{(2)} = 1 \\ {\mathbf{y}_l^{(1)}}^\top \mathbf{X}_l \mathbf{w}_l^{(2)} = 0 \end{cases} \quad , l = 1, \ldots, L.$$

Where:

- $\mathbf{w}_l^{(1)} \in \mathbb{R}^{J_l}$ is a the first block-weight vector.
- $\mathbf{w}_l^{(2)} \in \mathbb{R}^{J_l}$is a the second block−weight vector.

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$$\underset{\mathbf{w}_1^{(2)},\ldots,\mathbf{w}_L^{(2)}}{\operatorname{argmax}} \sum_{k,l=1}^{L} c_{kl} \quad g\left(\operatorname{Cov}\left(\mathbf{X}_k\mathbf{w}_k^{(2)}, \mathbf{X}_l\mathbf{w}_l^{(2)}\right)\right)$$

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- ❖ …

Optimization criterion: From Sequential to Global

$$\underset{\mathbf{w}_1^{(1)},\ldots,\mathbf{w}_L^{(1)}}{\text{argmax}} \sum_{k,l=1}^{L} c_{kl} \quad g\left(\text{Cov}\left(\mathbf{X}_k\mathbf{w}_k^{(1)}, \mathbf{X}_l\mathbf{w}_l^{(1)}\right)\right)$$

Where:

❖ $\mathbf{w}_l^{(1)} \in \mathbb{R}^{J_l}$is a the first block−weight vector.

Optimization criterion: From Sequential to Global

$$\underset{\mathbf{w}_1^{(r)},\ldots,\mathbf{w}_L^{(r)}}{\operatorname{argmax}} \sum_{k,l=1}^{L} c_{kl} \sum_{r=1}^{R} g\left(\operatorname{Cov}\left(\mathbf{X}_k\mathbf{w}_k^{(r)}, \mathbf{X}_l\mathbf{w}_l^{(r)}\right)\right)$$

Where:

- $\mathbf{w}_l^{(\mathrm{r})} \in \mathbb{R}^{J_l}$ is a the r^{th} block–weight vector.

Optimization criterion: From Sequential to Global

$$\underset{\mathbf{W}_1,\ldots,\mathbf{W}_L}{\operatorname{argmax}} \sum_{k,l=1}^{L} c_{kl} \operatorname{Trace}\left(g\left(\operatorname{Cov}(\mathbf{X}_k \mathbf{W}_k, \mathbf{X}_l \mathbf{W}_l)\right)\right)$$

Where:

- $\mathbf{w}_l^{(\mathrm{r})} \in \mathbb{R}^{J_l}$ is a the r^{th} block−weight vector.
- $\mathbf{W}_l = \left[\mathbf{w}_l^{(1)}, \ldots, \mathbf{w}_l^{(\mathrm{R})}\right] \in \mathbb{R}^{J_l \times R}$ is a block−weight matrix.

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Optimization criterion: From Sequential to Global

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Principle of the Global RGCCA Algorithm

Following the optimization framework of RGCCA, the core optimization problem is:

$$\underset{\mathbf{W}_l, \mathbf{W}_l^\top \mathbf{M}_l \mathbf{W}_l = \mathbf{I}_R}{\operatorname{argmax}} \quad \operatorname{Trace}(\boldsymbol{\nabla}_l f(\mathbf{W}^s)^\top \mathbf{W}_l)$$

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Pros:

- A single optimization problem allows to extract all components simultaneously.
- The obtain algorithm is rather simple (simple update) and is globally convergent.
- It is possible now to add constraints across components.

Cons:

- In this form, we have to extract the same number of component per block.

RGCCA framework - State of the Art

		Core Optimization Problem			
		$\max \boldsymbol{\nabla}_l f(\mathbf{w}^{\mathbf{s}})^\top \mathbf{w}_l$			
Constraints	$\mathbf{w}_l \in \omega_l$	RGCCA[1,2]			Constraints
	$\begin{cases} \lVert \mathbf{w}_l \rVert_2^2 = 1 \\ \lVert \mathbf{w}_l \rVert_1 \leq s_l \end{cases}$	SGCCA[3]			
	$\begin{cases} \mathbf{w}_l = \mathbf{w}_l^K \otimes \mathbf{w}_l^J \\ \mathbf{w}_l \in \omega_l \end{cases}$	MGCCA[4]/TGCCA[5]			

$$\omega_l = \{\mathbf{w}_l \in \mathbb{R}^{J_l};\ \mathbf{w}_l^\top \mathbf{M}_l \mathbf{w}_l = 1\}$$

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RGCCA framework - State of the Art

		Core Optimization Problem			
		Sequential	Global		
		$\max \nabla_l f(\mathbf{w}^{\mathbf{s}})^\top \mathbf{w}_l$			
Constraints	$\mathbf{w}_l \in \omega_l$	RGCCA[1,2]			Constraints
	$\begin{cases} \|\mathbf{w}_l\|_2^2 = 1 \\ \|\mathbf{w}_l\|_1 \leq s_l \end{cases}$	SGCCA[3]			
	$\begin{cases} \mathbf{w}_l = \mathbf{w}_l^K \otimes \mathbf{w}_l^J \\ \mathbf{w}_l \in \omega_l \end{cases}$	MGCCA[4]/TGCCA[5]			

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RGCCA framework - State of the Art

Constraints	Core Optimization Problem: Sequential	Core Optimization Problem: Global	Constraints
	$\max \boldsymbol{\nabla}_l f(\mathbf{w}^{\mathbf{s}})^\top \mathbf{w}_l$	$\max \mathbf{Tr}(\boldsymbol{\nabla}_l f(\mathbf{W}^{\mathbf{s}})^\top \mathbf{W}_l)$	
$\mathbf{w}_l \in \omega_l$	RGCCA[1,2]		
$\begin{cases} \Vert\mathbf{w}_l\Vert_2^2 = 1 \\ \Vert\mathbf{w}_l\Vert_1 \leq s_l \end{cases}$	SGCCA[3]		
$\begin{cases} \mathbf{w}_l = \mathbf{w}_l^K \otimes \mathbf{w}_l^J \\ \mathbf{w}_l \in \omega_l \end{cases}$	MGCCA[4]/TGCCA[5]		

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RGCCA framework - State of the Art

		Core Optimization Problem			
		Sequential	Global		
		$\max \boldsymbol{\nabla}_l f(\mathbf{w^s})^\top \mathbf{w}_l$	$\max \mathbf{Tr}(\boldsymbol{\nabla}_l f(\mathbf{W^s})^\top \mathbf{W}_l)$		
Constraints	$\mathbf{w}_l \in \omega_l$	RGCCA[1,2]		$\mathbf{W}_l \in \Omega_l$	Constraints
	$\begin{cases} \Vert\mathbf{w}_l\Vert_2^2 = 1 \\ \Vert\mathbf{w}_l\Vert_1 \le s_l \end{cases}$	SGCCA[3]			
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RGCCA framework - State of the Art

		Core Optimization Problem			
		Sequential	Global		
		$\max \nabla_l f(\mathbf{w^s})^\top \mathbf{w}_l$	$\max \mathbf{Tr}(\nabla_l f(\mathbf{W^s})^\top \mathbf{W}_l)$		
Constraints	$\mathbf{w}_l \in \omega_l$	RGCCA[1,2]	Global RGCCA[6,7]	$\mathbf{W}_l \in \Omega_l$	Constraints
	$\begin{cases} \lVert\mathbf{w}_l\rVert_2^2 = 1 \\ \lVert\mathbf{w}_l\rVert_1 \leq s_l \end{cases}$	SGCCA[3]			
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RGCCA framework - State of the Art

	Core Optimization Problem		
	Sequential	Global	
	$\max \boldsymbol{\nabla}_l f(\mathbf{w}^{\mathbf{s}})^\top \mathbf{w}_l$	$\max \mathbf{Tr}(\boldsymbol{\nabla}_l f(\mathbf{W}^{\mathbf{s}})^\top \mathbf{W}_l)$	
Constraints			**Constraints**
$\mathbf{w}_l \in \omega_l$	RGCCA[1,2]	Global RGCCA[6,7]	$\mathbf{W}_l \in \Omega_l$
$\begin{cases} \Vert\mathbf{w}_l\Vert_2^2 = 1 \\ \Vert\mathbf{w}_l\Vert_1 \leq s_l \end{cases}$	SGCCA[3]		
$\begin{cases} \mathbf{w}_l = \mathbf{w}_l^K \otimes \mathbf{w}_l^J \\ \mathbf{w}_l \in \omega_l \end{cases}$	MGCCA[4]/TGCCA[5]		$\begin{cases} \mathbf{W}_l = \mathbf{W}_l^K \odot \mathbf{W}_l^J \\ \mathbf{W}_l \in \Omega_l \end{cases}$

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RGCCA framework - State of the Art

		Core Optimization Problem			
		Sequential	Global		
		$\max \boldsymbol{\nabla}_l f(\mathbf{w}^{\mathbf{s}})^\top \mathbf{w}_l$	$\max \mathbf{Tr}(\boldsymbol{\nabla}_l f(\mathbf{W}^{\mathbf{s}})^\top \mathbf{W}_l)$		
Constraints	$\mathbf{w}_l \in \omega_l$	RGCCA[1,2]	Global RGCCA[6,7]	$\mathbf{W}_l \in \Omega_l$	Constraints
	$\begin{cases} \Vert\mathbf{w}_l\Vert_2^2 = 1 \\ \Vert\mathbf{w}_l\Vert_1 \leq s_l \end{cases}$	SGCCA[3]			
	$\begin{cases} \mathbf{w}_l = \mathbf{w}_l^K \otimes \mathbf{w}_l^J \\ \mathbf{w}_l \in \omega_l \end{cases}$	MGCCA[4]/TGCCA[5]	Global MGCCA[6,7]	$\begin{cases} \mathbf{W}_l = \mathbf{W}_l^K \odot \mathbf{W}_l^J \\ \mathbf{W}_l \in \Omega_l \end{cases}$	

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		Core Optimization Problem			
		Sequential	Global		
		$\max \boldsymbol{\nabla}_l f(\mathbf{w^s})^\top \mathbf{w}_l$	$\max \mathbf{Tr}(\boldsymbol{\nabla}_l f(\mathbf{W^s})^\top \mathbf{W}_l)$		
Constraints	$\mathbf{w}_l \in \omega_l$	RGCCA[1,2]	Global RGCCA[6,7]	$\mathbf{W}_l \in \Omega_l$	Constraints
	$\begin{cases} \lVert\mathbf{w}_l\rVert_2^2 = 1 \\ \lVert\mathbf{w}_l\rVert_1 \leq s_l \end{cases}$	SGCCA[3]			
	$\begin{cases} \mathbf{w}_l = \mathbf{w}_l^K \otimes \mathbf{w}_l^J \\ \mathbf{w}_l \in \omega_l \end{cases}$	MGCCA[4]/TGCCA[5]	Global MGCCA[6,7]	$\begin{cases} \mathbf{W}_l = \mathbf{W}_l^K \odot \mathbf{W}_l^J \\ \mathbf{W}_l \in \Omega_l \end{cases}$	
	Structured Sparsity				

$$\omega_l = \{\mathbf{w}_l \in \mathbb{R}^{J_l};\ \mathbf{w}_l^\top \mathbf{M}_l \mathbf{w}_l = 1\}$$

$$\Omega_l = \{\mathbf{W}_l \in \mathbb{R}^{J_l \times R};\ \mathbf{W}_l^\top \mathbf{M}_l \mathbf{W}_l = \mathbf{I}_R\}$$

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RGCCA framework - State of the Art

		Core Optimization Problem		
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	$\begin{cases} \lVert\mathbf{w}_l\rVert_2^2 = 1 \\ \lVert\mathbf{w}_l\rVert_1 \le s_l \end{cases}$	SGCCA[3]		
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	Structured Sparsity	(i). Group-Lasso in the same framework[8] (ii). Other structured sparse penalties in other frameworks[6,9,10,11]		Constraints

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RGCCA framework - State of the Art

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Fabien GIRKA
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Caroline PELTIER
CNRS, INRAE

Here are the contributors of the actual version of the package !!

Vincent GUILLEMOT
Institut Pasteur, Bioinformatics and Biostatistics Hub

Arnaud GLOAGUEN
Centre National de Recherche en Génomique Humaine, CEA

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elixir FRANCE

Other perpectives ?

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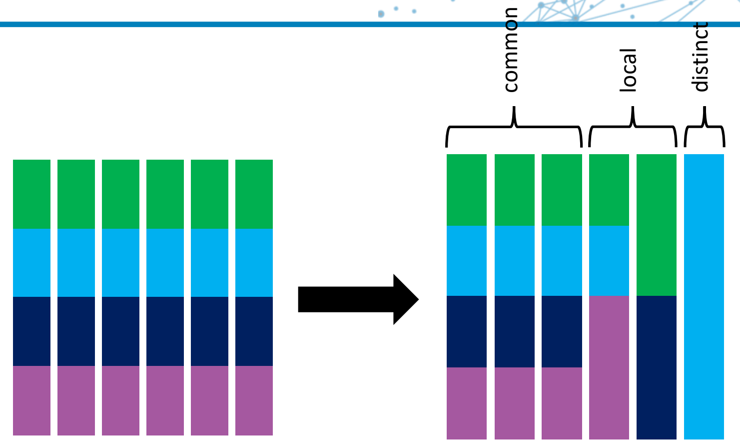
Axe 1: Use comon and specific information



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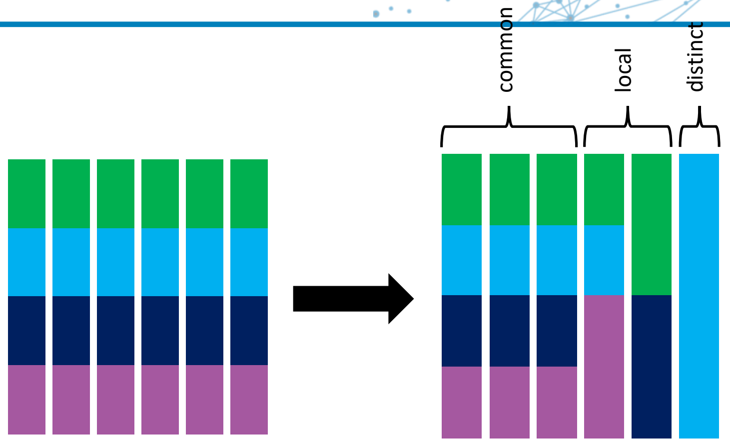
Vary the combination of omics data from which components are built.



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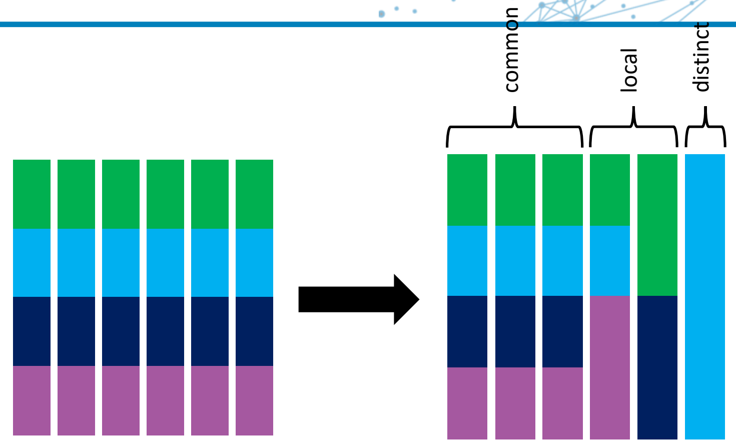

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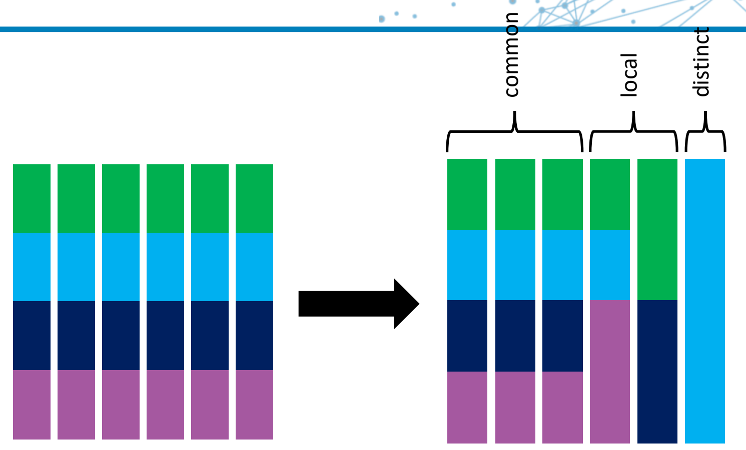

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Divide each omic matrix by biological pathways.

Allow to identify most important pathways (With L1 norm).

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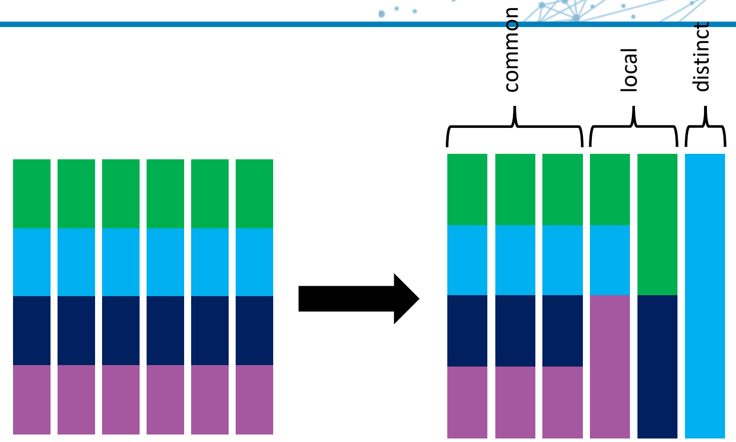

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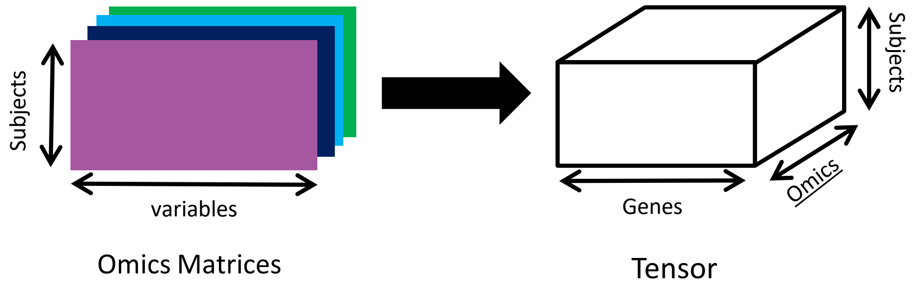
Regroup omic matrices along the third dimension (ex: by genes) to create a tensor.

Permet d'ajouter une notion biologique dans la définition du modèle



Courtesy to Vincent Le Goff.

Other perspectives ?

PhD of Vincent LE GOFF

Supervised by:

- **Edith Le Floch**
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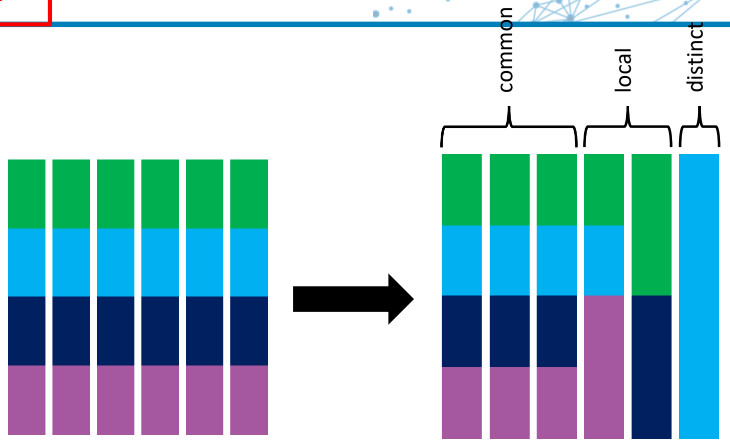
- **Arnaud Gloaguen**



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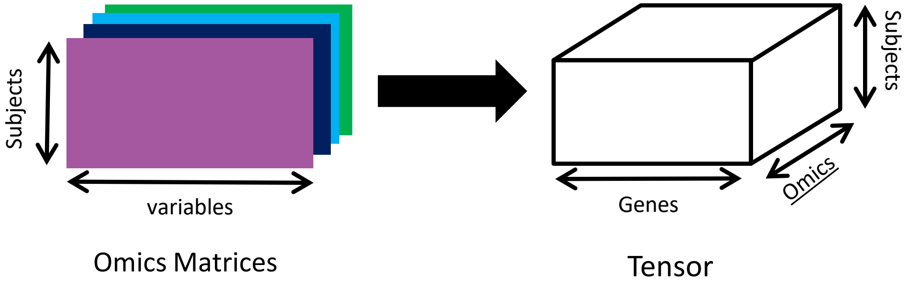

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Belzeaux Raoul

Gascon Gonzalo

Isabelle Mansuy

Summer School SIB/IFB:

Florence Mehl

Olivier Sand

Grégoire Rossier

Jimmy Vandel

Guillemette Marot

Marie-Galadriel Briere

Lucie Khamvongsa-Charbonnier

Morgane Terezol

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Maxime Delmas

Jean-Clément Gallardo

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Statomique:

Guillemette Marot (again !)

Christelle Hennequet-Antier

Julie Aubert

Marie-Agnès Dillies

Helene Touzet

Justine Merlan

Slides:

Arthur Tenenhaus

Laurent Le Brusquet

Julien Bect

Vincent Le Goff

Edith Le Floch

ETBII:

Lucie Khamvongsa-Charbonnier

Hélène Chiapello

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Thank you for your attention !