Genomics Data

Supervised learning for High-Dimensional Data

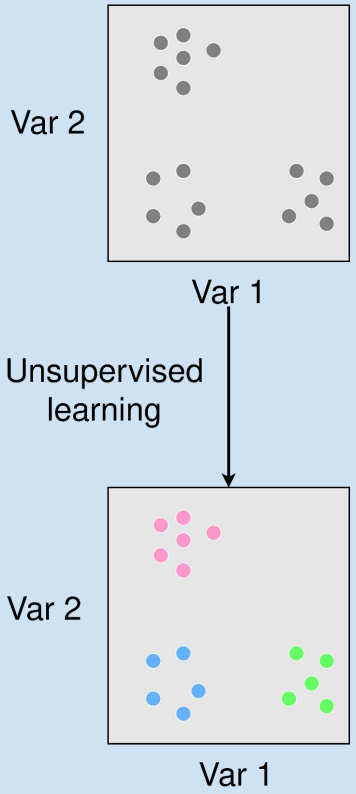
Supervised Learning

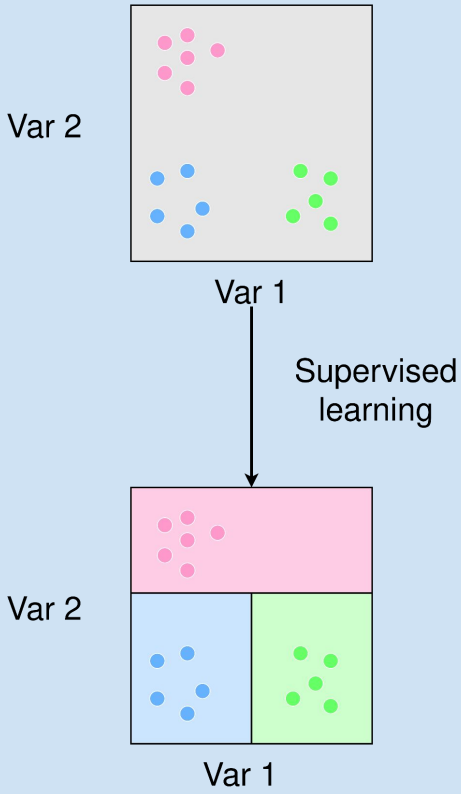
Unsupervised learning

- Exploring patterns in data
- No “correct” response
- PCA, clustering

Supervised learning

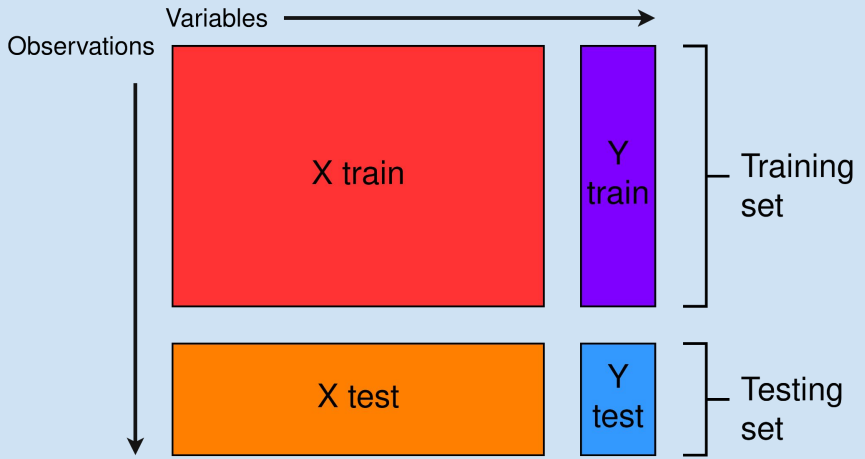
- Learn the relationship between predictors and a response
- Linear regression, random forest,...

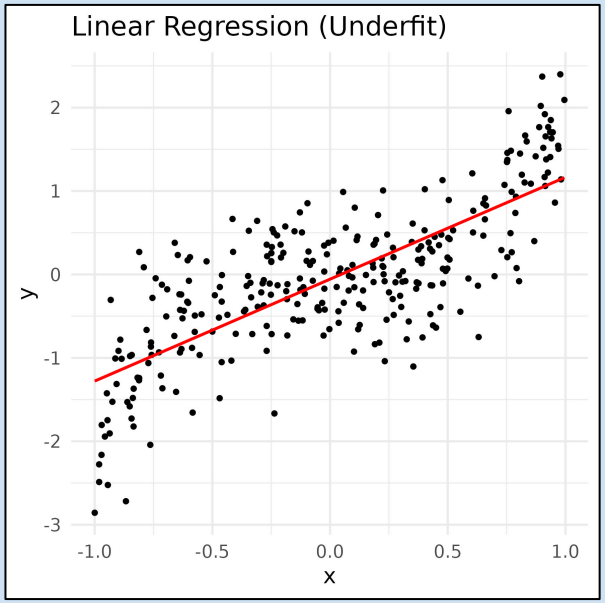


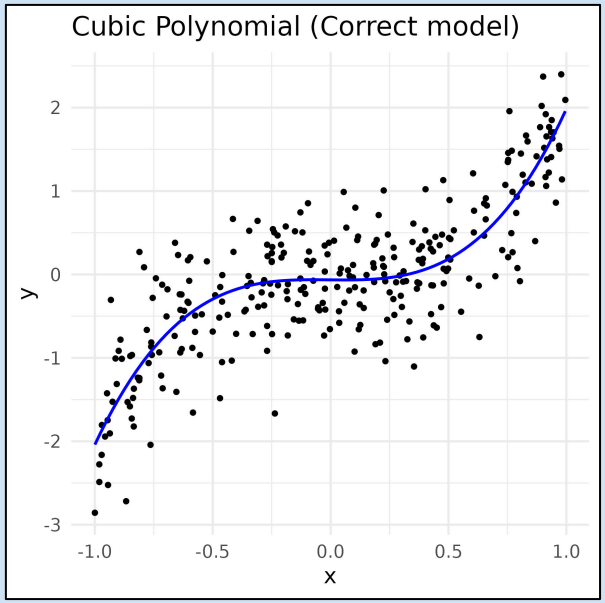


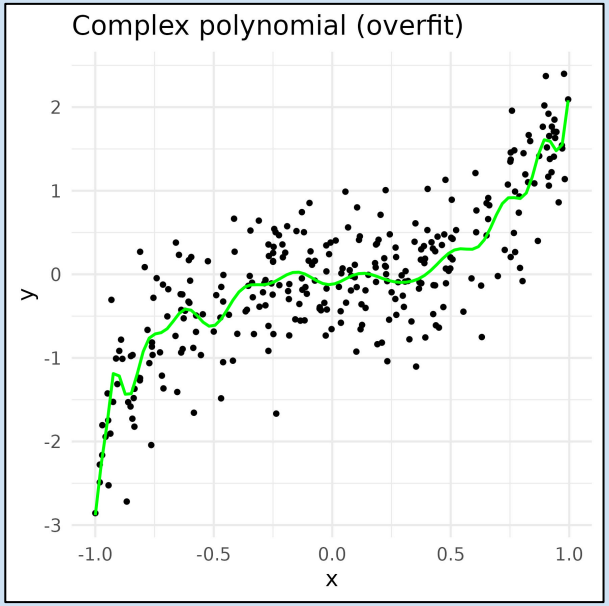
Terminology in supervised learning

- **Observations/Samples/Individuals :** set of input samples
- **Predictors/variables :** set of input variables used to predict, X
- **Response/outcome :** variable to be predicted, y
- **Training set :** data used to learn the model parameters
- **Testing set** : data used to evaluate the model's performance
- **Loss :** measure of how wrong a model's predictors were
- **Bias :** systematic error in predicting true relationship
- **Variance :** model dependency on training data





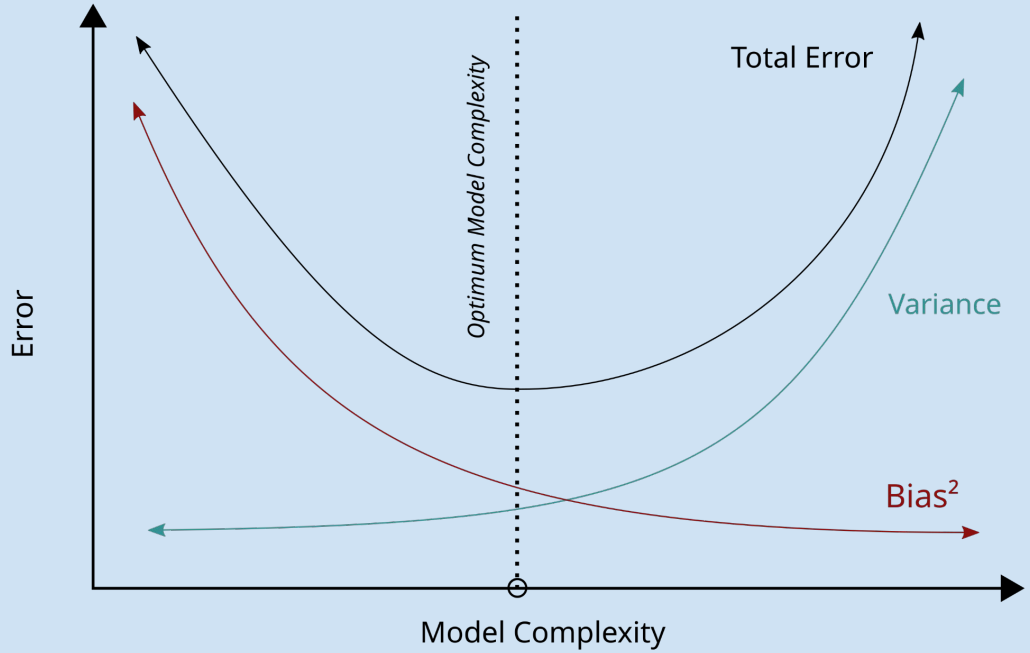




Underfitting = low variance, high bias

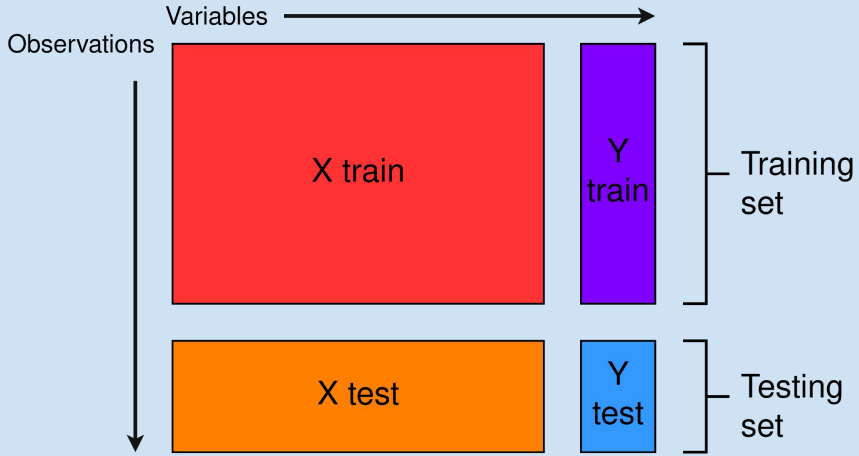
Overfitting = high variance, low bias

Bias-Variance trade-off

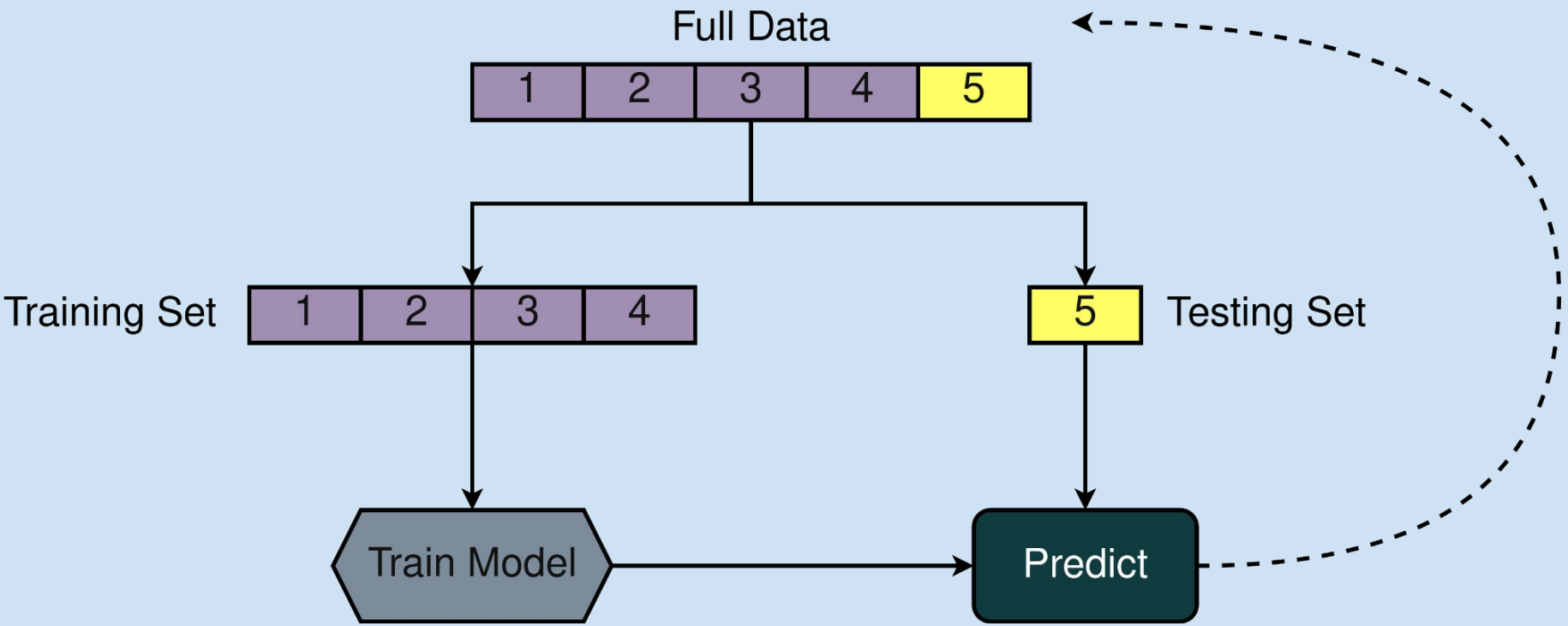


How to evaluate true model performance?

- Naïve approach : train/test split
- **Wasteful :** Reduce the size of the training set
- **Variable :** results will depend on the random data split



Cross-validation



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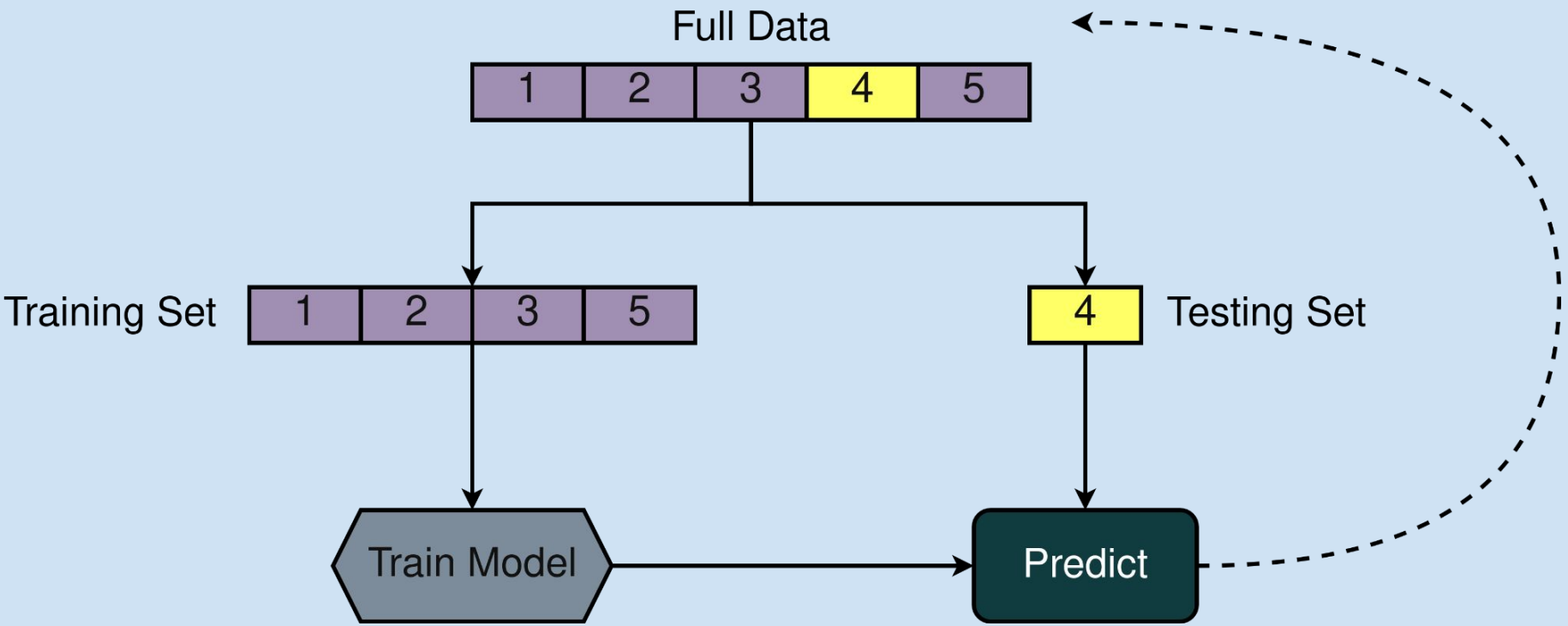
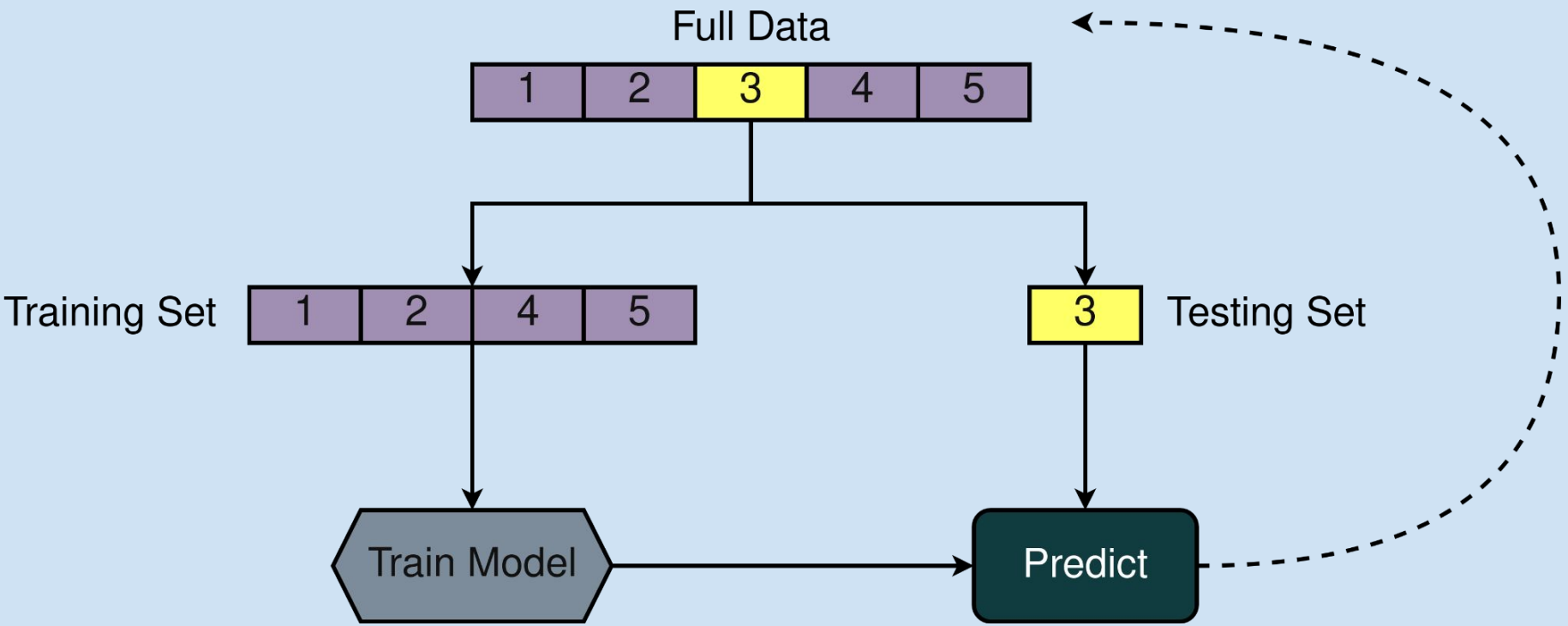


Cross-validation



The curse of dimensionality

Everything becomes worse in high dimensions…

- More risk to **overfit** by finding coincidental relationships in data
- Most predictors included in the model are **uninformative**
- Predictors are **multicollinear**
- **Signal is sparse** and drowned in noise
- Greater computational burden

Linear regression

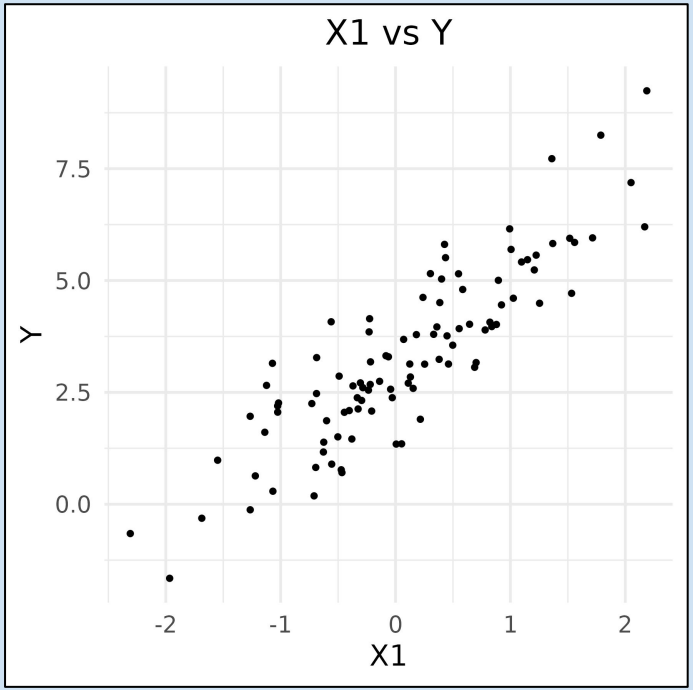
Motivation : Linear regression

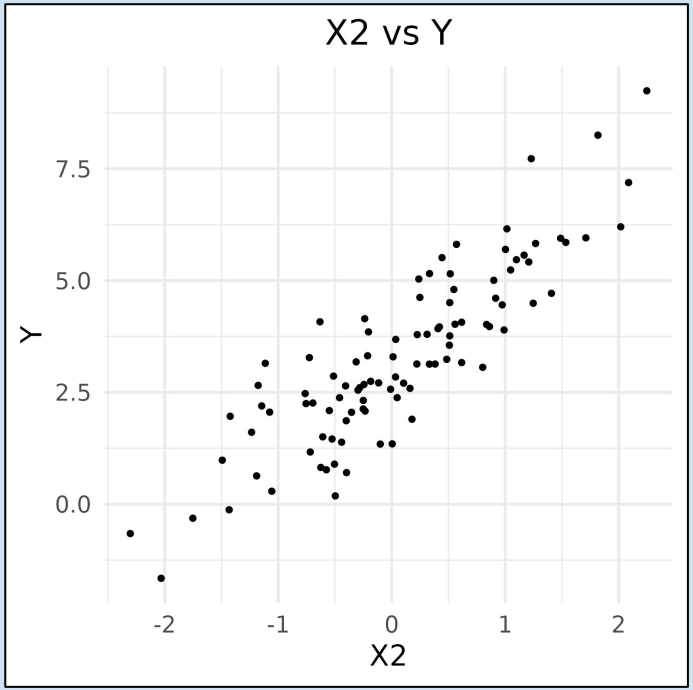
Simple data simulation

- response y
- two **highly correlated predictors x1, x2**

y	x1	x2
4.077859	-0.56047565	-0.63151630
3.852058	-0.23017749	-0.20448912
5.852272	1.55870831	1.53403913
3.684211	0.07050839	0.03575413
2.844236	0.12928774	0.03412588
5.953883	1.71506499	1.71056221

Both x1 and x2 are predictive of y





Regression of y on x1 and x2

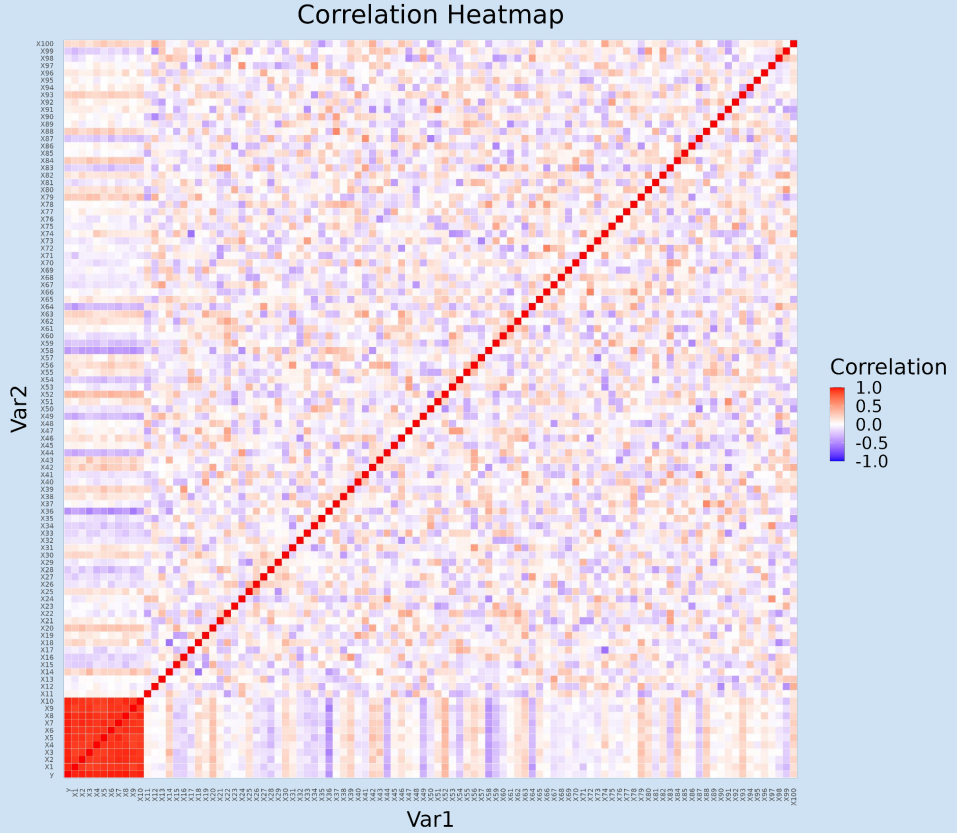
Model : y = $\alpha 0 + \alpha 1 * x1 + \alpha 2 * x2$

What is wrong here?

```
Coefficients:
            Estimate Std. Error t value Pr(>|t|)
(Intercept)  3.12389    0.09857  31.693   <2e-16 ***
x1           2.05465    0.95083   2.161   0.0332 *
x2          -0.26485    0.94944  -0.279   0.7809
```

What happens in high-dimension

- 100 predictors, 30 observations
- **First 10 predictors** multicollinear and correlated with true coefficients = 2
- **Other 90 are noise**



Linear regression output

```
Coefficients: (71 not defined because of singularities)
             Estimate Std. Error t value Pr(>|t|)
(Intercept)   6.09614        NaN     NaN      NaN
X1           17.19978        NaN     NaN      NaN
X2           -0.70897        NaN     NaN      NaN
X3           35.43475        NaN     NaN      NaN
X4          -16.38034        NaN     NaN      NaN
X5          -13.82239        NaN     NaN      NaN
```

…

```
X28         -10.63382        NaN     NaN      NaN
X29          -5.95420        NaN     NaN      NaN
X30                NA         NA      NA       NA
X31                NA         NA      NA       NA
X32                NA         NA      NA       NA
```

Some problems with linear regression

- OLS estimates are **not interpretable in multicollinear** settings
  - Coefficients are nonsensical and standard errors are high
- **In addition :** OLS is not possible when n<p!

Regularised methods

Ridge, lasso, elastic net regression

What are regularisation methods?

Regression methods estimate parameters by minimising a loss function :

$$\hat{\boldsymbol{\beta}} = \arg\min_{\beta} \underbrace{\mathcal{L}(\boldsymbol{\beta}; \boldsymbol{X}, y)}_{\text{loss function}},$$

For example :

- **Squared error loss (linear regression):**

$$\mathcal{L}(\beta; X, y) = \sum_{i=1}^{n} (y_i - x_i^\top \beta)^2$$

  - Measures the sum of squared differences between observed and predicted responses.

What are regularisation methods?

Regularised methods add a **penalty term** that *shrinks* the parameter estimates:

$$\hat{\boldsymbol{\beta}} = \arg\min_{\beta} \underbrace{\mathcal{L}(\boldsymbol{\beta}; \boldsymbol{X}, y)}_{\text{loss function}} + \underbrace{\lambda\, \Omega(\boldsymbol{\beta})}_{\text{penalty}},$$

- $\Omega(\boldsymbol{\beta})$ is a **penalty function** encoding preferences on the parameters (e.g., small magnitude, sparsity, smoothness).
- $\lambda \geq 0$ controls the strength of the penalty: higher λ imposes stronger regularisation.

What are regularisation methods?

Different penalty functions have different properties:

- **Ridge regression:**

$$\Omega(\boldsymbol{\beta}) = \sum_{j=1}^{p} \beta_j^2 = \|\boldsymbol{\beta}\|_2^2$$

- **Lasso regression:**

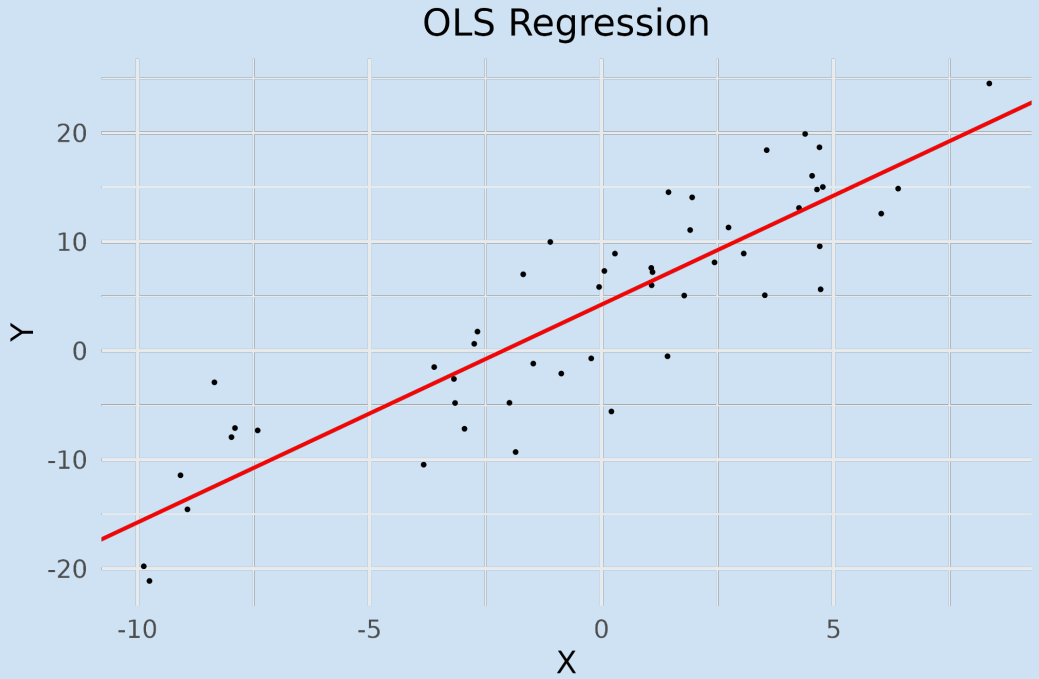
$$\Omega(\boldsymbol{\beta}) = \sum_{j=1}^{p} |\beta_j| = \|\boldsymbol{\beta}\|_1$$

- **Elastic net regression:**

$$\Omega(\boldsymbol{\beta}) = \alpha\|\boldsymbol{\beta}\|_1 + (1-\alpha)\|\boldsymbol{\beta}\|_2^2, \quad \alpha \in [0,1]$$

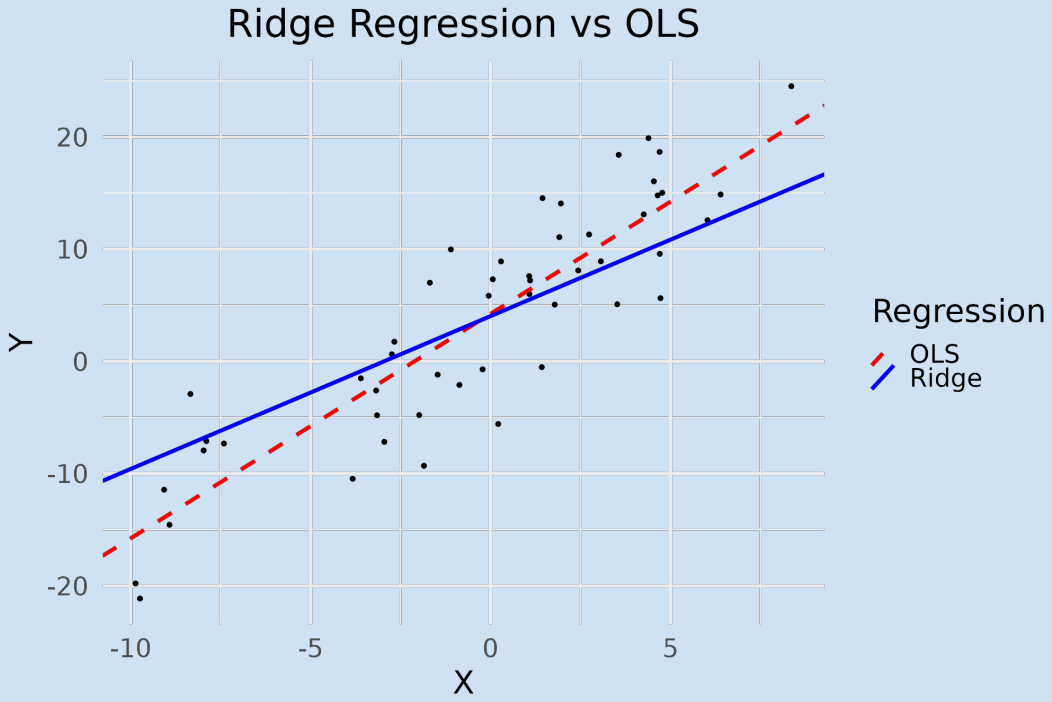
What does this mean in practice?

- OLS based on 1 predictor of Y



What does this mean in practice?

- Ridge regression *shrinks* the coefficient of X
- The line is **less specific to the training data**



What happens in high-dimension

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- **First 10 predictors** multicollinear and correlated with true coefficients = 2
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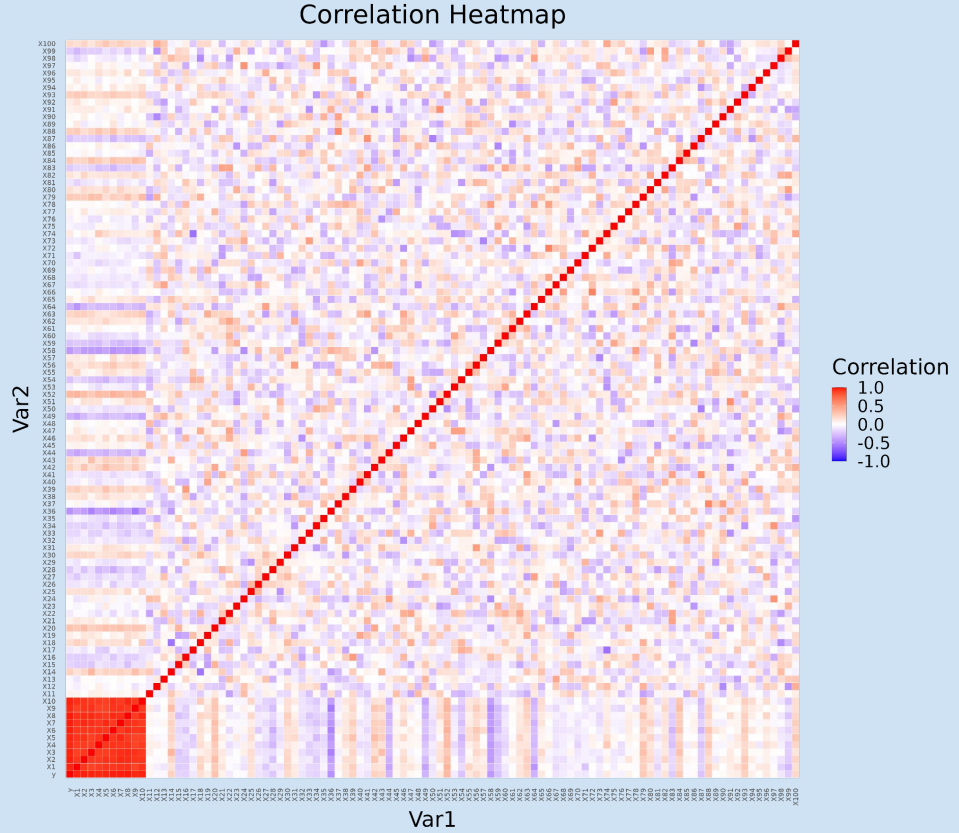


Ridge regression, small penalty term

Predictor	Coefficient
(Intercept)	4.199203850
X1	1.722511160
X2	1.563138138
X3	1.618239257
X4	1.545498028
X5	1.647217751
X6	1.653767428
X7	1.607043560
X8	1.602866955
X9	1.541996515
X10	1.522906678
X11	-0.083351967
X12	-0.217714240
X13	0.041424806

- Coefficients for first 10 predictors are **underestimated** (penalised), but reasonable

Ridge regression, large penalty term

Predictor	Coefficient
(Intercept)	5.824742599
X1	0.920329883
X2	0.874152089
X3	0.900291651
X4	0.876054764
X5	0.927766602
X6	0.921230947
X7	0.895915991
X8	0.892476809
X9	0.860369210
X10	0.887186751
X11	-0.068315490
X12	-0.169504537
X13	0.078989765

- Coefficients even more penalised
- However, coefficients for the noise predictors are still non-zero
- In fact, the ridge penalty **cannot** shrink coefficients all the way to zero

Lasso regression - regularisation and variable selection

- Lasso regression solves this problem by using a penalty which allows coefficients to be **shrunk to exactly 0**
- This allows uninformative features to be removed from the model and for informative features to be easier to interpret !

- **Lasso regression:**

$$\Omega(\boldsymbol{\beta}) = \sum_{j=1}^{p} |\beta_j| = \|\boldsymbol{\beta}\|_1$$

Lasso regression - small penalty term

Predictor	Coefficient
(Intercept)	3.2138461
X1	2.9146758
X2	2.6461699
X3	1.6067177
X4	0.8452229
X5	2.7256999
X6	2.0209490
X7	0.3937528
X8	2.2824053
X9	2.1998183
X10	2.2016101
X11	0.0000000
X12	0.0000000
X13	0.0000000

- Now, we only have non-zero coefficients for the first 10 predictors
- The model is more ***sparse and interpretable***

Lasso regression - large penalty term

Predictor	Coefficient
(Intercept)	5.7733620
X1	0.3473931
X2	0.0000000
X3	0.1216453
X4	0.0000000
X5	0.1664646
X6	2.9953686
X7	0.0000000
X8	0.0000000
X9	1.6641831
X10	1.3486280
X11	0.0000000
X12	0.0000000
X13	0.0000000

- A slight problem : if predictors are **multicollinear**, lasso tends to **select one** and discards the rest
- This could lead to **erroneous interpretations** of which predictors are important

Elastic Net regression - mix of lasso and ridge

- Elastic net regression solves this problem by *combining* the penalty terms of lasso and ridge

- **Elastic net regression:**

$$\Omega(\boldsymbol{\beta}) = \alpha\|\boldsymbol{\beta}\|_1 + (1-\alpha)\|\boldsymbol{\beta}\|_2^2, \quad \alpha \in [0,1]$$

Elastic Net regression - large penalty term

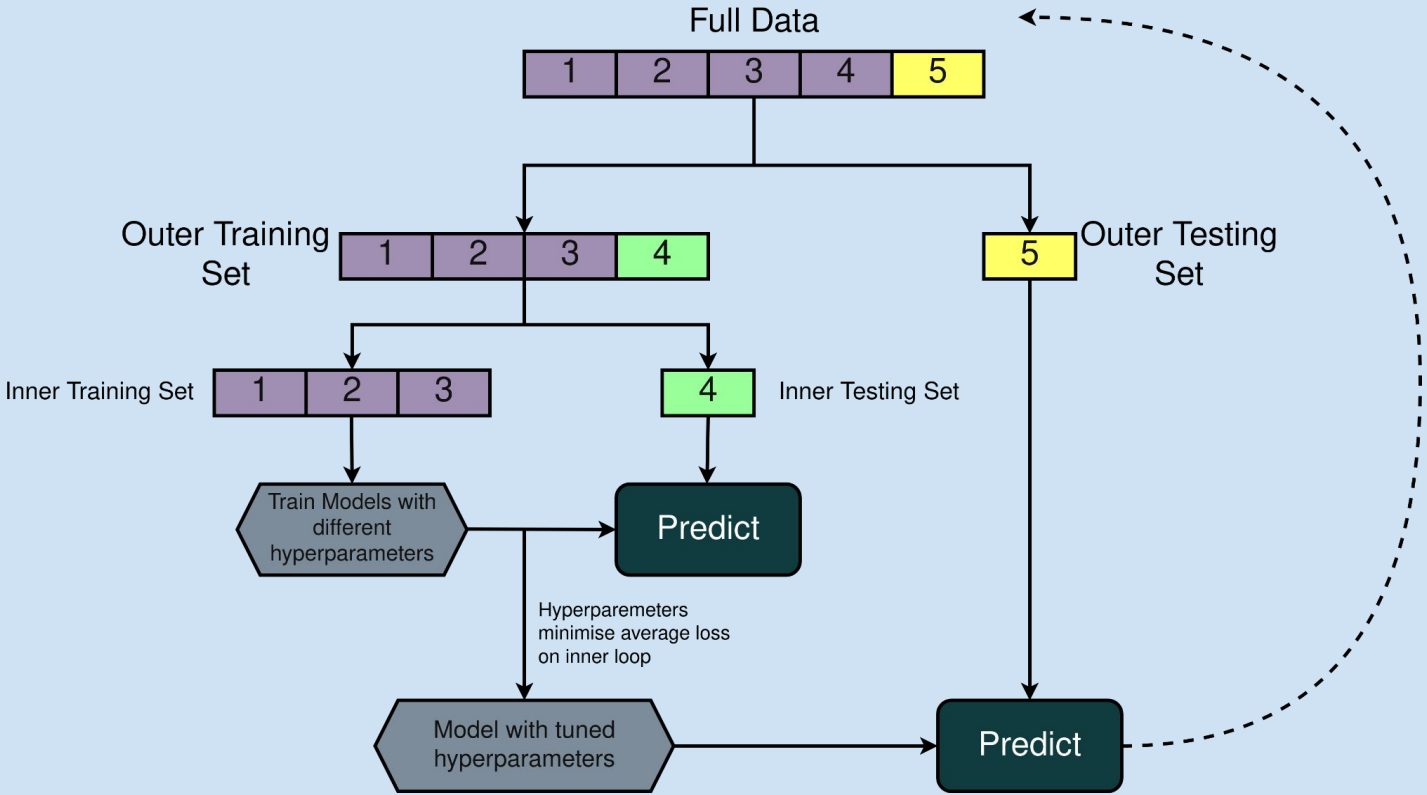
Predictor	Coefficient
(Intercept)	3.591873
X1	2.031664
X2	1.921551
X3	1.659616
X4	1.575456
X5	2.013029
X6	1.930660
X7	1.108460
X8	1.760805
X9	1.775735
X10	1.899880
X11	0.000000
X12	0.000000
X13	0.000000

- Elastic net combines the properties of ridge and lasso
- **Ridge :** tends to shrink multicollinear predictors in proportion, but cannot *select* predictors
- **Lasso :** can select predictors, but may discard important ones when multicollinear
- **Elastic Net :** Can select groups of multicollinear predictors

Summary on regularised methods

	Handles overfitting?	Handles multicollinearity?	Variable selection?
Linear regression	no	Nonsensical estimates, large error	no
Ridge regression	Reduces chance of overfitting with penalisation	yes	no
Lasso regression	Reduces chance of overfitting with penalisation	Yes, but tendency to discard predictors in multicollinear groups	yes
Elastic net regression	Reduces chance of overfitting with penalisation	Selects groups of multicollinear predictors	yes

How to choose the hyperparameters? Nested CV



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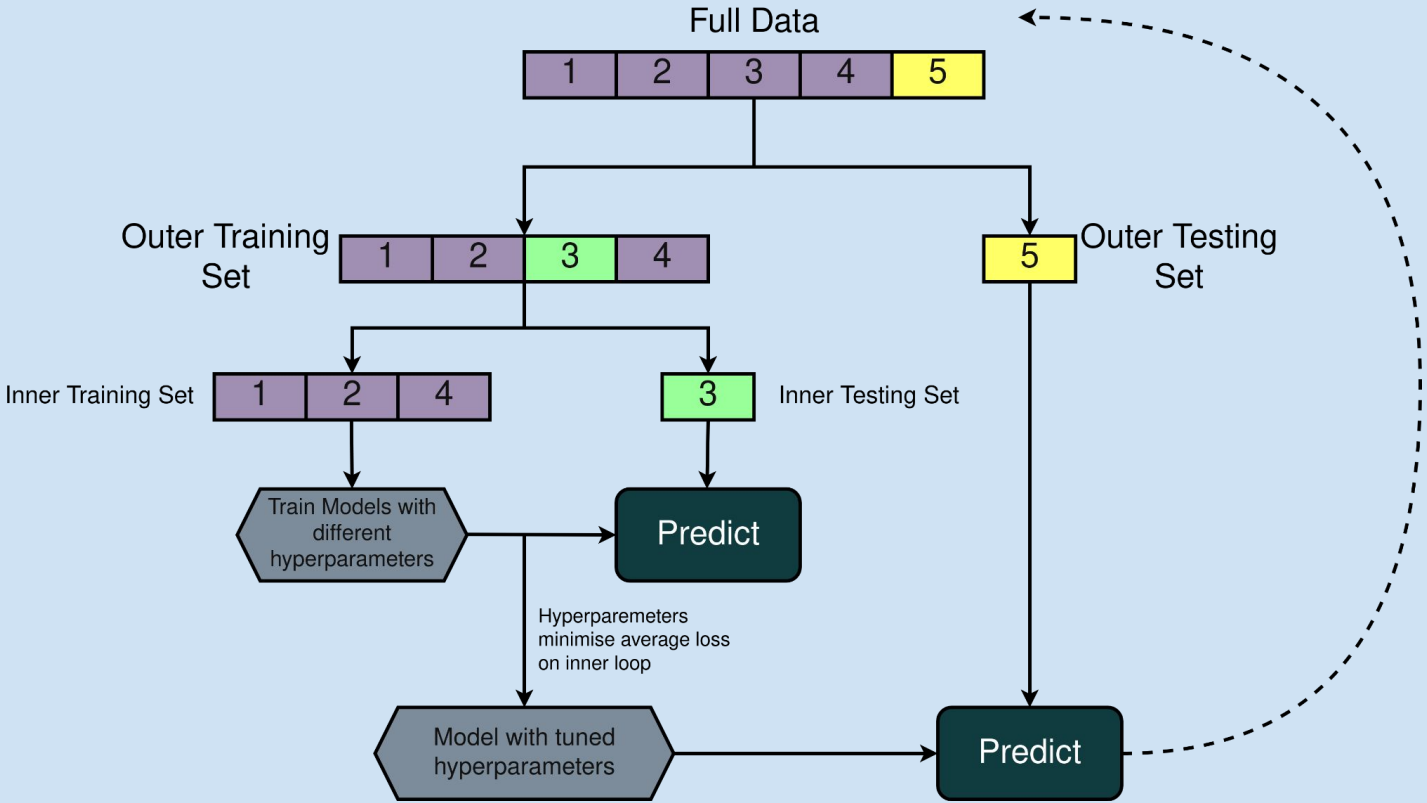

Latent Variable Methods

Principal Component Regression

Latent variable approaches

- ***Latent*** **= hidden**
- A latent variable cannot be observed but can be estimated from observable variables
- **Example :** socio-economic status
  - This variable cannot be directly measured but could be constructed from a combination of e.g. income, education level, occupation, housing quality

Motivation : Linear regression

Simple data simulation

- response y
- two **highly correlated predictors x1, x2**

y	x1	x2
4.077859	-0.56047565	-0.63151630
3.852058	-0.23017749	-0.20448912
5.852272	1.55870831	1.53403913
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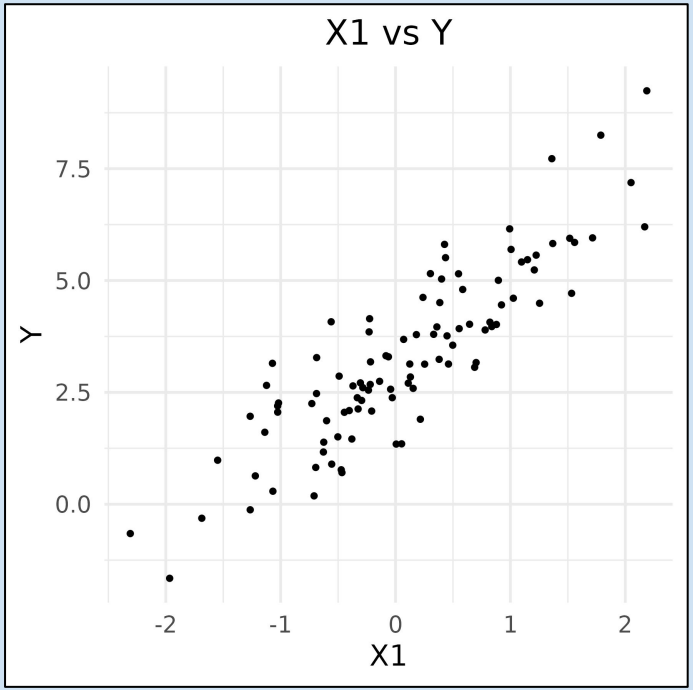
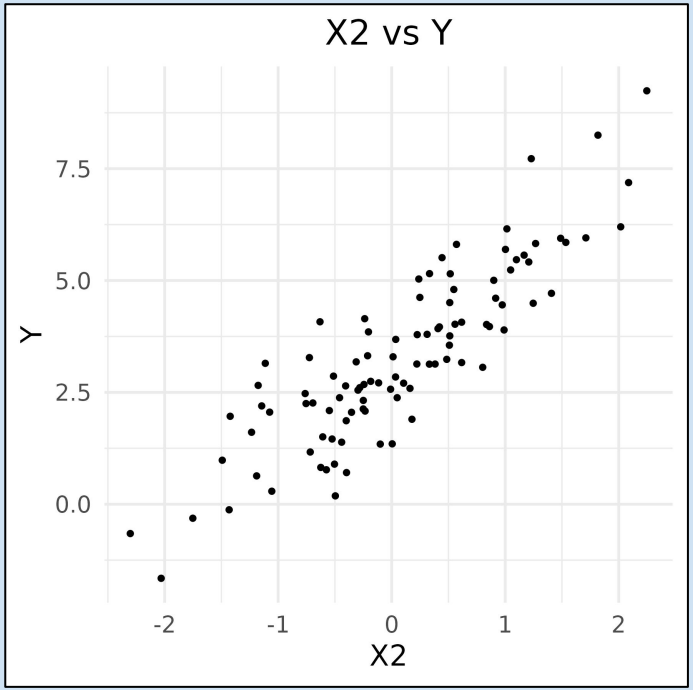
Both x1 and x2 are predictive of y





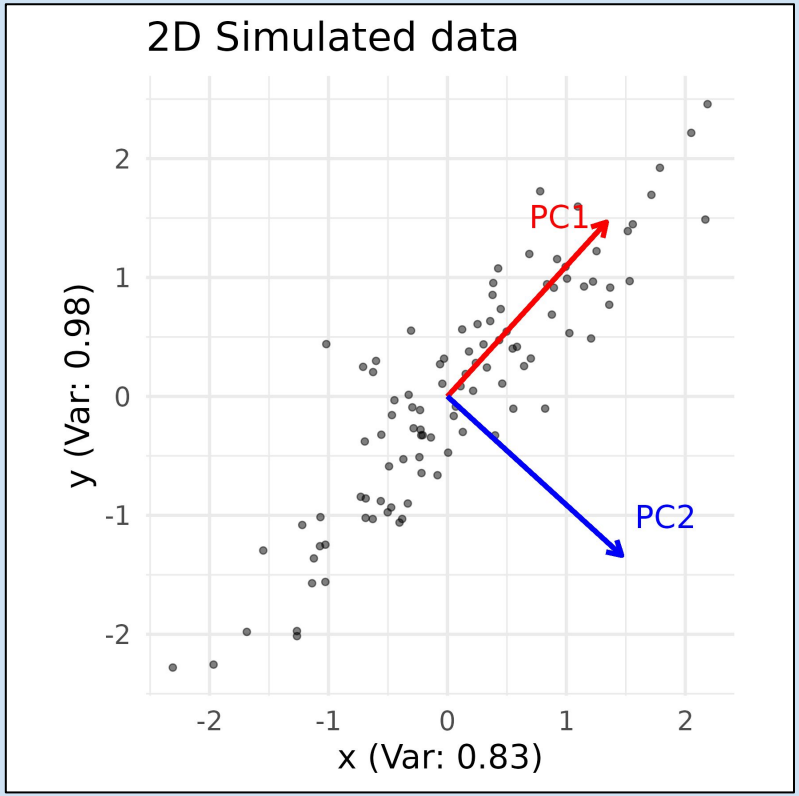
Linear regression fails with multicollinear predictors

```
Coefficients:
            Estimate Std. Error t value Pr(>|t|)
(Intercept)  3.12389    0.09857  31.693   <2e-16 ***
x1           2.05465    0.95083   2.161   0.0332 *
x2          -0.26485    0.94944  -0.279   0.7809
```

Idea : transform the data to capture signal in a smaller number of uncorrelated variables

Principal Component Analysis reminder

- **Principal Components** are weighted combinations of the original variables
- In this example :
  - PC1 = 0.67x + 0.74y
  - PC2 = 0.74x - 0.67y
- The first PCs capture the majority of the variability in the data
- By construction, PCs are completely uncorrelated (orthogonality)



Principal Component Regression

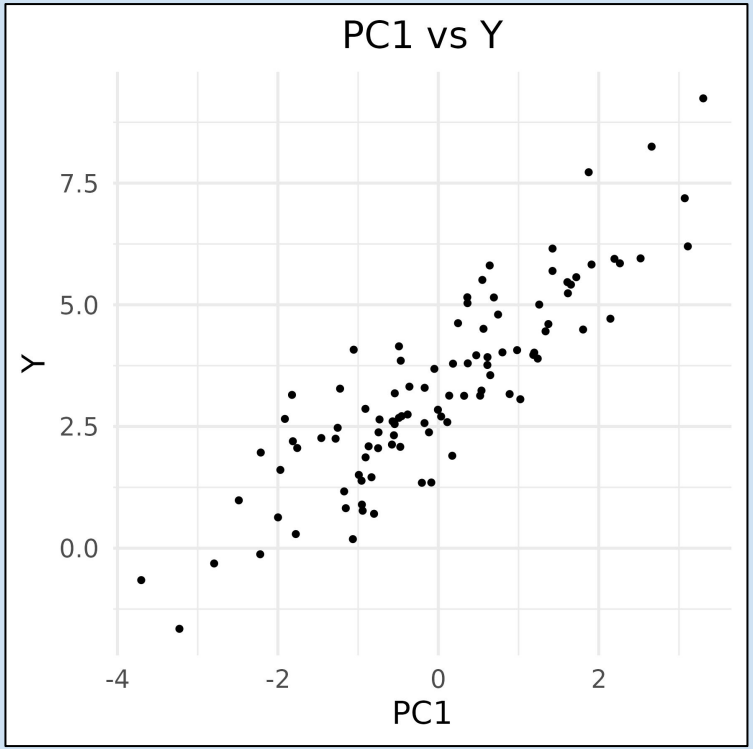
1. **Transform the data** with PCA
2. **Reduce the dimension** by discarding PCs which do not explain much of the variability in the data (scree plot)
3. **Perform regression** using reduced number of PCs instead of original predictors

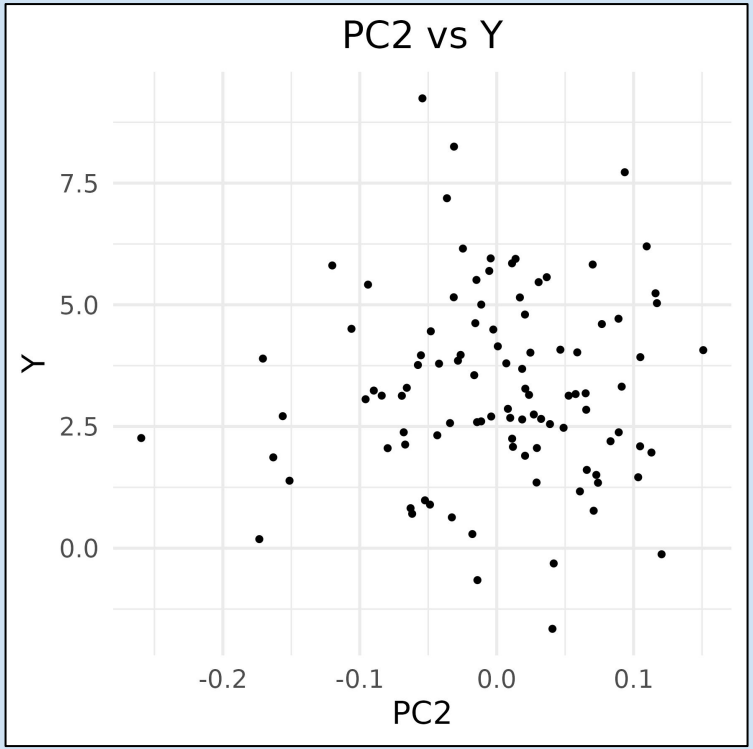
Transformation of the data

- PC1 = 0.71*x1 + 0.71*x2
- PC2 = 0.71*x1 - 0.71*x2
- cor(PC1, PC2) = 0

y	x1	x2	PC1	PC2
4.077859	-0.56047565	-0.63151630	-1.054901952	0.046499773
3.852058	-0.23017749	-0.20448912	-0.468365196	-0.028310420
5.852272	1.55870831	1.53403913	2.263632953	0.011188532
3.684211	0.07050839	0.03575413	-0.049405709	0.018578749
2.844236	0.12928774	0.03412588	-0.005133536	0.065372635
5.953883	1.71506499	1.71056221	2.521446325	-0.004383515

PC1 is related to Y but PC2 is not





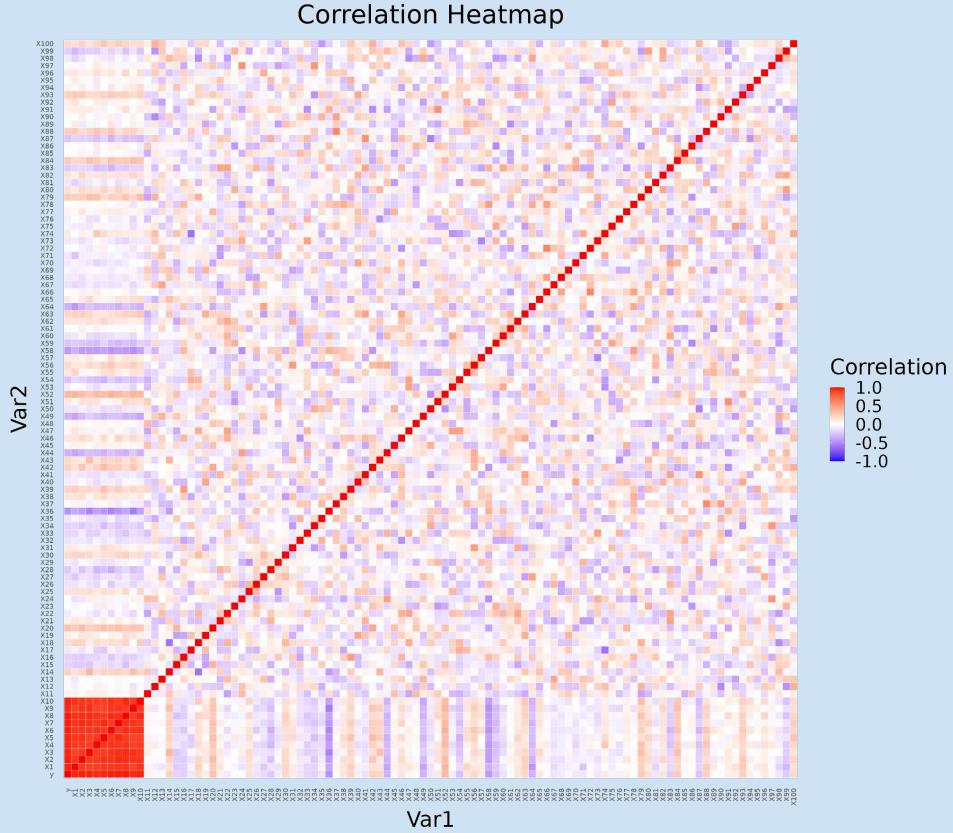
Linear regression on principal components

Model : y = $\alpha 0 + \alpha 1 * PC1 + \alpha 2 * PC2$

	Estimate	Std. Error	t value	Pr(>|t|)	
(Intercept)	3.30128	0.09513	34.703	<2e-16	***
PC1	1.20502	0.06770	17.799	<2e-16	***
PC2	0.89752	1.27661	0.703	0.484	

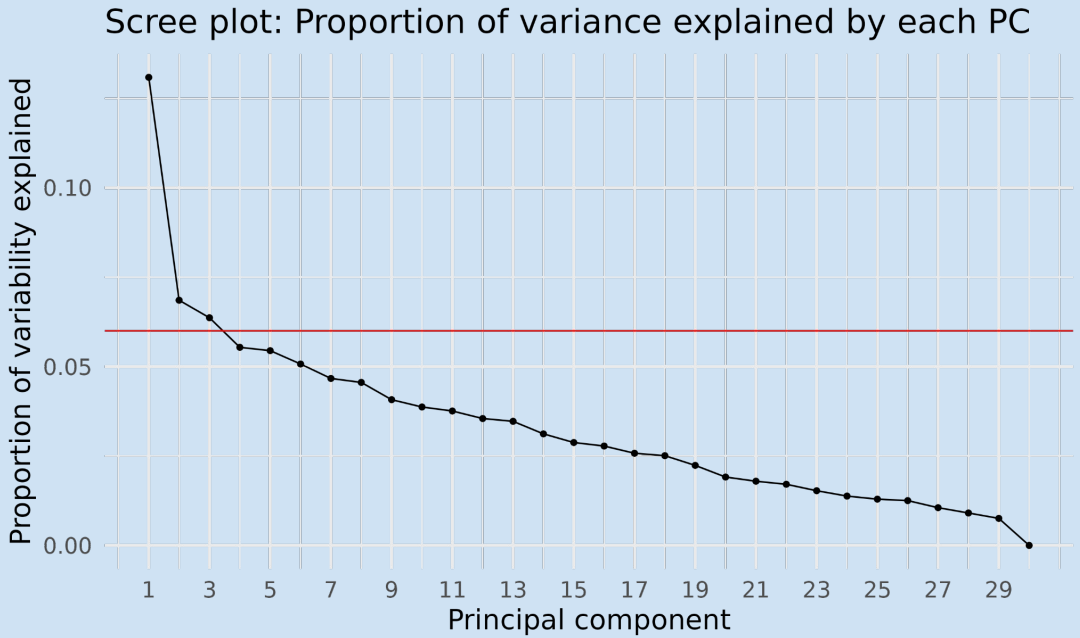
PCR in high-dimension

- 100 predictors, 30 observations
- **First 10 predictors** multicollinear and correlated with true coefficients = 2
- **Other 90 are noise**

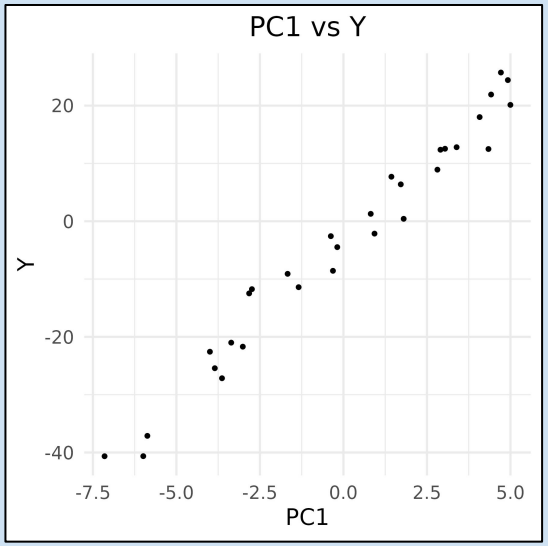


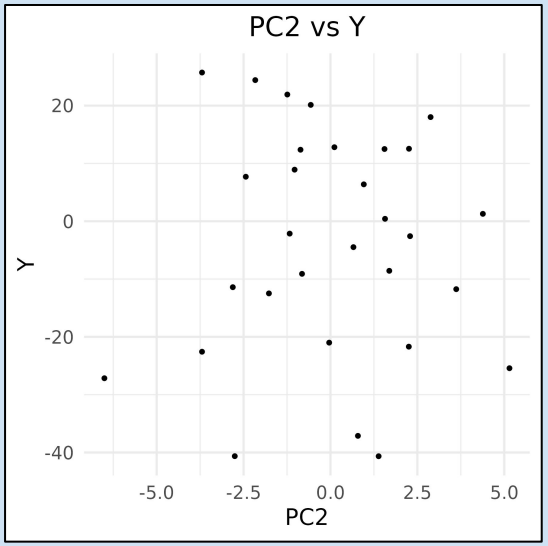
PCR in high-dimension : choosing the number of PCs

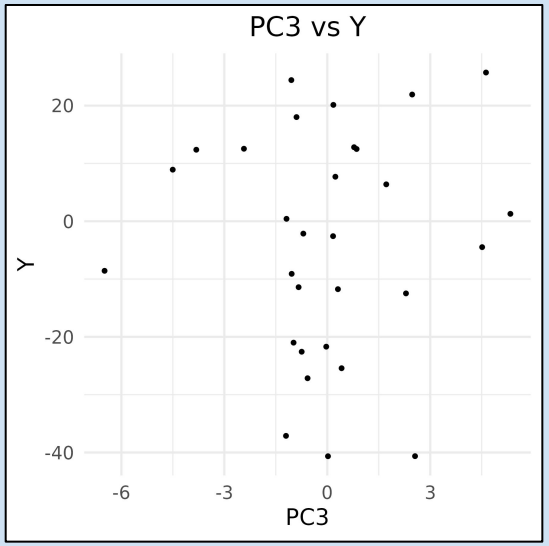
- First few PCs capture a lot of the variance
- We will keep 3 for the regression (elbow method)



Examine the new predictors







Linear regression output

```
Coefficients:
            Estimate Std. Error t value Pr(>|t|)
(Intercept) -3.78726    0.61919  -6.116 1.82e-06 ***
PC1          5.29136    0.17409  30.394  < 2e-16 ***
PC2         -0.03108    0.24054  -0.129    0.898
PC3          0.34242    0.24961   1.372    0.182
```

How can we interpret the results?

Look at the *loading weights* for the important PCs

These give the contributions of each variable to the PC

- As expected, the 10 truly associated predictors all contribute to PC1, the most predictive PC

	Predictor	Loading
X8	X8	0.26683184
X9	X9	0.26669971
X3	X3	0.26490462
X1	X1	0.26336880
X10	X10	0.26304947
X7	X7	0.26167679
X2	X2	0.26164914
X6	X6	0.25900956
X5	X5	0.25889924
X4	X4	0.25757469
X80	X80	-0.12902728
X49	X49	0.12614039
X45	X45	-0.12319149

Maths of PC regression

Principal Component Regression

- $X \in \mathcal{R}^{n \times p}$ matrix with n rows of observations of p columns of predictors,
- y a continuous outcome,
- both predictors and outcome centered, scaled

Maths of PC regression

1. **Find** $PC_1 \in \mathbb{R}^{n\times 1}$, a linear combination of the predictors:

$$PC_1 = Xw_1,$$

where

- $w_1 \in \mathbb{R}^{p\times 1}$ is the **weight** vector that defines the linear combination of the predictors, chosen to **maximize the variance** of the score:

$$w_1 = \arg\max_{\|w\|=1} \mathrm{Var}(Xw)$$

2. **Adjust** (deflate) X to remove the contribution of the first principal component:

$$p_1 = \frac{X^\top PC_1}{PC_1^\top PC_1} \qquad \text{(PC loading vector)}$$

$$X_1 = X - PC_1 p_1^\top.$$

Maths of PC regression

3. **Repeat** to find additional principal component scores $PC_2, PC_3, \ldots$ using deflated predictors $X_1, X_2, \ldots$.
4. **Keep** p^* informative PCs (choose with cumulative proportion of variance explained)
5. **Regression step:** regress y on $PC = (PC_1, ..., PC_{p^*})$

A couple of problems with PC regression

- **Explaining the variability in the predictors does not guarantee explaining the variability in the response!**
  - In this example, PC2 and PC3 were useless predictors

- **Every predictor contributes a non-zero weight to every PC**
  - i.e. the more useless predictors, the more we accumulate noise in the PCs
  - Perhaps this could be solved with regularisation on the loading weights?

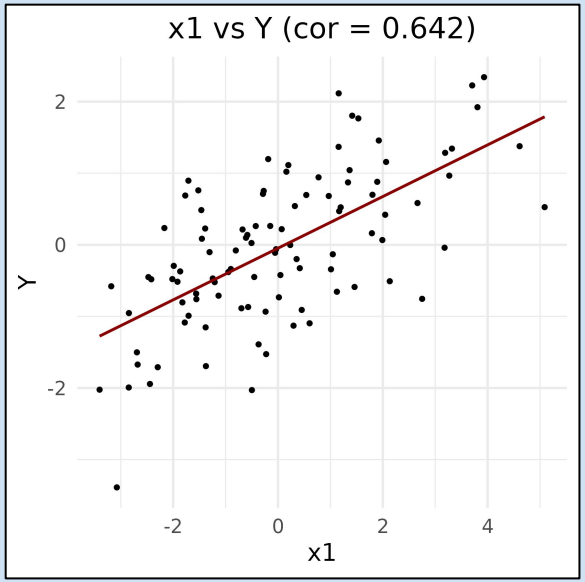
Latent Variable Methods

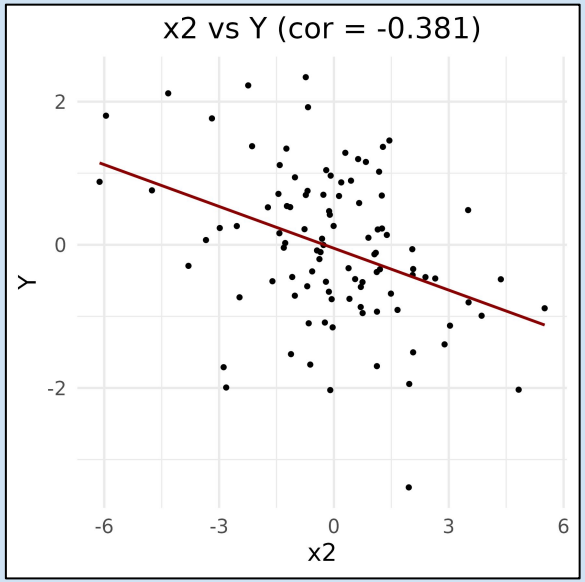
Partial Least Squares

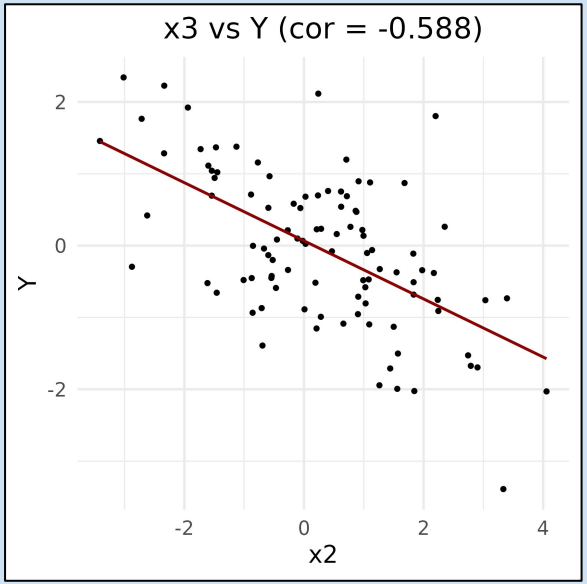
Idea of partial least squares

- PCA forms latent variables by linear combinations which best explain the variability in X
- PLS forms latent variables by linear combinations which best explain the variability in Y!
    - Like PCA, these latent variables are **uncorrelated**

Low dimensional example

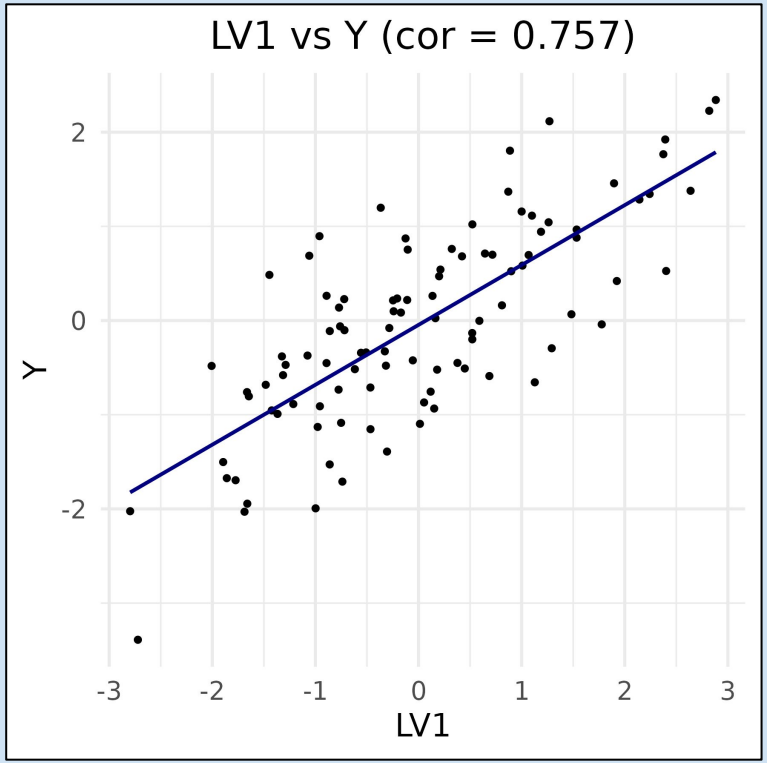






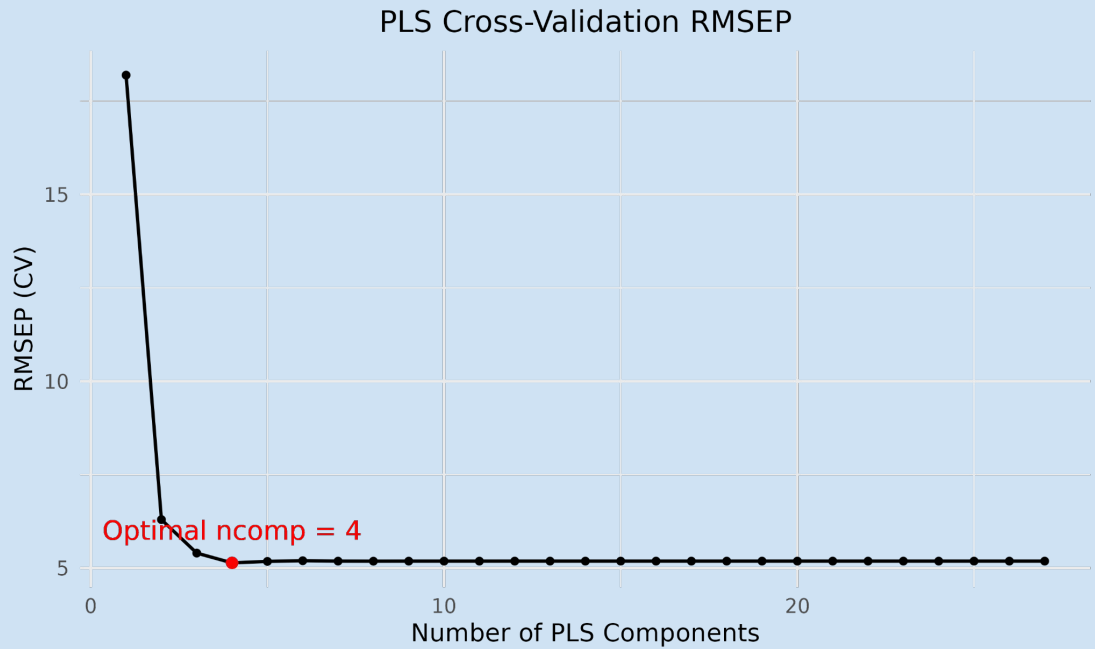
Low-dimensional example

- **We combine the original predictors** into a latent variable which has **more correlation with Y** than any of the original predictors alone



High-dimensional example - tuning number of LVs to keep

- CV error is pretty stable after 4 but we prefer smaller models (parsimony)
- We can therefore perform linear regression using the 4 first latent variables



High-dimensional example - linear regression output

- All 4 LVs are associated with Y, with decreasing strength

```
Coefficients:
                Estimate Std. Error t value Pr(>|t|)
(Intercept)      3.19182    0.06270  50.909  < 2e-16 ***
LV_scoresComp 1  5.04198    0.01826 276.195  < 2e-16 ***
LV_scoresComp 2  1.27878    0.02840  45.023  < 2e-16 ***
LV_scoresComp 3  0.64658    0.03839  16.844 3.72e-15 ***
LV_scoresComp 4  0.29620    0.03682   8.044 2.13e-08 ***
---
```

Interpretation of LV1

- Similar with PC regression, we can interpret the loading weights of the important LVs
- LV1 is dominated by the truly important variables X1,...,X10

variable	loading
X8	0.2756075
X2	0.2738030
X3	0.2736750
X1	0.2721593
X4	0.2690283
X7	0.2683456
X10	0.2663741
X9	0.2660805
X6	0.2658825
X5	0.2643691
X93	-0.1397060
X70	-0.1359411

Interpretation of LV2

- LV2 is correlated with Y, but it is formed of variables which are just noise…

variable	loading
X48	0.2727252
X55	0.2478832
X91	-0.2429874
X58	0.2019630
X87	0.1913649
X46	0.1901583
X67	-0.1892773
X88	0.1750529

Maths of PLS regression

Partial least squares

- $X \in \mathcal{R}^{n \times p}$ matrix with n rows of observations of p columns of predictors,
- y a continuous outcome,
- both predictors and outcome centered, scaled

Maths of PLS regression

1. **Find** $LV_1 \in \mathcal{R}^{n \times 1}$, linear combination of the predictors:

$$LV_1 = Xw_1$$

Where:

- $w_1 \in \mathcal{R}^{p \times 1}$ is the **weight vector** that defines the linear combination of the predictors, chosen to **maximize the covariance** between the latent variable LV_1 and y:

$$w_1 = \arg \max_{\|w\|=1} \text{Cov}(Xw, y)$$

2. **Adjust** (deflate) X to remove the influence of the first LV:

$$p_1 = \frac{X^\top LV_1}{LV_1^\top LV_1}.$$

$$X_1 = X - LV_1 p_1^T$$

Where p_1 is a vector that relates the first latent variable LV_1 back to the original predictors.

Maths of PLS regression

3. **Repeat** to find additional latent variables $LV_2, LV_3, \ldots$ using deflated predictors $X_1, X_2, \ldots$.
4. **Keep** p^* informative latent variables (choose with cross-validation)
5. **Regression step** : regress y on $LV = (LV_1, ..., LV_{p^*})$

Problems with PLS

- **Every predictor still contributes a non-zero weight to every LV**
  - This is likely to reduce predictive accuracy as we accumulate noise
- **High potential for overfitting**
  - The more predictors available, the more likely we are to find some combination of noise which produces a predictive latent variable

Latent Variable + Regularisation

Sparse Partial Least Squares

Idea of sparse partial least squares

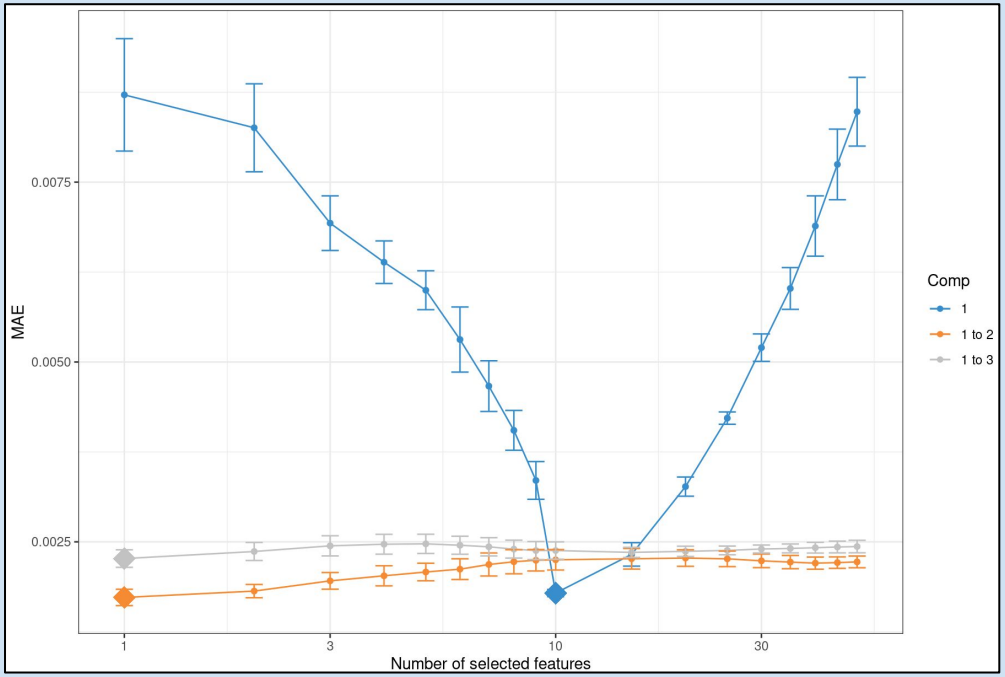
- Latent variable methods like PCr and PLSr deal well with multicollinearity but still suffer in the high-dimensional setting
  - Overfitting, poor performance due to noise accumulation, difficulties in interpretation…

- Idea : combine partial least squares with lasso regularisation to construct ***sparse latent variables***

sPLS = PLS + LASSO

High-dimensional example - tuning

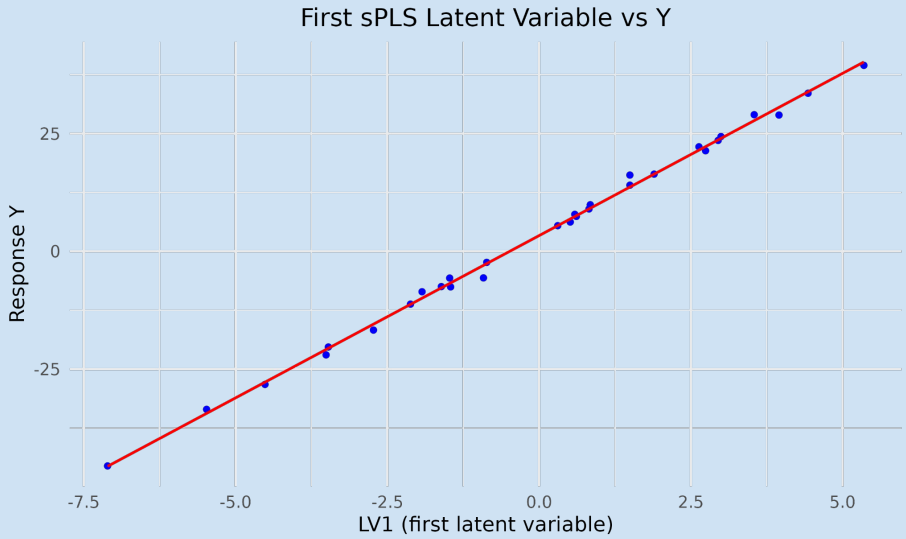
- In MixOmics package - 2 hyperparameters to tune for sPLS
  - Number of components to keep
  - Number of variables to keep on each component (equivalent to tuning sparsity parameter)
- This plot says 1 component with 10 features is optimal



Look at LV1

The 10 truly important variables were selected for LV1, no others were selected

	value.var
X7	0.3244752
X4	0.3193589
X5	0.3190780
X1	0.3173010
X8	0.3160257
X10	0.3153129
X6	0.3143405
X2	0.3137792
X9	0.3130805
X3	0.3092797



Maths of sPLS

Sparse partial least squares (sPLS)

- $X \in \mathcal{R}^{n \times p}$ matrix with n rows of observations of p columns of predictors,
- y a continuous outcome,
- both predictors and outcome centered, scaled

1. **Find** $LV_1 \in \mathcal{R}^{n \times 1}$, linear combination of the predictors:

$$LV_1 = Xw_1$$

Where:

- $w_1 \in \mathcal{R}^{p \times 1}$ is the **sparse weight vector** that defines the linear combination of the predictors, chosen to **maximize the covariance** between the latent variable LV_1 and y while enforcing sparsity via an L1 penalty:

$$w_1 = \arg \max_{\|w\|_2 = 1} \Big[\mathrm{Cov}(Xw, y) - \lambda \|w\|_1 \Big],$$

where $\|w\|_1 = \sum_{j=1}^{p} |w_j|$ is the L1 norm of w and $\lambda > 0$ controls the degree of sparsity (larger λ $\rightarrow$ more zeros in w_1).

Take-Home messages

	Regularisation?	Sparsity/variable selection?	Handles Multicollinearity?	Predictive power?
Linear regression	no	no	Fails in multicollinear settings	Bad
Ridge regression	Yes, L2 penalty	No	Yes	Good
Lasso regression	Yes, L1 penalty	Yes	Tendency to discard predictors in multicollinear groups	Slightly worse than ridge
Elastic net regression	Yes, L1 + L2 penalty	Yes	Yes, selects groups of multicollinear predictors	Good
Principal component regression	No	No	Yes	PCs are not necessarily predictive
Partial least squares	No	No	Yes	Good but can accumulate noise in predictors
Sparse partial least squares	Yes, L1 penalty	Yes	Yes	Good

Conclusion

- **Curse of high-dimensionality makes predictive modelling difficult**, specialist methods are required
  - Main problems : large amount of irrelevant predictors, multicollinearity, overfitting
- **Regularisation** approaches
  - **Mitigate overfitting** by reducing the impact of the data on the parameter estimates
  - Allow for **variable selection**
- **Latent variable** approaches allow to
  - Find **parsimonious “hidden” signals** in the data
- LV + regularisation approaches are powerful (sPLS)

Practical work

We are going to analyse a public dataset containing transcriptomic samples from participants vaccinated with seasonal influenza vaccine. The goal will be to predict the vaccine-induced immune response (antibodies) using the earlier gene expression response. We will focus on

- Implementation and evaluation of supervised regression methods with cross-validation
- Automation and optimisation of model tuning
- Model interpretability

Complete the R markdown file

PHDS_omics_supervisedlearning_2025_questions.Rmd