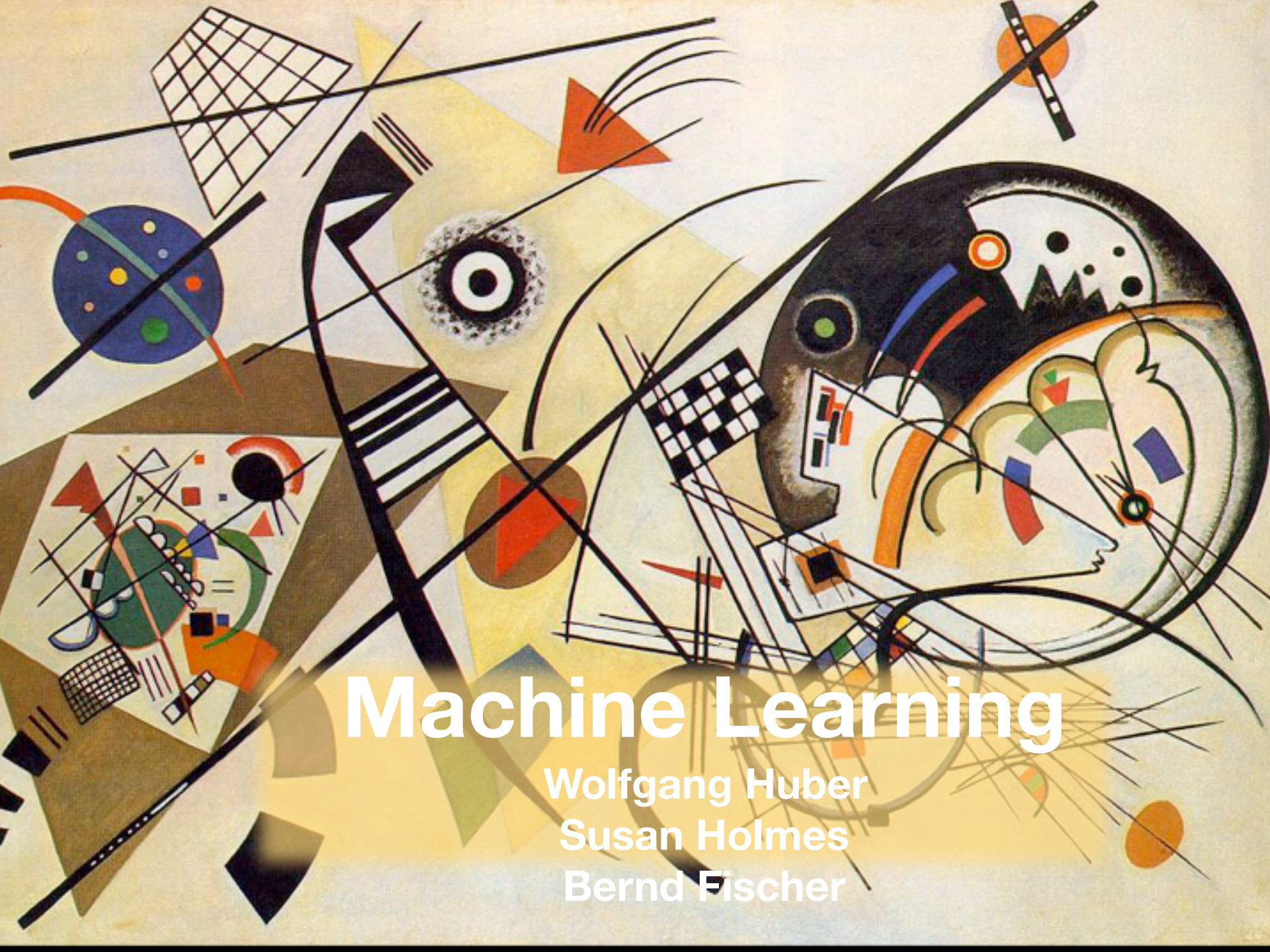


Machine Learning

Wolfgang Huber
Susan Holmes
Bernd Fischer

What you will learn in this lecture

- Exemplary applications
- Linear discriminant analysis
- How to get non-linear decision boundaries using kernel methods
- Overfitting
- Curse of dimensionality
- Regularization, generizability and model complexity
- Using cross-validation to
  - — tune parameters
  - — assess performance

The diabetes data

```
library("readr")
library("magrittr")
diabetes = read_csv("../data/diabetes.csv", col_names = TRUE)
diabetes

## # A tibble: 144 x 7
##       id relwt glufast glutest steady insulin group
##    <int> <dbl>   <int>   <int>  <int>   <int> <int>
##  1     1  0.81      80     356    124      55     3
##  2     3  0.94     105     319    143     105     3
##  3     5  1.00      90     323    240     143     3
##  4     7  0.91     100     350    221     119     3
##  5     9  0.99      97     379    142      98     3
##  6    11  0.90      91     353    221      53     3
##  7    13  0.96      78     290    136     142     3
##  8    15  0.74      86     312    208      68     3
##  9    17  1.10      90     364    152      76     3
## 10    19  0.83      85     296    116      60     3
## # ... with 134 more rows

diabetes$group %<>% factor
```

We used the forward-backward pipe operator `%<>%` to convert the `group` column into a factor. The plot is shown in Figure 13.4.

```
library("ggplot2")
library("reshape2")
ggplot(melt(diabetes, id.vars = c("id", "group")),
       aes(x = value, col = group)) +
 geom_density() + facet_wrap( ~variable, ncol = 1, scales = "free") +
 theme(legend.position="bottom")
```

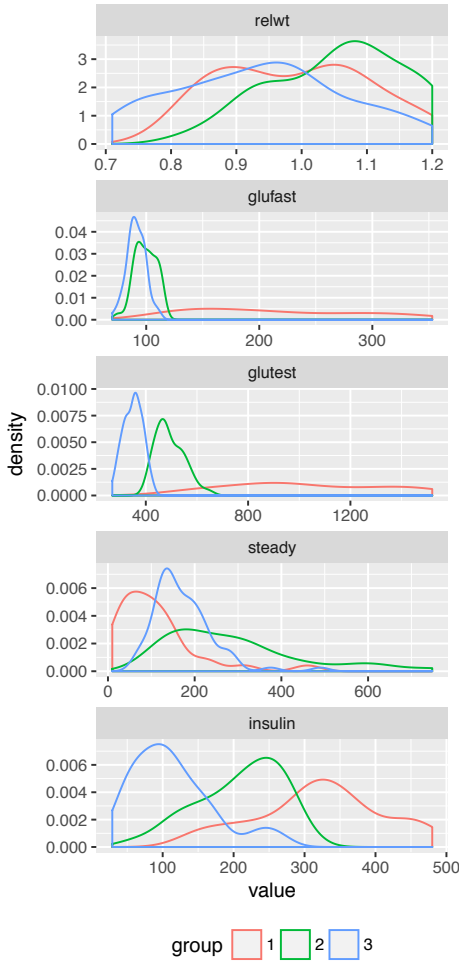
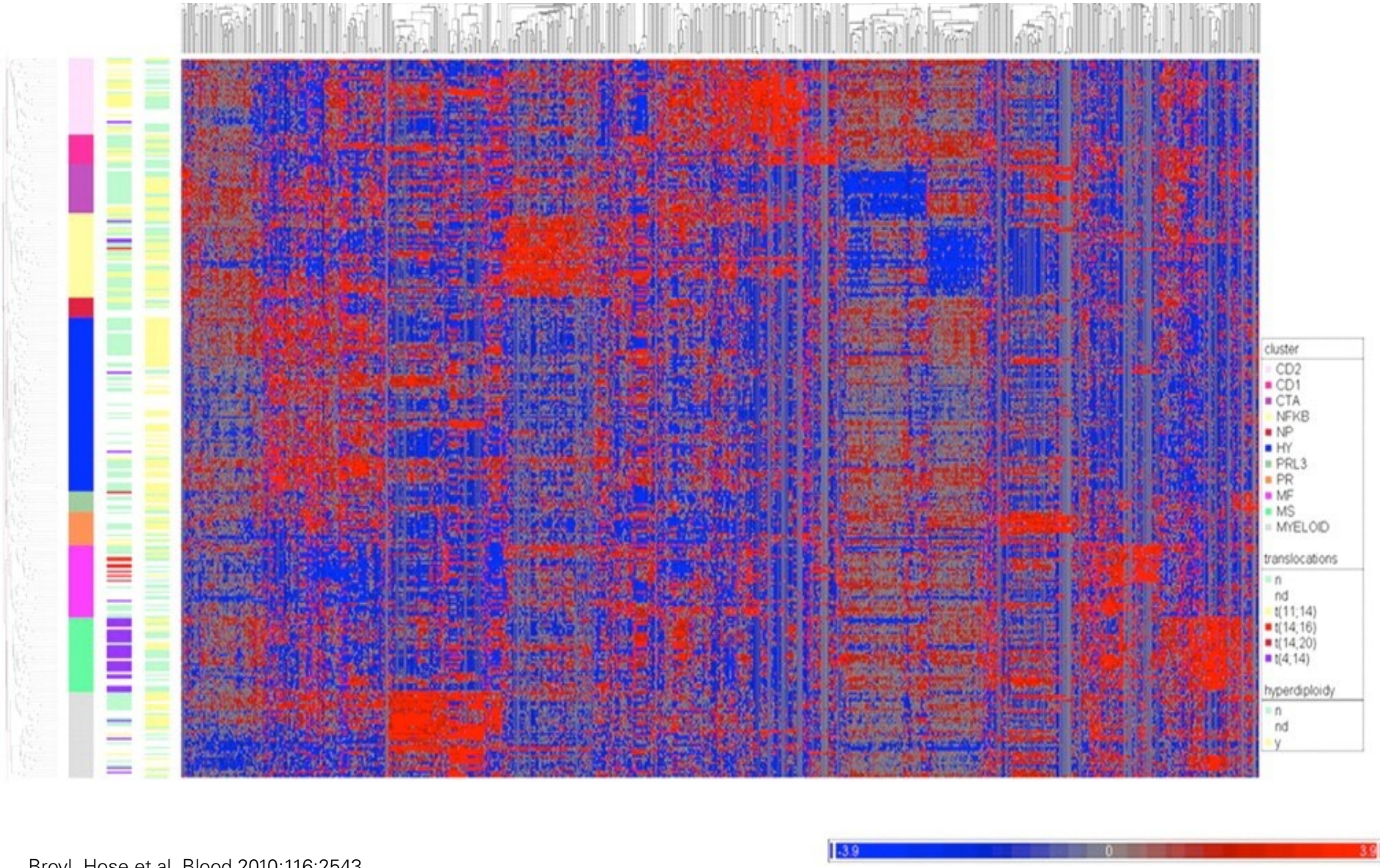


Figure 13.4: We see already from the one-dimensional distributions that some of the individual variables could potentially predict which group a patient is more likely to belong to. Our goal will be to combine variables to improve these one dimensional predictions.

Molecular classification of cancer

(multiple myeloma in newly diagnosed patients, gene expression profiling)



Broyl, Hose et al. Blood 2010;116:2543

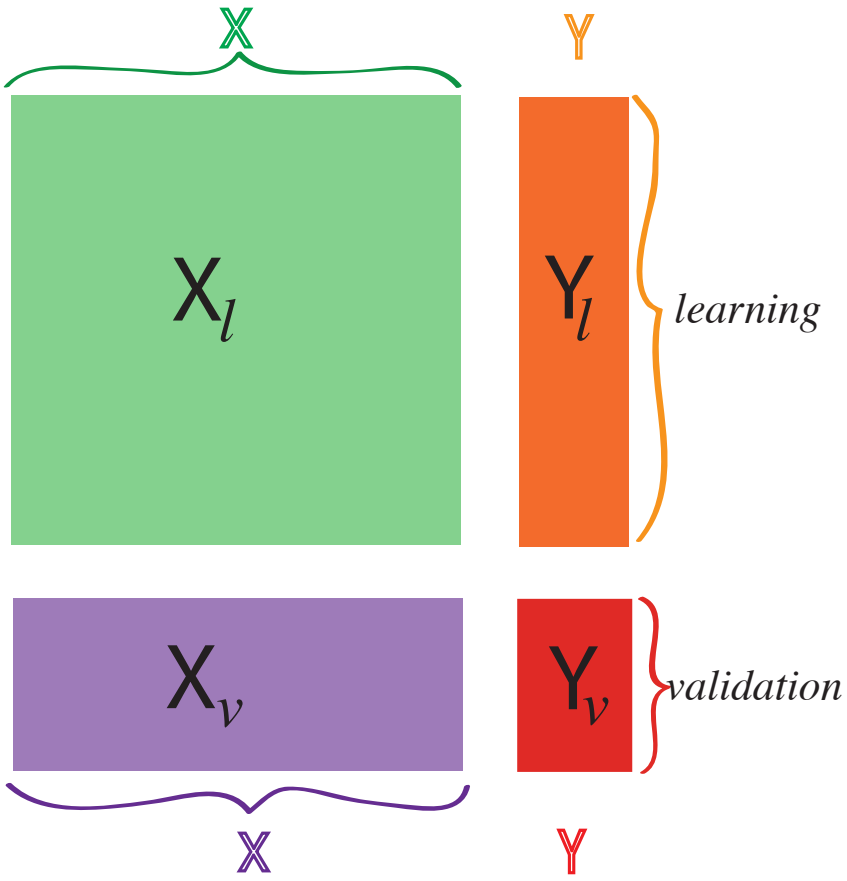


Figure 13.3: In supervised learning, we assign two different roles to our variables. We have labeled the explanatory variables X and the response variable(s) Y. There are also two different sets of observations: the training set X_ℓ and Y_ℓ and the validation set X_v and Y_v.

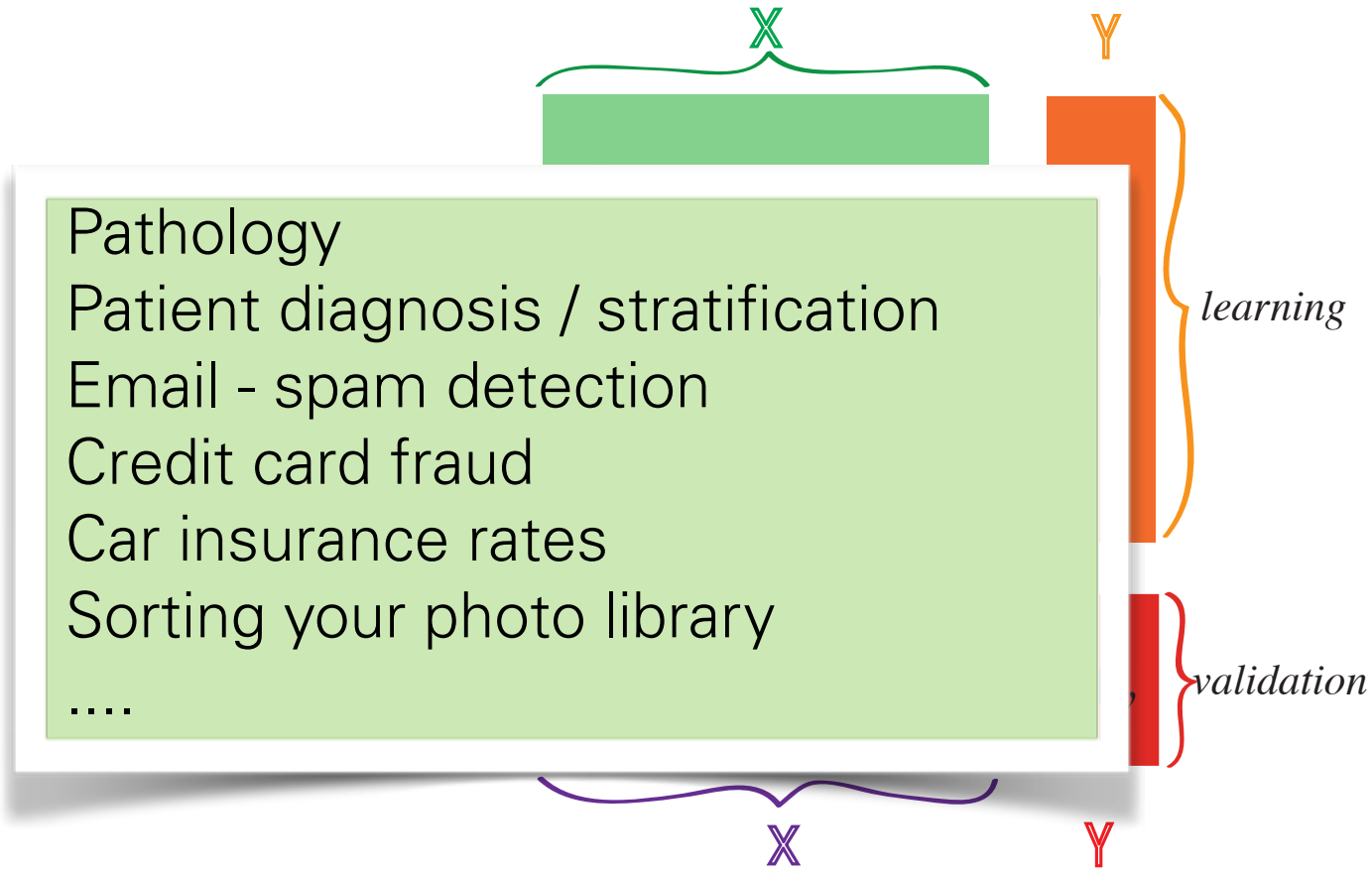


Figure 13.3: In supervised learning, we assign two different roles to our variables. We have labeled the explanatory variables X and the response variable(s) Y. There are also two different sets of observations: the training set X_ℓ and Y_ℓ and the validation set X_v and Y_v.

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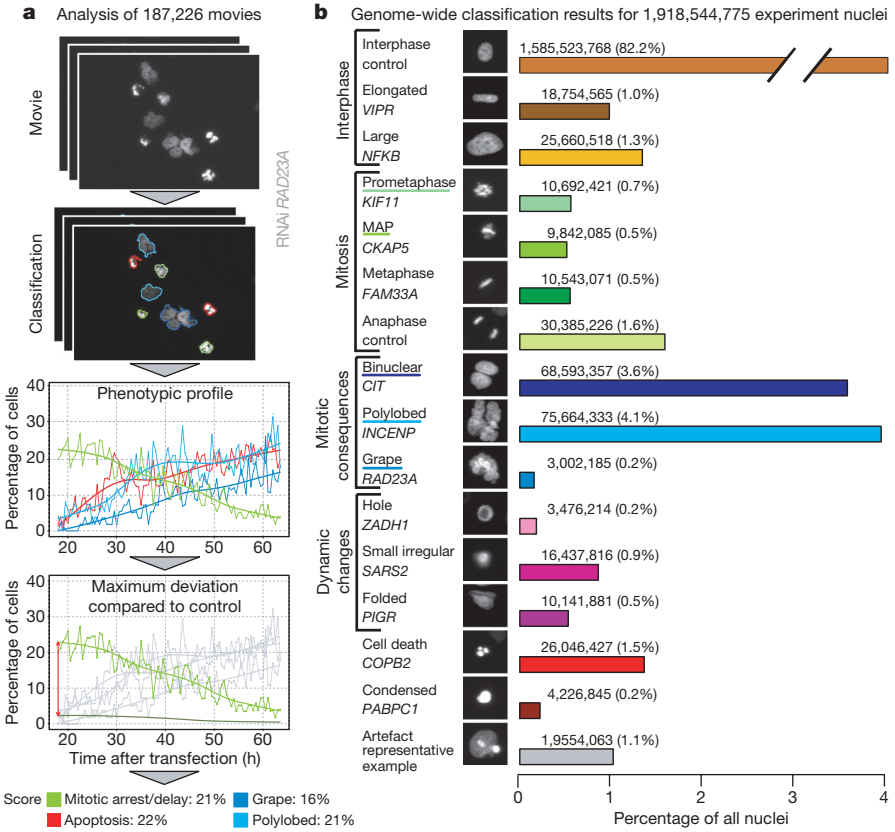
ARTICLES

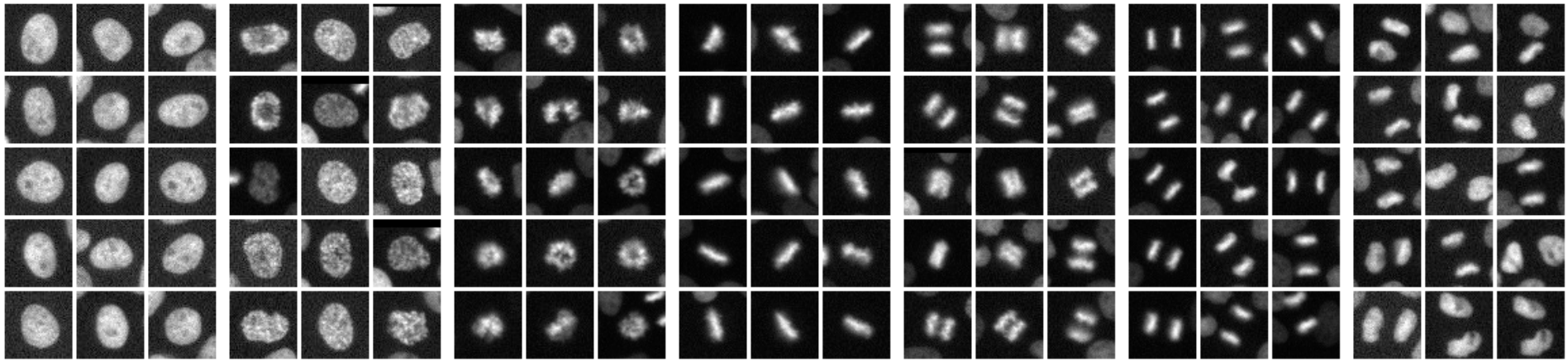
Phenotypic profiling of the human genome by time-lapse microscopy reveals cell division genes

Beate Neumann[1]*, Thomas Walter[1]*, Jean-Karim Hériché[5]†, Jutta Bulkescher[1], Holger Erfle[1,3]†, Christian Conrad[1,3], Phill Rogers[1]†, Ina Poser[6], Michael Held[1]†, Urban Liebel[1]† Gregoire Pau[9], Rolf Kabbe[10], Annelie Wünsche[2], Venkata Satagopam[4], Michael Daniel W. Gerlich[7], Reinhard Schneider[4], Roland Eils[10], Wolfgang Huber[9], Jan-Anthony A. Hyman[6], Richard Durbin[5], Rainer Pepperkok[3] & Jan Ellenberg[2]

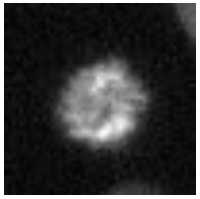


Morphological Phenotyping

Provide Human Annotation to a small set of cells:

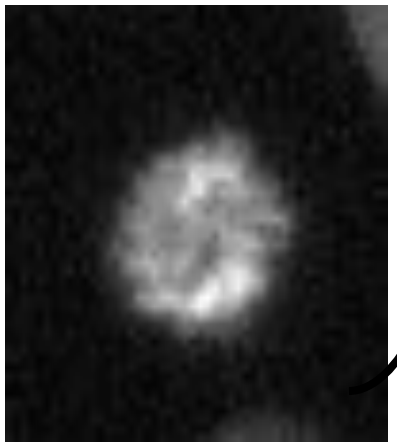


inter pro prometa meta earlyana lateana telo



Which mitotic phase is this?
Can we do this automatically?

Automatic Classification Workflow



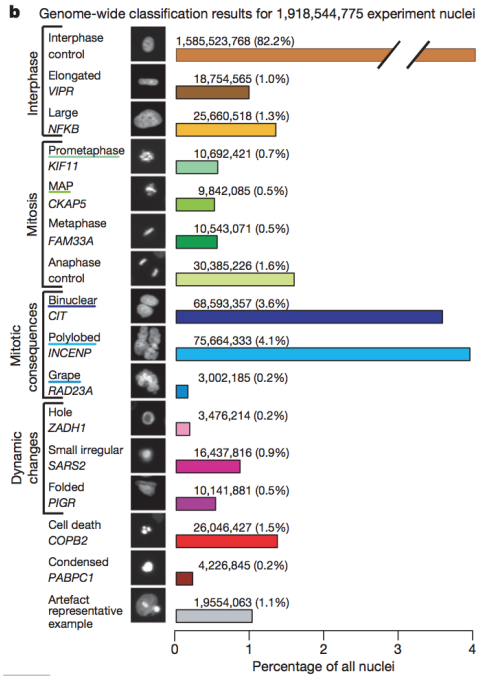
Preprocessing
e.g. normalization, background subtraction, …

Feature extraction
e.g. lightness, nucleus area, excentricity, …

Classification

Prophase

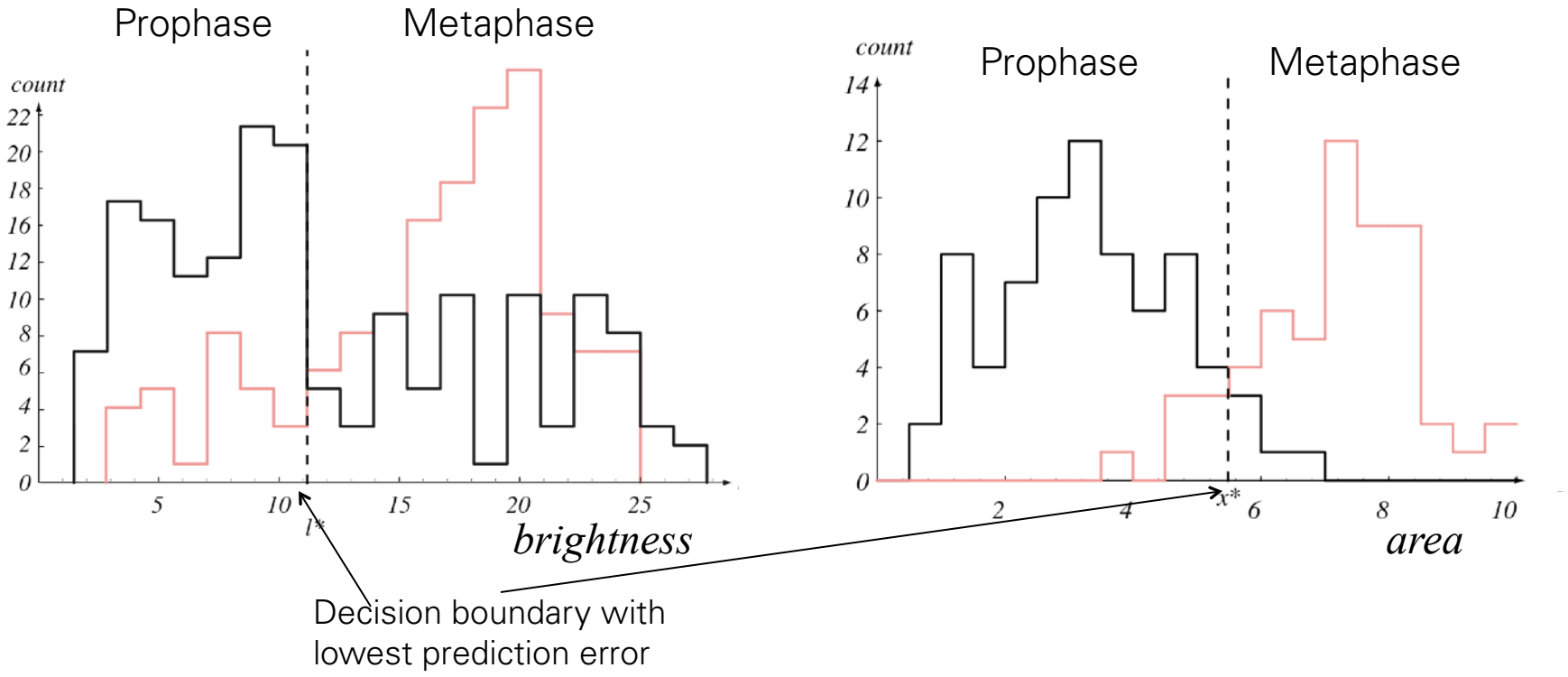
Metaphase



Prophase/ Metaphase Classification

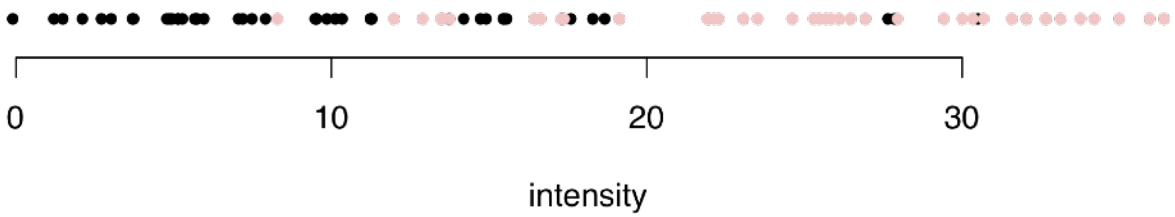
Predict mitotic state based on brightness

Predict mitotic state based on nucleus area

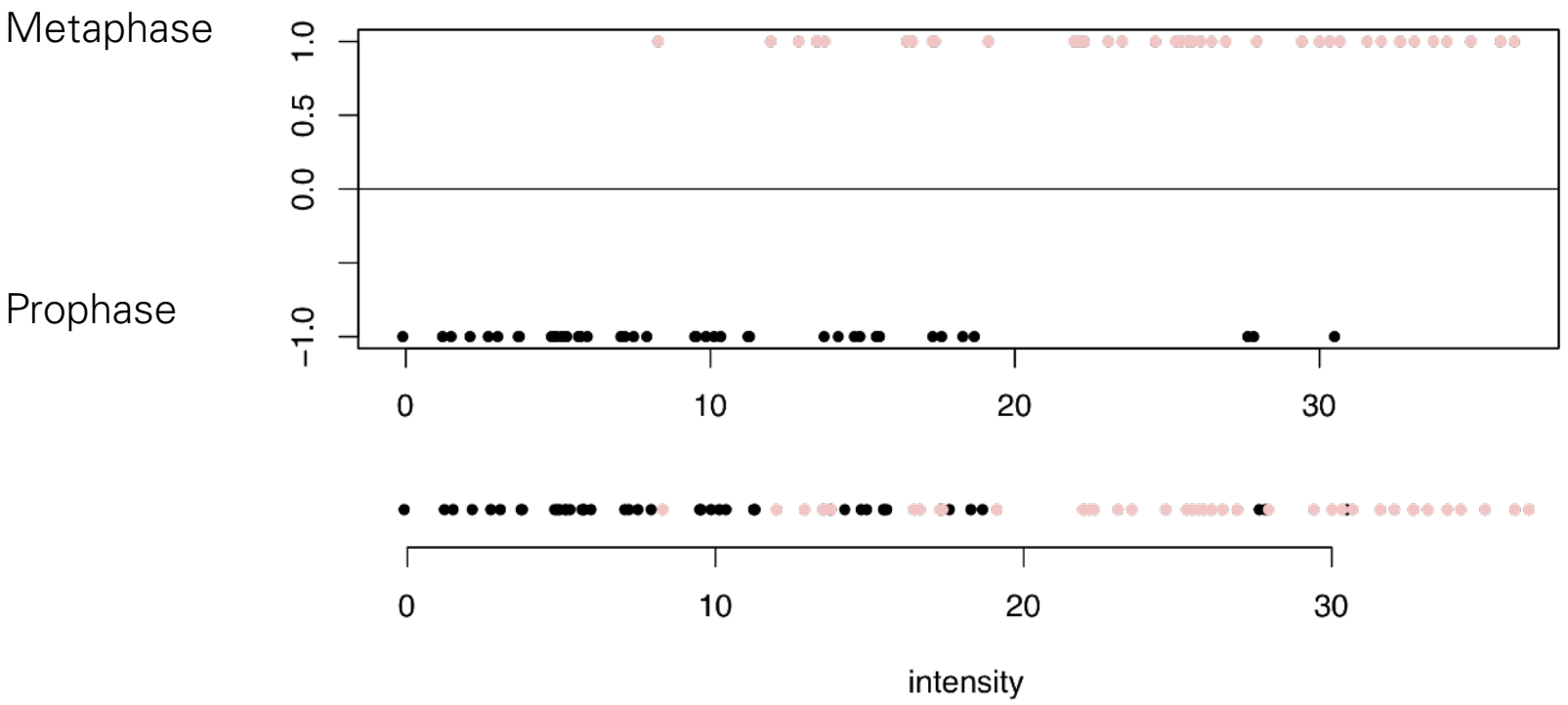


Both features are informative, but none of them individually has a good predictive power

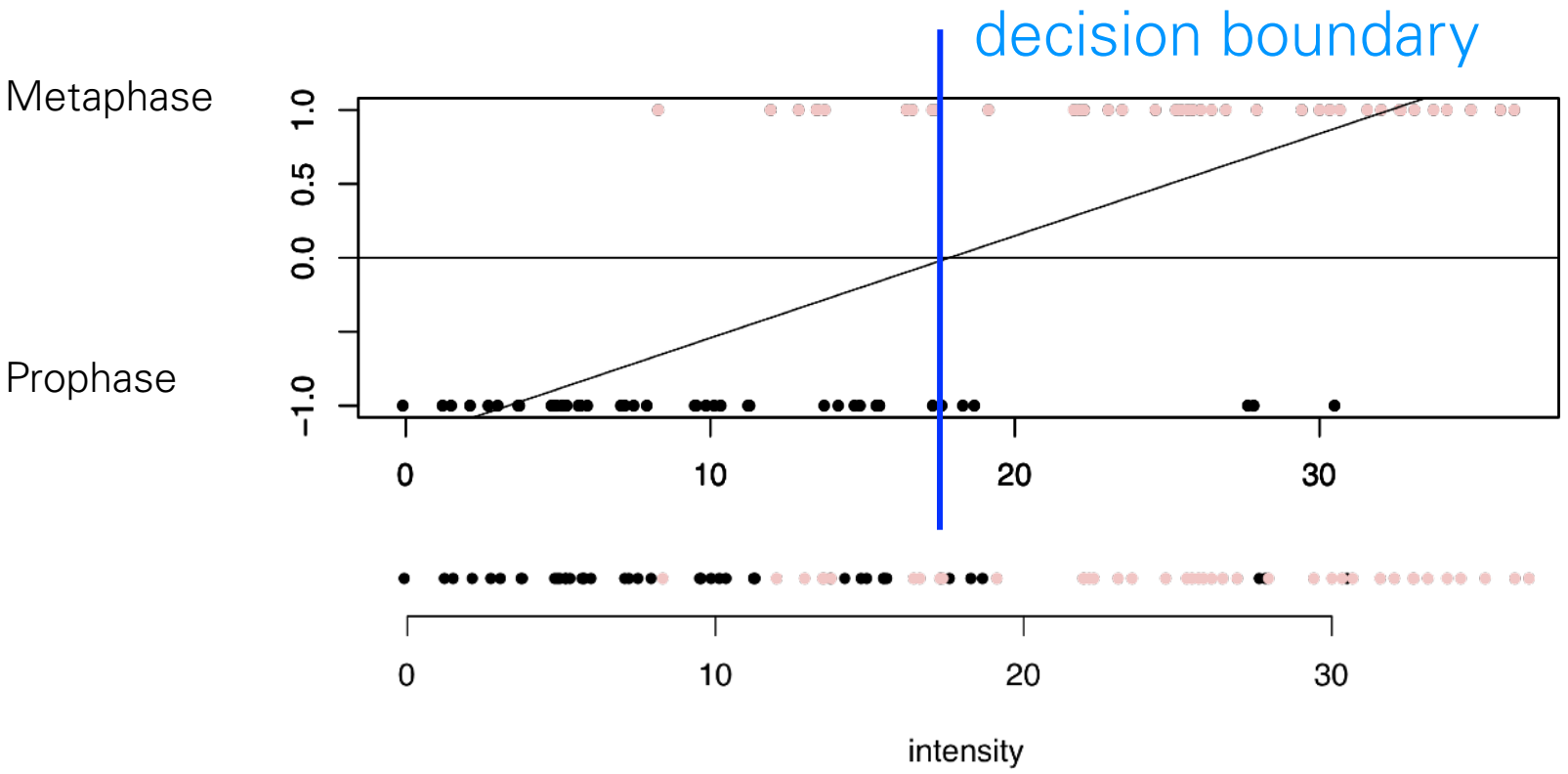
A Simple Least Squares Classifier (1D)



A Simple Least Squares Classifier (1D)



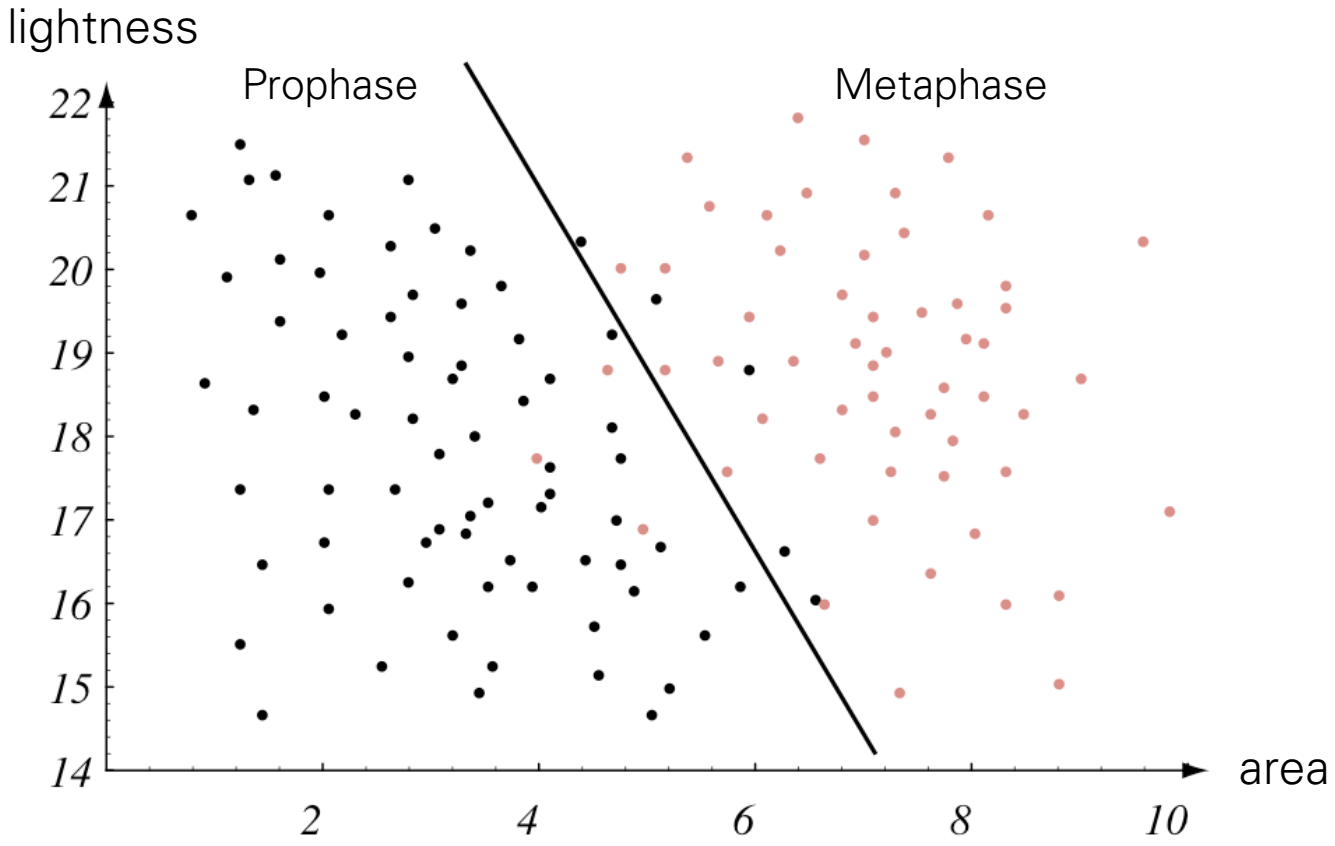
A Simple Least Squares Classifier (1D)




```
y[i] = -1 for prophase
y[i] = +1 for metaphase
x[i,] = c(area[i], intensity[i])
model = lm(y ~ x)
ynew = predict(model, newdata=newX)
ifelse(ynew < 0, “meta”, “pro”)
```

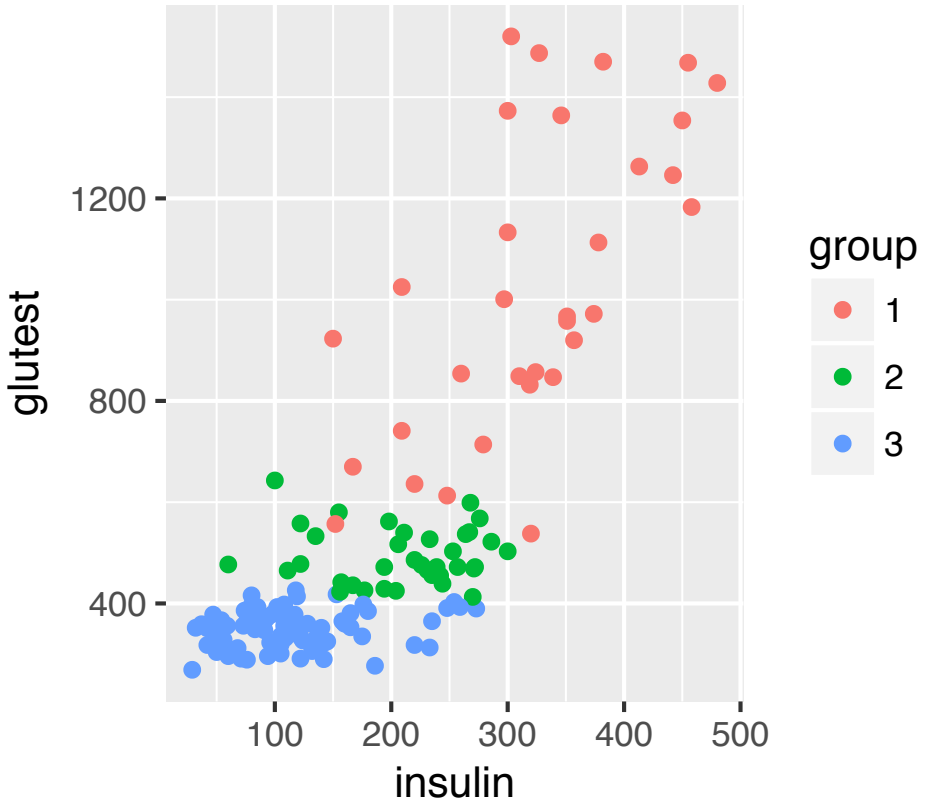
$$\Sigma_i (y_i - \beta x_i)^2 \rightarrow \min$$

A Simple Least Squares Classifier (2D)




```
y[i] = +1 for prophase
y[i] = -1 for metaphase
x[i,] = c(area[i],lightness[i])
model = lm.fit(x, y)
ynew = predict(model, Xnew)
            $fitted.values
ifelse(ynew < 0, “meta”, “pro”)
```

Linear discriminant Analysis (LDA) on the diabetes data



Linear discriminant Analysis (LDA) on the diabetes data

```
library("MASS")
diabetes_lda = lda(group ~ insulin + glutest, data = diabetes)
diabetes_lda

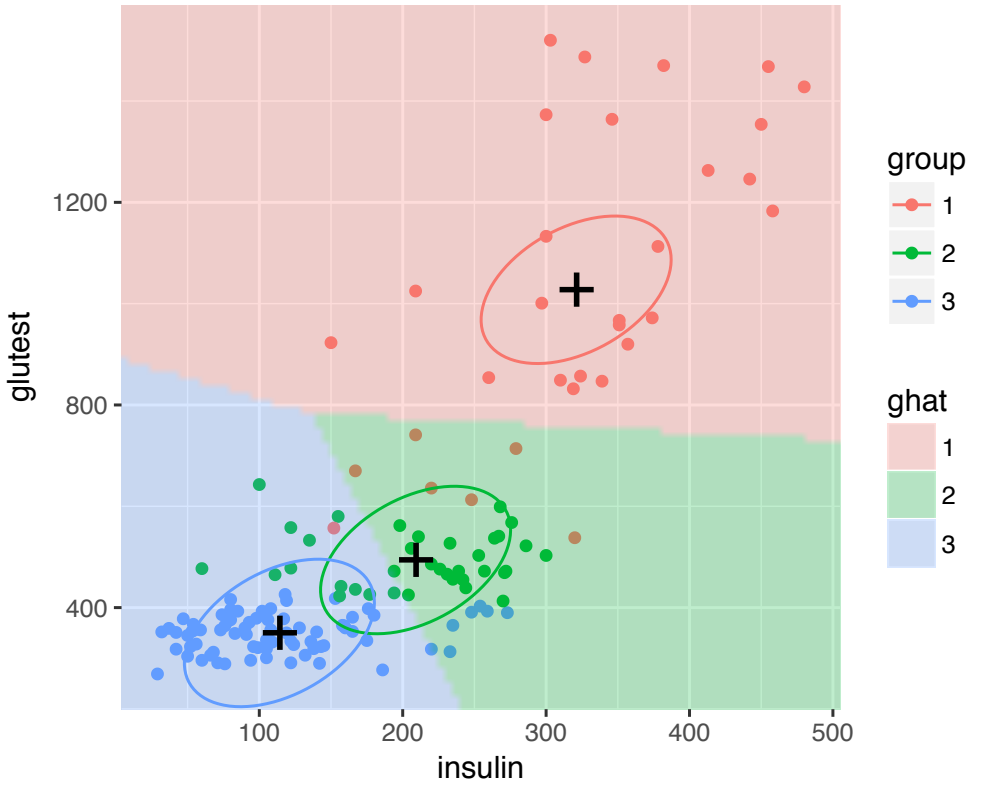
## Call:
## lda(group ~ insulin + glutest, data = diabetes)
##
## Prior probabilities of groups:
##         1         2         3
## 0.2222222 0.2500000 0.5277778
##
## Group means:
##    insulin   glutest
## 1 320.9375 1027.3750
## 2 208.9722  493.9444
## 3 114.0000  349.9737
##
## Coefficients of linear discriminants:
##                   LD1         LD2
## insulin -0.004463900 -0.01591192
## glutest -0.005784238  0.00480830
##
## Proportion of trace:
##    LD1    LD2
## 0.9677 0.0323

ghat = predict(diabetes_lda)$class
table(ghat, diabetes$group)

##
## ghat  1  2  3
##    1 25  0  0
##    2  6 24  6
##    3  1 12 70

mean(ghat != diabetes$group)

## [1] 0.1736111
```



QDA: Represent each group by a bivariate Normal $N(\mu_g, \Sigma_g)$

LDA: $\Sigma_g = \Sigma$

Linear discriminant Analysis (LDA) on the diabetes data

```
library("MASS")
```

Why is the boundary between the prediction regions for groups 1 and 2 not perpendicular to the line between the cluster centers?

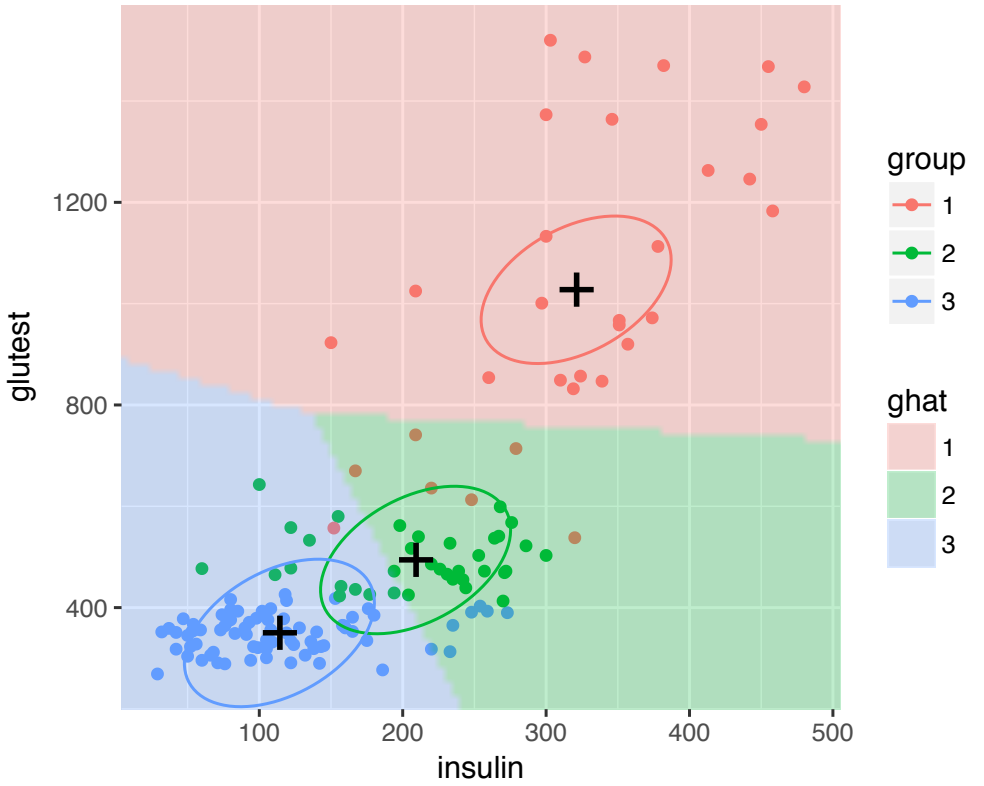
```
## 0.9677 0.0323

ghat = predict(diabetes_lda)$class
table(ghat, diabetes$group)

##
## ghat  1  2  3
##    1 25  0  0
##    2  6 24  6
##    3  1 12 70

mean(ghat != diabetes$group)

## [1] 0.1736111
```



QDA: Represent each group by a bivariate Normal $N(\mu_g, \Sigma_g)$

LDA: $\Sigma_g = \Sigma$

Linear discriminant Analysis (LDA) on the diabetes data

```
library("MASS")
```

How confident would you be about the predictions in those areas of the 2D plane that are far from all of the cluster centers?

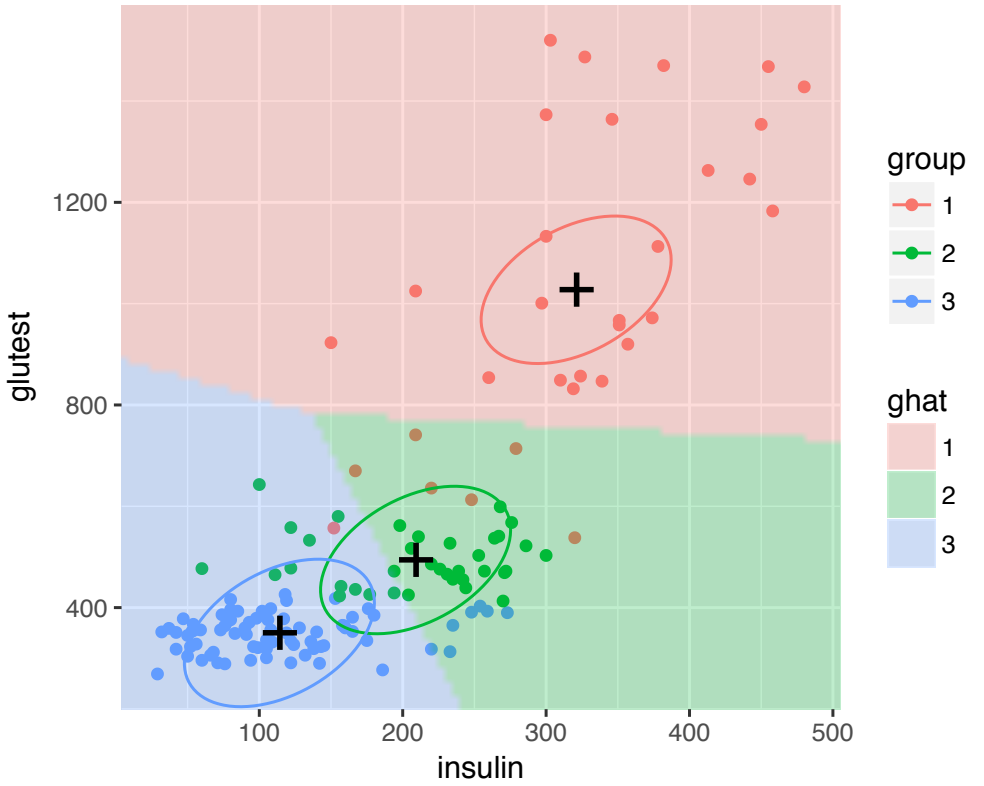
```
## 0.9677 0.0323

ghat = predict(diabetes_lda)$class
table(ghat, diabetes$group)

##
## ghat  1  2  3
##    1 25  0  0
##    2  6 24  6
##    3  1 12 70

mean(ghat != diabetes$group)

## [1] 0.1736111
```



QDA: Represent each group by a bivariate Normal $N(\mu_g, \Sigma_g)$

LDA: $\Sigma_g = \Sigma$

Linear discriminant Analysis (LDA) on the diabetes data

```
library("MASS")
```

Why is the boundary between the prediction regions for groups 2 and 3 not half-way between the centers?

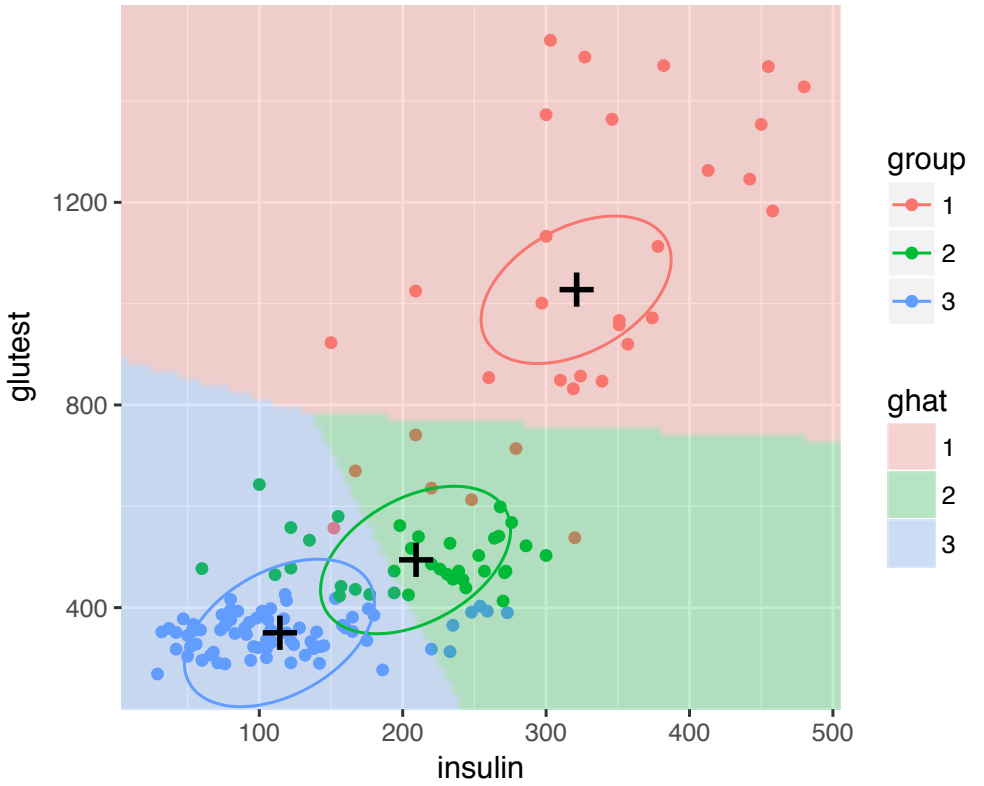
```
## 0.9677 0.0323

ghat = predict(diabetes_lda)$class
table(ghat, diabetes$group)

##
## ghat  1  2  3
##    1 25  0  0
##    2  6 24  6
##    3  1 12 70

mean(ghat != diabetes$group)

## [1] 0.1736111
```



QDA: Represent each group by a bivariate Normal $N(\mu_g, \Sigma_g)$

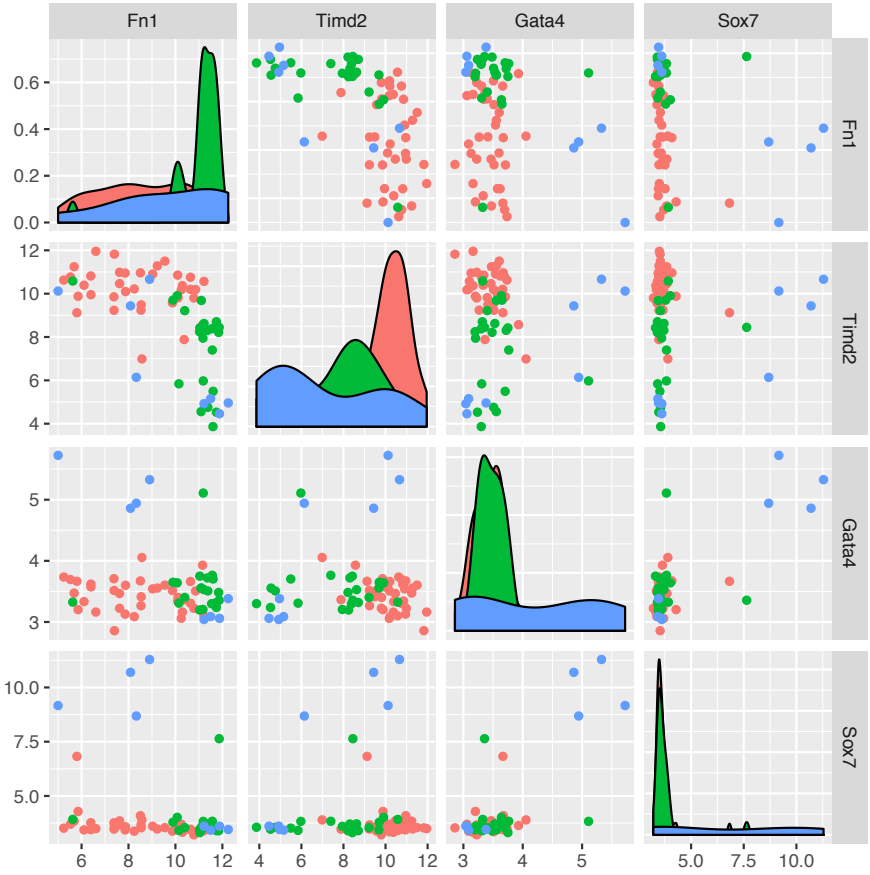
LDA: $\Sigma_g = \Sigma$

Hiiragi mouse embryo single cell expression data

```
library("Hiiragi2013")
data("x")
probes = c("1426642_at", "1418765_at", "1418864_at", "1416564_at")
embryoCells = t(exprs(x)[probes, ]) %>% as_tibble %>%
  mutate(Embryonic.day = x$Embryonic.day) %>%
  filter(x$genotype == "WT")
```

```
library("mouse4302.db")
anno = AnnotationDbi::select(mouse4302.db, keys = probes,
         columns = c("SYMBOL", "GENENAME"))
anno
```

```
##       PROBEID SYMBOL
## 1 1426642_at    Fn1
## 2 1418765_at  Timd2
## 3 1418864_at  Gata4
## 4 1416564_at   Sox7
##                                                GENENAME
## 1                                            fibronectin 1
## 2 T cell immunoglobulin and mucin domain containing 2
## 3                                  GATA binding protein 4
## 4                  SRY (sex determining region Y)-box 7
```



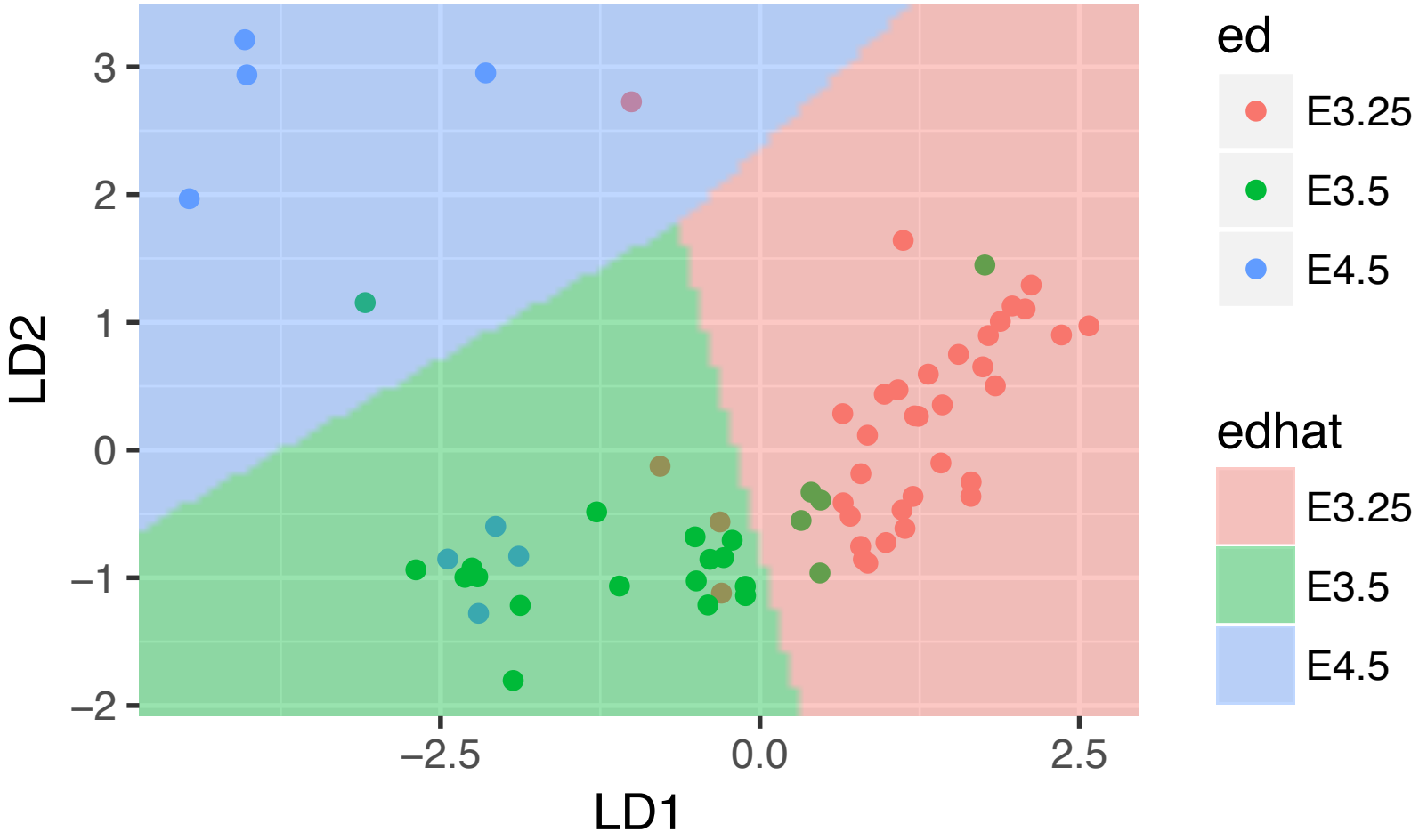


Figure 13.10: LDA classification regions for Embryonic.day.

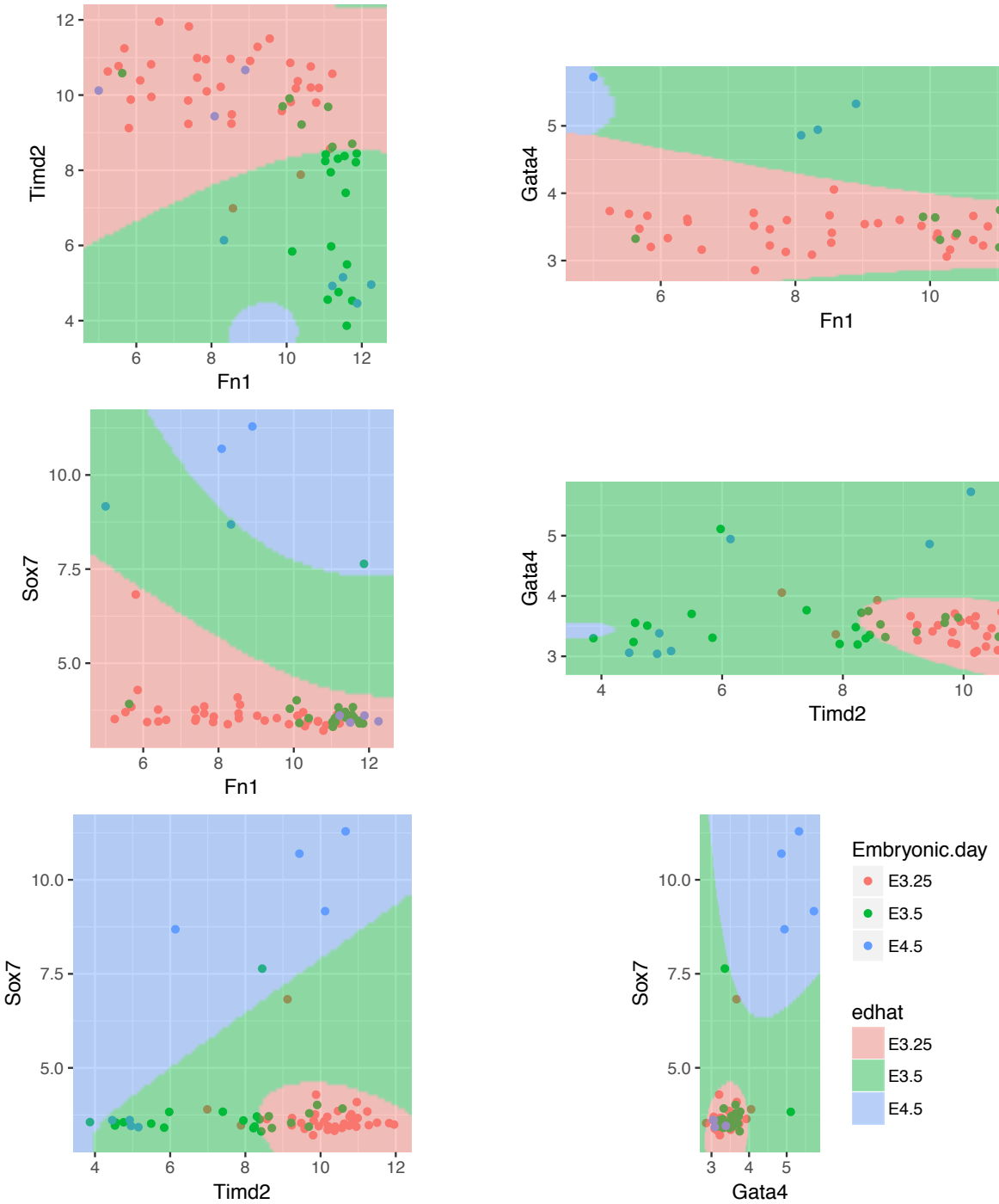
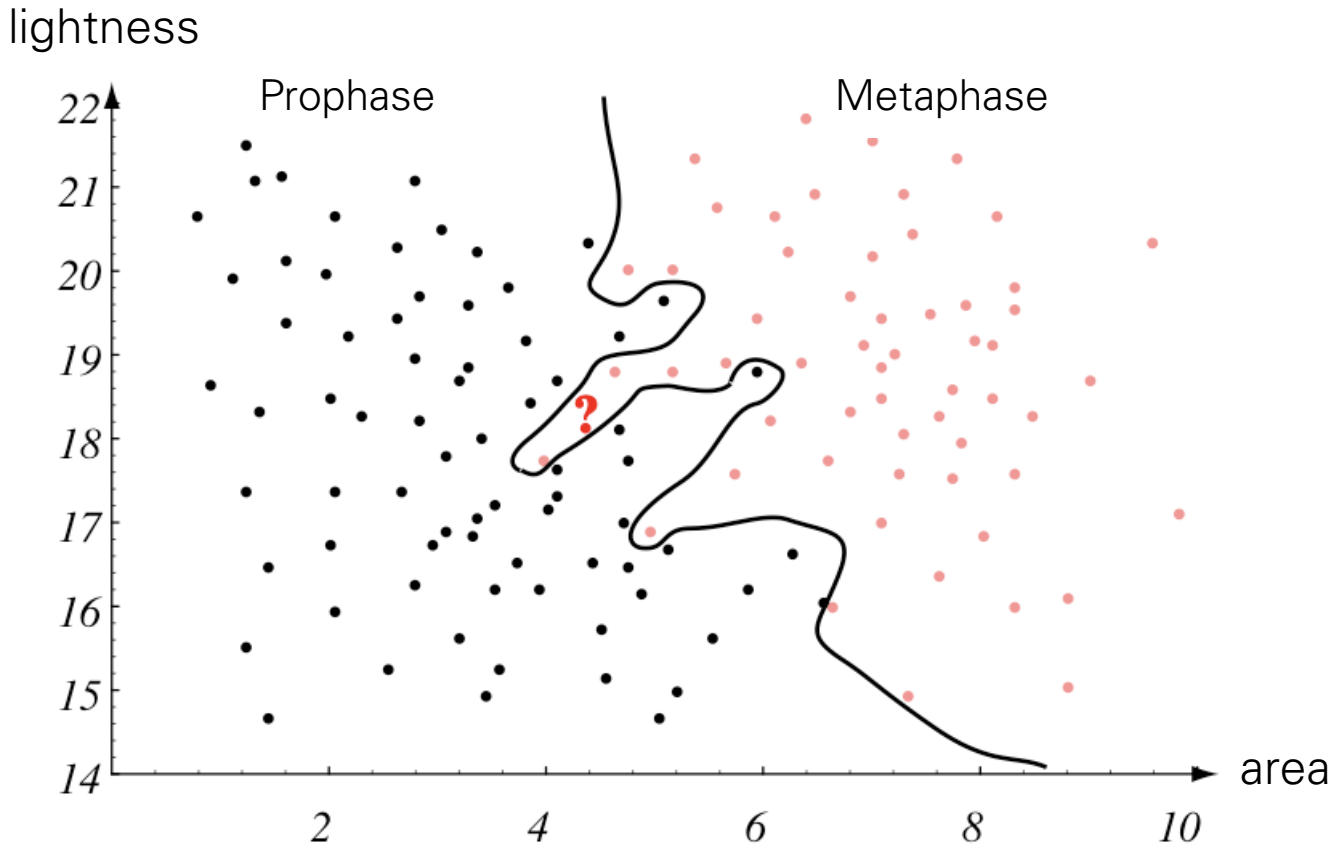


Figure 13.11: QDA for the mouse cell data. Shown are all pairwise plots of the four features.

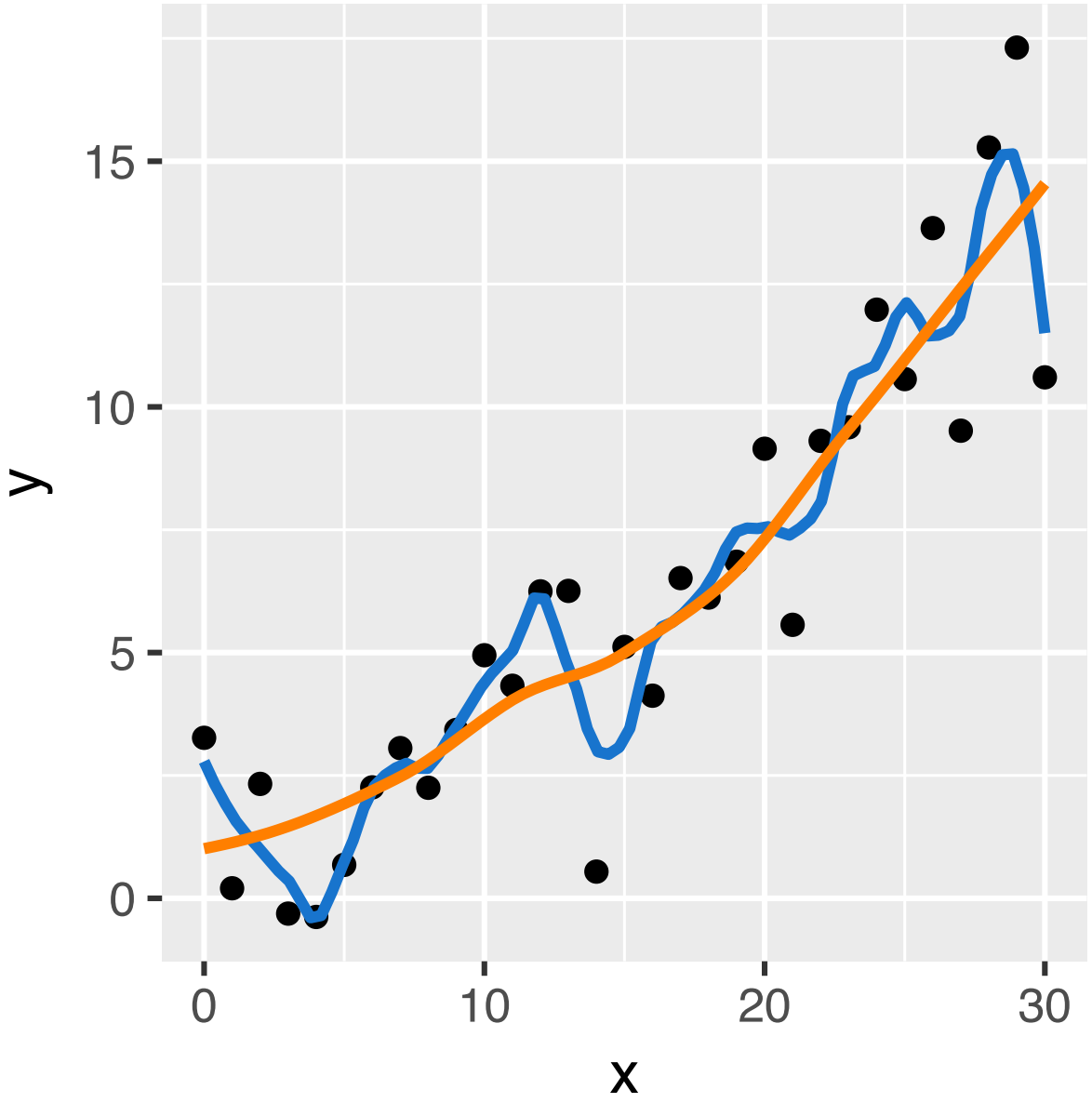
k-Nearest-Neighbor Classifier



Assign each new cell to the class of its nearest neighbor.
Black line shows decision boundary

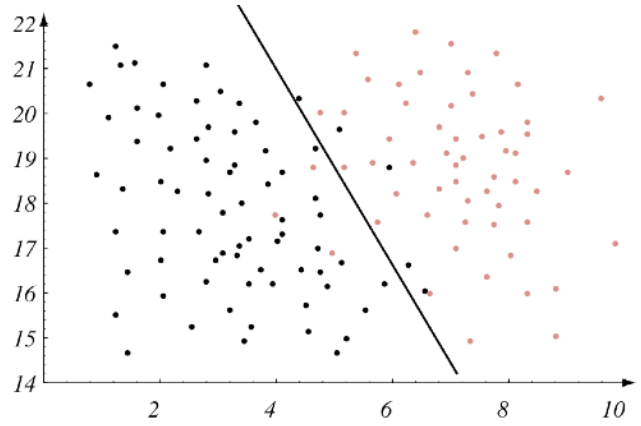
```
y[i] = +1 for pro phase
y[i] = -1 for meta phase
X[i,] = (area[i],lightness[i])
d = class::knn(X,Xnew,y,k=1)
```

Another example of overfitting

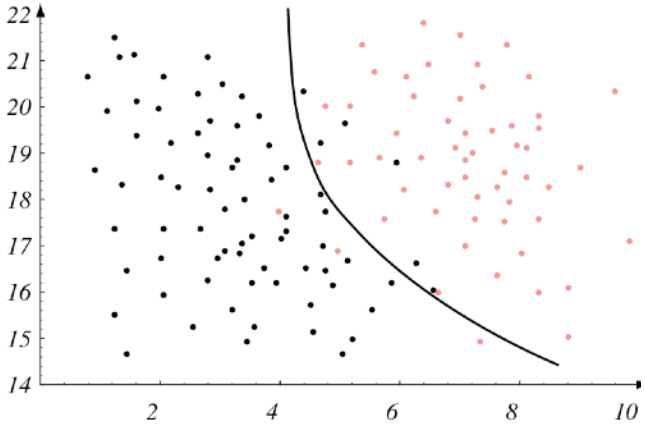


Which Decision Boundary?

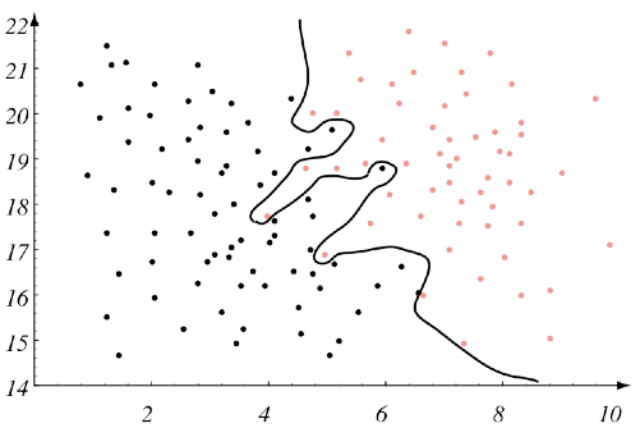
High bias
Low variance



low model complexity
(needs 2 parameters to describe the decision boundary)



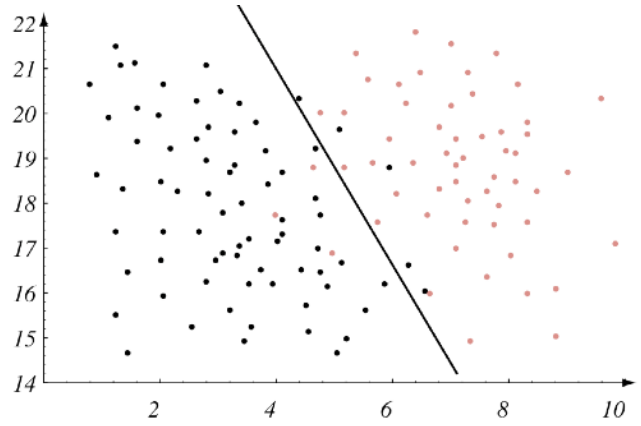
Low bias
High variance



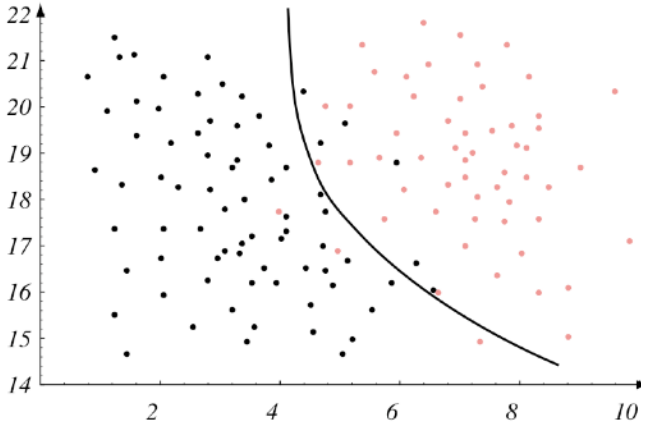
high model complexity
(need 100s of parameters to describe decision boundary)

Which Decision Boundary?

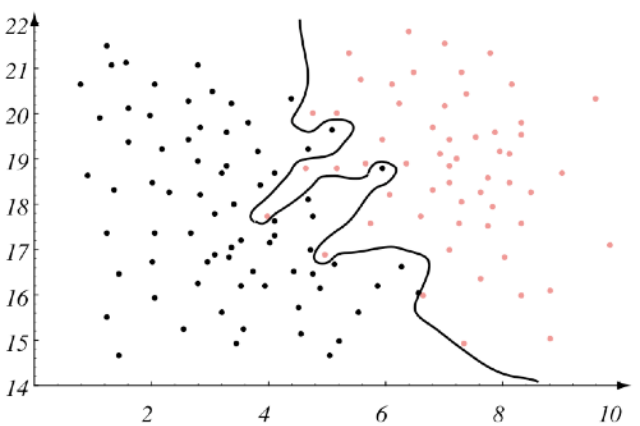
High bias
Low variance



low model complexity
(needs 2 parameters to describe the decision boundary)



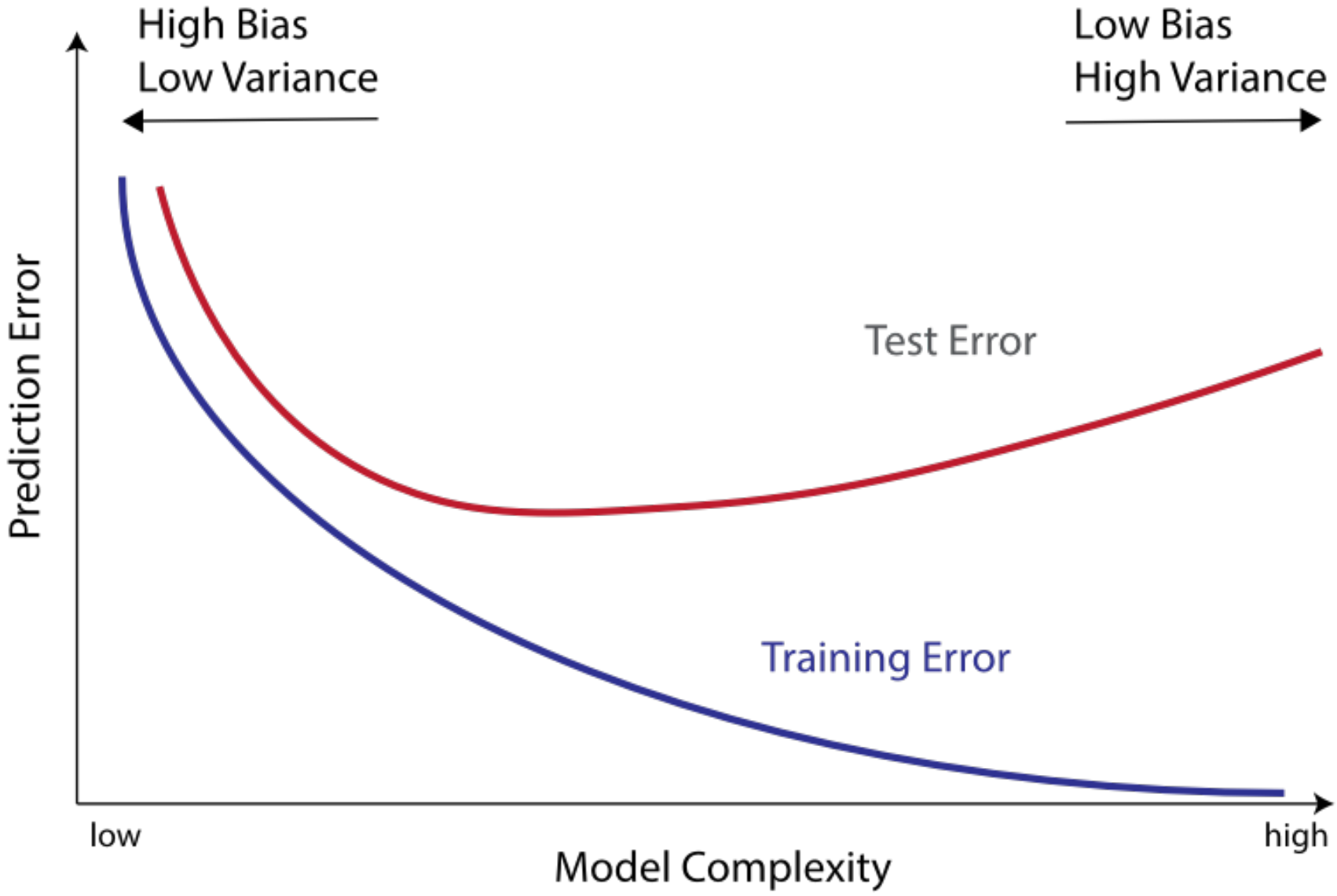
Low bias
High variance



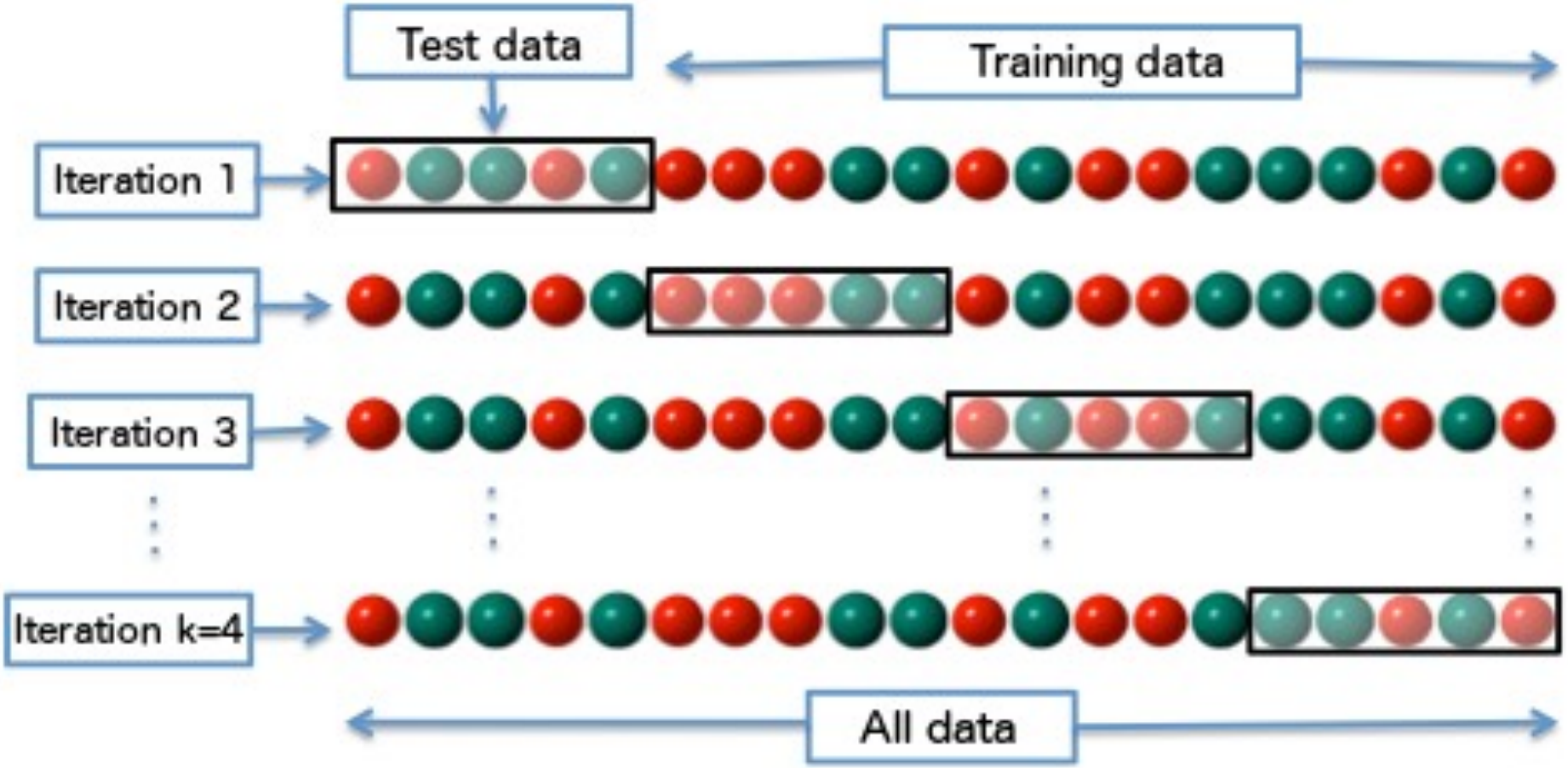
high model complexity
(need 100s of parameters to describe decision boundary)

Which decision boundary has the lowest prediction error?

Bias-Variance-Dilemma

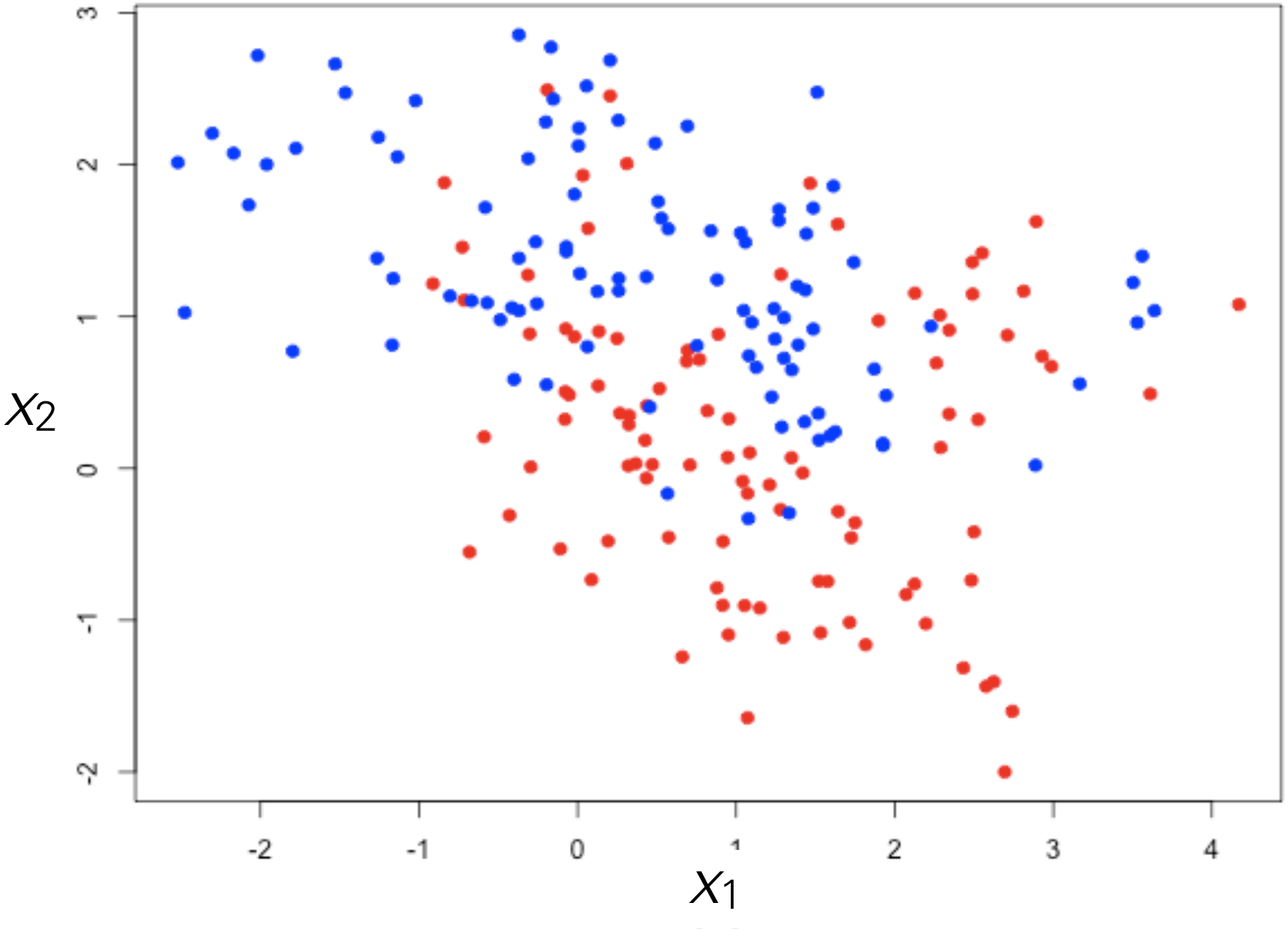


Cross-Validation

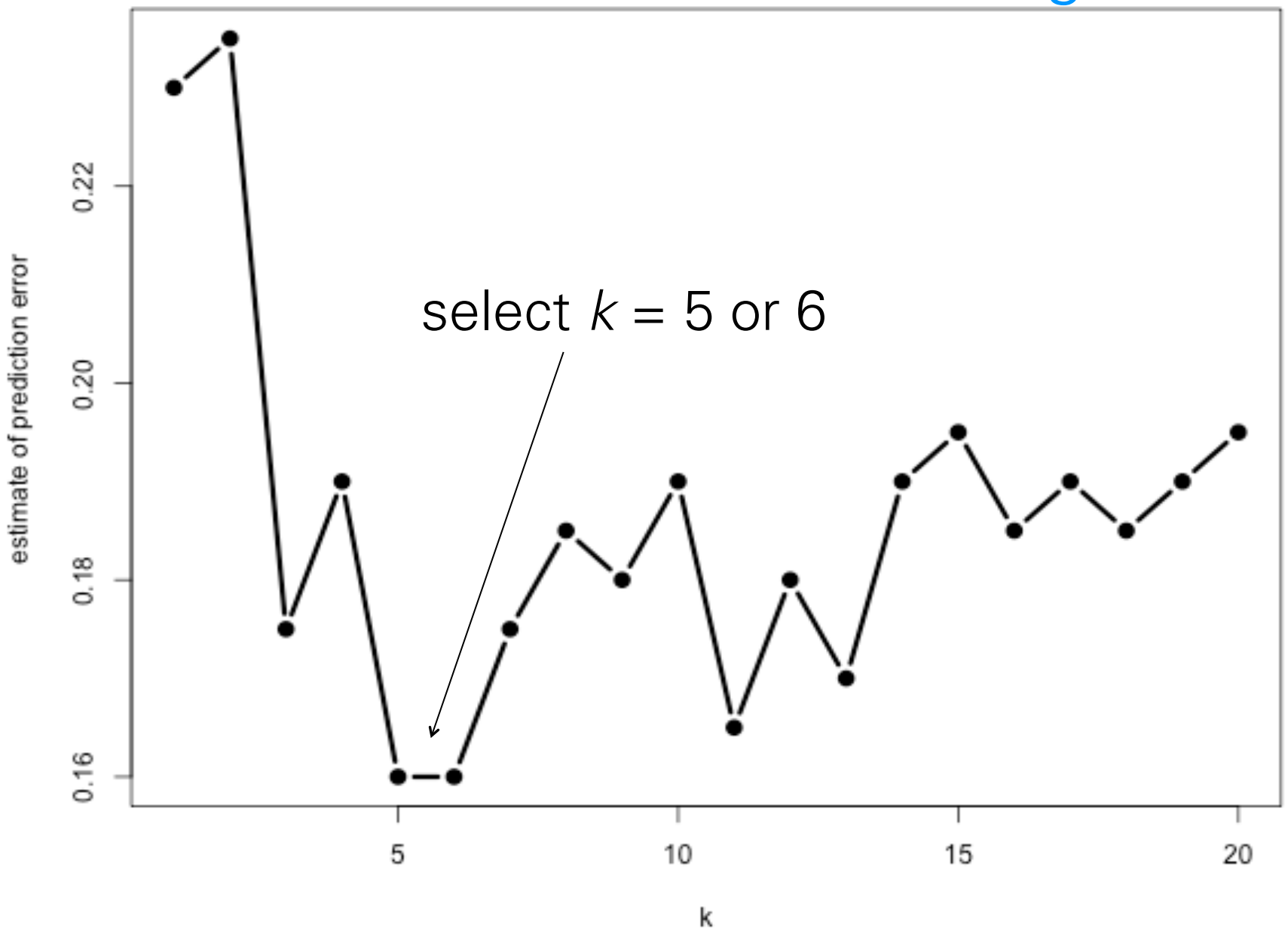


Wikipedia

Example: 2 classes, 2 variables, 200 objects

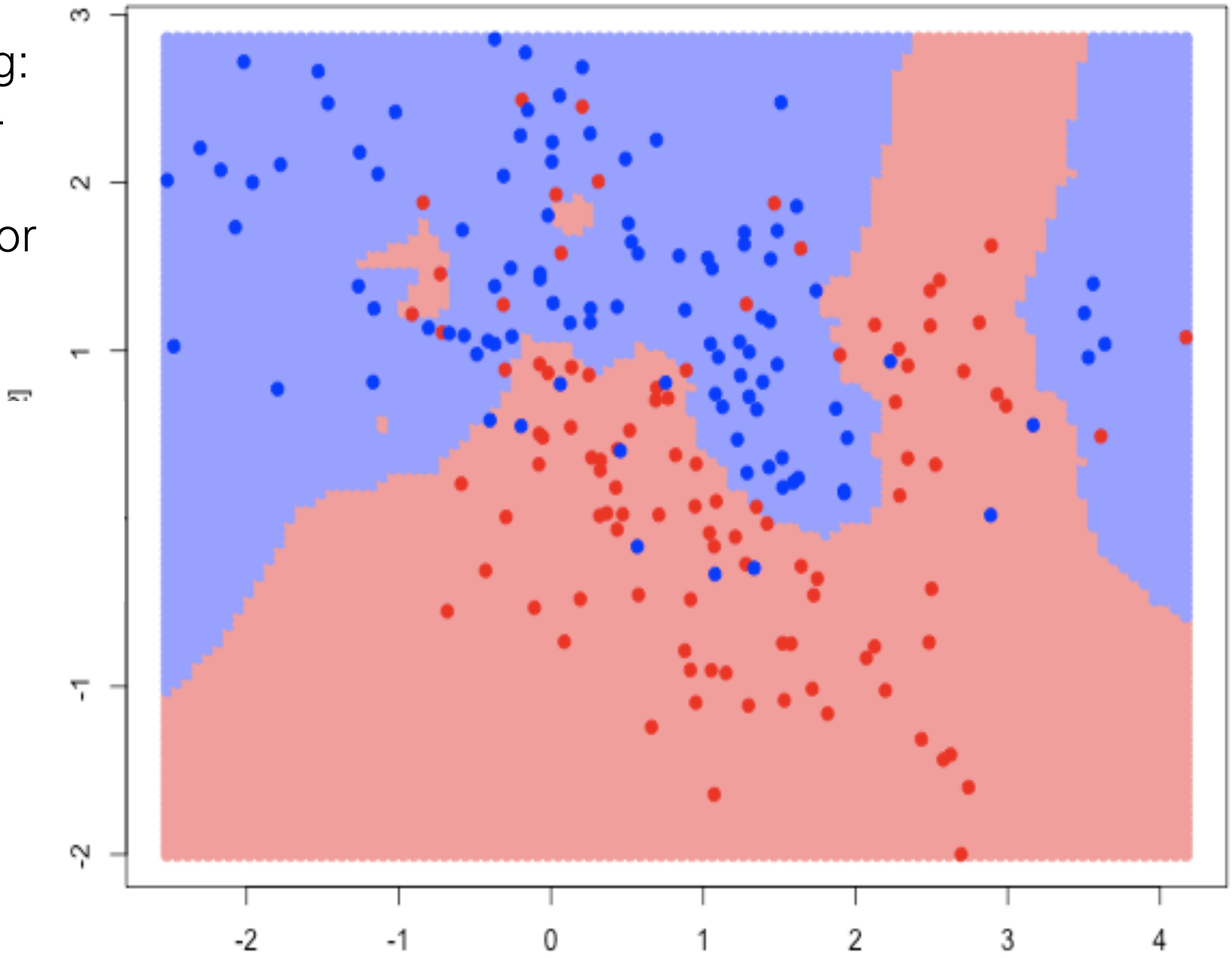


Cross-validation for *k* nearest neighbours



Cross-validation for *k* nearest neighbours

Shading: classifi-cation result for $k = 5$



Come back to the linear least squares classifier

X: *n* x *d* matrix with *d*-dimensional features for *n* samples
y: vector of length *n*: $y_i = 0$ for first class, 1 for second class
Fit linear model by minimizing the squared error:

$$\hat{\beta} = \arg\min_{\beta} \|X\beta - y\|_2^2$$

```
model = lm.fit(X, y)
ynew = predict(model, Xnew)$fitted.values
ifelse(ynew < 0,-1,1)
```

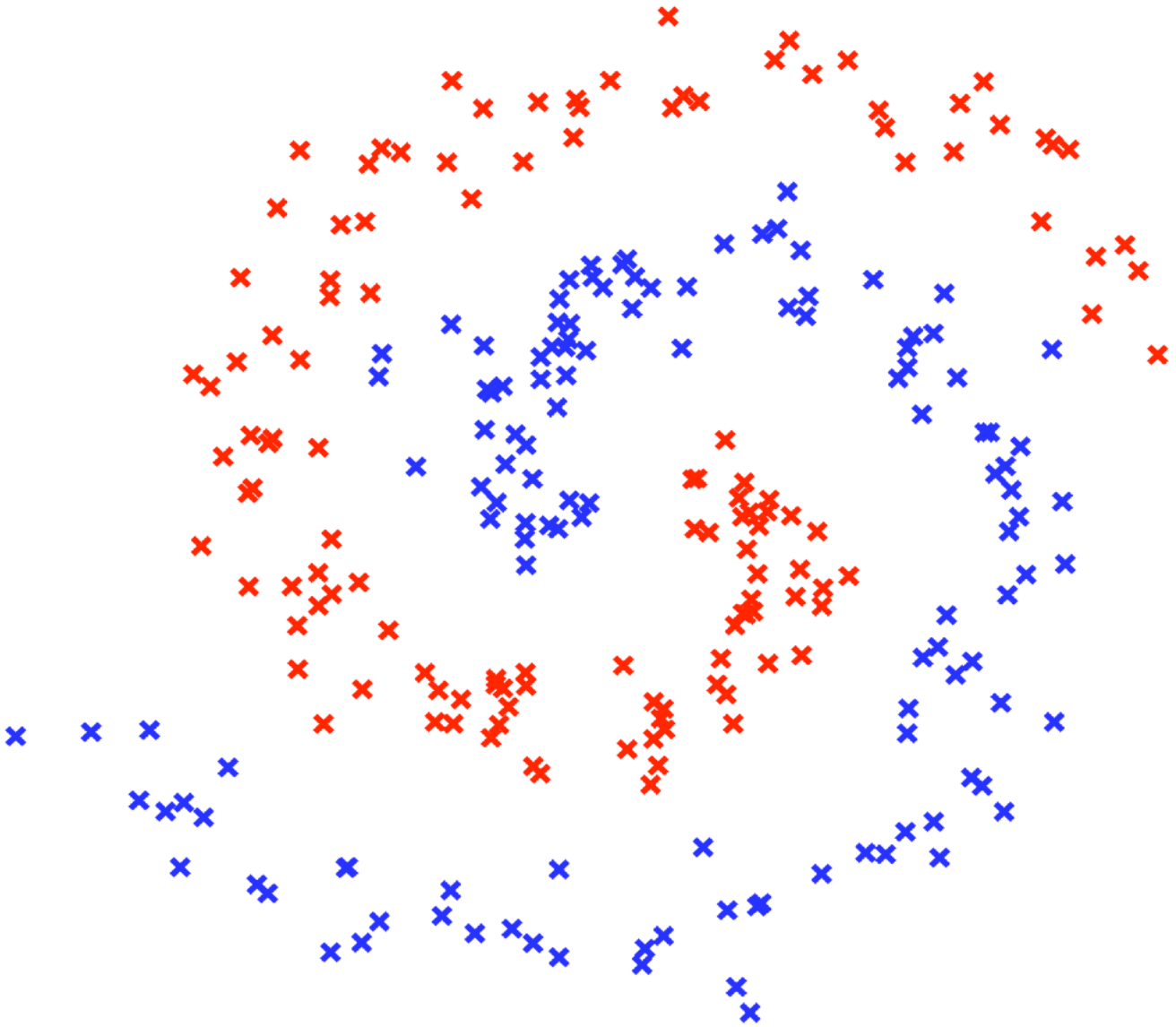
Extension to *k* classes:
Y: an *n* x *d* matrix of indicator variables

Class	1	2	3
a	1	0	0
b	0	1	0
c	0	0	1
b	0	1	0
a	1	0	0

In practice: lda (R-package MASS)

Non-Linear Classifiers?

These classes can not be separated by a straight line (hyperplane)



We could either

- bend our decision boundaries to be curvy, or
- bend our data space and stick with linear boundaries.

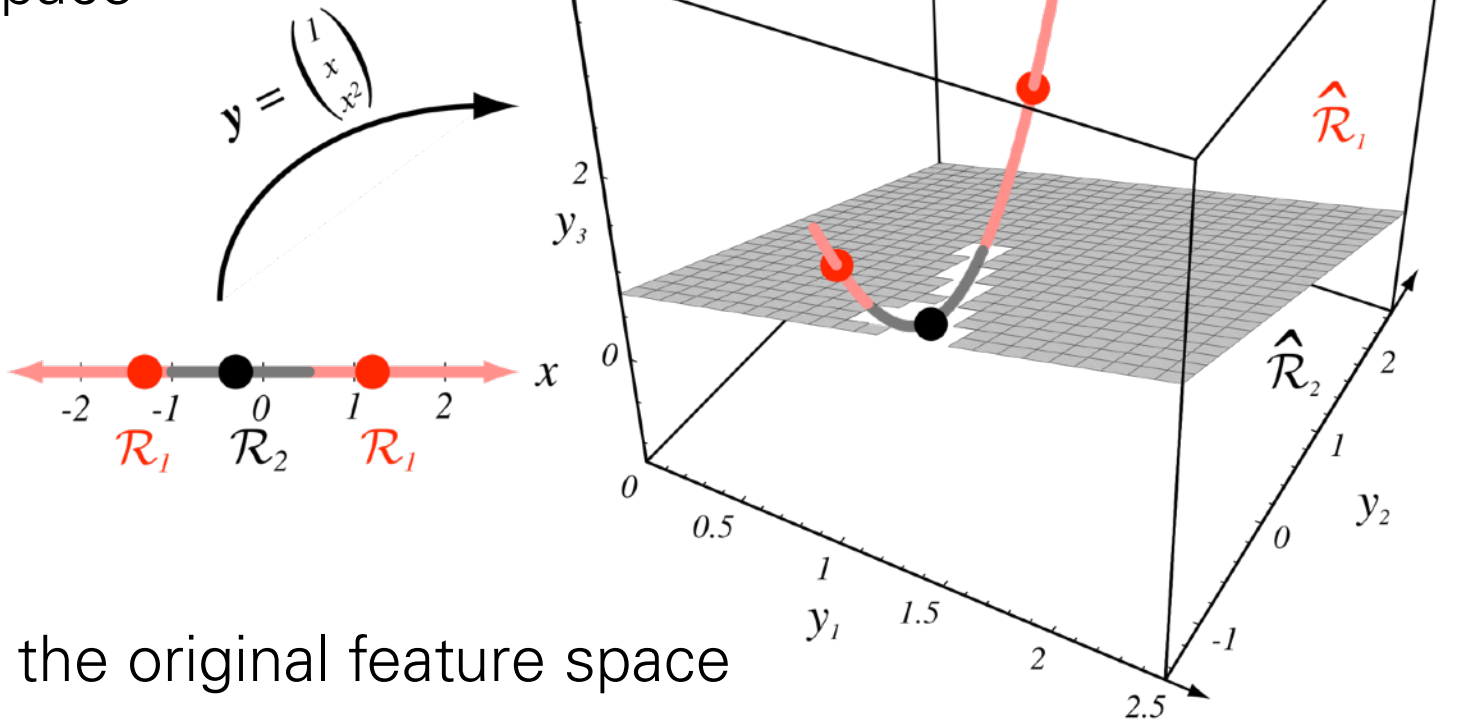
Guess what is simpler

Data Transformation & Augmentation

Apply non-linear functions, e.g.

$$f(x) = \left(1, x, x^2, x^3, \ldots\right)$$

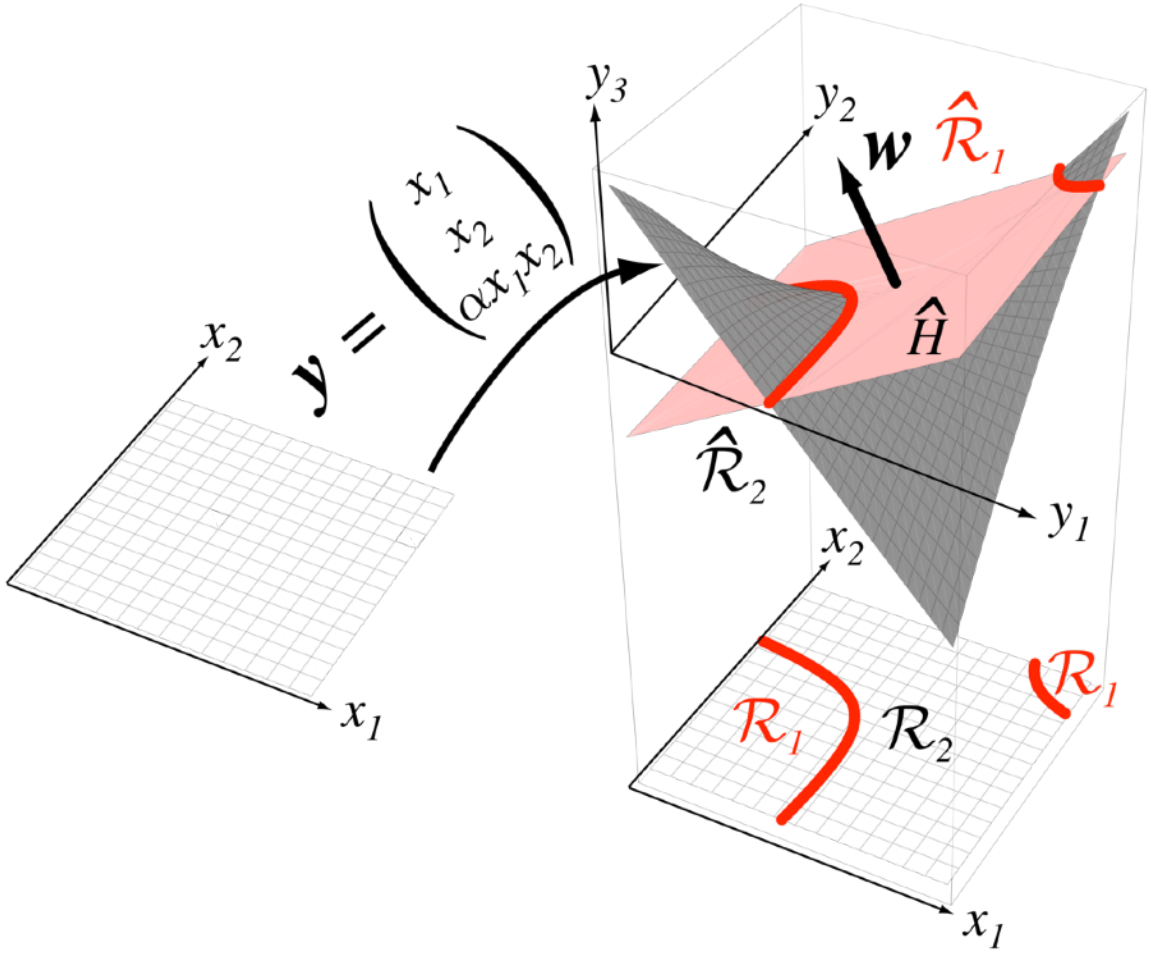
Train **linear** classifier in the new feature space



non-linear classifier in the original feature space

Quadratic Extension

Parabolic decision boundaries can be achieved by using the product x_1x_2



The Kernel Trick

You don’t even need to do the augmentation explicitly.

Remember that relative positions of all data points can be encoded by their distance matrix.

Now just replace Euclidean distance with some other, called “kernel”.

The Kernel Trick

Popular choices

Linear kernel

$$K(x_i, x_j) = x_i x_j$$

Radial basis functions

$$K(x_i, x_j) = \exp\left(-\frac{1}{2\sigma^2}\left\|x_i - x_j\right\|\right)$$

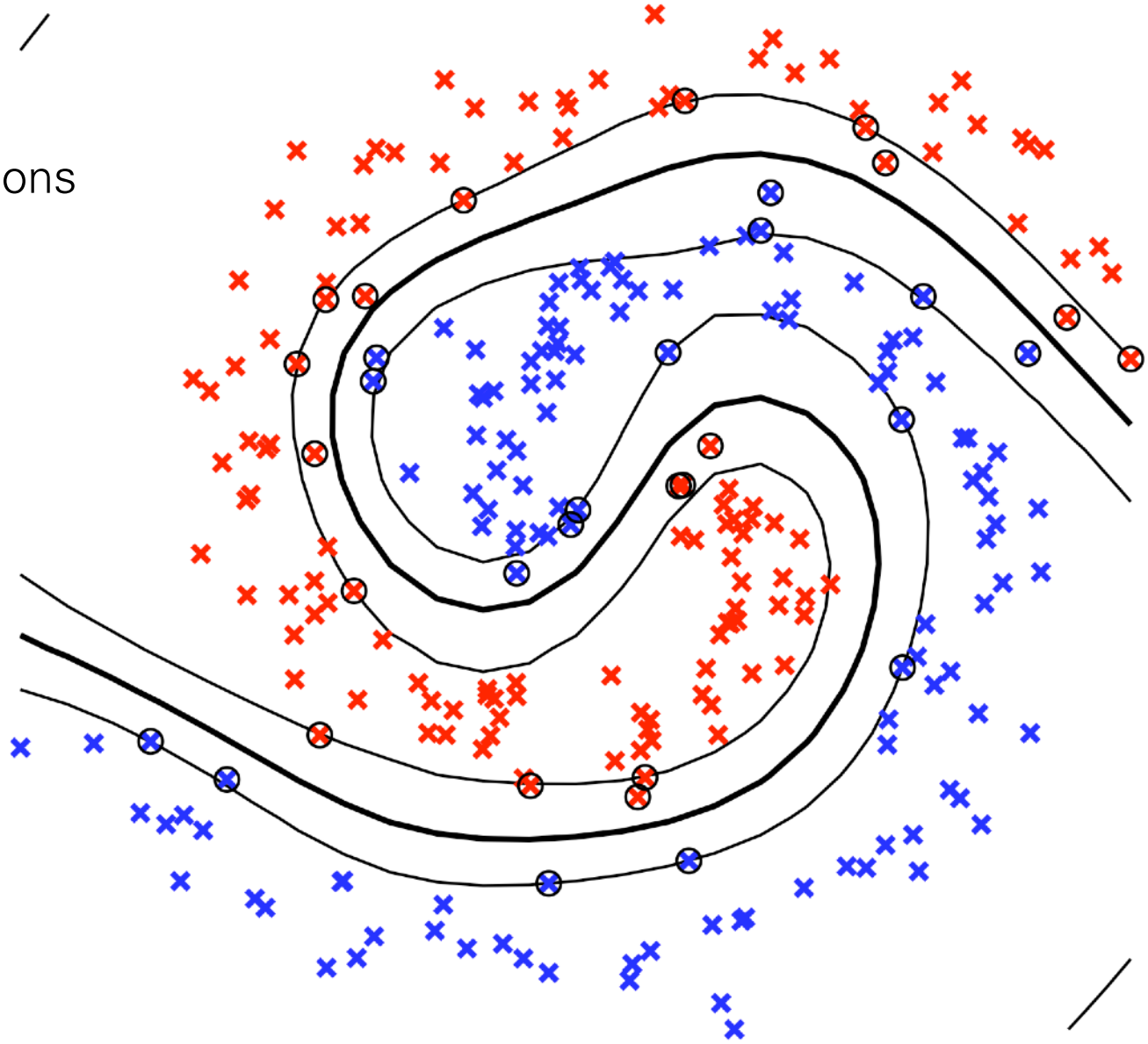
Polynomial

$$K(x_i, x_j) = (x_i x_j + 1)^d$$

Example

Radial Basis Functions

Kernel



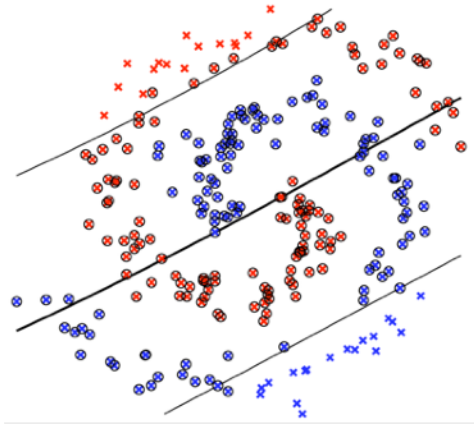
(SVM

Thick line: class separating hyperplane

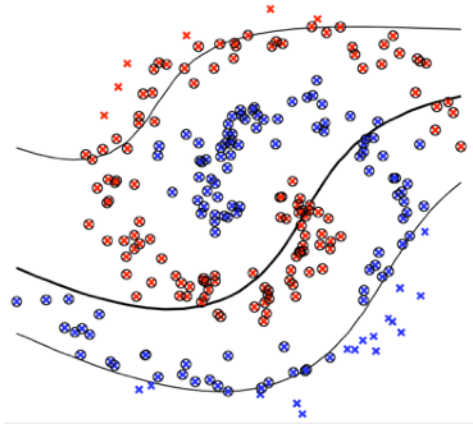
Thin line: margin

Circles: support vectors)

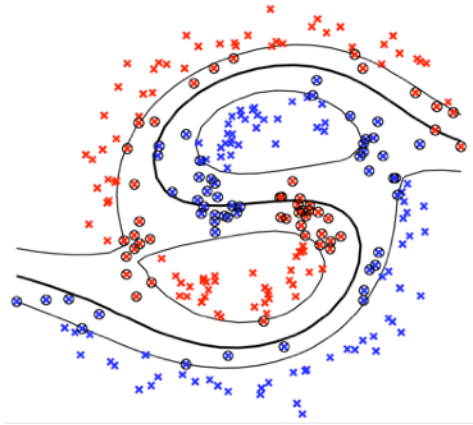
The Influence of the Kernel Parameter



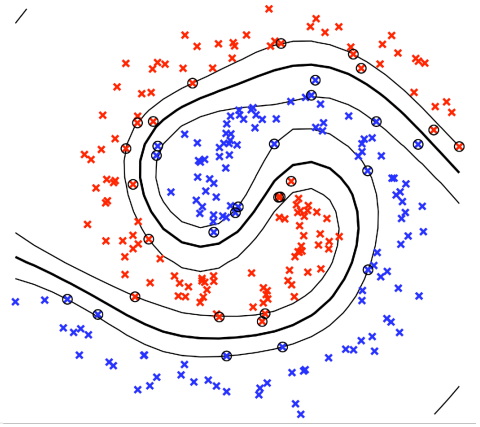
$\gamma = 0.001$



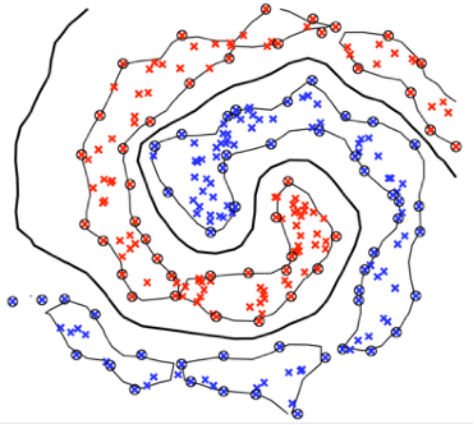
$\gamma = 0.005$



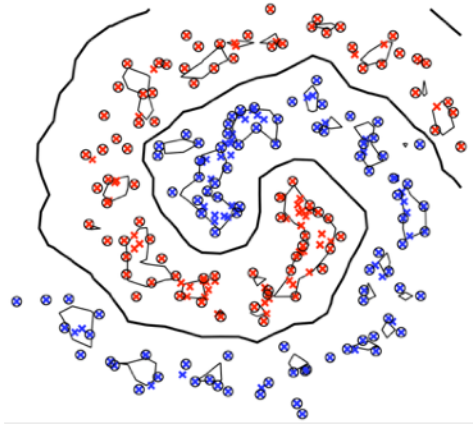
$\gamma = 0.03$



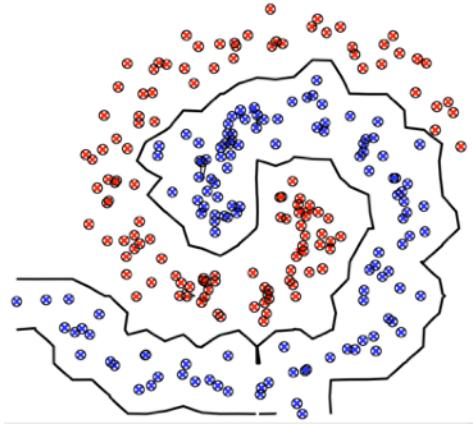
$\gamma = 0.1$



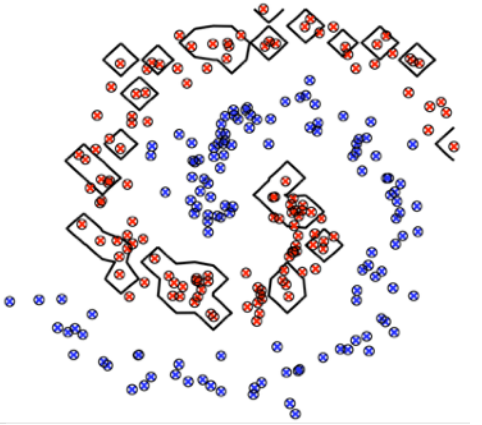
$\gamma = 1$



$\gamma = 2$



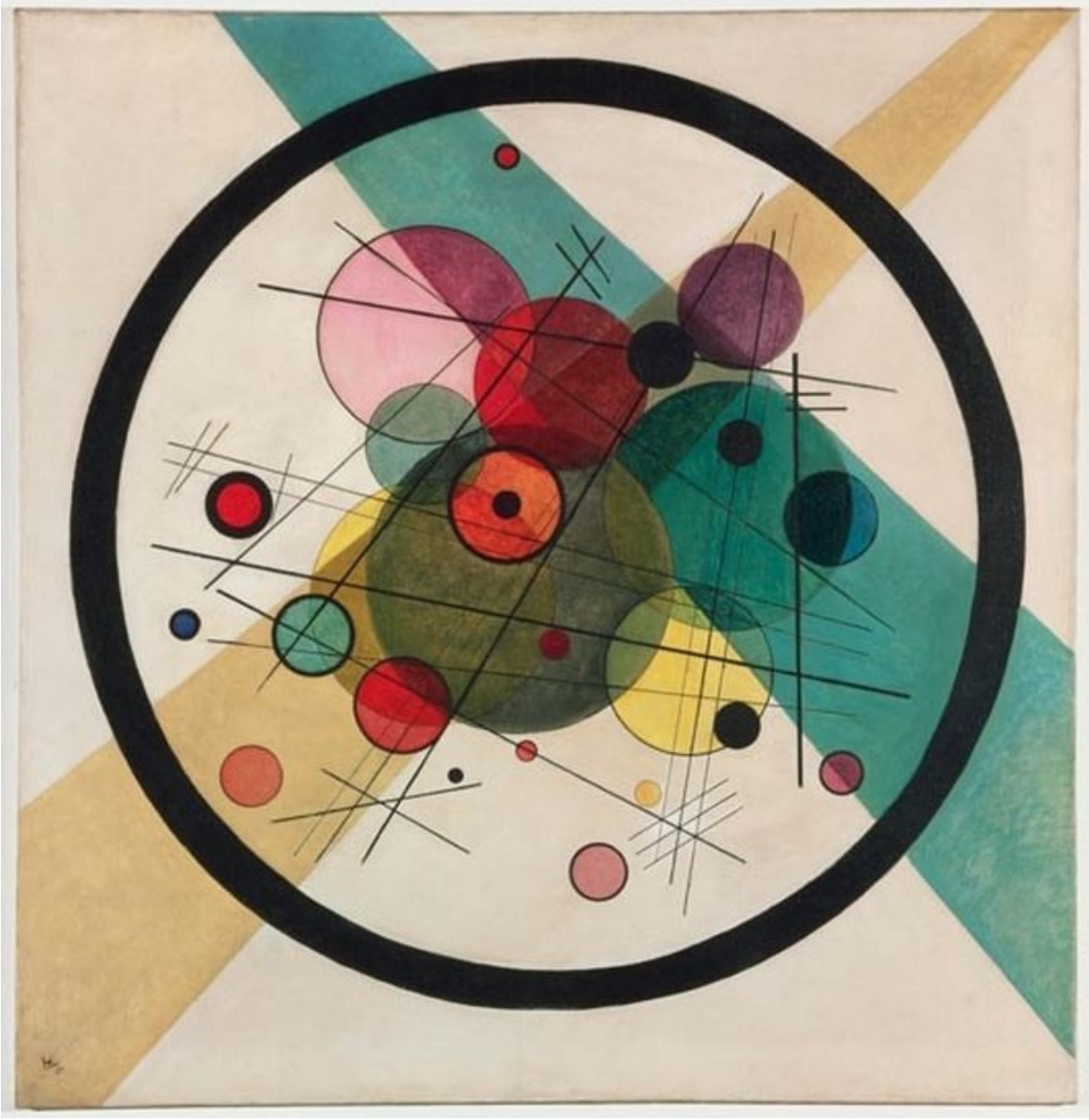
$\gamma = 20$

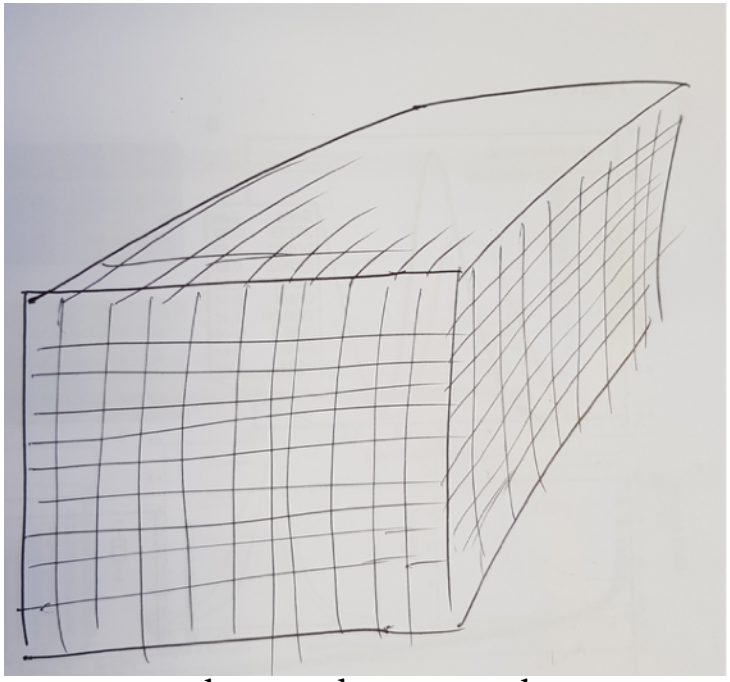


$\gamma = 200$

$\gamma = \sigma^{-2}$, RBF

The curse of dimensionality



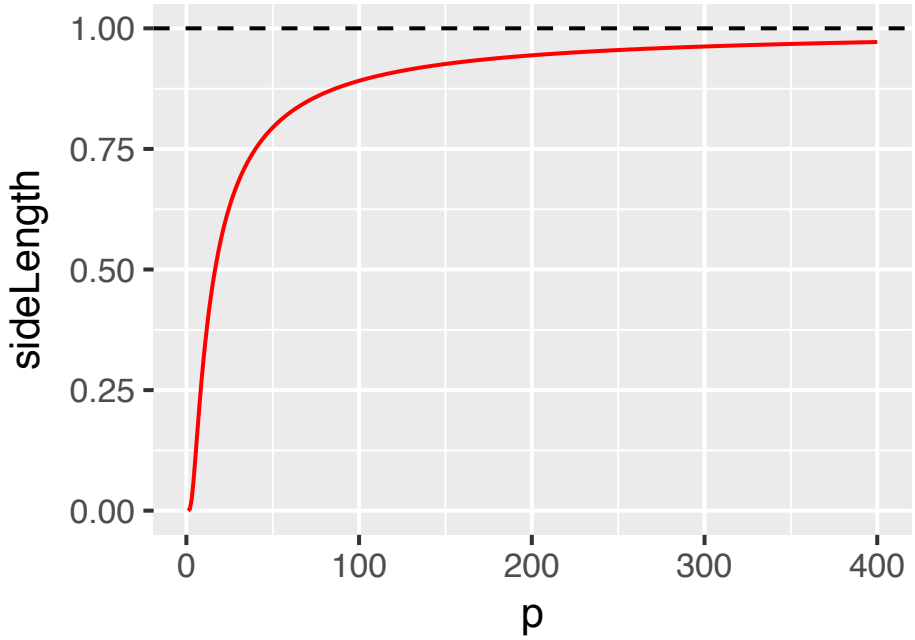


▶ Question **13.12** Assume you have a dataset with 1 000 000 data points in p dimensions. The data are uniformly distributed in the unit hybercube (i. e., all features lie in the interval $[0, 1]$). What's the side length of a hybercube that can be expected to contain just 10 of the points, as a function of p? ◀

▶ Solution **13.12**

See Figure 13.16.

```
sideLength = function(p, pointDensity = 1e6, pointsNeeded = 10)
   (pointsNeeded / pointDensity) ^ (1 / p)
ggplot(tibble(p = 1:400, sideLength = sideLength(p)),
       aes(x = p, y = sideLength)) + geom_line(col = "red") +
  geom_hline(aes(yintercept = 1), linetype = 2)
```



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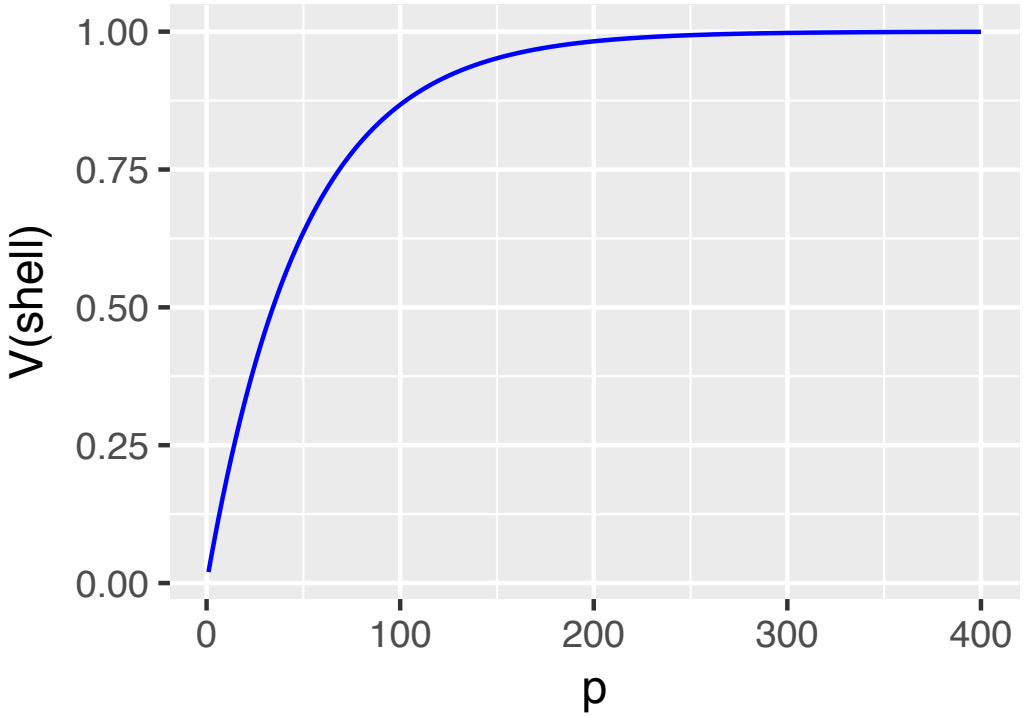
  geom_hline(aes(yintercept = 1), linetype = 2)
```

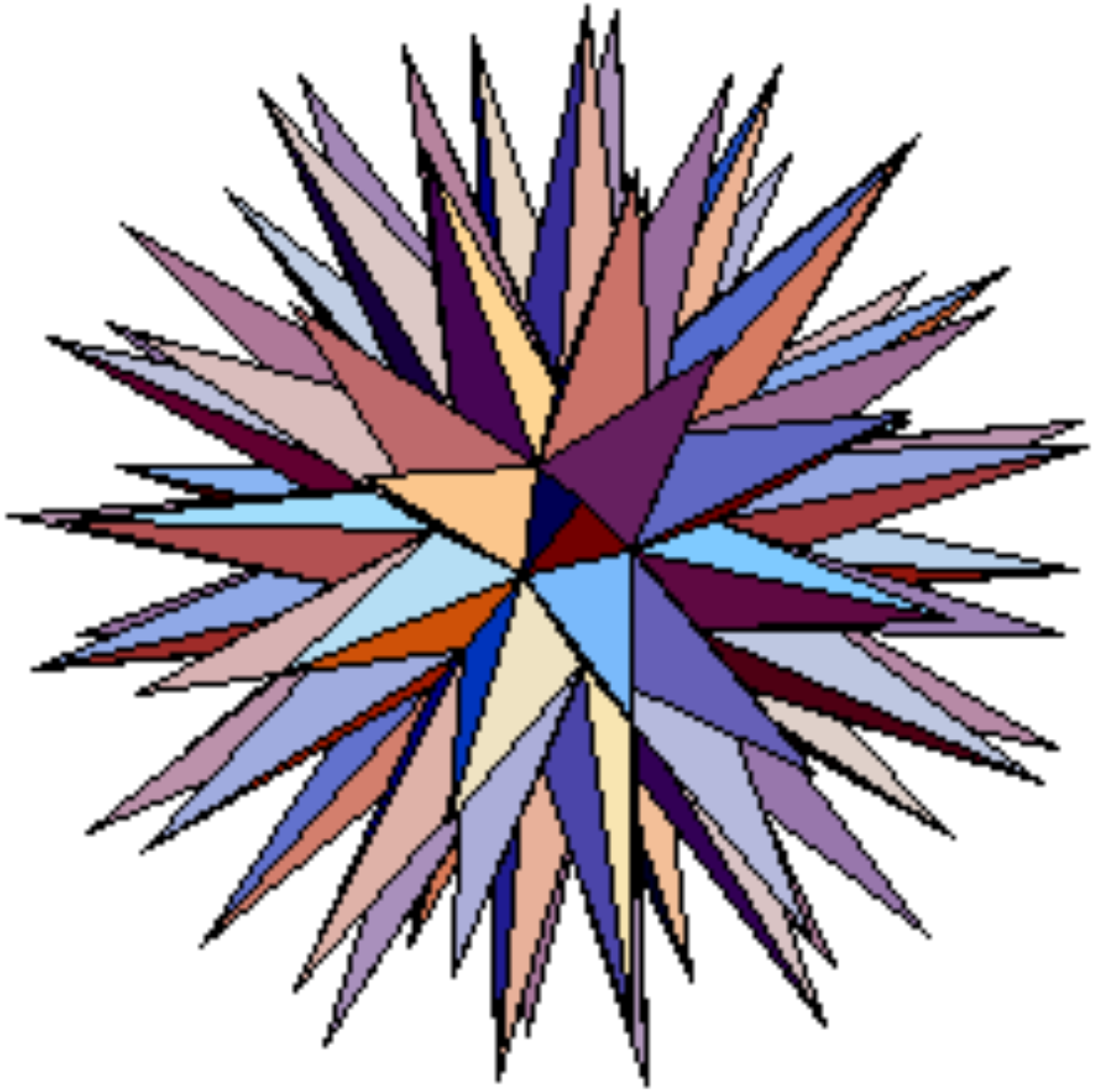


▶ Question **13.13** What fraction of a unit cube's total volume is closer than 0.01 to any of its surfaces, as a function of the dimension? ◀

▶ Solution **13.13**

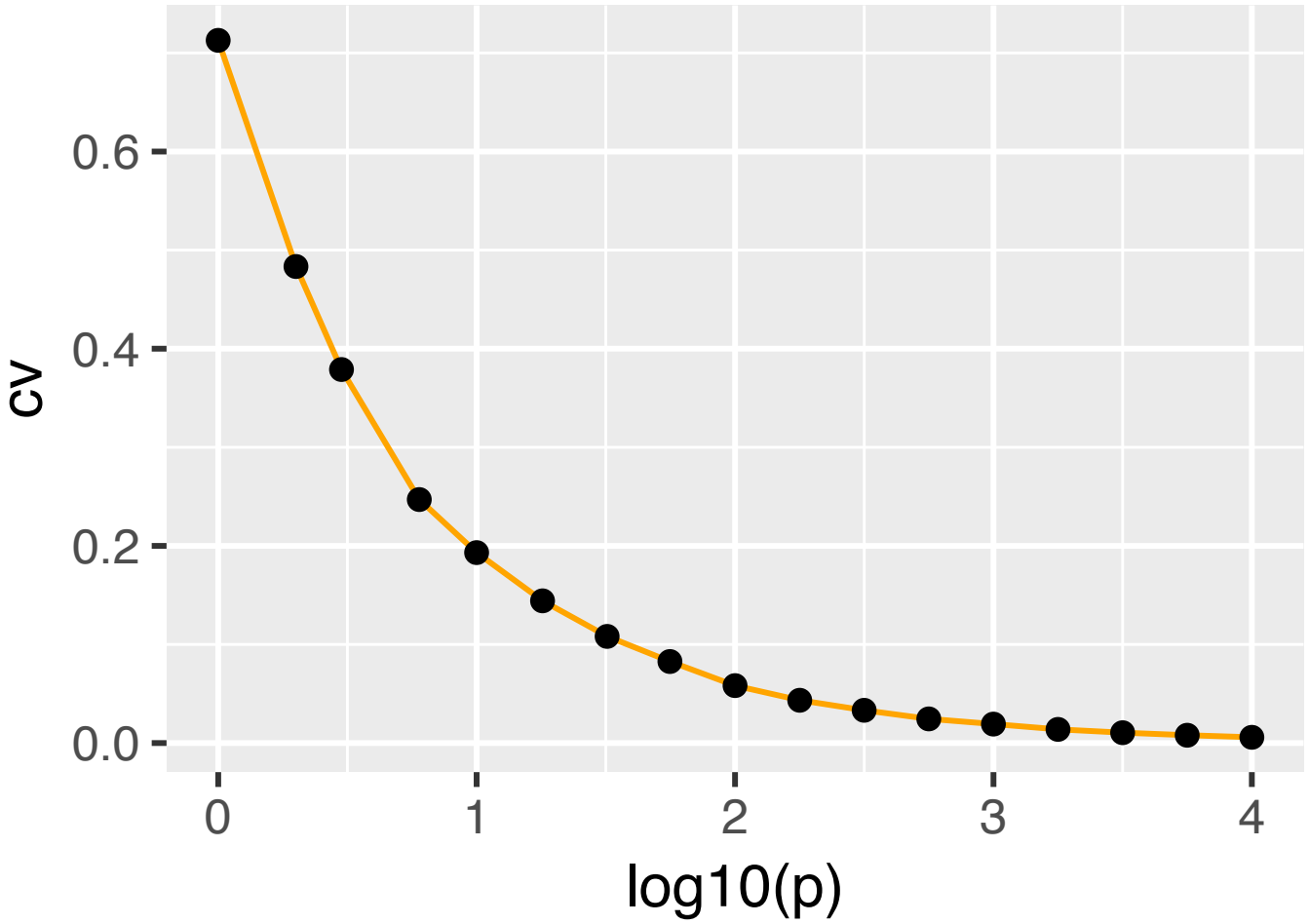
See code below and Figure 13.17.

```
tibble(
  p = 1:400,
  volOuterCube = 1 ^ p,
  volInnerCube = 0.98 ^ p,   # 0.98 = 1 - 2 * 0.01
  `V(shell)` = volOuterCube - volInnerCube) %>%
ggplot(aes(x = p, y =`V(shell)`)) + geom_line(col = "blue")
```



An attempt to visualize a 7-dim hypercube (2^7 = 128 corners)

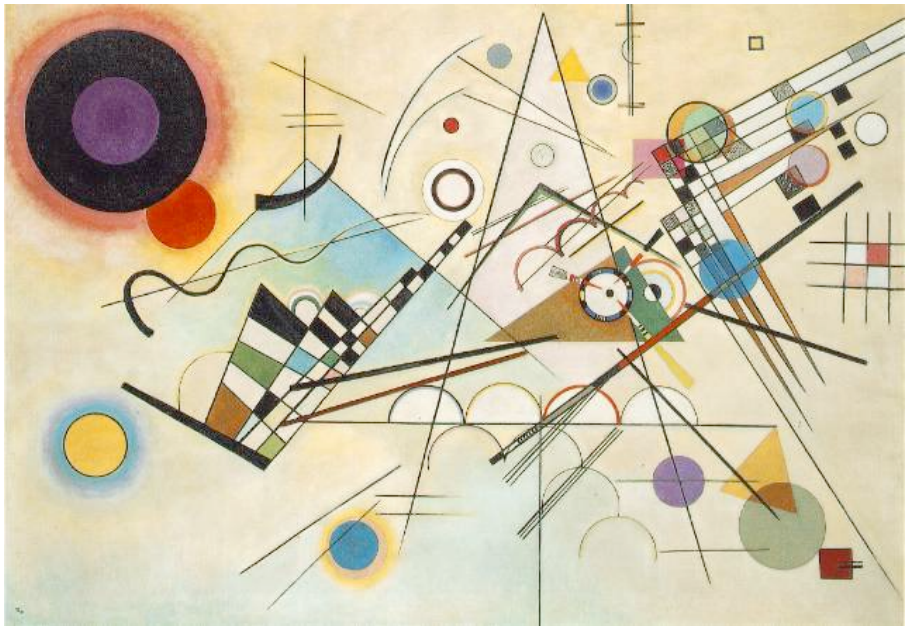
http://yaroslavvb.blogspot.com/2006/05/curse-of-dimensionality-and-intuition.html



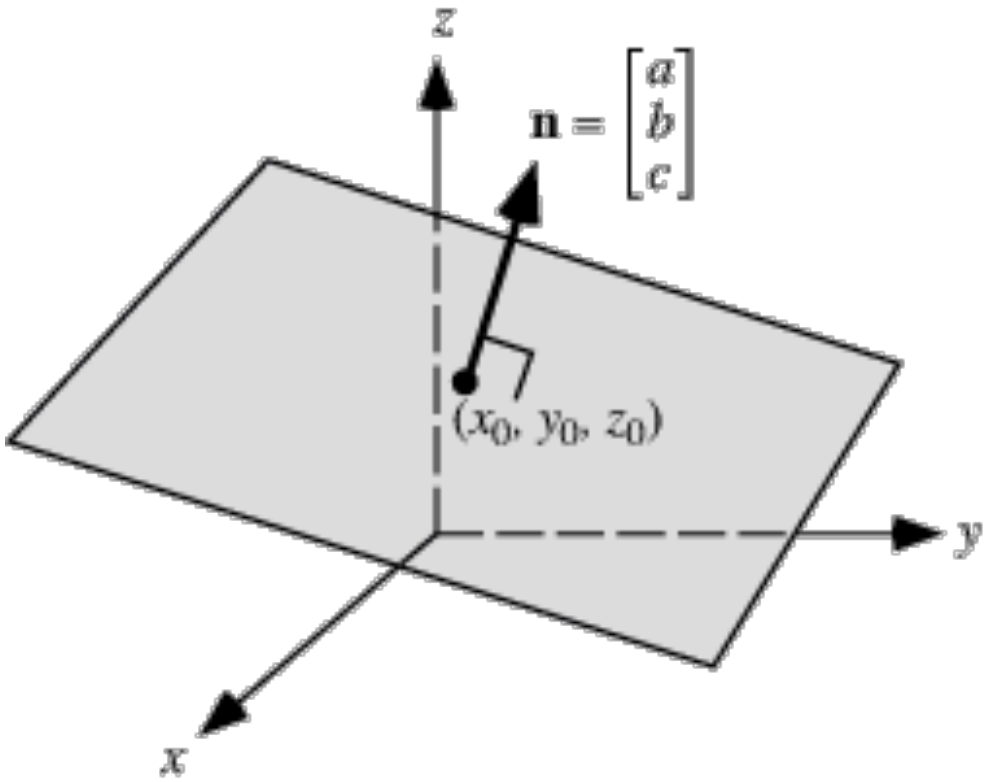
▶ Question **13.14** What is the coefficient of variation (ratio of standard deviation over average) of the distance between two randomly picked points in the unit hypercube, as a function of the dimension? ◀

Curse of Dimensionality: overfitting guaranteed

- Consider:
  - 10 samples per class
  - Each sample is characterised by several hundred features.
- Even a linear classifier will be (always) too complex: overfitting
- There is a need to lower the complexity even below that of the linear classifier



Regularisation



E.g.: decision rule:
x n - 1 > 0

Remember that a plane in 3D space can be represented by its normal vector.

Same for *n*-dim. space

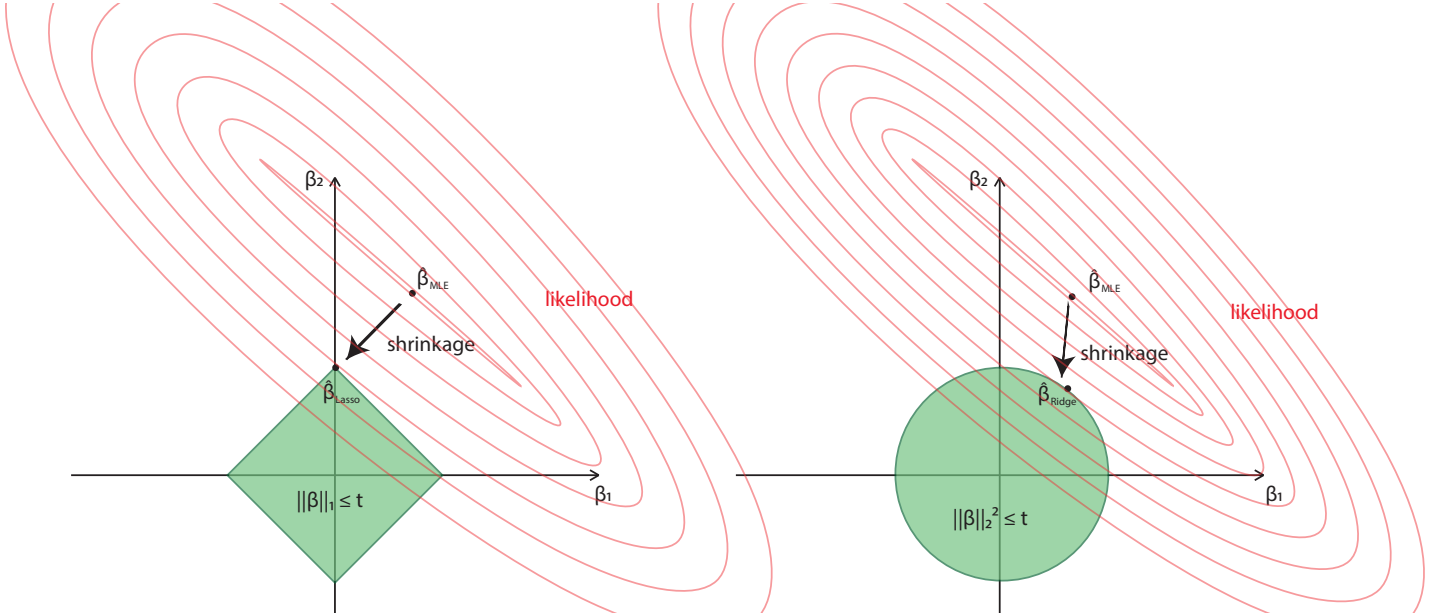
Idea: rather than allowing general vectors, ask for many of the coefficients to be small, or even zero.

Commonly used penalizations and their geometry

Lasso estimator: $p(\beta) = ||\beta||_1$ **Ridge estimator**: $p(\beta) = ||\beta||_2^2$

$$\hat{\beta} \in \arg\min_{\beta} \ell(\beta) + \lambda||\beta||_1 = \arg\min_{\beta} \ell(\beta) \; s.t. ||\beta||_1 \leq t,$$

$$\hat{\beta} \in \arg\min_{\beta} \ell(\beta) + \lambda||\beta||_2^2 = \arg\min_{\beta} \ell(\beta) \; s.t. ||\beta||_2^2 \leq t,$$



- Ridge just wants the $\boldsymbol{\beta}$ to be small
- Lasso snaps many of the elements to 0 ('sparsity')

(least absolute shrinkage and selection operator)

13.6.2 Example: predicting colon cancer from stool microbiome composition

Zeller et al. (2014) studied metagenome sequencing data from fecal samples of 156 humans that included colorectal cancer patients and tumor-free controls. Their aim was to see whether they could identify biomarkers (presence or abundance of certain taxa) that could help with early tumor detection. The data are available from Bioconductor through its **ExperimentHub** service under the identifier EH359.

```
library("ExperimentHub")
eh = ExperimentHub()
zeller = eh[["EH361"]]
```

```
table(zeller$disease)
```

```
##
##        cancer large_adenoma             n small_adenoma
##            53            15            61            27
```

```
pData(zellerNC)[ sample(ncol(zellerNC), 3), ]

##                    subjectID age gender bmi country disease
## CCIS71578391ST-4-0     FR-187  70   male  25  france       n
## CCIS50003399ST-4-0     FR-194  66 female  28  france       n
## CCIS38765456ST-20-0    FR-723  79 female  22  france  cancer
##                    tnm_stage ajcc_stage localization     fobt
## CCIS71578391ST-4-0       <NA>       <NA>         <NA> negative
## CCIS50003399ST-4-0       <NA>       <NA>         <NA> negative
## CCIS38765456ST-20-0    t4n1m1         iv           lc positive
##                    wif-1_gene_methylation_test   group
## CCIS71578391ST-4-0                    negative control
## CCIS50003399ST-4-0                    negative control
```

```
rownames(zellerNC)[1:4]

## [1] "k__Bacteria"
## [2] "k__Viruses"
## [3] "k__Bacteria|p__Firmicutes"
## [4] "k__Bacteria|p__Bacteroidetes"

rownames(zellerNC)[nrow(zellerNC) + (-2:0)] %>% formatfn

## [[1]]
## [1] "k__Bacteria| p__Proteobacteria| c__Deltaproteobacteria|"
## [2] "o__Desulfovibrionales| f__Desulfovibrionaceae|"
## [3] "g__Desulfovibrio| s__Desulfovibrio_termitidis"
##
## [[2]]
## [1] "k__Viruses| p__Viruses_noname| c__Viruses_noname|"
## [2] "o__Viruses_noname| f__Baculoviridae|"
## [3] "g__Alphabaculovirus|"
## [4] "s__Bombyx_mori_nucleopolyhedrovirus|"
## [5] "t__Bombyx_mori_nucleopolyhedrovirus_unclassified"
##
## [[3]]
## [1] "k__Bacteria| p__Proteobacteria| c__Deltaproteobacteria|"
## [2] "o__Desulfovibrionales| f__Desulfovibrionaceae|"
## [3] "g__Desulfovibrio| s__Desulfovibrio_termitidis|"
## [4] "t__GCF_000504305"
```

glmnet on the Zeller data

```
library("glmnet")
glmfit = glmnet(x = t(exprs(zellerNC)),
                y = factor(zellerNC$disease),
                family = "binomial")
```

```
predTrsf = predict(glmfit, newx = t(exprs(zellerNC)),
                   type = "class", s = 0.04)
table(predTrsf, zellerNC$disease)
```

```
##
## predTrsf cancer  n
##   cancer     51  0
##   n           2 61
```

```
plot(glmfit, col = brewer.pal(12, "Set3"), lwd = sqrt(3))
```

glmnet on the Zeller data

```
library("glmnet"
glmfit = glmnet
```

```
predTrsf = predi
```

```
table(predTrsf,
```

```
##
## predTrsf canc
##    cancer
##    n
```

```
plot(glmfit, co
```

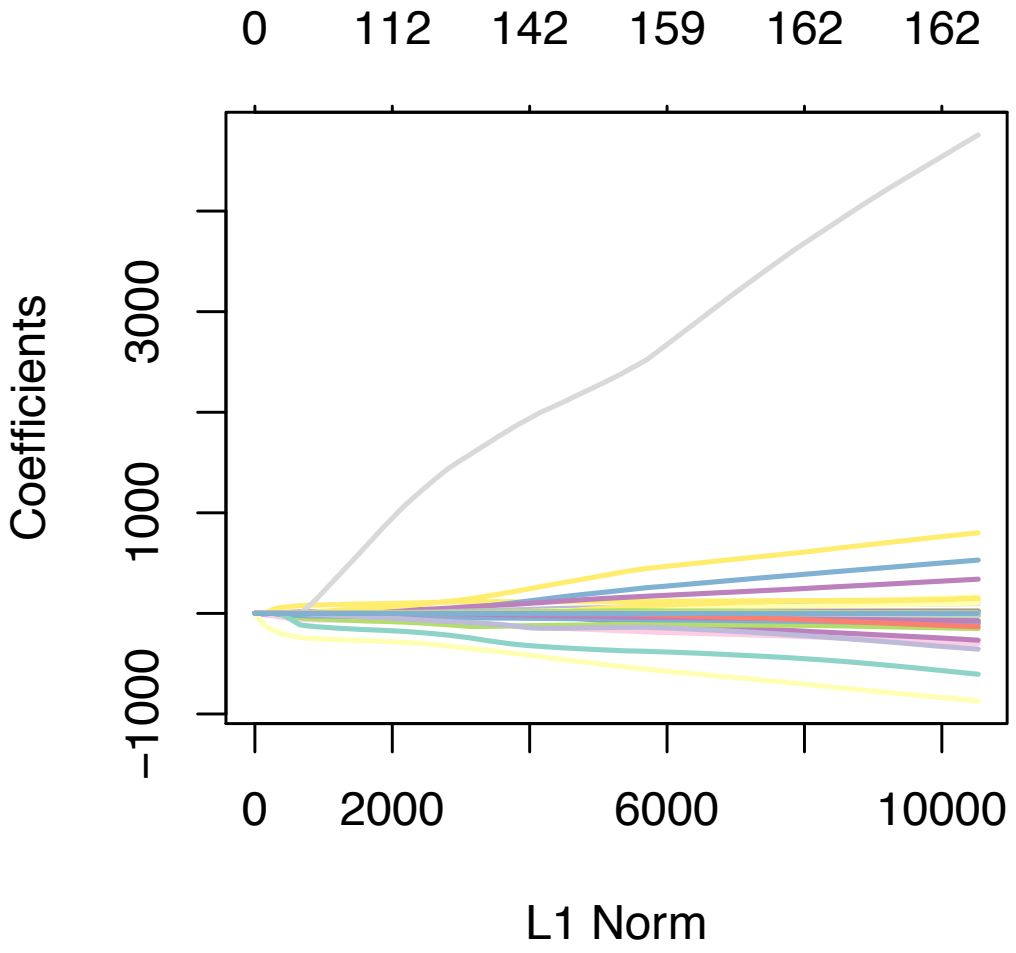
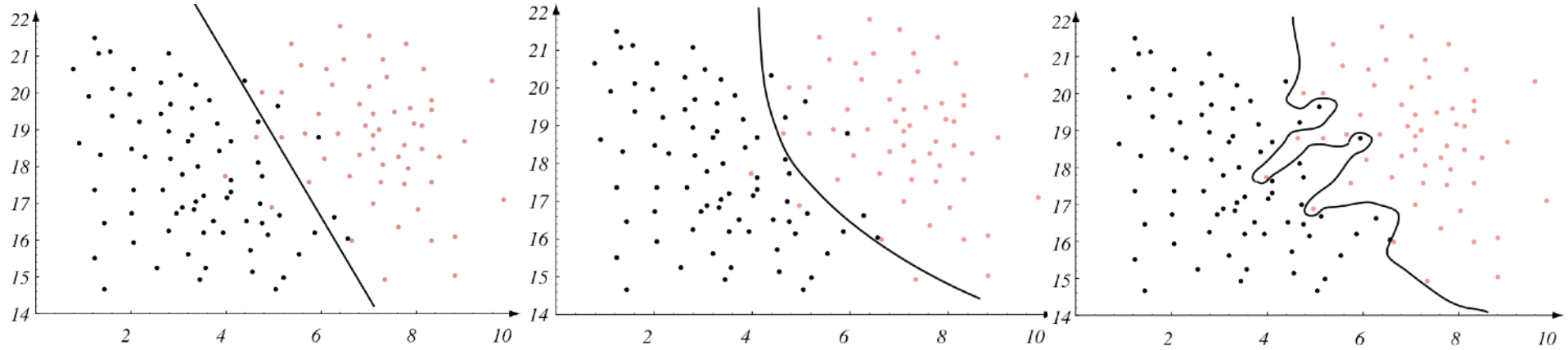


Figure 13.21: Regularization paths for `glmfit`.

Summary: It's all about adapting the complexity of the model to that of the data

High bias
Low variance

Low bias
High variance



low model complexity
(needs 2 parameters to describe the decision boundary)

high model complexity
(need 100s of parameters to describe decision boundary)

Reduce complexity: regularization (Lasso, ridge, …)
Increase complexity: data transformation, augmentation, kernels
Always assess classifiers by **cross-validation**