Supervised Learning: Classification

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- Classification problems tend to occur even more frequently than regression problems in biomedical applications.
- Just like regression,
  - Classification cannot be blindly performed in high-dimensions because you will get zero training error but awful test error;
  - Properly estimating the test error is crucial; and
  - There are a few tricks to extend classical classification approaches to high-dimensions, which we have already seen in the regression context!

Classification

- Categorical / qualitative variables take values in an unordered set: e.g.
  eye color $\in \{brown, blue, green\}$
  email $\in \{spam, not\ spam\}$.
- We want to build a function that takes as input the feature vector X and predicts the value for Y.
- Often we are more interested in estimating the probability that X belongs to a given category.
- For example: we might want to know the probability that someone will develop diabetes, rather than to predict whether or not they will develop diabetes.

Can't We Just Use Linear Regression?

- Classify an emergency room patient on the basis of her symptoms to one of three conditions:

$$Y = \begin{cases} 1 & \text{if stroke;} \\ 2 & \text{if drug overdose;} \\ 3 & \text{if epileptic seizure.} \end{cases}$$

- If we apply linear regression, then the results will depend on the choice of coding . . . and the coding implies an ordering among the medical conditions.
- A classification approach is more appropriate.

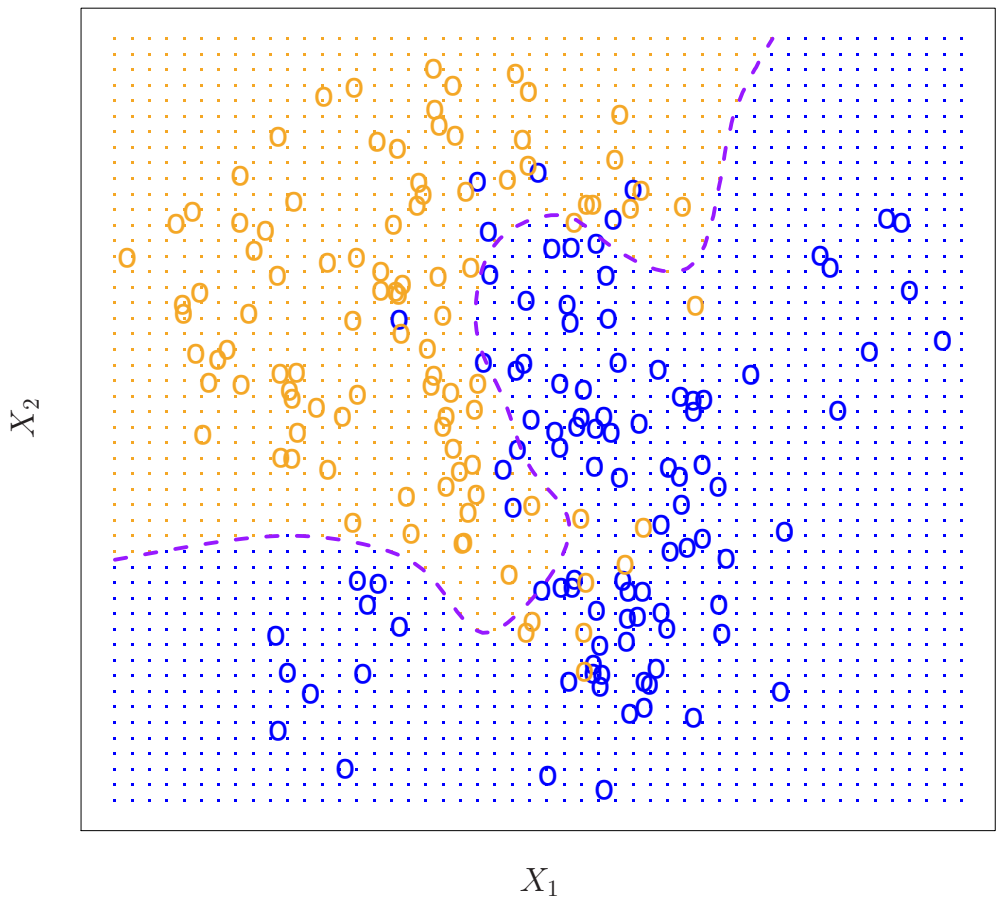
Classification

- There are many approaches out there for performing classification.
- We will discuss three: k-nearest neighbors, logistic regression, and support vector machines.

K-Nearest Neighbors

- Can I take a totally non-parametric (model-free) approach to classification?
- K-nearest neighbors:
  1. Identify the K observations whose X values are closest to the observation at which we want to make a prediction.
  2. Classify the observation of interest to the most frequent class label of those K nearest neighbors.

K-Nearest Neighbors



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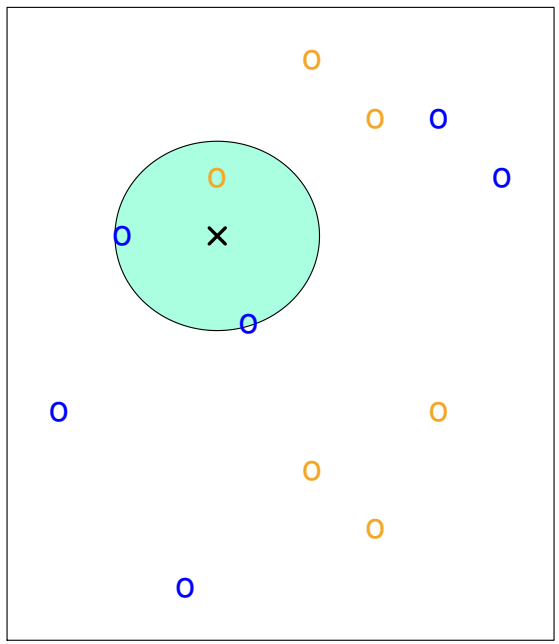

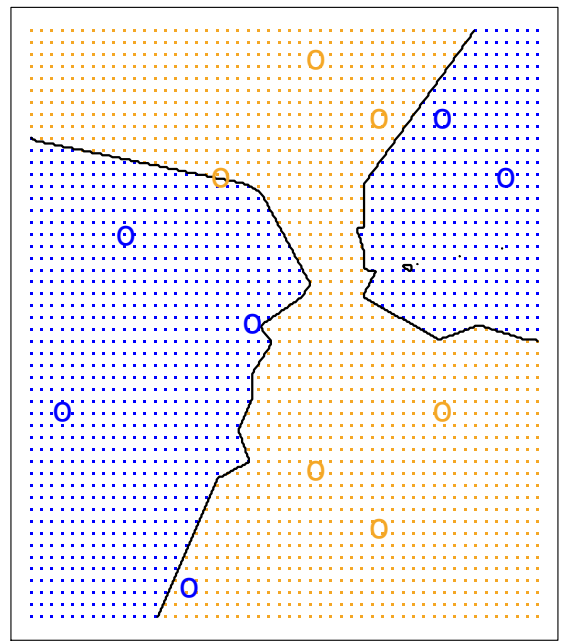

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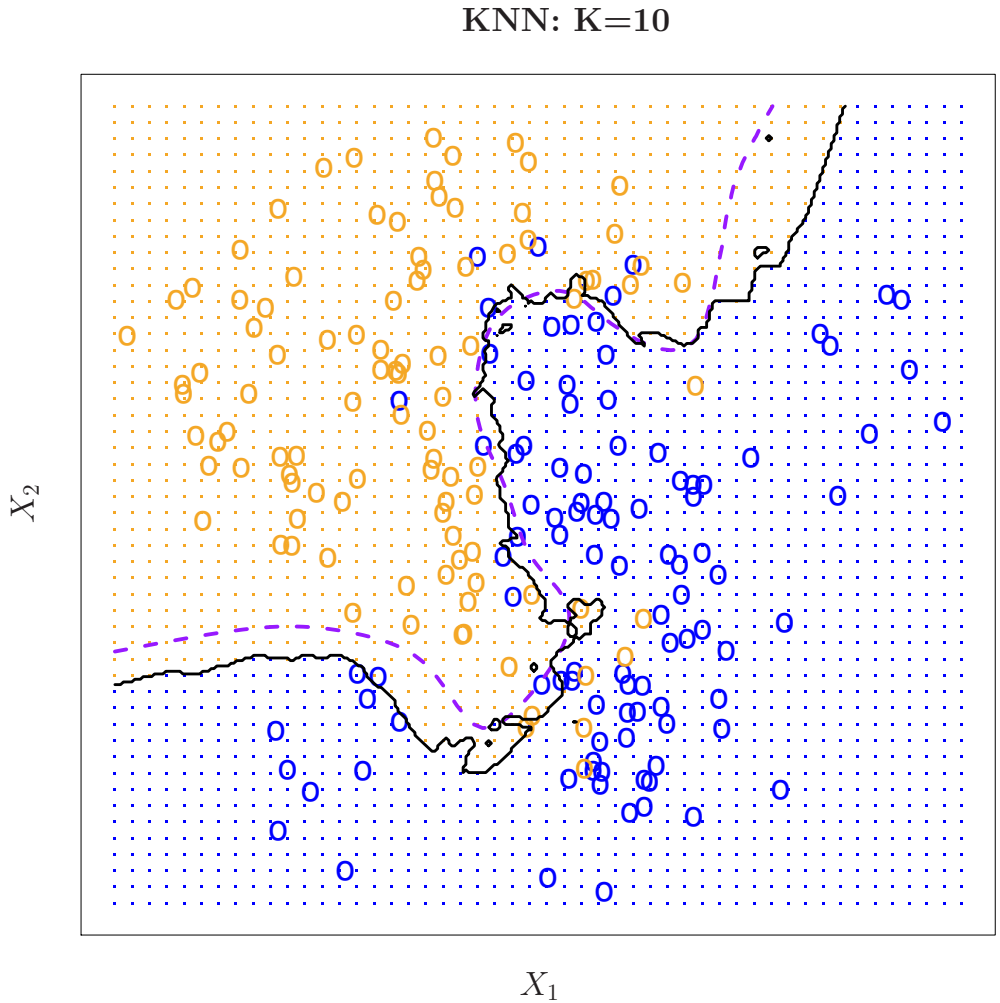
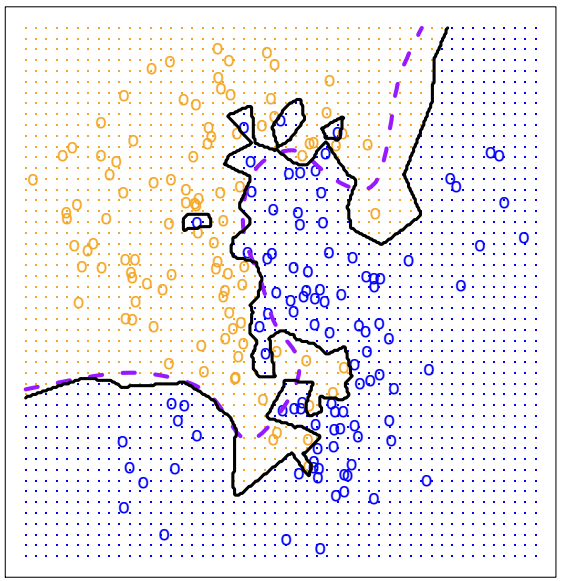
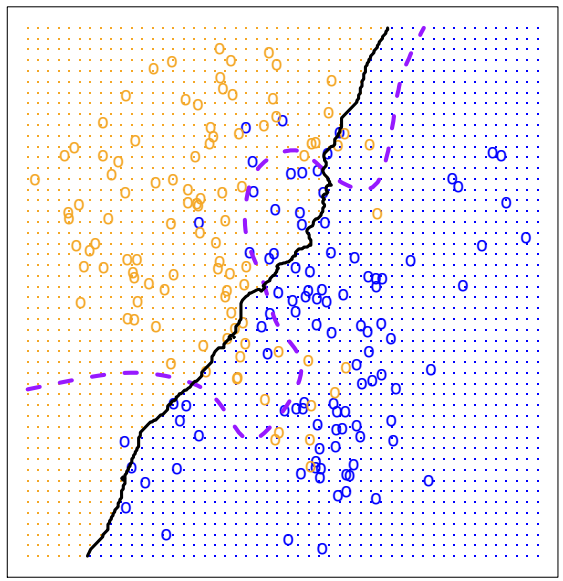


K-Nearest Neighbors

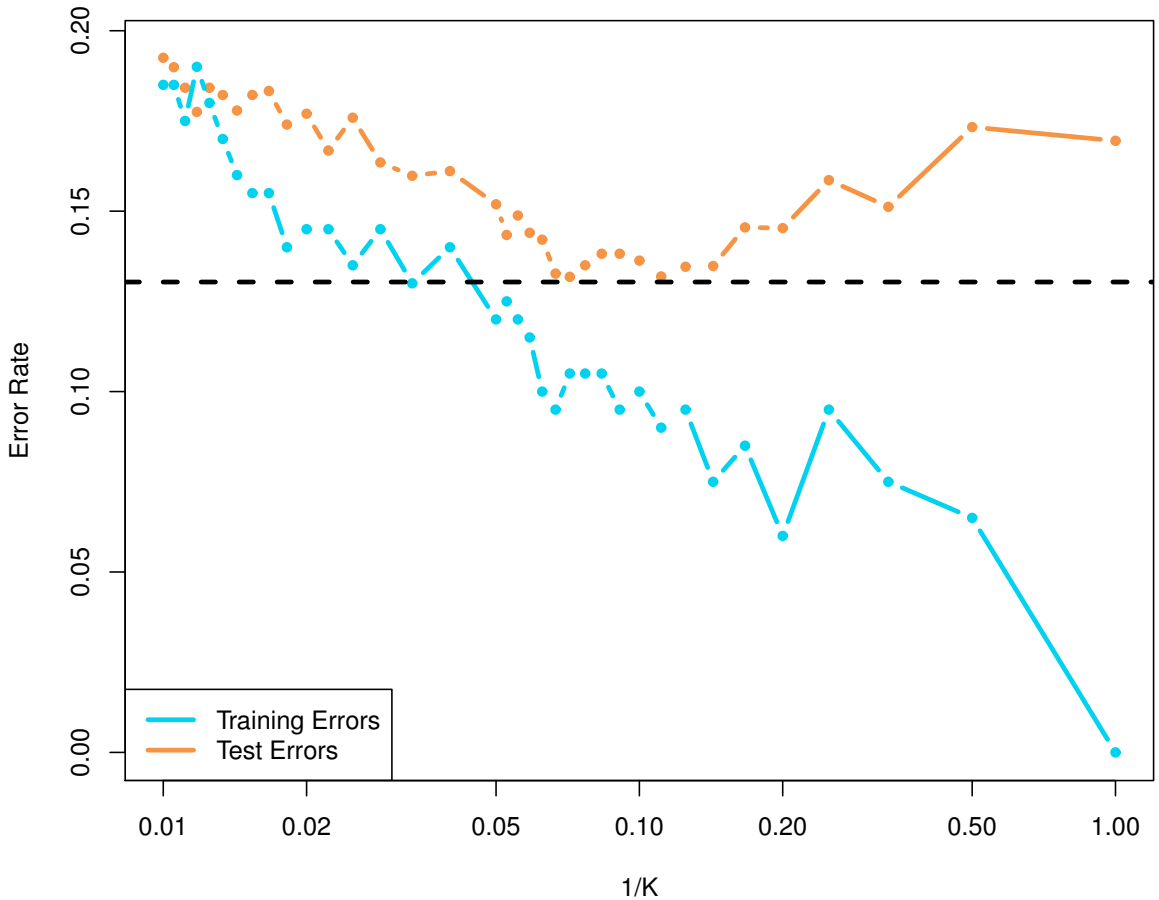
KNN: K=1



KNN: K=100



K-Nearest Neighbors



K-Nearest Neighbors

- Simple, intuitive, model-free.
- Good option when p is very small.
- Curse of dimensionality: when p is large, no neighbors are "near". All observations are close to the boundary.
- Do not use in high dimensions!

Logistic Regression

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- For simplicity, suppose $y \in \{0, 1\}$: a two-class classification problem.
- The simple linear model $y = X\beta + \epsilon$ doesn't make sense for classification.

Logistic Regression

- Let $p(X) = \Pr(Y = 1|X)$.
- Suppose we want to use biomarker level to predict probability of cancer.
- Logistic regression uses the form

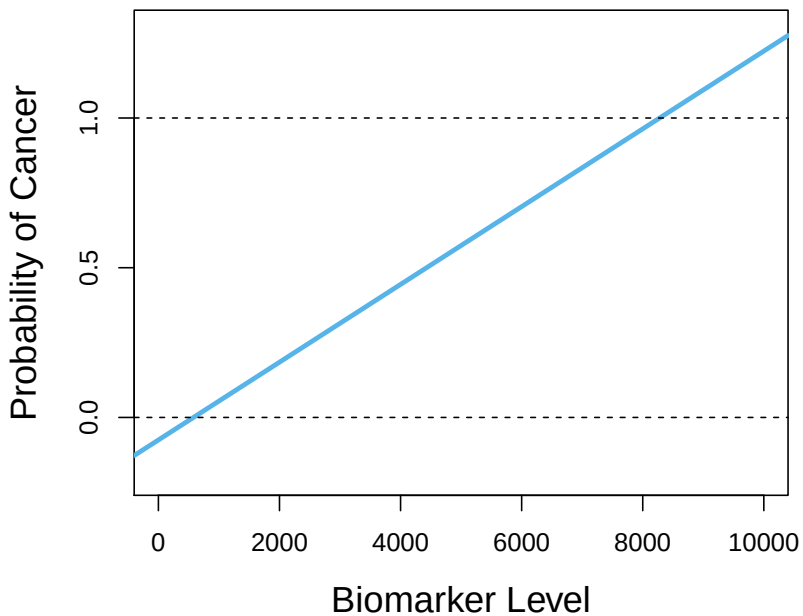
$$p(X) = \frac{e^{\beta_0+\beta_1 X}}{1 + e^{\beta_0+\beta_1 X}}.$$

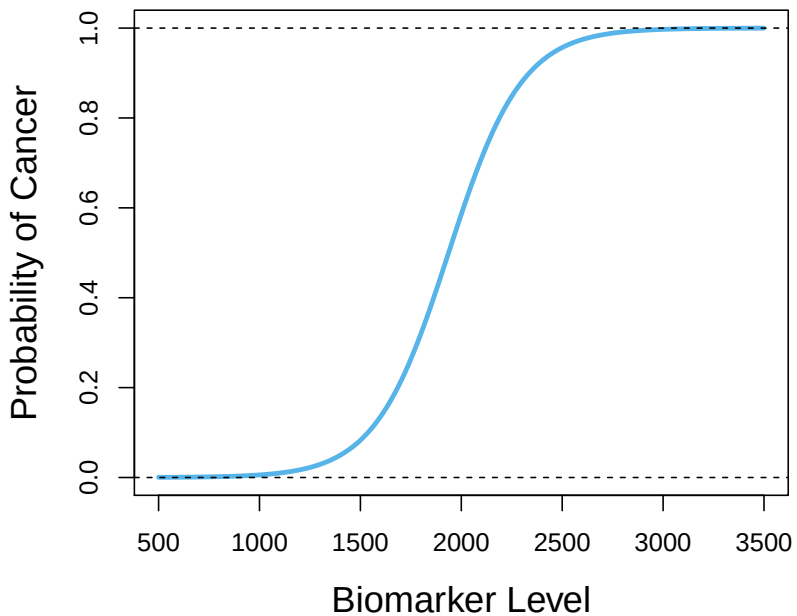
- $p(X)$ will lie between 0 and 1.
- Furthermore,

$$\log\left(\frac{p(X)}{1 - p(X)}\right) = \beta_0 + \beta_1 X.$$

- This function of $p(X)$ is called the logit or log odds.

Why Not Linear Regression?





- Left: linear regression.
- Right: logistic regression.

Multiple Logistic Regression

- Just like before:

$$p(X) = \frac{e^{\beta_0+\beta_1 X_1+\cdots+\beta_p X_p}}{1+e^{\beta_0+\beta_1 X_1+\cdots+\beta_p X_p}}.$$

- And just like before:

$$\log\left(\frac{p(X)}{1-p(X)}\right) = \beta_0+\beta_1 X_1+\cdots+\beta_p X_p.$$

Example in R

```
xtr <- matrix(rnorm(1000*20),ncol=20)
beta <- c(rep(1,10),rep(0,10))
ytr <- 1*((xtr%*%beta + .2*rnorm(1000)) >= 0)
mod <- glm(ytr~xtr,family="binomial")
print(summary(mod))
```

Five Ways to Extend Logistic to High Dimensions

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How to decide which approach is best, and which tuning parameter value to use for each approach? Cross-validation or validation set approach.

What is an appropriate validation measure?

For classification without a probability or score:

- Misclassification rate:

$$\frac{\#\text{test samples misclassified}}{\text{total \# of test samples}}$$

What is an appropriate validation measure?

For probablistic classification

- Can still use misclassification rate.
- Like in continuous regression could use SSE:

$$\sum_{i \in \text{test}} (y_i - \hat{p}_i)^2$$

- Often preferable to use "predictive [log]likelihood":

$$-\log \left[\prod_{i \in \text{test}} \hat{p}_i^{y_i} (1 - \hat{p}_i)^{1-y_i} \right]$$

- Can also use ROC-curve-based metric (eg. AUC)

Remember though; all of these must be conducted on a separate validation set.

Example in R: Lasso Logistic Regression

```
xtr <- matrix(rnorm(1000*20),ncol=20)
beta <- c(rep(1,5),rep(0,15))
ytr <- 1*((xtr%*%beta + .5*rnorm(1000)) >= 0)
cv.out <- cv.glmnet(xtr, ytr, family="binomial", alpha=1)
plot(cv.out)
```

Let's Try It Out in R!

Chapter 4 R Lab
Skip part on LDA & QDA
www.statlearning.com

Bayes-based classifiers

Suppose rather than knowing $P(y = j|x)$...

we have information on $f_j(x) = P(x|y = j)$, the feature distribution within each class

How do we use this to make predictions?

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How do we use this to make predictions?

Using Bayes Theorem:

$$P(y = j|x) = \frac{f_j(x)\pi_j}{\sum_k f_k(x)\pi_k}$$

here $\pi_k = P(y = k)$ is the prior probability of class k.

Estimating the Rule

To apply Bayes Theorem

$$P(y = j|x) = \frac{f_j(x)\pi_j}{\sum_k f_k(x)\pi_k}$$

we need

- $f_k(x)$ for $k = 1, \ldots, K$
- π_k for $k = 1, \ldots, K$

Estimating the π_k

π_k is generally simple to estimate

- If your data are a random sample; then can use the sample proportion

$$\hat{\pi}_k = \frac{\#\{y_i = k\}}{n}$$

- Otherwise can use outside information (eg. historical data)

If you change population proportions; it is easy to adjust the rule.

Estimating the $f_k(x)$

Estimate of $f_k(x) = P(x|y = k)$ is more difficult.

This is a density estimation problem.

The tools we discuss for this break down into 3 general categories

- flexible, non-parametric estimates
- parametric estimates
- shrunken parametric estimates

The above are ordered (more-or-less) by where they fall on bias/variance spectrum:

more flexible $\rightarrow$ less bias/more variance

Parametric $f_k(x)$ Estimate

Most well known estimator of this type is Linear/Quadratic Discriminant Analysis:

Here we assume that $f_k(x)$ is Gaussian density, $N(\mu_k, \Sigma_k)$

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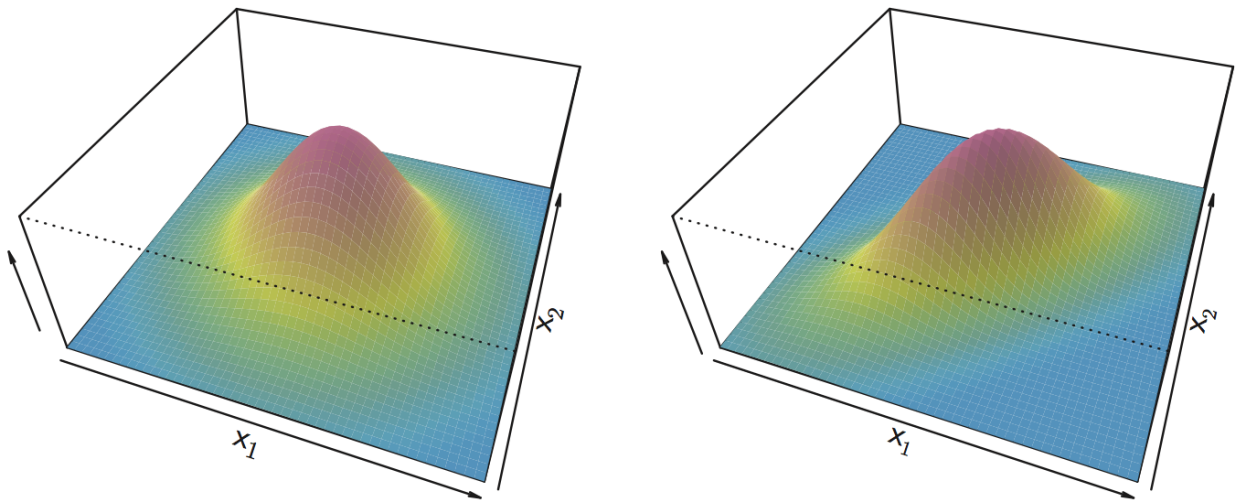

Discriminant Analysis

There are three main types of unpenalized discriminant analysis:

- Quadratic (QDA)
- Linear (LDA)
- Diagonal (DDA)

These make different assumptions on the covariance structure:

- QDA makes no assumptions
- LDA assumes a pooled variance $\Sigma = \Sigma_k$ for all k
- DDA assumes a pooled variance; and further that Σ is diagonal (i.e. no correlation among covariates!)

Discriminant Analysis

Why would we choose DDA over QDA?

Remember, *flexibility* comes at a price!

QDA will have the least bias; but has many more parameters to estimate

Often good estimates of the correlation don't improve classifications much

DDA takes into account the scale of each feature, but trades a bit of bias for potentially a large reduction in variance

LDA for $p = 1$

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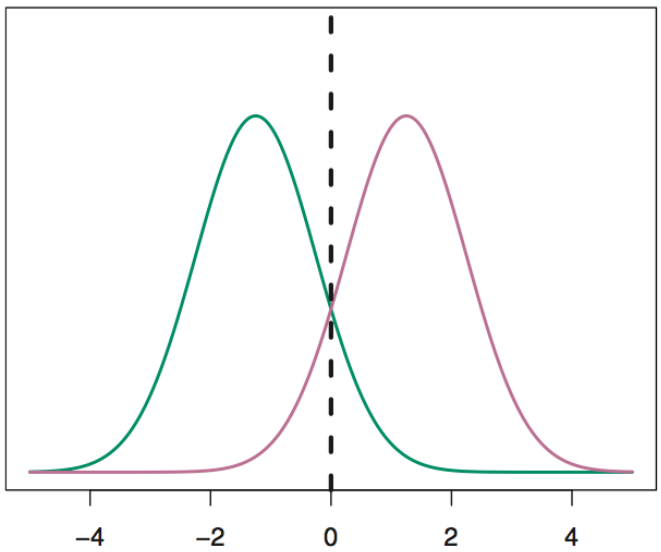

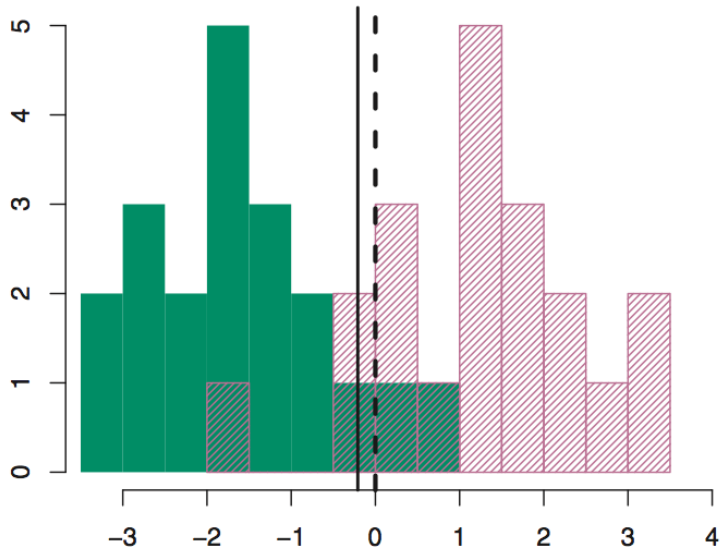

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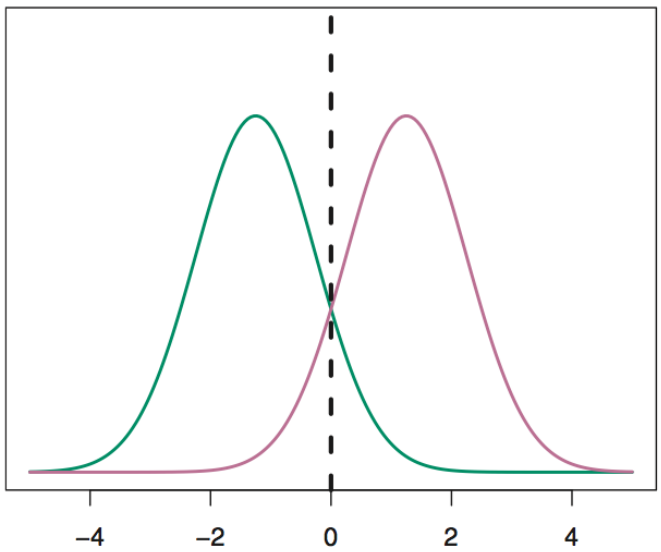

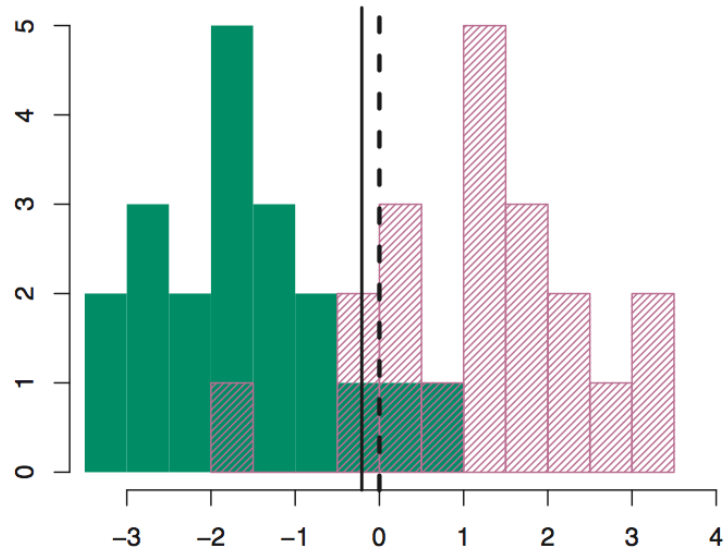

- To make this work, we need to estimate the parameters. The ML estimates are given by $\hat{\pi}_k = n_k/n$ and

$$\hat{\mu}_k = \frac{1}{n_k} \sum_{i:y_i=k} x_i \qquad \hat{\sigma}^2 = \frac{1}{n-K} \sum_{k=1}^{K} \sum_{i:y_i=k} (x_i - \hat{\mu}_k)^2$$

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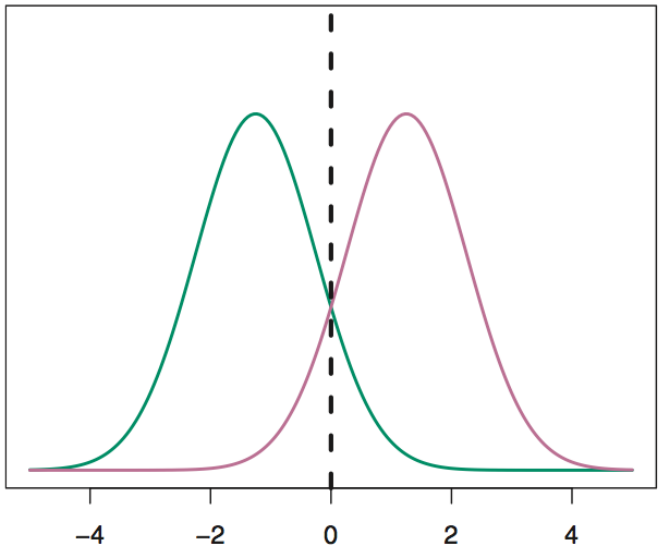

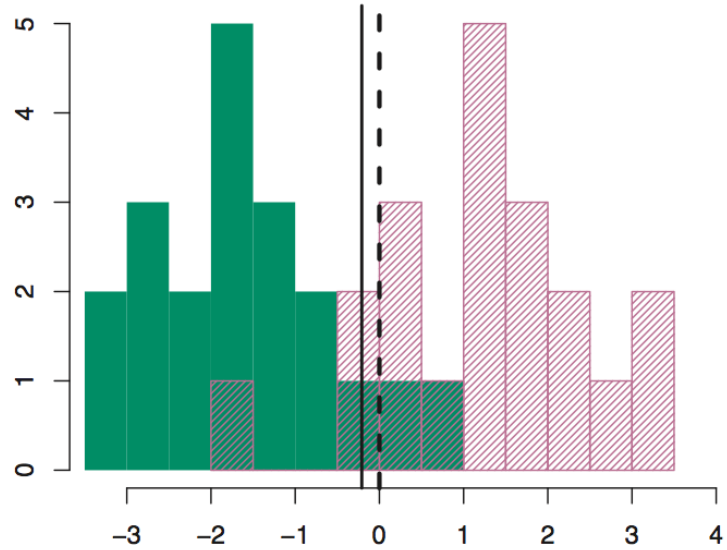

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- The picture is very similar if $K > 2$...or if $p > 1$

LDA for $p > 1$

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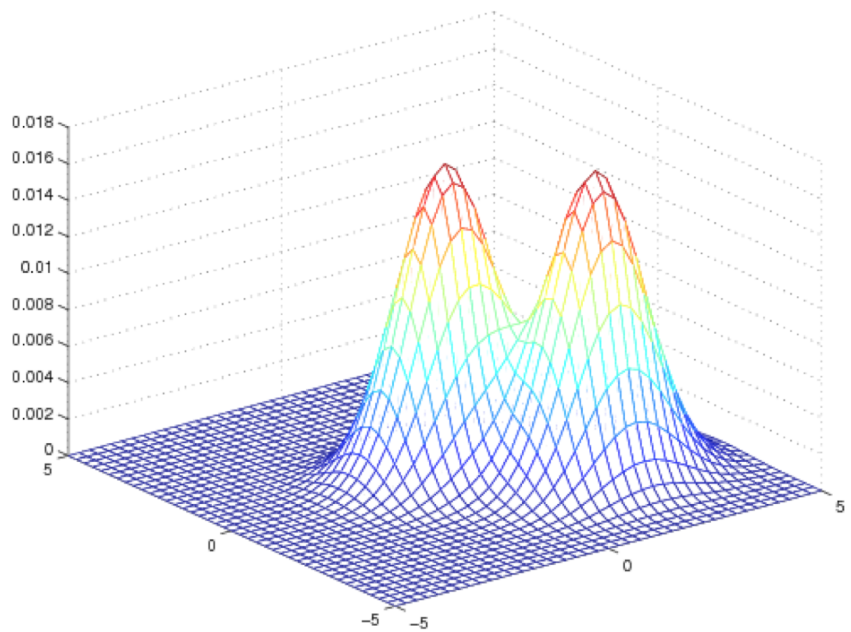
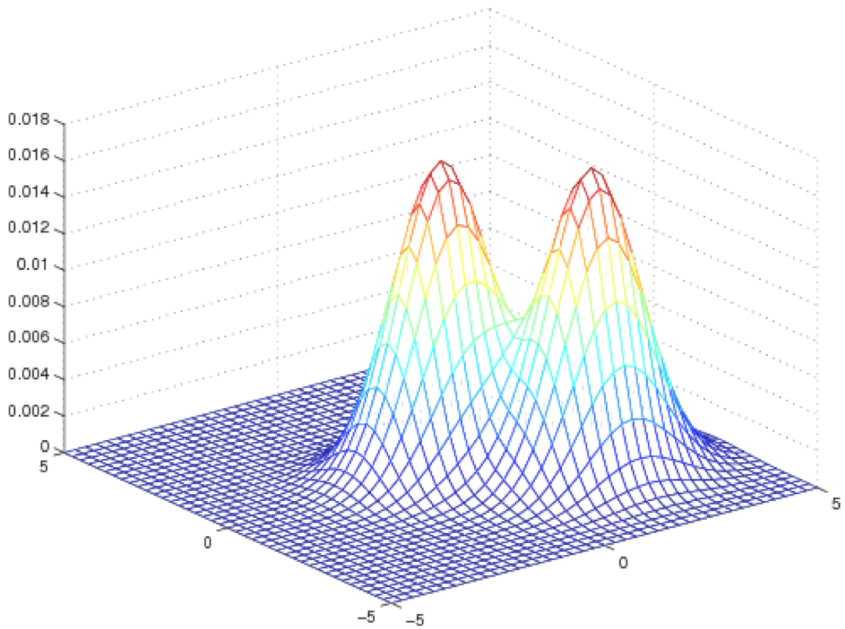


LDA for $p > 1$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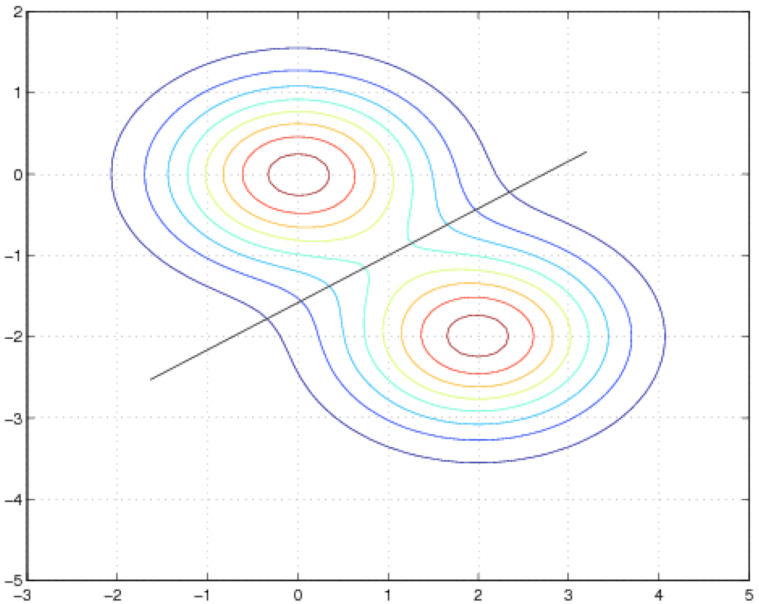
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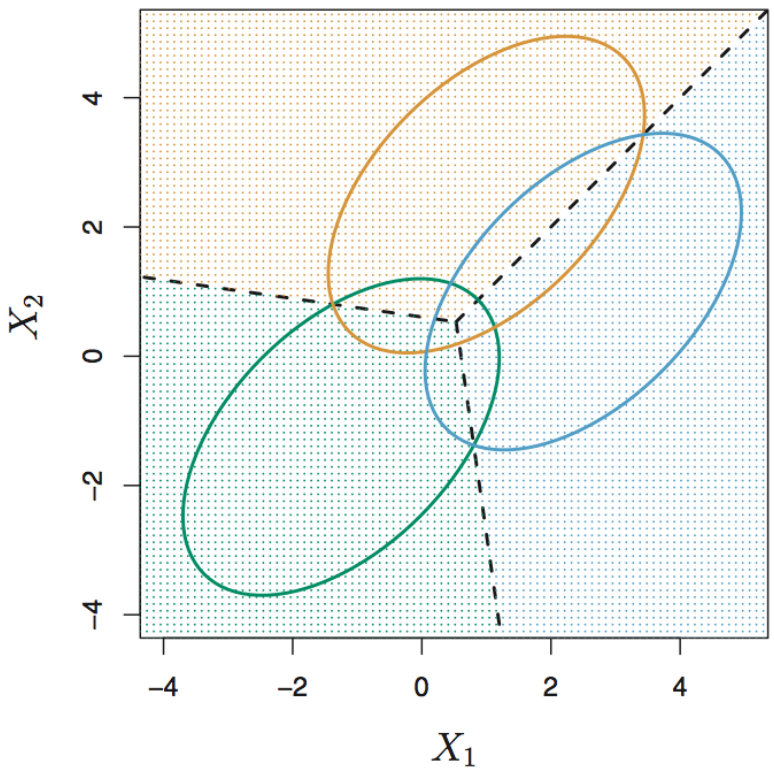
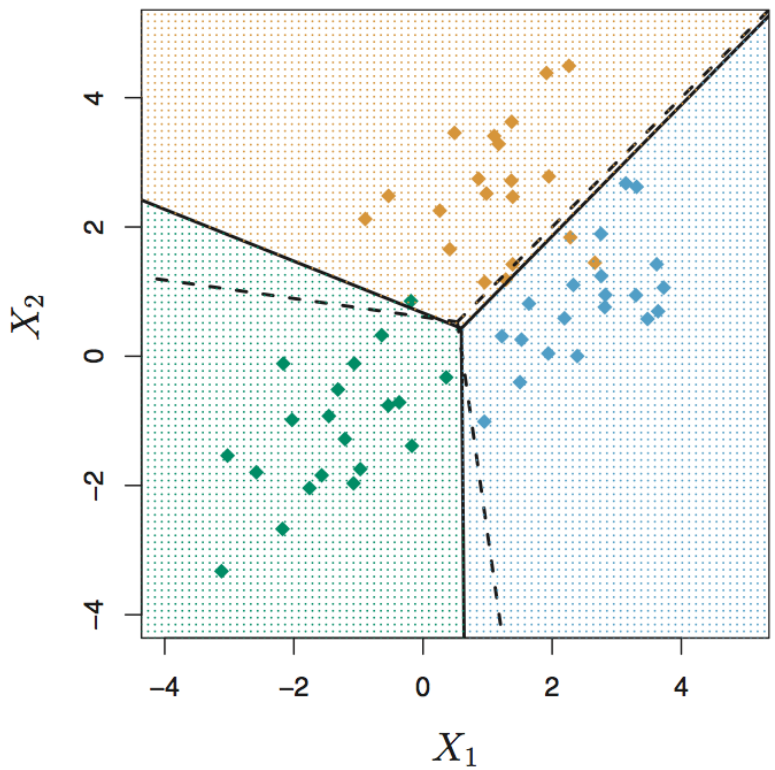


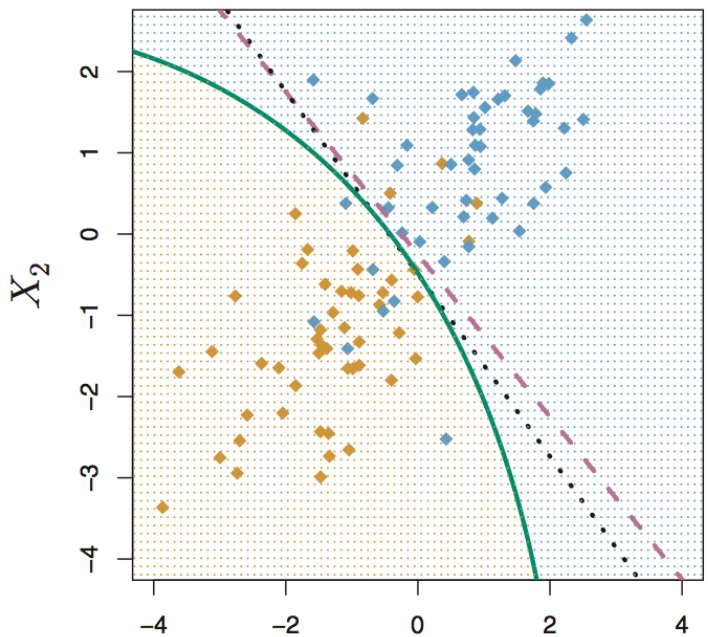


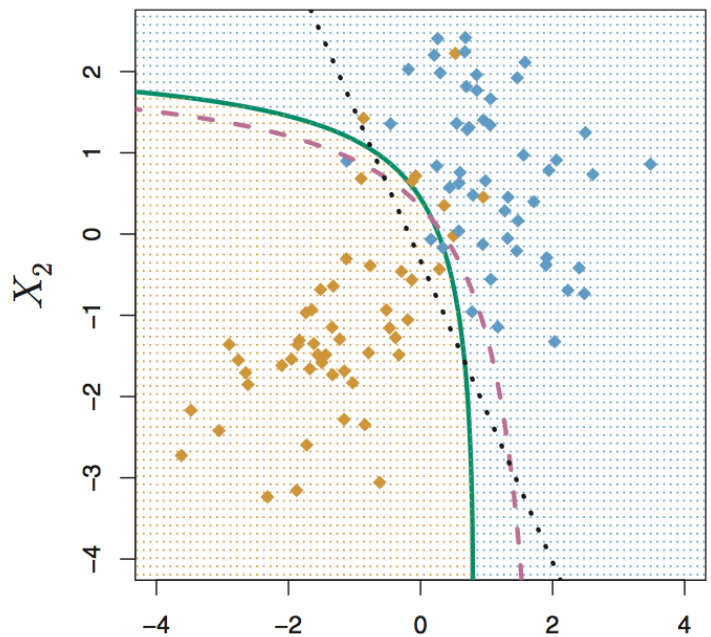
QDA vs LDA

The level-curves for each class look identical with LDA;

QDA allows for different classes to have differently shaped ellipsoids...

This results in decision boundaries that are non-linear (quadratic in fact)





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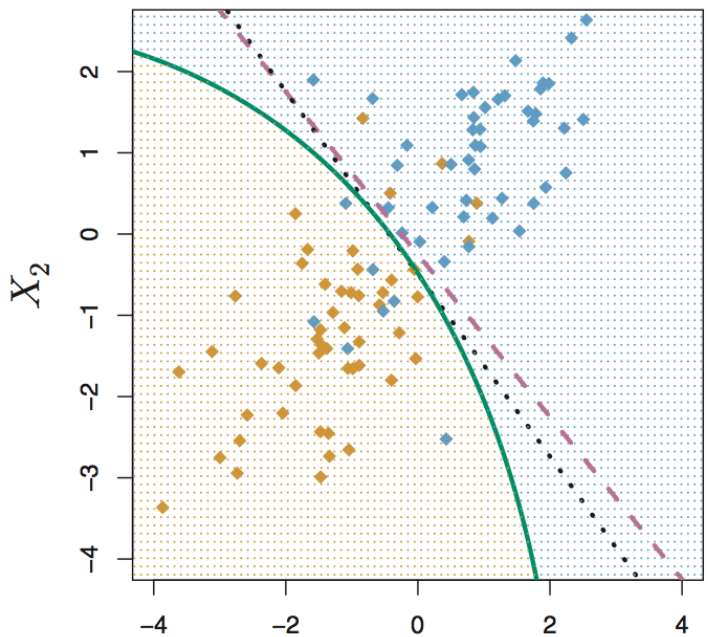
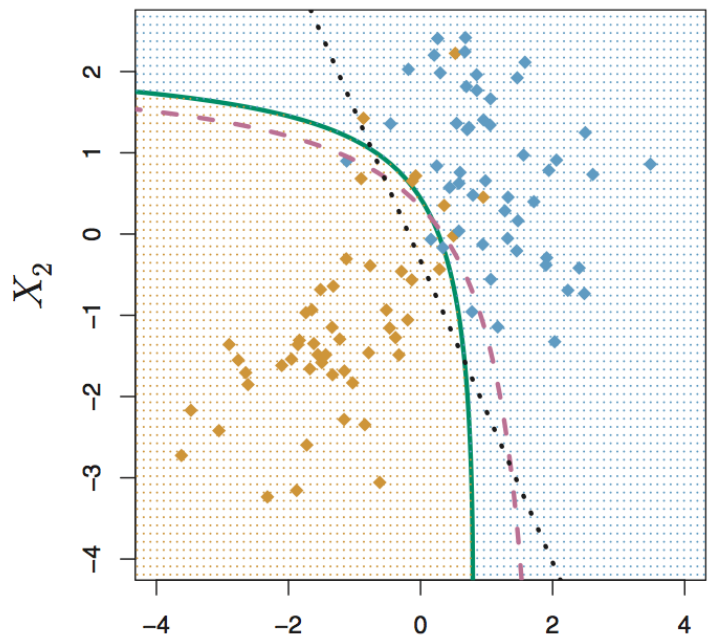




DDA

For DDA...

- level curves are spheres (not ellipsoids).
- decision boundaries are still linear
- sometimes called *naive bayes* (that doesn't mean it's bad though!)
- with $\pi_k = \frac{1}{K}$ for all k, and equal variances (ie. $\Sigma = \sigma I$); this is just the *nearest centroid* classifier

-DA vs logistic regression

Discriminant Analysis model can actually be rewritten as multinomial logistic models:

Beginning with

$$P(y = j|x) = \frac{f_j(x)\pi_j}{\sum_k f_k(x)\pi_k}$$

and

$$f_k(x) \propto \exp\left[-\frac{1}{2}(x - \mu_k)^\top \Sigma_k^{-1}(x - \mu_k)\right]$$

substituting and simplifying we get

$$P(y = j|x) = \frac{e^{\eta_j}}{\sum_k e^{\eta_k}}$$

-DA vs logistic regression

$$P(y = j|x) = \frac{e^{\eta_j}}{\sum_k e^{\eta_k}}$$

where

$$\eta_k = \beta_0 + x^\top \beta + x^\top \Sigma_k^{-1} x$$

This is just a multinomial logistic model with quadratic terms and interactions.

In particular for LDA (where $\Sigma_k = \Sigma$ is pooled) we have cancellation and get

$$\eta_k = \beta_0 + x^\top \beta$$

Simply a linear logistic model.

Shrunken Parametric Estimates

Sometimes the optimal bias/variance tradeoff is between two parametric classes.

For example: We may not have the data to estimate completely different covariance matrices for each class (i.e. QDA); but we may not want to use identical covariance matrices.

In this case we can take a weighted combination of our estimates. This is called regularized discriminant analysis.

This is a type of *shrunken parametric estimator*.

Regularized Discriminant Analysis

For shrinking between QDA/LDA we use:

$$\hat{\Sigma}_k^{RDA} = \lambda \hat{\Sigma}^{LDA} + (1 - \lambda)\hat{\Sigma}_k^{QDA}$$

For shrinking between LDA and Naive Bayes we use

$$\hat{\Sigma}^{RDA} = \lambda \hat{\Sigma}^{LDA} + (1 - \lambda)\hat{\Sigma}^{NB}$$

λ is a tuning parameter, and is generally selected via CV

DA in High Dimensions

All of the Discriminant Analysis techniques discussed so far use all the features.

For high dimensional problems this will lead to over-fitting

One popular solution is to shrink each class-mean estimate $\hat{\mu}_k$ towards the overall mean $\hat{\mu}$ using element-wise soft-thresholding

This method is called Nearest Shrunken Centroids (though it should probably more appropriately be "nearest shrunken DDA")

Nearest Shrunken Centroids (PAM)

Steps to the method:

1. Calculate our pooled, diagonal estimate of Σ; let s_j be the sd. estimate of gene j
2. Calculate the within class mean $\hat{\mu}_{jk}$ for each gene j, class k, and overall mean $\hat{\mu}_j$.
3. Set $\hat{\mu}_{jk}^{PAM}$ to be the shrunken difference:

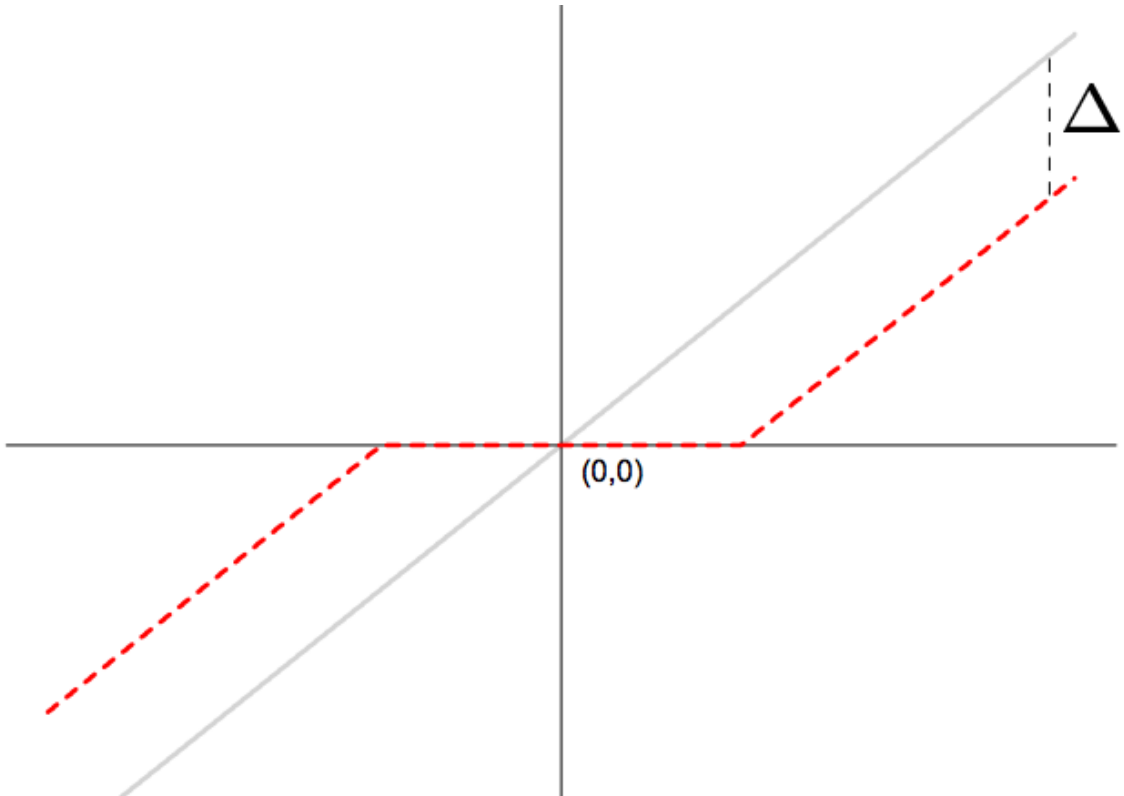
$$\hat{\mu}_{jk}^{PAM} = \hat{\mu}_{j\cdot} + s_j * SHRINK_{\Delta}\left(\frac{\hat{\mu}_{jk} - \hat{\mu}_{j\cdot}}{s_j}\right)$$

where $SHRINK_{\Delta}$ is the *Soft Thresholding Function*

Soft Thresholding

The soft thresholding shrinks its argument towards 0 — if it hits 0; then it stops!

Can be thought of as the continuous version of usual *thresholding*



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  Both of these are implemented in R-package `penalizedLDA`.
- Another option, which is especially helpful when using QDA is to penalize the covariance matrices Σ_k (or their inverses).

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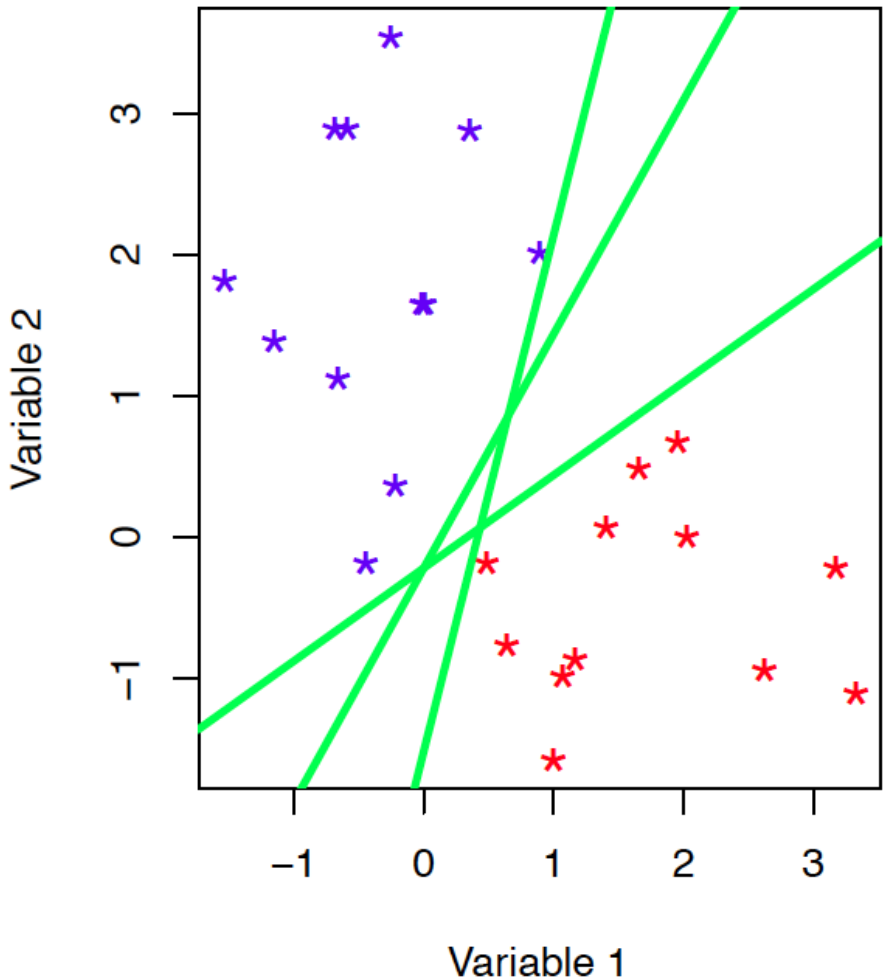
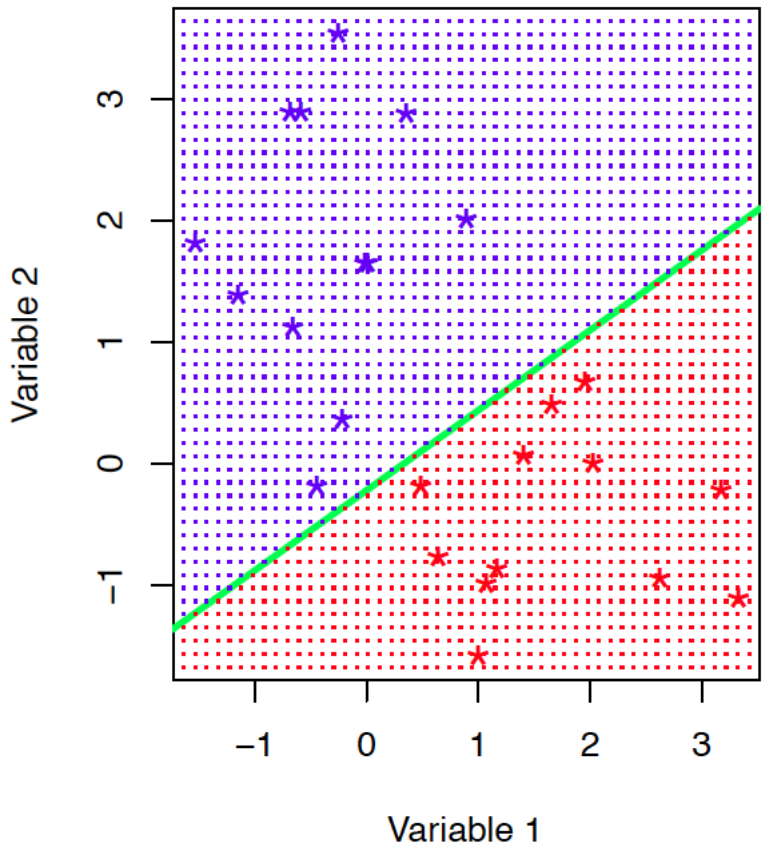
- But, it is a nice idea.

Separating Hyperplane

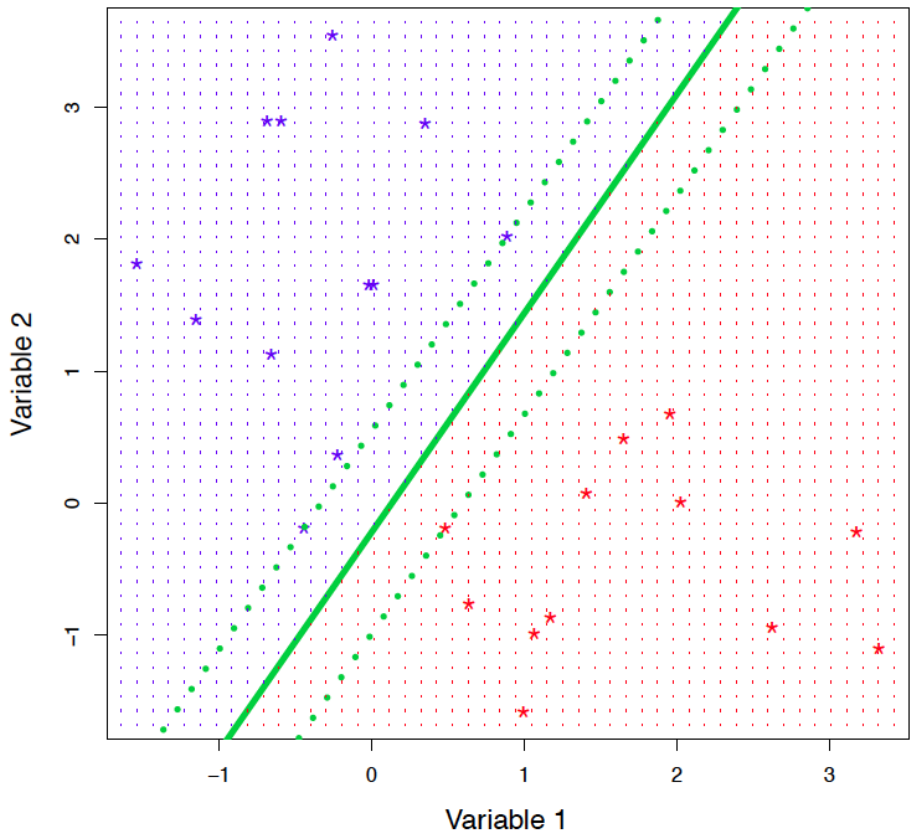


Classification Via a Separating Hyperplane



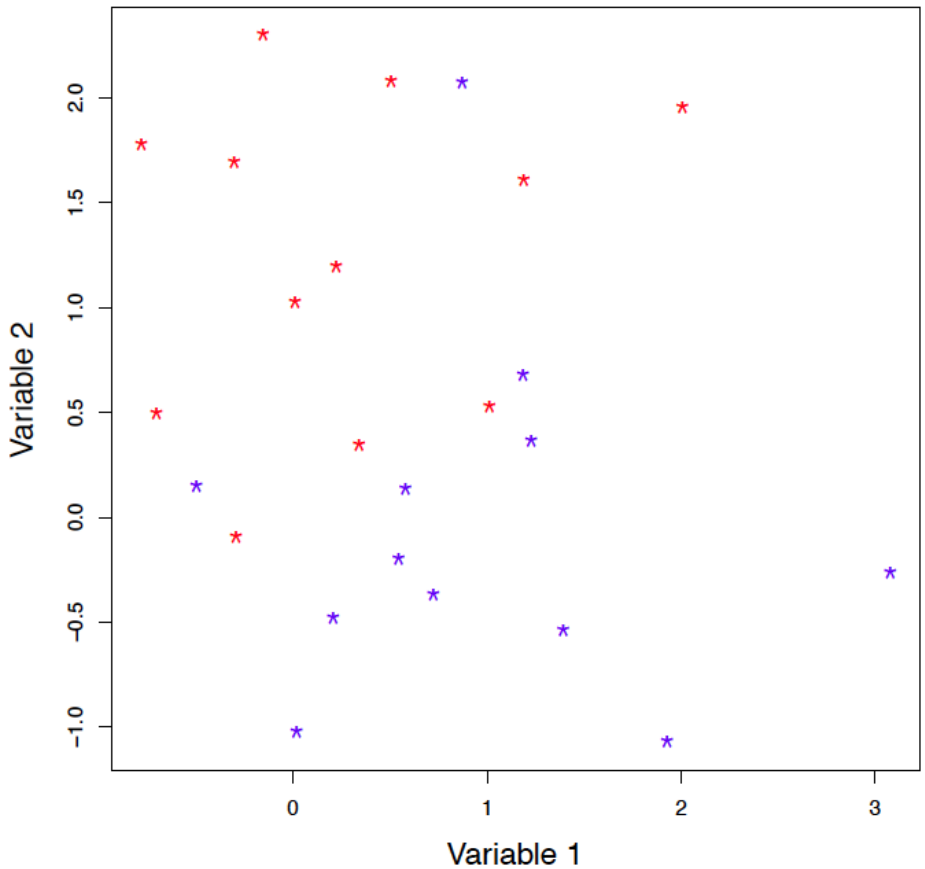
Blue class if $\beta_0 + \beta_1 X_1 + \beta_2 X_2 > c$; red class otherwise.

Maximal Separating Hyperplane

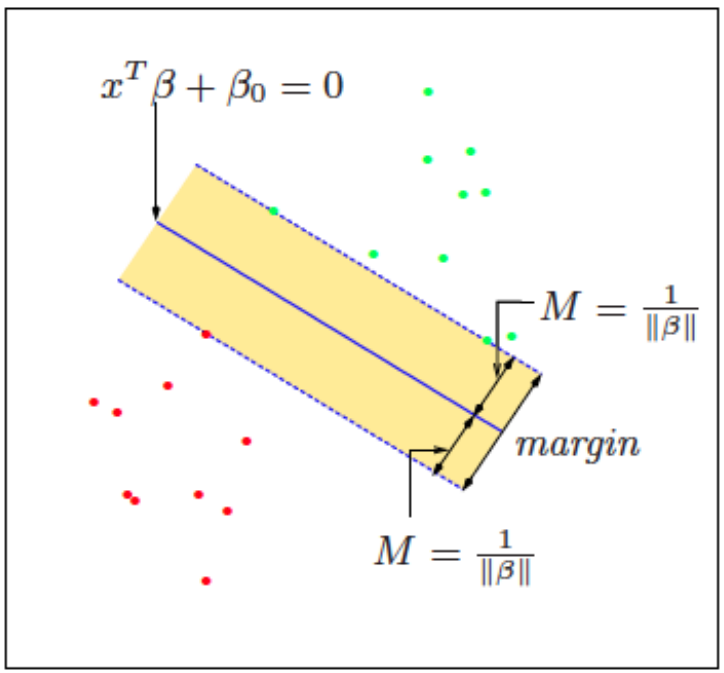


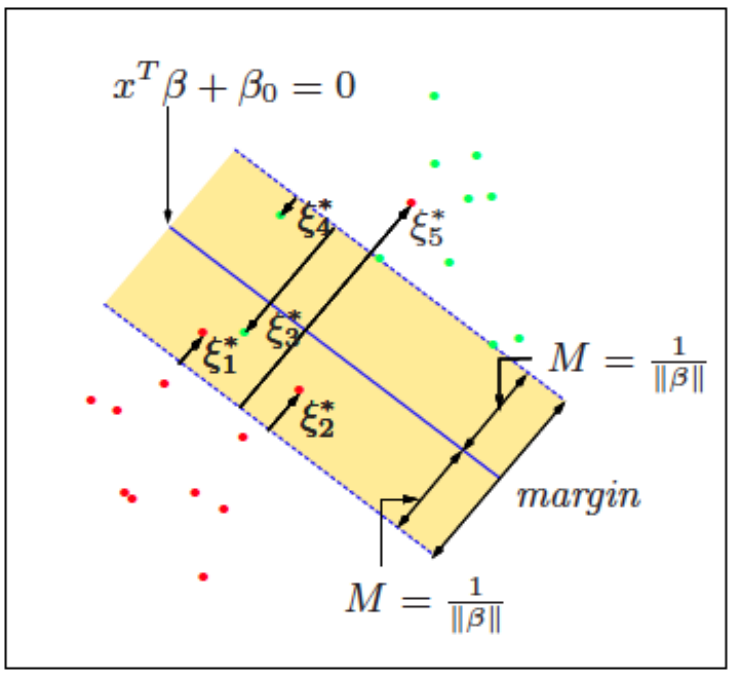
Note that only a few observations are on the margin: these are the support vectors.

What if There is No Separating Hyperplane?



Support Vector Classifier: Allow for Violations





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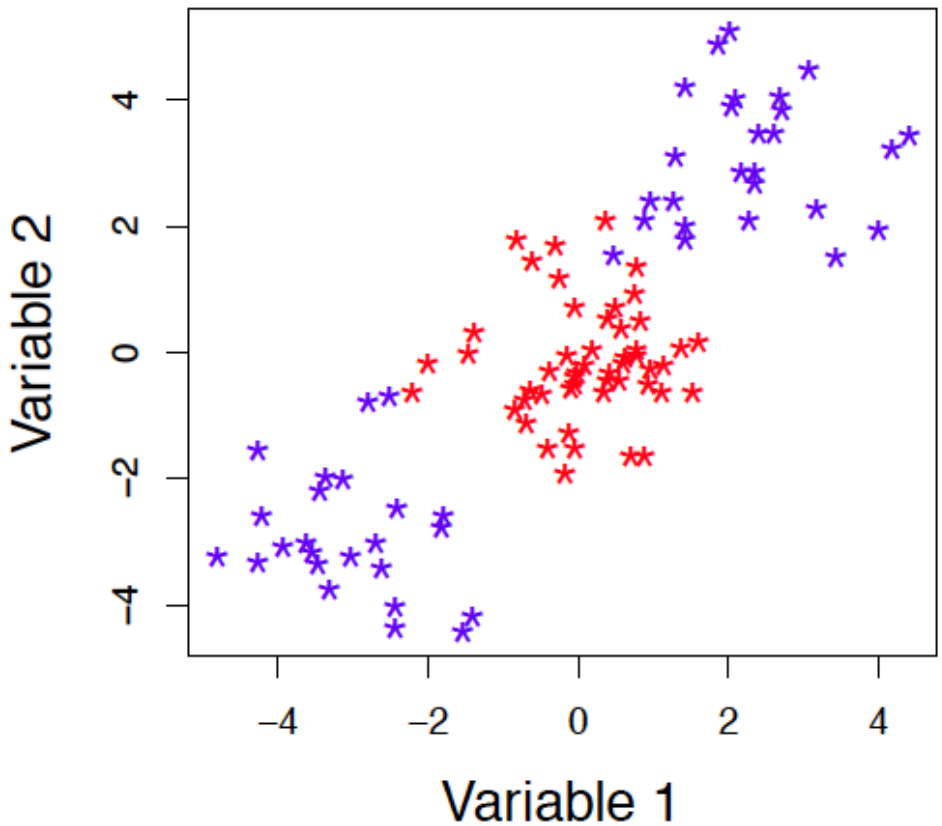
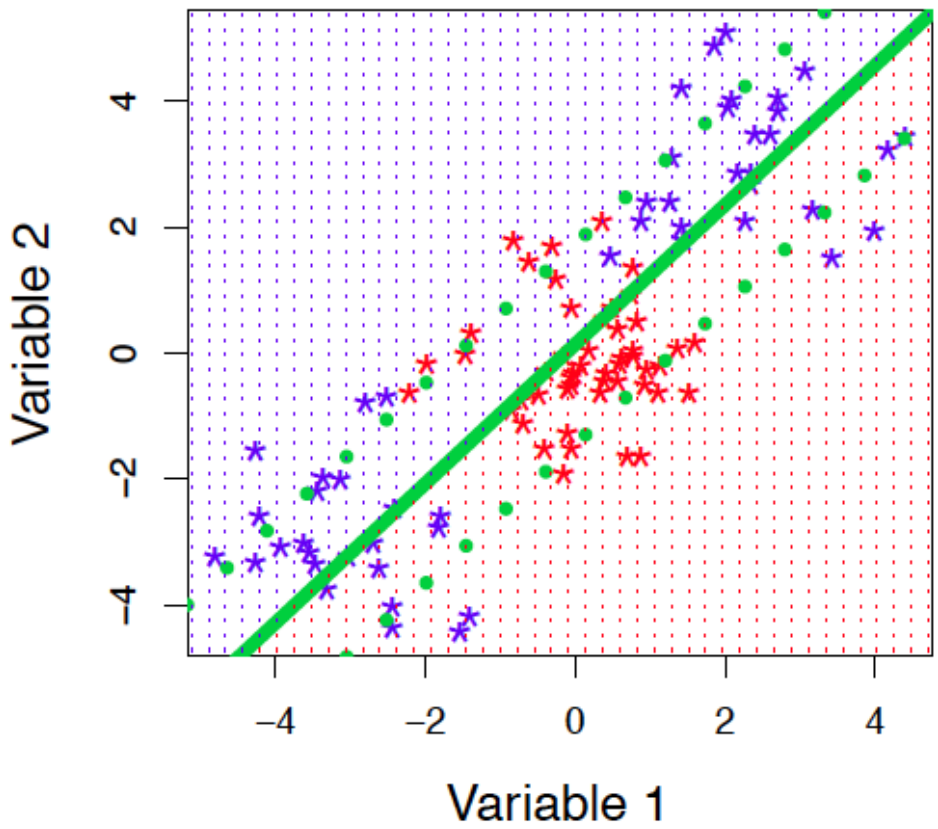
- However, linear regression, logistic regression, and other classical statistical approaches can also be applied to non-linear functions of the variables.
- For historical reasons, SVMs are more frequently used with non-linear expansions as compared to other statistical approaches.

Non-Linear Class Structure



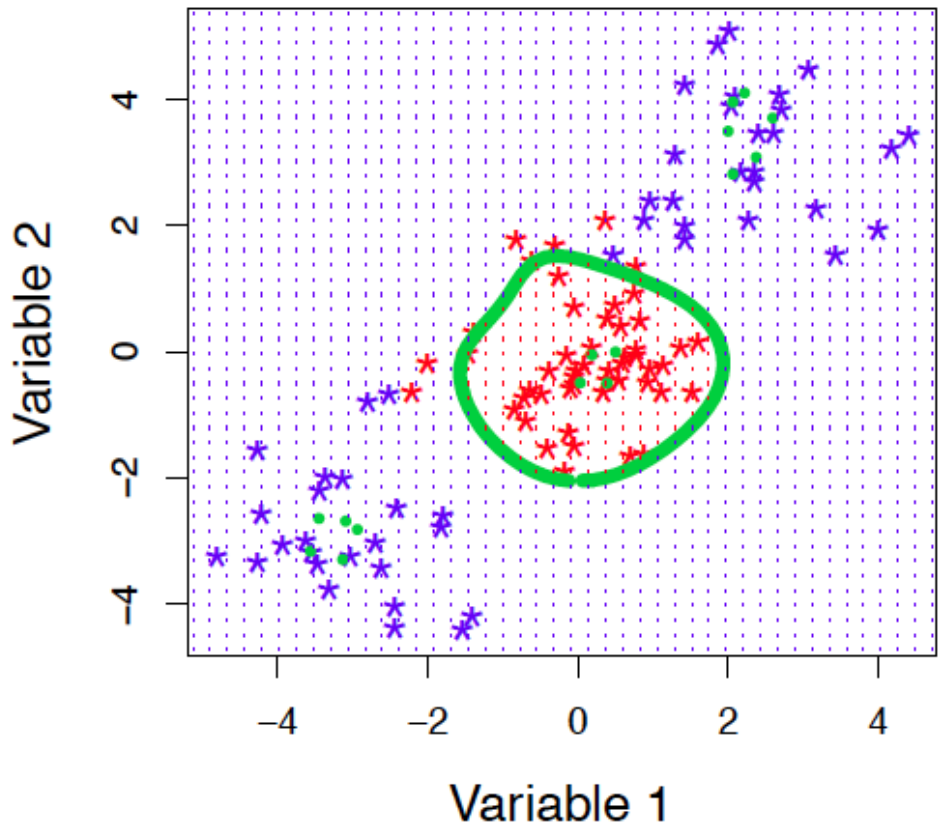
This will be hard for a linear classifier!

Try a Support Vector Classifier



Uh-oh!!

Support Vector Machine



Much Better.

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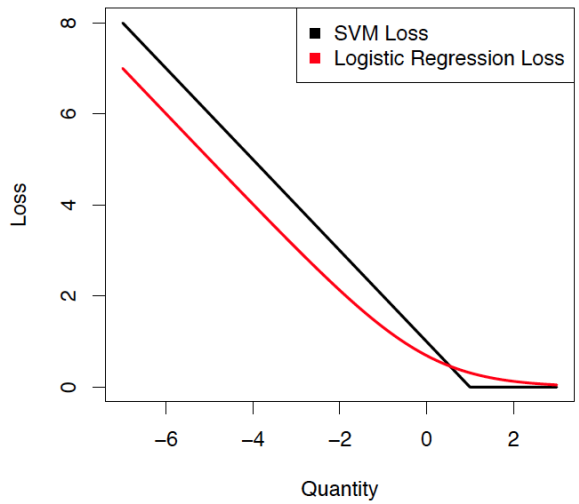
- No, if you are in a very high-dimensional setting such that estimating a non-linear decision boundary is hopeless.

Support Vector Classifier Versus Logistic Regression



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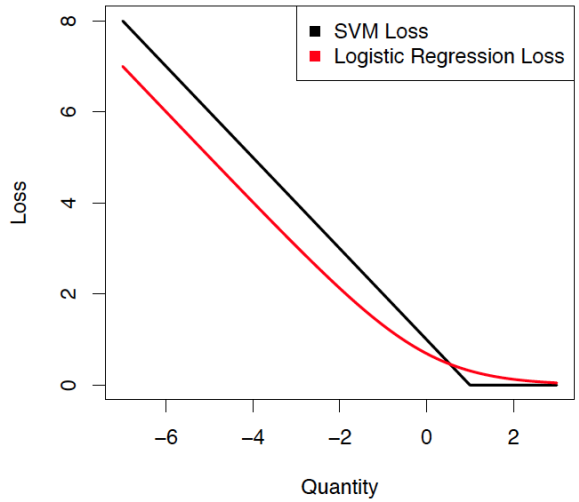

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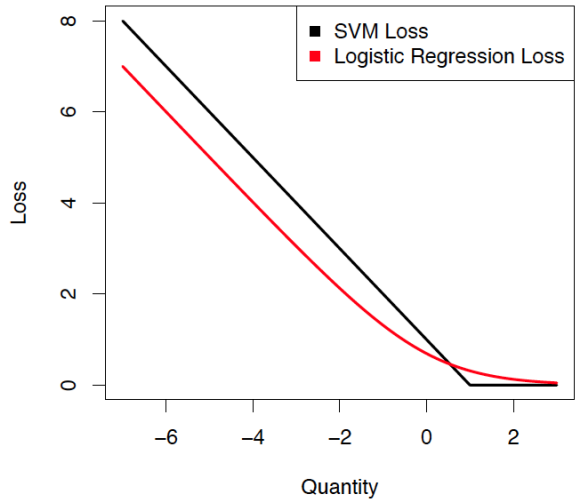

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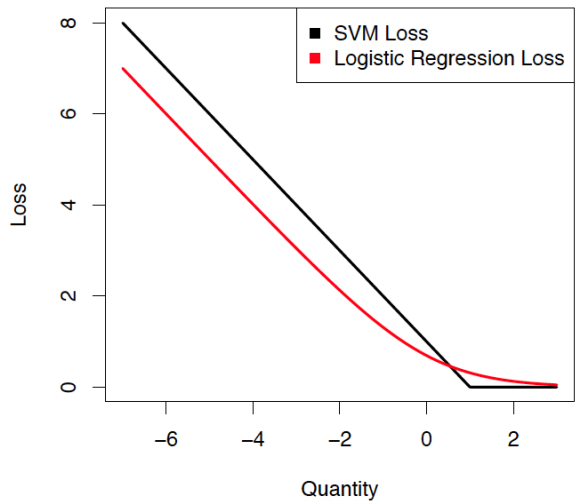

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- SVM uses a non-linear kernel... but could do that with logistic or linear regression too!

In High Dimensions...

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- Can get a sparse SVM using a lasso penalty; this yields a decision rule involving only a subset of the features.
- Logistic regression and other classical statistical approaches could be used with non-linear expansions of features. But this makes high-dimensionality issues worse.

Let's Try It Out in R!

Chapter 9 R Lab
www.statlearning.com

Batch Effects

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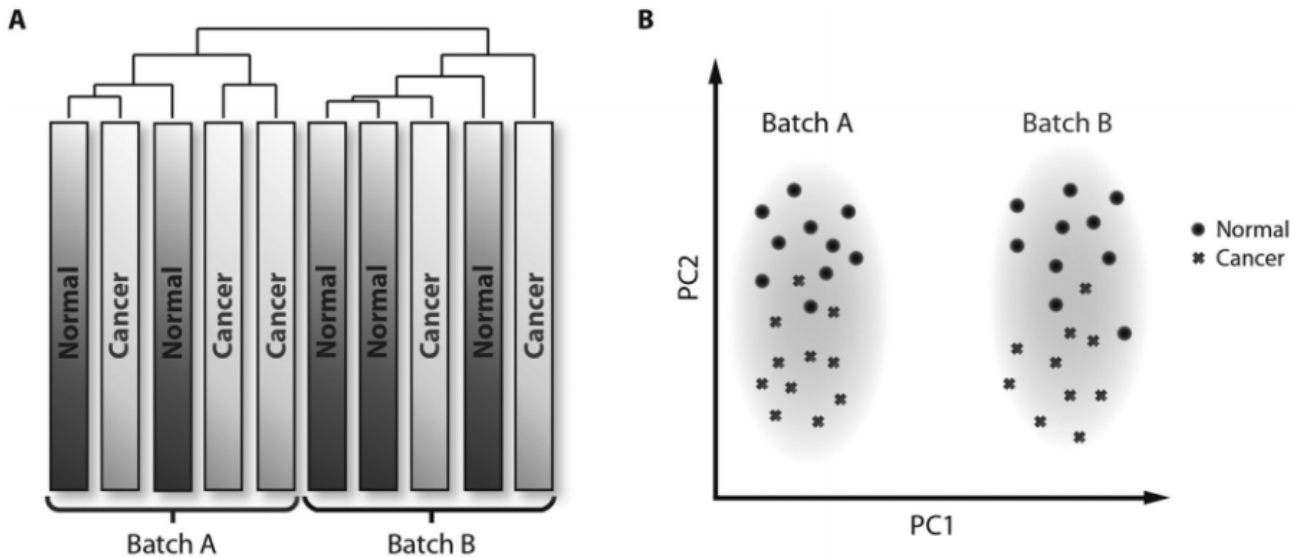
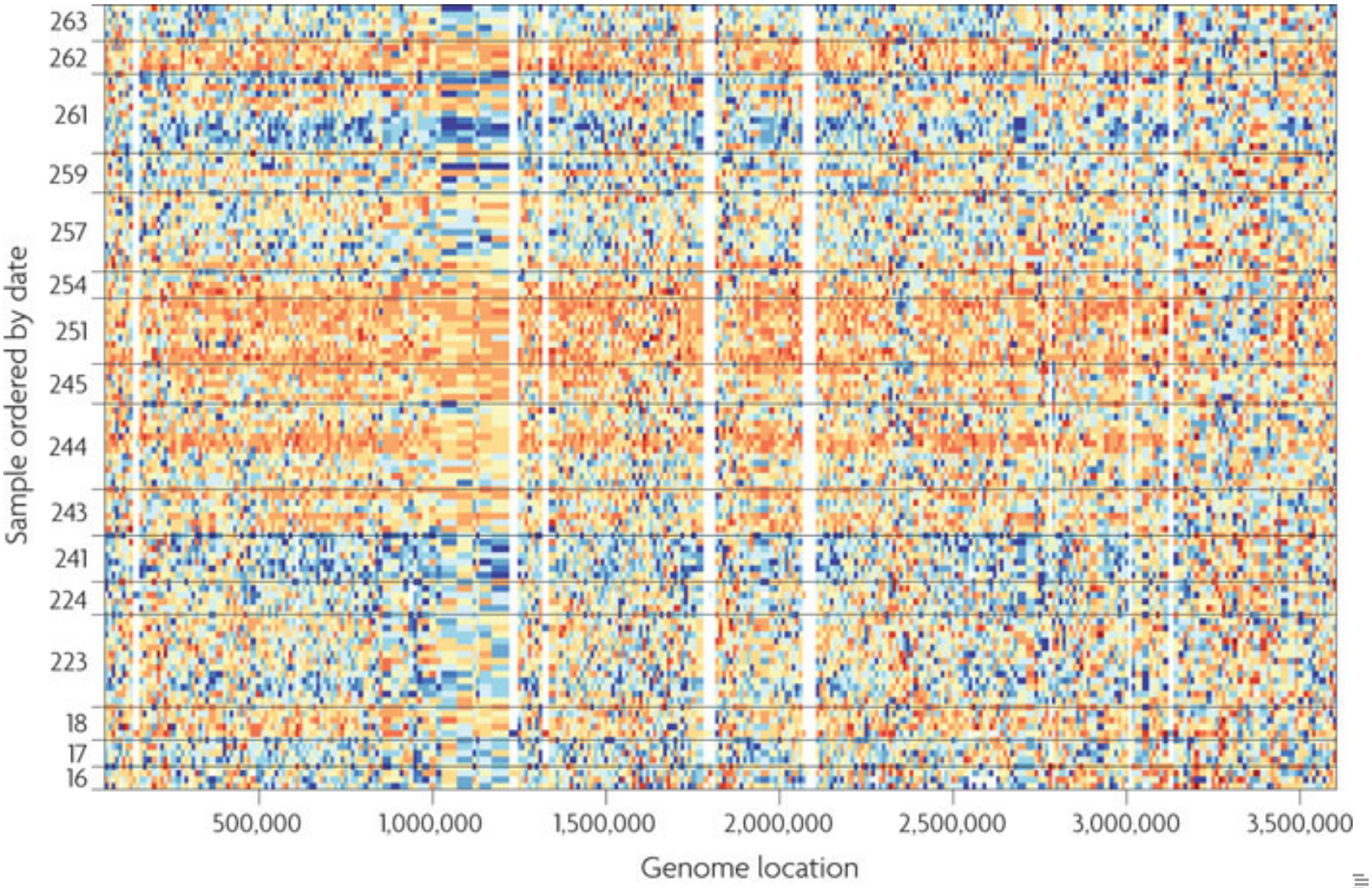
- Batch effects can make your data nonsense . . .

Batch Effects



Batch Effects in Practice



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Batch effects are almost inevitable. But you can do your best to design an experiment and analyze the data in such a way that batch effects do not compromise the results obtained.

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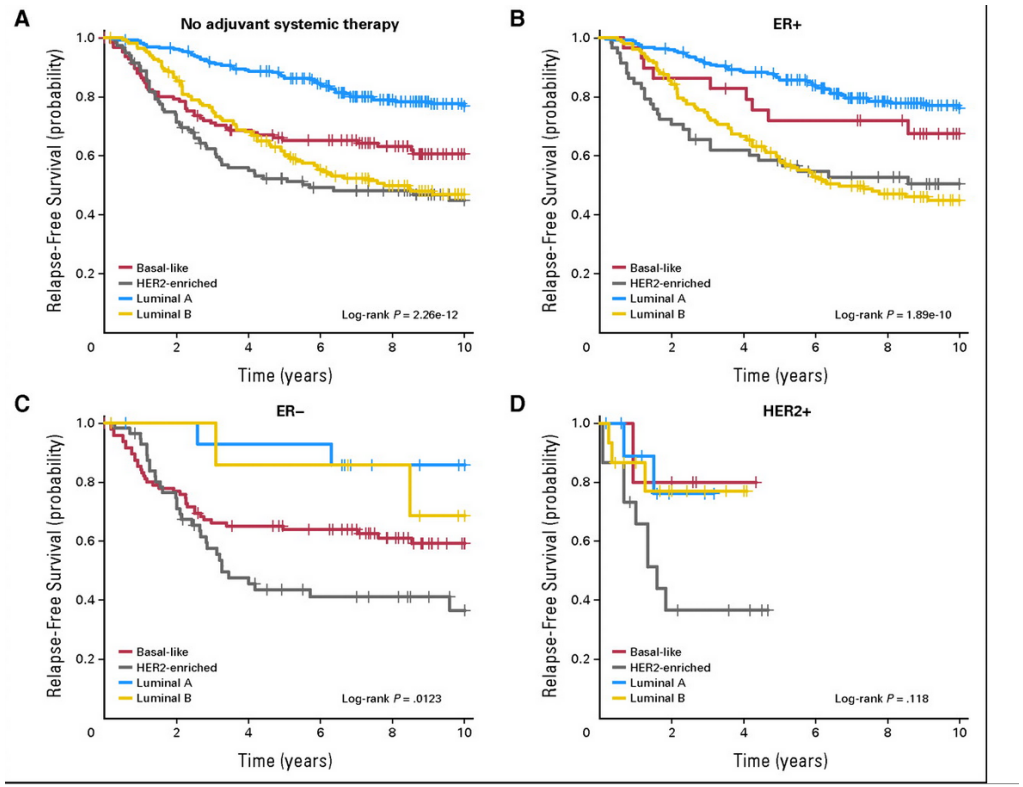
- Moving target: nobody knows the "true" subtype!
- Prat et al., Breast Cancer Res Treat, 2012

Why Do We Care About Subtypes?



Citation: Parker et al, Journal of Clinical Oncology, 2009

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- Great enthusiasm in the popular press and general public.
- Plans were made to begin marketing a test based on the reported diagnostic.

Not So Fast!!

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- In summary: the observed differences between cancer and normal proteomic patterns were attributable to "artifacts of sample processing, not the underlying biology of cancer."

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- This research was hailed as a major breakthrough in cancer treatment, and researchers from all over the world tried to use these sorts of techniques in their own labs.

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  - Reversal of sensitive/resistant labels
- A shocking paper published by Baggerly and Coombes in Annals of Applied Statistics, detailing all of the errors made: "One theme that emerges is that the most common errors are simple (e.g., row or column offsets); conversely, it is our experience that the most simple errors are common."

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- Need to have a proper independent test set, that you simply cannot peek at under any circumstances!
- Need to have clearly documented code that contains all steps of the analysis, from start to finish. You must be able to share this code with independent researchers, and you must be confident that your code is correct. If not, then your work isn't ready for prime time.

The Stakes are High!

At Duke:

- Dozens of papers retracted;
- Careers and reputations ruined;
- Patients endangered through unethical clinical trials.

Plus, a 60 Minutes special feature and an Institute of Medicine Committee!!!

Discussion Questions

Suppose someone came to a statistical consulting service you were running and said...

I want to try and classify patients as having breast cancer, or not based on gene expression in serum.

I'm pretty excited because I just found two awesome datasets:

The first, from the Farnsworth Lab, has serum expression measured using RNA-seq in 5000 *patients with breast cancer;*

The second, from the Wernstrom Lab, has serum expression measured using microarrays on 5000 *healthy patients.*

I wanted to combine them to build my classifier

What concerns, if any, come to mind?

Discussion Questions

Suppose we want to classify patients as having cancer/not having cancer using methylation on cf-dna fragments

In particular, say we initially consider 10000 cpg sites, and try to build a classification model that uses proportion of methylated fragments at each of those sites as features.

Would it make sense to run an SVM with a non-linear kernel here?

If we used cross-validation to select between both that SVM, and a LASSO-logistic regression, what might happen?