BIOST 546: Machine Learning for Biomedical Big Data

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Lecture 4: Classification for Biomedical Big Data - Part I
Spring 2017

Recap

- Bias-variance tradeoff & Training/Test error
- Cross validation and related procedures
- Methods for reducing model complexity:
  - subset selection (variable pre-selection, best subset selection, forward step-wise selection)
  - regularization (ridge and lasso)
  - dimension reduction (PCR and PLS)

Today & Next Lecture

- High dimensional classification:
  - Classification using linear regression
  - Logistic regression (& penalized logistic regression)
  - KNN classification
  - LDA & QDA
  - Support Vector Machines (SVM)

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  - You may need to preprocess the data and do preliminary analyses to remove batch effects etc (see BIOST 544, 545).
  - Please post your proposal as a discussion by the *end of next week*. If you don't have a topic in mind, I will try to match you with others.
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- Tentative schedule:
  - Finalize the project topic: Thursday April 27th
  - Proposal presentations: 5%
  - 2-page project proposal & progress report: 5%
  - Final Presentations: 10%
  - Full report (max 7 pages in ICML format (TBD)): 20%

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- Classification problems tend to occur even more frequently than regression problems in the analysis of biomedical data.
- 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

- There are many approaches out there for performing classification.
- We will discuss a few ideas
  - Model-based methods: logistic regression, LDA, QDA.
  - Non-parametric methods: KNN classification.
  - Margin-based classifiers: support vector machines (SVM).

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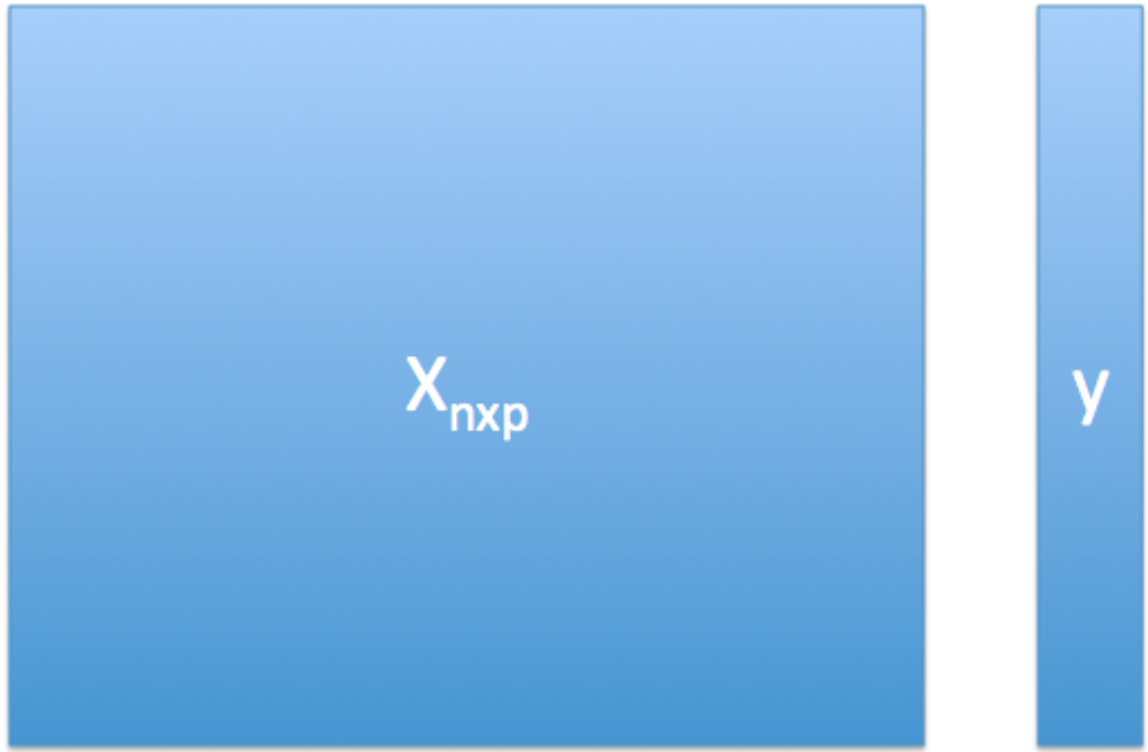

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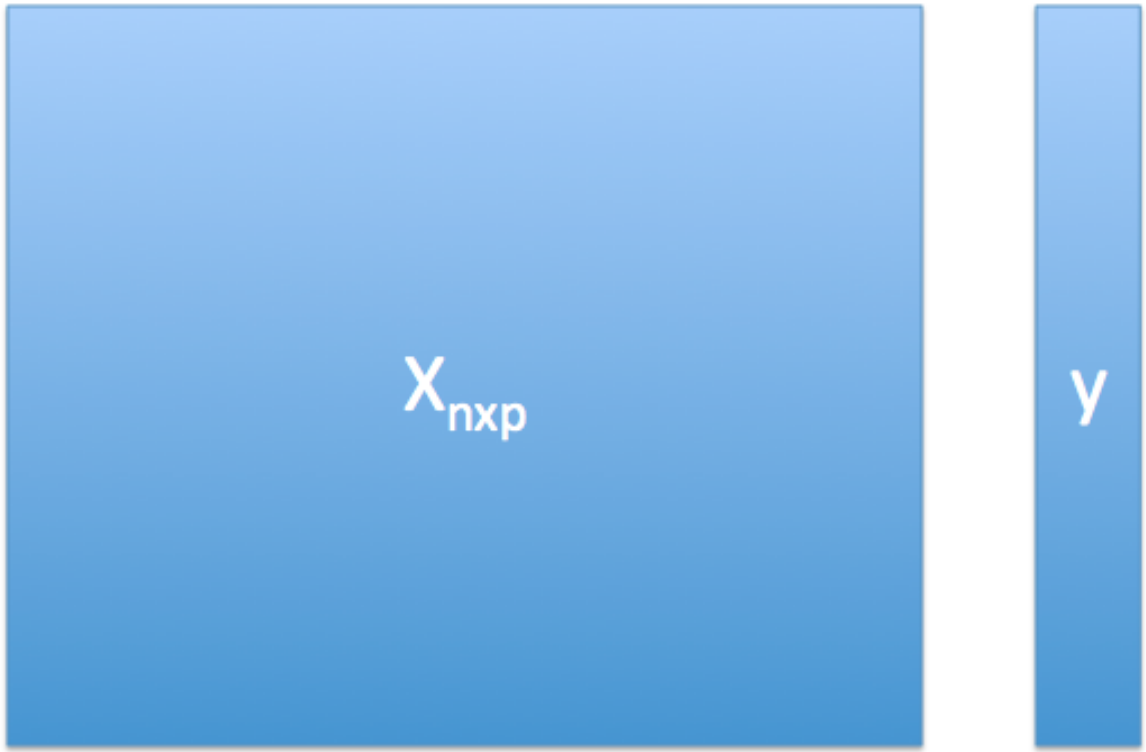

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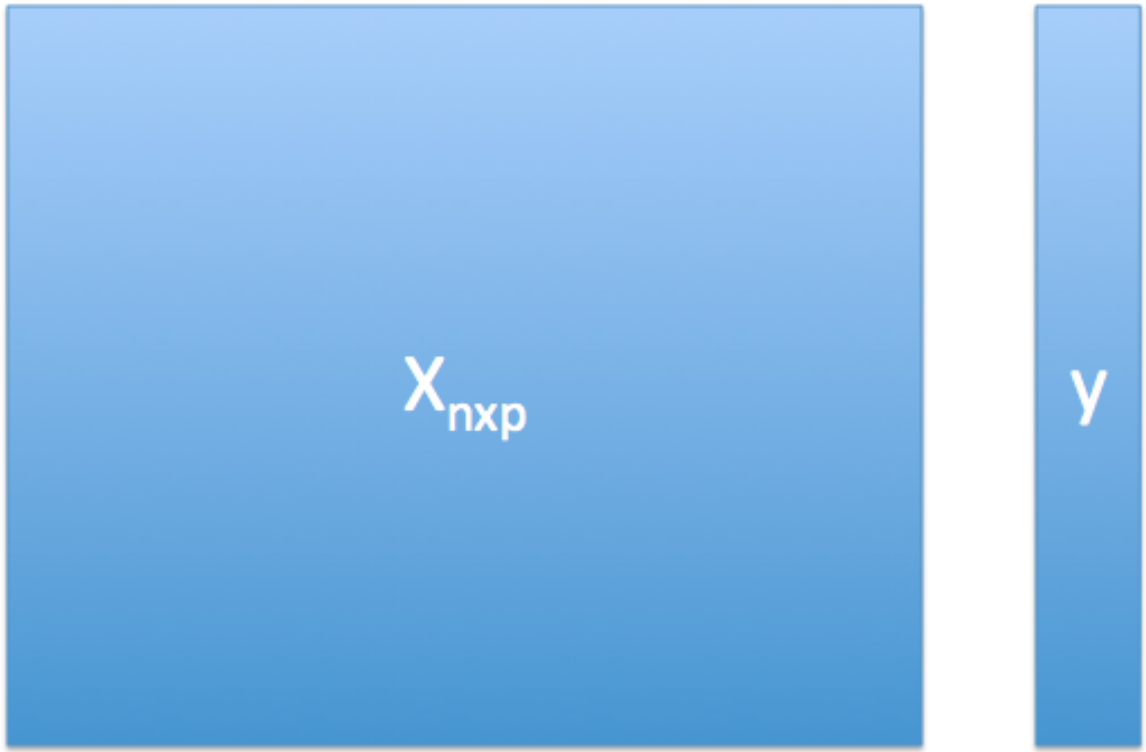

- The only difference is that the response y is a categorical variable with (in general) K categories
- We mostly focus on the case of $K = 2$, i.e. cancer vs benign, but the ideas are the same

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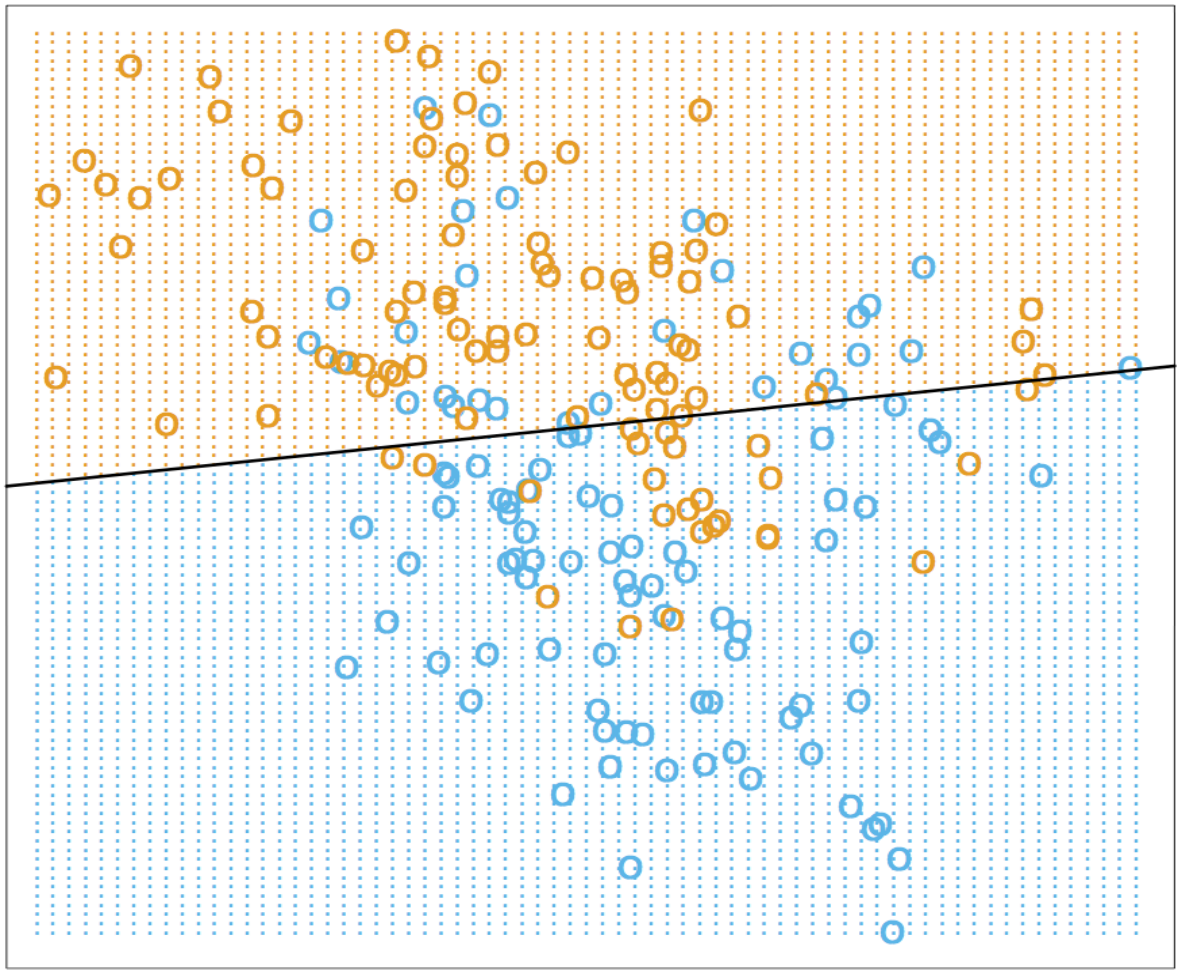

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- In this case, we set

$$C_i = \begin{cases} 1 & x_i\hat{\beta} > 0 \\ -1 & x_i\hat{\beta} \leq 0 \end{cases}$$

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- This suggest that so *sum of squared errors may not be the best loss function for categorical variables*!

Drawbacks of Linear Regression for Classification

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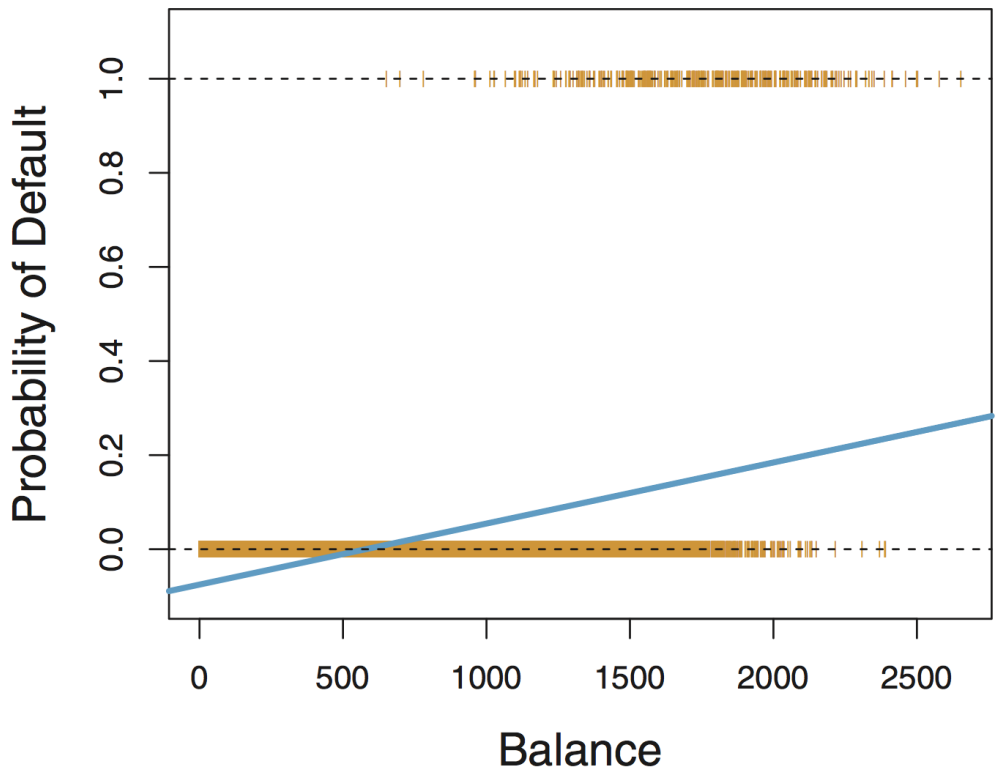

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  - Unfortunately, this coding implies an ordering on the outcomes, putting drug overdose in between stroke and epileptic seizure
  - In practice there is no particular reason that this needs to be the case and one could choose any other equally reasonable coding

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- Using this loss function, a good classifier is one for which the test error

$$E(y_0 \neq \hat{y}_0)$$

  is minimized.

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- We can also get the Bayes error rate, which is the *lowest test error we can get*

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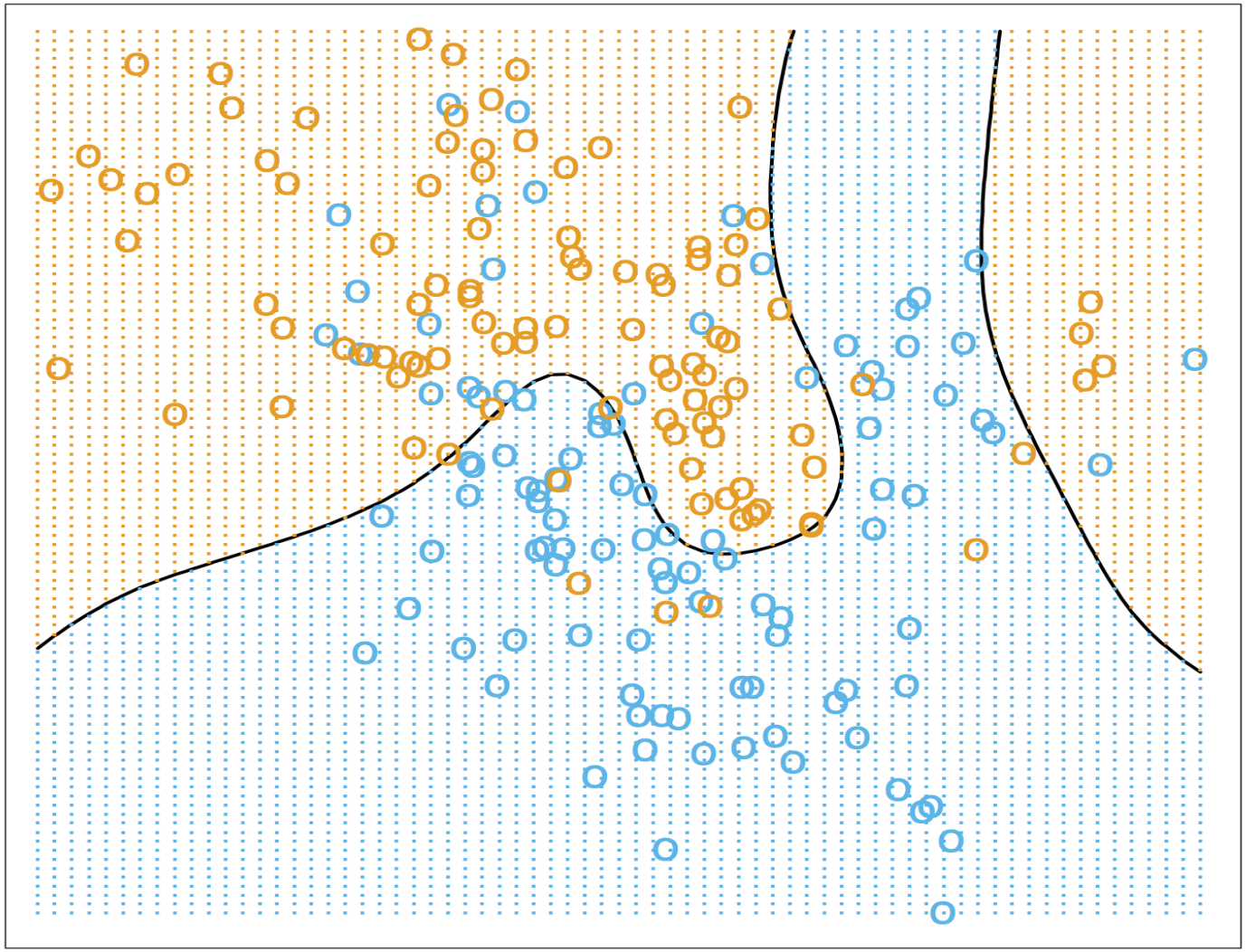

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- *If this assumption holds*, logistic regression, is a good model-based alternative to Bayes classifier.

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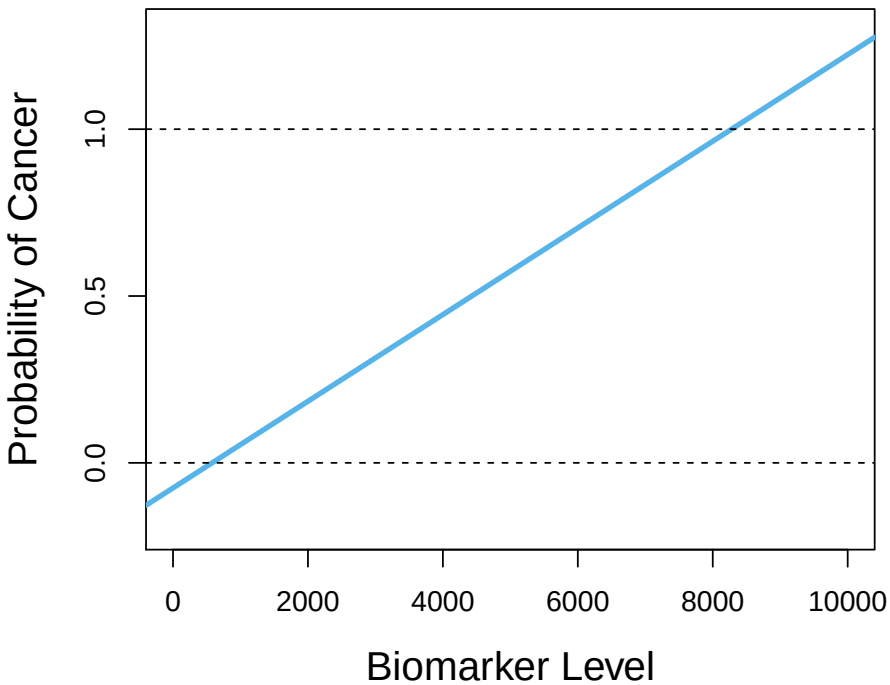
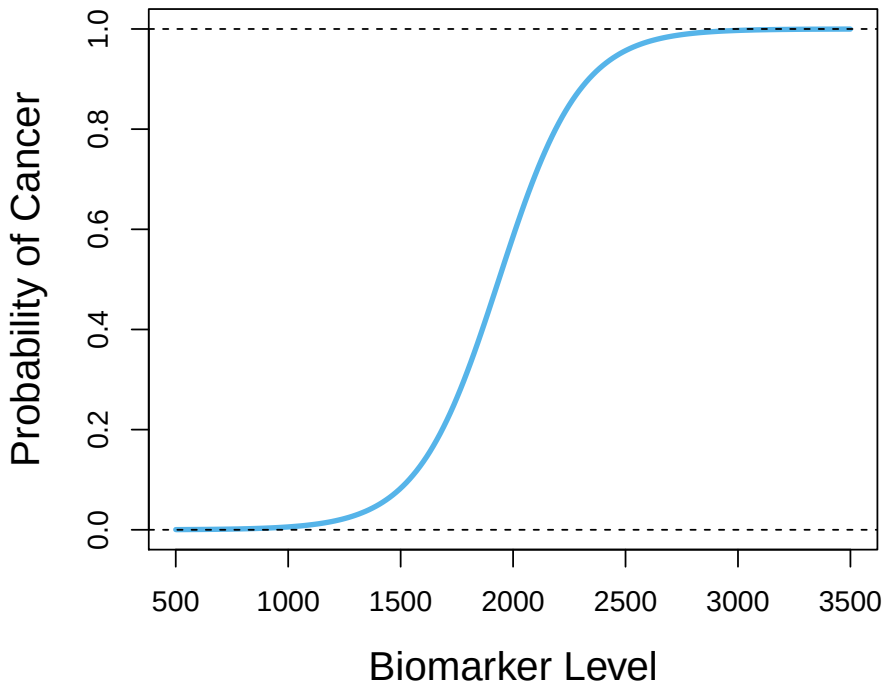
- We usually fit this model using maximum likelihood – like least squares, but for logistic regression.

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))
```

Logistic vs Linear Regression





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

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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.

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)
```

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- It has been shown many many times that batch effects can be much stronger than biological effects of interest!
- If you are not careful, batch effects can result in complete confounding, making your data worthless and your results nonsense.

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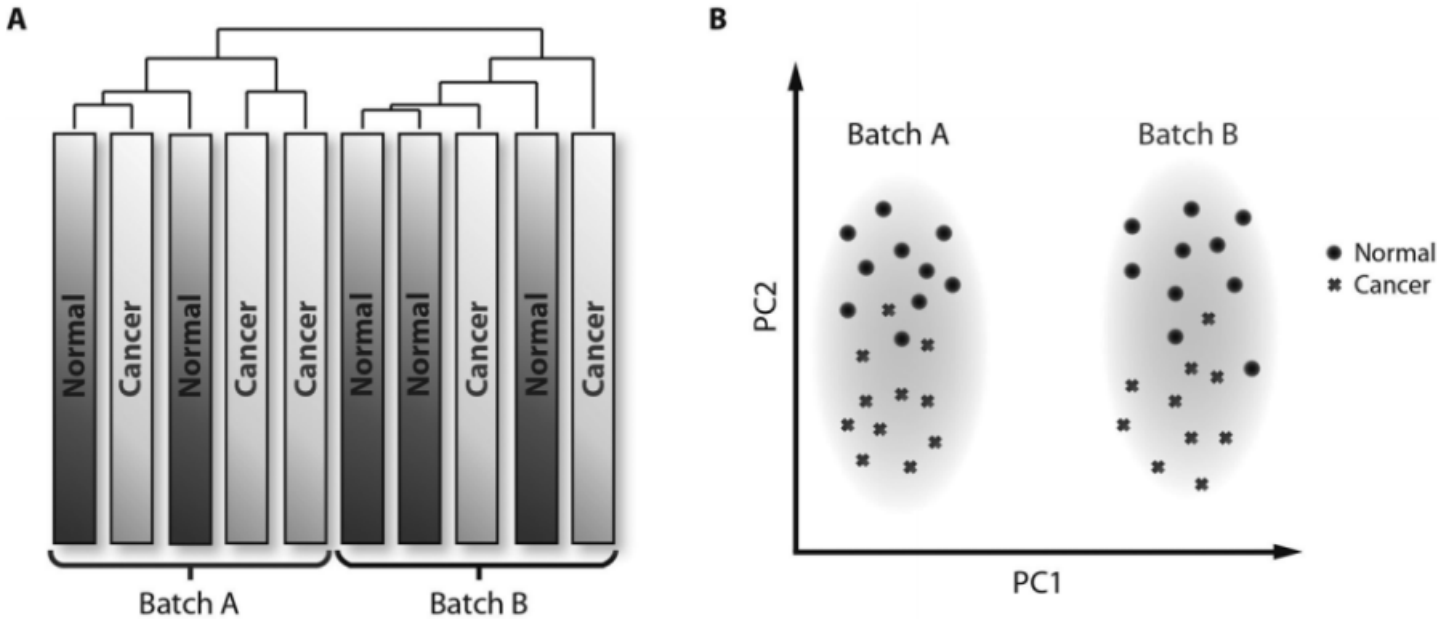

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Batch effects are almost inevitable. But you can do your best to design an experiment and analyze the data in such a way that batch effects do not compromise the results obtained.

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- Want to be able to determine the subtype for a new patient with breast cancer.
- Controversy over the best classifier for this task:
  - PAM50 classifier involves 50 genes.
  - More recent proposal involving three genes.

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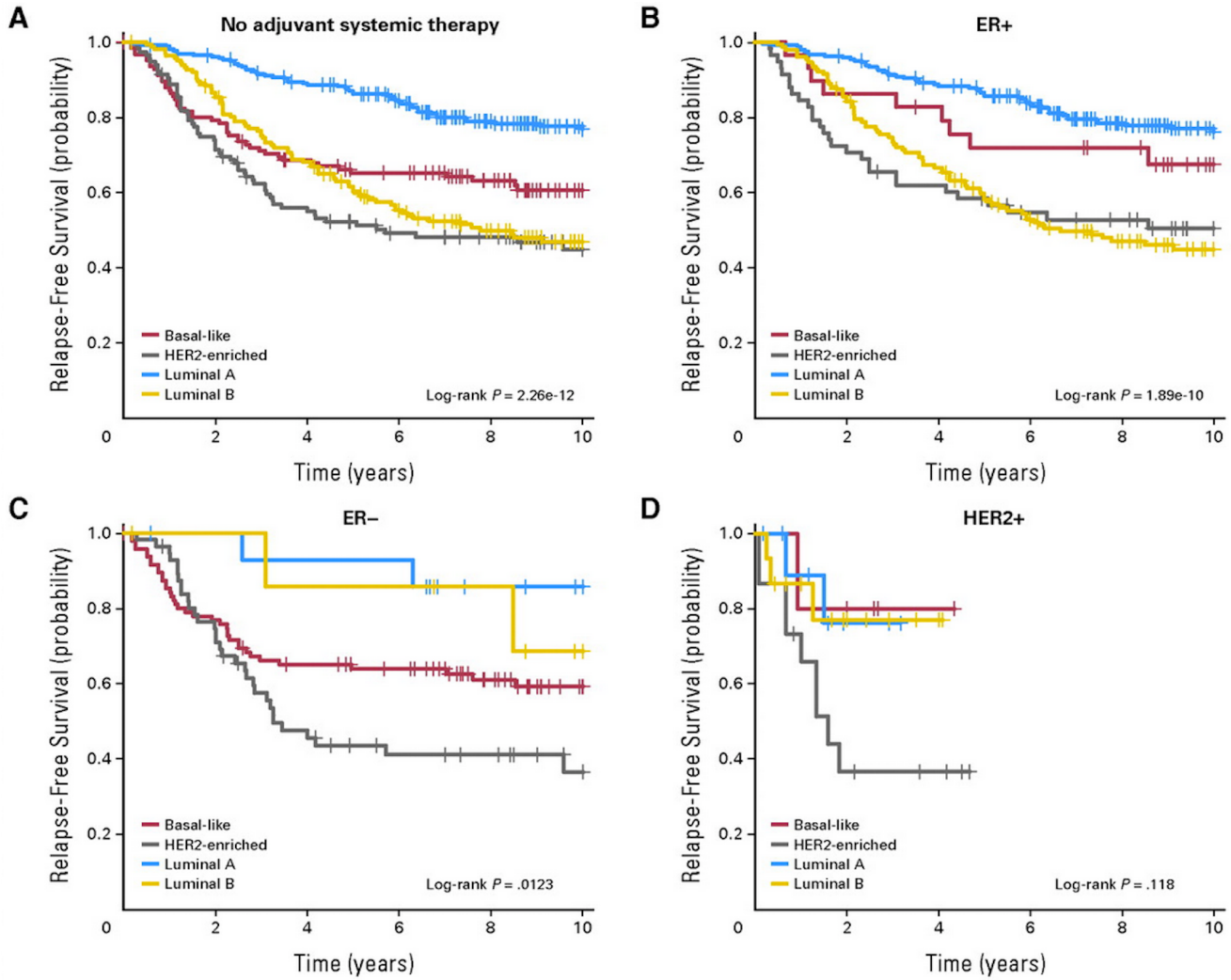
- Subgroups differ with respect to risk factors, incidence, baseline prognoses, responses to therapies.
- Want to be able to determine the subtype for a new patient with breast cancer.
- Controversy over the best classifier for this task:
  - PAM50 classifier involves 50 genes.
  - More recent proposal involving three genes.
- 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

Proteomics for Ovarian Cancer

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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!!

- Independent researchers took a look at the data, which was publicly available, and discovered:
  - inadvertent changes in protocol mid-experiment: i.e. major batch effects.
  - problems with instrument calibration.
  - difference in processing between tumor and normal samples.

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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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- 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!!!

Next Lecture

- Linear Discriminant Analysis (LDA)
- Quadratic Discriminant Analysis (QDA)
- KNN Classifier
- Support Vector Machines (SVM)