

# Resampling Methods

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# Outline and introduction

- ▶ Objectives: prediction or inference?
- ▶ Cross-validation
- ▶ Bootstrap
- ▶ Permutation Test
- ▶ Monte Carlo Simulation

ISLR Chapter 5: James, G. *et al.* An Introduction to Statistical Learning: with Applications in R. (Springer, 2013).  
This book can be downloaded for free at <http://www-bcf.usc.edu/~gareth/ISL/getbook.html>

# Why do regression?

## Inference

- ▶ Questions:
  - ▶ *Which* predictors are associated with the response?
  - ▶ *How* are predictors associated with the response?
  - ▶ Example: do dietary habits influence the gut microbiome?
- ▶ Linear regression and generalized linear models are the workhorses
  - ▶ We are more interested in interpretability than accuracy
  - ▶ Produce interpretable models for inference on coefficients

## Bootstrap, permutation tests

# Why do regression? (cont'd)

## Prediction

- ▶ Questions:
  - ▶ How can we predict values of  $Y$  based on values of  $X$
  - ▶ Examples: Framingham Risk Score, OncotypeDX Risk Score
- ▶ Regression methods are still workhorses, but also less-interpretable machine learning methods
  - ▶ We are more interested in accuracy than interpretability
  - ▶ e.g. sensitivity/specificity for binary outcome
  - ▶ e.g. mean-squared prediction error for continuous outcome

## Cross-validation

## Cross-validation

## Why cross-validation?

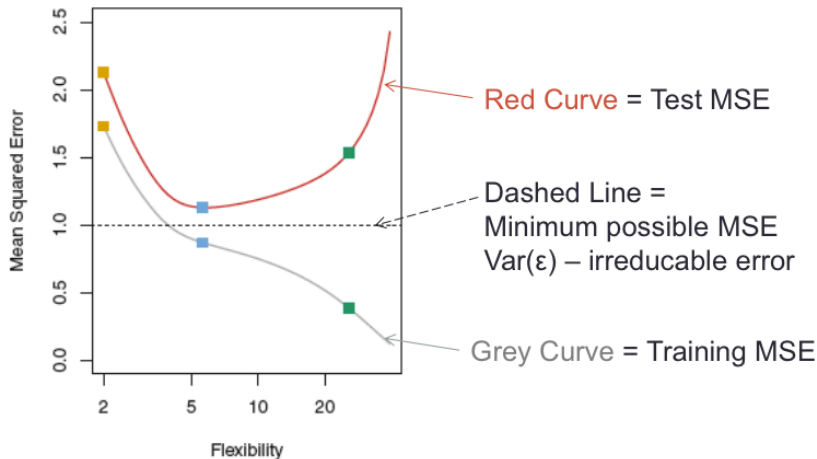


Figure 1: Figure 2.9 B

**Under-fitting, over-fitting, and optimal fitting**

## K-fold cross-validation approach

- ▶ Create  $K$  “folds” from the sample of size  $n$ ,  $K \leq n$
1. Randomly sample  $1/K$  observations (without replacement) as the validation set
  2. Use remaining samples as the training set
  3. Fit model on the training set, estimate accuracy on the validation set
  4. Repeat  $K$  times, not using the same validation samples
  5. Average validation accuracy from each of the validation sets

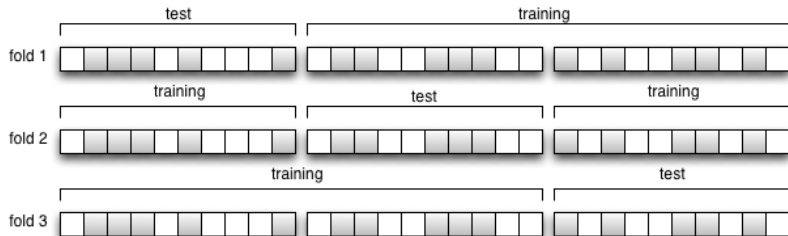


Figure 2: 3-fold CV

# Variability in cross-validation

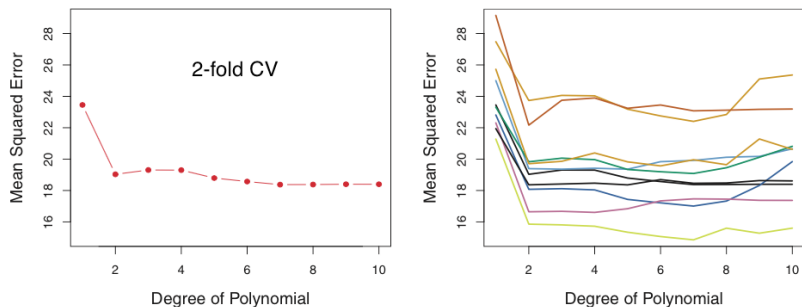


Figure 3: Variability of 2-fold cross-validation (ISLR Figure 5.2)



## Bias-variance trade-off in cross-validation

- ▶ *Key point:* we are talking about bias and variance of the overall accuracy estimate, not between the folds.
- ▶ 2-fold CV produces a *high-bias, low-variance* estimate:
  - ▶ training on fewer samples causes upward bias in error rate
  - ▶ low correlation between models means low variance in average error rate
- ▶ Leave-on-out CV produces a *low-bias, high-variance* estimate:
  - ▶ training on  $n - 1$  samples is almost as good as on  $n$  samples (almost no bias in prediction error)
  - ▶ models are almost identical, so average has a high variance
- ▶ Computationally,  $K$  models must be fitted
  - ▶ 5 or 10-fold CV are very popular compromises

## Cross-validation summary

- ▶ In prediction modeling, we think of data as *training* or *test*
  - ▶ Cross-validation estimates test set error from a training set
- ▶ Training set error always decreases with more complex (flexible) models
- ▶ Test set error as a function of model flexibility tends to be U-shaped
  - ▶ The low point of the U represents the optimal bias-variance trade-off, or the most appropriate amount of model flexibility

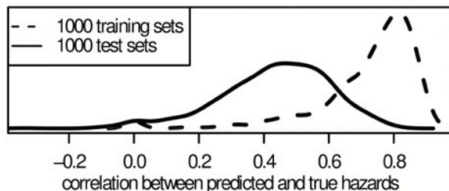
## Cross-validation caveats

- ▶ Be very careful of information “leakage” into test sets, e.g.:
  - ▶ feature selection using all samples
  - ▶ “human-loop” over-fitting
  - ▶ changing your mind on accuracy measure
  - ▶ try a different dataset

<http://hunch.net/?p=22>

## Cross-validation caveats (cont'd)

- ▶ Tuning plus accuracy estimation requires **nested** cross-validation
- ▶ Example: high-dimensional training and test sets simulated from identical true model
  - ▶ Penalized regression models tuned by 5-fold CV
  - ▶ Tuning by cross-validation does *not* prevent over-fitting



Waldron *et al.*: **Optimized application of penalized regression methods to diverse genomic data.** *Bioinformatics* 2011, 27:3399–3406.

## Cross-validation caveats (cont'd)

- ▶ Cross-validation estimates assume that the sample is representative of the population

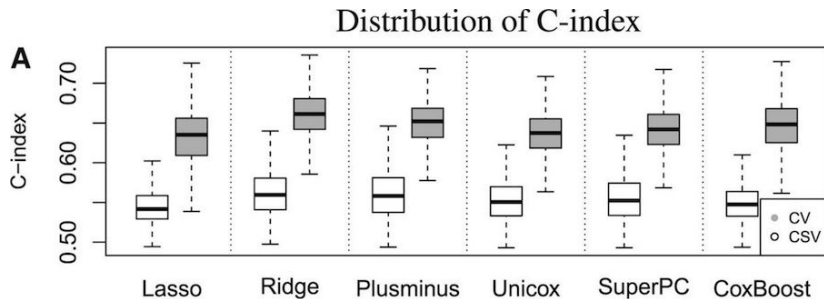


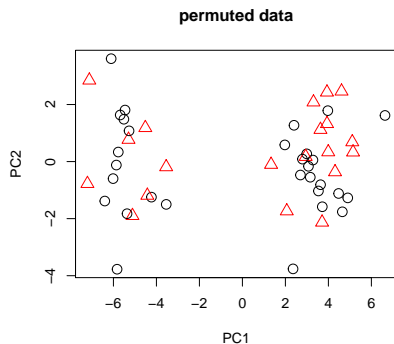
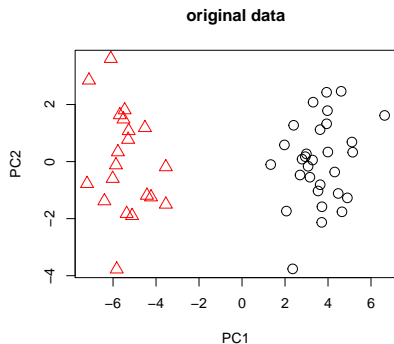
Figure 4: Cross-validation vs. cross-study validation in breast cancer prognosis

Bernau C *et al.*: **Cross-study validation for the assessment of prediction algorithms.** *Bioinformatics* 2014, 30:i105–12.

## Permutation test

# Permutation test

- ▶ Classical hypothesis testing:  $H_0$  of test statistic derived from assumptions about the underlying data distribution
  - ▶ e.g.  $t$ ,  $\chi^2$  distribution
- ▶ Permutation testing:  $H_0$  determined empirically using permutations of the data where  $H_0$  is guaranteed to be true



## Steps of permutation test:

1. Calculate test statistic (e.g.  $T$ ) in observed sample
2. Permutation:
  - 2.1 Sample without replacement the response values ( $Y$ ), using the same  $X$
  - 2.2 re-compute and store the test statistic  $T$
  - 2.3 Repeat  $R$  times, store as a vector  $T_R$
3. Calculate empirical p value: proportion of permutation  $T_R$  that exceed actual  $T$



## Calculating a p-value

$$P = \frac{\text{sum}(\text{abs}(T_R) > \text{abs}(T)) + 1}{\text{length}(T_R) + 1}$$

- ▶ Why add 1?
  - ▶ Phipson B, Smyth GK: **Permutation P-values should never be zero: calculating exact P-values when permutations are randomly drawn.** Stat. Appl. Genet. Mol. Biol. 2010, 9:Article39.

# Permutation test - pros and cons

- ▶ Pros:

- ▶ does not require distributional assumptions
- ▶ can be applied to any test statistic

- ▶ Cons:

- ▶ less useful for small sample sizes
- ▶ p-values usually cannot be estimated with sufficient precision for heavy multiple testing correction
- ▶ in naive implementations, can get p-values of “0”

## Example from (sleep) data:

- ▶ Sleep data show the effect of two soporific drugs (increase in hours of sleep compared to control) on 10 patients.

```
##      extra      group      ID
##  Min.    :-1.600   1:10    1    :2
##  1st Qu.: -0.025   2:10    2    :2
##  Median :  0.950           3    :2
##  Mean   :  1.540           4    :2
##  3rd Qu.:  3.400           5    :2
##  Max.   :  5.500           6    :2
##                                     (Other):8
```

## t-test for difference in mean sleep

```
##  
## Welch Two Sample t-test  
##  
## data: extra by group  
## t = -1.8608, df = 17.776, p-value = 0.07939  
## alternative hypothesis: true difference in means is not  
## 95 percent confidence interval:  
## -3.3654832 0.2054832  
## sample estimates:  
## mean in group 1 mean in group 2  
## 0.75 2.33
```

## Permutation test instead of t-test

```
set.seed(1)
permT = function(){
  index = sample(1:nrow(sleep), replace=FALSE)
  t.test(extra ~ group[index], data=sleep)$statistic
}
Tr = replicate(999, permT())
(sum(abs(Tr) > abs(Tactual)) + 1) / (length(Tr) + 1)

## [1] 0.079
```

Bootstrap

# The Bootstrap

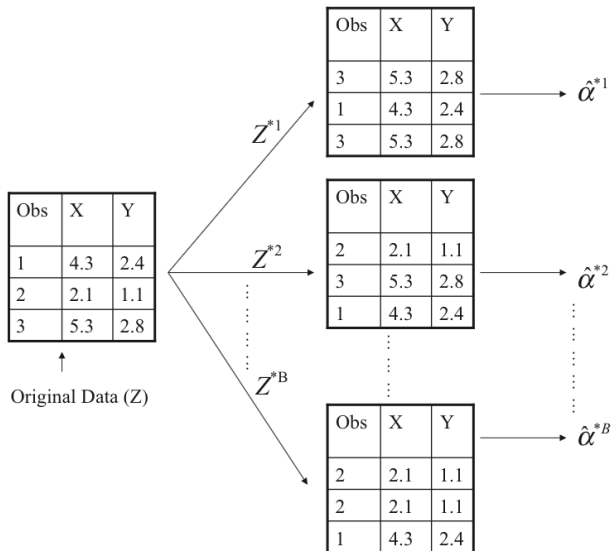


Figure 5: Schematic of the Bootstrap

# Uses of the Bootstrap

- ▶ The Bootstrap is a very general approach to estimating sampling uncertainty, e.g. standard errors
- ▶ Can be applied to a very wide range of models and statistics
- ▶ Robust to outliers and violations of model assumptions



# How to perform the Bootstrap

- ▶ The basic approach:
  1. Using the available sample (size  $n$ ), generate a new sample of size  $n$  (with replacement)
  2. Calculate the statistic of interest
  3. Repeat
  4. Use repeated experiments to estimate the variability of your statistic of interest

## Example: bootstrap in the sleep dataset

- ▶ We used a permutation test to estimate a p-value
- ▶ We will use bootstrap to estimate a confidence interval

```
t.test(extra ~ group, data=sleep)
```

```
##  
## Welch Two Sample t-test  
##  
## data: extra by group  
## t = -1.8608, df = 17.776, p-value = 0.07939  
## alternative hypothesis: true difference in means is not  
## 95 percent confidence interval:  
## -3.3654832 0.2054832  
## sample estimates:  
## mean in group 1 mean in group 2  
## 0.75 2.33
```

## Example: bootstrap in the sleep dataset

```
set.seed(2)
bootDiff = function(){
  boot = sleep[sample(1:nrow(sleep), replace = TRUE), ]
  mean(boot$extra[boot$group==1]) -
    mean(boot$extra[boot$group==2])
}
bootR = replicate(1000, bootDiff())
bootR[match(c(25, 975), rank(bootR))]
```

```
## [1] -3.32083333  0.02727273
```

note: better to use `library(boot)`

## Example: oral carcinoma recurrence risk

- ▶ Oral carcinoma patients treated with surgery
- ▶ Surgeon takes “margins” of normal-looking tissue around to tumor to be safe
  - ▶ number of “margins” varies for each patient
- ▶ Can an oncogenic gene signature in histologically normal margins predict recurrence?

Reis PP, Waldron L, *et al.*: **A gene signature in histologically normal surgical margins is predictive of oral carcinoma recurrence.** BMC Cancer 2011, 11:437.

## Example: oral carcinoma recurrence risk

- ▶ Model was trained and validated using the maximum expression of each of 4 genes from any margin

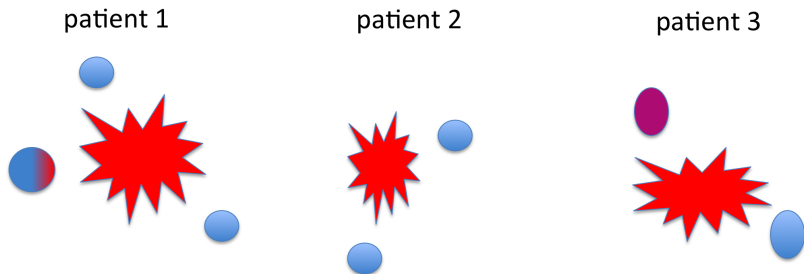


Figure 6: Oral carcinoma with histologically normal margins

## Bootstrap estimation of HR for only one margin

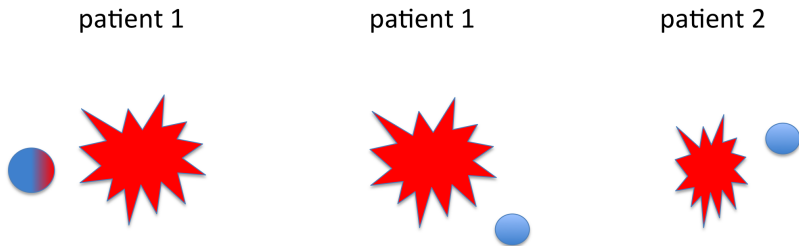


Figure 7: Bootstrap re-sample with randomly selected margin

## Example: oral carcinoma recurrence risk

From results:

*Simulating the selection of only a single margin from each patient, the 4-gene signature maintained a predictive effect in both the training and validation sets (median HR = 2.2 in the training set and 1.8 in the validation set, with 82% and 99% of bootstrapped hazard ratios greater than the no-effect value of HR = 1)*

Monte Carlo



# What is a Monte Carlo simulation?

- ▶ “Resampling” is done from known theoretical distribution
- ▶ Simulated data are used to estimate the probability of possible outcomes
  - ▶ most useful application for me is *power estimation*
  - ▶ also used for Bayesian estimation of posterior distributions

# How to conduct a Monte Carlo simulation

► **Steps of a Monte Carlo simulations:**

1. Sample randomly from the simple distributions in each step
2. Estimate the complex function for the sample
3. Repeat this a large number of times

# Random distributions form the basis of Monte Carlo simulation

Figure 6A.15: Distributional Choices

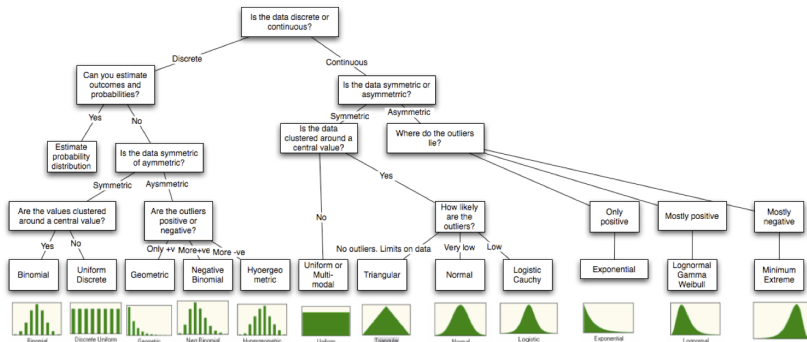


Figure 8:

Credit: Markus Gesmann <http://www.magesblog.com/2011/12/fitting-distributions-with-r.html>

## Power Calculation for a follow-up sleep study

- ▶ What sample size do we need for a future study to detect the same effect on sleep, with 90% power and  $\alpha = 0.05$ ?

```
power.t.test(power=0.9, delta=(2.33-.75),  
             sd=1.9, sig.level=.05,  
             type="two.sample", alternative="two.sided")
```

```
##  
##      Two-sample t test power calculation  
##  
##              n = 31.38141  
##            delta = 1.58  
##             sd = 1.9  
##    sig.level = 0.05  
##           power = 0.9  
## alternative = two.sided  
##  
## NOTE: n is number in *each* group
```

## The same calculation by Monte Carlo simulation

- ▶ Use `rnorm()` function to draw samples
- ▶ Use `t.test()` function to get a p-value
- ▶ Repeat many times, what % of p-values are less than 0.05?

## R script

```
set.seed(1)
montePval = function(n){
  group1 = rnorm(n, mean=.75, sd=1.9)
  group2 = rnorm(n, mean=2.33, sd=1.9)
  t.test(group1,group2)$p.value
}
sum(replicate(1000, montePval(n=32)) < 0.05) / 1000
```

```
## [1] 0.895
```

## Summary: resampling methods

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|                  | Procedure  | Application                                       |
|------------------|--|---|
| Cross-Validation | Data is randomly divided into subsets. Results validated across sub-samples. | Model tuning<br>Estimation of prediction accuracy |
| Permutation Test | Samples of size $N$ drawn at random <i>without</i> replacement.              | Hypothesis testing                                |

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## Summary: resampling methods

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|             | Procedure  | Application  |
|-------------|--|--|
| Bootstrap   | Samples of size $N$ drawn at random <i>with</i> replacement. | Confidence intervals, hypothesis testing           |
| Monte Carlo | Data are sampled from a known distribution                   | Power estimation, Bayesian posterior probabilities |

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