Resampling Methods

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July 13, 2016

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)

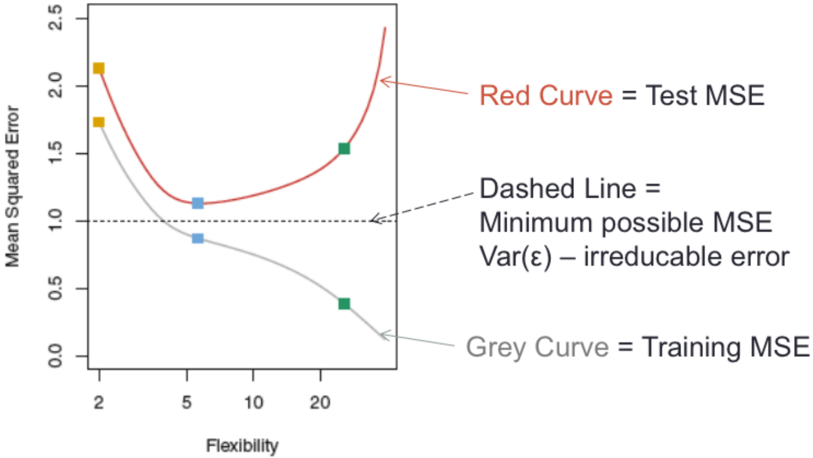
Prediction

- 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?



Red Curve = Test MSE

Dashed Line =
Minimum possible MSE
Var(ε) – irreducable error

Grey Curve = Training MSE

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

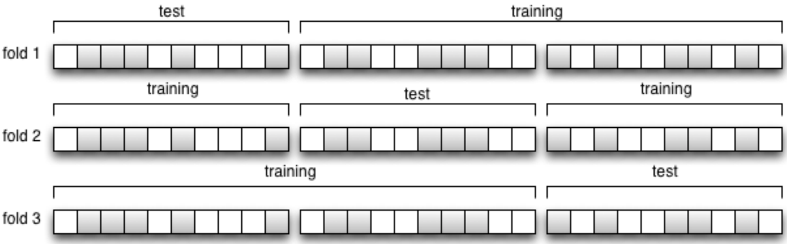


Figure 2: 3-fold CV

Variability in cross-validation

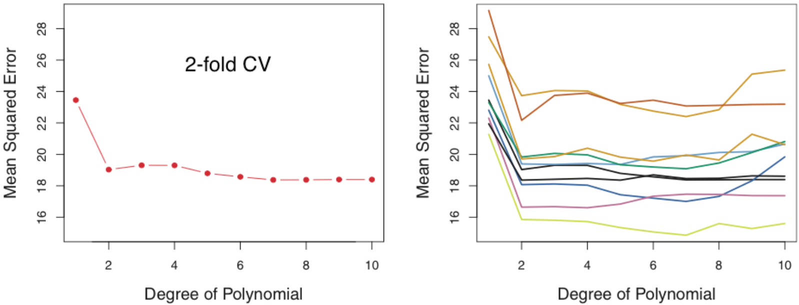


Figure 3: Variability of 2-fold cross-validation (ISLR Figure 5.2)

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

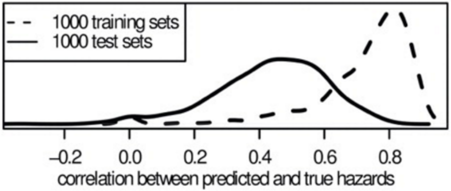
Cross-validation caveats

- 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

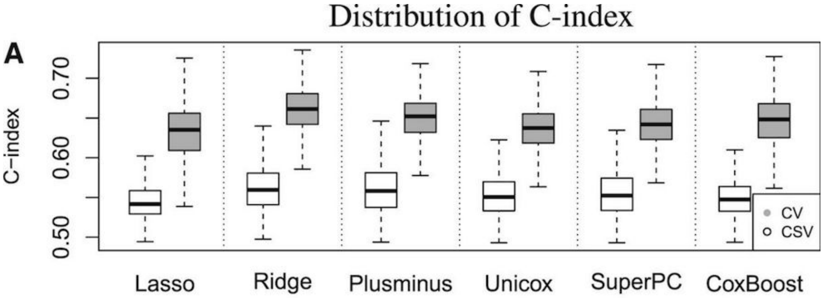


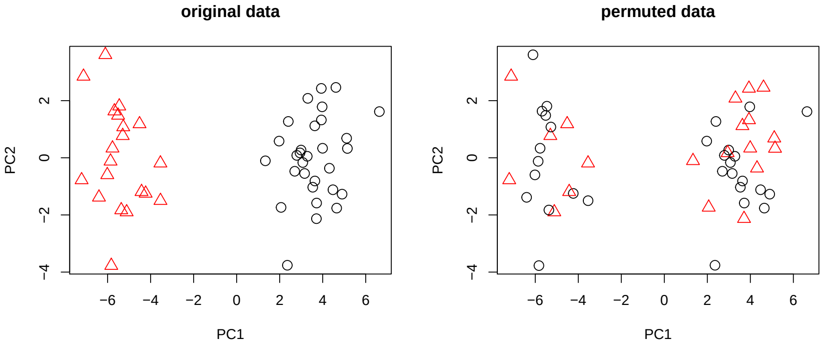
Figure 4: Cross-validation vs. cross-study validation in breast cancer prognosis

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, χ^2 distribution
- Permutation testing: H_0 determined empirically using permutations of the data where H_0 is guaranteed to be true


original data

permuted data

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

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

- 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
```

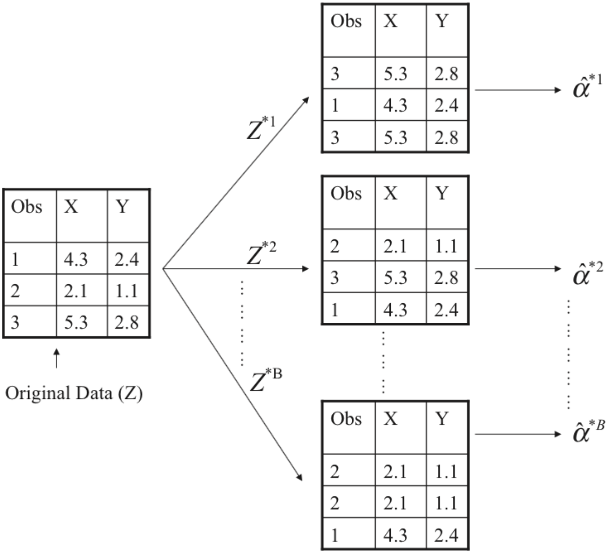
Permutation test instead of t-test

```r
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



Obs	X	Y
1	4.3	2.4
2	2.1	1.1
3	5.3	2.8

Obs	X	Y
3	5.3	2.8
1	4.3	2.4
3	5.3	2.8

Obs	X	Y
2	2.1	1.1
3	5.3	2.8
1	4.3	2.4

Obs	X	Y
2	2.1	1.1
2	2.1	1.1
1	4.3	2.4

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

```r
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

```r
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

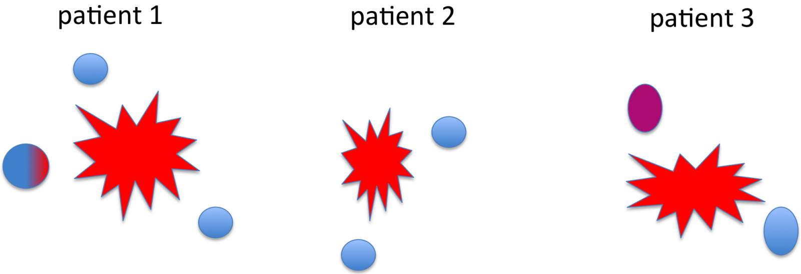


Figure 6: Oral carcinoma with histologically normal margins

Bootstrap estimation of HR for only one margin

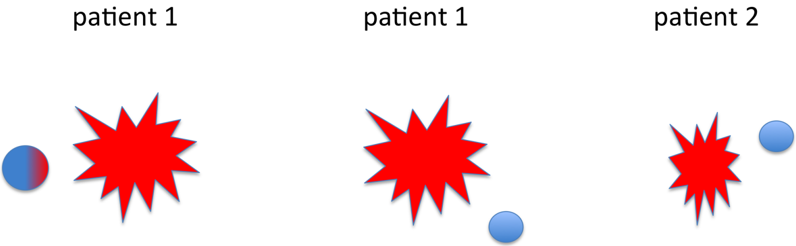


Figure 7: Bootstrap re-sample with randomly selected margin

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

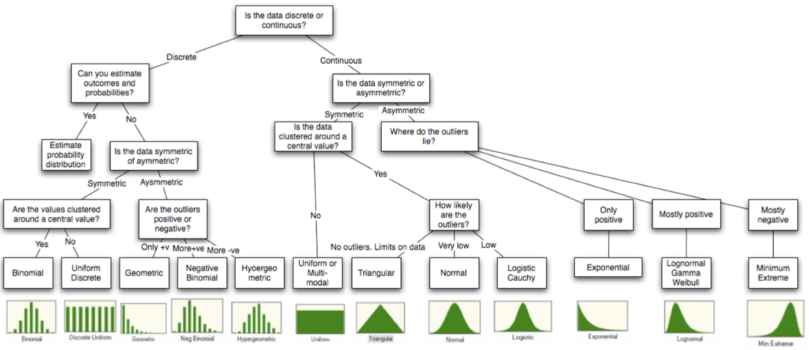


Figure 8:

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

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

Summary: resampling methods

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