Module 6, part II: Sparse regression and shrinkage

BIOS 526

Reading

- Sections 3.3 3.4 in Elements of Statistical Learning II (ESL II) (Hastie et al)
- Section 6.5 in Introduction to Statistical Learning (ISL) (James et al)

Concepts

- Ridge regression and L2 norm
- Sparsity
- Lasso and L1 norm
- Selecting the penalty / CV
- Correlated Variables and Elastic Net
- Bonferroni Correction

Motivation

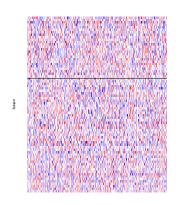
In modern applications, p is often very large relative to n.

A study is "high dimensional" if p is large.

There are a number of considerations:

- 1. Predictive Ability: OLS has low bias but high variance. Can we sacrifice bias to achieve lower variance, and thus greater accuracy?
- 2. Interpretability: with large p, our goal is to identify important variables. It would be helpful to have a model that does this, rather than rely upon forward/backward selection procedures and p-values.
- 3. Moreover, when p>n, we can't use multiple regression OLS estimators are not unique.
 - In $(\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}'\mathbf{Y}$, p > n then $(\mathbf{X}'\mathbf{X})$ not invertible

Motivating dataset: gene expression in leukemia



- Response: binary variable indicating whether the subject has leukemia. 25 subjects with leukemia, 47 controls. n=72.
- Covariates: Microarray data from p=3571 genes. Blue indicates negative values (lower expression), red indicates higher gene expression.

Review: Bias-Variance Trade-off

$$\begin{split} E\{g(\mathbf{x}_i) - \hat{g}(\mathbf{x}_i)\}^2 &= E[\{g(\mathbf{x}_i) - E\ \hat{g}(\mathbf{x}_i) + E\ \hat{g}(\mathbf{x}_i) - \hat{g}(\mathbf{x}_i)\}^2] \\ &= [g(\mathbf{x}_i) - E\ \hat{g}(\mathbf{x}_i)]^2 + E[\ \hat{g}(\mathbf{x}_i) - E\ \hat{g}(\mathbf{x}_i)]^2 \\ &= (\mathsf{Bias}\ \mathsf{of}\ \hat{g}(\mathbf{x}_i))^2 + \mathsf{Variance}\ \mathsf{of}\ \hat{g}(\mathbf{x}_i) \end{split}$$

where $\hat{g}(\mathbf{x}_i)$ is the estimate of $E(Y|\mathbf{x}_i) = g(\mathbf{x}_i)$.

Here,
$$g(\mathbf{x}_i) = \mathbf{x}_i' \boldsymbol{\beta}$$
.

When estimating a large number of parameters, we may overfit the data.

Sacrifice some bias to reduce variance, improve overall accuracy.

To estimate more parameters accurately, you need more data. A rough rule of thumb is 10 observations / parameter.

Model Complexity

7. Model Assessment and Selection

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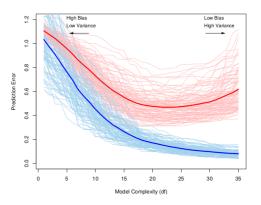


FIGURE 7.1. Behavior of test sample and training sample error as the model complexity is varied. The light blue curves show the training error $\overline{\text{err}}$, while the light red curves show the conditional test error $\overline{\text{Err}}_T$ for 100 training sets of size 50 each, as the model complexity is increased. The solid curves show the expected test error $\overline{\text{Err}}$ and the expected training error $\overline{\text{E[err]}}$.

Review

We discussed penalized regression in Module 5.

Recall the ridge regression penalty from M5.2:

$$\underset{\boldsymbol{\beta}}{\operatorname{argmin}} \quad \sum_{i=1}^{n} (y_i - \mathbf{x}_i' \boldsymbol{\beta})^2 + \lambda ||\boldsymbol{\beta}||_2^2$$

Here, λ is the penalty.

This problem can be equivalently formulated as

$$\underset{\boldsymbol{\beta}}{\operatorname{argmin}} \ (\mathbf{Y} - \mathbf{X}\boldsymbol{\beta})'(\mathbf{Y} - \mathbf{X}\boldsymbol{\beta}) \quad \text{with constraint } \boldsymbol{\beta}'\boldsymbol{\beta} \leq C$$

where there exists a one-to-one mapping between λ and C.



Closed-form solution

We derived the solution, which has a very convenient closed form:

$$\hat{\boldsymbol{\beta}} = (\mathbf{X}'\mathbf{X} + \lambda \mathbf{I})^{-1}\mathbf{X}'\mathbf{Y}$$

for some positive number λ .

Note:

- When $\lambda=0$, $\hat{\beta}$ becomes the ordinary least squares estimate. So no penalization is present $(C=\infty)$.
- When $\lambda \to \infty$, $(\mathbf{X}'\mathbf{X} + \lambda \mathbf{I})^{-1}$ becomes small, so $\hat{\boldsymbol{\beta}} \to \mathbf{0}$.
- $(\mathbf{X}'\mathbf{X} + \lambda \mathbf{I})$ is positive definite for $\lambda > 0$, so we can invert it even if p > n!

Important details

The penalty λ is unfair if the predictors are not on the same scale.

Consequently, we scale the columns of ${\bf X}$ to have unit variance. Then the penalty for each coefficient is equitable.

We often do not want to penalize the intercept:

$$\underset{\beta}{\operatorname{argmin}} \quad \sum_{i=1}^{n} (y_i - \beta_0 - \mathbf{x}_i' \boldsymbol{\beta})^2 + \lambda ||\boldsymbol{\beta}||_2^2$$

where β_0 is not penalized.

Similarly, we can center all columns of $\mathbf{X} \in \mathbb{R}^{n \times p}$ and center \mathbf{y} . Then $\hat{\beta}_0 = 0$. So one approach is to center your data and then penalize all terms.

Ridge regression versus sparsity

For variable selection, it would be nice to have estimates of β that include exact zeros.

If
$$\hat{\beta}_j \neq 0$$
, \mathbf{x}_j is selected.

If
$$\hat{\beta}_j = 0$$
, \mathbf{x}_j is not important.

Although $\hat{\beta}^{Ridge}$ may have reduced MSE relative to $\hat{\beta}^{OLS}$, it does not help us too much with variable selection.



Norms

We can measure the length of a vector using different metrics.

Ridge regression uses the squared L_2 norm, which is also called the Euclidean norm.

For a vector $oldsymbol{eta} \in \mathbb{R}^d$, an L_p norm has the general form

$$||\boldsymbol{\beta}||_p = \left(\sum_{j=1}^d |\beta_j|^p\right)^{1/p}$$

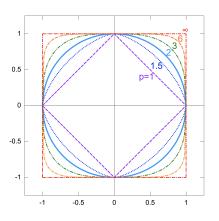


Figure: Illustration of the unit circles of some p-norms for p=1: sum norm, p=1.5, p=2: Euclidean norm, p=3, p=6, p= ∞ : max norm in two dimensions from

https://en.wikipedia.org/wiki/Lp_space#/media/File: Vector-p-Norms_qtl1.svg.

Lasso

We will assume all covariates and ${\bf y}$ are centered so that we don't need to estimate the intercept.

We will also assume they are scaled.

Let's consider using a different norm, the L_1 norm.

$$\hat{\boldsymbol{\beta}}^{Lasso} = \underset{\boldsymbol{\beta}}{\operatorname{argmin}} \quad \sum_{i=1}^{n} (y_i - \mathbf{x}_i' \boldsymbol{\beta})^2 + \lambda ||\boldsymbol{\beta}||_1$$

where $||\beta||_1 = \sum_{j=1}^p |\beta_j|$.

Statisticians call this the **LASSO**: Least absolute shrinkage and selection operator.

This penalty is chosen because it induces sparsity.

Sparsity is when we have many zeros and a relatively small number of non-zeros.

L_1 and L_2 constraints

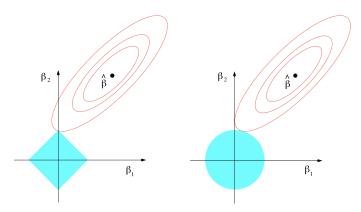


FIGURE 3.11. Estimation picture for the lasso (left) and ridge regression (right). Shown are contours of the error and constraint functions. The solid blue areas are the constraint regions $|\beta_1| + |\beta_2| \le t$ and $\beta_1^2 + \beta_2^2 \le t^2$, respectively, while the red ellipses are the contours of the least squares error function.

Figure: From ESLII p. 71

Lasso

Why does the Lasso induce sparsity?

For $||\beta||_1 \leq C$, the L_1 constraint creates sharp points at the boundary corresponding to $(\beta_1,\beta_2)=(C,0)$, (0,C), (-C,0), and (0,-C).

For $\beta = (\beta_1, \beta_2)$, consider where the contours of $(\mathbf{Y} - \mathbf{X}\beta)'(\mathbf{Y} - \mathbf{X}\beta)$ intersect the constraint .

For sufficiently small C, i.e., large λ , the constraint leads to the selection of either β_2 or β_1 .

In contrast, the smooth circle from the ridge regression, $\beta_1^2 + \beta_2^2 = C$, is tangent to the contours of $(\mathbf{Y} - \mathbf{X}\boldsymbol{\beta})'(\mathbf{Y} - \mathbf{X}\boldsymbol{\beta})$ at $\beta_1 \neq 0$ and $\beta_2 \neq 0$.

Obtaining Lasso estimates

Unfortunately, there is no closed form solution for the Lasso.

Fortunately, it is convex problem.

In the R package glmnet, there are efficient ways to calculate the solutions for a set of λ_k .

In the special case of orthogonal and standardized covariates, we have

$$\hat{\beta}_j^{Lasso} = \mathrm{sign}(\hat{\beta}_j^{OLS})(|\hat{\beta}_j^{OLS} - \lambda|)_+.$$

Perspectives on Lasso and Ridge: Orthonormal covariates

	Estimator	Formula	_
	Best subset (size M)	$\hat{\beta}_j \cdot I(\hat{\beta}_j \ge \hat{\beta}_{(M)})$	
	Ridge	$\hat{eta}_j/(1+\lambda)$	
	Lasso	$\operatorname{sign}(\hat{\beta}_j)(\hat{\beta}_j - \lambda)_+$	_
Best Subs	et Rid	ge	Lasso
(0,0		(0.0)	(0,0)

Figure: Table 3.4 from ESL II. Closed forms for Best Subset, Ridge, and Lasso for the special case of orthonormal covariates.

Ridge Regression and Bayes Estimates

In the Bayesian framework, $f(\beta|\mathbf{y}) \propto f(\mathbf{y}|\beta)f(\beta)$.

Let's assume a Gaussian likelihood with variance σ^2 and independent mean-zero Gaussian priors on β with common variance τ^2 :

$$f(\boldsymbol{\beta}|\mathbf{y}) \propto (2\pi\sigma^2)^{-n/2} \exp\left\{-\sum_{i=1}^n (y_i - \mathbf{x}_i'\boldsymbol{\beta})^2/(2\sigma^2)\right\}$$
$$\times (2\pi\tau^2)^{-p/2} \exp\left\{-\sum_{j=1}^p \beta_j^2/(2\tau^2)\right\}$$

Bayesian Perspective on Ridge Regression

Assumes σ^2 and τ^2 are given.

On the log scale, and dropping constants, the maximum a posteriori estimate (i.e., mode) is obtained as

$$\hat{\boldsymbol{\beta}}^{MAP} = \underset{\boldsymbol{\beta}}{\operatorname{argmax}} \quad -\frac{1}{2\sigma^2} \sum_{i=1}^{n} (y_i - \mathbf{x}_i' \boldsymbol{\beta})^2 - \frac{1}{2\tau^2} \sum_{j=1}^{p} \beta_j^2$$

$$= \underset{\boldsymbol{\beta}}{\operatorname{argmin}} \quad \sum_{i=1}^{n} (y_i - \mathbf{x}_i' \boldsymbol{\beta})^2 + \lambda \sum_{j=1}^{p} \beta_j^2.$$

for
$$\lambda = \sigma^2/\tau^2$$
.

Thus, $\hat{\beta}^{Ridge}$ can be derived from the Bayesian perspective in which the prior distribution is Gaussian and the prior precision determines the degree of shrinkage.

Bayesian Perspective on the Lasso

The Laplace distribution (also called double exponential) is a shrinkage prior.

For mean zero, $f(\beta_j)=\frac{1}{2\tau}\exp(-|\beta_j|/\tau)$, which has variance $2\tau^2$.

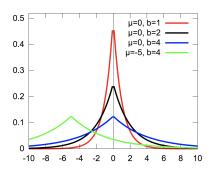


Figure: https://en.wikipedia.org/wiki/Laplace_distribution

Bayesian Perspective on the Lasso

Then we have

$$\hat{\boldsymbol{\beta}}^{MAP} = \underset{\boldsymbol{\beta}}{\operatorname{argmax}} \quad -\frac{1}{2\sigma^2} \sum_{i=1}^{n} (y_i - \mathbf{x}_i' \boldsymbol{\beta})^2 - \frac{1}{2\tau} \sum_{j=1}^{p} |\beta_j|$$
$$= \underset{\boldsymbol{\beta}}{\operatorname{argmin}} \quad \sum_{i=1}^{n} (y_i - \mathbf{x}_i' \boldsymbol{\beta})^2 + \lambda \sum_{j=1}^{p} |\beta_j|.$$

for
$$\lambda = \sigma^2/\tau$$
.

Thus, we again see a stronger prior (smaller τ) leads to greater shrinkage. For sufficiently large τ , we get variable selection.

Selecting λ : Cross-validation

Recall from M5.2:

In K-Fold CV, the data are divided into K subsets

$$MSE_k = \frac{1}{n/K} \sum_{i \in \mathcal{S}_k} (y_i - \hat{y}_i^{-\mathcal{S}_k})^2$$

$$CV = \widehat{MSE} = \frac{1}{K} \sum_{k=1}^{K} MSE_k$$

- Each partition has a training dataset with (K-1)*n/K observations and test dataset with n/K observations.
- Then the model is fit K times.
- LOOCV is a special case where the number of folds is n.

K-fold Cross-Validation

$$MSE_k = \frac{1}{n/K} \sum_{i \in \mathcal{S}_k} (y_i - \hat{y}_i^{-\mathcal{S}_k})^2$$

$$CV = \widehat{MSE} = \frac{1}{K} \sum_{k=1}^{K} MSE_k$$

1 2 3 4 5

Train Train Validation Train Train

Figure: R Tibshirani Lecture notes, http:

//www.stat.cmu.edu/~ryantibs/datamining/lectures/18-val1.pdf.

Prediction error to choose λ

Note: the goal of CV is to improve prediction.

The resulting choice of λ may not be optimal for addressing our goal, which is to select the most important covariates.

CV tends to over-select the number of parameters.

There are heuristics such as the one standard error rule:

- Find λ_{min} using 10-fold CV.
- Estimate the variance of the CV using each fold's MSE_k as a sample:

$$\frac{1}{K} \sum_{k=1}^{K} (MSE_k - \widehat{MSE}_k)^2$$

• Increase λ to result in an MSE that is +1 SE of CV for λ_{min} .



Correlated covariates

It turns out that variable selection via the Lasso is sensitive to correlation between your covariates.

For two correlated covariates, Lasso picks one but not the other, e.g., $\hat{\beta}_1$ is set to zero while $\hat{\beta}_2$ is not.

For small samples, which variable is chosen can be arbitrary.

Ridge regression is less sensitive to correlation between covariates, and shrinks covariates together.

Variable Selection Methods for Correlated Covariates

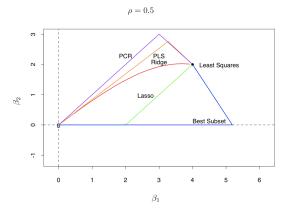


Figure: Figure 3.18 from ESL II. Correlation between \mathbf{x}_1 and \mathbf{x}_2 is 0.5. The true regression coefficients are (4,2). Note that Ridge and Lasso are estimated over a continuous range of λ , whereas other methods correspond to the discrete steps selecting 0, 1, or 2 variables.

Elastic Net

The elastic net offers a middle ground and uses a combination of the two. For $\alpha \in (0,1)$,

$$\hat{\boldsymbol{\beta}}^{ElNet} = \underset{\boldsymbol{\beta}}{\operatorname{argmin}} \quad \sum_{i=1}^{n} (y_i - \mathbf{x}_i' \boldsymbol{\beta})^2 + \lambda \sum_{j=1}^{p} (\alpha |\beta_j| + (1 - \alpha)\beta_j^2).$$

Elastic net tends to shrink some coefficients to zero, like the lasso, but shrinks correlated covariates together, like ridge.

In the R package glmnet, the penalty is $\lambda \sum_{j=1}^p \left\{ \alpha |\beta_j| + (1-\alpha)\beta_j^2/2 \right\}$.

According to the vignette, when variables are correlated in groups, $\alpha=0.5$ tends to result in variables in the group either all selected or dropped.

Note in glmnet, $\alpha=0=$ ridge, $\alpha=1=$ Lasso.



GLM Elastic Net

We can also use penalized regression in the generalized linear model framework. Let ℓ be the log density of y_i .

$$\hat{\beta}^{ElNet} = \underset{\beta}{\operatorname{argmin}} - \sum_{i=1}^{n} \ell(y_i; \mathbf{x}_i' \boldsymbol{\beta}) + \lambda \sum_{j=1}^{p} (\alpha |\beta_j| + (1 - \alpha)\beta_j^2).$$

Note that rather than penalizing the squared loss, here we penalize the negative log-likelihood.

With the penalty, the objective function is maximized at smaller values of β_j relative to the MLE.

Cross-validation and loss functions

For Gaussian data, we used the PMSE in cross-validation: $\sum_{i=1}^{n} (y_i - \hat{y}_i)^2$.

In GLMs, we use the negative log likelihood, which is often multiplied by two and called the deviance:

$$D = -2\sum_{i=1}^{n} \ell(y_i; \mathbf{x}_i'\boldsymbol{\beta})$$

.

Note that for iid Gaussian data with variance 1, the deviance equals $\sum_{i=1}^{n} (y_i - \hat{y}_i)^2$.

For CV, we can use the deviance in place of PMSE. Other options are available.

The R package glmnet

The R package glmnet contains a function, also called glmnet Some of the options are listed below:

```
glmnet(x, y, family = c("gaussian", "binomial", "poisson", "multinomial",
"cox", "mgaussian"), alpha = 1,nlambda = 100,
lambda = NULL, standardize = TRUE, intercept = TRUE,
```

A key parameter here is alpha: the elastic net mixing parameter with $0 \le \alpha \le 1$. The penalty is defined as

$$\frac{1-\alpha}{2}||\beta||_{2}^{2} + \alpha||\beta||_{1}$$

alpha=1 is the lasso penalty, and alpha=0 the ridge penalty.

Standardizes data by default.

No "data" argument.



Leukemia Dataset: Ridge Regression

```
> x = Leukemia$x
> v = Leukemia$v
> model.ridge = glmnet(x,y,alpha=0,family = 'binomial')
> print(model.ridge)
Call: glmnet(x = x, y = y, family = "binomial", alpha = 0)
     Df %Dev Lambda
   3571 0.00 409.30
   3571 18.35 390.70
   3571 19.01 372.90
   3571 19.69 356.00
   3571 20.38 339.80
   3571 21.09 324.40
   3571 21.82 309.60
   3571 22.56 295.60
   3571 23.32 282.10
10 3571 24.09 269.30
```

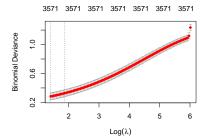
Leukemia Dataset: Ridge Regression

```
> dim(coef(model.ridge))
[1] 3572 100
> coef(model.ridge)[1:10,1:5]
10 x 5 sparse Matrix of class "dgCMatrix"
                                                                  s3
                                                                                s4
(Intercept) -6.312718e-01 -6.449201e-01 -6.459674e-01 -6.470840e-01 -6.482734e-01
V1
            -4.780168e-38 -1.203411e-04 -1.259193e-04 -1.317424e-04 -1.378195e-04
V2
             3.994960e-38 8.905586e-05 9.273885e-05 9.654906e-05 1.004888e-04
VЗ
             9.777714e-38 2.086957e-04 2.169559e-04 2.254734e-04
                                                                     2.342506e-04
V4
             3.692679e-38 7.792437e-05 8.089428e-05 8.394169e-05 8.706528e-05
V5
            -9.494342e-39 -1.533100e-05 -1.579680e-05 -1.626987e-05 -1.675012e-05
V6
            -3.815336e-38 -1.003254e-04 -1.050186e-04 -1.099108e-04 -1.150079e-04
            -7.641146e - 38 - 1.800051e - 04 - 1.878006e - 04 - 1.958899e - 04 - 2.042796e - 04
٧7
V8
            -8.192134e-38 -1.976823e-04 -2.064352e-04 -2.155335e-04 -2.249867e-04
V9
             2.647430e-38 4.418512e-05 4.547821e-05 4.677791e-05
```

Leukemia Dataset: Ridge Regression

Fit model using 10-fold CV to select lambda:

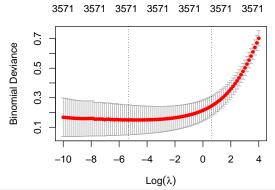
```
> set.seed(123)
> cv.model.ridge = cv.glmnet(x,y,alpha=0,family='binomial')
> plot(cv.model.ridge)
```



The default values of lambda did not work.

Leukemia Dataset: Ridge Regression Refit using smaller values of lambda to get a minimum:

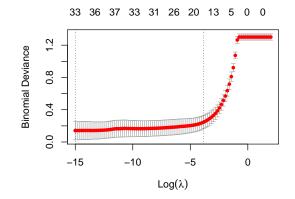
```
> lambda = exp(seq(4,-10,length=100))
> cv.model.ridge = cv.glmnet(x,y,alpha=0,lambda = lambda,family='binomial')
> cv.model.ridge$lambda.min
[1] 0.00482795
> cv.model.ridge$lambda.1se
[1] 1.833195
```



Leukemia Dataset: Lasso

```
> set.seed(123)
```

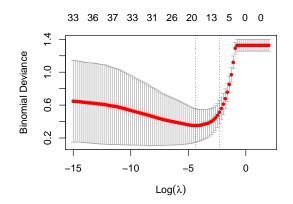
- > lambda = exp(seq(2,-15,length=100))
- > cv.model.lasso = cv.glmnet(x,y,alpha=1,lambda=lambda,family='binomial')
- > plot(cv.model.lasso)



Leukemia Dataset: Lasso

Unfortunately, the CV estimate can be highly variable.

This is running the same code but using a different random partition of the data into folds:

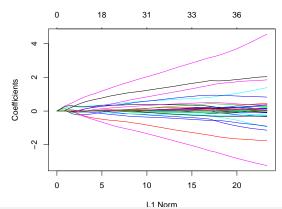


Coefficient Paths

We can also look at coefficient paths.

These plot the coefficients across the grid of λ .

Variables the enter the model first are more important (when using standardization).



Leukemia Dataset: Elastic Net

For elastic net, a typical default is $\alpha = 0.5$.

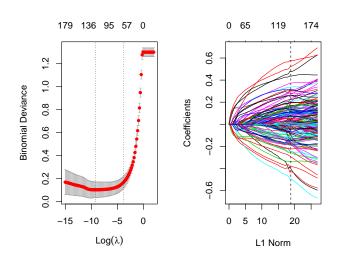
You could try to perform a 2D-CV varying λ and α , but this is computationally costly and may not work very well due to high CV variability.

Elastic net with $\alpha=0.5$ is a good default for high-dimensional regression. Tends to be more reliable than lasso, and unlike ridge, achieves variable selection.

To select fewer variables, increase α .

```
> set.seed(123)
> cv.model.elnet = cv.glmnet(x,y,alpha=0.5,lambda=lambda,family='binomial')
> elnet.estimates = coef(cv.model.elnet,s=cv.model.elnet$lambda.min)
> model.elnet = glmnet(x,y,alpha=0.5,lambda=lambda,family='binomial')
> plot(model.elnet)
> abline(v=sum(abs(elnet.estimates)),lty=2)
```

Leukemia Dataset: Elastic Net



What about inference?

Inference in the Lasso and penalized regression is an active area of research.

Recent distributional results are available when conditioning on the selection event: Lee, J. D., Sun, D. L., Sun, Y., & Taylor, J. E. (2016). Exact post-selection inference, with application to the lasso. *The Annals of Statistics*, 44(3), 907-927.

Since we are also choosing the tuning parameter via cross-validation, "conditioning on the selection event" is not incorporating all sources of uncertainty.

Another promising approach is "knockoffs," where you create "knockoffs" of \mathbf{X} unrelated to \mathbf{Y} and estimate the distribution of test statistics from these knockoffs: Barber, R. F., Candes, E. J., & Samworth, R. J. (2020). Robust inference with knockoffs. Annals of Statistics, 48(3), 1409-1431.

Other issues with inference

For elastic net and lasso using glmnet, we have replaced inference with variable selection and CV.

A common approach to large p (high dimensional) studies is to conduct thousands of univariate tests.

E.g., t tests for comparing cancer and control in gene expression.

Multiple comparisons is a problem: when conducting thousands of tests, we need to consider the probability that we falsely reject null hypotheses.

Note on Bonferroni Correction

When we conduct many hypothesis tests, we increase the chance of false detections.

Let H_1, \ldots, H_m be a family of null hypothesis tests, and p_1, \ldots, p_m their associated p-values.

Here we use m instead of p predictors due to notational conflict.

The family-wise error rate is the probability of at least one false positive.

Let $m_0 < m$ be the number of true null hypotheses.

We control the FWER if

$$P\left\{\bigcup_{j=1}^{m_0}\left(H_j \text{ is rejected } | H_j \text{ is true}\right)\right\} < \alpha.$$

Bonferroni correction, cont.

The Bonferroni correction is popular in part due to it simplicity: let $\alpha^* = \alpha/m$, where α is typically 0.05.

$$P\left\{\bigcup_{j=1}^{m_0} (p_j \le 0.05/m)\right\} \le \sum_{j=1}^{m_0} P\left(p_j \le 0.05/m\right)$$
$$= m_0 * 0.05/m$$
$$\le m * 0.05/m$$
$$= 0.05.$$

So when we control the individual tests at α^* , the FWER is less than or equal to α .

Bonferroni Correction, cont.

The Bonferroni Correction is a very conservative approach to correcting for multiple comparisons in variable selection.

It is often too conservative, and we will not find much (or even any) signal for very large p.

Other methods can be more powerful: controlling the false discovery rate (FDR), which is the proportion of falsely rejected null hypotheses, i.e., among the set of rejected null hypotheses, what proportion were in fact Type 1 errors.

There are also more powerful approaches to FWER, particularly under some types of dependence.