MA8701 Advanced methods in statistical inference and learning

W6: Statistical inference for penalized GLM methods

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1 Before we begin

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1.2 Literature

Main source:

- [HTW] Hastie, Tibshirani, Wainwright: "Statistical Learning with Sparsity: The Lasso and Generalizations". CRC press. Ebook. Chapter 6.0, 6.1, 6.2, 6.4, 6.5. (Results from 6.3 through Taylor and Tibshirani (2015))

Also: brush up on **bootstrap intervals from TMA4300**, where Givens and Hoeting (2013) is on the reading list. See specifically chapter 9 (9.2.1 and 9.3 will be used here). NTNU-access to the full book if you are on vpn.

Secondary sources:

- Short note on multiple hypothesis testing in TMA4267 Linear Statistical Models, Kari K. Halle, Øyvind Bakke and Mette Langaas, March 15, 2017.
- Single/multi-sampling splitting part of Dezeure, Bühlmann, Meier, Meinshausen (2015). "High-Dimensional Inference: Confidence Intervals, p-Values and R-Software hdi". Statistical Science, 2015, Vol. 30, No. 4, 533–558 DOI: 10.1214/15-STS527 (only the single/multiple sample splitting part in 2.1.1 and 2.2 for linear regression, and using the method in practice). Or Chapter 11 of Bühlmann and de Geer (2011)
- Taylor and Tibshirani (2015): Statistical learning and selective inference, PNAS, vol 112, no 25, pages 7629-7634. (Soft version of HTW 6.3.2)

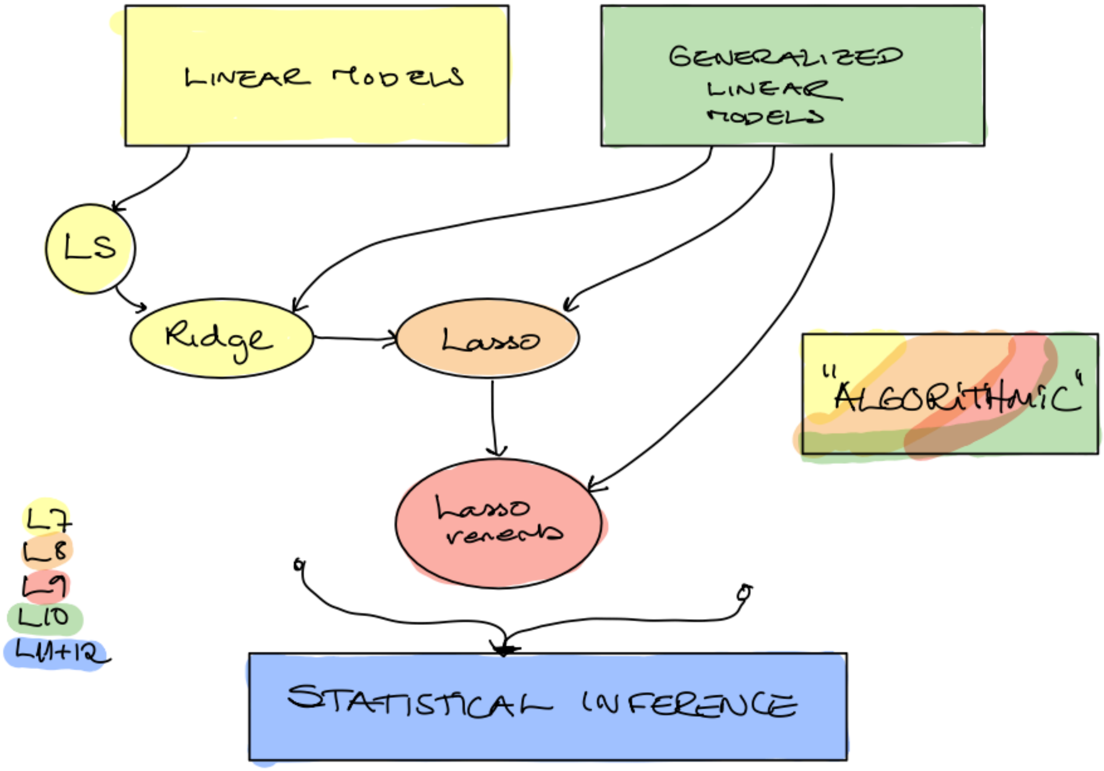


Figure 1: Overview of Part 2

2 Statistical inference

We have now heard about the South African heart disease data, and we will also look at at a regression problem with prediction of disease progression in diabetes.

2.1 Prediction vs statistical inference

2.1.1 Prediction

- Predict the value of the progression variable for a person with diabetes.
- Predict the probability of heart disease for a person from the population in the South African heart disease example.

2.1.2 Inference

- Assess the goodness of the prediction (MSE, error rate, ROC-AUC) - with uncertainty.
- Interpret the GLM-model - which covariates are included?
- Confidence interval for the model regression parameters.
- Testing hypotheses about the model regression parameters.

2.2 Statistics vs Machine learning

2.3 Known sampling distributions

For the linear regression and logistic regression we know the sampling distribution of the regression coefficient estimators.

Then it is easy to construct confidence intervals and perform hypothesis tests.

What are the known results?

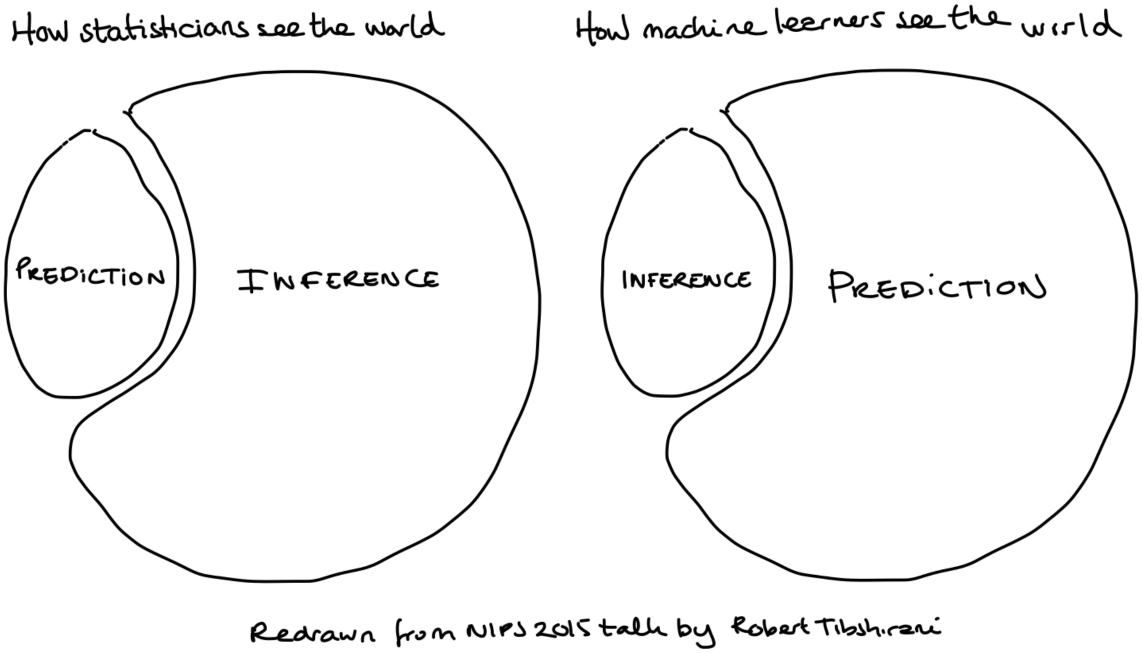

How statisticians see the world
How machine learners see the world
PREDICTION
INFERENCE
INFERENCE
PREDICTION
Redrawn from NIPS 2015 talk by Robert Tibshirani

Figure 2: Figures redrawn from Robert Tibshiran´s Breiman lecture at the NIPS 2015 https://www.youtube.com/watch?v=RKQJEvc02hc&t=81s. (Conference on Neural Information Processing System)

2.3.1 Multiple linear regression

$$Y = X\beta + \varepsilon$$

where $\varepsilon \sim N_N(0, \sigma^2 I)$ (independent observation pairs).

$$\hat{\beta}_{\text{LS}} = (X^T X)^{-1} X^T Y$$

with $\hat{\beta}_{\text{L}S} \sim N_p(\beta, \sigma^2 (X^T X)^{-1})$.

Restricted maximum likelihood estimator for σ^2:

$$\hat{\sigma}^2 = \frac{1}{N-p}(Y - X\hat{\beta}_{\text{LS}})^T (Y - X\hat{\beta}_{\text{L}S}) = \frac{\text{SSE}}{N-p}$$

with $\frac{(N-p)\hat{\sigma}^2}{\sigma^2} \sim \chi^2_{N-p}$.

Statistic for inference about β_j, c_{jj} is diagonal element j of $(X^T X)^{-1}$.

$$T_j = \frac{\hat{\beta}_{\text{L}S,j} - \beta_j}{\sqrt{c_{jj}}\hat{\sigma}} \sim t_{N-p}$$

or, inference can be done asymptotically and then replace the t with the normal distribution.

T_j is the starting point for constructing CIs for β_j and testing hypotheses about β_j.

Observe: the least squares estimator is *unbiased*!

2.3.2 Logistic regression

$\hat{\beta}$ is now not on closed form, but asymptotically when $N \to \infty$

$$\hat{\beta} \approx N_p(\beta, (X^T \hat{W} X)^{-1})$$

where $W = diag(\hat{\pi}_i(1 - \hat{\pi}_i))$, so that inference can be based on the asymptotic normality of each element of the regression estimate vector.

Observe: the logistic regression parameter estimator is *unbiased.*

2.4 Confidence interval — generic set-up

Set-up

- We have a random sample $Y_1, Y_2, \dots, Y_N$ from
- some distribution F with some (unkonwn) parameter θ.
- Let $y_1, y_2, \dots, y_N$ be the observed values for the random sample.

Statistics

- We have two statistics $\hat{\theta}_L(Y_1, Y_2, \dots, Y_N)$ and $\hat{\theta}_U(Y_1, Y_2, \dots, Y_N)$ so that

$$P(\hat{\theta}_L(Y_1, Y_2, \dots, Y_N) \leq \theta \leq \hat{\theta}_U(Y_1, Y_2, \dots, Y_N)) = 1 - \alpha$$

where $\alpha \in [0, 1]$

Confidence interval

The numerical interval

$$[\hat{\theta}_L(y_1, y_2, \dots, y_N), \hat{\theta}_U(y_1, y_2, \dots, y_N)]$$

is called a $(1 - \alpha)$ 100% confidence interval.

2.5 Sampling distribution for ridge and lasso?

2.5.1 Multippel linear ridge regression

$$\hat{\beta}_{\text{ridge}} = (X^T X + \lambda I)^{-1} X^T Y$$

$$\hat{\beta}(\lambda)_{\text{ridge}} \sim N\{(X^T X + \lambda I_p)^{-1} X^T X \beta,$$

$$\sigma^2 (X^T X + \lambda I_p)^{-1} X^T X (X^T X + \lambda I_p)^{-1}\}.$$

$$\text{df}(\lambda) = \text{tr}(H_\lambda) = \text{tr}(X(X^T X + \lambda I)^{-1} X^T) = \cdots = \sum_{j=1}^{p} \frac{d_j^2}{d_j^2 + \lambda}$$

- What can we do with that?
- What if the design matrix is orthogonal, does that help?

2.5.2 Logistic ridge

For large sample sizes the ridge logistic regression estimator is approximately multivariate normal (Wieringen (2021) Section 5.3).

$$\hat{\beta}(\lambda) \approx N_p(\beta - \lambda(X^T\hat{W}X + \lambda I)^{-1}\beta),$$
$$(X^T\hat{W}X + \lambda I)^{-1} - (X^T\hat{W}X + \lambda I)^{-2})$$

This is based on the asymptotic normality of the score function (gradient of the loglikelihood - here the penalized loglikelihood).

- What can we do with that?
- What if the design matrix is orthogonal, does that help?

2.5.3 Lasso

Some results using approximations to ridge (for mean and variance, see Wieringen (2021) p 97), but else *no parametric version of sampling distribution* known.

2.5.4 What is our aim?

Penalized estimation: reduce variance by introducing (strong) bias.

The squared bias then is a major part of the mean squared error, and the variance is thus a minor part.

But, do we need to use the ridge or lasso estimator to construct a confidence interval for β or test if $\beta_j = 0$?

- $p > N$
- $p < N$?

2.5.5 Debiased (desparsified) lasso

(HTW Section 6.4)

$$\hat{\beta}^d = \hat{\beta}_\lambda + \frac{1}{N} M X^T (Y - X\hat{\beta}_\lambda)$$

the matrix M is some approximation to the inverse of

$$\hat{\Sigma} = \frac{1}{N} X^T X$$

Use the debiased estimator to form CI from:

$$\hat{\beta}^d \sim N(\beta, \frac{\sigma^2}{N} M \hat{\Sigma} M^T)$$

Interpretation of debiasing: assume we want to minimize the residual sum of squares using an approximate Newton step starting at the lasso estimator.

Two solutions are based on

- neighbour-based methods to impose sparsity
- optimization problem to get $\hat{\Sigma}\hat{M} \approx I$ while the variance of the debiased estimator is small.

See Hastie, Tibshirani, and Wainwright (2015) page 159 for references to these solutions.

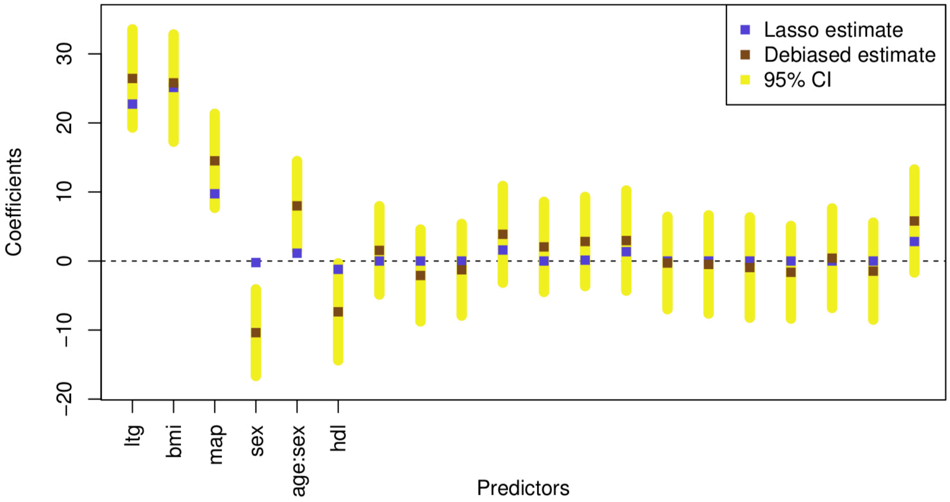


Figure 6.13 *Diabetes data: Lasso estimates, debiased lasso estimates, and confidence intervals from the debiasing approach. These intervals have not been adjusted for multiple comparisons. The first 6 predictors have intervals not containing zero: when Bonferroni-adjusted, this number drops to three.*

Figure 3: Figure 6.13 in Hastie, Tibshirani, and Wainwright (2015)

2.6 Conclusion

This is absolutely not straightforward.

The *adaptive and biased nature* of the estimation procedures makes it challenging to perform inference.

- We will *discuss* other (in addition to the debiasing) solutions to finding confidence intervals for regression parameters for lasso, and for constructing p-values for testing hypotheses about the regression parameters.
- We will address some *philosophical principles behind inference*
- and mention topics that can be studied further for the interested student!

Warning: there seems not to be consensus, but many interesting approaches and ideas that we may consider.

2.7 Diabetes data

In a medical study the aim was to explain the ethiology of diabetes progression. Data was collected from $n = 442$ diabetes patients, and from each patient the following measurements are available:

- `age` (in years) at baseline
- `sex` (0=female and 1=male) at baseline
- body mass index (`bmi`) at baseline
- mean arterial blood pressure (`map`) at baseline
- six blood serum measurements: total cholesterol (`tc`), ldl cholesterol (`ldl`), hdl cholesterol (`hdl`), `tch`, `ltg`, glucose `glu`, all at baseline,
- a quantitative measurement of disease progression one year after baseline (`prog`)

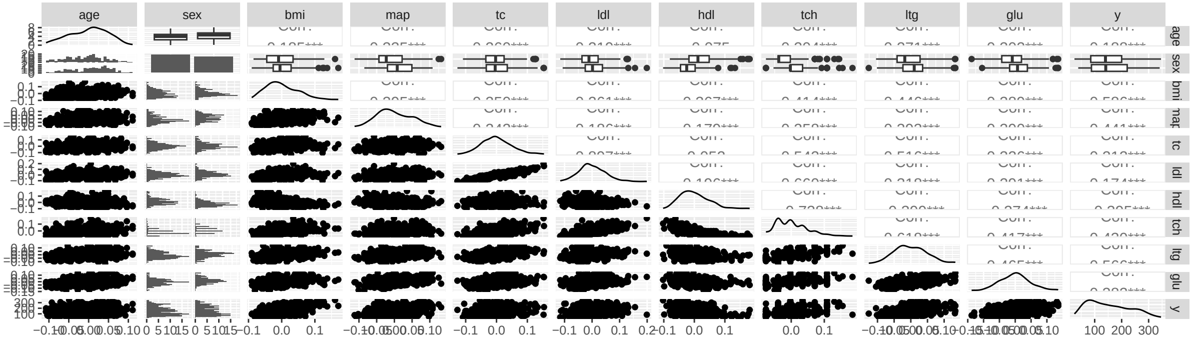
All measurements except `sex` are continuous. There are 10 covariates.

The response is the disease progression `prog` - thus a regression problem.

Data can be

- downloaded from https://web.stanford.edu/~hastie/StatLearnSparsity_files/DATA/diabetes.html in three variants: raw, standardized and 442 × 64 matrix with quadratic terms (not used here).

- Or, loaded from the `lars` package, that is automatically loaded in the `monomvn` package (where `blasso` is found).



3 Bayesian ridge and lasso

(HTW 6.1 for lasso, WNvW Section 5.5 and 6.6)

For penalized models there exists Bayesian equivalents. We will here focus on the multiple linear regression model.

3.1 Bayesian set-up

In the Bayesian statistics the regression parameters β are random quantities, and in addition to the likelihood also a prior for the regression parameters (and other parameters) are needed. When a *conjugate prior* the posterior distribution may be derived analytically.

Multiple linear regression: distribution of response - where we for simplicity assume that we have centred covariates and centred response (so no intercept term)

$$y \mid \beta, \sigma \sim N(X\beta, \sigma^2 I)$$

This gives the likelihood:

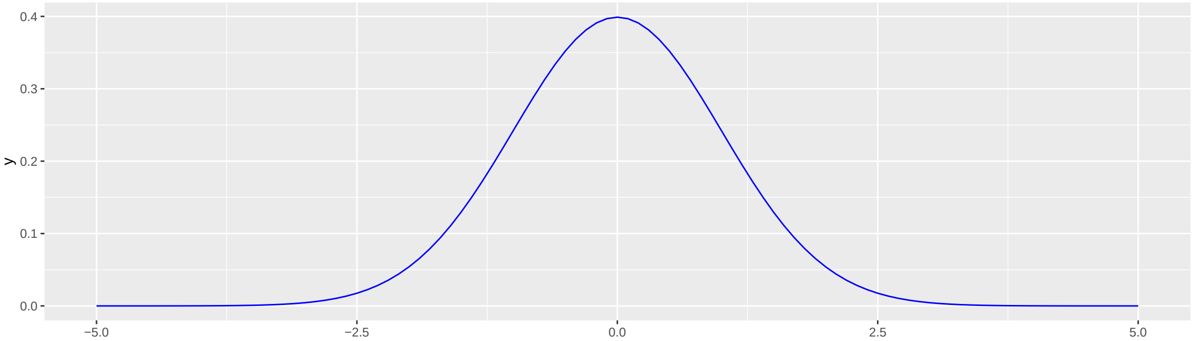
$$L(\beta \mid y, X, \sigma) \propto (\sigma^{-N/2}) \exp[-\frac{1}{2\sigma^2}(y - X\beta)^T(y - X\beta)]$$

3.2 Prior for regression parameters (ridge)

In Part 1 we worked with multiple imputation and one method for drawing observations was the Bayesian linear regression.

We will use the same priors here, for the σ^2 we use a inverse Gamma prior. For the regression coefficents a normal prior is used.

$$\beta \mid \sigma \sim \prod_{j=1}^{p} \sqrt{\frac{\lambda}{2\sigma^2}} \exp(-\frac{\lambda}{2\sigma^2}\beta_j^2)$$



3.3 Posterior for regression parameters (ridge)

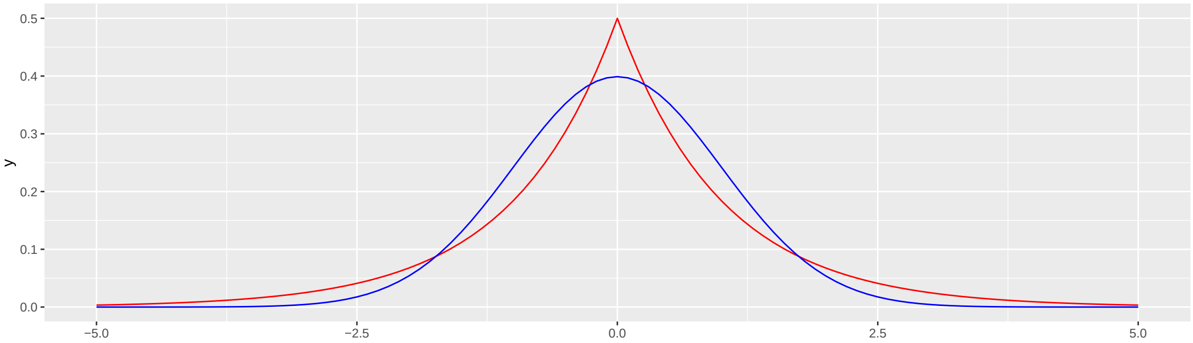
$$\beta, \mid X, Y\sigma^2 \propto \exp[-\frac{1}{2\sigma^2}](\beta - \widehat{\beta}(\lambda))^T(X^TX + \lambda I)(\beta - \widehat{\beta}(\lambda))]$$

The posterior mean is the ridge estimator $\widehat{\beta}(\lambda)$.

3.4 Prior for regression parameters (lasso)

$$\beta \mid \lambda, \sigma \sim \prod_{j=1}^{p} \frac{\lambda}{2\sigma} \exp(-\frac{\lambda}{\sigma}|\beta_j|)$$

This prior is called an i.i.d. *Laplacian* (or double exponential) prior.



3.5 Posterior for regression parameters (lasso)

It can be shown that the negative log of the posterior density for $\beta \mid y, \lambda, \sigma$ is (up to an additive constant)

$$\frac{1}{2\sigma^2}\|y - X\beta\|_2^2 + \frac{\lambda}{\sigma}\|\beta\|_1$$

Does this look familiar?

For a fixed value of σ and λ - the β giving the minimum of the negative log posterior is the *lasso* estimate where the regularization parameter is $\sigma\lambda$.

The minimum negative log posterior will then be the same as the maximum log posterior - and the maximum of a distribution is called the *mode* of the distribution.

The lasso estimate is the *posterior mode* in the Bayesian model.

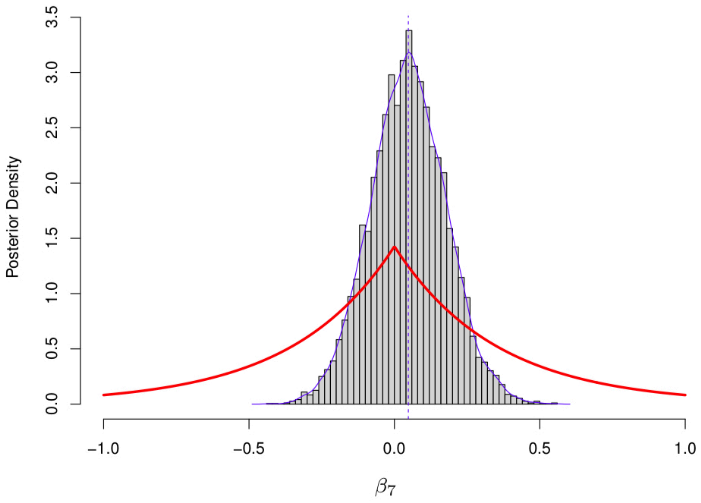


Figure 6.1 *Prior and posterior distribution for the seventh variable in the diabetes example, with λ held fixed. The prior in the figure is a double exponential (Laplace) distribution with density proportional to $\exp(-.0065|\beta_7|)$. The prior rate .0065 is a representative value just for illustration.*

Figure 4: Figure 6.1 in Hastie, Tibshirani, and Wainwright (2015)

From Hastie, Tibshirani, and Wainwright (2015): a 95% posterior credibility interval covers zero.

Hastie, Tibshirani, and Wainwright (2015): MCMC with 10 000 samples.

A full Bayesian approach requires priors for λ and σ, in addition to priors on the regression coefficient.

Markov Chain Monte Carlo MCMC is used efficiently sample realizations form the posterior distribution.

See Wieringen (2021) Chapter 2 for more on Bayesian regression and the connection to the ridge and Section 6.6 for connection to lasso.

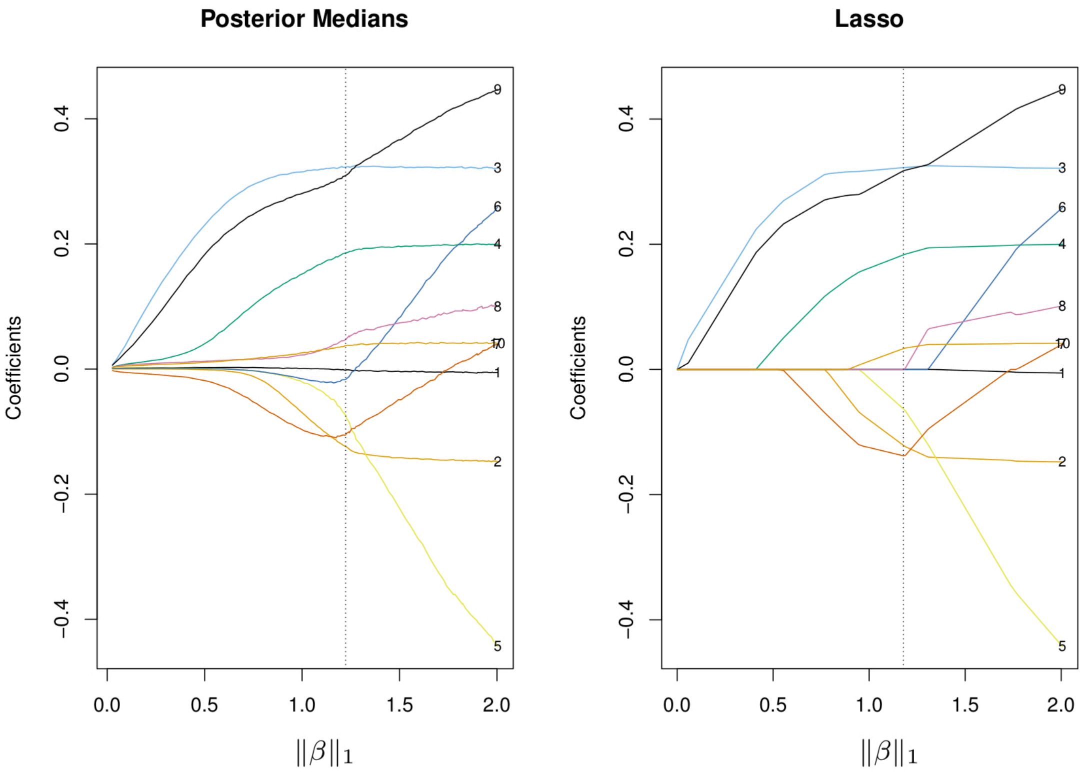


Figure 6.2 *Bayesian lasso on the diabetes data. The left plot shows the posterior medians from MCMC runs (conditional on λ). The right plot shows the lasso profile. In the left plot, the vertical line is at the posterior median of $\|\beta\|_1$ (from an unconditional model), while for the right plot the vertical line was found by N-fold cross-validation.*

Figure 5: Figure 6.2 in Hastie, Tibshirani, and Wainwright (2015)

3.6 Not only the point estimate

The posterior distribution gives the

- point estimates for the lasso (the mode of the distribution)

but

- also the *entire joint distribution*.

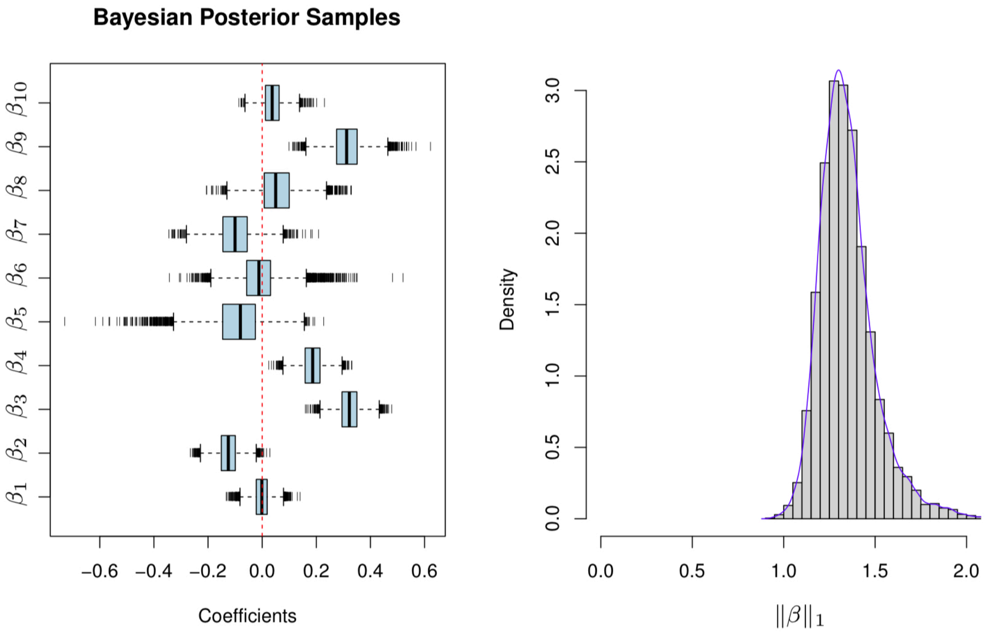


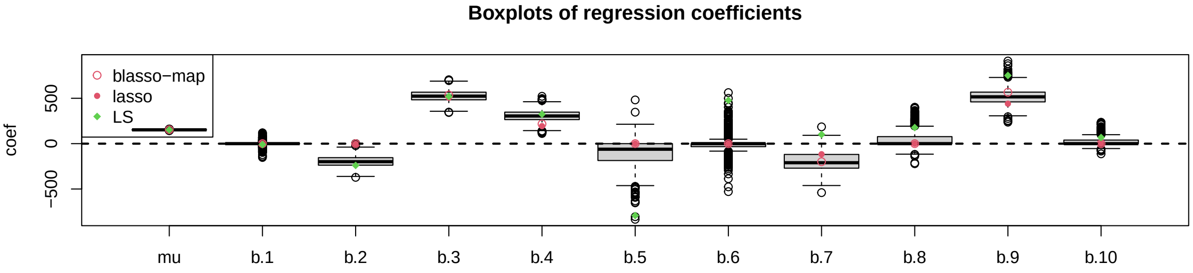
Figure 6.3 *Posterior distributions for the* β_j *and* $\|\beta\|_1$ *for the diabetes data. Summary of* 10,000 *MCMC samples, with the first* 1000 *"burn-in" samples discarded.*

Figure 6: Figure 6.3 in Hastie, Tibshirani, and Wainwright (2015)

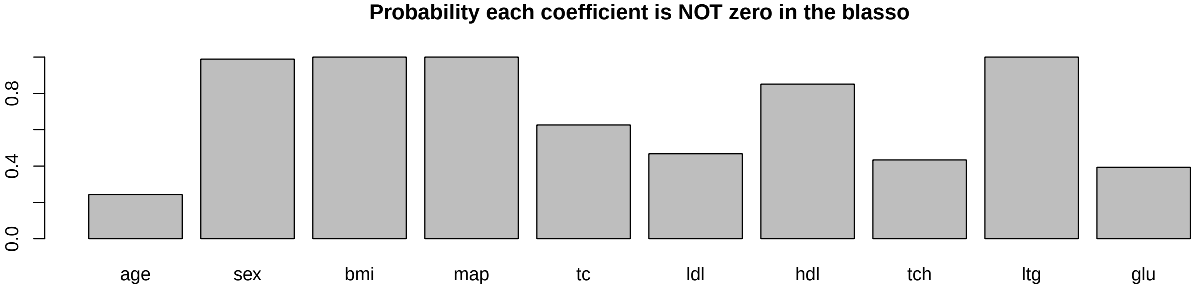
Hastie, Tibshirani, and Wainwright (2015): 10 000 samples from the posterior.

3.6.1 Diabetes example with `blasso`

```
## code below copied from the help(blasso)
## following the lars diabetes example
data(diabetes)
attach(diabetes)

## Ordinary Least Squares regression
reg.ols <- regress(x, y)

## Lasso regression
reg.las <- regress(x, y, method="lasso")

## Bayesian Lasso regression
reg.blas <- blasso(x, y,verb=0)
```



```
## plot the size of different models visited
#plot(reg.blas, burnin=200, which="m")

## get the summary
s <- summary(reg.blas, burnin=200)
```



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4 Bootstrap

(HTW 6.2)

4.1 Procedure to find lasso estimate $\hat{\beta}(\hat{\lambda}_{CV})$

(Copied word by word from HTW page 142)

Refer to these 6 steps as $\hat{\beta}(\hat{\lambda}_{CV})$-loop

1. Fit a lasso path to (X, y) over a dense grid of values $\Lambda = \{\lambda_l\}_{l=1}^{L}$.
2. Divide the training samples into 10 groups at random.
3. With the kth group left out, fit a lasso path to the remaining 9/10ths, using the same grid Λ.
4. For each $\lambda \in \Lambda$ compute the mean-squared prediction error for the left-out group.
5. Average these errors to obtain a prediction error curve over the grid Λ.
6. Find the value $\hat{\beta}(\hat{\lambda}_{CV})$ that minimizes this curve, and then return the coefficient vector from our original fit in step (1) at that value of λ.

Observe:

- λ-path is the same for each run of the lasso
- the chosen λ is then used on the orginal data

Q: Is it possible to use resampling to estimate the distribution of the lasso $\hat{\beta}$ estimator including the model selection (choosing λ)?

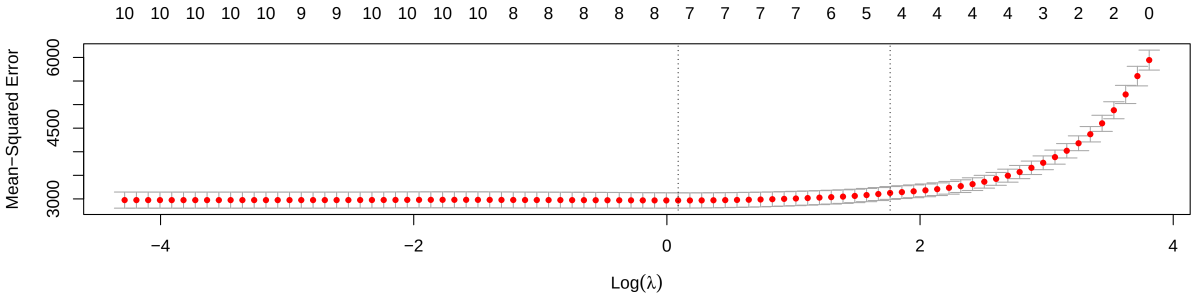
4.2 Non-parametric (paired) bootstrap

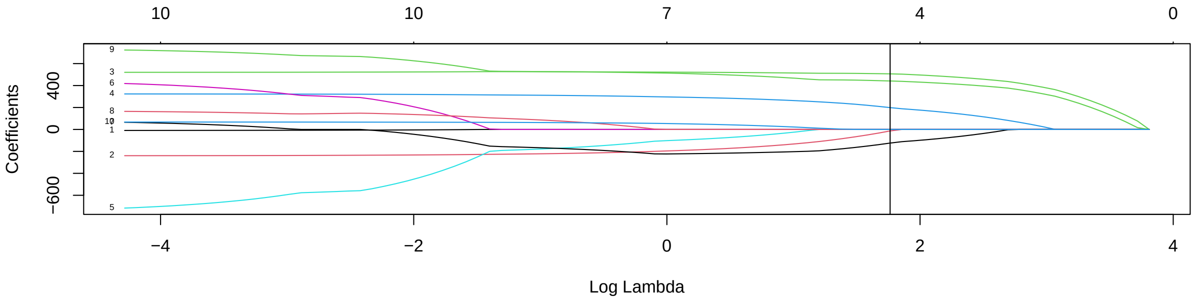
- Let F denote the joint distribution of (X, Y).
- The empirical $\hat{F}$ is $\frac{1}{N}$ for each observation (X, Y) in our training data (X_i, Y_i), $i = 1, \dots, N$.
- Drawing from $\hat{F}$ is the same as drawing from the N observations in the training data with replacement.

Now, we draw B bootstrap samples from the training data, and for each new bootstrap sample we run through the 6 steps in the $\hat{\beta}(\hat{\lambda}_{CV})$-loop.

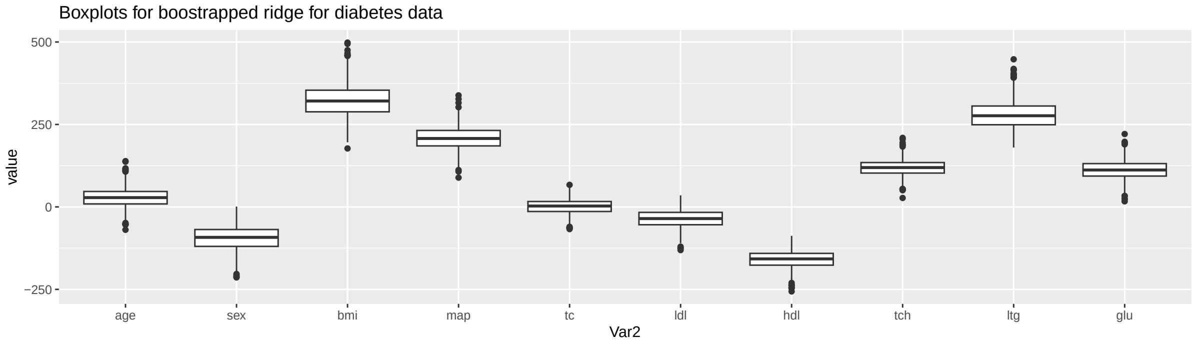
- The result is B vectors $\hat{\beta}(\hat{\lambda}_{CV})$.
- We plot the result as
    - boxplots,
    - proportion of times each element of $\hat{\beta}(\hat{\lambda}_{CV})$ is equal 0.

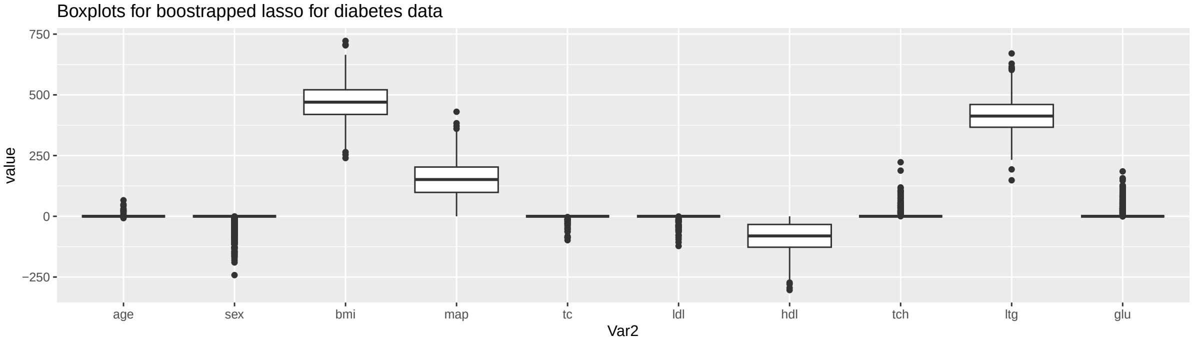
4.2.1 Diabetes example

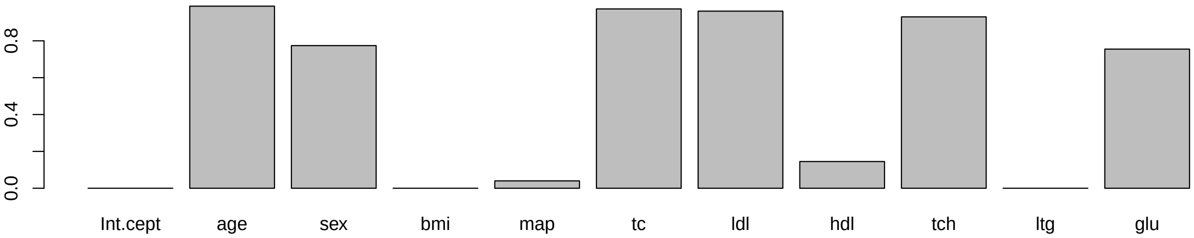




```
11 x 1 sparse Matrix of class "dgCMatrix"
                      s1
(Intercept)  152.13348
age              .
sex          -13.59236
bmi          506.66309
map          199.02672
tc               .
ldl              .
hdl         -124.16053
tch              .
ltg          441.69986
glu              .
```







4.3 Bootstrapping vs Bayesian lasso

The results from the Bayesian lasso on the proportion of times a coefficient is 0 and the boxplots are very similar to the results from the bootstrapping. The bootstrap seems to be doing the "same" as a Bayesian analysis with the Laplacian prior.

When the model is not so complex and the number of covariates is not too large ($p \sim 100$) the Bayesian lasso might be as fast as the bootstrapping, but for larger problems the bootstrap "scales better".

For GLMs the Bayesian solution is more demanding, but the bootstrap is as easy as for the linear model.

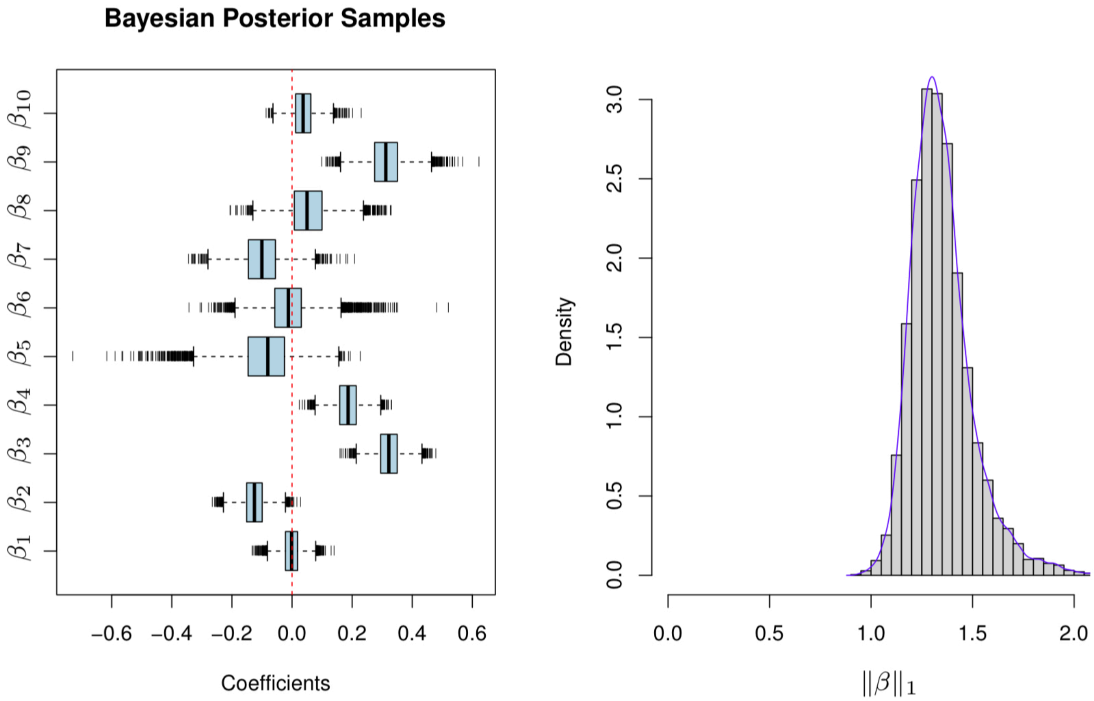


Figure 6.3 *Posterior distributions for the β_j and $\|\beta\|_1$ for the diabetes data. Summary of $10,000$ MCMC samples, with the first 1000 "burn-in" samples discarded.*

Figure 7: Figure 6.3 in Hastie, Tibshirani, and Wainwright (2015)

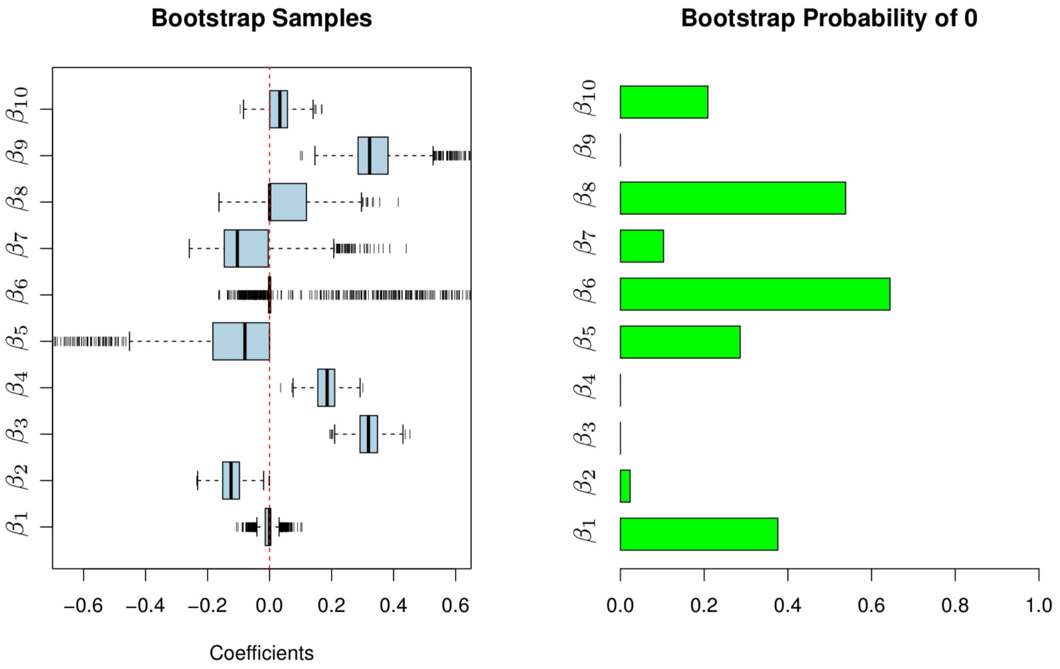


Figure 6.4 *[Left] Boxplots of 1000 bootstrap realizations of $\widehat{\beta}^*(\hat{\lambda}_{CV})$ obtained by the nonparametric bootstrap, which corresponds to re-sampling from the empirical CDF $\widehat{F}_N$. Comparing with the corresponding Bayesian posterior distribution in Figure 6.3, we see a close correspondence in this case. [Right] Proportion of times each coefficient is zero in the bootstrap distribution.*

Figure 8: Figure 6.4 in Hastie, Tibshirani, and Wainwright (2015)

4.4 Bootstrapt percentile CI

To construct a $(1-\alpha)\cdot 100\%$ CI:

- order the bootstrap sample for the estimate of interest
- read off the $(1-\alpha/2)\cdot 100$ percetile
- $(\alpha/2)\cdot 100$ percentile

These are now the lower and upper limit of the CI.

4.5 Bootstrap BCa CI

See page 34 of Bootstrap confidence intervals in the master thesis of Lene Tillerli Omdal Section 3.6.2 and teaching material from TMA4300: Givens and Hoeting (2013) chapter 9.3. NTNU-access to the full book if you are on vpn.

4.5.1 Diabetes example

What if we calculated percentile bootstrap intervals - could we use that to say anything about the true underlying regression coefficients?

```
[1] "Ridge first then lasso"
```

```
               2.5%         50%      97.5%        2.5%       50%     97.5%
Int.cept  147.08515  152.140842  157.48081  146.942231 152.17445 157.29619
age       -30.29701   28.233633   84.43224    0.000000   0.00000   0.00000
sex      -170.89169  -92.265146  -26.22187 -115.349163   0.00000   0.00000
bmi       232.35050  321.111896  421.01718  329.357643 469.97818 617.77346
map       140.21620  207.461944  278.29632    0.000000 151.40541 304.09469
tc        -45.76264    2.724457   43.62582   -4.357653   0.00000   0.00000
ldl       -91.46718  -35.412937   15.64376  -22.951886   0.00000   0.00000
hdl      -206.89616 -157.552738 -109.32657 -218.711400 -80.79045   0.00000
```

```
tch        69.30617  119.322597  165.46347    0.000000   0.00000  51.93353
ltg       206.74238  276.466411  369.93742  283.107398 412.68911 556.78790
glu        61.07588  111.952224  168.07668    0.000000   0.00000  90.18665
```

4.5.2 Medical example

(See Figures from study in class notes.)

4.6 Bootstrap CIs for β_j

Sadly, there are two main challenges:

- The percentile interval is not a good choice for biased estimators, and it is not clear if the bias-corrected accelerated intervals are better
- It has been shown that (for fixed p) the asymptotic ($N \to \infty$) distribution of the lasso has point mass at zero (which leads to that bootstrapping not having optimal properties).

The authors of the *penalized package* take the following view Section 6: A note on standard errors and confidence intervals in the Penalized user manual https://cran.r-project.org/web/packages/penalized/vignettes/penalized.pdf

"Unfortunately, in most applications of penalized regression it is impossible to obtain a sufficiently precise estimate of the bias. Any bootstrap-based calculations can only give an assessment of the variance of the estimates. Reliable estimates of the bias are only available if reliable unbiased estimates are available, which is typically not the case in situations in which penalized estimates are used."

"It is certainly a mistake to make confidence statements that are only based on an assessment of the variance of the estimates, such as bootstrap-based confidence intervals do."

Reliable confidence intervals around the penalized estimates can be obtained in the case of low dimensional models using the standard generalized linear model theory as implemented in lm, glm and coxph."

4.7 Outline

- Prediction vs statistics inference: what are the aims?
- Sampling distributions
- Debiased lasso
- Bayesian lasso
- Boostrapping

WE are here now!

- Sample splitting
- Inference after selection (forward regression example, polyhedral result, PoSI)
- Reproducibility crisis and selective inference
- Conclusions

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5 Sample splitting

5.1 What if we just split the data in two?

Linear regression or logistic regression.

Dataset with p covariates and N observations. Divided into a training set of size aN and a test set of $(1-a)N$, where $a \in [0, 1]$.

- Training data used to decide on λ using CV - gives final model where some coefficients is set to 0 and some are shrunken. (The 6 steps.)
- Test data:
  - Fit ordinary LS or GLM model with only the non-zero lasso covariates
  - present CI and p-values from LS

Group discussion: Is this ok? What is gained and what is lost?

5.2 From single to multiple hypotheses

In many situations we are not interested in testing only one hypothesis, but instead m hypotheses.

	Not reject H_0	Reject H_0	Total
H_0 true	U	V	m_0
H_0 false	T	S	$m - m_0$
Total	$m - R$	R	m

- Out of the m hypotheses tested, the (unknown) number of true null hypotheses is m_0.
- V: the number of type I errors (false positive findings) and
- T: the number of type II errors (false negative findings).
- U: the number of true null hypotheses that are not rejected and
- S: the number of false null hypotheses that are rejected.
- R: the number of hypoteses rejected for a specific cut-off

Observe: only m and R is observed!

5.3 Familywise error rate

The familywise error rate (FWER) is defined as *the probability of one or more false positive findings*

$$\text{FWER} = P(V > 0)$$

The number of false positive findings V is not known in a real life situation, but still we may find a cut-off on the p-value, called α_{loc}, that gives an upper limit to (controls) the FWER.

- Raw p-value, p_j, the lowest nominal level to reject the null hypothesis.

- Adjusted p-value, $\tilde{p}_j$, is the nominal level of the multiple (simultaneous) test procedure at which $H_{0j}, j = 1, \dots, m$ is just rejected, given the values of all test statistics involved.

The adjusted p-values can be defined as

$$\tilde{p}_j = \inf\{\alpha \mid H_{0j} \text{ is rejected at FWER level } \alpha\}$$

In a multiple testing problem where all adjusted p-value below α are rejected, the overall type I error rate (for example FWER) will be controlled at level α.

5.3.1 The Bonferroni method controls the FWER

Single-step methods controls for multiple testing by estimating one local significance level, α_{loc}, which is used as a cut-off to detect significance for each individual test.

The Bonferroni method is valid for all types of dependence structures between the test statistics.

The local significance level is

$$\alpha_{\text{loc}} = \frac{\alpha}{m}$$

The adjusted p-value is

$$\tilde{p}_j = \min(1, mp_j)$$

Read more here if needed: Short note on multiple hypothesis testing

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5.4 High-dimensional inference

(Dezeure, Bühlmann, Meier, Meinshausen, 2.1.1 + 2.2)

- The article has focus on frequentist methods for high-dimensional inference with confidence intervals and p-values in linear and generalized linear models.
- We will focus on linear models.

Set-up:

$$Y = X\beta^0 + \varepsilon$$

- X is $n \times p$ design matrix
- Y is an $n \times 1$ response vector
- ε is an $n \times 1$ error vector, independent of X and i.i.d. entries with $\mathrm{E}(\varepsilon)_i) = 0$.
- The number of parameters *may* be larger than the sample size (then the regression parameter is not identifiable in general).

The *active set* is

$$S_0 = \{j; \beta_j^0 \neq 0, j = 1, \dots, p\}$$

with cardinality (size) $|S_0|$.

Now: construct CI and p-values for *individual regression parameters* β_j^0, $j = 1, \dots, p$, and also with multiple testing adjustment.

Remark: We want inference for *all* coefficients - not only the ones that the lasso has selected.

- The lasso has desirable properties for estimating β^0 in high dimensional models, in particular for prediction $X\beta^0$ or a new response Y_{new}.
- But, the distribution of the estimator is hard to characterize, and
- it has been shown that (for fixed p) the asymptotic ($n \leftarrow \infty$) distribution of the lasso has point mass at zero (which leads to that bootstrapping not having optimal properties).

For the situation $p >> n$ extra assumptions are needed, called the *compatibility condition* on the design matrix, and this guarantees identifiability and socalled oracle optimality results for the lasso. However, this is reported to be *unrealistic in practical situations*.

5.5 Single-sample splitting

1) Split the data into two (equal) halves, I_1 and I_2, no observations in common.
2) I_1 is used for model selection (with the lasso), with active variables in $\hat{S}(I_1)$.
3) The selected covariates in $\hat{S}(I_1)$ is used for estimation in I_2. To construct p-values, P_j, for example use LS with t-tests. P-values for variables not selected is set to 1. Remark: then the number of covariates selected in I_1 need be smaller than the sample size for I_2.
4) The raw p-values is corrected for multiple testing (Bonferroni method controlling FWER)

$$P_{\text{corr},j} = \min(P_j \cdot |\hat{S}|, 1)$$

This avoids using the data twice! But, is very sensitive to the split - giving *wildly* different p-values=p-value lottery

How can this be amended?

5.6 Multiple-sample splitting

- The single-sample splitting routine is run B times giving $P^{[b]}_{\text{corr},j}$ for $b = 1, \ldots, B$ and $j = 1, \ldots, p$.
- Problem: how aggregate the B p-values for each j to give one p-value?
- The different b runs have many observations in common, so the p-values for covariate j are correlated.
- The authors have shown in a previous article that for dependent p-values that one solution (that gives valid p-values) is to take the median and multiply with 2.
- The result is more general, and γ is a general quantile ($\gamma = 0.5$ for the median):

$$Q_k(\gamma) = \min(\text{empirical } \gamma - \text{quantile}\{P^{[b]}_{\text{corr},j}/\gamma, b = 1, \ldots, B\}, 1)$$

- The authors get more advanced and choose to search all γ within the interval $(\gamma_{\min}, 1)$, where a common choice is $\gamma_{\min} = 0.05$, to get the smallest p-value. However there is a price to pay: $(1 - \log(\gamma_{\min}))$

$$P_j = \min((1 - \log(\gamma_{\min}) \cdot \inf_{\gamma \in (\gamma_{\min}, 1)} Q_j(\gamma)), 1)$$

for $j = 1, \ldots, p$.

Some assumptions are necessary to assure FWER control.

Confidence intervals are found

- from the adjusted p-values P_j
- using the duality of p-values and two-sided confidence intervals. That is,
- a $(1 - \alpha)$ 100% CI contains values c where the p-value is below α for testing $H_0 : \beta_j = c$. A closed form solution involving P_j is found.
- Both single testing and multiple corrected testing CIs are found. (Appendix A.2 in article)

```
data(diabetes)
x=cbind(diabetes$x)#,diabetes$x2)
y=diabetes$y

hdires=multi.split(x=x,y=y,B=1000,fraction=0.5,
                   ci.level=0.95, model.selector=lasso.cv,
                   classical.fit=lm.pval, classical.ci=lm.ci,
                   return.nonaggr = FALSE, #if not adj for multiple testing
                   return.selmodels=FALSE, #just to have a look!
                   verbose=FALSE)
dput(hdires,"hdires.dd")
```

```
hdires=dget("hdires.dd")
names(hdires)
```

```
 [1] "pval"              "pval.corr"         "pvals.nonaggr"     "ci.level"
 [5] "lci"               "uci"               "gamma.min"         "sel.models"
 [9] "method"            "call"              "clusterGroupTest"
```

```
hdires$gamma.min
```

```
 [1] 0.999 0.999 0.050 0.064 0.999 0.999 0.050 0.999 0.052 0.999
```

```
#summary(hdires$pvals.nonaggr) # if return.nonaggr=TRUE
hdires$pval.corr
```

```
         age          sex          bmi          map           tc          ldl
1.000000e+00 1.000000e+00 5.178832e-10 1.331537e-02 1.000000e+00 1.000000e+00
         hdl          tch          ltg          glu
4.533731e-01 1.000000e+00 6.863052e-08 1.000000e+00
```

```
cbind(hdires$lci, hdires$uci)
```

```
          [,1]      [,2]
age       -Inf       Inf
sex -435.92911 103.48598
bmi  363.10330 776.42063
map   66.58321 472.64439
```

```
tc        -Inf       Inf
ldl       -Inf       Inf
hdl -406.96777  14.72096
tch -764.32633 201.01275
ltg  301.70828 715.18364
glu -327.08642 254.88420
```

5.6.1 hdi with logistic regression

For modifications to the call to `mult.split` see the Appendix of the master thesis of

- Martina Hall: “Statistical Methods for early Prediction of Cerebral Palsy based on Data from Computer-based Video Analysis”.
- Dag J. Kristiansen: “Detecting Neuronal Activity with Lasso Penalized Logistic Regression”
- Haris Fawad: ” Modelling Neuronal Activity using Lasso Regularized Logistic Regression”(Modelling Neuronal Activity using Lasso Regularized Logistic Regression) - also git repo neuro-lasso.

5.6.2 hdi - also with other solutions

In the `hdi` package also solutions for *debiasing* the lasso estimator is included. (See HTW 6.4 or the Dezure et al article.)

5.6.3 Summing up

What is the take home message from this “Sample splitting” story?

6 Inference after selection

(Taylor and Tibshirani, 2015 and HTW 6.3)

6.1 The plot

Let us leave the lasso for a while.

1980: small data sets, planned hypothesis to test ready before data collected, no model selection. Only fit model and look at CI and p-values.

After 1980: larger data sets and looking at data to give best model. New challenge: *how to do inference after selection.*

This is an important topic that is not a part of ANY statistical courses at IMF.

The main question is:

- we have used a selection method (forward selection, lasso) to find potential association between covariates and response,
- with focus on interpreting the selected model: how can we assess the strength (read: CI and p-value) of these findings?

The answer includes:

- we have "cherry picked" the strongest associations, and we can thus not just report CI and p-values based on the final model - when all is done on the same data set.

In this story we now focus on *understanding how our model selection influences the inference on the final model.*

The technical solutions are of less importance, and is not presented with enough mathematical detail so that we understand the method in detail.

Remark: the single and multiple sample splitting strategy isvalid.

6.2 Forward stepwise regression

Aim: Multiple linear regression - where forward stepwise regression is used to select the model

$$y_i = \beta_0 + \sum_{j=1}^{p} x_{ij}\beta_j + \varepsilon_i$$

- Start with an empty model (only intercept)

While some stopping criterion not reach - perform step

- At step k add the predictor that gives the most decrease in the sums of squares of error (here now - to follow the notation denoted by RSS instead of what we previously called SSE)

$$\text{RSS} = \sum_{i=1}^{N} (y_i - \hat{y}_i)^2$$

where $\hat{y}_i$ is the predicted value for observation i in this model.

If we have a model with $k-1$ predictors and we would like to add one more predictor (the k to be added):

$$\text{R}_k = \frac{1}{\sigma^2}(\text{RSS}_{k-1} - \text{RSS}_k) \sim \chi^2_1$$

where here σ^2 is assumed known.

This can be seen as an hypothesis test:

H_0 : The new predictor is not relevant vs. H_1 : The new predictor is relevant with a p-value calculated from the upper tail of the χ^2_1-distribution.

Alternative scenario:

For simplicity - we look at the $k = 1$:

The order in which the predictors is to be entered in to the model was decided before the data was collected (or at least before the data was analysed or plottet).

Then: we are all good - and this p-value from the χ^2_1-distribution will be a valid p-value.

What does this mean in practice?

Back to original scenario:

Assume we are at step $k = 1$, and will add the first predictor which is the one with the largest R_1.

Will the distribution of the *maximal* R_1 be the same as the distribution of a given predefined R_1?

Distribution to the maximum given that we have p predictors:

$$P(\max R_1 \geq c) = 1 - P(\max R_1 < c) = 1 - P(\text{all p } R_1 \text{ are} < c)$$

Study Figure 1 in the article for a plot of nominal vs. actual p-value for $p = 10$ and $p = 50$. The figure was made using Monte Carlo sampling.

Moving on to $k > 1$

- We would like to obtain valid ("correct") p-values for all steps, not only for $k = 1$.
- Monte Carlo solution would be elaborate.

The method used in the article is to calculate a p-value for the covariate at step k by conditioning on the fact that already the strongest $k - 1$ predictors in this sequential set-up has already been chosen.

The p-value at step k would be dependent on the number of covariates p.

We now change focus and look at the distribution of the estimated regression coefficient for the covariate added at step k, because that can be used to construct both a CI for the coefficient and a p-value for testing if the coefficient is different from zero.

6.3 The polyhedral result

(for details consult HTW 6.3 or articles references to in the Taylor and Tibshirani article)

Distribution for regression coefficient:

- Assume that we are at some step k, and that $k - 1$ covariates are in the model.
- We have found the new covariate to include, and fitted the model with the k covariates.
- Standard theory tells us that the estimator $\widehat{\beta}$ for covariate k is unbiased and follows a normal distribution with some variance τ^2.

$$\hat{\beta} \sim N(\beta, \tau^2)$$

But, this is given that we only had these k covariates available at the start. We will instead *condition on* selection event.

It turns out that the selection event can be written in a *polyhedral form* $Ay \leq b$ for some matrix A and some vector b.

At each step of the forward selection we have a competition among all p variables, and the A and b is used to construct the competition.

The correct distribution of the estimator $\hat{\beta}$ for covariate now has a *truncated normal distribution*

$$\hat{\beta} \sim TN^{c,d}(\beta, \tau^2)$$

i.e. the *same* normal distribution, but scaled to lie within the interval (c, d).

The limits (c, d) depends on both the data and the selection evetns that lead to the current model.

The formulae for these limits are somewhat complicated but easily computable.

This truncated normal distribution is used to calculate *selection-adjusted* p-values and confidence interval.

(Study Figure 3. in the article by Taylor and Tibshirani.)

6.4 Polyhedral lasso result

The same methodology can be used for the lasso, here also the selection of predictors can be described as a polyhedral region of the form $Ay \leq b$ - for a fixed value λ.

For the lass the A and b will depend on

- the predictors
- the active set
- λ

but not on y.

The methods are on closed form, but the values c and d may be of complicated form.

The R package `selectiveInference` can be used to find post selection p-values both for forward stepwise selection and for the lasso.

See the package help for details.

Study Figure 5 from the article for an example of Naive and Selection-adjusted intervals for the lasso.

6.4.1 Further improvements

The method yields rather wide confidence intervals for the regression parameters (given that we translate the p-values into CIs).

There exists improvements to the results, in particular a method called *carving* which is explained in the you-tube videos from a course with Snigdha Paragrahi

- Tutorial I
- Tutorial II

6.5 PoSI

(HTW 6.5)

- The POSI method also fits a selected submodel and
- adjust the standard CIs by *accounting for all possible models that might have been delivered by the selection procedure.*
- This means the method can be used on published results where the complete selection process is not explained in detail.
- This lack of information of the selection process leads to *very wide CIs.*

Inference is based on the submodel M chosen, and on the projection of $X\beta$ onto the space spanned by the submodel M:

$$\beta_M = (X_M^T X_M)^{-1} X_M^T X\beta$$

The method considers a confidence interval for the jth element of β_M of the form

$$\mathrm{CI}_{jM} = \hat{\beta}_{jM} \pm K\hat{\sigma} v_{jM}$$

where $v_{jM}^2 = (X_M^T X_M)_{jj}^{-1}$

The constant K is found to satisfy

$$P(\beta_{jM} \in \mathrm{CI}_{jM}) \leq 1 - 2\alpha$$

over all possible selection models.

K is a function of the data matrix X and the maximum number of nonzero component allowed in β_M. An upper bound on K is known from a result on simultaneous intervals by Scheffe.

HTW page 161: Reports on the diabetes data with submodels of size 5, where the 95% CI value of K is 4.42 (“little less than 2 hours of computing”).

Details may be found in the PoSI 2013 article (reference Berk et al below).

6.5.1 PoSI R-package

In linear LS regression, calculate for a given design matrix the multiplier K of coefficient standard errors such that the confidence intervals [b - K*SE(b), b + K*SE(b)] have a guaranteed coverage probability for all coefficient estimates b in any submodels after performing arbitrary model selection.

Results for the Boston housing data is available in the help section.

https://cran.r-project.org/web/packages/PoSI/index.html

6.6 Post selection inference and the reproducibility crisis

The *incorrect* use of CIs and p-values in models found from model selection *and* inference on the same data - is though to be one of the main contributors to the *reproducibility crisis in science.*

Selective Inference: The Silent Killer of Replicability by Yoav Benjamini Published on Dec 16, 2020

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7 Conclusion

7.1 How will you perform inference

on Data Analysis Project 1?

We discuss:

1) You can afford a test set
2) You have no test set

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8 References

(also given in the text and not repeated here)

- Wessel N. van Wieringen: Lecture notes on ridge regression
- A. Chatterjee and S. N. Lahiri (2011). Bootstrapping Lasso Estimators. Journal of the American Statistical Association. Vol. 106, No. 494 (June 2011), pp. 608-625 (18 pages)
- Single/multi-sampling splitting part of Dezeure, Bühlmann, Meier, Meinshausen (2015). "High-Dimensional Inference: Confidence Intervals, p-Values and R-Software hdi". Statistical Science, 2015, Vol. 30, No. 4, 533–558 DOI: 10.1214/15-STS527 (only the single/multiple sample splitting part in 2.1.1 and 2.2 for linear regression, and using the method in practice).
- Taylor and Tibshirani (2015): Statistical learning and selective inference, PNAS, vol 112, no 25, pages 7629-7634. (Soft version of HTW 6.3.2)
- Berk, Richard; Brown, Lawrence; Buja, Andreas; Zhang, Kai; Zhao, Linda. Valid post-selection inference. Ann. Statist. 41 (2013), no. 2, 802–837. doi:10.1214/12-AOS1077.

9 Left overs

To check that all is here

9.1 Bootstrap confidence intervals

9.2 Percentile interval

9.3 Bias corrected accelerated interval

9.4 Single hypothesis test

$$H_0\colon \beta_j = 0 \quad \text{vs.} \quad H_1\colon \beta_j \neq 0$$

	Not reject H_0	Reject H_0
H_0 true	Correct	Type I error
H_0 false	Type II error	Correct

- Two types of errors are possible, type I error and type II error.

- A type I error would be to reject H_0 when H_0 is true, that is concluding that there is a linear association between the response and the predictor where there is no such association. This is called a *false positive finding.*
- A type II error would be to fail to reject H_0 when the alternative hypothesis H_1 is true, that is not detecting that there is a linear association between the response and the covariate. This is called a *false negative finding.*

9.5 p-value

- A p-value $p(X)$ is a test statistic satisfying $0 \leq p(Y) \leq 1$ for every vector of observations Y.
- Small values give evidence that H_1 is true.
- In single hypothesis testing, if the p-value is less than the chosen significance level (chosen upper limit for the probability of committing a type I error), then we reject the null hypothesis, H_0.
- The chosen significance level is often referred to as α.

A p-value is *valid* if

$$P(p(Y) \leq \alpha) \leq \alpha$$

for all α, $0 \leq \alpha \leq 1$, whenever H_0 is true, that is, if the p-value is valid, rejection on the basis of the p-value ensures that the probability of type I error does not exceed α.

An *exact* p-value satisfies

$$P(p(Y) \leq \alpha) = \alpha$$

for all α, $0 \leq \alpha \leq 1$.

- The exact p-value is uniformly distributed when the null hypothesis is true.
- This is a fact that is often misunderstood by users of p-values.
- The incorrect urban myth is that p-values from true null hypotheses are close to one, when the correct fact is that all values in intervals of the same length are equally probable (which is a property of the uniform distribution).

9.6 False discovery rate

The false discovery rate (FDR) is defined as

$$\text{FDR} = \text{E}(\frac{V}{R}) \text{ for } R > 0$$

and

$$\text{FDR} = 0 \text{ else}$$

Efron, Bradley, and Trevor Hastie. 2016. *Computer Age Statistical Inference - Algorithms, Evidence, and Data Science*. Cambridge University Press. https://hastie.su.domains/CASI/.

Hastie, Trevor, Roberg Tibshirani, and Martin Wainwright. 2015. *Statistical Learning with Sparsity: The Lasso and Generalizations*. CRC Press. https://hastie.su.domains/StatLearnSparsity/.

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