Knockoff filter

Patrick Breheny

April 15

Introduction

- Today we will discuss one final approach to inference in high-dimensional regression models called the *knockoff filter*
- There are two approaches to the knockoff filter:
  - In its simplest form, we can generate knockoffs without any assumptions on $\mathbf{X}$; however this approach only works if $\mathbf{X}$ is full rank (Barber and Candès 2015)
  - A later paper (Candès et al. 2018) extended this idea to the $p > n$ case, although in order to do so, we need to make some assumptions about $\mathbf{X}$
- Both approaches are implemented in the R package `knockoff`

Step 1: Construct knockoffs

- The basic idea of the knockoff filter is that for each feature $\mathbf{x}_j$ in the original feature matrix, we construct a *knockoff* feature $\tilde{\mathbf{x}}_j$
- We'll go into specifics on constructing knockoffs later; for now, we specify the properties that a knockoff $\tilde{\mathbf{x}}_j$ must have:

$$\begin{aligned} \widetilde{\mathbf{X}}^\top \widetilde{\mathbf{X}} &= \mathbf{X}^\top \mathbf{X} \\ \tilde{\mathbf{x}}_j^\top \mathbf{x}_k &= \mathbf{x}_j^\top \mathbf{x}_k \qquad \text{for all } k \neq j \\ \tfrac{1}{n}\tilde{\mathbf{x}}_j^\top \mathbf{x}_j &= 1 - s_j \qquad \text{where } 0 \leq s_j \leq 1 \end{aligned}$$

- In other words, the knockoff matrix $\widetilde{\mathbf{X}}$ differs from the original matrix $\mathbf{X}$, but has the same correlation structure and the same correlation with the original features

Step 2: Calculate test statistics

- With the knockoffs constructed, the next step is to fit a (lasso) model to the augmented $n \times 2p$ design matrix $[\mathbf{X}\ \widetilde{\mathbf{X}}]$
- At this point, we need some sort of test statistic that measures whether the original feature is better than the knockoff
- There are actually a variety of statistics we could use here, but in this lecture we'll focus on the point λ along the lasso path at which a feature enters the model, giving us a $2p$-dimensional vector $\{Z_1, \ldots, Z_p, \tilde{Z}_1, \ldots, \tilde{Z}_p\}$
- Our test statistic is then

$$W_j = \max(Z_j, \tilde{Z}_j) \cdot \operatorname{sign}(Z_j - \tilde{Z}_j);$$

i.e., W_j will be positive if the original feature is selected before the knockoff, and negative if the knockoff is selected first

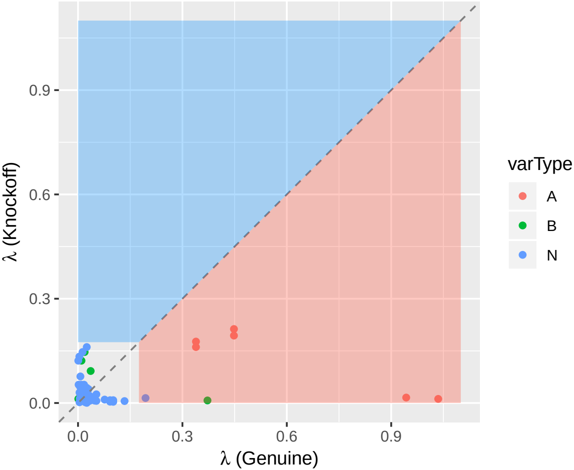
Step 3: Estimate false discovery rate

- Now, if we select features such that $W_j \geq t$ for some threshold t, we can use the knockoff features to estimate the false discovery rate
- Specifically, our knockoff estimate of the FDR is:

$$\widehat{\mathrm{FDR}} = \frac{\#\{j : W_j \leq -t\}}{\#\{j : W_j \geq t\}},$$

  with the understanding that $\widehat{\mathrm{FDR}} = 1$ if the numerator is larger than the denominator, or if the denominator is zero
- Typically, we would specify the desired FDR q and then choose t to be the smallest value satisfying $\widehat{\mathrm{FDR}}(t) \leq q$

Illustration: Augmented example data $(n = 200, p = 60)$



Power and $\{s_j\}$

- So, how do we actually construct these knockoffs?
- As we will see, the knockoff filter is valid provided that the knockoffs have the correlation structure outlined earlier; its power, however, depends on $\{s_j\}$
- For the greatest power, we want the knockoffs to be as different from the original features as possible (i.e, we want the $\{s_j\}$ terms to be as large as possible)

Nullspace, n, and p

- Let $\mathbf{X}^\perp$ denote the nullspace of $\mathbf{X}$, and let $\mathbf{N}$ denote a p-dimensional orthonormal basis for $\mathbf{X}^\perp$ (this can be constructed using the QR decomposition)
- Note that the nullspace of $\mathbf{X}$ has dimension $n - \mathrm{rank}(\mathbf{X})$
- Thus, for the matrix $\mathbf{N}$ to exist, it is not enough for $\mathbf{X}$ to be full rank; we also need $n \geq p + \mathrm{rank}(\mathbf{X})$, so $n \geq 2p$ in the full-rank case

Constructing knockoffs under equal correlation

- So, let's say we have a full rank $\mathbf{X}$ with $n \geq 2p$ and thus can construct an orthonormal $\mathbf{N}$ with $\mathbf{N}^\top \mathbf{X} = 0$
- Furthermore, suppose we require $s_j = s$ for all j and let $\frac{1}{n}\mathbf{C}^\top \mathbf{C} = 2s\mathbf{I} - s^2\boldsymbol{\Sigma}^{-1}$, where $\boldsymbol{\Sigma} = \frac{1}{n}\mathbf{X}^\top \mathbf{X}$
- **Proposition:** The matrix

$$\widetilde{\mathbf{X}} = \mathbf{X}(\mathbf{I} - s\boldsymbol{\Sigma}^{-1}) + \mathbf{N}\mathbf{C}$$

satisfies the requirements of a knockoff matrix

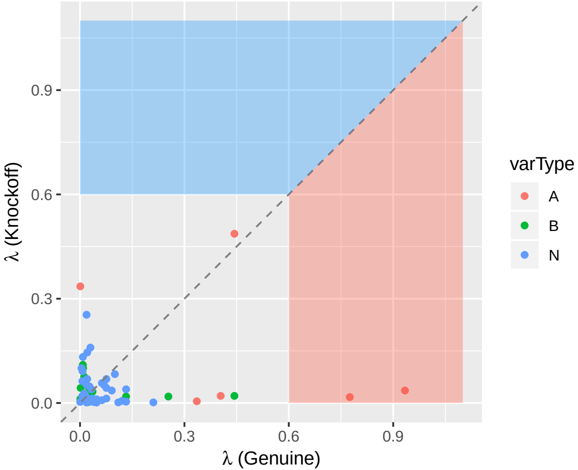
The non-full rank case

- What if $\mathbf{X}$ is not full rank?
- It turns out that the maximum value for s is 2 times the minimum eigenvalue of $\mathbf{\Sigma}$; thus, $s_j = s$ for all j cannot work in the case where $\mathbf{X}$ is not full rank
- In this case, we will have to set some of the $s_j = 0$ (meaning no power for those features) and try to maximize the rest as best we can
- In the `knockoff` package, a semidefinite programming approach is used to determine the values that minimize $\sum_j (1 - s_j)$ subject to the its constraints (`method='sdp'`; the earlier approach is `method='equi'`)

The $p < n < 2p$ case

- Now, what if $\mathbf{X}$ is full rank, but $n < 2p$?
- In this case, there is an interesting little data augmentation trick that can be used, provided that σ^2 can be estimated accurately
- To get our sample size up to $2p$, we can generate $2p - n$ additional rows of $\mathbf{X}$ that are simply all equal to $\mathbf{0}$ and $2p - n$ additional entries for $\mathbf{y}$ that are drawn from a $\mathrm{N}(0, \hat{\sigma}^2)$ distribution
- We now have a linear model with p features and $2p$ observations; the new observations carry no information about $\boldsymbol{\beta}$, but are useful for generating knockoffs

$p < n < 2p$ data augmentation applied to example data



FDR control

- So does this knockoff procedure actually control the FDR? Not quite
- Instead, Barber and Candès show that it controls a modified version of the FDR:

$$\mathbb{E}\left(\frac{|\mathcal{N} \cap \hat{\mathcal{S}}|}{|\hat{\mathcal{S}}| + q^{-1}}\right) \leq q,$$

  where $\hat{\mathcal{S}}$ is the set of features selected by the knockoff filter
- Alternatively, the knockoff filter controls the FDR if we add 1 to the numerator (i.e., to the number of knockoffs selected)
- The modifications have a nontrivial effect unless many features are selected

Coin flip lemma

- We won't go through the entire proof here, but just present a sketch of the main ideas
- The critical property that knockoffs have is a "coin flipping property": for $j \in \mathcal{N}$, we have $\text{sign}(W_j) \overset{\perp\!\!\!\perp}{\sim} \text{Bern}(1/2)$
- This coin flipping property derives from two exchangeability results: letting , then
    - $[\mathbf{X}\ \widetilde{\mathbf{X}}]^\top[\mathbf{X}\ \widetilde{\mathbf{X}}]$ is invariant to any exchange of original and knockoff features
    - The distribution of $[\mathbf{X}\ \widetilde{\mathbf{X}}]^\top\mathbf{y}$ is invariant to any exchange of *null* original and knockoff features

Sketch of proof

- With these lemmas in place, the FDR control proof follows from the inequality

$$\mathrm{FDR} \leq q \cdot \frac{\#\{j : \beta_j = 0 \text{ and } W_j > t\}}{1 + \#\{j : \beta_j = 0 \text{ and } W_j < -t\}};$$

  the coin flipping property ensuring that the expected value of this quantity is below q

- The argument can be extended to a random threshold T through use of martingales and the optional stopping theorem similar to our FDR proof at the beginning of the course

Modeling $\mathbf{X}$

- An obvious shortcoming of the previous approach is that it requires $n \geq p$
- Extending the idea to $p > n$ situations requires us to treat $\mathbf{X}$ as random and to model its distribution; Candès et al. refer to these as "model-X knockoffs" or just "MX" knockoffs
- Note that this is an interesting philosophical shift: the classical setup is to assume a very specific distribution for $\mathbf{y}$ but assume as little as possible about $\mathbf{X}$, whereas MX knockoffs assume that we know everything about the distribution of $\mathbf{X}$ but require no assumptions on the distribution of $Y|\mathbf{X}$

Knockoff properties in the random case

- Recall our exchangeability results from earlier; with these in mind, we can define knockoff conditions in the case where $\mathbf{X}$ is treated as a random matrix with IID rows
- A knockoff matrix $\widetilde{\mathbf{X}}$ satisfies
    - The distribution of $[X \ \tilde{X}]$ is invariant to any exchange of original and knockoff features
    - $\tilde{X} \perp\!\!\!\perp Y | X$
- Note that the second condition is guaranteed if $\widetilde{\mathbf{X}}$ is constructed without looking at $\mathbf{y}$

Gaussian case

- There are special cases in which we actually know something about the distribution of $\mathbf{X}$; in general, however, we would likely assume it follows a multivariate normal distribution
- The main challenge here is that now we must estimate $\mathbf{\Sigma}$, a $p \times p$ covariance matrix, or rather $\mathbf{\Sigma}^{-1}$, the precision matrix
- We will (time permitting) discuss this problem a bit later in the course; for now, although this is by no means trivial, let us assume that we can estimate $\mathbf{\Sigma}$ well enough to assume that we know $X \sim \mathrm{N}(\mathbf{0}, \mathbf{\Sigma})$

MX knockoffs in the Gaussian case

- In order to satisfy the knockoff property, let us assume the joint distribution $[X\ \tilde{X}] \sim \mathrm{N}(\mathbf{0}, \mathbf{G})$ where

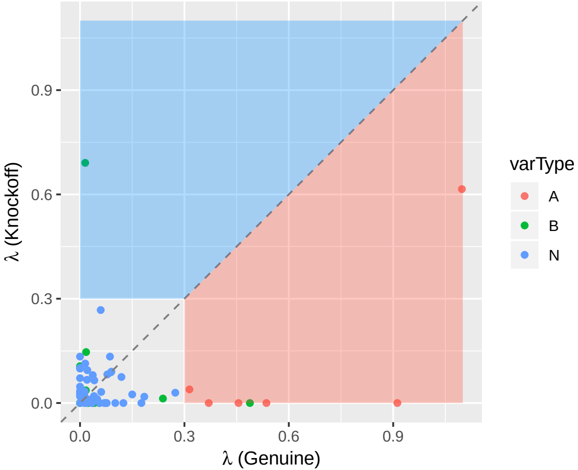
$$\mathbf{G} = \begin{bmatrix} \mathbf{\Sigma} & \mathbf{\Sigma} - \mathbf{S} \\ \mathbf{\Sigma} - \mathbf{S} & \mathbf{\Sigma} \end{bmatrix};$$

  here $\mathbf{S}$ is a diagonal matrix with entries $\{s_j\}$

- Now, we can draw a random $\widetilde{\mathbf{X}}$ from the conditional distribution $\tilde{X}|X$, which is normal with

$$\mathbb{E}(\tilde{X}|X) = X - \mathbf{S}\mathbf{\Sigma}^{-1}X$$
$$\mathbb{V}(\tilde{X}|X) = 2\mathbf{S} - \mathbf{S}\mathbf{\Sigma}^{-1}\mathbf{S}$$

Example data with modeled $\mathbf{X}$



TCGA data

- I tried applying the MX knockoff approach to the TCGA data using the `knockoff` package, but this crashed, being unable to allocate the RAM for a $17,322 \times 17,322$ matrix
- I even tried running it on our HPC cluster, but this also crashed
- So it would seem safe to say that at least in the current version (0.3.2), the `knockoff` package is not particularly scalable to high dimensions
- However, it is worth noting that in their paper, Candès et al. applied the MX knockoff filter to a problem with $p = 400,000$ by taking advantage of a special correlation structure in $\mathbf{X}$

Remarks: Some drawbacks

- The results I obtained for this example differed quite a bit depending on the random $\widetilde{\mathbf{X}}$ I drew; it would seem desirable to aggregate or average these results over the draws, although how exactly to do this is unclear
- In our examples, the knockoff filter seemed a bit less powerful than some of the other approaches we have discussed, although it's a fairly new method and at present it isn't fully understood (by me, at least) how it compares to the other inferential approaches we have discussed
- This is especially true in the MX case: "Admittedly, this paper may pose more problems than it solves"
- Furthermore, scaling the method to very high dimensions is not trivial

Remarks: Some advantages

- However, the knockoff filter also has some nice advantages
- In particular, none of its theory involves any asymptotics, or anything special about the statistic W, or about the lasso, which means:
  - The theory holds exactly in finite dimensions
  - We can use other statistics, such as the lasso coefficient difference: $W_j = |\widehat{\beta}_j(\lambda)| - |\widehat{\beta}_{j+p}(\lambda)|$
  - Perhaps most appealing, we can apply this reasoning to all kinds of other methods – other penalties of course, but also much more ambitious problems: forward selection, random forests, even deep learning