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Discussion of Sesia et al. and the Knockoff Framework

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1. ON THE MOTIVATION

The authors of Sesia et al. (2018) set out to design a procedure for variable selection with provable statistical guarantees. The *knockoff* algorithm proposed by Sesia et al. (2018), provably controls the FDR of conditionally independent variables. Denoting with x and y the predictor and outcome variables, respectively. The *false detection proportion*, a.k.a. the *false selection proportion*, is defined as V/R where R is the number of variables selected, and V is the number of such variables where $y|x_{-j}$ is independent of x_j. The knockoff algorithm of Sesia et al. (2018) provably control the $FDR := \mathbb{E}[FDP]$, at some user selected magnitude.

The fundamental idea of the method is to generate variables that have all the properties of the original x_j, only that they are conditionally uncorrelated to y. These are termed *knockoff* variables. The method then proceeds to compute a test statistic that captures the difference in the strength of the dependence of the knockoff, and the original variable. This statistic is then compared to it resampling distribution: the distribution over resampled knockoffs.

Crucially for our comments: (1) The FDR is an expectation with respect to variability in x and y, i.e., a *random design* guarantee. (2) The procedure is *model free*, or *non-parametric* in that nothing is assumed on the parametric form of $y|x$. (3) The proofs assume full knowledge of F_x, i.e., the joint distribution of predictors, marginalized over y. (4) The method aims at good variable selection, not prediction.

We think of the method in Sesia et al. (2018) as an adaptation of Candès et al. (2018) to genome-wide association studies (GWAS). The differences between the two: (1) The non-null variables in Candès et al. (2018) are those that belong to the minimal set that renders all others independent. The non-null variables in Sesia et al. (2018) are those with non-null partial correlation. (2) Candès et al. (2018) discusses a multivariate Gaussian model, while Sesia et al. (2018) a hidden Markov model. Each paper offers an sampling algorithm for sampling knockoffs from the assumed model.

The method of Sesia et al. (2018) is similar in flavor to Barber & Candès (2015), but Sesia et al. (2018) is quite more general: (1) Barber & Candès (2015) assume a linear generative model, so that the null is simply $H_j : \beta_j = 0$. (2) Barber & Candès (2015) crucially assume $n > p$, and Gaussian distributed errors.

2. ON OTHER KNOCKOFFS

The idea of augmenting design matrices with random variables is not new. It has been suggested many times, for the purposes of prediction, variable ranking, consistent support recovery, etc. Some notable examples include the authors' own Candès et al. (2006). Tusher et al. (2001) have already proposed the idea of permuting the original variables for FDR control on selected variables. While intuitive and elegant, their algorithm did not have any provable guarantees. Some more algorithms adding "fake", "phony", "probes" or "pseudo variables", are reviewed in Guyon & Elisseeff (2003).

Perhaps the most similar work is that of Wu et al. (2007), which not only propose adding 'pseudo-variables" for the purpose of estimating the variable selection FDR, but also require two conditions very similar to the knockoff conditions. Wu et al. (2007) require that: (A1) "real unimportant variables and phony unimportant variables have the same probability of being selected on average", and (A2)"real important variables have the same probability of being selected whether or not phony variables are present". These two conditions cannot be satisfied, but they are clearly related to the *pairwise exchangeability* and *nullity condition* in Sesia et al. (2018) and Candès et al. (2018).

The impossibility to satisfy A1 and A2 was already observed by Wu et al. (2007). One may thus view the two knockoff conditions as a satisfiable version of A1 and A2. To the credit of Wu et al. (2007) we quote their insights, which already hint at what will be later formalized in the knockoff conditions: "Permutation produces pseudovariables that when appended to the real data create what are essentially matched pairs. To each real variable there corresponds a pseudo variable with identical sample moments and also with preservation of correlations".

3. ON THE PROBLEM SETUP

The problem setup in Candès et al. (2018) and Sesia et al. (2018) deals with random design inference, in a non-parametric generative model. We find this to be a very useful setup for screening problems: It is consistent with the random designs typically found in observational studies, and it avoids the very-useful-yet-controversial linearity assumption.

A more surprising component of the problem setup is the knowledge of F_x, i.e., the joint distribution of predictors, marginalized over y. Many authors would consider this an Oracle assumption, and given the difficulty of estimating joint distributions, an unrealistic one. We, on the other hand, do not find this such a troubling assumption for the following reasons: (1) In many applications the dimensionality of F_x can be reduced to a tractable one. The HMM assumption of Sesia et al. (2018) is an example. (2) The preliminary results of Candès et al. (2018) show that FDR-control is quite robust to errors in F_x. We expect this matter to be further investigated in the future.

4. ON VARIABLE SELECTION AND NULL HYPOTHESES

The problem of variable selection with error guarantees is not new. Previously proposed algorithms include, for instance, Stability Selection (Meinshausen & Bühlmann, 2010), SURE Screening (Fan & Lv, 2008), BOLASSO (Bach, 2008), Benjamini-Gavrilov (Benjamini & Gavrilov, 2009), and many more. These procedures propose varying algorithms, with varying statistical guarantees in varying scenarios. We do not review this literature for the sake of brevity. We do, however, wish to discuss the matter of identifiability and estimability. I.e., is the parameter well defined, and is the estimation problem well-posed?

When doing variable selection, one will always require some assumption to ensure that "a good" selection is well defined. For this purpose a linear generative model is typically assumed. In the linear generative case multicollinearity will render the problem non-identifiable. To ensure identifiability in the fixed design, authors have proposed various conditions such as *Sparse Eigenvalue*, *Sparse Riesz Condition*, *Neighbourhood Stability*, *Irrepresentable Condition*, and *Exact Recovery Criterion*. See Meinshausen & Bühlmann (2010, Sec 3.1.1) for a review. In the random-design literature, identifiability is typically ensured with some restriction on the condition number of $Cov[x]$, or with some strong-convexity assumption on the risk surface. How is identifiability ensured in the knockoff framework?

The (later version of the) knockoff framework does not deal with the linear generative case, so that null and alternative cannot be stated in terms of β coefficients. On the other hand, support recovery is a more modest goal than consistent estimation, which does not require an identifiable model. Errors, and thus FDR, can thus be defined without identifiable parameters.

Lacking a parametric generative model, null and alternative have a more information-theoretic flavor, and are stated in terms of dependence. Candès et al. (2018) define the null using a Markov-Blanket, and

Sesia et al. (2018) use conditional independence. This raises several questions: Are these hypotheses consistent with the motivating problems? Why this change in hypotheses?

Screening problems, such as GWAS, are good examples of variable selection: The inference has no causal aspirations[1]; and the design is random. We find that the conditional independence assumption is not quite consistent with the GWAS motivation. To see this, consider two perfectly correlated SNPs. One causal and the other not, but for the purpose of a screening study, both belong to the alternative. Using the conditional independence hypotheses in Sesia et al. (2018), however, they will both belong to the null. Using the Markov-Blanket hypotheses in Candès et al. (2018), they will also belong to the null. It seems to us that for the purpose of screening, marginal hypotheses, such as the ones in Tusher et al. (2001), are more appropriate. If the purpose were not screening for associations, but rather, causal inference, then clearly the definition of hypotheses, and errors, would have required a different language altogether.

5. Permutation Testing and Symmetries

6. Future Research

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[1] Otherwise, stating hypotheses with *Do-Calculus* (Pearl, 1995) may be more appropriate