AUTO ENCODING KNOCKOFF GENERATOR FOR FDR CONTROLLED VARIABLE SELECTION

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ABSTRACT

A new statistical procedure (Model-X Candès et al. (2018)) has provided a way to identify important factors using any supervised learning method controlling for FDR. This line of research has shown great potential to expand the horizon of machine learning methods beyond the task of prediction, to serve the broader needs in scientific researches for interpretable findings. However, the lack of a practical and flexible method to generate knockoffs remains the major obstacle for wide application of Model-X procedure. This paper fills in the gap by proposing a model-free knockoff generator which approximates the correlation structure between features through latent variable representation. We demonstrate our proposed method can achieve FDR control and better power than two existing methods in various simulated settings and a real data example for finding mutations associated with drug resistance in HIV-1 patients.

1 INTRODUCTION

In the past decades, the machine learning methods have achieved great advancement in improving prediction accuracy. However, prediction accuracy is not the sole quest of 'big data' analysis. A universal aim across a lot of scientific disciplines is to identify the causes of certain outcome. For example, in new drug development, a personalized medicine strategy can be formed by identifying the gene markers that is biologically linked to certain drug response or resistance. In electronic health record analysis, the goal is to identify 'actionable' factors for the purpose of reducing cost and improving the quality of care. In epidemiology or sociology studies, it is of interest to identify protection or risk factors, especially those that can be changed through public policy or civil planning to improve public welfare. In these scientific endeavors, the need is to identify the important factors associated with a certain outcome, so that further confirmatory investigation (e.g. randomized international studies) could be conducted to expand knowledge or change future actions for a better outcome. For this purpose, we are interested in procedures that control the Type I error, which is the chance of a false discovery. With a large amount of factors to test, controlling the chance of any false discovery (family-wise error) is too stringent. Therefore the objective is usually relaxed to control the False Discovery Rate (FDR) (Benjamini & Hochberg, 1995).

A recent breakthrough in the statistical theory, i.e. the Model-X framework(Barber & Candès, 2015; Candès et al., 2018), provided a general solution. It can be incorporated with any machine learning models to select true signals associated with the outcome, with rigorous control for FDR. This line of research shed light on expanding the horizon of supervised learning methods beyond prediction. However, the implementation of Model-X requires the generation of the so called 'knockoffs', which has limited existing methods. The goal of our paper is to fill in the gap by proposing a model-free method for generating knockoffs with relaxed assumptions for the data, leveraging the power of the recent development in deep generative models. Specifically, we propose a framework to generate knockoffs based on latent variable Z which captures the correlation structure of X. This provide a great generalization from the existing knockoff generation methods for HMM and mixture Gaussian to (but not limited to) Hidden Markov Random Field. The contribution of this paper is in two folds: first, we tackles the problem of generating Model-X knockoffs for any data set by proposing and justifying a framework based on latent variable Z; second, the proposed framework is a novel application for variational auto encoder and its variants. Compared with other deep learning architecture to generate knockoff, the proposed framework has the advantage in less computational complexity and easier to be implemented by domain scientists.

2 BACKGROUND

The model-X framework (Candès et al., 2018) is proposed for the following problem. There are N i.i.d. samples $(X^{(i)}, Y^i)$ from a population, where the predictors are random variables $X = (X_1, \ldots, X_p)$. The outcome Y only depend on a subset of predictors $S \in \{1, 2, \ldots, p\}$, i.e. given $\{X_j, j \in S\}$, Y is independent of the other X_j's. The smallest set S that satisfy this requirement is considered as the true predictors. The goal is to find a good estimator $\hat{S}$ for S with control of the $FDR = E\left(\frac{\#\{j:j\in\hat{S}\setminus S\}}{\#\{j:j\in\hat{S}\}\vee 1}\right)$. Barber & Candès (2015) first proposed the method for linear regression with Gaussian errors, where the design matrix $\boldsymbol{X}$ is assumed to be fixed. Candès et al. (2018) greatly generalized it to the Model-X framework. In contrast to the traditional statistical models focusing on the conditional distribution $Y|X_1, \ldots, X_p$, Model-X makes no assumption for the conditional distribution, but assume X has a known distribution for the purpose of generating knockoffs $\tilde{X}$ that satisfies Definition 2.1.

Definition 2.1 Model-X knockoffs *for the family of random variables $X = (X_1, \ldots, X_p)$ are a new family of random variables $\tilde{X} = (\tilde{X}_1, \ldots, \tilde{X}_p)$ constructed with the following two properties: (1) for any subset $S \subset \{1, \ldots, p\}$, $(X, \tilde{X})_{swap(S)} =_d (X, \tilde{X})$; (2) $\tilde{X} \perp\!\!\!\perp Y|X$ if there is a response Y. (2) is guaranteed if $\tilde{X}$ is constructed without looking at Y.*

Proposition 1 (Candès 2018) *The random variables $\tilde{X} = (\tilde{X}_1, \ldots, \tilde{X}_p)$ are model-X knockoffs for $X = (X_1, \ldots, X_p)$ if and only if the joint distributions are equal after swapping X_j and $\tilde{X}_j$, i.e. $(X_j, X_{-j}, \tilde{X}_j, \tilde{X}_{-j}) =_d (\tilde{X}_j, X_{-j}, X_j, \tilde{X}_{-j})$, for any $j \in \{1, \ldots, p\}$, where X_{-j} denote the other variables. And $Y \perp\!\!\!\perp \tilde{X}|X$.*

Suppose one can generate Model-X knockoffs, the features are selected through the model-specific feature statistics $W_j = w_j([X, \tilde{X}], y)$. Intuitively, the signs for the W_j's from the null variables ($X_j \notin S$) need to symmetric conditioning on its magnitude $|W_j|$. Which is formalized as the flip-sign property,

$$W_j([X, \tilde{X}]_{swap(S)}, y) = (1 - 2\mathbf{1}_{\{\mathrm{j}\in\mathrm{S}\}})w_j([X, \tilde{X}], y).$$

According to Thm 3.4 in Candès et al. (2018), the following procedure (Knockoff) can estimate the $\hat{S}$ controlling for modified FDR, i.e. $E\left(\frac{\#\{j:j\in\hat{S}\setminus S\}}{\#\{j:j\in\hat{S}\}+q^{-1}}\right) \leq q$. First, compute the threshold $\tau = \min\left\{t > 0 : \frac{\#\{j:W_j\leq -t\}}{\#\{j:W_j\geq t\}} \leq q\right\}$, then the selected set is

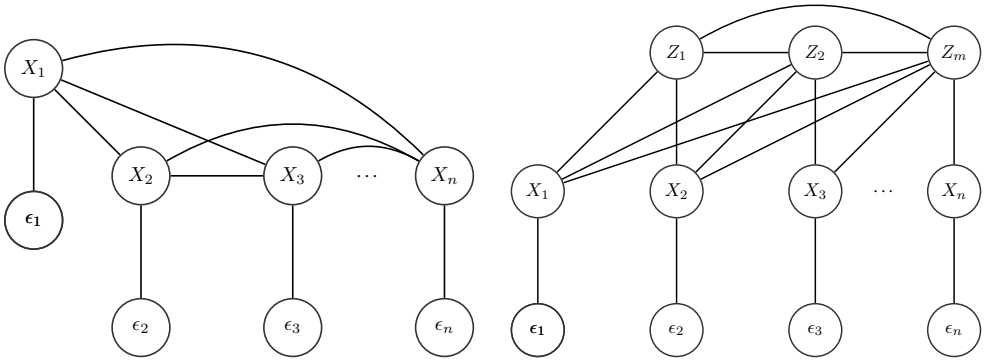
$$\text{(Knockoff): } \hat{S} = \{j : W_j \geq \tau\}. \tag{1}$$

More conservatively, the following procedure (Knockoff+) can control for the FDR, choose a threshold $\tau+ = \min\left\{t > 0 : \frac{1+\#\{j:W_j\leq -t\}}{\#\{j:W_j\geq t\}} \leq q\right\}$, and select the variables in the set

$$\text{(Knockoff+): } \hat{S} = \{j : W_j \geq \tau+\}. \tag{2}$$

An example of the feature statistics is the signed max lambda statistics in L_1 penalized regressions Barber & Candès (2015): for the concatenated design matrix $[X, \tilde{X}]$, define $\hat{\beta}(\lambda) = \arg\min_b \left\{Loss(y, [X\tilde{X}]b) + \lambda\|b\|_{L1}\right\}$. Intuitively, the true predictors with strong signals would have entered the LASSO selection with large λ and X_j is entering the model with larger λ than its knockoff $\tilde{X}_j$. The null variables will enter the model with smaller penalty. Thus the signed max lambda statistic is defined as $W_j = (Z_j \vee \tilde{Z}_j)\text{sign}(Z_j - \tilde{Z}_j)$. Where $Z_j = \sup\{\lambda : \hat{\beta}_{2j-1}(\lambda) \neq 0\}$ and $\tilde{Z}_j = \sup\{\lambda : \hat{\beta}_{2j}(\lambda) \neq 0\}$. Various feature statistics has been proposed for common learning methods (Candès et al., 2018; Gimenez et al., 2018), however the current knockoff generation methods are still limited to make Model-X generally applicable on any real data set.

Although Candès et al. (2018) provided a general algorithm for generating Model-X knockoffs, i.e. the Sequential Conditional Independent Pairs algorithm, it needs to sample from the conditional distribution of $\tilde{X}_j$ from $f(X_j|X_{-j}, \tilde{X}_{1:j-1})$ which becomes intractable with slightly complex distributional assumption for X. Candès et al. (2018) also proposed a second-order approach by matching



(a) Observed Data (b) Latent Variable Z to Block X

Figure 1: Hidden Markov Field

first two moments of $(X, \tilde{X})_{swap(S)}$ and $(X, \tilde{X})$, which satisfies Def. 2.1 when X is from Gaussian distribution. Sesia et al. (2018) proposed an algorithm to sample knockoffs when X is from Hidden Markov Model. Gimenez et al. (2018) proposed algorithm that applicable for X from simple Bayesian network models (such as mixture Gaussian) with distributional assumptions for certain conditional probabilities which need to be estimated and sampled from.

3 A Model-Free Knockoff Generator With Latent Encoding Variables.

3.1 Existence of Desired Latent Variable Z

Conceptually, the Model-X focuses on controlling for the FDR of testing the null hypotheses $X_j \perp\!\!\!\perp Y | X_{-j}$, where $j = 1, \ldots, p$, and X_{-j} denote the variables except X_j. Thus, a necessary condition for X_j to be chosen by Model-X is that it contains signals not contained in the other variables, i.e. X_j can not be a determinant function of X_{-j}. In the knockoff generating process, any component of X_j's that is independent from X_{-j} is easy to generate. The difficulty and necessity to consider complex conditional distribution is introduced by the correlated component. Thus we formed a general framework based on the assumption that there exists some latent variable Z so that X_j's are mutually independent conditional on Z.

Such Z always exists for any X, one can take $Z = X$ or $Z = f(X)$, such that f is an one-on-one mapping between X and Z. However, to generate powerful knockoff, we want smaller mutual information between $\tilde{X}_j$ and X_j, which means that we need large variation of $X|Z$, or at least conditional densities, $p(X|Z)$ is not degenerated.

A general class of models satisfies this assumption is the Hidden Markov Random Field as illustrated by the undirected graphical models in Figure 1. The latent variables are from a Markov Random Field and the observed random variables X_j's are generated from $Z's$ with independent errors.If X's are from binomial (for binary data) or multinomial distribution (for categorical data) with positive probability mass, the desired latent variable Z always exists as a categorical variable with probabilities from the tensor decomposition of multi-way contingency array of probability for X Bhattacharya & Dunson (2012). Then $X_i|Z$'s are generated from Bernoulli or multinomial with parameters as functions of Z and thus $p(X_i|Z)$'s are not degenerate.

For continuous or infinite discrete state X, there is no general theory to characterize the existence of such latent Z. de Finetti's theorem states that if the distribution $(X_1, X_2, \ldots, X_n)$ is exchangeable then there exists a one dimensional non-degenerate latent variable Z, such that $p(X_1, X_2, \ldots, X_n|Z) = \prod_{j=1}^{n} p(X_j|Z)$. Thus the desired Z exists for the multivariate normal distribution or trans-elliptical distribution (i.e., any distribution that can be transformed into multivariate normal distribution by element-wise transformation). The mixture of trans-elliptical distribution also has the desired latent Z as the combination of the single latent variable which indicate the cluster and the latent Z for each cluster. The knockoff generator for HMM Sesia et al. (2018) can

be viewed as a special case of our general framework that Z is restricted to be finite state discrete variables from a Markov chain with pre-specified edges and $f(X_i|Z) = f(X_i|Z_i)$. Our work gives a general representation of the latent variable solution for generating knockoffs from the Hidden Markov Random Field without pre-specified structure.

Even for the non Gibbs Random Field (X is not from Markov Random Field), the latent Z can exist, for example $f(x_1, x_2) = 2\mathbf{1}_{\{}x_1 + x_2 \leq 1, x_1 \geq 0$ and $x_2 \geq 0\}$. Consider the partition of the support $\{x_1 + x_2 \leq 1, x_1 \geq 0$ and $x_2 \geq 0\}$ into countable many squares. The desired Z can be defined as the indicator whether X belong to the squares. $X|Z$ is then the uniform distribution on that square, X_1 and X_2 are independent given Z. More generally, for non-degenerate X, we can consider the support of the joint density $f(x_1, x_2, \cdots, x_p)$ into a partition of countable many cells. If $f(x_1, x_2, \cdots, x_p)$ on each cell is from the above mentioned examples, for which Z exist, then the desired Z exist as indicators of X belong to each cell and Z for each cell. Notice that this general case is very broad that for real data, it is hardly possible to reject the null hypothesis that X belong to this broad class of distributions where the desired Z exist.

To sum up, the assumption of our framework includes a large class of distributions that offers a knockoff generation solution for all discrete predictors, and continuous predictors with a mild distributional assumption.

3.2 Method and Algorithm

Our procedure first generate Z's knockoff from conditional $Z|X$ and then generate X's knockoff from $X|Z$. In practice, we assume Z and the conditional distributions are from parametric families and the parameters can be approximated through variational inference. Specifically, in simulation and real data example of this paper, we provide results based on state of art Variational Auto Encoder to estimated the conditional distributions. Gao et al. (2018) point out under certain conditions, the ELBO for VAE is equivalent to a lower bound for the Total Correlation Explanation, for which one component of the objective is optimized when Z fully decorrelate (disentangle) the X (i.e. conditional of Z, X is mutually independent).

The objective function of our learning framework is then target on the reconstruction of X, the data's compatibility with variational model assumptions for $Z|X$ and $X|Z$. Alternatively, if one construct knockoff directly from deep neural network with input X and random noise E, $\tilde{X} = f(X, E)$. The objective is the discrepancy between $(X, \tilde{X})$ and $(X, \tilde{X})_{swap}$. There are $2^p - 1$ ways of swapping, thus the objective is more complicated. The latter may have benefits over our approach when the 'working' variational auto encoding model is not compatible with the true data distribution. However the pros and cons of our method and various other deep learning based knockoff generator await to be evaluated and compared case by case in various real data sets.

The random vector of covariates $X = (X_1, X_2, \ldots, X_p)$ are from $p_X(x)$ (X can be continuous, discrete or mixed). There exists a vector of continuous latent random variables Z from distribution $p_Z(z)$. Each component of the covariates $X_j \sim p_\epsilon(f_i(Z)), j = 1, \ldots, p$, such that ϵ_j's are mutually independent given Z. For example, when the predictor is continuous, $X_j \sim \mathcal{N}(f_j(Z), \sigma_j^2)$; and when the predictor is binary, $X_j \sim$ Bernoulli$(f_j(Z))$. Given the observed samples $\{\boldsymbol{x}^{(i)}\}_{i=1}^N$ from $p_X(x)$, to estimate $p_Z(z)$ and $p_{X|Z}$ may not be an identifiable problem. However, we just need to find one Z that approximately satisfy the above condition in practice for our purpose of knockoff generation.

We denote there are two working models from parametric families: a) an encoder $Q_{Z|X}(z|x;\theta)$ to approximate $p_{Z|X}(z|x)$; b) a decoder $Q_{X|Z}(x|z; f, q_\epsilon)$ to approximate $p_{X|Z}(x|z)$. Where θ denote the parameter for the encoder, and f denote the parameters for decoder. And q_ϵ denote the working noise distribution to generate $\tilde{X}$ given $\hat{f}(\tilde{Z})$, and ϵ is element-wise independent $q_\epsilon = \prod_j q_{\epsilon_j}$. And $\hat{\theta}$, $\hat{f}$ denote the estimates for these parameters. Then we propose to generate knockoff $\tilde{X}$ as Algorithm 1.

Notice that the Step 2 in Algorithm 2 is different from the usual VAE implementation. In the latter, $\tilde{Z}$ is usually generated from a prior distribution $p_Z(z)$, however in our algorithm $\tilde{Z}$ is generated from the conditional distribution $Q_{Z|X}$. The following Theorem 3.1 justifies why our procedure is so.

Algorithm 1 Auto-encoding Knockoff Generator.

1: Train model parameters to get estimates $\hat{\theta}, \hat{f}$.
2: Generate $\tilde{Z}$ from $Q_{Z|X}(z|X;\hat{\theta})$.
3: Generate $\tilde{X}$ from $Q_{X|Z}(x|\tilde{Z};\hat{f},q_\epsilon)$.

The state of art Variational Auto Encoder (VAE) (Kingma & Welling, 2014; Rezende et al., 2014; Maddison et al., 2017; Jang et al., 2017) provide a way to estimate the working models in Step 1. For example, in the common variational auto encoder, $Z \sim N(0, I_q)$, the working model $Q_{Z_i|X}$ is assumed to be from $\mathcal{N}(\mu_i(X), \sigma_i^2(X))$, and $Q_{X_i|Z}$ is $\mathcal{N}(f_i(Z), \sigma^2)$, where $\mu_i(\bullet)$ and $\sigma_i^2(\bullet)$ and $f(\bullet)$ are functions to be approximated by neural networks. The q_ϵ in this case is i.i.d. normal distribution with infinitesimal variance. So in practice people generate $\tilde{X}$ as $\hat{f}(\tilde{Z})$. Another example is to approximate discrete Z's by the concrete distribution Jang et al. (2017); Maddison et al. (2017). In this case $\tilde{X}$ is generated from $Bernoulli(\hat{f}(\tilde{Z}))$ and $\epsilon = \tilde{X} - \hat{f}(\tilde{Z})$ are element-wise independent.

3.3 Theoretical Results

The following theorems justifies our two step generating approach. Theorem 3.1 shows that if X is mutually independent conditional on Z, then the generated knockoffs $\tilde{X}$ satisfies the swap condition. Theorem 3.3 provide the FDR bound given the discrepancy of the variational approximation for the encoder and decoder are bounded.

Theorem 3.1 *For any vector of random variables Z, such that conditional on Z, X_i's are mutually independent. If $\tilde{Z}$ is from $p_{Z|X}(\bullet|X)$, then $\tilde{X}$ from $p_{X|Z}(\bullet|\tilde{Z})$ is model-X knockoffs.*

Proof: For any $j \in 1, \ldots, p$ and sets A_j, B_j, A_{-j}, B_{-j},

$$
\begin{aligned}
& P(X_j \in A_j, \tilde{X}_j \in B_j, X_{-j} \in A_{-j}, \tilde{X}_{-j} \in B_{-j}) = \int p_{X|Z}(A_j, A_{-j}|Z) p_{X|Z}(B_j, B_{-j}|Z) dF(Z) \\
= & \int p_{X_j|Z}(A_j|Z) p_{X_{-j}|Z}(A_{-j}|Z) p_{X_j|Z}(B_j|Z) p_{X_{-j}|Z}(B_{-j}|Z) dF(Z) \\
= & \int p_{X_j|Z}(B_j|Z) p_{X_{-j}|Z}(A_{-j}|Z) p_{X_j|Z}(A_j|Z) p_{X_{-j}|Z}(B_{-j}|Z) dF(Z) \\
= & \int p_{X|Z}(B_j, A_{-j}|Z) p_{X|Z}(A_j, B_{-j}|Z) dF(Z) = P(X_j \in B_j, \tilde{X}_j \in A_j, X_{-j} \in A_{-j}, \tilde{X}_{-j} \in B_{-j})
\end{aligned}
$$

We have shown X_j and $\tilde{X}_j$ are exchangeable in the joint distribution, then $\tilde{X}$ is the Model-X knockoff by Proposition 1.

To provide the FDR bound for the knockoffs generated from the estimated encoder and decoder, we do not assume there exists a Z satisfies the condition of Theorem 2.1 exactly. Instead, we assume the working models and observed distribution of X are approximately compatible as in the following theorem. We then apply the results per Barber et al. (2018) to show FDR control, where they showed the FDR derived from approximate knockoffsis bounded by a function of the observed KL divergence between $(X_j, \tilde{X}_j, X_{-j}, \tilde{X}_{-j})$ and $(\tilde{X}_j, X_j, X_{-j}, \tilde{X}_{-j})$ as below:

$$
\widehat{KL}_j = \log\left(\frac{P(X_j, \tilde{X}_j, X_{-j}, \tilde{X}_{-j})}{P(\tilde{X}_j, X_j, X_{-j}, \tilde{X}_{-j})}\right) = \sum_{i=1}^{n} \log\left(\frac{P(X_{ij}, \tilde{X}_{ij}, X_{i,-j}, \tilde{X}_{i,-j})}{P(\tilde{X}_{ij}, X_{ij}, X_{i,-j}, \tilde{X}_{i,-j})}\right)
$$

Theorem 3.2 *Assume the observed marginal distribution $p_X(x)$ and the working models ($Q_{Z|X}$, $Q_{X|Z}$, q_ϵ estimated in Algorithm 1) are approximately compatible as following: there exists a random vector Z from certain distribution $p_Z(z)$ and $a_n \to 0$, such that*

$$
\sup_x |\log\left(\frac{q_\epsilon(x)}{p_{\hat{\epsilon}}(x)}\right)| \le a_n \text{ and } \sup_{z,x} |\log\left(\frac{p_{Z|\hat{X}}(z|x)}{Q_{Z|X}(z|x)}\right)| \le a_n.
$$

Where the density of $\hat{\epsilon} = X - \hat{f}(Z)$ is denoted as $p_{\hat{\epsilon}}$, considering $\hat{f}$ as a fixed function. And denote $\hat{X} = \hat{f}(Z) + \epsilon$ as a random variable generated from the decoder $Q_{X|Z}(x|z = Z; \hat{f}, q_\epsilon)$.

Then the FDR can be controlled at $q \exp\{8na_n^2 + 8\sqrt{n \log(p)}a_n\}$.

Proof of Theorem 3.2 is in Appendix A.

4 Goodness of Fit

Theorem 3.2 provide FDR bound given the variational models is able to approximate the $Z|X$ and $X|Z$ sufficiently close. However, the convergence and its rate of VAE and any general deep generative models is a hard problem. Thus the rate provided in Theorem 3.2 is not a guarantee of the FDR control. One evaluation approach proposed by Candès et al. (2018) is to estimate the empirical FDR for simulated Y and X of the real data, and compare the power and FDR control performance of knockoffs from various generator. One can also compose some goodness of fit metrics based on the distributional discrepancy between $(X, \tilde{X})$ and $(X, \tilde{X})_{swap}$. In addition to the metrics shared with other knockoff generator, our framework has a unique measurement of goodness of fit, which is the $X|Z$ are independent. Specifically, if the q_ϵ is assumed to be additive error, i.e. $\tilde{X}_j = \hat{f}_j(\tilde{Z}) + \epsilon_j$. The residuals $X - \hat{f}(\tilde{Z})$ of the real data X and the fitted means, is mutually independent. In the following numerical studies, we focus on the first evaluation strategy which is based on FDR control for simulated Y. We include preliminary graphical check for the independence criterion in Appendix C and some further discussion in Section 7 .

5 Simulation

In the simulation, we compare three knockoff generation schemes: a) our proposed method implemented through VAE b) the fixed knockoff generation method in Barber & Candès (2015) c) the second order matching in Candès et al. (2018). We demonstrate the performance of these methods in two simulation scenarios. In both scenarios, the sample size is 200, and number of potential predictors is 100, where the first m variables are the true signals. The coefficients β for the true predictors are alternating ρ and $-\rho$, where ρ is the magnitude of the signal. In Figures 23, the power and FDR are drawn as curves with respect to ρ.

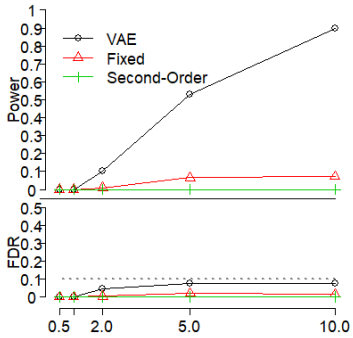
We generated two types of outcomes: the continuous outcomes are generated with errors from standard normal distribution; the binary outcomes are generated from Bernoulli with probabilities $1/(1 + \exp(-X\beta))$. And we used the L_1 penalized linear and logistic regression correspondingly. Results based on 100 replications are presented for two different numbers of true signals $m = 10, 20$.

Setting 1. In this setting, we simulate a set of lightly correlated non-normal distributed continuous predictors: a) Generate independent uniform $(0, 1)$ distributed 200 by 200 random matrix. b) Let C be the Cholesky decomposition of the correlation matrix with 0.1 on the off diagonal entries and compute $Z = UC$. c) Even column X_{2i} is generated as $Z_{4i} + 0.5 * Z_{4i+1}^3$, and odd column X_{2i+1} is generated as $Z_{4i+2} - 0.5Z_{4i+2}^2 + 0.5\exp(Z_{4i+3})$, where $i = 0, \ldots, 49$. d) Rescale X's to be within range $[0, 1]$ by subtracting the column $\min$ and divided by column $\max - \min$. Empirically, the pairwise correlation X ranges from -0.3 to 0.6 and the absolute value of the correlation has mean 0.07. The signal to noise ratios of the Gaussian case approximately has the range of $0.25 - 0.3\rho^2$ for $m = 10$ and $0.7 - 0.85\rho^2$ for setting with $m = 20$.

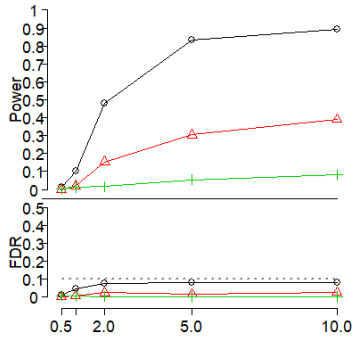
Setting 2. The second setting generates correlated categorical predictors :a) Generate independent standard Gaussian distributed 200 by 100 random matrix. b) Let C be the Cholesky decomposition of the correlation matrix with 0.1 on the off diagonal entries. Let $Z = UC$. c) X is the categorized Z matrix, where $X_{ij} = \mathbf{1}(Z_{ij} > 0)$. Approximately, the signal to noise ratio for the Gaussian case is $2\rho^2$ for $m = 10$ and $4\rho^2$ for $m = 20$. We present results for FDR controlled at 0.1.

Results

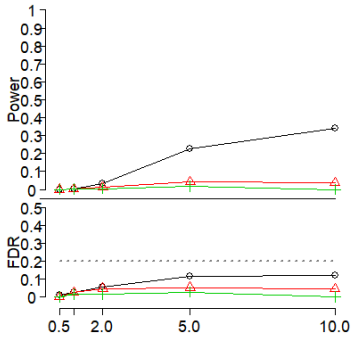
According to Figures 2 3, our proposed method implemented through VAE has FDR controlled below the predetermined threshold, and it demonstrates higher power than its two competitors. Cases with more true signals $m = 20$ demonstrate better power for Gaussian outcomes, since we control



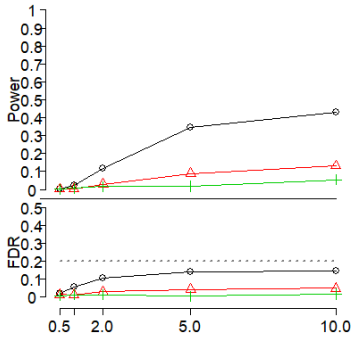
(a) Linear Regression $m = 10$, FDR$= 0.1$



(b) Linear Regression $m = 20$, FDR$= 0.1$



(c) Logistic Regression $m = 10$, FDR$= 0.2$



(d) Logistic Regression $m = 20$, FDR$= 0.2$

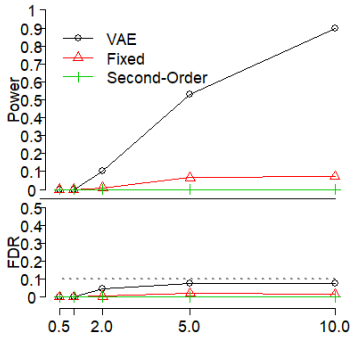
Figure 2: Power and FDR with respect to signal magnitude ρ for Setting 1.

for the proportion of false discoveries, the criterion can tolerate more false discoveries with larger number of true discoveries it detect. The second-order matching method proposed for the gaussian predictors has very low power due to the violation of its assumption that our generated X are not from Gaussian distribution. The assumptions for Fixed Knockoff generator is satisfied for the linear regression settings(with gaussian errors) but violated for the logistic regression setting. In the simulation, the FDR is still controlled for cases these assumptions are violated. However the powers are low.

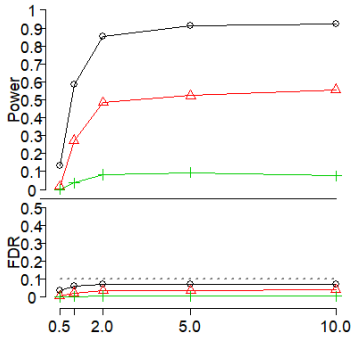
Implementation details. For both settings, we implemented our method with VAE Kingma & Welling (2014). We defer the training details to Appendix B. We use the signed max lambda statistics in Barber & Candès (2015) (see definition on page 2). We implemented the L_1 penalized linear and logistic regression with R package 'glmnet' with a finer grid of tuning parameter to break ties in Z_j and $\tilde{Z}_j$. We used the more conservative Knockoff+ as in (2).

6 Real Data Experiment

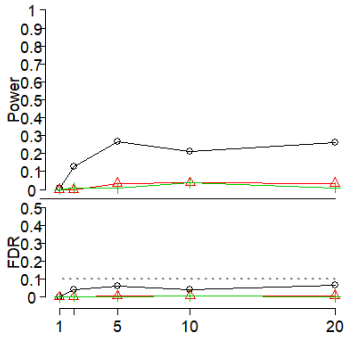
In the real data experiment, we demonstrate the performance of our proposed method on generating knockoffs for sparse genetic mutation data. The dataset and scientific problem is from a study aiming at detecting mutations associated with drug resistance in patients with Human Immunodeficiency Virus Type 1 (HIV-1) Rhee et al. (2006). Due to the space limit, here we present results for the 7 protease inhibitors. There is no ground truth for which subset of mutations caused the drug resistance. Nevertheless, there is a set of 73 treatment-selected mutations (TSMs) identified



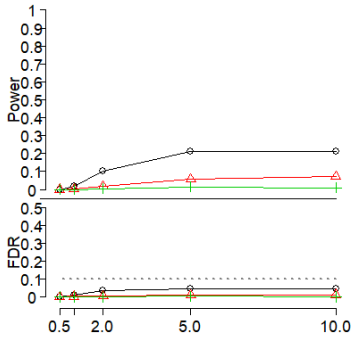
(a) Linear Regression $m = 10$, FDR$= 0.1$



(b) Linear Regression $m = 20$, FDR$= 0.1$



(c) Logistic Regression $m = 10$, FDR$= 0.1$



(d) Logistic Regression $m = 20$, FDR$= 0.1$

Figure 3: Power and FDR with respect to signal magnitude ρ for Setting 2.

from a separate study Rhee et al. (2005), which are selected as the mutations marginally correlated with the patient treatment history with protease inhibitors. Thus to evaluate the performance of the knockoffs, we first simulates the outcome for which we know the true signal, and evaluate the FDR control and power as shown in Figure 4, and then we used the real data outcome and compared our selected mutations with the TSM. Notice that the TSM is not drug specific and can not be considered as ground truth, by showing number of selected mutations in TSM set we are not showing the FDR control but demonstrate reproducibility across studies.

The normal distributed Z does not fit the discrete and sparse nature of the genetic mutation data. Thus we adopted the Categorical Variation Auto-Encoder (CAT-VAE) Jang et al. (2017); Maddison et al. (2017), where in our implementation, the latent variables Z are 20 Gumbel-Softmax distributed variable with temperature 1, each with 10 categories; both the encoder and decoder has one hidden layer of dimension 200.

Figure 4 demonstrates the results for simulated outcomes using the real data X. Overall speaking, our proposed method still achieves the FDR control and demonstrates the highest power among the three. The correlation is smaller than the previous simulation settings (since the X is a sparse matrix), so the other two methods has better power. Controlled for a FDR level of 0.2, all three methods achieve a high power of 80% very large signal at $\rho = 10$ in the Gaussian case. For the binary case, our proposed method shows greater advantage in achieving more than 2-times the power of the other two methods.

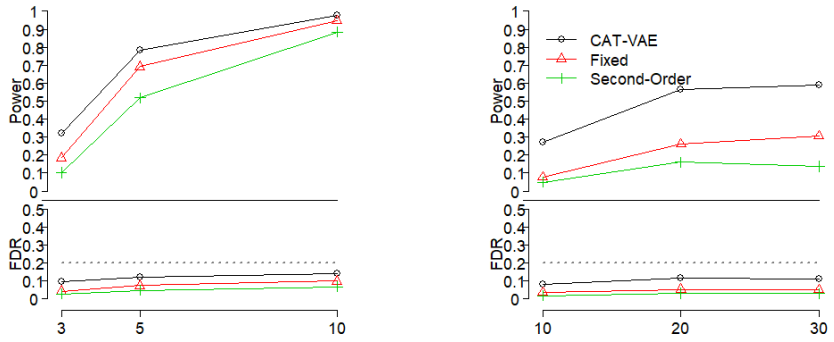
Table 1 presents the number of selected and matched selection of mutations with the 73 TSMs. Here we present results controlled by both Knockoff+ (as in (2)) and Knockoff (as in (1)) controlled

Table 1: Number of TRM mutations/ total number of selected mutations controlled for FDR at 0.2

		APV	ATV	IDV	LPV	NFV	RTV	SQV
	Sample Size	767	328	825	515	842	793	824
Knockoff+	CAT-VAE	28/28	8/31	34/49	27/37	42/54	38/48	39/52
	Fixed	25/25	2/10	0	0	0	35/44	23/25
	Second-Order	0	0	0	0	5/5	5/5	0
Knockoff	CAT-VAE	32/40	9/38	34/49	28/38	42/54	38/48	38/50
	Fixed	30/35	0	14/14	0	26/26	34/43	25/27
	Second-Order	24/24	4/11	4/4	17/24	29/29	35/42	17/17

at FDR level 0.2. Similar to the simulated settings, our proposed method select more mutations than the other methods, the average proportion of selected mutation that is in the TSM set for our proposed method is 75.3%, which demonstrate reproducibility across studies. With less conservative Knockoff procedure, Fixed and Second-Order methods are able to select more mutations, where our proposed method seems be less sensitive to choice of Knockoff or Knockoff+.

Implementation details For these analysis, the CAT-VAE knockoffs are generated for 186 mutations with ($\geq$ 4) occurrence in the data set and the number of patients is 846. Since each drug resistance outcome is observed in a subset of samples, when conduct analysis for each drug, we only consider mutations with ≥ 2 occurrence. Following analysis in Rhee et al. (2006), the outcome is a continuous variable, which is the log transformed drug susceptibility. For results in Figure 4, the linear signal is simulated as following: in each replication, randomly chose 50 predictors from 186 mutations , and compute μ as sum of ρx_j's with alternating signs. The Gaussian outcome is μ plus a standard normal noise and the binomial outcome is generated from Bernoulli$(\frac{1}{1+\exp(-\mu_i)})$.



(a) Gaussian, FDR= 0.2

(b) Binary, FDR= 0.2

Figure 4: Capture of simulated signals with real data generated knockoffs

7 Conclusion and Discussion

In this paper, we propose a knockoff generating framework based on a latent variable Z to decorrelate X. We noticed there are two independent works on deep learning generators for knockoff. (For double blind review consideration, I exclude the citations at this time.) Compared with other possible framework for deep generative models of knockoffs, our framework is the only framework directly target on the reconstruction of X from Z, as a surrogate to approximate the solution where X are mutually independent given Z. We illustrate such Z exists for a lot of general cases. Our framework offers a computational light solution, and if the data and variational model are compatible, our framework may offers an computationally efficient solution to be easily implemented by scientist on their own data set.

It calls for future research to compare these deep knockoff generators in terms of their goodness-of-fit of the generated knockoffs, and also in terms of their power and FDR control performance in simulated Y's. Notice that the non-convexity nature of the deep learning, makes it a hard problem to justify the FDR control from theoretical stand point. To solve this problem, one preprint on arXiv (name omitted for double blind review) proposed several goodness of fit statistics to compare deep generative models.

In addition to these metrics, the unique structure of our framework offers a diagnostic based on conditional independence as introduced in section 4. We include the graphical check in Appendix C. From these initial independence check for the two simulation settings and the real HIV dataset, the estimated Z does attenuate X's correlation. For the binary simulated X and HIV data set, the attenuation is closer to independence compared with the continuous simulated X. It remains for further investigation that if we can adjust the objective function of VAE to improve the goodness-of-fit in terms of independence. For example, adding a penalization term with the Maximum Mean Discrepancy metric between distribution of $X - f(\tilde{Z})$ and the element wise independent distribution from the product of marginal distributions.

To sum up, this paper propose a framework of deep knockoff generator based on latent variable Z. This framework, as a new application of the VAE and its variations, offers a computationally light solution to generate knockoffs. The promising numerical results demonstrated in this paper and the easiness of implementation makes it a promising tool among the choice of deep generating models for FDR controlled variables selection.

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A. Proof of Theorem 3.2

Proof: Consider $\tilde{\hat{X}}$ which is another independent sample from $Q_{X|Z}(x|z = Z; q_\epsilon)$ when sampling $\hat{X}$ using the same Z. Since q_ϵ is element-wise independent, conditions in Theorem 2.1 holds, thus $\tilde{\hat{X}}$ is a model-X knockoff of $\hat{X}$ and

$$\log\left(\frac{P(\hat{X}_j \in A_j, \tilde{\hat{X}}_j \in B_j, \hat{X}_{-j} \in A_{-j}, \tilde{\hat{X}}_{-j} \in B_{-j})}{P(\hat{X}_j \in B_j, \tilde{\hat{X}}_j \in A_j, \hat{X}_{-j} \in A_{-j}, \tilde{\hat{X}}_{-j} \in B_{-j})}\right) = 0.$$

Notice that by our assumptions

$$\sup_x |\log\left(\frac{p_{\hat{X}}(x)}{p_X(x)}\right)| \leq \sup_{x,z} |\log\left(\frac{p_{\hat{X}|Z}(x|z)}{p_{X|Z}(x|z)}\right)| = \sup_{x,z} |\log\left(\frac{q_\epsilon(x - \hat{f}(z))}{p_{\hat{\epsilon}}(x - \hat{f}(z))}\right)| \leq a_n$$

$$\sup_{x,\tilde{x}} |\log\left(\frac{p_{\tilde{\hat{X}}|\tilde{X}}(\tilde{x}|x)}{p_{\tilde{X}|X}(\tilde{x}|x)}\right)| = \sup_{x,z,\tilde{x}} |\log\left(\frac{\int q_\epsilon(\tilde{x} - \hat{f}(z)) p_{Z|\hat{X}}(z,x)dz}{\int q_\epsilon(\tilde{x} - \hat{f}(z)) Q_{Z|X}(z,x)dz}\right)| \leq \sup_{z,x} |\log\left(\frac{p_{Z|\hat{X}}(z|x)}{Q_{Z|X}(z|x)}\right)| \leq a_n$$

So $\sup_{x,\tilde{x}} |\log\left(\frac{p_{(\hat{X},\tilde{\hat{X}})}(x,\tilde{x})}{p_{(X,\tilde{X})}(x,\tilde{x})}\right)| \leq 2a_n$ and we can bound the log likelihood ratio by

$$\begin{aligned}
&\log\left(\frac{P(X_j \in A_j, \tilde{X}_j \in B_j, X_{-j} \in A_{-j}, \tilde{X}_{-j} \in B_{-j})}{P(X_j \in B_j, \tilde{X}_j \in A_j, X_{-j} \in A_{-j}, \tilde{X}_{-j} \in B_{-j})}\right) \\
= \quad &\log\left(\frac{P(\hat{X}_j \in A_j, \tilde{\hat{X}}_j \in B_j, \hat{X}_{-j} \in A_{-j}, \tilde{\hat{X}}_{-j} \in B_{-j})}{P(\hat{X}_j \in B_j, \tilde{\hat{X}}_j \in A_j, \hat{X}_{-j} \in A_{-j}, \tilde{\hat{X}}_{-j} \in B_{-j})}\right) + \log\left(\frac{P(X_j \in A_j, \tilde{X}_j \in B_j, X_{-j} \in A_{-j}, \tilde{X}_{-j} \in B_{-j})}{P(\hat{X}_j \in A_j, \tilde{\hat{X}}_j \in B_j, \hat{X}_{-j} \in A_{-j}, \tilde{\hat{X}}_{-j} \in B_{-j})}\right) \\
&+ \log\left(\frac{P(\hat{X}_j \in B_j, \tilde{\hat{X}}_j \in A_j, \hat{X}_{-j} \in A_{-j}, \tilde{\hat{X}}_{-j} \in B_{-j}))}{P(X_j \in B_j, \tilde{X}_j \in A_j, X_{-j} \in A_{-j}, \tilde{X}_{-j} \in B_{-j})}\right) \leq 0 + 2a_n + 2a_n = 4a_n
\end{aligned}$$

So we can bound

$$\max_{j=1,\cdots,p} \widehat{KL}_j \leq 8na_n^2 + 8\sqrt{n\log(p)}a_n.$$

And FDR has the bound in the statement by applying Lemma 2 in Barber et al. (2018). Specifically, if $a_n = o((n\log(p))^{-1/2})$, then FDR will be asymptotically bounded by $q + o(1)$.

B. Implementation Details for Neural Networks in Simulation

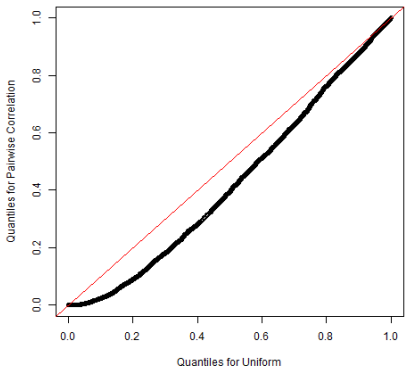
The latent variables are multivariate normal with 300 dimensions. The models were trained with batch size 25 and for 20 epochs with the default 'adam' optimizer in 'keras'Chollet et al. (2015). The architecture of VAE for setting 1 is as following, the encoder networks for μ_z and $\log(\sigma)$ have

two hidden layers with 500 and 400 neurons with 'tanh' activation and L_2 regularization with tuning parameter 0.2. The activation for the output layer is 'linear'. The decoder network has two hidden layers with the same specifications, followed by a batch-normalization layer and output with linear activation. The architecture of VAE for setting 2 is as following, the encoder networks has two hidden layers with 500 and 400 neurons with 'relu' activation and L_2 regularization with tuning parameter 0.3. The activation for the output layer is 'linear'. The decoder is an one layer network with the 'sigmoid' activation function and then threshold by 0.5.

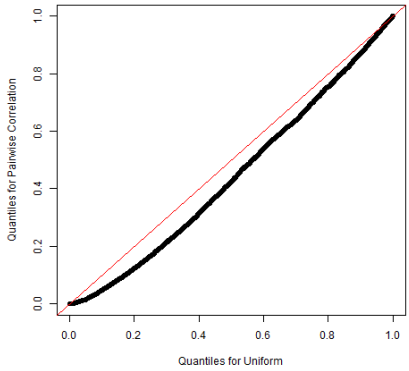
C. ILLUSTRATION FOR DISENTANGLEMENT OF Z.

Here we present the Q-Q plots for the p-values for pairwise correlation test for X and $X|Z$. Where the correlation of $X|Z$ is estimated as the pairwise correlation of $X - \hat{f}(\tilde{Z})$. When $X|Z$ are mutually independent, the p-values would be from the uniform distribution and the Q-Q plot will coincide with the diagonal line $y = x$. For the simulated settings, it is the result from one replication.

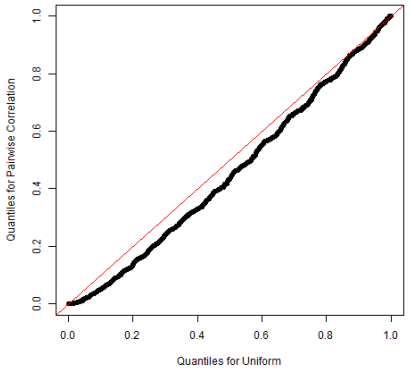
We see for the HIV real data example in Figure A1 (e) (f), the correlation is greatly attenuated by conditioning on Z. For the simulation studies, the Q-Q plot in setting 2 (Figure A1 (c) and (d)) almost coincide with the diagonal line after conditioning on Z, which indicates good fit of the model. Interestingly the above two settings, X's are binary. In simulation setting 1 (Figure A1 (a) and (b)), when X's are continuous, the disentanglement effect is still visible but not as strong as setting 2 and the HIV example.



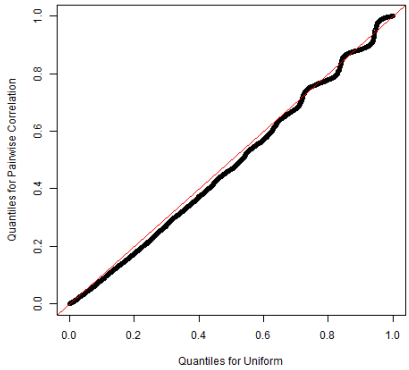
(a) Q-Q plot for p-values of correlation of X in simulation setting 1



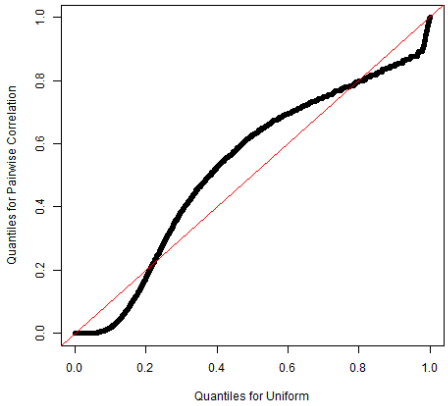
(b) Q-Q plot for p-values of correlation of $X - \hat{f}(\tilde{Z})$ in simulation setting 1



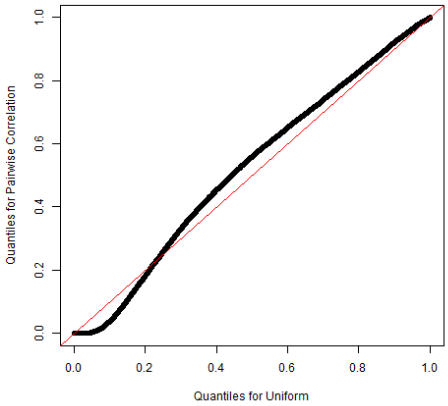
(c) Q-Q plot for p-values of correlation of X in simulation setting 2



(d) Q-Q plot for p-values of correlation of $X - \hat{f}(\tilde{Z})$ in simulation setting 2



(e) Q-Q plot for p-values of correlation of X in the HIV example



(f) Q-Q plot for p-values of correlation of $X - \hat{f}(\tilde{Z})$ in the HIV example

Figure A1. Illustration of Attenuation Effect of Z for X's Correlation.