Deep IV GWAS: Milestone

Category: Health / Genomics

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1 Introduction

The genome-wide association study (GWAS) is an experimental design used to detect associations between genetic variants and traits in samples from populations and has served as a main driver of understanding the relationship between gene expression and phenotype.[2,3] However, since traditional GWAS study designs run several thousand to million t-tests simultaneously they can only identify gene variants with large effect size. This is in contrast with the current hypothesis of genetic architecture that posits many gene variants acting in tandem to produce a phenotypic trait, each with small effect size.[4]

Despite the development of many sophisticated modern statistical techniques to deal with complicated interactions like the ones between genes, GWAS is plagued by counfoundedness. Gene expression and phenotype directly influence each other, rendering simple prediction or correlations between the two useless. While neural networks seem to provide the best ability to uncover complicated interactions between genes, they are not built to parse through endogeneity. To address these shortcomings we will employ the Deep IV methodology, a two-stage multiplayer perceptron model designed to use exogenous instruments z to identify the direct causal relationship of some policy variable p on outcome y. In our case, we want to use random gene mutations to characterize the causal effect of gene expression on phenotype.

@jandaraka Write about why this is such a big deal for GWAS and then why GWAS is such a big deal.

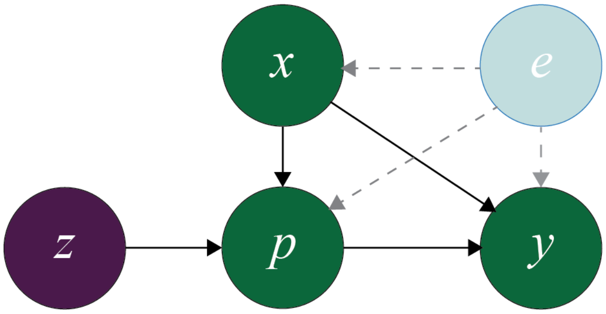
2 Algorithm

2.1 Overview

We implement the method described in "Deep IV: A Flexible Approach for Counterfactual Prediction" to identify the effect of a policy variable p on outcome y under confoundedness.[5] Instrumental variables (IV) are a well-developed tool for remedying endogeneity, but require a strong prior understanding of the data generating process and are not well equipped to deal with a large number of covariates. Deep IV promises to marry the best qualities of DNNs and IV, and we believe GWAS are a prime use case.

To perform IV analysis one needs to find an exogenous variable that affects the outcome variable only through the endogenous covariate of interest. More specifically, the instrument z must be conditionally independent of the error (Figure 1).

Figure 1: Generalized Deep IV



Traditional IV can be estimated through a procedure called two-stage least squares (2SLS): in the first stage you regress your endogenous variable of interest, p, on the exogenous instrument, z, to create a predicted $\hat{p}$ constructed only with the exogenous variation of z. In the second stage, you regress your outcome variable, y, on the predicted $\hat{p}$ from the first stage.[1]

2.2 Model Architectures

To adapt this procedure for the DeepIV method, we replace the two-stage least squares with two-stage multilayer perceptrons. We call the first stage our *policy network* and the second our *response network*. Our first iteration is modeled off of the specification in the appendix of the seminal DeepIV paper from Hartford et al. (2017).[6]

The policy and response networks have three hidden layers with 128, 64, and 32 hidden units respectively. The policy network takes in the exogenous z and control variables x as input to predict p using tanh acitvation functions for each layer and a mixture of Gaussian output with 10 components. The predicted $\hat{p}$ from the policy network and x are then fed into the response network to yield predictions $\hat{y}$. The repsone network performs ReLU activation functions for the three hidden layers and linear activation for the output.

Both networks use Adam Optimization with learning rate $= 0.001$, $\beta_1 = 0.9$, $\beta_2 = 0.999$, and $\epsilon = 1e - 08$. For training we use L2 weight decay with penalty parameter 0.001, a dropout rate of $\min(1000/(1000+n); 0.5)$, $(1.5 \times 10^6/n)$ epochs, and batch size 100.

3 Experiment

3.1 Motivation and Design

As a proof-of-concept, we evaluate our approach on simulated data, testing DeepIV's ability to recover an underlying causal relationship in a low-dimensional domain. We compared our DeepIV architecture to a single-stage feed-forward network with the same architecture as our DeepIV *response* stage.

3.2 Simulated Data

Our simulation models a DGP similar to that described in Section 2. For ease of explanation, we ground our simulation in a typical real-world IV application: estimating the effect of price on sales of some product (say, hotel bookings). We begin by assuming seven customer types, $s \in \{1, ..., 7\}$ which each exhibit different levels of price sensitivity. Customer price sensitivity varies according to a complex non-linear function of time.

$$\psi_t = 2\big((t-5)^4/600 + \exp\big[-4(t-5)^2\big] + t/10 - 2\big)$$
$$t \sim \text{unif}(0, 10)$$

Prices are a function of observed variable t and some instrument z, on the basis that the hotel chooses their price to move with average price sensitivity. In the hotel example, the high demand resulting from some unobserved confounding variable (e.g. a nearby conference) breaks the conditional independence between our policy variable p (price) and the latent effects e. We model this by generating our errors e with parameter ρ that denotes the correlation between p and e; in other words, it reflects the extent of endogeneity in our population model. Our outcome variable y (sales) is then generated as:

$$y = 100 + (100 + p)s\psi_t - 2p + e$$
$$p = 25 + (z + 3)\psi_t + v$$
$$z, v \sim \mathcal{N}(0, 1)$$
$$e \sim \mathcal{N}(\rho v, 1 - \rho^2)$$

The causal relationship we wish to uncover is $h(t, s, p) = (10 + p)s\psi_t - 2p$, but the correlation between the error e and p in our population model violates the unconfoundedness assumption necessary for causal interpretation, thus requiring the use of some instrument z.

Since we have our ground truth causal relationship, we evaluate our model by first generating features $[t, s, p]$, but then change p to a fixed grid of price values p'. This allows us to compare our predicted sales, $\hat{h}$ against the ground truth h.

3.3 Preliminary Results

Results of @billyf and @cwalker4 simulations.

[1] Chapter 4 of Angrist and Pischke's *Mostly Harmless Econometrics: an Empiricist's Companion* provides a good introduction to instrumental variables.

4 Data

@jandraka

5 Next Steps

This milestone was a proof of concept, showing that the DeepIV method effectively uncovers causal relationships that are glossed over by a naive Feed Forward Neural Net. Crucially, first implementing our architecture on simulated data provided a sanity check of our code before moving forward with our real life dataset where the true causal relationship is unknown.

Just recently we were granted access to breast cancer genetic data. The path forward entails cleaning this data, running our baseline model described above on the genetic data, and then tuning our hyperparameters. Additionally, we would like to include the standard 2SLS as another baseline to judge the effectiveness of the DeepIV architecture against the standard IV method.