Analysis of Encouragement Trials

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1 Introduction

Many studies with human subjects can be difficult or even unethical to conduct under normal circumstances. One issue is non-compliance, i.e. assignment of subjects to treatment does not ensure that the treatment is actually received. Another issue occurs when there is evidence that the treatment under consideration is clearly beneficial. Is it ethical to withhold this treatment for the sake of creating a control group?

These problems can be alleviated if the assignment, or encouragement, to a treatment and the actual receipt of the treatment are considered separately. In this arrangement, there are now two effects for the analyst to consider. First, we must consider the effect of encouragement on the receipt of the treatment. Secondly, but most importantly, we are interested in the direct effect of the treatment on the outcome.

Trials that are designed to address these issues are called *encouragement trials*. Imbens, Rubin, and others have developed a Bayesian based methodology for analyzing encouragement trials by treating encouragement as an instrumental variable. We will first review the fundamental concepts of instrumental variables and then review the Bayesian methodology for estimating direct causal effects of treatments.

2 Instrumental Variables and ITT Analysis

Instrumental variables are used to model a common situation in causal inference. Suppose we have a variable Z_i, a treatment variable W_i, and a response variable Y_i. If Z_i has a causal effect on Y_i without a direct casual effect on Y_i, i.e. the effect of Z_i passes through the treatment variable W_i, then Z_i is an instrumental variable. A simple diagram is shown below:

$$Z_i \rightarrow W_i \rightarrow Y_i$$

This diagram indicates that instrumental variables can be thought of as fitting multiple regressions, which is the approach we will see later.

Instrumental variables were first developed in the field of economics during the early 20th century and are still in use today. For an example in tourism economics, Thrane (2015) uses length of stay as an instrumental variable to predict total trip expenditure.

In the case of encouragement trials, the instrumental variable is usually the *assignment* to treatment, the effect of which first must pass through *receipt* of treatment and then to the outcome. Alternatively, we can think of this instrumental variables approach as a method that addresses non-compliance in the study.

The three traditional ways to handle non-compliance are *intention-to-treat* analysis (ITT), *per-protocol* analysis and *as-treated* analysis. ITT analysis considers the assignment and receipt of treatment to be one and the same and therefore analyzes subjects as they are assigned to treatment groups, regardless of whether the subjects actually receive the correct treatment. On

the other hand, per-protocol analysis drops participants who do not receive treatment, receive treatment when not assigned, or, more generally, receive the incorrect treatment based on their assignment. Finally, in an as-treated analysis, subjects are analyzed as the treatment they actually took, but this time they are included in the analysis instead of dropping them as in an a per-protocol analysis. These methods of handling non-compliance have shortcomings. Both *per-protocol* and *as-treated* analyses are naive in that they ignore the initial randomization of encouragement, which leads to biased estimates of the treatment effect for each "principle compliance strata", which will be defined later. ITT can give better estimates than the naive methods, but it ignores the actual treatment effect and we are therefore left with only the effect of the encouragement on the response'. However, to answer the scientific question of how the treatment affects the outcome, we need to estimate the causal effect of the *treatment* and not the causal effect of the assignment or the encouragement of treatment.

At an initial glance this might seem difficult, but there are some simple ways to disentangle these causal effects. For example, to estimate the causal effect of the treatment W_i on the outcome Y_i, given 2 simple assumptions , Imbens and Rubin propose the *Local Average Treatment Effect* (LATE)

$$\tau_{late} = \text{ITT}_{Y,co} = \frac{\text{ITT}_Y}{\text{ITT}_W}$$

where ITT_Y is the intention to treat effect on the outcome and ITT_W is the intention to treat effect on the receipt of treatment. In other words, it is possible to estimate the causal effect of the treatment by combining two

intention to treat analyses. The assumptions needed are:

1. Assignment has no effect on the outcome for noncompliers

2. Assignment has no effect on the outcome for compliers.

Things can get more complicated as assumptions change, but this example should give some of the flavor of the types of analyses that are possible using an instrumental variables approach.

Note while this discussion has been very informal for ease of understanding, there is a mathematical formulation of these topics using Rubin's potential outcomes causal model. Future sections will define concepts with more formal mathematical notation.

3 Analyzing an Encouragement Trial: A Practical Example

Hirano, Imbens, Rubin, and Zhou (2000) present a framework for analyzing encouragement trials using instrumental variables and Bayesian methods. They then use this framework to analyze the results of an influenza encouragement trial.

In the trial, physicians were randomized to encouragement and control groups. Physicians in the encouragement group were sent a reminder when one of their patients was eligible to receive the influenza vaccine. This structure allows the researchers to observe the effect of higher vaccine usage in a group without explicitly withholding it from the control group.

Let Z_i^{obs} be the instrumental variable that assigns doctor i to either the encouragement ($Z_i^{obs} = 1$) or control group ($Z_i^{obs} = 0$). Similarly, let the treatment variable D_i^{obs} be equal to 1 if the patient received the influenza vaccine and let the response variable Y_i^{obs} equal 1 if the patient was hospitalized for influenza in the following flu season. Otherwise, $Z_i^{obs}, D_i^{obs}, Y_i^{obs}$ will be equal to 0. Therefore we wish to investigate the following relationship.

$$Z_i^{obs} \rightarrow D_i^{obs} \rightarrow Y_i^{obs}$$

The authors first start by estimating the ITT effect, which can formally be defined as

$$ITT = \frac{1}{N}\sum_{i=1}^{N}(Y_i(1) - Y_i(0))$$

where $Y_i(z)$ is the outcome of patient i for $Z_i^{obs} = z$, $z = 0, 1$. Note that either $Y_i(1)$ or $Y_i(0)$ is observed but not both at the same time. This naturally leads to a missing data problem, which can easily be handled from a Bayesian perspective.

Since this is an ITT analysis, we need only model the relationship

$$Z_i^{obs} \rightarrow Y_i^{obs}$$

Because Y_i^{obs} is a binary variable, the authors used logistic regression to model the probability of hospitalization of a patient given that their doctor received the encouragement. Note that the use of a regression model allows for the inclusion of covariates X_{i1}^{obs} and X_{i2}^{obs}, which are in this case age and an indicator for chronic obstructive pulmonary disease. Their full model

therefore is

$$P\left(Y_i^{obs} = 1 | Z_i^{obs}, X_{i1}^{obs}, X_{i2}^{obs}\right) = \frac{\exp\left(\beta_0 + \beta_1 Z_i^{obs} + \beta_2 X_{i1}^{obs} + \beta_3 X_{i2}^{obs}\right)}{1 + \exp\left(\beta_0 + \beta_1 Z_i^{obs} + \beta_2 X_{i1}^{obs} + \beta_3 X_{i2}^{obs}\right)}$$

Usually for logistic regression, we would directly be interested in the regression parameters, but in this case we are more interested in the predictions made by the model. We can use the fitted model to fill in the missing $Y_i(1)$ and $Y_i(0)$ potential outcomes and in turn use these to estimate ITT.

Applying a Bayesian approach, the authors end up with a posterior distribution of ITT effects with posterior probability $P(ITT_{posterior} < 0) = 0.97$. Therefore, one could reasonably conclude that sending reminders to physicians decreases flu hospitalizations.

However, this analysis is not very interesting if you want to know the effect of the flu vaccine itself. The effect that we see in this study might just be from the assignment of encouragement to the doctors and might not have anything to do with whether or not the vaccine was actually administered. Therefore, we will have to disentangle the treatment effect from the encouragement effect.

Imbens, Hirano, Rubin, and Zhou analyze the direct effect of the vaccine using the instrumental variable approach discussed earlier. To do this, they categorization patient units into 4 different classes based on compliance behavior. Let $D_i(z)$ be an indicator that represents the receipt of the vaccine

given the encouragement $Z_i = z$. Therefore, D defines the classes as

$$C_i = \begin{cases} c & D_i(z) = z \\ n & D_i(z) = 0 \\ a & D_i(z) = 1 \\ d & D_i(z) = 1 - z \end{cases}$$

Thus we have compliers, never-takers, always-takers, and defiers respectively. For each of these classes, we can consider the probability of hospitalization given Z_i, i.e. $P(Y_i(Z_i, D_i(Z_i))$. There are 4 classes of compliance behavior and 2 levels of Z_i so we will need to model 8 different probabilities using logistic regression similar to the ITT analysis.

However, the authors note that if the assumption

$$D_i(1) \geq D_i(0)$$

is made, then the number of probabilities to model decreases to 6. In words, this statement makes the assumption that there are no defiers. The authors justify this assumption by reasoning that the encouragement to vaccinate can only increase the the actual receipt of the vaccine.

Ten Have, Elliot, Joffe, Zanutto, and Datto (2004) address this assumption in more detail. They note that in some contexts, for example in doctors treating depression, defiers exist and can have a significant effect on the results if not included as part of the analysis. Their work suggests that it could be helpful for Imbens, Hirano, Rubin, and Zhou to include a sensitiv-

ity analysis of the no defiers assumption. Unfortunately, such an analysis is not included so the sensitivity of the model to the no defiers assumption is unknown.

Note that the compliance behavior class C_i is unobserved and will have to be estimated from the observed data. To do this, the authors use the multinomial logistic regression model to model the probabilities

$$P(C_i = c|X_{i1}, X_{i2}), P(C_i = n|X_{i1}, X_{i2}), P(C_i = a|X_{i1}, X_{i2})$$

Combining this regression with the earlier logistic regression for $P(Y_i(Z_i, D_i(Z_i))$, the authors obtain a likelihood function for the observed data, which they combine with a vague proper prior distribution to obtain the posterior distribution.

Based on this posterior, the authors conclude that the there is little evidence that the influenza vaccine had any benefit. They reach this conclusion by noting that the effect of encouragement seems to be the same for always-takers and for compliers, i.e. the actual receipt of the vaccine did not matter. Therefore, the ITT analysis overstates the effectiveness of the shot.

In summary, the bayesian instrumental variables approach presented by Imbens, Hirano, Rubin, and Zhou is a very powerful tool for determining the casual effect of a treatment in an encouragement trial because it allows for analysis by compliance behavior type, incorporation of prior information, and handling of different stability assumptions not mentioned.

4 Clustering in Encouragement Trials

Recall that in the influenza trial described in Imbens, Hirano, Rubin, and Zhou assigned encouragement to individual doctors who then would be responsible for delivering the treatment to their groups of patients. This introduces a natural clustering where the effect might differ with each doctor having his or her own distribution of effects. Frangakis, Rubin, and Zhou (2002) generalize the methods in the previous paper to account for the physician-level clustering.

Similar to the last model, we will model classification of each physician into"compliance principal strata" and then model the potential outcome using the results from the classification. As before, these will be logistic regression models, but this time with a probit link function in stead of a logit. The authors do not explain the change in link function, but it does not matter too much since we do not care about interpreting the regression coefficients. If for patient i, X_i is the vector of observed covariates, Q_i is the physician of patient i, and W_i is the vector of covariates in X_i that vary from physician to physician, then we have the models

$$P(C_i = n|X_i, Q_i) = 1 - \Phi(X_i'\alpha^{(C,1)} + W_i' b_{Q_i}^{(C,1)})$$

$$P(C_i = c)|X_i, Q_i) = [1 - P(C_i = n|X_i, Q_i)] \left[1 - \Phi(X_i'\alpha^{(C,2)} + W_i' b_{Q_i}^{(C,2)})\right]$$

where $\alpha^{(C,1)}$, $\alpha^{(C,2)}$, $b_{Q_i}^{(C,1)}$, and $b_{Q_i}^{(C,2)}$ are parameter vectors. Note that the $b_{Q_i}^{(C,1)}$ and $b_{Q_i}^{(C,2)}$ are specific to each physician, i.e. this is a mixed effects model where the physicians are considered to be sampled from some larger

population.

The potential outcomes are modeled as

$$P(Y_i(z) = 1|C_i = t, X_i, Q_i) = \Phi\left(f^{(1)}(X_i, t, z)\alpha^{(Y)} + f^{(2)}(W_i, t)b^{(Y)}_{Q_i}\right)$$

Similar to the last model, $\alpha^{(Y)}$, $b^{(Y)}_{Q_i}$ are parameter vectors with $b^{(Y)}_{Q_i}$ being unique to each physician. $f^{(1)}$ and $f^{(2)}$ are link functions with some flexibility in how they can be defined. In their example, Frangakis et. al. specify $f^{(1)}$ and $f^{(2)}$ using indicator functions in order to define effects for each compliance strata. Also note that the physician-level effects are assumed random with distribution

$$(b^{C,1}_q, b^{(C,2)}_q, b^{(Y)}_q)|D^{(b)} \sim N(0, D^{(b)})$$

Similar to the simpler model from last time, these component models are combined in order to estimate the joint distribution $P(D_i, Y_i, X_i, Q_i)$. This combined model is then used to generate the missing potential outcomes in order to estimate the ITT effect.

Frangakis et. al. were able to apply this model to analyze a study were doctors were reminded to discuss advanced directive (AD) forms with patients in order to increase the percentage of forms being completed. An initial IIT analysis showed that the encouragement of physicians only increased the completion rate of AD forms by 11%. However, approximately 75% of the physician-patient pairs did not discuss the forms, despite being in the encouragement group. Because there was such a large imbalance in

the compliance classes, Frangakis et. al. were interested in the effect of the discussion, i.e. when the doctor and patient actually had the conversation, on AD form completion. This group of doctors and patients are the compliers. After fitting the instrumental variable model with clustering, the results were that the effect had a posterior mean of a 62% increase in completion rate with 95% posterior interval of (34.7, 79.5). In other words, the causal effect of the discussions was much larger than what the ITT analysis initially showed.

5 Conclusion

In this report, we reviewed the fundamental concepts of encouragement trials and how causal effects can be estimated using instrumental variables. To give an idea of how this approach is actually used, we reviewed two papers, one by Imbens et. al. and the other by Frangakis et. al., that show how to use the Bayesian instrumental variable approach to estimate causal effects of the treatment in encouragement trials. Like many topics in causal inferences, the techniques presented in these papers are clever uses of standard statistical tools that are powerful, yet easy to understand.

6 References

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