1. Abstract

This research considers the problem of assessing causal effect moderation in longitudinal settings in which treatment/exposure is time-varying and so are the covariates said to moderate its effect. Conditional Intermediate Causal Effects that describe time-varying causal effects of treatment conditional on past covariate history are introduced and considered as part of Robins’ Structural Nested Mean Model (SNMM). Two estimators of the intermediate causal effects are presented and discussed. The first is a proposed 2 Stage Regression Estimator, which can be implemented using standard regression software. The second is Robins’ G-Estimator. We present preliminary results of simulation studies that aim to understand some of the asymptotic and small sample properties of the two estimators. The methodology is motivated by the PROSPECT Study. The objective is to model the time-varying effects of adherence to the randomized PROSPECT intervention, conditional on time-varying covariates that may modify these effects. The outcome of interest is end of study levels of depression.

2. The Time-Varying Setting

Baseline
4-month Visit
8-month Visit
Suicidal
Ideation
0
Suicidal
Ideation
40 to 4 Months
Adherence
4 to 8 Months
Adherence

3. Conceptualizing Time-Varying Effect Moderation

The Conditional Intermediate Causal Effect at \( t = 8 \): The \( k = 2 \) Time-Point Effect

\[
\mu_{2}(s_k, a_k) \equiv E\left( Y(\alpha_1, \alpha_2) - Y(\alpha_1, 0) \mid S_k(a_k) = s_k \right)
\]

The Conditional Intermediate Causal Effect at \( t = 4 \): The \( k = 1 \) Time-Point Effect

\[
\mu_{1}(s_k, a_k) \equiv E\left( Y(\alpha_1, 0) - Y(0, 0) \mid S_k(a_k) = s_k \right)
\]

4. Two Problems With The Classical Regression Model

\[
E(Y(a_1, a_2) \mid \tilde{S}_1(a_1) = \tilde{s}_1) = \beta_0^\ast + \eta s_0 + a_1 \times (\beta_1^\ast + \beta_2^\ast s_0) + \eta s_1 + a_2 \times (\beta_1^\ast + \beta_2^\ast s_0)/2
\]

Problem 1: Are You Getting the Effect You Really Want?

Baseline 4-month Visit 8-month Visit

Problem 2: Spurious Effects Due to Covariates \( V_1 \) that Affect \( S_1(a_1) \) and \( Y(a_1, a_2) \)

5. Robins’ Structural Nested Mean Model

\[
E(Y(\alpha_1) \mid \tilde{S}_1(a_1)) = \beta_0 + \epsilon_1(s_0) + \mu_1(s_0, a_1) + \epsilon_2(s_1, a_2) + \mu_2(s_1, a_2),
\]

where \( \beta_0 \) is an intercept term.


Does Not Require Models for the Nuisance Functions

Set the following equations to zero and solve for \( (\beta_1, \beta_2) \):

\[
P_n\left( Y - H_{2A_0} - b_2(S_0, A_1) \right) + \left( Y - H_{A_2} - H_{A_1} \beta_1 - b_3(S_0) \right) \times \left( A_1 - p_1(S_0) \right) = \Delta(H_{1A_1}) \times \left( H_{1A_1} \right)^T
\]

7. Estimation II: Parametric 2-Stage Regression Estimator

Requires Models for the Nuisance Functions

Models for the nuisance functions must have conditional mean zero; they may take the following form:

\[
\epsilon_1(S_0, s_0, \gamma_1) = \eta_1(s_0 - m_0(\gamma_1)) = \eta_1 G_1(\gamma_1)
\]

where \( m_0(\gamma_1) = E(S_0) \), and \( m_0(\gamma_1) = E(S_0 | S_0, A_1) \).

Stage 1: Estimate \( \gamma_1 \) and \( \gamma_2 \) using GLM, and calculate \( G_1(\gamma_1) \) and \( G_2(\gamma_2) \)

Stage 2: OLS Regression of \( Y \sim [1, G_1(\gamma_1), H_1 G_2(\gamma_2), H_2] \)

Both estimators require the assumption of Sequential Ignorability for appropriate causal inference.

8. Simulation Experiments: Bias-Variance Trade-off

Mis-specifying the 2-Stage Estimator using a Multiplicative Error Method

Mis-specify the 2-Stage Estimator by replacing \( \hat{S} \) in the models for the nuisance functions (in both \( m_0, G_1, G_2 \) by \( \hat{S} \times \omega \), where \( \omega \sim N(1, \epsilon) \)

Correctly specified estimator when \( \epsilon = 0 \)

Compare Mean Squared Error of G-Estimator versus Miss-specified 2-Stage Estimator

Results with \( K = 3 \) time points, \( N = 3000 \) data sets, and sample size \( n = 500 \)