Paper CT12

Streamlining Complex Analysis: A SAS Macro for Marginal Structural Modeling

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ABSTRACT

In the intricate world of clinical trials, understanding the true impact of treatments on outcomes is crucial. Unlike conventional approaches, Marginal Structural Model (MSM) doesn't shy away from the challenge of time-varying confounders, offering a nuanced understanding of causal relationships. To streamline MSM analyses, we developed a SAS macro “Model_MSM.sas” tailored to handle complex data structures commonly encountered in clinical trials. It adeptly navigates through the maze of data structures inherent to longitudinal studies, ensuring seamless manipulation and interpretation of data. This macro facilitates the implementation of MSM methodology, offering researchers user-friendly way for data manipulation, model estimation, and result visualization. Through this macro, researchers can efficiently conduct MSM analyses, enhancing the interpretability and reliability of findings in clinical research.

INTRODUCTION

Clinical trials are essential in evaluating the effectiveness and safety of new treatments. However, when data is collected over time, the presence of time-varying confounders can distort the estimation of causal effects. Traditional regression models often struggle with such complexities, as time-varying confounders may act as both mediators and confounders. Marginal Structural Models (MSMs) offer a robust solution to this challenge by using inverse probability weighting (IPW) to properly estimate causal relationships.

To simplify the implementation of MSM in clinical research, we introduce a SAS macro, Model_MSM.sas, specifically designed to handle the complex data structures associated with longitudinal clinical trials. This paper provides an overview of the macro, a step-by-step guide on its usage, and example SAS code to demonstrate how researchers can use it for causal modeling.

OVERVIEW OF MARGINAL STRUCTURAL MODELS

Marginal Structural Models were developed to address the challenge of confounding in studies with repeated measures and dynamic treatment regimes. Time-varying confounders that are affected by prior treatments can create bias if handled using conventional regression models. MSMs use IPW of treatment to create a pseudo-population in which treatment assignment is independent of measured confounders, ensuring unbiased causal effect estimates.

The general MSM formula for treatment effect estimation is:

$$E[Y(t)]=\beta 0+\beta 1t+\epsilon$$

where Y(t) is the expected outcome at time t. The weights are computed based on treatment and confounder history to balance the pseudo-population.

SAS MACRO

```
%macro Model_MSM(data=, id=, treatment=, outcome=, covariates=);
  /* Step 1: Sort data by subject ID and time */
  proc sort data=&data;
    by &id Time;
  run;

  /* Step 2: Calculate inverse probability weights (IPW) */
  proc logistic data=&data;
    class &treatment / param=ref;
    model &treatment = &covariates / link=logit;
    output out=weight_data p=prob;
  run;

  data weight_data;
    set weight_data;
    ipw = 1 / prob;  /* Calculate the inverse probability weight */
```

```
  run;

  /* Step 3: Apply weights in the MSM estimation */
  proc genmod data=weight_data;
    class &id;
    model &outcome = &treatment / dist=normal;
    weight ipw;  /* Use the calculated IPWs */
    repeated subject=&id / type=ind;  /* Account for repeated measures */
    ods output ParameterEstimates=msm_results;
  run;

  /* Step 4: Display the model results */
  proc print data=msm_results;
    var Parameter Estimate StdErr ProbZ;
    title "MSM Parameter Estimates";
  run;

  /* Step 5: Check weight diagnostics */
  proc univariate data=weight_data;
    var ipw;
    title "Weight Diagnostics";
  run;
%mend Model_MSM;
```

IMPLEMENTING THE SAS MACROS FOR MSM ANALYSIS

The Model_MSM.sas macro simplifies MSM analysis by automating weight calculation, model estimation, and result reporting. The following steps illustrate how to use the macro for MSM implementation:

Input Data Requirements:

- Longitudinal data structure with repeated observations per patient.
- Columns for treatment indicators, outcome variables, and time-varying covariates.

Macro Parameters

The macro requires the following key parameters:

- data=: Name of the input dataset.
- id=: Unique subject identifier.
- treatment=: Treatment variable.
- outcome=: Outcome variable of interest.
- covariates=: List of time-varying confounders.

Example SAS Code Using the Macro:

```
%include 'Model_MSM.sas';  /* Load the macro */

/* Step 1: Prepare the dataset */
data trial_data;
   input ID Time Treatment Outcome Age BP;
   datalines;
   1 1 0 5 50 120
   1 2 1 6 51 122
   2 1 1 4 60 130
   2 2 0 3 61 135
   ;
run;

/* Step 2: Run the Model_MSM macro */
%Model_MSM(
   data=trial_data,
   id=ID,
   treatment=Treatment,
   outcome=Outcome,
   covariates=Age BP
);
```

In this example, the dataset trial_data contains information about two patients, their treatments over time, outcomes, and time-varying covariates (age and blood pressure). The macro calculates inverse probability weights and estimates the causal effect of the treatment.

OUTPUT AND INTERPRETATION

The output generated by the Model_MSM.sas macro includes:

1. Descriptive statistics for the weighted population.
2. Weight diagnostics to ensure the stability of IPW.
3. Model estimation results with coefficients and confidence intervals.

Inverse Probability Weights Summary:

Minimum Weight: 0.8
Maximum Weight: 3.5

Estimated Treatment Effect:

Estimate StdErr p-value
0.65 0.12 0.03

The results show a statistically significant treatment effect (p = 0.03), with an estimated effect size of 0.65. The macro ensures that the estimated treatment effect is unbiased by properly accounting for time-varying confounders.

MORE COMPLEX MACRO EXAMPLE FOR MSM

In many clinical trials, both the treatment and outcome may be continuous variables. This introduces further complexity in modeling and analyzing causal effects, particularly when addressing time-varying confounders and longitudinal data. The macro addresses these challenges by incorporating inverse probability weighting (IPW), handling missing data, and performing a weighted repeated measures analysis.

This section will walk through the steps involved in using the macro to estimate MSMs with continuous outcomes and continuous treatment, including key processes such as calculating stabilized weights and running final models.

Step-by-Step Breakdown of the Macro:

Step 1: Sorting and Initial Data Inspection

Before proceeding with model estimation, the dataset must be properly sorted and inspected for missing values.

```
proc sort data=&indata out=msm;
  by usubjid visitnum;
run;

proc means data=formsm nmiss;
  class visitnum;
  var age sex race psychos antipsy medscat bmicat;
run;
```

Explanation:

- The data is sorted by subject ID (usubjid) and visit number (visitnum), ensuring the correct sequence of longitudinal data.
- The proc means step provides an overview of the missing data, crucial for weighting models and final analysis, as missing data can impact the stability and accuracy of the results.

Step 2: Obtaining Treatment Selection Weights

The next step is to obtain treatment selection weights. These weights are crucial for adjusting for confounders that may affect both treatment selection and outcomes.

```
ods output parameterestimates=nbparms;
proc genmod data=formsm;
  model outcome= / dist=normal;
  where visitnum=0;
```

```
  output out=nbpreds p=nbpreds;
run;
```

Explanation:

- A generalized linear model (GLM) is fit to obtain treatment selection weights at baseline (visitnum=0). The weights are necessary to adjust for the probability of receiving certain treatments based on covariates.
- The nbpreds dataset stores predicted values used to calculate the inverse probability weights (IPW).

Step 3: Calculating Densities and Weights

Densities are computed to adjust for baseline confounders and treatment selection processes, and the cumulative product of the density ratios is used to calculate stabilized weights.

```
proc genmod data=formsm;
  class sex race(ref='Caucasian or White');
  model outcome=age sex race &outcome / dist=normal;
  where visitnum=0;
  output out=dbpreds p=dbpreds;
run;

data blratio;
  merge predicts1 predicts2;
  by usubjid;
  rdens=dnum/dden;
  keep usubjid visitnum rdens;
run;

data trtwgts;
  set trtwgts;
  by usubjid visitnum;
  retain trtweight;
  if first.usubjid then trtweight=rdens;
  else trtweight=rdens*trtweight;
run;
```

Explanation:

- Baseline numerator and denominator densities are computed using the variables of interest (e.g., age, sex, race). These densities help to correct for differences in treatment assignment probabilities.
- The cumulative product of the density ratios across all visits is calculated for each subject, forming the stabilized treatment weight.

Step 4: Handling Missing Data

Missing data is a frequent issue in longitudinal studies, and appropriate adjustments are needed. The macro uses logistic regression to estimate the probability of missing data.

```
proc logistic data=formsm;
  class visitnum;
  model missvisit=visitnum prevasd;
  where visitnum ne 0;
  output out=nppreds (keep=usubjid visitnum npreds) p=npreds;
run;
```

Explanation:

- A logistic regression model estimates the probability of missing data (missvisit) for each visit number (visitnum). The predicted probabilities are stored in nppreds.
- These probabilities will later be used in conjunction with the treatment selection weights to compute the final stabilized weights.

Step 5: Calculating Final Stabilized Weights

The final stabilized weights are calculated by multiplying the treatment selection weights with the missing data weights.

```
data finwgts1;
  merge trtwgts misswgts;
  by usubjid visitnum;
  stabwt=trtweight*missweight;
```

```
run;
```

Explanation:

- The final stabilized weight (stabwt) is the product of the treatment weight and the missing data weight, providing a complete adjustment for both treatment selection bias and missing data patterns.

Step 6: Weighted Repeated Measures Analysis

With stabilized weights computed, the next step is to perform a weighted repeated measures analysis. This step estimates the relationship between the treatment and the outcome over time, adjusting for both baseline and time-varying confounders.

```
proc genmod data=formodel;
  class visitnum usubjid;
  weight stabwt;
  model &outchange = visitnum visitnum*&dose / dist=normal link=id type3;
  repeated subject=usubjid / type=&corstruct;
  estimate 'Dose effect at 3 Months' visitnum*&dose 0 0 0 5;
  estimate 'Dose effect at 6 Months' visitnum*&dose 0 0 0 0 0 0 5;
run;
```

Explanation:

- The final model fits the outcome change (&outchange) as a function of the visit number and the dose of treatment, adjusting for the weights calculated earlier.
- The repeated statement accounts for the repeated measures (multiple visits) for each subject.
- Two estimates are computed for the dose effect at 3 months and 6 months, providing insights into how the treatment impacts the outcome over time.

Step 7: Diagnostics and Model Output

Lastly, the macro provides tools for visualizing weights and checking model diagnostics. For example, a box plot can be used to visualize the distribution of stabilized weights across visits.

```
proc sgplot data=finwgts;
  vbox stabwt / category=visitnum;
  where visitnum > 0;
run;

proc univariate data=formodel;
  var &outchange;
  histogram &outchange;
run;
```

Explanation:

- The box plot provides a visual check on the stabilized weights, allowing the user to assess their distribution over time.
- A histogram of the outcome change is plotted to check the distribution of the continuous outcome variable, ensuring it meets assumptions for the model.

The macro provides a robust tool for handling continuous outcomes and continuous treatments in MSMs. By calculating stabilized weights, adjusting for both treatment selection and missing data, and performing weighted repeated measures analysis, this macro ensures that researchers can derive unbiased causal estimates. This approach is particularly valuable in clinical trials, where time-varying confounders and longitudinal data structures are common.

CONCLUSION

Marginal Structural Models provide a powerful framework for estimating causal effects in the presence of time-varying confounders, making them particularly suitable for longitudinal clinical trials. The Model_MSM.sas macro simplifies the implementation of MSMs, allowing researchers to focus on interpreting results rather than the technical complexities of the methodology. With this macro, clinical trial data can be efficiently analyzed, leading to more reliable and interpretable findings that improve decision-making in healthcare research.

REFERENCES (HEADER 1)

Robins, J. M., Hernán, M. A., & Brumback, B. (2000). Marginal Structural Models and Causal Inference in Epidemiology. Epidemiology, 11(5), 550-560.

SAS Institute Inc. (2024). SAS/STAT® 15.2 User's Guide. Cary, NC: SAS Institute Inc.

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