Synthetic and negative control evaluation framework for large-scale propensity score survival analysis

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Propensity Score Adjustment

- PS = estimated probability of treatment assignment address confounding in observational studies
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How is the PS Estimated?
Propensity Score Adjustment

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How is the PS Estimated?

Logistic Regression
Propensity Score Adjustment

- PS = estimated probability of treatment assignment address confounding in observational studies

How is the PS Estimated?
- Logistic Regression

How are Covariates Selected?
Propensity Score Adjustment

- PS = estimated probability of treatment assignment address confounding in observational studies

How is the PS Estimated?
Logistic Regression

How are Covariates Selected?
Thousands of potential confounders
PS Model Selection

• Traditionally: Investigator Selection

• high-dimensional Propensity Score algorithm (hdPS) univariate screen for significant covariates based on exposure or outcome association

  “exposure-based” : relative risk with treatment exposure
  “bias-based” : relative risk with outcome of interest

• L1-regularization (LASSO) multivariate model selection via penalized likelihood coefficients of unimportant covariates shrunk to zero
Study Goals

• Detail framework to evaluate propensity score estimation method performance
  
  - simulations
  
  - negative control experiments

• Use evaluation to compare:
  
  - hdPS Algorithm : “exposure-based” and “bias-based”
  
  - L1-regularization (LASSO)
PS Details

- **hdPS Algorithm** prescribes a certain set of data preprocessing:
  - aggregate covariates by coding
  - limit considered covariates to most prevalent
  - augment covariates by individual level frequency
  - 180 day lookback windows

- **FeatureExtraction default** uses more expansive set of covariates
  - eras, exposures, observations, measurements, scores
  - 30 day, 365 day, all day lookback windows

- We used **L1-regularization on both (hdPS and CDM)**
Simulations

• Keep treatment exposure and covariates from real-world data

• Simulate outcomes times under a survival model

• Simulate under known hazard ratio and with different outcome prevalences

• Extends the “plasmode” framework by Franklin et al. (2014)
Simulations

• Simulate realistic survival data under a known hazard ratio in Cox proportional hazards model

Empirical Cohorts Data

- Empirical values
- Fitted Cox regression
- Breslow estimator
- Nelson-Aalen estimator

Cox Model Components:

- Treatment data
- Covariate data
- Covariate effect sizes
- Baseline survival function
- Censoring function
Negative Control Experiments

- Downside to simulations:
  Do not capture full complexity of real-world data

- Negative controls:
  Outcomes unaffected by the studied treatments

Dabigatran \rightarrow \text{Outcome of Interest: Major Bleeding} \rightarrow \text{Warfarin}

Unknown relative hazard ratio
Negative Control Experiments

- Downside to simulations:
  Do not capture full complexity of real-world data

- Negative controls:
  Outcomes unaffected by the studied treatments

Dabigatran \[\rightarrow\] Negative Control Outcome: Lyme Disease \[\rightarrow\] Warfarin

Presumed relative hazard ratio: 1
Empirical Data Used - Anticoagulants

- Replication of dabigatran vs warfarin observational study by Graham et al. (2014)
- Database: Truven Health Marketscan Medicare Supplemental and Coordination of Benefits Database
- Cohorts:
  - 19768 dabigatran users, 52721 warfarin users
  - 192 intracranial hemorrhage 0.26%
  - 98118 unique covariates
PS Distribution

AUC: 0.793

L1 Regularization (CDM)

AUC: 0.760

L1 Regularization (hdPS)

AUC: 0.737

exposure-based hdPS

Empirical:

bias-based hdPS (empirical)

AUC: 0.747
PS Distribution

AUC: 0.793

L1 Regularization (CDM)

AUC: 0.760

L1 Regularization (hdPS)

AUC: 0.747

exposure-based hdPS

AUC: 0.742

bias-based hdPS (simulation)

Empirical:

Simulation:
Covariate Balance

• standardized difference of covariates before and after propensity score matching

Which covariates to consider?

• All covariates

• “true confounders”
  - approximated by simulation model covariates
  - note: these include “hdPS Algorithm Covariates” and “CDM Covariates”
All Covariates

10:1 variable ratio matching
All Covariates

10:1 variable ratio matching
Simulation Model Covariates

10:1 variable ratio matching
Simulation Model Covariates

10:1 variable ratio matching
Bias Reduction: Simulations

Simulation Estimation Bias

Simulation Parameters

- HR: 1.0 | OP: 0.5%
- HR: 1.5 | OP: 0.5%
- HR: 2.0 | OP: 0.5%
- HR: 1.0 | OP: 1%
- HR: 1.5 | OP: 1%
- HR: 2.0 | OP: 1%
- HR: 1.0 | OP: 5%
- HR: 1.5 | OP: 5%
- HR: 2.0 | OP: 5%
- HR: 1.0 | OP: 10%
- HR: 1.5 | OP: 10%
- HR: 2.0 | OP: 10%

log HR bias

method
- L1-Reg (CDM)
- L1-Reg (hdPS)
- exp-hdPS
- bias-hdPS
- unadjusted

Outcome
Dependent
Metric

10:1 variable ratio matching
Bias Reduction: Simulations

Simulation Estimation Bias

Outcome Dependent Metric

10:1 variable ratio matching
Simulation Bias

Survival Simulation; consider 1:1 matching

\[ \hat{\eta} = \log N_1 - \log N_0 \]

\( N_1 \): exposed has event, time before unexposed
\( N_0 \): unexposed has event, time before exposed

\[ \Pr(\text{set in } N_1) = \int_0^\infty \left( \frac{\partial}{\partial t} S(t) \exp\{\theta_1, k\} \right) S(t) \exp\{\theta_0, k\} C(t) C(t) \, dt \]

- Survival function
- Censoring function
- Exposed hazard contains true effect size
- Unexposed hazard
Simulation Bias

Survival Simulation; consider 1:1 matching

\[ \hat{\eta} = \log N_1 - \log N_0 \]

\( N_1 \): exposed has event, time before unexposed
\( N_0 \): unexposed has event, time before exposed

\[ \text{Pr(set in } N_1) = \int_0^\infty \left( \frac{\partial}{\partial t} S(t)^{\exp\{\theta_1, \kappa\}} \right) S(t)^{\exp\{\theta_0, \kappa\}} C(t)C(t)dt \]

Not unbiased when there is variance in baseline hazards
Negative Controls

Coverage: 0.53±0.07
Bias Reduction: Negative Outcomes

<table>
<thead>
<tr>
<th>Outcome Dependent Metric</th>
<th>Coverage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposure-based hdPS</td>
<td>0.80±0.06</td>
</tr>
<tr>
<td>Bias-based hdPS</td>
<td>0.86±0.05</td>
</tr>
<tr>
<td>L1 Reg (CDM)</td>
<td>0.90±0.04</td>
</tr>
<tr>
<td>L1 Reg (hdPS)</td>
<td>0.86±0.05</td>
</tr>
</tbody>
</table>

10:1 variable ratio matching
Outcome Dependent Metrics
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- Susceptible to bias:
  - PS adjustment techniques
  - simulation design choices
  - negative control misspecification
Outcome Dependent Metrics

• Susceptible to bias:
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• Different outcomes can yield different results
Outcome Dependent Metrics

- Susceptible to bias:
  - PS adjustment techniques
  - simulation design choices
  - negative control misspecification

- Different outcomes can yield different results

- Outcome independent metrics more generalizable
Instrument Variables

- Variables that predict treatment exposure but has no effect on outcome (or correlation with any confounder)

- Inclusion in PS can increase bias and variance of estimate

Suppose:

- eye color perfectly separates treatment groups (all blue eyed receive A, all brown eyed receive B)
- eye color does not influence outcome
- no power in experiment
Instrument Variables

- Variables that predict treatment exposure but has no effect on outcome (or correlation with any confounder)

- Inclusion in PS can increase bias and variance of estimate

Suppose:

- absent of IV, PS correlated with outcome hazard, PS matches patients with similar baseline outcome hazard
- add in IV, PS of many exposed people increases
- exposed people now matched with higher hazard
- negative bias results
Instrument Variables

- True IV are rare, impact on real-world data unproven

- IV only problematic if uncorrelated with any confounders - unlikely situation in real-world data

- Identifying IV’s is difficult

- bias-based hdPS uses outcome information in PS to avoid IV’s, but breaks Rubin’s unconfoundedness assumption
Instrument Variables - Solution?

- If certain IV’s are suspected, stratify on them in the PS logistic regression -> conditional logistic regression (CLR)

- CLR avoids estimating any effect size from IVs

- Keeps unconfoundedness while eliminates effects on PS

- Issue:
  CLR computationally expensive for large strata
  CLR approximations can be very inaccurate

- Future direction:
  Efficient CLR implementation, apply to PS
Take Away Points

• L1 Regularization favorable over hdPS Algorithm

• Simulations and negative controls provided useful evidence

• Regularization solves PS “convergence” problem (no MLE for regression exists)