A Bayesian Approach for Integrating External Data in Clinical Trials using Overlap Prior

Fan Li

Department of Statistical Science
Duke University

October 12, 2022

Bayesian Biostatistics 2022
Bethesda, Maryland
joint work with Yanxun Xu (Johns Hopkins)

Real World Data (RWD)

- FDA establishes a framework to evaluate the potential use of real-world evidence (RWE) in 2018 to:
  - Support a new indication for a drug approved
  - Satisfy post-approval study requirements
- RWE is generated from Real World Data (RWD):
  - electronic health records (EHR)
  - medical claims
  - disease registries
- A prominent use of RWD is external controls in clinical trials

External Controls from RWD

- In clinical trials on treatments of rare or severe diseases, challenging to recruit patients into the control arm
- RWD available: past trials or EHR on the population with the same disease
- External controls: construct synthetic controls from external RWD, to substitute or supplement concurrent controls
- Two popular classes of methods: propensity score and Bayesian dynamic borrowing

Notations

- $A = 1$: active treatment; $A = 0$: control
- $Z = 1$: in concurrent data; $Z = 0$: in external data
- In single arm trial: $Z_i = A_i$; we will focus on this case
- Outcome: Y; potential outcomes $Y_i(a), a = 0, 1$
- covariates: X
- Denote concurrent and external data $D = \{A, Y, X\}$ in by D_{con}, D_{ext}
- Estimand: average treatment effect (ATE)

$$\tau = \mathrm{E}\{Y_i(1) - Y_i(0)\}$$

- ATE... but in what population? the whole population (ATE)? the concurrent trial (similar to ATT), or the population in clinical equipoise (similar to ATO)?

Method 1: Propensity Scores

- Propensity score: $e(x) = \Pr(Z = 1|X = x)$, a scalar summary of the multi-dim covariates
- PS Methods: (1) balance covariates between concurrent and external data using PS via e.g. matching or weighting; (2) calculate the matched or weighted difference in outcome between two data
- Pros:
  - Model-free (for outcomes)
  - Easy to understand and implement with single-arm trials
  - available software (e.g. `PSweight` R package)
- Cons:
  - How to deal with hybrid trials? How to differentiate the controls between D_{ext} and D_{con}?
  - How to handle multiple external sources?
  - Only capture difference in covariates, not outcomes

Method 2: Bayesian dynamic borrowing

- The Bayes theorem: $p(\theta|D) \propto p_0(\theta)L(\theta|D)$, where $L(\theta|D)$ is based on an outcome model, e.g. $Y \sim \beta X + \theta Z$

- Bayesian dynamic borrowing: use external data D_{ext} to inform the prior:

$$p(\theta|D) \propto p_0(\theta|D_{ext}, \alpha)L(\theta|D)$$

- Power prior (Ibrahim and Chen, 2000):

$$p_0(\theta|D_{ext}, \alpha) \propto p_0(\theta)\{L(\theta|D_{ext})\}^{\alpha}$$

  α: power – strength of borrowing, $\alpha = 1$: full borrowing

- Later proposals: commensurate prior (Hobbs et al, 2011); MAP prior (Neuenschwander et al. 2010)
- Only capture difference in outcomes, not covariates

Combining the Two Methods

- Combine PS methods and dynamic borrowing to capture difference in both covariates and outcomes
- Wang et al. (2019, JPS): (1) stratify units by PS; (2) within each stratum, use a specific power prior for all units
- Liu et al. (2021): combine PS and a MAP prior
- Golchi (2021): individual weights (IW) prior

$$p_0(\theta|D_{ext}, \alpha) \propto p_0(\theta) \prod_{i}^{N_{ext}} p(y_{ext,i}; \theta)^{\alpha_i}$$

α_i: the Mahalanobis distance between the covariates in the external individual and the concurrent sample

  - Challenge: Mahalanobis dist is hard to compute for even moderate dimensions

Our proposal: Individual Overlap Prior

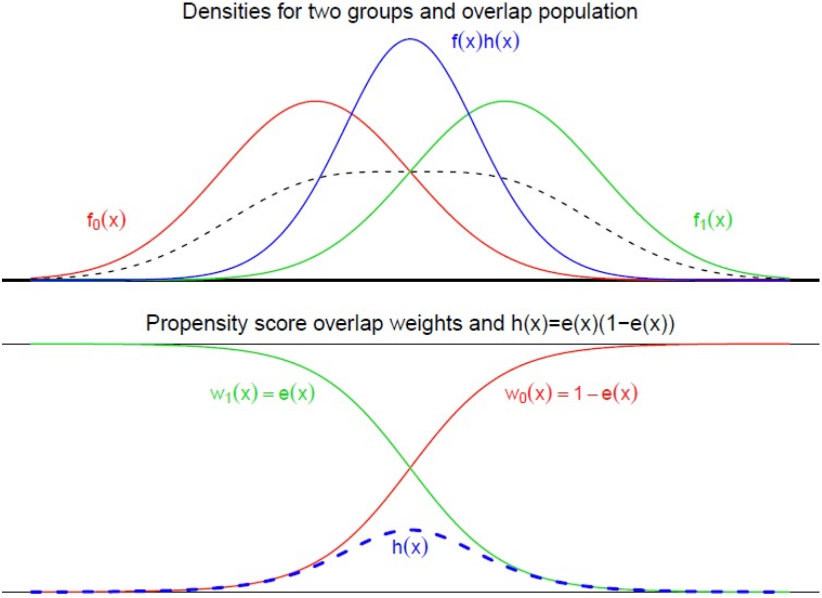
- Our proposal imposes individual weights, but different distance metric

$$p_0(\theta|D_{ext},\alpha) \propto p_0(\theta)\prod_{i}^{N_{ext}} p(y_{ext,i};\theta)^{f(e_i)} \qquad (1)$$

  where $f(e_i) = 2\{e_i(1-e_i)\}^{1/2}$

- The function $h(x) = e(x)\{1-e(x)\}$ is motivated from the overlap weighting (Li, Morgan, Zaslavsky, 2018) in propensity score literature
  - proportional to the harmonic mean of e_i and $1-e_i$
  - the function leading to the optimal covariate overlap between external and concurrent sample
  - A related overlap coefficient of two distributions: $\min(e(x), 1-e(x))$ (Inman and Bradley, 1989)

The Overlap Function $h(x) = e(x)\{1 - e(x)\}$



Simulation Design

- Single arm: $N_c = 50, 100$, $N_e = 200$
- Covariates ($p = 6$)
  - Concurrent: $X_c \sim MVN(\mu_c, \Sigma)$, with $diag(\Sigma) = 1$ and other entries 0.5
  - External: $X_e \sim MVN(\mu_e, \Sigma)$
- Outcome
  - Concurrent: $Y_c \sim MVN(X\beta + Z\theta, 1)$; θ: treatment effect
  - External: $Y_e \sim MVN(X\beta + \delta_e, 1)$; δ_e: a mean shift of external data not explained by X

Simulation Design

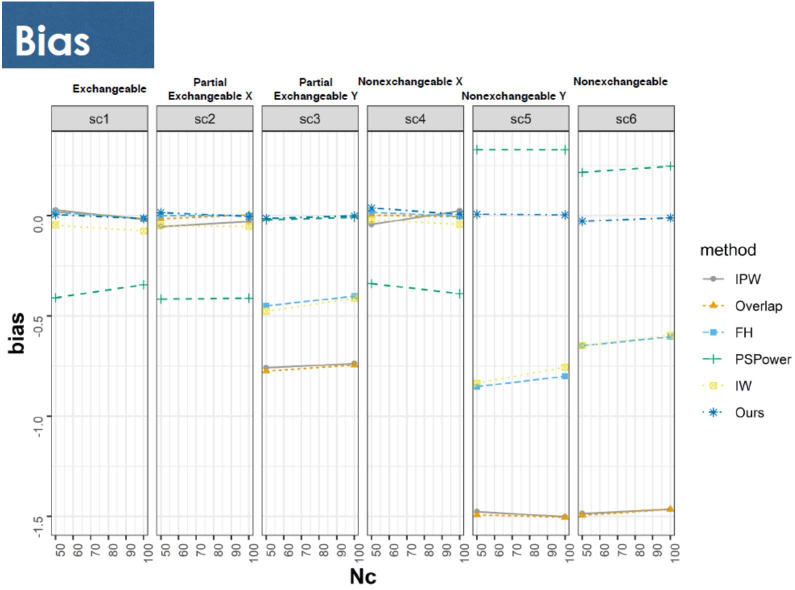
- $X_c \sim MVN(\mu_c = 1, \Sigma)$
- $Y_c \sim MVN(X\beta + Z, 1)$ (true eff $\theta = 1$),
  $Y_e \sim MVN(X\beta + \delta_e, 1)$
- Six simulation scenarios (same setup in Golchi, 2020)

	exchangeable: X, Y	μ_e	δ_e	expectation
sc1	Yes, Yes	μ_c	0	all good
sc2	partially Yes, Yes	μ_c or $2\mu_c$	0	PS good, Bayes poor
sc3	Yes, partially Yes	μ_c	0 or 1.5	PS poor, Bayes good
sc4	No, Yes	$2\mu_c$	0	PS good, Bayes poor
sc5	Yes, No	μ_c	1.5	PS poor, Bayes good
sc6	No, No	$2\mu_c$	1.5	PS poor, Bayes poor

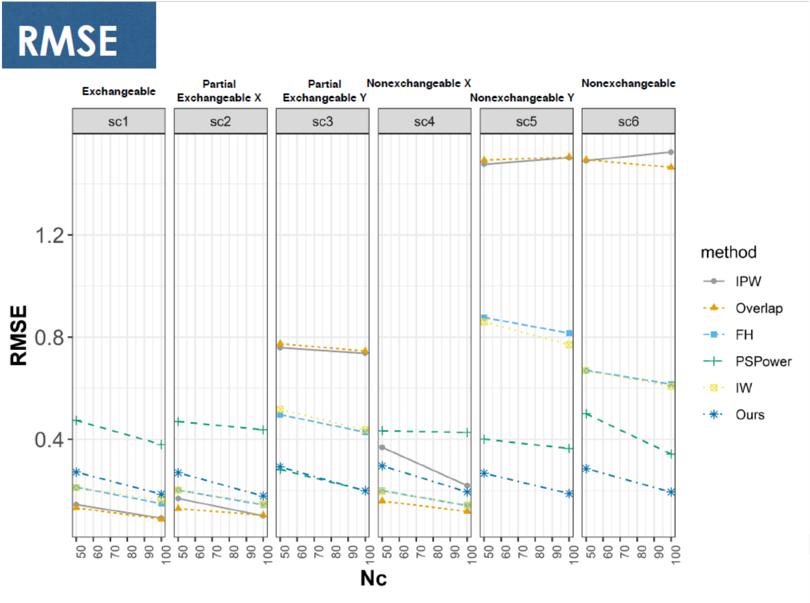
Methods under Comparison

- Propensity score methods
  - Inverse probability weighting (IPW)
  - Overlap weights (Overlap)
- Bayesian dynamic borrowing: Power prior with full history borrowing (FH, $\alpha = 1$)
- Hybrid
  - Stratified PS + Power prior (PSPower)
  - Individualized weights (IW)
  - Our approach (Ours)

Simulation Results

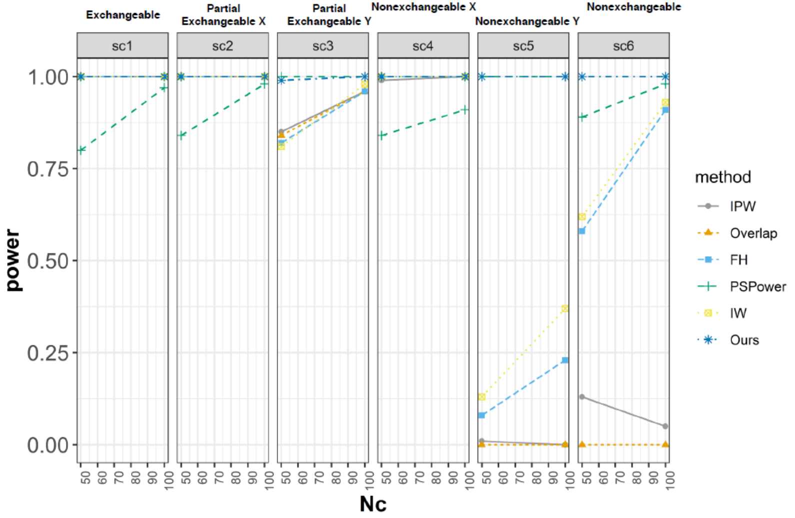


Simulation Results

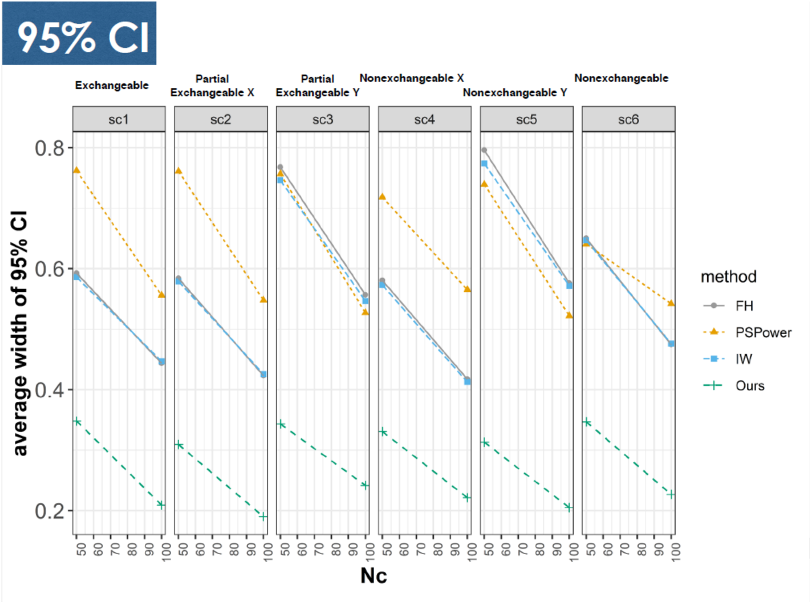


Simulation Results

Power



Simulation Results



Discussion

- Two classes of methods for external control (outcome-based and covariated-based)
- We develop a Bayesian approach with overlap prior to combine both
- Extensions
  - different types of outcomes and multiple external data sources
  - Adaptive borrowing during the recruitment of a concurrent control via several interim analyses
  - embed in the Go/no-Go framework in Phase II trials.
- Ongoing real applications