Combining weighting and regression adjustments under a Bayesian framework largely overcomes limitations caused by unstable weights. The resulting performance is similar to parametric G-computation

Regression augmented weighting adjustment for indirect comparisons

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Introduction

- Head-to-head randomized controlled trials, the gold standard in assessing treatment efficacy, often lack comparisons against all potential competitors necessary for funding decisions.
- Indirect comparisons serve as a viable alternative, estimating effects of A vs B tthrough the relative effects estimated from two trials comparing A and B to a common control C
- Indirect comparisons are only unbiased if no effect modifying variables differ across the two trials, in which case population adjustment is required
- Data accessibility poses a challenge: only **aggregate-level data (ALD)** from the competitor trial, despite the accessibility to **individual patient data (IPD)** for sponsored trials
- Standard methods like inverse propensity score weighting not applicable due to data accessibility, and existing population adjustment methods can be assumption-heavy and unstable.
- Our proposed solution is a novel Bayesian framework method that combines weighting and regression adjustment to tackle these issues.

Methods

Existing methods

- Weighting-Based: Matching-adjusted indirect comparisons (MAIC) **(Signorovitch et al. 2010, 2012)**:
  - Pros: Dependent on few assumptions; easy to implement; fast to compute;
  - Cons: tend to give unreliable estimates under poor population overlap and small sample(IPD) size;
- Regression-Based: Parametric G-computation **(Remiro-Azócar, Heath, and Baio 2022)**:
  - Pros: More flexible - can extrapolate beyond the covariate range of the IPD; minimal impact of low population overlap;
  - Cons: relies heavily on correct parametric modelling of the covariate distribution in the ALD trial;

Proposed methods: G-MAIC

Three stages for estimating population-adjusted relative effects of A vs B Δ^*:

1. Outcome regression using IPD: this aims to build a model for the conditional mean μ
2. Weight estimation: this can be any procedure for estimating the calibration weights, including MAIC weights
3. Uncertainty quantification: Bayesian bootstrap with estimated weights as 'pseudo frequency'

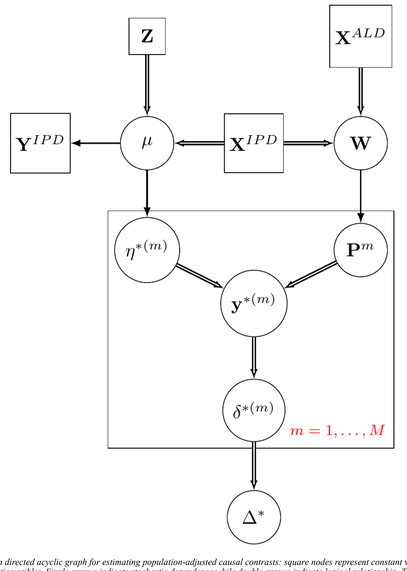


Figure 1: Bayesian directed acyclic graph for estimating population-adjusted causal contrasts: square nodes represent constant variables, circular nodes for stochastic varibles. Single arrows indicate stochastic dependence while double arrows indicate logical relationship. The plate notation indicates repeated analysis

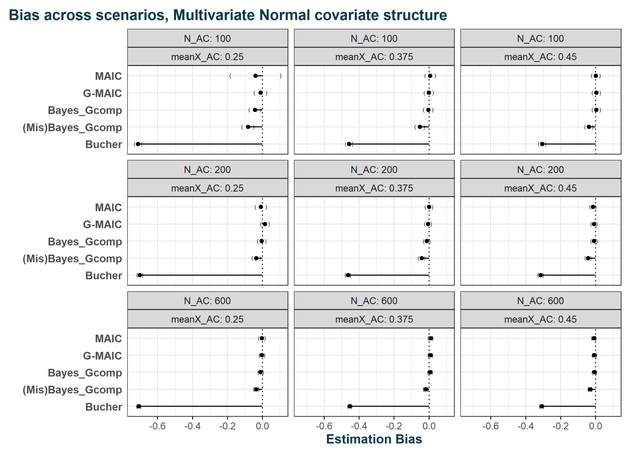
Simulation Studies

- General set-up: AC is the IPD trial, BC is the ALD trial. We first generate the IPD for both trials and summarise the data to obtain the ALD for BC trial.
- Aim: Benchmarking the proposed method against existing methods in estimating A vs B effects in the BC population
- Data Generating mechanisms: we consider one binary outcome and five covariates for both trials using the following outcome model:

$$\text{logit}(\theta_i) = \beta_0 + \beta_{\mathbf{1}}\mathbf{X}_{\mathbf{EM}} + (\beta_{trt} + \beta_{\mathbf{EM}}\mathbf{X}_{\mathbf{EM}})T_i.$$

  We then vary the IPD sample size, population overlap and covariate structure in a combination of 18 scenarios
- Estimand: The marginal treatment effect of A vs B in the BC population
- Methods:
  - **MAIC;;**
  - **Proposed method: G-MAIC;**
  - **Bayesian Parametric G-computation;**
  - **Bayesian Parametric G-computation under mis-specified covariate model;**
  - **Bucher's method (standard indirect comparison);**
- Performance measures:
  - Bias;
  - Average model standard errors;
  - Empirical standard errors;
  - Coverage

Simulation Results



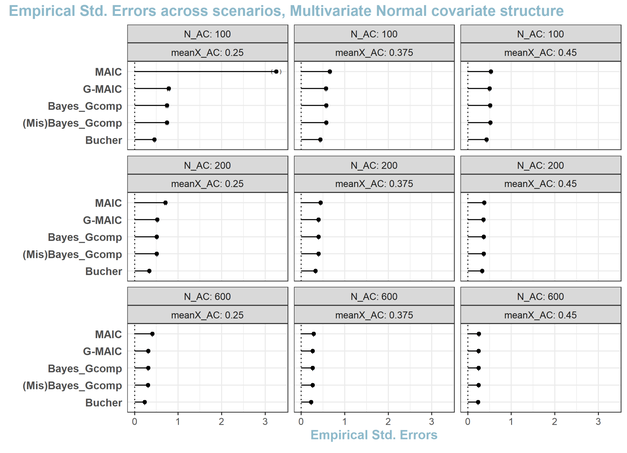


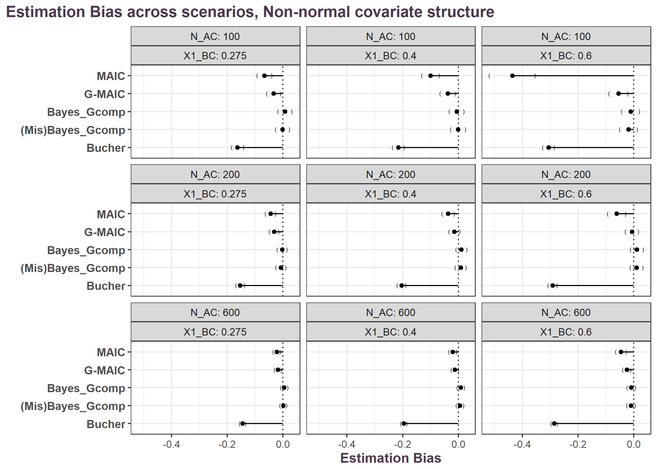
Figure 2: Results under multivariate Normal covariate structure with varying overlap and sample size: from left to right average sample size reductions are 82.7%, 55%, 31%. From top to bottom, methods are displayed in the order of: MAIC, G-MAIC, Bayesian Parametric G-computation, Bayesian Parametric G-computation under mis-specified covariate model, Bucher's method

Findings

- When the implied the trial assignment model is correct (the Normal scenario), the proposed method overcomes the limitations caused unstable weight estimation in small samples with poor overlap;
- Under mild mis-specifications of trial assignment model, the problem of unstable weights from MAIC exacerbates, leading to even larger bias than standard indirect comparison. While using MAIC weights, the performance of proposed method in this scenario is still comparable to parametric G-computation but with fewer assumptions

Future directions

- G-MAIC does not extrapolate beyond the covariate range of IPD, but extrapolation is necessary under no/minimal population overlap:
  - Explore the application of model averaging for robust extrapolation, value of information analysis for uncertainty quantification
  - Quantify the loss due to naive linear extrapolation when the underlying surface is non-linear



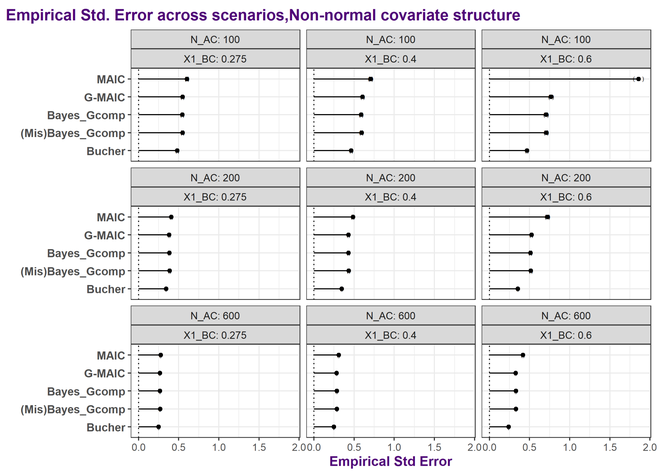


Figure 3: Results under non-Normal covariate structure with varying overlap and sample size: from left to right average sample size reductions are 32.7%, 55%, 81%. From top to bottom, methods are displayed in the order of: MAIC, G-MAIC, Bayesian Parametric G-computation, Bayesian Parametric G-computation under mis-specified covariate model, Bucher's method

References

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Signorovitch, James E, Eric Q Wu, Andrew P Yu, Charles M Gerrits, Evan Kantor, Yanjun Bao, Shiraz R Gupta, and Parvez M Mulani. 2010. "Comparative Effectiveness Without Head-to-Head Trials: A Method for Matching-Adjusted Indirect Comparisons Applied to Psoriasis Treatment with Adalimumab or Etanercept." *Pharmacoeconomics* 28 (10): 935–45.