Predictive-adjusted indirect comparison (PAIC): a novel method for population-adjusted indirect comparison

An accurate, unbiased alternative to MAIC

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Background

Population-adjusted indirect comparisons are increasingly used to compare treatment outcomes across clinical trials. Such methods are utilised when:

- There are no head-to-head trials comparing the interventions of interest
- Individual patient data (IPD) are available for an intervention, e.g. through the sponsor company's own trial, but are unavailable for comparator(s)
- There are cross-trial differences in patients' baseline characteristics

Suppose that we want to compare treatment A with treatment B in the absence of a head-to-head randomised controlled trial. An **indirect** comparison is required. We shall assume that this is **anchored**: a connected treatment network is available through a common comparator C, e.g. placebo. We have IPD for the index trial AC but only aggregate-level data (ALD), available from publications, for trial BC.

Standard methods for indirect comparisons allow for the use of ALD and maintain randomisation. However, such methods are biased when the distribution of effect modifiers differs between trials. Population-adjusted indirect comparisons adjust for cross-trial differences in observed covariates. Recently proposed approaches for population adjustment are:

1. **Matching-adjusted indirect comparison (MAIC)** [1] reweights the patients in the AC trial so that the weighted moments of their covariates match those in the published BC summary data. Weights derived from the IPD are applied to the outcome model to generate adjusted outcomes. As MAIC is a weighting method, it will always reduce the effective sample size. If too many covariates are included in the weighting procedure, the precision of the treatment effect estimate may be negatively affected [2].
2. **Simulated treatment comparison (STC)** [3] involves creating an outcome regression model. A regression model is fitted in the AC population, including all effect modifiers in imbalance, and then used to predict outcomes in the BC trial population. The current implementation of STC is systematically biased for non-linear outcomes because the mean outcome depends on the full distribution of the covariates and not just their mean [2, 4].

To overcome possible shortcomings of current population adjustment methods, we propose a multiple imputation-based algorithm called **predictive-adjusted indirect comparison (PAIC)**.

Methodology

Available data

For the AC (IPD) trial, we have:

- A vector of K observed baseline characteristics for each patient i, $\boldsymbol{X}_i = (X_{i1}, \dots, X_{iK})$
- A treatment indicator T_i ($T_i = 1$ for active treatment and $T_i = 0$ for the common comparator)
- An observed outcome Y_i, e.g. a binary or time-to-event outcome

For the BC (ALD) trial, we have:

- The published summary values $\boldsymbol{\theta}$ of the covariates, e.g. proportions for discrete X_{ik}
- An estimate of the B vs. C treatment effect (in the BC population), $\hat{\Delta}_{CB}$

Predictive-adjusted indirect comparison

Predictive-adjusted indirect comparison consists of six steps: **first-stage regression**, **covariate sampling**, **outcome prediction**, **second-stage regression**, **pooling** and **comparison**. The algorithm methodology is summarised in **Figure 1**. A regression fitted in the AC (IPD) population (step 1) is used to create a large number of "synthetic" datasets/imputations (steps 2 and 3); these consist of predicted individual-level covariates and outcomes under treatments A and C in the BC population, $(T_i, \boldsymbol{X}_i^*, Y_i^*)$. The A vs. C treatment effect on such population is estimated in a second-stage regression for each imputation (step 4). After pooling over imputations (step 5), the average A vs. C treatment effect can be compared with $\hat{\Delta}_{CB}$ (step 6) to obtain an unbiased estimate of comparative efficacy for A vs. B.

Simulation Study

A simulation study is performed to benchmark the performance of PAIC against that of MAIC and STC. Binary outcomes and four binary covariates (two effect modifiers and two purely prognostic variables) are considered. 1000 Monte Carlo replicates are generated and analysed per simulation scenario. The study follows a fully factorial structure with $3 \times 3 \times 3 \times 2 \times 3 = 162$ scenarios. The following parameters are varied:

- $N_{AC} \in \{300, 450, 600\}$ under a 2:1 active treatment vs. placebo allocation ratio
- $\beta_{1k} \in \{-\log(0.67), -\log(0.5), -\log(0.33)\}$ (weak, moderate and strong prognostic effect)
- $\beta_{2k} \in \{-\log(0.67), -\log(0.5), -\log(0.33)\}$ (weak, moderate and strong effect modification)
- $\text{cor}(X_{ij}, X_{ik}) \in \{0, 0.35\}, j \neq k$ (zero and strong covariate correlation)
- $p_k \in \{0.4, 0.35, 0.3\}$, $X_{ik} \sim \text{Bernoulli}(p_k)$ for the AC trial (simultaneously varying $p_k \in \{0.6, 0.65, 0.7\}$ for the BC trial, respectively, yielding weak, moderate and strong covariate imbalance)

Binary outcomes Y_i are simulated from Bernoulli distributions with probabilities of success generated from logistic regression. For each trial:

$$\text{logit}\big(P(Y_i|T_i, \boldsymbol{X}_i)\big) = \beta_0 + \boldsymbol{X}_i\boldsymbol{\beta}_1 + (\beta_T + \boldsymbol{X}_i^{EM}\boldsymbol{\beta}_2)\mathbf{1}(T_i = 1),$$

with $\beta_T = \log(0.17)$, β_0 set to fix the baseline event rate at 0.35 and $N_{BC} = 600$ (2:1 allocation). For PAIC, the number of imputations is set to $M = 100$.

Conclusions

- PAIC produces more accurate estimates (lower mean absolute error) than MAIC and STC on a consistent basis
- PAIC withstands extreme conditions better than MAIC and STC; MAIC is less robust to strong covariate imbalances and STC breaks down with strong prognostic variable effects and is more sensitive to low numbers of patients in the IPD trial
- PAIC provides unbiased estimates when all effect modifiers are accounted for
- In general, PAIC's coverage rates were not statistically significantly different from 0.95

1. Fit a first-stage regression to the AC IPD:

$$g(\hat{Y}_i) = \beta_0 + \boldsymbol{X}_i\boldsymbol{\beta}_1 + (\beta_T + \boldsymbol{X}_i^{EM}\boldsymbol{\beta}_2)\mathbf{1}(T_i = 1),$$

where $\boldsymbol{X}_i^{EM}$ are effect modifying covariates, $g(\cdot)$ is a suitable link function, β_0 is an intercept, $\boldsymbol{\beta}_1$ are regression coefficients for the prognostic variables, $\boldsymbol{\beta}_2$ are interaction coefficients for the effect modifiers and β_T is an A vs. C treatment coefficient.

↓

2. For $m = 1, \dots, M$ imputations, "forward sample" $\boldsymbol{\theta}$ to **simulate individual-level covariates in the BC population**, $\boldsymbol{X}_i^{*(m)}$. The joint distribution of the covariates is captured by simulating from a copula, which uses the correlation structure and approximate marginal distribution types observed in the IPD.

↓

3. Draw predicted outcomes $Y_i^{*(m)}$ for each imputation **from their posterior predictive distribution** (conditional on the sampled covariates). This requires drawing first-stage regression coefficients $\hat{\boldsymbol{\beta}}^{(m)}$ from their approximate posterior beforehand; $\hat{\boldsymbol{\beta}}^{(m)} \sim \text{MVN}\big(\hat{\boldsymbol{\beta}}, \hat{\boldsymbol{V}}(\hat{\boldsymbol{\beta}})\big)$.

↓

4. Fit a second-stage regression to each imputed dataset:

$$g(\hat{Y}_i^{*(m)}) = \beta_0^{(m)} + \Delta_{CA}^{*(m)}T_i,$$

to find $\hat{\Delta}_{CA}^{*(m)}$, the A vs. C treatment effect estimate (on the BC population).

↓

5. Pool the treatment effect estimates and their variances across M imputations. The average A vs. C treatment effect and its estimated variance are:

$$\hat{\Delta}_{CA}^{*} = \frac{1}{M}\sum_{m=1}^{M}\hat{\Delta}_{CA}^{*(m)} \qquad \hat{V}(\hat{\Delta}_{CA}^{*}) = \Big(1 + \frac{1}{M}\Big)b - \hat{w},$$

where $b = \frac{1}{M-1}\sum_{m=1}^{M}(\hat{\Delta}_{CA}^{*(m)} - \hat{\Delta}_{CA}^{*})^2$ is the between-imputation variance and $\hat{w} = \frac{1}{M}\sum_{m=1}^{M}\hat{V}(\hat{\Delta}_{CA}^{*(m)})$ is the average within-imputation variance.

↓

6. Perform a standard indirect comparison in the BC population:

$$\hat{\Delta}_{BA} = \hat{\Delta}_{CA}^{*} - \hat{\Delta}_{CB},$$

where $\hat{\Delta}_{BA}$ is the estimated marginal A vs. B treatment effect. The variance is estimated by summing the variances of the within-trial relative effects. Inferences can be based on normal distributions if M, N_{AC} and the number of samples in step 2 are relatively large.

Figure 1: Predictive-adjusted indirect comparison

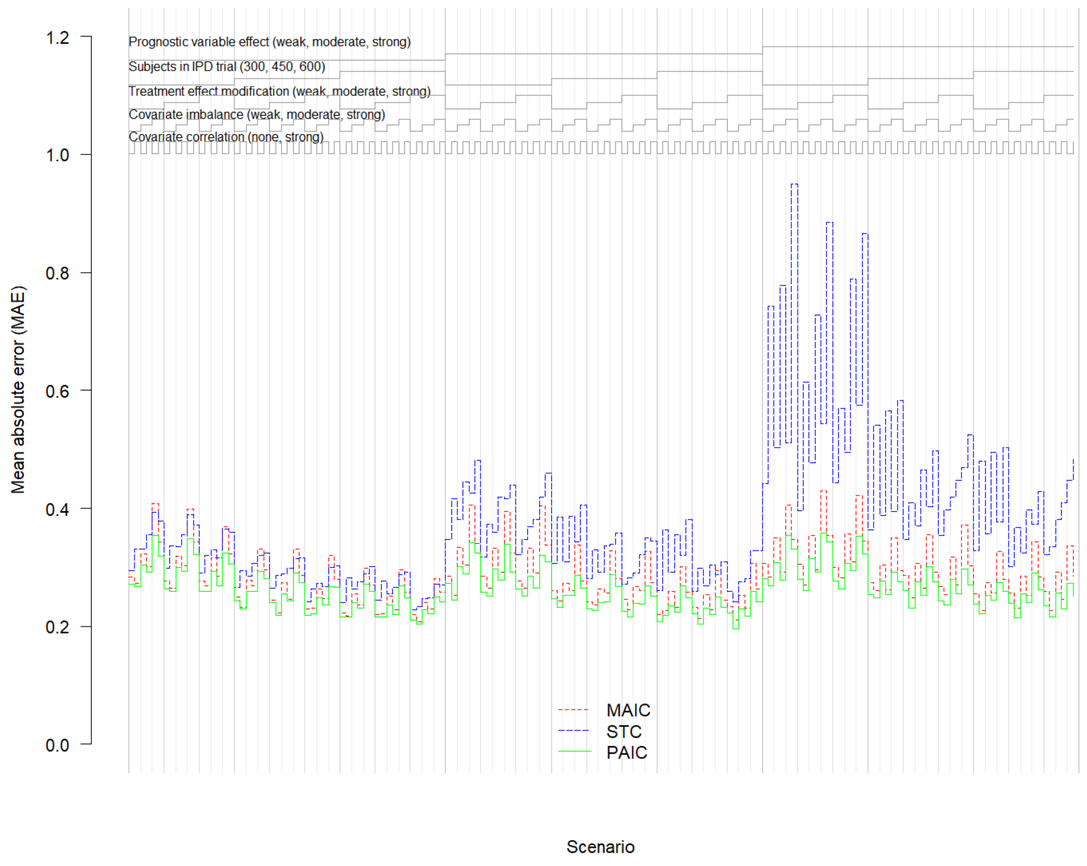

Figure 2: Mean absolute error

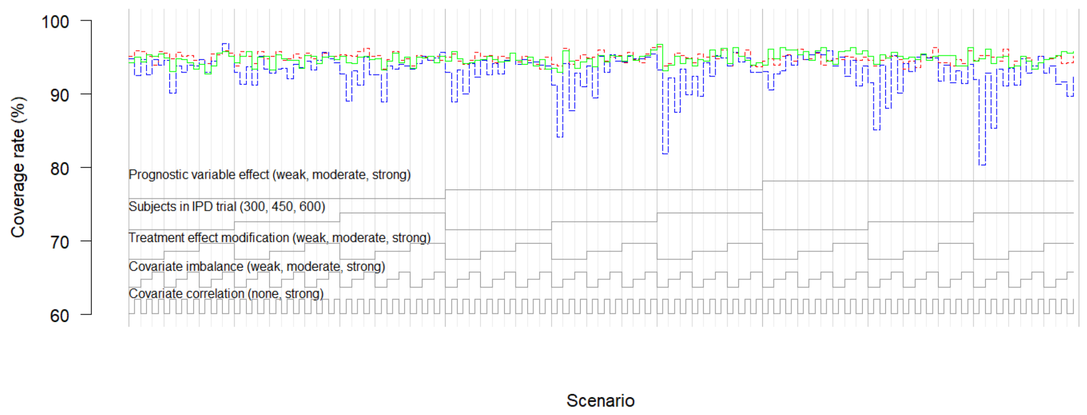

Figure 3. Coverage rate of 95% confidence intervals

References

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