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# Entropy Balance Weighting and Power Priors: Its use in Real World Data (RWD) and Disproportionate Randomized-Controlled Trials (RCTs)

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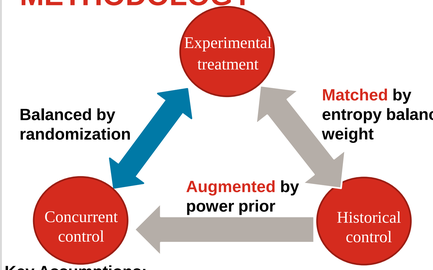
## INTRODUCTION & OBJECTIVE

- Disproportionate randomized-controlled trials (RCTs) are more appealing and feasible than adequate RCTs for:
  - Pediatric populations, orphan medicines, ethical issues or concerns
- Augmenting the disproportionate RCTs with the real world data (RWD) is prevalent
- **OBJECTIVE: Augment the disproportionate randomized-controlled trial by leveraging the real world data (RWD).**
  - **Adjust the heterogeneity of the data from the current trial and historical studies**
  - **Control the amount of historical information borrowing**

## METHODOLOGY




**Key Assumptions:**

Patients in the control arm in current RCT and historical studies received the same active control treatment or placebo.

## SIMULATION SETUP

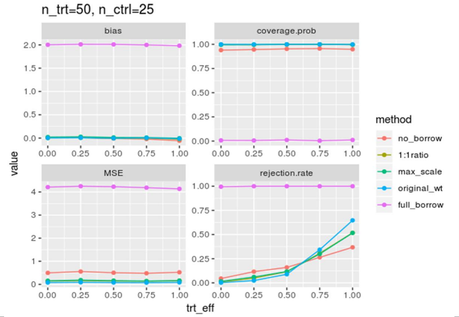
**Data generation:**

- Generate two heterogeneous patients populations $\boldsymbol{X}_{ki}$
- Sample from these two populations to form current RCT and historical trial patients.
- Generate the outcome data $Y_{ki} \sim N(\tilde{\boldsymbol{\beta}}^T \boldsymbol{X}_{ki} + \beta_1 * Z_{ki}, \sigma^2)$ with $\tilde{\boldsymbol{\beta}}$ as the prognostic effects.

**Operating setting:**

- For current RCT, $N_{trt}$ : $N_c$ = 2:1;
- For historical control patients, $N_{c0}$ : $N_c$ = 3:1;
- Consider treatment effect $\beta_1$= 0, 0.25, 0.5, 0.75, 1;
- Define the decision rule as Pr($\beta_1$ >0| $\boldsymbol{D}_1$, $\boldsymbol{D}_0$ )> 0.95

## KEY RESULT




## CONCLUSIONS

- Poor estimation when borrowing historical information without adjusting the heterogeneity.
- The proposed method improves the efficiency of estimation (lower MSE and higher coverage probability), especially when the current study is a small scaled trial.
- The proposed method results in a low type 1 error and an increasing power when effect size is larger.
- The amount of information borrowing is flexible and can be calibrated by a scalar.
- Enables a more comprehensive evaluation on treatment effect than frequentist inference approach.

## Notations

**Patient-level data**

$D_{ki}$**= (Y$_{ki}$, Z$_{ki}$, X$_{ki}$),** k = 0,1; $i = 1, \ldots N_k$

$Y_{ki}$ **= Outcome variable;**

$Z_{ki}$ **= Treatment group indicator:** 1-treatment, 0- control

$\boldsymbol{X}_{ki}$**= baseline characteristics covariates vector which may confound the outcome** $Y_{ki}$

**k = data source indicator:** 0- historical data; 1-current RCT data

## Entropy Balancing Weight ($w_{ki}$)

$$\min_{w_{ki}} H(w) = \sum_{\{i|k=0\}} h(w_{ki}),\ h(.) \text{ is the distance metric}$$

Subject to balance and normalization constraints:

$$\sum_{\{i|k=0\}} w_{ki} c_{ri}(\boldsymbol{X}_{ki}) = \boldsymbol{m}_r$$ with r ϵ 1,.., R and $\boldsymbol{m}_r$ as a set of balance constraints

and

$$\sum_{\{i|k=0\}} w_{ik} = c_0 \qquad w_{ki} \geq 0 \text{ for all } i$$

Compared to propensity score based method, entropy balancing is **advantageous** in terms of

- No model is required.
- No covariates balance check is needed.
- Achieves a better covariate distributions balance.

## Likelihood

**Outcome variables:** $Y_{ki} \sim N(\mu_{ki}, \sigma^2)$,

where $\mu_{ki} = \beta_0 + \beta_1 * Z_{ki}$ (after the confounding covariates vector $X_{ki}$ is **balanced** between the treatment and control patients)

- $\beta_0$ – control mean; $\beta_1$ – treatment effect
- Non-informative priors on $\beta_1$ and $\sigma^2$
- Power prior on $\beta_0$

## Power Prior

$$\pi(\beta_0 \,|\boldsymbol{\alpha}_0, \boldsymbol{D}_0) \propto \prod_{i=1}^{N_0} L(\beta_0 \,|D_{0,i})^{\alpha_{0i}} \pi(\beta_0)$$

**The discounting factor** $\boldsymbol{\alpha}_0 = (w_{0,1}, \ldots w_{0,N_0}) \times c_0$

Entropy balancing weight — Scalar to adjust the amount of information borrowing

Consider the following **weight scaling**:

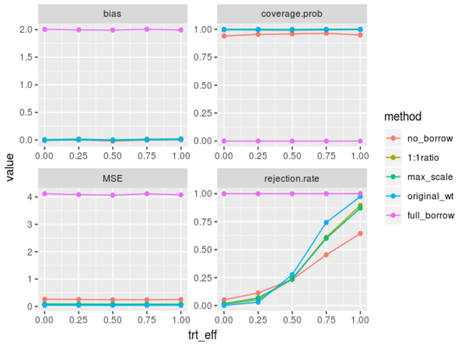
- $c = 1$, no scaling
- $c = 1/\max(w_{0,1}, \ldots, w_{0,N_0})$, scaling the weight to be between 0 and 1.
- $c = \tilde{c}_0$, such that 1:1 trt vs. augmented control allocation

## Joint posterior distribution

$$q(\boldsymbol{\beta}, \sigma^2 | \boldsymbol{D}_1, \boldsymbol{D}_0, \boldsymbol{\alpha}_0) \propto L(\boldsymbol{\beta}, \sigma^2 | \tilde{\boldsymbol{X}}, \boldsymbol{Y}) \pi(\boldsymbol{\beta}, \sigma^2) \left[ \prod_{i=1}^{N_0} f(Y_{0,i} | \beta_0, \sigma^2)^{\alpha_{0,i}} \right]$$

- $\boldsymbol{\beta} = (\beta_0, \beta_1)$
- $\tilde{\boldsymbol{X}} = (\tilde{X}_1, \ldots, \tilde{X}_{N_1})'$ with $\tilde{X}_i = (1, Z_i)'$ where $N_1$ is the sample size of the current RCT.
- $\boldsymbol{D}_1, \boldsymbol{D}_0$denote the data from current RCT and RWD from historical studies, respectively.
- $Y_{0,i}$ is the outcome of $i$-th patient from the historical control.

## MORE RESULT




**Note:** R package **"ebal"** was used to calculate the entropy balancing weights in the simulation.

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**Disclosures:** GY, YB, and MG are full employees of Eli Lilly and Company.