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A Comprehensive Bayesian Double-Adjustment Approach to Dynamic Borrowing of External Data

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Outline

- // Bayesian dynamic borrowing of external data
- // Bayesian double-adjustment approach
- // Case analysis
- // Simulations
- // Discussion

Bayesian Dynamic Borrowing of External Data

A Brief Review

Bayesian Dynamic Borrowing Approaches

A brief review

- Methods addressing background/baseline differences
  - PS matching for selection of patients: non-dynamic
  - PS-integrated methods: use discounted external data as priors
- Methods addressing outcome differences
  - Elastic prior approach: discounts external data by the degree of outcome difference
  - Random effects, hierarchical, shrinkage models: borrow through co-modeling of current and external data by the assumption of exchangeability
  - Commensurate prior approach: allows lack of exchangeability in co-modeling

Power Prior Approach

Ibrahim and Chen (2000), Ibrahim et al (2015), Neuenschwander et al (2009)

- In Bayesian inference of parameter θ, likelihood $L(\theta|D)$ given current data D is analyzed with a power prior constructed from external data D_0:

$$L(\theta|D_0)^{\alpha_0}\pi_0(\theta),$$

  $L(\theta|D_0)$ is the likelihood given D_0, $0 \leq \alpha_0 \leq 1$ is a scalar parameter, $\pi_0(\theta)$ is an initial prior
- α_0 (fixed or random) controls the weight of influence of D_0 in the analysis of D; the higher, the more borrowing from D_0
- When α_0 is assumed random (modified power prior), the correct inference would depend on whether priors for θ and α_0 are independently or jointly assigned
- Not straightforward to assign a prior for α_0, so suggest using fixed α_0 at various values to assess prior sensitivity in practice

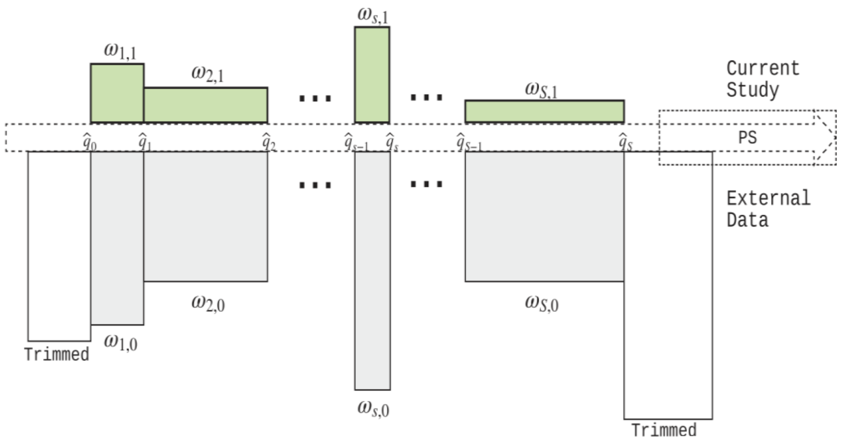
PS-integrated Power Prior Approach

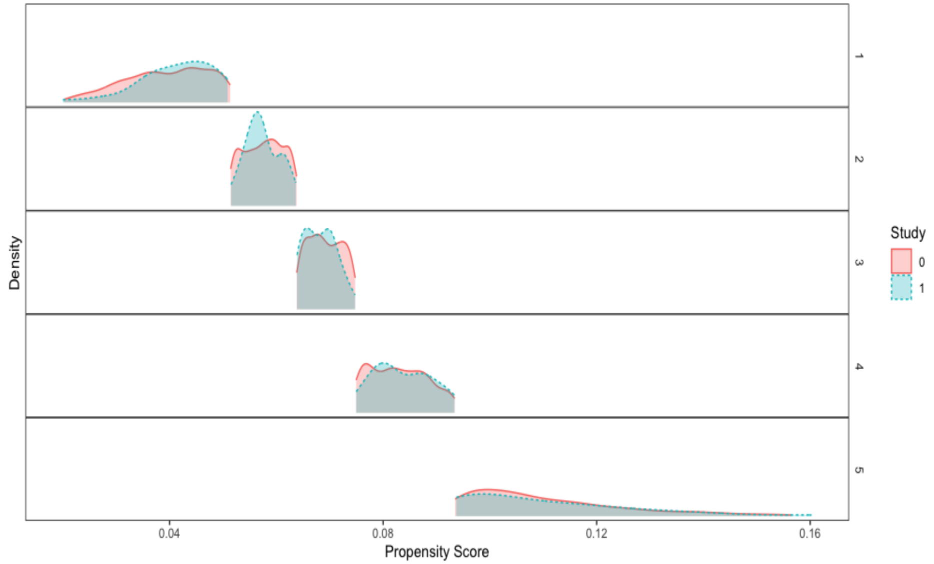
Wang et al (2019) - adjusts borrowing through power prior based on PS

- Borrow **A** patients from external data to analyze current data for the inference of θ
- Borrowing based on stratified similarity of PS
  - **S1: Model and estimate** PSs of current and external patients
  - **S2: Trim** off external patients whose PSs fall outside the range of PSs of current patients
  - **S3: Stratify** external patients into S (e.g. S=5) strata defined by PSs of current patients, $n_{0,s}$ in each stratum
  - **S4: Calculate** the overlapping probability of PS distributions of current and external patients for each stratum, denoted as r_s
  - **S5: Adjust** the proportion to borrow from each stratum as $v_s = {}^{r_s}/_{\sum_{i=1}^{S} r_s}$
  - **S6: Specify** the power parameter of external patients,

$$\alpha_s = \min(1, \frac{A}{n_{0,s}} v_s)$$

  - **S7: Analyze** to obtain stratum-specific posterior θ_s
  - **S8: Summarize** the posterior estimation of θ as weighted mean of θ_s's, $\sum_{s=1}^{S} \theta_s / S$ if same number of current patients in each stratum

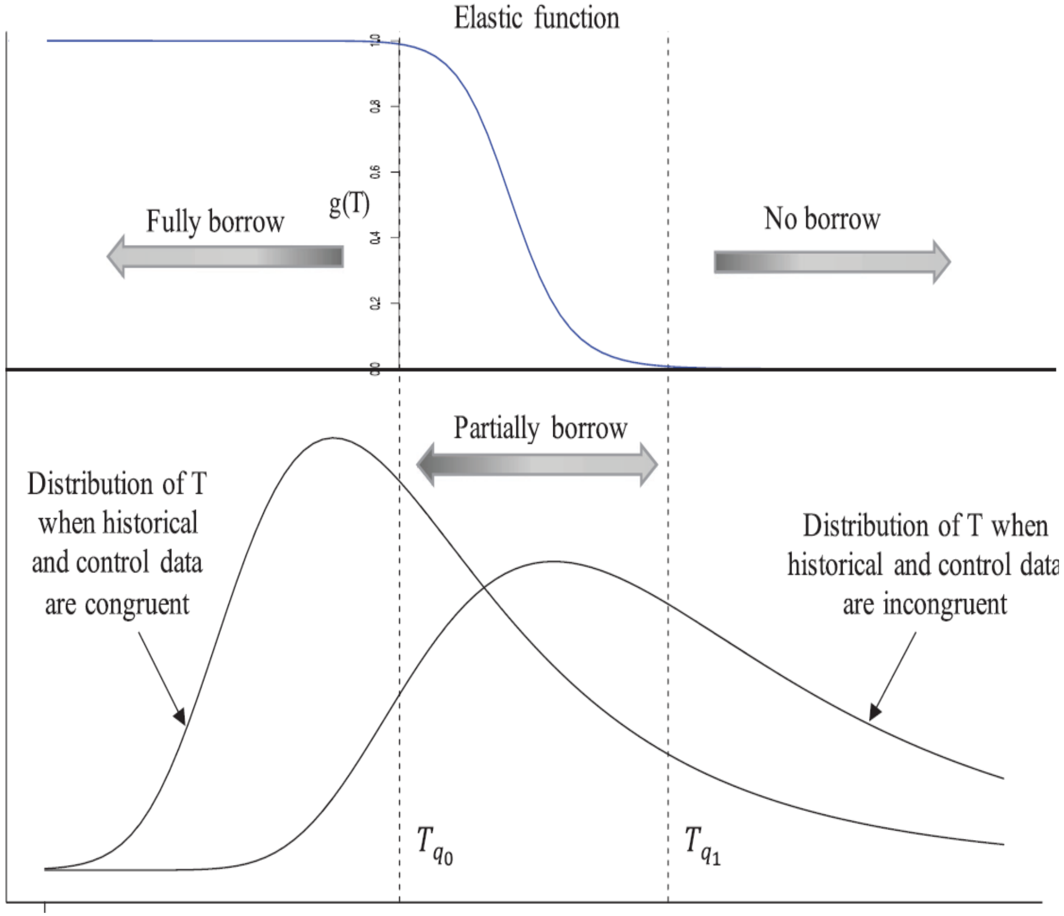




Elastic Prior Approach

Jiang et al (2021)

- Discounts external data (D_0) by the degree of incongruence between current data and external data
  - A congruence measure to assess similarity of current and external data, such as by a test statistic T for mean difference
  - An elastic function $g(T)$ is defined to determine how much to borrow, e.g. a logistic function
  - Use $g(T)$ to downweight prior information, e.g. in a normal case if the full prior from D_0 is $N(\theta_0, \tau^2)$, the elastic prior is $N(\theta_0, \tau^2/g(T))$
- $g(T)$ can be defined with clinical input



Bayesian Double-Adjustment Approach

A comprehensive integrated method

Proposed Double-Adjustment Approach

Adjust borrowing for both baseline and outcome differences

- Instead of assessing similarity of current data (D) and external data (D_0) by a statistical test as in Jiang et al (2021), calibrate the posterior predictive probability (ppp) of observing a value more extreme than a summary of D given D_0:

$$ppp = \Pr(\widetilde{D_0}^{\,S} > D^S | D_0)$$

- If D_0 and D are similar, ppp would be closer to 0.5
- Binary case: $S \rightarrow$ sample mean
- Normal case: $S \rightarrow$ sample mean (if same variance) or standardized sample mean (if different variances)

Proposed Double-Adjustment Approach

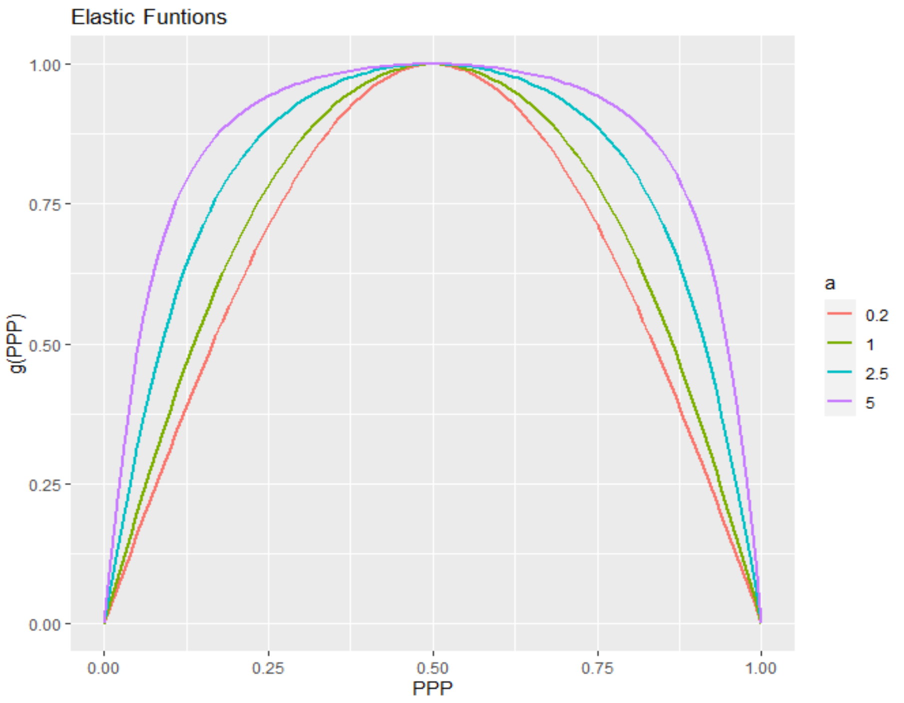
Adjust borrowing for both baseline and outcome differences

- Use the elastic function

$$g(ppp) = \frac{\arctan(a \times \sin(ppp * \pi)\ )}{\arctan(a)}$$

to determine a further discounting factor for each stratum

- The value of a can be tuned with clinical input
- For example, $g(ppp = 0.25) = 0.75$, then a can be calculated to be 0.675



Proposed Double-Adjustment Approach

Adjust borrowing for both baseline and outcome differences

- At S6 of the PS-integrated power prior approach, further adjust the power prior parameter by ppp
  - Overall adjustment: $\alpha_s = \min(1, \frac{A}{n_{0,s}} v_s * ppp)$
  - Stratum-specific adjustment: $\alpha_s = \min(1, \frac{A}{n_{0,s}} v_s * ppp_s)$

A Case Analysis

Addressing both baseline and outcome differences

Case Analysis

A Phase 2 study borrowing external control (EC)

- We applied the proposed double-adjustment BDB approach to a Ph2 trial, utilizing data from a real-world health care data source
- The Ph2 trial has 2 active dose groups + control group
- The outcome is a binary event variable
- Borrow only EC to augment comparison with treatment groups combined

Summary of Current and External Data

A Phase 2 study borrowing external control (EC)

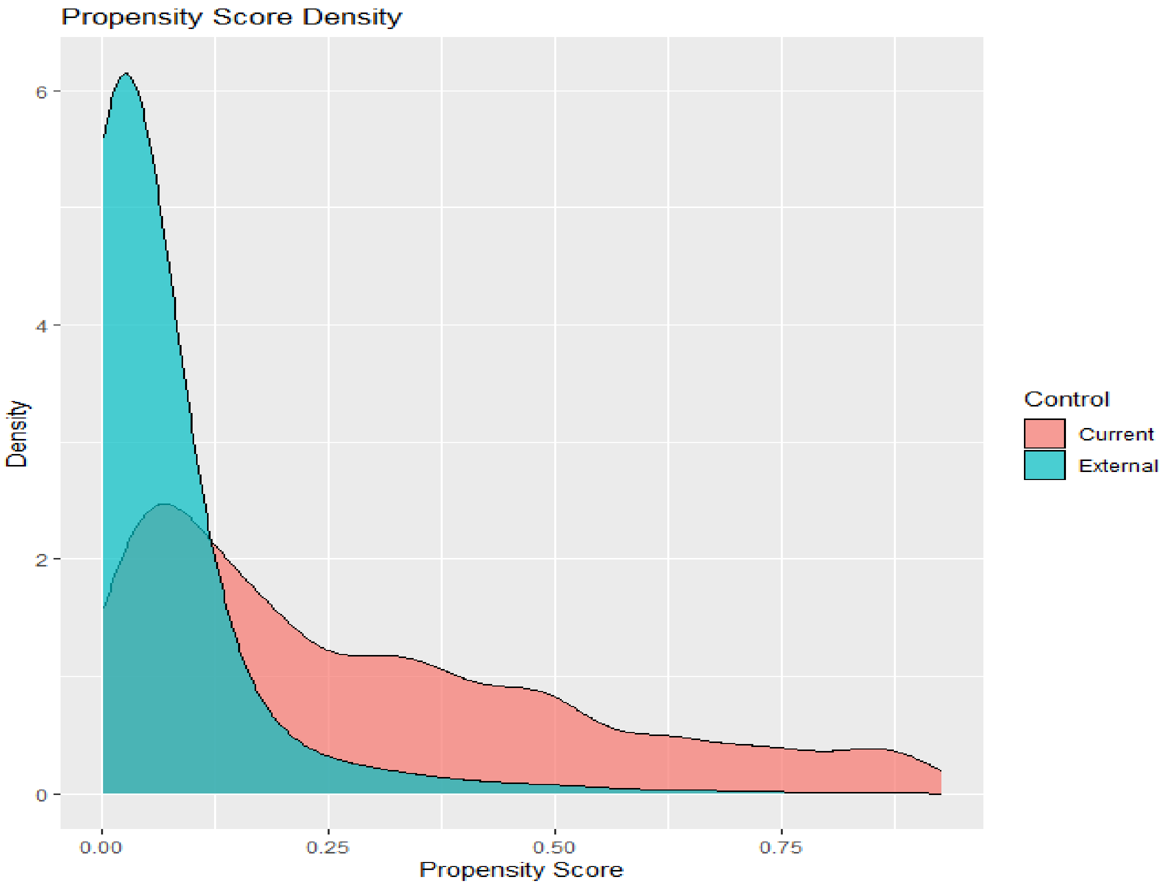
- A subset of EC was identified from the data source
- Summary

	Current Treatment	Current Control	External Control
Number of Patients	505	250	3327
Number of Events	4	6	206
Event rate (%)	0.8	2.4	6.2

PS Modeling, Calculation, Trimming

Similarity of baseline data – current vs. external control

- Logistic regression was applied to current and external control data to obtain propensity scores
- After trimming, 3013 of 3327 EC patients are kept



Stratification

A Phase 2 study borrowing external control data

- Current and external control patients are divided into S=5 strata, with equal number (n=50) of current control patients in each stratum
- Summary of Strata

		Stratum				
		1	2	3	4	5
Current	No. of pts	2266	473	169	77	28
	No. of events	139	31	12	6	1
	Event rate (%)	6.1	6.6	7.1	7.8	3.6
External	No. of pts	50	50	50	50	50
	No. of events	2	0	0	2	2
	Event rate (%)	4.0	0	0	4.0	4.0

Overlapping, Weighing, Discounting

A Phase 2 study borrowing external control data

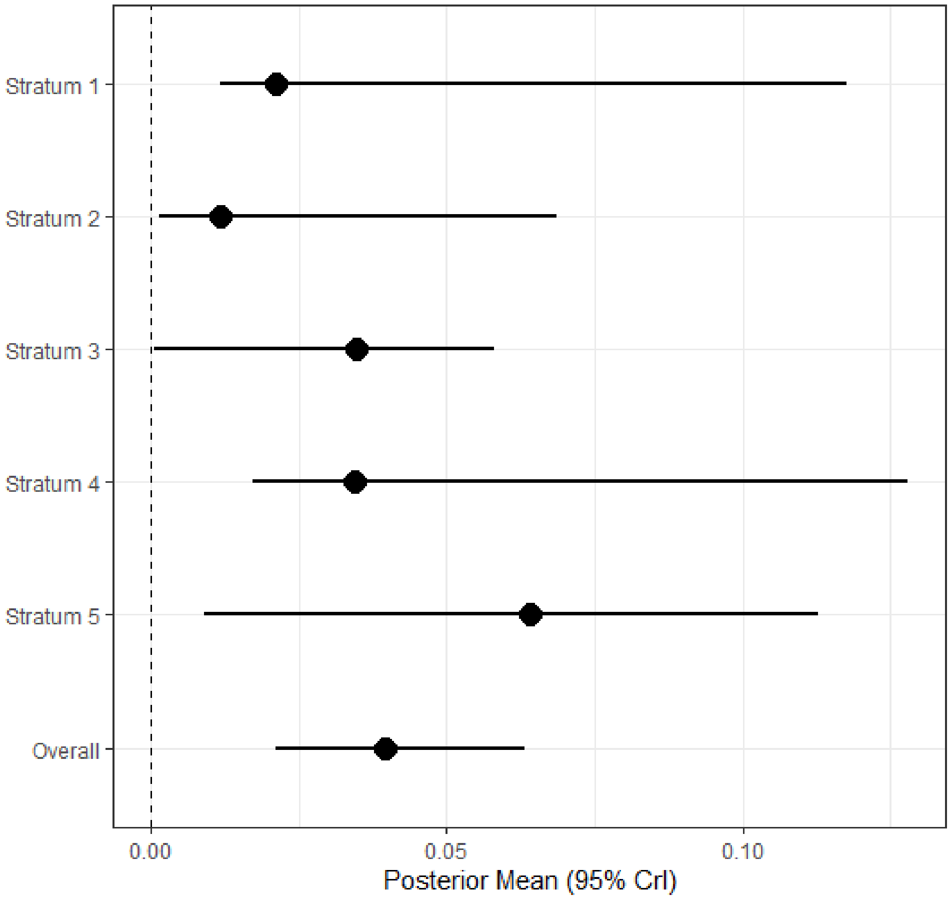
- Current and external control patients are divided into S=5 strata, with equal number (n=50) of current control patients in each stratum
- Summary of EC

	Stratum				
	1	2	3	4	5
r_s	0.66	0.91	0.92	0.95	0.74
v_s	0.16	0.22	0.22	0.23	0.18
a_s	0.017	0.115	0.326	0.736	1
r_s: overlapping prob. Of PS dist'ns; v_s: r_s-adjust weight; a_s: power prior parameter					

Mapping, Discounting, Analysis

A Phase 2 study borrowing external control data

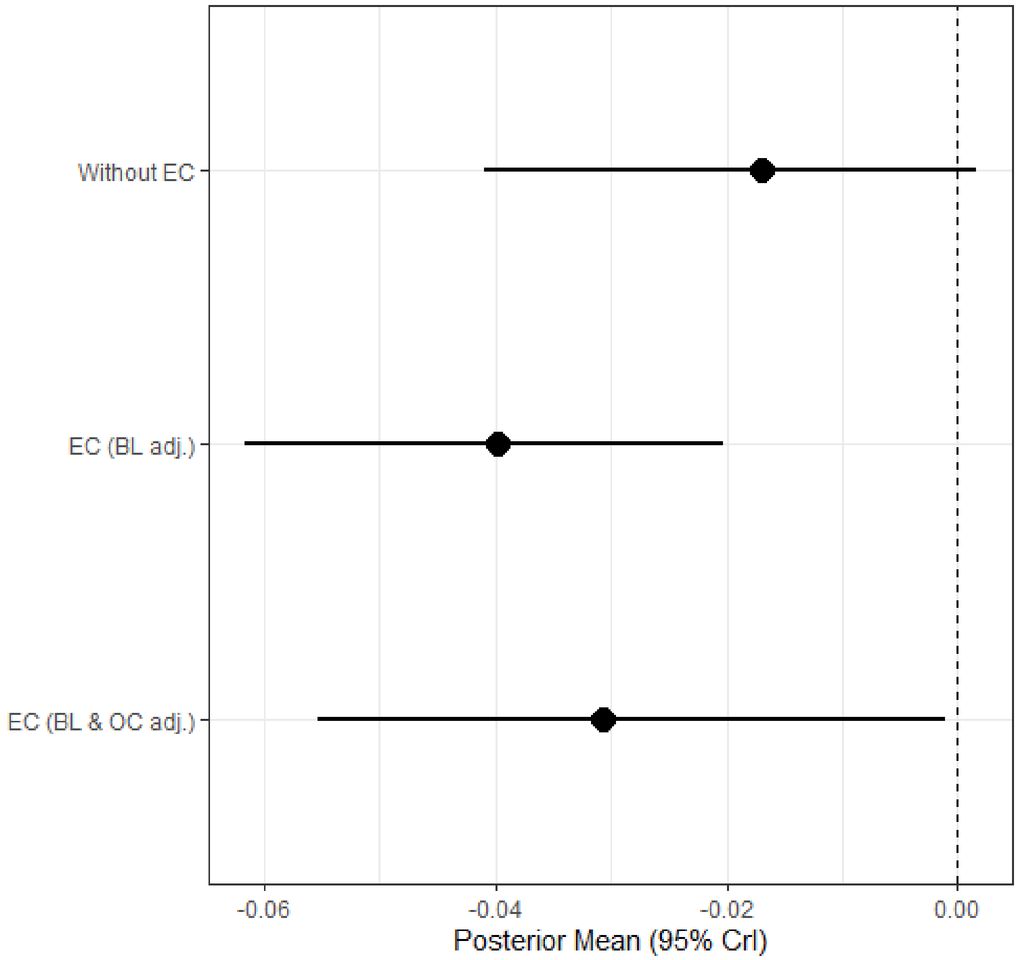
- PPP of current control given EC: <0.01
- Tuning parameter of the arctangent elastic function: a=25
- Discounting for outcome difference: g(PPP)=0.28
- Instead of A=250, borrowing from 0.28*A=70 EC patients



Comparison of Analyses

Comparison of analyses

- Bayesian analysis was conducted for
  - Without EC
  - With EC (adj. for BL)
  - With EC (adj. for BL & OC)
- Excessive influence of EC was attenuated by adj. for outcome differences
- Analysis with EC (adj. for BL & OC) shows higher variability, which might have been caused by small samples/events in strata



Simulations - Normal Response

Adjust for both baseline and outcome differences

Simulation Scenarios

- Data generating scenarios modified from Wang et al (2019)
- A vector $\boldsymbol{X}$ of 10 covariates
  - $F_{X|Z} = MVN(\mu_z, \Sigma_z), z = 0$ (external), 1 (current)
  - Σ_z: same variances (σ_Z^2), same covariances ($0.1\sigma_Z^2$)
  - First 4 covariates are further converted to be binary by cut at 0
- Outcome Y_i for subject i
  - $Y_i|\boldsymbol{X_i}, Z_i = \beta_0 + \boldsymbol{\beta^T X_i} + \epsilon_i + \boldsymbol{O_i}$
    - ϵ_i is the random error
    - O_i is a random outcome disturbance by unaccounted sources

Simulation Scenarios (Cont.)

- Data generating scenarios
  - $\mu_1 = (1, \dots, 1)^t$, $\mu_0 = (1.2, \dots, 1.2)^t$
  - $\sigma_1^2 = 1$, $\sigma_0^2 = 1.5$
  - $\beta_0 = 0$, $\boldsymbol{\beta} = (1, \dots, 1)^t$, $\epsilon_i \sim N(0, 1)$
  - $O_1 = 0$, $O_0 \sim N(d, var = 1.5)$
  - Current $n = 100$, external $n = 1{,}000$

Simulation Results

- Summary of simulation results:

Scenario	d	A	$\hat{\theta}$	Bias	Var	ESS	Cover	Width
1	2	20	9.37	0.008	0.058	12	0.82	0.96
2	2	100	9.59	0.222	0.064	59	0.62	0.99
3	1	20	9.37	0.002	0.061	16	0.81	0.97
4	1	100	9.53	0.161	0.057	82	0.70	0.94

$\hat{\theta}$: posterior mean; Bias: deviation from mean of current data

ESS: effective sample size borrowed from EC

Cover: coverage probability of the true mean by 90% CrI; Width: width of 90% CrI

- Borrowing is less with more outcome differences

Discussion

Remarks and Further work

Conclusion

- Clinical justification is indispensable for application of dynamic borrowing
- The proposed approach provides a reasonable solution for addressing both baseline and outcome differences if dynamic borrowing is warranted
- Both clinical and statistical insights/inputs are needed for realistic and acceptable implementation of the proposed approach as required of other methods
- Dynamic borrowing requires good planning, extensive simulation work, and well-engaged regulatory communication to pre-address potential concerns

Further Work

- Investigate further on application to small-sample/rare-disease scenarios
  - High vs. low event rates
- Look into other data types, including time-to-event variables
- Explore other clinically elicited elastic functions
- Consider utilizing other types of priors than power prior for double adjustment

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Thank you!

Questions?