PSI Conference

A Comprehensive Self-Adaptive Mixture Prior Approach to Dynamic Borrowing from External Data

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Outline

Introduction

Motivation and challenges

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Motivation and challenges in leveraging external data for the analysis of RCTs

Randomized Control Trials (RCTs)

- Considered the “gold standard” to evaluate efficacy and safety of treatments
- Randomization aims to **balance** observed covariates across treatments
- Randomization not always feasible (recruitment, ethical, duration, costs, etc.)

External Data Sources (e.g., historical trials, RWD)

- Issues to be considered when using external data:
  - The **similarity** between trial patients and those from external data sources
  - The **amount of information** that the external data contributes to the statistical inference

Our Goal

- Develop a comprehensive, **self-adaptive** Bayesian dynamic borrowing approach that adjust for both **baseline** and **outcome** differences to determine the **amount of information** borrowing

Bayesian Dynamic Borrowing from External Data

A Brief Review

Power Prior Approach

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

- Bayesian inference of parameter θ, given current data D_1 and external data D_0 is through the following expression:

$$\underbrace{\pi(\theta|D_1)}_{\text{Posterior}} \propto \underbrace{L(D_1|\theta)}_{\text{Likelihood}}\underbrace{L(D_0|\theta)^{\boldsymbol{\alpha_0}}\ \pi_0(\theta)}_{\text{Power prior}}$$

Idea: construct informative prior from historical data; define power parameter to down-weight the influence of historical data on the analysis

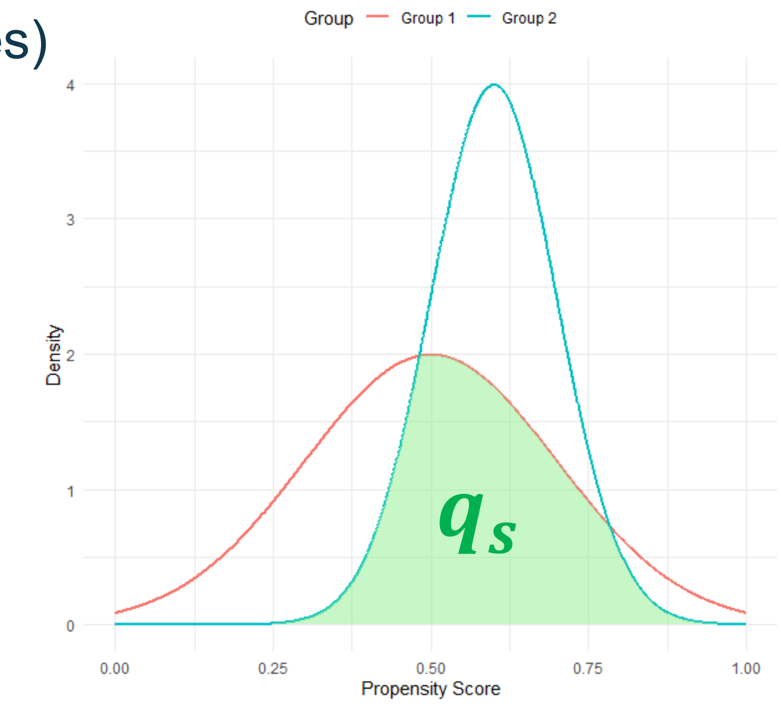
- $\boldsymbol{L(D_1|\theta)}$ is the likelihood of the **current data** given parameter θ
- $\boldsymbol{L(D_0|\theta)}$ is the likelihood of **external data** given parameter θ
- $0 \leq \boldsymbol{\alpha_0} \leq 1$ is a scalar parameter (fixed or random) that controls the weight of influence of D_0 in the analysis of D_1; with higher values of α_0, more information is borrowed from D_0
- $\pi_0(\theta)$ is an initial prior

Propensity Score-Integrated Power Prior (PSIPP)

Wang et al (2019): Adjusts borrowing based on stratified propensity score (PS) similarity

// Stratify current and external subjects into S strata (PS percentiles)

Idea: use overlap of stratified PS distributions of current and external patients to down-weight the external data in the analysis



// q_s: overlapping area of PS distributions of current and external patients

// A : number of subjects to borrow

// $n_{0,s}$: number of external subjects in strata s

// Discount power parameter: $\alpha_s = \min\left(1, \frac{A}{n_{0,s}} \frac{q_s}{\sum_{i=1}^{S} q_s}\right)$

$$q_s = \int_0^1 \min[p_{s,0}(x), p_{s,1}(x)]\, dx$$

// **Power prior**: $\pi(\theta_1, \ldots, \theta_S) \propto \prod_{s=1}^{S} \left[L(D_{s,0}|\theta_s)\right]^{\alpha_s} \pi_0(\theta_1, \ldots, \theta_S)$

Mixture Prior Approach

Schmidli et al. (2014)

To account for the possibility of prior-data conflict and improve the robustness of the inference, fixed-weight mixture prior have been proposed:

$$\pi_{mixture}(\theta) = \tilde{\omega}\pi_{informative}(\theta) + (1 - \tilde{\omega})\pi_{vague}(\theta)$$

Idea: combine and informative prior with a non-informative or vague prior into a single distribution, through a mixing weight

$\pi_{informative}(\theta)$: Informative prior constructed from external data

$\pi_{vague}(\theta)$: Non-informative or vague prior

$\tilde{\omega}$: **prespecified fixed** mixing weight (representing the prior probability of no prior-data conflict between D_1(current) and D_0(external))

Propensity Score Integrated Self Adaptive Mixture Prior

A comprehensive integrated method

Proposed Self-Adaptive Mixture Prior Approach

Define self-adaptive mixture weight

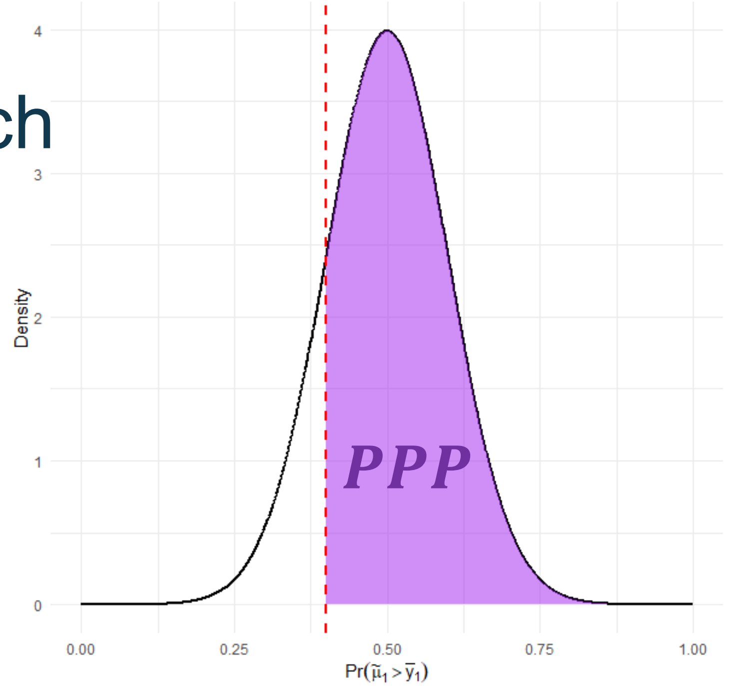
- Assess similarity between current and external data via the **predictive probability of observing the current data given the external data** via the Posterior Predictive Probability:

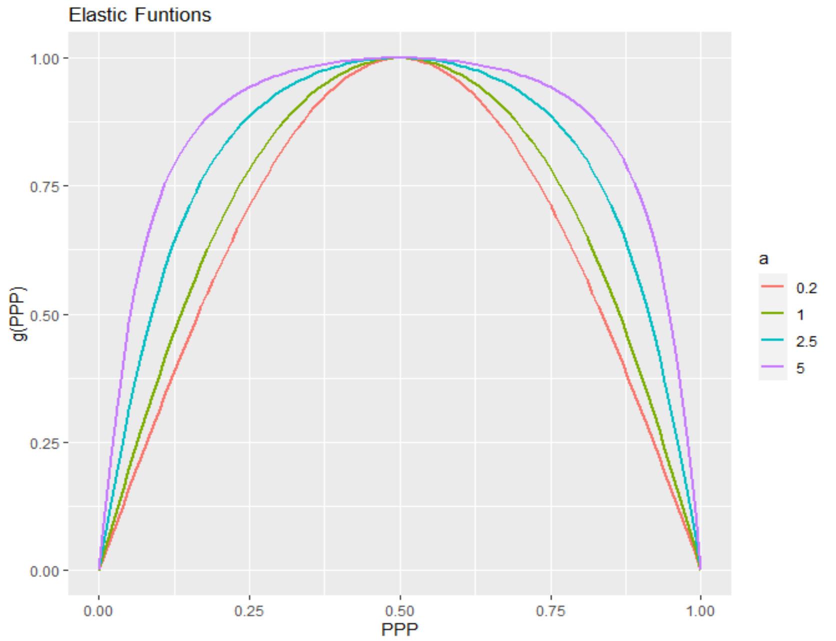
$$PPP = \Pr(\tilde{\mu}_1 > \bar{y}_1 | y_0)$$

  - ➢ $\tilde{\mu}_1$ is the predictive sample mean given external data y_0
  - ➢ $\bar{y}_1$ is the sample mean of the current data

- If external and current data are similar, $PPP \approx 1/2$
- Elastic function $g(PPP) = \dfrac{\arctan(a \times \sin(PPP * \pi)\ )}{\arctan(a)}$
- The value of a can be tuned with clinical input

Self-adaptive mixture weight: $\boldsymbol{\omega} = \boldsymbol{g(PPP)}$





Proposed Self-Adaptive Mixture Prior Approach

The self-adaptive mixture prior for stratum $s = 1,2,3 \ldots, S$, is given by:

$$\pi_{SAMP,s}(\theta) = \boldsymbol{\omega_s}(\boldsymbol{PPP_s})\boldsymbol{\pi_{informative,s}}(\boldsymbol{\theta}) + [1 - \boldsymbol{\omega_s}(\boldsymbol{PPP_s})]\boldsymbol{\pi_{vague,s}}(\boldsymbol{\theta})$$

$\boldsymbol{\pi_{informative,s}}(\boldsymbol{\theta})$: Informative prior for stratum s (derived via PSIPP)

$\boldsymbol{\pi_{vague,s}}(\boldsymbol{\theta})$: Non-informative or vague prior for stratum s

$\boldsymbol{\omega_s}(\boldsymbol{PPP_s})$: Self-adaptive mixture weight for stratum s (depends on PPPs through the elastic function $g(*)$)

Simulation Results

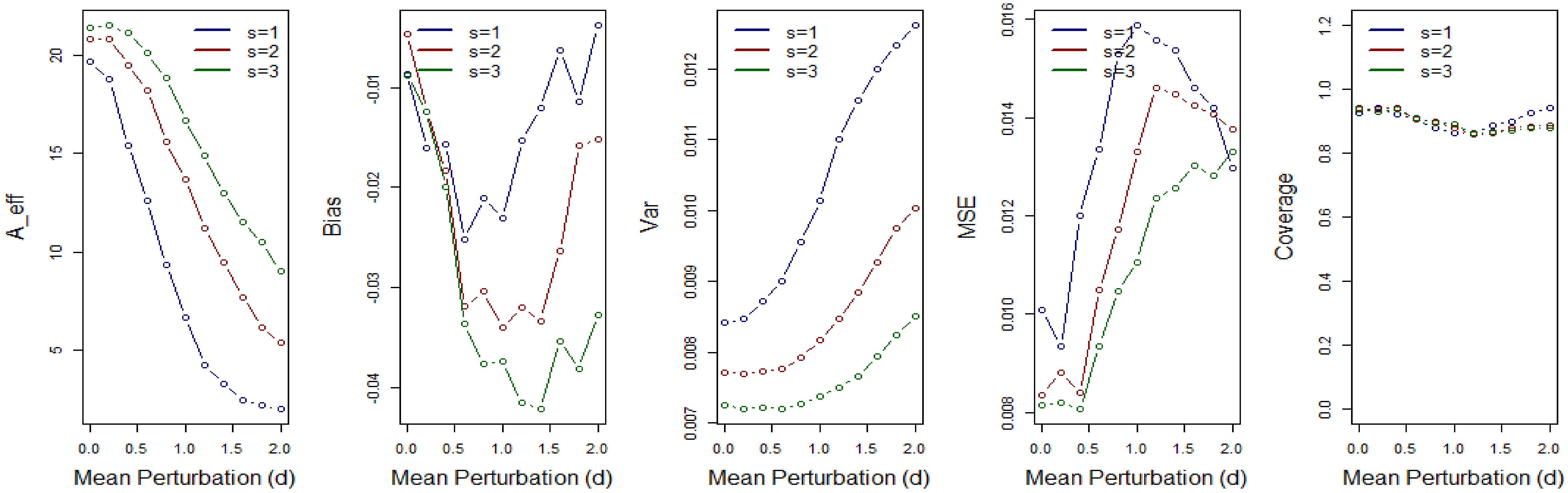
Binary Outcomes

Binary Outcome – Hybrid Control Arm

N1=75 (current), 2:1 treatment-to-control, A=25 (no. to borrow), N0=3000 (external), and s=3 (strata)

$$logit(Y_i|\boldsymbol{X_i}, Z_i) = \beta_0 + \boldsymbol{\beta}^{\boldsymbol{T}}\boldsymbol{X_i} + O_i\ ;\ \boldsymbol{X} = (X_1, \dots, X_{10})^{\boldsymbol{T}};\ \beta_0 = -10.48\ ;\ \boldsymbol{\beta} = (1, \dots, 1)^T;\ F_{X|Z} = MVN(\mu_z, \Sigma_z)$$

$Z = 1$ (current)	$\mu_1 = (1, \dots, 1)^T$	$\sigma_1^2 = 0.1$	$O_1 = 0$
$Z = 0$ (external)	$\mu_0 = (1.02, \dots, 1.02)^T$	$\sigma_0^2 = 0.12$	$O_0 \sim N(d, 0.25)$ (random perturbation)



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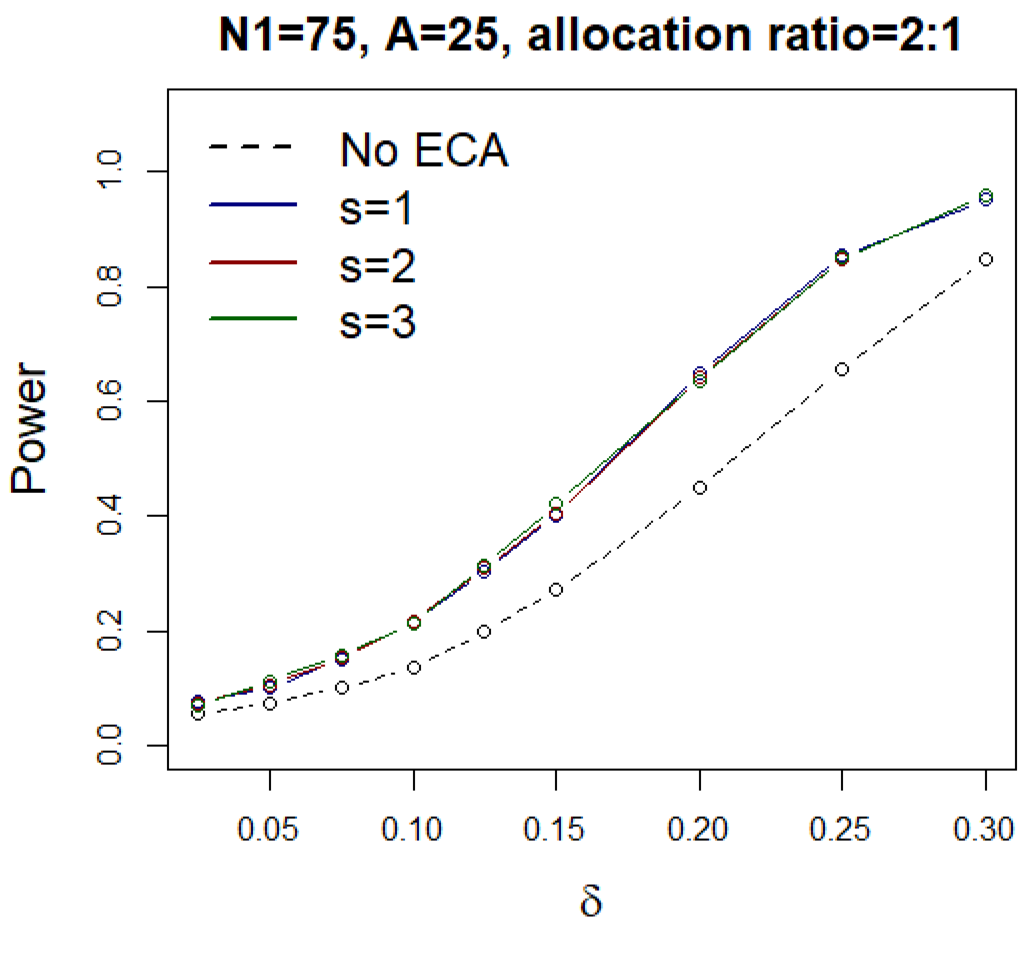
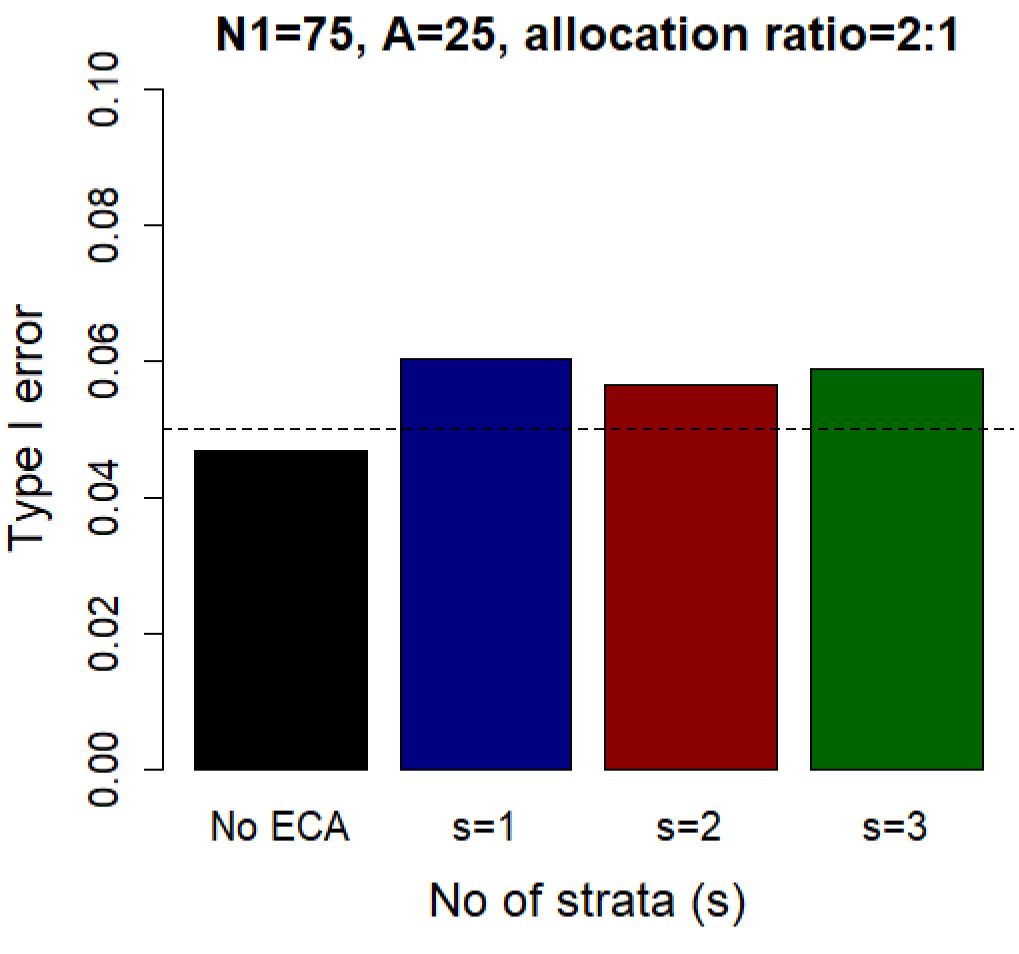




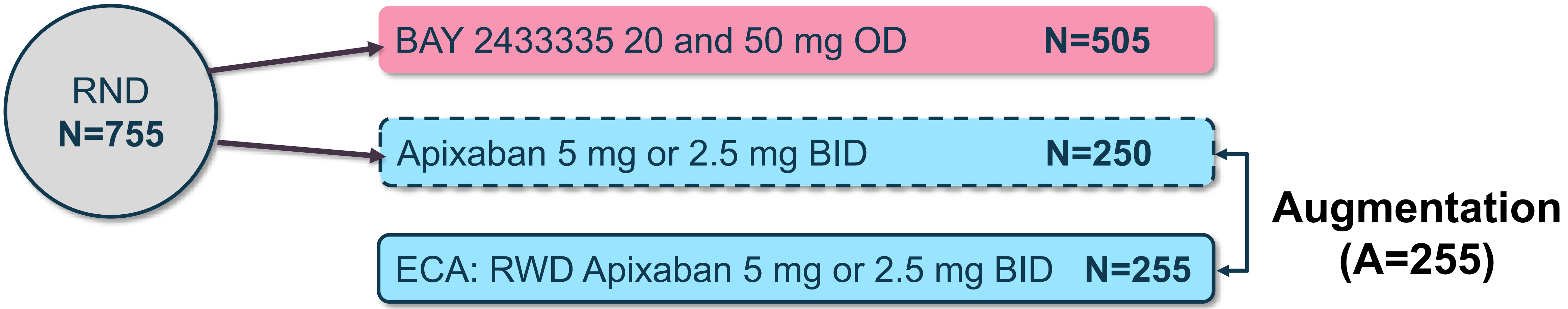
Illustrative Example

Addressing both baseline and outcome differences

Illustrative Example

PACIFIC-AF Phase II trial and External RWD

- **Trial data**: Phase II trial (PACIFIC-AF) to compare efficacy and safety of new factor XIa inhibitor against Apixaban. Two active dose groups and control arm (**N=755, ≈ 2:1 ratio**)
- **External data**: RWD with identical selection criteria as in the trial (N=3327)
- **Outcome**: Major bleeding within 90-days
- **Key Idea**: Augment control arm by borrowing information **equivalent to 255** patients from RWD to attain 1:1 ratio of treatment to control



PS Modeling, Estimation, Trimming

Similarity of baseline data – current vs. external control

- Propensity scores estimated via logistic regression (trial: 755, RWD: 3327)
- 33 baseline covariates as additive linear terms
- Trimming: 3204 of the 3327 external patients were retained (123 excluded)
- Number of strata **s=3**

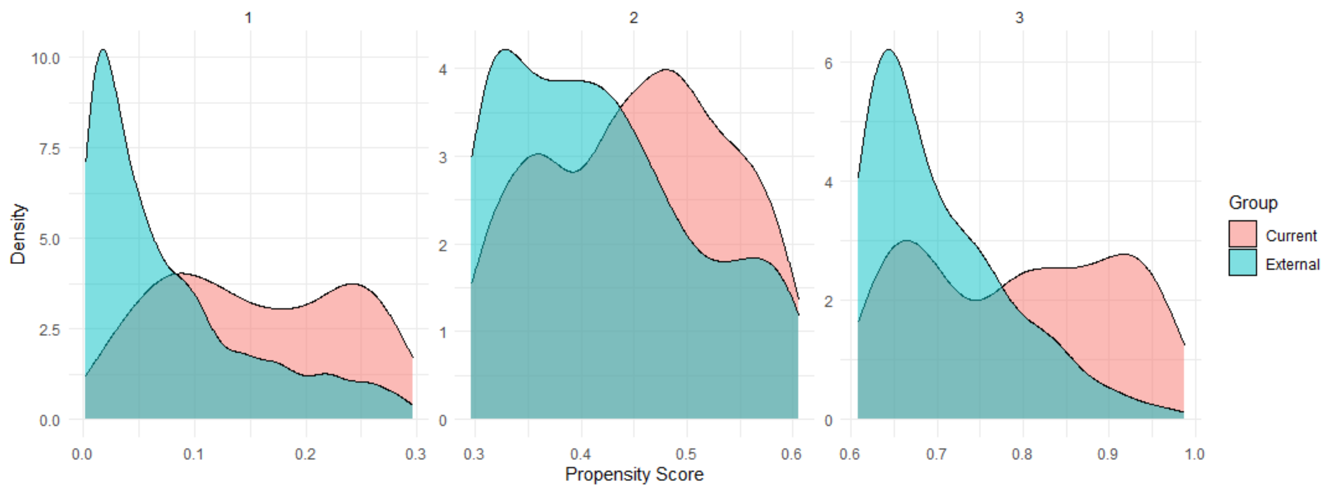


Figure. Propensity score densities by stratum

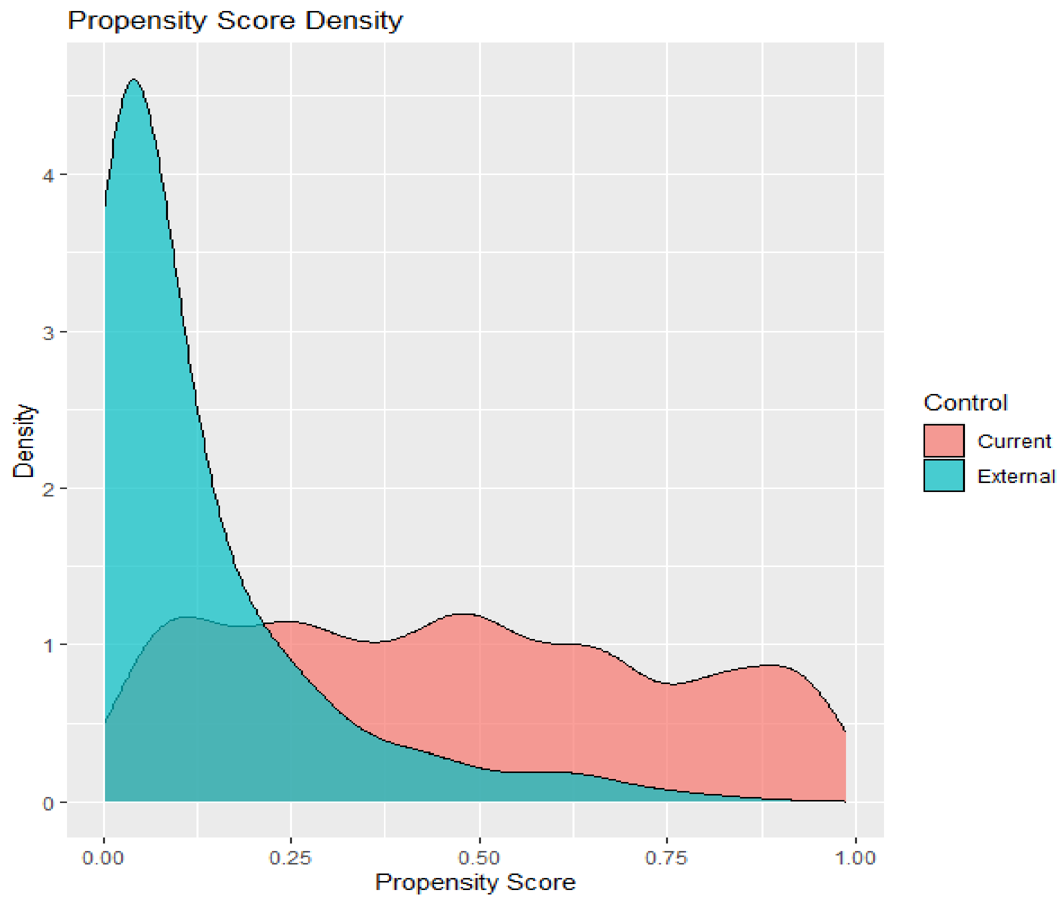


Figure. Propensity score densities for the current study and external data for the illustrative example.

Summary of Current and External Data

PACIFIC-AF Phase II trial and External RWD

Parameter		Stratum			Total
		$s = 1$	$s = 2$	$s = 3$	
Current Study (sample size)	n_{s1}	252	251	252	755
Treatment	n_{s11}	172	172	161	505
Control	n_{s10}	80	79	91	250
Current Study (no. of events)					
Treatment	ne_{s11}	1	1	2	4
Control	ne_{s10}	2	1	3	6
External data (sample size)	n_{s0}	2823	294	87	3204
External data (no. of events)	ne_{s0}	86	8	1	95

Parameters of the self-adaptive mixture prior approach

PACIFIC-AF Phase II trial and External RWD

Parameter		Stratum*			Total
		$s = 1$	$s = 2$	$s = 3$	
Overlapping coefficient	q_s	0.62	0.82	0.64	
Overlapping coefficient normalized	v_s	30%	39%	31%	100%
Discount power parameter	α_s	0.027	0.341	0.904	
Posterior Predictive Probability	PPP_s	0.451	0.626	0.129	
Self-adaptive mixture weight $(a = 0.1)$*	ω_s	0.988	0.923	0.395	
Effective sample size	A_{eff}	77	96	48	**221**

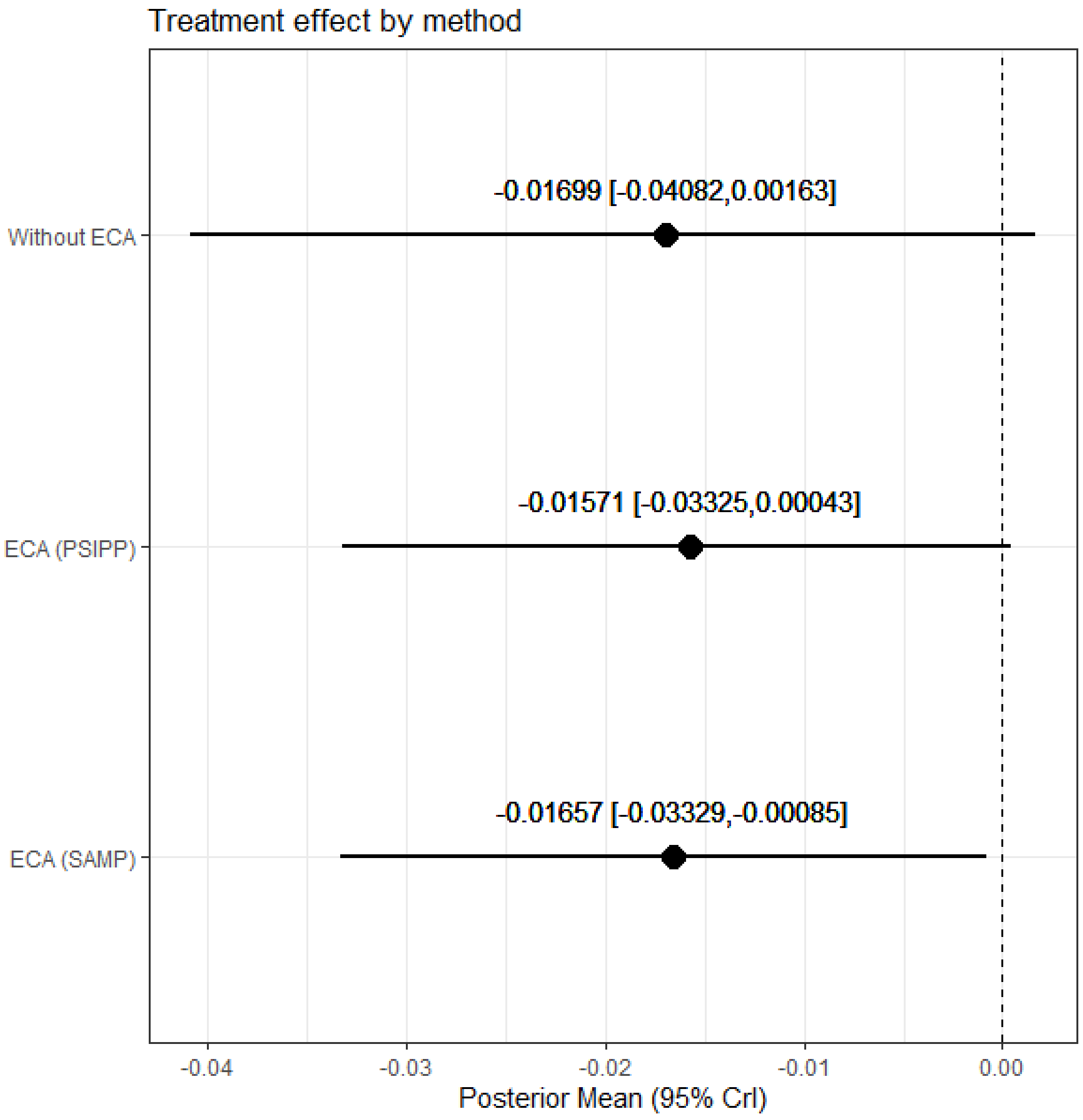
* Number of strata (s) and tuning parameter (a) can be chosen through a grid search aimed at minimizing the MSE

Comparison of Analyses

PACIFIC-AF Phase II trial and External RWD

- Bayesian analysis:
  - Without ECA (Trial data)
  - With ECA (PSIPP)
  - With ECA (PSI-SAMP)

- Adjusting for baseline only, increases precision but slightly shifts the estimate
- Analysis adjusting for baseline & outcome differences attenuates the bias resulted from borrowing from the ECA



Discussion

Summary and Conclusions

Summary and Conclusions

- We propose an integrated self-adaptive Bayesian dynamic borrowing approach
- Baseline differences are accounted for by the overlap of the stratified propensity score distributions
- Self-adaptive mixture weights are function of the predictive posterior probability of observing the current outcome given the outcome of the external data
- The target number of external subjects A is discounted according to the observed degree of difference between current and external data
- Simulations show desirable operating characteristics and adaptive information borrowing
- The proposed approach is intuitive, allows flexibility for adjusting the amount of borrowing, and it enables the incorporation of expert opinion

Key References

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Thank you!

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Back up

Elastic Prior Approach

Jiang et al (2021)

- **Key idea**: Use of “congruence measure” (e.g. T-test) to assess similarity of current D_1 and external data D_0.
- An “elastic function” $\boldsymbol{g(T)}$ is used to map the congruence measure to the interval (0,1)
- The mapped value is used to adjust the prior variance, controlling how much the external data influences the analysis

- Example: Normal endpoint
  - $y_{1,i} \sim N(\theta, \sigma^2)$, $y_{0,i} \sim N(\theta_0, \sigma_0^2)$, with interest in estimating θ
  - Assuming that D_1 and D_0 are incongruent
  - **Elastic prior**: $\pi^*(\theta|D_0) = N\left(\bar{y}_0, \frac{\sigma_0^2}{n_0 \boldsymbol{g(T)}}\right)$

variance is inflated with the elastic function $\boldsymbol{g(T)}$

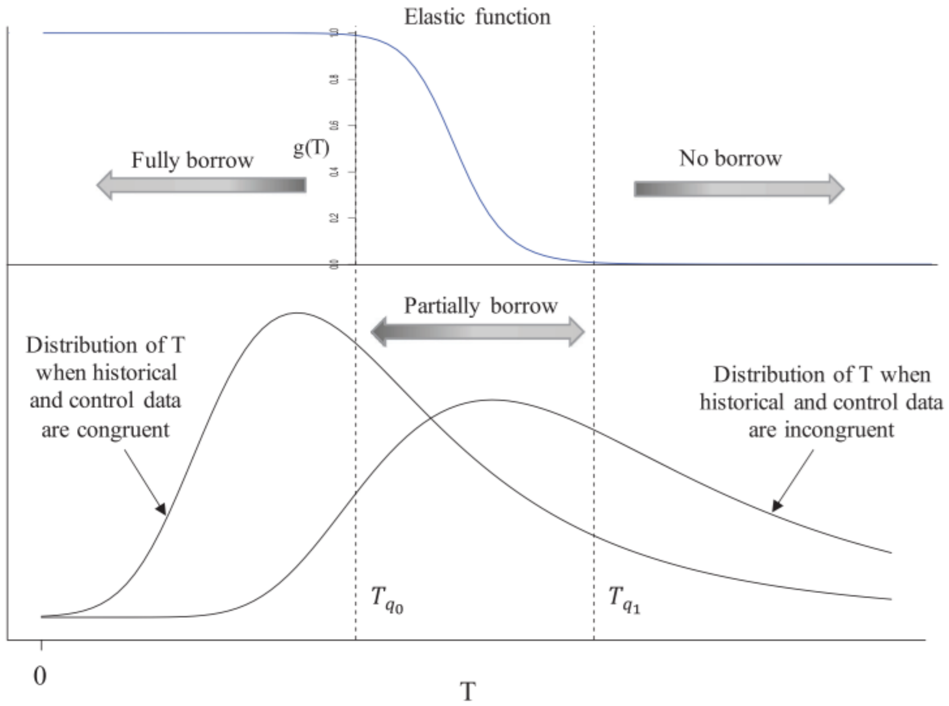


Figure (Jiang et al 2021). Dynamic information borrowing through elastic function

How to choose tuning parameter (a) and number of strata (s)?

Practical recommendations for user-specified parameters

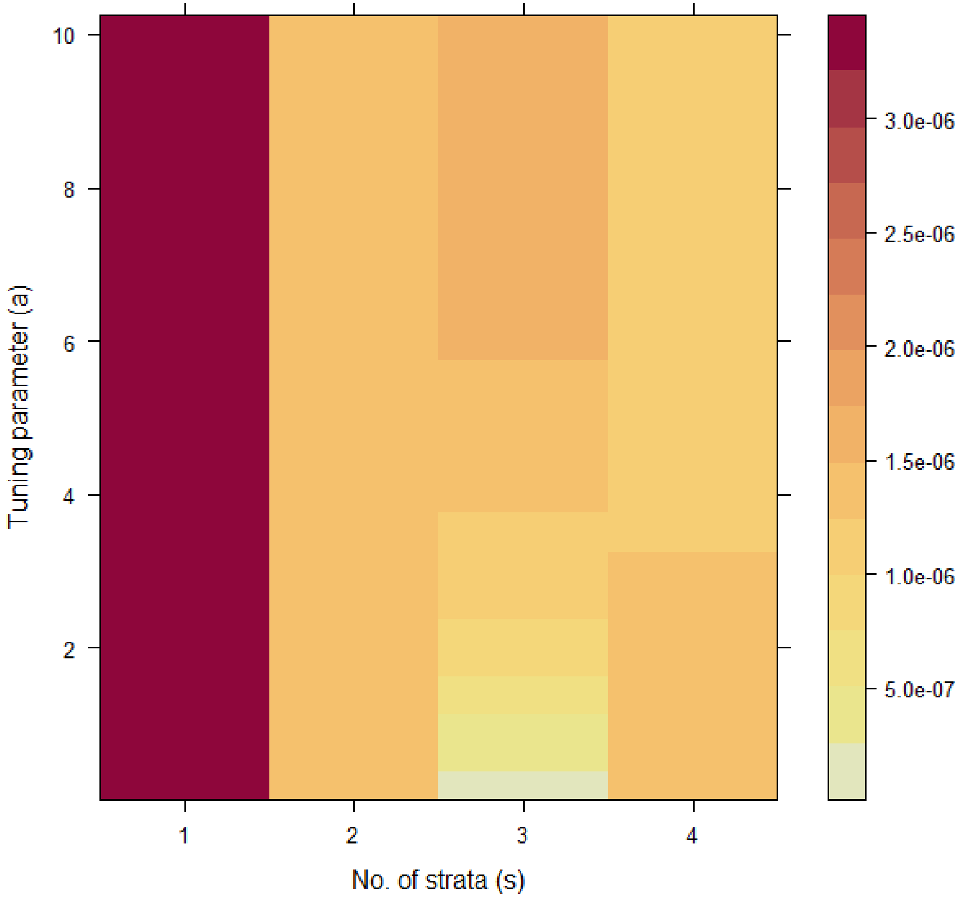
1) Use as reference θ_T (treatment effect from current trial)

2) Define:

$$MSE(s,a) = \left(\hat{\theta}(s,a) - \theta_T\right)^2 + Var\left(\hat{\theta}(s,a)\right)$$

where $\hat{\theta}(s,a)$) is the double adjustment estimator

3) Do a grid search over parameters a and s to minimize MSE



Heatmap of mean squared error *MSE(s,a)*. Minimum is attained at ***a*=0.1** and ***s*=3**

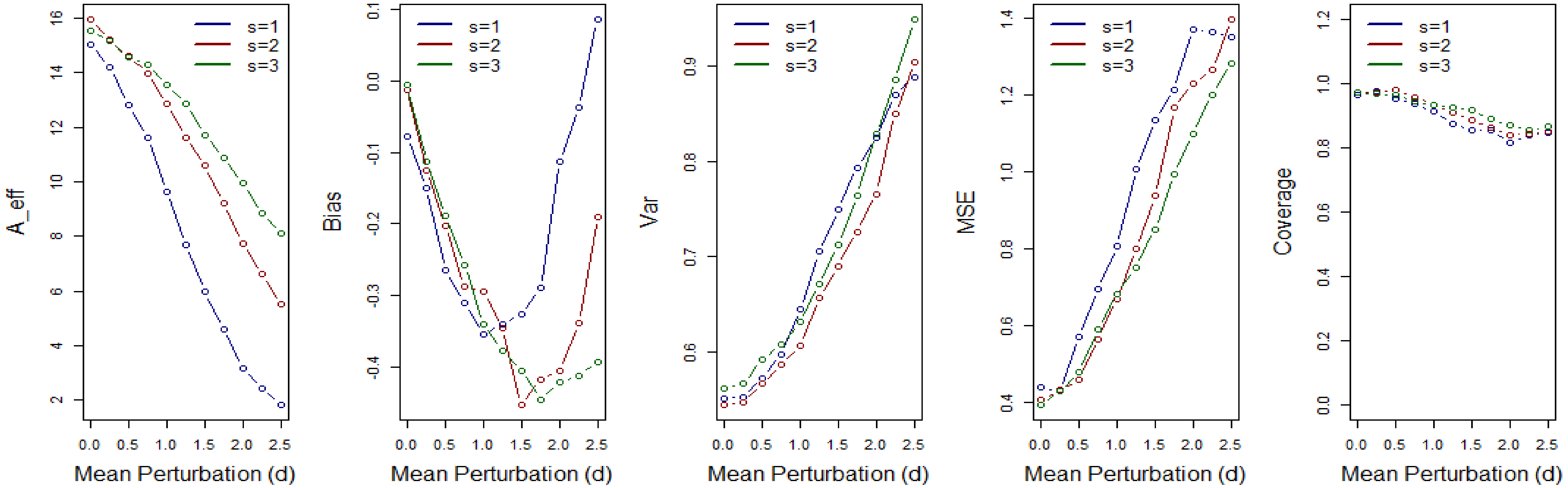
Continuous Outcome – Hybrid Control Arm

Effective SS, bias, variance, MSE and coverage for N1=75 (current), N0=3000 (external), and s=3 (strata)

$Y_i|\boldsymbol{X_i}, Z_i = \beta_0 + \boldsymbol{\beta^T X_i} + \epsilon_i + O_i$; $\boldsymbol{X} = (X_1, \dots, X_{10})^T$; $\beta_0 = 0$; $\boldsymbol{\beta} = (1, \dots, 1)^T$; $\epsilon_i \sim N(0,1)$; $F_{X|Z} = MVN(\mu_z, \Sigma_z)$

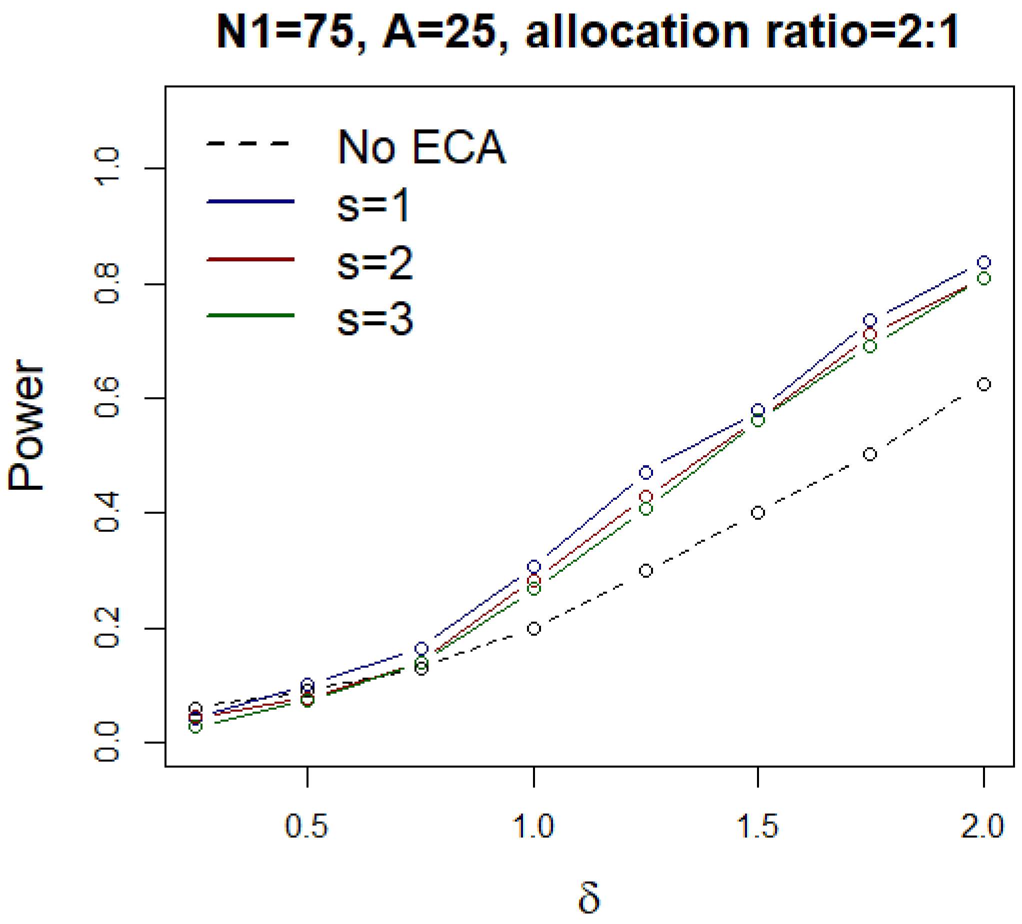
$Z = 1$ (current) $\mu_1 = (1, \dots, 1)^T$; $\sigma_1^2 = 1$; $O_1 = 0$

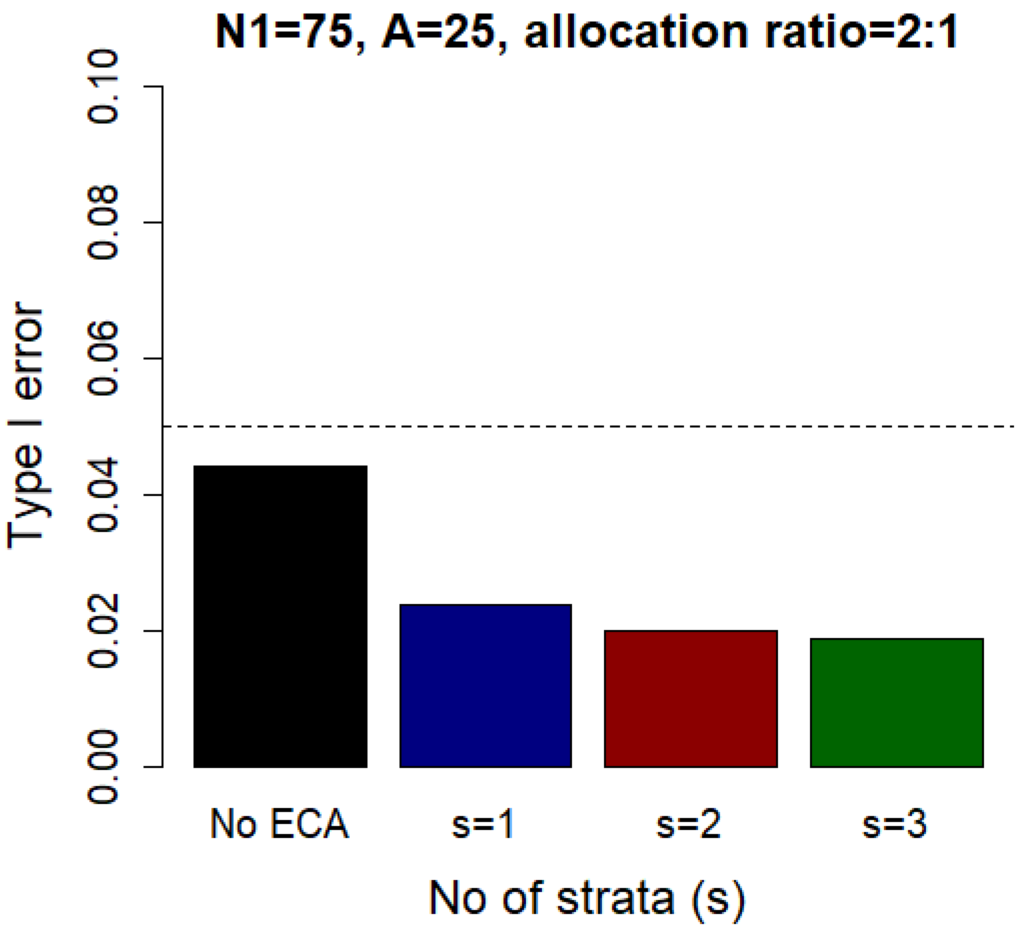
$Z = 0$ (external) $\mu_0 = (1.05, \dots, 1.05)^T$; $\sigma_0^2 = 1.5$; $O_0 \sim N(d, 1.5)$ (random perturbation)



Continuous Outcome – Hybrid Control Arm

Power and Type I error, N1=75, N0=3000, treatment-to-control allocation ratio 2:1, A=25, s=3





Event Rates and Treatment Effect Estimates by Stratum

PACIFIC-AF Phase II trial and External RWD