Regularized MAIC as a Modern Solution for Indirect Treatment Comparison Challenges

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Abstract

The modern era of targeted therapies and narrowed indications may be a benefit for patients but can make indirect comparisons of health technologies difficult. Applications of Matching-Adjusted Indirect Comparison (MAIC) may attempt to match many characteristics, eroding effective sample size (ESS), or failing entirely to find a solution. The objective of this research is to determine whether regularization of MAIC is a viable solution to these challenges. The results of statistical simulation show that regularized MAIC involves a bias-variance tradeoff, with smaller errors for the regularized weights and better ESS compared to the standard method. Moreover, if the two cohorts have large imbalances, the regularized method succeeds where the standard method fails.

Introduction

- MAIC[1] is a method of indirect treatment comparison in which patients from one trial are weighted so that their average characteristics match the average characteristics reported by the competitor. A weighted comparison of outcomes under different treatments follows.

- The goal is to account for differences in sampling between the two trials that would confound the comparison.

- Matching many characteristics is challenging and reduces the information available for comparison (small ESS)[2]. In extreme cases, MAIC can fail entirely.

Methods

- MAIC weights patients in Trial 1 (treatment A) to appear as though they were sampled according to Trial 2 (treatment C).

- Patient characteristics to be balanced are those which modify the treatment effect, and those which modify the outcome if the comparison is not anchored to a common treatment B.
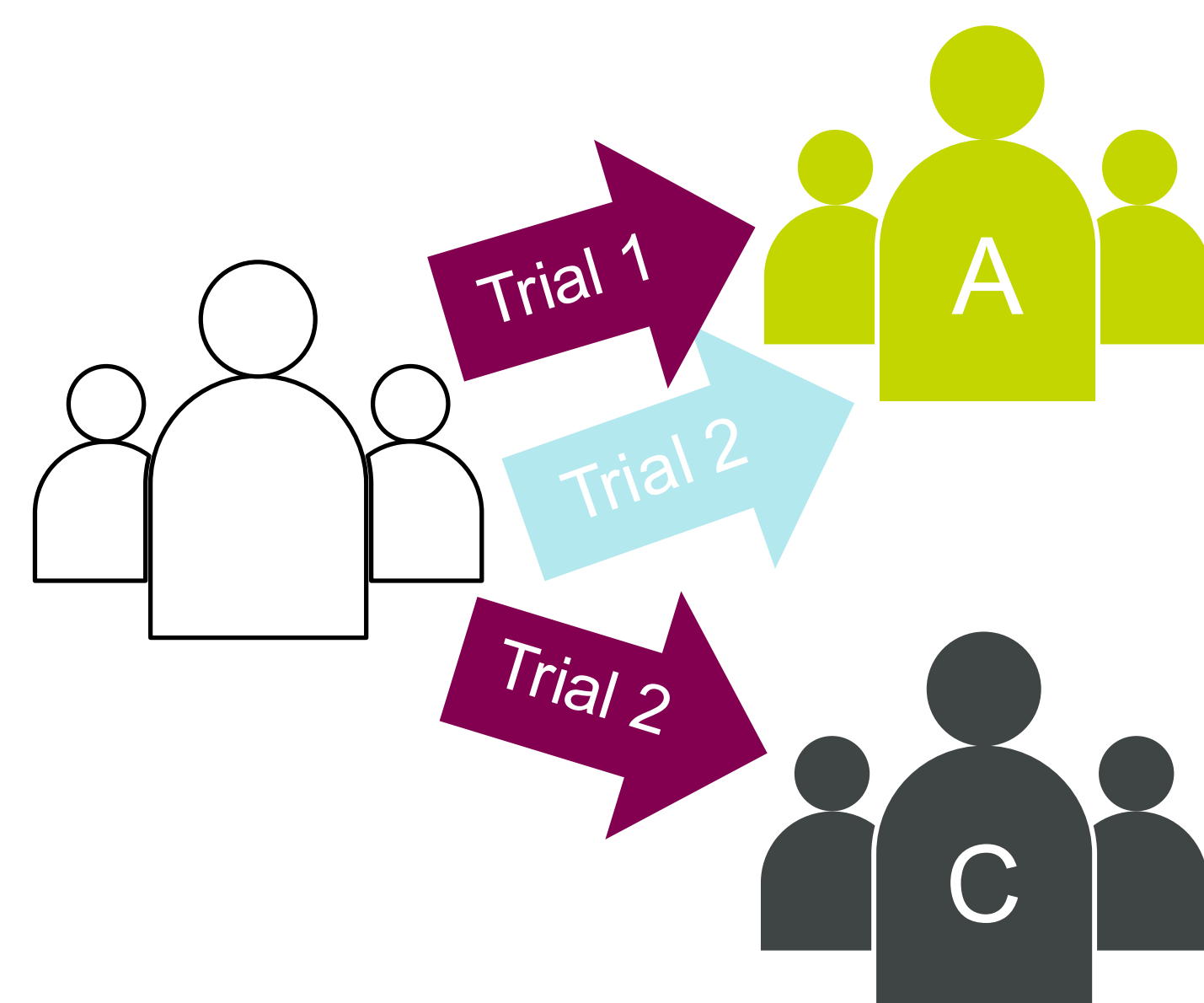
Trials 1 and 2 have different sampling schemes. To compare treatment A vs C, MAIC weights patients from Trial 1 to appear on average as though they were sampled like those in Trial 2.

Standard MAIC[1]

MAIC uses the concept of propensity score weighting, but only moments are available from Trial 2. The propensity score is estimated using:

$$\text{logit}\big(P(T_i = 2|X_i)\big) = \alpha_0 + X_i\alpha$$

where X_i is a vector of covariates to be matched for patient i, α_0 is an intercept term, and α is the vector of coefficients to be estimated.

Weights are proportional to odds of being in trial 2:

$$w_i \propto \left(\frac{P(T_i = 2|X_i)}{1 - P(T_i = 2|X_i)}\right)$$

The $\hat{\alpha}$ is found by moment matching. After some simplification, this amounts to solving

$$\Sigma_i \exp(\tilde{X}_i\hat{\alpha})\tilde{X}_i = 0$$

where $\tilde{X}$ are the covariates centered on average values from trial 2. This is equivalent to optimizing

$$g(\hat{\alpha}) = \Sigma_i \exp(\tilde{X}_i\hat{\alpha})$$

Regularized MAIC

The coefficients $\hat{\alpha}$ are shrunk towards zero. Note that when $\hat{\alpha} = 0$, there is no weighting.

- Ridge: minimize $g(\hat{\alpha}) + \frac{\lambda}{2}\Sigma_j \hat{\alpha}_j^2$ given λ

- Lasso: minimize $g(\hat{\alpha}) + \lambda \Sigma_j |\hat{\alpha}_j|$ given λ

- Elastic net: minimize $g(\hat{\alpha}) + \lambda_1 \Sigma_j |\hat{\alpha}_j| + \frac{\lambda_2}{2}\Sigma_j \hat{\alpha}_j^2$

Statistical simulation

Simulations included 100 patients in each trial, with 10 patient characteristics to match.

- $X_i \sim N(0,1)$ in Trial 1
- $X_i \sim N(\mu,1)$ in Trial 2, with
- $\mu \sim N(0,0.1)$ difference between trials

Two hundred simulations were performed. λ was set so that the standardized mean difference (SMD) was less than 0.1 for all patient characteristics[3,4].
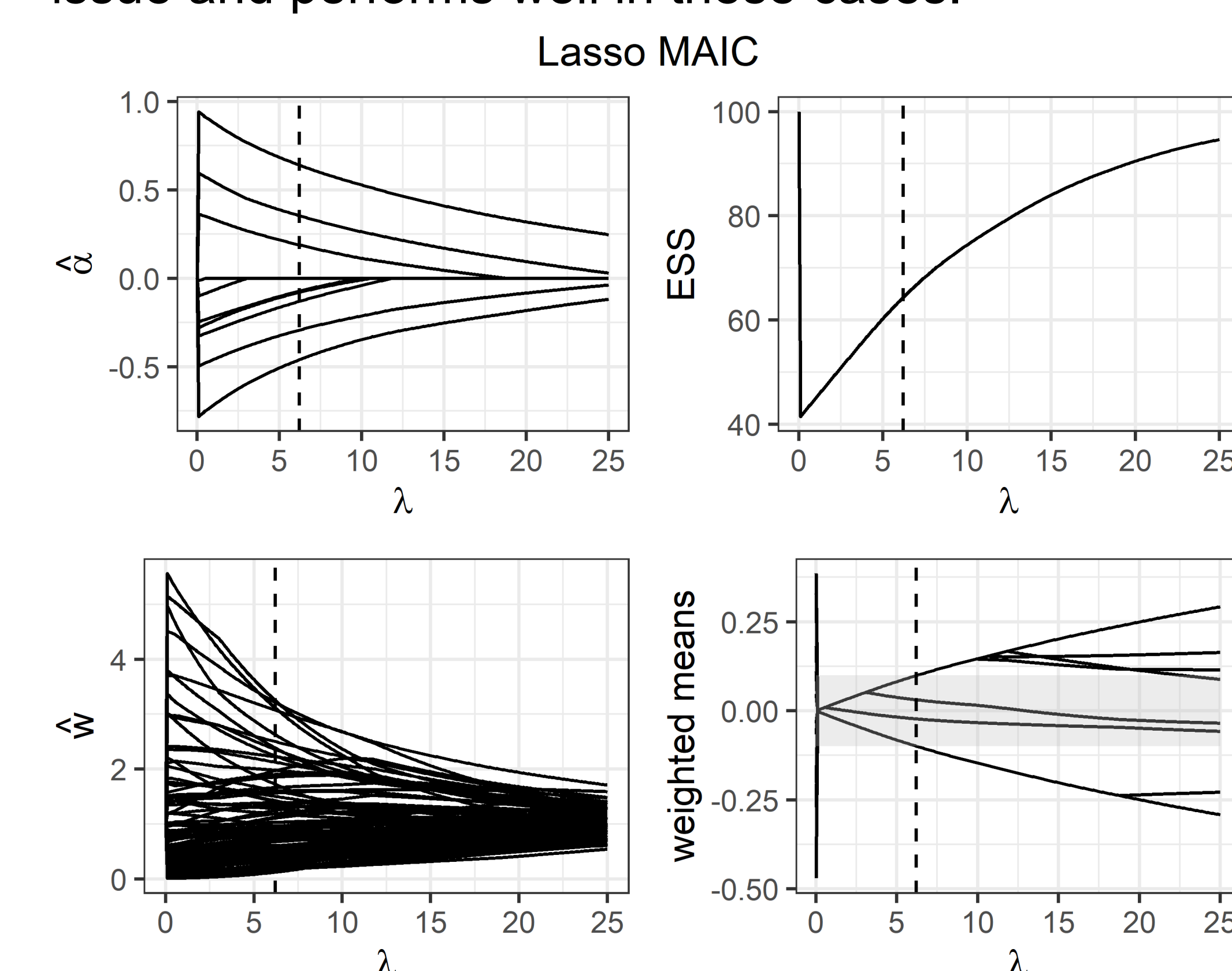
Results

Regularized MAIC performs as expected

Across simulations, the SMD ≤ 0.1 strategy led to reduced root mean squared error (RMSE) and increased ESS at the expense of bias. This tradeoff could be tailored to a given situation as needed. Individual simulations show that significant gains in ESS can be made under modest regularization.

Ridge MAIC
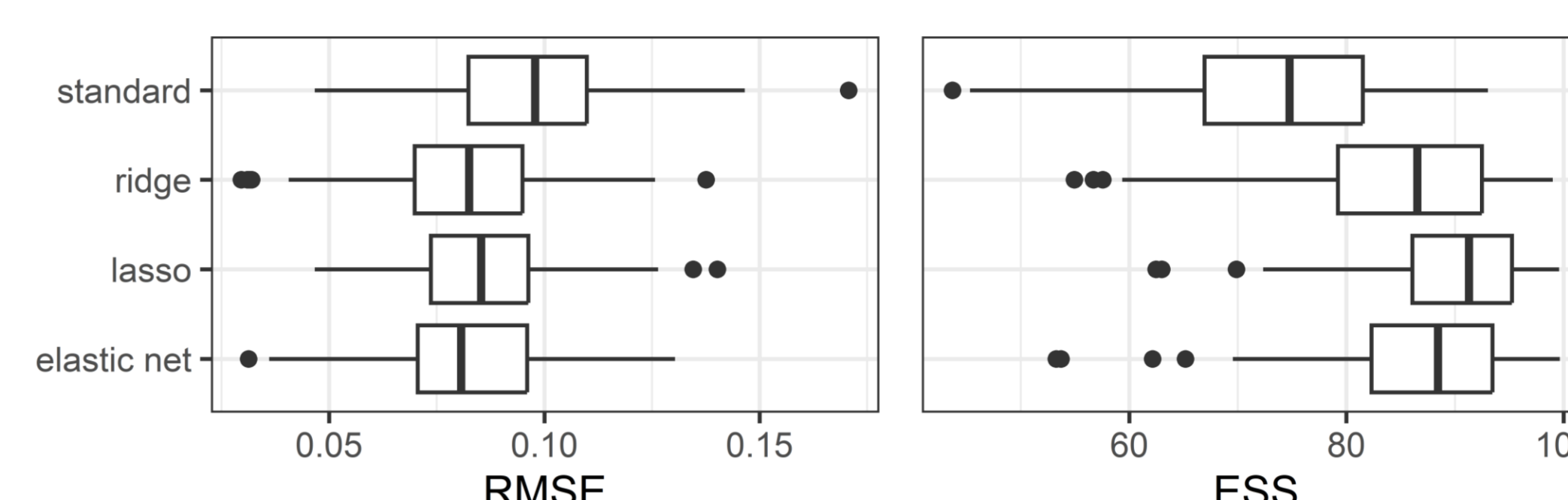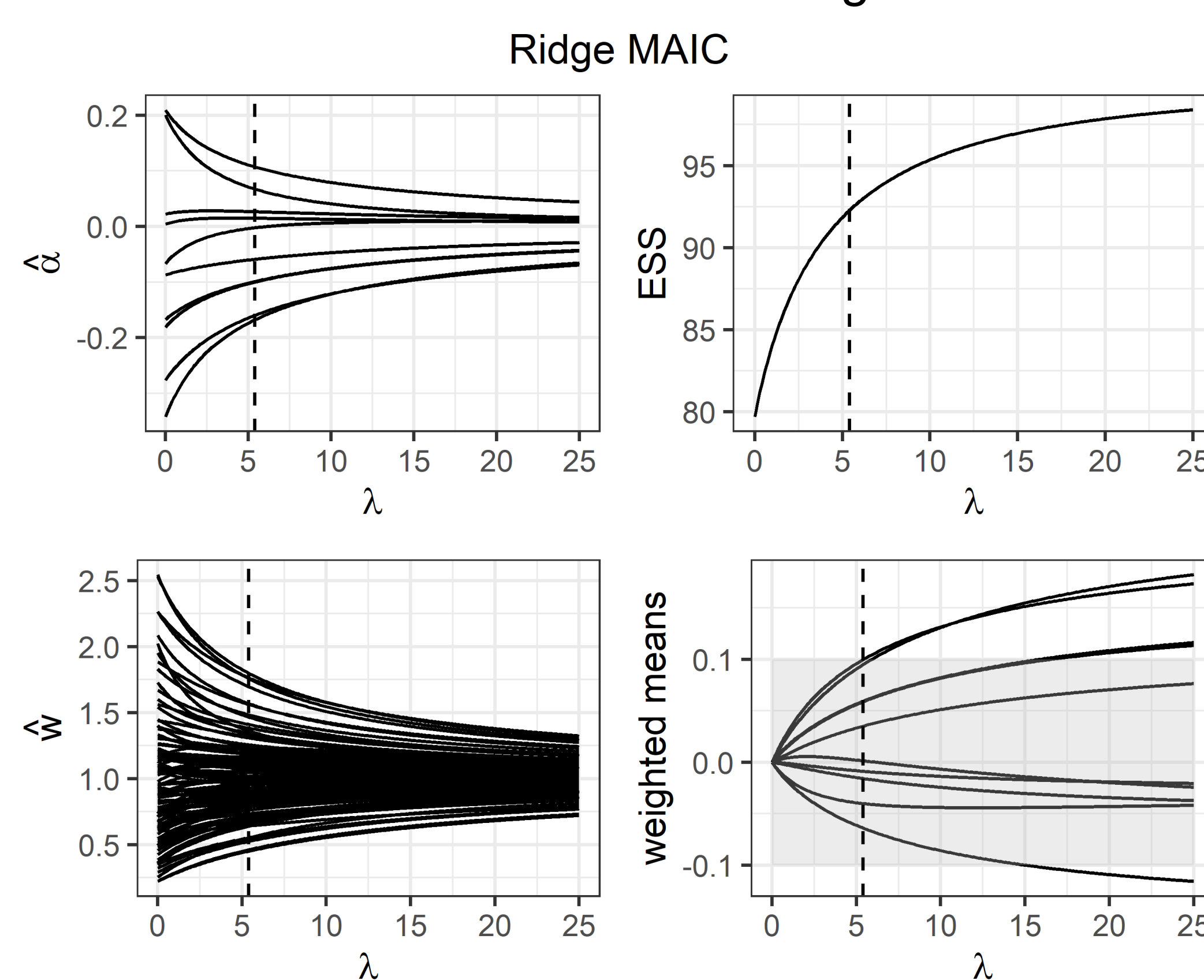
The regularized MAIC methods have improved root-mean-squared-error (RMSE) performance compared to standard MAIC, and meaningfully improved ESS as well.

Simulation with $\mu \sim N(0,0.25)$ can result in failure of the standard MAIC. Regularized MAIC has no issue and performs well in these cases.

Lasso MAIC

Left: Results of a single simulation with a ridge penalty. The gray region shows SMD ≤ 0.1, and the dashed line is the resulting λ value. NB: $\lambda = 0$ corresponds to standard MAIC.

Above: A single simulation in which standard MAIC fails. As expected, the lasso results in a solution.

Conclusions

MAIC is often applied in difficult situations with limited alternatives, and uncertainty can lead to matching many confounders, eroding effective sample size or precluding a solution.

- Regularization is an automatic approach which retains ESS and has smaller RMSE.

- Regularized MAIC can work in tough cases where standard MAIC fails

- The general machinery is well-understood from other regression contexts[5]

References
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