**Description of the simulation scripts**

We performed extensive simulations to study the performance of the proposed method, CAMT, compared to competing methods including AdaPT, IHW, FDRreg, BL, SABHA, ST and BH. The "simulate.data" function in the provided "CAMT" package implements all the simulation settings used in the manuscript. For each setting, the simulation was repeated 100 times and these repetitions were run simultaneously on the institutional HPC cluster ("cluster\_Mayo.R" contains the code for running on the cluster using Open Grid Scheduler). We provided all the simulation codes for reproduction purpose. Each simulation script contained codes for a specific setting. The names of these simulation scripts were mainly in the format of cov\_{norm， gamma}\_k\_{0, 1}\_r\_{0, 1}, where {norm, gamma} indicates the distribution of the z-score under the alternative, k\_{0, 1} indicates whether the covariate also affects the alternative distribution and r\_{0, 1} indicates whether to simulate correlations among the z-scores. For each main setting, there may be variants and were indicated with additional numbers or suffixes. Specifically, we have the following scripts

**cov\_gamm\_k\_0\_r\_0.v2.R**: 10,000 features are simulated, one covariate (normally distributed) affects pi0 only, z-score under H1 follows a noncentral [gamma] distribution, z-score under H0 follows a standard normal distribution (uniform distribution for p-value), and no correlation exists among the z-scores. One-sided p-values are calculated. The "knockoff+" procedure is used for CAMT. Different levels of signal density, covariate strength and signal strength are simulated.

**cov\_norm\_k\_0\_r\_0\_1.v2.R**: 10,000 features are simulated, one covariate (normally distributed) affects pi0 only, z-score under H1 follows a noncentral [normal] distribution, z-score under H0 follows a standard normal distribution (uniform distribution for p-value), and no correlation exists among the z-scores. One-sided p-values are calculated. The "knockoff+" procedure is used for CAMT. Different levels of signal density, covariate strength and signal strength are simulated.

**cov\_norm\_k\_0\_r\_0\_2.v2.R**: 10,000 features are simulated, one covariate (normally distributed) affects pi0 only, z-score under H1 follows a noncentral normal distribution, z-score under H0 follows a standard normal distribution (uniform distribution for p-value), and no correlation exists among the z-scores. One-sided p-values are calculated. The ["hybrid"] procedure is used for CAMT. Different levels of signal density, covariate strength and signal strength are simulated.

**cov\_norm\_k\_0\_r\_0\_3.v2.R**: 10,000 features are simulated, one covariate (normally distributed) affects pi0 only, z-score under H1 follows a noncentral normal distribution, z-score under H0 follows a normal distribution with a negative mean ([a left skewed distribution for p-value under H0, increasing f0]), and no correlation exists among the z-scores. One-sided p-values are calculated. The "knockoff+" procedure is used for CAMT. Different levels of signal density, covariate strength and signal strength are simulated.

**cov\_norm\_k\_0\_r\_0\_4.v2.R**: 10,000 features are simulated, one covariate (normally distributed) affects pi0 only, z-score under H1 follows a noncentral normal distribution, z-score under H0 follows a normal distribution with a positive mean ([a right skewed distribution for p-value under H0, decreasing f0]), and no correlation exists among the z-scores. One-sided p-values are calculated. The "knockoff+" procedure is used for CAMT. Different levels of signal density, covariate strength and signal strength are simulated.

**cov\_norm\_k\_0\_r\_0\_5.v2.R**: 10,000 features are simulated, one covariate ([T-distributed (df = 5)]) affects pi0 only, z-score under H1 follows a noncentral normal distribution, z-score under H0 follows a standard normal distribution (uniform distribution for p-value), and no correlation exists among the z-scores. One-sided p-values are calculated. The "knockoff+" procedure is used for CAMT. Different levels of signal density, covariate strength and signal strength are simulated.

**cov\_norm\_k\_0\_r\_0.v2.1000.R**:[1,000] features are simulated, one covariate (normally distributed) affects pi0 only, z-score under H1 follows a noncentral normal distribution, z-score under H0 follows a standard normal distribution (uniform distribution for p-value), and no correlation exists among the z-scores. One-sided p-values are calculated. The "knockoff+" procedure is used for CAMT. Low signal density, moderate covariate strength and signal strength are simulated.

**cov\_norm\_k\_0\_r\_0.v2.100000.R**: [100,000] features are simulated, one covariate (normally distributed) affects pi0 only, z-score under H1 follows a noncentral normal distribution, z-score under H0 follows a standard normal distribution (uniform distribution for p-value), and no correlation exists among the z-scores. One-sided p-values are calculated. The "knockoff+" procedure is used for CAMT. [Extremely low signal density (>99%), moderate covariate strength and low signal strength are simulated. This simulation setting tries to mirror the signal structure in the EWAS data.]

**cov\_norm\_k\_0\_r\_1\_1.v2.R**: 10,000 features are simulated, one covariate (normally distributed) affects pi0 only, z-score under H1 follows a noncentral normal distribution, z-score under H0 follows a standard normal distribution (uniform distribution for p-value), and [block correlation structure (positive correlations)] exists among the z-scores. One-sided p-values are calculated. The "knockoff+" procedure is used for CAMT. Different levels of signal density, covariate strength and signal strength are simulated.

**cov\_norm\_k\_0\_r\_1\_2.v2.R**: 10,000 features are simulated, one covariate (normally distributed) affects pi0 only, z-score under H1 follows a noncentral normal distribution, z-score under H0 follows a standard normal distribution (uniform distribution for p-value), and [block correlation structure (both positive and negative correlations)] exists among the z-scores. One-sided p-values are calculated. The "knockoff+" procedure is used for CAMT. Different levels of signal density, covariate strength and signal strength are simulated.

**cov\_norm\_k\_0\_r\_1\_3.v2.R**: 10,000 features are simulated, one covariate (normally distributed) affects pi0 only, z-score under H1 follows a noncentral normal distribution, z-score under H0 follows a standard normal distribution (uniform distribution for p-value), and [AR1 correlation structure (all positive correlations)] exists among the z-scores. One-sided p-values are calculated. The "knockoff+" procedure is used for CAMT. Different levels of signal density, covariate strength and signal strength are simulated.

**cov\_norm\_k\_0\_r\_1\_4.v2.R**: 10,000 features are simulated, one covariate (normally distributed) affects pi0 only, z-score under H1 follows a noncentral normal distribution, z-score under H0 follows a standard normal distribution (uniform distribution for p-value), and [AR1 correlation structure (positive and negative correlations)] exists among the z-scores. One-sided p-values are calculated. The "knockoff+" procedure is used for CAMT. Different levels of signal density, covariate strength and signal strength are simulated.

**cov\_norm\_k\_1\_r\_0\_1.v2.R**: 10,000 features are simulated, two covariates (normally distributed) affect [pi0 and mean of f1 (z-score)] respectively, z-score under H1 follows a noncentral normal distribution, z-score under H0 follows a standard normal distribution (uniform distribution for p-value), and no correlation exists among the z-scores. One-sided p-values are calculated. The "knockoff+" procedure is used for CAMT. Different levels of signal density, covariate strength and signal strength are simulated.

**cov\_norm\_k\_1\_r\_0\_2.v2.R**: 10,000 features are simulated, two covariates (normally distributed) affect [pi0 and mean of f1 (z-score) respectively, where we further reduce the s.d. of f1 to simulate a stronger effect], z-score under H1 follows a noncentral normal distribution, z-score under H0 follows a standard normal distribution (uniform distribution for p-value), and no correlation exists among the z-scores. One-sided p-values are calculated. The "knockoff+" procedure is used for CAMT. Different levels of signal density, covariate strength and signal strength are simulated.

The above simulation scripts are designed to run on the HPC cluster (OGS). To run these scripts, create a folder with the same name as the script. Please change the working directory in these files. Then put **“cluster\_Mayo.R”** in the same folder and source the script in the R environment. Since the HPC environment for different institutions may be different, additional configurations are needed to run the simulations. After running the simulations, the results will be collected in an R data object with the same name as the simulation script. The following scripts will be used to generate the plots:

**SimResultProcess\_powercurve.R**: generate plots for all the simulation settings except **cov\_norm\_k\_0\_r\_0.v2.100000.R**. The script produces combined plots of power and FDR curves at different signal strengths. Only FDRreg with theoretical null is included.

**SimResultProcess\_powercurve(EmpricalNull).R**: generate plots for **cov\_norm\_k\_0\_r\_0\_4.v3.R and cov\_norm\_k\_0\_r\_0\_4.v2.R,** where the null p-values are not uniformly distributed. The script produces combined plots of power and FDR curves at different signal strengths. FDRreg with [both theoretical and empirical null] are included.

**SimResultProcess\_powercurve(m=100000).R**: generate plots for **cov\_norm\_k\_0\_r\_0.v2.100000.R,** where we only simulate one level of signal strength, signal density and covariate strength. The script produces combined plots of power and FDR curves [at different FDR target levels]. Only FDRreg with theoretical null is included.

Finally, the script **SurrogateLikelihoodFitExample.R** is used to study the fit of the surrogate likelihood.