Accurate and Computationally Efficient Analysis of Longitudinal fMRI data

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Introduction

There is growing need for longitudinal analyses of structural and functional MRI data. Standard software, SPM and FSL in particular, cannot accurately model these data when there are $k > 2$ visits, and cannot accommodate between-subject covariates (e.g. gender) within their repeated measures models.

In this work we propose the use of Ordinary Least Squares (OLS) combined with sandwich estimator (SwE) standard errors [1] to provide fast and valid inferences. We compare this approach to the naive OLS (N-OLS) longitudinal model typically used in FSL & SPM, and Generalized Least Square (GLS) [2]. N-OLS is obtained by including subject indicator variables as covariates; while this is fast, it is only correct for balanced designs with a certain "compound symmetric" covariance structure, and it precludes fitting subject-level covariates. GLS is the gold standard (used in R's lmer & SAS's proc_mix) but is slow and may fail to converge.

Methods

We compare three univariate models for inference on longitudinal data: N-OLS, GLS, and SwE via Monte Carlo simulation (10,000 simulations for each setting). For a range of subject sample sizes ($n = 12, 25, 50, 100, 200$) and number of visits ($k = 3, 5, 8$), and compound symmetric ($\rho = 0.9$) and non-compound symmetric (Toeplitz, $[0.9, 0.8, \ldots]$) intra-visit correlation structure. We evaluate the properties of the estimates of a within-subject covariate (the linear effect of visit number), and of a pure between-subject covariate (a random covariate value assigned to each subject, akin to initial age). We also compare those 3 methods with an unbalanced design matrix taken from a real fMRI study with 41 subjects and from 2 to 3 visits [3].

For each setting, we evaluate: (1) relative SE (Standard Error) Bias, the relative average error in the estimated variance of the parameter of interest, (2) relative P-value Bias, the mismatch between nominal α and observed false positive rate (FPR), and (3) relative SE Stdev, the standard deviation of the standard error estimates (normalized to the mean Monte Carlo standard error). We also evaluate 4 different versions of the SwE that differ by the assumption of homogeneity ("Hom") or heterogeneity ("Het", as suggested in [4]) between subject, and by the use of unstandardized residuals ("type A") or standardized residuals ("type B", as suggested in [5] and [6]).

Results

Under CS and a balanced design, N-OLS and GLS give identical performance, and the SwE similar performance (Fig. 1). But with a non-CS (Toeplitz) correlation N-OLS and GLS give appreciable bias, with false positives up to 7× nominal (Fig. 2). For a between-subject covariate, N-OLS cannot be used, and SwE gives similar performance to GLS (Fig. 3). In each instance, the "SwE Hom Type B" was the most accurate, i.e. SwE assuming homogeneous variance over subjects & using standardized residuals. With the design from the real study, we find similar results, with SwE giving performance similar to GLS & N-OLS under CS and the best performance without CS correlation (Fig. 4).

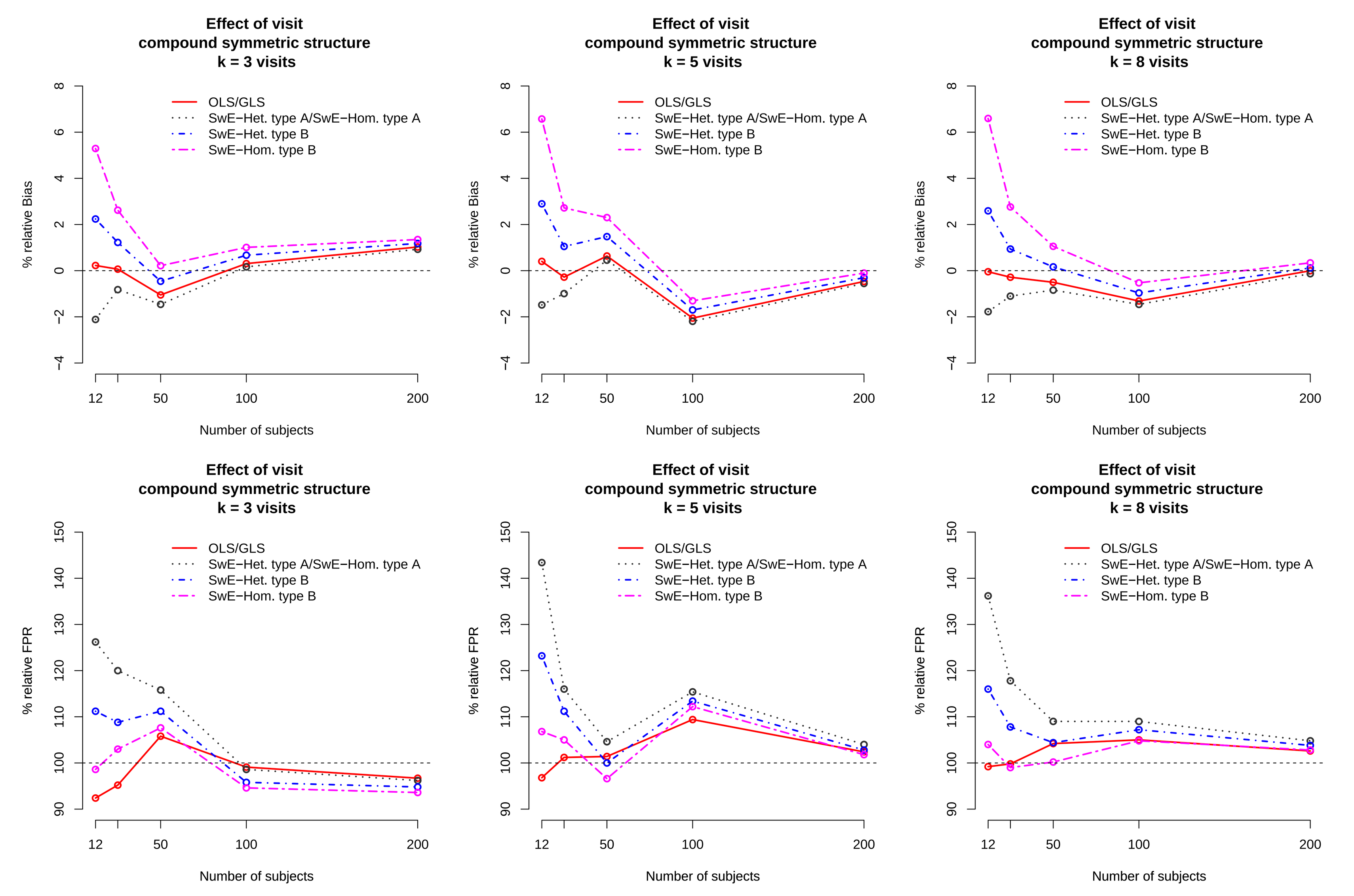

Figure 1: Linear effect of visit with compound symmetry, in the rows are relative bias in the standard error, and relative FPR of N-OLS, GLS and SwE.

Discussion

Our results show that OLS with Sandwich Estimator standard errors provides accurate inferences in a variety of settings and the ability to estimate between-subject effects without resorting to GLS.

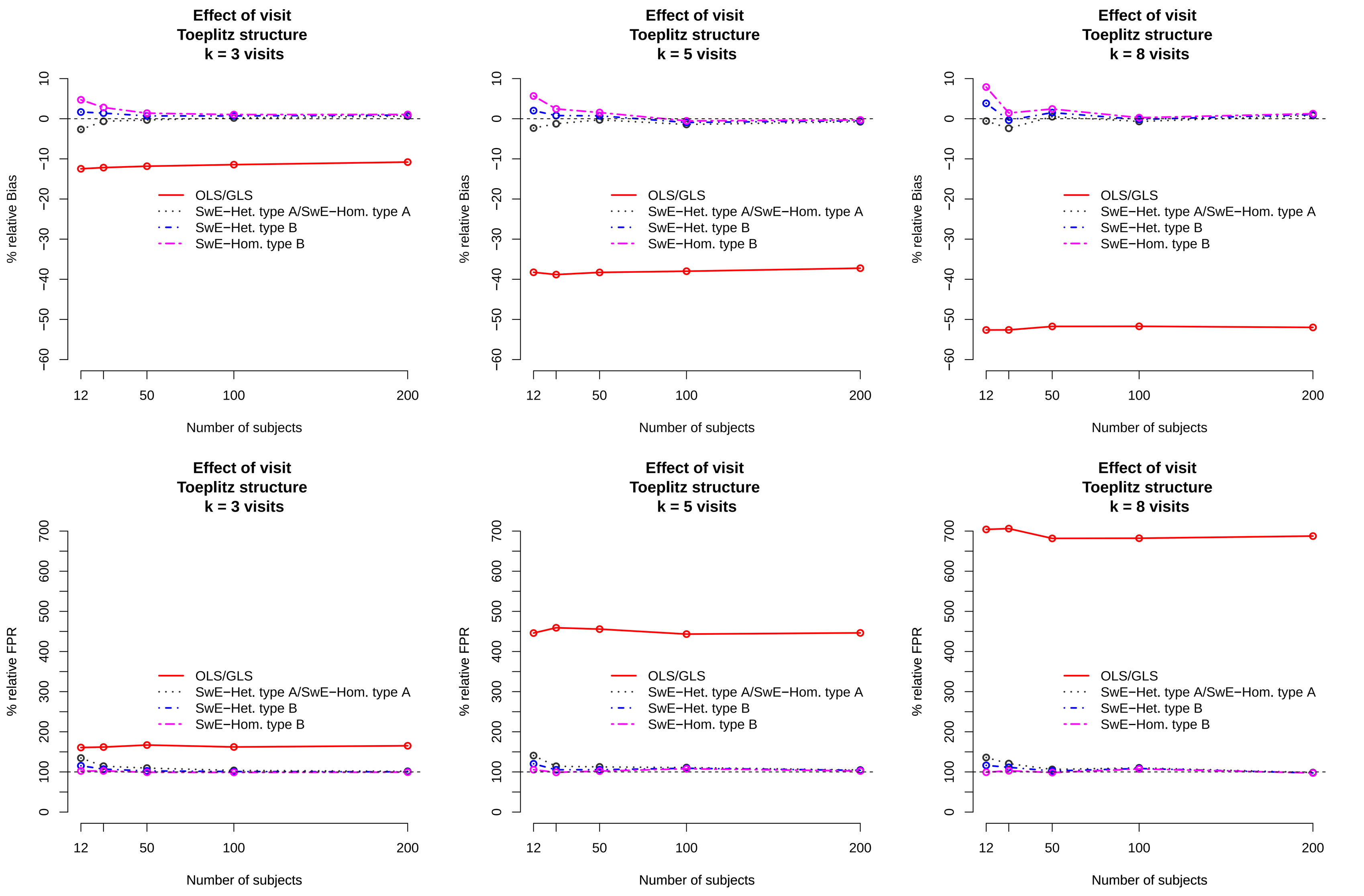

Figure 2: Linear effect of visit with non-compound symmetry (Toeplitz structure); same format as Figure 1 otherwise.

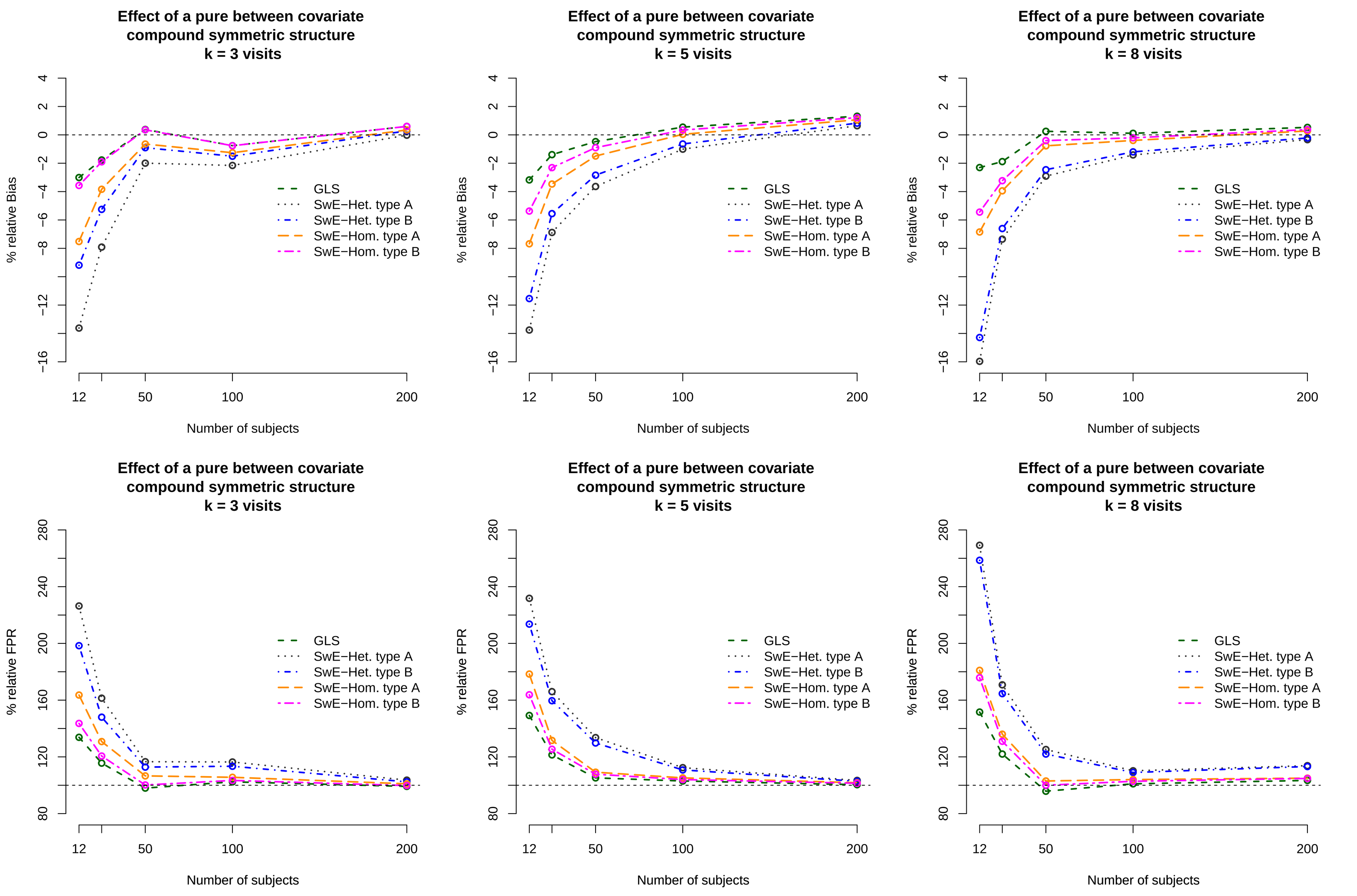

Figure 3: Effect of a pure between covariate with compound symmetry, in the rows are relative bias in the standard error, and relative FPR of GLS and SwE.

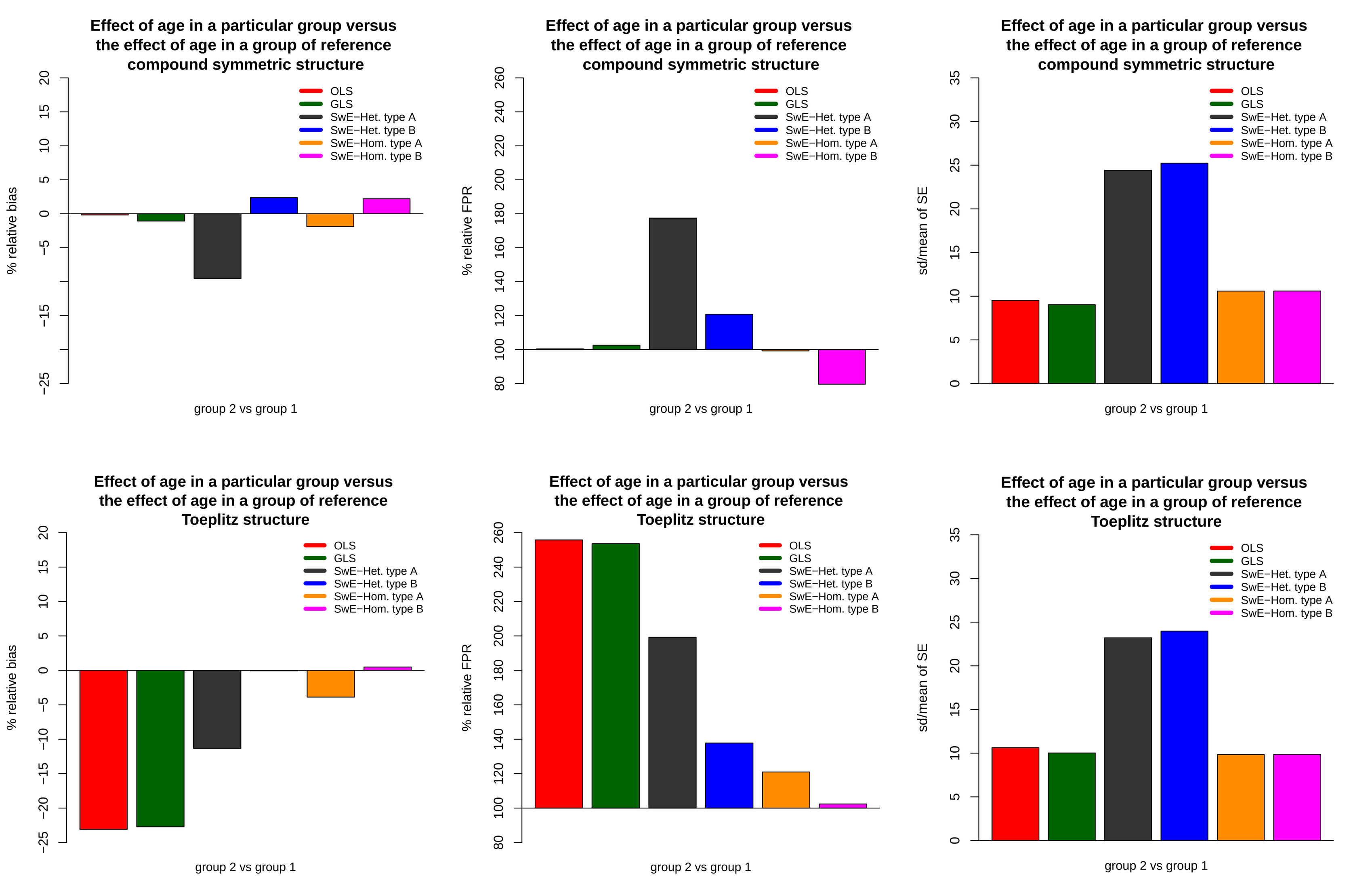

Figure 4: Performance with imbalanced real study design, inference on difference of slopes (age-dependent BOLD) between two groups. In the columns are relative bias in the standard error, relative FPR, and relative SE stdev of N-OLS, GLS and SwE, in the rows are compound symmetric, and Toeplitz structure for the intra-visit correlation

References

[1] White (1981). JASA, 76(374), 419-433.
[2] Laird & Ware (1982). *Biometrics*, 38(4):963-974.
[3] Heitzeg et al. (2008). *Alcoholism: Clin. & Exp. Res.* 32:414426.
[4] Diggle, et al. (1994). *Analysis of Longitudinal Data*. OUP.
[5] MacKinnon & White (1985). *J. Econometrics*, 29:305-325.
[6] Long & Ervin (2000). *Am. Statistician*, 54:217-224.

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