Robust testing in generalized linear models by sign-flipping score contributions

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Outline

1. Motivation
2. Flip score test (known nuisance parameters)
3. Effective Flip score test
4. Standardized Flip Score Test
5. Extensions (Multivariate + Clustered)

Permutation tests

Usually

- require less assumptions
- exact control of Type I Error, even for small sample size
- converge to parametric counterpart
  (ie asymptotically same power)
- multivariate (multiplicity correction): easy and powerful

A major limitation: Continuous Confounders

Example: Poisson model ($g() = log()$ link function)

$$log(E(y_i)) = g(\mu) = \eta = \gamma_0 + \gamma_1 z_i + \beta x_i, \;\; i = 1, \dots, n$$

$$H_0: \;\beta = 0 \;\; \forall\, \gamma = (\gamma_0, \gamma_1)$$

- Z is **categorical**: y_i are exchangeable **within levels**. Permute y_i within levels to get the null distribution.
- Z is **continuous**: Residualization is problematic: $V(y_i) = e^{\gamma_0 + \gamma_1 z_i}$ depends on the covariates.

Solutions with some limitations: Gail et al., (1988), Heller et al., (2009), Parhat et al. (2014), Pauly et al (2015).

Flip Score test

In this presentation we focus on GLM:

- Effective Flip Score test: Hemerik, Goeman, Finos. *Robust testing in generalized linear models by sign-flipping score contributions*. JRSS-B `doi:10.1111/rssb.12369`
- Standardized Flip Score test: De Santis, Goeman, Hemerik, Finos
  `https://arxiv.org/abs/2209.13918`.

Both approaches are:

- **Robust**: allow for biased variance estimators (i.e. overdispersion, heteroscedastic, etc)
- **Flexible**: general approach, many extensions

Outline

The parametric score test

$$
\begin{aligned}
Score &= \left.\frac{\partial \ell(\beta|x,z,y)}{\partial \beta}\right|_{\beta=0} \\
&= \sum_{i=1}^{n} \frac{\partial}{\partial \beta} \log f_\gamma(y_i) = \\
&= \sum_{i=1}^{n} \nu_i \underset{H_0}{\dot\sim} N(0,\mathcal{I}) \ \ \text{(asymptotically, under } H_0\text{)} \\
&\quad \mathcal{I}\text{: Fisher Information Matrix}
\end{aligned}
$$

$\nu_i \sim NOTnormal(0, var(\nu_i))$ + Centr.Lim.Thm =
Approximated Type I Error control, but very good in practice.

Sign-Flip Score test with known γ_0 and γ_1

$$
\begin{aligned}
S^* : &= \sum_{i=1}^{n} \pm\nu_i \\
(Poisson) &= \sum_{i=1}^{n} \pm x_i (y_i - e^{\gamma_0 + z_i \gamma_1}) = \sum_{i=1}^{n} \pm x_i (y_i - \mu_i)
\end{aligned}
$$

- Observed test statistic: $S^{obs} = \sum_{i=1}^{n} +\nu_i$
- p-value: $\frac{\#(|S^*| \geq |S^{obs}|)}{\#resamplings}$

Properties

Second-moment Null-invariance (NI2)

- 0-mean: $E(y_i - \mu_i) = 0 \Rightarrow E(\pm x_i(y_i - \mu_i)) = 0$
- $y_i \perp\!\!\!\perp y_i$
- constant variance:
  $V(+x_i(y_i - \mu_i)) = V(-x_i(y_i - \mu_i)) \Rightarrow V(S^*) = V(S^{obs})$

Properties

It converges to parametric score test (i.e. asymptotically):

i. is normal $N(0, \mathcal{I})$
ii. is exact
iii. is locally most powerful (LMP)
iv. if the parametric S test is UMP (UMPU),
    S^* is asymptotically UMP (UMPU)

Outline

Flip score test with UNknown nuisance parameters

- Model: $log(E(y_i)) = \gamma_0 + \gamma_1 z_i + \beta x_i, \;\; i = 1, \ldots, n$
- $H_0: \;\beta = 0 \;\forall\; \gamma = (\gamma_0, \gamma_1)$

In most applications, γ is unknown and we **plug-in an estimate** (under H_0).

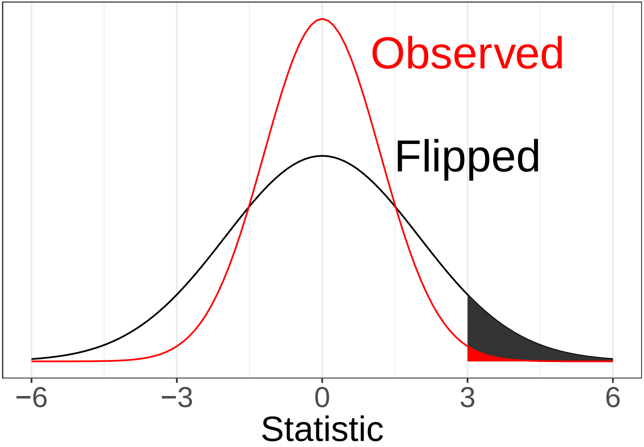
e.g. Poisson model:

$$S = \sum_{i=1}^{n} x_i \left(y_i - e^{\hat{\gamma}_0 + z_i \hat{\gamma}_1} \right) = \sum_{i=1}^{n} x_i \left(y_i - \hat{\mu}_i \right)$$

Does it has any consequences?

YES, Observed test statistic has lower variance than flipped ones :(

The test becomes conservative



Solution: Effective flip score test (or doubly residualized)

YES, Observed test statistic has lower variance than flipped ones :(

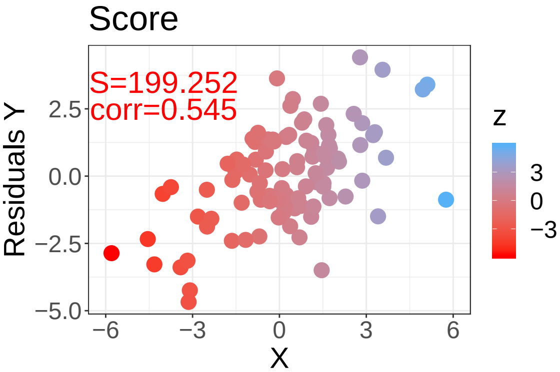
Intuition for **linear model**
$H = Z(Z'Z)^{-1}Z'$

$$
\begin{aligned}
S^*(d(\pm 1)) &= \sum_{i=1}^{n} \pm x_i(y_i - \hat{\mu}_i) \\
&= X'd(\pm 1)(I-H)Y = \\
&= X'(I-H+H)'d(\pm 1)(I-H)Y = \\
&= \mathbf{X}'(\mathbf{I}-\mathbf{H})\mathbf{d}(\pm\mathbf{1})(\mathbf{I}-\mathbf{H})\mathbf{Y} + X'Hd(\pm 1)(I-H)Y
\end{aligned}
$$

Observed score test: $X'Hd(+1)(I-H)Y = X'H(I-H)Y = 0$
Random flip: $X'Hd(\pm 1)(I-H)Y \neq 0$
(0 mean, positive variance)

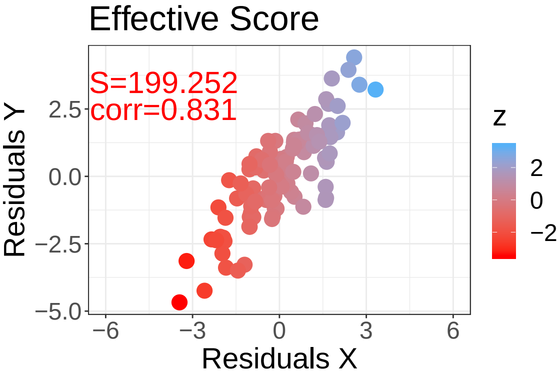
Toy Data

Linear model $y \sim 1 + z + x + \varepsilon, \quad \varepsilon \sim N(0, 1)$, $\mathbf{corr}(\mathbf{x}, \mathbf{z}) = \mathbf{.8}$



Toy Data

Linear model $y \sim 1 + z + x + \varepsilon, \quad \varepsilon \sim N(0,1)$, $\mathbf{corr}(\mathbf{x}, \mathbf{z}) = .8$



Double residualization in GLM

- W diagonal matrix with $w_i = (\partial\mu_i/\partial\eta_i)^2/var(y_i)$
- $I - H = I - WZ(Z'WZ)^{-1}Z'$

The Score test statistic:

$$S^{obs} = X'(Y - \hat{\mu})$$

The **Effective** (Observed) Score test statistic:

$$S_E^{obs} = X'(I - H)(Y - \hat{\mu})$$

and Flipped: $S_E^* = X'(I - H)d(\pm 1)(Y - \hat{\mu})$

General Solution: Effective Score

For every $1 \leq i \leq n$, let

$$\nu_{\hat{\gamma},i}^{(k-1)} = \frac{\partial}{\partial \gamma} \log f_{\beta,\gamma,X_i}(Y_i)\Big|_{\beta=0,\gamma=\hat{\gamma}} \in \mathbb{R}^{k-1},$$

Then

$$S^*_{\hat{\gamma}} = \sum_i \pm(\nu_{\hat{\gamma},i} - \hat{\mathcal{I}}'_{XZ}\hat{\mathcal{I}}_{ZZ}^{-1}\nu_{\hat{\gamma},i}^{(k-1)})$$

with $\hat{\mathcal{I}}$ the Observed Fisher Information under H_0:

$$\hat{\mathcal{I}} = \begin{bmatrix} \hat{\mathcal{I}}_{XX} & \hat{\mathcal{I}}'_{XZ} \\ \hat{\mathcal{I}}_{XZ} & \hat{\mathcal{I}}_{ZZ}. \end{bmatrix}$$

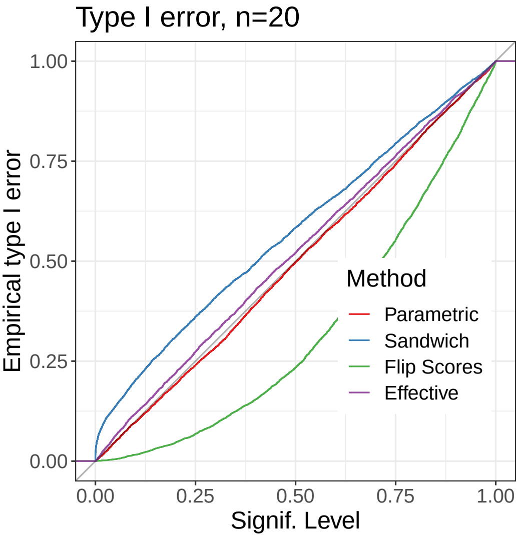
Remark: The effective score is strongly connected with the (parametric) Efficient Score (Cox and Hinkley, 1979).

Simulation: Poisson

Setting

- $y_i \sim Poisson(\mu_i = \exp(1 + 1 \cdot z_i + \beta x_i))$,
- $H_0 : \beta = 0 \ \forall(\gamma_0, \gamma_1)$
- Simulation under $H_0 : \beta = 0$ (nuisance $\gamma_1 = \gamma_0 = 1$)
- (x, z) multivariate normal with high correlation: $corr(xz) = 0.8$ (and variance 1)
- 2000 sign-flips, 10000 datasets

Poisson



Type I error, n=20
Empirical type I error
1.00
0.75
0.50
0.25
0.00
0.00
0.25
0.50
0.75
1.00
Signif. Level
Method
Parametric
Sandwich
Flip Scores
Effective

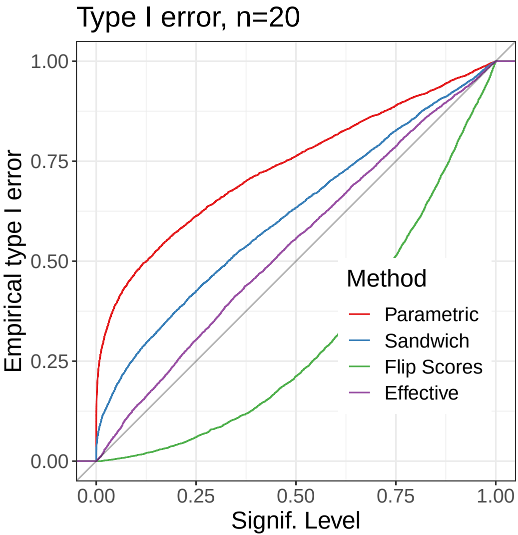
Simulation: overdispersion

The Effective Score Statistic is robust to biased estimate of W (i.e. variance).

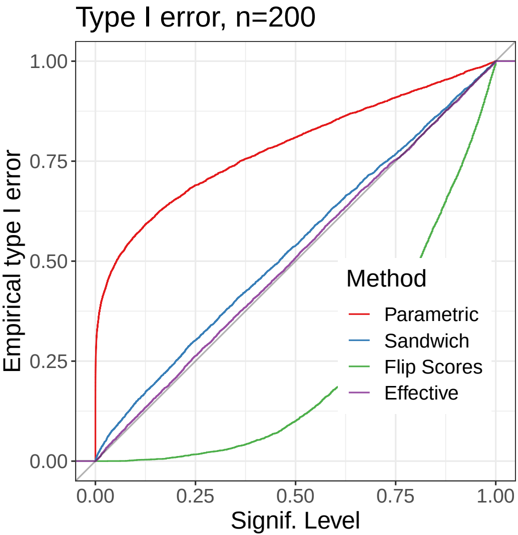
Setting

- $y_i \sim NegBinom(\mu_i = \exp(1 + 1 \cdot z_i + \beta x_i), \phi = 1.2)$,
- $H_0: \ \beta = 0 \ \forall(\gamma_0, \gamma_1)$ but WRONG Poisson model used
- Simulation under $H_0 : \beta = 0$ (nuisance $\gamma_1 = \gamma_0 = 1$)
- (x, z) multivariate normal with high correlation: $corr(xz) = 0.8$ (and variance 1)
- 2000 sign-flips, 10000 datasets

Overdispersion



Overdispersion



Effective Flip Score is Asymptotically Exact

- We need: $\nu_i \perp\!\!\!\perp \nu_{i'}$.
- However, when we plug $\hat{\gamma}$ into $S_{\hat{\gamma}}$, the $\nu_{\hat{\gamma},i}$ become dependent (e.g. in linear model the effective d.f. are $n - \mathrm{rank}(Z)$).
- The correlation disappears when $n \to \infty$

We get **asymptotically exact** test (with any variance estimates).

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We propose the **Standardized** Flip Score for small (and large) sample size!

Outline

Standardized Flip Scores

It is easy to derive: $Var\{S(d(\pm 1))\} =$
$n^{-1}X^TW^{1/2}(I-H)d(\pm 1)(I-H)d(\pm 1)(I-H)W^{1/2}X + o_p(1)$
Standardized flipscores:

$$S^*(d(\pm 1)) = S(d(\pm 1))/Var\{S(d(\pm 1))\}^{1/2}$$

Results: the anti-conservativeness disappears:

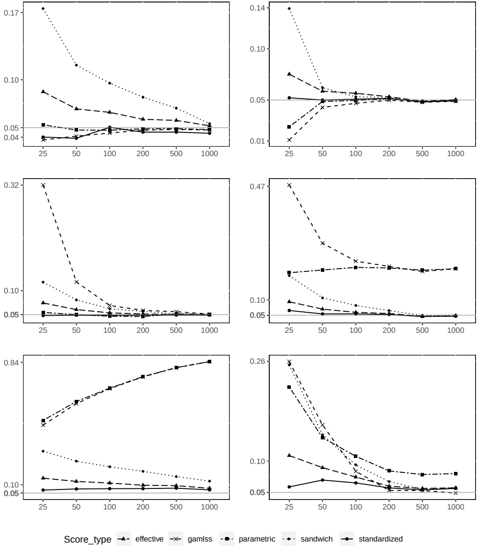
- with unbiased estimate of $\hat{\mu}$: **Second Moment Null Invariant (NI2)** (almost exact, see later)
- with unbiased estimate of $\hat{\mu}$ + normality (lm): **Exact**

Simulation: Type I error control

Top: correct Poisson and Logistic model.

Middle Normal, heteroscedasticity nuisance / target.

Bottom: false Poisson model, two groups Negative-binomial.



Standardized vs Effective Flip Scores

Property: **second-moment null-invariant (NI2)** means that S^* and S^{obs} have zero mean and same variance (i.e. it is not an exact test, same as for parametric score).

When $\hat{W}$ is **unbiased** estimate of true W:

- **Effective** flip Score is only *Asymtotically* NI2
- **Standardized** flip Score is (finite sample) NI2

When $\hat{W}$ is **biased** estimate of true W:

- **Effective** flip Score is only *Asymtotically* NI2
- **Standardized** flip Score is Asymtotically NI2,
  but it converges faster.

Standardized is anyway better than Effective.

Outline

Multivariate

Multivariate Hypotheses

$$H_{0j}:\ \beta_j = 0 \mid (\gamma_{0j}, \tau_{0j}) \in \mathbb{G}_j \times \mathbb{T}_j, \quad H_0 : \bigcap_{j=1}^{q} H_{0j} \tag{1}$$

$$H_{1j}:\ \beta_j > 0 \mid (\gamma_{0j}, \tau_{0j}) \in \mathbb{G}_j \times \mathbb{T}_j, \quad H_1 : \bigcup_{j=1}^{q} H_{1j}$$

Multivariate Test Statistic:

$$S^*_{Oj} = X'_j(I - H)Ud(\pm)U'(Y - \hat{\mu}), \quad S_O = (S_{O1}, \dots, S_{Oq})'$$

Resampled S^*_O: same sign-flipping $d(\pm)$ for all tests $S^*_{O1}, \dots, S^*_{Oq}$.
This ensure same covariance, that is **Multivariate NI2**.

Multivariate: example

- $log(E(Y)) = Z\gamma + X_1\beta_1$
- $log(E(Y)) = Z\gamma + X_2\beta_2$

$$H_0: \ \beta_1 = 0 \cap \ \beta_2 = 0$$

i.e. Same estimate under H_0 (= same H and W)
Examples:

- post-hoc ANOVA with covariates (Z)
- GWAS: case-control (binomial Y) with individual covariates (Z)

Clustered Observations (e.g. mixed-models)

Examples: Mixed-models, Repeated measures, GEE
Clustered observations: true W is BLOCK matrix (not diagonal).
Solution: Flipping matrix $d(\pm 1)$ has same sign within blocks (i.e. signs are flipped block-wise)
Remarks:

- doesn't need balanced designs
- when correlation within clusters is misspecified:
  GEE has unbiased estimate, but loses type I error control
  Flipscores has unbiased estimate AND good type I error control

R package: `flipscores`

Same syntax as `glm()`

An Example:

- Response: Binomial, logit link
- Predictors: x(3-groups) + z(continuous)+interaction
- Clustered observations (15 clusters)

```
set.seed(1)
x=factor(rep(LETTERS[1:3],15))
D=data.frame(y=rbinom(45,1,.05+(x=="C")*.8),x=x,
             z=rnorm(45),id=rep(1:15,each=3))
```

R package: flipscores

```
library(flipscores)
mod=flipscores(y~x*z,data=D,family = binomial, data = D, id = D$id)
summary(mod)
```

```
##
## Call:
## flipscores(formula = y ~ x * z, family = binomial, data = D,
##     id = D$id)
##
## Coefficients:
##                Estimate      Score Std. Error z value Pr(>|z|)
## (Intercept) -2.057e+01 -7.211e+00  2.772e+00  -2.601    0.054 .
## xB          -6.564e-11 -5.673e-16  4.881e-16  -1.162    0.384
## xC           2.195e+01  5.861e+00  3.239e+00   1.810    0.020 *
## z           -4.722e-09 -3.166e-16  3.952e-16  -0.801    0.442
## xB:z         4.722e-09 -5.008e-16  4.076e-16  -1.229    0.278
## xC:z        -5.465e-03  2.433e-16  5.275e-09   0.000    1.000
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

R package: flipscores

```
anova(mod,type=3)

## Analysis of Deviance Table: Type III test
## Model: binomial, link: logit
## Inference is provided by FlipScores approach (5000 sign flips).
##
## Response: y
##      Score Df Pr(>Score)
## x   7.6516  2     0.0020 **
## z   0.5828  1     0.4484
## x:z 0.0001  2     0.9904
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

Conclusion

Standardized Flip Score Test

- for GLM
- gooood control of the type I error

Effective Flip Score Test:

- general: any score statistics
- Asymtotically exact

Both

- assume the link function to be right ($E(\hat{\mu}) = \mu$)
- very **robust** (heteroscedasticity, overdispersion etc)
- Multivariate: easy (even $\mathbf{p} >> \mathbf{n}$)
- quite **fast** to compute
- R package: `https://github.com/livioivil/flipscores`
- some relationship with solution of F. Pesarin (2001) to Behrens-Fisher problem

Extensions

- Spatial/Penalized Models (Ferracioli, Sangalli, Finos. Nonparametric tests for semiparametric regression models DOI, 10.1007/s11749-023-00868-9)
- Confidence Intervals (??)
- more on Multivariate (with A. Vesely; arXiv:2210.02794 + arXiv:2205.12563)
- Median unbiased estiamators (with E.C. Kenne Pagui)
- survival analysis (De Santis), others non-linear models ...