Statistics 360: Advanced R for Data Science

Penalized logistic regression

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Motivation: GWAS for binary outcomes

- Genome-wide association study (GWAS) analyses typically consist of estimating and testing associations between a disease trait (phenotype) and genetic markers called single nucleotide variants (SNVs).

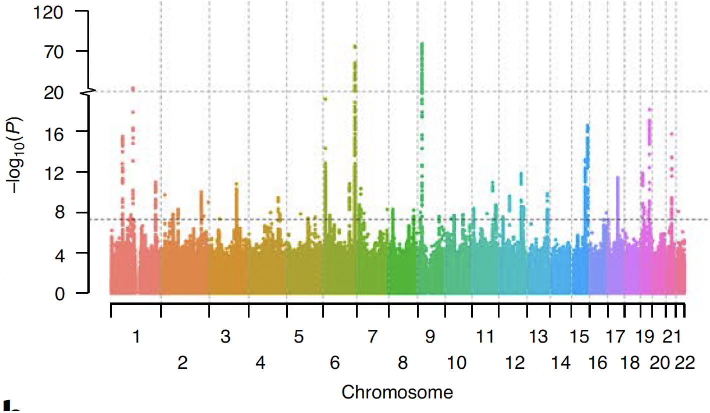


Figure 1: Manhattan plot for Coronary Artery Disease, UK Biobank data

Maximum likelihood inference of SNV effects

- The maximum likelihood estimator (MLE) is the maximizer of the **likelihood**, the probability of the data as a function of the regression parameters.
- Let $Y_i = 1$ if subject i has the disease and 0 if not and X_i take value 0, 1 or 2 for the number of copies of the variant that subject i carries. Then the model is for the log-odds

$$\log \frac{P(Y=1|X)}{P(Y=0|X)} = \alpha + \beta X_i$$

- The log-OR β describes how (if) the log odds changes with X.
- The likelihood is

$$f(y|\beta,\alpha) = \prod_i \frac{\exp(y_i(\alpha + X_i\beta))}{1+\exp(\alpha + X_i\beta)},$$

Sparse data bias

- Despite huge sample sizes in modern GWAS (e.g., about 500,000 in UK Biobank), inference of phenotype-SNV associations is prone to sparse data bias.
- With a categorical exposure, sparse means small cell entries in the table of phenotype x exposure
- Well-known: Do not use asymptotic distributions when there are small cell counts
- Less well known: MLE of log-ORs is biased away from zero

Avoiding sparse data bias in GWAS

- One approach is to use *penalized* likelihood, using Firth's method, which shrinks estimates of log-ORs toward 0

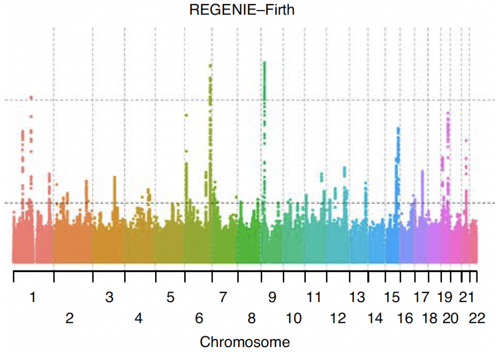


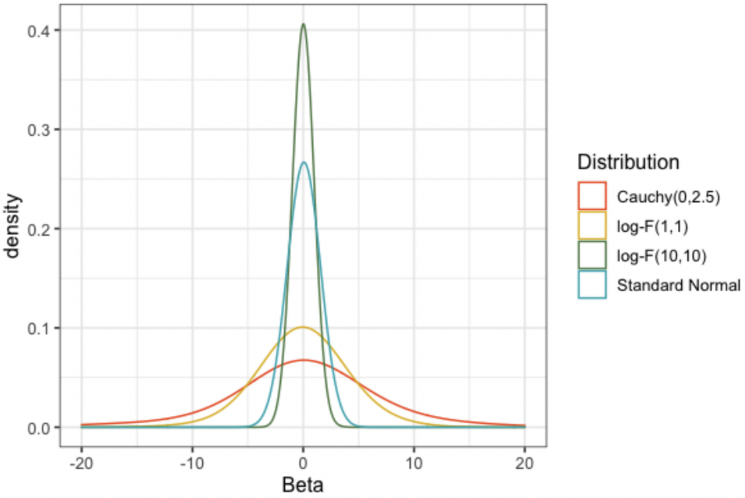
Figure 2: Firth vs SPA for Coronary Artery Disease, UK Biobank data

Alternatives to Firth penalization

- A penalty is a function with maximum at zero and the penalized likelihood is the likelihood times the penalty function.
- The maximizer of the penalized likelihood will be shifted, or "shrunken" towards zero.
- Penalty terms are often chosen to be known **prior** distributions; see Stat 460 for Bayesian inference.
- Firth's penalty corresponds to the Jeffreys prior (Jeffreys 1946)

Log-F penalties

- Greenland and Mansournia (2015) suggest penalization by a log-$F(m, m)$ distribution



More on log-F

- Distribution of $\log \beta$ for $\beta \sim F(m, m)$; a "Type IV" logistic distribution (Johnson, Kotz, and Balakrishnan 1994).
- For logistic regression, it is easy to implement log-$F(m, m)$ penalization with a simple data augmentation trick.

	Response							
	Success	**Failure**	**Intercept**	**X**	Z_1	Z_2	$\dots$	Z_p
Original Dataset	1	0	1	0	x_{11}	x_{21}	$\dots$	x_{p1}
	0	1	1	2	x_{12}	x_{22}	$\dots$	x_{p2}
	$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\ddots$	$\vdots$
	0	1	1	1	x_{1n}	x_{2n}	$\dots$	x_{pn}
Augmented Dataset	$m/2$	$m/2$	0	1	0	$\dots$	$\dots$	0

Figure 3: Data augmentation for log-$F(m, m)$

Extension to adjust for covariates and offsets

- Covariates Z: Adjust for covariates like age and sex
- Offsets $\hat{b}$: Adjustment for population structure and hidden relatedness is through a "whole genome regression".
  - Model includes random effects for a GW panel of SNVs.
  - To keep computation manageable, fit the WGR once and include estimated polygenic effects $\hat{b}$ as "offsets".
- Extended logistic regression likelihood is:

$$f(y|\alpha, \theta, \beta) = \prod_i \frac{\exp(y_i(\alpha + Z_i\theta + \hat{b}_i + X_i\beta))}{1 + \exp(\alpha + Z_i\theta + \hat{b}_i + X_i\beta)},$$

  where θ is a vector of confounder effects.
- No change to the prior/penalty – don't penalize confounder effects.

References I

Greenland, Sander, and Mohammad Ali Mansournia. 2015. "Penalization, Bias Reduction, and Default Priors in Logistic and Related Categorical and Survival Regressions." *Statistics in Medicine* 34 (23): 3133–43.

Jeffreys, Harold. 1946. "An Invariant Form for the Prior Probability in Estimation Problems." *Proceedings of the Royal Society of London. Series A. Mathematical and Physical Sciences* 186 (1007): 453–61.

Johnson, Norman Lloyd., Samuel Kotz, and N. Balakrishnan. 1994. *Continuous Univariate Distributions*. Wiley.