Previous' lecture

- P-value based combination.
- Fixed vs random effects models.
- Meta vs. pooled- analysis.
- New random effects testing.

Interaction

Outline:

- Definition of interaction
- Additive versus multiplicative interaction
- Testing G$\times$E under the additional restriction of G and E independence
- Empirical Bayes (weighted) estimator of interaction
- General regression and likelihood function

Definition and Overview

- Broad notion: Effect of one factor on an outcome depends in some way on the presence of another factor
- These two factors can be two genes, two environmental factors, or a gene (G) and and environmental (E) factor
- Outcome: binary, continuous, time-to-event
- Focus on the binary case in depth as many of the intuitions and observations translate to general regression models

Notation

- Y: Disease status
- G: Genotype (0 and 1)
- E: Exposure (0 and 1)
- p_{ge}: $P(D = 1|G = g, E = e)$, $g = 0, 1, e = 0, 1$

	$G = 0$		$G = 1$	
	$E = 0$	$E = 1$	$E = 0$	$E = 1$
p_{ge}	p_{00}	p_{01}	p_{10}	p_{11}

Additive Interaction

- Lung cancer risk in smokers and non-smokers by asbestos exposure (Hill et al. 1986).

	No Asbestos		Asbestos	
	Non-Smoker	Smoker	Non-Smoker	Smoker
P_{ge}	$p_{00} = 0.0011$	$p_{01} = 0.0095$	$p_{10} = 0.0067$	$p_{11} = 0.0450$

- Effect of asbestos exposure alone (for non-smokers):

$$p_{10} - p_{00} = 0.0056$$

- Effect of smoking alone (in absence of asbestos):

$$p_{01} - p_{00} = 0.0084$$

- Effect of both in reference to absence of both:

$$p_{11} - p_{00} = 0.0439$$

- Difference in effect of both factors compared to sum of individual effects:

$$(p_{11} - p_{00}) - \{(p_{10} - p_{00}) + (p_{01} - p_{00})\} = p_{11} - p_{10} - p_{01} + p_{00} = 0.0299$$

Multiplicative Interaction

- Instead of using risk differences, use risk ratios
- Lung cancer risk in smokers and non-smokers by asbestos exposure (Hill et al. 1986).

	No Asbestos		Asbestos	
	Non-Smoker	Smoker	Non-Smoker	Smoker
P_{ge}	$p_{00} = 0.0011$	$p_{01} = 0.0095$	$p_{10} = 0.0067$	$p_{11} = 0.0450$

- Effect of asbestos exposure alone:

$$RR_{01} = p_{10}/p_{00} = 6.09$$

- Effect of smoking alone:

$$RR_{01} = p_{01}/p_{00} = 8.64$$

- Effect of both factors:

$$RR_{11} = p_{11}/p_{00} = 40.91$$

- Measure of interaction on a multiplicative scale:

$$\frac{RR_{11}}{RR_{10}RR_{01}} = 0.78$$

Scale Dependence of Interaction (Rothman et al 2008)

- If both factors have some effect on the outcome, absence of interaction on the multiplicative scale implies the presence of additive interaction, and likewise, the absence of interaction on additive scale implies presence of multiplicative interaction
- If there is no multiplicative interaction, i.e., $p_{11} = (p_{10}p_{01})/p_{00}$
- Additive interaction

$$\begin{aligned} p_{11} - p_{10} - p_{01} + p_{00} &= \frac{p_{10}p_{01}}{p_{00}} - p_{10} - p_{01} + p_{00} \\ &= \frac{(p_{01} - p_{00})(p_{10} - p_{00})}{p_{00}} \\ &\neq 0 \end{aligned}$$

Statistical Models for Interaction in Case-control Data

- Logistic regression model.

$$\text{logit}\{\Pr(Y = 1|G, E)\} = \beta_0 + \beta_1 G + \beta_2 E + \beta_3 G \times E$$

- $OR \approx RR$ if the disease is rare ($<$5%)
- Multiplicative interaction is quantified by

$$\exp(\beta_3) = \frac{OR_{11}}{OR_{10} OR_{01}}$$

- Testing $G \times E$ multiplicative interaction is to test

$$H_0 : \beta_3 = 0$$

- Wald, likelihood ratio or score tests can be used

Inference for Additive Interaction

- Relative excess risk due to interaction (*RERI*).

$$\begin{aligned} RERI &= (p_{11} - p_{10} - p_{01} + p_{00})/p_{00} \\ &= RR_{11} - RR_{10} - RR_{01} + 1 \\ &= (RR_{11} - 1) - \{(RR_{10} - 1) + (RR_{01} - 1)\} \end{aligned}$$

- When the disease is rare,

$$\begin{aligned} RERI &\approx OR_{11} - OR_{10} - OR_{01} + 1 \\ &= \exp(\beta_1 + \beta_2 + \beta_3) - \exp(\beta_1) - \exp(\beta_2) + 1 \end{aligned}$$

- Testing additive interaction is to test

$$H_0 : \exp(\beta_3) = \frac{1 - \exp(\beta_1) - \exp(\beta_2)}{\exp(\beta_1 + \beta_2)}$$

- Plug in $\widehat{\beta}_{ML}$ and use the delta theorem for standard errors.

Additive versus Multiplicative

- Additive scale is useful for public health relevance of an interaction in different subgroups.
- Additive scale more closely corresponds to mechanistic interaction ((both exposures together turns the outcome on and the removal of one turns the outcome off), which requires stronger assumptions than statistical interaction.
- Multiplicative models are easier to fit.
- Some noted less heterogeneity in multiplicative interaction while meta-analyzing interactions.
- When the main effects are weak, the difference between additive versus multiplicative interaction is small.

A Data Example

Odds ratios (OR) for Joint Associations of Smoking Status (ever vs. never) and 12 Susceptibility Loci with Bladder Cancer Risk

					Observed Ors			Expected OR joint		P-values interaction	
Location (gene/s in neighbouring region)	N	Cases	Controls	RAF	OR SNP	OR smoking	OR joint	Additive	Multi.	Additive	Mult.
Chr 8p22 *(NAT2)*	8	4,061	5,667	0.77	0.98	2.07	2.55	2.06	2.04	$6.8\text{x}10^{-4}$	0.036
Chr 1p13.3 *(GSTM1)*	6	3,745	3,930	0.71	1.7	3.35	4.7	4.05	5.7	0.011	0.097
Chr 8q24.21 *(MYC)*	5	3,525	5,108	0.45	1.34	2.79	3.59	3.13	3.74	0.034	0.743
Chr 3q28 *(TP63)*	5	3,519	5,110	0.74	1.41	2.93	3.8	3.34	4.12	0.24	0.722
Chr 8q24.3 *(PSCA)*	6	3,843	5,438	0.47	1.07	2.41	2.91	2.48	2.59	0.017	0.325
Chr 5p15.33 *(CLPTM1L)*	5	3,526	5,117	0.55	1.06	2.53	2.9	2.59	2.68	0.141	0.579
Chr 4p16.3 *(TMEM129 TACC3-FGFR3)*	8	4,063	5,668	0.2	1.23	2.41	2.8	2.65	2.98	0.354	0.582
Chr 22q13.1 *(CBX6, APOBEC3A)*	8	4,066	5,643	0.65	1.13	2.07	2.73	2.2	2.34	0.02	0.362
Chr 19q12 *(CCNE1)*	8	4,068	5,668	0.33	1.32	2.59	2.93	2.91	3.42	0.919	0.139
Chr 2q37.1 *(UGT1A family)*	8	4,062	5,660	0.92	1.24	2.34	2.95	2.58	2.9	0.088	0.904
Chr 2q37.1 *(UGT1A6)*	8	4,048	5,304	0.97	1.44	1.73	3.47	2.17	2.48	$2.0\text{x}10^{-4}$	0.254
Chr. 18q12.3 *(SLC14A1)*	8	4,017	5,640	0.43	1.19	2.35	2.88	2.54	2.8	0.046	0.811

Test for multiplicative interaction: empirical-Bayes (EB) shrinkage estimator exploiting the assumption of gene-environment independence.

Test for additive interaction: likelihood-ratio (LRT) test comparing saturated and additive model for joint effects using logistic regression models.

Garcia-closas et al. (2013)

Power of $G \times E$ Interaction

- Power for identifying GxE is typically low. It needs ~ 4 times as many subjects to test for an interaction that is equally powerful as a main effect test.
- G and E may be assumed to be independent in many situations.
- Under the additional restriction for G–E independence, more efficient estimates may be obtained by exploiting this assumption.

Case-only Estimation

Table: A binary G and a binary E.

	$G=0$		$G=1$	
	$E=0$	$E=1$	$E=0$	$E=1$
$Y=0$	p_{01}	p_{02}	p_{03}	p_{04}
$Y=1$	p_{11}	p_{12}	p_{13}	p_{14}

- Multiplicative interaction

$$\text{logit}\{\Pr(Y=1|G,E)\} = \beta_0 + \beta_1 G + \beta_2 E + \beta_3 G \times E.$$

$$\begin{aligned}\exp(\beta_3) &= \frac{OR_{11}}{OR_{10}OR_{01}} \\ &= \frac{p_{11}p_{14}}{p_{12}p_{13}} \Big/ \frac{p_{01}p_{04}}{p_{02}p_{03}} \\ &= \frac{GE \text{ odds ratio in cases}}{\underbrace{GE \text{ odds ratio in controls}}_{\text{becomes 1 under G–E independence}}}\end{aligned}$$

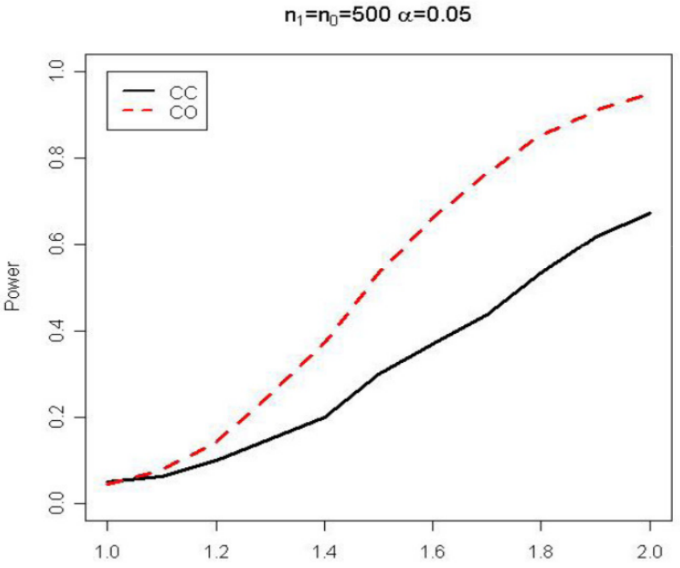
Case-only Estimation

- Model

$$\frac{\Pr(G=1|E,Y=1)}{\Pr(G=0|E,Y=1)}$$
$$= \frac{\Pr(Y=1|G=1,E)/\Pr(Y=0|G=1,E)}{\Pr(Y=1|G=0,E)/\Pr(Y=0|G=0,E)} \cdot \frac{\Pr(Y=0,G=1,E)}{\Pr(Y=0,G=0,E)}$$
$$= \frac{\exp(\beta_0+\beta_1+\beta_2 E+\beta_3 E)}{\exp(\beta_0+\beta_2 E)} \cdot \frac{\Pr(G=1|Y=0,E)}{\Pr(G=0|Y=0,E)}$$
$$= \exp(\beta_1+\beta_3 E) \cdot \frac{\Pr(G=1)}{\Pr(G=0)}$$

- The last equality holds if G and E are independent in controls.

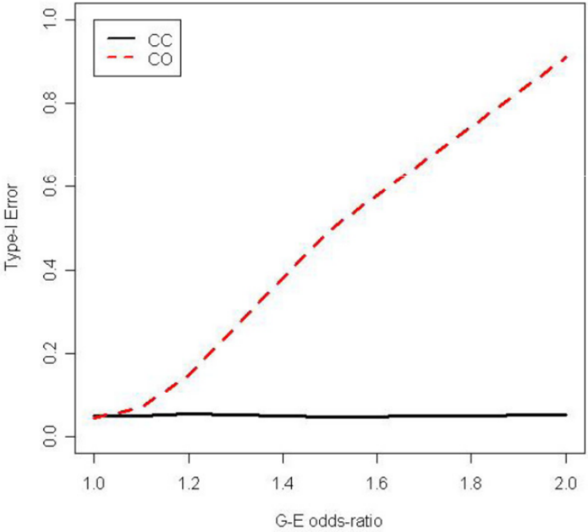
Power Comparison Between Case-Control versus Case-only



Type 1 Error

- Type I error is inflated if G–E independence doesn't hold.

$n_1=n_0=500\ \alpha=0.05$



Independence Assumption

- Natural for external exposure (e.g., exposure to pollution, pesticide).
- True for treatment in a randomized clinical trial.
- Tricky for behaviour exposures (e.g., smoking, alcohol)

Measure of $G - E$ Independence

- Measure of G and E association in controls, $\widehat{\theta}_{GE}$ =log (odds ratio) of G and E in controls.

$$\widehat{\theta}_{GE} \sim N(\theta_{GE}, \sigma^2)$$

- Since we are not sure about the $G - E$ independence assumption

$$\theta_{GE} \sim N(0, \tau^2)$$

- If $\tau^2 = 0$, uses the case-only estimator, if $\tau^2 = \infty$, uses the case control estimator.

- Since $\widehat{\theta}_{GE} \sim N(0, \sigma^2 + \tau^2)$, one may estimate unknown hyperparameter τ^2 by

$$\widehat{\tau}^2 = \max(0, \widehat{\theta}^2_{GE} - \widehat{\sigma}^2)$$

- One could be conservative and use $\widehat{\tau}^2 = \widehat{\theta}^2_{GE}$

Empirical Bayes (EB) Estimator of Interaction

- A weighted average estimator of interaction

$$\widehat{\beta}_{EB} = \frac{\widehat{\sigma}^2_{CC}}{\widehat{\theta}^2_{GE} + \widehat{\sigma}^2_{CC}} \widehat{\beta}_{CO} + \frac{\widehat{\theta}^2_{GE}}{\widehat{\theta}^2_{GE} + \widehat{\sigma}^2_{CC}} \widehat{\beta}_{CC}$$

- $\widehat{\beta}_{CO}$: case-only estimator; $\widehat{\beta}_{CC}$: case-control estimator.
- th$\widehat{\beta}_{EB}$ can be viewed as a shrinkage estimator, where the robust $\widehat{\beta}_{CC}$ has been shrunk toward the efficient $\widehat{\beta}_{CO}$ under the assumption of G-E independence
- The specific form of the ”shrinkage” weights resembles the form of a posterior mean obtained in a classical Bayesian analysis under a normal-normal model (Berger, 1985, p. 131), with the prior variance substituted by an estimate obtained using a method of moments approach.

Inference

- The EB-estimator can be re-written as

$$\widehat{\beta}_{EB} = \widehat{\beta}_{CO} - \frac{\widehat{\theta}^2_{GE}}{\widehat{\theta}^2_{GE} + \widehat{\sigma}^2_{CC}} \widehat{\theta}_{GE}$$

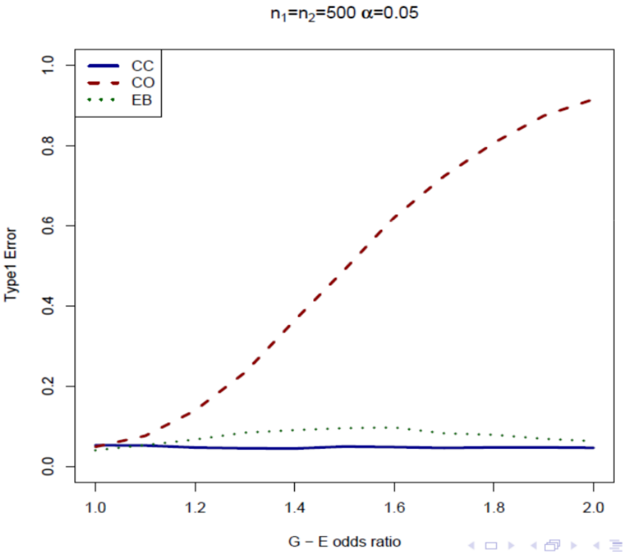
- By using the delta-method

$$V(\widehat{\beta}_{EB}) \approx \sigma^2_{CO} + \left(\frac{\widehat{\theta}^2_{GE}(\widehat{\theta}^2_{GE} + 3\widehat{\sigma}^2_{CC})}{(\widehat{\sigma}^2_{CC} + \widehat{\theta}^2_{GE})^2} \widehat{\sigma}^2_{\theta_{GE}} \right)$$

- Wald test based on this variance can be constructed to test $\beta_3 = 0$

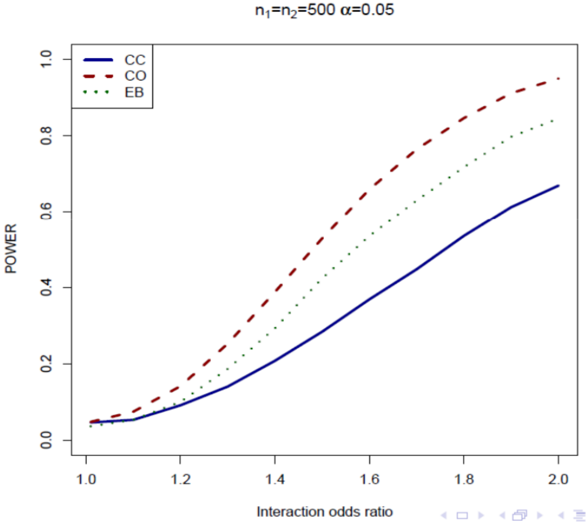
Type I Error

- Empirical Bayes (EB) estimator has better control of type I error than case-only under independence.



Power

- EB estimator has power gain over case-control under independence.



General Regression Set-up

- Likelihood

$$P(G, E|Y) = \frac{\Pr(Y|G, E)P(G|E)P(E)}{\sum_{G^* E^*} P(Y|G^*, E^*)P(G^*|E^*)P(E^*)}$$

- Logistic regression model

$$\text{logit}\{\Pr(Y = 1|G, E)\} = \beta_0 + \beta_1 G + \beta_2 E + \beta_3 GxE$$

  where $\beta = (\beta_0, \beta_1, \beta_2, \beta_3)$

- $P(G|E)$: dependence parameter θ. If $\theta = 0$, G and E are independent.
- $P(E)$ is a non-parametric function.
- Unconstrained model: estimate (β, θ) allowing for dependence $\theta \neq 0$.
- Constrained model: estimate β assuming $\theta = 0$.

Estimation

- β: parameters of interest; θ: nuisance parameter
- Under the independence assumption, $\theta = 0$
- Relaxing the independence assumption, postulate a prior distribution of the form, $\theta \sim N(0, \tau^2)$
- Define $\widehat{\beta}_{ML}(\theta)$ as the profile MLE of β for fixed θ from the retrospective likelihood (Chatterjee and Carroll 2005)
- Constrained MLE for β with $\theta = 0$

$$\widehat{\beta}^0_{ML} = \widehat{\beta}_{ML}(\theta = 0)$$

- Unconstrained MLE for β

$$\widehat{\beta}_{ML} = \widehat{\beta}_{ML}(\theta = \widehat{\theta}_{ML})$$

Profile MLE (Chatterjee and Carroll 2005)

An interesting result

- Lemma 1 (Identifiability). Under the assumption that G and E are independent, for all $\beta' = (\beta_1, \beta_2, \beta_3) \in \mathcal{B}$,

  $$\Pr(E = e, G = g | Y = d, \beta_0, \beta', Q, F) = \Pr(E = e, G = g | Y = d, \beta_0^*, \beta', Q^*, F^*)$$

  if and only if $\beta_0 = \beta_0^*$, $Q = Q^\star$, $F = F^\star$, where Q and F are the distributions of G and E, respetively, and d = 0, 1.

- Sketch of proof: The probability equality holds only if

  $$d\mathcal{H}^*(G, E) = constant \cdot \frac{1 + \exp(\beta_0^* + m(G, E, \beta'))}{1 + \exp(\beta_0 + m(G, E, \beta'))} d\mathcal{H}(G, E)$$

  If H is of the product form QxF, $\mathcal{H}^\star \neq \mathcal{H}$ could be of the product form only if β' has only the main effect of either G or E. Thus, for any β', then $F = F^*$ and $Q = Q^*$. Moreover, since $\mathcal{H} = \mathcal{H}^*$, it also follows that $\beta_0 = \beta^*$.

Empirical Bayes Estimation

- Consider a general function $\beta(\theta)$, and θ has a prior, $MVN(0, A)$. By applying Taylor's expansion at $\theta = 0$, the prior for $f(\theta)$ is

$$\beta(\theta) \sim MVN(\beta(0), [\beta'(0)]^T A[\beta'(0)])$$

  where $\beta'(\theta) = \partial\beta^T(\theta)/\partial\theta$.

- The profile MLE

$$\widehat{\beta}_{ML} \sim N(\beta(\theta), V)$$

- Posterior mean

$$E(\beta(\theta)|\widehat{\beta}_{ML}) = V[V + \{\beta'(0)\}^T A\beta'(0)]^{-1}\beta(0) + \{\beta'(0)\}^T A\beta'(0)[V + \{\beta'(0)\}^T A\{\beta'(0)\}]^{-1}\widehat{\beta}_{ML}$$

Variance-Covariance Matrix

- $\widehat{\beta}_{EB}$ is a function of MLE, $(\widehat{\beta}_{ML}, \widehat{\theta}_{ML}, \widehat{\beta}^{0}_{ML})$

$$\begin{pmatrix} \widehat{\beta}_{ML} \\ \widehat{\theta}_{ML} \\ \widehat{\beta}^{0}_{ML} \end{pmatrix} \sim N\left(\begin{pmatrix} \beta \\ \theta \\ \beta_0 \end{pmatrix}, \Sigma \right)$$

- Apply the multivariate Taylor's expansion provides the variance-covariance expression matrix.

Revisit the 2×4 Case

- The unconstrained MLE $\widehat{\beta}_{ML} = \widehat{\beta}_{cc} = \widehat{\beta}_{co} - \theta_{GE}$
- The constrained MLE (G-E independence) $\widehat{\beta}^{0}_{ML} = \widehat{\beta}_{co}$
- Replace V by $\widehat{\sigma}^2_{cc}$, A by $(\widehat{\beta}_{cc} - \widehat{\beta}_{co})^2 = \widehat{\theta}^2_{GE}$, and $\beta'(0) = \frac{\partial \beta_{ML}}{\partial \theta_{GE}} = -1$,

$$
\begin{aligned}
\beta^*(\theta) =& V[V + \{\beta'(0)\}^T A \beta'(0)]^{-1} \beta(0) \\
&+ \{\beta'(0)\}^T A \beta'(0)[V + \{\beta'(0)\}^T A\{\beta'(0)\}]^{-1} \beta(\theta) \\
=& \frac{\widehat{\sigma}^2_{cc}}{\widehat{\sigma}^2_{cc} + \widehat{\theta}^2_{GE}} \widehat{\beta}_{co} + \frac{\widehat{\theta}^2_{GE}}{\widehat{\sigma}_{cc} + \widehat{\theta}^2_{GE}} \widehat{\beta}_{cc} \\
=& \widehat{\beta}_{EB}
\end{aligned}
$$

Power Comparison

How does the general estimator perform?

$n_0 = n_1$		β_{G*E_1}	β_{G*E_2}	$MSE1$ $(G*E_1)$	$MSE2$ $(G*E_2)$	$MSE1$ $+MSE2$
100	Dependence	0.7308	0.7890	0.4564	0.4797	0.9361
	Independence	0.7278	1.1369	0.1994	0.3875	0.5869
	EB	0.7215	0.9320	0.2881	0.3593	0.6474
200	Dependence	0.7420	0.6849	0.2071	0.2055	0.4126
	Independence	0.7153	1.1039	0.0966	0.2603	0.3599
	EB	0.7294	0.8284	0.1455	0.1634	0.3089
500	Dependence	0.7015	0.7075	0.0805	0.0897	0.1702
	Independence	0.6980	1.1041	0.0393	0.2089	0.2482
	EB	0.6988	0.8178	0.0601	0.0862	0.1463

Simulation Setting: $E = (E_1, E_2)$, $P(E_1 = 1) = 0.3$, $P(E_2 = 1) = 0.3$ $OR_{E_1\ E_2} = 2.0$, $P(G = 1) = 0.3$, $OR_{GE_1} = 1$, $OR_{GE_2} = 1.5$ in controls. Interactions: $\beta_{G*E_1} = \beta_{G*E_2} = \log(2)$, no main effects. Thus we have G-E_1 independence and G-E_2 dependence.

Effect size estimation: Winner's curse

- Combine $\widehat{\beta}_{\text{MLE}}$ that accounts for selection $|\widehat{\beta}| > c\widehat{\sigma}$ and $\widehat{\beta}$ is estimated directly from the data

$$\widehat{\beta}_w = \frac{\widehat{\sigma}^2}{\widehat{\sigma}^2 + (\widehat{\beta} - \widehat{\beta}_{\text{MLE}})^2}\widehat{\beta} + \frac{(\widehat{\beta} - \widehat{\beta}_{\text{MLE}})^2}{\widehat{\sigma}^2 + (\widehat{\beta} - \widehat{\beta}_{\text{MLE}})^2}\widehat{\beta}_{\text{MLE}}$$

- It has a similar form to the Empirical-Bayes estimator
- Zhong et al. (2012) argued the weight from the MSE perspective, $MSE(\widehat{\beta}) = \widehat{\sigma}^2 + (\widehat{\beta} - \beta_0)^2$

EB-estimator

- EB-estimator as posterior mean also minimizes MSE,

$$MSE = \int \int (\theta - \widehat{\theta})^2 f(x, \theta) dx d\theta$$

where $f(x, \theta)$ is the joint density of the observations and the parameter. To minimize the integral with respective to $\widehat{\theta}$, we rewrite using the laws of conditional probability as

$$MSE = \int f(x) \int (\theta - \widehat{\theta}(x))^2 f(\theta|x) d\theta dx$$

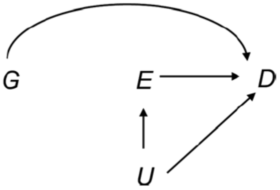
- To minimize MSE, we must minimize the inner integral for each value of x because the integral is weighted by a positive quantity. Hence, the estimator is $E(\theta|x)$.

Empirical Bayes

- Empirical Bays (EB) is a pragmatic Bayesian paradigm, between the extreme Bayesian and frequentist standpoints.
- Comparison with two-stage testing procedure.
  - Test $H_0 : \theta_{GE} = 0$.
  - If reject, use case-control estimator; If not, use case-only.
  - The second-stage testing needs to account for the uncertainty of the decision rule associated with independence testing.
- EB depends on θ on a continuous scale, which has less bias and MSE.
- Computationally feasible for large-scale GWAS. In large scale association studies: Average performance is of interest.

Confounding in $G \times E$

- We need to account for confounding not only for G, but also for E.
- When G is independent of E and U, as long as there is no interaction effect between G and U, the interaction effect of GxE is not biased despite the main effect for E is biased (VanderWeele, 2011)



Simple derivation for confounding

- Suppose U is an unobserved confounder associated with E and Y

$$\frac{\Pr(Y=1|G=1,E=1)}{\Pr(Y=1|G=0,E=1)}$$

$$= \frac{\int \Pr(Y=1|G=1,E=1,u)f(u|G=1,E=1)du}{\int \Pr(Y=1|G=0,E=1,u)f(u|G=0,E=1)du}$$

$$= \frac{\int \Pr(Y=1|G=1,E=1,u)/\Pr(Y=1|G=0,E=0,u_0)f(u|G=1,E=}{\int \Pr(Y=1|G=0,E=1,u)/\Pr(Y=1|G=0,E=0,u_0)f(u|G=0,E=}$$

$$= \frac{\int RR_G RR_E RR_U RR_{GE} RR_{GU} RR_{EU} f(u|G=1,E=1)du}{\int RR_E RR_U RR_{EU} f(u|G=0,E=1)du}$$

$$= RR_G RR_{GE} \frac{\int RR_U RR_{GU} RR_{EU} f(u|E=1)du}{\int RR_U RR_{EU} f(u|E=1)du}$$

- The last equality holds because G is independent of U

Main effect of E

- The effect effect of E is biased.

$$\frac{\Pr(Y=1|G=0,E=1)}{\Pr(Y=1|G=0,E=0)}$$

$$= \frac{\int \Pr(Y=1|G=0,E=1,u)f(u|G=0,E=1)du}{\int \Pr(Y=1|G=0,E=0,u)f(u|G=0,E=0)du}$$

$$= \frac{\int \Pr(Y=1|G=0,E=1,u)/\Pr(Y=1|G=0,E=0,u_0)f(u|G=0,E=}{\int \Pr(Y=1|G=0,E=0,u)/\Pr(Y=1|G=0,E=0,u_0)f(u|G=0,E=}$$

$$= \frac{\int RR_E RR_U RR_{EU} f(u|G=0,E=1)du}{\int RR_U f(u|G=0,E=0)du}$$

$$= RR_E \frac{\int RR_U RR_{EU} f(u|E=1)du}{\int RR_U f(u|E=0)du}$$

- The last equality holds because G is independent of U
- The consequence is that even though the interaction effect can be estimated consistently, the joint effects of G and E are biased. The effect of G stratified by E can be estimated consistently.

Summary

- Additive versus multiplicative interaction.
- Empirical Bayes estimator.
- General regression and likelihood function.

Recommended Reading

- Chatterjee N & Carroll RJ (2005). Semiparametric maximum likelihood estimation exploiting gene-environment independence in case-control studies, *Biometrika* 92: 399–418.
- Mukherjee B & Chatterjee N (2008). Exploiting gene-environment independence for analysis of case–control studies: an empirical Bayes-type shrinkage estimator to trade-off between bias and efficiency. *Biometrics* 64: 685–94.
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- Thomas DC (2010). Gene-environment-wide association studies: emerging approaches. *Nature Rev Genet* 11: 259–72.
- VanderWeele TJ et al. (2011) Sensitivity analysis for interactions under unmeasured confounding. *Stat in Med 31*: 2552–64.