# STAT 545: Categorical Data Analysis (Part II)

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# Overview of Part II of this class

Oct 19, 2015 to December 2, 2015. There will be homework/projects and a final exam

- Regression model for binary data
- Regression model for ordinal data
- Regression model for counts data
- Extensions of standard regression models for categorical data
- Marginal models for longitudinal categorical data
- Conditional models for longitudinal categorical data

# Logistic Regression

# Logistic Regression Model

$$\pi(x) = P(Y = 1|X = x) = 1 - P(Y = 0|X = x)$$
$$= \text{expit}\,(\alpha + \beta x) = \frac{\exp(\alpha + \beta x)}{1 + \exp(\alpha + \beta x)} \in (0, 1)$$
$$\text{logit}\,[\pi(x)] = \log \frac{\pi(x)}{1 - \pi(x)} = \alpha + \beta x \in (-\infty, \infty)$$

1. Binary outcome; for binomial outcome, the model is similar
2. Interpretation of $\beta$ (log odds ratio)
3. Simple visual model checking by grouping (§ 5.1.2)
4. Logistic regression with retrospective studies (§ 5.1.4)
5. Model fitting through maximum likelihood estimation (§ 5.5)
6. Inference about model parameters and probabilities (§ 5.2.1)
7. Checking goodness of fit (§ 5.2.5)

# The (log) odds ratio and its interpretation

$$\text{logit}\left[\pi(x)\right] = \alpha + \beta x$$

$$\text{logit}\left[\pi(\mathbf{x})\right] = \alpha + \beta_1 x_1 + \beta_2 x_2 + ...\beta_p x_p$$

# Simple visual model checking by grouping

1. Group the (continuous) covariate into 10 categories by cutoffs at the quantiles, with $n_i$ subjects in each group ($i = 1, 2, ..., 10$)
2. Calculate the average covariate within each group ($\bar{x}_i$)
3. Calculate the proportion of $Y = 1$ within each group ($\bar{y}_i$)
4. Plot logit of $\bar{y}_i$ vs. $\bar{x}_i$. It should be approximately a straight line
5. Note: may need correction when $\bar{y}_i = 0$ or 1.

$$\log \frac{\bar{y}_i}{n_i - \bar{y}_i} \Rightarrow \log \frac{\bar{y}_i + 0.5}{n_i - \bar{y}_i + 0.5}$$

6. Only work with a single covariate

# Logistic regression with retrospective studies (§ 5.1.4)

# Model fitting through maximum likelihood estimation (§ 5.5)

# Inference on parameters and probabilities (§ 5.2.1)

Test $H_0 : \beta = 0$ in logistic model $\text{logit}\,[\pi(x)] = \alpha + \beta x$

1. Wald, Likelihood ratio, and Score tests are applicable (§ 1.3.3)
2. The predicted probability and its confidence interval

# Checking goodness of fit (§ 5.2.3)

$$\text{logit}\left[\pi(\mathbf{x})\right] = \alpha + \beta_1 x_1 + \beta_2 x_2$$

1. Visual checking through grouping (works best with a single covariate)
2. Adding interactions, quadratic terms, etc., and testing for significance or looking at AIC/BIC: problematic but widely used
3. Making the model more flexible by using splines
4. Global goodness of fit checking by *Hosmer & Lemeshow test*

$$\sum_{i=1}^{g} \frac{\left(\sum_j y_{ij} - \sum_j \hat{\pi}_{ij}\right)^2}{n_i \left(\sum_j \hat{\pi}_{ij}/n_i\right)\left[1 - \left(\sum_j \hat{\pi}_{ij}\right)/n_i\right]} \quad \sim \quad \chi^2_{g-2}$$

- A large value of any global fit statistic merely indicates *some* lack of fit but provides no insight about its nature

# Logistic models with categorical predictors (§ 5.3)

- When there is a single categorical predictor, the data can be arranged in an $I \times 2$ contingency table (e.g., Table 5.3)
- When the categories are unordered (e.g., nominal data), the (saturated) model is $\text{logit}(\pi_i) = \beta_i$ ($i = 1, 2, ..., I$), with $I$ unknown parameters.
- We may write the model as $\text{logit}(\pi_i) = \alpha + \beta_i$ with set-to-zero constraint $\beta_1 = 0$ or sum-to-zero constraint $\sum_i \beta_i = 0$
- The model for subject $j$ ($j = 1, 2, ..., n$) is $\text{logit}(\pi_j) = \alpha + \sum_{i=1}^{I} \beta_i 1\{j \in \text{group } i\}$
- When the categories are ordered (e.g., ordinal data), we may assume that $\text{logit}(\pi_i) = \alpha + \beta x_i$
  - The number of parameters reduced with the linear assumption.
  - Be careful about coding $x_i$ (i=1,2,...,I): (1,2,3) or (1,4,9)?
  - Treat the $x_i$ like a continuous variable.

# Cochran-Armitage Trend Test (§ 5.3.5)

- Developed by Armitage (1955) and Cochran (1954) for $I \times 2$ tables with ordered rows
- They used a linear probability model $\pi = \alpha + \beta x_i$
- It is a chi-square test of the independence between rows and columns under the linear assumption. $H_0 : \beta = 0$.
- This test is equivalent to the score statistic for testing $H_0 : \beta = 0$ in the linear logit model.
- Using directed models can improve inferential power
  - If the trend is indeed linear, making use of the linear trend (as in Cochran-Armitage test) is more powerful than not making use of the linear trend (as in $\text{logit}(pi_i) = \beta_i$)

# Model Selection (§ 6.1)

The data set is $\{Y_i, X_{1i}, X_{2i}, ..., X_{pi}; i = 1, 2, ..., n\}$. The logistic regression model is

$$\pi(\mathbf{X}_i) = \text{expit}\left(\beta_0 + \beta_1 X_{1i} + \beta_2 X_{2i} + ... + \beta_p X_{pi}\right)$$

The $p$ covariates include interactions, quadratic terms, etc. We want to retain only the predictive covariates in the model.

- Model selection is both science and art
- The same principles that you learned in linear model class still apply
- Two goals: (1) complex enough to fit the data well; (2) relatively simple to interpret (avoid overfitting) 
- Confirmatory studies vs. exploratory studies

# How many covariates can be included in the model?

$$Y_i \sim \text{Bernoulli with } \pi(\mathbf{X}_i) = \text{expit}\left(\beta_0 + \beta_1 X_{1i} + \beta_2 X_{2i} + ... + \beta_p X_{pi}\right)$$

- The effective sample size of a logistic regression is either $\sum_i Y_i$ or $n - \sum_i Y_i$, whichever is smaller
- **The rule of thumb**: no more than the effective sample size divided by 10 (or, 10 events per covariate)
- Including too many covariates may cause non-convergence 
- Avoid multicollinearity, as in linear regression (  Page 209, Table 6.1)
  - The overall test is highly significant ($p < 0.0001$)
  - The individual covariates are, in general, not very significant due to the multicollinearity between the horseshoe crab's width and weight ($r = 0.887$)

# Forward, backward, and stepwise model selection

$$Y_i \sim \text{Bernoulli with } \pi(\mathbf{X}_i) = \text{expit}\left(\beta_0 + \beta_1 X_{1i} + \beta_2 X_{2i} + ... + \beta_p X_{pi}\right)$$

- Forward procedure: (1) start with just the intercept (2) at each step, add the covariate with the smallest p-value in likelihood ratio or Wald test (3) stop when no more significant covariate is available (However, it can stop prematurely due to lack of power)
- Stepwise procedure: at each step, retest the significance of the terms added at previous stages
- Backward procedure: (1) start with full model (2) at each step, remove the covariate with the largest p-value (3) stop when all remaining covariates are significant. (However, full model may not be stable)
- The dummy variables for a single categorical covariate should be added or removed together (likelihood ratio test); do not place an interaction in the model without the main effect terms
- SAS PROC LOGISTIC offers additional entry and exit p-value criteria

# Further comment on forward, backward, and stepwise model selection

$$Y_i \sim \text{Bernoulli with } \pi(\mathbf{X}_i) = \text{expit}\left(\beta_0 + \beta_1 X_{1i} + \beta_2 X_{2i} + ... + \beta_p X_{pi}\right)$$

-  Page 211, Table 6.2 illustrates
  - three-way interaction is usually not significant (e.g., lack of power) and not desirable (hard to interpret)
  - dropping multiple covariates at once using likelihood ratio test (LRT) or dropping them one at a time (Wald or LRT)
- All these procedures are not rigorously justified (*ad hoc*); use with caution!
- Modern approaches are available (LASSO, bagging, etc.)
- Philosophically, there is no such thing as "the correct model" or "the true model": ALL MODELS ARE WRONG, SOME ARE USEFUL — George Box

# Akaike Information Criterion (AIC)

Select the model with smaller AIC or BIC ($L$: maximized log likelihood; $m$: number of parameters in the model; $n$: sample size)

$$AIC = -2L + 2m$$
$$BIC = -2L + \log(n)m$$

- **Rationale**: Including more covariates will always include the log likelihood, but may cause overfitting; so we put a "penalty" by adjusting for the size of the model. There are mathematical reasons why the penalty must take this form.
- Other penalties are available: HQ, DIC, etc.
- BIC puts more penalty on larger model, and therefore tends to select the simpler model  Page 213
- Like scatter plot smoothing, the "desired" amount of penalty is a somewhat subjective choice 
- Need a comprehensive assessment of AIC/BIC, significance, residuals, scientific rationale, parsimony and interpretability, etc.

# Residuals: Pearson, Deviance, Standardized

Let $y_i$ denote the binomial outcome for $n_i$ trials at setting $i$ of the explanatory variables, $i = 1, 2, ..., N$. Let $\hat{\pi}_i$ denote the model estimate of $P(Y = 1)$.

- Pearson residual is like the residual for linear regression, but with standardization
- Deviance residual is motivated from the likelihood and deviance (which resembles the sum of squares in linear regression)
- Standardized residual has an approximate $N(0, 1)$ distribution and is the one that we usually use, BUT:
  - use it with grouped data (binomial instead of binary). Page 217, Table 6.5

# Influence diagnosis for logistic regression

- A single observation can have a much more exorbitant influence in linear regression than in logistic regression, since linear regression has no bound on the distance of $y_i$ from the expected value.
- Points that have extreme predictor values need not have high leverage. In fact, the leverage can be relatively small if $\hat{\pi}_i$ is close to 0 or 1.

# Predictive power of a logistic regression model: pseudo $R^2$

- For linear regression $Y_i = \mathbf{X}_i^T \beta + \epsilon_i$, the $R^2$ is

$$R^2 = 1 - \frac{\sum_i \left( Y_i - \mathbf{X}_i^T \hat{\beta} \right)^2}{\sum_i \left( Y_i - \bar{Y} \right)^2}$$

- For logistic regression, the analog

$$1 - \frac{\sum_i \left( Y_i - \hat{\pi}_i \right)^2}{\sum_i \left( Y_i - \bar{Y} \right)^2}$$

may not be nondecreasing as the model gets more complex (undesirable)

# Predictive power of a logistic regression model: pseudo $R^2$

For logistic regression, a more widely used measure is the pseudo $R^2$ of McFadden (1974): $\frac{L_M - L_0}{L_S - L_0} = 1 - \frac{L_M}{L_0}$

$$L = \log \prod_{i=1}^{N} \left[\pi_i^{y_i}(1-\hat{\pi}_i)^{1-y_i}\right] = \sum_{i=1}^{N} \left[y_i \log \hat{\pi}_i + (1-y_i)\log(1-\hat{\pi}_i)\right]$$

- $L_M$ is the log likelihood evaluated at the MLE $\hat{\pi}_i = \text{expit}(\mathbf{X}_i^T \hat{\beta})$
- $L_0$ is the log likelihood evaluated under the MLE of the null model: $\hat{\pi}_i = N^{-1} \sum_i y_i$
- $L_S$ is the log likelihood evaluated under the saturated model with $\hat{\pi}_i = y_i$. $L_S = 0$

# Receiver Operative Characteristics (ROC) curve

- $Y_i = 0$ (non disease) or 1 (disease). Estimated viral load $\hat{\pi}_i \in (0, 1)$. We classify the subject as a case ($Y = 1$) when $\hat{\pi} > c$ and control ($Y = 0$) when $\hat{\pi} \leq c$.
- Sensitivity $P(\hat{\pi} > c | Y = 1) \Leftarrow \frac{\sum_i 1\{\hat{\pi}_i > c\}}{\sum_i Y_i}$ 
- Specificity $P(\hat{\pi} \leq c | Y = 0) \Leftarrow \frac{\sum_i 1\{\hat{\pi}_i \leq c\}}{\sum_i (1 - Y_i)}$ 
- ROC curve  p225
- The area under the ROC curve (AUC) is reported as c-statistic in SAS PROC LOGISTIC. It is a number between 0 and 1. AUC $= 0.5$ is like flipping a coin. So AUC $< 0.5$ is unlikely. Good classification requires AUC $> 0.80$ (excellent, $> 0.9$).

# ROC Curve

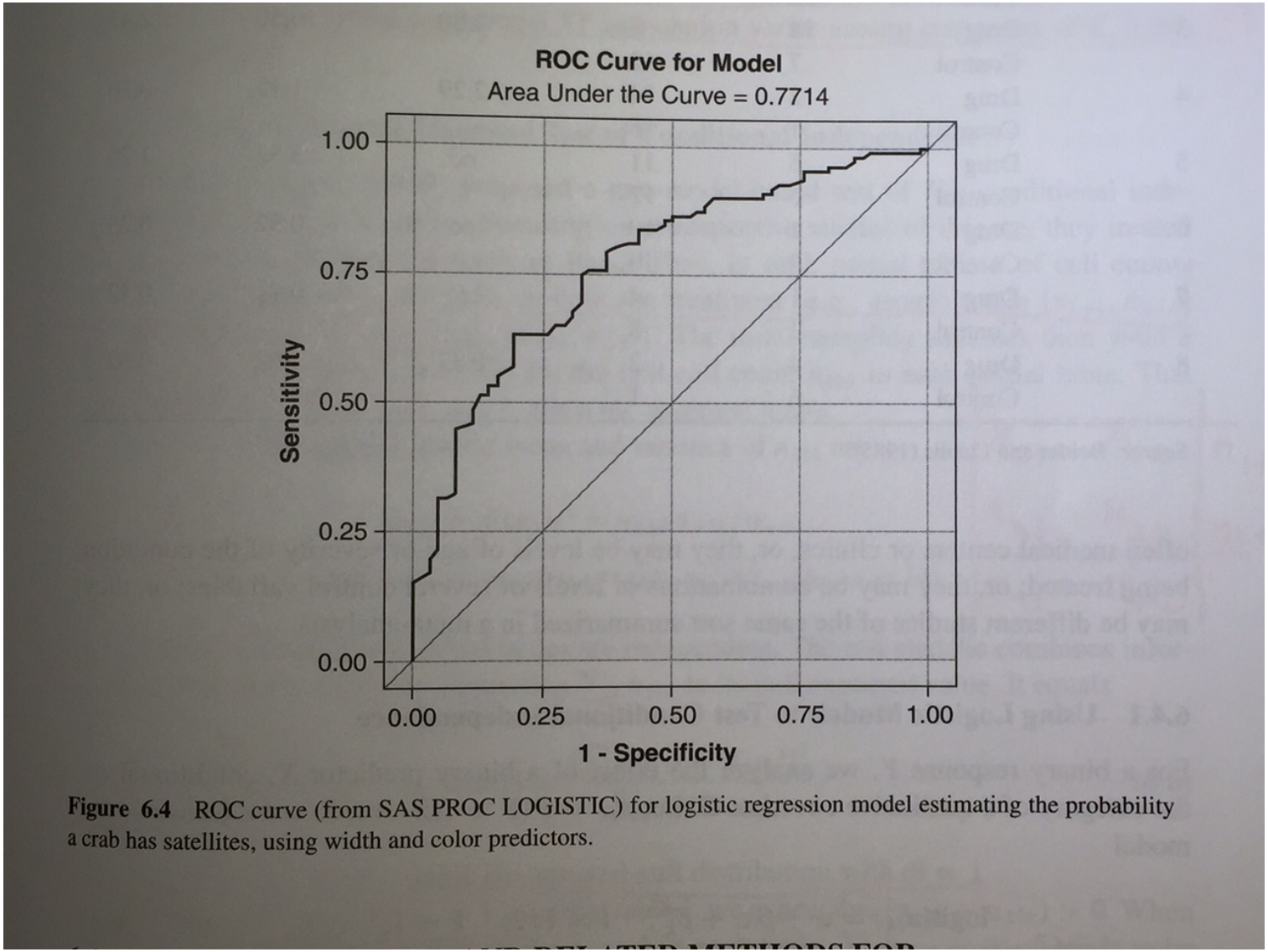



**Figure 6.4** ROC curve (from SAS PROC LOGISTIC) for logistic regression model estimating the probability a crab has satellites, using width and color predictors.

# Cochran-Mantel-Haenszel Test (§ 6.4)

- Study the association between a treatment variable (e.g., binary) and a disease outcome (e.g., binary) after adjusting for a possibly confounding variable (e.g., categorical or continuous but grouped) that might influence that association
- Example in Table 6.9: multicenter randomized clinical trial comparing treatment vs. placebo on a binary outcome (cured vs. not)
- The logistic regression approach ($i = 1, 2; k = 1, 2, ..., K; x_i = 1 \text{ or } 2$):

$$\pi_{ik} = P(Y = 1 | X = i, Z = k)$$
$$logit(\pi_{ik}) = \alpha + \beta x_i + \beta_k^Z$$

- Test $H_0$: $\beta = 0$ using Wald or likelihood ratio test
- What if there is interaction between $X$ and $Z$, i.e., $\beta$ depends on $Z$?

# Table 6.9



**Table 6.9 Clinical Trial Relating Treatment to Response for Eight Centers, with Expected Value and Variance (of Success Count for Drug) Under Conditional Independence**

| | | Response | | | | |
|---|---|---|---|---|---|---|
| Center | Treatment | Success | Failure | Odds Ratio | $\mu_{11k}$ | $\text{var}(n_{11k})$ |
| 1 | Drug | 11 | 25 | 1.19 | 10.36 | 3.79 |
| | Control | 10 | 27 | | | |
| 2 | Drug | 16 | 4 | 1.82 | 14.62 | 2.47 |
| | Control | 22 | 10 | | | |
| 3 | Drug | 14 | 5 | 4.80 | 10.50 | 2.41 |
| | Control | 7 | 12 | | | |
| 4 | Drug | 2 | 14 | 2.29 | 1.45 | 0.70 |
| | Control | 1 | 16 | | | |
| 5 | Drug | 6 | 11 | $\infty$ | 3.52 | 1.20 |
| | Control | 0 | 12 | | | |
| 6 | Drug | 1 | 10 | $\infty$ | 0.52 | 0.25 |
| | Control | 0 | 10 | | | |
| 7 | Drug | 1 | 4 | 2.0 | 0.71 | 0.42 |
| | Control | 1 | 8 | | | |
| 8 | Drug | 4 | 2 | 0.33 | 4.62 | 0.62 |
| | Control | 6 | 1 | | | |

*Source*: Beitler and Landis (1985).

often medical centers or clinics; or, they may be levels of age or severity of the condition

# Cochran-Mantel-Haenszel Test (§ 6.4)

Data from Center $k$ $(k = 1, 2, ..., K)$

| | cured | not | Total |
|---|---|---|---|
| Treatment | $n_{11k}$ | $n_{12k}$ | $n_{1+k}$ |
| placebo | $n_{21k}$ | $n_{22k}$ | $n_{2+k}$ |
| Total | $n_{+1k}$ | $n_{+2k}$ | $n_{++k}$ |

- Test $H_0$: Treatment and outcome independent conditional on center
- Both the treatment (row) and outcome (column) totals fixed, $n_{11k} \sim$ hypergeometric distribution
- Under the null, the hypergeometric mean and variance of $n_{11k}$ are

$$\mu_{11k} = E(n_{11k}) = n_{1+k}n_{+1k}/n_{++k}$$

$$var(n_{11k}) = n_{1+k}n_{2+k}n_{+1k}n_{+2k}/[n_{++k}^2(n_{++k} - 1)]$$

- The CMH statistic is $CMH = \frac{[\sum_k (n_{11k} - \mu_{11k})]^2}{\sum_k var(n_{11k})}$, which has a large sample chi-squared null distribution with $df = 1$.

# Cochran-Mantel-Haenszel Test vs. Logistic Regression

- When the sample size per center (also called strata) is moderately large, the two produce similar results (CMH is a score test of the logistic model)
- When the number of strata is large (like matched pairs data), the logistic regression does not apply but CMH still applies
- A point estimator of the overall odds ratio is available from CMH 

$$\hat{\theta}_{CMH} = \frac{\sum_k (n_{11k} n_{22k} / n_{++k})}{\sum_k (n_{12k} n_{21k} / n_{++k})} = \frac{\sum_k n_{++k} p_{11|k} p_{22|k}}{\sum_k n_{++k} p_{12|k} p_{21|k}}$$

- CMH is the standard method for stratified analysis of categorical data, applicable to $I \times J \times K$ contingency table
- If the treatment effect differs across strata (interaction), use logistic model with interaction

# Quasi-complete Separation in Logistic Regression

- Be careful about excessively large (or small) odds ratios or excessively large standard errors
  - multi-colinearity; remove one of the correlated covariates
  - complete or quasi-complete separation
- Complete separation: there exists a vector $\mathbf{b}$ such that $\mathbf{b}^T\mathbf{x}_i > 0$ whenever $y_i = 1$ and $\mathbf{b}^T\mathbf{x}_i < 0$ whenever $y_i = 0$. (more likely with continuous covariates)
- Quasi-complete separation: $\mathbf{b}^T\mathbf{x}_i \geq 0$ whenever $y_i = 1$ and $\mathbf{b}^T\mathbf{x}_i \leq 0$ whenever $y_i = 0$. (more likely with categorical covariates)
- Not a problem with linear regression

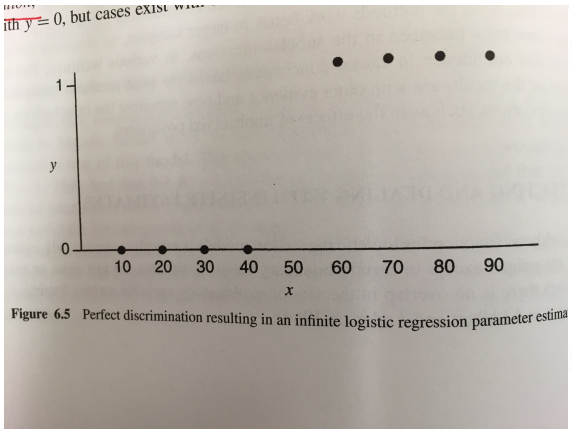


Figure 6.5 Perfect discrimination resulting in an infinite logistic regression parameter estima

# Chapter 8

## Regression Models for Multinomial Data

# Models for Multinomial Responses (§ 8)

- Nominal data vs. ordinal data: presence or absence of intrinsic order
- For nominal outcome variable $Y = 1, 2, ..., J$. We need to model $\pi_j(\mathbf{x}) = P(Y = j|\mathbf{x})$ under constraint $\sum_j \pi_j(\mathbf{x}) = 1$.
- $Y$ follows a multinomial distribution with probabilities $\{\pi_1(\mathbf{x}), ..., \pi_J(\mathbf{x})\}$.
- Baseline-category logit model (e.g., pick $J$ as the baseline/reference category)

$$\log \frac{\pi_j(\mathbf{x})}{\pi_J(\mathbf{x})} = \alpha_j + \boldsymbol{\beta}_j^T \mathbf{x} \quad , \qquad j = 1, 2, ..., J-1$$

- These $J-1$ equations determine parameters for logits with other pairs of response categories, as well as the response probabilities:

$$\log \frac{\pi_a(\mathbf{x})}{\pi_b(\mathbf{x})} = \log \frac{\pi_a(\mathbf{x})}{\pi_J(\mathbf{x})} - \log \frac{\pi_b(\mathbf{x})}{\pi_J(\mathbf{x})}$$

# Models for Multinomial Responses: baseline-category logit model

- The constraint leads to: $\pi_J(x) = \dfrac{1}{1 + \sum_{j=1}^{J-1} \exp\left(\alpha_j + \boldsymbol{\beta}_j^T \mathbf{x}\right)}$
- The probability for the $j$-th category ($j = 1, 2, ..., J-1$):

$$\pi_j(x) = \frac{\exp\left(\alpha_j + \boldsymbol{\beta}_j^T \mathbf{x}\right)}{1 + \sum_{j=1}^{J-1} \exp\left(\alpha_j + \boldsymbol{\beta}_j^T \mathbf{x}\right)}$$

- With more than two response categories ($J > 2$), the probability of a given category need not continuously increase or decrease (e.g., $\pi_j(x)$ may not be a monotone function of $x$) 
- The model is fit by maximum likelihood. Let $\mathbf{y}_i = (y_{i1}, y_{i2}, ..., y_{iJ})$, where $y_{ij} = 1$ when the response is in category $j$ and 0 otherwise, so that $\sum_j y_{ij} = 1$. The log likelihood is:

$$\sum_{i=1}^{n} \log \left[ \prod_{j=1}^{J} \pi_j(\mathbf{x}_i)^{y_{ij}} \right]$$

# Models for Ordinal Responses (§ 8.2)

- $Y = 1, 2, ..., J$. We need to model $\pi_j(\mathbf{x}) = P(Y = j|\mathbf{x})$ under constraint $\sum_j \pi_j(\mathbf{x}) = 1$.
- Due to the intrinsic ordering of the response categories, we model the cumulative probabilities

$$P(Y \leq j|\mathbf{x}) = \pi_1(\mathbf{x}) + ... + \pi_j(\mathbf{x})$$

- The cumulative logits are defined as:

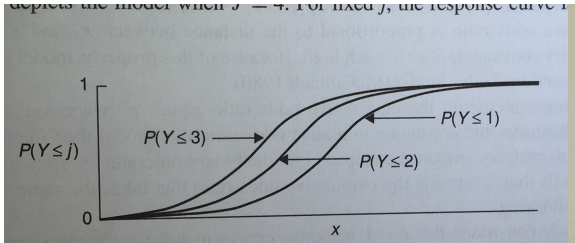
$$logit[P(Y \leq j|\mathbf{x})] = \log \frac{P(Y \leq j|\mathbf{x})}{1 - P(Y \leq j|\mathbf{x})} = \log \frac{\pi_1(\mathbf{x}) + ... + \pi_j(\mathbf{x})}{\pi_{j+1}(\mathbf{x}) + ... + \pi_J(\mathbf{x})}$$

- Cumulative logit model

$$logit[P(Y \leq j|\mathbf{x})] = \alpha_j + \boldsymbol{\beta}^T\mathbf{x} \quad , \qquad j = 1, 2, ..., J-1$$

- The cumulative logit is monotone in $\mathbf{x}$; this feature not available in baseline-category logit model

# Proportional Odds Model




umulative logit model with the same effect on each of three cumulative probabili
se.

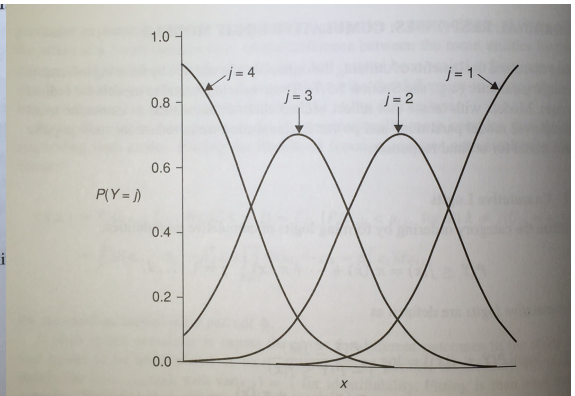



Figure 8.3 Individual category probabilities in cumulative logit model with four response categories.

- Proportional odds model $logit[P(Y \leq j|\mathbf{x})] = \alpha_j + \boldsymbol{\beta}^T\mathbf{x}$, where $j = 1, 2, ..., J-1$
- Need to assume the same $\beta$ for each logit. Therefore, *cumulative logit model* is also called the *proportional odds model*

$$logit[P(Y \leq j|\mathbf{x}_1)] - logit[P(Y \leq j|\mathbf{x}_2)] = \boldsymbol{\beta}^T(\mathbf{x}_1 - \mathbf{x}_2)$$

- Cumulative odds ratio $\exp(\boldsymbol{\beta})$ does not depend on $j$, i.e., $\boldsymbol{\beta}_j \equiv \boldsymbol{\beta}, \forall j$
- We cannot make the model more generalizable by letting replacing $\boldsymbol{\beta}$ with $\boldsymbol{\beta}_j$: the different cumulative probabilities may cross, which is impossible

# Proportional Odds Model



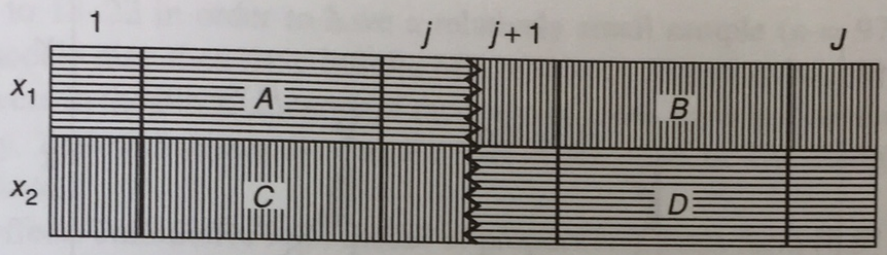



**Figure 8.4** Uniform odds ratios $AD/BC$ whenever $x_1 - x_2 = 1$, for all binary collapsings of the response in cumulative logit model of proportional odds form.

likelihood function is

$$\prod_{i=1}^{n}\left[\prod_{j=1}^{J}\pi_j(\boldsymbol{x}_i)^{y_{ij}}\right] = \prod_{i=1}^{n}\left\{\prod_{j=1}^{J}\left[P(Y \le j|\boldsymbol{x}_i) - P(Y \le j-1|\boldsymbol{x}_i)\right]^{y_{ij}}\right\}$$

$$= \prod_{i=1}^{n}\left\{\prod_{j=1}^{J}\left[\frac{\exp(\alpha_j + \boldsymbol{\beta}^T\boldsymbol{x}_i)}{1+\exp(\alpha_j + \boldsymbol{\beta}^T\boldsymbol{x}_i)} - \frac{\exp(\alpha_{j-1} + \boldsymbol{\beta}^T\boldsymbol{x}_i)}{1+\exp(\alpha_{j-1} + \boldsymbol{\beta}^T\boldsymbol{x}_i)}\right]^{y_{ij}}\right\}, \quad (8.6)$$

viewed as a function of $(\{\alpha_j\}, \boldsymbol{\beta})$. This can be maximized to obtain the ML estimates us-

- The model parameters are estimated by maximum likelihood

# Latent Variable Motivation for Proportional Odds Model

- A continuous latent variable $y^*$ with $y^* = \tilde{\boldsymbol{\beta}}^T \mathbf{x} + \epsilon$ and the distribution function of $\epsilon$ is $G(.)$ (not mean zero)
- Thresholds $-\infty = \tilde{\alpha}_0 < \tilde{\alpha}_1 < ... < \tilde{\alpha}_J = \infty$
- The observed response $y$ satisfies $y = j$ if $\tilde{\alpha}_{j-1} < y^* \leq \tilde{\alpha}_j$

$$P(Y \leq j|\mathbf{x}) = P(y^* \leq \tilde{\alpha}_j|\mathbf{x}) = G(\tilde{\alpha}_j - \tilde{\boldsymbol{\beta}}^T \mathbf{x})$$

- The proportional odds model

$$P(Y \leq j|\mathbf{x}) = expit\left(\alpha_j + \boldsymbol{\beta}^T \mathbf{x}\right)$$

- $G(.) \sim expit(.)$, $G^{-1}(.) \sim logit(.)$, $\tilde{\alpha}_j = \alpha_j$, $\tilde{\boldsymbol{\beta}} = -\boldsymbol{\beta}$

# Proportional Odds Model: Interpretation using latent variable

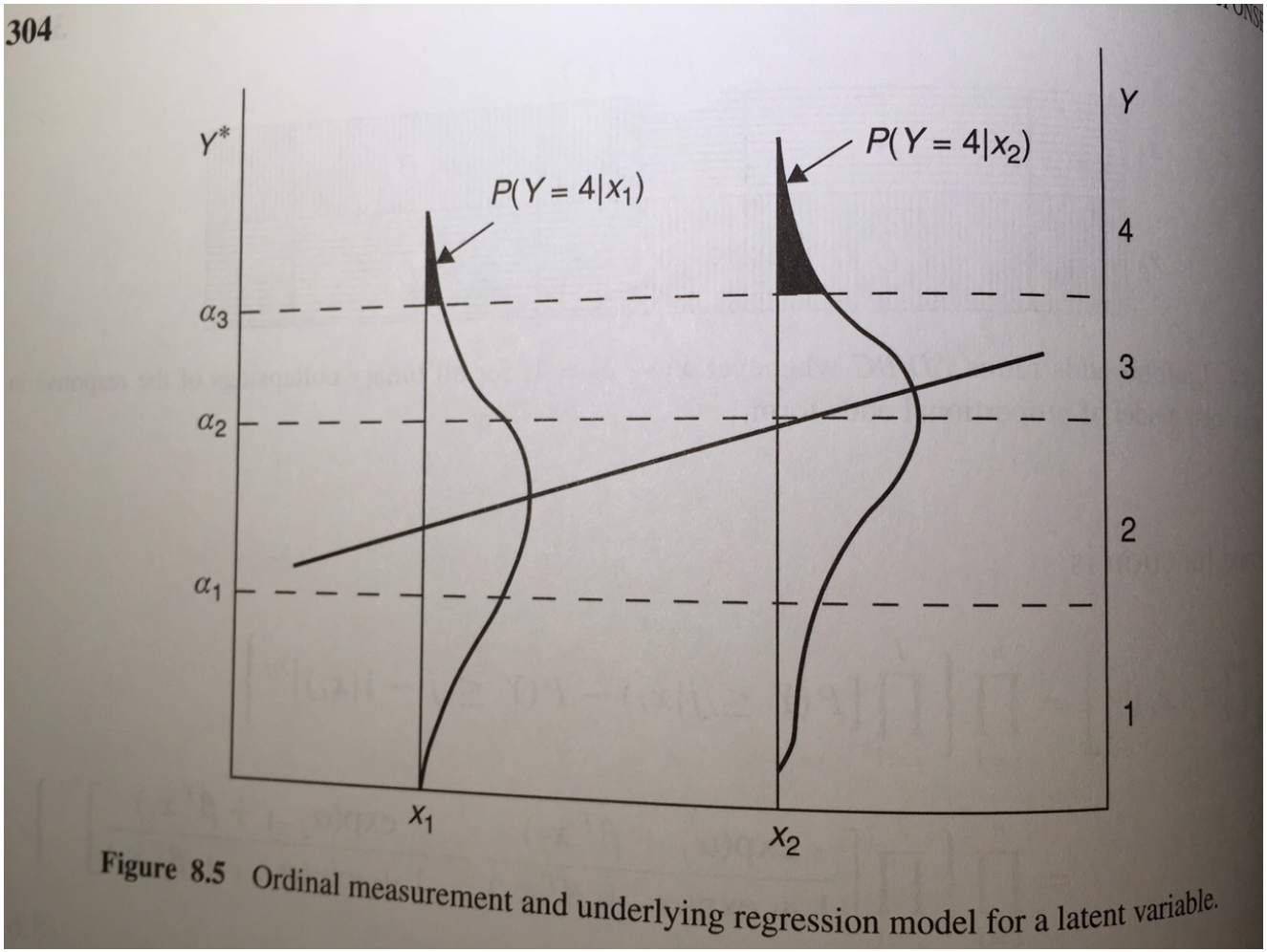



Figure 8.5 Ordinal measurement and underlying regression model for a latent variable.

# Probit and Logit: Latent Variable Motivation for Binary Outcome Model

- A continuous latent variable $y^*$ with $y^* = \tilde{\boldsymbol{\beta}}^T \mathbf{x} + \boldsymbol{\epsilon}$ (no intercept) and the distribution function of $\boldsymbol{\epsilon}$ is $G(.)$
- Threshold $-\infty < \tilde{\alpha} < \infty$. The observed response $y$ satisfies $y = 1$ if $y^* \leq \tilde{\alpha}$ and $y = 0$ otherwise

$$P(Y = 1|\mathbf{x}) = P(y^* \leq \tilde{\alpha}|\mathbf{x}) = G(\tilde{\alpha} - \tilde{\boldsymbol{\beta}}^T \mathbf{x})$$

- The logistic regression model: $P(Y = 1|\mathbf{x}) = \textit{expit}\left(\alpha + \boldsymbol{\beta}^T \mathbf{x}\right)$.
$$G(.) \sim \textit{expit}(.),\ G^{-1}(.) \sim \textit{logit}(.),\ \tilde{\alpha} = \alpha,\ \tilde{\boldsymbol{\beta}} = -\boldsymbol{\beta}$$
- The probit regression model: $P(Y = 1|\mathbf{x}) = \Phi\left(\alpha + \boldsymbol{\beta}^T \mathbf{x}\right)$.
$$G(.) \sim \Phi(.),\ G^{-1}(.) \sim \Phi^{-1}(.),\ \tilde{\alpha} = \alpha,\ \tilde{\boldsymbol{\beta}} = -\boldsymbol{\beta}$$

# Check the Proportional Odds Assumption

$$P(Y \leq j|\mathbf{x}) = expit\left(\alpha_j + \boldsymbol{\beta}^T\mathbf{x}\right)$$

- Proportional odds model is parsimonious and easy to interpret
- Replacing $\beta$ with $\beta_j$ may cause the cumulative probabilities to cross
- A score test of proportional odds model is available (SAS PROC LOGISTIC)
- Retain proportional odds model unless there is strong deviation from this assumption
- What to do when the proportional odds assumption is violated:
  - Adding additional terms, such as interaction
  - alternative ordinal model (next slides)
  - partial proportional odds model (SAS PROC LOGISTIC)
  - baseline category logit model

# Alternative Models for Ordinal Data

- Cumulative link model: $G^{-1}\left[P(Y \leq j|\mathbf{x})\right] = \alpha_j + \boldsymbol{\beta}^T\mathbf{x}$
- Cumulative probit model: $\Phi^{-1}\left[P(Y \leq j|\mathbf{x})\right] = \alpha_j + \boldsymbol{\beta}^T\mathbf{x}$
- Cumulative complementary log-log model: $\log\left\{-\log\left[1 - P(Y \leq j|\mathbf{x})\right]\right\} = \alpha_j + \boldsymbol{\beta}^T\mathbf{x}$
  - Equivalent to a latent variable model with extreme value distribution for the residuals
  - Equivalent to proportional hazard model in for discrete survival data analysis (e.g., year of death at 1, 2, 3, ... )
  - Rare event logistic regression
- Adjacent category logit model
- Continuation ratio logit model

# Regression Models for Counts Data

# Poisson Regression: introduction

- Applicable to counts data $0, 1, 2, .....$ Popularized in the 1970s and 1980s.
- Suppose $Y$ has Poisson distribution with mean $\mu$

$$P(Y = y) = \frac{e^{-\mu}\mu^y}{y!}, \quad y = 0, 1, 2, ... \tag{1}$$

and $E(Y) = var(Y) = \mu$

- Suppose we want to relate $Y$ to a covariate $X$, we assume $g(\mu) = \alpha + \beta X$. What choices do we have for the link function $g(.)$? Any monotone mapping from $(0, \infty)$ to $(-\infty, \infty)$?
- Log link (log linear model) $\mu = \exp(\alpha + \beta X)$: the multiplicative effect of $X$ on $\mu$. Interpret $\exp(\beta)$ as a rate ratio.
- Example: A study of 400 patients with malignant melanoma. $Y$: tumor counts; $X$: tumor type (Hutchinson's, Superficial, Nodular, Indeterminate) and tumor site (Head & Neck, Trunk, Extremities)

# Poisson Regression: Offset

- Frequently, discrete counts represent information collected over time (days, years) or in space (volume for bacteria counts) and interest lies in modeling rates. Denote the exposure time or volume by $N$, then the rate is $Y/N$, which has expectation $\mu/N$.
- Modeling this rate with a log linear model as $\log \frac{\mu}{N} = \alpha + \beta X$. That is $\log \mu = \alpha + \beta X + \log(N)$ or $\mu = N \exp(\alpha + \beta X)$.
- $Y \sim Poisson(\mu)$.
- The log-likelihood is 

$$L = \log \prod_{i=1}^{n} \mu_i^{Y_i} \{\exp(-\mu_i)\}/Y_i! \quad , \quad \mu_i = N_i \exp(\alpha + \beta X_i)$$

# Poisson Regression: Example with Offset

- Table 12.2 of "Categorical Data Analysis with the SAS System".

| Region | Age Group | Cases | Total |
|---|---|---|---|
| North | $< 35$ | 61 | 2,880,262 |
| South | $35 - 44$ | 76 | 564,535 |
| ... | ... | ... | ... |

- **Counts**: number of new cases in 1961-1971; **offset**: size of the populations at risk; **covariates**: age group and region
- Can this example be analyzed with binomial regression? 

```
proc genmod data = melanoma order = data ;
class age region ;
model cases = age region / dist = poisson link = log offset = ltotal ;
run ;
```

# Poisson Regression: Overdispersion

- Real data often have more variation than expected from a Poisson distribution (due to unobserved heterogeneity not captured by the covariates); $var(Y) > E(Y)$.
- Discover overdispersion through overdispersion parameter (next slide)
- Three ways to correct for overdispersion
  - Overdispersion model
  - Negative binomial regression
  - Poisson regression with random effect (later)

# Overdispersion Model

- $var(Y) = \phi E(Y)$. $\phi > 1$ is the dispersion parameter. ($0 < \phi < 1$ is called under dispersion)
- $\mu_i = E(Y_i|\mathbf{X}_i) = N_i \exp(\mathbf{X}_i^T \theta)$ and $var(Y_i|\mathbf{X}_i) = \phi\mu_i$. In a Poisson regression model, we model the mean as a function of covariates, but not $\phi$
- The likelihood equation $0 = \sum_{i=1}^{n} \left(Y_i - N_i \exp(\mathbf{X}_i^T \theta)\right) \mathbf{X}_i$, which uses only the mean function. So the point estimator is always correct even when overdispersion is ignored; but variance estimation and p-values will be incorrect.
- Estimate $\phi$  , and then multiply the ordinary standard error estimates by $\sqrt{\hat{\phi}}$. Example in page 150 
- An approximate method motivated from quasi-likelihood ideas
- Maybe wrong if the mean function is misspecified (major weakness)

# Overdispersion with Binomial Model

- $y_i$ is the sample proportion from $n_i$ Bernoulli trials with parameter $\pi_i$, $i = 1, 2, ..., n$.
- According to binomial model $E(Y_i) = \pi_i$ and $var(Y_i) = \pi_i(1 - \pi_i)/n_i$.
- $v(\pi_i) = \phi\pi_i(1 - \pi_i)/n_i$
- Estimate $\phi$ by $X^2/(n - p)$ and multiply the standard error by $\sqrt{(\hat{\phi})}$
- Not applicable when some $n_i = 1$ (and some not) because $\phi$ can only be 1 in this case.

# Negative Binomial Regression §4.3.4

- If $Y$ has a Poisson distribution with both mean and variance equal to $\lambda$, and $\lambda$ has a gamma distribution (extra variation; overdispersion) with mean $\mu$ and variance $\mu^2/k$, then marginally $Y$ has a negative binomial distribution with mean $\mu$ and variance $\mu + \gamma\mu^2$ ($\gamma = 1/k > 0$) 
- When $\gamma \to 0$ (random effect variance approaches zero), the NB distribution approaches Poisson
- Like the overdispersion model, we let $\gamma$ to be a overdispersion constant and model the mean $\mu = N\exp(\mathbf{X}^T\theta)$.
- Standard error will become larger after applying negative binomial regression
- Preferred over overdispersion model
- Available in SAS PROC GENMOD

# Conditional Logistic Regression for Binary Matched Pairs

# Clustered / Longitudinal vs. Cross-sectional Data

- Longitudinal data is a special kind of clustered data; sometimes also called repeated measures data
- Cross-sectional data: each subject is one row 
- Longitudinal data: the long format (most common) and the short format (rarely used; do not work for irregularly measured time points) 
- Notation for longitudinal and cross-sectional data 

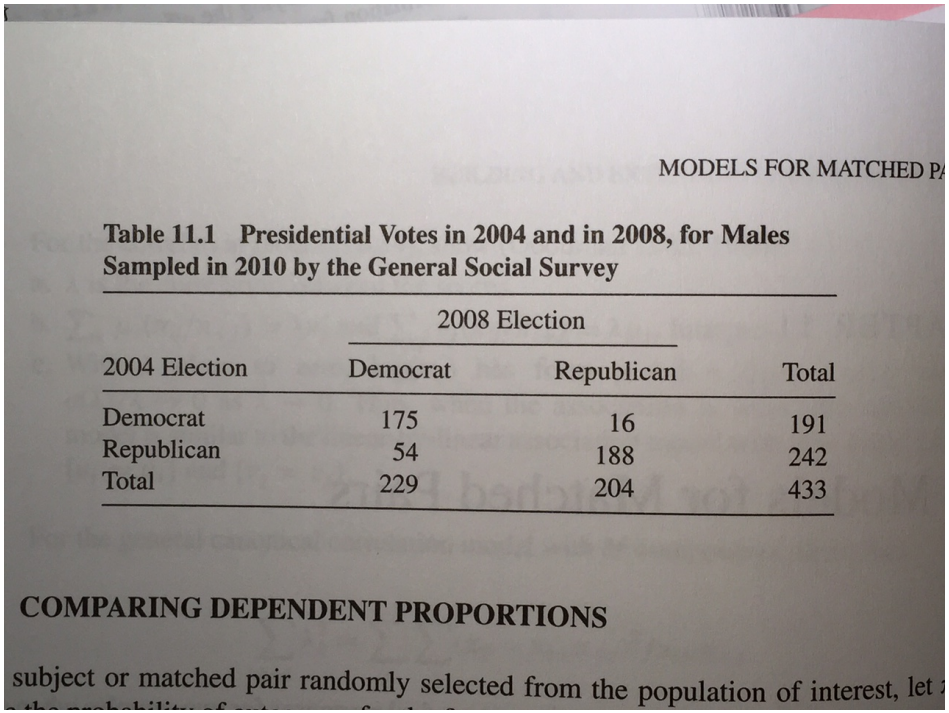
# Conditional Logistic Regression

- (Positively) correlated continuous data
- (Positively) correlated binary data
- For the example in Table 11.1 , let $(Y_{i1}, Y_{i2})$ denote the data pair, $i = 1, 2, ..., n$. The conditional logistic regression model is ($x_t = 0$ or 1)

$$\text{logit}[P(Y_{ij} = 1)] = \mu + \beta x_t + \alpha_i \quad , \quad t = 1, 2$$

- $\alpha_i$ is the random intercept, analogous to the linear regression case. It has a distribution, but the advantage of the methodology here is that it works without making any assumption on the form of that distribution
- Note: $\beta$ is NOT the marginal odds ratio ( , SAS)

# Conditional Logistic Regression Example



MODELS FOR MATCHED PA

**Table 11.1 Presidential Votes in 2004 and in 2008, for Males Sampled in 2010 by the General Social Survey**

| | 2008 Election | | |
|---|---|---|---|
| 2004 Election | Democrat | Republican | Total |
| Democrat | 175 | 16 | 191 |
| Republican | 54 | 188 | 242 |
| Total | 229 | 204 | 433 |

**COMPARING DEPENDENT PROPORTIONS**

subject or matched pair randomly selected from the population of interest, let

- 2004 Odds $(D/R) = 191/243$ ; 2008 Odds $(D/R) = 229/204$ ; log OR (2008 vs. 2004) $= 0.35$
- Conditional logistic regression code below gives $\beta = 1.22$, $p < 0.0001$ (actually, $\exp(\beta) = 54/16$)
- McNemar test has $p < 0.0001$.

# SAS code

```
proc logistic ;
strata pair ;
model Vote(event = 'D') = Year ; run ;
(long format)
```

```
proc freq ;
tables Y2004 * Y2008 / agree ;
run ;
(short format)
```

# Fit Conditional Logistic Regression

$$\text{logit}[P(Y_{ij} = 1)] = \alpha_i + \beta^T X_{it} \quad , \quad t = 1, 2$$

- Maximize the likelihood by treating $\alpha_i$ as fixed parameters?
- Maximize the likelihood by treating $\alpha_i$ as random parameters (effects)?
- Eliminate all the $\alpha_i$'s by using a conditional likelihood.

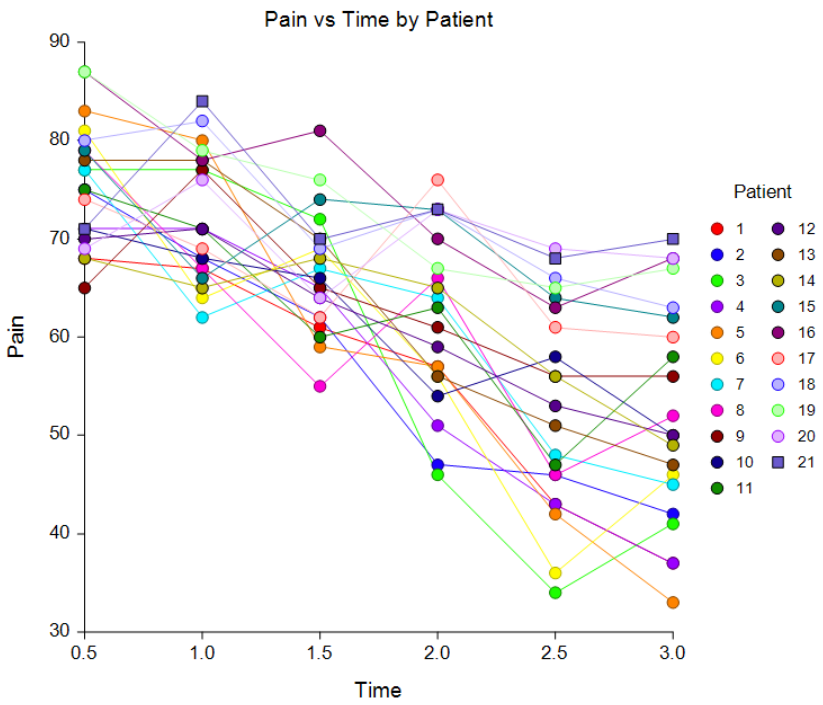
# A Few Notes on Fitting Conditional Logistic Regression

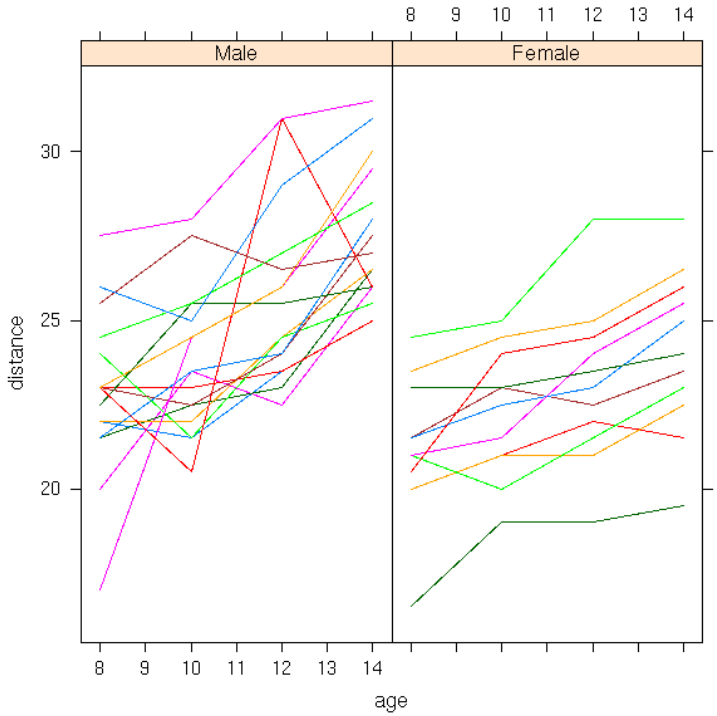
$$\text{logit}[P(Y_{ij} = 1)] = \alpha_i + \beta^T X_{it} \quad , \quad t = 1, 2$$

- If $X_{it}$ is the same for each subject, then $\beta$ cannot be estimated with this method. Example: $Y_{it}$ is the outcome at week 1 and week 4 after surgery, and $X_{it}$ is the intra-operative treatment.
- When $X_{i1} = 0$ and $X_{i2} = 1$, the test of $\beta = 0$ is equivalent to McNemar test. Also, it can be shown that $\exp(\beta)$ is estimated by $n_{12}/n_{21}$ where $n_{12}$ and $n_{21}$ are off-diagonal counts in the McNemar test table 
- Since the likelihood conditioned on the discordant pairs ($Y_{i1} \neq Y_{i2}$), the concordant pairs ($Y_{i1} = Y_{i2}$) are non-informative and thus can be ignored (as in McNemar test). What is the intuition behind it?
- An analog in the case of a continuous outcome and linear model with random intercept. 

# Longitudinal Data Analysis: Marginal Model

# Longitudinal Data Example




- Repeated measures ANOVA may be applicable (at treatment by time combination)
- Ignoring **intrasubject correlation** may cause bias to the point estimator (sometimes, depending on methods) and estimated variance (almost always, even if the point estimator is unbiased )

# Marginal Longitudinal Data Model for Continuous Outcome

$$Y_{ij} = X_{ij}^T \beta + \epsilon_{ij}$$

$\epsilon_{ij}$ and $\epsilon_{ij'}$ may be correlated. In matrix notation

$$\begin{aligned} \mathbf{Y}_i &= \mathbf{X}_i \beta + \boldsymbol{\epsilon}_i \\ \boldsymbol{\epsilon}_i &\sim MVN(\mathbf{0}, \boldsymbol{\Sigma}) \end{aligned}$$

- The log likelihood is proportional to a weighted least squares 
- The likelihood equation is

$$\mathbf{0} = \sum_{i=1}^{n} \mathbf{X}_i^T \boldsymbol{\Sigma}^{-1} (\mathbf{Y}_i - \mathbf{X}_i \beta) = \sum_{i=1}^{n} \frac{\partial \mathbf{X}_i^T \beta}{\partial \beta} \boldsymbol{\Sigma}^{-1} (\mathbf{Y}_i - \mathbf{X}_i \beta)$$

- Even when $\boldsymbol{\epsilon}_i$ is not MVN, as long as $E(\boldsymbol{\epsilon}_i) = \mathbf{0}$, we can use this **unbiased estimating equation** to estimate $\beta$ (assuming $\boldsymbol{\Sigma}$ known)

# Marginal Longitudinal Data Model for Continuous Outcome

- An **unbiased estimating equation** for i.i.d. data takes the form:

$$\mathbf{0} = \sum_{i=1}^{n} \mathbf{f}(\mathbf{Y}_i, \mathbf{X}_i, \beta)$$

  There are as many equations as the number of parameters in $\beta$. As long as $E(\mathbf{f}(\mathbf{Y}_i, \mathbf{X}_i, \beta)) = \mathbf{0}$, solving this equation gives us consistent estimator of $\beta$
- Question: is $\mathbf{0} = \sum_{i=1}^{n} \mathbf{X}_i^T(\mathbf{Y}_i - \mathbf{X}_i\beta)$ an unbiased estimating equation? Is it the previous equation with misspecified $\mathbf{\Sigma}$ matrix?
- $\mathbf{\Sigma}$ is treated known in the equation, but what value does it take?
- **G**eneralized **E**stimating **E**quation:

$$\mathbf{0} = \sum_{i=1}^{n} \frac{\partial \mu_i(\beta)}{\partial \beta} var(\mathbf{Y}_i)^{-1}(\mathbf{Y}_i - \mu_i(\beta))$$

# Marginal Longitudinal Data Model for Continuous Outcome

- We don't know $\mathbf{\Sigma}$, and need to make some assumptions about it.
- With a MVN $\epsilon_i$ (that is an assumption), $\mathbf{\Sigma}$ is the variance covariance matrix.
- Without the MVN assumption, we can use some **working assumption**: 
  1. Independent (ignore intrasubject correlation)
  2. Exchangeable
  3. Auto-regressive (AR-1)
  4. Unstructured
- **Important**: unlike the usual likelihood inference, if we misspecify the working assumption about $var(\mathbf{Y}_i)$, the point estimator is still consistent, but may lose efficiency
- **But** the best efficiency is achieved with a correctly specified variance function

# Marginal Longitudinal Data Model for Continuous Outcome

- GEE algorithm step 1: Give an initial values to $\beta$ and $\mathbf{\Sigma}$
- step 2: Given $\mathbf{\Sigma}$, solve the GEE for $\beta$
- step 3: Given the solution of $\beta$ from step 2, calculate residuals $\mathbf{Y}_i - \mathbf{X}_i\hat{\beta}$, and estimate $\mathbf{\Sigma}$
  - Illustrate with matched pairs data 
- step 4: iterate between step 2 and 3 till convergence

# Generalized Estimating Equation for Categorical Outcomes (Section 12.3.4)

$$\mathbf{0} = \sum_{i=1}^{n} \frac{\partial \boldsymbol{\mu}_i(\boldsymbol{\beta})}{\partial \boldsymbol{\beta}} var(\mathbf{Y}_i)^{-1}(\mathbf{Y}_i - \boldsymbol{\mu}_i(\boldsymbol{\beta}))$$

- Model assumption on mean and variance functions (in the natural exponential family notation) 
- The specification of working covariance matrix for $\mathbf{Y}_i$ 
- Connection with quasi-likelihood (Section 12.3.2) 
- Model-based vs. empirical (sandwich) standard error (Section 12.3.4) 
- Section 12.3.5 and above are advanced topics

# GEE: Summary §12.3

- Estimate the **marginal** mean of the outcome  . Also called repeated measures ANOVA when all covariates are categorical
- Marginal interpretation: how the mean of the outcome change with treatment by time combination in a given population
- Only specifies the mean and variance function, and a working correlation (weaker assumption than full likelihood modeling)
- Variance function and working correlation are allowed to be wrong (but the best efficient is achieved with their are right)
- Techinical details in Section 12.3.2 and 12.3.4

# GEE: Iteration in SAS PROC GENMOD (documentation)

$$E(Y_{ij}) = \mu_{ij}(\beta) \quad \text{and} \quad var(Y_{ij}) = \phi v(\mu_{ij})$$

$$\mathbf{0} = \sum_{i=1}^{n} \mathbf{D}_i^T V_i^{-1}(\mathbf{Y}_i - \boldsymbol{\mu}_i(\beta))$$

$$\mathbf{D}_i = \frac{\partial \boldsymbol{\mu}_i(\beta)}{\partial \beta} \quad \text{and} \quad \mathbf{V}_i = \mathbf{B}_i^{1/2}\mathbf{R}(\alpha)\mathbf{B}_i^{1/2}\phi \quad , \quad \text{diag}\{\mathbf{B}_i\} = \{v(\mu_{ij})\}$$

1. Compute initial value of $\beta$ by assuming independence (ordinary GLM)
2. Compute the working correlation matrix $\mathbf{R}$ based on the standardized residuals, the current $\beta$, and the assumed structure of $\mathbf{R}$
3. Compute an estimate of the covariance: $\mathbf{V}_i = \mathbf{B}_i^{1/2}\mathbf{R}(\alpha)\mathbf{B}_i^{1/2}\phi$
4. Update $\beta$:

$$\beta_{(l+1)} = \beta_{(l)} + \left(\sum \mathbf{D}_i^T \mathbf{V}_i^{-1} \mathbf{D}_i\right)^{-1} \left(\sum \mathbf{D}_i^T \mathbf{V}_i^{-1}(\mathbf{Y}_i - \boldsymbol{\mu}_i)\right)$$

# GEE: Model-based and empirical SE §12.3.3, 12.3.4

- Model-based covariance matrix for $\hat{\beta}$ is $[\sum \mathbf{D}_i^T \mathbf{V}_i^{-1} \mathbf{D}_i]^{-1}$ (§12.3.4, p 470)
- The empirical (sandwich, robust) covariance matrix is given on p 469. See the "bread" and "meat" in the "sandwich". It reduces down to the model-based one when the variance is correctly specified.
- By default, SAS PROC GENMOD report the empirical SE; model based SE is requested from the `modelse` option (repeated statement)
- Even when variance is misspecified, the empirical SE is still valid; when the variance is correctly specified, model-based SE is better in the sense that it is less variable with better finite sample performance
- See the Poisson mean example on page 467 (NOT for longitudinal data, but a good illustration). 
- Inference through Wald method (CI, test)

# GEE Example in §12.2.2

- Longitudinal mental depression data 📖
- data in long format; SAS code below; all covariates are categorical
- Result in Table 12.5
- Empirical SE is similar to Model-based SE ($n_i \equiv 3$)

```
case severity treat time Y
1 0 0 0 1
1 0 0 1 1
1 0 0 2 1

2 0 0 0 1
2 0 0 1 1
2 0 0 2 1
```

```
proc genmod data = one desc ;
    class case ;
    model Y = severity treat time
        treat*time / link = logit dist = bin ;
    repeated subject = case
        / type = exch modelse corrw ;
run ;
```

# Chapter 13

## Longitudinal Data Analysis: Conditional Model

# Conditional Model / Random Effect Model / Subject-specific Modeling

- Conditional Model / Random Effect Model / Hierarchical Modeling / Subject-specific Modeling
- Marginal Model / Population-averaged Modeling

# Random Effect Model for Continuous Data

$$
\begin{aligned}
Y_{ij} &= \beta_{0i} + \beta_{1i} t_{ij} + \epsilon_{ij} \quad \text{(random intercept slope model)} \\
&= (\beta_0 + \beta_1 t_{ij}) + (u_{0i} + u_{1i} t_{ij}) + \epsilon_{ij} \\
&= \mathbf{x}_{ij}^T \boldsymbol{\beta} + \mathbf{z}_{ij}^T \mathbf{u}_i + \epsilon_{ij} \\
Y_{ij} &= \beta_{0i} + \beta_1 X_{ij} + \epsilon_{ij} \quad \text{(random intercept model)} \\
&= (\beta_0 + \beta_1 X_{ij}) + u_i + \epsilon_{ij} \\
&= \mathbf{x}_{ij}^T \boldsymbol{\beta} + \mathbf{z}_{ij}^T \mathbf{u}_i + \epsilon_{ij} \\
\mathbf{Y}_i &= \mathbf{X}_i \boldsymbol{\beta} + \mathbf{Z}_i \mathbf{u}_i + \boldsymbol{\epsilon}_i \ , \ \mathbf{u}_i \sim N(\mathbf{0}, \boldsymbol{\Sigma}) \\
\mathbf{Y} &= \mathbf{X}\boldsymbol{\beta} + \mathbf{Z}\mathbf{u} + \boldsymbol{\epsilon}
\end{aligned}
$$

- Two-stage hierarchical structure (1) $\mathbf{Y}|\mathbf{u}$ (2) $\mathbf{u} \sim\sim N(\mathbf{0}, \boldsymbol{\Sigma})$
- Linear mixed effect (fixed / random) model for continuous data (LMM): R packages `nlme`, `lme`, `lme4`; SAS PROC MIXED
- Within- and between- cluster covariates (§13.2.3)

# Generalized linear mixed model (GLMM), §13.1.1

- Generalized linear mixed model (GLMM): R packages `nlme`; SAS PROC NLMIXED & PROC GLIMMIX
- Extended from LMM by adding link function (the same as extending from GLM to GEE)
- $Y_{ij}$, $i = 1, 2, ..., n$, $j = 1, 2, ..., n_i$. Let $\mu_{ij} = E(Y_{ij}|\mathbf{u}_i)$

$$g(\mu_{ij}) = \mathbf{x}_{ij}^T \boldsymbol{\beta} + \mathbf{z}_{ij}^T \mathbf{u}_i \qquad \mathbf{u}_i \sim N(\mathbf{0}, \boldsymbol{\Sigma})$$

- The variability of $\mathbf{u}_i$ induces non-negative associations among the outcome (§13.2.1) 
- The random effect reparameterized as an unmeasured subject-specific covariate: $u_i \sim N(0, \sigma^2)$, $u_i = \sigma u_i^*$.

$$g(\mu_{ij}) = \mathbf{x}_{ij}^T \boldsymbol{\beta} + u_i = \mathbf{x}_{ij}^T \boldsymbol{\beta} + \sigma u_i^*$$

- Interpretation of $\beta$ as usual

# Logistic GLMM with random intercept for binary matched pairs, §13.1.2

- The conditional logistic regression model

$$\text{logit}\left[P(Y_{ij}=1)\right]=\alpha_i+\beta x_{ij}=\alpha_i+\beta x_j \quad , \quad j=1,2$$

- The logistic GLMM model

$$\text{logit}\left[P(Y_{ij}=1|u_i)\right]=\beta_0+\beta_1 x_j+u_i \quad \& \quad u_i\sim N(0,\sigma^2)$$

- The conditional logistic regression (CLR) estimate of $\beta$ is the same as the MLE of $\beta_1$ from the GLMM (to be discussed later)
- The same model, two methods, different assumptions
  - CLR only estimates within-cluster fixed effects; does not make distribution assumption on random effect
  - GLMM estimates everything, including random effects; need normality assumption on random effect; generally more efficient than CLR when the model assumptions are correct

# Connection between Conditional (GLMM) and Marginal (GEE) Models (§13.2.3)

- The conditional model (GLMM)

$$g(\mu_{ij}) = \mathbf{x}_{ij}^T \boldsymbol{\beta} + \mathbf{z}_{ij}^T \mathbf{u}_i \qquad \mathbf{u}_i \sim N(\mathbf{0}, \boldsymbol{\Sigma})$$

- The marginal model (GEE)

$$g(\mu_{ij}) = \mathbf{x}_{ij}^T \boldsymbol{\beta} \qquad \text{var}(Y_{ij}) = v(\mu_{ij}) \qquad \text{var}(\mathbf{Y}_i) = \phi \mathbf{B}_i^{1/2} \mathbf{R}(\boldsymbol{\alpha}) \mathbf{B}_i^{1/2}$$

- How to interpret the two $\boldsymbol{\beta}$'s in GLMM and GEE?
- Do we get the same $\boldsymbol{\beta}$ from GLMM and from GEE? No.
- Illustrate with a logistic GLMM with random intercept 

# Logistic-Normal Approximation

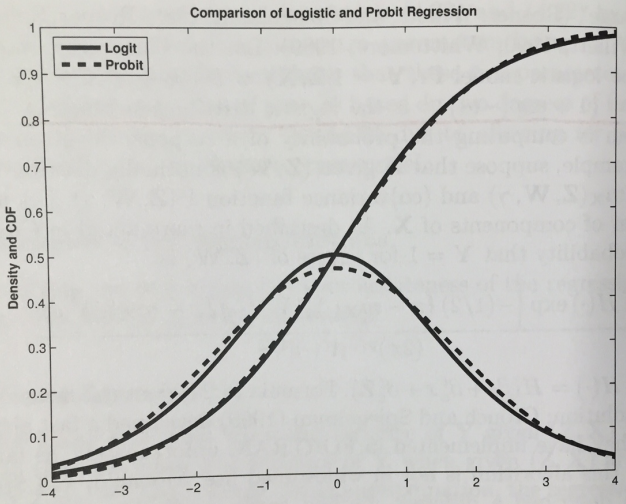



Figure 4.9 *The standard logistic distribution and density functions compared to the normal distribution and density functions with standard deviation 1.70. The point of the graph is to show how close the two are.*

effect. For a single explanatory variable $x$, the figure shows subject-specific

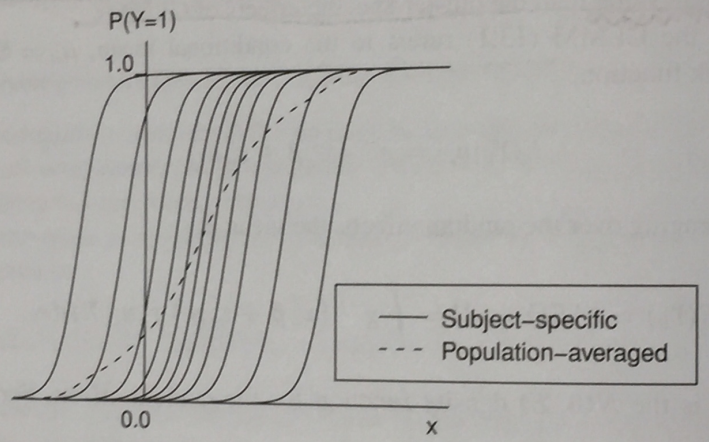



**Figure 13.1** Logistic random-intercept model, showing its subject-specific curves and the populati marginal curve averaging over these.

- Read and understand §13.2.4

# GLMM Fitting, Prediction, and Inference (§13.6)

- The GLMM is

$$g(\mu_{ij}) = \mathbf{x}_{ij}^T \boldsymbol{\beta} + \mathbf{z}_{ij}^T \mathbf{u}_i \qquad \mathbf{u}_i \sim N(\mathbf{0}, \boldsymbol{\Sigma})$$

- The marginal likelihood is:

$$\prod_{i=1}^{n} \int \left\{ \prod_{j=1}^{n_i} f(Y_{ij}|\mathbf{u}_i) \right\} f(\mathbf{u}_i)\, d\mathbf{u}_i$$

- The challenge is to maximize this likelihood and deal with the (multi-dimensional) integration
- No closed form expression for the integral; must use numerical integration