Generalized Linear Models and their Applications

STAT 431/STAT 831[*]

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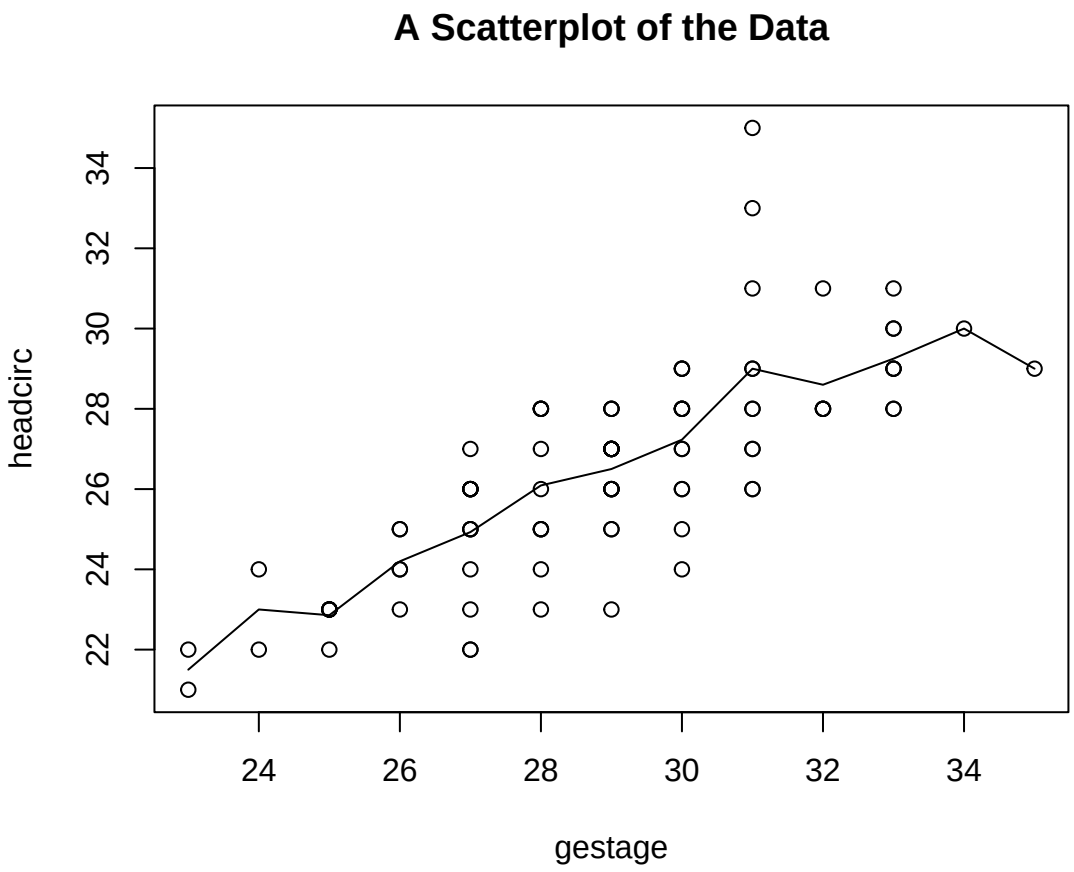
Contents

Topic 1a: Review of Linear Regression

Example: low birthweight infants study[1]

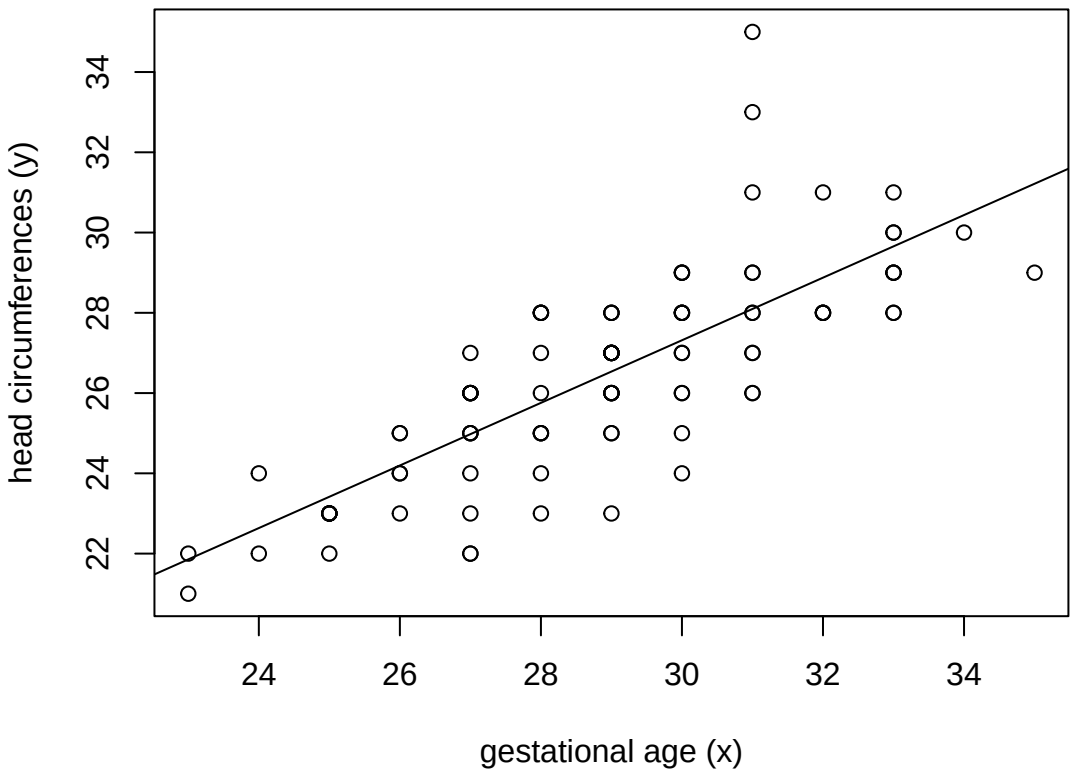
A study was conducted at two teaching hospitals in Boston, Massachusetts, where the head circumference, gestational age and some other variables are recorded for 100 low birth weight infants.

Question: what is the relationship between *gestational age* & head circumference?



We wish to model the relationship between *gestational age* and *head circumference* using a straight line!

[1] Principles of Biostatistics 2nd Edition by Marcello Pagano, Kimberlee Gauvreau.



The Model Fitting Process

1. Model Specification: select a probability distribution for the response variable and a linear equation linking the response to the explanatory variables.
2. Estimation: finding the equation (the parameters of the model).
3. Model checking: how well does the model fit the data?
4. Inference: interpret the fitted model, calculate confidence intervals, conduct hypothesis tests.

1 Model Specification

Notation

For each subject $i = 1, \ldots, n$ we have:

- $Y_i =$ random variable representing the response, and
- $\boldsymbol{x}_i = (1, x_{i1}, \ldots, x_{ip})^\top$ a vector of explanatory variables.

Specification for Multiple Linear Regression

- Linear regression equation:

$$Y_i = \beta_0 + \beta_1 x_{i1} + \cdots + \beta_p x_{ip} + \varepsilon_i \text{ where } \varepsilon_i \overset{\text{iid}}{\sim} \mathcal{N}(0, \sigma^2).$$

- Equivalently, Y_i's are independent $\mathcal{N}(\mu_i, \sigma^2)$ random variables or

$$\mu_i = \mathbb{E}[Y_i] = \beta_0 + \beta_1 x_{i1} + \cdots + \beta_p x_{ip}.$$

- For convenience, we often write linear regression models in matrix form as

$$\boldsymbol{Y} = \boldsymbol{X}\boldsymbol{\beta} + \boldsymbol{\varepsilon},$$

where

$$\boldsymbol{Y} = \begin{bmatrix} Y_1 \\ Y_2 \\ \vdots \\ Y_n \end{bmatrix}, \quad \boldsymbol{X} = \begin{bmatrix} 1 & x_{11} & \cdots & x_{1p} \\ 1 & x_{21} & \cdots & x_{2p} \\ \vdots & \vdots & \ddots & \vdots \\ 1 & x_{n1} & \cdots & x_{np} \end{bmatrix}, \quad \boldsymbol{\beta} = \begin{bmatrix} \beta_0 \\ \beta_1 \\ \vdots \\ \beta_p \end{bmatrix}, \quad \boldsymbol{\varepsilon} = \begin{bmatrix} \varepsilon_1 \\ \varepsilon_2 \\ \vdots \\ \varepsilon_n \end{bmatrix}$$

and

$$\boldsymbol{\varepsilon} \sim \text{MVN}(\boldsymbol{0}, \sigma^2 \boldsymbol{I}).$$

2 Estimation

Least Squares Method

We wish to minimize a loss function:

$$\begin{aligned} S(\boldsymbol{\beta}) &= \sum_{i=1}^{n} (y_i - \hat{y}_i)^2 \\ &= \sum_{i=1}^{n} \big(y_i - (\beta_0 + \beta_1 x_{i1} + \cdots + \beta_p x_{ip})\big)^2 \\ &= (\boldsymbol{Y} - \boldsymbol{X}\boldsymbol{\beta})^\top (\boldsymbol{Y} - \boldsymbol{X}\boldsymbol{\beta}). \end{aligned}$$

The least squares estimators (LSE) are the solutions to the equations:

$$\frac{\partial S}{\partial \boldsymbol{\beta}} = \frac{\partial}{\partial \boldsymbol{\beta}} (\boldsymbol{Y} - \boldsymbol{X}\boldsymbol{\beta})^\top (\boldsymbol{Y} - \boldsymbol{X}\boldsymbol{\beta}) = 0.$$

Maximum Likelihood Method

The probability density function for Y_i is:

$$f(y_i) = \frac{1}{\sqrt{2\pi\sigma^2}} \exp\left\{ -\frac{1}{2\sigma^2} \big(y_i - (\beta_0 + \beta_1 x_{i1} + \cdots + \beta_p x_{ip})\big)^2 \right\}.$$

The log-likelihood function is therefore:

$$\begin{aligned}\ell(\boldsymbol{\beta}, \sigma^2) &= \log\left(\prod_{i=1}^{n} f(y_i)\right) \\ &= \sum_{i=1}^{n}\left(-\frac{1}{2}\log(2\pi\sigma^2) - \frac{1}{2\sigma^2}\left(y_i - (\beta_0 + \beta_1 x_{i1} + \cdots + \beta_p x_{ip})\right)^2\right) \\ &= -\frac{n}{2}\log(2\sigma^2) - \frac{1}{2\sigma^2}(\boldsymbol{Y} - \boldsymbol{X}\boldsymbol{\beta})^\top(\boldsymbol{Y} - \boldsymbol{X}\boldsymbol{\beta}).\end{aligned}$$

The maximum likelihood estimators (MLE) of $\boldsymbol{\beta}$ are obtained by solving:

$$\frac{\partial \ell}{\partial \boldsymbol{\beta}} = \frac{\partial}{\partial \boldsymbol{\beta}}\left[-\frac{1}{2\sigma^2}(\boldsymbol{Y} - \boldsymbol{X}\boldsymbol{\beta})^\top(\boldsymbol{Y} - \boldsymbol{X}\boldsymbol{\beta})\right] = 0.$$

- Parameter Estimates: For linear regression LSE and MLE of $\boldsymbol{\beta}$ are the same

$$\hat{\boldsymbol{\beta}} = (\boldsymbol{X}^\top\boldsymbol{X})^{-1}\boldsymbol{X}^\top\boldsymbol{Y}.$$

- Fitted values: $\hat{\boldsymbol{Y}} = \boldsymbol{X}\hat{\boldsymbol{\beta}}$.
- Residuals: $\hat{r}_i = (y_i - \hat{y}_i)$.
- Variance estimates:
  - An unbiased estimate of σ^2 is:

$$\hat{\sigma}^2 = \frac{1}{n - (p+1)}\sum_{i=1}^{n}\hat{r}_i^2.$$

  - An estimate of the variance of $\hat{\boldsymbol{\beta}}$ is:

$$\widehat{\mathrm{V}}(\hat{\boldsymbol{\beta}}) = \hat{\sigma}^2(\boldsymbol{X}^\top\boldsymbol{X})^{-1}.$$

Low Birthweight Infant Data Example

- For $n = 100$ infants, we have observed Y_i = head circumference and x_i = gestational age for baby i, $i = 1, \ldots, 100$.
- Consider a simple linear regression model:

$$Y_i = \beta_0 + \beta_1 x_i + \varepsilon_i.$$

- We can fit the model and obtain LSE/MSE using the `lm()` function in R.

```
lowbwt <- read.table("lowbwt.txt", header = T)
fit <- lm(headcirc ~ gestage, data = lowbwt)
summary(fit)
```

```

Call:
lm(formula = headcirc ~ gestage, data = lowbwt)

Residuals:
    Min      1Q  Median      3Q     Max
-3.5358 -0.8760 -0.1458  0.9041  6.9041
```

```
Coefficients:
            Estimate Std. Error t value Pr(>|t|)
(Intercept)  3.91426    1.82915    2.14   0.0348 *
gestage      0.78005    0.06307   12.37   <2e-16 ***
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Residual standard error: 1.59 on 98 degrees of freedom
Multiple R-squared:  0.6095,Adjusted R-squared:  0.6055
F-statistic: 152.9 on 1 and 98 DF,  p-value: < 2.2e-16
```

- What is the interpretation of regression parameters β_0 and β_1?
  - β_0 (intercept): expected `headcirc` for a baby of a gestational age zero ($x = 0$).
  - β_1 (slope): expected change in `headcirc` associated with a one unit increase in gestational age.

(3) Model Checking

Standardized Residuals:

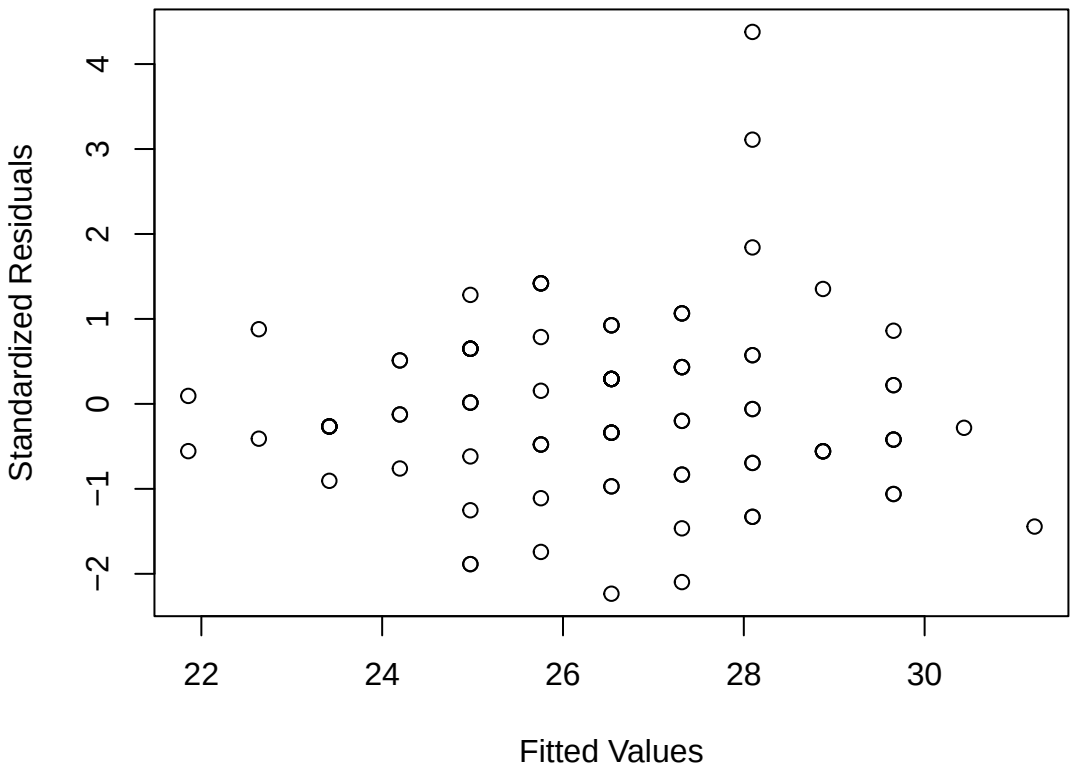
$$d_i = \frac{r_i}{\sqrt{\hat{\sigma}^2(1 - h_{ii})}},$$

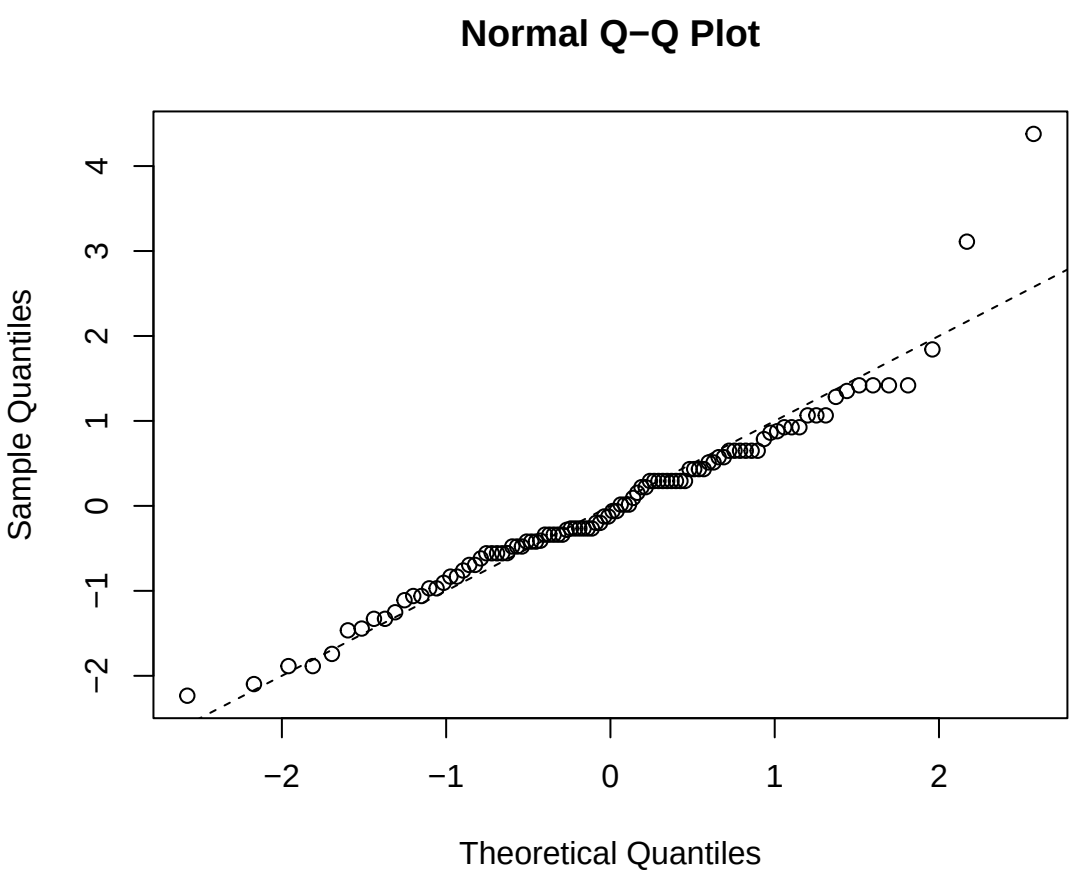
where h_{ii} is the (i, i) element of $\boldsymbol{H} = (\boldsymbol{X}^\top \boldsymbol{X})^{-1}\boldsymbol{X}^\top$. By asymptotic theory, if the model provides a good fit to the data then we should expect that:

$$d_i \overset{\text{iid}}{\sim} \mathcal{N}(0, 1).$$

We visually check this by examining residual plots such as:

- Standardized residuals versus the fitted values.
- Standardized residuals versus the explanatory variable(s).
- Normal probability plot (QQ plot) of the standardized residuals.


Standardized Residuals
−2
−1
0
1
2
3
4
22
24
26
28
30
Fitted Values



④ Inference

- Under suitable assumptions, the fitted regression parameters are asymptotically normally distributed:

$$\hat{\boldsymbol{\beta}} \sim \text{MVN}(\boldsymbol{\beta}, \sigma^2(\boldsymbol{X}^\top \boldsymbol{X})^{-1}),$$
$$\hat{\beta}_j \sim \mathcal{N}(\beta_j, \sigma^2 v_{jj}), \qquad \text{where } v_{jj} = \left[(\boldsymbol{X}^\top \boldsymbol{X})^{-1}\right]_{(j,j)}.$$

- Since σ^2 is generally unknown, we replace it with the unbiased estimate $\hat{\sigma}^2$, and obtain $\mathsf{se}(\hat{\beta}_j) = \sqrt{\hat{\sigma}^2 v_{jj}}$.
- The inference is then based on the t-distribution result:

$$\frac{\hat{\beta}_j - \beta_j}{\mathsf{se}(\hat{\beta}_j)} \sim t_{n-p-1}.$$

Low Birthweight Infant Data Example

- Is there a significant (linear) relationship between head circumference and gestational age?
  We wish to test H_0: $\beta_1 = 0$ vs H_A: $\beta_1 \neq 0$.

$$t = \frac{\hat{\beta}_1 - (0)}{\mathsf{se}(\hat{\beta}_1)} \sim t_{98},$$

  if H_0 is true, and we reject H_0 if $|t| > t_{98,0.975} = 1.985$. Here we have $t = 0.78/0.063 = 12.37 \gg 1.985$, so we reject H_0.

- What is the $95\,\%$ confidence interval for the expected increase in head circumference when the gestational age of a baby increases by 1 week?

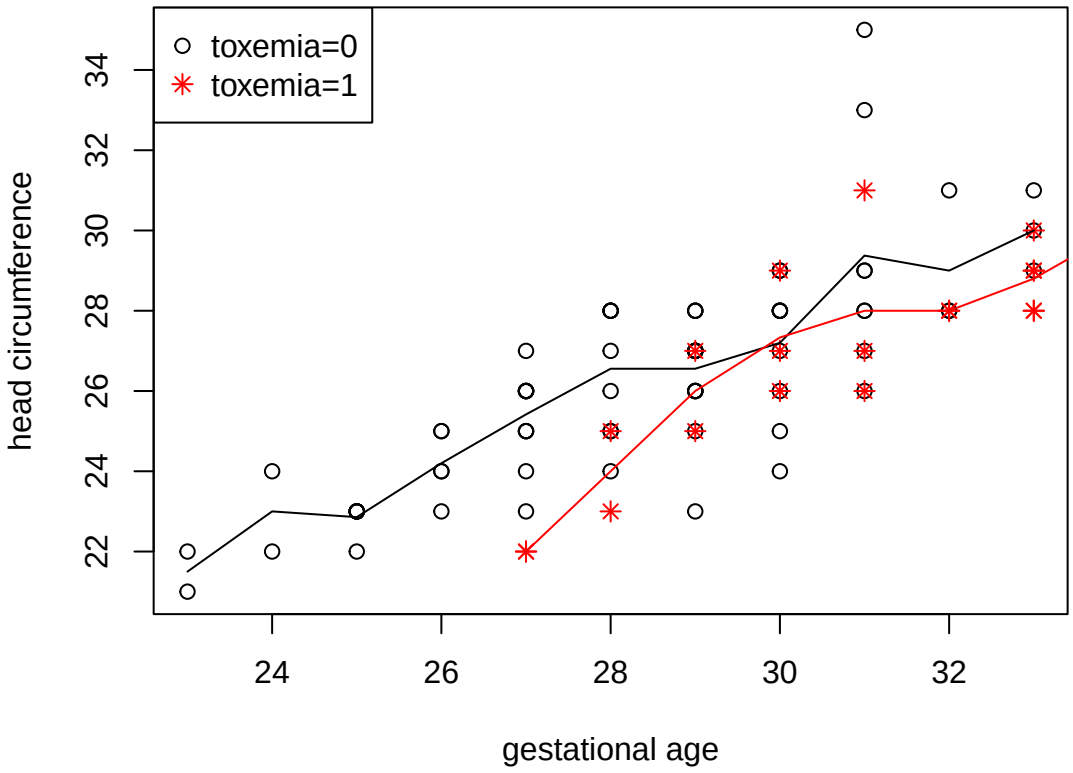
  A $95\,\%$ CI for β_1:

$$\hat{\beta}_1 \pm t_{98,0.975}\,\mathsf{se}(\hat{\beta}_1) = 0.78 \pm 1.985(0.063) = (0.665, 0.905).$$

Linear models with multiple predictors

Low Birthweight Infant Data Example

- *Toxemia*, a pregnancy complication characterized by high blood pressure and signs of damage to liver and kidneys, may also have an impact on the development of babies.



- Does *toxemia*, after adjustment for gestational age, also affect the head circumference?

```
fit <- lm(headcirc ~ gestage + factor(toxemia), data = lowbwt)
summary(fit)


Call:
lm(formula = headcirc ~ gestage + factor(toxemia), data = lowbwt)

Residuals:
    Min      1Q  Median      3Q     Max
```

```
-3.8427 -0.8427 -0.0525  0.8109  6.4092

Coefficients:
                 Estimate Std. Error t value Pr(>|t|)
(Intercept)       1.49558    1.86799   0.801  0.42530
gestage           0.87404    0.06561  13.322  < 2e-16 ***
factor(toxemia)1 -1.41233    0.40615  -3.477  0.00076 ***
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Residual standard error: 1.507 on 97 degrees of freedom
Multiple R-squared:  0.6528,Adjusted R-squared:  0.6456
F-statistic: 91.18 on 2 and 97 DF,  p-value: < 2.2e-16
```

What is the interpretation of β_2?

$\hat{\beta}_3 = -1.41233$. After adjustment of gestational age, the babies whose mothers had toxemia have smaller (by $1.41\,\text{cm}$) than those whose mothers did not. This difference is significant (test H_0: $\beta_2 = 0$, p-value $= 0.0076 < 0.05$).

- Is the rate of increase of head circumference with gestational age the same for infants whose mothers with toxemia as those whose mother without it?

$$Y_i = \beta_0 + \beta_1 x_{i1} + \beta_2 x_{i2} + \beta_3 x_{i1} x_{i2} + \varepsilon_i.$$

```
fit <- lm(headcirc ~ gestage * factor(toxemia), data = lowbwt)
summary(fit)


Call:
lm(formula = headcirc ~ gestage * factor(toxemia), data = lowbwt)

Residuals:
    Min      1Q  Median      3Q     Max
-3.8366 -0.8366 -0.0928  0.7910  6.4341

Coefficients:
                         Estimate Std. Error t value Pr(>|t|)
(Intercept)               1.76291    2.10225   0.839    0.404
gestage                   0.86461    0.07390  11.700   <2e-16 ***
factor(toxemia)1         -2.81503    4.98515  -0.565    0.574
gestage:factor(toxemia)1  0.04617    0.16352   0.282    0.778
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Residual standard error: 1.515 on 96 degrees of freedom
Multiple R-squared:  0.6531,Adjusted R-squared:  0.6422
F-statistic: 60.23 on 3 and 96 DF,  p-value: < 2.2e-16
```

What is the interpretation of β_3?

β_3 is the differences in slopes between the two groups (`toxemia=1` vs `toxemia=0`). We want to test H_0: $\beta_3 = 0$, $t = 0.282$, p-value $= 0.778 > 0.05$. No evidence to reject H_0.

Limitations of Linear Regression

Linear regression models can be very useful but may not be appropriate to use when response Y is not continuous and can not be assumed to be normally distributed, e.g.,

- Binary data ($Y = 0$ or $Y = 1$),
- Count data ($Y = 0, 1, 2, 3, \ldots$).

Generalized Linear Models (GLM) extend the linear regression framework to address the above issue.

- Suitable for continuous and discrete data.
- Normal/Gaussian linear regression is a special case of GLM.
- Inference based on maximum likelihood methods (review next class — 431 Appendix, Stat 330 notes).

WEEK 2
13th to 17th September

Topic 1b: Review of Likelihood Methods

Distributions with a Single Parameter

Setup

- Suppose Y is a random variable with probability density (or mass) function $f(y; \theta)$, where $\theta \in \Omega$ is a continuous parameter.
- The true value of θ is unknown.
- We wish to make inferences about θ (i.e., we may want to estimate θ, calculate a $95\,\%$ CI or carry out tests of hypotheses regarding θ).

Likelihood Function

- The Likelihood function is any function which is proportional to the probability of observing the data one actually obtained, i.e.,
$$L(\theta; y) = cf(y; \theta) = c\,\mathbb{P}(Y = y; \theta),$$
where c is a *proportionality constant* that does not depend on θ.
- $L(\theta; y)$ contains all the information regarding θ from the data.
- $L(\theta; y)$ ranks the various parameter values in terms of their consistency with the data.
- Since $L(\theta; y)$ is defined in terms of the random variable y, it is itself a random variable.

Maximum Likelihood Estimator

- For the purposes of estimation we typically want to find θ value that makes the observed data the most likely (hence the term maximum likelihood).
- The maximum likelihood estimator (MLE) of θ is
$$\hat{\theta} = \arg\max_{\theta} L(\theta; y).$$
- Estimation becomes a simple optimization problem!

- It is often easier to work with the logarithm of the likelihood function, i.e., the log-likelihood function

$$\ell(\theta; y) = \log\big(L(\theta; y)\big).$$

- Equivalently, since the $\log(\,\cdot\,)$ function is monotonic, the value of θ that maximizes $L(\theta; y)$ also maximizes the log-likelihood $\ell(\theta; y)$.
- For simplicity, we drop the y and use $L(\theta) = L(\theta; y)$ and $\ell(\theta) = \ell(\theta; y)$.

A List of Important Functions

- Log-likelihood function: $\ell(\theta) = \log\big(L(\theta)\big)$.
- Score function: $S(\theta) = \frac{\partial \ell(\theta)}{\partial \theta} = \ell'(\theta)$.
- Information function: $I(\theta) = -\frac{\partial^2 \ell(\theta)}{\partial \theta^2} = -\ell''(\theta)$.
- Fisher information function: $\mathcal{I}(\theta) = \mathbb{E}\big[I(\theta)\big]$.
- Relative likelihood function: $R(\theta) = L(\theta)/L(\hat{\theta})$.
- Log relative likelihood function: $r(\theta) = \log\big(L(\theta)/L(\hat{\theta})\big) = \ell(\theta) - \ell(\hat{\theta})$.

Maximum Likelihood Estimation

- Want θ that maximizes $\ell(\theta)$, or equivalently solves $S(\theta) = 0$.
- Sometimes $S(\theta) = 0$ can be solved explicitly (easy in this case), but often we must solve iteratively.
- Check that the solution corresponds to a maxima of $\ell(\theta)$ by verifying the value of the second derivative at $\hat{\theta}$ is negative, or

$$I(\hat{\theta}) = -\ell''(\hat{\theta}) > 0.$$

- Invariance property of MLEs: if $g(\theta)$ is any function of the parameter θ, then the MLE of $g(\theta)$ is $g(\hat{\theta})$.

  If $\hat{\theta}$ is the MLE of θ, then $\mathrm{e}^{\hat{\theta}}$ is the MLE of e^{θ}.

Example: Binomial Distribution

Example: Binomial Distribution

- A study was conducted to examine the risk for hormone use in healthy postmenopausal women.
- Suppose a group of n women received a combined hormone therapy, and were monitored for the development of breast cancer during 8.5 years follow-up.
- Let

$$Y_i = \begin{cases} 1 & \text{, if woman } i \text{ developed breast cancer,} \\ 0 & \text{, otherwise,} \end{cases}$$

  for $i = 1, \ldots, n$.
- Suppose $Y_i \overset{\text{iid}}{\sim} \text{BERN}(\pi)$ where $\pi = \mathbb{P}(Y_i = 1)$, then the total number of woman developed breast cancer is:

$$Y = \sum_{i=1}^{n} Y_i \sim \text{BIN}(n, \pi).$$

- We wish to find the MLE of unknown parameter π (probability of cancer).

- Likelihood function:
$$L(\pi; y) = c\,\mathbb{P}(Y = y; \pi) = \pi^y (1-\pi)^{n-y},$$
where we take $c = 1/\binom{n}{y}$ to simplify the likelihood.

- Log-likelihood function:
$$\ell(\pi) = y \log(\pi) + (n-y)\log(1-\pi).$$

- Score function:
$$S(\pi) = \frac{y}{\pi} - \frac{n-y}{1-\pi}.$$

- Maximum Likelihood Estimator:
$$S(\pi) = 0 \implies \hat{\pi} = \frac{\sum_{i=1}^n y_i}{n} = \bar{y}.$$

- Second derivative test using information function:
$$I(\pi) = -\ell''(\pi) = \frac{y}{\pi^2} + \frac{n-y}{(1-\pi)^2} > 0 \; \forall \pi \in (0,1).$$

Example: Hormone Therapy Data

- A group of $n = 8506$ postmenopausal women aged 50-79 received EPT and $Y = 166$ developed invasive breast cancer during the follow-up.
- Assume $Y \sim \text{BIN}(n, \pi)$ with unknown parameter π.
- The maximum likelihood estimate of π is:
$$\hat{\pi} = \bar{y} = \frac{y}{n} = \frac{166}{8506} = 0.0195.$$

Example: Poisson Distribution

Suppose $y_1, \ldots, y_n$ is an iid sample from a Poisson distribution with probability mass function:

$$f(y; \lambda) = \mathbb{P}(Y = y; \lambda) = \frac{\lambda^y \mathrm{e}^{-\lambda}}{y!}, \; \lambda > 0, \; y = 0, 1, 2, \ldots.$$

- Likelihood function:
$$L(\lambda; y_1, \ldots, y_n) = \prod_{i=1}^n f(y_i; \lambda) = \frac{\lambda^{\sum y_i} \mathrm{e}^{-n\lambda}}{\prod_i y_i!}.$$

- Log-likelihood function:
$$\ell(\lambda) = \left(\sum_i y_i\right) \log(\lambda) - n\lambda - \sum_{i=1}^n \log(y_i!).$$

- Score function:
$$S(\lambda) = \frac{\sum_i y_i}{\lambda} - n = 0 \implies \hat{\lambda} = \frac{\sum_{i=1}^n y_i}{n} = \bar{y}.$$

Newton Raphson Algorithm For Finding MLE

- Sometimes, solving $S(\theta) = 0$ can be challenging and closed form solutions may not be obtained, iterative method need to be used to find the MLE.
- Recall Taylor Series expansion of a differentiable function $f(x)$ about a point a:

$$f(x) = f(a) + \frac{f'(a)}{1!}(x-a) + \frac{f''(a)}{2!}(x-a)^2 + \cdots .$$

- Now suppose we wish to find $\hat{\theta}$, the root of $S(\theta) = 0$ and $\theta^{(0)}$ is a guess that is "close" to $\hat{\theta}$.
- Consider the Taylor series expansion of $S(\theta)$ about $\theta^{(0)}$:

$$S(\theta) = S(\theta^{(0)}) + \frac{S'(\theta^{(0)})}{1!}(\theta - \theta^{(0)}) + \frac{S''(\theta^{(0)})}{2!}(\theta - \theta^{(0)})^2 + \cdots .$$

- For $|\theta - \theta^{(0)}|$ very small, the second and higher order terms can be dropped to a good approximation:

$$S(\theta) \simeq S(\theta^{(0)}) + S'(\theta^{(0)})(\theta - \theta^{(0)}).$$
$$S(\theta) \simeq S(\theta^{(0)}) - I(\theta^{(0)})(\theta - \theta^{(0)}).$$

- Then at $\theta = \hat{\theta}$,

$$\begin{aligned} S(\hat{\theta}) &\simeq S(\theta^{(0)}) - I(\theta^{(0)})(\hat{\theta} - \theta^{(0)}) \\ I(\theta^{(0)})(\hat{\theta} - \theta^{(0)}) &\simeq S(\theta^{(0)}) \\ (\hat{\theta} - \theta^{(0)}) &\simeq I^{-1}(\theta^{(0)})S(\theta^{(0)}) \\ \hat{\theta} &\simeq \theta^{(0)} + I^{-1}(\theta^{(0)})S(\theta^{(0)}). \end{aligned}$$

- This suggests a revised guess for $\hat{\theta}$ is:

$$\theta^{(1)} = \theta^{(0)} + I^{-1}(\theta^{(0)})S(\theta^{(0)})$$

Newton Raphson Algorithm for finding the MLE

- Begin with an initial estimate $\theta^{(0)}$.
- Iteratively obtain updated estimate by using:

$$\theta^{(i+1)} = \theta^{(i)} + I^{-1}(\theta^{(i)})S(\theta^{(i)}).$$

- Iteration continues until $\theta^{(i+1)} \simeq \theta^{(i)}$ within a specified tolerance.
- Then set $\hat{\theta} = \theta^{(i+1)}$, check that $I(\hat{\theta}) > 0$.

Inference for Scalar Parameters θ

- So far we have discussed estimation of $\hat{\theta}$, next we want to conduct inference about θ, i.e., carry out hypothesis tests and construct confidence intervals of θ.
- Likelihood inference relies on the following asymptotic distribution results:

Useful asymptotic distributional results

- (log) Likelihood ratio statistic: $-2\log\big(R(\theta)\big) = -2r(\theta) \sim \chi^2_{(1)}$.
- Score statistic: $\big(S(\theta)\big)^2 / I(\theta) \sim \chi^2_{(1)}$.
- Wald statistic: $(\hat{\theta} - \theta)^2 I(\hat{\theta}) \sim \chi^2_{(1)}$ or $(\hat{\theta} - \theta)\sqrt{I(\hat{\theta})} \sim \mathcal{N}(0,1)$ since $Z \sim \mathcal{N}(0,1) \implies Z^2 \sim \chi^2_1$.

Confidence Interval (CI)

Suppose we want a $100(1-\alpha)\,\%$ confidence interval for θ.

- The Likelihood ratio (LR) based pivotal gives a confidence interval:

$$\big\{\theta : -2r(\theta) < \chi^2_1(1-\alpha)\big\},$$

  where $\chi^2_1(1-\alpha)$ is the upper α percentage point of the χ^2_1 distribution.

- The Wald-based pivotal gives an interval:

$$\Big\{\theta : (\hat{\theta} - \theta)^2 I(\hat{\theta}) < \chi^2_1(1-\alpha)\Big\},$$

  or equivalently

$$\hat{\theta} \pm Z_{1-\alpha/2}\big(I(\hat{\theta})\big)^{-1/2},$$

  where $Z_{1-\alpha/2}$ is the upper $\alpha/2$ percentage point of the standard normal.

Example: Hormone Therapy Data

Likelihood Ratio based $95\,\%$ CI: $\big\{\theta : -2r(\theta) < \chi^2_1(0.95)\big\}$ where $r(\theta) = \ell(\theta) - \ell(\hat{\theta})$.

- For the Binomial distribution: $\hat{\theta} = y/n$, and

$$r(\theta) = \big(y\log(\theta) + (n-y)\log(1-\theta)\big) - \left(y\log\left(\frac{y}{n}\right) + (n-y)\log\left(1 - \frac{y}{n}\right)\right).$$

- To find the root of $-2r(\theta) = \chi^2_1(0.95)$:

```
y = 166
n = 8506
LRCI = function(theta, y, n) {
  -2 * (y * log(theta) + (n - y) * log(1 - theta) - y * log(y/n) -
    (n - y) * log(1 - y/n)) - qchisq(0.95, 1)
}
mle = y/n
uniroot(LRCI, c(0, mle), y = y, n = n)$root

[1] 0.01673867

uniroot(LRCI, c(mle, 1), y = y, n = n)$root

[1] 0.02260709
```

- The likelihood ratio based $95\,\%$ CI is $(0.017, 0.023)$.

Wald based $95\,\%$ CI: $\hat{\theta} \pm Z_{0.975}\big(I(\hat{\theta})\big)^{-1/2}$.

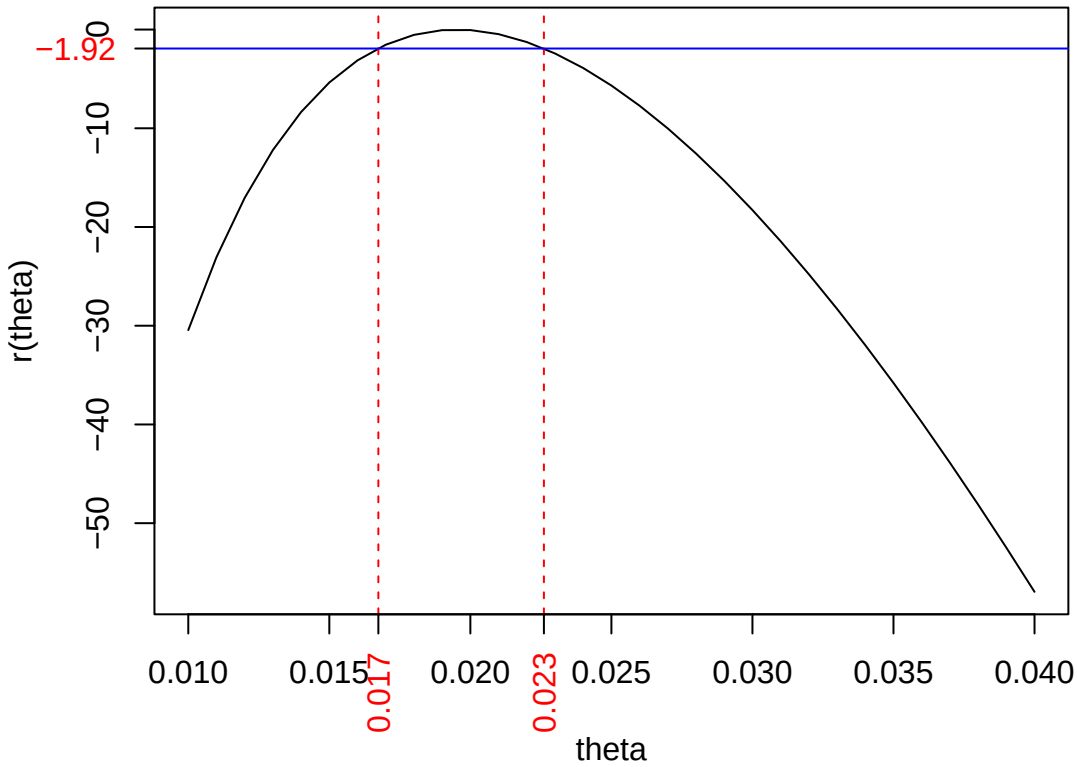
- For Binomial distribution $\hat{\theta} = y/n$ and

$$I(\hat{\theta}) = \frac{y}{\hat{\theta}^2} + \frac{n-y}{(1-\hat{\theta})^2} = n^2\left(\frac{1}{y} + \frac{1}{n-y}\right).$$

- So we solve:

$$\begin{aligned}\hat{\theta} \pm 1.96\big(I(\hat{\theta})\big)^{-1/2} &= 0.0195 \pm 1.96(0.0015)\\ &= (0.017, 0.022).\end{aligned}$$

- The Wald based $95\,\%$ CI is: $(0.017, 0.022)$.



Hypotheses Test

Suppose we are interested in testing hypotheses:

$$H_0\text{: } \theta = \theta_0 \text{ vs } H_A\text{: } \theta \neq \theta_0.$$

- Likelihood ratio (LR) test: p-value $= \mathbb{P}\big(\chi^2_1 > -2r(\theta_0)\big)$.

- Score test: p-value $= \mathbb{P}\Big(\chi_1^2 > \big(S(\theta)\big)^2 / I(\theta_0)\Big)$.
- Wald test:

$$p\text{-value} = \mathbb{P}\Big(\chi_1^2 > (\hat{\theta} - \theta_0)^2 I(\hat{\theta})\Big), \text{ or } p\text{-value} = \mathbb{P}\left(|Z| > |\hat{\theta} - \theta_0|\sqrt{I(\hat{\theta})}\right).$$

Example: Hormone Therapy Data

Suppose we wish to test if women received EPT would have a risk of breast cancer same as that of the general population, say about $1.5\,\%$.

$$H_0\text{: } \theta = 0.015 \text{ vs } H_A\text{: } \theta \neq 0.015.$$

- Likelihood Ratio based test:

$$\begin{aligned} r(\theta_0 = 0.015) &= \Big(y \log(0.015) + (n-y)\log(1-0.15)\Big) - \left(y \log\Big(\frac{y}{n}\Big) + (n-y)\log\Big(1 - \frac{y}{n}\Big)\right) \\ &= -5.3637. \end{aligned}$$

  Thus, the p-value for the test is given by:

$$p = \mathbb{P}\Big(\chi^2_{(1)} > -2r(0.015)\Big) = \mathbb{P}\Big(\chi^2_{(1)} > 10.7274\Big) = 0.001.$$

  Therefore, we *reject* H_0 and conclude that the risk of breast cancer for women received EPT is significantly different from $1.5\,\%$.

Notes on Asymptotic Inference

- Asymptotic results: approximation improves as sample size increases.
- Results are exact for a Normal linear model if θ is the mean parameter and σ^2 is known.
- LR approach:
  - Need to evaluate (log) likelihood at two locations.
  - Not always a closed from solution for a CI.
  - Usually the best approach.
- Score approach:
  - Usually the least powerful test.
  - Don't actually need to find MLE to use.
- Wald's approach:
  - Always get a closed form solution for a CI.
  - May not behave well for skewed likelihoods (transform?).
- All three are asymptotically equivalent!

Likelihood Methods for Parameter Vectors

Suppose $\boldsymbol{\theta} \in \Omega$ is a continuous $p \times 1$ parameter vector indexing a probability density (or mass) function $f(\boldsymbol{y}; \boldsymbol{\theta})$. The likelihood and log-likelihood functions are defined as before, but

- $\boldsymbol{S}(\boldsymbol{\theta}) = \frac{\partial \ell(\boldsymbol{\theta})}{\partial \boldsymbol{\theta}}$ is the $p \times 1$ Score vector, i.e.,

$$\boldsymbol{S}(\boldsymbol{\theta}) = \begin{bmatrix} \frac{\partial \ell(\theta)}{\partial \theta_1} \\ \vdots \\ \frac{\partial \ell(\theta)}{\partial \theta_p} \end{bmatrix}.$$

- $\boldsymbol{I}(\boldsymbol{\theta}) = -\frac{\partial^2 \ell(\boldsymbol{\theta})}{\partial \boldsymbol{\theta}^\top \partial \boldsymbol{\theta}}$ is the $p \times p$ Information matrix, i.e.,

$$\boldsymbol{I}(\boldsymbol{\theta}) = \begin{bmatrix} -\frac{\partial^2 \ell(\theta)}{\partial \theta_1^2} & -\frac{\partial^2 \ell(\theta)}{\partial \theta_1 \partial \theta_2} & \cdots & \frac{\partial^2 \ell(\theta)}{\partial \theta_1 \partial \theta_p} \\ & -\frac{\partial^2 \ell(\theta)}{\partial \theta_2^2} & \cdots & \frac{\partial^2 \ell(\theta)}{\partial \theta_1 \partial \theta_p} \\ & & \ddots & \frac{\partial^2 \ell(\theta)}{\partial \theta_p^2} \end{bmatrix}.$$

- The Newton Raphson algorithm applies as before, but with vectors and matrices as follows:

$$\boldsymbol{\theta}^{(i+1)} = \boldsymbol{\theta}^{(i)} + \boldsymbol{I}^{-1}(\boldsymbol{\theta}^{(i)}) \boldsymbol{S}(\boldsymbol{\theta}^{(i)}).$$

- Again, we apply iteratively until we obtain convergence, but now check to see if $\boldsymbol{I}(\hat{\boldsymbol{\theta}})$ is a positive definite matrix.

- Analogues to the LR, Score and Wald results apply based on partitioning the Information matrix by $\boldsymbol{\theta} = (\boldsymbol{\alpha}, \boldsymbol{\beta})^\top$, where $\boldsymbol{\alpha}$ is a $p \times 1$ vector of nuisance parameters and $\boldsymbol{\beta}$ is a $q \times 1$ vector of parameters of interest:

$$\boldsymbol{I} = \boldsymbol{I}(\boldsymbol{\alpha}, \boldsymbol{\beta}) = \begin{pmatrix} \boldsymbol{I}_{\boldsymbol{\alpha}\boldsymbol{\alpha}}(\boldsymbol{\alpha}, \boldsymbol{\beta}) & \boldsymbol{I}_{\boldsymbol{\alpha}\boldsymbol{\beta}}(\boldsymbol{\alpha}, \boldsymbol{\beta}) \\ \boldsymbol{I}_{\boldsymbol{\beta}\boldsymbol{\alpha}}(\boldsymbol{\alpha}, \boldsymbol{\beta}) & \boldsymbol{I}_{\boldsymbol{\beta}\boldsymbol{\beta}}(\boldsymbol{\alpha}, \boldsymbol{\beta}) \end{pmatrix},$$

  where $\boldsymbol{I}_{\boldsymbol{\alpha}\boldsymbol{\alpha}}(\boldsymbol{\alpha}, \boldsymbol{\beta}) = -\frac{\partial^2 \ell}{\partial \boldsymbol{\alpha} \partial \boldsymbol{\alpha}^\top}$ is $p \times p$, $\boldsymbol{I}_{\boldsymbol{\alpha}\boldsymbol{\beta}}(\boldsymbol{\alpha}, \boldsymbol{\beta}) = -\frac{\partial^2 \ell}{\partial \boldsymbol{\alpha} \partial \boldsymbol{\beta}^\top}$ is $p \times q$, $\boldsymbol{I}_{\boldsymbol{\beta}\boldsymbol{\alpha}}(\boldsymbol{\alpha}, \boldsymbol{\beta}) = -\frac{\partial^2 \ell}{\partial \boldsymbol{\beta} \partial \boldsymbol{\alpha}^\top}$ is $q \times p$, and $\boldsymbol{I}_{\boldsymbol{\beta}\boldsymbol{\beta}}(\boldsymbol{\alpha}, \boldsymbol{\beta}) = -\frac{\partial^2 \ell}{\partial \boldsymbol{\beta} \partial \boldsymbol{\beta}^\top}$ is $q \times q$.

Topic 2a: Formulation of Generalized Linear Models

The Exponential Family

Definition (Exponential Family)

Consider a random variable Y with probability density (or mass) function $f(y; \theta, \phi)$, we say that the distribution is a member of the exponential family if we can write

$$f(y; \theta, \phi) = \exp\left\{ \frac{y\theta - b(\theta)}{a(\phi)} + c(y; \phi) \right\},$$

for some functions $a(\,\cdot\,)$, $b(\,\cdot\,)$, and $c(\,\cdot\,)$.

- The parameter θ is called the canonical parameter, and it is unknown.
- The parameter ϕ is called the scale/dispersion parameter, is constant, and assumed to be known.

Many well known distributions (continuous/discrete) can be shown to be a member of the exponential family.

Examples

- Poisson Distribution: $Y \sim \text{POI}(\lambda)$,

$$f(y;\lambda) = \frac{\lambda^y \mathrm{e}^{-\lambda}}{y!},\ \lambda > 0,\ y = 0, 1, \ldots.$$

Show that Poisson is a member of exponential family and identify the canonical parameter and the functions $a(\,\cdot\,)$, $b(\,\cdot\,)$, and $c(\,\cdot\,)$.

Solution. $f(y;\lambda) = \exp\big\{\log(f(y;\lambda))\big\} = \exp\Big\{\frac{y\log(\lambda)-\lambda}{1} - \log(y!)\Big\}$. Therefore,

$$\begin{aligned}
\theta &= \log(\lambda) \qquad \text{(canonical/natural parameter)},\\
b(\theta) &= \lambda = \mathrm{e}^{\theta},\\
\phi &= 1,\\
a(\phi) &= 1,\\
c(y;\phi) &= -\log(y!).
\end{aligned}$$

- Normal Distribution: $Y \sim \mathcal{N}(\mu, \sigma^2)$ and σ^2 known,

$$f(y;\theta,\phi) = \frac{1}{\sqrt{2\pi\sigma^2}} \exp\left\{-\frac{(y-\mu)^2}{2\sigma^2}\right\}.$$

Show that this Normal distribution is a member of the exponential family.

Solution.

$$\begin{aligned}
f(y;\mu,\sigma^2) &= \exp\left\{-\frac{y^2 - 2\mu y + \mu^2}{\sigma^2} - \frac{1}{2}\log(2\pi\sigma^2)\right\}\\
&= \exp\left\{\frac{y\mu - \mu^2/2}{\sigma^2} - \frac{y^2}{2\sigma^2} - \frac{1}{2}\log(2\pi\sigma^2)\right\}.
\end{aligned}$$

Therefore,

$$\begin{aligned}
\theta &= \mu,\\
\phi &= \sigma^2,\\
a(\phi) &= \phi = \sigma^2,\\
b(\theta) &= \frac{\mu^2}{2} = \frac{\theta^2}{2},\\
c(y;\phi) &= -\frac{y^2}{2\sigma^2} - \frac{1}{2}\log(2\pi\sigma^2).
\end{aligned}$$

Properties of Exponential Family

Consider a single observation y from the exponential family.

$$L(\theta,\phi;y) = f(y;\theta,\phi) = \exp\left\{\frac{y\theta - b(\theta)}{a(\phi)} + c(y;\phi)\right\}.$$

$$\ell(\theta,\phi;y) = \log\big(f(y;\theta,\phi)\big) = \frac{y\theta - b(\theta)}{a(\phi)} + c(y;\phi).$$

$$S(\theta) = \frac{\partial \ell}{\partial \theta} = \frac{y - b'(\theta)}{a(\phi)}.$$

$$I(\theta) = -\frac{\partial^2 \ell}{\partial \theta^2} = \frac{b''(\theta)}{a(\phi)}.$$

$$\mathcal{I}(\theta) = \mathbb{E}\left[-\frac{\partial^2 \ell}{\partial \theta^2}\right] = I(\theta).$$

Some General Results for Score and Information

Result # 1

The expectation of the score function is zero.

$$\mathbb{E}\big[S(\theta)\big] = 0.$$

Proof:

$$\begin{aligned}
\int f(y;\theta,\phi)\,\mathrm{d}y &= 1 \\
\frac{\partial}{\partial\theta}\int f(y;\theta,\phi)\,\mathrm{d}y &= 0 \\
\int \frac{\partial}{\partial\theta} f(y;\theta,\phi)\,\mathrm{d}y &= 0 \\
\int \left(\frac{\partial}{\partial\theta}\log\big(f(y;\theta,\phi)\big)\right) f(y;\theta,\phi)\,\mathrm{d}y &= 0 \qquad (1) \\
\int S(\theta) f(y;\theta,\phi)\,\mathrm{d}y &= 0 \\
\mathbb{E}\big[S(\theta)\big] &= 0
\end{aligned}$$

Result # 2

The expectation of the score function squared is the expected information.

$$\mathbb{E}\big[S(\theta;y)^2\big] = \mathbb{E}\big[I(\theta;y)\big]$$

Proof: Differentiate (1) again,

$$\begin{aligned}
\int \left(\frac{\partial}{\partial\theta}\log\big(f(y;\theta,\phi)\big)\right) f(y;\theta,\phi)\,\mathrm{d}y &= 0 \\
\int \left(\frac{\partial^2}{\partial\theta^2}\log\big(f(y;\theta,\phi)\big)\right) f(y;\theta,\phi)\,\mathrm{d}y + \int \left(\frac{\partial}{\partial\theta}\log\big(f(y;\theta,\phi)\big)\right) \frac{\partial}{\partial\theta} f(y;\theta,\phi)\,\mathrm{d}y &= 0 \\
\int \frac{\partial^2}{\partial\theta^2}\log\big(f(y;\theta,\phi)\big) f(y;\theta,\phi)\,\mathrm{d}y + \int \left(\frac{\partial}{\partial\theta} f(y;\theta,\phi)\right)^2 f(y;\theta,\phi)\,\mathrm{d}y &= 0 \\
\int -I(\theta) f(y;\theta,\phi)\,\mathrm{d}y + \int S(\theta)^2 f(y;\theta,\phi)\,\mathrm{d}y &= 0 \\
\mathbb{E}\big[-I(\theta;y)\big] + \mathbb{E}\big[S(\theta;y)^2\big] &= 0
\end{aligned}$$

Now for the exponential family, we apply above results and obtain:

$$\begin{aligned}
\mathbb{E}\big[S(\theta)\big] &= 0, \\
\mathbb{E}\left[\frac{Y - b'(\theta)}{a(\phi)}\right] &= 0, \\
\mathbb{E}[Y] &= b'(\theta),
\end{aligned}$$

$$\begin{aligned}
\mathbb{E}\big[S(\theta)^2\big] &= \mathbb{E}\big[I(\theta)\big], \\
\mathbb{E}\left[\left(\frac{Y - b'(\theta)}{a(\phi)}\right)^2\right] &= \mathbb{E}\left[\frac{b''(\theta)}{a(\phi)}\right], \\
\frac{1}{a(\phi)^2}\,\mathbb{E}\Big[\big(Y - \mathbb{E}[Y]\big)^2\Big] &= \frac{b''(\theta)}{a(\phi)}, \\
\mathsf{Var}(Y) &= b''(\theta)a(\phi).
\end{aligned}$$

Mean and Variance for the Exponential Family

- Mean: $\mathbb{E}[Y] = b'(\theta) = \mu$.
- Variance: $\mathsf{Var}(Y) = b''(\theta)a(\phi)$.

Note that:

- $b'(\theta) = \mu$ tells the relationship between *canonical* parameter θ and μ.
- $b''(\theta)$ is a function of θ and hence can be also expressed as a function of μ.
- Thus, we write $b''(\theta) = \mathsf{V}(\mu)$ and call $\mathsf{V}(\mu)$ the variance function.
- Subsequently, we have:
$$\mathsf{Var}(Y) = b''(\theta)a(\phi) = \mathsf{V}(\mu)a(\phi),$$
which is the mean-variance relationship for the exponential family.

Link Functions

Definition (Link Function)

The link function relates the linear predictor $\eta = \boldsymbol{x}^\top\boldsymbol{\beta}$ to the expected value μ of the random variable Y, i.e.,

$$g(\mu) = \eta = \boldsymbol{x}^\top\boldsymbol{\beta},$$

where $g(\,\cdot\,)$ is the link function.

Definition (Canonical Link Function)

When Y is a member of the exponential family we define the canonical link function to be:

$$g(\mu) = \theta = \eta = \boldsymbol{x}^\top\boldsymbol{\beta}$$

(i.e., the choice of $g(\,\cdot\,)$ that sets canonical parameter = linear predictor).

Examples

Recall that POI(λ) is a member of exponential family,

$$f(y;\lambda) = \frac{\lambda^y \mathrm{e}^{-\lambda}}{y!} = \exp\left\{\frac{y\log(\lambda) - \lambda}{1} - \log(y!)\right\}$$

where $\theta = \log(\lambda)$, $\phi = 1$, $b(\theta) = \lambda = \mathrm{e}^\theta$, and $a(\phi) = 1$. Now to find the mean, variance function, and canonical link function:

- Mean: $\mathbb{E}[Y] = b'(\theta) = \mathrm{e}^\theta = \mu \implies \theta = \log(\mu)$.
- Variance Function: $\mathsf{V}(\mu) = b''(\theta) = \mathrm{e}^\theta \implies \mathsf{V}(\mu) = \mu$.
- Variance: $\mathsf{Var}(Y) = \mathsf{V}(\mu)a(\phi) = \mu$ (mean-variance relationship).
- Canonical link: set $\theta = \eta$ using $\theta = \log(\mu) = \eta = \boldsymbol{x}^\top\boldsymbol{\beta}$, i.e., $g(\mu) = \log(\mu)$ where $\log(\cdot)$ is the canonical link.

Moving forward, we consider a log-linear model: $\log(\mu_i) = \boldsymbol{x}_i^\top\boldsymbol{\beta}$.

Remarks on Link Function

- We can choose any function $g(\cdot)$ as the link function in theory.
- The canonical link is a special link function, we often choose to use canonical link for its good statistical properties.
- Context and goodness of fit should motivate the choice of link function in practice.

Generalized Linear Models

Definition (Generalized Linear Model (GLM))

A Generalized Linear Model (GLM) is composed of three components:

- Random Component: The responses $Y_1, \ldots, Y_n$ are independent random variables and each Y_i is assumed to come from a parametric distribution that is a member of the exponential family.
- Systematic Component (or linear predictor):

  $$\eta_i = \boldsymbol{x}_i^\top\boldsymbol{\beta},$$

  a linear combination of explanatory variables $\boldsymbol{x}_i$ and regression parameters $\boldsymbol{\beta}$.
- Link function:

  $$g(\mu_i) = \eta_i = \boldsymbol{x}_i^\top\boldsymbol{\beta},$$

  a function that relates the mean of response to the linear predictor.

Topic Summary

1. Definition of the Exponential Family.
   - Exponential form of the probability density (or mass) function.
   - Derivation of Score and Information.
   - Properties of exponential family, mean-variance relationship.
   - Definition of canonical link.

2. Definition of a Generalized Linear Model.

Next Topic: 2b Estimation for Generalized Linear Models.

WEEK 3
20th to 24th September

Topic 2b: Maximum Likelihood Estimation for Generalized Linear Models

Generalized Linear Models

Suppose for each subject $i = 1, \ldots, n$ in a random sample:

- Y_i is the response variable.
- $x_{i1}, \ldots, x_{ip}$ are explanatory variables associated with Y_i.

We consider a Generalized Linear Model (GLM) for the data, by definition the GLM is composed following three components:

(1) Random Component:

$$Y_i \sim \text{exponential family}, \qquad Y_1, \ldots, Y_n \text{ are independent.}$$

(2) Systematic Component (or linear predictor):

$$\eta_i = \boldsymbol{x}_i^\top \boldsymbol{\beta} = \beta_0 + \beta_1 x_{i1} + \cdots + \beta_p x_{ip}.$$

- $\boldsymbol{x}_i = (1, x_{i1}, \ldots, x_{ip})^\top$ is a covariate vector.
- $\boldsymbol{\beta} = (\beta_0, \beta_1, \ldots, \beta_p)^\top$ is a vector of regression coefficients.

(3) Link function: a function $g(\,\cdot\,)$ links $\mathbb{E}[Y_i] = \mu_i$ to a linear prediction η_i:

$$g(\mu_i) = \eta_i = \boldsymbol{x}_i^\top \boldsymbol{\beta}.$$

Example: A Poisson Regression Model

Suppose $Y_i \overset{\text{ind}}{\sim} \text{POI}(\lambda_i)$ with mean $\mathbb{E}[Y_i] = \lambda_i$, $i = 1, \ldots, n$:

$$f(y_i) = \frac{\mathrm{e}^{-\lambda_i} \lambda_i^{y_i}}{y_i!} = \exp\{y_i \log(\lambda_i) - \lambda_i - \log(y_i!)\}.$$

Poisson distribution is a member of exponential family with:

- Canonical parameter: $\theta_i = \log(\lambda_i)$.
- Canonical link: $\theta_i = \eta_i \implies \log(\lambda_i) = \boldsymbol{x}_i^\top \boldsymbol{\beta}$ (log link).

A Poisson regression model with the canonical link takes the form:

$$\log(\lambda_i) = \boldsymbol{x}_i^\top \boldsymbol{\beta} = \beta_0 + \beta_1 x_{i1} + \cdots + \beta_p x_{ip} \qquad \text{(log-linear model)}.$$

Example: A Normal Regression Model

Assume $Y_i \overset{\text{ind}}{\sim} \mathcal{N}(\mu_i, \sigma^2)$ and σ^2 is known, $i = 1, \ldots, n$:

$$\begin{aligned} f(y_i) &= (2\pi\sigma^2)^{-1/2} \exp\left\{ -\frac{(y_i - \mu_i)^2}{2\sigma^2} \right\} \\ &= \exp\left\{ \frac{y_i\mu_i - \mu_i^2/2}{\sigma^2} - \frac{1}{2}\left(\frac{y_i^2}{\sigma^2} + \log(2\pi\sigma^2) \right) \right\}. \end{aligned}$$

A Normal distribution (σ^2 known) is a member of exponential family with:

- Canonical parameter: $\theta_i = \mu_i$.
- Canonical link: $\theta_i = \eta_i \implies \mu_i = \boldsymbol{x}_i^\top \boldsymbol{\beta}$ (identity link).

A Normal regression model with the canonical link takes the form:

$$\mu_i = \boldsymbol{x}_i^\top \boldsymbol{\beta} = \beta_0 + \beta_1 x_{i1} + \cdots + \beta_p x_{ip} \qquad \text{(linear model)}.$$

Linear regression model (STAT 331) is a Normal GLM using the canonical link!

Likelihood for Generalized Linear Models

We wish to use likelihood methods for the estimation of the regression parameter $\boldsymbol{\beta}$ from the GLM: $g(\mu_i) = \boldsymbol{x}_i^\top \boldsymbol{\beta}$. Consider the log-likelihood for a *single* observation from the exponential family:

$$\ell(\theta, \phi; y) = \frac{y\theta - b(\theta)}{a(\phi)} + c(y; \phi).$$

- ℓ is a function of θ (assume that ϕ is known).
- θ is related to μ through the result:
$$\mu = b'(\theta).$$
- η can be expressed in terms of μ through the link function:
$$g(\mu) = \eta.$$
- $\boldsymbol{\beta}$ can be expressed in terms of η through the linear predictor:
$$\eta = \boldsymbol{x}^\top \boldsymbol{\beta}.$$

Score Vector

To find the maximum likelihood estimator for $\boldsymbol{\beta}$, we must solve $\boldsymbol{S}(\boldsymbol{\beta}) = \frac{\partial \ell}{\partial \boldsymbol{\beta}} = \mathbf{0}$. Consider taking derivative with respect to β_j using the chain rule:

$$\frac{\partial \ell}{\partial \beta_j} = \frac{\partial \ell}{\partial \theta} \frac{\partial \theta}{\partial \mu} \frac{\partial \mu}{\partial \eta} \frac{\partial \eta}{\partial \beta_j},$$

where

$$\begin{aligned} &\frac{\partial \ell}{\partial \theta} = \frac{y - b'(\theta)}{a(\phi)}, \\ &\frac{\partial \theta}{\partial \mu} = \left(\frac{\partial \mu}{\partial \theta} \right)^{-1} = \frac{1}{b''(\theta)} && \text{since } \mu = b'(\theta), \\ &\frac{\partial \mu}{\partial \eta} = \frac{\partial \mu}{\partial \eta}, \\ &\frac{\partial \eta}{\partial \beta_j} = x_j && \text{since } \eta = \beta_0 + \beta_1 x_1 + \cdots + \beta_j x_j + \cdots + \beta_p x_p. \end{aligned}$$

Hence, we have:

$$\begin{aligned}
\frac{\partial \ell}{\partial \beta_j} &= \frac{y - b'(\theta)}{a(\phi)} \frac{1}{b''(\theta)} \frac{\partial \mu}{\partial \eta} x_j \\
&= \frac{y - \mu}{\mathsf{Var}(Y)} \frac{\partial \mu}{\partial \eta} x_j && \text{since } \mu = b'(\theta),\ \mathsf{Var}(Y) = a(\phi) b''(\theta) \\
&= \frac{y - \mu}{\mathsf{Var}(Y)} \left(\frac{\partial \mu}{\partial \eta} \right)^2 \frac{\partial \eta}{\partial \mu} x_j && \text{since } \frac{\partial \mu}{\partial \eta} \frac{\partial \eta}{\partial \mu} = 1 \\
&= (y - \mu) \left(\mathsf{Var}(Y) \left(\frac{\partial \mu}{\partial \eta} \right)^2 \right)^{-1} \frac{\partial \eta}{\partial \mu} x_j \\
&= (y - \mu) W \frac{\partial \eta}{\partial \mu} x_j,
\end{aligned}$$

where $W^{-1} = \mathsf{Var}(Y) \left(\frac{\partial \eta}{\partial \mu} \right)^2$. Note that generally $\frac{\partial \eta}{\partial \mu}$ is easier to calculate than $\frac{\partial \mu}{\partial \eta}$ since we define the link as $\eta = g(\mu)$.

For a random sample $Y_1, \ldots, Y_n$ from exponential family and each Y_i has a probability density function

$$f(y_i; \theta, \phi) = \exp\left\{ \frac{y_i \theta_i - b(\theta_i)}{a(\phi)} + c(y_i, \phi) \right\}.$$

We write likelihood and log-likelihood functions as:

$$\begin{aligned}
L &= \prod_{i=1}^{n} f(y_i; \theta_i, \phi) = \prod_{i=1}^{n} \exp\left\{ \frac{y_i \theta_i - b(\theta_i)}{a(\phi)} + c(y_i, \phi) \right\}, \\
\ell &= \sum_{i=1}^{n} \ell_i = \sum_{i=1}^{n} \frac{y_i \theta_i - b(\theta_i)}{a(\phi)} + c(y_i, \phi).
\end{aligned}$$

The element of the score vector is:

$$\big[\boldsymbol{S}(\boldsymbol{\beta}) \big]_j = \frac{\partial \ell}{\partial \beta_j} = \sum_{i=1}^{n} \frac{\partial \ell_i}{\partial \beta_j} = \sum_{i=1}^{n} (y_i - \mu_i) W_i \frac{\partial \eta_i}{\partial \mu_i} x_{ij}$$

where $W^{-1} = \mathsf{Var}(Y_i) (\frac{\partial \eta_i}{\partial \mu_i})^2$, $g(\mu_i) = \eta_i = \boldsymbol{x}_i^\top \boldsymbol{\beta}$. In vector and matrix form we can write:

$$\boldsymbol{S}(\boldsymbol{\beta}) = \boldsymbol{X} \boldsymbol{\mathcal{W}} \boldsymbol{\mathcal{A}} (\boldsymbol{y} - \boldsymbol{\mu}),$$

where

- $\boldsymbol{y} = (y_1, \ldots, y_n)^\top$ and $\boldsymbol{\mu} = (\mu_1, \ldots, \mu_n)^\top$ are $n \times 1$ vectors,
- $\boldsymbol{X} = (\boldsymbol{x}_1, \ldots, \boldsymbol{x}_n)$ is a $(p+1) \times n$ matrix,
- $\boldsymbol{\mathcal{W}} = \mathsf{diag}(W_1, \ldots, W_n) = \begin{bmatrix} W_1 & 0 & \cdots & 0 \\ \vdots & \ddots & \ddots & \vdots \\ 0 & \cdots & 0 & W_n \end{bmatrix}$, and
- $\boldsymbol{\mathcal{A}} = \mathsf{diag}\Big(\frac{\partial \eta_1}{\partial \mu_1}, \ldots, \frac{\partial \eta_n}{\partial \mu_n} \Big)$.

Example: Poisson Regression Model (Problem 1.4)

For a random sample from Poisson distribution, $Y_i \sim \text{POI}(\lambda_i)$, $i = 1, \ldots, n$,

$$\ell_i = \log\big(f(y_i; \lambda_i) \big) = \big(y_i \log(\lambda_i) - \lambda_i - \log(y_i!) \big).$$

Poisson regression with a log-link:

$$\log(\lambda_i) = \eta_i = \boldsymbol{x}_i^\top \boldsymbol{\beta}.$$

To write down the score vector for the regression coefficients $\boldsymbol{\beta}$, we may calculate the derivative using standard methods, i.e.,

$$\begin{aligned}
\big[\boldsymbol{S}(\boldsymbol{\beta})\big]_j &= \sum_i \frac{\partial \ell_i}{\partial \beta_j} \\
&= \sum_i \frac{\partial}{\partial \beta_j}\big(y_i \log(\lambda_i) - \lambda_i - \log(y_i!)\big) \\
&= \sum_i \big(y_i x_{ij} - \mathrm{e}^{\boldsymbol{x}_i^\top \boldsymbol{\beta}} x_{ij}\big).
\end{aligned}$$

Or we can use the general results derived for the GLMs on the previous slides.

Solving $\boldsymbol{S}(\boldsymbol{\beta}) = \boldsymbol{0}$ for MLE

1. Newton Raphson update equation is:

$$\hat{\boldsymbol{\beta}}^{(r+1)} = \hat{\boldsymbol{\beta}}^{(r)} + \boldsymbol{I}^{-1}(\hat{\boldsymbol{\beta}}^{(r)})\boldsymbol{S}(\hat{\boldsymbol{\beta}}^{(r)}),$$

   where $\boldsymbol{I}$ is the observed information matrix.

   - This requires us to find and repeatedly evaluate the information $\boldsymbol{I}$ (possibly computationally intensive).
   - Fisher suggested using the expected information matrix $\boldsymbol{\mathcal{I}}$ rather than the observed information matrix.

2. Fisher Scoring update equation is:

$$\hat{\boldsymbol{\beta}}^{(r+1)} = \hat{\boldsymbol{\beta}}^{(r)} + \boldsymbol{\mathcal{I}}^{-1}(\hat{\boldsymbol{\beta}}^{(r)})\boldsymbol{S}(\hat{\boldsymbol{\beta}}^{(r)}).$$

Information Matrix

Consider the (j, k) element of the Information matrix:

$$\begin{aligned}
\boldsymbol{I}_{jk} &= -\frac{\partial^2 \ell}{\partial \beta_j \, \partial \beta_k} \\
&= -\frac{\partial}{\partial \beta_k}\frac{\partial \ell}{\partial \beta_j} \\
&= \sum_i -\frac{\partial}{\partial \beta_k}\left[(y_i - \mu_i) W_i \left(\frac{\partial \eta_i}{\partial \mu_i}\right) x_{ij}\right] \\
&= \sum_i -(y_i - \mu_i)\left\{\frac{\partial}{\partial \beta_k}\left[W_i\left(\frac{\partial \eta_i}{\partial \mu_i}\right)x_{ij}\right]\right\} - W_i\left(\frac{\partial \eta_i}{\partial \mu_i}\right)x_{ij}\left(\frac{\partial}{\partial \beta_k}(y_i - \mu_i)\right) \\
&= \sum_i -(y_i - \mu_i)\left\{\frac{\partial}{\partial \beta_k}\left[W_i\left(\frac{\partial \eta_i}{\partial \mu_i}\right)x_{ij}\right]\right\} + W_i\left(\frac{\partial \eta_i}{\partial \mu_i}\right)x_{ij}\frac{\partial \mu_i}{\partial \eta_i}\frac{\partial \eta_i}{\partial \beta_k} \\
&= \sum_i -(y_i - \mu_i)\frac{\partial}{\partial \beta_k}\left[W_i\left(\frac{\partial \eta_i}{\partial \mu_i}\right)x_{ij}\right] + x_{ij} W_i x_{ik}.
\end{aligned}$$

Fisher Information

To get an element of the Expected/Fisher Information matrix:

$$\begin{aligned}
\boldsymbol{\mathcal{I}}_{jk} &= \sum_i \mathbb{E}\left[-\frac{\partial^2 \ell}{\partial\beta_j\,\partial\beta_k}\right] \\
&= \sum_i \mathbb{E}\left[-(y_i-\mu_i)\frac{\partial}{\partial\beta_k}\left[W_i\left(\frac{\partial\eta_i}{\partial\mu_i}\right)x_{ij}\right] + x_{ij}W_i x_{ik}\right] \\
&= \sum_i -\mathbb{E}\left[(y_i-\mu_i)\right]\frac{\partial}{\partial\beta_k}\left[W_i\left(\frac{\partial\eta_i}{\partial\mu_i}\right)x_{ij}\right] + x_{ij}W_i x_{ik} \\
&= \sum_i x_{ij}W_i x_{ik}.
\end{aligned}$$

Therefore, we can write the (j,k) element of the Fisher information as:

$$\boldsymbol{\mathcal{I}}_{jk} = \sum_{i=1}^{n} x_{ij}W_i x_{ik} = [\boldsymbol{X}\boldsymbol{\mathcal{W}}\boldsymbol{X}^\top]_{jk}$$

where again, $\boldsymbol{\mathcal{W}} = \mathsf{diag}(W_1,\ldots,W_n)$ and $W_i^{-1} = \mathsf{Var}(Y_i)\left(\frac{\partial\eta_i}{\partial\mu_i}\right)^2$.

When is Fisher Scoring Equivalent to Newton Raphson?

Recall information matrix:

$$\boldsymbol{I}_{jk} = \sum_i -(y_i-\mu_i)\frac{\partial}{\partial\beta_k}\left[W_i\left(\frac{\partial\eta_i}{\partial\mu_i}\right)x_{ij}\right] + x_{ij}W_i x_{ik}.$$

Now examine:

$$\begin{aligned}
W_i\left(\frac{\partial\eta_i}{\partial\mu_i}\right)x_{ij} &= \left(\mathsf{Var}(Y_i)\left(\frac{\partial\eta_i}{\partial\mu_i}\right)^2\right)^{-1}\left(\frac{\partial\eta_i}{\partial\mu_i}\right)x_{ij} \\
&= \left(a(\phi)b''(\theta_i)\frac{\partial\eta_i}{\partial\mu_i}\right)^{-1}x_{ij} && \text{since } \mathsf{Var}(Y_i) = a_i(\phi)b''(\theta_i) \\
&= \left(a(\phi)\frac{\partial\mu_i}{\partial\theta_i}\frac{\partial\eta_i}{\partial\mu_i}\right)^{-1}x_{ij} && \text{since } b'(\theta_i)=\mu_i,\ b''(\theta_i)=\frac{\partial\mu_i}{\partial\theta_i} \\
&= \left(a(\phi)\right)^{-1}x_{ij} && \text{under the canonical link } \theta_i=\eta_i.
\end{aligned}$$

So under the canonical link,

$$\frac{\partial}{\partial\beta_k}\left[W_i\left(\frac{\partial\eta_i}{\partial\mu_i}\right)x_{ij}\right] = \frac{\partial}{\partial\beta_k}\left[\left(a(\phi)\right)^{-1}x_{ij}\right] = 0,$$

therefore information matrix is same as the Fisher information:

$$\boldsymbol{I}_{jk} = \sum_i x_{ij}W_i x_{ij} = \boldsymbol{\mathcal{I}}_{jk}$$

and Fisher Scoring is equivalent to Newton Raphson.

Iteratively Reweighted Least Squares

The Fisher Scoring is also called iteratively reweighted least squares (IRWLS). The reason is that the update equation can be rewritten as:

$$\hat{\boldsymbol{\beta}}^{(r+1)} = \left(\boldsymbol{X}\boldsymbol{\mathcal{W}}(\hat{\boldsymbol{\beta}}^{(r)})\boldsymbol{X}^{\top}\right)^{-1}\boldsymbol{X}\boldsymbol{\mathcal{W}}(\hat{\boldsymbol{\beta}}^{(r)})\boldsymbol{Z}(\hat{\boldsymbol{\beta}}^{(r)})$$

where $\boldsymbol{Z}$ is a transformation of the response vector $\boldsymbol{Y}$ such that:

$$\boldsymbol{Z} = \boldsymbol{\eta} + (\boldsymbol{Y} - \boldsymbol{\mu}) * \frac{\partial \boldsymbol{\eta}}{\partial \boldsymbol{\mu}}$$

- See manipulation in Section 1.2.3 of course notes.
- Same form as the weighted LS estimate of $\boldsymbol{\beta}$ with dependent variable $\boldsymbol{Z}$ and weight matrix $\boldsymbol{\mathcal{W}}$.
- $\boldsymbol{Z}$ and $\boldsymbol{\mathcal{W}}$ are updated at each iteration.

Topic Summary

2b Maximum Likelihood Estimation of Generalized Linear Models:

- When Y_i come from a distribution in the exponential family, we can use the theory of Generalized Linear Models to fit the regression equations of the form:

$$g(\mu_i) = \boldsymbol{x}_i^{\top}\boldsymbol{\beta}.$$

- The link function $g(\,\cdot\,)$ may be the canonical link, but its choice should come from model interpretation and fit.
- Can use Fisher Scoring (also known as IRWLS) to estimate the regression parameters $\boldsymbol{\beta}$ from any GLM based on general forms for $\boldsymbol{I}(\boldsymbol{\beta})$ and $\boldsymbol{S}(\boldsymbol{\beta})$.
- PRACTICE: Chapter 1 review problems.

Topic 3a: Binary Data and Odds Ratios

Binary Data Set-up

Consider the simplest case with two *binary* variables:

- COVID-19: infected or not infected (response).
- Vaccination: yes or no (explanatory variable).

Use a 2×2 table to summarize the data:

	COVID-19		
Vaccination	infected	not infected	
yes	y_1	$m_1 - y_1$	m_1
no	y_2	$m_2 - y_2$	m_2
Total	$y_\bullet$	$m_\bullet - y_\bullet$	$m_\bullet$

Treat m_1 and m_2 as fixed, assume Y_1 and Y_2 are independent binomial r.v.'s

$$Y_k \sim \text{BIN}(m_k, \pi_k), \qquad k = 1, 2,$$

where $\pi_k = \mathbb{P}(\text{infection} \mid \text{group } k)$.

How do we measure the associate between COVID-19 infection and vaccination?

Measures of Association

Definition (Odds Ratio)

The Odds Ratio (OR) is the ratio of the odds of an event occurring in one group to the odds of the event in another group (e.g., not vaccinated):

$$\text{Odds Ratio} = \frac{\pi_1/(1-\pi_1)}{\pi_2/(1-\pi_2)}.$$

Interpretation of OR:

$$\begin{array}{lcccl} \pi_1 = \pi_2 & \Longrightarrow & \text{OR} = 1 & \Longrightarrow & \text{equal risk (no association)} \\ \pi_1 > \pi_2 & \Longrightarrow & \text{OR} > 1 & \Longrightarrow & \text{higher risk in group 1} \\ \pi_1 < \pi_2 & \Longrightarrow & 0 < \text{OR} < 1 & \Longrightarrow & \text{higher risk in group 2} \end{array}$$

Relative Risk (RR)

The Relative Risk (RR) is the ratio of the probability of an event occurring in one group versus another group:

$$\text{Relative Risk} = \frac{\pi_1}{\pi_2}$$

In the case of a rare disease (i.e., when π_1 and π_2 are very small),

$$\text{OR} = \frac{\pi_1/(1-\pi_1)}{\pi_2/(1-\pi_2)} = \frac{\pi_1}{\pi_2}\underbrace{\left(\frac{1-\pi_2}{1-\pi_1}\right)}_{\approx 1} \approx \frac{\pi_1}{\pi_2} = \text{RR},$$

then

$$\text{OR} \approx \text{RR}.$$

Maximum Likelihood Estimation of Odds Ratio

Goal: Estimate odds ratio $\psi = \frac{\pi_1/(1-\pi_1)}{\pi_2/(1-\pi_2)}$ using likelihood method. Based on "grouped" binomial data,

$$Y_k \sim \text{BIN}(m_k, \pi_k),\ k = 1, 2$$

$$\begin{aligned} L(\pi_1, \pi_2) &= \binom{m_1}{y_1}\pi_1^{y_1}(1-\pi_1)^{m_1-y_1}\binom{m_2}{y_2}\pi_2^{y_2}(1-\pi_2)^{m_2-y_2} \\ &\propto \left(\frac{\pi_1/(1-\pi_1)}{\pi_2/(1-\pi_2)}\right)^{y_1}\left(\frac{\pi_2}{1-\pi_2}\right)^{y_2+y_1}(1-\pi_1)^{m_1}(1-\pi_2)^{m_2}. \end{aligned}$$

Note that $\pi_1, \pi_2 \in [0, 1]$ and odds ratio $\psi \in (0, \infty)$ are restricted, we consider re-parameterize:

$$\theta_1 = \log\left(\frac{\pi_1/(1-\pi_1)}{\pi_2/(1-\pi_2)}\right) = \log(\psi), \qquad \theta_2 = \log\left(\frac{\pi_2}{1-\pi_2}\right),$$

and now $\theta_1, \theta_2 \in (-\infty, \infty)$.

Our re-parameterization implies:

$$\pi_1 = \frac{e^{\theta_1+\theta_2}}{1+e^{\theta_1+\theta_2}}, \qquad \pi_2 = \frac{e^{\theta_2}}{1+e^{\theta_2}}.$$

Now the likelihood becomes:

$$\begin{aligned} L(\theta_1, \theta_2) &= (e^{\theta_1})^{y_1}(e^{\theta_2})^{y_1+y_2}(1+e^{\theta_1+\theta_2})^{m_1}(1+e^{\theta_2})^{-m_2}, \\ \ell(\theta_1, \theta_2) &= y_1\theta_1 + (y_1+y_2)\theta_2 - m_1\log(1+e^{\theta_1+\theta_2}) - m_2\log(1+e^{\theta_2}). \end{aligned}$$

The score vector is:

$$S(\theta_1,\theta_2)=\begin{pmatrix}\frac{\partial \ell}{\partial \theta_1}\\ \frac{\partial \ell}{\partial \theta_2}\end{pmatrix}=\begin{pmatrix} y_1-m_1\left(\frac{e^{\theta_1+\theta_2}}{1+e^{\theta_1+\theta_2}}\right)\\ y_1+y_2-m_1\left(\frac{e^{\theta_1+\theta_2}}{1+e^{\theta_1+\theta_2}}\right)-m_2\left(\frac{e^{\theta_2}}{1+e^{\theta_2}}\right)\end{pmatrix}.$$

Solving $\boldsymbol{S}(\theta_1,\theta_2)=\mathbf{0}$ gives us the MLEs:

$$\hat{\theta}_1=\log\left(\frac{y_1/(m_1-y_1)}{y_2/(m_2-y_2)}\right),\qquad \hat{\theta}_2=\log\left(\frac{y_2}{m_2-y_2}\right).$$

So by the invariance property of MLEs, we have:

$$\hat{\pi}_1=\frac{y_1}{m_1},\qquad \hat{\pi}_2=\frac{y_2}{m_2},\qquad \hat{\psi}=\frac{\hat{\pi}_1/(1-\hat{\pi}_1)}{\hat{\pi}_2/(1-\hat{\pi}_2)}=\frac{y_1/(m_1-y_1)}{y_2/(m_2-y_2)}.$$

Inference for Odds Ratio

In order to do inference we will need the Information Matrix:

$$\boldsymbol{I}(\theta_1,\theta_2)=\begin{bmatrix}I_{11} & I_{12}\\ I_{21} & I_{22}\end{bmatrix}\qquad \text{where } I_{jk}=-\frac{\partial^2}{\partial\theta_j\,\partial\theta_k}\ell(\theta_1,\theta_2).$$

Here, we have:

$$\begin{aligned} I_{11}&=m_1\left(\frac{e^{\theta_1+\theta_2}}{(1+e^{\theta_1+\theta_2})^2}\right),\\ I_{12}=I_{21}&=m_1\left(\frac{e^{\theta_1+\theta_2}}{(1+e^{\theta_1+\theta_2})^2}\right),\\ I_{22}&=m_1\left(\frac{e^{\theta_1+\theta_2}}{(1+e^{\theta_1+\theta_2})^2}\right)+m_2\left(\frac{e^{\theta_2}}{(1+e^{\theta_2})^2}\right).\end{aligned}$$

We are interested in doing inference on $\theta_1=\log(\psi)$ (while θ_2 is nuisance).

Recall the asymptotic distribution result of a Wald statistic:

Wald Statistic

For a vector $\boldsymbol{\theta}=(\theta_1,\theta_2)^\top$ where $\theta_1=\log(\psi)$ is a scalar parameter of interest:

$$(\hat{\theta}_1-\theta_1)^2\big(I^{11}(\hat{\theta}_1,\hat{\theta}_2)\big)^{-1}\sim\chi^2_{(1)},$$

where I^{11} is the $(1,1)$ element of $\boldsymbol{I}^{-1}$ evaluated at MLE $\hat{\theta}_1$ and $\hat{\theta}_2$.

- Calculation of I^{11} by using a general result:

$$\boldsymbol{I}=\begin{pmatrix}I_{11} & I_{12}\\ I_{21} & I_{22}\end{pmatrix},\qquad \boldsymbol{I}^{-1}=\begin{pmatrix}I^{11} & I^{12}\\ I^{21} & I^{22}\end{pmatrix},\qquad I^{11}=\big(I_{11}-I_{12}I_{22}^{-1}I_{21}\big)^{-1}.$$

- We can use the Wald result to find a confidence interval for $\theta_1=\log(\psi)$.

Confidence Interval for Odds Ratio

Here, we obtain:

$$I^{11}(\hat{\theta}_1,\hat{\theta}_2)=\frac{1}{y_1}+\frac{1}{m_1-y_1}+\frac{1}{y_2}+\frac{1}{m_2-y_2}.$$

Thus, a Wald-based $95\,\%$ confidence interval for $\theta_1 = \log(\psi)$ is:

$$\hat{\theta}_1 \pm 1.96\sqrt{\frac{1}{y_1} + \frac{1}{m_1 - y_1} + \frac{1}{y_2} + \frac{1}{m_2 - y_2}} = (\hat{\theta}_{1\mathrm{L}}, \hat{\theta}_{1\mathrm{U}}).$$

A $95\,\%$ confidence interval for the Odds Ratio ψ is:

$$\big(\exp\{\hat{\theta}_{1\mathrm{L}}\}, \exp\{\hat{\theta}_{1\mathrm{U}}\}\big).$$

Example: Prenatal Care from Two Clinics

Consider the data below for the relationship between:

- Response: Fetal Mortality.
- Explanatory variable: Level of Care.

	Fetal Mortality		
Level of Care	Died	Survived	Total
Intensive	20	316	336
Regular	46	373	419
	66	689	755

- Using the above data, we obtain MLE of odds ratio ψ:

$$\hat{\psi} = \frac{y_1/(m_1 - y_1)}{y_2/(m_2 - y_2)} = \frac{20/316}{46/373} = 0.51.$$

  $\hat{\psi} = 0.51 < 1$, the risk of mortality is lower with intensive care.

- A $95\,\%$ CI for $\theta_1 = \log(\psi)$:

$$\log(0.51) \pm 1.96\sqrt{\frac{1}{20} + \frac{1}{316} + \frac{1}{46} + \frac{1}{373}} = (-1.219, -0.127).$$

- A $95\,\%$ CI for odds ratio ψ:

$$\big(\exp\{-1.219\}, \exp\{-0.127\}\big) = (0.30, 0.89).$$

  Note that the CI does not cover the value $\psi = 1$ (no association), so we reject the null hypothesis of no association between fetal mortality and level of care. In other words, there is evidence of association.

Example: Prenatal Care from Two Clinics

There is an additional explanatory variable: Clinic (A vs B).

Prenatal Care Data Stratified by Clinic

	Clinic A			*Clinic B*		
Level of Care	Died	Survived	Total	Died	Survived	Total
Intensive	16	293	309	4	23	27
Regular	12	176	188	34	197	231
	28	469	497	38	220	258

- $\hat{\psi}_{\mathrm{A}} = 0.80$ $(0.37, 1.73)$ and $\hat{\psi}_{\mathrm{B}} = 1.01$ $(0.33, 3.10)$. These cover value 1, different from the results from the pooled analysis on the previous slide.
- These results do NOT agree with the results from the pooled analysis on the previous slide.

Association Between Clinic and Level of Care

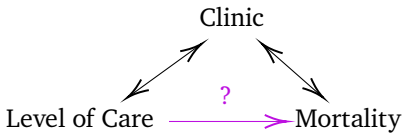
	A	B	
Intensive	309	27	336
Regular	118	231	419
	497	258	755

- $\hat{\psi} = 14.06$ $(9.12, 21.76)$.

Association Between Clinic and Mortality

	A	B	
Died	28	38	66
Survived	469	220	689
	497	258	755

- $\hat{\psi} = 0.35$ $(0.21, 0.58)$.
- The initial strong association between Level of Care and Infant Morality disappeared when we stratified by clinic.



- Instead of having to examine multiple 2×2 tables we'd like to estimate the OR and compute associations using a multiple regression model.
- One way to do this is by fitting a Binomial GLM to the data.

WEEK 4
0927 to 1st October

Topic 3b: Binomial Regression Models for Binary Data

Recall Topic 3a: Binary Data and Odds Ratios

Last week, we introduce a simple method for association between two binary variables, 2×2 contingency table analysis: Measure of Association: OR $= \psi = \dfrac{\pi_1/(1-\pi_1)}{\pi_2/(1-\pi_2)}$,

	Mortality		
Level of Care	Died	Survived	
Intensive	y_1	$m_1 - y_1$	$Y_1 \sim \text{BIN}(m_1, \pi_1)$
Regular	y_2	$m_2 - y_2$	$Y_2 \sim \text{BIN}(m_2, \pi_2)$

- OR $= 1$ (equal risk).
- $0 <$ OR < 1 (lower risk in group 1).
- OR > 1 (higher risk in group 1).

Maximum likelihood estimator for OR is:

$$\hat{\psi} = \frac{y_1/(m_1 - y_1)}{y_2/(m_2 - y_2)},$$

and a Wald-based $95\,\%$ CI is:

$$\exp\left\{\log(\hat{\psi}_1) \pm 1.96 \underbrace{\sqrt{\frac{1}{y_1} + \frac{1}{m_1 - y_1} + \frac{1}{y_2} + \frac{1}{m_2 - y_2}}}_{\mathsf{se}(\log(\hat{\psi}))}\right\}.$$

Prenatal Care Data Example

OR (Mortality and Care)	Est.	$95\,\%$ CI
Intensive vs Regular	0.51	$(0.30, 0.89)$

Table 1: $1 \notin (0.30, 0.89) \implies$ evidence of association between Mortality and Care.

However, Mortality and Care are also related to another variable, Clinic:

OR (Mortality and Clinic)	Est.	$95\,\%$ CI
Clinic A vs Clinic B	0.35	$(0.12, 0.58)$

Table 2: Association between Mortality and Clinic.

OR (Care and Clinic)	Est.	$95\,\%$ CI
Clinic A vs Clinic B	14.06	$(9.12, 21.76)$

Table 3: Association between Care and Clinic.

- Therefore, we wish to consider how a variable, e.g., Mortality (Y), is related to multiple explanatory variables together, e.g., Care (x_1) and Clinic (x_2).
- This can be done using multiple regression methodology for binary data $\implies$ Topic 3b: Binomial Regression Models for Binary Data.

Multiple Regression for Binary Data

- Often we need to consider the relationship between a binary outcome and multiple explanatory variables, using multiple regression methodology.
- This is because we may want to:
  - control for cofounding variables and hence want to examine the effect of several variables simultaneously;
  - examine the effect of categorical variables (> 2 levels) or continuous covariates;
  - develop sophisticated models that describe complex relationship.
- Suppose *subject level data* is binary with a value of 1 indicating that an event of interest occurs and a value of 0 indicating that event doesn't occur.
- Subjects can be classified according to the values of explanatory variables into n groups (i.e., common covariates values within each group), so we have *grouped data* such that:

- m_i denotes number of subjects in group i;
- Y_i denotes number of subjects experienced the event in group i;
- $x_{i1}, \ldots, x_{ip}$ denote the covariates values associated with group i where $i = 1, \ldots, n$.

Set-up of a Binomial Regression Model

(1) Response Variable: $Y_i \sim \text{BIN}(m_i, \pi_i)$, $i = 1, \ldots, n$, and Binomial distribution is a member of Exponential family!

$$\begin{aligned} f(y_i) &= \binom{m_i}{y_i} \pi_i^{y_i} (1-\pi_i)^{m_i - y_i} \\ &= \exp\left\{ y_i \log\left(\frac{\pi_i}{1-\pi_i}\right) + m_i \log(1-\pi_i) + \log\left(\binom{m_i}{y_i}\right) \right\}, \end{aligned}$$

where

$$\begin{aligned} \theta_i &= \log\left(\frac{\pi_i}{1-\pi_i}\right), \\ a(\phi) &= \phi = 1, \\ b(\theta_i) &= -m_i \log(1-\pi_i) = m_i \log(1+\mathrm{e}^{\theta_i}). \\ c(y_i; \phi) &= \log\left(\binom{m_i}{y_i}\right). \end{aligned}$$

(2) Linear Predictor:

$$\eta_i = \boldsymbol{x}_i^\top \boldsymbol{\beta} = \beta_0 + \beta_1 x_{i1} + \cdots + \beta_p x_{ip}.$$

(3) Link Function: Recall that for Binomial distribution, we have $\mathbb{E}[Y_i] = \mu_i = m_i \pi_i$, therefore we typically re-write the link function in terms of π_i,

$$g(\pi_i) = \boldsymbol{x}_i^\top \boldsymbol{\beta}.$$

As $\pi_i \in (0, 1)$, any function $g \colon (0, 1) \to (-\infty, \infty)$ may work, and here are some link functions we can consider:

log-log	$g(\pi) = \log\big(-\log(\pi)\big)$
complementary log-log	$g(\pi) = \log\big(-\log(1-\pi)\big)$
Probit[a]	$g(\pi) = \Phi^{-1}(\pi)$
Logit (canonical)	$g(\pi) = \log\big(\pi/(1-\pi)\big)$

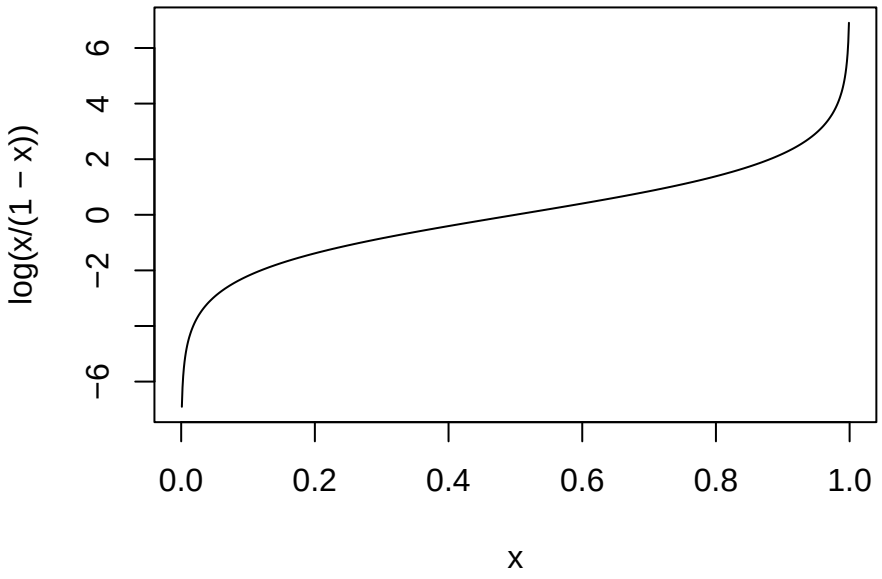
[a] For the Probit link, $\Phi(\,\cdot\,)$ is the *CDF* of $\mathcal{N}(0, 1)$.

Canonical Link and Logistic Regression

Recall for Binomial distribution $\theta_i = \log\left(\frac{\pi_i}{1-\pi_i}\right)$, and by setting $\theta_i = \eta_i$, we have:

$$\log\left(\frac{\pi_i}{1-\pi_i}\right) = \eta_i.$$

The Logit link, $g(\pi_i) = \log\big(\pi_i/(1-\pi_i)\big)$, is the canonical link for the Binomial!



This leads to a Logistic Regression Model:

$$\log\left(\frac{\pi_i}{1-\pi_i}\right) = \boldsymbol{x}_i^\top \boldsymbol{\beta} = \beta_0 + \beta_1 x_{i1} + \cdots + \beta_p x_{ip}.$$

Prediction from Logistic Regression

Aside: The inverse of the logit function is called the expit function:

$$\text{logit}(\pi_i) = \log\left(\frac{\pi_i}{1-\pi_i}\right) = \boldsymbol{x}_i^\top \boldsymbol{\beta} \iff \pi_i = \frac{\exp\{\boldsymbol{x}_i^\top \boldsymbol{\beta}\}}{1+\exp\{\boldsymbol{x}_i^\top \boldsymbol{\beta}\}} = \text{expit}(\boldsymbol{x}_i^\top \boldsymbol{\beta}).$$

Suppose we have found MLE $\hat{\boldsymbol{\beta}}$ using Fisher scoring, then the fitted value for the probability of response π_i given explanatory variables $\boldsymbol{x}_i$ is:

$$\hat{\pi}_i = \frac{\exp\{\boldsymbol{x}_i^\top \hat{\boldsymbol{\beta}}\}}{1+\exp\{\boldsymbol{x}_i^\top \hat{\boldsymbol{\beta}}\}}.$$

The predicted number of responses are: $\hat{Y}_i = m_i \hat{\pi}_i$.

Interpretation of β in Logistic Regression

- Consider a simple logistic model with a single binary explanatory variable:

$$\log\left(\frac{\pi_i}{1-\pi_i}\right) = \beta_0 + \beta_1 x_{i1},$$

  where $x_{i1} = 0$ (group 0) and $x_{i1} = 1$ (group 1).
- Let's compare the model when $x_{i1} = 1$ vs $x_{i1} = 0$.
- We subtract line 2 from line 1 to isolate β_1 and find its interpretation.
- $\beta_1 =$ log odds ratio of response for subjects with $x_{i1} = 1$ vs $x_{i1} = 0$.
- Please see Section 2.4.2 for general interpretations of $\boldsymbol{\beta}$'s in multiple logistic regression models.

Group	$\boldsymbol{x}_i^\top$	η_i	$= \log\big(\pi_i/(1-\pi_i)\big)$
1	$(1,1)^\top$	$\beta_0 + \beta_1$	$= \log\big(\pi_1/(1-\pi_1)\big)$
0	$(1,0)^\top$	β_0	$= \log\big(\pi_0/(1-\pi_0)\big)$
		β_1	$= \log\left(\frac{\pi_1/(1-\pi_1)}{\pi_0/(1-\pi_0)}\right) = \log(\text{OR})$

Logistic Regression for Prenatal Care Example

- Response: Fetal Mortality, that is,

$$Y_i \sim \text{BIN}(m_i, \pi_i),\ i = 1, 2, \ldots.$$

- Explanatory Variables:

$$x_{i1} = \begin{cases} 1 & \text{Intensive Care} \\ 0 & \text{Regular Care} \end{cases}$$

$$x_{i2} = \begin{cases} 1 & \text{Clinic A} \\ 0 & \text{Clinic B} \end{cases}$$

$$x_{i3} = x_{i1}x_{i2} = \begin{cases} 1 & \text{Intensive care and Clinic A} \\ 0 & \text{Otherwise} \end{cases}$$

- We will use the context of this example to illustrate how to:
  - fit (simple and multiple) logistic regression models using R, and
  - interpret regression parameters.

Model 1: Level of Care only model

$$\log\left(\frac{\pi_i}{1-\pi_i}\right) = \beta_0 + \beta_1 x_{i1}.$$

Level of Care	Clinic	$\boldsymbol{x}_i^\top$	$\log\big(\pi_i/(1-\pi_i)\big)$
Intensive	—	$(1,1)^\top$	$\beta_0 + \beta_1$
Regular	—	$(1,0)^\top$	β_0

- $\beta_0 =$ log odds of mortality for babies born to mothers treated with regular care.
- $\beta_1 =$ log odds ratio of mortality for babies born to mothers treated with intensive vs regular care.

Model 2: Main effects model

$$\log\left(\frac{\pi_i}{1-\pi_i}\right) = \beta_0 + \beta_1 x_{i1} + \beta_2 x_{i2}.$$

- $\beta_0 =$ log odds of mortality with regular care at Clinic B.
- $\beta_1 =$ log odds ratio of mortality for babies born to mothers treated with intensity vs regular care at the *same clinic*.
- $\beta_2 =$ log odds ratio of mortality for babies born to mothers treated at Clinic A vs Clinic B at the *same level of care*.

Level of Care	Clinic	$\boldsymbol{x}_i^\top$	$\log(\pi_i/(1-\pi_i))$
Intensive	A	$(1,1,1)^\top$	$\beta_0+\beta_1+\beta_2$
Regular	A	$(1,0,1)^\top$	$\beta_0+\beta_2$
Intensive	B	$(1,1,0)^\top$	$\beta_0+\beta_1$
Regular	B	$(1,0,0)^\top$	β_0

Model 3: Interaction model

$$\log\left(\frac{\pi_i}{1-\pi_i}\right) = \beta_0 + \beta_1 x_{i1} + \beta_2 x_{i2} + \beta_3 x_{i3}.$$

Level of Care	Clinic	$\boldsymbol{x}_i^\top$	$\log(\pi_i/(1-\pi_i))$
Intensive	A	$(1,1,1)^\top$	$\beta_0+\beta_1+\beta_2+\beta_3$
Regular	A	$(1,0,1)^\top$	$\beta_0+\beta_2$
Intensive	B	$(1,1,0)^\top$	$\beta_0+\beta_1$
Regular	B	$(1,0,0)^\top$	β_0

- $\beta_0 =$ log odds ratio of mortality for babies born to mothers treated with intensity vs regular care at *Clinic B*.
- $\beta_1+\beta_3 =$ log odds ratio of mortality for babies born to mothers treated with intensity vs regular care at *Clinic A*.
- $\beta_2 =$ log odds ratio of mortality for babies born to mothers treated at Clinic A vs Clinic B with *regular* care.
- $\beta_2+\beta_3 =$ log odds ratio of mortality for babies born to mothers treated at Clinic A vs Clinic B with *intensive* care.
- β_3 represents the difference in log odds ratios.
- If $\beta_3 = 0$ then association between mortality and level of care does not dependent on clinic.
- Equivalently, if $\beta_3 = 0$ then the association between mortality and clinic does not depend on level of care.

Data file `prenatal.dat`

```
  clinic loc  y   m
1      0   0 34 231
2      0   1  4  27
3      1   0 12 188
4      1   1 16 309
```

- The first line contains the variable names/labels.
- We are using indicator variables for the explanatory variables:

$x_{i1} =$ `loc` (1 for Intensive, 0 for Regular)
$x_{i2} =$ `clinic` (1 for Clinic A, 0 for Clinic B)

- The variable y records the number of deaths (events).

Fit GLMs using R

The `glm()` function in R is used to fit the generalized linear models:

`fit = glm(formula, family = (link = ), data = ).`

- `formula`: a linear formula describing the model, e.g.,

  `resp ~ loc + clinic.`

- `family`: a description of the exponential family distribution and link function to be used in the model, e.g.,

  `family = binomial, gaussian, poisson, Gamma, etc..`

  `link = logit, log, loglog, cloglog, identity, probit, etc..`

- The default is the canonical link.

R Code and Output for Analysis of Prenatal Care data

```r
# read file prenatal.data
prenatal.dat = read.table("prenatal.dat", header = T)
# construct the binomial response for the logistic regression
# analysis
prenatal.dat$resp = cbind(prenatal.dat$y, prenatal.dat$m - prenatal.dat$y)
prenatal.dat
```

```
  clinic loc  y   m resp.1 resp.2
1      0   0 34 231     34    197
2      0   1  4  27      4     23
3      1   0 12 188     12    176
4      1   1 16 309     16    293
```

The logistic regression models are fit using the `glm()` commands like:

```r
# fit the logistic model using the glm function
model1 = glm(resp ~ loc, family = binomial(link = logit), data = prenatal.dat)
summary(model1)
```

Fit of Model 1: Level of Care Model

$$\log\left(\frac{\pi_i}{1-\pi_i}\right) = \beta_0 + \beta_1 x_{i1}.$$

```r
# fit the logistic model using the glm function
model1 = glm(resp ~ loc, family = binomial(link = logit), data = prenatal.dat)
summary(model1)$coefficients
```

```
              Estimate Std. Error    z value     Pr(>|z|)
(Intercept) -2.0929370  0.1562692 -13.393150 6.630754e-41
loc         -0.6670729  0.2785400  -2.394891 1.662530e-02
```

Components of the `summary()` output for `glm` objects:

- `Estimate`: the maximum likelihood estimates of the regression coefficients $\hat{\beta}_0$ and $\hat{\beta}_1$.
- `Std. Error`: estimated standard errors, the square root of the diagonal of the inverse of the Information matrix:
$$\mathsf{se}(\hat{\beta}_j) = \sqrt{\left[\boldsymbol{I}^{-1}(\hat{\boldsymbol{\beta}})\right]_{jj}} = \sqrt{I^{jj}(\hat{\boldsymbol{\beta}})}.$$
- `z value`: Wald-type test statistics for testing the hypotheses:
$$H_0\text{: } \beta_j = 0 \text{ vs } H_A\text{: } \beta_j \neq 0.$$
- `Pr(>|z|)`: p-value for above Wald test.

For this model:

- β_1 is the log odds ratio of mortality for infants born to mothers treated with intensive versus regular care.

Hypothesis test for β_j

- We may wish to test:
$$H_0\text{: } \beta_j = \beta^\star \text{ versus } H_A\text{: } \beta_j \neq \beta^\star.$$
- The general Wald result for a single parameter β_j is:
$$(\hat{\beta}_j - \beta^\star)^2 \left(I^{jj}(\hat{\boldsymbol{\beta}})\right)^{-1} \sim \chi^2_1,$$
equivalently $\dfrac{\hat{\beta}_j - \beta^\star}{\mathsf{se}(\hat{\beta}_j)} \sim \mathcal{N}(0,1)$ where $\mathsf{se}(\hat{\beta}_j) = \sqrt{I^{jj}(\hat{\boldsymbol{\beta}})}$.
- We can find the p-value of this test using:
$$p = 2\,\mathbb{P}\left(Z > \frac{|\hat{\beta}_j - \beta^\star|}{\mathsf{se}(\hat{\beta}_j)}\right).$$
- The `summary()` output gives the test statistics and p-values for testing
$$H_0\text{: } \beta_j = 0 \text{ vs } H_A\text{: } \beta_j \neq 0.$$

Hypothesis test for β_1 from Model 1: Level of Care Model

```
summary(model1)$coefficients
```

```
             Estimate Std. Error    z value     Pr(>|z|)
(Intercept) -2.0929370  0.1562692 -13.393150 6.630754e-41
loc         -0.6670729  0.2785400  -2.394891 1.662530e-02
```

- We wish to test:
$$H_0\text{: } \beta_1 = 0 \text{ vs } H_A\text{: } \beta_1 \neq 0$$
- Wald test:
$$z = \frac{\hat{\beta}_1 - 0}{\mathsf{se}(\hat{\beta}_1)} = \frac{-0.6671}{0.2785} = -2.3949$$

- p-value:
$$p = 2\,\mathbb{P}(Z > |-2.3949|) = 0.0166 < 0.05$$
- Therefore, we reject the null hypothesis that $\beta_1 = 0$.
- Estimate of OR for Mortality for Intensive vs Regular Care:
$$\hat{\psi} = \exp\{\hat{\beta}_1\} = \exp\{-0.6670729\} = 0.51.$$
- Confidence Interval for OR:
$$\begin{aligned}\exp\{\hat{\beta}_1 \pm 1.96\,\mathrm{se}(\hat{\beta}_1)\} &= \exp\{-0.6671 \pm 1.96(0.2785)\} \\ &= (\exp\{-1.2130\}, \exp\{-0.1211\}) \\ &= (0.30, 0.89)\end{aligned}$$
- The estimate and Wald $95\,\%$ CI here match those found previously from the 2×2 table analysis. That is, the 2×2 table analysis is equivalent to a simple logistic regression with a single binary covariate.

Fit of Model 2: Main Effects Model

$$\log\left(\frac{\pi_i}{1-\pi_i}\right) = \beta_0 + \beta_1 x_{i1} + \beta_2 x_{i2}.$$

```
model2 <- glm(resp ~ loc + clinic, family = binomial(link = logit),
  data = prenatal.dat)
summary(model2)$coefficients

             Estimate Std. Error    z value     Pr(>|z|)
(Intercept) -1.7410476  0.1784691 -9.7554560 1.748132e-22
loc         -0.1503053  0.3301670 -0.4552402 6.489365e-01
clinic      -0.9862793  0.3089322 -3.1925427 1.410261e-03
```

- What is the OR for mortality for Intensive vs Regular Care, now controlling for Clinic?
$$\widehat{\mathrm{OR}} = \hat{\psi} = \exp\{-0.1503\} = 0.86.$$
- $95\,\%$ CI:
$$\exp\{-0.1503 \pm 1.96 \times 0.3302\} = (0.4505, 1.6436).$$

Fit of Model 3: Interaction Model

$$\log\left(\frac{\pi_i}{1-\pi_i}\right) = \beta_0 + \beta_1 x_{i1} + \beta_2 x_{i2} + \beta_3 x_{i3}.$$

```
model3 <- glm(resp ~ loc + clinic + loc * clinic, family = binomial(link = logit),
  data = prenatal.dat)
summary(model3)$coefficients

               Estimate Std. Error     z value     Pr(>|z|)
(Intercept) -1.756843204  0.1857092 -9.46018403 3.074017e-21
loc          0.007643349  0.5726827  0.01334657 9.893513e-01
clinic      -0.928734141  0.3514300 -2.64272868 8.224091e-03
loc:clinic  -0.229649891  0.6949054 -0.33047646 7.410400e-01
```

Level of Care	Clinic	$\boldsymbol{x}_i^\top$	$\log(\pi_i/(1-\pi_i))$
Intensive	A	$(1,1,1)^\top$	$\beta_0+\beta_1+\beta_2+\beta_3$
Regular	A	$(1,0,1)^\top$	$\beta_0+\beta_2$
Intensive	B	$(1,1,0)^\top$	$\beta_0+\beta_1$
Regular	B	$(1,0,0)^\top$	β_0

- What is the OR for Mortality for Intensive vs Regular Care at Clinic A?

$$\text{OR} = \psi = \exp\{\beta_1+\beta_3\} \implies \hat{\psi} = \exp\{0.0076 - 0.2296\} = 0.8.$$

- $\text{se}(\hat{\beta}_1+\hat{\beta}_3)$ is required for calculation of 95 % CI.
  - Recall $\text{Var}(\hat{\beta}) = \boldsymbol{I}^{-1}(\hat{\boldsymbol{\beta}})$, now for any linear function of $\boldsymbol{\beta}$'s, e.g., $\boldsymbol{c\beta}$ where $\boldsymbol{c}$ is a row vector of constants, then MLE of $\boldsymbol{c\beta}$ is $\boldsymbol{c}\hat{\boldsymbol{\beta}}$, and $\text{se}(\widehat{\boldsymbol{c\beta}}) = \sqrt{\boldsymbol{c}\boldsymbol{I}^{-1}(\hat{\boldsymbol{\beta}})\boldsymbol{c}^\top}$.
- Therefore, $\log(\psi) = \beta_1+\beta_3 = \boldsymbol{c\beta}$, $\boldsymbol{c} = (0,1,0,1)^\top$. In R, `vcov(model3)` gives $\boldsymbol{I}^{-1}(\hat{\boldsymbol{\beta}})$.
- What is OR for Mortality for Intensive vs Regular Care at Clinic B?

$$\text{OR} = \psi = \exp\{\beta_1\} \implies \hat{\psi} = \exp\{0.0076\} = 1.01.$$

Topic 3c: Likelihood Ratio Test for Logistic Regression Models

Logistic Regression Models

Recall major developments of Binomial logistic regression from last topic 3b: $Y_i \sim \text{BIN}(m_i, \pi_i)$, $i = 1,\ldots,n$ independently, with covariate vector $\boldsymbol{x}_i$ and

$$\log\left(\frac{\pi_i}{1-\pi_i}\right) = \boldsymbol{x}_i^\top\boldsymbol{\beta}.$$

- Estimation: $\hat{\boldsymbol{\beta}}$ come from Fisher scoring using R function `glm()`.
- Interpretation: $\exp\{\beta_j\}$ has OR interpretation.
- Hypothesis tests of H_0: $\beta_j = 0$ using Wald statistic.
- Confidence Intervals: $\hat{\beta}_j \pm z_{1-\alpha/2}\,\text{se}(\hat{\beta}_j)$.

Likelihood for Logistic Regression Models

- Log-likelihood for Binomial Distribution:

$$\begin{aligned}\ell &= \log\left(\prod_{i=1}^n \pi_i^{y_i}(1-\pi_i)^{m_i-y_i}\right)\\ &= \sum_{i=1}^n y_i\log\left(\frac{\pi_i}{1-\pi_i}\right) + m_i\log(1-\pi_i).\end{aligned}$$

- Using logit link we can re-parameterize the log-likelihood in terms of $\boldsymbol{\beta}$:

$$\log\left(\frac{\pi_i}{1-\pi_i}\right) = \boldsymbol{x}_i^\top\boldsymbol{\beta}, \qquad \pi_i = \frac{\exp\{\boldsymbol{x}_i^\top\boldsymbol{\beta}\}}{1+\exp\{\boldsymbol{x}_i^\top\boldsymbol{\beta}\}}.$$

- Log likelihood for logistic regression:

$$\ell = \sum_{i=1}^{n} y_i \boldsymbol{x}_i^\top \boldsymbol{\beta} - m_i \log\big(1 + \exp\{\boldsymbol{x}_i^\top \boldsymbol{\beta}\}\big).$$

- Maximization of log-likelihood $\ell(\boldsymbol{\beta})$ gives MLE $\hat{\boldsymbol{\beta}}$, and
  - estimated probability of response:

$$\hat{\pi}_i = \mathrm{e}^{\boldsymbol{x}_i^\top \hat{\boldsymbol{\beta}}}/(1 + \mathrm{e}^{\boldsymbol{x}_i^\top \hat{\boldsymbol{\beta}}}) = \mathsf{expit}(\boldsymbol{x}_i^\top \hat{\boldsymbol{\beta}}),$$

  - estimated number of responses: $\hat{y}_i = m_i \hat{\pi}_i$.
- Questions:
  - How good is the model? How well do the estimated number of events $\hat{y}_i$ approximate the observed data y_i? (goodness of fit).
  - How much worse is the fit of a model when several of the covariates are excluded? (nested models):

$$H_0\text{: } \beta_k = \beta_{k+1} = 0 \text{ vs } H_A\text{: } \beta_k \neq 0 \text{ or } \beta_{k+1} \neq 0.$$

Likelihood Ratio Test (General Setting)

- Suppose $\ell(\boldsymbol{\theta})$ is the likelihood for a q-dimension parameter vector $\boldsymbol{\theta}$ and let
  - $\tilde{\boldsymbol{\theta}}$ be the q-dim MLE of $\boldsymbol{\theta}$ (unconstrained/saturated, $q = n$),
  - $\hat{\boldsymbol{\theta}}$ be the p-dim MLE of $\boldsymbol{\theta}$ (constrained/unsaturated, $p < q$).
- Hypotheses:
  - H_0: the constrained model is adequate (i.e., as good as the unconstrained).
  - H_A: constrained model is not adequate.
- Recall the Likelihood Ratio (LR) result:

$$\text{Under } H_0\text{:} \quad -2\log\left(\frac{L(\hat{\boldsymbol{\theta}})}{L(\tilde{\boldsymbol{\theta}})}\right) = -2\big[\ell(\hat{\boldsymbol{\theta}}) - \ell(\tilde{\boldsymbol{\theta}})\big] \sim \chi^2_{q-p}.$$

- Reject H_0 at θ if

$$p\text{-value} = \mathbb{P}(\chi^2_{q-p} > -2\big[\ell(\hat{\boldsymbol{\theta}}) - \ell(\tilde{\boldsymbol{\theta}})\big]) < \alpha.$$

Likelihood Ratio Test (Logistic Regression Model)

- Saturated (unconstrained) model MLEs:

$$\tilde{\pi}_i = \frac{y_i}{m_i},\ i = 1, \ldots, n.$$

  - Binomial MLE without imposing any constraint.
  - We will have $\tilde{y}_i = m_i \tilde{\pi}_i = y_i$, a perfect fit!
- Unsaturated (constrained) model MLEs:

$$\hat{\pi}_i = \mathsf{expit}(\boldsymbol{x}_i^\top \hat{\boldsymbol{\beta}}).$$

  - Regression models are a way of imposing constraints on the estimation of π_i through p-dim regression coefficients $\boldsymbol{\beta}$.

  - We will have fitted number of responses $\hat{y}_i = m_i\hat{\pi}_i = m_i \,\text{expit}(\boldsymbol{x}_i^\top \hat{\boldsymbol{\beta}})$.

- Hypotheses:
  - H_0: the p-dim model, e.g., $\text{logit}(\pi_i) = \boldsymbol{x}_i^\top \boldsymbol{\beta}$ is adequate.
  - H_A: the p-dim model, e.g., $\text{logit}(\pi_i) = \boldsymbol{x}_i^\top \boldsymbol{\beta}$ is not adequate *compared to the n-dim saturated model*.

- Likelihood Ratio Statistic (also referred to as the Deviance):

$$\begin{aligned} D &= -2\big[\ell(\hat{\boldsymbol{\pi}}) - \ell(\tilde{\boldsymbol{\pi}})\big] \\ &= -2\left(\sum_{i=1}^n \Big(y_i \log(\hat{\pi}_i) + (m_i - y_i)\log(1-\hat{\pi}_i)\Big) - \sum_{i=1}^n \Big(y_i \log(\tilde{\pi}_i) + (m_i - y_i)\log(1-\tilde{\pi}_i)\Big)\right) \\ &= -2\sum_{i=1}^n \left(y_i \log\left(\frac{y_i}{m_i\hat{\pi}_i}\right) + (m_i - y_i)\log\left(\frac{m_i - y_i}{m_i(1-\hat{\pi}_i)}\right)\right). \end{aligned}$$

- The LR/Deviance can also be written in a general form as:

$$D = 2\sum_{i=1}^n \sum_{j=1}^2 \left(O_{ij} \log\left(\frac{O_{ij}}{E_{ij}}\right)\right).$$

  - $O_{i1} = y_i$, $E_{i1} = m_i\hat{\pi}_i$ (observed and expected # of events).
  - $O_{i2} = m_i - y_i$, $E_{i2} = m_i(1-\hat{\pi}_i)$ (observed and expected # of non-events).

- We expect $D \sim \chi^2_{n-p}$ under H_0, and reject H_0 if $\mathbb{P}(\chi^2_{n-p} > D) < \alpha$.
  - Unfortunately, this is not a great approximation.
  - Approximation is much better for testing nested unsaturated models though.

Example: Prenatal Care Data

- Model 2: Main Effects Model,

$$\text{logit}(\pi_i) = \beta_0 + \beta_1 x_{i1} + \beta_2 x_{i2}.$$

  - H_0: Model 2 is adequate.
  - H_A: Model 2 is not adequate compared to the saturated model.

- In R, the `summary()` output D is reported as the Residual Deviance.

```
model2 = glm(resp ~ loc + clinic, family = binomial(link = logit),
  data = prenatal.dat)
summary(model2)
```

```
Call:
glm(formula = resp ~ loc + clinic, family = binomial(link = logit),
    data = prenatal.dat)

Deviance Residuals:
       1         2         3         4
-0.08521   0.25805   0.13909  -0.11719

Coefficients:
            Estimate Std. Error z value Pr(>|z|)
```

```
(Intercept)  -1.7410     0.1785  -9.755  < 2e-16 ***
loc          -0.1503     0.3302  -0.455  0.64894
clinic       -0.9863     0.3089  -3.193  0.00141 **
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

(Dispersion parameter for binomial family taken to be 1)

    Null deviance: 16.91763  on 3  degrees of freedom
Residual deviance:  0.10693  on 1  degrees of freedom
AIC: 23.262

Number of Fisher Scoring iterations: 3
```

  - Deviance: $D = 0.10693$.
  - p-value: $\mathbb{P}(\chi^2_{n-p} > D) = \mathbb{P}(\chi^2_1 > D) = 0.7436689 \gg 0.05$.

- Do not reject the null hypothesis that Model 2 is adequate.

Pearson Statistic

- The Pearson statistic is another statistic that can be used for assessing "overall" fit (or goodness of fit) of a Binomial model:

$$P = \sum_{i=1}^{n} \frac{(y_i - m_i\hat{\pi}_i)^2}{m_i\hat{\pi}_i(1-\hat{\pi}_i)}.$$

  - As with LR/Deviance statistic, $P \sim \chi^2_{n-p}$ under H_0: the model is adequate.
  - Note that P has the general form:

$$P = \sum_i \frac{(O_i - E_i)}{V_i}.$$

  - The χ^2 approximation is a bit better than for deviance statistic D.
  - Both are poor if the sample size (m_i) is small though.

Testing Nested Non-saturated Models

- The previous LR/Deviance test was for an unsaturated model vs a saturated model.
- Now consider two unsaturated models ($p < q < n$).

$$\text{logit}(\pi_i) = \beta_0 + \beta_1 x_{i1} + \cdots + \beta_{p-1} x_{ip-1} \quad (1)$$
$$\text{logit}(\pi_i) = \beta_0 + \beta_1 x_{i1} + \cdots + \beta_{p-1} x_{ip-1} + \cdots + \beta_{q-1} x_{iq-1} \quad (2)$$

- Model (1) is *nested* within Model (2).
- H_0: Model (1) fits the data as well as Model (2).
  - H_0: $\beta_p = \cdots = \beta_{q-1} = 0$.
- H_A: Model (1) is inadequate compared to Model (2).
  - H_A: at least one of $\beta_p, \ldots, \beta_{q-1} \neq 0$.

Model	Dimension	MLEs
(1) Reduced model	p	$\hat{\pi}_i$
(2) Full model	q	$\tilde{\pi}_i$
Saturated model	n	$\tilde{\tilde{\pi}}_i$

- LR/Deviance test of Model (1) vs Saturated Model:

$$D_0 = -2\big(\ell(\hat{\boldsymbol{\pi}}) - \ell(\tilde{\tilde{\boldsymbol{\pi}}})\big).$$

- LR/Deviance test of Model (2) vs Saturated Model:

$$D_{\text{A}} = -2\big(\ell(\tilde{\boldsymbol{\pi}}) - \ell(\tilde{\tilde{\boldsymbol{\pi}}})\big).$$

- Now, we wish to conduct LR test of Model (1) vs Model (2):

$$\Delta D = D_0 - D_{\text{A}} = -2\big(\ell(\hat{\boldsymbol{\pi}}) - \ell(\tilde{\boldsymbol{\pi}})\big).$$

- It can be shown that under H_0: Model (1) is as adequate as Model (2),

$$\Delta D \sim \chi^2_{q-p}.$$

  - This approximation is much better than when testing an unsaturated model vs the saturated model.
- If $p = \mathbb{P}(\chi^2_{q-p} > \Delta D) < \alpha$ then reject H_0.
  - Reduced model does not fit the data as well as Full model.
  - One or more of covariates $x_{ip}, \ldots, x_{iq-1}$ is important (i.e., associated with the response).

Example: Prenatal Care Data

- Summary of Deviance ("`residual deviance`") from R output:

Model	Covariates	Deviance	Parameters	$n-p$
1	`loc`	10.814378	2	2
2	`loc + clinic`	0.106928	3	1
3	`loc + clinic + loc*clinic`	0	4	0
4	`clinic`	0.314841	2	2

- Compare nested models:
  - Model 2: $\text{logit}(\pi_i) = \beta_0 + \beta_1 x_{i1} + \beta_2 x_{i2}$.
  - Model 4: $\text{logit}(\pi_i) = \beta_0 + \beta_2 x_{i2}$.
- Is level of care associated with fetal mortality after accounting for clinic?
  - H_0: Model 4 is as adequate as Model 2 (e.g., $\beta_1 = 0$).
  - H_A: Model 4 is inadequate compared to Model 2 (e.g., $\beta_1 \neq 0$).
- LR test for comparing Model 4 vs Model 2, or equivalently testing hypotheses:

$$H_0\text{: } \beta_1 = 0 \text{ vs } H_A\text{: } \beta_1 \neq 0.$$

  - We do not reject H_0 of no association between level and care and fetal mortality after controlling for Clinic.

```
model2 = glm(resp ~ loc + clinic, family = binomial, data = prenatal.dat)
model4 = glm(resp ~ clinic, family = binomial, data = prenatal.dat)
D = model4$deviance - model2$deviance
1 - pchisq(D, 2 - 1)
```

```
[1] 0.6484081
```

  - This implies that level of care is no longer important when clinic is included in the model.
  - It also implies that Model 4 is as adequate compared to Model 2.

- Finally, when testing a single parameter, e.g., H_0: $\beta_1 = 0$, LR/Deviance test result is consistent with the Wald test result provided in the R output:

```
model2 = glm(resp ~ loc + clinic, family = binomial, data = prenatal.dat)
summary(model2)
```

```

Call:
glm(formula = resp ~ loc + clinic, family = binomial, data = prenatal.dat)

Deviance Residuals:
       1         2         3         4
-0.08521   0.25805   0.13909  -0.11719

Coefficients:
            Estimate Std. Error z value Pr(>|z|)
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clinic       -0.9863     0.3089  -3.193  0.00141 **
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

(Dispersion parameter for binomial family taken to be 1)

    Null deviance: 16.91763  on 3  degrees of freedom
Residual deviance:  0.10693  on 1  degrees of freedom
AIC: 23.262

Number of Fisher Scoring iterations: 3
```

Summary of LR/Deviance Test for Logistic Regression

- For Binomial GLM with logit link the LR/Deviance test statistic is:

$$D = \sum_{i=1}^{n} 2\left(y_i \log\left(\frac{y_i}{m_i\hat{\pi}_i}\right) + (m_i - y_i)\log\left(\frac{m_i - y_i}{m_i(1-\hat{\pi}_i)}\right)\right).$$

- This is reported as the "`Residual Deviance`" in R `glm` summary output.
- Deviance statistic D can be used to:
  - Test adequacy/goodness of fit of a non-saturated logistic model:

$$D \overset{H_0}{\sim} \chi^2_{n-p}.$$

– Compare the fit of two nested-non saturated logistic models:

$$\Delta D = D_0 - D_A \overset{H_0}{\sim} \chi^2_{q-p}.$$

WEEK 5
3rd to 8th October

Topic 3d: Residuals for Binomial Data and Neuroblastoma Example

Recall: Residuals in Linear Regression Models

- Normal linear regression models (STAT 331),

$$y_i = \boldsymbol{x}_i^\top \boldsymbol{\beta} + \varepsilon_i, \qquad \varepsilon_i \overset{\text{iid}}{\sim} \mathcal{N}(0, \sigma^2).$$

- Fitted values:

$$\hat{y}_i = \boldsymbol{x}_i^\top \hat{\boldsymbol{\beta}}.$$

- Residuals:

$$r_i = y_i - \hat{y}_i.$$

- The overall fit of the model and validity of the model assumptions are assessed using various *residual plots*, e.g.,
  - Residuals r_i vs fitted value $\hat{y}_i$ plot (check normality and constant variance).
  - QQ plot of residuals r_i's (check normality).

Residuals for Binomial Data

- When fit a logistic regression model to Binomial data, we evaluate the adequacy of the model by using the LR deviance test statistic:

$$\begin{aligned} D &= \sum_{i=1}^{n} 2\left(y_i \log\left(\frac{y_i}{m_i \hat{\pi}_i}\right) + (m_i - y_i) \log\left(\frac{m_i - y_i}{m_i(1-\hat{\pi}_i)}\right)\right) \\ &= \sum_{i=1}^{n} d_i. \end{aligned}$$

- Deviance Residual:

$$r_i^D = \mathsf{sign}(y_i - m_i\hat{\pi}_i)\sqrt{|d_i|}.$$

- Under H_0: the model is adequate:

$$D = \sum_{i=1}^{n} d_i \overset{\text{approx}}{\sim} \chi^2_{n-p} \implies r_i^D \overset{\text{approx}}{\sim} \mathcal{N}(0,1).$$

- We can use the plots of deviance residuals to assess whether r_i^D's look independent observations from $\mathcal{N}(0,1)$.

Example: Prenatal Care Data

$$\mathsf{logit}(\pi_i) = \beta_0 + \beta_1 \texttt{clinic}_i$$

	Stage				
Age (months)	I	II	III	IV	V
0-11	11/12	15/16	2/4	5/18	18/19
12-23	3/4	3/7	5/8	0/25	1/3
24+	4/5	4/12	3/15	3/93	2/5

```r
model4 <- glm(resp ~ clinic, family = binomial(link = logit), data = prenatal.dat)
summary(model4)
```

```
Call:
glm(formula = resp ~ clinic, family = binomial(link = logit),
    data = prenatal.dat)

Deviance Residuals:
       1         2         3         4
-0.00432   0.01262   0.43671  -0.35206

Coefficients:
            Estimate Std. Error z value Pr(>|z|)
(Intercept)  -1.7560     0.1757  -9.996  < 2e-16 ***
clinic       -1.0624     0.2621  -4.053 5.06e-05 ***
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

(Dispersion parameter for binomial family taken to be 1)

    Null deviance: 16.91763  on 3  degrees of freedom
Residual deviance:  0.31484  on 2  degrees of freedom
AIC: 21.47

Number of Fisher Scoring iterations: 4
```

- Pearson Residual:

$$r_i^P = \frac{y_i - m_i\hat{\pi}_i}{\sqrt{m_i\hat{\pi}_i(1-\hat{\pi}_i)}} = \frac{O_i - E_i}{\sqrt{V_i}}.$$

- Under H_0: the model is adequate,

$$r_i^P \sim \mathcal{N}(0,1).$$

- Note: if $m_i\hat{\pi}_i < 5$ (or $m_i(1-\hat{\pi}_i) < 5$) for one or more cases, we should be concerned about the validity of the approximation (χ^2 or $\mathcal{N}(0,1)$) and hence our conclusions.

Prognosis for Children with Neuroblastoma

- A study is conducted to investigate the probability of *disease-free survival* (surviving 2 years free of disease) following the treatment for neuroblastoma.
- Associated risk factors include *age at diagnosis* and *stage of disease at diagnosis*.
  - Cell entries are of the form y/m with y representing the number of patients surviving 2 years, and m representing the number of patients in that age-stage combination at the start of the study.

	Stage					
Age (months)	I	II	III	IV	V	Total
0-11	11/12	15/16	2/4	5/18	18/19	51/69
12-23	3/4	3/7	5/8	0/25	1/3	12/47
24+	4/5	4/12	3/15	3/93	2/5	16/130
Total	18/21	22/35	10/27	8/136	21/27	79/246

- As an initial look at the data, consider the marginal distributions.
  - Higher chance of survival at younger age at diagnosis.
  - Higher chance of survival with lower stage of disease at diagnosis.

Setup Regression Models for Neuroblastoma Data

- Response Variable:
  - Y_i is the number of 2-yr disease-free survivors out of m_i total children in group i, assume $Y_i \sim \text{BIN}(m_i, \pi_i)$, $i = 1, \ldots, 15$, and

$$\pi_i = \mathbb{P}(\text{2-yr disease-free survival in group } i).$$

- Explanatory Variables:
  - Age (0-11, 12-23, 24+ months); age 0-11 month is the baseline/reference,

$$x_{i1} = \begin{cases} 1 & \text{if age 12-23 months} \\ 0 & \text{o.w.} \end{cases} \qquad x_{i2} = \begin{cases} 1 & \text{if age 24+ months} \\ 0 & \text{o.w.} \end{cases}$$

  - Stage (I, II, III, IV, V); stage 1 is the baseline/reference,

$$x_{i3} = \begin{cases} 1 & \text{stage II} \\ 0 & \text{o.w.} \end{cases} \qquad x_{i4} = \begin{cases} 1 & \text{if stage III} \\ 0 & \text{o.w.} \end{cases}$$
$$x_{i5} = \begin{cases} 1 & \text{if stage IV} \\ 0 & \text{o.w.} \end{cases} \qquad x_{i6} = \begin{cases} 1 & \text{if stage V} \\ 0 & \text{o.w.} \end{cases}$$

- Consider the following logistic regression models:
  - Model 1: Age & Stage

$$\text{logit}(\pi_i) = \beta_0 + \underbrace{\beta_1 x_{i1} + \beta_2 x_{i2}}_{\text{Age}} + \underbrace{\beta_3 x_{i3} + \beta_4 x_{i4} + \beta_5 x_{i5} + \beta_6 x_{i6}}_{\text{Stage}}.$$

  - Model 2: Age only

$$\text{logit}(\pi_i) = \beta_0 + \beta_1 x_{i1} + \beta_2 x_{i2}.$$

  - Model 3: Stage only

$$\text{logit}(\pi_i) = \beta_0 + \beta_3 x_{i3} + \beta_4 x_{i4} + \beta_5 x_{i5} + \beta_6 x_{i6}.$$

Fitting Logistic Regression Models Using R

```r
neuro.dat = read.table("neuro.dat", header = T)
neuro.dat
```

```
   age stage  y  m
1    1     1 11 12
2    1     2 15 16
3    1     3  2  4
4    1     4  5 18
5    1     5 18 19
6    2     1  3  4
7    2     2  3  7
8    2     3  5  8
9    2     4  0 25
10   2     5  1  3
11   3     1  4  5
12   3     2  4 12
13   3     3  3 15
14   3     4  3 93
15   3     5  2  5
```

```r
# here we construct the response variable for logistic
# regression
neuro.dat$resp = cbind(neuro.dat$y, neuro.dat$m - neuro.dat$y)
neuro.dat
```

```
   age stage  y  m resp.1 resp.2
1    1     1 11 12     11      1
2    1     2 15 16     15      1
3    1     3  2  4      2      2
4    1     4  5 18      5     13
5    1     5 18 19     18      1
6    2     1  3  4      3      1
7    2     2  3  7      3      4
8    2     3  5  8      5      3
9    2     4  0 25      0     25
10   2     5  1  3      1      2
11   3     1  4  5      4      1
12   3     2  4 12      4      8
13   3     3  3 15      3     12
14   3     4  3 93      3     90
15   3     5  2  5      2      3
```

Summary of Model 1: Age & Stage

$$\text{logit}(\pi_i) = \beta_0 + \underbrace{\beta_1 x_{i1} + \beta_2 x_{i2}}_{\text{Age}} + \underbrace{\beta_3 x_{i3} + \beta_4 x_{i4} + \beta_5 x_{i5} + \beta_6 x_{i6}}_{\text{Stage}}.$$

```
Call:
glm(formula = resp ~ factor(age) + factor(stage), family = binomial(link = logit),
    data = neuro.dat)

Deviance Residuals:
```

```
     Min        1Q    Median        3Q       Max
-1.47408  -0.61913  -0.09643   0.53163   1.52114

Coefficients:
              Estimate Std. Error z value Pr(>|z|)
(Intercept)      3.3175     0.7721   4.297 1.73e-05 ***
factor(age)2    -2.1181     0.5736  -3.693 0.000222 ***
factor(age)3    -2.6130     0.5017  -5.208 1.91e-07 ***
factor(stage)2  -1.2529     0.7837  -1.599 0.109860
factor(stage)3  -1.7759     0.8003  -2.219 0.026478 *
factor(stage)4  -4.3678     0.7902  -5.528 3.25e-08 ***
factor(stage)5  -1.0222     0.8644  -1.183 0.236980
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

(Dispersion parameter for binomial family taken to be 1)

    Null deviance: 162.832  on 14  degrees of freedom
Residual deviance:   9.625  on  8  degrees of freedom
AIC: 55.382

Number of Fisher Scoring iterations: 4
```

- Before interpreting these results too much, we should look to see how good the fit is to the data.

```
y = neuro.dat$y
m = neuro.dat$m
fv1 = model1$fitted.values
yhat = m * fv1
rd1 = residuals.glm(model1, "deviance")
rp1 = (y - m * fv1)/sqrt(m * fv1 * (1 - fv1))
cbind(rd1, rp1, yhat, y)

           rd1         rp1      yhat  y
1  -0.77808711 -0.91184050 11.580304 11
2   0.68559153  0.63381666 14.198641 15
3  -1.47407847 -1.69888561  3.294804  2
4   0.17884403  0.18019371  4.665014  5
5   0.63431439  0.58779486 17.261237 18
6  -0.08658336 -0.08736144  3.073705  3
7  -0.30801258 -0.30734393  3.406432  3
8   1.52114028  1.56325351  2.877982  5
9  -1.43545385 -1.02556686  1.009324  0
10 -0.73520283 -0.73328264  1.632557  1
11  0.64949774  0.62163765  3.345991  4
12 -0.23825133 -0.23663531  4.394927  4
13 -0.50305728 -0.48993834  3.827214  3
14  0.42894854  0.44782015  2.325662  3
15 -0.09643089 -0.09619454  2.106206  2
```

- Residuals are a random scatter around 0 and $\in (-2, 2)$ therefore r_i^D (or r_i^P) $\sim \mathcal{N}(0, 1)$. Therefore, model 1 is adequate.

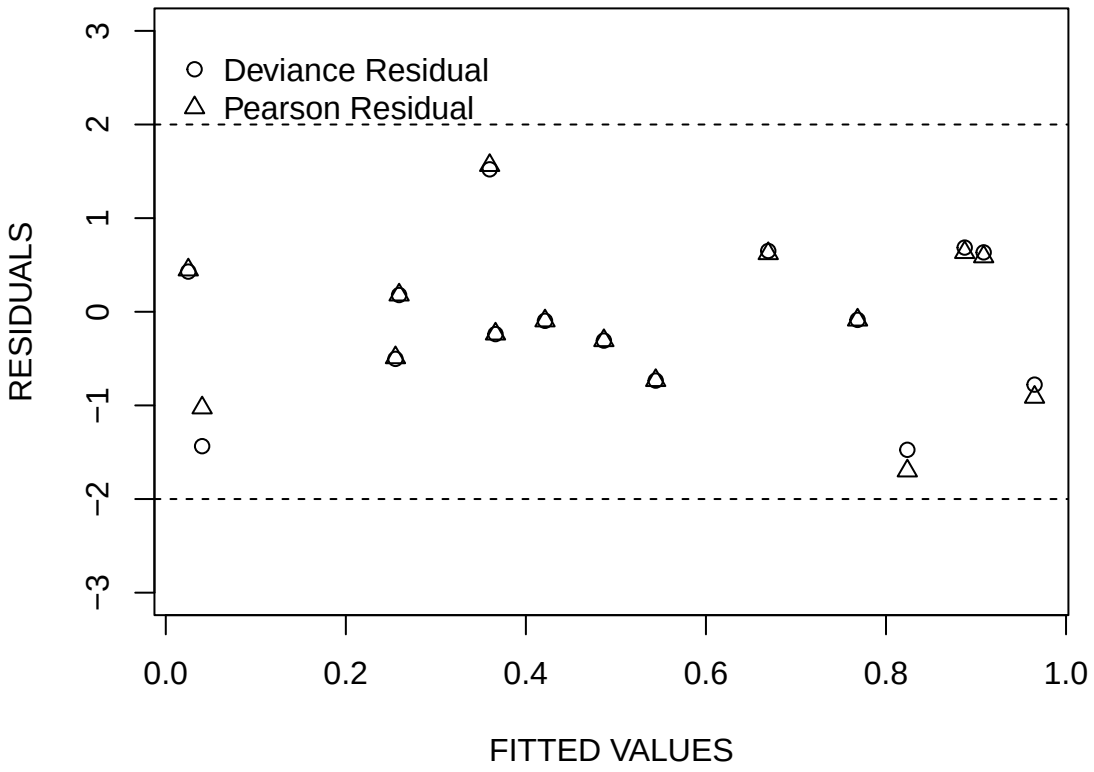


Figure 1: Plot of Residuals by Fitted Values for Neuroblastoma Data based on Logistic Regression Model with main effects of Age and Stage.

- We can test H_0: model 1 is adequate using LR/D statistic p-value $= \mathbb{P}(\chi^2_8 > 9.625) < 0.05$, do not reject H_0.

Summary of Model 2: Age only

- Now we consider simplifying the model further by examining the decrease in the quality of the fit that results from dropping the stage variable(s).

$$\text{logit}(\pi_i) = \beta_0 + \beta_1 x_{i1} + \beta_2 x_{i2}.$$

```
model2 = glm(resp ~ factor(age), family = binomial(link = logit),
  data = neuro.dat)
summary(model2)
```

```

Call:
glm(formula = resp ~ factor(age), family = binomial(link = logit),
    data = neuro.dat)

Deviance Residuals:
    Min       1Q   Median       3Q      Max
-4.0853  -0.3591   1.5613   2.0684   3.4667

Coefficients:
             Estimate Std. Error z value Pr(>|z|)
(Intercept)    1.0415     0.2742   3.799 0.000145 ***
factor(age)2  -2.1119     0.4325  -4.883 1.05e-06 ***
factor(age)3  -3.0051     0.3827  -7.853 4.06e-15 ***
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

(Dispersion parameter for binomial family taken to be 1)

    Null deviance: 162.832  on 14  degrees of freedom
Residual deviance:  83.583  on 12  degrees of freedom
AIC: 121.34

Number of Fisher Scoring iterations: 5
```

Summary of Model 3: Stage only

- Now we fit the model excluding the age variable to examine the drop in the quality of fit from model 1.

$$\text{logit}(\pi_i) = \beta_0 + \beta_3 x_{i3} + \beta_4 x_{i4} + \beta_5 x_{i5} + \beta_6 x_{i6}.$$

```
model2 = glm(resp ~ factor(stage), family = binomial(link = logit),
  data = neuro.dat)
summary(model3)
```

```
Call:
glm(formula = resp ~ loc + clinic + loc * clinic, family = binomial(link = logit),
    data = prenatal.dat)

Deviance Residuals:
[1]  0  0  0  0

Coefficients:
             Estimate Std. Error z value Pr(>|z|)
(Intercept) -1.756843   0.185709  -9.460  < 2e-16 ***
loc          0.007643   0.572683   0.013  0.98935
clinic      -0.928734   0.351430  -2.643  0.00822 **
loc:clinic  -0.229650   0.694905  -0.330  0.74104
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

(Dispersion parameter for binomial family taken to be 1)

    Null deviance:  1.6918e+01  on 3  degrees of freedom
Residual deviance: -4.3521e-14  on 0  degrees of freedom
AIC: 25.155

Number of Fisher Scoring iterations: 3
```

Testing Nested Models

- Now we can compare nested models using LR/Deviance Tests:

Model	Covariates	Deviance (D)	Parameters (p)	DF ($n-p$)
M1	Age & Stage	9.625	7	8
M2	Age	83.583	3	12
M3	Stage	42.446	5	10

- Recall:

$$\Delta D = D_0 - D_{\text{A}} = -2\big(\ell(\hat{\boldsymbol{\pi}}) - \ell(\tilde{\boldsymbol{\pi}})\big) \sim \chi^2_{q-p}$$

  - D_0 and D_{A} are deviances from the reduced and full models respectively.
  - $\hat{\boldsymbol{\pi}}$ and $\tilde{\boldsymbol{\pi}}$ represents the MLEs from the reduced and full models respectively.

Objective: Pick the model that best represents the important associations between the outcome and explanatory variables.

1. Is Stage important?

H_0: $\beta_3 = \cdots = 0$ (Model 2 is as adequate as Model 1)
H_A: at least one of them is not 0 (Model 2 is not adequate)

$$\Delta D = D_2 - D_1 = 83.583 - 9.625 = 73.958$$
$$p = \mathbb{P}(\chi^2_{7-3} > 73.958) < 0.001$$

```
1 - pchisq(83.583 - 9.625, 7 - 3)

[1] 3.330669e-15
```

We reject H_0 and conclude that there is evidence that Stage is important.

2. Is Age important?

H_0: $\beta_1 = \beta_2 = 0$ (Model 3 is as adequate as Model 1)
H_A: at least one of them is not 0 (Model 3 is not adequate)

$$\Delta D = D_3 - D_1 = 42.446 - 9.625 = 32.821$$
$$p = \mathbb{P}(\chi^2_{7-5} > 32.821) < 0.001$$

```
1 - pchisq(42.446 - 9.625, 7 - 5)

[1] 7.464666e-08
```

We reject H_0 and conclude that there is evidence that Age is important.

3. Do we need an Age$*$Stage interaction?

```
1 - pchisq(model1$deviance, model1$df.residual)

[1] 0.292341
```

- Model with age, stage, and age$*$stage is the saturated model!
- Do not reject H_0: model 1 is as adequate as the saturated model (interaction model).
- Do not need to consider age$*$stage.

Interpret the Selected Model

So we select Model 1 for interpretation.

```
model1 = glm(resp ~ factor(age) + factor(stage), family = binomial(link = logit),
  data = neuro.dat)
summary(model1)


Call:
glm(formula = resp ~ factor(age) + factor(stage), family = binomial(link = logit),
    data = neuro.dat)

Deviance Residuals:
     Min        1Q    Median        3Q       Max
-1.47408  -0.61913  -0.09643   0.53163   1.52114

Coefficients:
              Estimate Std. Error z value Pr(>|z|)
(Intercept)      3.3175     0.7721   4.297 1.73e-05 ***
```

```
factor(age)2    -2.1181     0.5736  -3.693 0.000222 ***
factor(age)3    -2.6130     0.5017  -5.208 1.91e-07 ***
factor(stage)2  -1.2529     0.7837  -1.599 0.109860
factor(stage)3  -1.7759     0.8003  -2.219 0.026478 *
factor(stage)4  -4.3678     0.7902  -5.528 3.25e-08 ***
factor(stage)5  -1.0222     0.8644  -1.183 0.236980
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

(Dispersion parameter for binomial family taken to be 1)

    Null deviance: 162.832  on 14  degrees of freedom
Residual deviance:   9.625  on  8  degrees of freedom
AIC: 55.382

Number of Fisher Scoring iterations: 4
```

Q1: What is the odds ratio of 2 yr disease-free survival for a child aged 24+ months versus aged $<$ 12 months?

Age	Stage	$\boldsymbol{x}_i^\top$	$\log(\pi_i/(1-\pi_i))$
0-11	—	$(1,0,0,x_{i3},x_{i4},x_{i5},x_{i6})^\top$	$\beta_0+\beta_3x_{i3}+\beta_4x_{i4}+\beta_5x_{i5}+\beta_6x_{i6}$
24+	—	$(1,0,1,x_{i3},x_{i4},x_{i5},x_{i6})^\top$	$\beta_0+\beta_2+\beta_3x_{i3}+\beta_4x_{i4}+\beta_5x_{i5}+\beta_6x_{i6}$

- The odds ratio is therefore $\psi=\exp\{\beta_2\}$, its MLE is:

$$\hat{\psi}=\exp\{\hat{\beta}_2\}=\exp\{-2.614\}=0.0733.$$

- The 95 % CI for this odds ratio is:

$$\exp\{\hat{\beta}_2\pm 1.96\,\mathrm{se}(\hat{\beta}_2)\}=\exp\{-2.613\pm 1.96\times 0.5017\}=(0.0274,0.1960).$$

- *When controlling for stage at the diagnosis, the odds of 2-yr DFS for children aged 24+ months is only about 7 % [95 % CI: (0.0274,0.1960)] of that for those aged less than 12 months.*

Q2: What is the odds ratio of 2 yr disease-free survival for a child with stage V versus stage II cancer?

Age	Stage	$\boldsymbol{x}_i^\top$	$\log(\pi_i/(1-\pi_i))$
—	V	$(1,x_{i1},x_{i2},0,0,0,1)^\top$	$\beta_0+\beta_1x_{i1}+\beta_2x_{i2}+\beta_6$
—	II	$(1,x_{i1},x_{i2},1,0,0,0)^\top$	$\beta_0+\beta_1x_{i1}+\beta_2x_{i2}+\beta_3$

- The odds ratio is therefore $\psi=\exp\{\beta_6-\beta_3\}$, its MLE is:

$$\hat{\psi}=\exp\{\hat{\beta}_6-\hat{\beta}_3\}=\exp\{-1.022+1.253\}=1.26.$$

- *When controlling for age at the diagnosis, the odds of a 2-yr DFS for those diagnosed in stage V is 1.26 times of that for those diagnosed in stage II.*

Q3: What is the 95 % CI for OR $\psi=\exp\{\beta_6-\beta_3\}$?

1. Finding the 95 % CI for $\eta=\beta_6-\beta_3=\boldsymbol{c}^\top\boldsymbol{\beta}$, where

$$\boldsymbol{c}^\top=\begin{bmatrix}0&0&0&-1&0&0&1\end{bmatrix},\qquad \boldsymbol{\beta}=\begin{bmatrix}\beta_0\\ \beta_1\\ \vdots\\ \beta_6\end{bmatrix}.$$

Standard error for $\hat{\eta} = \hat{\beta}_6 - \hat{\beta}_3 = \boldsymbol{c}^\top \hat{\boldsymbol{\beta}}$:

$$\widehat{\mathsf{Var}}(\hat{\boldsymbol{\beta}}) = \boldsymbol{I}^{-1}(\hat{\boldsymbol{\beta}})$$
$$\mathsf{se}(\boldsymbol{c}^\top \boldsymbol{\beta}) = \sqrt{\boldsymbol{c}\boldsymbol{I}^{-1}(\hat{\boldsymbol{\beta}})\boldsymbol{c}^\top}.$$

```
C = c(0, 0, 0, -1, 0, 0, 1)
se = sqrt(C %*% vcov(model1) %*% C)
se

          [,1]
[1,] 0.6729361
```

The $95\,\%$ CI for $\eta = \beta_6 - \beta_3$ is:

$$\hat{\eta} \pm 1.96\,\mathsf{se}(\hat{\eta}) = (-1.0222 + 1.2529) \pm 1.96 \times 0.6729 = (-1.0882, 1.5496).$$

2. Exponentiate it to obtain the $95\,\%$ CI for $\psi = \exp\{\eta\} = \exp\{\beta_6 - \beta_3\}$:

$$\exp\{\hat{\eta} \pm 1.96\,\mathsf{se}(\hat{\eta})\} = (0.3368, 4.7098).$$

Topic 3e: Dose-Response Models

Bioassay Experiments

- Bioassay experiment: Several groups of subjects are exposed to varying levels of a drug/toxin to determine how many responses within a fixed period of time.
- Stimulus: Each group is subjected to a particular dose of the drug/toxin:

$$\text{dose} = \log(\text{concentration})$$

- Response: As a result of the stimulus, subjects will often manifest a binary response indicating the occurrence of an adverse event (e.g., death).
- Tolerance: We assume that for each subject there is a certain dose level above which the response will always occur.
  - This level is called the tolerance or threshold.
  - The tolerance varies from one individual to another in the population and therefore from subject to subject in the sample.
  - We can therefore ascribe a distribution to it.

The Tolerance Distribution

- $z =$ concentration of the stimulus (toxin/drug).
- $x = \log(z) =$ dose/intensity of the stimulus.
- $f(x) =$ pdf for the distribution of the tolerance in the population (*i.e., the distribution for the stimulus/dose at which response occurs*).
- Suppose a dose of x_0 were applied to the population. What proportion would respond?

$$\pi_0 = \int_{-\infty}^{x_0} f(s)\,\mathrm{d}s = F(x_0)$$

- If $x_0 < x_1$, then $\pi_0 < \pi_1$.

Modelling the Dose-Response Relationship

For each group $i = 1, \ldots, n$ let:

- $x_i =$ dose applied to subjects in group i,
- $m_i =$ number of subjects in group i,
- $y_i =$ the number of subjects with response in group i.

Dose x_i	Responders y_i	Total m_i	y_i/m_i
1.6907	6	59	0.10
1.7242	13	60	0.22
1.7552	18	62	0.29
⋮	⋮	⋮	⋮

- Assume

$$Y_i \sim \text{BIN}(m_i, \pi_i), \ i = 1, \ldots, n,$$

$$\pi_i = \text{probability of response in group } i \text{ with dose } x_i.$$

- Objective: To model probability of response π_i as a function of dose x_i.
- Binomial Regression Models:

$$g(\pi) = \beta_0 + \beta_1 x_i,$$

where $g(\,\cdot\,)$ is a choice of link function.

- Then we have:

$$\pi_i = g^{-1}(\beta_0 + \beta_1 x_i),$$

that is, the probability of response as a function of dose x_i via $g^{-1}(\,\cdot\,)$.

- Question: What link function should we select?
- Realize that:
  - If we assume a tolerance distribution $f(x)$, the probability of response to dose x_i is:

$$\pi_i = \int_{-\infty}^{x_i} f(x)\,\mathrm{d}x = F(x_i).$$

  - With a Binomial regression model and a link function $g(\,\cdot\,)$, we have:

$$\pi_i = g^{-1}(\beta_0 + \beta_1 x_i).$$

- These suggest that the choice of the tolerance distribution determines the form of the link function, i.e., selecting $g(\,\cdot\,)$ such that $g^{-1}(\,\cdot\,)$ is a cdf:

$$\pi_i = g^{-1}(\beta_0 + \beta_1 x_i) = F^{\star}(\beta_0 + \beta_1 x_i).$$

Some Choices for the Tolerance Distribution

(1) Normal Tolerance Distribution:

$$\begin{aligned}\pi(x) &= \int_{-\infty}^{x} f(s)\,\mathrm{d}s \\ &= \int_{-\infty}^{x} \frac{1}{\sqrt{2\pi\sigma^2}} \exp\left\{-\frac{1}{2}\left(\frac{s-\mu}{\sigma}\right)^2\right\}\mathrm{d}s \\ &= \Phi\left(\frac{x-\mu}{\sigma}\right)\end{aligned}$$

where Φ is the $\mathcal{N}(0,1)$ cdf. This implies that

$$\Phi^{-1}(\pi) = \frac{x-\mu}{\sigma},$$

i.e., the Probit link s.t.,

$$g(\pi) = \Phi^{-1}(\pi) = -\frac{\mu}{\sigma} + \frac{1}{\sigma}x = \beta_0 + \beta_1 x.$$

A Binomial Probit Model:

$$\Phi^{-1}(\pi) = \beta_0 + \beta_1 x.$$

How do we interpret β_0 and β_1?

- They are no longer log odds ratios (as with logistic link)
- Interpretation is in terms of μ and σ the parameters of the Normal distribution for tolerance, i.e.,

$$\beta_0 = -\frac{\mu}{\sigma}, \qquad \beta_1 = \frac{1}{\sigma}.$$

(2) Logistic Distribution:

$$f(x;\mu,s) = \frac{\exp\left\{-\frac{x-\mu}{s}\right\}}{s\left[1+\exp\left\{-\frac{x-\mu}{s}\right\}\right]^2},\ s>0,\ \mathbb{E}[X]=\mu.$$

The probability of response:

$$\begin{aligned}\pi(x) &= \int_{-\infty}^{x} f(x;\mu,s)\,\mathrm{d}s = \left[1+\exp\left\{-\frac{x-\mu}{s}\right\}\right]^{-1} \\ 1-\pi(x) &= \frac{\exp\left\{-\frac{x-\mu}{s}\right\}}{1+\exp\left\{-\frac{x-\mu}{s}\right\}} \\ \log\left(\frac{\pi(x)}{1-\pi(x)}\right) &= \frac{x-\mu}{s}.\end{aligned}$$

This implies the Logit link s.t.,

$$g(\pi) = \mathrm{logit}(\pi) = -\frac{\mu}{s} + \frac{1}{s}x = \beta_0 + \beta_1 x.$$

(3) Extreme Value Distribution:

$$f(x;\mu,s) = \frac{1}{s}\exp\left\{\frac{x-\mu}{s} - \exp\left\{\frac{x-\mu}{s}\right\}\right\},\ s>0.$$

The probability of response:

$$\begin{aligned}\pi(x) &= \int_{-\infty}^{x} f(x;\mu,s)\,\mathrm{d}s \\ &= 1-\exp\Big\{-\exp\Big\{-\frac{x-\mu}{s}\Big\}\Big\} \\ \log\Big(-\log\big(1-\pi(x)\big)\Big) &= \frac{x-\mu}{s}.\end{aligned}$$

This implies the Complementary log-log link s.t.,

$$g(\pi) = \log\big(-\log(1-\pi)\big) = -\frac{\mu}{s} + \frac{1}{s}x = \beta_0 + \beta_1 x.$$

Tolerance Distribution	Link Function	Dose-Response Model
Normal	Probit	$\Phi^{-1}(\pi) = \beta_0 + \beta_1 x$
Logistic	Logit	$\text{logit}(\pi) = \beta_0 + \beta_1 x$
Extreme Value	Complementary log-log	$\log\big(-\log(1-\pi)\big) = \beta_0 + \beta_1 x$

Median Lethal/Effective Dose

- The median lethal/effective dose (ED50) is the dose at which $50\,\%$ of the population has the response.
- That is, if we let δ be the ED50, then by definition:

$$\pi(\delta) = \int_{-\infty}^{\delta} f(x)\,\mathrm{d}x = 0.50.$$

- How do we find the expression of δ given a Dose-Response model? Suppose we fit a Binomial Probit model (i.e., Normal tolerance distribution):

$$\Phi^{-1}(\pi) = \beta_0 + \beta_1 x.$$

Note that at dose δ (ED50), $\pi = 0.50$.

$$\begin{aligned}\Phi^{-1}(0.50) &= \beta_0 + \beta_1\delta \\ 0 &= \beta_0 + \beta_1\delta \\ \delta &= -\frac{\beta_0}{\beta_1}\end{aligned}$$

A Dose-Response Example — Beetle Mortality

Beetle Mortality

Consider an experiment by Bliss (Annals of Applied Biology, 1935) in which groups of beetles were exposed to varying concentrations of carbon disulphide (CS_2) gas.

Dose (x_i)	# of insects killed (x_i)	# of insects m_i	y_j/m_i
1.6907	6	59	0.10
1.7242	13	60	0.22
1.7552	18	62	0.29
1.7842	28	56	0.50
1.8113	52	63	0.83
1.8369	53	59	0.89
1.8610	61	62	0.98
1.8839	60	60	1.00

- Objective: modelling the dose-response relationship.
- We will fit several binomial regression models to this data:

$$g(\pi_i) = \beta_0 + \beta_1 x_i,$$

  where $x_i =$ dose in group i, $i = 1, \ldots, 8$.
- Various link functions will be used to find the best fitted model:
  - `Logistic` link.
  - `Probit` link.
  - `Cloglog` link.

Dose-Response Analysis using R

```r
# read beetle data
beetle.dat = read.table("beetle.dat", header = T)
# here we construct the response variable for Binomial
# regression
beetle.dat$resp <- cbind(beetle.dat$y, beetle.dat$m - beetle.dat$y)
beetle.dat
```

```
    dose  y  m resp.1 resp.2
1 1.6907  6 59      6     53
2 1.7242 13 60     13     47
3 1.7552 18 62     18     44
4 1.7842 28 56     28     28
5 1.8113 52 63     52     11
6 1.8369 53 59     53      6
7 1.8610 61 62     61      1
8 1.8839 60 60     60      0
```

Fit of the Logistic Model

```r
model1 = glm(resp ~ dose, family = binomial(link = logit), data = beetle.dat)
summary(model1)
```

```
Call:
glm(formula = resp ~ dose, family = binomial(link = logit), data = beetle.dat)

Deviance Residuals:
    Min       1Q   Median       3Q      Max
-1.5941  -0.3944   0.8329   1.2592   1.5940

Coefficients:
            Estimate Std. Error z value Pr(>|z|)
(Intercept)  -60.717      5.181  -11.72   <2e-16 ***
dose          34.270      2.912   11.77   <2e-16 ***
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

(Dispersion parameter for binomial family taken to be 1)

    Null deviance: 284.202  on 7  degrees of freedom
Residual deviance:  11.232  on 6  degrees of freedom
AIC: 41.43

Number of Fisher Scoring iterations: 4
```

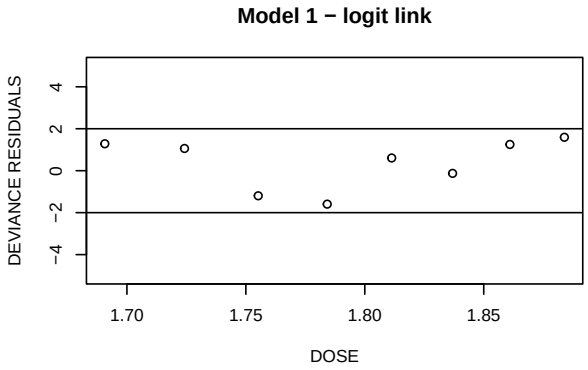
Fit of the Probit Model

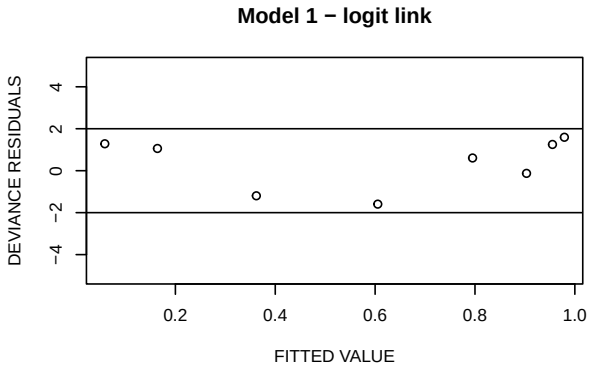
```
model2 = glm(resp ~ dose, family = binomial(link = probit), data = beetle.dat)
summary(model2)


Call:
glm(formula = resp ~ dose, family = binomial(link = probit),
    data = beetle.dat)

Deviance Residuals:
    Min       1Q   Median       3Q      Max
-1.5714  -0.4703   0.7501   1.0632   1.3449

Coefficients:
            Estimate Std. Error z value Pr(>|z|)
(Intercept)  -34.935      2.648  -13.19   <2e-16 ***
dose          19.728      1.487   13.27   <2e-16 ***
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

(Dispersion parameter for binomial family taken to be 1)

    Null deviance: 284.20  on 7  degrees of freedom
Residual deviance:  10.12  on 6  degrees of freedom
AIC: 40.318

Number of Fisher Scoring iterations: 4
```

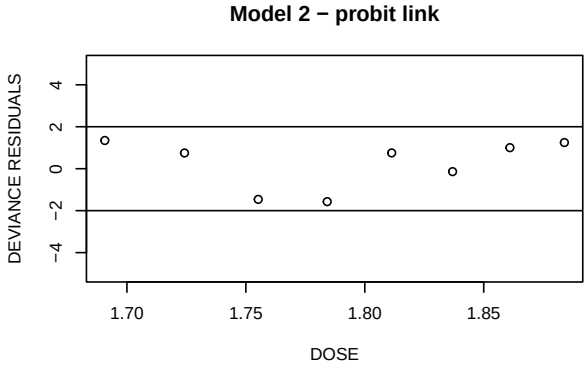
Fit of the Complementary Log-log Model

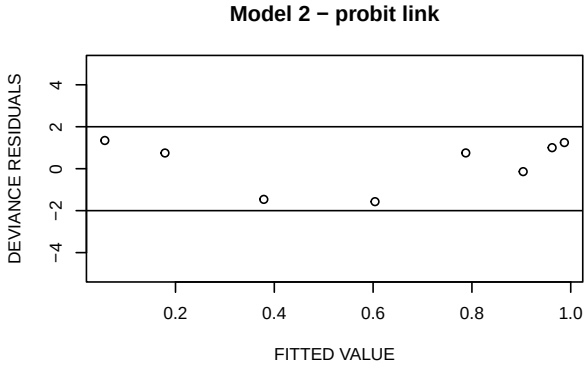
```
model3 = glm(resp ~ dose, family = binomial(link = cloglog), data = beetle.dat)
summary(model3)


Call:
glm(formula = resp ~ dose, family = binomial(link = cloglog),
    data = beetle.dat)

Deviance Residuals:
     Min        1Q    Median        3Q       Max
-0.80329  -0.55135   0.03089   0.38315   1.28883

Coefficients:
            Estimate Std. Error z value Pr(>|z|)
(Intercept)  -39.572      3.240  -12.21   <2e-16 ***
dose          22.041      1.799   12.25   <2e-16 ***
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

(Dispersion parameter for binomial family taken to be 1)

    Null deviance: 284.2024  on 7  degrees of freedom
Residual deviance:   3.4464  on 6  degrees of freedom
AIC: 33.644

Number of Fisher Scoring iterations: 4
```

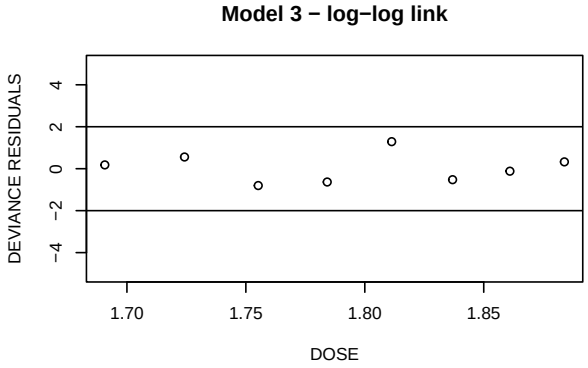
Deviance Residual Plots

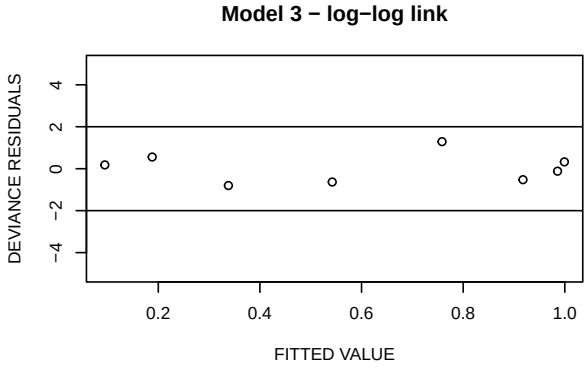










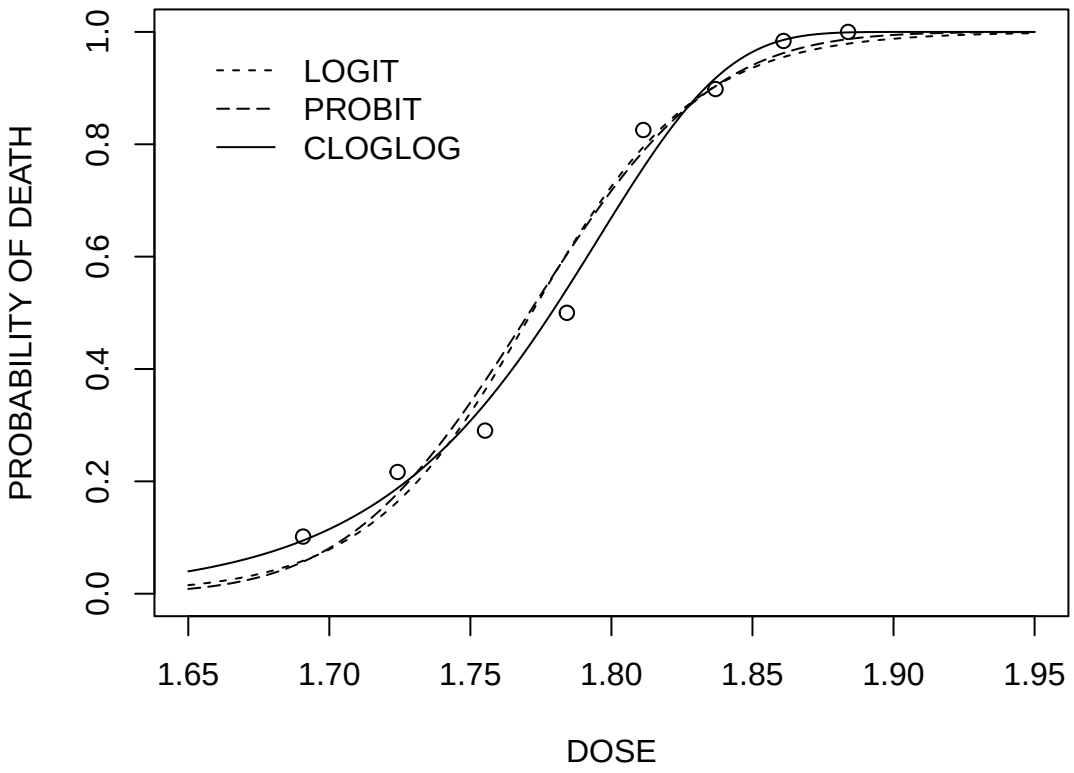


Choice of Tolerance Distribution or Binomial Model

- Observed probability of response:
$$\tilde{\pi}_i = \frac{y_i}{m_i}.$$
- Fitted probability of response:
$$\hat{\pi}_i = g^{-1}(\hat{\beta}_0 + \hat{\beta}_1 x_i).$$
- The tolerance distribution (or the Binomial model) that provides the "best" agreement between the observed and fitted probability of response is the one that fits the data the "best."
- We can check this by plotting the observed and fitted probability of response $\tilde{\pi}_i$ and $\hat{\pi}_i$, against dose x_i.

Fitted Dose-Response Curves

```
# Plot the dose-response curves
plot(beetle.dat$dose, beetle.dat$y/beetle.dat$m, xlim = c(1.65, 1.95),
  ylim = c(0, 1), xlab = "DOSE", ylab = "PROBABILITY OF DEATH")
x = seq(1.65, 1.95, by = 0.001)
prob = as.vector(rep(1, length(x)))
beta = as.vector(model1$coefficients)  # logistic model
for (i in 1:length(x)) {
  prob[i] = exp(beta[1] + beta[2] * x[i])/(1 + exp(beta[1] + beta[2] *
    x[i]))
}
lines(x, prob, lty = 2)
beta = as.vector(model2$coefficients)  # probit model
for (i in 1:length(x)) {
  prob[i] = pnorm(beta[1] + beta[2] * x[i])
}
lines(x, prob, lty = 5)
beta = as.vector(model3$coefficients)  # cloglog model
for (i in 1:length(x)) {
  prob[i] = 1 - exp(-exp(beta[1] + beta[2] * x[i]))
}
lines(x, prob, lty = 1)
legend(1.65, 1, c("LOGIT", "PROBIT", "CLOGLOG"), lty = c(2, 5, 1),
  bty = "n")
```



- Note that the curve for the complementary log-log link fits the data better than the other two, as expect from the residual plots and the deviance statistics.
- (The R code for generating above plot see course notes, 2.10.3, page 47).

Interpretation of Dose-Response Models

- Interpretation of regression parameter β_1 will depend on the link function.
  - Logistic model: $\text{logit}(\pi) = \beta_0 + \beta_1 x$.
    - $\beta_1 =$ log odds ratio for response associated with a one unit increase in dose.
  - Probit model: $\Phi^{-1}(\pi) = \beta_0 + \beta_1 x$, or Complementary log-log model $\log\big(-\log(1-\pi)\big) = \beta_0 + \beta_1 x$, interpretation of β parameters is not as natural as in logistic models.
- Estimation of δ (ED50) from a Binomial model $g(\pi) = \beta_0 + \beta_1 x$:

$$g(\pi = 0.5) = \beta_0 + \beta_1 \delta \implies \hat{\delta} = \frac{g(0.5) - \hat{\beta}_0}{\hat{\beta}_1}.$$

- Exercise: What is $\delta_{0.25}$, the dose at which $25\,\%$ of the population has the response?

WEEK 6
11th to 15th October

Reading week.

WEEK 7
18th to 22nd October

Topic 3f: Summary of Binomial Regression Models

Binomial GLM Specification

- $Y_i \sim \text{BIN}(m_i, \pi_i)$, $i = 1, \ldots, n$ independently and

$$g(\pi_i) = \boldsymbol{x}_i^\top \boldsymbol{\beta},$$

where

  - $\boldsymbol{x}_i$ is a vector of explanatory variables,
  - π_i is the probability of event of interest,
  - $g(\,\cdot\,)$ is a link function that relates explanatory variables $\boldsymbol{x}_i$ to probability π_i, and
  - $\boldsymbol{\beta}$ is a vector of regression parameters.

- When using the canonical link of Binomial distribution, i.e., $g(\,\cdot\,) = \mathsf{logit}()$, we have

$$\mathsf{logit}(\pi_i) = \mathsf{log}\left(\frac{\pi_i}{1-\pi_i}\right) = \boldsymbol{x}_i^\top \boldsymbol{\beta},$$

which is called a *logistic regression model* which is commonly used in practice.

Parameters Estimation

- Likelihood methods are used for parameter estimating and inference.
- MLE $\hat{\boldsymbol{\beta}}$ come from Fisher Scoring using R function `glm()`.
- Interpretation: β_k has a log OR interpretation for logistic models.
- Variance covariance estimate for $\hat{\boldsymbol{\beta}} = \widehat{\mathsf{Var}}(\hat{\boldsymbol{\beta}}) = \boldsymbol{I}^{-1}(\hat{\boldsymbol{\beta}})$, where $\boldsymbol{I}^{-1}$ is the inverse of the information matrix evaluated at MLE $\hat{\boldsymbol{\beta}}$.
- Standard error: $\mathsf{se}(\hat{\beta}_k) = \sqrt{\left[\boldsymbol{I}^{-1}(\hat{\boldsymbol{\beta}})\right]_{kk}} = \sqrt{I^{kk}(\hat{\boldsymbol{\beta}})}$.
- Wald-test of a single parameter: H_0: $\beta_k = \beta^\star$ vs H_A: $\beta_k \neq \beta^\star$:

$$\frac{(\hat{\beta}_k - \beta^\star)^2}{I^{kk}(\hat{\beta}_k)} \overset{H_0}{\sim} \chi^2_1,$$

or

$$\frac{\hat{\beta}_k - \beta^\star}{\mathsf{se}(\hat{\beta}_k)} \sim \mathcal{N}(0,1) \text{ under } H_0.$$

For testing H_0: $\beta_k = 0$, we have $\frac{\hat{\beta}_k}{\mathsf{se}(\hat{\beta}_k)}$, reported as "`z-value`" in `glm()` summary.

- Confidence interval for a single β_k:

$$\hat{\beta}_k \pm Z_{1-\alpha/2}\, \mathsf{se}(\hat{\beta}_k).$$

- Confidence interval for $\eta_i = \boldsymbol{x}_i^\top \boldsymbol{\beta}$:

$$\boldsymbol{x}_i^\top \hat{\boldsymbol{\beta}} \pm Z_{1-\alpha/2} \sqrt{\boldsymbol{x}_i^\top I^{-1}(\hat{\boldsymbol{\beta}}) \boldsymbol{x}_i},$$

or equivalently

$$\boldsymbol{x}_i^\top \hat{\boldsymbol{\beta}} \pm Z_{1-\alpha/2} \sqrt{\boldsymbol{x}_i^\top \widehat{\mathsf{Var}}(\boldsymbol{x}_i^\top \hat{\boldsymbol{\beta}}) \boldsymbol{x}_i}.$$

How about CI for $\pi_i = \mathsf{expit}(\boldsymbol{x}_i^\top \boldsymbol{\beta})$?

Model Checking and Selection

- LR/Deviance: Recall $\text{LR} = -2\log\left(\frac{L(\tilde{\boldsymbol{\pi}})}{L(\hat{\boldsymbol{\pi}})}\right) = -2\big(\ell(\hat{\boldsymbol{\pi}}) - \ell(\tilde{\boldsymbol{\pi}})\big)$.

$$\begin{aligned} D &= -2\big[\ell(\hat{\boldsymbol{\pi}}) - \ell(\tilde{\boldsymbol{\pi}})\big] \\ &= -2\sum_{i=1}^{n}\left(y_i \log\left(\frac{y_i}{m_i\hat{\pi}_i}\right) + (m_i - y_i)\log\left(\frac{m_i - y_i}{m_i(1-\hat{\pi}_i)}\right)\right) \\ &= \sum_{i=1}^{n} d_i. \end{aligned}$$

- LR/Deviance test for *adequacy of a model* (H_0: fitted model is as adequate as the saturated model):

$$D \sim \chi^2_{n-p} \text{ under } H_0.$$

- LR/Difference in Deviance test for *comparing nested models* (H_0: reduced/simpler model is as adequate as the fitted model):

$$\Delta D = D_0 - D_\text{A} \sim \chi^2_{p-q} \text{ under } H_0.$$

- Deviance Residuals:

$$r_i^D = \text{sign}(y_i - m_i\hat{\pi}_i)\sqrt{|d|},$$

  where r_i^D's should behave like an iid sample from $\mathcal{N}(0,1)$ for a well-fitted model.

- Residuals plots:
  - *deviance residual vs fitted value* (i.e., r_i^D vs $\hat{\pi}_i$),
  - *deviance residual vs covariate* (i.e., r_i^D vs $\boldsymbol{x}_i$).
  - In both cases, we expect a pattern of random scatter around 0, within $(-2, 2)$.

- Residual plots can be used to evaluate the fit of a model or compare multiple models in general.
  - For example, non-nested models, using different link functions.

Binomial Model for Dose-Response Relationship

- Dose: $X = \log(\text{concentration})$.
- Tolerance distribution is $f(x)$ and probability of responding to dose x is:

$$\pi(x) = \mathbb{P}(X \le x) = \int_{-\infty}^{x} f(x)\,\mathrm{d}x = F(x).$$

- Binomial GLMs can be utilized to evaluate the dose-response relationship:

$$g(\pi) = \beta_0 + \beta_1 x$$

  In every case,

Link	Tolerance Distribution
Logit	Logistic(μ, s)
Probit	Normal(μ, s)
Cloglog	Extreme Value(μ, s)

$$\beta_0 = -\frac{\mu}{s}, \qquad \beta_1 = \frac{1}{s}.$$

- Estimation of the *median lethal/effective dose* ($\delta_{0.5}$):

$$g(0.5) = \hat{\beta}_0 + \hat{\beta}_1 \delta_{0.5} \implies \delta_{0.5} = \frac{g(0.5) - \hat{\beta}_0}{\hat{\beta}_1}.$$

- Calculation of dose related to q^{th} percentile of response.

Topic 4a: Poisson GLMs for Count Data

The Poisson Distribution

- Recall for $Y \sim \text{POI}(\mu)$,

$$f(y) = \frac{\mu^y e^{-\mu}}{y!} = \exp\big\{y \log(\mu) - \mu - \log(y!)\big\},\ \mu > 0,\ y = 0, 1, 2, \ldots.$$

  Examples of count data:

  - Health service, # of emergency visits, # of hospitalizations.
  - Insurance, # of claims.
  - Engineering/manufacturing, # of defects.

- The Poisson is a member of the *exponential family* with

$$\begin{aligned} \theta &= \log(\mu), \\ a(\phi) &= \phi = 1, \\ b(\theta) &= e^\theta = \mu, \\ c(y; \theta) &= -\log(y!). \end{aligned}$$

- Mean and variance:

$$\begin{aligned} \mathbb{E}[Y] &= b'(\theta) = e^\theta = \mu, \\ \text{Var}(Y) &= b''(\theta) a(\phi) = e^\theta = \mu. \end{aligned}$$

  Therefore, $\mathbb{E}[Y] = \text{Var}(Y)$.

- The *Canonical link*:

$$\theta = \eta \implies \log(\mu) = \eta = x^\top \beta,$$

  the log link, $g(\mu) = \log(\mu)$, is the canonical link.

Poisson Log Linear Model and Likelihood Function

- Now, suppose we have a random sample of size n:

$$Y_i \sim \text{POI}(\mu_i),\ i = 1, 2, \ldots, n,$$

  and association with each y_i there is a covariate vector $\boldsymbol{x}_i^\top = (1, x_{i1}, \ldots, x_{ip-1})^\top$.

- The likelihood and log-likelihood are then

$$\begin{aligned} L(\boldsymbol{\mu}) &= \prod_{i=1}^n \frac{\mu_i^{y_i} e^{-\mu_i}}{y_i!}, \\ \ell(\boldsymbol{\mu}; \boldsymbol{y}) &= \sum_{i=1}^n \big(y_i \log(\mu_i) - \mu_i - \log(y_i!)\big). \end{aligned}$$

- Using the Canonical link (i.e., log link):

$$\log(\mu_i) = \boldsymbol{x}_i^\top \boldsymbol{\beta} = \sum_{j=0}^{p-1} x_{ij}\beta_j,$$

  which is referred to as log linear regression because the use of the log link.

- We can obtain the log-likelihood in terms of β by substitution:

$$\begin{aligned}\ell(\boldsymbol{\mu}; \boldsymbol{y}) &= \sum_{i=1}^{n} \big(y_i \log(\mu_i) - \mu_i - \log(y_i!)\big) \\ &= \sum_{i=1}^{n} \big(y_i \boldsymbol{x}_i^\top \boldsymbol{\beta} - \exp\{\boldsymbol{x}_i^\top \boldsymbol{\beta}\} - \log(y_i!)\big).\end{aligned}$$

Estimation of β from log linear regression

- The j^{th} contribution to the Score vector is:

$$\frac{\partial \ell}{\partial \beta_j} = \sum_{i=1}^{n} \big(y_i x_{ij} - x_{ij} \exp\{\boldsymbol{x}_i^\top \boldsymbol{\beta}\}\big).$$

- The (j, k) element of the Information Matrix is:

$$-\frac{\partial^2 \ell}{\partial \beta_j \, \partial \beta_k} = \sum_{i=1}^{n} \big(x_{ij} x_{ik} \exp\{\boldsymbol{x}_i^\top \boldsymbol{\beta}\}\big).$$

- These can also be found using general exponential family results.
- Use the above to estimate $\hat{\boldsymbol{\beta}}$ via Fisher Scoring.

Poisson Deviance/LR Tests

- Let $\tilde{\mu}_i$ be the MLE under the saturated model (i.e., $\tilde{\mu}_i = y_i$ which is the Poisson MLE for μ_i).
- Let $\hat{\mu}_i$ be the MLE under a p-dimensional constrained model (e.g., $\hat{\mu}_i \exp\{\boldsymbol{x}_i^\top \hat{\boldsymbol{\beta}}\}$).
- Recall the Likelihood Ratio or Deviance Statistic has the form:

$$D = -2 \log\left(\frac{L(\hat{\boldsymbol{\mu}})}{L(\tilde{\boldsymbol{\mu}})}\right) = 2\big(\ell(\tilde{\boldsymbol{\mu}}) - \ell(\hat{\boldsymbol{\mu}})\big).$$

- Under H_0: constrained model is as adequate as saturated model, we have the following asymptotic distribution result:

$$D \sim \chi^2_{n-p}.$$

- For the Poisson we have:

$$\begin{aligned}D &= 2 \sum_{i=1}^{n} \Big(\big(y_i \log(\tilde{\mu}_i) - \tilde{\mu}_i\big) - \big(y_i \log(\hat{\mu}_i) - \hat{\mu}_i\big) \Big) \\ &= 2 \sum_{i=1}^{n} \left(y_i \log\left(\frac{y_i}{\hat{\mu}_i}\right) - (y_i - \hat{\mu}_i) \right) \\ &= 2 \sum_{i=1}^{n} \left(O_i \log\left(\frac{O_i}{E_i}\right) - (O_i - E_i) \right).\end{aligned}$$

- Question: does the Deviance Statistic have the form as the Binomial case, i.e.,

$$D = 2\sum O_i \log\left(\frac{O_i}{E_i}\right) \text{ ?}$$

When there is an intercept included in the Poisson log-linear model:

$$\frac{\partial \ell}{\partial \beta_0} = \frac{\partial}{\partial \beta_0}\left[\sum_{i=1}^{n} y_i \boldsymbol{x}_i^\top \boldsymbol{\beta} - \exp\{\boldsymbol{x}_i^\top \boldsymbol{\beta}\}\right] = \sum_{i=1}^{n}(y_i - \mu_i) \implies \sum_{i=1}^{n}(y_i - \hat{\mu}_i) = 0,$$

then the Deviance takes the form

$$D = 2\sum_{i=1}^{n} y_i \log\left(\frac{y_i}{\hat{\mu}_i}\right) = 2\sum_{i=1}^{n} O_i \log\left(\frac{O_i}{E_i}\right).$$

- Use the Deviance to test nested models:
  - H_0: the reduced model with p parameters is adequate versus

$$\log(\mu_i) = \beta_0 + \beta_1 x_{i1} + \cdots + \beta_{p-1} x_{ip-1}$$

  - H_A: the full model with q parameters ($p < q$)

$$\log(\mu_i) = \beta_0 + \beta_1 x_{i1} + \cdots + \beta_{p-1} x_{ip-1} + \cdots + \beta_{q-1} x_{iq-1}.$$

- LR/Difference in Deviance test statistic:

$$\Delta D = D_0 - D_\text{A} \sim \chi^2_{q-p} \text{ under } H_0.$$

- The p-value for this test is given by:

$$p\text{-value} = \mathbb{P}(\chi^2_{q-p} > \Delta D).$$

Deviance Residuals

- We can write the Deviance as a sum:

$$D = 2\sum_{i=1}^{n}\left(y_i \log\left(\frac{y_i}{\hat{\mu}_i}\right) - (y_i - \hat{\mu}_i)\right) = \sum_{i=1}^{n} d_i.$$

- The Deviance Residuals are given by:

$$r_i^D = \text{sign}(y_i - \hat{\mu}_i)\sqrt{|d_i|},$$

and are approximately $\mathcal{N}(0,1)$ if H_0 holds.

- We can use the residual plots to evaluate the fit of a model.

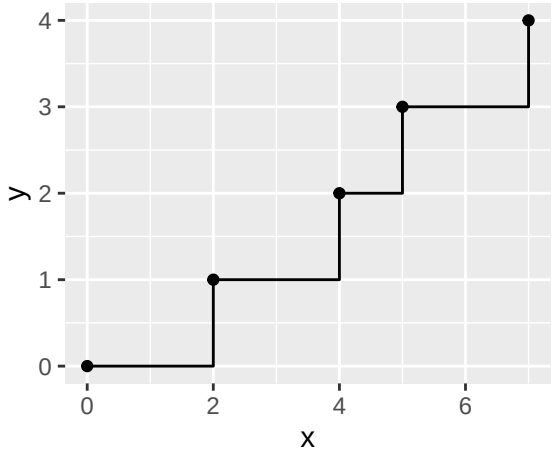
Regression for Poisson Processes

- The Poisson distribution assumes a *common observation period* for all individuals, so that the number of event does not depend on the time at risk.
- However, this may not be the case for many situations in practice.

Counting Process $N(t)$

A counting process $N(t)$ is any non-decreasing integer function of time such that $N(0) = 0$ and $N(t)$ is the number of events occurring in $(0, t]$.

- Example: Suppose events occurred at times $(2, 4, 5, 7)$.
- Draw a plot of $N(t)$ versus t:



Poisson Process $N(t)$

A counting process $N(t)$ is a Poisson process if it satisfies:

1. Independent increments: For $s_1 < t_1 < s_2 < t_2$:

$$N(t_1) - N(s_1) = \#\text{ events in } (s_1, t_1],$$

is independent of

$$N(t_2) - N(s_2) = \#\text{ events in } (s_2, t_2].$$

2. The number of events over $(0, t]$ has a Poisson distribution, i.e.,

$$\mathbb{P}\big(N(t) = n; \lambda\big) = \frac{(\lambda t)^n e^{-\lambda t}}{n!}, \ \lambda > 0, \ n = 0, 1, 2, \ldots.$$

- Expected number of events in $(0, t]$ is

$$\mathbb{E}\big[N(t)\big] = \mu(t) = \lambda t.$$

Parameter λ is a constant representing the *rate of occurrence of the event per unit of time*:

$$\lambda = \text{rate parameter},$$
$$t = \text{length of observation period}.$$

- Since λ is constant (not a function of t) we call this a time homogeneous Poisson process.
- Use the log link to do regression:

$$\log\big(\mu(t)\big) = \log(\lambda t) = \log(\lambda) + \log(t).$$

For each subject $i = 1, \ldots, n$ we observe:

- $N_i(t_i) =$ the number of events observed over $(0, t_i]$.
- Explanatory variables: $\boldsymbol{x}_i = (1, x_{i1}, \ldots, x_{ip-1})^\top$.

Log Linear Regression Model for a Time Homogeneous Poisson Process

$$\begin{aligned} \log\big(\mu_i(t_i)\big) &= \log(\lambda_i) + \log(t_i) \\ &= \boldsymbol{x}_i^\top \boldsymbol{\beta} + \log(t_i) \end{aligned} \qquad \text{e.g., } \log(\lambda_i) = \boldsymbol{x}_i^\top \boldsymbol{\beta}.$$

- The term $\log(t_i)$ is called an "*offset term*".
- It accounts for different lengths of observation.
- It *explains* some variation in the event counts across subjects, but does so in a deterministic way.

Next week: an example of fitting Poisson GLM using R.