Kurs Bio144: Datenanalyse in der Biologie

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Lecture 10: Modelling binary data 11./12. May 2017

Overview

- Binary response variables
- ullet Contingency tables, χ^2 test
- Odds and (log) odds ratios
- Logistic regression
- Residual analysis / model checking / deviances
- Interpretation of the results

Course material covered today

The lecture material of today is based on the following literature:

- Repetition: Chapter 9.4 about χ^2 -Tests in the Luchsinger script
- Chapters 9.1 9.3 from *The new statistics with R* (Hector book).

Recap of last week: GLMs and Poisson regression

- We introduced generalized linear models (GLMS) and key terms:
 Family Linear predictor Link function
- GLMs are useful when the response variable y is not continuous (→ residuals are not Gaussian).
- Count data usually lead to Poisson regression.
- However, for count data it may sometimes be ok to use linear regression with log(y) in the response.

Introduction

- Today, we will look at the case where the response variable is binary (0 or 1) or binomial (e.g. 5 out of 7 trials).
- In binary/binomial regression, the question will be: "Which variables influence the probability *p* of the outcome?"

Examples:

- Outcome: Heart attack (yes=1, no=0).
 Question: which variables lead to higher or lower risk of heart attack?
- Outcome: Survival (yes=1, no=0).
 Question: which variables influence the survival probability of premature babies (Frühgeburten)?

Some repetition: The χ^2 test

You have dealt with binary (categorical) data in Mat183! Remember the χ^2 test for contingency tables (simplest: 2×2 tables).

Example: Heart attack and hormonal contraception (Verhütungspille) (from Stahel):

		Herzinfarkt (B)			
		ja	nein	Summe	
Verhütungspille	ja	23	34	57	
(A)	nein	35	132	167	
	\mathbf{Summe}	58	166	224	

"Hormonal contraception" is the predictor (x) and "heart attack" the outcome (y).

Question: Does hormonal contraception (x) have an influence on heart attacks (y)?

This question is equivalent to asking whether the proportion of patients with heart attack is the same in both groups.

The respective test-statistic can be calculated as

$$\mathcal{T} = \sum_{\text{all entries}} \frac{(\text{observed} - \text{expected})^2}{\text{expected}} \ .$$

By hand, T is obtained as

$$\frac{(23-14.8)^2}{14.8} + \frac{(34-42.2)^2}{42.2} + \frac{(35-43.2)^2}{43.2} + \frac{(132-123.8)^2}{123.8} = 8.329$$

and is expected to be χ_1^2 distributed (one degree of freedom: $(2-1)\cdot (2-1)$).

The *p*-value of this test is given as $Pr(X \ge 8.329) = 0.003902$.

> pchisq(8.329,1,lower.tail=F)

[1] 0.003901713

Of course, R can do this for us:

Please note: You may sometimes prefer to have correct=TRUE to obtain a better approximation to the χ^2 distribution when expected values in the cells are small (continuity correction of Yates):

In any case, there is strong evidence for an association of hormonal contraception with heart attacks!

Quantification of a dependency

If two variables are not independent, it is often desired to quantify the dependency.

Let one variable be the grouping variable (e.g., hormonal contraception vs no hormonal contraception). Then π_1 and π_2 are the relative frequencies (proportions) observed in the two groups. For example:

$$\pi_1 = 23/57 = 0.404$$

$$\pi_2 = 35/167 = 0.210$$

are the proportions of females with a heart attack in the two groups.

There are at least three numbers that can be calculated to quantify how the two groups differ:

- Risk difference: $\pi_1 \pi_2 = 0.404 0.210 = 0.194$
- Relative risk: $\pi_1/\pi_2 = 0.404/0.210 = 1.92$
- Odds ratio ("Chancenverhältnis"):

$$OR = \frac{\pi_1/(1-\pi_1)}{\pi_2/(1-\pi_2)} = \frac{0.404/(1-0.404)}{0.210/(1-0.210)} = 2.55 \ ,$$

where $\pi/(1-\pi)$ is the odds (die "Chance").

Interpretation:

- \bigcirc $OR = 1 \rightarrow$ the two groups are independent.
- 2 $OR > 1 \rightarrow \text{positive dependency}$.
- $OR < 1 \rightarrow \text{negative dependency}$.

The odds and the odds ratio

- The **odds** ("Wetteverhältnis"): For a probability π the odds is $\pi/(1-\pi)$. For example, if the probability to win a game is 0.75, then the odds is given as 0.75/0.25 or 3:1.
- The odds ratio is given on the previous slide. It is a ratio of two ratios, or, the ratio of two odds.
- Often the log odds ratio is used:

$$\log(\mathit{OR}) = \log\left(\frac{\pi_1/(1-\pi_1)}{\pi_2/(1-\pi_2)}\right) \; .$$

Why is this simpler? Look at the interpretation:

Please go to the following webpage for a short klicker exercise: http://www.klicker.uzh.ch/bkx

Binomial and binary regression

Usually the situation is more complicated than

binary covariate $(x) \rightarrow$ binary outcome (y)

Often, we are interested in a relationship

Continuous/categ./binary variables $x^{(1)}$, $x^{(2)}$,... \rightarrow binary outcome (y)

 $\rightarrow \text{A regression model is needed again!}$

Illustrative/working example

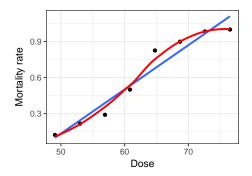
Let us look at an example from chapter 9.2 in Hector (2015):

Eight groups of beetles were exposed to carbon disulphide (an insecticide) for 5h. For each beetle it was then reported if it was killed or not (1 or 0), but the data were reported aggregated:

	Dose	Number_tested	Number_killed	Mortality_rate
1	49.06	49	6	0.1224490
2	52.99	60	13	0.2166667
3	56.91	62	18	0.2903226
4	60.84	56	28	0.5000000
5	64.76	63	52	0.8253968
6	68.69	59	53	0.8983051
7	72.61	62	61	0.9838710
8	76.54	60	60	1.0000000

Question: (How) does the insecticide (x) affect the survival probability (y) of the beetles?

As always, start with a graph:



with linear (blue) and smoothed line (red).

What can we see from the plot?

- Mortality increases with higher doses of the herbicide (not surprising, right?).
- ullet The linear line seems unreasonable. In particular, if one extrapolates to lower or higher doses, mortality would become <0 or >1, which is not possible. (Remember: A probability is between 0 and 1 by definition.)

How does one analyze these data correctly?

- So far, we know linear and Poisson regression.
- Both of these are not the correct approaches here.

The 'wrong' analyses

Linear regression

We could simply use

$$\mathsf{E}(y_i) = \beta_0 + \beta_1 \mathsf{Dose}_i$$

with $E(y_i) = \pi_i = \text{probability to die for individuals } i \text{ with } Dose_i$.

R does this analysis without complaining (!!):

```
> lm(Mortality_rate ~ Dose, data=beetle)
```

This leads to $\hat{\beta}_0 = -1.71$ and $\hat{\beta}_1 = 0.037$. This means for instance that, for a zero dose, the probability to die would be $\mathsf{E}(y_i) = -1.71$.

Problems:

- Linear regression leads to impossible predicted probability values!
 Unrealistic predictions!
- For $y_i = \beta_0 + \beta_1 Dose_i + e_i$, residuals e_i are **not** normally distributed!

Poisson regression

What about Poisson regression with the counts "Number_killed" in the response? We could use

$$\log(\mathsf{E}(y_i)) = \beta_0 + \beta_1 Dose_i$$

with $E(y_i)$ = number killed. Again, R does this analysis without complaining, although these are not 'real' counts:

> glm(Number_killed ~ Dose, data=beetle,family=poisson)

This leads to $\hat{\beta}_0 = -0.77$ and $\hat{\beta}_1 = 0.067$.

Problem: This means for instance that, for a dose of 76, one expects that $E(y_i) = \exp(\hat{\beta}_0 + \hat{\beta}_1 \cdot 76) = 73.80$ beetles die. However, there are only around 60 beetles in each group, so the predicted number killed is more than what is available. \Rightarrow Unrealistic predictions!

Sidenote: count vs. binomial data

Clarification of the difference between count data and binomial data:

Count data:

- Theoretically no upper limit on number of times an "event" (e.g., number of birds observed in a forest plot)
- Counts cannot be expressed as a proportion.

Binomial data:

- Aggregated version of many binary experiments, that is, each can be 0 or 1
- Therefore, there is an upper limit on the number of times an "event" can be observed (e.g., number of deaths cannot be greater than number of living individuals).
- Successes can be expressed as proportion (number of successes/number of trials).

A model for binary data?

I hope you remember the Bernoulli distribution from Mat183:

The probability distribution of a binary random variable $Y \in \{0,1\}$ with parameter π is defined as

$$Pr(Y = 1) = \pi$$
, $Pr(Y = 0) = 1 - \pi$.

Characteristics of the Beroulli distribution:

- $\mathsf{E}(Y) = \pi = \mathsf{Pr}(Y = 1)$ (useful to remember)
- $Var(Y) = \pi(1 \pi)$.
 - \rightarrow The variance of the distribution is determined by its mean.

From binary to binomial data

Binomial data is an aggregation of binary data:

- Repeat the experiment with $Pr(Y = 1) = \pi$ a total number of n times, calculate how often a success was observed (k times).
- The expected proportion of successes ("success rate", here k/n) has then the same expectation as the success probability of a single experiment:

$$\mathsf{E}\left(\frac{\sum_{i=1}^n Y}{n}\right) = \pi = \mathsf{E}(Y) \; .$$

Example: In the beetle data 49 beetles were tested for the lowest dose, of which k=6 died, thus $\hat{\pi}=6/49=0.122$.

The binomial distribution

The **binomial distribution** assigns the probability of seeing k success out of n trials, where the success probability of a single trial is π .

$$\Pr(Y = k) = \binom{n}{k} \pi^k (1 - \pi)^{n-k}, \quad k = 0, 1, 2, ..., n$$

In short:

$$Y \sim \mathsf{Binom}(n,\pi)$$
.

Characteristics of the binomial distribution:

• Mean: $E(Y) = n \cdot \pi$

• Variance: $Var(Y) = n \cdot \pi(1 - \pi)$

 \rightarrow For given *n*, the variance is determined by its mean.

R functions: rbinom(), dbinom()

Doing it right: Logistic regression

We can again use the GLM machinery from last week! The linear predictor is as always:

$$\eta_i = \beta_0 + \beta_1 x_i^{(1)} + \beta_2 x_i^{(2)} + \ldots + \beta_p x_i^{(p)}.$$

We again need a link function that relates the linear predictor η_i to the expected value $E(y_i)$.

Remember we used the log link last week, but that seems a bad idea here (see slide 18).

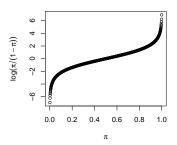
The link function must be chosen such that the expected value $E(y_i)$ is always between 0 and 1!

Link function: The logistic transformation

A transformation that assigns a probability (π) between 0 and 1 a value between $-\infty$ and ∞ is the logit-transformation:

$$g(\pi) = \log\left(rac{\pi}{1-\pi}
ight) = \log(\pi) - \log(1-\pi) \; .$$

A graph depicts the functional form of $g(\cdot)$:



See also Box 9.2 (p. 123) in The new statistics with R.

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The logistic regression model

In order to prevent the expected value $E(y_i)$ of a binary experiment (0/1) to attain unreasonable values, we thus formulate the logistic regression model as

$$\log\left(\frac{\mathsf{E}(y_i)}{1-\mathsf{E}(y_i)}\right) = \beta_0 + \beta_1 x_i^{(1)} + \beta_2 x_i^{(2)} + \ldots + \beta_p x_i^{(p)}$$

with $E(y_i) = Pr(y_i = 1)$.

- The link function is called the logistic link.
- The family is binomial.

Doing it right: Fitting a logistic regression

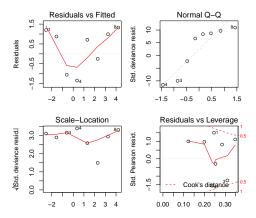
- As for the Poisson GLM, we can estimate the parameters β_0, β_1, \ldots by maximum-likelihood estimation.
- Luckily, the glm() function in R can also handle binomial and binary data!
- A complication comes from the fact that we need to tell the function two numbers for the response:
 - The number of successes, encoded as 1 (here: number killed)
 - The number of failures, encoded as 0 (here: number died)

```
> beetle$Number_survived <- beetle$Number_tested - beetle$Number_killed
> beetle.glm <- glm(cbind(Number_killed,Number_survived) ~ Dose,</pre>
```

+ data = beetle, family = binomial)

Doing it right: Model diagnostics

As always, before looking at the regression output, let's do some model diagnostics:



- As in Poisson regression, it is not clear how do define residuals, there are many ways...
- Again, different types of residuals are used in the plots.
- Be careful: such plots are only reasonable for aggregated data (which
 we have here)! The larger the groups, the more precise are the
 underlying assumptions (approximate equality of distributions).
- See example on slide 42 for an example with non-aggregated (binary)

Doing it right: Interpreting the coefficients

Let's look at the results, for the moment on the coefficients:

```
> summary(beetle.glm)$coef
```

```
Estimate Std. Error z value
                                                Pr(>|z|)
(Intercept) -14.5780604 1.2984622 -11.22717 2.999201e-29
             0.2455399 0.0214937 11.42381 3.179900e-30
Dose
```

The intercept and slope are estimated as

$$\hat{\beta}_0 = -14.578$$
 and $\hat{\beta}_1 = 0.246$,

with standard errors and p-values. Very clearly, the dose influences the survival probability ($p \ll 0.001$), and $\hat{\beta}_1 > 0$, thus, the larger the dose, the larger the mortality probability (positive relation; be careful, this is wrong in the Hector book!!).

This is a qualitative interpretation of the coefficients.

Note: The β coefficients are approximately normally distributed as $N(\hat{\beta}, \hat{\sigma}_{\beta}^2)$. → confidence intervals etc. can be calculated as in the linear case!

Quantitative interpretation of the coefficients

Remember the regression model

$$\log\left(\frac{\mathsf{E}(y_i)}{1-\mathsf{E}(y_i)}\right) = \beta_0 + \beta_1 \mathsf{Dose}_i \ .$$

To understand what β_1 tells us, let's transform the equation such that $E(y_i) = \Pr(y_i = 1)$ is on the left. Some algebra leads to

$$\Pr(y_i = 1) = \frac{\exp(\beta_0 + \beta_1 Dose_i)}{1 + \exp(\beta_0 + \beta_1 Dose_i)}. \tag{1}$$

It is then possible to calculate the odds ("Chance")

$$\mathsf{odds}(y_i = 1 \,|\, \mathsf{Dose}_i) = \frac{\mathsf{Pr}(y_i = 1 \,|\, \mathsf{Dose}_i)}{\mathsf{Pr}(y_i = 0 \,|\, \mathsf{Dose}_i)} = \mathsf{exp}(\beta_0 + \beta_1 \mathsf{Dose}_i) \;.$$

If the $Dose_i$ is then increased by 1 unit in concentration (from x to x + 1), the odds ratio is given as

$$\frac{\text{odds}(y_i = 1 \mid Dose_i = x + 1)}{\text{odds}(y_i = 1 \mid Dose_i = x)} = \exp(\beta_1) = \exp(0.246) = 1.28 .$$

Interpretation: When the dose is increased by 1 unit, the odds to die increases by a factor of 1.28.

Moreover, taking the log on the above equation shows that β_1 can be interpreted as a log odds ratio:

$$\beta_1 = \log \left(\frac{\operatorname{odds}(y_i = 1 \mid Dose_i = x + 1)}{\operatorname{odds}(y_i = 1 \mid Dose_i = x)} \right)$$

Doing it right: The anova() table

We can look at the Analysis of Deviance table (directly using test="Chisq"):

```
> anova(beetle.glm,test="Chisq")

Analysis of Deviance Table

Model: binomial, link: logit

Response: cbind(Number_killed, Number_survived)

Terms added sequentially (first to last)

Df Deviance Resid. Df Resid. Dev Pr(>Chi)

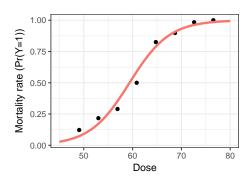
NULL 7 267.662

Dose 1 259.23 6 8.438 < 2.2e-16 ***
---
Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

Interpretation: The total deviance is 267.66, and of this 259.23 is explained by Dose (using 1 degree of freedom). This seems really good, because the χ^2 test gives a *p*-value that is reeeeallly small (< 2.2e - 16).

Plotting the fit

A fitted curve can be added to the raw data by plotting $Pr(y_i = 1)$ against the Dose, using equation (1):



Overdispersion

Remember:

- Slide 22: $E(Y) = \pi$ and $Var(Y) = \pi(1 \pi)$, thus the variance is determined by the mean!
- "Overdispersion" means "extra variability" (larger than the model predicts).
- Reason: Variables are missing in the model!
- Overdispersion leads to too small p-values.
- Detectable by looking at the residual deviance:

Residual deviance >> df \to Overdispersion

Also possible: underdispersion (dependency in the data), if:

Residual deviance << df

Here, the residual deviance is **8.44** with **6** degrees of freedom. Is this good or bad?

```
> 1-pchisq(8.438,6)
```

[1] 0.2077375

 $\rightarrow p = 0.21$ seems not problematic.

One can nevertheless account for overdispersion by switching to a **quasibinomial** model. This allows to estimate the dispersion parameter separately.

```
> beetle.glm2 <- glm(cbind(Number_killed, Number_survived) ~ Dose,
                data = beetle, family = quasibinomial)
> summary(beetle.glm2)
Call:
glm(formula = cbind(Number killed, Number survived) ~ Dose, family = guasibinomial,
   data = beetle)
Deviance Residuals:
   Min 1Q Median 3Q
                                    Max
-1.3456 -0.4515 0.7929 1.0422 1.3262
Coefficients:
           Estimate Std. Error t value Pr(>|t|)
(Intercept) -14.57806 1.46611 -9.943 5.98e-05 ***
         0.24554 0.02427 10.118 5.42e-05 ***
Dose
Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
(Dispersion parameter for quasibinomial family taken to be 1.274895)
   Null deviance: 267.6624 on 7 degrees of freedom
Residual deviance: 8.4379 on 6 degrees of freedom
ATC: NA
Number of Fisher Scoring iterations: 4
```

Binary response / non-aggregated data

- In the beetle example, we were in a comfortable situation: For each level of the does, we had several beetles. For instance, 55 beetles at lowest dose (49.06), of which 6 died (1) and 49 survived (0). This was binomial data, an aggregated version of 55 trials with 0 or 1 outcome.
- In reality, one often has only one trial (0/1) for a (combination of) covariate(s).
- The analysis is the same as for aggregated data, however there are a few complications with graphical descriptions and model checking.

Example: Blood screening (see week 1; data from Hothorn & Everitt 2014, chapter 7.3)

Blood screening example

- > library(HSAUR3)
- > data("plasma",package="HSAUR3")
- > plasma\$y <- as.integer(plasma\$ESR)-1

fibrinogen	globulin	ESR	У	fibrinogen	globulin	ESR	У
2.52	38	ESR < 20	0	2.88	30	ESR < 20	0
2.56	31	ESR < 20	0	2.65	46	ESR < 20	0
2.19	33	ESR < 20	0	2.28	36	ESR < 20	0
2.18	31	ESR < 20	0	2.67	39	ESR < 20	0
3.41	37	ESR < 20	0	2.29	31	ESR < 20	0
2.46	36	ESR < 20	0	2.15	31	ESR < 20	0
3.22	38	ESR < 20	0	2.54	28	ESR < 20	0
2.21	37	ESR < 20	0	3.34	30	ESR < 20	0
3.15	39	ESR < 20	0	2.99	36	ESR < 20	0
2.60	41	ESR < 20	0	3.32	35	ESR < 20	0
2.29	36	ESR < 20	0	5.06	37	ESR > 20	1
2.35	29	ESR < 20	0	3.34	32	ESR > 20	1
3.15	36	ESR < 20	0	2.38	37	ESR > 20	1
2.68	34	ESR < 20	0	3.53	46	ESR > 20	1
2.60	38	ESR < 20	0	2.09	44	ESR > 20	1
2.23	37	ESR < 20	0	3.93	32	ESR > 20	1

Question: Is a high ESR (erythrocyte sedimentation rate) an indicator for certain diseases (rheumatic disease, chronic inflammations)?

Specifically: Is there an association between ESR level ESR< 20mm/hr and the concentrations of the plasma proteins Fibrinogen and Globulin (which are disease indicators)?

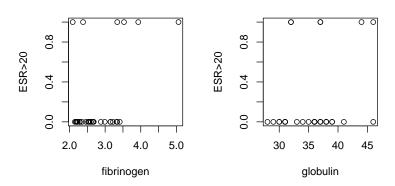
The model to be fitted:

$$\log\left(\frac{\mathsf{E}(y_i)}{1-\mathsf{E}(y_i)}\right) = \beta_0 + \beta_1 \mathit{fibrinogen}_i + \beta_2 \mathit{globulin}_i \ ,$$

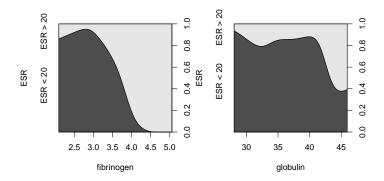
with
$$E(y_i) = Pr(y_i = 1) = \pi_i$$
, or, equivalently: $y_i \sim Bern(\pi_i)$.

Complication 1 with binary data: Graphical description

Plotting the response y (indictor for ESR> 20) against the covariats does not lead to very illustrative graphs:



It is a bit more illustrative to give a conditional density plot (cdplot()):

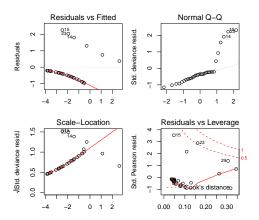


Complication 2: Model diagnostics

a) Residuals plots:

Plotting the residuals is possible, but not meaningful.

Why? Becasue the model checking assumptions rely on aggregated data!



b) Residual deviance:

For non-aggregated data, the residual deviance vs. df relation cannot be used to detect overdispersion!!

Your turn!

Apart from the above complications, fitting and interpreting the model is analogous to aggregated binary data. Let's continue with the blood screening example:

```
> plasma.glm <- glm(y ~ fibrinogen + globulin, data = plasma, family = binomial)
```

Please look at the model outcomes (summary and anova table) on the next slides and answer the following questions:

- Is there an an effect of figrinogen and/or globulin on the outcome (ESR> 20)?
- **②** What is the *quantitative* interpretation of the β_1 coefficient (what happens to Pr(ESR > 20) when fibrinogen incrases by 1 unit)?
- Is a quaisbinomial model more suitable for these data?

> summary(plasma.glm)

```
Call:
glm(formula = y ~ fibrinogen + globulin, family = binomial, data = plasma)
Deviance Residuals:
   Min
            10 Median
                                     Max
-0.9683 -0.6122 -0.3458 -0.2116 2.2636
Coefficients:
           Estimate Std. Error z value Pr(>|z|)
(Intercept) -12.7921 5.7963 -2.207 0.0273 *
fibrinogen 1.9104 0.9710 1.967 0.0491 *
globulin 0.1558 0.1195 1.303 0.1925
---
Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
(Dispersion parameter for binomial family taken to be 1)
   Null deviance: 30.885 on 31 degrees of freedom
Residual deviance: 22.971 on 29 degrees of freedom
ATC: 28 971
Number of Fisher Scoring iterations: 5
```

Analysis of Deviance Table Model: binomial, link: logit Response: y Terms added sequentially (first to last) Df Deviance Resid. Df Resid. Dev Pr(>Chi) NULL 31 30.885 fibrinogen 1 6.0446 30 24.840 0.01395 * globulin 1 1.8692 29 22.971 0.17156

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

> anova(plasma.glm,test="Chisq")

Summary

- Logistic regression is useful to model binary/binomial data.
- The link function is the logistic link.
- The coefficients of logistic regression are log odds ratios
 - \Leftrightarrow exp(β) is an odds ratio
- Differences between aggregated (binomial) and binary data.
- Overdispersion not detectable for binary data!