Biostatistics, Week 10

- > Logistic regression for binary outcome
 - > Interpretation of the coefficients
 - > Cl of the coefficients
 - Using logistic regression to predict (Y=1|x)

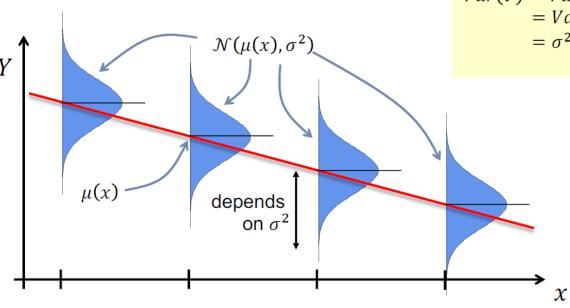
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Recap: Linear regression for continuous outcomes

1.
$$(Y|X=x)^{\sim}N(\underbrace{\beta_0+\beta_1x}_{\mu(x)},\sigma^2)$$

2.
$$Y = \beta_0 + \beta_1 x + \varepsilon$$

• $\varepsilon \sim N(0, \sigma^2)$



$$E(Y) = E(\beta_0 + \beta_1 x + \varepsilon)$$

$$= \beta_0 + \beta_1 x + E(\varepsilon)$$

$$= \beta_0 + \beta_1 x$$

$$Var(Y) = Var(\beta_0 + \beta_1 x + \varepsilon)$$

$$= Var(\varepsilon)$$

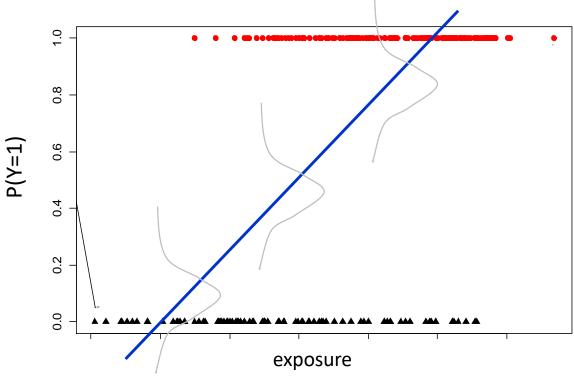
$$= \sigma^2$$

What if outcome is binary? Logistic Regression

Why switching from linear to logistic regression?

Visualize the fitted model together with data.

fit = lm(y ~ exposure, data=my.dat)



Problems:

- 1) linear model can yield impossible Expected values for p outside [0,1]
- 2) model assumptions are violated, since residuals are not $^{\sim}N(0,\sigma^2)$

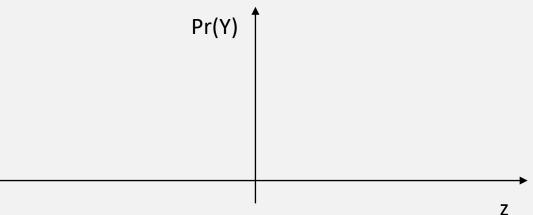
Find a suitable squeezing function



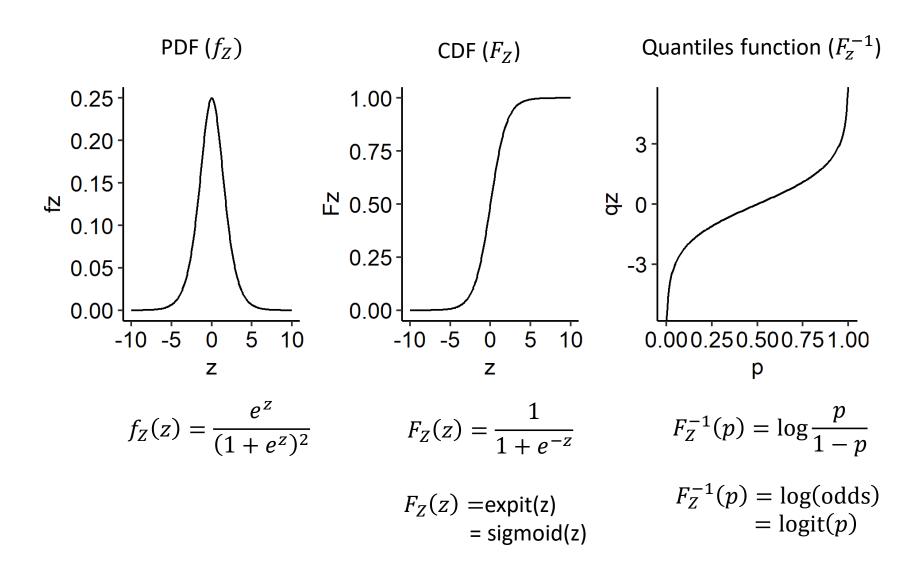
- Idea of logistic regression
- Take output of linear regression

•
$$z = a \cdot x + b$$
 $z \in [-\infty, \infty]$

- •and squeeze it to [0 and 1]
- Task: Draw a function which could do that.
 - Discuss with your neighbor



Logistic Distribution



Logistic regression

Logit transformation:
$$h(\pi) = \log\left(\frac{\pi}{1-\pi}\right) = \log\left(\text{odds}\right)$$

Approach: probabilities are transformed to **logged odds** which can then be modeled linearly.

Logistic regression:

$$h(\pi) = \log \left(\frac{P(Y=1|\vec{X})}{1 - P(Y=1|\vec{X})} \right) = \beta_0 + \beta_1 x_1 + \dots + \beta_n x_p$$
Linear predictor η_i

Remark: the logistic regression model does not contain an error term, since the data variability is captured by the conditional Bernoulli distribution (lin reg is an exception, since only μ but not σ is modeled.

Logistic Regression

Idea:

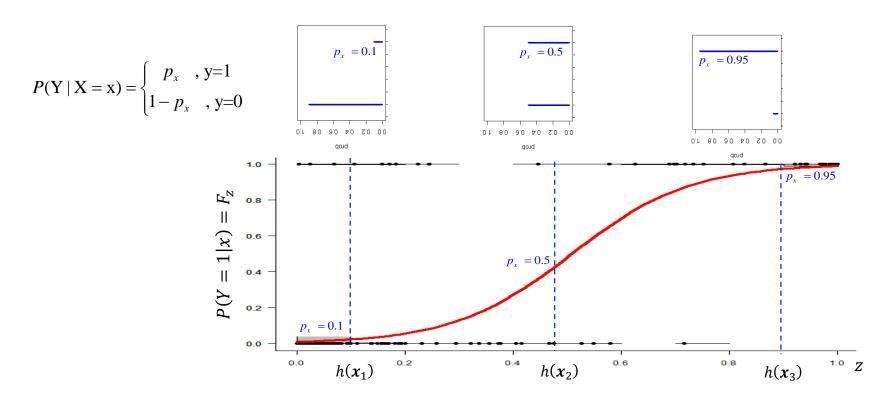
a continuous latent (unobserved) variable determines the probability to observe Y=1

CPD:
$$Y_{X_i} = (Y|X_i) \sim \text{Ber}(p_{x_i})$$

 $Y_x \in \{0,1\}$, $p_x = P(Y=1|x) \in [0,1]$

We don't model the p_x directly, but a value h(x) indicating a point in the latent variable z yielding via the CDF F_z the p_x :

$$p_{x} = F_{z}(h(x))$$



The conditional expected value in a logistic regression model

Logistic Regression Model

- The binary (Y|x) has a conditional Bernoulli distribution $B(\pi(x))$.
- The parameter of this distribution is $\pi(x)$, the disease probability which might be different for each subject depending on its co-variables X.

Now please note that:
$$\pi_i(x) = P(Y_i = 1 \mid x) = E[Y_i \mid x]$$

A common notion of the logistic regression model is to see it as a model where we try to find a relation between the probability for the outcome "1" (= the expected value of the binary response Y) and the predictors $X_1,...X_p$

Important: linear regression is not appropriate!

Estimating the coefficients in logistic regression

$$\log\left(\frac{P(Y=1|X)}{1-P(Y=1|X)}\right) = \beta_0 + \beta_1 x_1 + \dots + \beta x_p \qquad P(Y=1|X) = \frac{e^{\beta_0 + \beta_1 X_1 + \dots + \beta_p X_p}}{1+e^{\beta_0 + \beta_1 X_1 + \dots + \beta_p X_p}}$$

$$P(\mathbf{Y}_{i} = 1 \mid X_{i}) = \pi_{i} \; , \; P(\mathbf{Y}_{i} = 0 \mid X_{i}) = 1 - \pi_{i} \xrightarrow{\text{useful notation} \atop \text{coding } Y \in \{0,1\}} \\ P(\mathbf{Y}_{i} \mid X_{i}) = \pi_{i}^{Y_{i}} \cdot (1 - \pi_{i})^{1 - Y_{i}}$$

We estimate the coefficients by maximizing the Likelihood

(the coefficients β are contained in π since π is determined as a function of the linear predictor)

$$L(\beta) = \prod_{i=1}^{n} P(Y_i | X_i) \qquad l(\beta) = \sum_{i=1}^{n} y_i \log(\pi_i) + (1 - y_i) \log(1 - \pi_i)$$

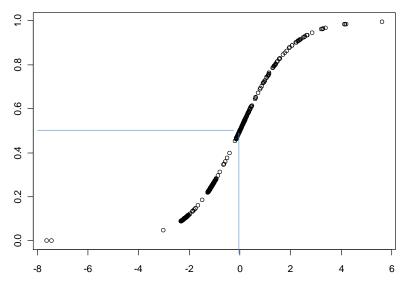
There is no closed formula for the MLE of the coefficient since they are determined in an iterative approach (IRLS).

Back transformation to probabilities

log-odds:
$$\log(\text{odds}) = \beta_0 + \beta_1 x_1 + \cdots + \beta_p x_p$$

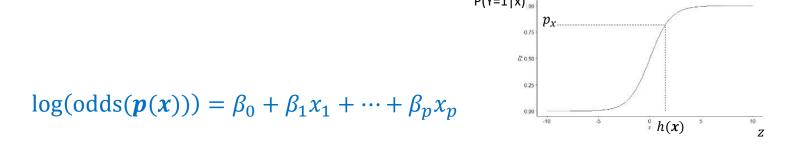
Probability:
$$P(Y = 1|x) = \frac{1}{1 + e^{-(\beta_0 + \beta_1 x_1 + \cdots + \beta_p x_p)}}$$

$$P(Y = 1|x) = \frac{1}{1 + e^{-(\beta_0 + \beta_1 x_1 + \dots + \beta_p x_p)}}$$



$$\log(\text{odds}) = \beta_0 + \beta_1 x_1 + \dots + \beta_p x_p$$

Interpretation of the coefficients in a logistic regression model



The **coefficient** β_k as the **log-odds-ratio** for Y=1 when comparing a situation where x_k is increases by 1 unit (while fixing all other variables) with the situation before increasing x_k

$$\log(\mathsf{OR}_k) = \log\left(\frac{\mathsf{odds}(x_1,\dots,x_k+1,\dots,x_p)}{\mathsf{odds}(x_1,\dots,x_k,\dots,x_p)}\right) = \log\left(\frac{e^{\beta_0} \cdot e^{\beta_1 x_1} \cdot \dots \cdot e^{\beta_k (x_k+1)} \cdot \dots \cdot e^{\beta_p x_p}}{e^{\beta_0} \cdot e^{\beta_1 x_1} \cdot \dots \cdot e^{\beta_k x_k} \cdot \dots \cdot e^{\beta_p x_p}}\right) = \log(e^{\beta_k}) = \beta_k$$

$$\Rightarrow e^{\beta_k} = OR_{x_k \to x_k + 1}$$

Interpretation of the coefficients in logistic regression

Interpretation of Regression Coefficient (β_k): response_i = $\hat{\beta}_0 + \hat{\beta}_1 \cdot x_{i1} + ... + \hat{\beta}_n \cdot x_{in}$

response_i =
$$\hat{\beta}_0 + \hat{\beta}_1 \cdot x_{i1} + ... + \hat{\beta}_p \cdot x_{ij}$$

In logistic regression, we have the following relationship:

$$\log(\hat{o}dds) = \hat{\beta}_0 + \hat{\beta}_1 X_1 + \dots + \hat{\beta}_p X_p$$

- In linear regression, the slope coefficient β_k gives the difference in the expected response (here: log(odds)) as x_k increases by 1 unit (while fixing all other variables)

$$\beta_k = \left(\log(\operatorname{odd}_{x_k+1}) - \log(\operatorname{odd}_{x_k})\right) = \log\left(\frac{\operatorname{odd}_{x_k+1}}{\operatorname{odd}_{x_k}}\right) = \log(\operatorname{OR}_{x_k \to x_k+1})$$

$$\Rightarrow e^{\beta_k} = OR_{x_k \to x_k + 1}$$

- Thus e^{β_k} gives the OR when the risk factor x_k is increased by 1 unit (and all other variables hold fix)
- If $\beta_k = 0$, the odds (and probability) is equal at all x_k levels ($e^{\beta_k} = 1$)
- If $\beta_k > 0$, the odds (and probability) increases as x_k increases ($e^{\beta_k} > 1$)
- If $eta_{\rm k}$ < 0 , the odds (and probability) decreases as ${\bf x}_{\rm k}$ increases (e^{eta_k} <1)

Confidence intervals for the coefficients in logistic regression

- \triangleright Note, that the coefficients β in logistic regression
 - > are, asymptotically, normally distributed
 - Don't have a t distribution (as in linear regression)
- > Therefore quantiles of the N(0,1) distribution are used
- \triangleright For a 95% confidence interval for β

$$\hat{\beta} \pm 1.96 \cdot \text{se}(\hat{\beta})$$

Confidence intervals for the odds ratio

Determine the 95% CI for

$$\beta_k = \left(\log(\operatorname{odd}_{x_k+1}) - \log(\operatorname{odd}_{x_k})\right) = \log\left(\frac{\operatorname{odd}_{x_k+1}}{\operatorname{odd}_{x_k}}\right) = \log(\operatorname{OR}_{x_k \to x_k+1})$$

95% CI for log(OR_{$$x_k \to x_k + 1$$}): $\left[\hat{\beta}_k - 1.96 \cdot se(\hat{\beta}_k) , \hat{\beta}_k + 1.96 \cdot se(\hat{\beta}_k) \right]$

95% CI for OR_{$$x_k \to x_k + 1$$}: $\left[e^{\hat{\beta}_k - 1.96 \cdot se(\hat{\beta}_k)}, e^{\hat{\beta}_k + 1.96 \cdot se(\hat{\beta}_k)} \right]$

A confidence interval for $\beta = logOR$ is symmetric

A confidence interval for $OR = e^{\beta}$ is skewed - the further OR is from 1, the more skewed is the confidence interval.

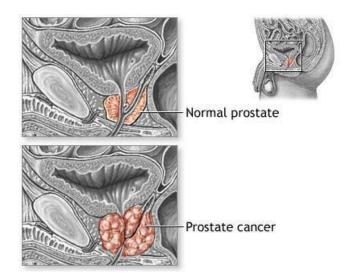
Example: Prostate Cancer

From a biopsy medical doctors can determine different continuous scores which might help to predict if the cancer is aggressive or not.

Target variable Y is binary (0 or 1):

 $Y_i = 1$ if tumor is aggressive

 $Y_i = 0$ if is not aggressive



Predictor or Covariates variables X_i are continuous

X₁: PSA: concentration of a predictive antigen

X₂: GS: gleason score is grading the cells

Goal:

We'd like to formulate a model that predicts the Y-value from the values of the two predictors or a probability for Y=1.

Modeling the prostate data by logistic regression in R

1.059344 0.158327 6.691 2.22e-11 ***

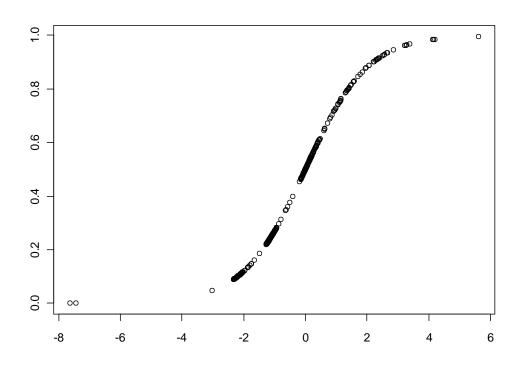
$$\log(\hat{o}dds) = \log(\frac{\pi}{1-\pi}) = -7.6 + 0.027 \cdot psa + 1.06 \cdot gs$$

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qs

Logistic regression model for the prostate data

$$P(Y = 1|x) = \frac{1}{1 + e^{-(-7.6 + 0.027 \cdot \text{psa} + 1.06 \cdot \text{gs}}}$$



 $h = \text{lin.predictor} = -7.6 + 0.027 \cdot \text{psa} + 1.06 \cdot \text{gs}$

Interpretation of the R output in the prostate example

$$\log(\hat{o}dds) = \log(\frac{\pi}{1-\pi}) = -7.6 + 0.027 \cdot psa + 1.06 \cdot gs$$

Which meaning has the estimated qs-coefficient 1.06?

- for two men who have same psa but a difference in their gs of one unit the expected difference of log(odds) or logOR is 1.06.

We usually look at the exponential of the coefficient:

- $-\exp(\beta_2) = \exp(1.06) = 2.88$
- The expected odds for having an aggressive tumor is 2.88-times higher for man with qs=7 than for a man with qs=6
- The odds ratio OR for a 1 unit difference in gs is $OR_{qs->qs+1} = e^{1.06} = 2.88$

- You also need to interpret changes as 'adjusting for PSA'

Interpretation of the coefficients in logistic regression Case 1: Continuous explanatory variable (reminder)

Let X_k be a continuous explanatory variable (e.g. PSA-value in the prostate example)

Interpretation of Regression Coefficient:

$$\log(\hat{o}dds) = \hat{\beta}_0 + \hat{\beta}_1 X_1 + \dots + \hat{\beta}_p X_p$$

- In logistic regression, the intercept (β_0) gives the log-odds of Y=1 (disease) amongst the subjects who have the value zero in all explanatory variables (*)
- the slope coefficient β_k gives the difference in the expected response (here: $\log (odds)$) as x_k increases by 1 unit (while fixing all other variables)

$$\beta_k = \left(\log(\operatorname{odd}_{x_k+1}) - \log(\operatorname{odd}_{x_k})\right) = \log\left(\frac{\operatorname{odd}_{x_k+1}}{\operatorname{odd}_{x_k}}\right) = \log(\operatorname{OR}_{x_k \to x_k+1})$$

$$\Rightarrow e^{\beta_k} = OR_{x_k \to x_k + 1}$$

– Thus e^{β_k} gives the OR when the risk factor x_k is increased by 1 unit (and all other variables hold fix)

(*) this interpretation is valid for cohort or cross-sectional studies, but not for case-control studies where #D is fixed and therefore the odds for disease cannot be estimated from the collected data

Interpretation of the coefficients in logistic regression Case 2: Binary explanatory variable

Let X_1 be a binary explanatory variable.

$$\log(\hat{o}dds) = \hat{\beta}_0 + \hat{\beta}_1 X_1$$

We first consider one binary exposure variable X_1 taking on only two values, say, $x_1=1$ (exposed) and $X_1=0$ (unexposed).

First consider
$$X_1$$
=0: $\log(odds(X_1 = 0)) = \hat{\beta}_0 + \hat{\beta}_1 \cdot 0 = \hat{\beta}_0$

 \Rightarrow The intercept (β_0) gives the log odds of Y=1 (disease) amongst the subjects in the reference level $X_1=0$ meaning here among the unexposed (*).

Now consider
$$X_1 = 1$$
: $\log(odds(X_1 = 1)) = \hat{\beta}_0 + \hat{\beta}_1 \cdot 1 = \hat{\beta}_0 + \hat{\beta}_1$

$$\Rightarrow \log\left(\mathrm{OR}_{x_1=0\to x_1=1}\right) = \log\left(\mathrm{odds}(X_1=1)\right) - \log\left(\mathrm{odds}(X_1=0)\right)$$
$$= \hat{\beta}_0 + \hat{\beta}_1 - \hat{\beta}_0 = \hat{\beta}_1$$

Thus e^{β_1} gives the OR when the risk factor X_1 goes from the reference level (X_1 =0, unexposed) to the observed level (X_1 =1, exposed). It is essential to choose a good reference level (many observations with typical value.

Interpretation of the coefficients in logistic regression Case 1: Categorical explanatory variable (>2 levels)

Consider a categorical explanatory variable with k>2 different levels.

(e.g. drug with 4 levels: alcohol, heroin, cannabis, ecstasy)

For an exposure with $\mathbb K$ distinct levels, one level is first chosen as the baseline or reference group (e.g. alcohol). Refer to that level as level 0. Then the following $\mathbb K-1$ indicator variables $\mathbb X_{\pm}$ are defined, which allow to specify the exposure level of a subject:

 X_1 =1 if an individual's exposure is at level 1, and X_1 =0 otherwise.

 X_2 =1 if an individual's exposure is at level 2, and X_2 =0 otherwise.

• •

 X_{K-1} =1 if an individual's exposure is at level K-1, and X_{K-1} =0 otherwise.

$$\log(\hat{o}dds) = \hat{\beta}_0 + \hat{\beta}_1 X_1 + ... + \hat{\beta}_{k-1} X_{k-1}$$

 e^{β_j} is the OR comparing exposure level j to the reference level 0.

 $e^{\beta_4-\beta_2}$ is the OR comparing exposure level 4 to exposure level 2.

The pancreatic cancer and coffee drinking example

We take the case-control study of coffee drinking and pancreatic cancer (MacMahon et al., 1981) as an example for the further discussion.

		Pancrea	tic Cancer	
crude table		Cases	Controls	
Coffee drinking (cups per day)	>1	347	555	902
	0	20	88	108
		367	643	1010

stratified table

		Co	Coffee Drinking (Cups per Day)					
Sex	Disease Status	0	1–2	3–4	≥5	Total		
Men	Case	9	94	53	60	216		
	Controls	32	119	74	82	307		
Women	Case	11	59	53	28	151		
	Controls	56	152	80	48	336		
	Total	108	424	260	218	1010		

Ungrouped and grouped data

When collecting data, the observed variable values corresponding to one study subject (or patient) are typically collected in one row of the original data set. This is called *ungrouped* data.

If the study subjects have many identical values in their variables, which is often the case if the variables are categorical, a more compact way of representing the data by forming groups with identical variable setting. This is as "grouped data".

Coffee data in ungrouped and grouped representation

Ungrouped data – 1010 x 4 1 row for each patient

	case	coffee	sex	index.coffee				
1	0	3	0	1				
2	0	3	0	1				
3	0	C	ase:					
4	0			no cancer)				
5	0	7	1=case (cancer)					
6	0	3	0	1				
7	0	3	0	1				
8	0	3	0	1				

:			Coffe	ee:		
81	0	3	Leve	l of co	offee	
82	0	3	drin	king		
83	0	2	0	1		
84	0	2	0	1		
85	0	2	0	1		
86	0	2	0	1		
87	0	2	0	1		Sex:
÷						0=male 1=female

Grouped data: -8 x 4

1 row for each risk factor setting defining a patient-group

(8 groups = 2 Gender x 4 coffee-levels)

	Coffee	Sex	Count.Ctrl	Count.Case	Count
1	0	0	32	9	41
2	0	1	56	11	67
3	1	0	119	94	213
4	1	1	152	59	211
5	2	0	74	53	127
6	2	1	80	53	133
7	3	0	82	60	142
8	3	1	48	28	76

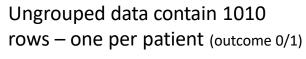
Count.Ctrl: # 0-outcome in this group Count n_i in ith group: #patients with this variable setting

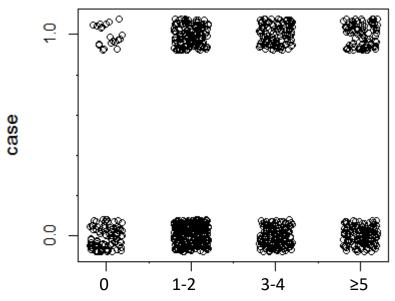
Count.Case: # 1-outcome in this group

How to get from grouped to ungrouped data using R Coffee data in ungrouped and grouped representation

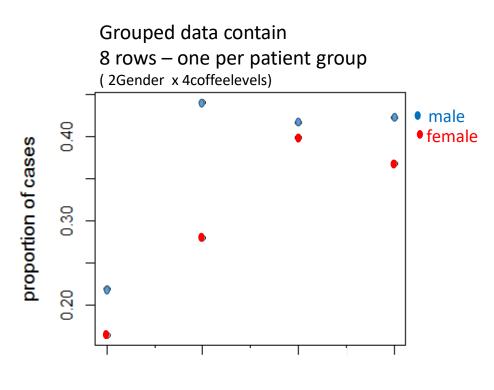
```
co.gr <- read.csv("coffee.csv", sep=";")

co.ungr = data.frame(case = as.factor(unlist(mapply(rep, x=co.gr$Case, times=co.gr$Count))))
co.ungr$coffee = unlist(mapply(rep, x=co.gr$Coffee, times=co.gr$Count))
co.ungr$sex = as.factor(unlist(mapply(rep, x=co.gr$Sex, times=co.gr$Count)))
co.ungr$index.coffee=as.factor(1*(co.ungr$coffee>0))
```





cups of coffee per day



cups of coffee per day

Logistic regression using the ungrouped data

```
> fit.ungr=glm(case~as.factor(coffee), family=binomial(link="logit"),data=co.ungr)
> summary(fit.ungr)
Call:
glm(formula = case ~ as.factor(coffee), family = binomial(link = "logit"),
    data = co.ungr)
Deviance Residuals:
               1Q
                    Median
    Min
                                  3Q
                                           Max
-1.0234 -1.0168 -0.9462
                              1.3470
                                       1.8365
Coefficients:
                                                                     Do not over-interpret these p-
                    Estimate Std. Error z value Pr(>|z|)
                                                                    values, but compare models with
                     -1.4816
                                  0.2477
                                           ~5.981 2.22e-09 ***
(Intercept)
as.factor(coffee)1
                      0.9099
                                  0.2676
                                            3.401 0.000672 ***
                                                                     and w/o this covariate (via \chi2
as.factor(coffee)2
                                  0.2780
                                            3.986 6.73e-05 ***
                      1.1081
                                                                    test using the R function anova)
                      1.0914
                                  0.2836
                                            3.849 0.000119 ***
as.factor(coffee)3
                                                                      to asses if this covariate is
                                                                            significant.
                 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
Signif. codes:
(Dispersion parameter for binomial family taken to be 1)
    Null deviance: 1323.8 on 1009
                                      degrees of freedom
Residual deviance: 1303.6 on 1006
                                      degrees of freedom
AIC: 1311.6
Number of Fisher Scoring iterations: 4
                                              #steps in IRLS estimation
```

Logistic regression using the grouped data

```
> fit.gr=glm(cbind(Count.Case,Count.Ctrl)~as.factor(Coffee),
             family=binomial(link="logit"),data=co.gr)
> summary(fit.gr)
Call:
glm(formula = cbind(Count.Case, Count.Ctrl) ~ as.factor(Coffee),
    family = binomial(link = "logit"), data = co.gr)
Deviance Residuals:
 0.5534 -0.4495 2.4125 -2.5053 0.2206 -0.2161
Coefficients:
                   Estimate Std. Error z value Pr(>|z|)
                    -1.4816
                                        -5.981 2.22e-09 ***
(Intercept)
                                0.2477
as.factor(Coffee)1
                     0.9099
                                0.2676
                                          3.401 0.000672 ***
as.factor(Coffee)2
                    1.1081
                                0.2780 /3.986 6.73e=05
as.factor(Coffee)3
                     1.0914
                                0.2836
                                                      We get the same estimates & se with
                                                      grouped or ungrouped data
Signif. codes: 0 '*** 0.001 '** 0.01 '* 0.05
(Dispersion parameter for binomial family taken to be 1)
    Null deviance: 33.469 on 7 degrees of freedom
Residual deviance: 13.306 on 4 degrees of freedom
ATC: 61, 257
                                                      The resulting deviances are
Number of Fisher Scoring iterations: 4
                                                      different with grouped or
                                                      ungrouped data
```

Comparing two nested models in R

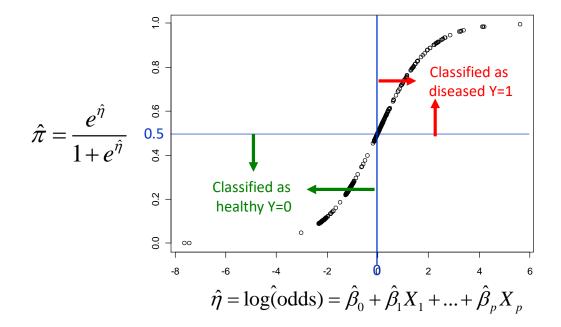
```
> anova(fit.gr,fit.gr2,test="Chisq")
Analysis of Deviance Table
Model 1: cbind(Count.Case, Count.Ctrl) ~ as.factor(Coffee)
Model 2: cbind(Count.Case, Count.Ctrl) ~ as.factor(Coffee)(+ Sex
  Resid. Df Resid. Dev Df Deviance Pr(>Chi)
                13.306
                 4.268 1 (9.0378 0.002644 **
                                              Adding of the explanatory
                                              variable Sex improves the
> drop1(fit.gr2, test="Chisq")
Single term deletions
                                              model fit.
Model:
cbind(Count.Case, Count.Ctrl) ~ as.factor(Coffee) + Sex
                   Df Deviance AIC
                                          LRT Pr(>Chi)
                         4.268 54.219
<none>
as.factor(Coffee) 3 21.870 65.822 17.6024 0.0005312 ***
                        13.306 61.257 9.0378 0.0026445
Sex
```

Using logistic regression for binary classification

A logistic regression model is not only used explaining the relation between predictors and outcome which is captured in the coefficients — we can also use it to make predictions based on the predictor values.

Fitted probability:

$$\hat{\pi}_{i} = g^{-1}(\eta_{i}) = \frac{e^{\hat{\eta}_{i}}}{1 + e^{\hat{\eta}_{i}}} = \frac{e^{\hat{\beta}_{0} + \hat{\beta}_{1}X_{1} + \dots + \hat{\beta}_{p}X_{p}}}{1 + e^{\hat{\beta}_{0} + \hat{\beta}_{1}X_{1} + \dots + \hat{\beta}_{p}X_{p}}}$$



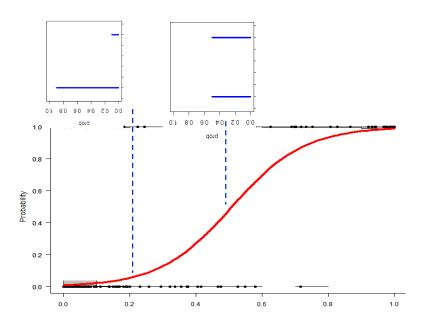
Comparison Logistic Regression / Linear

Logistic Regression

$$p(x) = a \cdot x + b$$

 $Y \sim Bern(p(x))$

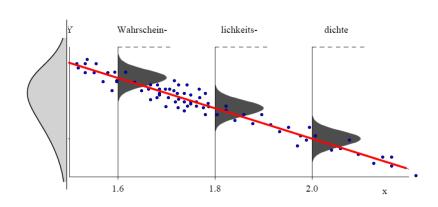
glm(y ~ ., binomial(logit))



Linear Regression

$$\mu(x) = a \cdot x + b$$
$$Y \sim N(\mu(x), \sigma = 1)$$

glm(y ~ ., gaussian(identity))



Summary

- Logistic regression can model the association between a binary outcome and a exposure and allows to adjust for confounders of any data type
 - The coefficients in a logistic regression model can be interpreted as log-OR when the corresponding predictor increases by one and all other predictors stay constant
 - Bernoulli logistic regression works on ungrouped data (1 observation = 1 row in data matrix)
 - Binomial logistic regression works on grouped data (only possible with categorical predictors)
 - When working with factor variables it is important to choose a good reference level

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