Lecture 4: Regression (continued) and multiple regression

BIO144 Data Analysis in Biology

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Recap of last week

- Why use linear regression?
- Fitting the line (least squares).
- Is the linear model good enough – the five assumptions.
- What if something goes wrong (transformations and handling outliers)?

Overview of this week

Regression continued...

- How well does the model describe the data: Correlation and R^2
- Are the parameter estimates compatible with some specific value (t-test)?
- What range of parameters values are compatible with the data (confidence intervals)?
- What regression lines are compatible with the data (confidence band)?
- What are plausible values of other data (prediction band)?

Multiple regression:

- Multiple linear regression $x_1, x_2, \ldots, x_m$
- Checking assumptions
- R^2 in multiple linear regression
- t-tests, F-tests and p-values

Course material covered today

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

- Chapters 3.1, 3.2a-q of *Lineare Regression*
- Chapters 4.1 4.2f, 4.3a-e of *Lineare Regression*

How good is the regression model?

This is, per se, a difficult question. . . .

One often considered index is the **coefficient of determination (Bestimmtheitsmass)** R^2. Let us again look at the regression output form the bodyfat example:

```
summary(r.bodyfat)$r.squared
```

```
## [1] 0.5390391
```

Compare this to the squared correlation between the two variables:

```
cor(d.bodyfat$bodyfat,d.bodyfat$bmi)^2
```

```
## [1] 0.5390391
```

$\rightarrow$ In simple linear regression, R^2 is the squared correlation between the independent and the dependent variable.

- R^2 indicates the proportion of variability of the response variable y that is **explained by the ensemble of all covariates**.
- Its value lies between 0 and 1.

The **larger** R^2

$\Rightarrow$ the **more** variability of y is captured ("explained") by the covariate
$\Rightarrow$ the **"better"** is the model.

(However, it's a bit more complicated, as we will see in the multiple regression later in the lecture today)

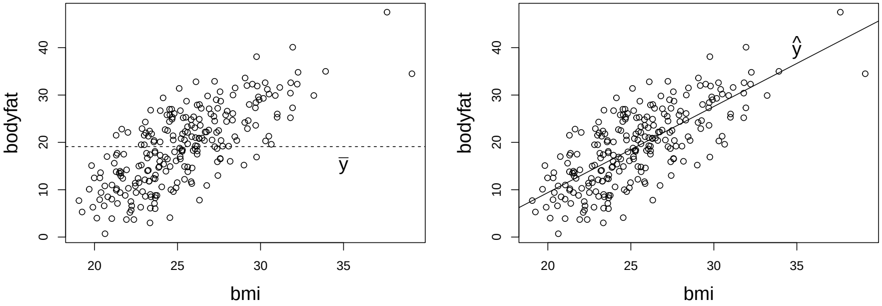
R^2 is also called the *coefficient of determination* or "Bestimmtheitsmass", because it measures the proportion of the reponse's variability that is explained by the ensemble of all explanatory variables:

$$R^2 = SSQ^{(R)}/SSQ^{(Y)} = 1 - SSQ^{(E)}/SSQ^{(Y)}$$

With

$$\begin{array}{ccccc} \text{total variability} & = & \text{explained variability} & + & \text{residual variability} \\ \sum_{i=1}^{n}(y_i - \overline{y})^2 & = & \sum_{i=1}^{n}(\hat{y}_i - \overline{y})^2 & + & \sum_{i=1}^{n}(y_i - \hat{y}_i)^2 \\ SSQ^{(Y)} & = & SSQ^{(R)} & + & SSQ^{(E)} \end{array}$$

This can be visualized for a model with only one predictor:



Are the parameter estimates compatible with some specific value (t-test)?

Important: $\hat{\beta}_0$ and $\hat{\beta}_1$ are themselves random variables and as such contain uncertainty!

Let us look again at the regression output, this time only for the coefficients. The second column shows the *standard error* of the estimate:

```
summary(r.bodyfat)$coef
```

```
##               Estimate Std. Error   t value     Pr(>|t|)
## (Intercept) -26.984368  2.7689004 -9.745518 3.921511e-19
## bmi           1.818778  0.1083411 16.787522 2.063854e-42
```

$\rightarrow$ The logical next question is: what is the distribution of the estimates?

Distribution of the estimators for $\hat{\beta}_0$ and $\hat{\beta}_1$

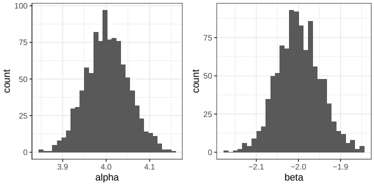
To obtain an idea, we generate data points according to model

$$y_i = 4 - 2x_i + \epsilon_i \ , \quad \epsilon_i \sim N(0, 0.5^2).$$

In each round, we estimate the parameters and store them:

```
niter <- 1000
pars <- matrix(NA,nrow=niter,ncol=2)
for (ii in 1:niter){
  x <- rnorm(100)
  y <- 4 - 2*x + rnorm(100,0,sd=0.5)
  pars[ii,] <- lm(y~x)$coef
}
```

Doing it 1000 times, we obtain the following distributions for $\hat{\beta}_0$ and $\hat{\beta}_1$:



This looks suspiciously normal!

In fact, from theory it is known that

$$\hat{\beta}_1 \sim N(\beta_1, \sigma^{(\beta_1)2}) \qquad \text{and} \qquad \hat{\beta}_0 \sim N(\beta_0, \sigma^{(\beta_0)2})$$

For formulas of the variances $\sigma^{(\beta_1)2}$ and $\sigma^{(\beta_0)2}$, please consult Stahel 2.2.h.

To remember:

- $\hat{\beta}_0$ and $\hat{\beta}_1$ are unbiased estimators of β_0 and β_1.
- the parameters estimates $\hat{\beta}_0$ and $\hat{\beta}_1$ are normally distributed.
- the formulas for the variances depend on the residual variance σ^2, the sample size n and the variability of X ($\text{SSQ}^{(X)(\star)}$).

$(\star)$

$$\text{SSQ}^{(X)} = \sum_{i=1}^{n} (x_i - \overline{x})^2$$

With all this, we can calculate a standardised measure of the uncertainty in the parameter estimates, known as the *standard error*, or *SE*:

Standard error of parameter estimate: $se^{(\beta_1)} = \sqrt{\frac{\hat{\sigma}^2}{SSQ^{(X)}}}$

Estimated residual variance: $\hat{\sigma}^2 = \frac{1}{n-2} \sum_{i=1}^{n} R_i^2$

Residuals (also sometimes e_i): $R_i = Y_i - (\hat{\beta}_0 + \hat{\beta}_1 x_i)$

Sum of squares of X: $SSQ^{(X)} = \sum_{i=1}^{n} (x_i - \bar{x})^2$

Are the parameter estimates compatible with some specific value (t-test)?

Let's first go back to the output from the bodyfat example:

```r
summary(r.bodyfat)$coef
```

```
##                Estimate Std. Error   t value     Pr(>|t|)
## (Intercept) -26.984368  2.7689004 -9.745518 3.921511e-19
## bmi           1.818778  0.1083411 16.787522 2.063854e-42
```

Besides the estimate and the standard error (which we discussed before), there is a `t value` and a probability `Pr(>|t|)` that we need to understand.

How do these things help us?

Testing the “effect” of a covariate

Remember: in a statistical test you first need to specify the *null hypothesis*. Here, typically, the null hypothesis is

$$H_0 : \quad \beta_1 = 0 \ .$$

In words: H_0 = "no association"

Here, the *alternative hypothesis* is given by

$$H_A : \quad \beta_1 \neq 0$$

Remember: To carry out a statistical test, we need a *test statistic*.

What is a test statistic?

$\rightarrow$ It is some type of **summary statistic** that follows a known distribution under H_0.
For our purpose, we use the so-called T**-statistic**

$$T = \frac{\hat{\beta}_1 - \beta_{1,H_0}}{se(\beta_1)} \ . \qquad (1)$$

Again: typically, $\beta_{1,H_0} = 0$, so the formula simplifies to $T = \frac{\hat{\beta}_1}{se(\beta_1)}$.

Under H_0, T has a t-distribution with $n - 2$ degrees of freedom ($n =$ number of data points).

(You should try to recall the t-distribution. Check Mat183, keyword: t-test.)

So let's again go back to the bodyfat regression output:

```
summary(r.bodyfat)$coef
```

```
##              Estimate Std. Error   t value     Pr(>|t|)
## (Intercept) -26.984368  2.7689004 -9.745518 3.921511e-19
## bmi           1.818778  0.1083411 16.787522 2.063854e-42
```

Task:
→ Please use equation (1) to find out how the first three columns (Estimate, Std. Error and t value) are related! Check by a calculation...

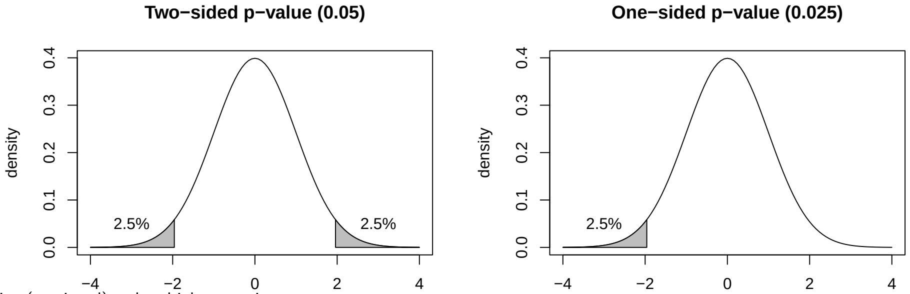
Note: The last column contains the *p*-**value** of the test of the null hypothesis of $\beta_1 = 0$.

Recap: Formal definition of the p-value

The **formal definition of p-value** is the probability to observe a data summary (e.g., an average) that is at least as extreme as the one observed, given that the Null Hypothesis is correct.

Example (normal distribution): Assume that we calculated that t-value = -1.96

$\Rightarrow Pr(|t| \geq 1.96) = 0.05$ and $Pr(t \leq -1.96) = 0.025$.



The regression output from R indicates that the p-value for BMI is very small ($p < 0.0001$).

Conclusion: there is **very strong evidence** that the BMI is associated with bodyfat, because p is extremely small (thus it is very unlikely that such a slope $\hat{\beta}_1$ would be seen if there was no association of BMI and body fat).

This basically answers question 1: "Are the parameters compatible with some specific value?"

A cautionary note on the use of p-values

Maybe you have seen that in statistical testing, often the criterion $p \leq 0.05$ is used to test whether H_0 should be rejected. This is often done in a black-or-white manner.

However, we will put a lot of attention to a more reasonable and cautionary interpretation of p-values in this course!

What range of parameters values are compatible with the data (confidence intervals)?

To answer this question, we can determine the confidence intervals of the regression parameters.

Facts we know about $\hat{\beta}_1$

- $\hat{\beta}_1$ is estimated with a standard error of $\sigma^{(\beta_1)}$
- The distribution of $\hat{\beta}_1$ is normal, namely $\hat{\beta}_1 \sim N(\beta_1, \sigma^{(\beta_1)2})$.
- However, since we need to estimate $\sigma^{(\beta_1)}$ from the data, we have a t-distribution.

Doing some calculations (similar to those in chapter 8.2.2 of Mat183 script) leads us to the 95% confidence interval

$$[\hat{\beta}_1 - c \cdot \hat{\sigma}^{(\beta_1)}; \hat{\beta}_1 + c \cdot \hat{\sigma}^{(\beta_1)}] \ ,$$

where c is the 97.5% quantile of the t-distribution with $n-2$ degrees of freedom.

Doing this for the bodfat example "by hand" is not hard. We have 241 degrees of freedom:

```
coefs <- summary(r.bodyfat)$coef
beta <- coefs[2,1]
sdbeta <- coefs[2,2]
beta + c(-1,1) * qt(0.975,241) * sdbeta
```

```
## [1] 1.605362 2.032195
```

Even easier: directly ask R to give you the CIs.

```r
confint(r.bodyfat,level=c(0.95))
```

```
##                  2.5 %     97.5 %
## (Intercept) -32.438703 -21.530032
## bmi           1.605362   2.032195
```

In summary,

	Coefficient	95%-confidence interval	*p*-value
Intercept	-26.98	from -32.44 to -21.53	< 0.0001
bmi	1.82	from 1.61 to 2.03	< 0.0001

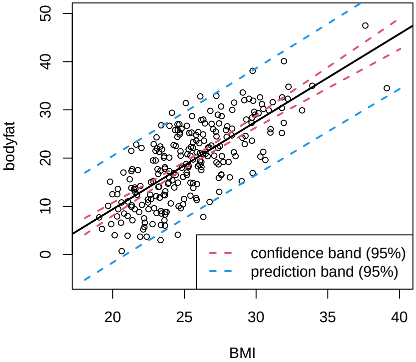
Interpretation: for an increase in the bmi by one index point, roughly 1.82% percentage points more bodyfat are expected, and all true values for β_1 between 1.61 and 2.03 are compatible with the observed data.

Confidence and Prediction Bands

- Remember: When another sample from the same population was taken, the regression line would look slightly different.
- There are two questions to be asked:

1. Which other regression lines are compatible with the observed data?
   $\Rightarrow$ This leads to the **confidence band**.
2. Where do future observations with a given x coordinate lie?
   $\Rightarrow$ This leads to the **prediction band**.

Bodyfat example



Note: The prediction band is much broader than the confidence band.

Calculation of the confidence band

Given a fixed value of x, say x_0. The question is:

Where does $\hat{y}_0 = \hat{\beta}_0 + \hat{\beta}_1 x_0$ lie with a certain confidence (i.e., 95%)?

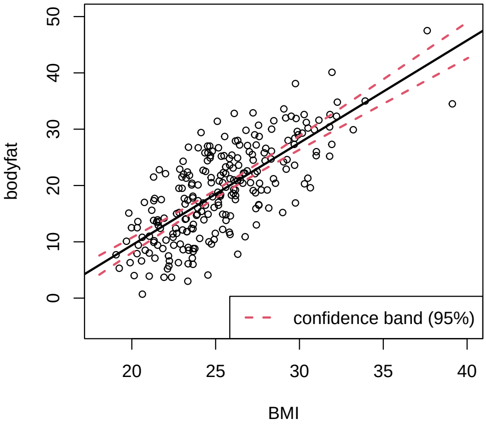
This question is not trivial, because both $\hat{\beta}_0$ and $\hat{\beta}_1$ are estimates from the data and contain uncertainty.

The details of the calculation are given in Stahel 2.4b.

Plotting the confidence interval around all $\hat{y}_0$ values one obtains the **confidence band** or **confidence band for the expected values** of y.

Note: For the confidence band, only the uncertainty in the estimates $\hat{\beta}_0$ and $\hat{\beta}_1$ matters.

Confidence band



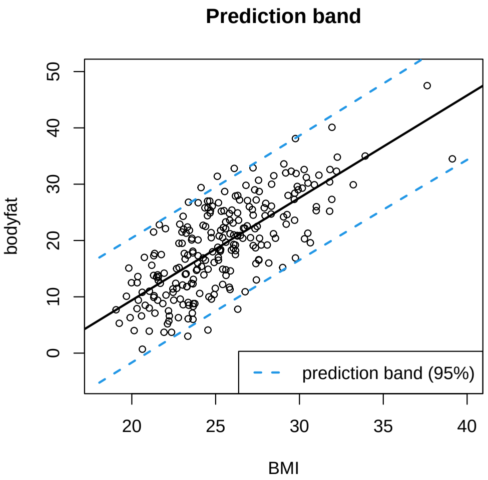
Calculations of the prediction band

Given a fixed value of x, say x_0. The question is:

Where does a **future observation** lie with a certain confidence (i.e., 95%)?

To answer this question, we have to consider not only the uncertainty in the predicted value $\hat{y}_0 = \hat{\beta}_0 + \hat{\beta}_1 x_0$, but also the error in the equation $\epsilon_i \sim N(0, \sigma^2)$.

This is the reason why the **prediction band is always wider than the confidence band.**



Prediction band
bodyfat
BMI
0
10
20
30
40
50
20
25
30
35
40
prediction band (95%)

That is regression done (at least for our current purposes)

- Why use (linear) regression?
- Fitting the line (= parameter estimation)
- Is linear regression good enough model to use?
- What to do when things go wrong?
- Transformation of variables/the response.
- Handling of outliers.
- Goodness of the model: Correlation and R^2
- Tests and confidence intervals
- Confidence and prediction bands

(Homework and Practical class: Presentation of findings)

Multiple linear regression

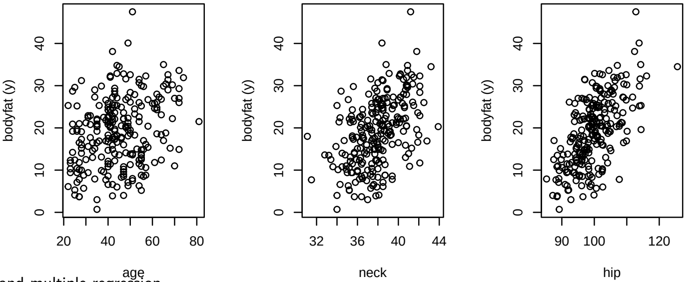
Multiple continuous explanatory variables.

- Question 1: Are the explanatory variables (i.e. more than one) associated with the response?
- Question 2: Which variables are associated with the response?
- Question 3: What proportion of variability is explained?

Bodyfat example

We have so far modeled bodyfat in dependence of bmi, that is:
$(bodyfat)_i = \beta_0 + \beta_1 \cdot bmi_i + \epsilon_i$.
However, other explanatory variables might also be relevant for an accurate prediction of bodyfat.

Examples: Age, neck fat (Nackenfalte), hip circumference, abdomen circumference etc.



Multiple linear regression is when we have more than one explanatory variable. We can then ask three questions:

1. Is the **ensemble** of all explanatory variables associated with the response?
2. If yes, which explanatory variables are associated with the response?
3. What proportion of response variability ($SSQ^{(Y)}$) is explained by the model?

Multiple linear regression model

The idea is simple: Just **extend the linear model by additional predictors**.

- Given several influence explanatory variables $x_i^{(1)}, \ldots, x_i^{(m)}$, the straightforward extension of the simple linear model is

$$
\begin{aligned}
y_i &= \beta_0 + \beta_1 x_i^{(1)} + \beta_2 x_i^{(2)} + \ldots + \beta_m x_i^{(m)} + \epsilon_i \\
\text{with} \quad \epsilon_i &\sim N(0, \sigma^2).
\end{aligned}
$$

- The parameters of this model are $\beta = (\beta_0, \beta_1, \ldots, \beta_m)$ and σ^2.

The components of β are again estimated using the **least squares** method. Basically, the idea is (again) to minimize

$$\sum_{i=1}^{n} e_i^2$$

with

$$e_i = y_i - (\beta_0 + \beta_1 x_i^{(1)} + \beta_2 x_i^{(2)} + \ldots + \beta_m x_i^{(m)})$$

It is a bit more complicated than for simple linear regression, see Section 3.4 of the Stahel script.

Some **linear algebra** is needed to understand these sections; we look at this in Lecture 7.

Multiple linear regression for bodyfat

Let us regress the proportion (%) of bodyfat (from last week) on the predictors **bmi** and **age** simultaneously. The model is thus given as

$$
\begin{aligned}
(bodyfat)_i &= \beta_0 + \beta_1 \cdot bmi_i + \beta_2 \cdot age_i + \epsilon_i \ , \\
\text{with} \quad \epsilon_i &\sim N(0, \sigma^2) \ .
\end{aligned}
$$

Multiple linear regression with R

Let's now fit the model with R, and quickly glance at the output:

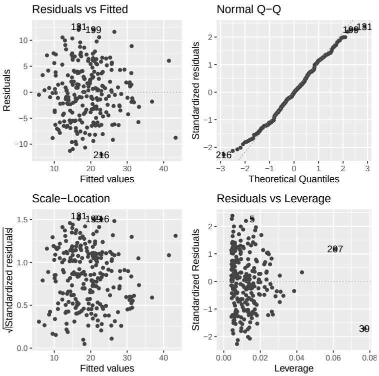
```
r.bodyfatM <- lm(bodyfat ~ bmi + age, d.bodyfat)

summary(r.bodyfatM)
```

```
##
## Call:
## lm(formula = bodyfat ~ bmi + age, data = d.bodyfat)
##
## Residuals:
##      Min       1Q   Median       3Q      Max
## -12.0415  -3.8725  -0.1237   3.9193  12.6599
##
## Coefficients:
##              Estimate Std. Error t value Pr(>|t|)
## (Intercept) -31.25451    2.78973 -11.203  < 2e-16 ***
## bmi           1.75257    0.10449  16.773  < 2e-16 ***
## age           0.13268    0.02732   4.857 2.15e-06 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Residual standard error: 5.329 on 240 degrees of freedom
## Multiple R-squared:  0.5803, Adjusted R-squared:  0.5768
## F-statistic: 165.9 on 2 and 240 DF,  p-value: < 2.2e-16
```

Model checking

Before we look at the results, we must check if the modelling assumptions are fulfilled (check our 'chute before we jump):



This seems ok, so continue with answering questions 1-3.

Question 1: Are the explanatory variables associated with the response?

To answer question 1, we need to perform a so-called F-test. The results of the test are displayed in the final line of the regression summary. Here, it says:

```
F-statistic:  165.9 on 2 and 240 DF,  p-value: < 2.2e-16
```

So apparently (and we already suspected that) the model has some explanatory power.

*The F-statistic and -test is briefly recaptured in 3.1.f) of the Stahel script, but see also Mat183 chapter 6.2.5. It uses the fact that

$$\frac{SSQ^{(R)}/m}{SSQ^{(E)}/(n-p)} \sim F_{m,n-p}$$

follows an F-distribution with m and $(n-p)$ degrees of freedom, where m are the number of variables, n the number of data points, p the number of β-parameters (typically $m+1$). $SSQ^{(E)} = \sum_{i=1}^n R_i^2$ is the squared sum of the residuals, and $SSQ^{(R)} = SSQ^{(Y)} - SSQ^{(E)}$ with $SSQ^{(y)} = \sum_{i=1}^n (y_i - \overline{y})^2$.

n is the number of data points

m is the number of explanatory variables in the regression model

p is the number of beta parameters estimated (e.g. intercept, plus a slope for each explanatory variable, hence $p = m + 1$)

And the degrees of freedom for error are $n - p$

Question 2: Which variables are associated with the response?

```
summary(r.bodyfatM)$coef
```

```
##                Estimate Std. Error    t value     Pr(>|t|)
## (Intercept) -31.2545057 2.78973238 -11.203406 1.039096e-23
## bmi           1.7525705 0.10448723  16.773060 2.600646e-42
## age           0.1326767 0.02731582   4.857137 2.149482e-06
```

To answer this question, again look at the *t-tests*, for which the *p*-values are given in the final column. Each *p*-value refers to the test for the null hypothesis $\beta_0^{(j)} = 0$ for explanatory variable $x^{(j)}$.

As in simple linear regression, the T-statistic for the j-th explanatory variable is calculated as

$$T_j = \frac{\hat{\beta}_j}{se^{(\beta_j)}} \ , \qquad (2)$$

with $se^{(\beta_j)}$ given in the second column of the regression output.

The distribution of this statistic is $T_j \sim t_{n-p}$.

Therefore: A "small" p-value indicates that the variable is relevant in the model.

Here, we have

- $p < 0.001$ for bmi
- $p < 0.001$ for age

Thus both, bmi and age seem to be associated with bodyfat.

Again, a 95% CI for $\hat{\beta}_j$ can be calculated with R:

```
confint(r.bodyfatM)
```

```
##                   2.5 %      97.5 %
## (Intercept) -36.7499929 -25.7590185
## bmi           1.5467413   1.9583996
## age           0.0788673   0.1864861
```

(The CI is again $[\hat{\beta} - c \cdot \sigma^{(\beta)}; \hat{\beta} + c \cdot \sigma^{(\beta)}]$, where c is the 97.5% quantile of the t-distribution with $n - p$ degrees of freedom; compare to slides 38-40 of last week).

!However!:

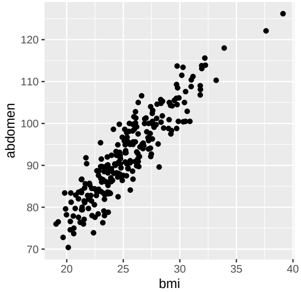
The p-value and T-statistics should only be used as a **rough guide** for the "significance" of the coefficients.

For illustration, let us extend the model a bit more, including also neck, hip and abdomen:

	Coefficient	95%-confidence interval	p-value
Intercept	-7.75	from -22.13 to 6.63	0.29
bmi	0.43	from -0.03 to 0.88	0.066
age	0.015	from -0.04 to 0.07	0.60
neck	-0.80	from -1.18 to -0.43	$<$ 0.0001
hip	-0.32	from -0.53 to -0.11	0.003
abdomen	0.84	from 0.67 to 1.00	$<$ 0.0001

It is now much less clear how strongly age ($p = 0.60$) and bmi ($p = 0.07$) are associated with bodyfat.

Basically, the problem is that the variables in the model are correlated and therefore explain similar aspects of bodyfat. **Example:** Abdomen (Bauchumfang) seems to be a relevant predictor and it is obvious that abdomen and BMI are correlated:



This problem of collinearity is at the heart of many confusions of regression analysis, and we will talk about such issues later in the course (lectures 8 and 9).

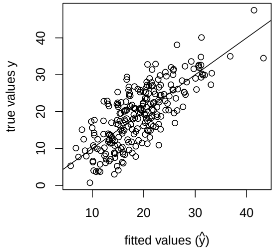
Please see also IC: practical 4 (milk example) for an analysis and more thoughts.

Question 3: Which proportion of variability is explained?

To answer this question, we can look at the multiple R^2 (see Stahel 3.1.h). It is a generalized version of R^2 for simple linear regression:

R^2 **for multiple linear regression** is defined as the squared correlation between $(y_1, \ldots, y_n)$ and $(\hat{y}_1, \ldots, \hat{y}_n)$, where the $\hat{y}$ are the fitted values

$$\hat{y}_i = \hat{\beta}_0 + \hat{\beta}_1 x^{(1)} + \ldots + \hat{\beta}_m x^{(m)}$$



Let us look at the R^2s from the three bodyfat models

model r.bodyfat: $y \sim bmi$

model r.bodyfatM: $y \sim bmi + age$

model r.bodyfatM2: $y \sim bmi + age + neck + hip + abdomen$:

```r
summary(r.bodyfat)$r.squared
```

```
## [1] 0.5390391
```

```r
summary(r.bodyfatM)$r.squared
```

```
## [1] 0.5802956
```

```r
summary(r.bodyfatM2)$r.squared
```

```
## [1] 0.718497
```

The models explain 54%, 58% and 72% of the total variability of y.

It thus *seems* that larger models are "better". However, R^2 does always increase when new variables are included, but this does not mean that the model is more reasonable.

Adjusted R^2

When the sample size n is small with respect to the number of variables m included in the model, an adjusted R^2 gives a better ("fairer") estimation of the actual variability that is explained by the explanatory variables:

$$R_a^2 = 1 - (1 - R^2)\frac{n-1}{n-m-1}$$

Why R_a^2?

It **penalizes for adding more variables** if they do not really improve the model!

Note: R_a may decrease when a new variable is added.

Interpretation of the coefficients

Apart from model checking and thinking about questions 1-3, it is probably even **more important to understand what you *see*.** Look at the output and ask yourself:

What does the regression output actually *mean*?

	Coefficient	95%-confidence interval	p-value
Intercept	-31.25	from -36.75 to -25.76	< 0.0001
bmi	1.75	from 1.55 to 1.96	< 0.0001
age	0.13	from 0.08 to 0.19	< 0.0001

Table 1: Parameter estimates of model 2.

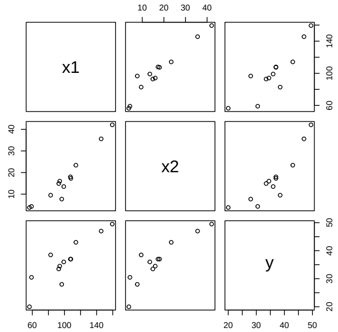
Task in teams: Interpret the coefficients, 95% CIs and p-values.

Example: Catheter Data

Catheter length (y) for heart surgeries depending on two characteristic variables $x^{(1)}$ and $x^{(2)}$ of the patients.

Aim: estimate y from $x^{(1)}$ and $x^{(2)}$ ($n = 12$).

Again look at the data first ($x^{(1)}$ and $x^{(2)}$ are highly correlated!):



Regression results with both variables: $R^2 = 0.81$, $R^2 = 0.76$, F-test $p = 0.0006$.

	Coefficient	95%-confidence interval	p-value
Intercept	21.09	from 1.25 to 40.93	0.04
x1	0.077	from -0.25 to 0.40	0.61
x2	0.43	from -0.41 to 1.26	0.28

With x_1 only: $R^2 = 0.78, R_a^2 = 0.75$, F-test $p = 0.0002$

	Coefficient	95%-confidence interval	p-value
Intercept	12.13	from 2.66 to 21.59	0.017
x1	0.24	from 0.15 to 0.33	0.0002

With x_2 only: $R^2 = 0.80, R_a^2 = 0.78$, F-test $p = 0.0001$

	Coefficient	95%-confidence interval	p-value
Intercept	25.63	from 21.16 to 30.09	< 0.0001
x2	0.62	from 0.40 to 0.83	< 0.0001

Questions to consider:

1. Is x_1 an important explanatory variable?
2. Is x_2 an important explanatory variable?
3. Are both explanatory variables needed in the model?
4. Interpretation of the results?

Recap

- How well does the model describe the data: Correlation and R^2
- Are the parameter estimates compatible with some specific value (t-test)?
- What range of parameters values are compatible with the data (confidence intervals)?
- What regression lines are compatible with the data (confidence band)?
- What are plausible values of other data (prediction band)?

Multiple regression:

- Multiple linear regression $x_1, x_2, \ldots, x_m$
- Checking assumptions
- R^2 in multiple linear regression
- t-tests, F-tests and p-values

Next steps

- Homework.
- Practical.
- Then week 5: Binary/categorical explanatory variables, and interactions