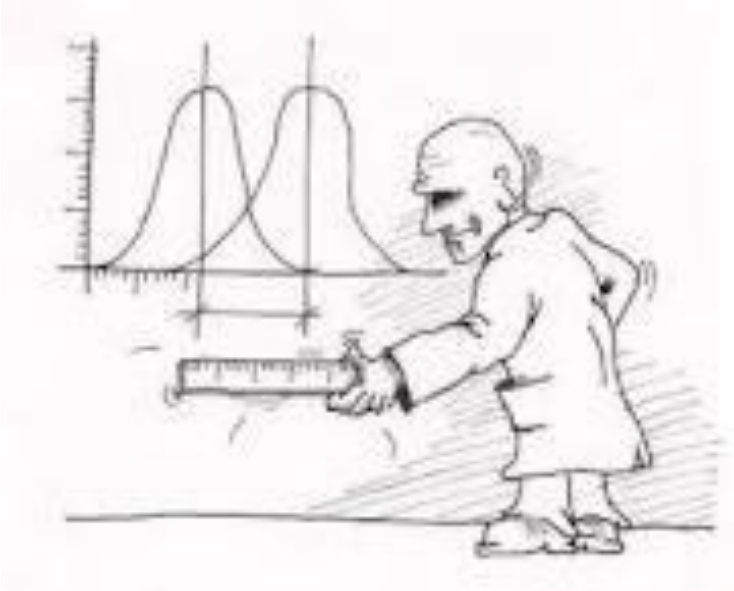
Biostatistics

Formalia

- **Lectures: Tuesdays , 10:10-11:45 , HG E21, Beate Sick**
- **Exercises: Tuesdays, 16:15-17:00, HG D7.1, Lisa Herzog**
- **Material: https://bsick.github.io/Biostatistics-Fall-2018/**



1

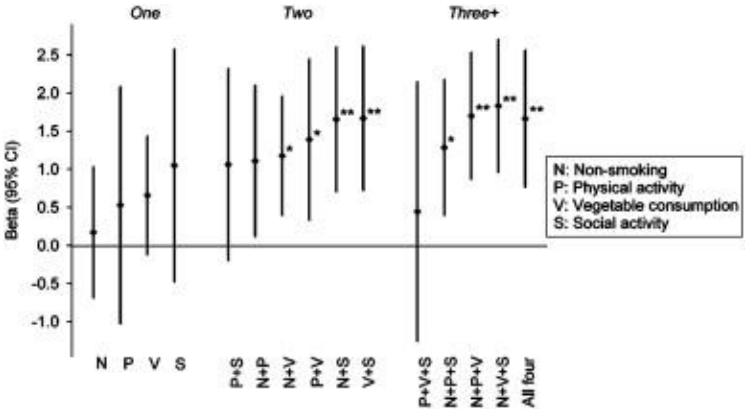
Goal of the module "Biostatistics"

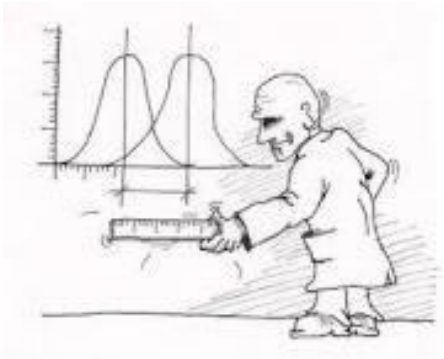
- **Goal is to get more confident…**

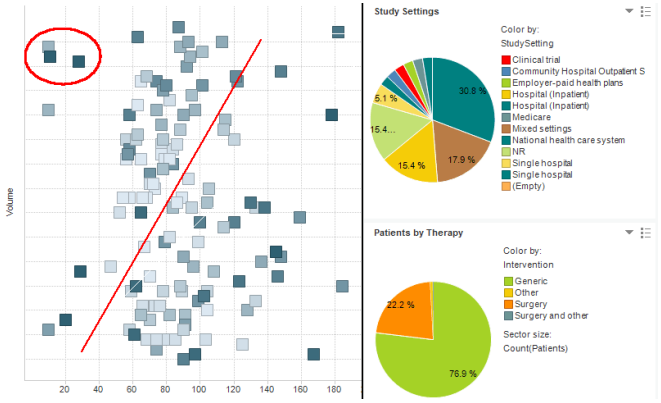
  - in the most widely used statistical methods

  - in reading data analysis sections in in scientific articles, especially in medical or biological journals

  - Visualizing and analyzing own data







Biostatistics for Medical Physicists

Topics

Exam is on these topics, written, 45 minutes

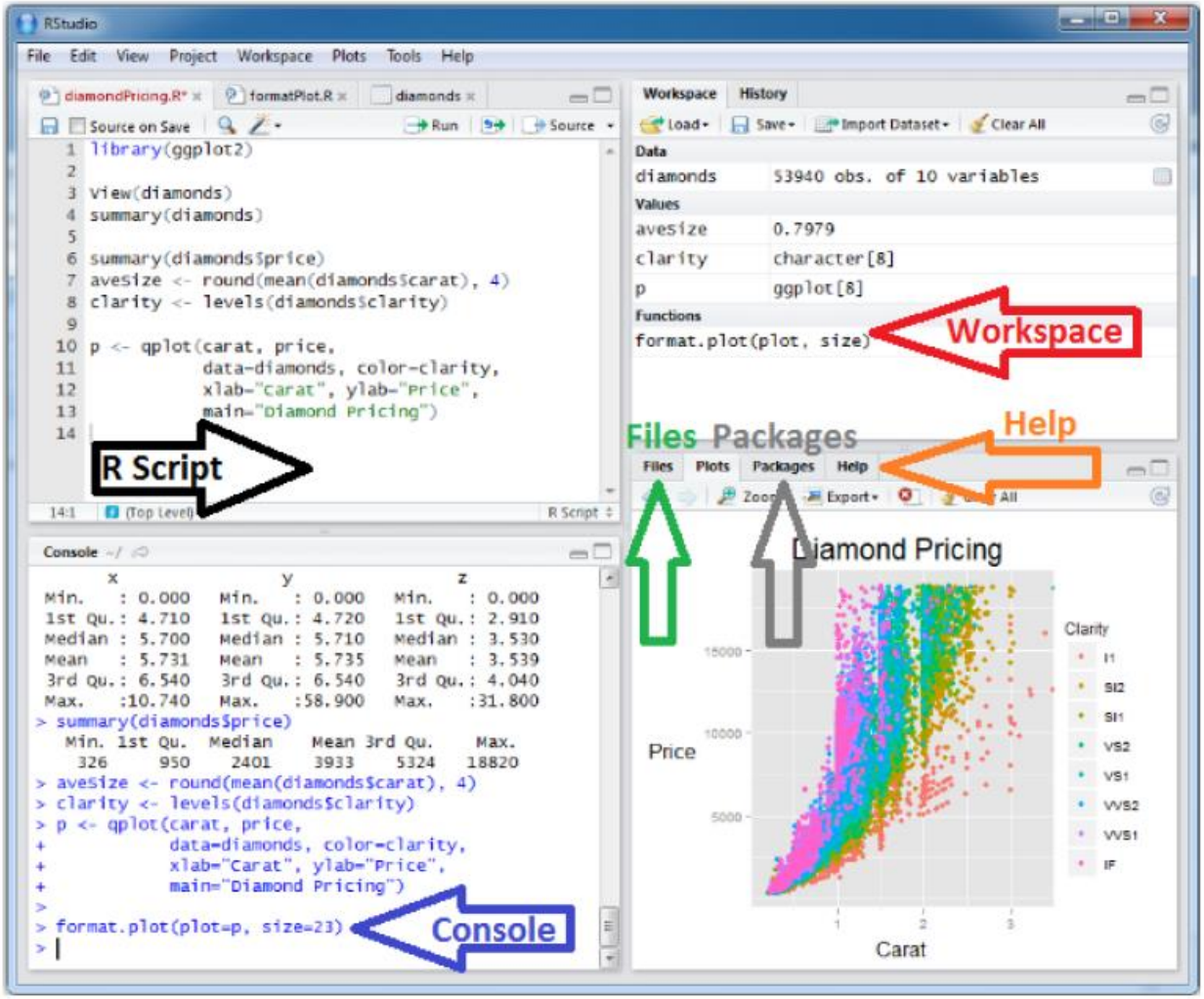
- data visualization
- basic terms and summary statistics
- study types, confounding
- diagnostic tests
- models/distribution-types
- parameter estimation
- testing, confidence intervals, p-values
- linear regression
- reliability analysis
- logistic regression
- outlook on more advanced or modern regression methods

3

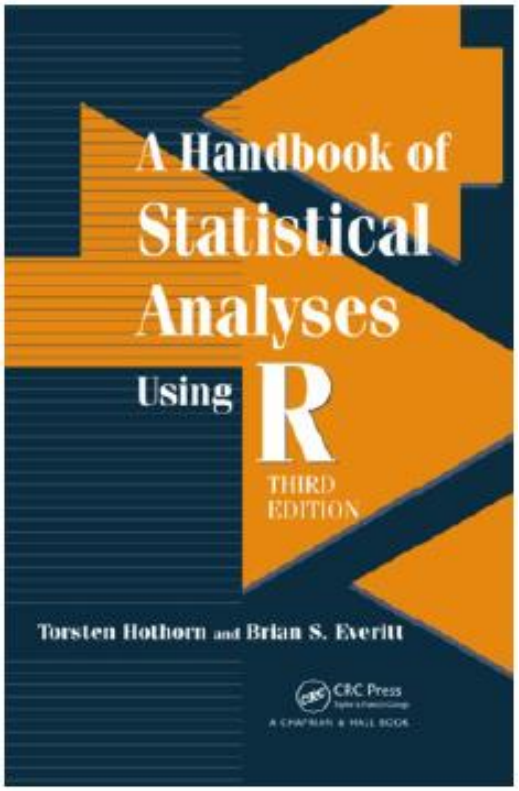
We use R for performing statistical data analysis
Recommended environment: RStudio

Main reasons:

- open source
- powerful
- wide spread
- reproducible
- transparent



Literature: no book needs to be purchased



Selected chapters from "A Handbook of Statistical Analysis Using R" by Torsten Hothorn, UZH, serve as recommended readings for this course and are provided on the course website. In addition some selected method articles will be recommended.

The R package HSAUR3 provides the selected chapters as PDF besides all data sets, examples and R code

http://CRAN.R-project.org/package=HSAUR3

Torsten.Hothorn@R-project.org

My background: Important stations

Head of bioinformatics & biostatistics at DNA Array Facility UNIL

Prof. for applied statistics & Scientist

Providing trainings for life science researcher

Scientific collaborator, consultant, and lecturer in the field of biostatistics and medical research

Biostatistics for Medical Physicists
Week 1

Topics this week:

- **Goals of this module**
- **Data types**
- **methods for uni-variate data visualization**
- **terms and key numbers**

Research Article Example:
Paper on hyperactivity form McCann et al.

Food additives and hyperactive behaviour in 3-year-old and 8/9-year-old children in the community: a randomised, double-blinded, placebo-controlled trial

Donna McCann, Angelina Barrett, Alison Cooper, Debbie Crumpler, Lindy Dalen, Kate Grimshaw, Elizabeth Kitchin, Kris Lok, Lucy Porteous, Emily Prince, Edmund Sonuga-Barke, John O Warner, Jim Stevenson

Lancet 2007; 370: 1560–67

Published Online September 6, 2007
DOI:10.1016/S0140-6736(07)61306-3

See Comment page 1524

See Department of Error page 1542

School of Psychology

Summary

Background We undertook a randomised, double-blinded, placebo-controlled, crossover trial to test whether intake of artificial food colour and additives (AFCA) affected childhood behaviour.

Methods 153 3-year-old and 144 8/9-year-old children were included in the study. The challenge drink contained sodium benzoate and one of two AFCA mixes (A or B) or a placebo mix. The main outcome measure was a global hyperactivity aggregate (GHA), based on aggregated z-scores of observed behaviours and ratings by teachers and parents, plus, for 8/9-year-old children, a computerised test of attention. This clinical trial is registered with Current Controlled Trials (registration number ISRCTN74481308). Analysis was per protocol.

What does it mean?

Typical "table 1" in a medical research article

Table. Patient Clinical Characteristics

	All, n=68 (%)	No Recurrent Event Observed, n=54 (%)	Recurrent Event Observed, n=14 (%)	*P* Value
Demographic data				
Age, y (range)	65 (30–90)	64.7(30–88)	65.5 (47–90)	0.96
Men	47 (69)	38 (70.4)	9 (64.3)	0.75
Type of event				
TIA	5 (7.4)	4 (7.4)	1 (7.1)	0.6
Retinal ischemia	5 (7.4)	3 (5.6)	2 (14.3)	0.2
Stroke	58 (85.3)	47 (87)	11 (78.6)	0.2
Medical history, n (%)				
Smoking	29 (43)	20 (37)	9 (64.3)	0.21
Hypertension	49 (72)	37 (68.5)	12 (85.7)	0.32
Diabetes mellitus	13 (19)	7 (13.0)	6 (42.9)	0.02*
...				

Clinical characteristics of all 68 patients (all) and patient groups without or with ipsilateral recurrent ischemic event. Number (n) and percentage or median and IQR are shown. CAD indicates coronary artery disease; IQR, interquartile range; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; pAOD, peripheral artery occlusive disease; TIA, transient ischemic attack; and TOAST, Trial of ORG 10172 in Acute Stroke Treatment classification scheme for stroke etiology.

*P values <0.05 in Mann–Whitney U test or Fisher exact test.

***Stroke*. 2015;46:3274-3276.**

Research Articel Example:
Paper on hyperactivity form McCann et al.

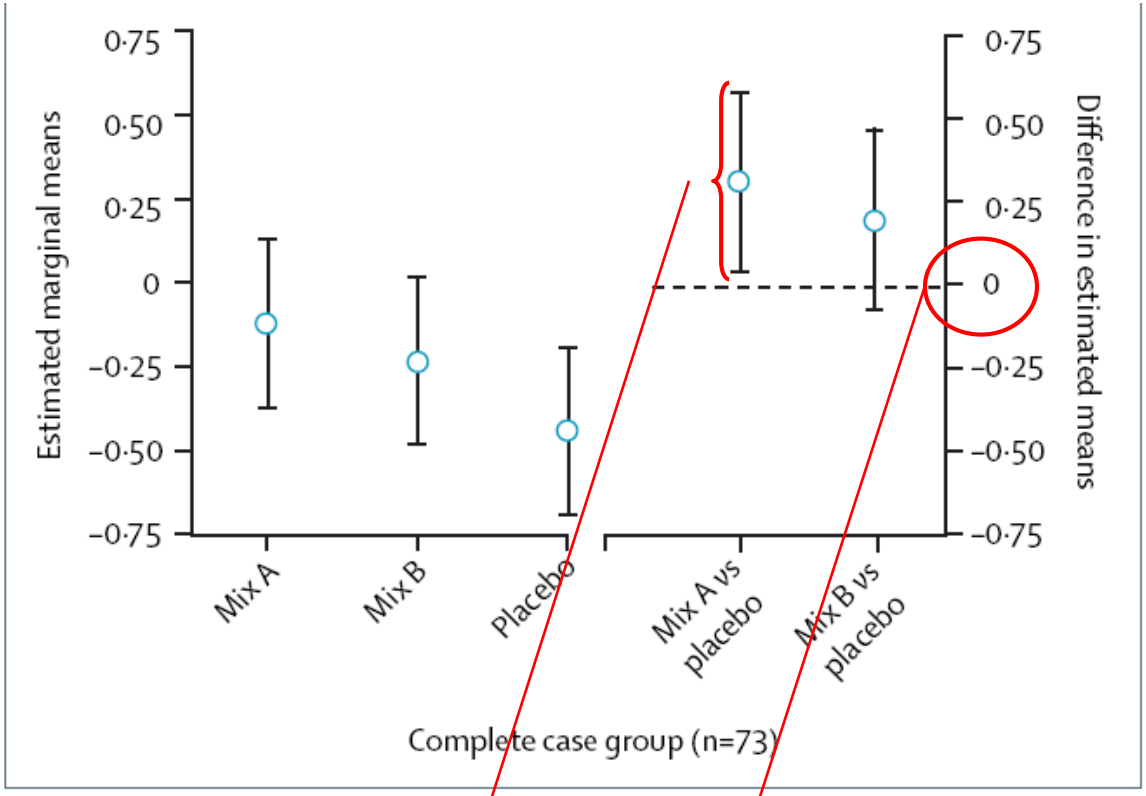


Figure 3: Estimated marginal means by challenge type and difference in estimated means in GHA under model 2 for 3-year-old children

What do bars indicate?

What is special with the 0-line?

Research Article Example:
Paper on hyperactivity form McCann et al.

	Entire sample (n=140)	Group with ≥85% consumption (n=130)
Model 1 **Unadjusted**		
Intercept	−0·31 (−0·49 to −0·13)*	−0·33 (−0·53 to −0·13)†
Challenge type		
Mix A *vs* placebo	0·20 (0·01 to 0·40)‡	0·24 (0·02 to 0·47)‡
Mix B *vs* placebo	0·16 (−0·04 to 0·35)	0·16 (−0·07 to 0·38)
Model 2 **Adjusted**		
Intercept	−0·54 (−0·89 to −0·18)*	−0·51 (−0·92 to −0·11)
Challenge type		
Mix A *vs* placebo	0·20 (0·01 to 0·39)‡	0·28 (0·05 to 0·51)‡
Mix B *vs* placebo	0·17 (−0·03 to 0·36)	0·19 (−0·04 to 0·41)

In model 2, in addition to challenge type, the effects of the following factors were adjusted for: week during study, sex, GHA in baseline week, number of additives in pretrial diet, maternal educational level, and social class.

What does "adjusted" mean?

How is it done?

What does * mean?

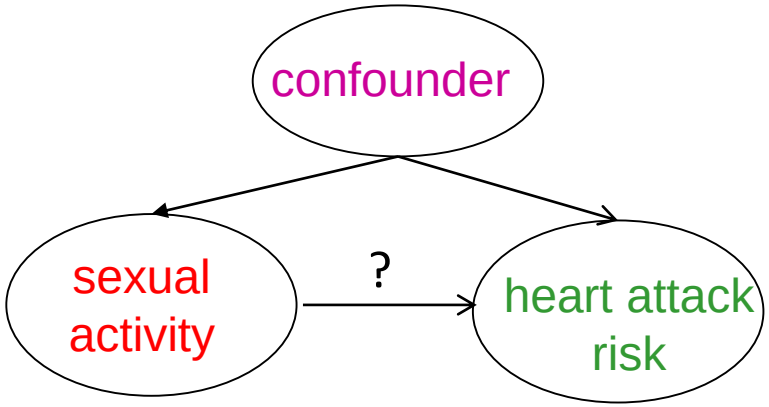
Example: Study in Caerphilly (Wales), 1979-2003

914 healthy men, between 45 and 95 years old, were chosen at random and followed over 10 years where they were interviewed e.g. about their sexual live. Moreover it was followed who suffered a heart attack in this period.

Result:

group	# men	# sexual active men	# sexual inactive men
all men	914	231	197
men suffering heart attack	11% 105	8% 19	17% 33

What can we conclude?



Why do we need statistics?

Data vary!

Samples are random!

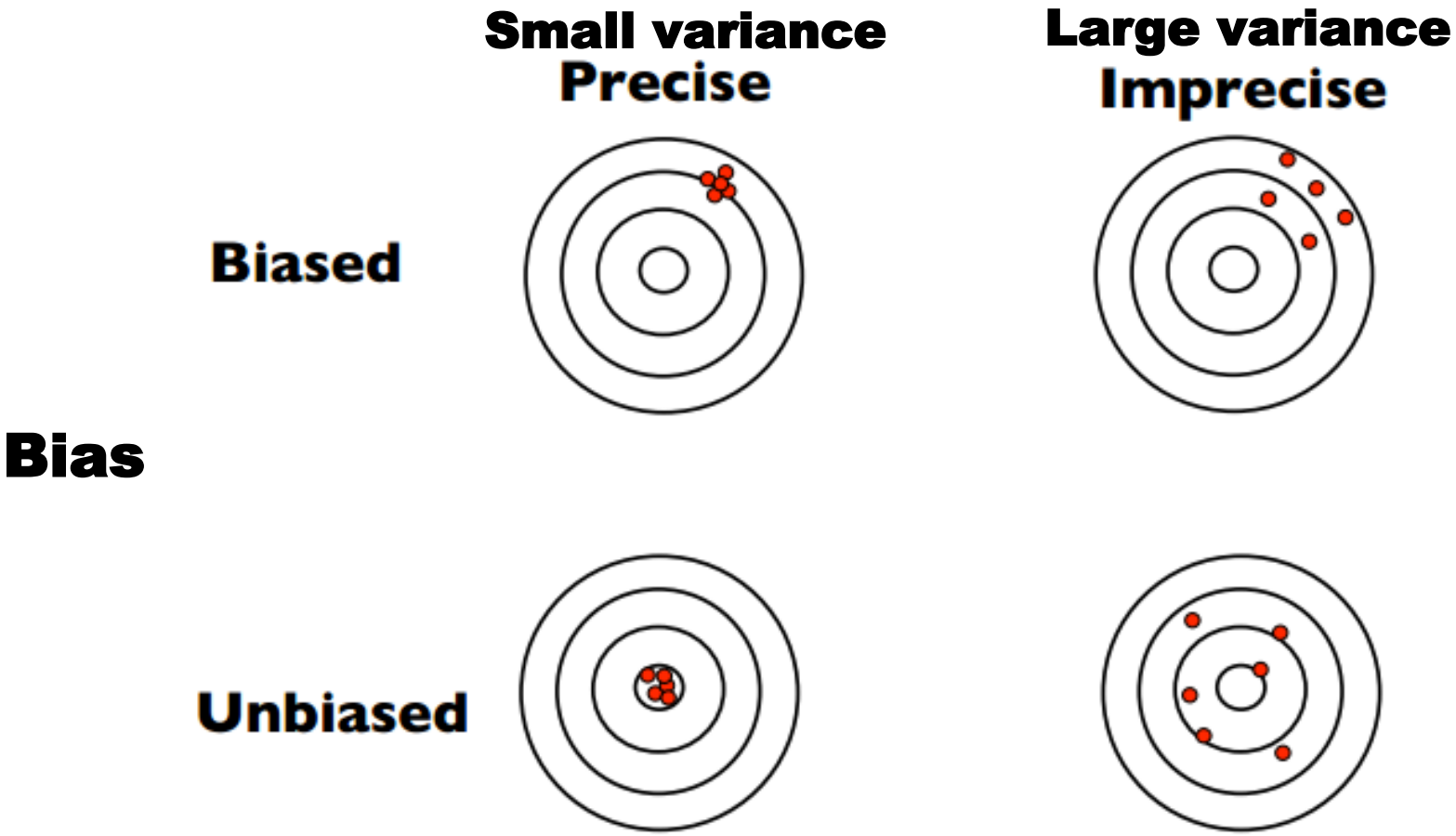
„We need statistics to draw intelligent decisions in the presence of uncertainty.“

Numbers and Data

Numbers in mathematics	Number in data
exact	imprecise: random errors
certain	uncertain: “biased”, faked, accidental coarse error
Just a number	Need for interpretation
Two number are either equal or different	Two observations are normally not exactly equal, but are they significantly different?

What kind of errors do we usually see?

Variance: by random errors

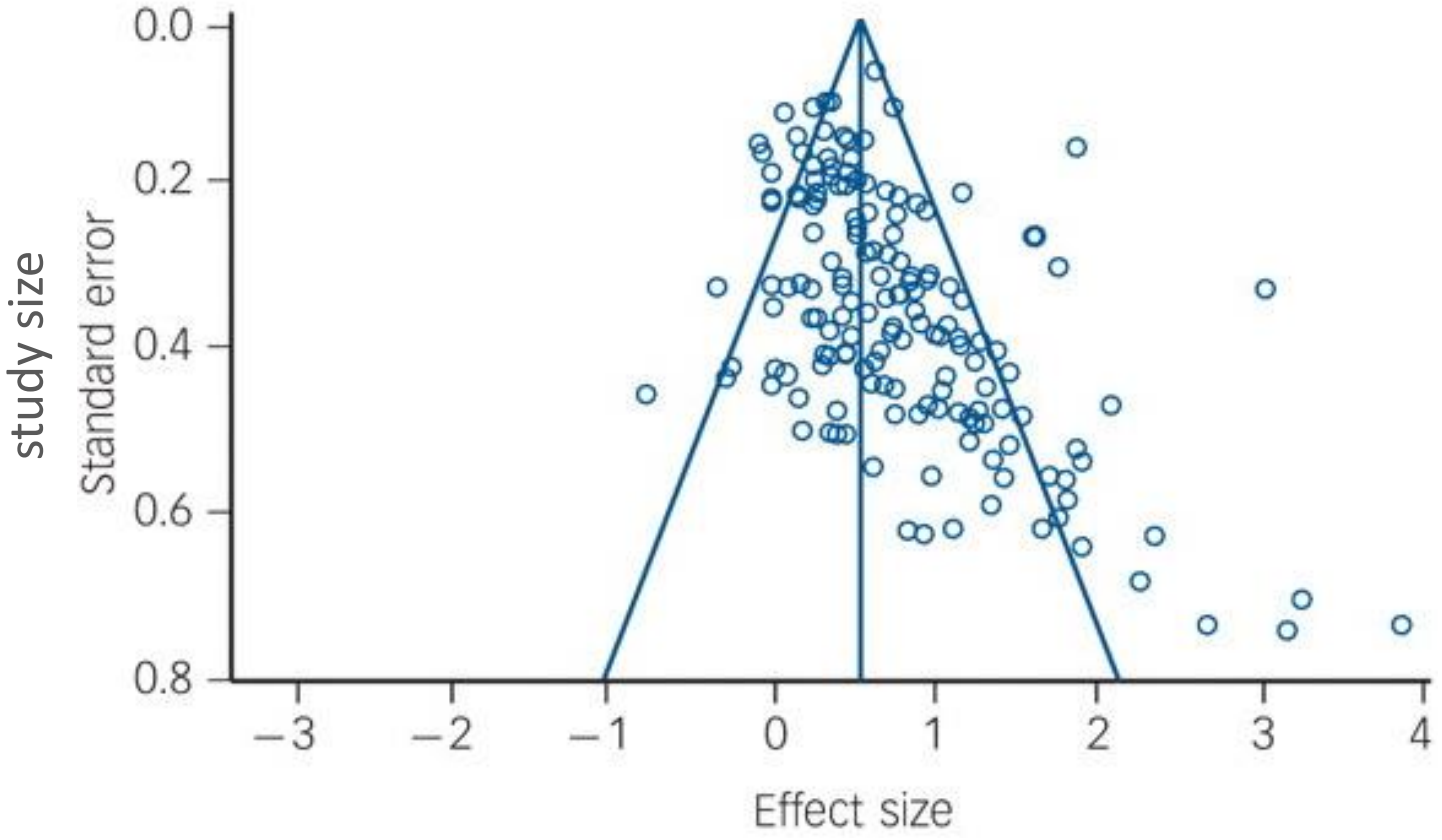


Systematic error or bias, accidental coarse error

Wrong basic calibration

Accidently shifted comma suggested wrongly high iron content in spinach

What is a publication bias?



Publication bias is the tendency to more likely publish results that are positive (i.e. showing a significant finding) than negative results, leading to a misleading bias in the overall published literature. This is often visible in a funnel plot, where smaller studies with higher standard error tend to report more often positive results than large studies which are published irrespectively of the result.

Willful error or fake: the case of Henrik Schön

- 2001 each week a paper, many in Nature or Scienceach
  - Proposed as youngest Max Plank direktor in Stuttgart
  - Candidate for Nobelpreis
  - …
- 2002 Beasley Kommision…

- Withdrawl of PhD title because of dishonorable behaviour, but he did not fake during his PhD time in Konstanz

Der internationale Braunschweig-Preis geht an die Forschergruppe mit (von links) Jan Hendrik Schön, Christian Kloc (beide Bell Labs, Lucent Technologies, New Jerseey) und Professor Bertram Batlogg (ETH Zürich) als Gruppenleiter.

picture:
ETH-Zürich

Fake: same noise implies same data -> data substitution

II. Data Substitution: Ambipolar triode characteristics

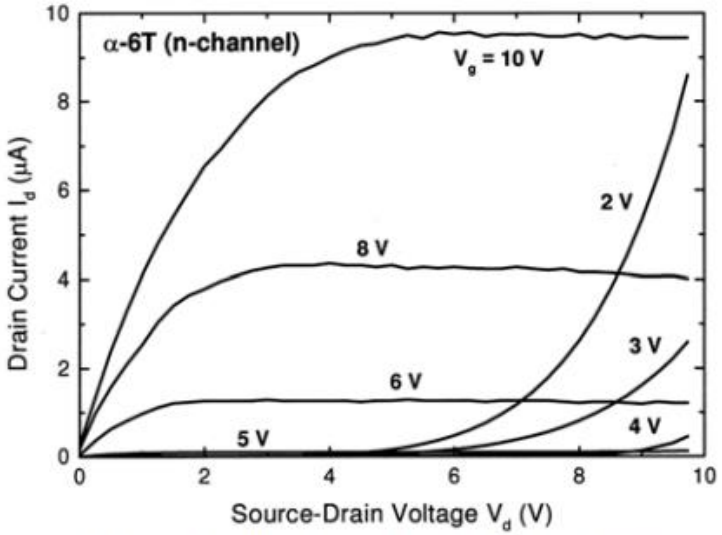


Figure 7. Triode characteristic from "LightEmitting" Paper (V), Fig. 1.: "alpha-sexithiophene (α-6T)"

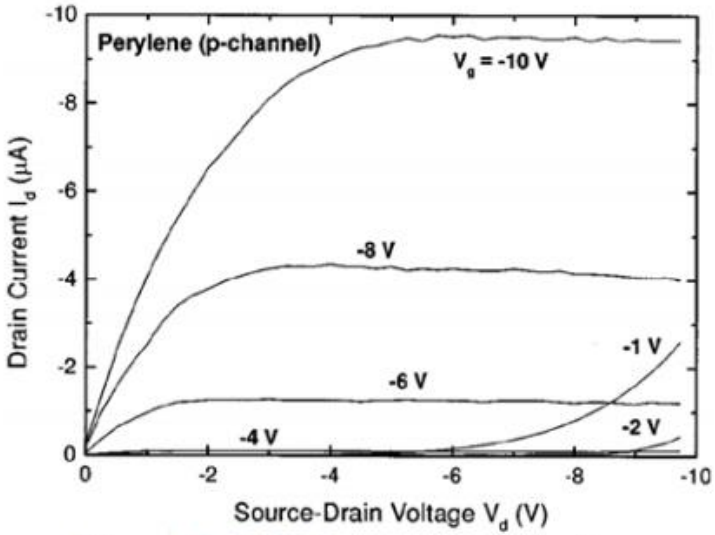


Figure 8. Triode characteristic from "Perylene" (VI), Fig. 2: "perylene". Note the sign change from Figure 7. One curve is missing.

Same data, different effects, different publications

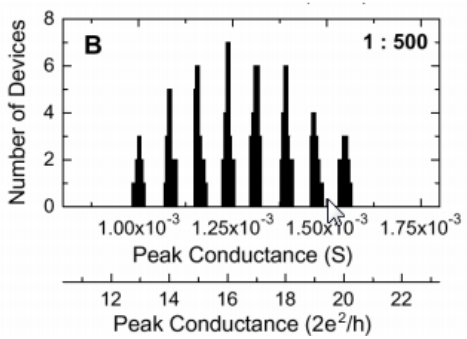
(V) "A Light-Emitting Field-Effect Transistor," J. H. Schön, A. Dodabalapur, Ch. Kloc, and B. Batlogg, Science 290, 963 (November 3, 2000)

(VI) "Perylene: A promising organic field-effect transistor material," J. H. Schön Ch. Kloc, and B. Batlogg, Appl. Phys. Lett. 77, 3776 (December 4, 2000)

http://publish.aps.org/reports/lucentrep.pdf

Pitfall when faking: precision

Presented data



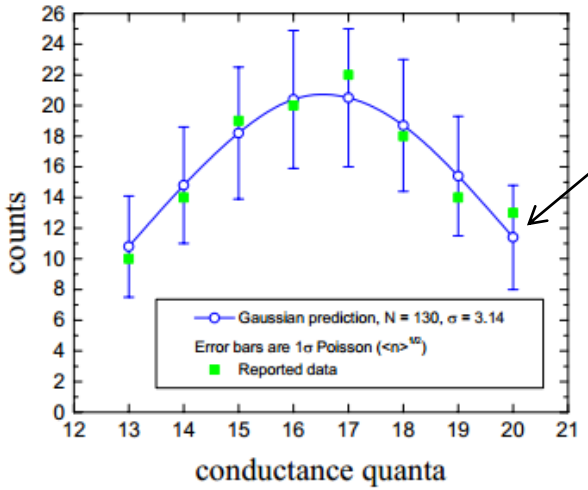


Figure 47. Comparison of reported number of devices in each conductance quantum bin with a fit to a Gaussian distribution. The reported data are extracted from original plotting data for Figure 46 from an electronic draft. The agreement exceeds the expected variation for such a small number of devices.

Blue: Theory

green: «observations»

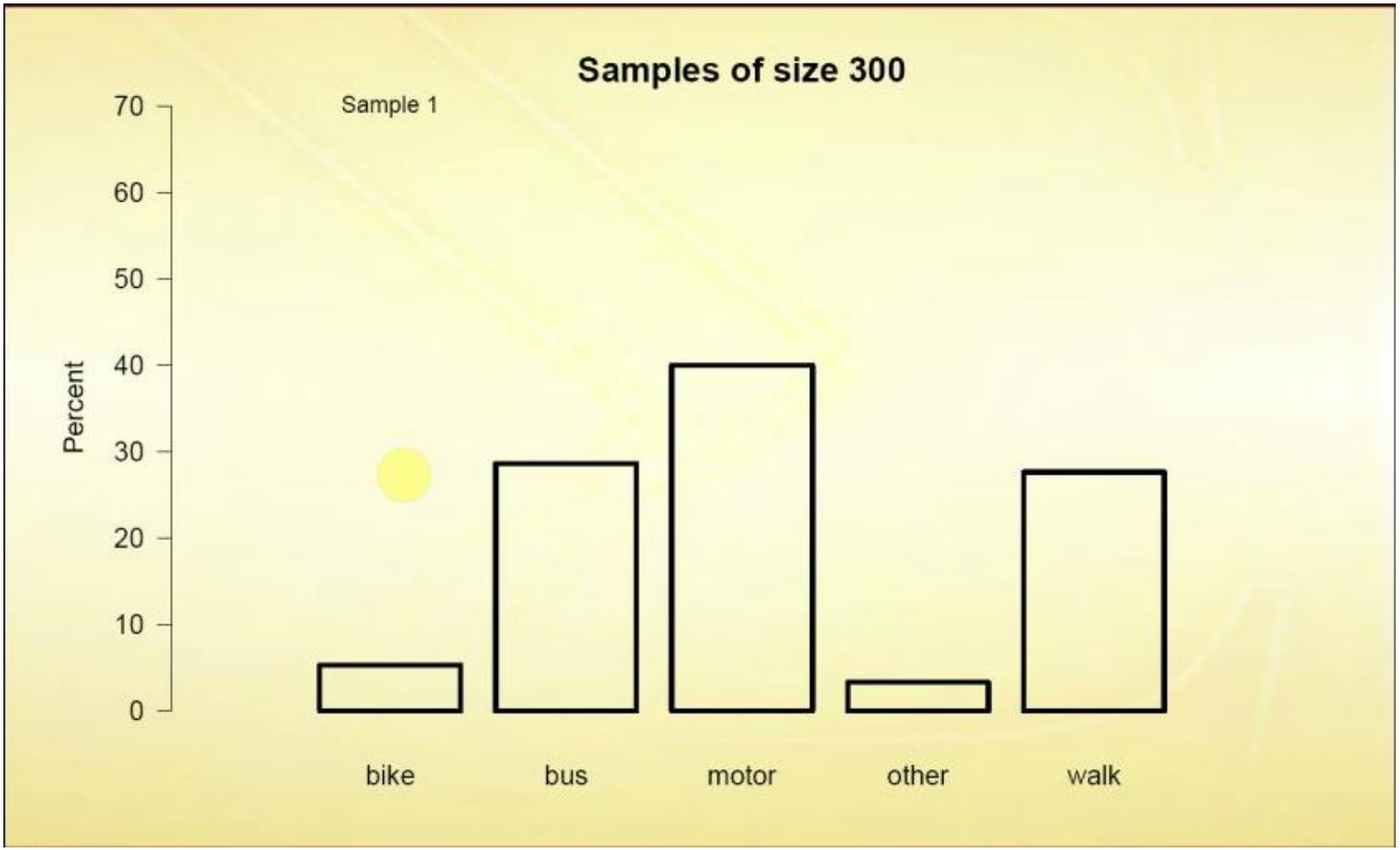
Blue standard error bar:
1/3 of all observations should outside of the bars.

Probability to see such data by chance: 0.0012:

"Field-Effect Modulation of the Conductance of Single Molecules," Jan Hendrik Schön, Hong Meng, Zhenan Bao, Science 294, 2140 (December 7, 2001).

How reliable are the bar-heights in a barplot?

How do pupils get to school?



Balkendiagramm mit Gedächtnis

Quelle: http://www.stat.auckland.ac.nz/~wild/09.USCOTSTalk.html

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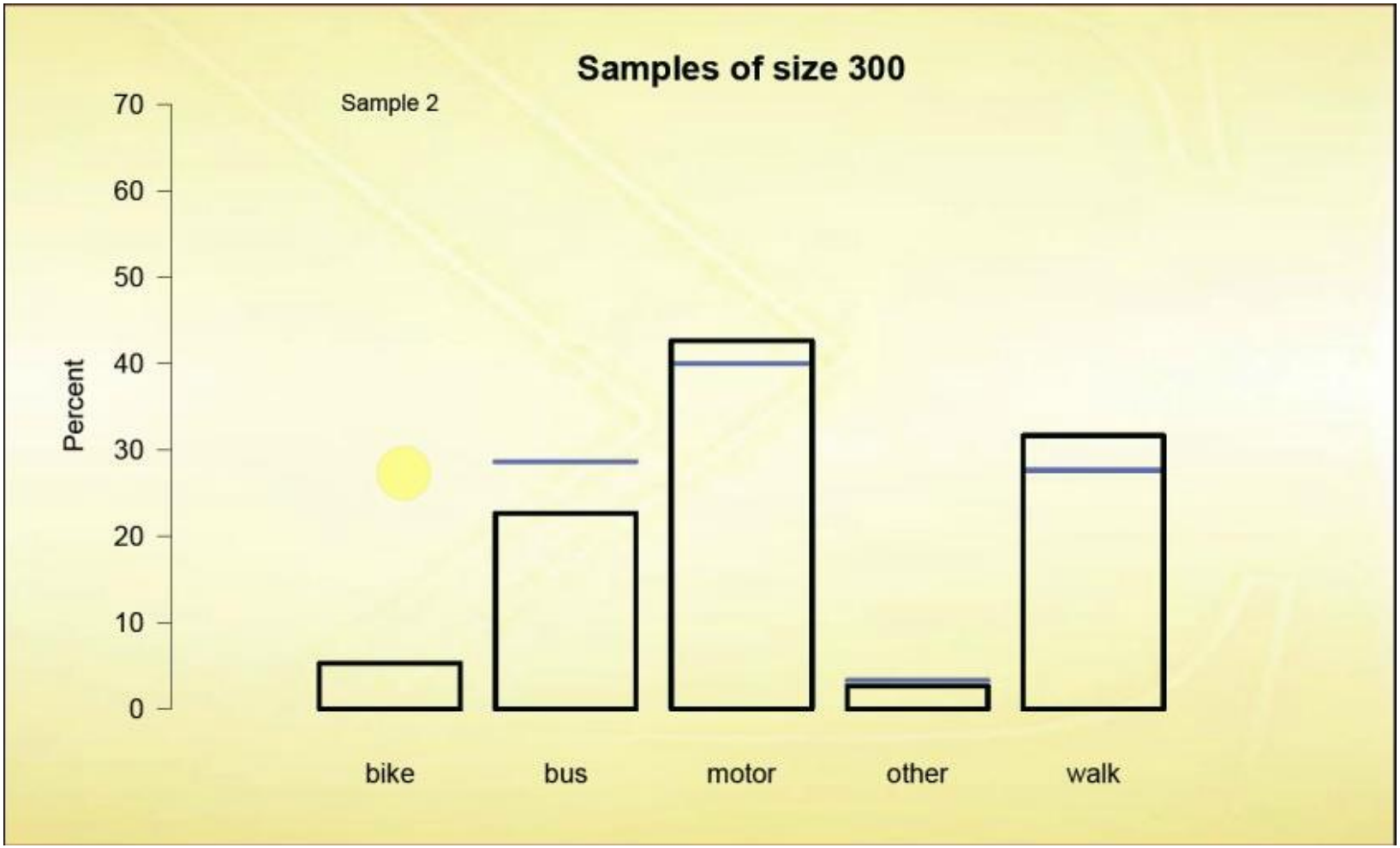

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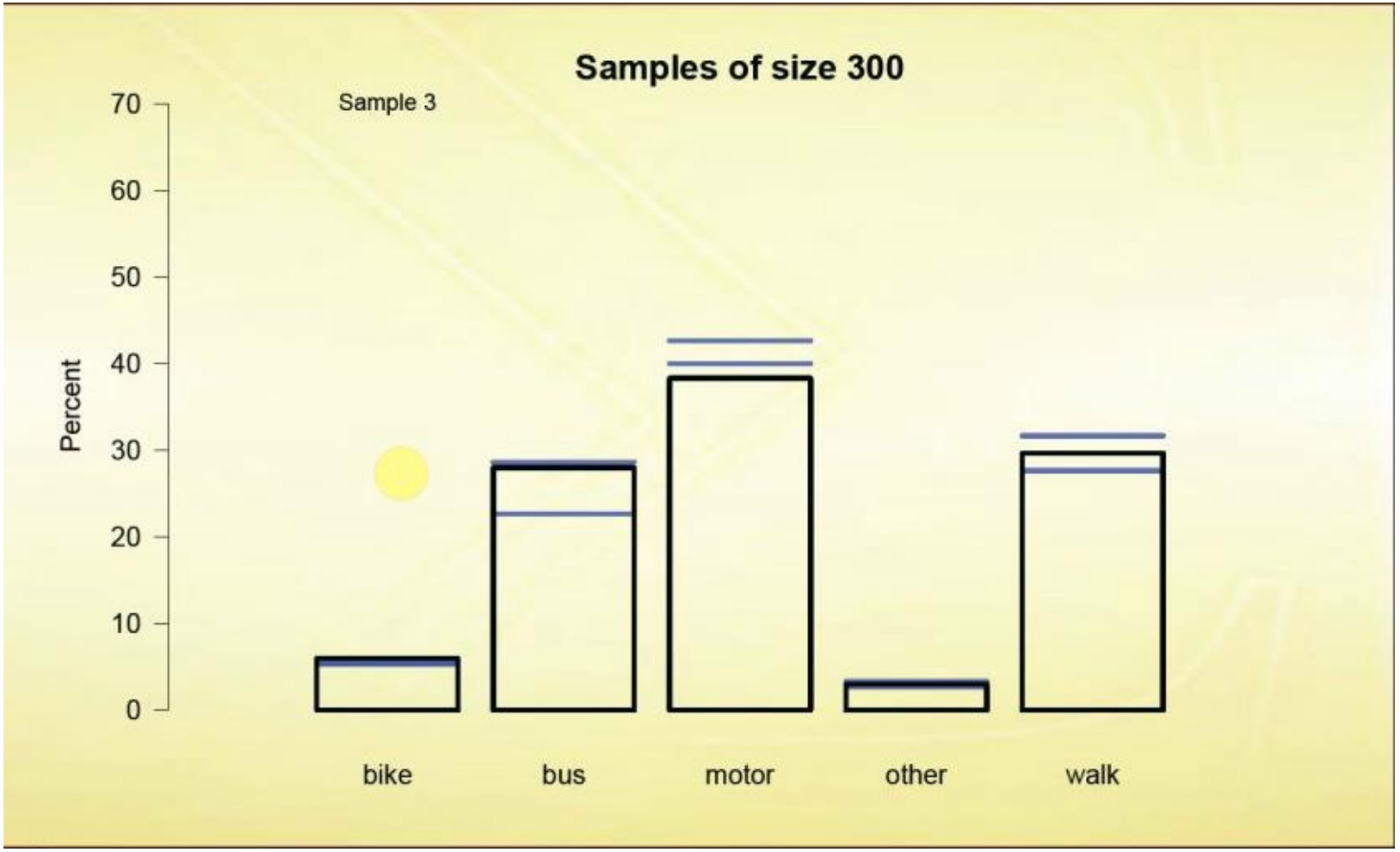

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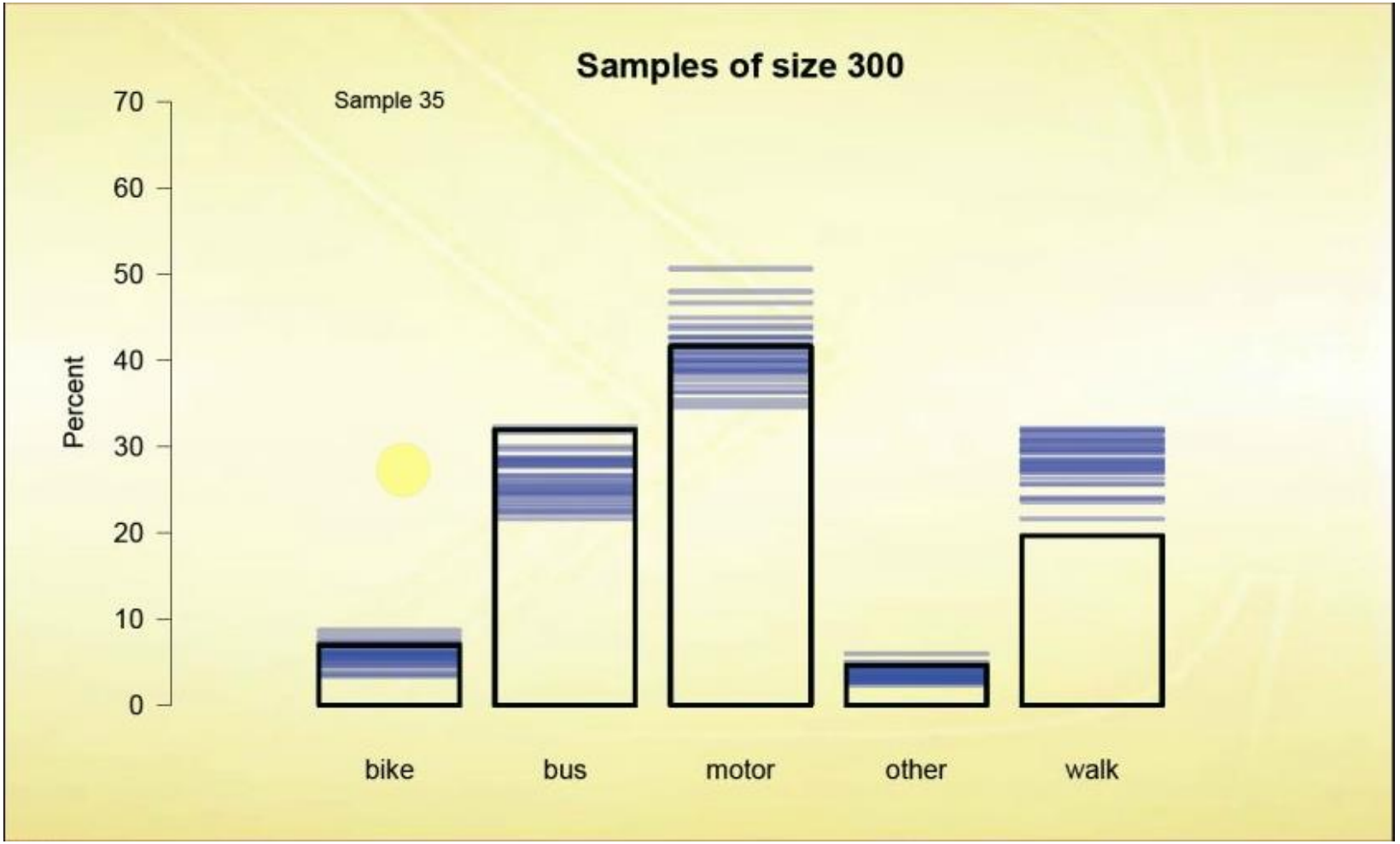

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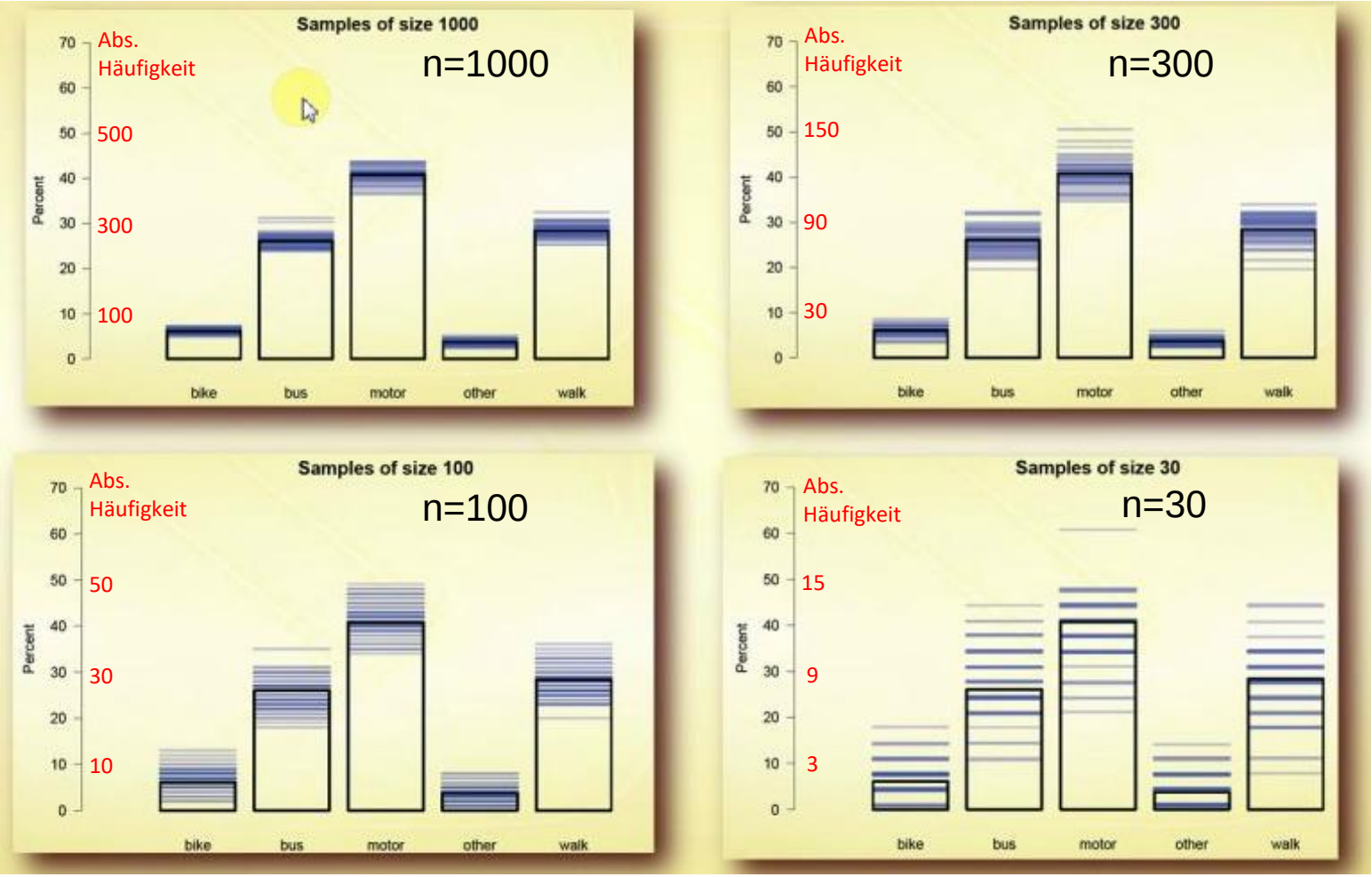

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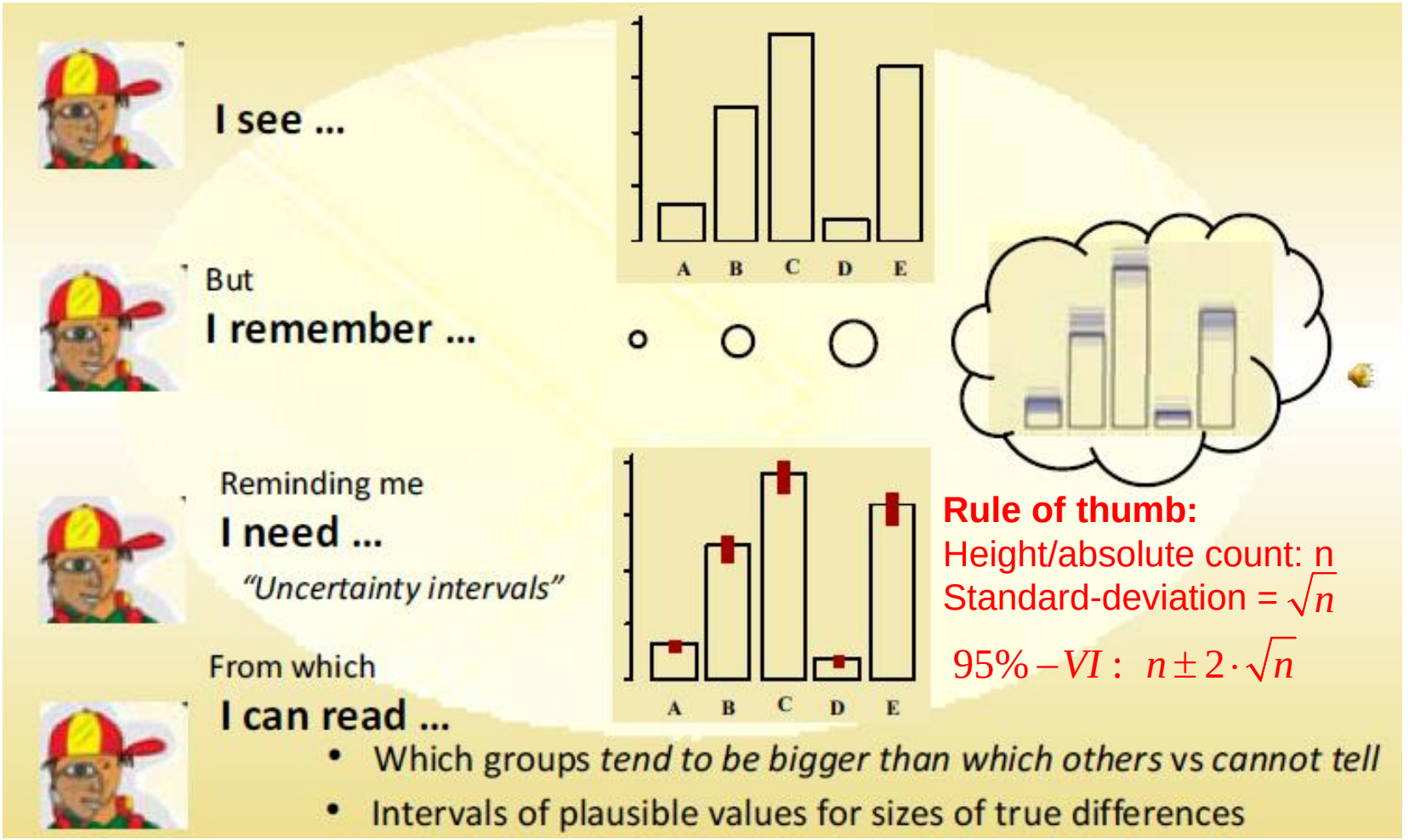


Balkendiagramm mit Gedächtnis

Quelle: http://www.stat.auckland.ac.nz/~wild/09.USCOTSTalk.html

Fundamental terms

- **Feature or variable**:
  Properties which can take different values
  - Age of a patient
  - Sex of a student
  - braking distance from 100 km/h for different car types

- **Population**:

  The complete set of all items that are relevant for the investigation
  - All persons suffering a heart attack
  - All at ETH inscribed students
  - All uranium atoms

- **Sample**:

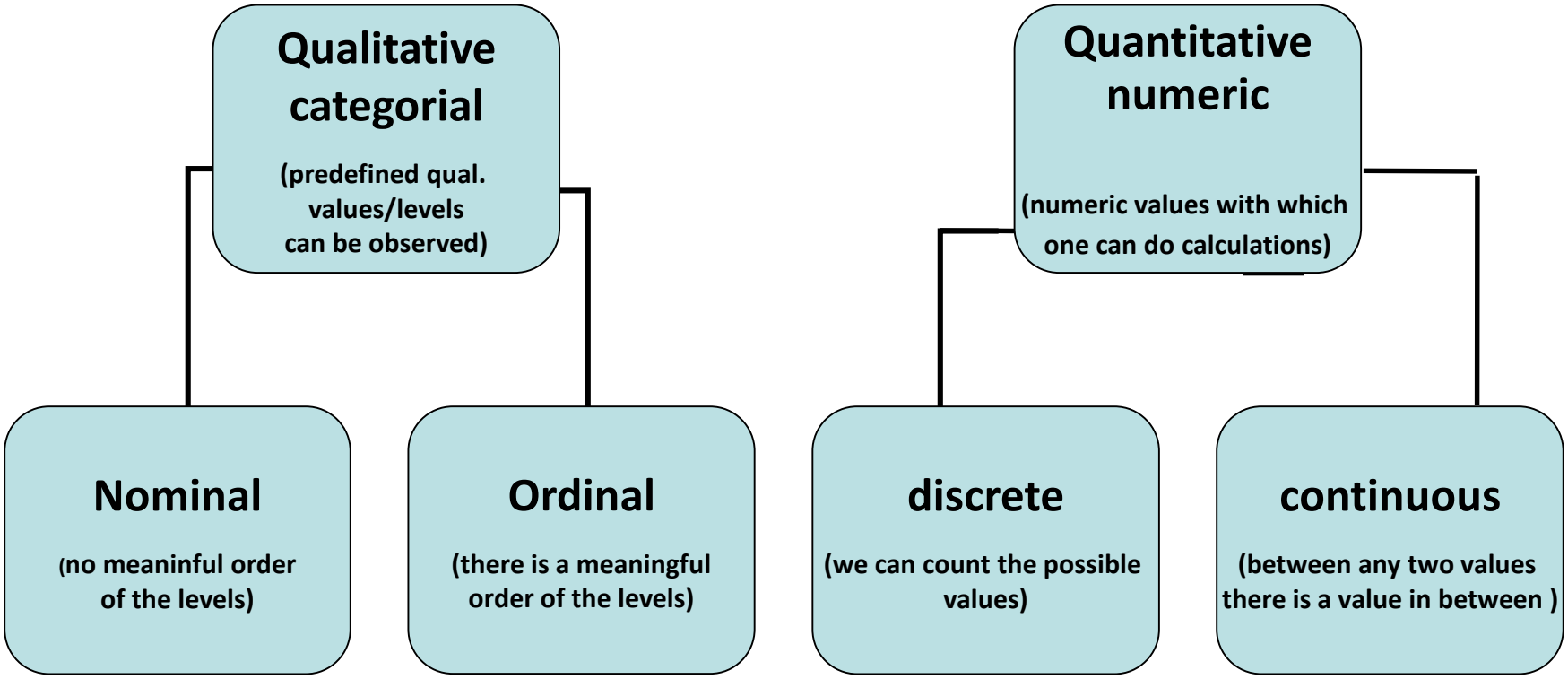
  A subgroup of the entire population which have been selected in a certain manner (systematically, arbitrary, at random, stratified)

We can collect some data from each student

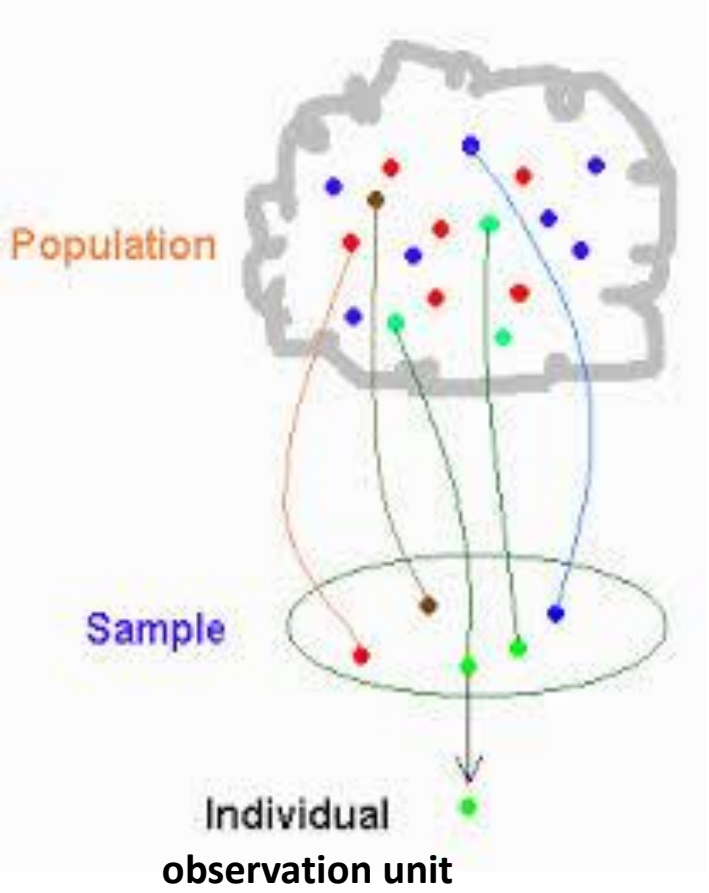
1) Age
2) Sex
3) Nationality
4) Height
5) Arm span
6) Number of siblings
7) Handedness
8) Rate the quality of the ETH Mensa food (0, 1, …, 9)

How do the type of collected data differ?
How could we visualize the answers from the class for each question?

There are different types of data



We use a sample to learn about the population



Results from statistical inference are only correct, if the sample was representative.

A sample is representative if it does not systematically differ from the population (e.g. the percentages of male and female are similar in the sample than in the population).

In-class-exercise 1
Topic: When is a sample representative?

In the following examples we have a short description of research questions (RQ). Please answer for each example the 2 following questions (ignore the issue of sample sizes for the moment):

a) What is the population for which the results should be generalized?

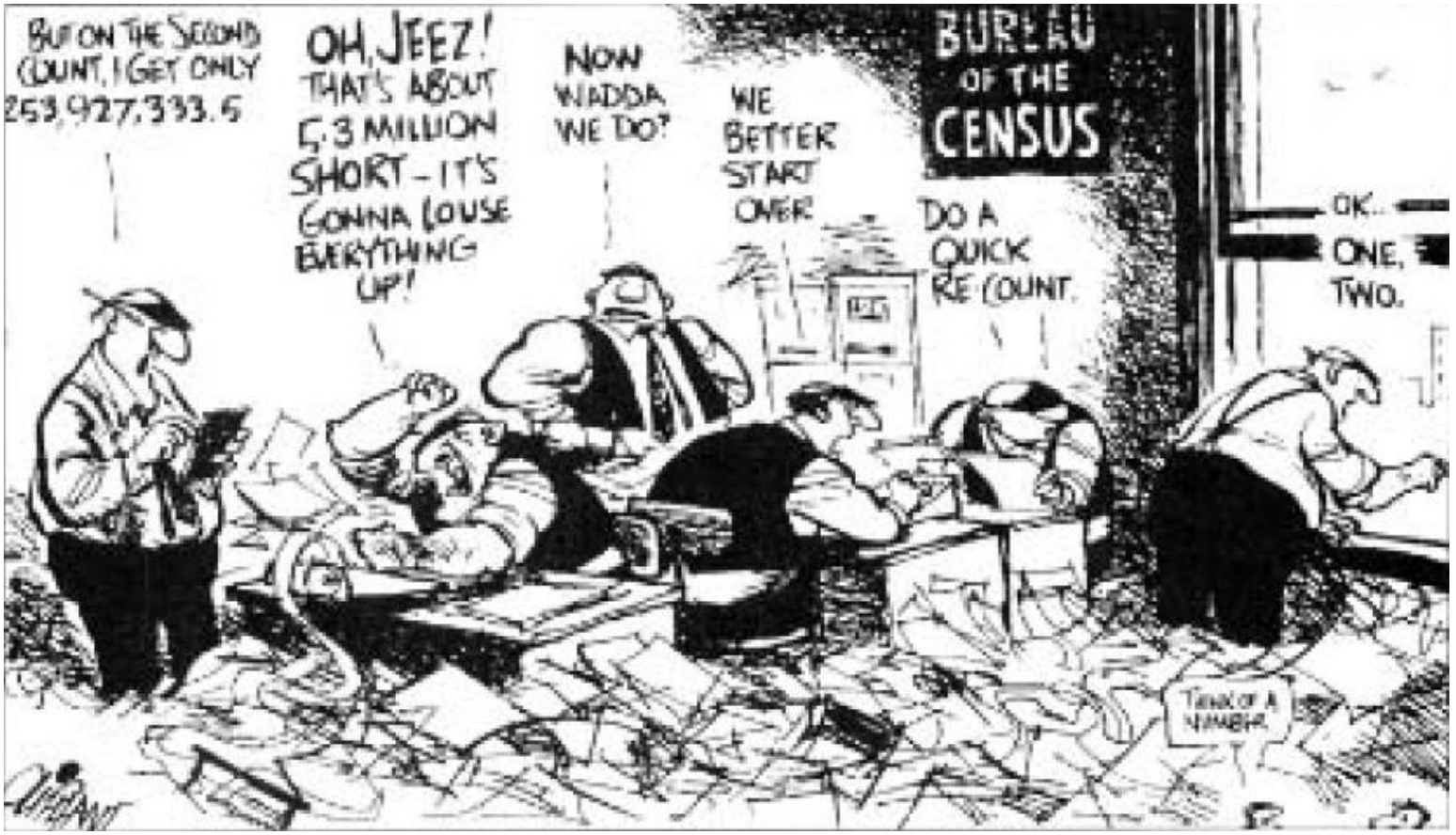
b) Is the sample appropriate to answer the RQ for this population?

1) **RQ:** „How strong is the pain during tooth drilling by a dentist without local anesthetics?“
Sample: Patients who decided to take the treatment without local anesthetics.
□ good □ reasonable □ bad

2) **RQ:** Is the volume reading correct in a delivery of 1000 Micropipettes?
Sample: 100 Micropipettes picked at random.
□ good □ reasonable □ bad

4) **RQ:** „what is the average hemoglobin level in females? “
Sample: Women who donate blood at the university medical center of Zurich.
□ good □ reasonable □ bad

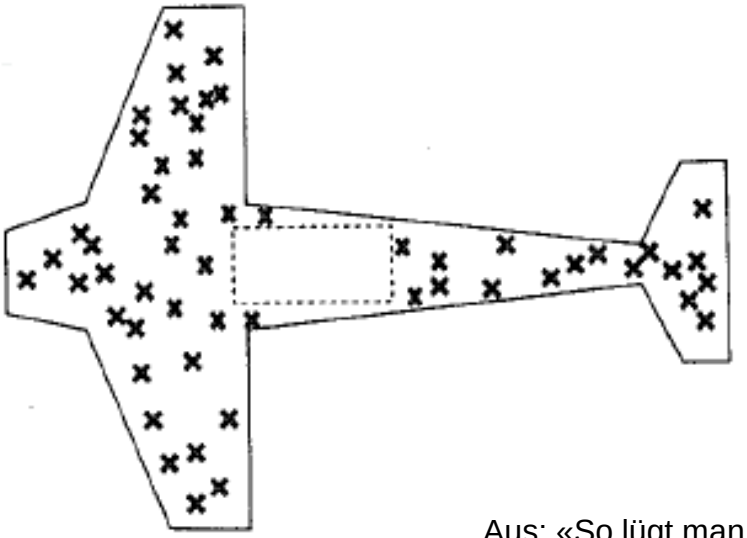
Census or Sample?



- In 2000 we had the last census (Vollerhebung) in Switzerland
- sampling is some times better, because of practical and data quality reasons

Representative Sample?

- Question:
  Which parts of bombers were most often hit? Which do we need to reinforce?
- *Population: all bomber which came into operation*
- *Sample: 100 returned bombers . representative?*

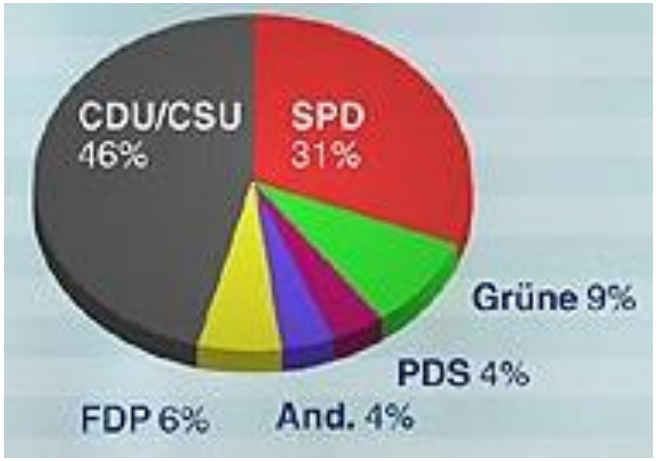


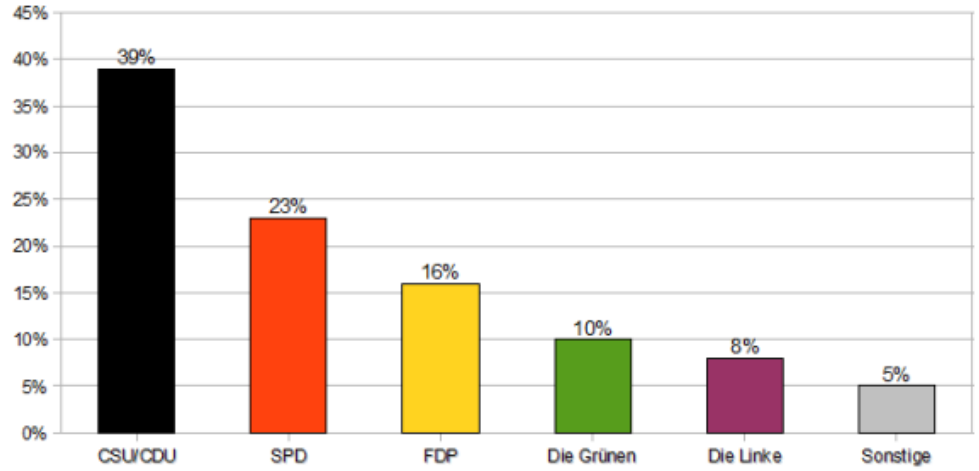
Aus: «So lügt man mit Statistik»

"selection bias"

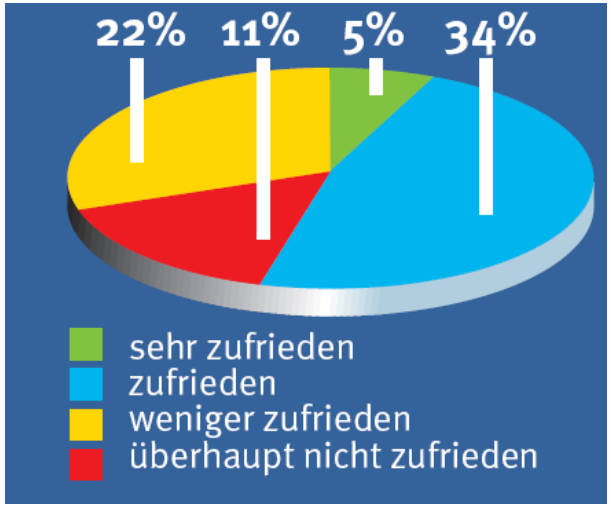
Visualizing categorical data by Bar-Chart or Pie-Chart

These charts are simple – is there room form manipulation?





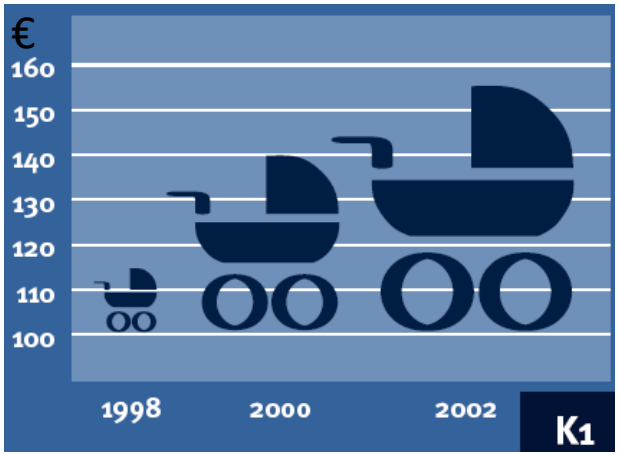
Half of all reader are satisfied with Klinsmann - true?



Pie-Chart from the German newspaper „Bild“ . Reader were asked how satisfied they are with soccer trainer Klinsmann.

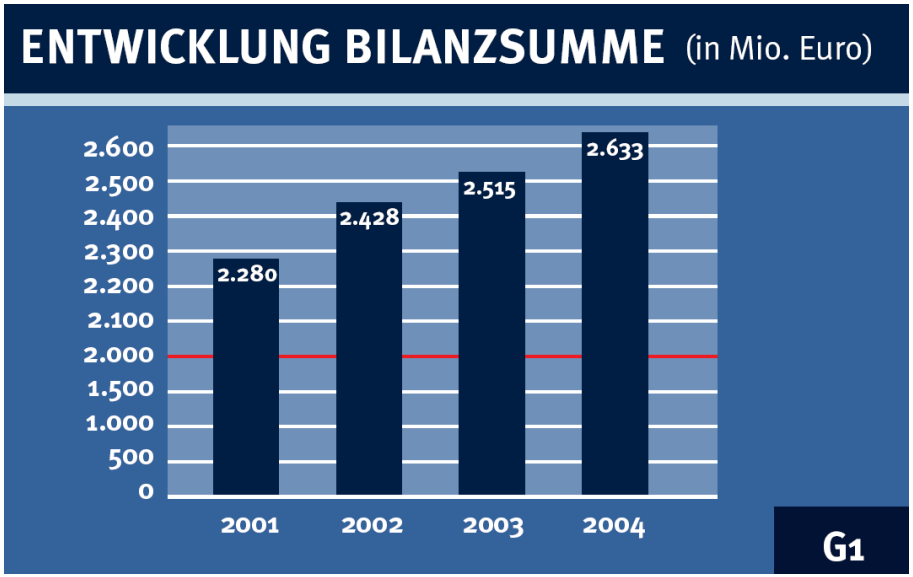
Quelle: http://www.wdr.de.varnish.gl-systemhaus.de/tv/quarks/sendungsbeitraege/2006/1017/002_zahlen.jsp?smonat=2009-10

Generous increase of child allowance - true?



Graph from government statement in the German red-green agenda 2010.

Good business development - true?



Bar Chart in the business report of a german bank
(psd-Bank Rhein-Ruhr 2004)

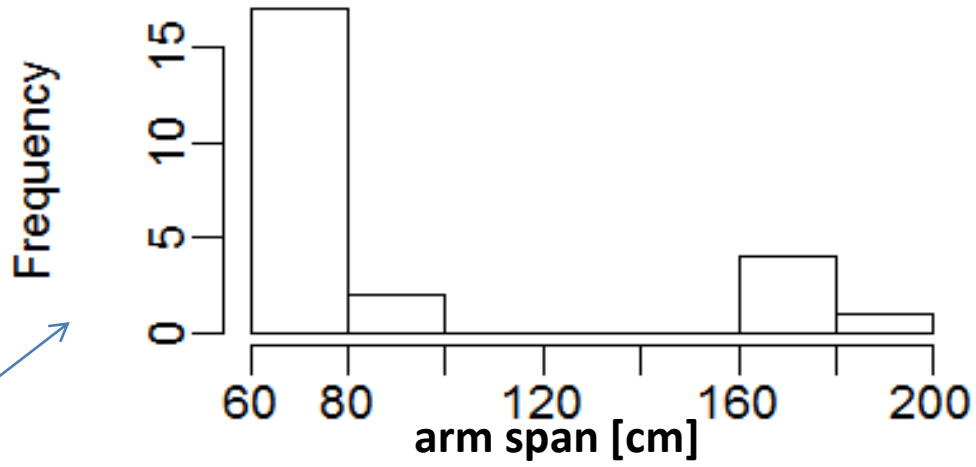
How can we visualize continuous data?

1) Age
2) Sex
3) Nationality
4) Height
5) Arm span
6) Number of siblings
7) Handedness
8) Rate the quality of the ETH Mensa food (0, 1, …, 9)

How to summarize continuous data – e.g. arm span?

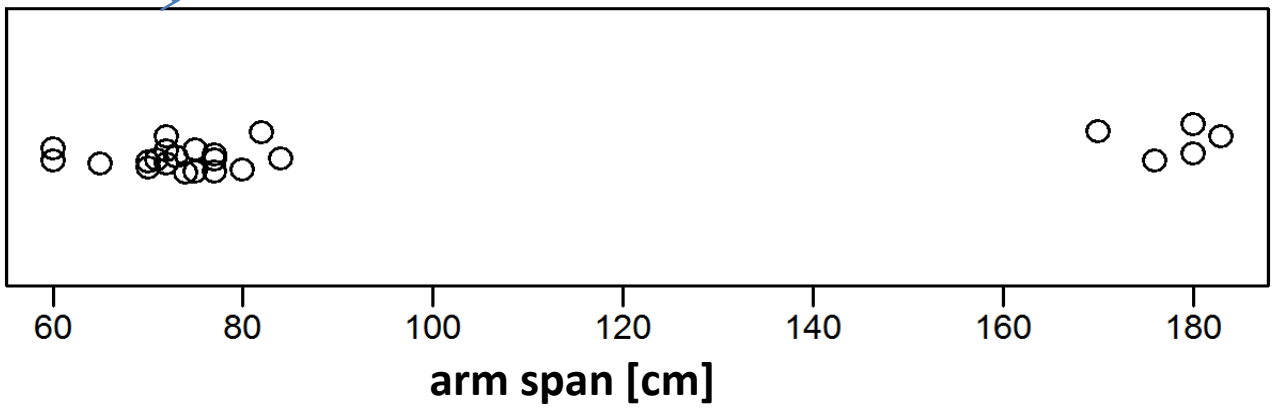
X: arm span	frequency
[60, 80)	17
[80,100)	2
[100,120)	0
[120,140)	0
[140,160)	0
[160,180)	4
[180,200)	1

- define non-overlapping classes/bins
- count number of observation per class
- draw histogram (no gaps between bars)




```
hist(x)
```

```
stripchart(x,method="jitter")
```



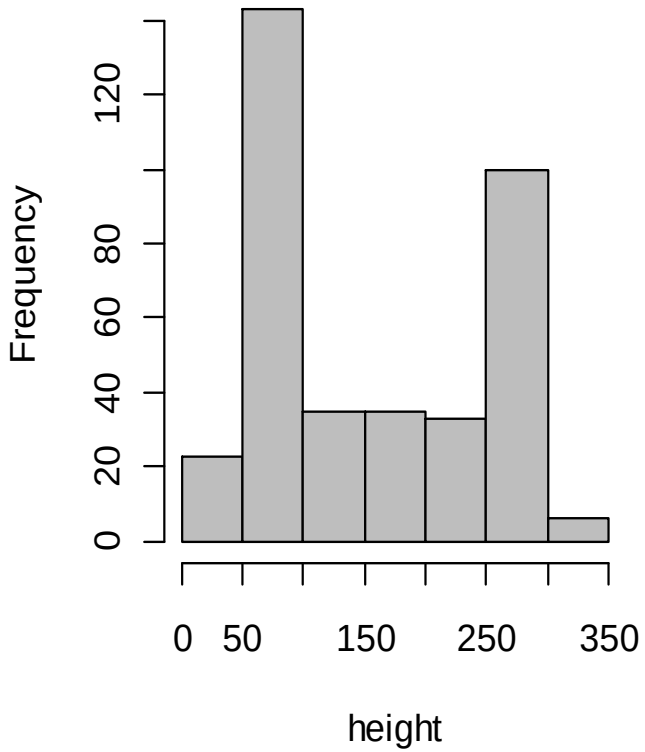
How to visualize continuous data?

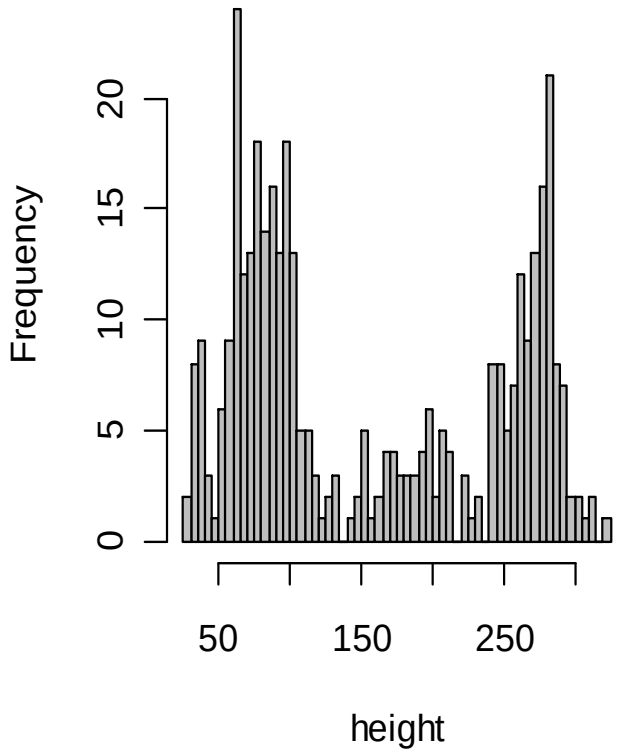
The height (cm) of 376 plants were measured.

```
head(dat$height)
```

G
height
57.9
62.1
55.8
61.5
68
52.8
70.5
60.4
75.2
77.1
70.4
70.1
27.6
35
⋮

```
# hist, few classes, big bin width
hist(dat$height, nclass=7)
# hist, many classes, small bin width
hist(dat$height, nclass=100)
```

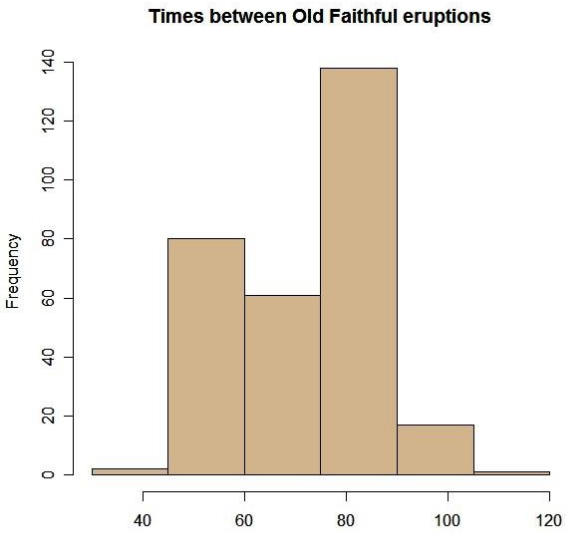


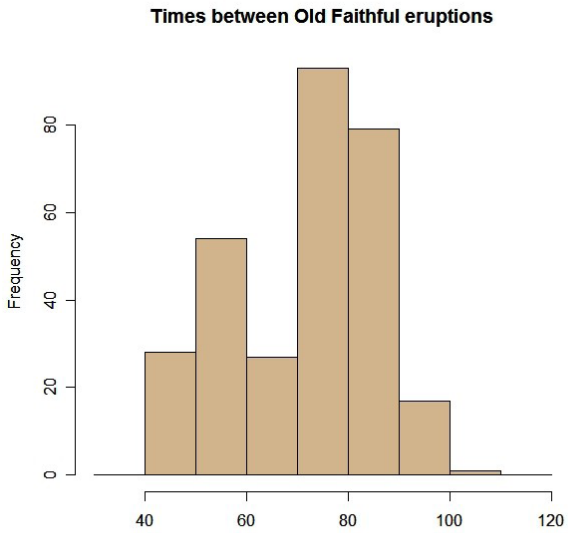


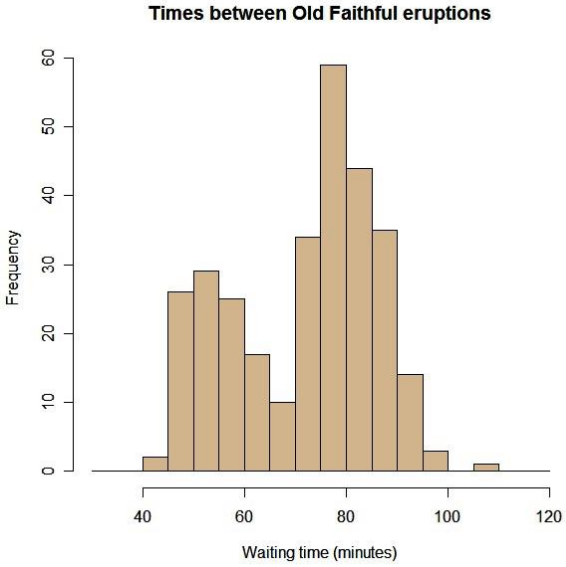
Are there subgroups? If yes – how many?

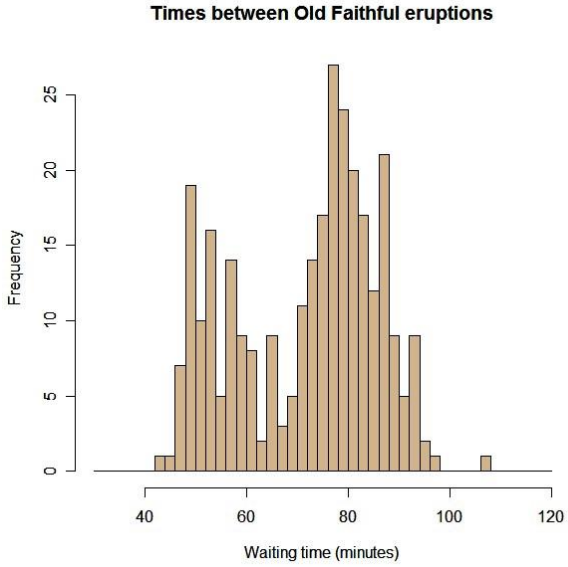
How reliable is the height of a bar?

How many classes do we need?









http://www.amstat.org/publications/jse/v6n3/applets/Histogram.html

299 eruption intervals were observed

Shape of the histogram may depend on the class choices

Rules for histograms

Zurich University of Applied Sciences

zh aw

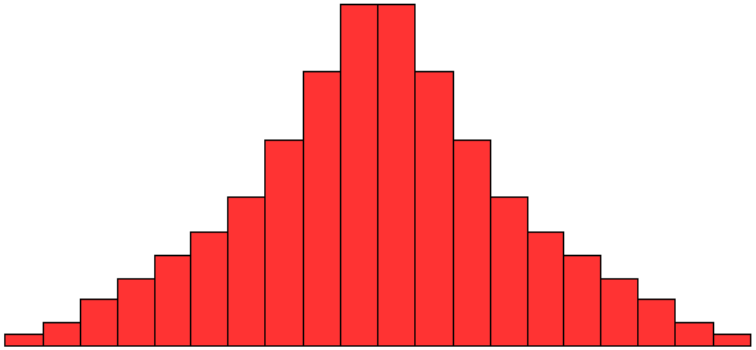
- Avoid classes with different width! (shape will change)

- How many classes: $\sqrt{n}$ classes for n observations.

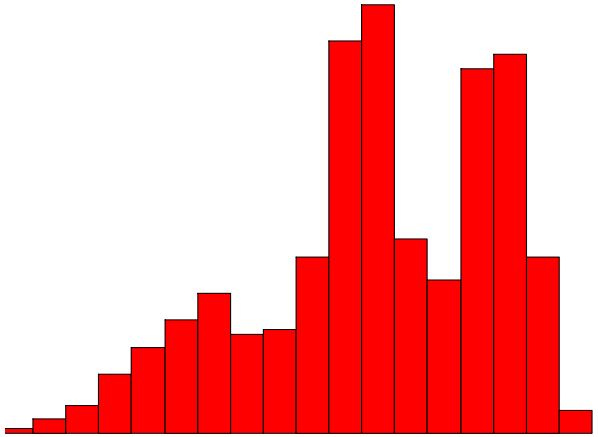
- The shape can depend on the number classes and the class limits.

Attention: in a scaled histogram the ***area*** of the bar indicates the relative frequency, whereas in a unscaled histogram the ***height*** of the bar indicates the absolute frequency -> in case of unequal bin-widths the shape of the unscaled and scaled histograms can differ substantially.

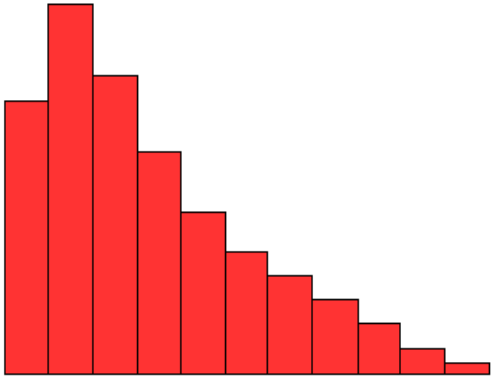
Shapes of distributions



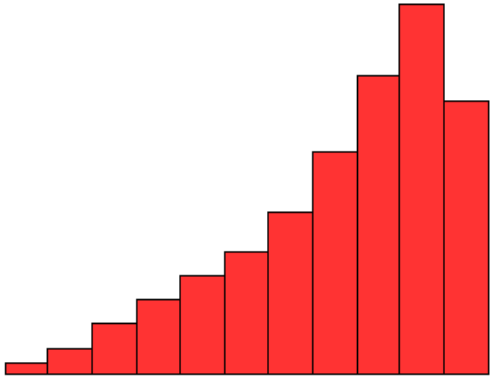
Symmetric, uni-modale



Multi-modale, slightly left-skewed



Right-skewed, uni modale



Left-skewed, uni-modale

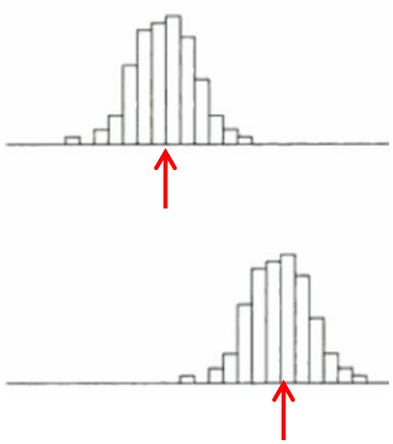
Measures for the location and variation

Data can be summarized by summary statistics. Most important key figure describe the center and the width of a distribution..

Measures for the location

Where is the center?

What is a typical value?



Measures for the variation

A number which quantifies the width of the distribution.

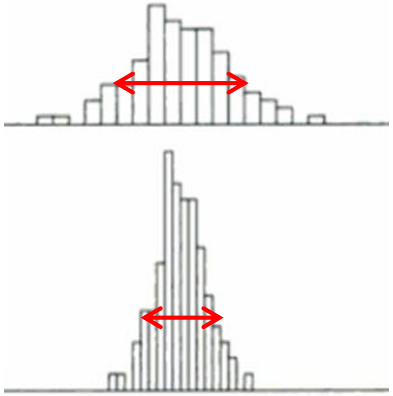


Bild: W. Stahel

Is the mean salary a «typical salary»?

The mean salary for Novartis employees was in 2009 around 220'000 CHF.

Schweizer Arbeitsplätze

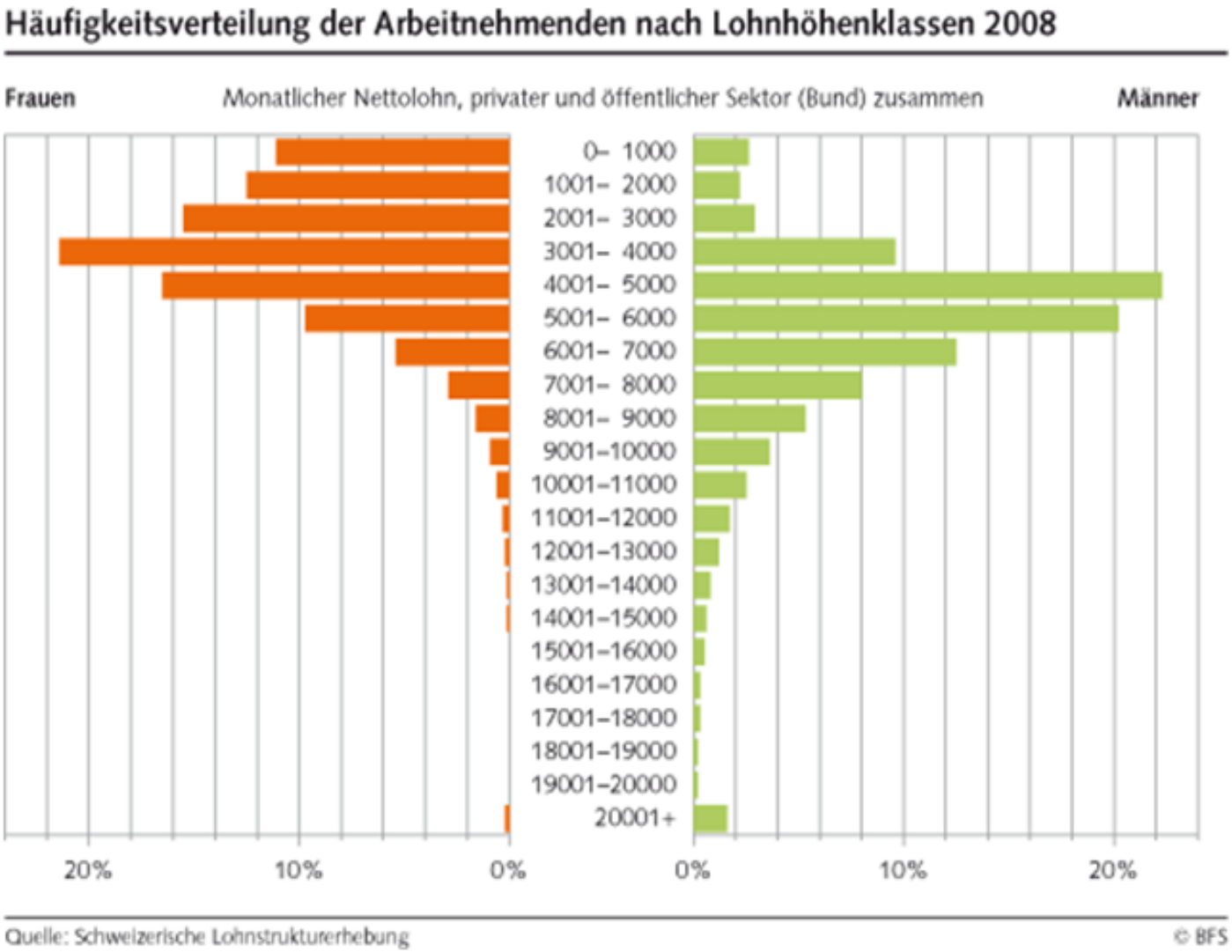
Grafik vergrössern

Novartis beschäftigt weltweit zurzeit rund 99.800 Mitarbeitende. Davon arbeiten rund 12.000 in der Schweiz – verteilt auf die acht Standorte in Basel BS/BL, Stein AG, Embrach ZH, Cham ZG, Bern BE, St-Aubin FR, Nyon VD und Locarno TI. Eine kürzlich veröffentlichte Studie hat ergeben, dass für jeden direkten Arbeitsplatz bei Novartis in der Schweiz indirekt 2,5 weitere Arbeitsplätze geschaffen werden.

Die Gesamtsumme der Lohn- und Sozialleistungen für Mitarbeitende von Novartis in der Schweiz betrug im Jahr 2009 rund 2,6 Milliarden Franken.

$$\text{mean.salary} \approx \frac{2.6 Mrd.}{12000}$$
$$\approx 220000 \ CHF$$

Distribution of salaries in Switzerland



46

For right-skewed distributions the mean is not a typical value

The mean corresponds to the center of mass (balance point of a see-saw), very big values have a big leverage and can increase the mean above any threshold – the mean is not robust!