Data exploration: why and how

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Data, knowledge & data analysis

Data

Knowledge

In *omic* sciences, bioinformatics, statistics, … provide the tools to:

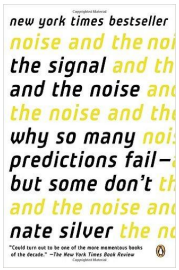
- Promote the incremental progress of science
- Guarantee the validity and the correctness of the results
- Facilitate the production of "scientific" results (of general validity …)
- Be consistent
- Get the maximum from complex data

Di che numeri parliamo ...

- Metabolomica Untargeted: ~10k variabili
- Metabolomica Targeted : ~ 300 molecole
- Proteomica: ~ 1k variabili
- Genomica e Metagenomica: 😱

Signal, Noise & Data Driven Science

Measuring more does not necessarily mean understanding more



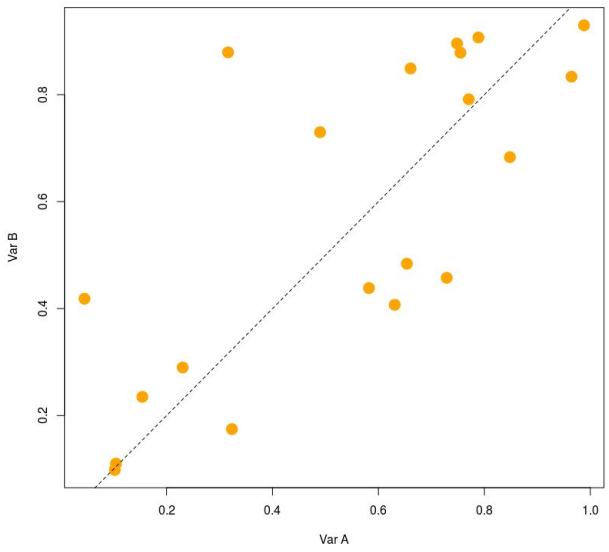
Nate Silver
"The Signal and the Noise: Why So Many Predictions Fail, but Some Don't"

“Noise” & false positives

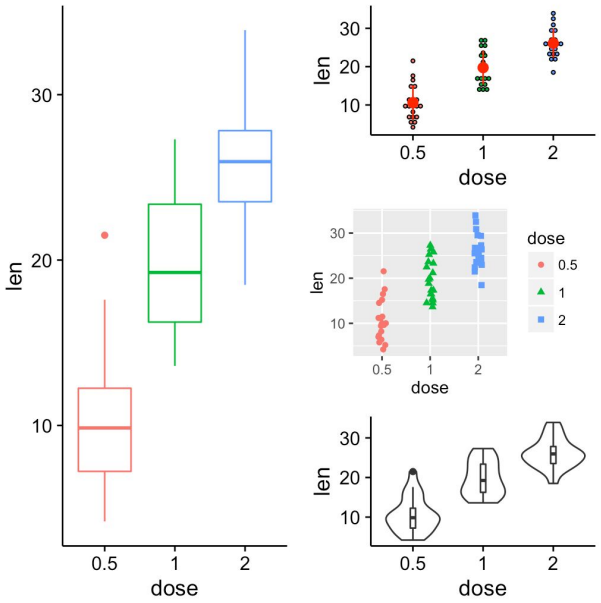
Data mining in a nutshell ...

- Look for true Information (signal) inside a complex dataset ...
- Look for organization inside the data ...

Two examples of organization ….



Two variables
highly “correlated”

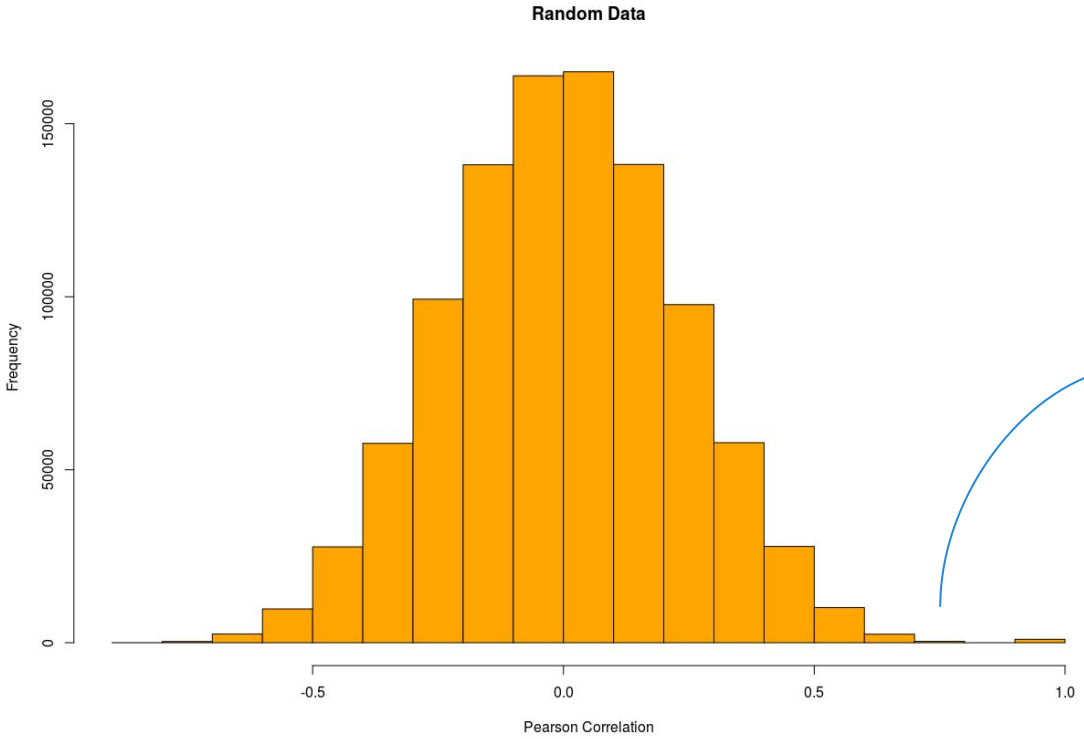


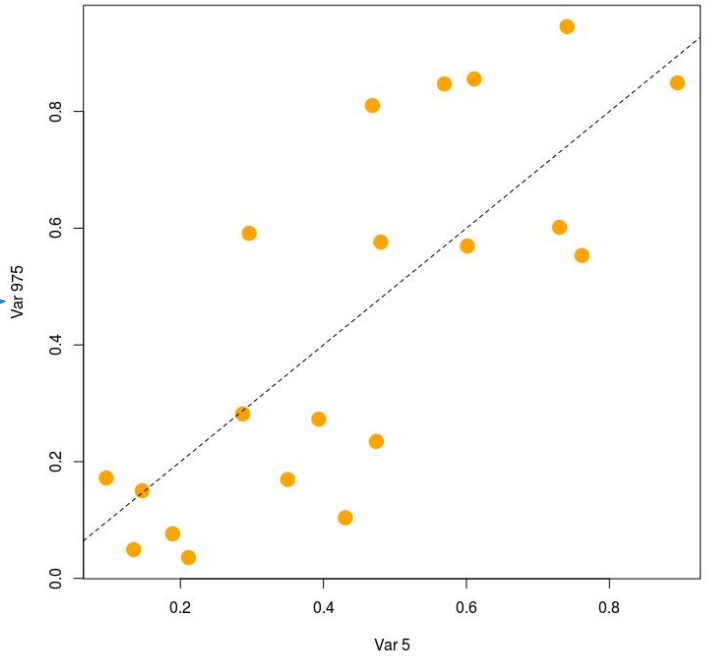
Biomarkers ...

The challenge

- We construct a “fake” data matrix of 20 samples and 1000 variables
- We look correlated variables (organized Information)
- There is not “true” information in the data

An example of “self - organization” ?





ALL FOR YOU

Questions for you ...

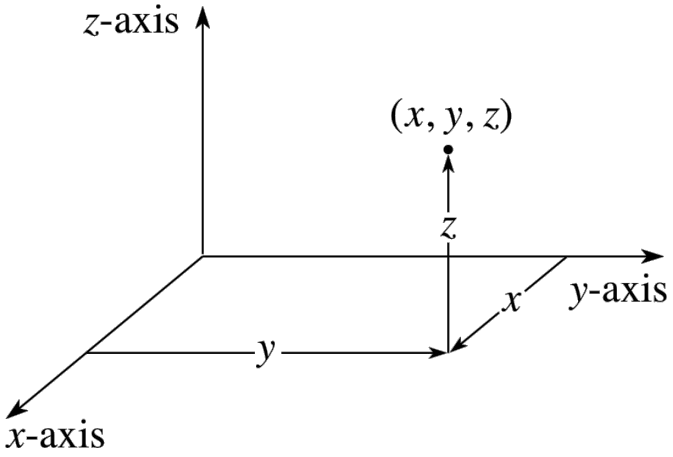
- Am’I playing fair?
- Where is the trick?
- Why I call this “false positive”?
- Is there an error somewhere?

Organized “by chance”

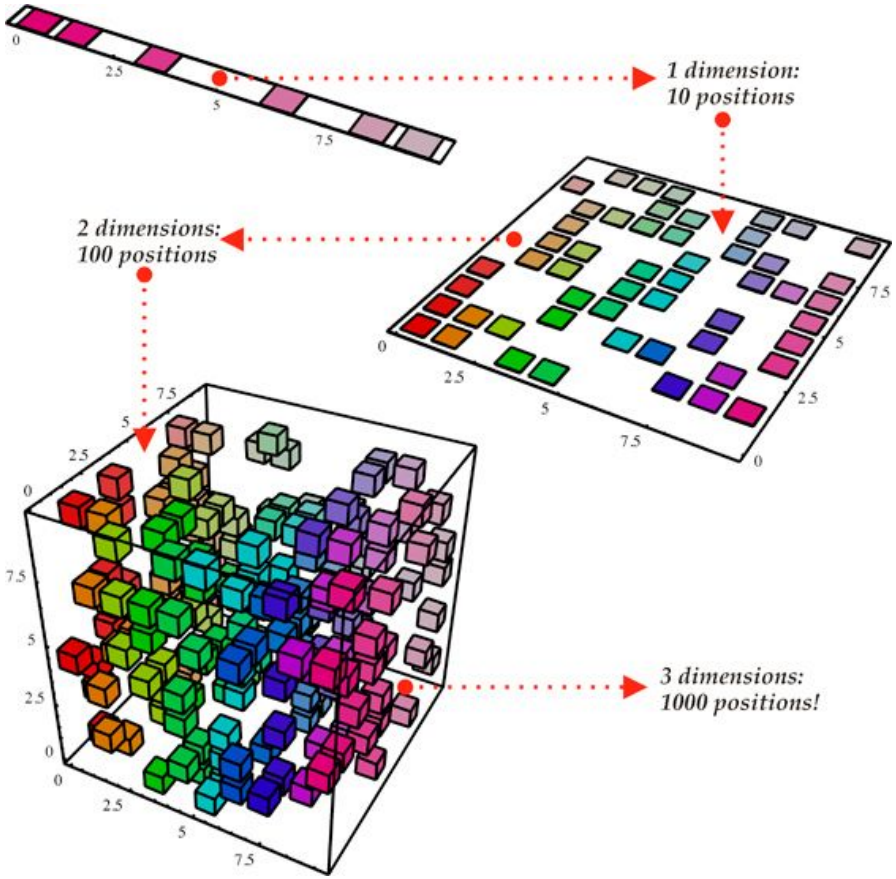
- We find true organization
- This is not the result of a true chemical/biological/physical process
- This organization is “true” only for my dataset
- There are no errors and no tricks
- Do you see the scientific consequences?

n variables, n dimensions

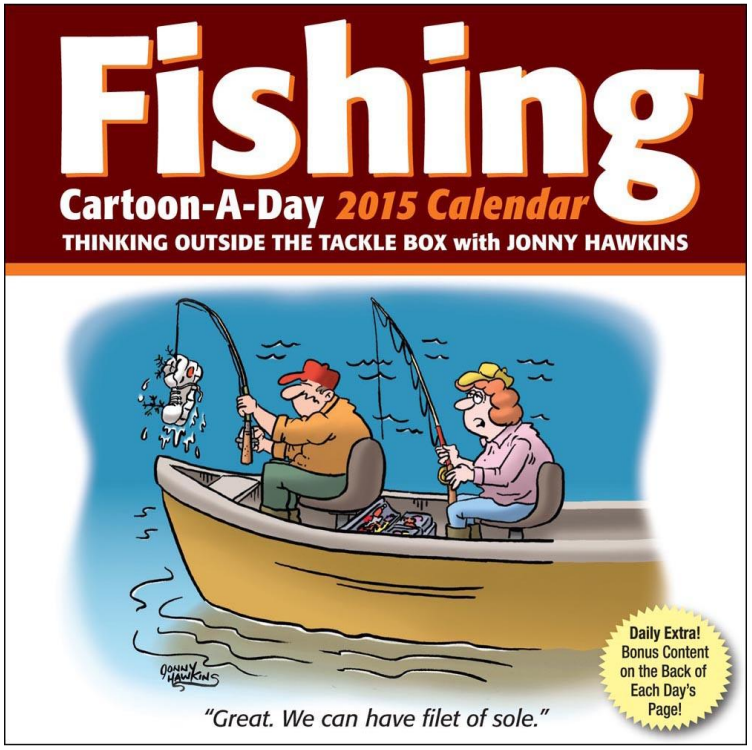
In a multivariate setting, each sample is a point in the multidimensional space



Empty Space


1 dimension:
10 positions
2 dimensions:
100 positions
3 dimensions:
1000 positions!

Be careful, it could be a sole …

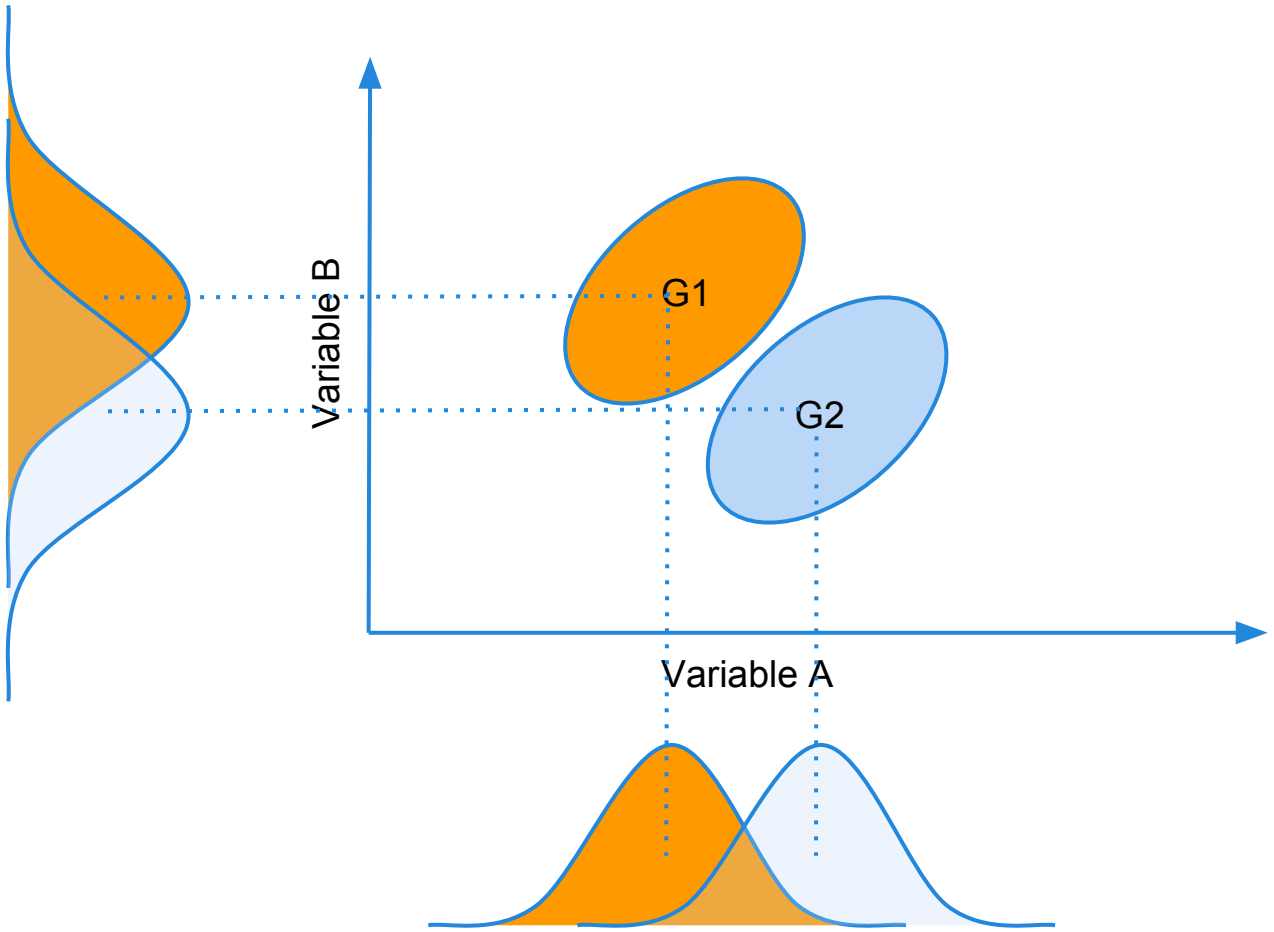


Luckily enough ..

The variables are not independent

- Biological dependence
- Chemical dependence
- ….

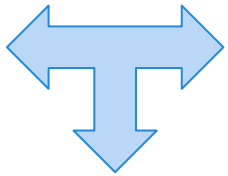
Multivariate vs Univariate



There ain't no such thing as a free lunch.

... IN STATISTICS

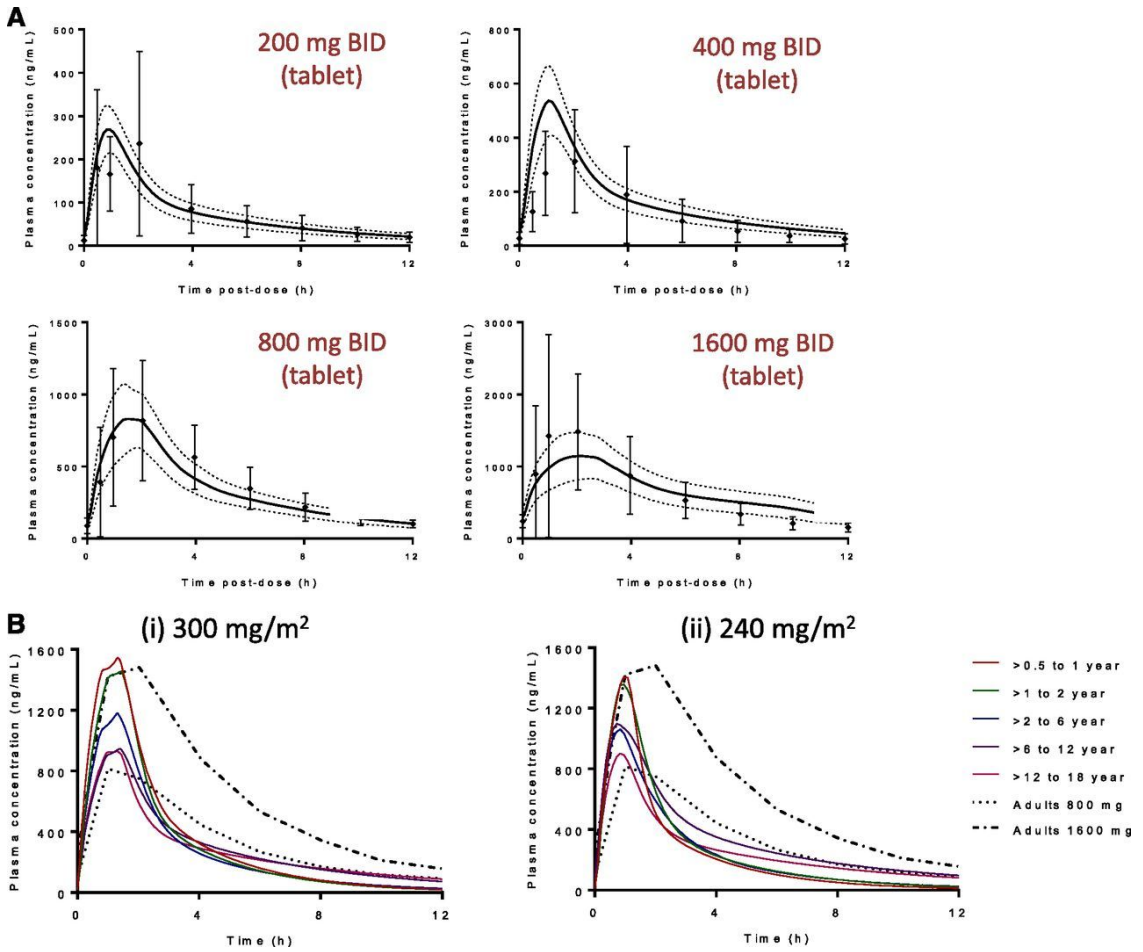
SAMPLES



MODEL COMPLEXITY

KNOWLEDGE

Pharmacokinetics



Understanding (Modelling) vs Classifying

To classify something it is not necessary to understand why ...

To recognize a tree your brain does not need to know the details of photosynthesis

The NEW ENGLAND JOURNAL of MEDICINE

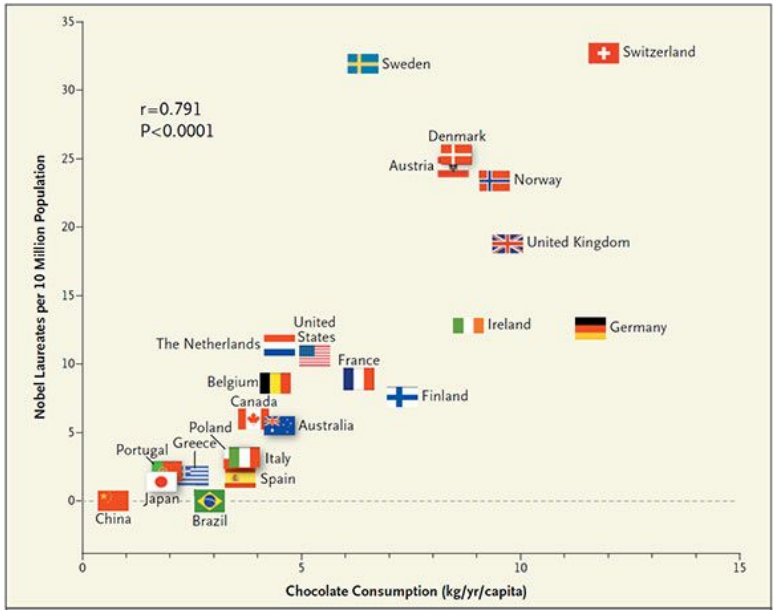
Chocolate Consumption, Cognitive Function, and Nobel Laureates

Franz H. Messerli, M.D.

N Engl J Med 2012; 367:1562-1564 October 18, 2012 DOI: 10.1056/NEJMon1211064

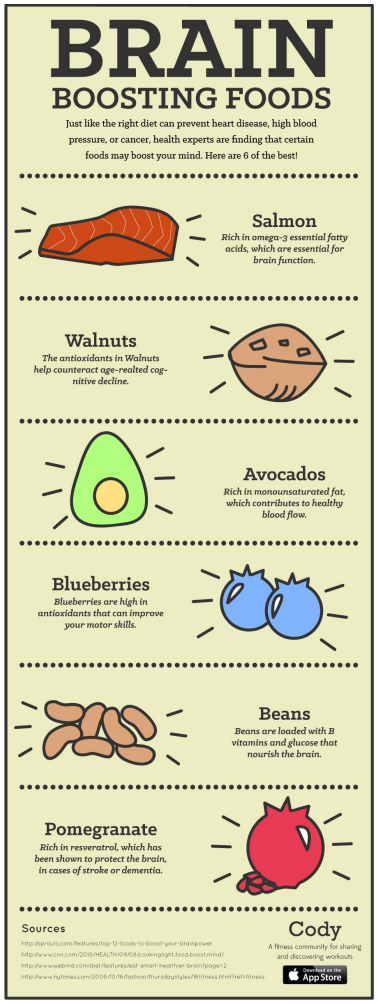
Chocolate consumption could hypothetically improve cognitive function not only in individuals but in whole populations. Could there be a correlation between a country's level of chocolate consumption and its total number of Nobel laureates per capita?

There was a close, significant linear correlation (r=0.791, P<0.0001) between chocolate consumption per capita and the number of Nobel laureates per 10 million persons in a total of 23 countries (Fig. 1)



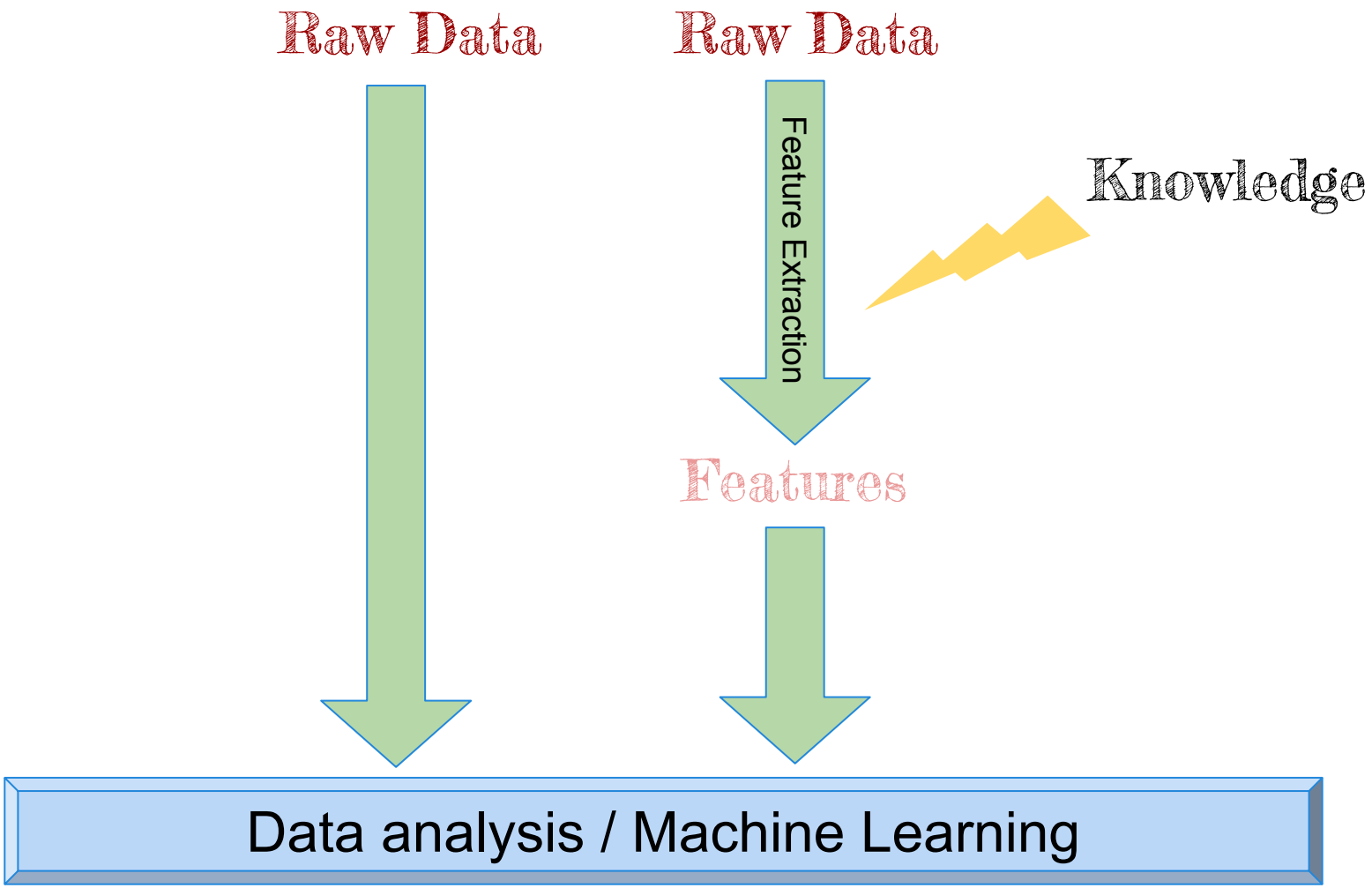
… food for brain

- It could be not easy to spot the predicting variables if you use a complex “predictor” (classifier,...)
- Sometimes is not needed! (Think to google)
- Modeling and predicting are not synonyms
- It depends on what is your objective ...



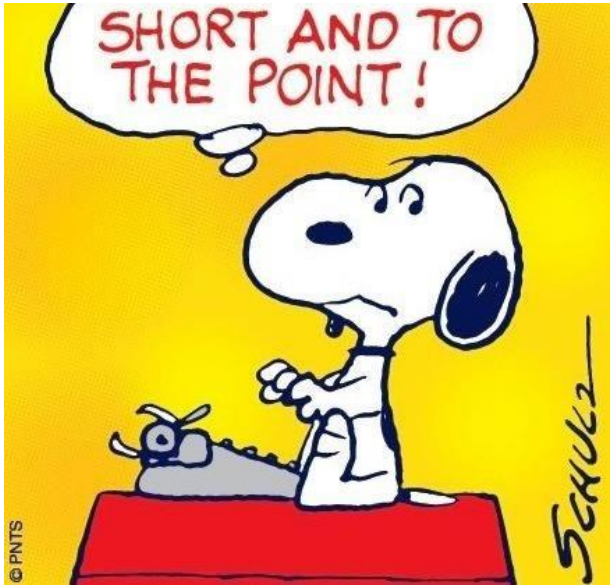
Things to look at ...

What variables should I use?

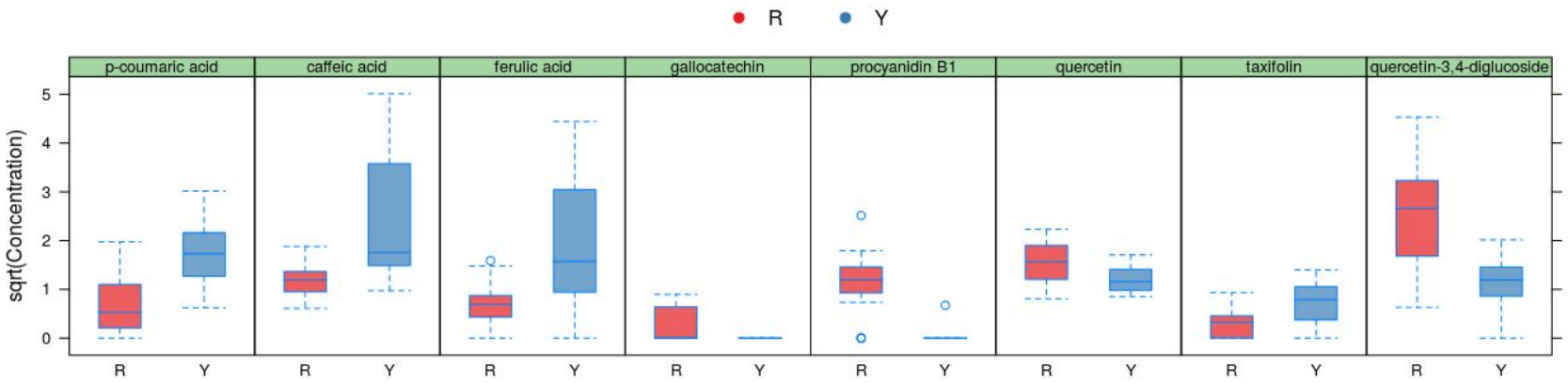


… food for brain

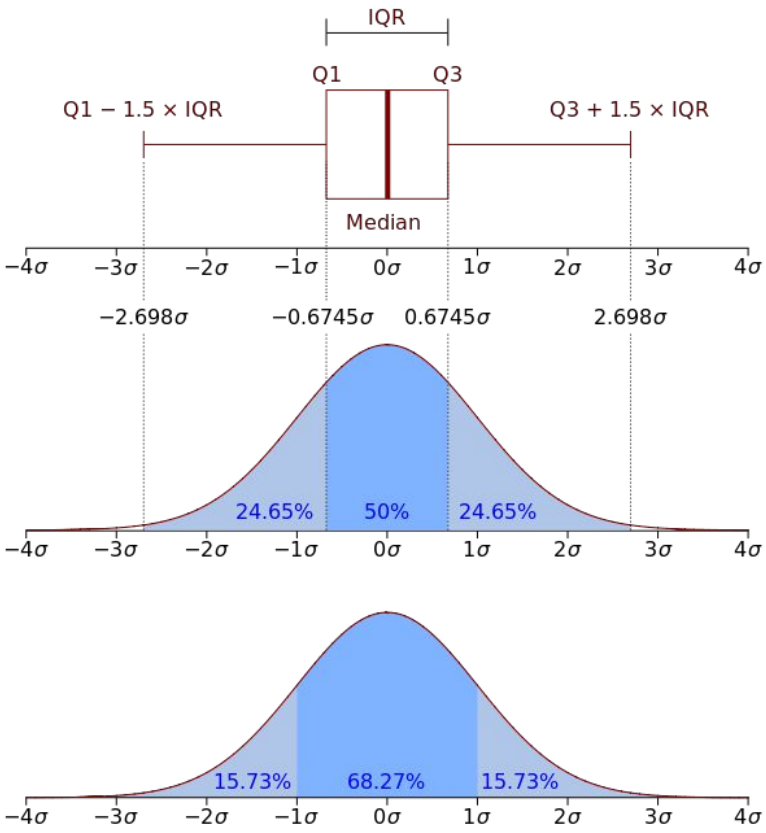
- The “raw” content of information in the raw data is bigger … but also the noise is bigger
- The process of feature extraction distill useful knowledge from noise
- Something can get lost
- It really depends on the problem …
- What would you do in image analysis, metabolomics, metagenomics?



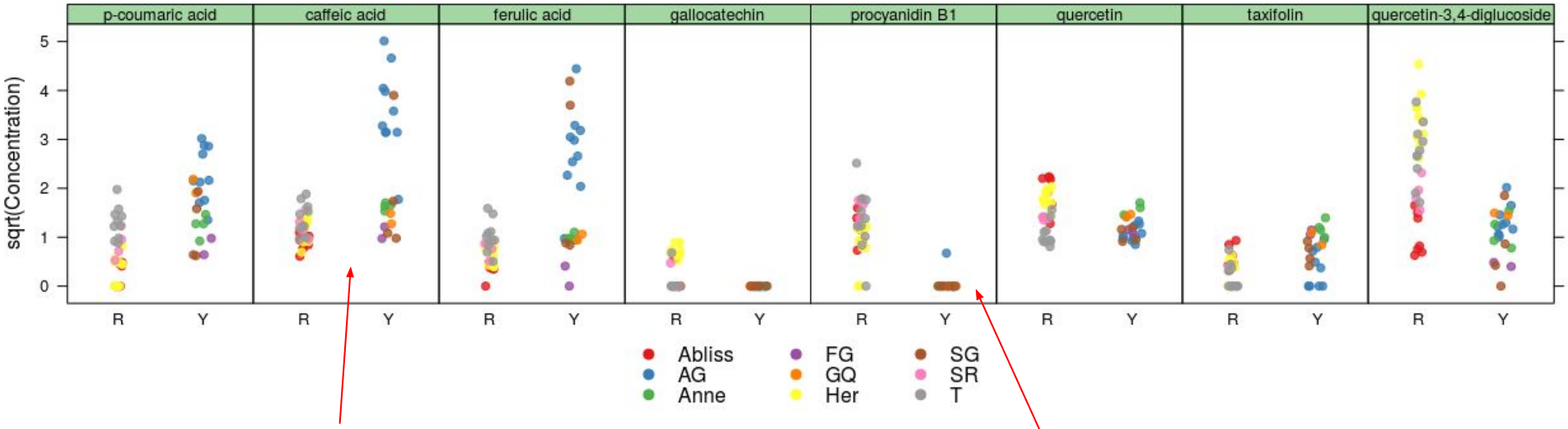
Confounding Factors



Box plots …. ;-)


IQR
Q1
Q3
Q1 − 1.5 × IQR
Q3 + 1.5 × IQR
Median
−4σ
−3σ
−2σ
−1σ
0σ
1σ
2σ
3σ
4σ
−2.698σ
−0.6745σ
0.6745σ
2.698σ
24.65%
50%
24.65%
15.73%
68.27%
15.73%

Confounding Factors

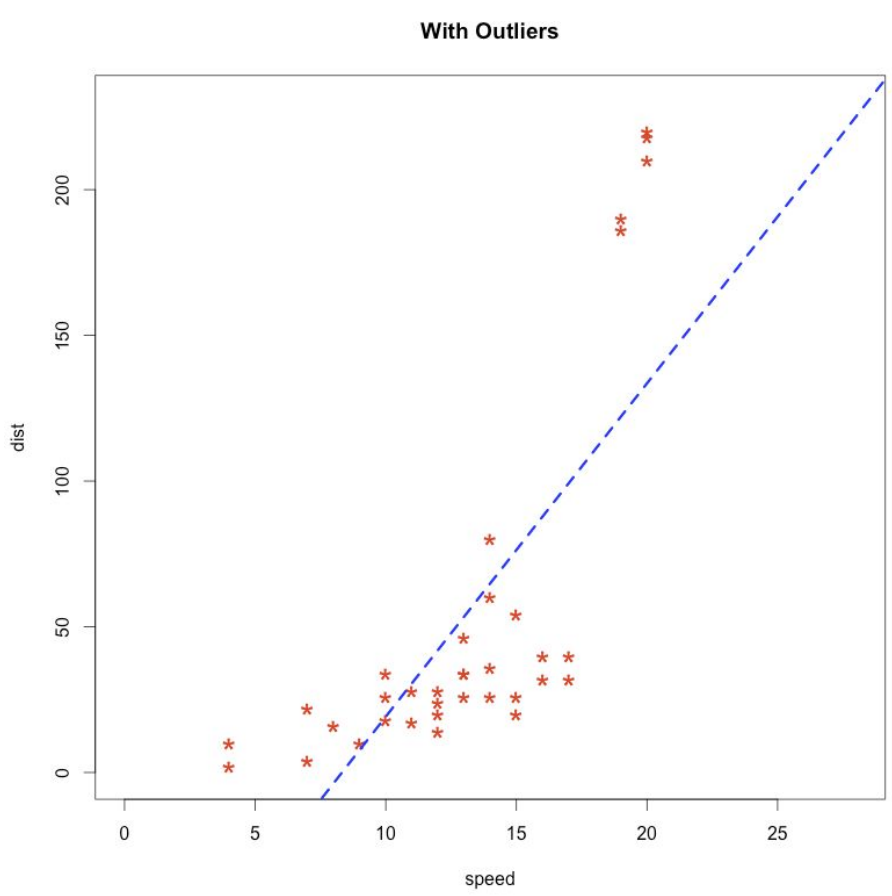


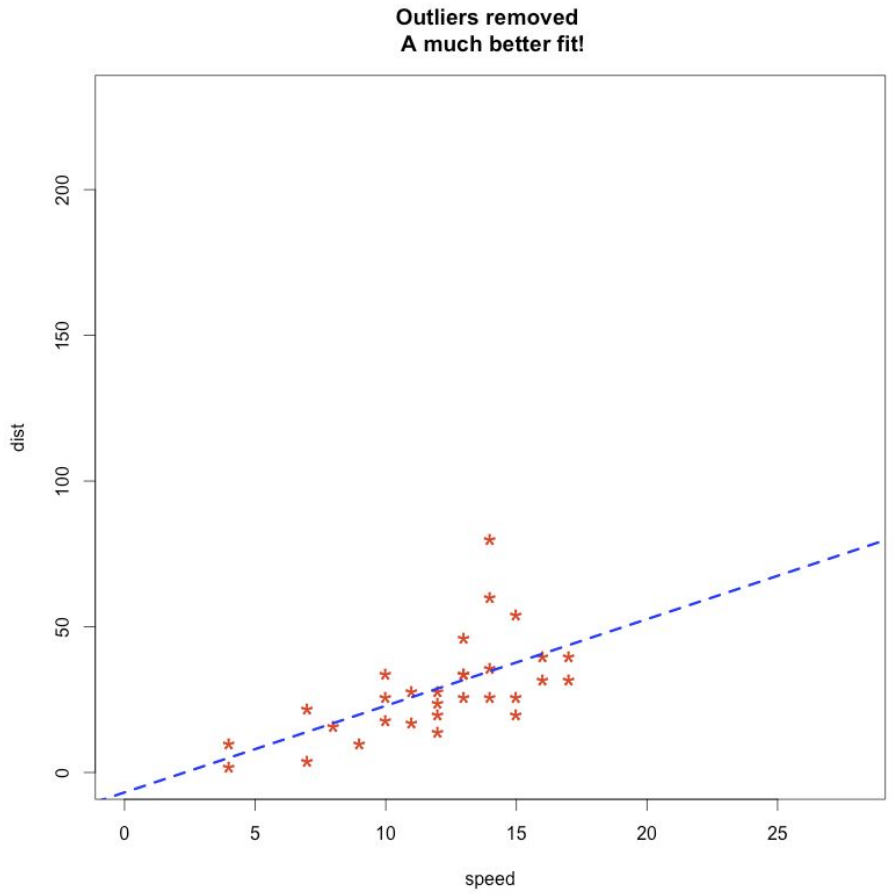
This seems to be not related to color ....

These look like zeroes … what does zero mean?

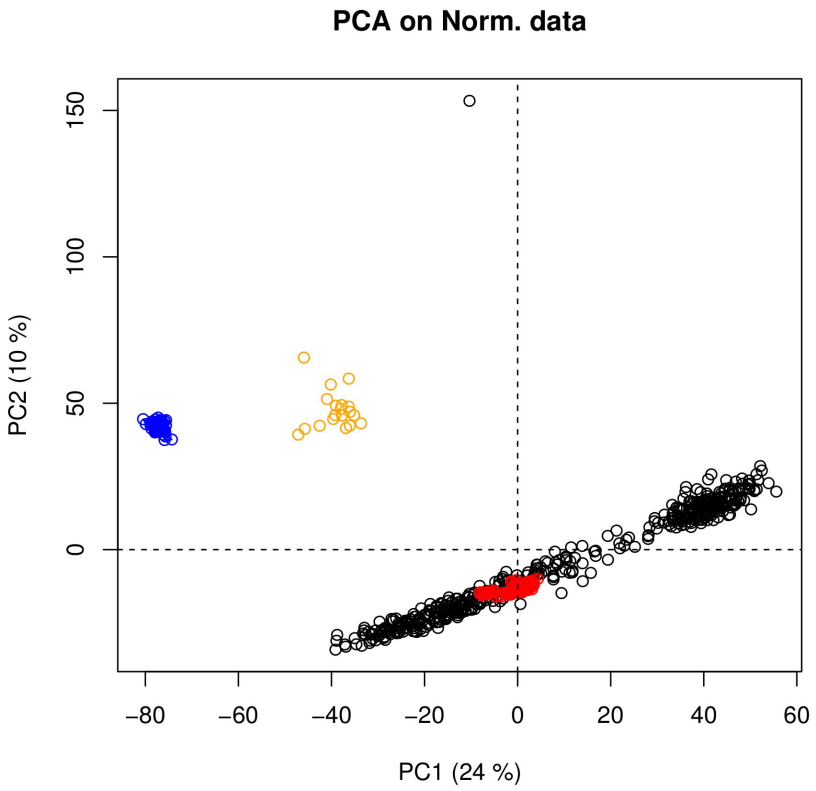
In machine learning , hidden confounding factors could bias validation schemes

Outliers


With Outliers
dist
speed
0
50
100
150
200
0
5
10
15
20
25


Outliers removed
A much better fit!
dist
speed
0
50
100
150
200
0
5
10
15
20
25

Outliers



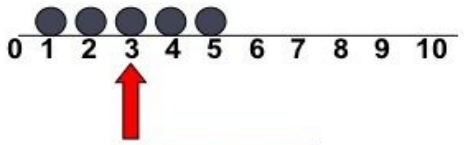
… let's discuss …

- What is an outlier?
- How should I treat it?
- When is fair to get rid of a sample?

Rely on robust statistics and methods ...

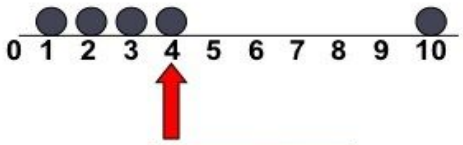
The Mean: Sensitive To Outliers

- The most common measure of the central tendency
- Affected by extreme values (outliers)



Mean = 3

$$\frac{1+2+3+4+5}{5} = \frac{15}{5} = 3$$



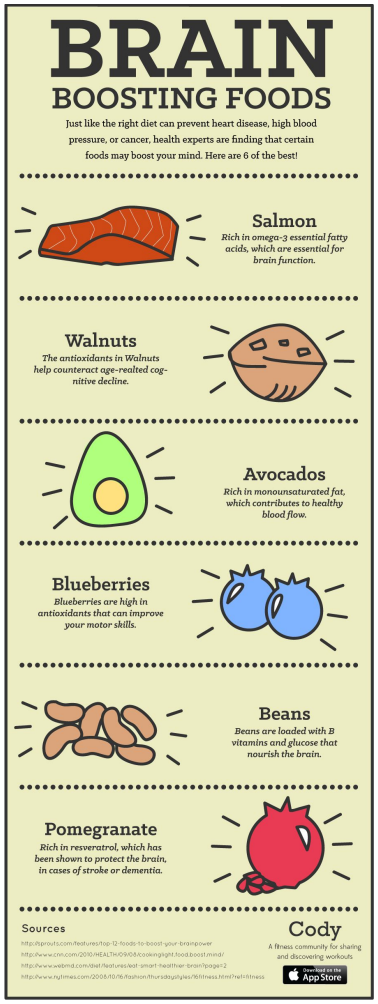
Mean = 4

$$\frac{1+2+3+4+10}{5} = \frac{20}{5} = 4$$

The mean is not robust the median is better

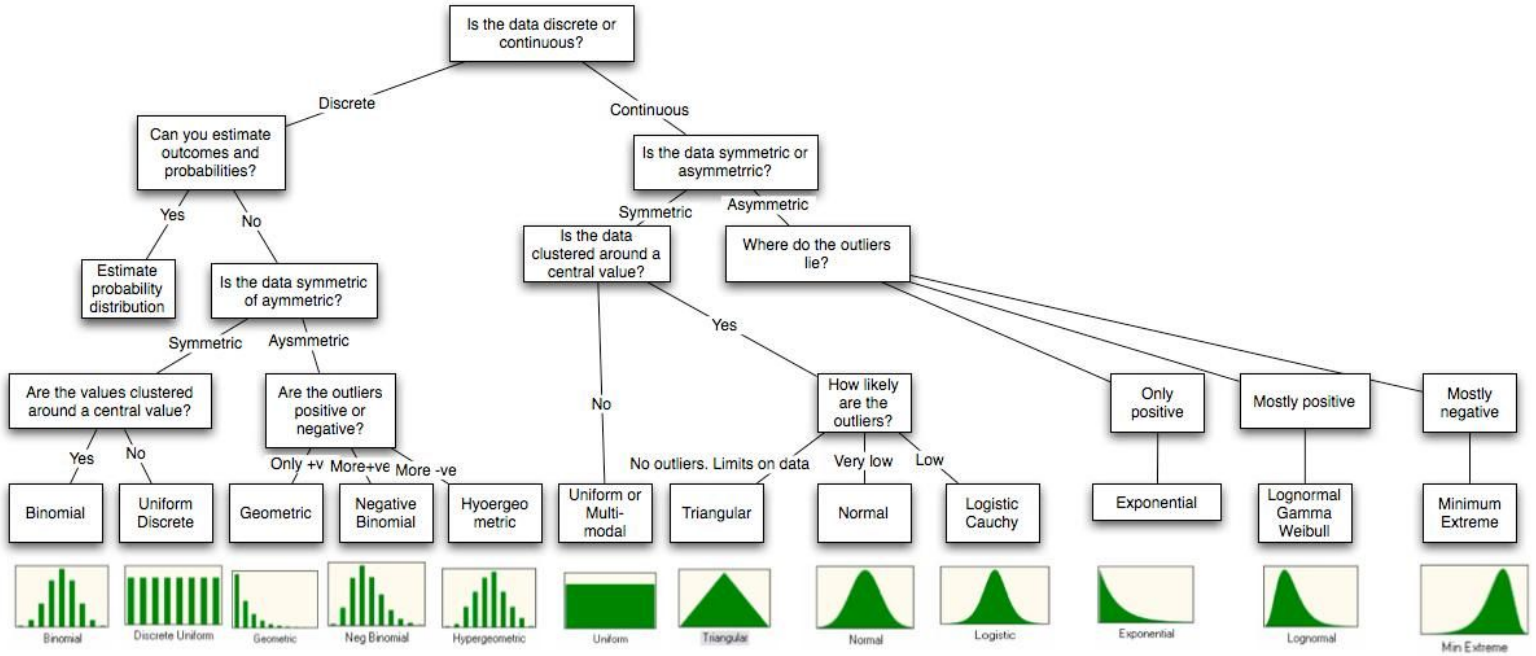
… food for brain

- Use boxplots wisely and not to hide the fact that you have few samples.
- If a sample looks as an outlier go back to the data and try to discover there are good reasons to discard it
- If not try to rely on robust statistics



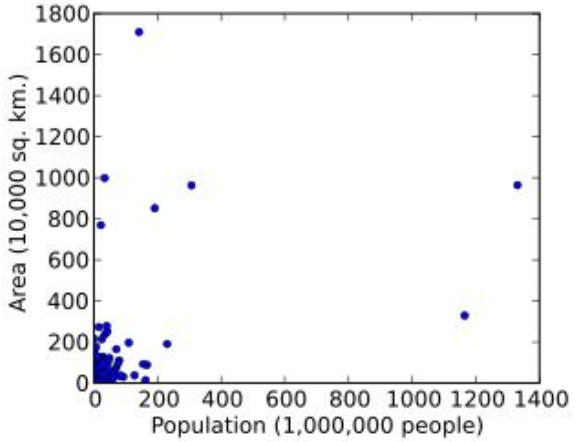
Which is the distribution of your data?

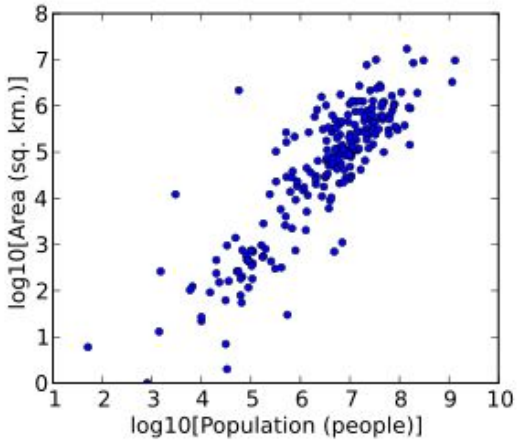
Many statistical methods contains hidden assumptions on the "acceptable" distribution of the data. As a rule, everything works better if data are normally distributed



Data transformation

In many cases “normality” can be restored by data transformation
Common transformations are square root or logarithm





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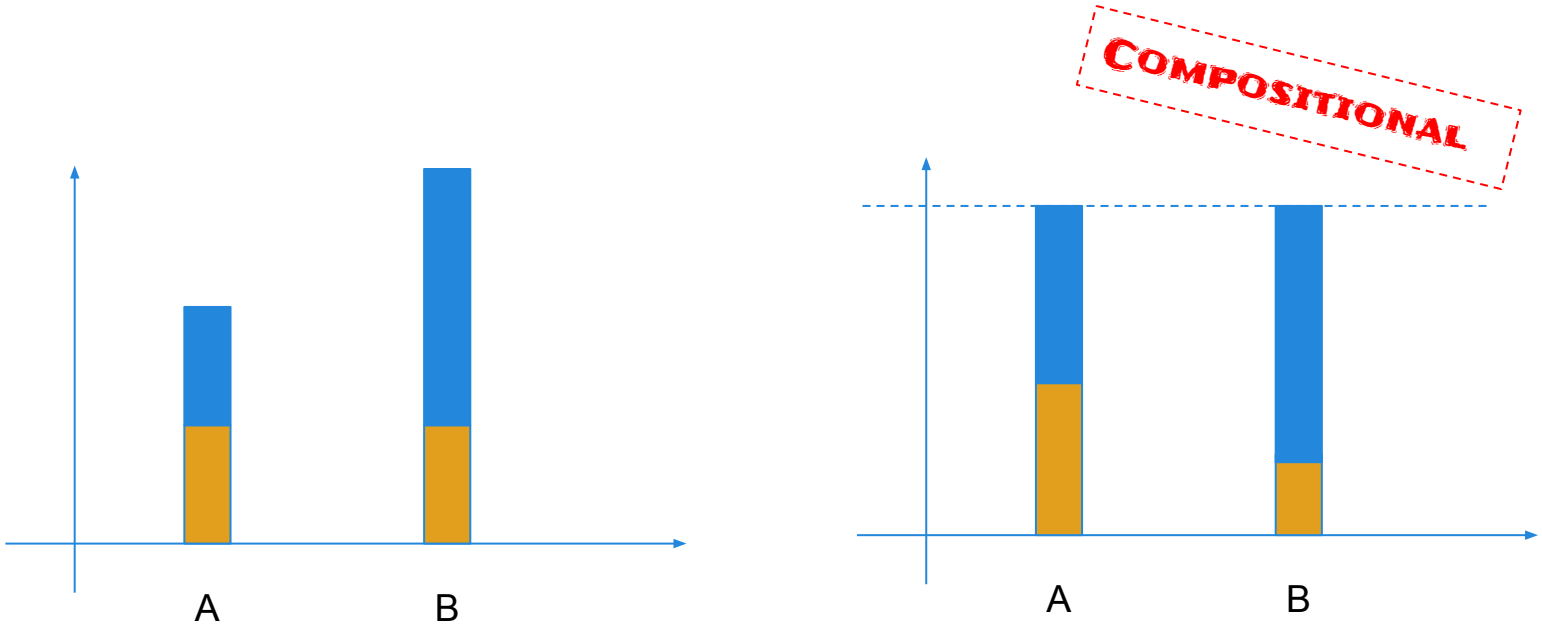
Compositional data

From Wikipedia, the free encyclopedia

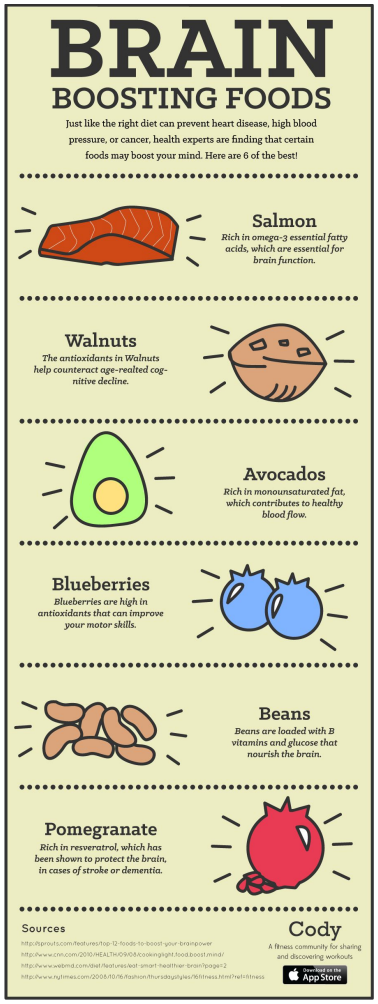
In statistics, **compositional data** are quantitative descriptions of the parts of some whole, conveying exclusively relative information. Measurements involving probabilities, proportions, percentages of ppm can all be thought of as compositional data.

Relative Abundances/ Relative concentrations



… food for brain

- The fact that in conditions A and B the sum of the variables should be the same introduces correlation
- In the first case the variable “blue” is a marker and “yellow” is not.
- In the second case both are markers!



… let's discuss …

- Can omic- data be compositional?
- Why?
- Is this a problem?

Variable range and magnitude

Almost invariably, we are dealing at the same time with variables of low and high intensity (concentrations, abundances, ...)

The “structure” of our dataset could then be dominated by high intensity variables.

Scaling

The process of making variable comparable is called scaling.

As usual this can be done in many different way - unit variance scaling is popular - and the scaling will affect the outcomes of the analysis

Mean centering is also a commonly applied strategy to make variable comparison easier

… let's discuss …

- Is scaling always fair?
- Do you see its limitations?
- How can I decide the "best" scaling approach?

Making samples comparable …

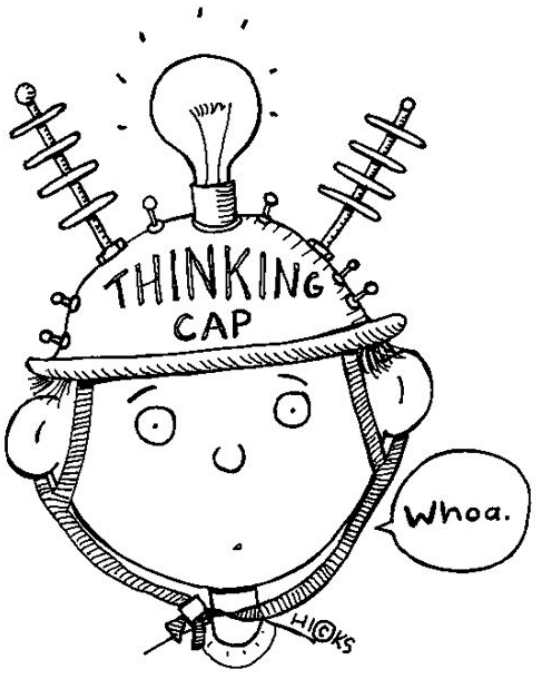
In many cases (metabolomics, metagenomics, ...) the overall response of the data acquisition pipeline is not constant across the samples.

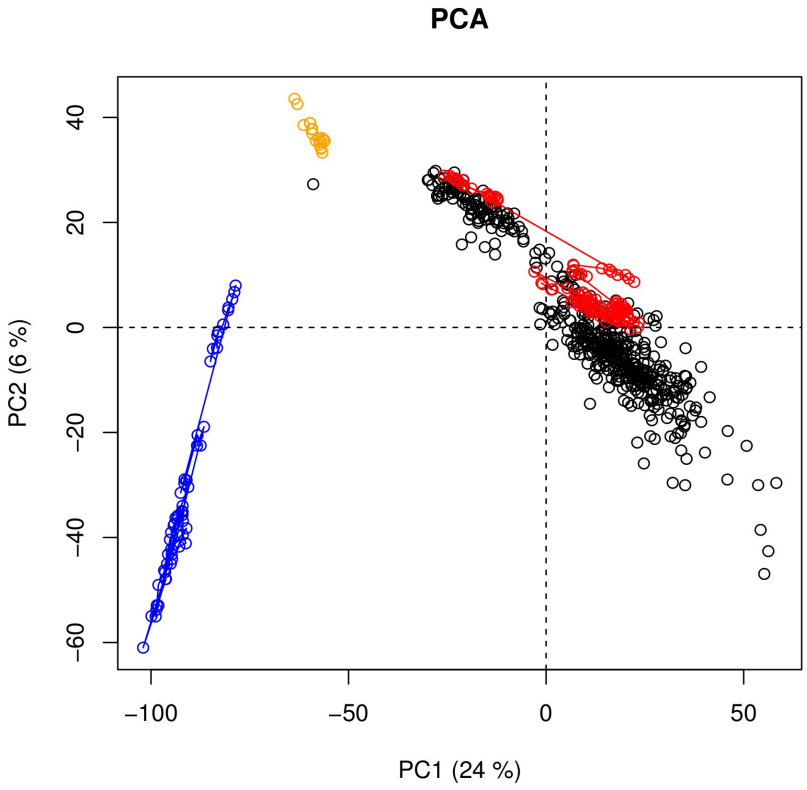
To look for biomarkers it is necessary to correct for that

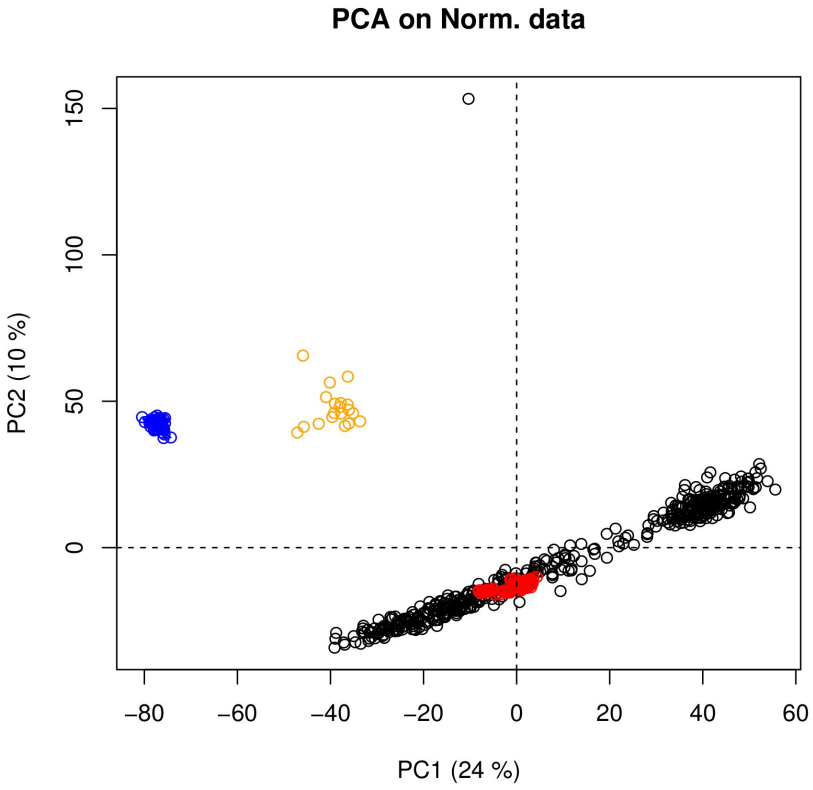
Normalization

… food for brain

- It would be better to avoid normalization
- If normalization is done relying on relative abundances the data are becoming compositional!
- A wise organization of the “sample list” taking into account the experimental design is of great help
- Normalization strategies are domain specific!




PCA
PC2 (6 %)
PC1 (24 %)
40
20
0
−20
−40
−60
−100
−50
0
50

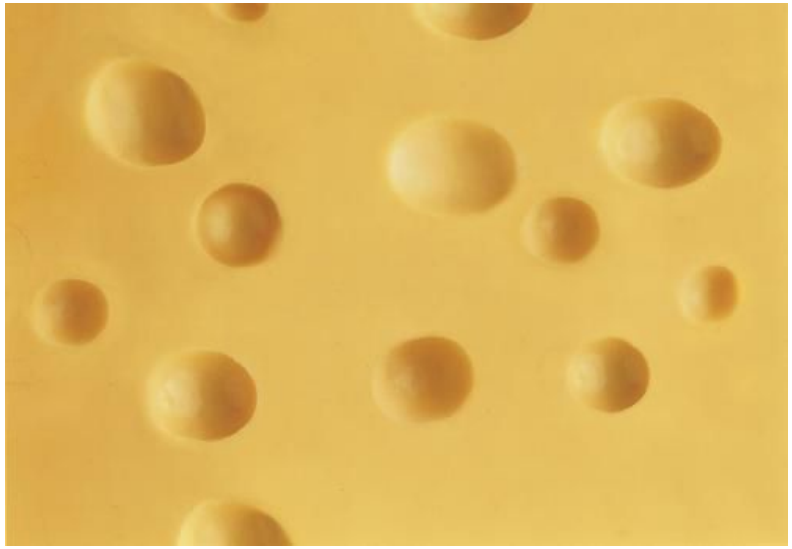

PCA on Norm. data
PC2 (10 %)
PC1 (24 %)
150
100
50
0
−80
−60
−40
−20
0
20
40
60

Missing data

From Wikipedia, the free encyclopedia

In statistics, **missing data**, or **missing values**, occur when no data value is stored for the variable in an observation. Missing data are a common occurrence and can have a significant effect on the conclusions that can be drawn from the data.

- Preprocessing errors
- Low intensity
- Low abundance
- ...



I could ...

- Forget them and live in peace
- Fill them with a value … which one?
- Take out the features with too many nas …
- … but then what I can do with the rest?

The process of substituting missing values with meaningful number is called imputation

… let's discuss …

Which is the best way to perform imputation?


#1
LETS GO
LIVE!!!

Towards Statistical Significance

Data, knowledge & data analysis

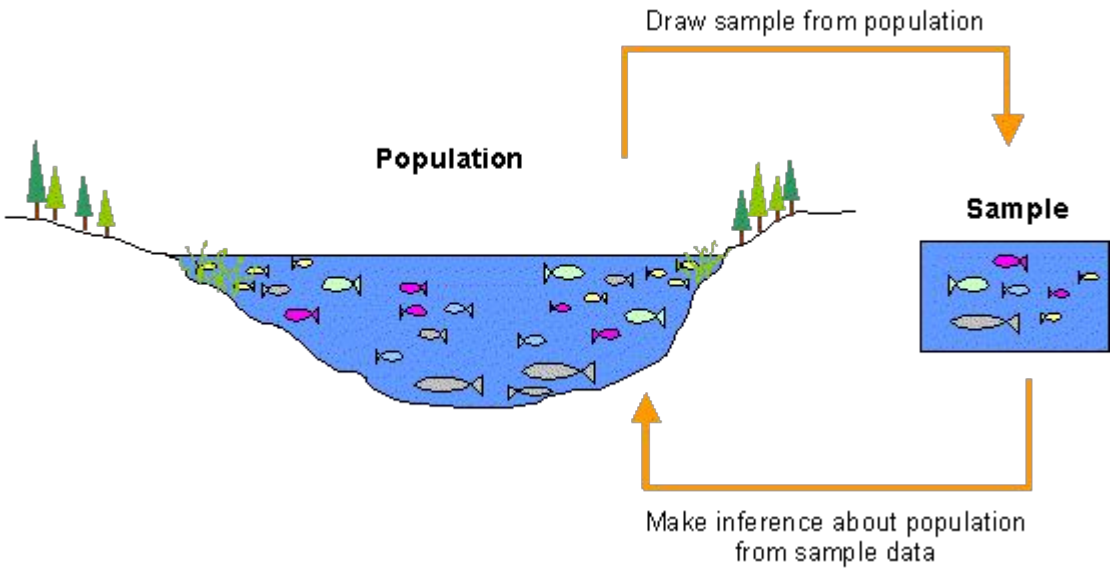
Data

Knowledge

In *omic* sciences, bioinformatics, statistics, … provide the tools to:

- Promote the incremental progress of science
- Guarantee the validity and the correctness of the results
- Facilitate the production of “scientific” results (of general validity …)
- Be consistent
- Get the maximum from complex data

Population, sampling and inference



The challenge

- A sampling can be unlucky … but the bigger the better ;-) !
- Organization can be true only for the sample and not for the population
- We cannot eliminate this, so we are never sure that what we see has general validity

The best we can do is to try to quantify our uncertainty

A reasonable approach … in words

- Suppose that the organization is absent at the population level (H0)
- Chose a “statistic” to quantify organization
- Calculate the probability of obtaining “at least” the observed level of organization only by chance (p-value!)
- Set a threshold of acceptable incertitude (1%, 5%)

If the probability is below the threshold, one can reasonably expect that the observed organization is true at the population level

… food for brain

- In all this approach I'm only testing the absence of organization … not the presence of a specific level of organization (H0, not H1)
- In any case I'm never sure!
- The best I can do is quantify the incertitude ...