

author

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DATA ANALYSIS AND REPORTING

Biostatistical Challenges in R&D

Conflicting regulators, upbeat
developers and big data:
How to bring them together?

Gonne van Osta
Author! et al. BV

Introduction

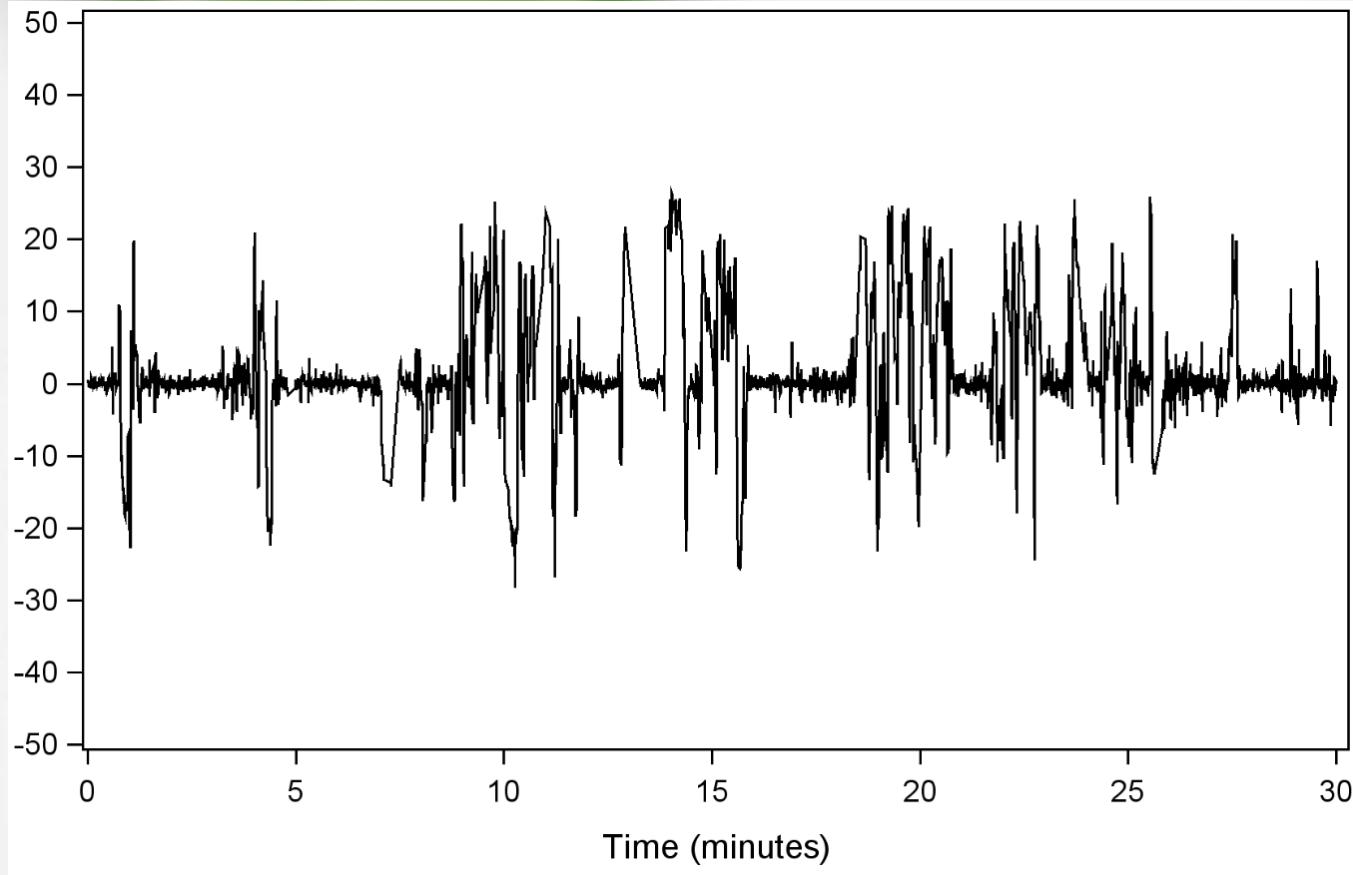
- ! Gonne van Osta (Goes, 1962)
- ! First year, Human Movement Studies VU, 80s
- ! MSc in Mathematical Statistics UvA, 80s
- ! 3 years, statistical consultant DLO Wageningen
- ! 22 years in development (biometrics, quality, clinical, regulatory, pharmaceutical) Organon etc, Oss
- ! Registered biostatistician, 2000
- ! Scientific meeting organiser PSDM/EFSPI, 2002-2006
- ! Lean six sigma black belt, 2012
- ! Currently: statistical consultant at AUTHOR!

Example: Diagnostic Medical Device

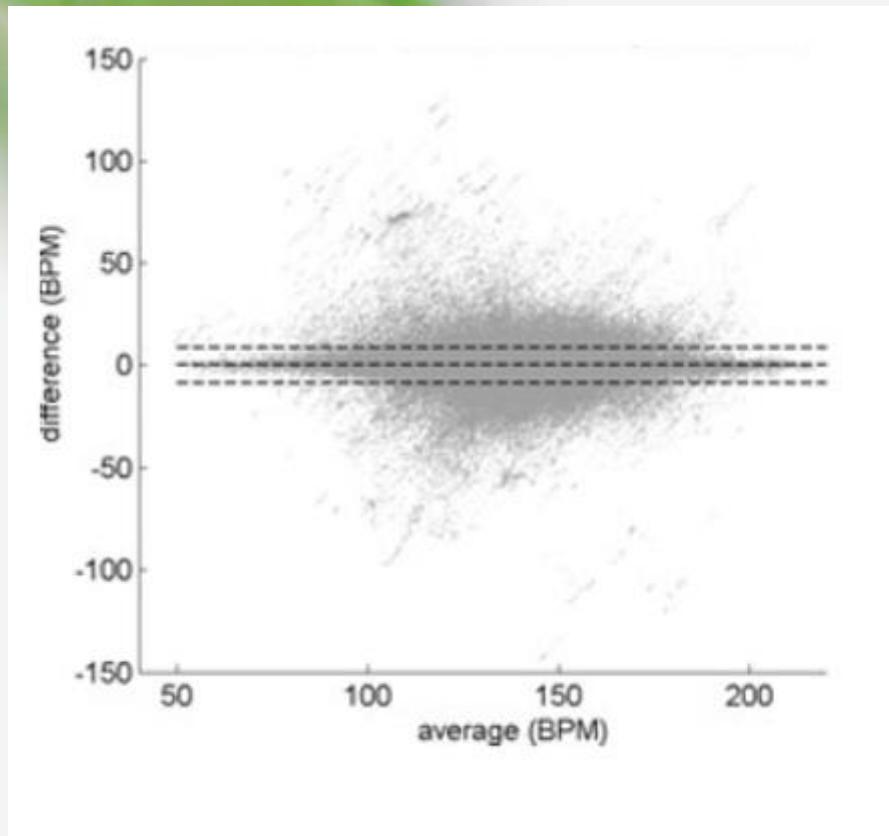
- ! New device to measure heartbeat, less invasive
- ! Aim: to replace the existing device with the new device
- ! Request: Study design/power calculations to show that the new device is as good as the golden standard
- ! What is measured?
 - 2 Devices in parallel (paired)
 - Heartbeat (periferal), in various stages of physical effort
 - Periods: several hours
 - 4 observations per second

→ Lots and lots of data

The data, one patient, ± 7000 points



Indication literature

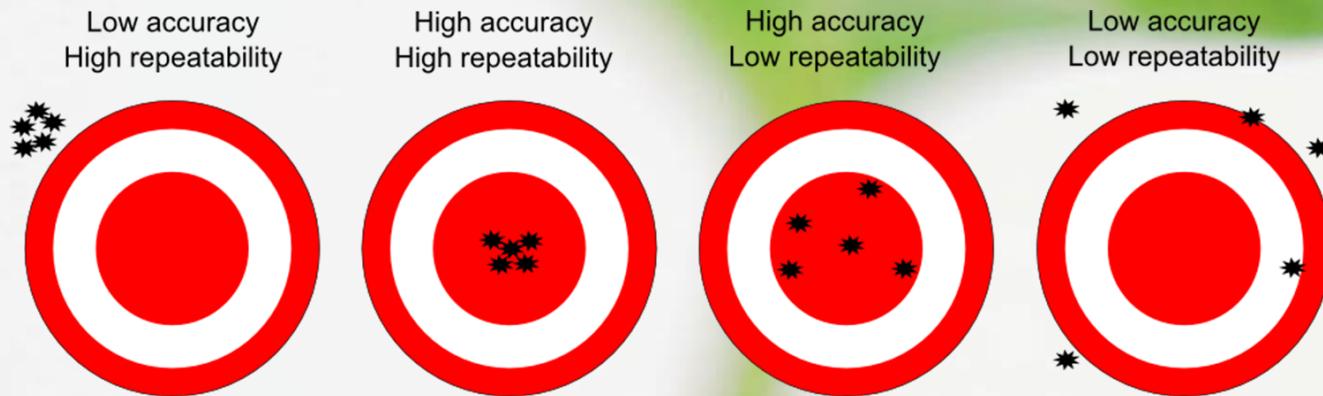


Challenge

- ! Input: sponsor, indication literature, hospital EC, regulators
- ! Sponsor/Literature:
 - Literature, 3 arm study showing superiority of one new devices over another existing device.
 - Reliability=Percentage Positive Agreement=Percentage Time Heart Beat of 2 systems is within 10 beats
 - Accuracy: root MSE of differences (or against the regression of Bland-Altman plot?)
 - 3-arm study not feasible: non-inferiority 2-arm

Aim for a reliability and accurate method

- Reliability=Percentage Positive Agreement=Percentage Time Heart Beat of 2 systems is within 10 beats
- Accuracy: SD estimation of paired differences
- Literature: Greenwood 1950: Sample Size Required For Estimating The Standard Deviation as a Percent of Its True Value, used for military (seemed appropriate), N=80



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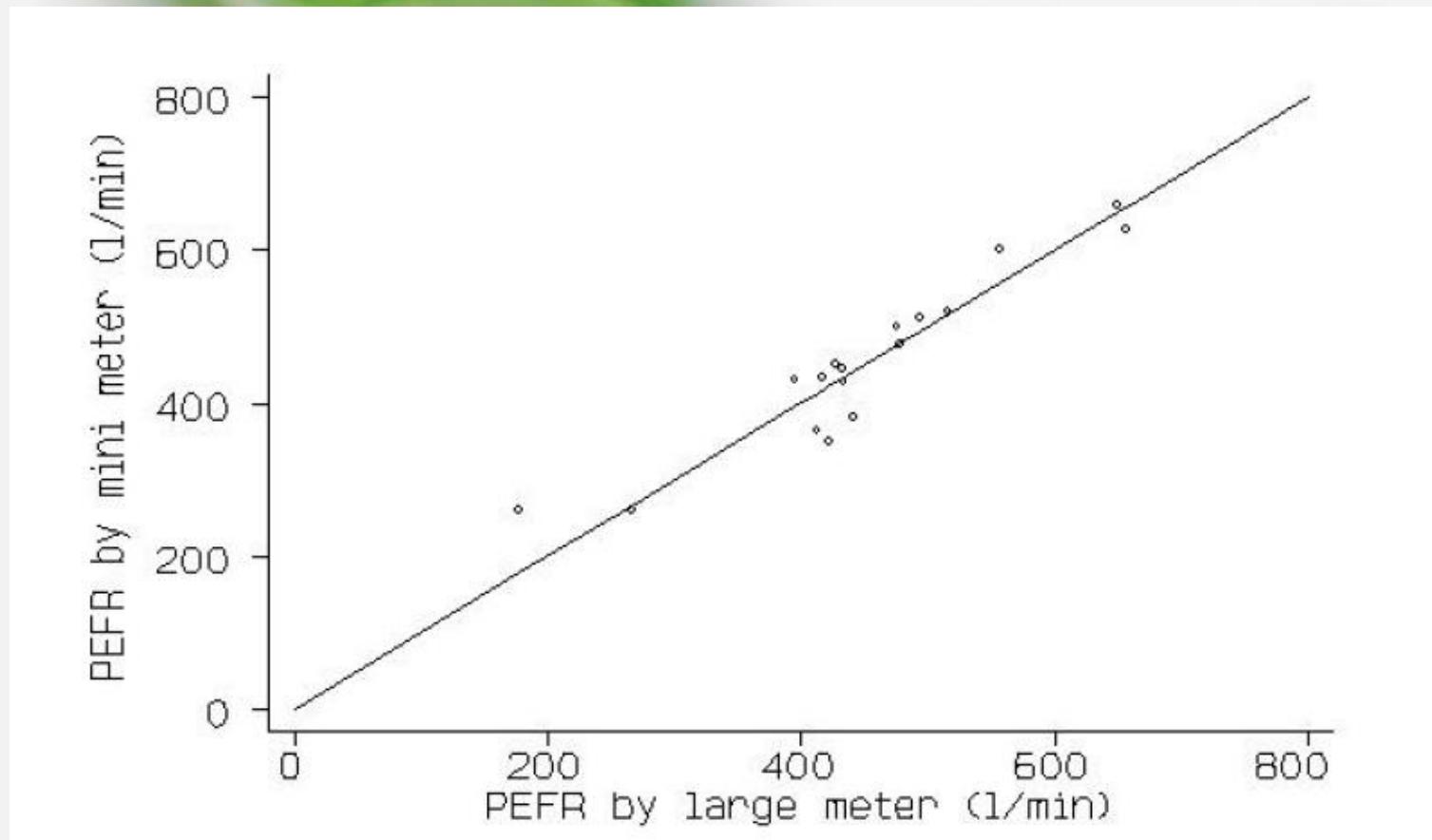
Challenge

- ! Regulators, show reliability and accuracy against golden standard:
 1. Reliability and Accuracy: N=80 seems low, use Bland/Altman 1983 to determine sample size for limits of agreement and bias estimation
 2. Reliability: Proposed definition of reliability is loss of information and repeated measures, use Deming regression ($\beta_0=0$, $\beta_1=1$).
 3. Accuracy: there are correlated repeated measures, use bootstrapping methods when constructing CIs for bias, Bland-Altman (2007) analysis including plots.

Limits of agreement is the new definition of reliability.
What is this new definition?

Bland & Altman, Agreement between methods of measurement with multiple observations per individual. Journal of Biopharmaceutical Statistics, 17: 571–582, 2007

Bland-Altman (1983) side-step



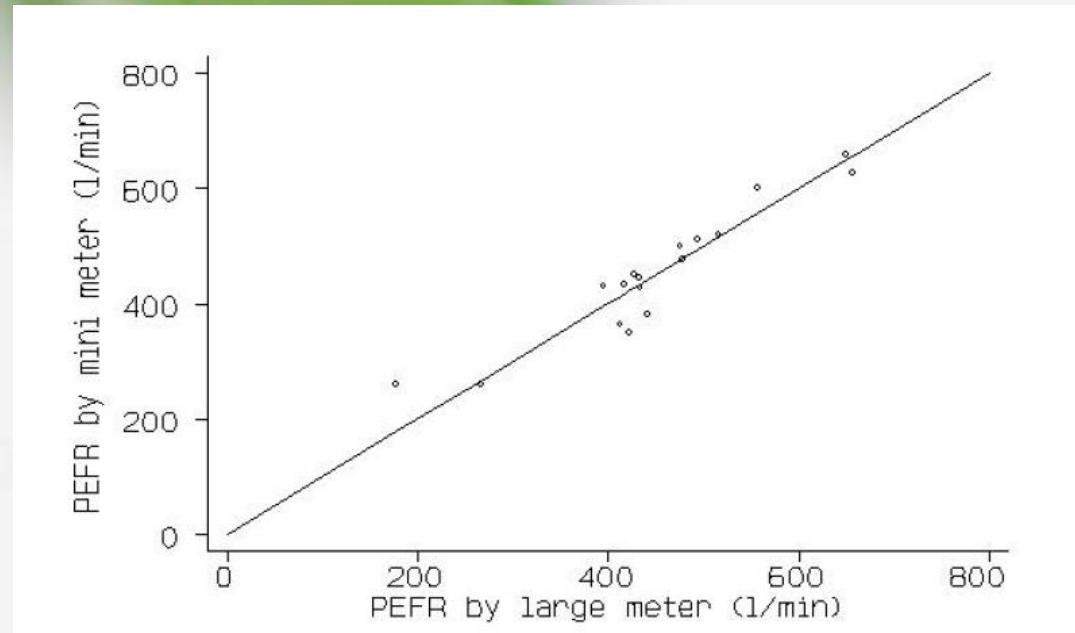
Altman DG, Bland JM. Measurement in medicine: the analysis of method comparison studies.

Statistician 1983;32:307–17

23 November 2018

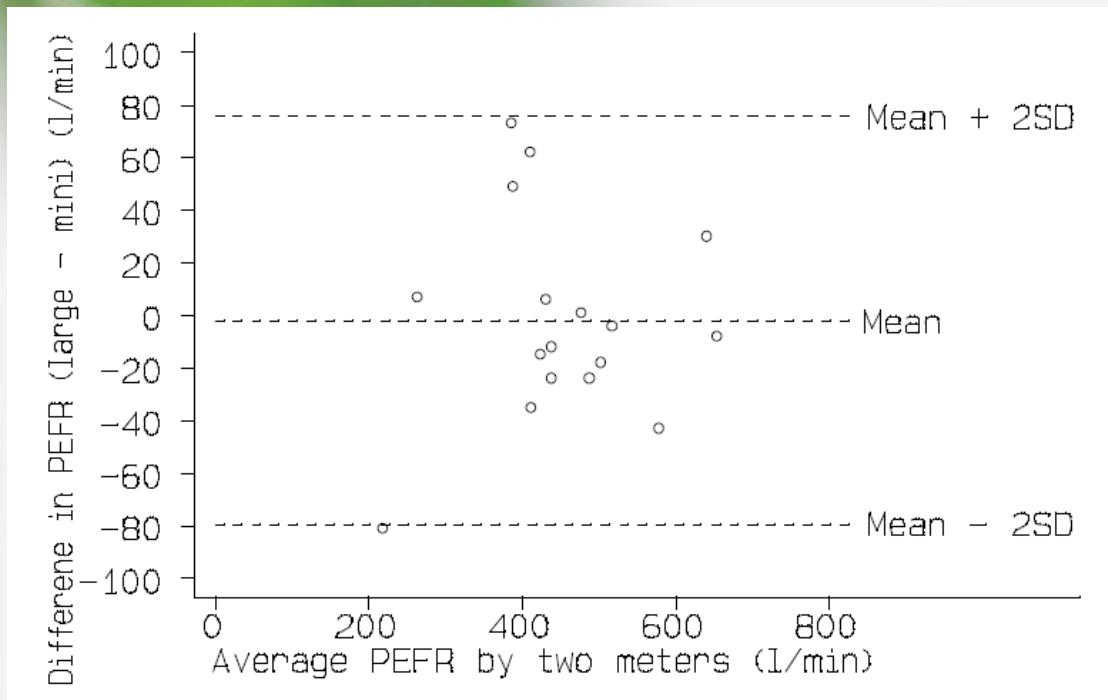
Gonne van Osta

Bland-Altman (1983) side-step



- Data will cluster around a regression line
 - The greater the range of measurements the greater the agreement will appear to be.
- regression is not the way

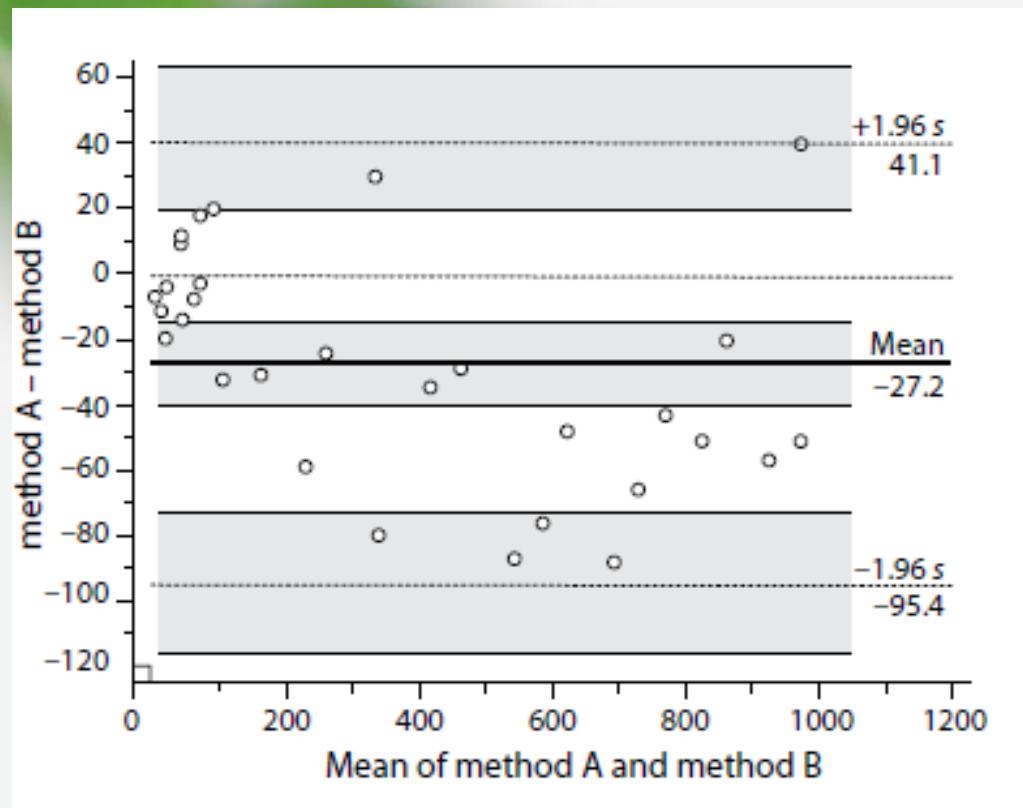
Bland-Altman (1983) side-step



Bland-Altman plot:

- Difference against average
- Error and bias are much easier to assess
- Bias -2.1, mean \pm 2*SD ranges from -80 to +76, this lack of agreement not clear from regression figure

Bland-Altman: Limits of agreement



Bland-Altman plot (continued):

- Estimation of precision of SD/limits of agreement depends on sample size, SE of limits is $\sqrt{3S^2/n}$

Giavarina (2015), Lessons in Biostatistics: Understanding Bland Altman analysis

Bland-Altman side-step

Conclusions:

- ! Correlation does not measure agreement
- ! Least square regression does not measure comparability
- ! This is not calibration. Since calibration is the situation where the true value is known

Summary/Assumptions:

- ! Paired (single readings)
- ! Uncorrelated
- ! Repeatability/plots: Investigate the between method differences and relation with the size of the measurements

Example: Diagnostic Medical Device

So far, straightforward, use Bland-Altman.

- ! But which one? 1983 or 2007?

In the mean time:

- ! Trouble managing the large amounts of data
- ! Lots of (test) data
 - Not keen on bootstrapping
 - Plotting to check B&A assumptions is a challenge
 - Deming regression ($\beta_0=0$, $\beta_1 = 1$) or Bland-Altman (dif vs average regression)?
 - Accounting for correlated repeated data

Bland-Altman side-step

Our example

- ! Paired observations ✓
- ! Independent observations X
- ! No relation between difference(bias) and mean ?

Example: Diagnostic Medical Device

Our test data:

! Independent: X

! Relation Bias and mean ?

! Bland&Altman 1999/2007:

- Number of obs per patient varies (2-5)
- True value varies

→ One way analysis, estimate residual mean square (1 summary per patient).

But: observations within a patient are assumed independent

Example: Diagnostic Medical Device

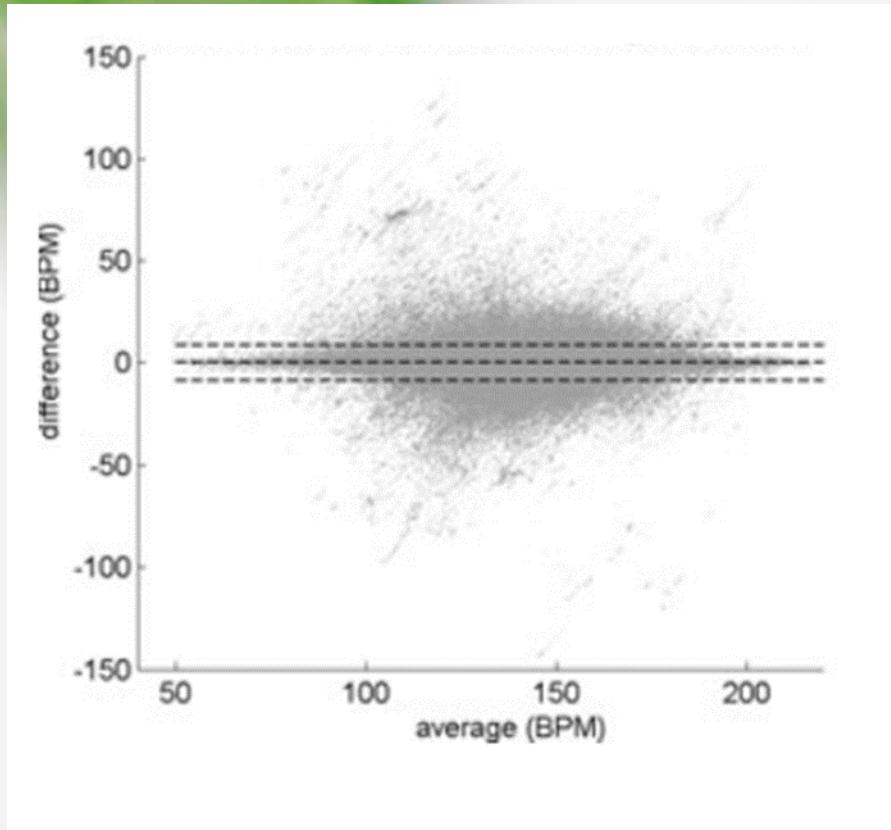
Our test data:

- ! Independent: X
- ! Relation Bias and mean ?
- ! Dependency
 - Estimate correlation or use only one data-point?

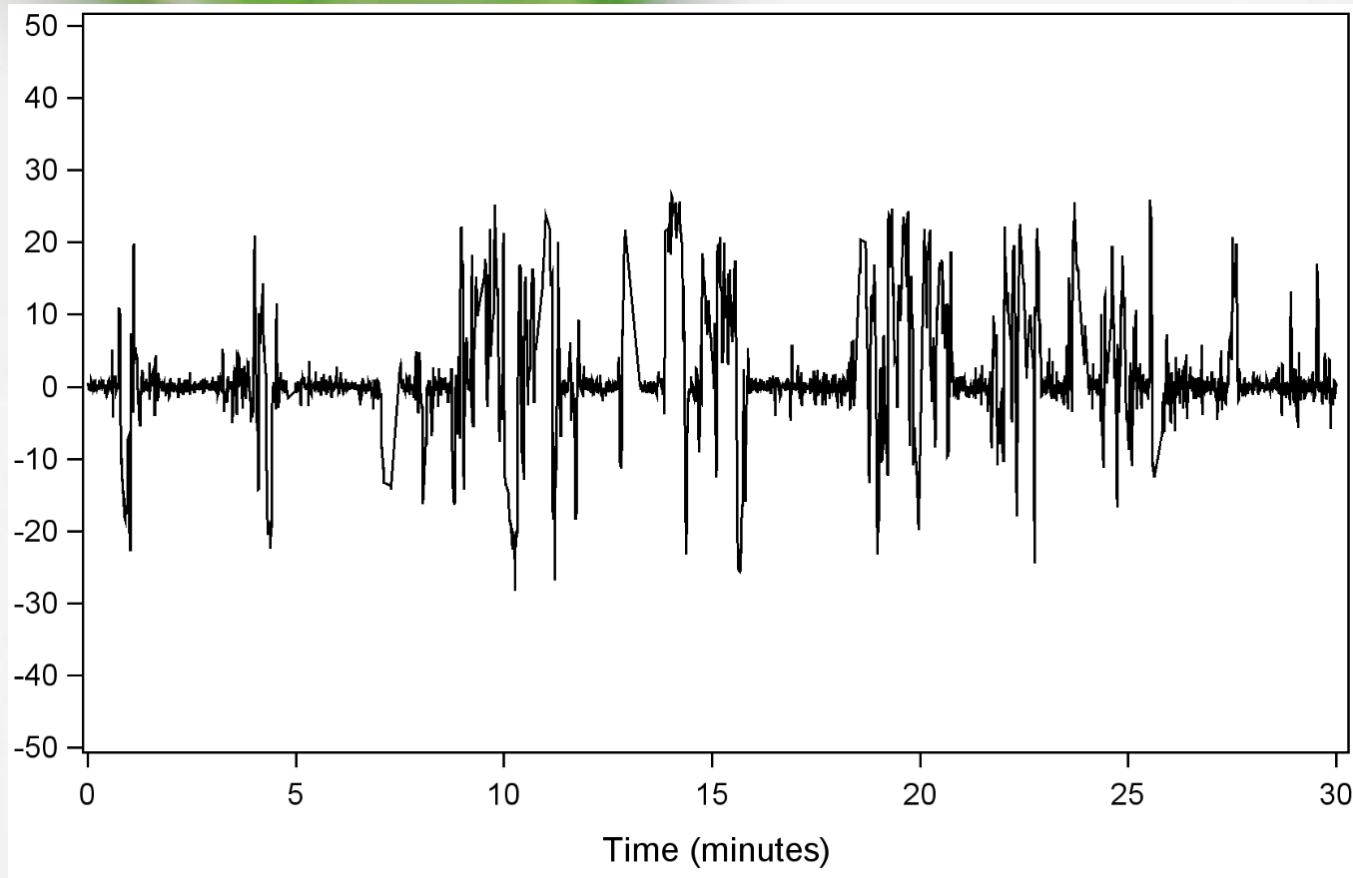
Hours*minutes*seconds*4 >100.000 paired observations per patient

- Hard to estimate/model correlation
- Hard to explore graphically (B&A plot or Regression plot)

Literature: Bland-Altman plots



The data, one patient, ± 7000 points



Example: Diagnostic Medical Device

- ! Our final data (average ~55.000 paired points per patient)

How can it be that I am longing for fewer data-points?



So, what did we do?

For regulators that were not concerned with repeated measures:

- ❗ Bland & Altman 1983, bias and limits of agreement testing based on summaries per patient
- ❗ Percentage time < 10 bpm

So, what did we do?

- ! For regulators that were concerned with repeated measures:
- ! Same as for 1)
- ! Plus: Bootstrapping, one observation per patient, estimate the Mean accuracy and Limits of Agreement and associated Bootstrap confidence limits
- ! Bland-Altman plots investigating bias vs mean
- ! Added value of Deming regression not really understood

Result

- ! First regulatory review resulted in certification
- ! Awaiting the second regulatory review