Establishing upper reference limits

For left-censored and contaminated data

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Section 1

Introduction

In collaboration with

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The initiating case

1. How do you find upper an reference limit when more than 50% of data has values at a lower limit of detection, i.e., are non-detectable?
   - The classical methods if working lead to too high upper reference limit
   - The use of limits of detection (LOD) is not recommended, Hewett and Ganser (2007) and Helsel (2010)
2. What if the data is also contaminated the right by a distribution of extreme values?
3. What if data isn't normal?

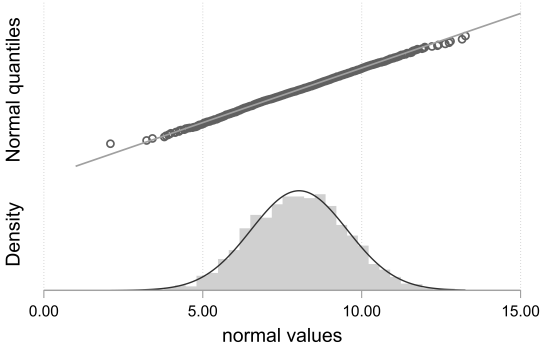
This is a work in progress!!

A stata command is to appear soon on the SSC: -ssc install ros-

Normal quantile plots

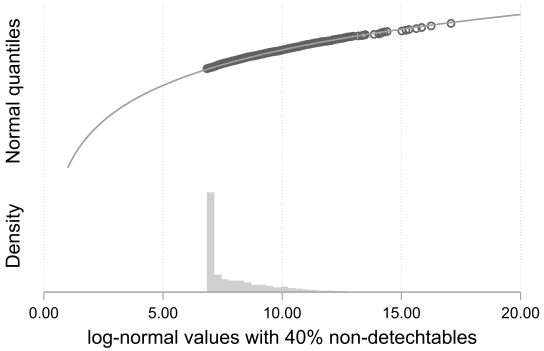
- Drawing normal quantiles against observations
  - If the oberservations are normally distributed, the curve is linear
  - The slope of the line is $1/\sigma$
  - The intercept is μ/σ
- One could do regressions instead of drawing
- The regression goodness of fit is measured by R^2_{adj}
  - number of parameters are always 2
  - AIC and BIC behaves strange with Box-Cox transformations
- The Box-Cox transformation *bct* used is:

$$bct(x;\theta) = \begin{cases} x^{\theta}/\theta & if\ \theta \neq 0 \\ log(x) & if\ \theta = 0 \end{cases}$$



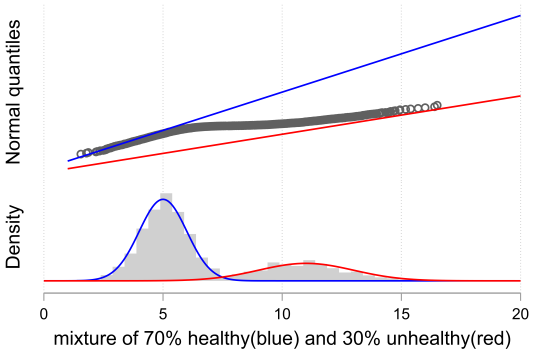
Non-detectable data, environmental statistics

- The regression on order statistics (ROS) is recommended if there is a high proportion of non-detectables, see Helsel (2010), Huston2009, and Hewett and Ganser (2007)
- The principle of ROS is that log-normal quantile plots are extrapolated to get quantiles
  - The curvature on the graph indicates the need for a log transformation of the data



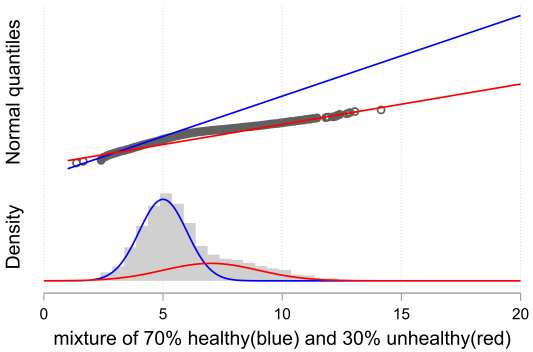
Contaminated (mixed) data, laboratory medicine, clinical biochemistry

- The Hoffmann method, Hoffmann (1963) and Jensen et al. (2006), uses normal quantile plots to separate the "healthy" from the "unhealthy".
- Non-detectables (in a large scale) are not considered.
- The log-transformation or the Box-Cox transformations are often used



When the mixed distributions are close

- the separation of the mixed parts still works
- A Box-Cox transformation might be equally good



The command -ros-

- A command for finding upper reference bounds when the data has non-detechtable values and possibly are contaminated to the right by an extreme value distribution
- Contamination of data is visually identified from a normal quantile plot
- Data are assumed to be from a Box-Cox distribution
  - Data is normally distributed after a Box-Cox transformation
- Optimal Box-Cox transformation is chosen by selecting a theta with a high adjusted R squared
  - The Box-Cox command gives biased estimates when there are non-detectables
  - Always only two parameters in the regressions, so adjusted R squared is an acceptable measure
  - AIC and BIC does not work with the current Box-Cox transformation formulas
- Regressing (ROS) the observed values on the emperical (normal) z-values
  - Estimation of the mean (the intercept) and standard deviation (the slope)
  - The mean and standard deviation are used to estimate the quantiles

Real life applications

- The -ros- command has been applied in Andersen et al. (2022) and Uldall Torp et al. (2022)
  - for finding upper reference bounds
  - Follow-up in Danish nationwide registers
  - Empirical quantile method lead to too high upper reference bounds

Section 2

The savona example dataset, Huston and Juarez-Colunga (2009)

Description

- Provided by the British Columbia Ministry of Environment
- Information on orthophosphate concentrations taken at the Thompson River from Savona
- Contains 32 oberservations of four variables:
  - The date of the measurement taken
  - Indication on whether a measurement is below the detection limit
  - Concentration is the level of orthophosphate observed
  - Censored also indicates whether an observation is below the detection limit or not

The -ros- command and output

Some of the options for -ros-

- **censor** A variable indicating whether a value is censored (1) or not (0)
- **scatter** Generates a qnorm scatterplot as model control
- **rsqrtheta** Generates a line plot of adjusted R squares by thetas (Box-Cox transformation)
- **theta(#)** for the choice of Box-Cox transformation, default = 1 (No transformation)

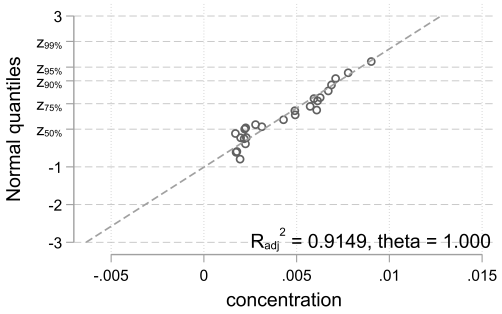
```
use concentration censored using "savona (NADA).dta", clear
```

```
ros concentration, censor(censored) rsqrtheta scatter
Adjusted Rsquared is 0.9149
Percentiles
  50.00%    0.0032
  75.00%    0.0054
  90.00%    0.0073
  95.00%    0.0085
  99.00%    0.0106
```

The -ros- diagnostics, the scatter plot

Look for contamination and/or transformation

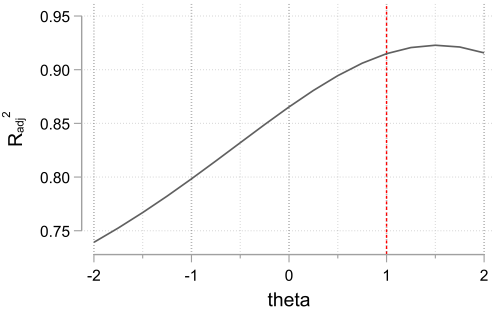
- Works for a small sample, N = 32
- Contamination is (probably) not detectable
- No transformation seems necessary



The -ros- diagnostics, the R2 adj vs theta plot

Look for an optimal transformation

- Optimal transformation is around 1.5, $R^2_{adj} = 0.923$
- Little gain from the chosen transformation 1, $R^2_{adj} = 0.915$
- The log transformation (default in Helsel (2010) and Hewett and Ganser (2007)) is relatively bad, $R^2_{adj} = 0.865$



Section 3

The TGAb eaxmple dataset

Description

- A random subsample of 1000 TGAb values from the North Denmark region pregnancy cohort
  - variable *tgab*
- Non-detectables are set at 7 (59.4%)
  - variable *tgab_c*

The -ros- command and output

- Data are assumed to be contaminated when TGAb > 20
  - see why at next slide
- Compare emperical percentiles (from -sumat-) with -ros- percentiles
- The 75% percentiles are the almost same
  - See the yellow line on the next slide
- The 95% percentile differ from 33 (-ros-) to 140 (empirical)

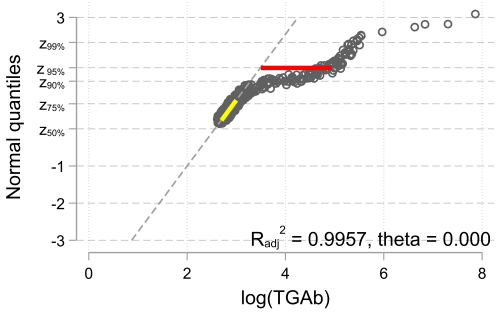
```
sumat tgab, statistics(p50 p75 p90 p95 p99)

------------------------------------------------
              p50    p75    p90     p95     p99
------------------------------------------------
TGAb(IU/ml)  7.00  19.10  50.60  140.18  233.54
------------------------------------------------
```

```
ros tgab if tgab < 20, censor(tgab_c) scatter ///
  rsqrtheta theta(0)
Adjusted Rsquared is 0.9957
Percentiles
  50.00%   12.9897
  75.00%   19.0034
  90.00%   26.7636
  95.00%   32.8506
  99.00%   48.2492
```

The -ros- diagnostics, the scatter plot

Look for contamination and/or transformation

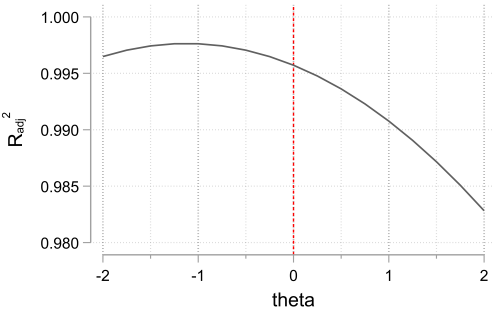
- Data are assumed to be contaminated when TGAb > 20
  - straight line only present at TGAb < 20
- **The distribution of the contaminated is ignored (ignore extreme values??)**
- Percentiles are extrapolated from around 160 (out of 1000) measurements (the yellow line)
- The red line is the change in 95% upper bound for TGAb from 140 UI/ml to 33 UI/ml
- At the yellow line the ROS upper bound estimates are the same as the emperical upper bound estimates



The -ros- diagnostics, the R2 adj vs theta plot

Look for an optimal transformation

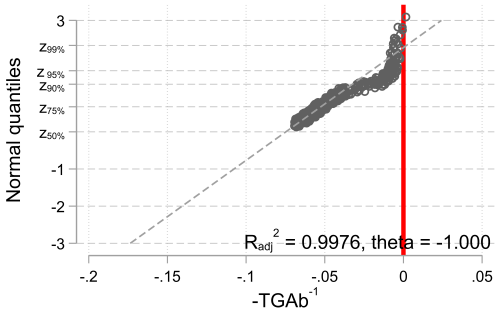
- Data are contaminated when TGAb > 20
- Optimal Box-Cox transformation is around -1, $R^2_{adj} = 0.998$
  - negative thetas does not behave well
  - negative value for the 99% upper bound
  - negative thetas implies negative values
  - asymptotic vertical behavior for values close to zero
- Little gain from the chosen log transformation (theta $= 0$), $R^2_{adj} = 0.996$
- No transformation (theta $= 1$) would be acceptable too, $R^2_{adj} = 0.991$



Limitations of the Box-Cox transformation

- The transformed values becomes negative with the negative thetas
  - can not cross the red line (jitter is used here)
  - the predictions can giving opposite signs

```
ros tgab if tgab < 20, censor(tgab_c) scatter theta(-1)
Adjusted Rsquared is 0.9976
Percentiles
  50.00%    13.3796
  75.00%    19.0435
  90.00%    30.7648
  95.00%    48.7057
  99.00%   -5.2e+02
```



Section 4

The final

Summary

We combine two classical graphical methods into a simple one

- to identify and handle possible contamination in data
- to identify a Box-Cox transformation to yield a better fit
  - and a better estimation
- to estimate upper bounds for reference intervals
  - to estimate the mean and standard deviations are means to an end, not the goal
- most times external validation of the bounds is necessary
- using simple regression estimates instead of using quantile plots
- "All models are wrong, but some are useful", so there might be more than one acceptable solution
  - in most cases with similar bounds
- This approach can handle mixtures of data with different limits of detection

TO DO

- How to predict confidence intervals for the estimated upper bounds
- To explore GLS estimation for the location-scale models, Rinne (2010)
- To explore the relation to the truncated finite mixed models (FMM)
- To explore the relation to the Tobit regression
- To explore the relation to parametric quantile models, Bottai (2021)
- To find a better class of distributions than the Box-Cox distributions
  - A challenge is negative data values and negative exponentiation
- Investigate whether regression modeling be done in this setup

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