Stat^{4tox}: An open-source R-GUI for the statistical evaluation of in vitro assays in toxicology

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This is joint work of

Statistics (Leibniz Universität Hannover)

- Ludwig A. Hothorn
- Daniel Gerhard
- Frank Schaarschmidt
- Mario Hasler
- Kornelius Rohmeyer
- Martin Sill
- Frank Konietschke (Universitätsklinikum Göttingen)
- Gemechis Dilba Djira (South Dakota State University)

Graphical user interface

- Bernd Bischl (Technische Universität Dortmund)
- Kornelius Rohmeyer (Leibniz Universität Hannover)
- Uwe Ligges (Technische Universität Dortmund)

Motivation

Background: Statistical methods for (in vitro) toxicology

Data structure:

- A number of well defined biological assays
- Dichotomous, count, continous data
- In simple one-way layouts or hierarchical layouts

Experimental questions:

- Proof of equivalence or proof of hazard vs. a control group
- In both settings: relevance of the effect size is of interest
- Often, relevance can be most easily defined as ratio (fold change)

$\longrightarrow$ **Focus is on confidence intervals for ratio parameters**

$\longrightarrow$ **Unadjusted and simultaneous confidence intervals needed**

Availability of statistical methods for toxicologists

- Confidence intervals for dissimilarity among groups
- For relevant distributions
- Trend or multiple dose comparisons to an untreated control
- Often **not available in standard statistical software**
- Available in R
- Plain R-code is **a hurdle for many users**.

Hence:

- Selected statistical methods
- Accessable via Graphical User Interface (GUI)

Funding

Part of the project

- 'Quality assessment and novel statistical analysis techniques for toxicological data'
- Lot 2: ANOVA techniques for ratios (Grant number: 2006/S 237-252824)
- ECVAM (European Center for Validation of Alternative Methods)
- IHCP (Institute for Health and Consumer Protection)
- JRC (Joint Research Center, European Commission)

Statistical methods

General concepts

Unadjusted confidence intervals

- **Proof of Safety:** Marginal $(1 - 2\alpha)$ confidence intervals or $(1 - \alpha)$ confidence limits
- Post-hoc interpretation of confidence limits
- Test decisions by graphical presentation of confidence intervals and relevance margins

Simultaneous confidence intervals

- Simultaneous confidence intervals for multiple contrasts in the generalized linear model [Hothorn et al. (2008)]
- Comparisons to control (analogous to [Dunnett (1955)])
- Williams type of trend test vs. a control [Williams (1971), Bretz (2006)]
- Down-turn-protected trend test [Bretz and Hothorn (2003)]

Statistical methods I

Dichotomous data in cross tables

- One-way layout only
- Odds ratio, risk ratio and risk difference
- Cochran-Armitage test

[Holford (1989), Agresti (1990), Piegorsch (1991), Piegorsch and Bailer (1997), Hothorn and Bretz (2000), Gerhard (2007, technical report), Sill(2007, technical report), Schaarschmidt et al. (accepted a), Schaarschmidt et al. (accepted b), Schaarschmidt(2008, technical report)]

Statistical methods II

Dichotomous data in higher layouts

- Layouts with covariates or secondary factors in the generalized linear model (logit-link)
- Odds ratio
- Binomial, quasibinomial and betabinomial assumption

[McCullagh and Nelder (1989), Chambers (1992), Hothorn et al. (2008), Gerhard (2007, technical report)]

Count data

- One-way layout and layouts with covariates or secondary factors in the generalized linear model (log-link)
- Ratio
- Poisson, quasipoisson and negative binomial assumption

[McCullagh and Nelder (1989), Chambers (1992), Venables and Ripley (2002), Hothorn et al. (2008), Gerhard (2008, technical report)]

Statistical methods III

Continuous data, Gaussian response

- Ratios and differences
- Assuming homogeneous or heterogeneous variances
- Higher layouts: confidence intervals for differences, assuming homogeneous variances

[Dilba et al. (2006), Schaarschmidt (2007b, technical report), Hasler (2008b, technical report), Hasler and Hothorn (accepted), Hothorn et al. (2008)]

Statistical methods IV

Solutions for some special problems

- Comparisons to negative and positive control for Gaussian data): multiple three arm design [Pigeot et al. (2003), Hasler et al. (2008), Hasler and Hothorn (accepted)]
- Simultaneous confidence intervals for equivalence in comparisons to control [Bofinger and Bofinger (1995), Hauschke et al. (1999)]
- Proof of equivalence and proof of hazard for multiple endpoints with Gaussian response [Quan et al. (2001), Hasler (2008a, technical report)]
- Non-parametric unadjusted and simultaneous confidence intervals for relative effects [Konietschke (2008, internal report)]
- Variance components and fixed effects inference in nested models [Pinheiro and Bates (2000)]
- Unadjusted confidence intervals for differences and ratios of means assuming log normal distribution [Chen and Zhou (2006)]
- Power calculation for two sample and multiple comparisons settings [Bock (1998), Genz and Bretz (1999), Bretz and Hothorn (2002), Hauschke (1999)]

Graphical user interface

Graphical user interface - Structure I

Free software, written in Java

Data import

- xls (properly filled sheets without formula)
- txt
- csv

Descriptive graphics

- Based on available R-packages `grid` and `lattice`
- Box-Whisker plots including jittered dots of single observations
- Mosaic plots for table data
- Scatterplots
- Possibly grouped by secondary factors

Graphical user interface - Structure II

Statistical methods accessable:

- Via statistical terminology
  - Scale of measurements
  - Experimental design
  - Experimental questions
- Via example evaluations of assays
  - Local lymph node assay
  - Ames assay
  - Micronucleus assay (in vitro and in vivo)
  - Comet assay
  - BALB/3T3c cell transformation assay

Graphical tools following model fit and inference

- Residual plot
- QQ-Plot
- Plots of confidence intervals

Graphical user interface - Structure III

Export of results

- PDF file summarizing the user information, the data set, statistical methods, results and graphics
- Export of selected tables in formats compatible to HTML and LaTeX
- Export of selected graphics as PDF, PNG, GIF and JPEG

Help

- HTML pages for all items in the menus
- Explaining arguments in the GUIs menus
- Short methodological description
- References

Installation and Dependencies I

Plattforms

- Microsoft Windows
- Linux
- Mac OS X

Different versions

- With R server (Web start, without local R installation!)
- With local R (Web start)
- With local R (Installer)

Installation and Dependencies II

Dependencies

- Current version of Java: Java Runtime Environment (JRE)
- Adobe Reader or Xpdf
- For versions with local `R`: `R-2.7.1` and the packages `mratios`, `multcomp`, `binMto`, `MCPAN`, `xtable`, `cluster`, `Hmisc`, `vcd`, `MultEq`, `ETC`, `nparcomp`, `exactRankTests`, `pairwiseCI`

  [CRAN - The Comprehensive R Archive Network]

Detailed description of installation at:
`http://130.75.68.4:8080/rjavaclient/install.php`

Contact: `help@biostat.uni-hannover.de`

We would appreciate, if you use the *Stat*^{4tox} and send us your comments!

Thank you for your attention!

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Software


R Development Core Team (2008). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, URL http://www.R-project.org.


CRAN - The Comprehensive R Archive Network. http://cran.r-project.org/, last visit: 23. Januar 2008

Supplementary - The GUI in action

Example 1: Ames assay

- Response variable: number revertant colonies on a plate
- One control group, five dose groups (008, 04, 21, 106, 532)
- Three replications each
- A negative binomial model to account for potential overdispersion

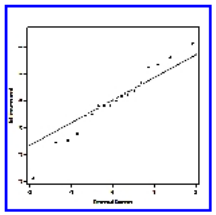
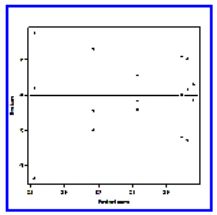
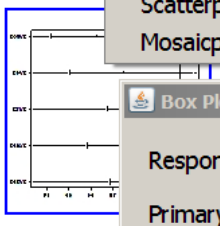
For which of the dose groups can a non-relevant increase (say, less than 1.2 times as many revertants as in the control) be inferred with 5% type-I-error probability?

stat4tox

File | Descript. Stats | Statistical Analysis | Assays | Graphics | Power | Extras | Help

Graphics menu: Boxplot, Scatterplot, Mosaicplot

Output

k-Sample comparisons for count data

Procedure:
Many-to-one comparisons by Dunnett-type contrasts for the ratio.
Comparing estimates of a GLM under assumption of a negative binomial

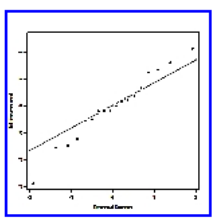
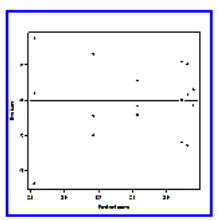
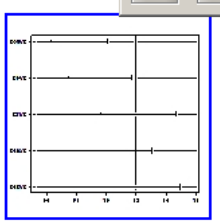
Comparisons:
Response variable: TA1535
Group variable: Dose
Control: C
Versus: D008, D04, D21, D106, D532
Testing against the margin: 1.2

Estimated overdispersion parameter of the negative binomial model: 218
(A small overdispersion parameter indicates a high amount of extra varia

Results:

	Estimate	lwr	upr	adj.pvalue
D008 / C	0.627	0.000	1.005	0.005
D04 / C	0.746	0.000	1.167	0.036
D21 / C	0.966	0.000	1.467	0.353
D106 / C	0.847	0.000	1.306	0.128
D532 / C	0.983	0.000	1.490	0.394

Simultaneous 95%-confidence intervals and adjusted p-values for ratios for Dunnett-contrasts.

Box Plot

Response: TA1535

Primary Factor: Dose

Level Order: C, D008, D04, D21, D106

Secondary Factors: Dose

Jitter Points ☑

SD Bars ☑

Title ☐

Label Y Axis ☐

Label X Axis ☐

Ok | Cancel

Data - am

Dose	TA1535	TA1537	TA98	TA100	WP2
C	19	15	22	117	35
	21	11	29	113	52
	19	5	34	118	62
	13	9	29	111	38
	19	17	34	102	35
	5	6	16	129	39
	11	16	32	107	31
	13	16	34	119	46
	20	15	25	136	39
	14	17	44	126	29
	24	18	56	106	39
	19	23	60	103	38
	16	128	129	152	41
	15	128	117	134	46
	19	147	114	167	44
	14	303	43	732	49
	24	184	51	734	48
	20	277	115	653	45

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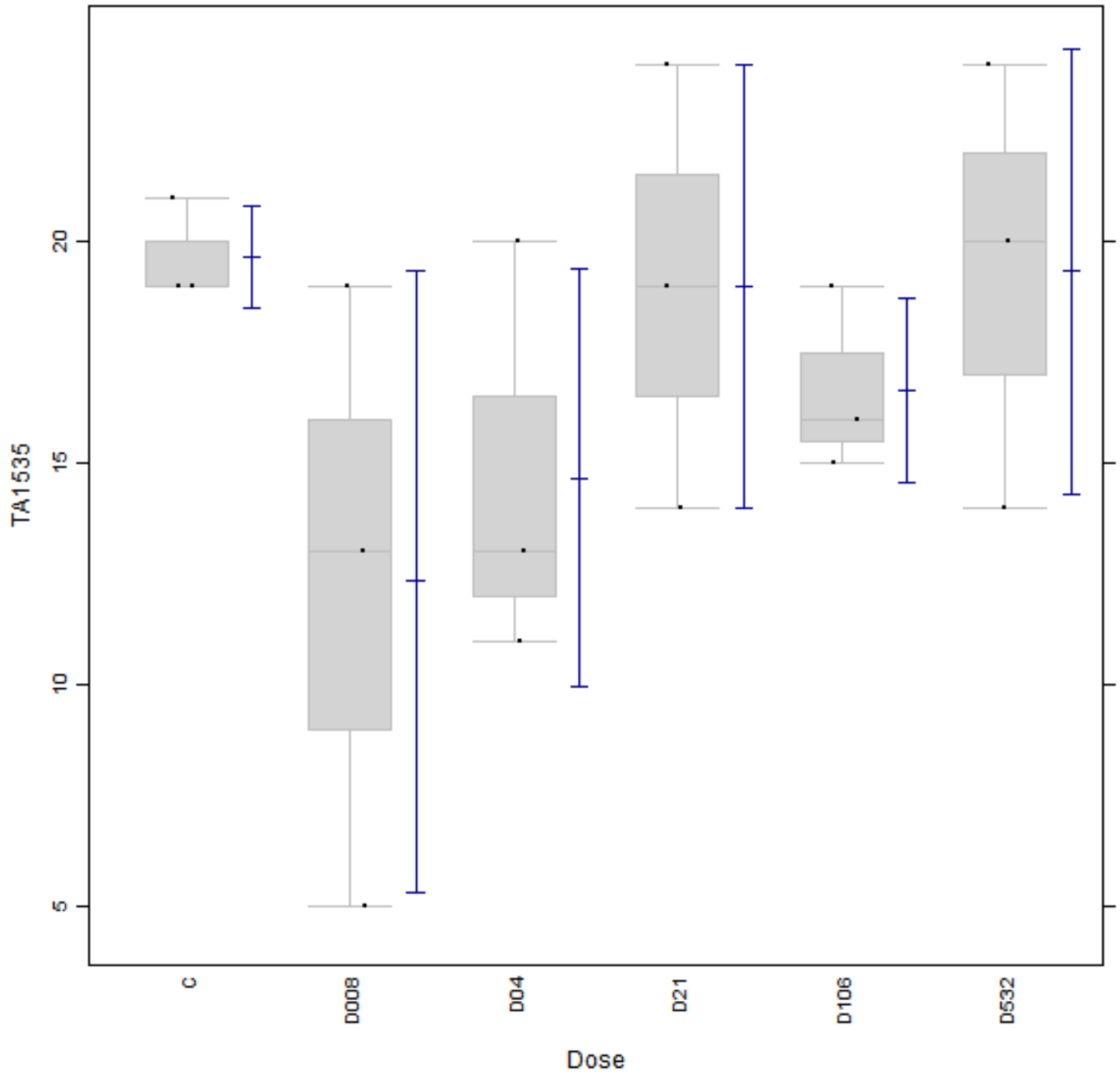

TA1535
5
10
15
20
C
D008
D04
D21
D106
D532
Dose

stat4tox

File | Descript. Stats | Statistical Analysis | Assays | Graphics | Power | Extras | Help

Two treatments / doses
k treatments / doses (Multipl. adj.)
Proof of Hazard (Without multipl. adj.)
Layouts with further factors or covariates
Multiple Endpoints
Hierarchical Layouts

Gaussian
Non-parametric
Counts
Proportions / Binomials

Assay Ames salm

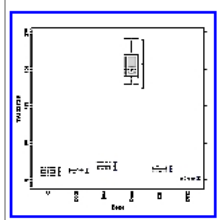
You can load appropriate Data your own data or the example

You can take a look at the ass article.

The Ames data example is not one study, these are many strains with/without metabolic activation. We analyse strains separately.

Highlighting the problem: Perform the box-plot for TA1537S9.

It should look like this:



- **Data characteristics:**
  - data are counts,
  - counts may be over-dispersed,
  - sample size is tiny,
  - a downturn effect occurs (muta-tox problem)
  - only increasing number of revertants are of interest
- The relevance criteria is the two-fold rule, i.e. ratio-based inference is needed
- Commonly a proof of hazard is used
- Over-dispersed counts can be modeled by the negative binomial distribution within the generalized linear model (glm)
- A downturn-protected modification of the Williams-type

Counts

Response	TA1535
Group	Dose
Level Order	D532 → C, D008, D04, D21, D106
Confidence Level	0.95
Alternative	two-sided
Type	Ratio
Margin	1
Comparison	Comparison to Control
Distribution	Negative Binomial

Ok | Cancel

Data - am

Dose	TA1535	TA1537	TA98	TA100	WP2
C	19	15	22	117	35
C	21	11	29	113	52
C	19	5	34	118	62
D008	13	9	29	111	38
D008	19	17	34	102	35
D008	5	6	16	129	39
D04	11	16	32	107	31
D04	13	16	34	119	46
D04	20	15	25	136	39
D21	14	17	44	126	29
D21	24	18	56	106	39
D21	19	23	60	103	38
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D532	24	184	51	734	48
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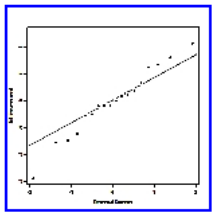
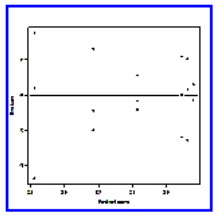
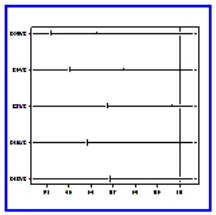
File Descript. Stats Statistical Analysis Assays Graphics Power Extras Help

Output

k-Sample comparisons for count data

Procedure:
Many-to-one comparisons by Dunnett-type contrasts for the ratio.
Comparing estimates of a GLM under assumption of a negative binomial distributed response.

Comparisons:
Response variable: TA1535
Group variable: Dose
Control: C
Versus: D008, D04, D21, D106, D532
Testing against the margin: 1.2

Estimated overdispersion parameter of the negative binomial model: 218711.81 (with std.err: 7898781.87)
(A small overdispersion parameter indicates a high amount of extra variability)

Results:

	Estimate	lwr	upr	adj.pvalue
D008 / C	0.627	0.000	1.005	0.005
D04 / C	0.746	0.000	1.167	0.036
D21 / C	0.966	0.000	1.467	0.353
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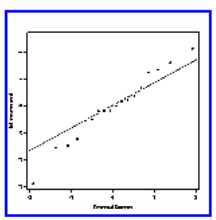
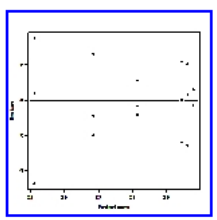
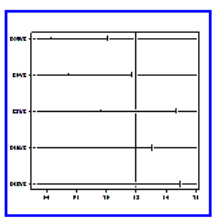

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D008	5	6	16	129	39
D04	11	16	32	107	31
D04	13	16	34	119	46
D04	20	15	25	136	39
D21	14	17	44	126	29
D21	24	18	56	106	39
D21	19	23	60	103	38
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Color key: Numeric Integer Factor

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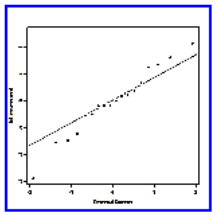
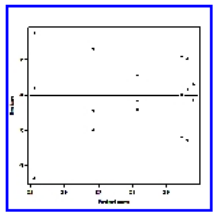
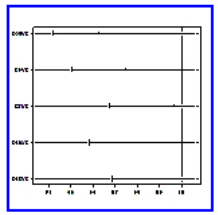
stat4tox

File Descript. Stats Statistical Analysis Assays Graphics Power Extras Help

Output

k-Sample comparisons for count data

Procedure:
Many-to-one comparisons by Dunnett-type contrasts for the ratio.
Comparing estimates of a GLM under assumption of a negative binom

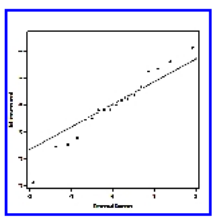
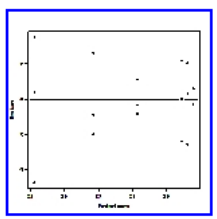
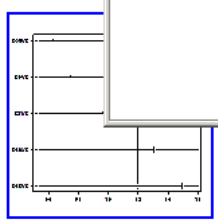
Comparisons:
Response variable: TA1535
Group variable: Dose
Control: C
Versus: D008, D04, D21, D106, D532
Testing against the margin: 1.2

Estimated overdispersion parameter of the negative binomial model: 21
(A small overdispersion parameter indicates a high amount of extra va

Results:

	Estimate	lwr	upr	adj.pvalue
D008 / C	0.627	0.000	1.005	0.005
D04 / C	0.746	0.000	1.167	0.036
D21 / C	0.966	0.000	1.467	0.353
D106 / C	0.847	0.000	1.306	0.128
D532 / C	0.983	0.000	1.490	0.394

Simultaneous 95%-confidence intervals and adjusted p-values for ratios for Dunnett-contrasts.

Data - am

Dose	TA1535	TA1537	TA98	TA100	WP2
C	19	15	22	117	35
C	21	11	29	113	52
C	19	5	34	118	62
D008	13	9	29	111	38
D008	19	17	34	102	35
D008	5	6	16	129	39
D04	11	16	32	107	31
D04	13	16	34	119	46
D04	20	15	25	136	39
D21	14	17	44	126	29
D21	24	18	56	106	39
D21	19	23	60	103	38
D106	16	128	129	152	41
D106	15	128	117	134	46
					44
					49
					48
					45

Color key: Numeric Integer Factor

The following code was copied to the clipboard:

```
% latex table generated in R 2.7.1 by xtable 1.5-2 package
% Thu Aug 28 17:12:34 2008
\begin{table}[ht]
\begin{center}
\begin{tabular}{rrrrr}
  \hline
 & Estimate & lwr & upr & adj.pvalue \\
  \hline
D008 / C & 0.627 & 0.000 & 1.005 & 0.005 \\
  D04 / C & 0.746 & 0.000 & 1.167 & 0.036 \\
  D21 / C & 0.966 & 0.000 & 1.467 & 0.353 \\
  D106 / C & 0.847 & 0.000 & 1.306 & 0.128 \\
  D532 / C & 0.983 & 0.000 & 1.490 & 0.394 \\
   \hline
\end{tabular}
\caption{Simultaneous 95%-confidence intervals and adjusted p-values for ratios for Dunnett-contrasts.}
\end{center}
\end{table}
```

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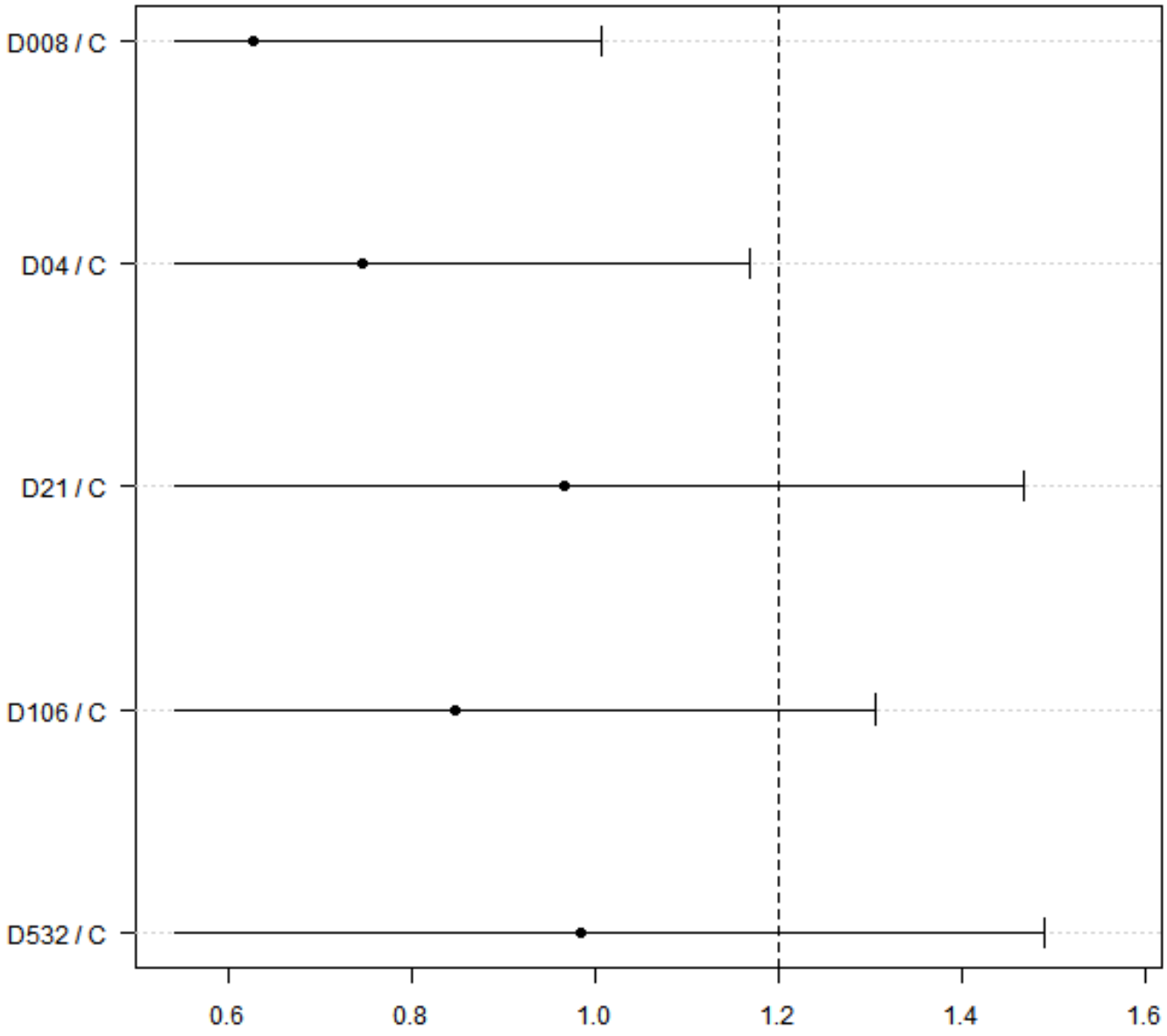
Results

Comparison	Estimate	Lower	Upper	adj. p-value
D008 / C	0.627	0.000	1.005	0.005
D04 / C	0.746	0.000	1.167	0.036
D21 / C	0.966	0.000	1.467	0.353
D106 / C	0.847	0.000	1.306	0.128
D532 / C	0.983	0.000	1.490	0.394

Table: Simultaneous 95%-confidence intervals and adjusted p-values for ratios for Dunnett-contrasts.


D008 / C
D04 / C
D21 / C
D106 / C
D532 / C
0.6
0.8
1.0
1.2
1.4
1.6

Example 2: Micronucleus assay

- Response variable: Number cells with micronuclei relative to the total of 1000 cells per observation
- One control and six dose groups (05, 10, 25, 50, 100, 200)
- A secondary factor with 2 levels (donor)
- A quasibinomial model, with donor included like a block

Can an increasing trend in the odds to observe micronuclei be inferred for increasing dose levels? - Williams-type trend test

stat4tox

File | Descript. Stats | Statistical Analysis | Assays | Graphics | Power | Extras | Help

- Two treatments / doses
- k treatments / doses (Multipl. adj.)
- Proof of Hazard (Without multipl. adj.)
- Layouts with further factors or covariates
  - Gaussian
  - Count
  - Proportions / Binomials
    - kx2 Table
    - Dichotomous
- Multiple Endpoints
- Hierarchical Layouts

Output

biostat.rinterface.exceptions.
haben falsche Länge

biostat.rinterface.exceptions.
dieselbe Länge haben wie der

= 1:length(Response)) : angegebene Zeilennamen

uss

k-Sample comparisons for binomial data with additional covariates

Procedure:
Many-to-one comparisons by Dunnett-type contrasts.
Comparing estimates of a GLM under assumption of a Bin
Estimating extra variability by a quasilikelihood approach.

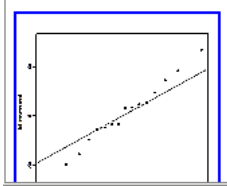
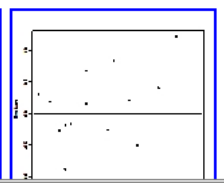
Comparisons:
Odds-Ratios are calculated with ntotal as successess and n
Group variable: group
Control: control
Versus: d02, d05, d10, d25, d50, d100, d200
Accounting for covariates: donor

Estimated dispersion parameter of the QuasiBinomial model
(A parameter > 1 indicates the occurrence of extra variabili

Results:

	Estimate	lwr	upr	adj.pvalue
d02 / control	1.200	0.519	2.772	0.977
d05 / control	1.534	0.693	3.396	0.491
d10 / control	1.534	0.693	3.395	0.492
d25 / control	2.399	1.150	5.004	0.013
d50 / control	3.058	1.502	6.226	0.000
d100 / control	4.899	2.490	9.639	0.000
d200 / control	9.170	4.792	17.549	0.000

Simultaneous 95%-confidence intervals and adjusted p-values for odds ratios for Dunnett-contrasts.

Layouts with further factors or covariates - kx2-table

Success: ntotal
Failure: none
Primary Group Var.: group
Level Order: control, d02, d05, d10, d25
Covariates: NC, one, two, three, total, ntotal, none, group → donor
Confidence: 0.95
Alternative: greater
Comparison: Trend
Distribution: Quasibinomial
Ok | Cancel

Data - D:\Aktuell\TALK Leuven\ScreenshotEx...

one	two	three	total	ntotal	none
8	0	0	8	8	992
10	0	0	10	10	990
16	0	0	16	16	984
14	0	0	14	14	986
23	1	0	24	25	977
24	2	0	26	28	976
36	5	0	41	46	964
53	7	2	62	73	947
7	0	0	7	7	993
8	0	0	8	8	992
7	0	0	7	7	993
9	0	0	9	9	991
11	0	0	11	11	989
16	1	0	17	18	984
24	2	0	26	28	976
56	4	1	61	67	944

Color key: Numeric Integer Factor

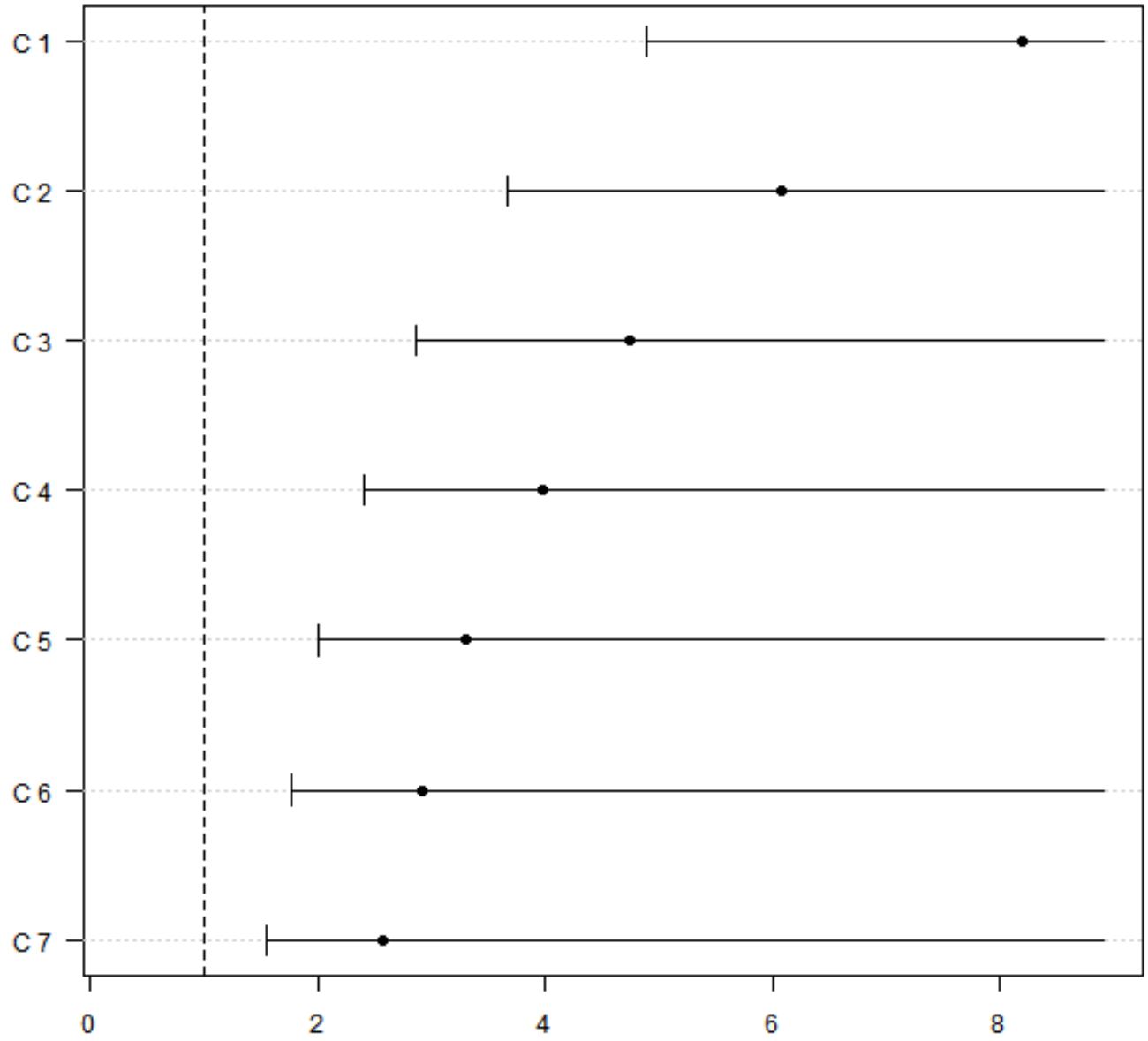
Start | Se... | st... | D:... | Te... | Po... | G:... | Su... | Un... | Plots | Plots | Plots | Plots | Plots | 12:25

Comparisons	control	0.02	0.05	0.1	0.25	0.5	1.0	2.0
C 1	−1	0	0	0	0	0	0	1
C 2	−1	0	0	0	0	0	0.5	0.5
C 3	−1	0	0	0	0	0.33	0.33	0.33
C 4	−1	0	0	0	0.25	0.25	0.25	0.25
C 5	−1	0	0	0.20	0.20	0.20	0.20	0.20
C 6	−1	0	0.17	0.17	0.17	0.17	0.17	0.17
C 7	−1	0.14	0.14	0.14	0.14	0.14	0.14	0.14

Table: Coefficients of contrasts calculated on scale of the odds.

Comparison	Estimate	Lower	Upper	adj. p-value
C 1	9.170	5.666	Inf	0.000
C 2	6.703	4.166	Inf	0.000
C 3	5.160	3.211	Inf	0.000
C 4	4.261	2.654	Inf	0.000
C 5	3.473	2.162	Inf	0.000
C 6	3.031	1.888	Inf	0.000
C 7	2.655	1.654	Inf	0.000

Table: Simultaneous 95%-confidence intervals and adjusted p-values for odds ratios for Williams-contrasts.


C 1
C 2
C 3
C 4
C 5
C 6
C 7
0
2
4
6
8

For more examples...

See the Assays menu in *Stat*^{4tox}!