Statistische Beurteilung von Dosiswirkungsbeziehungen

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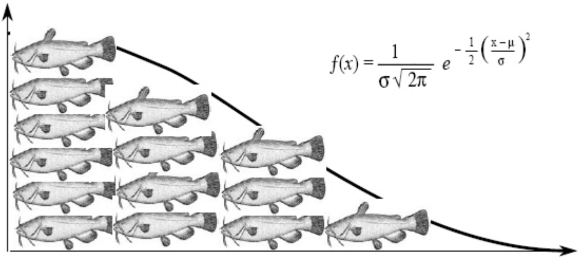


Agenda

algae bacteria bees butterflies bugs cell-cultures cucumber daphniae dogs ducks fish guinea-pigs hen's eggs humans limb-buds mice rabbits rats whole-embryo worms yeast zebrafish-embryos

Some Construction Lots

- Quantal response – (quasi) complete separation
- Teratology – clustered data
- Time is Information – time-dose-response models
- A general Risk Measure

Quantal Response – Basics

Data and Model

data $(d_i, r_i, n_i), i = 1, \ldots, k; \quad d_1 < d_2 < \cdots < d_k$

distribution $r_i \sim binom(\pi_i, n_i)$

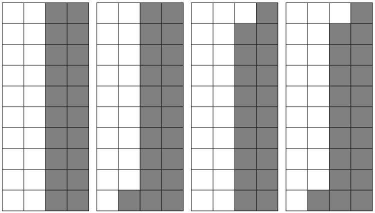
model $\pi_i = p(d_i); \;\; F^{-1}(\pi) = \alpha + \beta\, d = \dfrac{\mu - d}{\sigma} = \dfrac{ED_{0.5} - d}{c\;(ED_{0.5} - ED_q)}$

likelihood $L(model|data) = \prod_{i=1}^{k} \binom{r_i}{n_i} \pi_i^{r_i}\;(1 - \pi_i)^{n_i - r_i}$

Separated Data

monotonicity	$r_1/n_1 \leq r_2/n_2 \leq \cdots \leq r_k/n_k$
complete	$\max_i r_i\ (n_i - r_i) = 0$
quasi complete	$\exists i^* : \max_{i \neq i^*} r_i\ (n_i - r_i) = 0, \quad r_{i^*}\ (n_{i^*} - r_{i^*}) > 0$

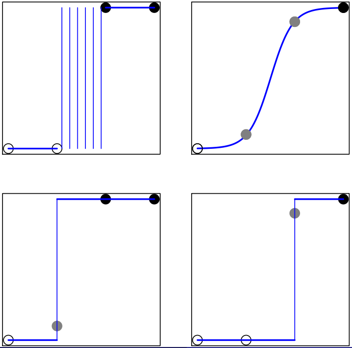
complete quasi quasi overlap



Quantal Response – Likelihood

sup L under (quasi) complete separation

always	$L(\pi \mid data) \leq 1$
complete sep.	$\sup L = 1$
quasi complete	$\sup L = dbinom(r_{i^*}, n_{i^*}, r_{i^*}/n_{i^*})$
quasi&complete	$\sup L = L(\pi_i = r_i/n_i)$ saturated model



complete	overlap
quasi	quasi

Quantal Response – Benchmarks

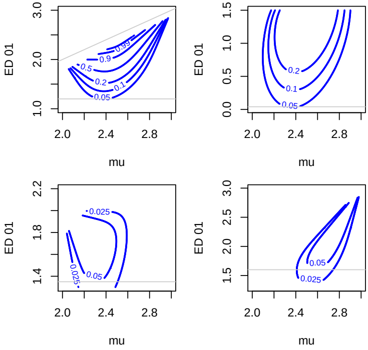
Likelihood intervals under separation

new parameters $(\alpha, \beta) \to \boldsymbol{\theta} = (ED_q, ED_{0.5})$

LR-statistic $LR(\boldsymbol{\theta}) = L(\boldsymbol{\theta}) / \sup L$

complete sep. $LR(\boldsymbol{\theta}) = L(\boldsymbol{\theta}) = P(data|\boldsymbol{\theta})$

quasi complete $Dev(\boldsymbol{\theta}) = -2 \log\{L(\boldsymbol{\theta})/dbinom(r_{i^*}, n_{i^*}, r_{i^*}/n_{i^*})\} \sim \chi^2_{k-2}$



complete	overlap
quasi	quasi

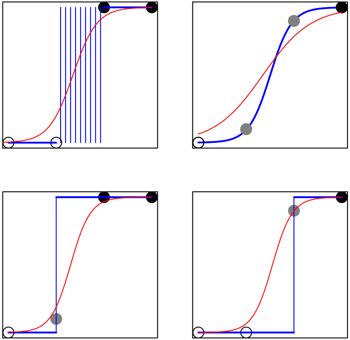
doses: $1, 2, 3, 4$

logit-link

Quantal Response – Benchmarks

Results Example BD01, $\alpha = 0.05$

- assume logistic model with $ED_{0.5} = 2.5, ED_{0.01} = 2$ then $P(\bigcup data) \approx 1,\ P(overlap) = 0.008$
- benchmarks appear reasonable
- ATTENTION! choice of model is crucial

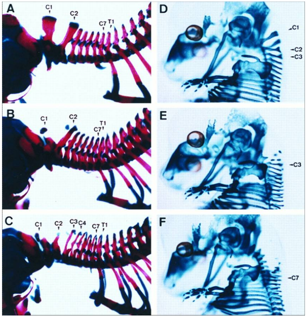


complete (1.2)	overlap (0.04)
quasi(1.35)	quasi (1.6)

Experiments in Teratology

Dose-Response Studies

- treat pregnant animals (rodents), randomized to dose groups
- record no. of implantations, resorptions, anomalies, etc per litter
- rather large litters, 8–15 in mice and rats



Yamaguchi et al,PNAS June 23, 1998 vol. 95 no. 13 7491-7496

Clustered Data in Teratology

Decomposition with Structured Noise

- data = signal + noise
- noise caused by litters b_i and by fetuses e_{ij}
  $i = 1, \ldots, I; \quad j = 1, \ldots, n_i$ for simplicity assume all n_i equal
- $y_{ij} = \mu + b_i + e_{ij}$, assumptions: b_i, e_{ij} independent,
  $Eb_i = Ee_{ij} = 0$, $Var(b_i) = \sigma_b^2$, $Var(e_{ij}) = \sigma^2$.
- data correlated within litters, no totally independent information

$$Corr(y_{ij}, y_{ik}) = \sigma_b^2 / (\sigma_b^2 + \sigma^2) = \rho$$

$$Var(\overline{y}_{..}) = \frac{1}{I}\left(\sigma_b^2 + \frac{\sigma^2}{n}\right) = \frac{1}{I \times n}\left(1 + n \times \frac{\rho}{1-\rho}\right)\sigma^2$$

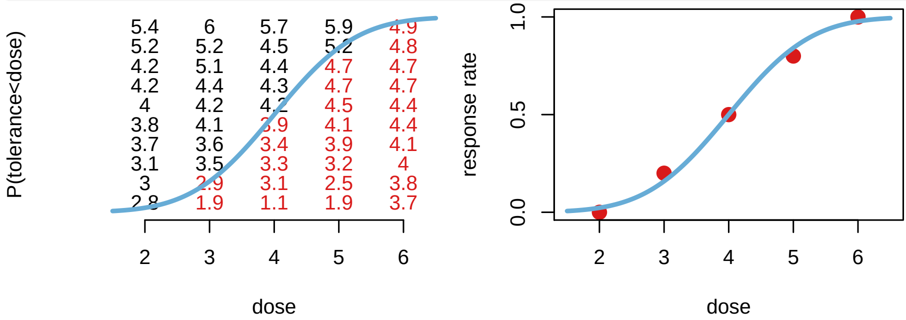
Intra-litter correlation causes variance inflation of the mean

Tolerance and Quantal Data

Distribution of individual tolerances determines response probabilities

Hypothetical tolerances for 50 individuals randomly assigned to 5 dose groups.

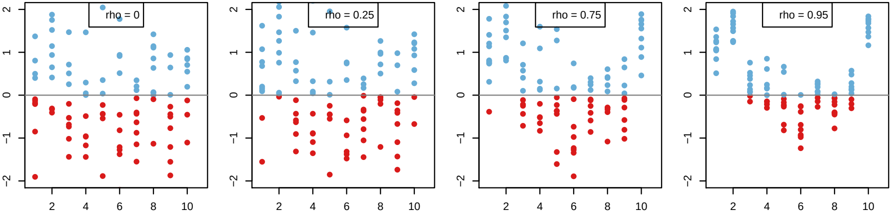
Fit of quantal response model: Maximum Likelihood for binomial data.



Quantal response allows indirect estimation of tolerance distribution

How intra-litter correlation changes pattern of reactions

Tolerances with litter effects, 10 fetuses for 10 litters. Increasing intra-litter correlation.

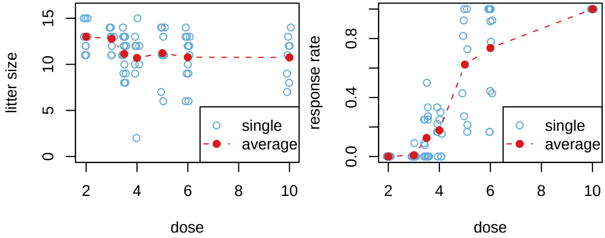


Litter effects increase dissimilarities of response rates between litters

Cleft palate induced by MNU

Raw data from Platzeck et al

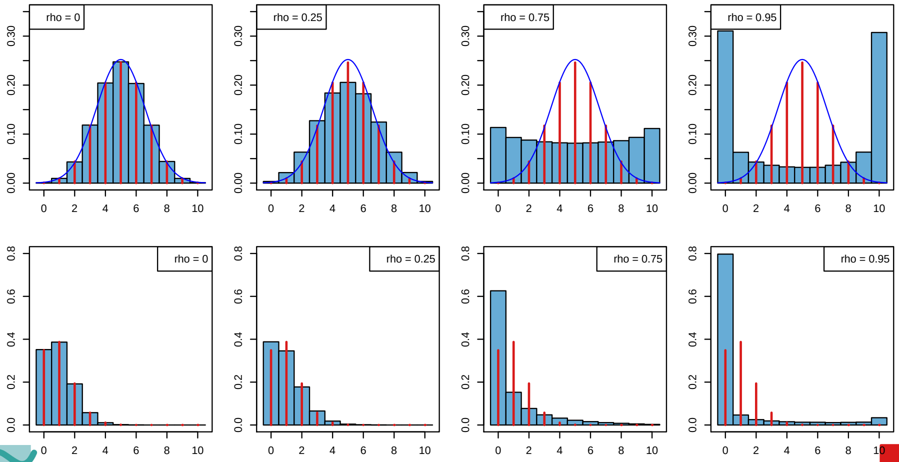
dose	reactions/litter size	$\sum r_i / \sum n_i$	litter effect
2	0/11 0/11 0/12 0/12 0/13 0/13 0/15 0/15 0/15	0	
3	0/11 1/11 0/12 0/13 0/13 0/13 0/14 0/14 0/14	0.009	–
3.5	0/8 2/8 0/9 3/9 5/10 1/11 3/11 0/12 0/12 3/12 3/12 0/13 0/13 1/13 0/14	0.13	**
4	0/2 2/9 0/10 3/10 0/12 2/12 2/12 3/12 2/13 5/15	0.18	–
5	1/6 7/7 3/11 8/11 9/11 12/13 3/14 6/14 14/14	0.62	**
6	6/6 6/6 4/9 7/9 10/10 11/11 2/12 2/12 11/12 12/13 13/13 13/13 6/14	0.74	**
10	7/7 8/8 9/9 11/11 12/12 12/12 13/13 14/14	1	



Results: slightly decreasing litter size, increase in response rate

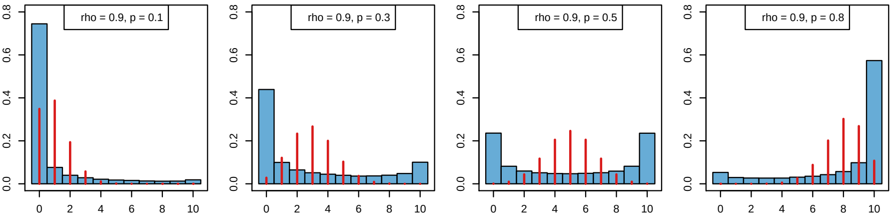
Simulations Litter Effect and Quantal Data

How intra-litter correlation changes distribution $p = 0.5, 0.1$



Intra-litter correlation results in overdispersed number of reactions per litter

How response probability changes distribution



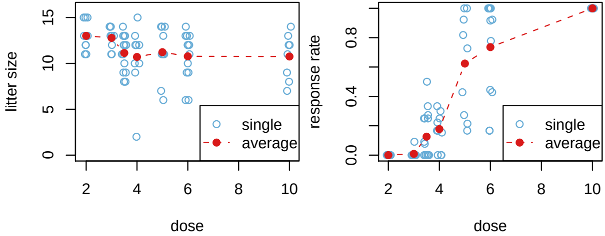
probability p	0.1	0.3	0.5	0.8
mean	1	3	5	8
variance	0.52	1.32	1.60	0.98
binomial variance	0.09	0.21	0.25	0.16
over-dispersion	5.73	6.30	6.41	6.11

Intra-litter correlations induces nearly constant overdispersion

Raw data from Platzeck et al(1988)

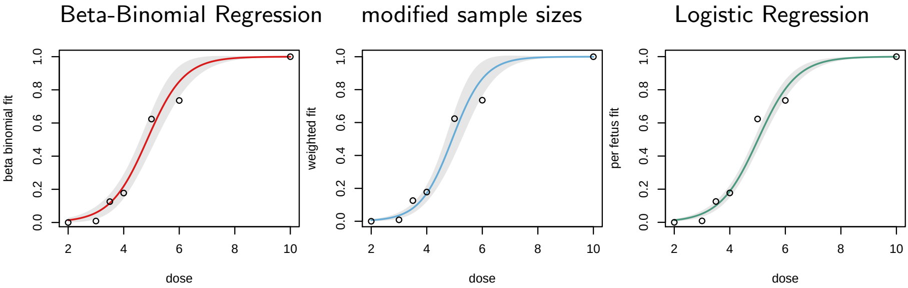
The Teratogenic Potency of MNU in Mice. Arch.Toxicol. 62: 411-423

dose	reactions/litter size	$\sum r_i / \sum n_i$	litter effect
2	0/11 0/11 0/12 0/12 0/13 0/13 0/15 0/15 0/15	0	
3	0/11 1/11 0/12 0/13 0/13 0/13 0/14 0/14 0/14	0.009	–
3.5	0/8 2/8 0/9 3/9 5/10 1/11 3/11 0/12 0/12 3/12 3/12 0/13 0/13 1/13 0/14	0.13	**
4	0/2 2/9 0/10 3/10 0/12 2/12 2/12 3/12 2/13 5/15	0.18	–
5	1/6 7/7 3/11 8/11 9/11 12/13 3/14 6/14 14/14	0.62	**
6	6/6 6/6 4/9 7/9 10/10 11/11 2/12 2/12 11/12 12/13 13/13 13/13 6/14	0.74	**
10	7/7 8/8 9/9 11/11 12/12 12/12 13/13 14/14	1	



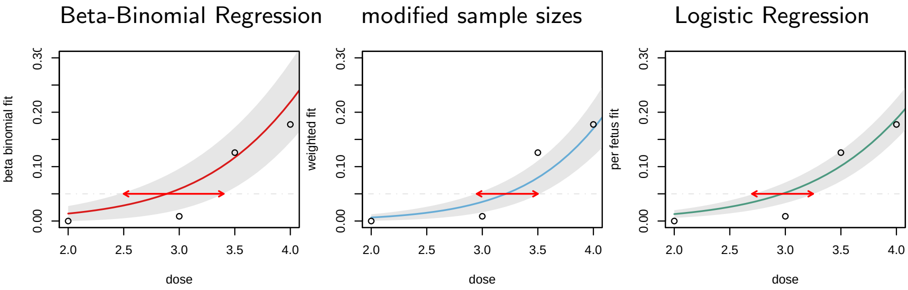
Results: slightly decreasing litter size, increase in response rate

How different treatment of litter-effect changes fit



litter effects cause weighted fit to data
ignoring litter effects gives too narrow confidence bands

How different treatment of litter-effect changes benchmarks

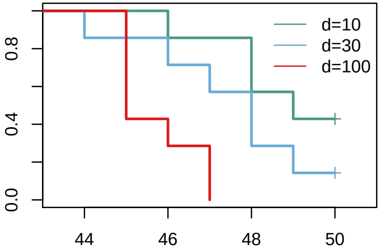


Selected method influences value **and** width of confidence interval
beta binomial fit recommended

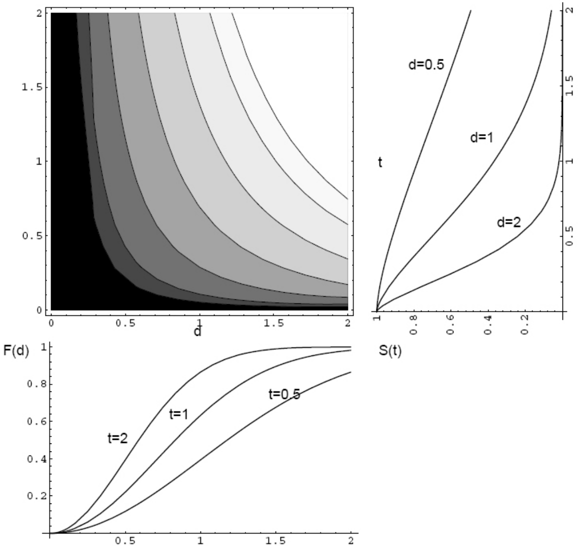
Example Labour Induction in Guinea-Pigs

	Time (days post conception)								
Dose	44	45	46	47	48	49	50	> 50	Total
10	0	0	1	0	2	1	0	3	7
30	1	0	1	1	2	1	0	1	7
100	0	4	1	2	0	0	0	0	7

Time to first abortion by dose of a Progesterone Antagonist (mg/a/d). Data from Elger (1999), pers. commun.



More Information Time-Dose-Response Models



Example: Moskito Fish (Newman/Huscher)

Zeitintervall bis Tod (in h)	Konzentration (in ppt)							Total
	0	10.3	10.8	11.6	13.2	15.8	20.1	
(. – 8]	0	0	0	0	0	9	77	86
(8 – 16]	0	0	0	0	0	26	0	26
(16 – 24]	0	0	0	0	3	28	0	31
(24 – 32]	0	0	0	1	10	11	0	22
(32 – 40]	0	0	2	2	10	2	0	16
(40 – 48]	0	5	6	8	10	2	0	31
(48 – 56]	0	2	2	9	10	0	0	23
(56 – 64]	0	2	5	4	10	0	0	21
(64 – 72]	0	3	3	7	5	0	0	18
(72 – 80]	0	1	0	2	6	0	0	9
(80 – 88]	0	2	0	3	4	0	0	9
(88 – 96]	0	1	4	4	1	0	0	10
zensiert	*78*	*60*	*57*	*37*	*7*	*0*	*0*	*239*
Total	78	76	79	77	76	78	77	541

Dörte Huscher (1999) Diploma Thesis TFH Berlin
„Statistische Methoden der Risikoabschätzung bei zeitabhängiger Exposition“

Time-Dose-Response Models

Data: Types of Recording

C (quasi) continuous

D discrete

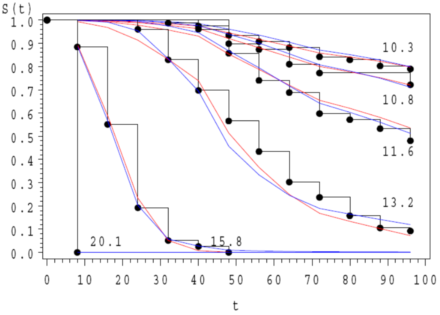
G grouped (*interval censored*)

Analysis: Types of Models

- parametric models C D G
  accelerated failure time
  glm with $f(time)$ as covariate
- semi parametric models
  Cox prop hazard C (D)
  glm for ordered categorical G

Choice of model defines type of dose-relation.

Example: Moskito Fish (Newman/Huscher)



fit: glm ordered categorical

link=cloglog, $c^{2.1}$

→prop. hazard

link=logit, $c^{2.8}$

→prop. odds

$$S(t_i) = 1 - link^{-1}(\alpha_i + \beta\ c^k); \quad t_i \in \{8, 16, 24, 32, 40, 48, 56, 64, 72, 80, 88, 96\}$$

General Measure of Risk

differential effects

data Let $X_i \sim F_i, \quad i = 1, 2$ be independent. Small values indicating *bad* state.

effect $p(X_1, X_2) = P(X_2 < X_1) + (1/2)P(X_2 = X_1)$
$= \int F_2(x)dF_1(x)$
modified version of F for discontinuous distributions .

origin Brunner, Akritas *differential treatment effect*

differential effects are invariant under strictly monotonous transformations

General Measure of Risk

differential effects for selected models

normal data $X_i \sim \Phi(\mu_i, \sigma^2), \; i = 1, 2$

$$p(X_1, X_2) = \Phi\{(\mu_1 - \mu_2)/(\sqrt{2}\sigma)\}$$

prop. hazards $1 - F_2(x) = \{1 - F_1(x)\}^\gamma$

$$p(X_1, X_2) = \gamma/(\gamma + 1)$$

binary data $X_i \sim B(1, q_i), i = 1, 2$

$$p(X_1, X_2) = (1/2) + (1/2)(p_2 - p_1)$$

differential effects are easily expressed as function of parameters

General Measure of Risk

Dose-Response for Differential Effects

data	$X_1 = X(0)$ controls, $X_2 = X(d)$ exposed
normalize	$\pi(d) = 2\{p(X(0), X(d)) - 1/2\}$
normal data	$\pi(d) = 2(\Phi\{(\mu(0) - \mu(d))/(\sqrt{2}\sigma)\} - 1/2)$
prop.hazard	$\pi(d) = \{\gamma(d) - 1\}/\{\gamma(d) + 1\}$
binary data	$\pi(d) = p(d) - p(0)$

normalized differential effects define risk function

Benchmark Doses for Normalized Differential Effects

parametric models use plug-in estimates of model parameters

ordered categorical use rank-sum estimate:

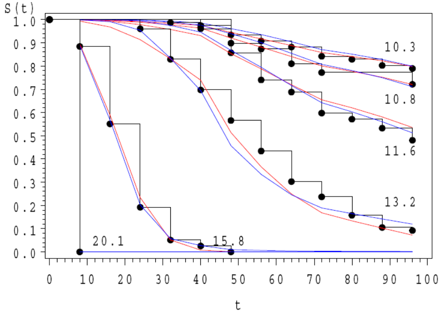
$$\widehat{\pi}(d) = 2[(1/n_d)\{(1/n_0)\sum_{i=1}^{n_0} R_{0,i} - (n_0+1)/2\} - (1/2)]$$

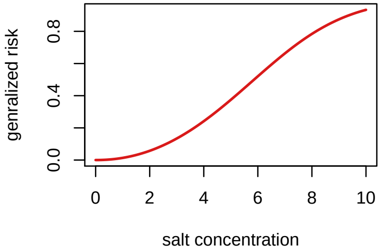
conf. bounds as usual, delta method, profile likelihood, bootstrap

benchmarks can be derived for differential effects

General Measure of Risk: Time-Dose-Response

Example: Moskito Fish (Newman/Huscher)





$$\pi(c) = \frac{\exp(0.0268 \times c^{2.1}) - 1}{\exp(0.0268 \times c^{2.1}) + 1}$$

Final Remarks

- Benchmarks can be derived for quantal response data when (quasi) complete separation occurs. ATTENTION model dependence
- Simple simulation is a good tool for analyzing clustered binary data. Beta-binomial regression provides reliable models for teratological data.
- Event history modeling extracts more and better information than quantal response approach.
- Stochastic order expressed by normalized differential effects is a suitable general measure of risk.

Frohe Adventszeit

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