Behavioral Testing of Antidepressant Compounds: An Analysis of Crossover Design for Correlated Binary Data

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Overview

- Behavioral testing of anti depressant compound
- The DRL-72 experiment and Study design
- Analysis of response rate using random effects model – three approaches
    1. Generalized linear mixed model for Binary data
    2. Hierarchical Bayesian model: Joint binomial-Poisson model
    3. Hierarchical Bayesian model: Joint binomial-Poisson model with extra Poisson variability
- Application to the data
- Conclusions

Behavioral Testing of Antidepressant Compounds

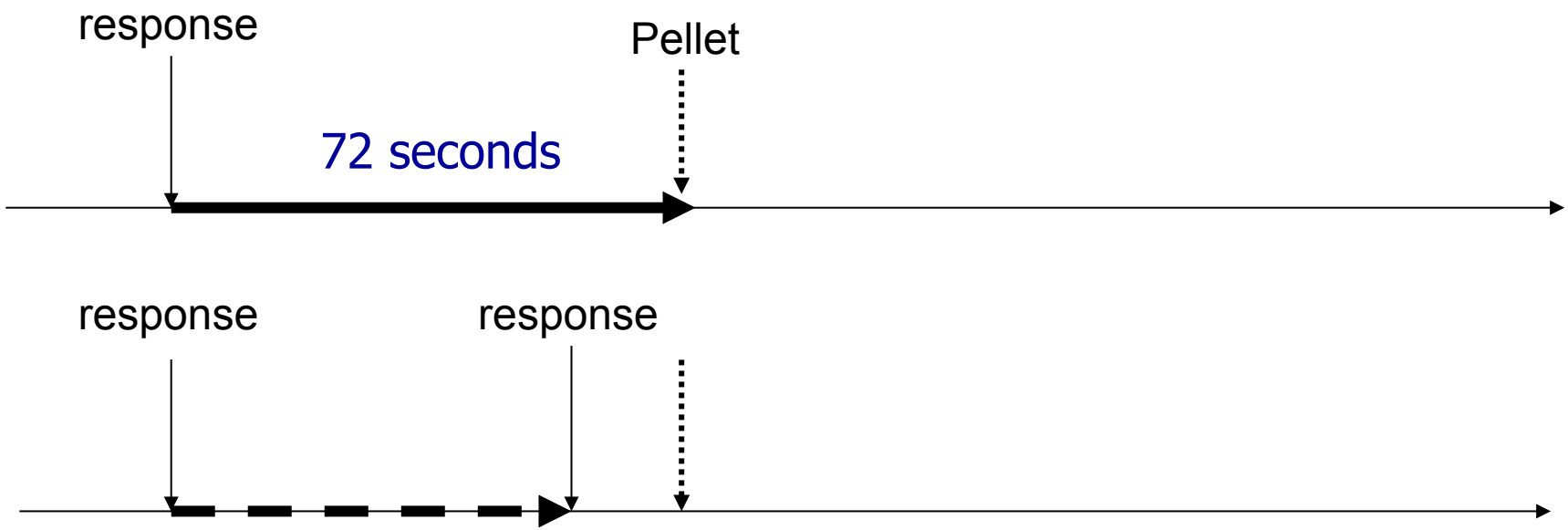
- Rat are used as a model (surrogate) to test compounds for their activity
- The DRL 72 is a protocol that is commonly used for screening of compounds (Evenden et al. 1993)
- Animals are treated with several treatments using crossover designs

DRL-72 Experiment

Z : total number of responses

Y : number of pellets

Press the lever and wait 72sd



Press the lever and wait less than 72sd

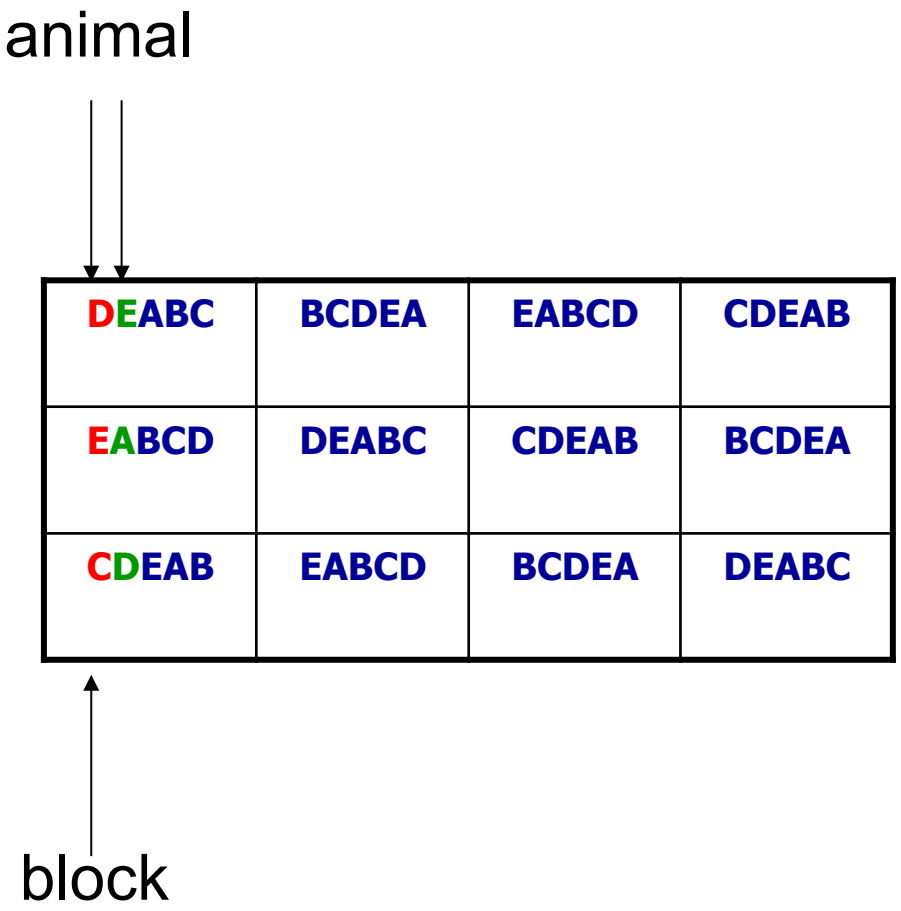
DRL-72 Experiment

- Rats have to press a lever in order to get a reward (food pellet)
- Only if they press the lever after a period of 72 sec they get a reward
- If they lose interest before the 72 sec period they do not get a reward
- Clinically active antidepressant drugs introduce a change in this behavior
- The success ratio (rewards over attempts) should increased with active drugs

Study design

- Cross-over design with 5 treatments, 3 periods and 4 blocks
- In total, 20 animals were randomized into a 3 periods sequences
- Five dose levels:

A=0
B=1.25
C=2.5
D=5
E=10 (mg/kg)



3 versus 5 periods

- 1 dose per week

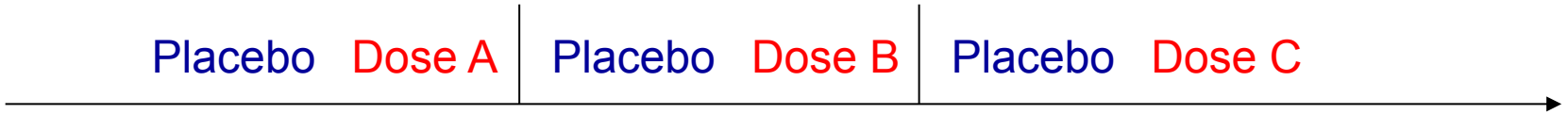
- 3 period fractional design

  1. Cross over experiments are very efficient

  2. Drop out after 5 weeks can be high

3 periods experiment

Each rat receive only three dose levels



Day 1 Day 2

period

Possible effects:

1. Animal (random effect)

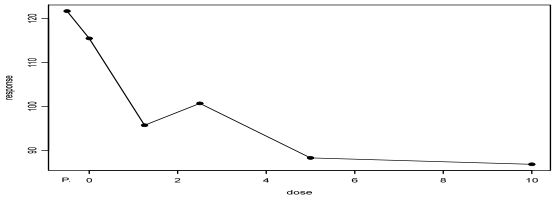
2. Dose

3. Period

4. Carry-over

Descriptive Analysis (1)

- Mean number of responses decrease with dose level

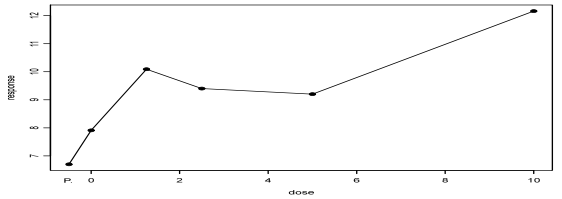


Dose	N	Mean
Placebo	55	121.7
0	12	115.5
1.25	11	95.72
2.5	10	100.7
5	10	88.30
10	12	86.83

This pattern is the main motivation for the second modeling approach !!

Descriptive Analysis (2)

- Mean number of pellets by dose level
- Increasing trend with dose level

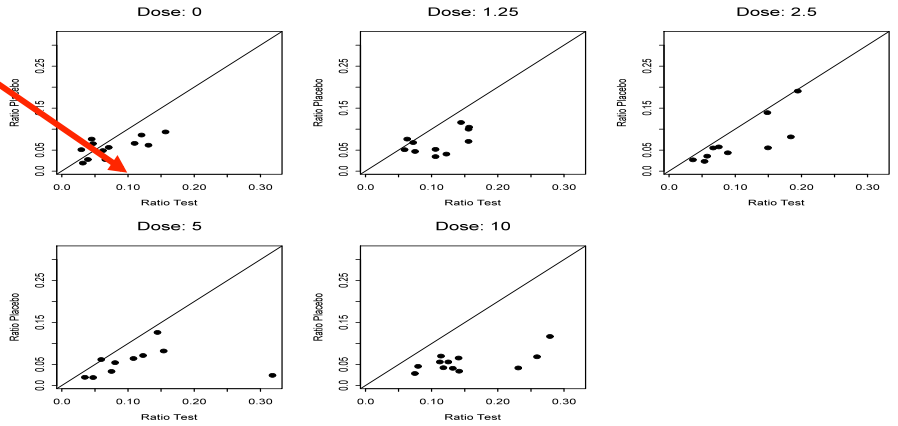


Dose	N	Mean
Placebo	55	6.60
0	12	7.91
1.25	11	10.09
2.5	10	9.40
5	10	9.20
10	12	12.6

Descriptive Analysis (3)

- The ratio pellets/ responses

  by dose group.
- Placebo versus test drug.



The ratio pellets/responses:
success rate

Three Modeling Approaches

- Generalized linear mixed model (GLMM) for binary data:

Logistic regression with normally distributed random effects.

- Joint model for Binomial and Poisson random variables :

Hierarchical Bayesian model with subject-specific random effects for both Binomial and Poisson variables

Joint Poisson/Binomial with extra Poisson variation

Generalized Linear Mixed Model

- The number of pellets is the response variable, we assume

$$pellets \sim B(\#responses, \pi)$$

- Here, π is the probability that the animal will wait 72 seconds and receive a pellet

- The primary of interest: how π influenced by the dose level ?

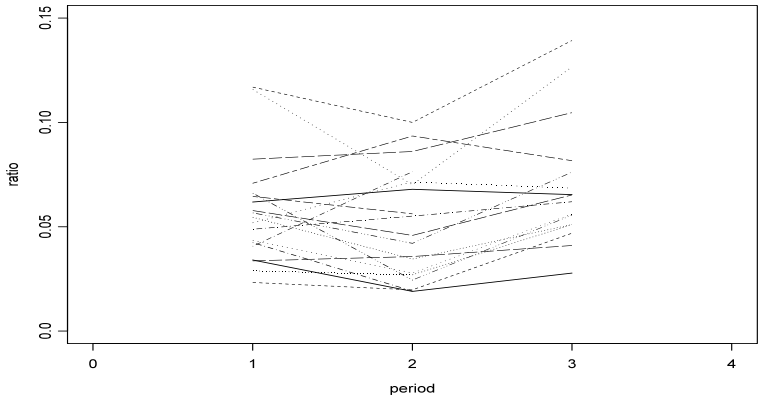
Generalized Linear Mixed Model

$$y_{ij} \mid z_{ij} \sim B(z_{ij}, \pi_{ij})$$

$$\text{logit}(\pi_{ij}) = X\beta_{ij} + b_i$$

$$b_i \sim N(0, \sigma_b^2)$$

Animal-specific random intercept



Mean Structure

- Carryover effect is possible only in period 2 and 3
- Suppose that an animal was randomized to the sequence ABC, then:

PERIOD 1: $logit(\pi_{ij}) = b_i + overall\ mean + dose_A$

PERIOD 2: $logit(\pi_{ij}) = b_i + overall\ mean + dose_B + carryover_A + period_2$

PERIOD 3: $logit(\pi_{ij}) = b_i + overall\ mean + dose_C + carryover_B + period_3$

Results

- The parameter estimate of the treatment variable from the GLMM is the log odds ratio
- The odds ratios has a very easy interpretation: success ratio of dose x versus success ratio of dose 0
- One value per dose summarizes the treatment effect

Results

DOSE	OR	CI
1.25 - 0	1.35	0.98 - 1.86
2.5 - 0	1.22	1.01 - 1.49
5.0 - 0	1.68	1.19 - 2.37
10.0 - 0	2.13	1.50 - 3.02

Why a Second Modeling Approach ?

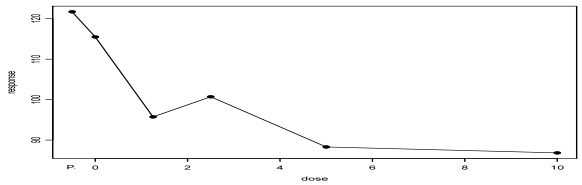
GLMM

$$y_{ij} \mid z_{ij}, \pi_{ij} \sim Binomial(z_{ij}, \pi_{ij})$$

$$\text{logit}(\pi_{ij}) = X\beta + b_i$$

$$b_i \sim N(0, \sigma_b^2)$$

The number of responses is **fixed**



Binomial-Poisson

$$y_{ij} \mid z_{ij}, \pi_{ij} \sim Binomial(z_{ij}, \pi_{ij})$$

$$\text{logit}(\pi_{ij}) = X\beta + b_i$$

$$z_{ij} \mid \mu_{ij} \sim Poisson(\mu_{ij})$$

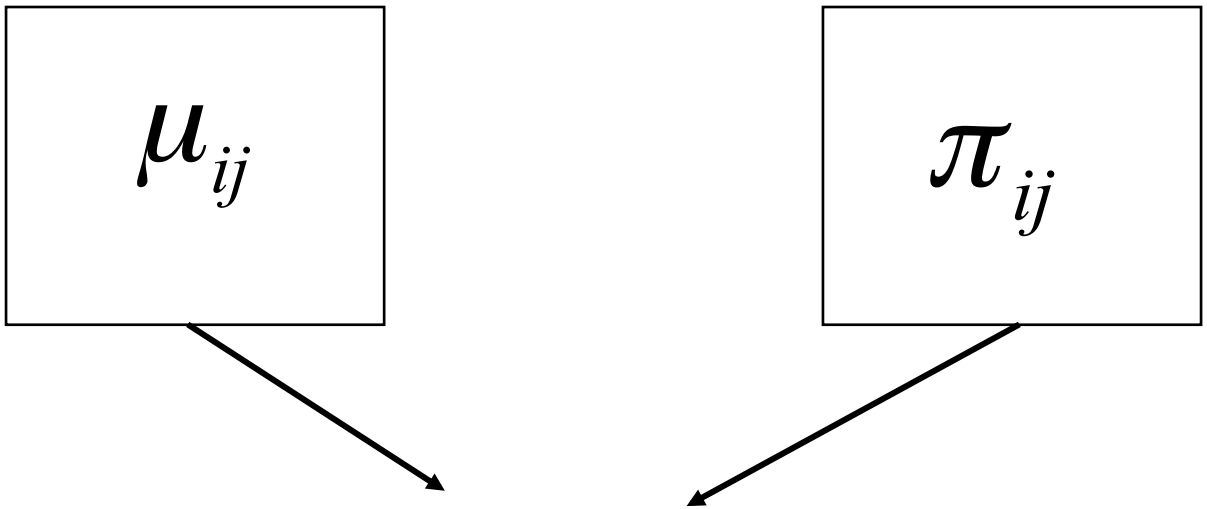
$$\log(\mu_{ij}) = X\alpha + a_i$$

The number of responses is Poisson **random variable**

Parameters of Primary Interest

- Mean number of responses
- Probability to obtain a reward

Poisson μ_{ij} π_{ij} Binomial



1. **How to model the association between the probability to obtain reward and the mean number of responses ?**
2. **Treatment effect ?**

Modeling Association

- Recall that $\text{logit}(\pi_{ij}) = X\beta + b_i$ and $\log(\mu_{ij}) = X\alpha + a_i$

- Hence, the association between μ_{ij} and π_{ij} can be modeled by

$$\begin{bmatrix} b_i \\ a_i \end{bmatrix} \sim N\left(\begin{bmatrix} 0 \\ 0 \end{bmatrix}, D \right)$$

- where

$$D = \begin{bmatrix} d_{bb} & d_{ab} \\ d_{ab} & d_{bb} \end{bmatrix} \Rightarrow \rho = \frac{d_{ab}}{\sqrt{d_{aa}}\sqrt{d_{bb}}}$$

Treatment Effects

- Suppose that an animal was randomized to the sequence ABC, then the linear predictors are given by:

- PERIOD 2:

(1) $logit(\pi_{ij}) = b_i + \text{overall mean} + dose_B + carryover_A + period_2$

(2) $log(\mu_{ij}) = a_i + \text{overall mean} + dose_B + carryover_A + period_2$

$$\rho = \frac{d_{ab}}{\sqrt{d_{aa}}\sqrt{d_{bb}}}$$

association

treatment effects

Hierarchical Bayesian Model

- First Level of the model (the likelihood)

Model for the number of pellets

$$y_{ij} \mid z_{ij}, \pi_{ij} \sim Binomial(z_{ij}, \pi_{ij})$$
$$\text{logit}(\pi_{ij}) = X\beta + b_i$$

Model for the number of responses

$$z_{ij} \mid \mu_{ij} \sim Poisson(\mu_{ij})$$
$$\log(\mu_{ij}) = X\alpha + a_i$$

- Second level of the model: prior model for random effects

$$\begin{bmatrix} b_i \\ a_i \end{bmatrix} \sim N\left(\begin{bmatrix} 0 \\ 0 \end{bmatrix}, D \right)$$

Hierarchical Bayesian Model

- Prior for the "fixed" effects (treatment, period, carry-over): we use non informative independent normal priors

$$\beta_i \sim N(0, \sigma^2_{\beta_i})$$ ← Priors for the fixed effects for number of pellets

$$\alpha_i \sim N(0, \sigma^2_{\alpha_i})$$ ← Priors for the fixed effects for number of responses

- Third level of the model (hyperprior for the covariance matrix D)

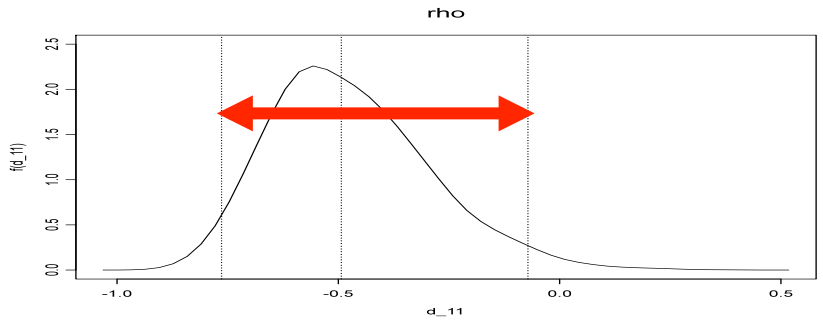
$$D^{-1} \sim W(R)$$

Parameters of Primary Interest

Correlation between the random effects	ρ
Treatment effects (binomial Variable): Log(OR)	$\beta_k - \beta_0$
Treatment effects (Poisson Variables): Log (RR)	$\alpha_k - \alpha_0$

Association Between Pellets and Responses

- Posterior mean for ρ is -0.4723 with 95% credible interval (-0.76, -0.07).
- Negative association between pellets and responses !!



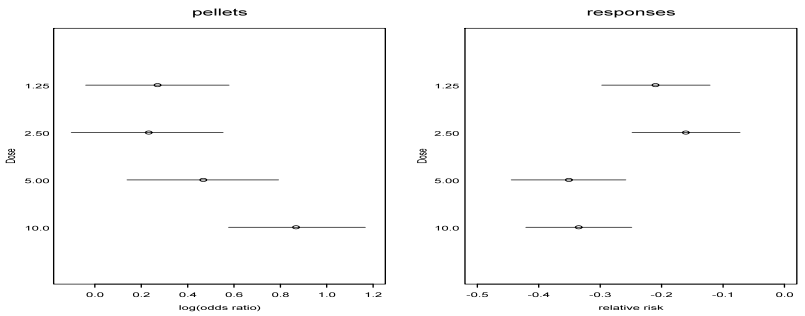
Odds Ratios and Relative

- Number of responses decreases with dose.
- Number of pellets increases with dose.

Posterior means and 95% credible intervals

Pellet

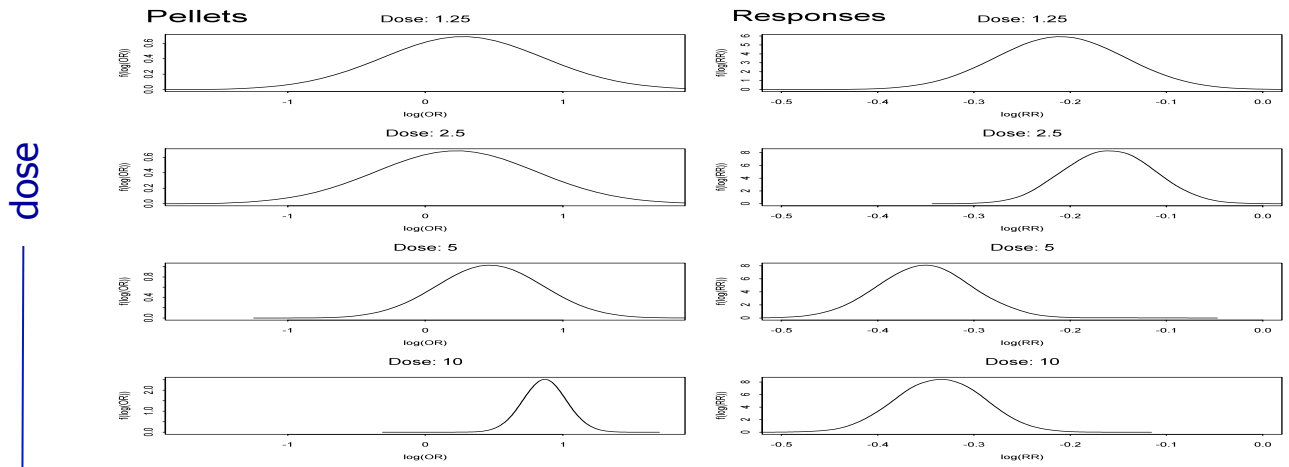
Responses



dose

Dose level K versus dose 0

Odds Ratios and Relative



Joint binomial/Poisson model with over overdispersion parameter for the Poisson model

For the number of responses:

$$z_{ij} \mid \mu_{ij} \sim Poisson(\mu_{ij})$$
$$\log(\mu_{ij}) = X\alpha + a_i$$
$$E(z_{ij}) = \mu_{ij} \qquad V(z_{ij}) = \mu_{ij}$$

In many application the mean and the variance for the count variable (responses in our example) are not equal.

We would like to model the data taking into account a possible overdispersion problem.

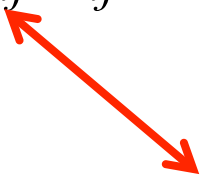
Joint binomial/Poisson model with over overdispersion parameter for the Poisson model

$$y_{ij} \mid z_{ij}, \pi_{ij} \sim Binomial(z_{ij}, \pi_{ij})$$

$$\text{logit}(\pi_{ij}) = X\beta + b_i$$

$$z_{ij} \mid \mu_{ij} \sim Poisson(\eta_{ij}\mu_{ij})$$

$$\log(\mu_{ij}) = X\alpha + a_i$$



overdispersion parameter in order to take into account extra Poisson variability.

Joint binomial/Poisson model with over overdispersion parameter for the Poisson model

$$y_{ij} \mid z_{ij}, \pi_{ij} \sim Binomial(z_{ij}, \pi_{ij})$$

$$\text{logit}(\pi_{ij}) = X\beta + b_i$$

$$z_{ij} \mid \mu_{ij} \sim Poisson(\eta_{ij}\mu_{ij})$$

$$\log(\mu_{ij}) = X\alpha + a_i$$

$$\eta_{ij} \sim gamma(\delta, \frac{1}{\delta})$$

$$\begin{bmatrix} b_i \\ a_i \end{bmatrix} \sim N\left(\begin{bmatrix} 0 \\ 0 \end{bmatrix}, D\right)$$

Joint binomial/Poisson model with over overdispersion parameter for the Poisson model

$$z_{ij} \mid \mu_{ij} \sim Poisson(\eta_{ij}\mu_{ij})$$

$$\log(\mu_{ij}) = X\alpha + a_i$$

$$\eta_{ij} \sim gamma(\delta, \frac{1}{\delta}) \quad \Rightarrow \quad E(\eta_{ij}) = 1, \quad V(\eta_{ij}) = \frac{1}{\delta}$$

For large value of δ the variance (of eta) is very small which implies that we do not have a problem of overdispersion since the mean is equal to 1.

Joint binomial/Poisson model with over overdispersion parameter for the Poisson model

Posterior mean for the correlation is negative: as dose increases the rats have less responses with more rewards (high success rate).

Posterior mean for the variance of the overdispersion parameter is 0.235.

$$\overline{\rho} = -0.3742$$

$$\overline{V}(\eta_{ij}) = 0.235$$

Discussion

- Proposal for the statistical analysis of the DRL-72 protocol.
- Hierarchical GLMM and GEE (number of responses is fixed) and full Bayesian Binomial-Poisson model (number of responses in random variables)

- All models can be fitted using standard software:

  SAS: NLMIXED, GENMOD (GEE), MCMC

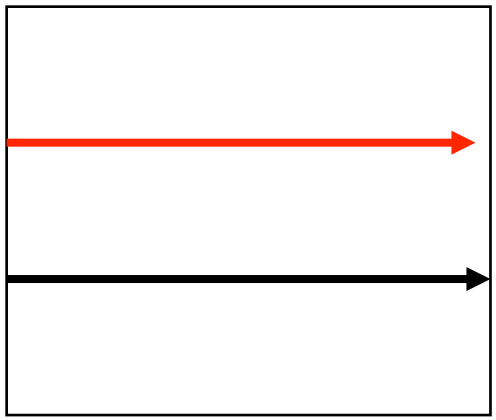
  WINBUGS 1.4 (Hierchical GLMM and the Binomial-Poisson models)

Thank you !!!

Why a Second Modeling Approach ?

CONSTANT SUCSESS RATE

A



dose

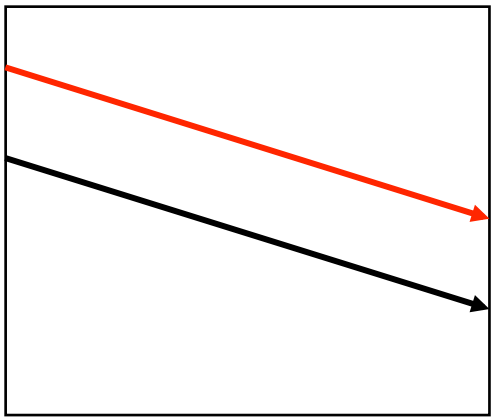
GLMM: NO TREATMENT EFFECT

BINOMIAL-POISSON: NO TRETMNET EFFECTS

Number of responses

Number of rewards

B



dose

GLMM: NO TREATMENT EFFECT

BINOMIAL-POISSON: NO TRETMNET EFFECTS

FOR THE SUCCESS RATE, BUT (!!!)

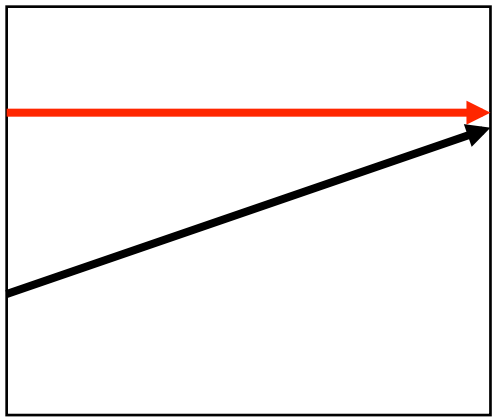
DECREASING TREATMENT EFFCTS

FOR NUMBER OF RESPONSES

Why a Second Modeling Approach ?

INCREASING SUCSESS RATE

C

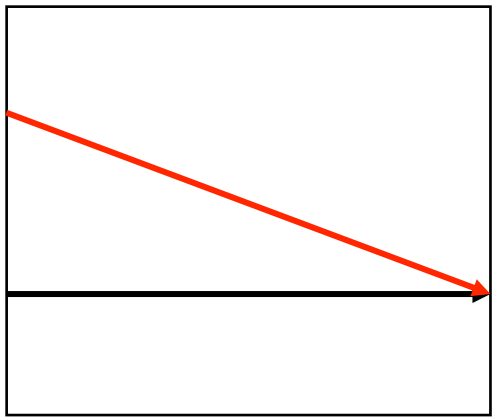


dose

GLMM: INCREASING SUCSESS RATE

BINOMIAL-POISSON: INCREASING SUCSESS RATE,
NO TREATMENT EFFECT FOR THE NUMBER
OF RESPONSES

D



dose

GLMM: INCREASING SUCSESS RATE

BINOMIAL-POISSON: NO TRETMNET EFFECTS
FOR THE SUCCESS RATE, BUT (!!!)
DECREASING TREATMENT EFFCTS
FOR NUMBER OF RESPONSES