

Development of a New Mixed Poisson-Gaussian Model for Count Data from Rodent Brief-Access Taste Aversion Experiments

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INTRODUCTION

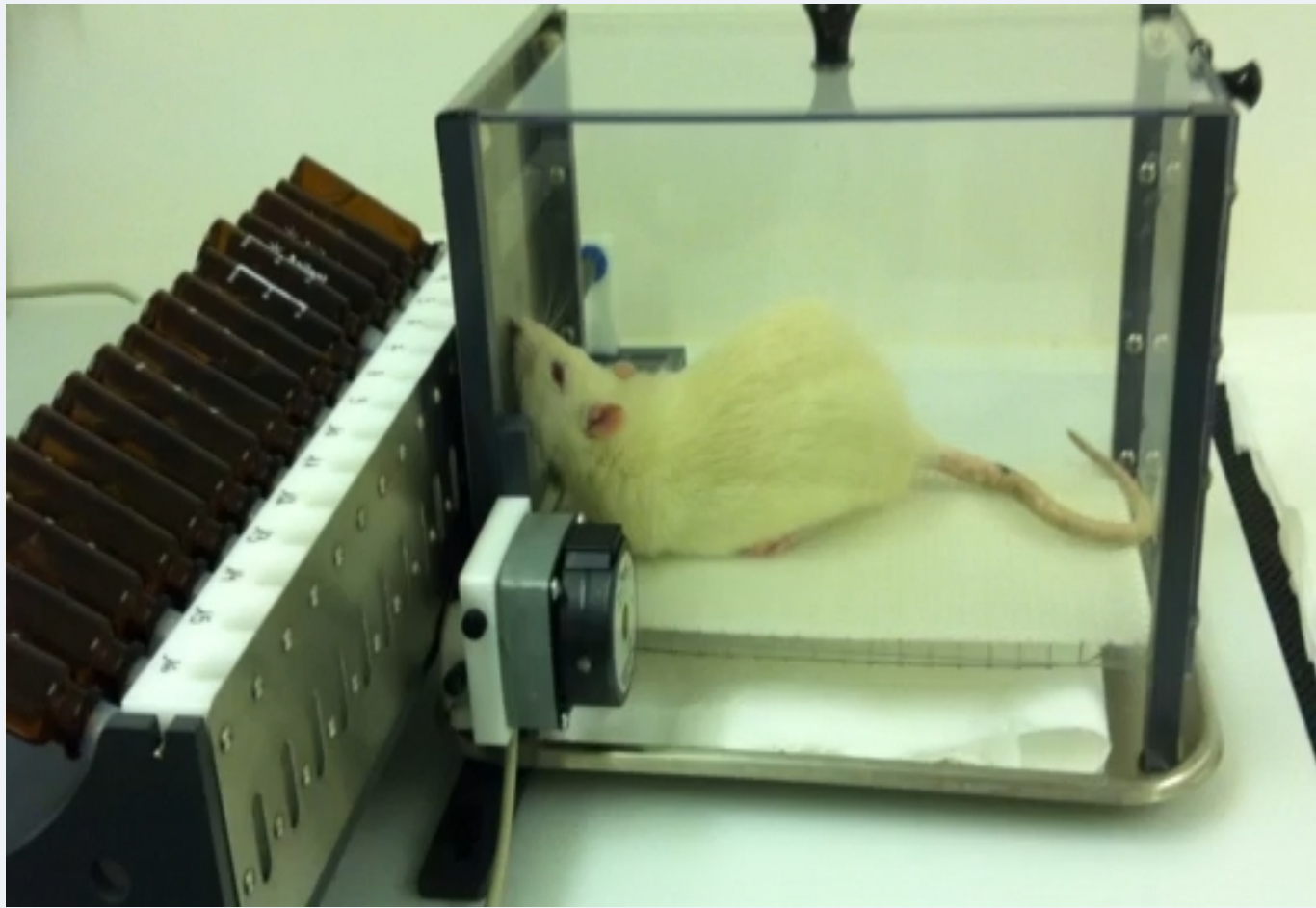
Taste assessment has become an important element of pharmaceutical drug development for patients with a chronic disease and the paediatric population. Evaluating the taste of different derivatives of new chemical entities (NCE) at a early stage of the drug development process is essential to increase the acceptability for the patient. Rodent Brief-Access Taste Aversion (BATA) experiment is a common in-vivo screening tool to evaluate the taste of a drug [1]. Published models that based on the “lick ratios” from the means are not ideal for analyzing these data.

MATERIALS AND METHODS

Brief Access Taste Aversion (BATA) experiments

- Mildly water-deprived rats (22 hours) exposed to different solutions at different concentrations for a period of time (8s)
- Taste is assessed by the number of licks which are recorded by a lickometer connected to a computer
- Deionised water and six concentrations (0.01, 0.03, 0.1, 0.3, 1 and 3 mM) of quinine hydrochloride dihydrate (QHD) were tested by 10 rats from 8 weeks study

Day 1	Water-bottles removed from animals' cages. Free access to food.
Day 2	Training session 1 (only on 1 st week): rodent in Davis Rig with free access to one water-bottle (not moving).
Day 3	Training session 2: rodent in Davis Rig, access to water-bottles moving to acclimatise it to the protocol.
Day 4	Test session 1: randomised presentation of up to 14 test samples.
Day 5	Test session 2: randomised presentation of up to 14 test samples.



Modelling and validation

Several single distribution models were tried [2,3].

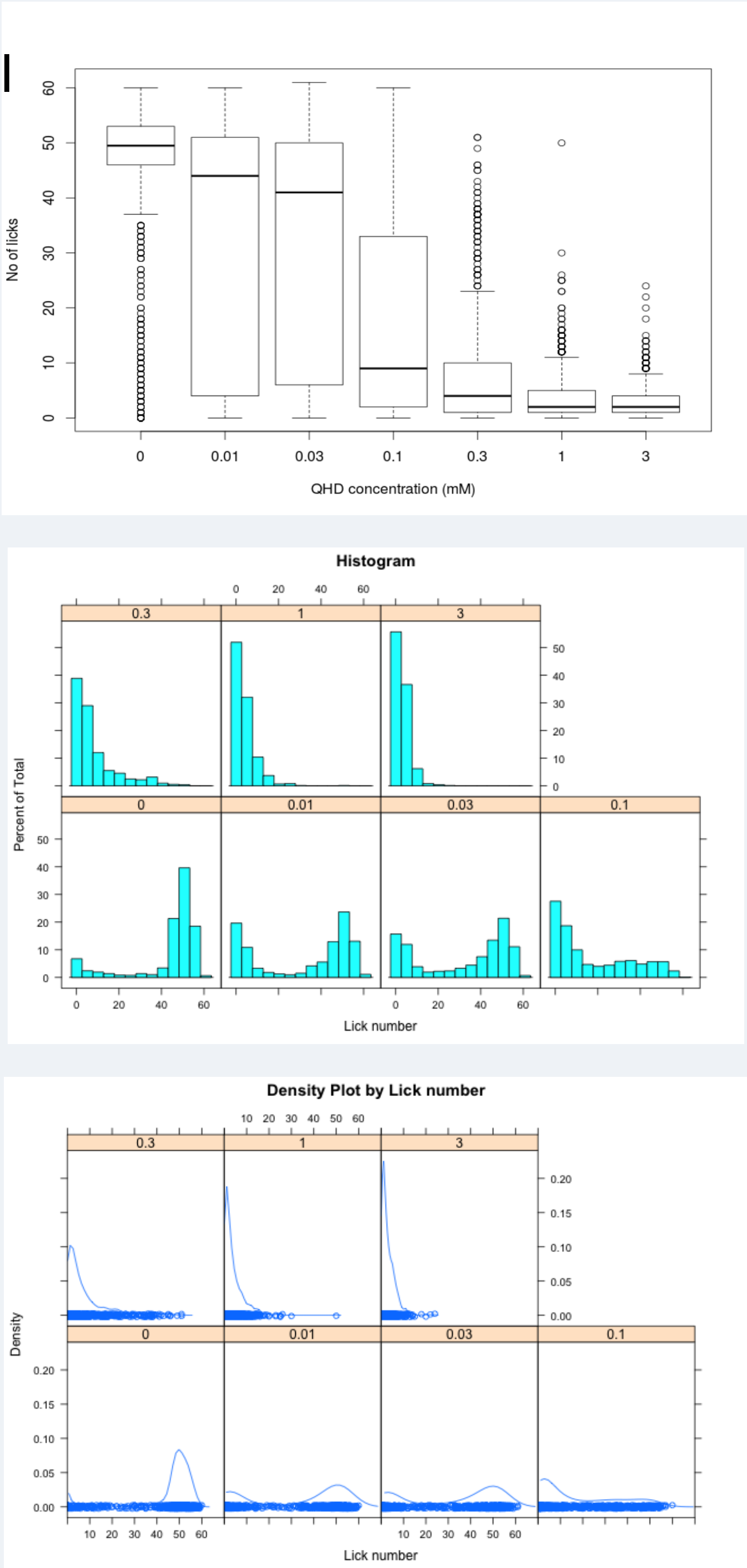
- Emax Model & Sigmod Emax Model
- Poisson Model
- Generalized Poisson (GP) model
- Negative Binomial (NB) model

Mixed models were also tested.

- Zero-Inflated Poisson (ZIP) model
- Zero-inflated negative binomial(ZINB) Model
- Poisson with mixture distribution(PMIX) model
- Poisson-Normal mixture distribution model

A total of 1000 bootstrap replicate datasets were generated by sampling randomly from the original data.

Categorical visual predictive check (VPC) based on 1000 simulations for the final model was used to evaluate the model.



RESULTS AND DISCUSSION

A total number of 5400 licks recorders for deionised water and 6 QHD concentrations were obtained from 10 rat BATA experiments. A large variability was shown in ‘lick numbers’ . From the histogram and distribution plot for each concentration of QHD, as the QHD concentration rises,the proportion of first distribution will decrease and the second distribution will increase.

QHD data can be well described by the new mixed distribution model. The proportion of the first distribution was defined as a logistic function and effects linked to QHD concentrations through the sigmoid Emax equation. The changes among different concentrations were captured by the logistic and Emax functions.

VPC demonstrated this new model is reasonable for BATA data.

Table 1. Parameter estimates for the Poisson-Normal mixture distribution model

Parameter	Estimate	(Bootstrap 95%CI)
Baseline	-2.3	(-2.69~-2.13)
Emax	5.7	(5.63~6.9)
IC ₅₀	0.231	(0.133~0.453)
λ	2.73	(2.69~3.33)
μ	50.5	(44.2~55.5)
σ	28.3	(19.4~32.8)
η _{Emax}	2.43	(0.321~2.43)
η _{IC50}	0.0205	(0.001~0.071)
η _{Baseline}	0.052	(0.021~0.072)
η _λ	1.11	(0.317~1.19)
η _E	0.726	(0.182~0.726)

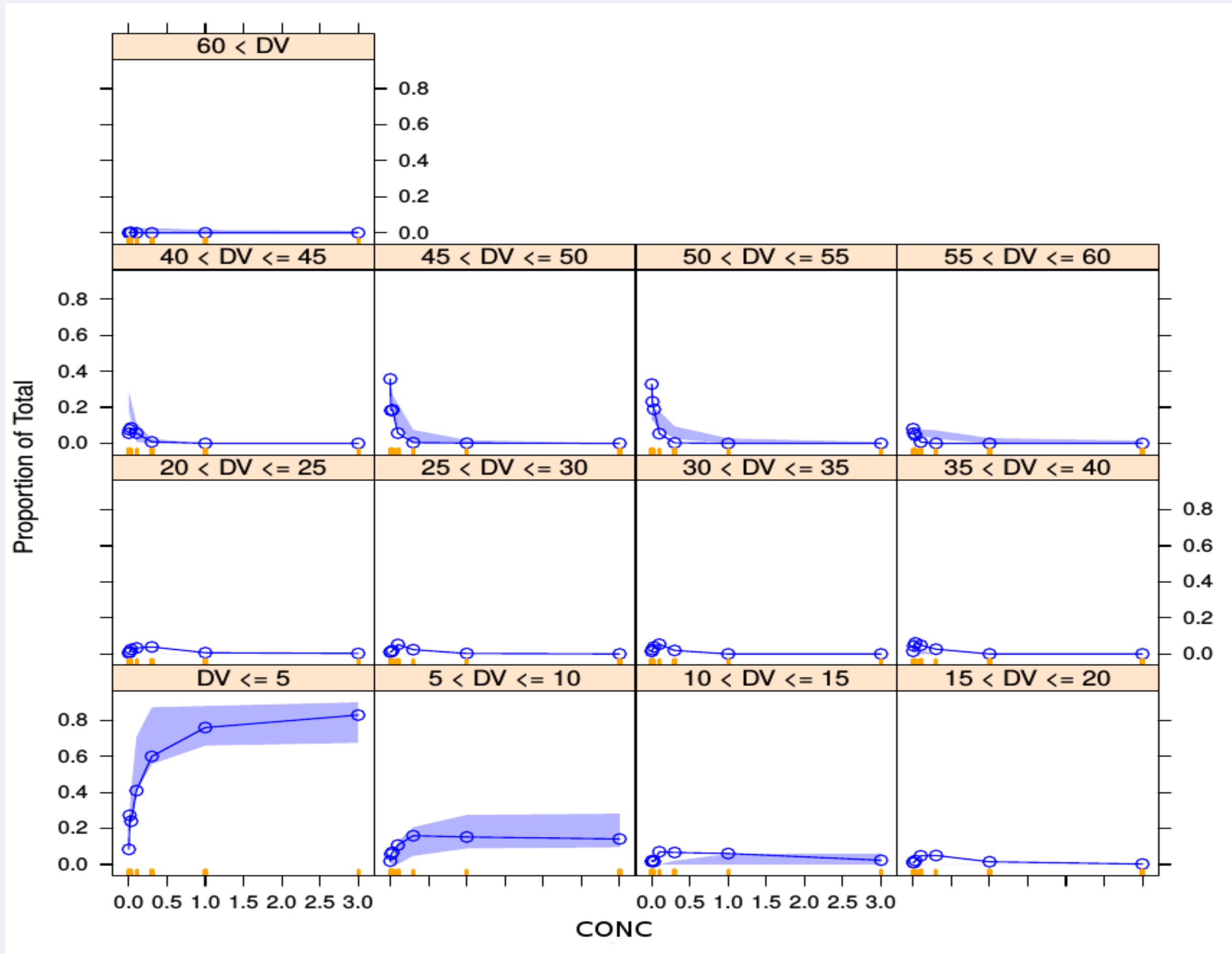
$$P(Y_i = n) = MP \times \frac{e^{-\lambda} \lambda^n}{n!} + (1 - MP) \times \frac{e^{-\frac{(n-\mu)^2}{2\sigma^2}}}{\sqrt{2\pi\sigma} \times P_{truncate}}$$

$$P_{truncate} = \sum_{n=0}^{66} P(n|N(\mu, \sigma^2)) \quad n \in [0, 66]$$

$$E = Baseline + \frac{Emax \times Conc}{IC_{50} + Conc} + \eta_E$$

$$MP = \frac{e^E}{1 + e^E}$$

```
PTRUNC=0
NN=0
DOWHILE(NN<66)
  PNN=EXP(-((NN-MEAN)**2)/
    (2*(SD**2)))/
    (SD*SQRT(2*3.1416))
  PTRUNC=PTRUNC+PNN
  NN=NN+1
ENDDO
```



CONCLUSION

The new Mixed Poisson-Gaussian Model is well suited for count data from rodent brief-access taste aversion (BATA) experiments. The results from any concentrations of QHD can be reasonable predicted by this model.

References:

- [1] Devantier HR, Long DJ, Brennan FX, et al. Quantitative assessment of TRPM5-dependent oral aversiveness of pharmaceuticals using a mouse brief-access taste aversion assay. Behave Pharmacol. (2008)19:673–82.
- [2] Plan, E. L. Modeling and simulation of count data. CPT pharmacometrics Syst. Pharmacol. (2014)3:e129.
- [3] Plan, E. L., Elshoff, J.-P., Stockis, A., et al. Likert pain score modeling: a Markov integer model and an autoregressive continuous model. Clin. Pharmacol. Ther. (2012)91:820–8.



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