Use of a generalized Poisson model to describe micturition frequency in patients with overactive bladder disease.

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Introduction:

Daily micturition frequency is a key endpoint for assessing overactive bladder disease activity.

Micturitions are count data and are commonly modeled assuming the Poisson distribution,.

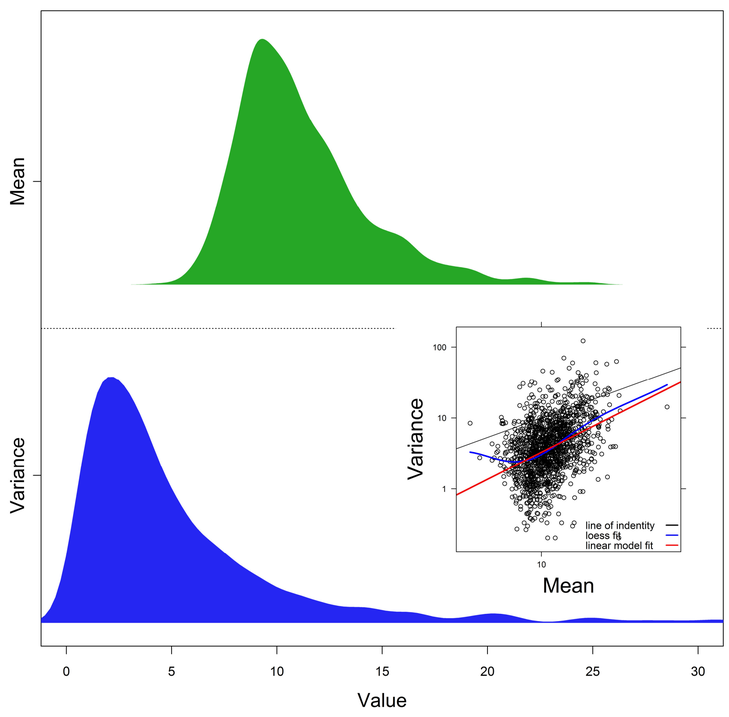
Although Poisson process assumes equi-dispersion, which means that mean and variance are the same, observed within-individual variance is consistently lower than within-individual mean micturition frequency (Figure 1).

Being encouraged by a recent study addressing under dispersion in Likert pain rating scales [3], we wanted to evaluate if the generalized Poisson (GP) that flexibly describes under and over dispersion describes micturition counts better than the standard Poisson (PS) distribution.

Objectives:

To evaluate if the generalized Poisson describes micturition counts better than the Poisson distribution.

Figure 1. Distribution of individual means and variances



Equations and examples of dispersion

$$P(Y=n)=\frac{e^{-\lambda}\cdot\lambda^{n}}{n!}$$ *Poisson*

$$P(Y=n)=\frac{e^{-\lambda-n\delta}\cdot\lambda(\lambda+n\delta)^{n-1}}{n!}$$ *Generalized Poisson*

Parameters in ***green*** are estimated

Thus, a Poisson distribution is a generalized Poisson distribution with dispersion factor δ = 0. Mean count and variance are given by:

$$\bar{x}=\frac{\lambda}{1-\delta}\qquad var(x)=\frac{\lambda}{(1-\delta)^3}$$

δ < 0 *under dispersion*

δ = 0 *equi dispersion*

δ > 0 *over dispersion*

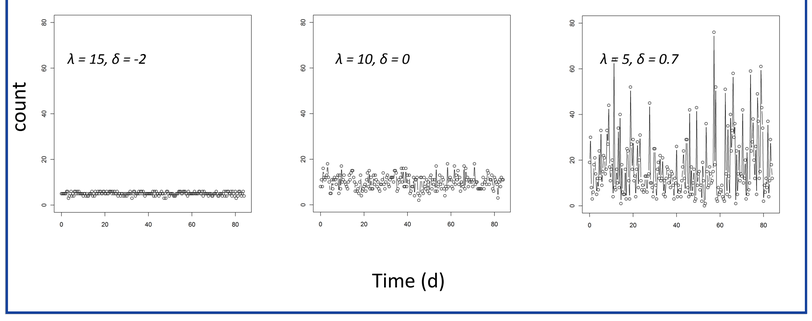


Figure 2. VPC of Poisson model

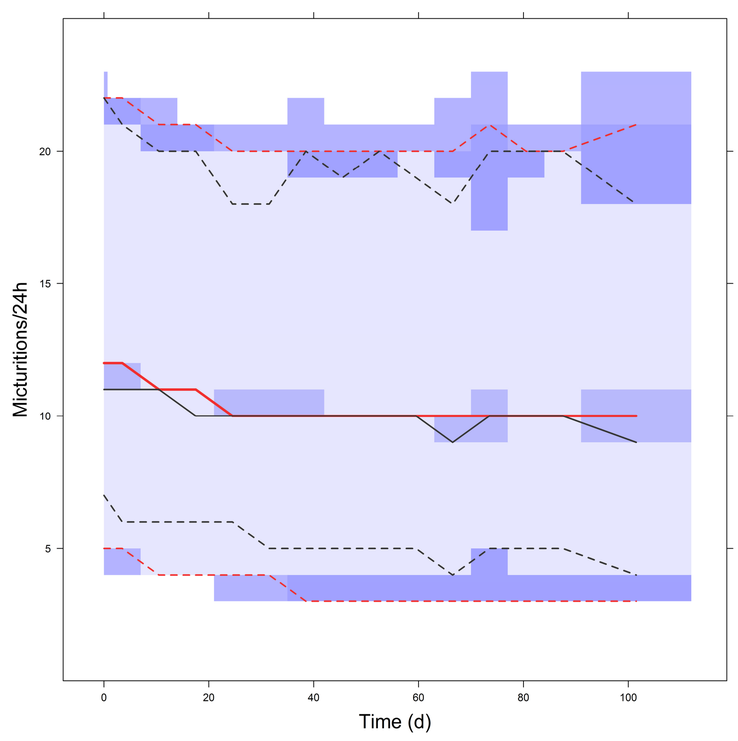
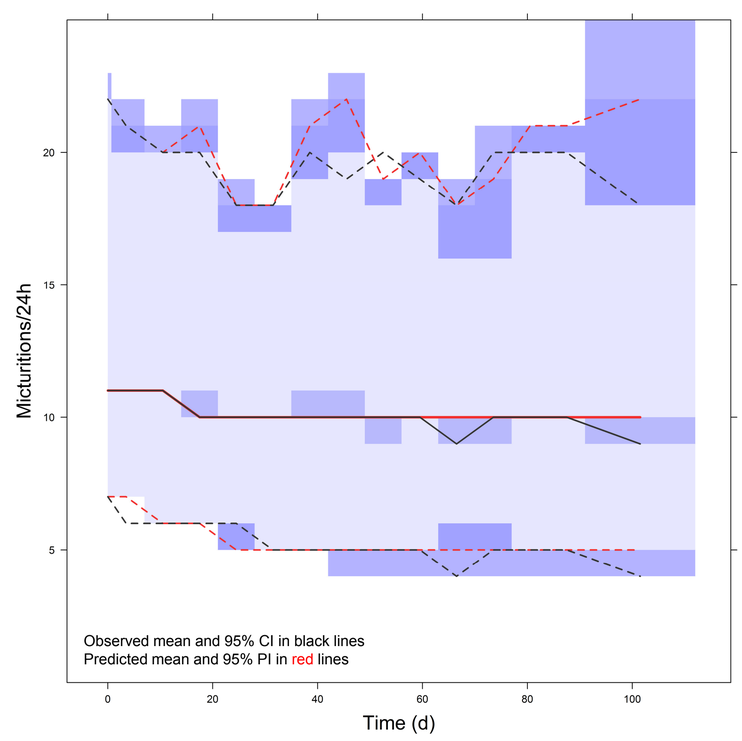


Figure 3. VPC of Generalized Poisson model



Methods:

Data

Placebo micturition count data from 1480 patients participating in 7 studies were used.

Model

Micturition counts (mict) were modeled as follows:

$$mict_{i,t}=mict_{base}\cdot\left(1-Eff\cdot\left(1-e^{-\theta_4\cdot t}\right)\right)$$

$$mict_{base}=\theta_1\cdot e^{\eta_1}$$

$$Eff=\frac{e^{\theta}}{1+e^{\theta}}+\eta_3,\qquad 0.01\le Eff\le 0.99$$

$$mict_{i,t}\sim genPoisson(\lambda,\delta)$$

$$\delta=\theta_2\cdot e^{\eta_2}$$

Where $mict_{i,t}$ is the micturition count in the i^{th} individual at time t. Lognormal between subject variability (BSV) was assumed on λ (PS) or λ1 (GP) and additive BSV was assumed on Eff (PS, GP).

FOCE LAPLACE did not prove stable for the generalized Poisson model, thus resampling tools were used: SAEM followed by MCMC BAYES. The SAEM was merely aiming to get some priors, hence 50 burn-in and 50 sampling iterations were requested:

```
$EST METH=SAEM LAPLACE -2LL NBURN=50 NITER=50 PRINT=1
```

The MCM Bayesian option was used for the final regression:

```
$EST METH=BAYES CTYPE=3 NITER=2000 NBURN=2000 PRINT=50
FILE=run1.bay
```

In the special case of δ=0, the GP model collapses to a PS. Since the likelihood functions for PS and GP are exactly the same the OFV of these models can be compared.

Models were compared by :

- Objective Function Value (OFV)
- ability to capture mean trends and observed variability using Visual Predictive Check (VPC) using the vpc tool from Perl-speaks-NONMEM
- precision of parameter estimates.

Results:

- The GP model was significantly better than the PS model as compared by the lower mean OFV (90382 vs. 73020) which is a >17,362 point drop (~12 points per individual).
- The mean trend was better captured with the GP model.
- The VPC (Figure 2 and 3) showed that the PS model under predicted the 5th and over predicted the 95th confidence interval, while the GP model captured them remarkably well.
- Parameter estimates $mict_{base}$ and k (rate of effect onset) were 41 and 46% more precise for the GP model. The parameter for placebo effect size was 25% less precise.

	Poisson			Generalized Poisson		
Parameter	Estimate	SE	CV (%)	Estimate	SE	CV (%)
lambda	11.7	0.0823	0.7	19.7	0.144	0.7
delta	0.0	--	--	-0.688	0.00823	1.2
$mict_{base}$	11.7	0.0823	0.7	11.54	0.0437	0.4
Eff	0.132	0.0054	4.1	0.119	0.00607	5.1
k (d^{-1})	0.0649	0.00529	8.2	0.0608	0.00292	4.8

Note: $mict_{base}$ was derived by λ/(1-δ)

Key References

[1] Consul PC. (1989) Generalized Poisson Distributions. Properties and Applications. Statistics: textbooks and monographs Vol 99. Marcel Dekker, Inc.

[2] Consul & Jain (1973). A Generalization of the Poisson distribution. Technometrics 15, 791-799

[3] Plan & Karlsson (2009). New models for handling correlated underdispersed Likert pain scores. PAGE 2009.

Conclusions

- The GP model was found to be superior to the PS model
- GP better described variability observed in micturition count data
- GP yielded more precise estimates but not for all parameters.
- As a result, the GP model is expected to provide more accurate inferences, such as drug efficacy predictions and clinical trial simulations.