

ptmixed: an R package for flexible modelling of overdispersed longitudinal counts



Mirko Signorelli¹
Twitter: @signormirko

Joint work with Roula Tsonaka¹ and Pietro Spitali²

¹ Department of Biomedical Data Sciences, Leiden University Medical Center

² Department of Human Genetics, Leiden University Medical Center

June 19, 2020
e-Rum2020



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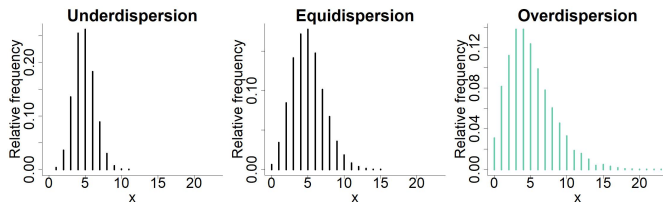
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Slides: github.com/m-signo/erum2020

Count data come in different shapes



- ▶ Count data typically classified as
 - ▶ Underdispersed: $Var(X) < E(X)$
 - ▶ Equidispersed: $Var(X) = E(X)$
 - ▶ **Overdispersed**: $Var(X) > E(X)$



- ▶ Most common models for overdispersed counts: **negative binomial (NB)** GLM and GLMM

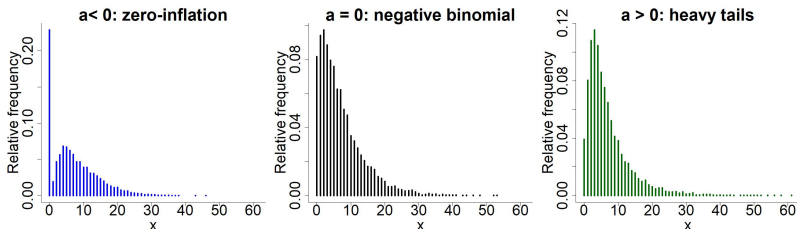
Poisson-Tweedie: fifty shades of overdispersion



- ▶ El-Shaarawy et al. (2011) showed that NB can't capture well different levels of **zero-inflation (ZI)** and **heavy-tails (HT)** commonly observed with overdispersed counts
- ▶ Alternative: use the **Poisson-Tweedie (PT)** distribution

$$Y \sim \text{PT}(\mu, D, a)$$

- ▶ Power $a \leq 1$ models extra **ZI** and **HT** for given dispersion D :



ptmixed: flexible modelling of longitudinal counts



Applicability of Poisson-Tweedie:

- ▶ cross-sectional data → PT GLM (Esnaola et al., 2013) ✓
- ▶ longitudinal data → no GLMM extension ✗

Our proposal: ptmixed

- ▶ We propose a **Poisson-Tweedie GLMM** to flexibly model **longitudinal counts** with different levels of **zero-inflation** and **heavy-tails**
- ▶ Implementation: R package **ptmixed** (published on CRAN)

Poisson-Tweedie GLMM

$$\begin{aligned} Y_{ij} \mid v_i &\sim \text{PT}(\mu_{ij}, D, a) \\ \log(\mu_{ij}) &= x_{ij}^T \beta + z_{ij}^T v_i \\ v_i &\stackrel{\text{i.i.d.}}{\sim} N(0, \Sigma) \end{aligned}$$

where $\beta \rightarrow$ fixed effects, $v_i \rightarrow$ random effects

How to estimate this model?

- ▶ Likelihood evaluation: approximation of PT pmf (Esnaola et al., 2013) + adaptive Gauss-Hermite quadrature
- ▶ Model estimation: maximum likelihood estimation

More details \rightarrow Signorelli et al. (2020, in press), [arXiv:2004.11193](#)

Data preparation



1) Load package and data

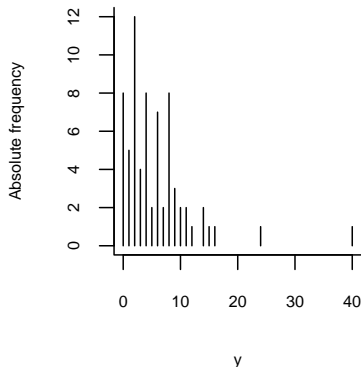
```
library(ptmixed)
head(data.long)
```

```
##      y id  group time
## 1  6  1 placebo    0
## 2  0  1 placebo    1
## 3  2  1 placebo    2
## 4  1  1 placebo    3
## 5  1  1 placebo    4
## 6 12  2 placebo    0
```

- ▶ $y \rightarrow$ response variable
- ▶ $id \rightarrow$ subject id ($1, \dots, n$)
- ▶ $group \rightarrow$ 2 groups (treated / placebo)
- ▶ $time \rightarrow$ 5 time points ($0 \rightarrow 4$)

2) Visualize distribution of the response

```
pmf(data.long$y)
```

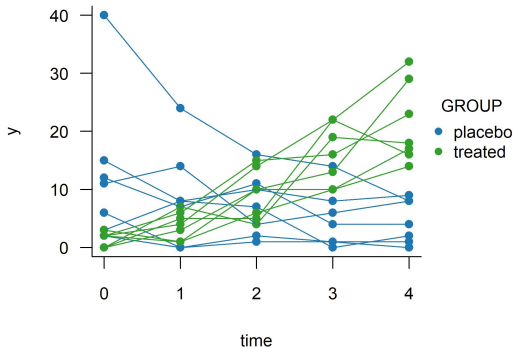


`make.spaghetti()`



3) Visualize longitudinal trajectories

```
make.spaghetti(x = time, y = y, id = id,  
               group = group, data = data.long)
```



make.spaghetti()



```
make.spaghetti(x, y, id, group, data)
```

... even easier than making spaghetti!



ptmixed(): estimate the Poisson-Tweedie GLMM!



4) Fit the Poisson-Tweedie GLMM

```
fit <- ptmixed(fixef.formula = y ~ group*time,  
              id = id, data = data.long)
```

The package also allows to estimate a few simpler models:

Function	Model
nbglm	Negative binomial GLM
nbmixed	Negative binomial GLMM
ptglm	Poisson-Tweedie GLM
ptmixed	Poisson-Tweedie GLMM

- 5) View estimated $\hat{\beta}$, \hat{D} , $\hat{\alpha}$, $\hat{\sigma}_0^2$, standard errors and univariate Wald tests

```
summary(fit)
```

```
## Loglikelihood: -140.539
## Parameter estimates:
##               Estimate Std. error      z p.value
## (Intercept)      2.0012     0.2888  6.9286  0.0000
## grouptreated     -1.4546     0.4677 -3.1102  0.0019
## time             -0.1360     0.0765 -1.7784  0.0753
## grouptreated:time  0.5115     0.1465  3.4908  0.0005
##
## Dispersion = 1.64
## Power = -0.14
## Variance = 0.42
```

6) Compute the best linear unbiased predictor of the random effects

```
ranef(fit)
```

```
##          1          2          3          4          5          6
## -0.7467  0.3204  1.1391 -1.1709  0.4988  0.4097
##          7          8          9         10         11         12
## -0.2220  0.3224 -0.3528 -0.0221  0.1815 -0.2705
##         13         14
## -0.1814  0.6586
```

7) Test more complex hypotheses, e.g. $H_0 : \beta_1 = \beta_3 = 0^1$:

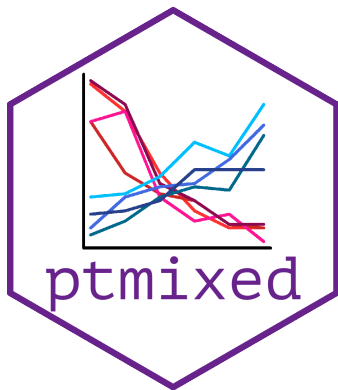
```
L = matrix(0, nrow = 2, ncol = 4)
L[1, 2] = L[2, 4] = 1
ptmixed::wald.test(fit, L = L, k = c(0, 0))
```

```
##          chi2 df          P
## 1 14.1051  2 0.0008651998
```

- Likelihood ratio test also possible, see sec. 2.4 of Signorelli et al. (2020)

¹NB: the hypothesis is coded in the form $L\beta = k$

Useful resources



More info about ptmixed here:

- 1) [arXiv:2004.11193](#) preprint of Signorelli et al. (2020, in press)
- 2) CRAN [package page](#)
- 3) [Vignette](#) of the R package:

```
browseVignettes("ptmixed")
```

El-Shaarawi, A. H., Zhu, R., & Joe, H. (2011). Modelling species abundance using the poisson–Tweedie family. *Environmetrics*, 22(2), 152–164.

Esnaola, M., Puig, P., Gonzalez, D., Castelo, R., & Gonzalez, J. R. (2013). A flexible count data model to fit the wide diversity of expression profiles arising from extensively replicated RNA-seq experiments. *BMC Bioinformatics*, 14(1), 254.

Signorelli, M., Spitali, P., & Tsonaka, R. (2020). Poisson-Tweedie mixed-effects model: a flexible approach for the analysis of longitudinal RNA-seq data. *To Appear in Statistical Modelling*.
<https://arxiv.org/abs/2004.11193>