Parameter estimations for various distributed data with observations below a lower limit of quantification

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Background

Pharmacokinetic and pharmacodynamic data could frequently exhibit observations below the lower limit of quantification (LLOQ). An adequate handling of data below the LLOQ is important for reducing bias in parameter estimates. For normally distributed data some methods to estimate the mean were suggested by Beal [1]. If data are non-normally distributed these approaches may cause additional bias. We propose new methods for estimating the mean of exponentially or Poisson distributed data and show the properties of the newly derived methods by evaluating the mean squared error (MSE) and bias (δ_i) in a simulation study.

Methods

In the case of N observations $y_1, \dots, y_N$ with $y_1, \dots, y_k < LLOQ := c$ (i.e. $N - k$ exact observations) with $c \in \mathbb{N}$ let F_λ be the underlying cumulative distribution function of a random value Y ($y_1, \dots, y_N \geq 0$ random realizations of Y).

Simulation Settings

For the simulation study the value of the LLOQ was set fix to $c = 4$. For each distribution type $B = 20000$ data sets were generated with sample sizes $N \in \{80, 1000\}$. To achieve different censored proportions (from $40\% - 90\%$) for a fixed LLOQ, the settings from Table 1 were generated.

Table 1: Settings of the simulation study

		Exp	Pois
		λ	λ
censored rate	~40%	0.13	4.15
	~50%	0.17	3.70
	~60%	0.23	3.20
	~70%	0.30	2.80
	~80%	0.40	2.30
	~90%	0.58	1.75

Evaluation criteria

In our simulation study we applied our maximum likelihood estimates to the data from the respective distribution and evaluated the results with regard to mean squared error and bias:

- mean squared error: $MSE := (\bar{\hat{\theta}} - \bar{\theta})^2 + \frac{1}{B-1}\sum_{i=1}^{B}(\hat{\theta}_i - \bar{\hat{\theta}})^2$,
- bias: $\delta_i := \theta_i - \hat{\theta}_i$, for $i = 1, \dots, B$,

where θ_i is the exact parameter of the distribution of the i-th dataset, $\hat{\theta}_i$ is the parameter estimation for the i-th dataset, $\bar{\hat{\theta}}$ is the mean of all estimated parameters from one method and B is the number of estimation replications.

Results

We derived maximum likelihood estimates for the truncated and censored sample methods under the exponential and Poisson distribution assumption [2].

Truncated sample methods

- For the **truncated sample methods (tru$_F$)** the following maximum likelihood estimations for the parameter mean are derived:

$$Y \sim \begin{cases} Exp(\lambda) & \Rightarrow \textbf{tru}_{Exp}\text{: } \hat{\mu} = \frac{1}{\hat{\lambda}} = \frac{1}{N-k}\left(\sum_{i=k+1}^{N} y_i\right) - c. \\ Pois(\lambda) & \Rightarrow \textbf{tru}_{Pois}\text{: } \hat{\lambda} \to \frac{-(N-k)\frac{\lambda^{c-1}}{(c-1)!}}{e^{\lambda} - \sum_{j=0}^{c-1}\frac{\lambda^j}{j!}} - (N-k) + \frac{1}{\lambda}\sum_{i=k+1}^{N} y_i = 0. \end{cases}$$

The equation for $Y \sim Pois(\lambda)$ was solved using the Newton-Raphson method.

Censored sample methods

- For the **censored sample methods (cen$_F$)** the following maximum likelihood estimations for the parameter mean are derived:

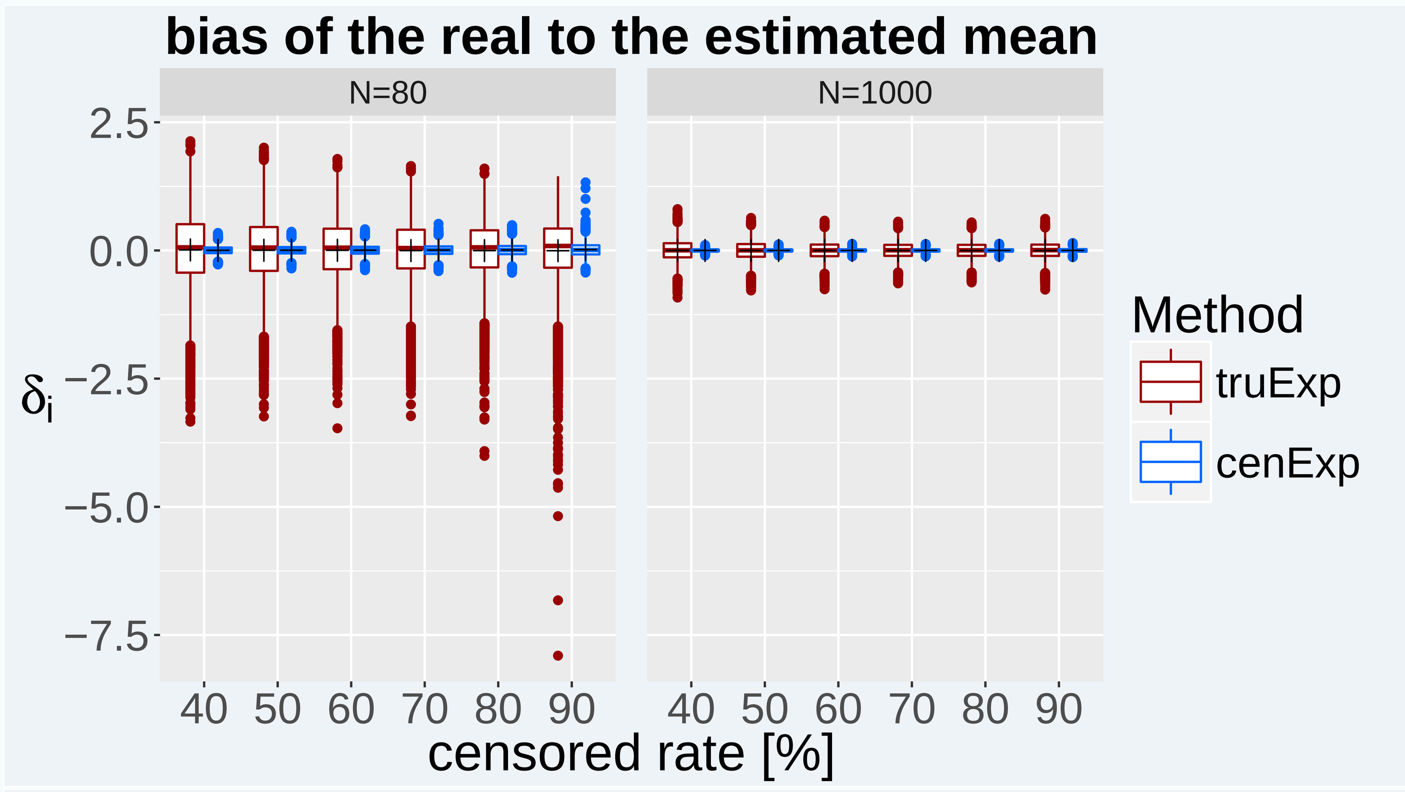
$$Y \sim \begin{cases} Exp(\lambda) & \Rightarrow \textbf{cen}_{Exp}\text{: } \hat{\mu} = \frac{1}{\hat{\lambda}} \to \frac{kc}{e^{\lambda c}-1} + \frac{N-k}{\lambda} - \sum_{i=k+1}^{N} y_i = 0. \\ Pois(\lambda) & \Rightarrow \textbf{cen}_{Pois}\text{: } \hat{\lambda} \to -N + k\frac{\sum_{j=0}^{c-1}\frac{\lambda^{j-1}j}{j!}}{\sum_{j=0}^{c-1}\frac{\lambda^j}{j!}} + \frac{1}{\lambda}\sum_{i=k+1}^{N} y_i = 0. \end{cases}$$

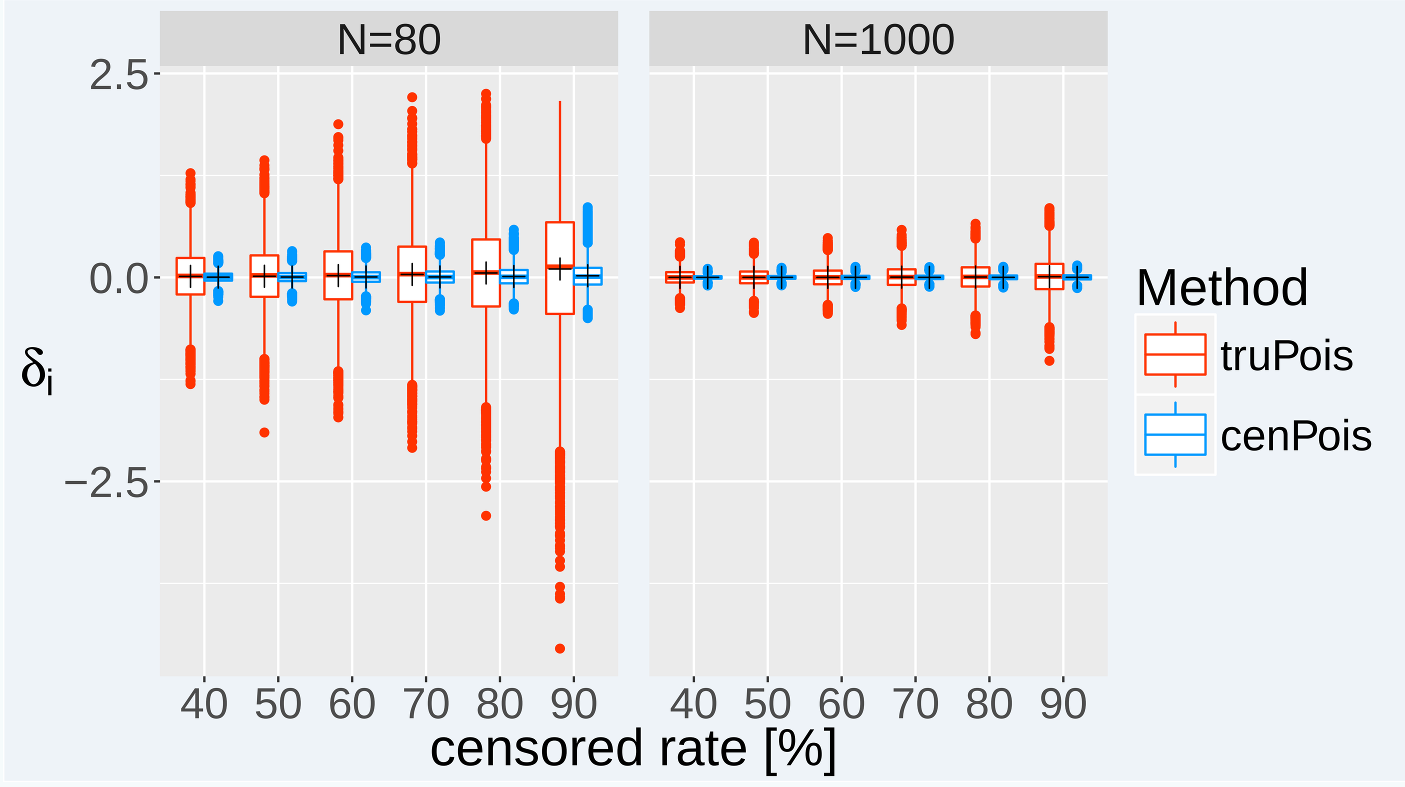
Both equations were solved using the Newton-Raphson method.

Evaluation of the Simulation Study

- For all investigated sample sizes and censored rates method cen$_F$ performed much better than method tru$_F$ regarding bias and MSE (the estimations varied less for method cen$_F$).
- With increasing sample size N the performance of all methods got more stable.
- With increasing censored rate the estimates got more unstable and worse with regard to bias and MSE.
- The averaged bias for the respective methods and distributions were all close to zero, except for method tru$_{Pois}$.

Simulation Study





The method tru$_{Exp}$ could not give estimates in all of the B repetitions for $N = 80$ and 90% censored data and tru$_{Pois}$ could not give estimates in all of the B repetitions for $N = 80$ and 80% and 90% censored data.

Conclusion

- We derived formulas for the maximum likelihood estimates of the distribution parameters if the data is exponentially or Poisson distributed.
- We evaluated the performance of the methods with respect to bias and mean squared error for the respective distribution.
- All methods performed quite well and with similar results as the truncated and censored sample methods under normal distribution from Beal [1] as it is shown by Senn [3].
- Outlook: In the next step we will evaluate the performance of our maximum likelihood estimates under distributional misspecification.

References

[1] Beal, S. L.: Ways to Fit a PK Model with Some Data Below the Quantification Limit. Journal of Pharmacokinetics and Pharmacodynamics, Vol. 28, No. 5, p.481-504, 2001.

[2] Berger, T.: Estimation Approaches for Distribution Parameters in the Case of Observations Under Multiple Lower Limits of Quantification. Master's thesis, Department of Medical Statistics, RWTH Aachen University, 2016.

[3] Senn, S.; Holford, N.; Hockey, H.: The ghosts of departed quantities: approaches to dealing with observations below the limit of quantification. Statistics in Medicine, 31(30), p.4280-4295, 2012.

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