

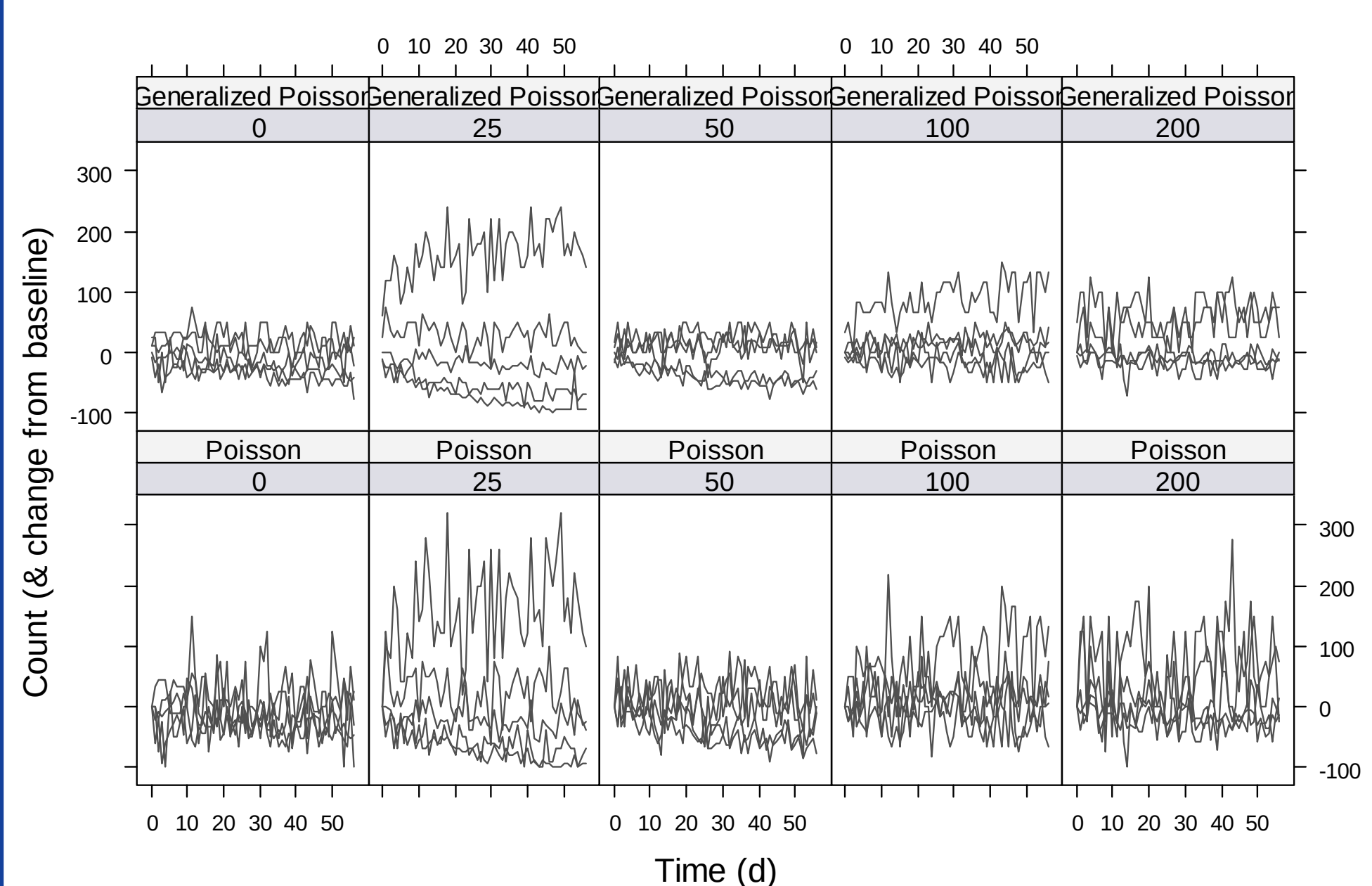
Introduction:

Traditionally, count data are modeled using the Poisson distribution that assumes mean and variance are the same. However, there are examples where variance is less (under dispersion) or more (over dispersion) than the mean count. A variety of distributions, including the Generalized Poisson (GP, [2]) are used to model the central tendency and data dispersion. Generally, the model fits improve substantially by estimating dispersion [1,3], and the Visual Predictive Checks look good instead of sloppy, the latter due to over estimating count variance. But it has not been reported yet if the model fit improvement also leads to increased power to detect a certain intrinsic effect. In the current simulation study using a case of under dispersion this will be investigated.

Objective:

To asses if modeling the true dispersion in under dispersed count data is associated with a different power to detect underlying central tendencies in the data.

Figure 1. Example simulated dataset



Simulated count data for a 5 subjects / arm trial,. The same seed was used for simulations for both distributions, making them easier comparable

The (Generalized) Poisson Distribution

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

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

Parameters in green are estimated

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

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

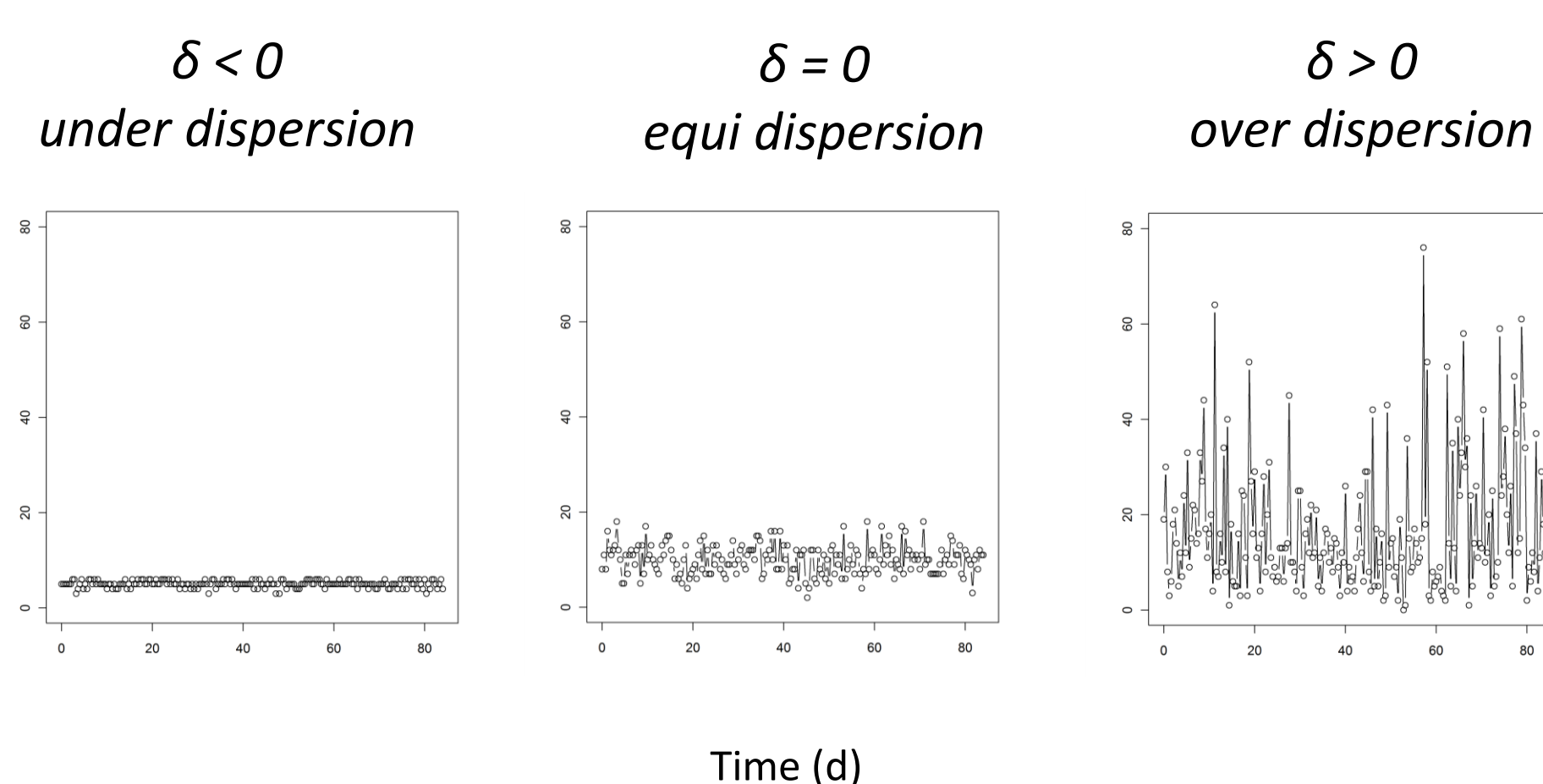
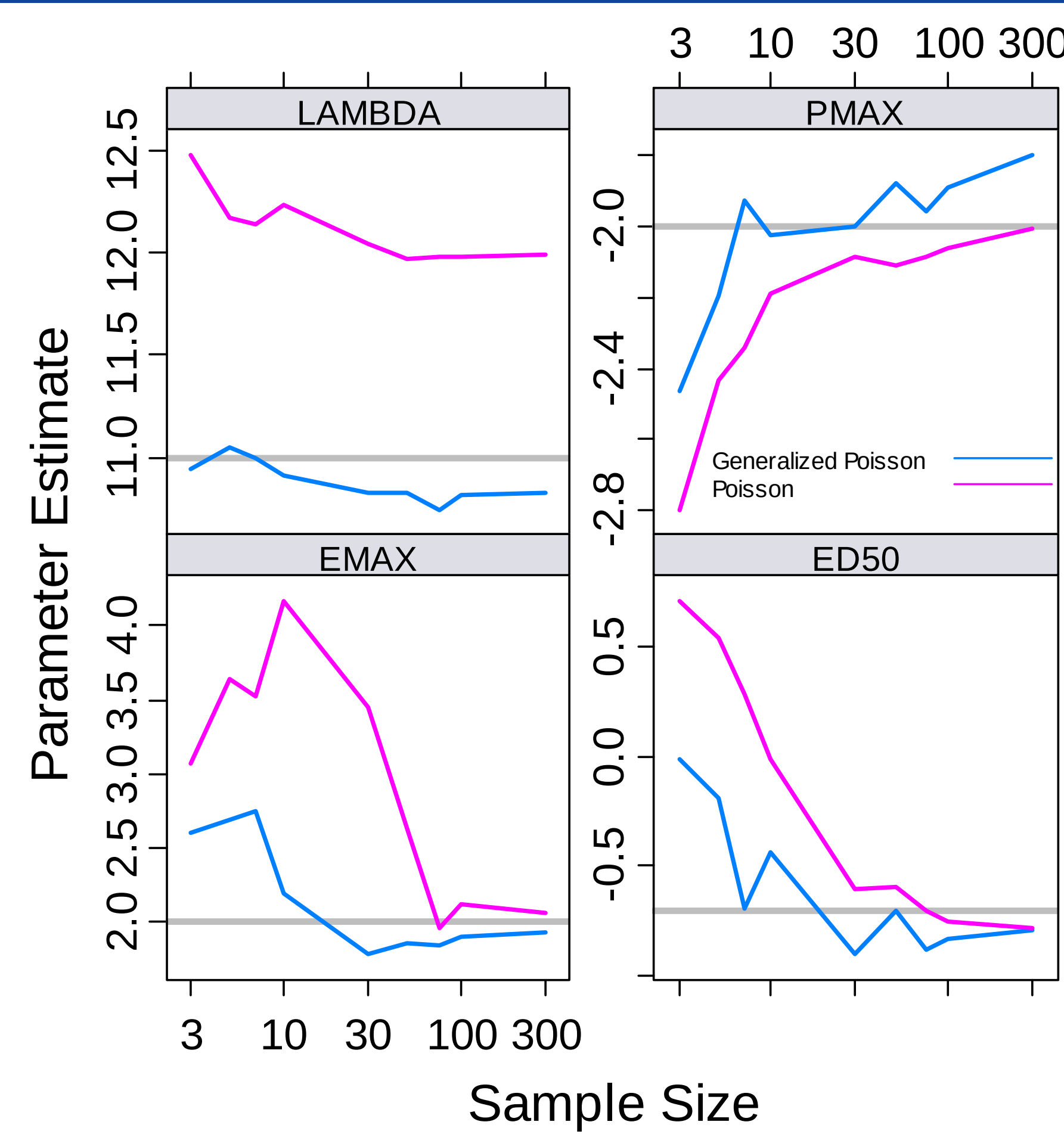


Figure 2. Mean Bayesian parameter estimates (true value as horizontal gray line)



Methods:

The true model was based on under dispersed daily micturition frequency. The placebo model included a mono-exponential decrease in base count (11 voids/d) reaching steady state effect after 8 weeks. The drug effect was modeled directly proportional to placebo effect via an Emax model (ED_{50} defined at 100 mg, and modeled as $\log_{10}[ED_{50}]$).

Using PsN's [4] stochastic simulation-estimation (sse), an under dispersed data set ($\lambda=22$, $\text{dispersion}=1$) was simulated using a datasets of varying treatment arm size ($n=3, 5, 7, 10, 30, 50, 75, 100$) including placebo, 25, 50, 100 and 200mg as treatments.

$$E = \text{base} \cdot (1 - \text{Eff} \cdot (1 - \exp(-\text{tslp} \cdot \text{time})))$$

$$\text{logit}(\text{Eff}) = P_{\text{max}}$$

$$\text{logit}(\text{Eff}) = P_{\text{max}} \cdot (1 + E_{\text{max}} \cdot \frac{\text{dose}}{\text{dose} + ED_{50}})$$

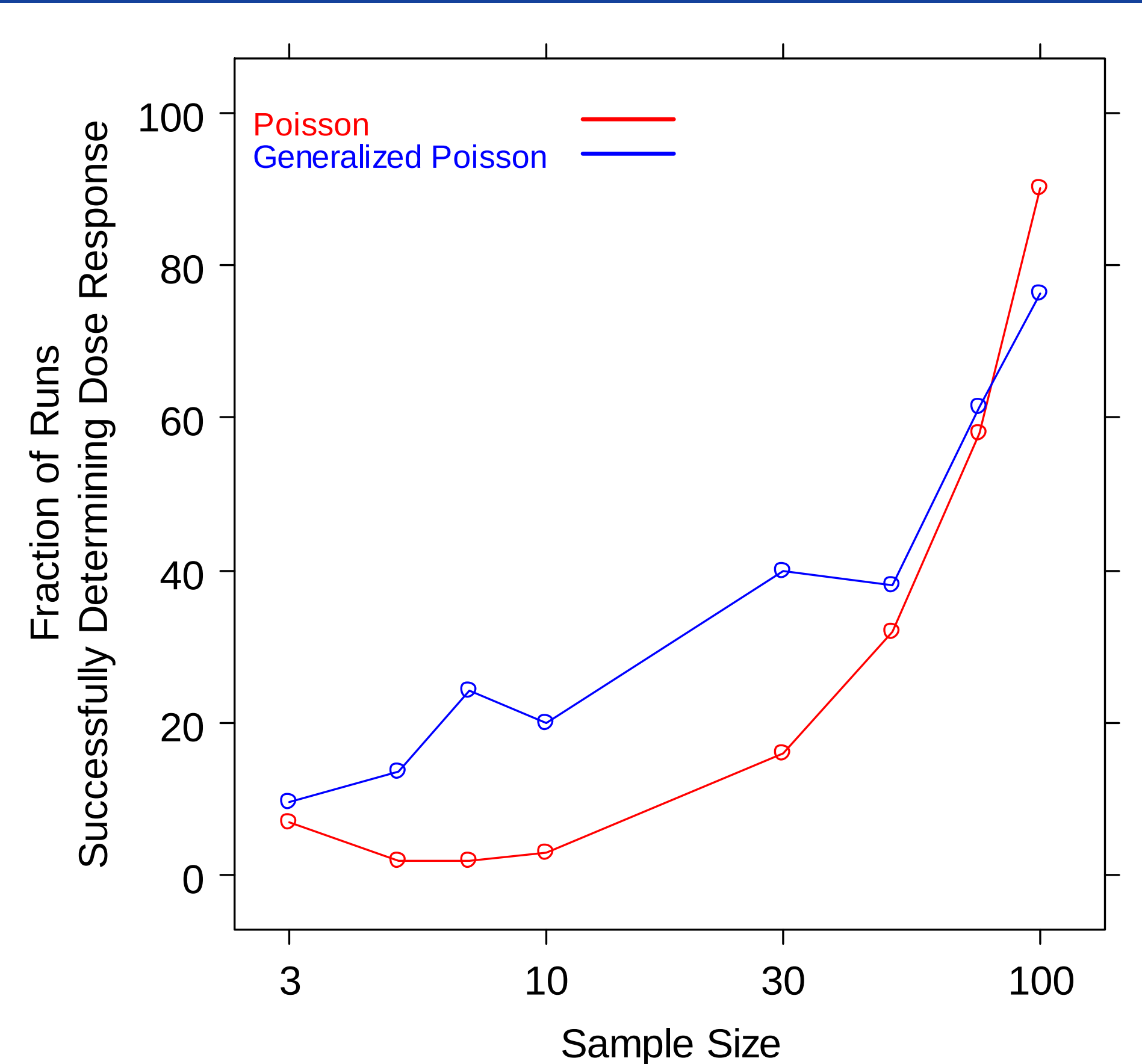
Placebo effect size was set to 11.9% inhibition of base count by setting $\log[P_{\text{max}}]$ to -2, $\log[E_{\text{max}}]$ was set at -0.7, which was associated with 35% inhibition change from baseline at infinite dose, resulting in a 2.5 point drop in count as compared to placebo. Non-correlated lognormal between-subject variability (38.7%) was placed on base (baseline count) and on E_{max} .

The model was re-estimated with a placebo (P_{max}) and a placebo + drug effect model (P_{max} , E_{max} and ED_{50}) and the proportion of placebo + drug effect models being statistically superior to their corresponding placebo model was used to define the power to detect a drug effect ($\alpha = 1\%$). Success was thus defined as the ability to achieve a significant drop in OFV by estimating E_{max} and ED_{50} in addition to P_{max} .

For each scenario, $M=100$ replicates were simulated / re-estimated.

This modeling procedure was performed under the GP (estimating dispersion) and the Poisson distribution (by fixing dispersion to zero, making the GP collapse to a Poisson) and the success rates were compared between the two distributions. For estimation MCMC BAYES method was used with settings $\text{CTYPE}=3$, $\text{NBURN}=2000$ and $\text{NITER}=1000$. The Bayesian engine in NONMEM was previously found to be suitable for generalized Poisson modeling, where FOCE-I failed.

Figure 3. Power to detect dose response signal as a function of sample size



Results:

- Up to 100 subjects per arm in this simulation exercise, the GP model had more power to recover the dose response relationship embedded in the data.
- From approximately 75 subjects per arm, the success rate was similar between the distributions. Apparently sufficient data were available to get this main trend, and ignoring data dispersion did not lead to lower performance to establish dose response.
- Parameters were closer to their true value at lower sample size for the GP model. The Poisson model always overestimated baseline.
- The jittery curvature of the simulated statistics vs. sample size indicate the replicate size ($M=100$) needs to be boosted substantially for stationary results.

Conclusions

- Acknowledging dispersion in models for under dispersed count data by using the GP distribution:
 - Increases the power to estimate central tendencies at relatively low sample size
 - improves ability to estimate the true parameter estimate
- At larger sample size the power to detect central tendencies and estimate parameters (except base lambda) converges to about the same for both Poisson and GP.
- Irrespective of sample size the Poisson model overestimates baseline count.

Key References

- [1] Plan (2014) Modeling and Simulation of Count Data. CPT-PSP
- [2] Consul & Jain (1973). A Generalization of the Poisson distribution. Technometrics 15, 791-799
- [3] Prins et al. (2011). Use of a generalized Poisson model to describe micturition frequency in patients with overactive bladder disease. PAGE-meeting 2011 Athens
- [4] Lindbom et al. (2005) PsN-Toolkit -- A collection of computer intensive statistical methods for non-linear mixed effect modeling. Comp Meth Prog Biomed.