UPPSALA UNIVERSITET

Maximum Likelihood estimation methods: performance in count response model's population parameters

Elodie Plan (1), Alan Maloney (1,2),

Iñaki F. Trocóniz (3), Mats O. Karlsson (1)

(1) Division of Pharmacokinetics and Drug Therapy, Department of Pharmaceutical Biosciences, Faculty of Pharmacy, Uppsala University, Uppsala, Sweden;

(2) Exprimo NV, Mechelen, Belgium;

(3) Department of Pharmacy and Pharmaceutical Technology, School of Pharmacy, University of Navarra, Pamplona, Spain.

University of Navarra

UPPSALA UNIVERSITET

- Background
- Aim
- Methodology
- Results
- Discussion
- Conclusion

Rationale

- Estimation methods properties:

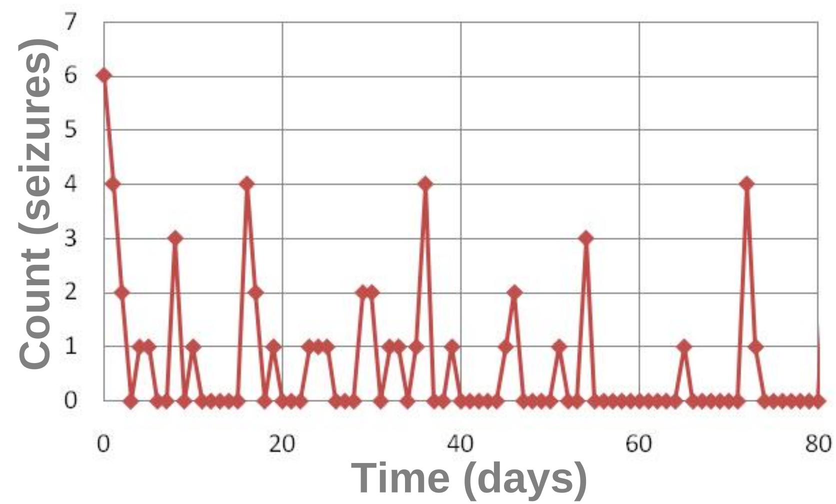
Be confident?

Be cautious?

Be aware!

Count response

- Count (PD) clinical outcomes
  - Discrete data
  - Integer positive values
  - Number of events within an observation time



- E.g. # of acid refluxes per min, # of emetic episodes per h, # of epilepsy seizures per day …

Count response modelling

➢ Background
➢ Aim
➢ Methodology
➢ Results
➢ Discussion
➢ Conclusion

- Count response probability
  - Calculation of the probability of an observation
  - Non linear mixed effects approach

$$\Phi_{ij} = h(\Psi, Z_{ij}).\exp(\eta_i); \quad \eta_i \sim N(0,\Omega); \quad \Phi_i > 0$$

  - Contribution to the likelihood of the prediction

$$\boxed{L(\psi,\Omega) = \prod_{i=1}^{N} L_i(\psi,\Omega \mid y_i)}$$

Wang Y. Derivation of various NONMEM estimation methods. *Journal of Pharmacokinetics and pharmacodynamics*. 34:575-93 (2007)

UPPSALA UNIVERSITET

- ➢ *Background*
- ➢ *Aim*
- ➢ *Methodology*
- ➢ *Results*
- ➢ *Discussion*
- ➢ *Conclusion*

Background

Maximum likelihood estimation

- Individual likelihood function

$$\boxed{P(y_i \mid \Psi,\Omega) = L_i(\psi,\Omega \mid y_i) = \int P(y_i \mid \eta_i,\Psi).P(\eta_i \mid \Omega).d\eta_i}$$

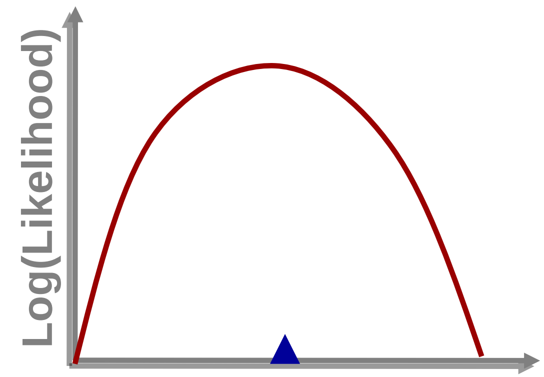
- No High nonlinearity in random effects with count models

➔ No closed-form expression for analytical solution
➔ Approximation of the marginal likelihood integral
➔ Methods other than model linearization based

Beal SL, Sheiner LB. *NONMEM Users Guides (I–VIII).* NONMEM Project Group, San Francisco.(1989–98)

Maximum likelihood approximation

- Methods approximating the logarithm of the integrand
  - Laplacian approximation
    - ✓ Second order Taylor expansion



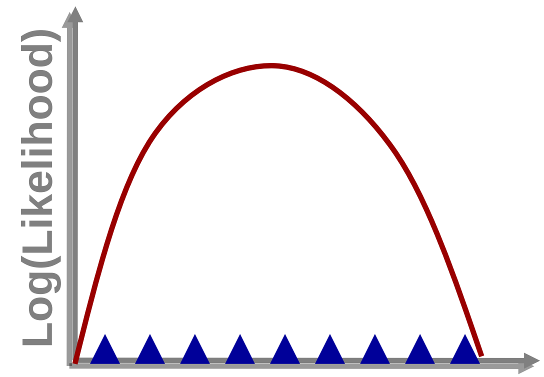
Pinheiro JC, Bates DM. Approximations to the log-likelihood function in nonlinear mixed-effects models. *Journal of Computational and Graphical Statistics.* 4:12-35 (1995)

UPPSALA UNIVERSITET

- ➢ Background
- ➢ Aim
- ➢ Methodology
- ➢ Results
- ➢ Discussion
- ➢ Conclusion

Maximum likelihood approximation

- Methods approximating the logarithm of the integrand



  - Laplacian approximation
    - ✓ Second order Taylor expansion
  - Gaussian quadrature
    - ✓ Numerical weighted approximation

1 quadrature point Gaussian = Laplacian approximation

Pinheiro JC, Bates DM. Approximations to the log-likelihood function in nonlinear mixed-effects models. *Journal of Computational and Graphical Statistics.* 4:12-35 (1995)

UPPSALA UNIVERSITET

- Background
- Aim
- Methodology
- Results
- Discussion
- Conclusion

- *Objective of the study*

To explore the accuracy and the precision of estimation methods for population parameters of different probability distribution models

UPPSALA UNIVERSITET

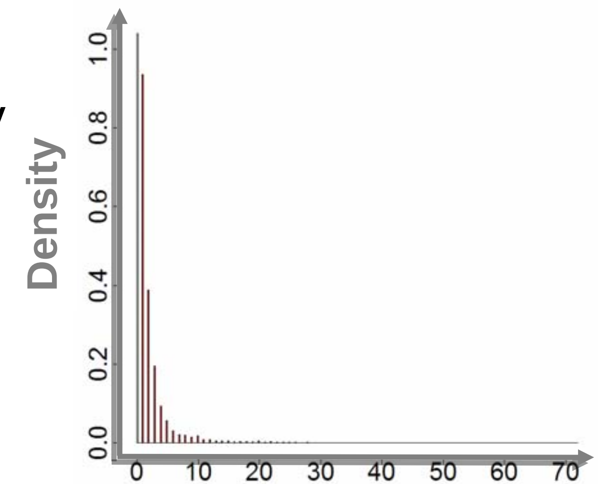
Simulations and estimations

- Monte Carlo study:
  - 100 **S**tochastic **S**imulations followed by re-**E**stimations with studied methods
- Statistical computations
  - ✓ Relative estimation error (RER)

$$RER(\%) = \left(\frac{Est - True}{True} \right) \times 100$$

Methodology
Simulations settings

- Study design based on a real case trial
  - ✓ 551 epileptic patients
    - ➔ record daily seizure activity
  - ✓ 12 weeks screening phase
    - ➔ 84 obs. each on average



- Parameters based on fit to the observed data
  - Estimation with studied models
  - Final estimates used to simulate

Trocóniz IF, Plan EL, Miller R, Karlsson MO. Modelling Overdispersion and Markovian Features in Count Data. *American Conference on Pharmacometrics, Tucson, Arizona*. (2008)

Estimation methods

- In NONMEM VI
  - LAPLACE

```
$PRED
...
Y = -2 * LOG(PROB)
$ESTIMATION MAXEVAL=9999 METHOD=COND LAPLACE -2LL
```

- In SAS Software (procedure NLMIXED)
  - LAPLACE + Gaussian Quadrature (GQ)

```
proc nlmixed data = dat qpoints=1 tech = quanew;
...
LL = log(prob);
model dv ~ general(LL);
...
run;
```

Probability distribution models

- 6 count models

  - Poison (PS)
  - Poisson with Markovian features (PMAK)
  - Poisson with a mixture distribution for individual observations (PMIX)
  - Zero Inflated Poisson (ZIP)
  - Generalized Poisson (GP)
  - Inverse (Negative) Binomial (INB)

Del Castilloa J, Pérez-Casany M. Overdispersed and underdispersed Poisson generalizations. *Journal of Statistical Planning and Inference*. 134,2:486-500 (2005)

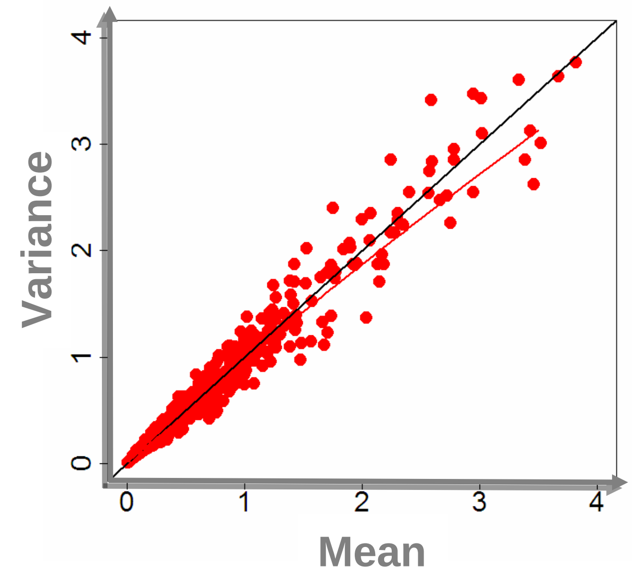
Probability distribution models

- Assumption of independence

  Of event from previous

- Assumption of equidispersion

  Variance (counts) = mean (counts)



- Poisson (PS)
  - ✓ 1 Φ: λ [individual mean of counts]

Methodology

Probability distribution models

- Violation of independence

  Event conditional on previous

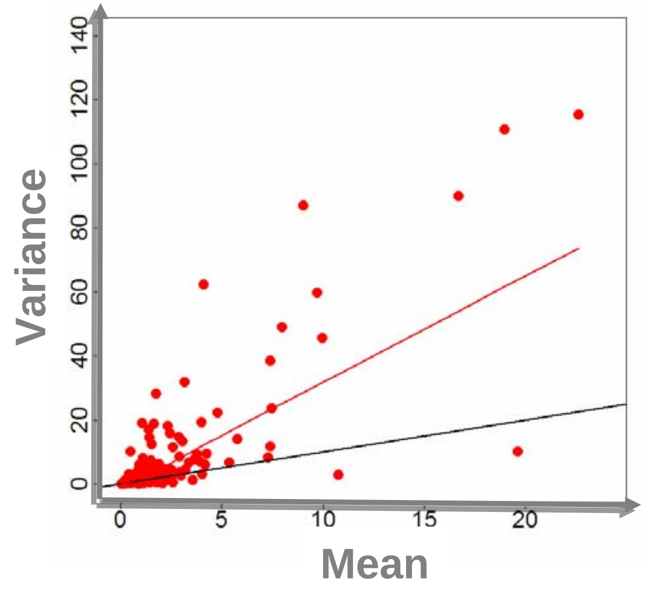
- Assumption of equidispersion

  Variance (counts) = mean (counts)

- Poisson with Markovian features (PMAK)
  - ✓ 2 Φ : λ_1 and λ_2 depending on previous day

Probability distribution models

- Violation of equidispersion
  Variance (counts) ≠ mean (counts)
- Assumption of independence
  Of event from previous



- Poisson with a mixture distribution for individual observations (PMIX)
  - ✓ 3 Φ : λ_1, λ_2 and MP [mixture probability]

Probability distribution models

- Background
- Aim
- Methodology
- Results
- Discussion
- Conclusion

- Violation of equidispersion
  - Zero Inflated Poisson (ZIP)

    When excess of zeros

    ✓ 2 Φ : λ and P_0 [probability of 0 count]
  - Generalized Poisson (GP)

    When heterodispersion

    ✓ 2 Φ : λ and δ [dispersion parameter in [max(-1, -λ/4),1]]
  - Negative (Inverse) Binomial (NB)

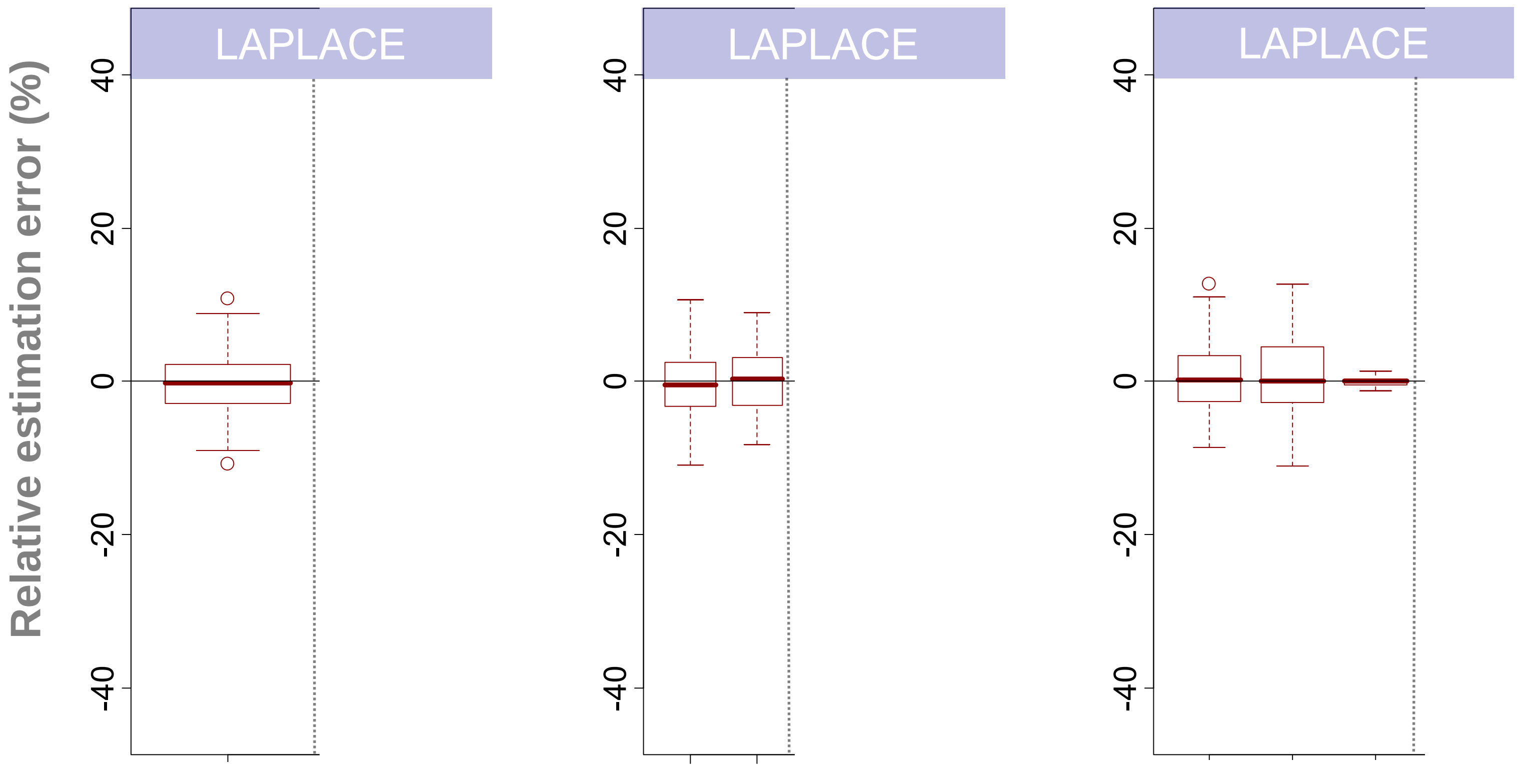
    When overdispersion

    ✓ 2 Φ : λ and OVDP [degree of overdispersion]

Results
Fixed effects

- Background
- Aim
- Methodology
- **Results**
- Discussion
- Conclusion

PS model | **PMAK model** | **PMIX model**

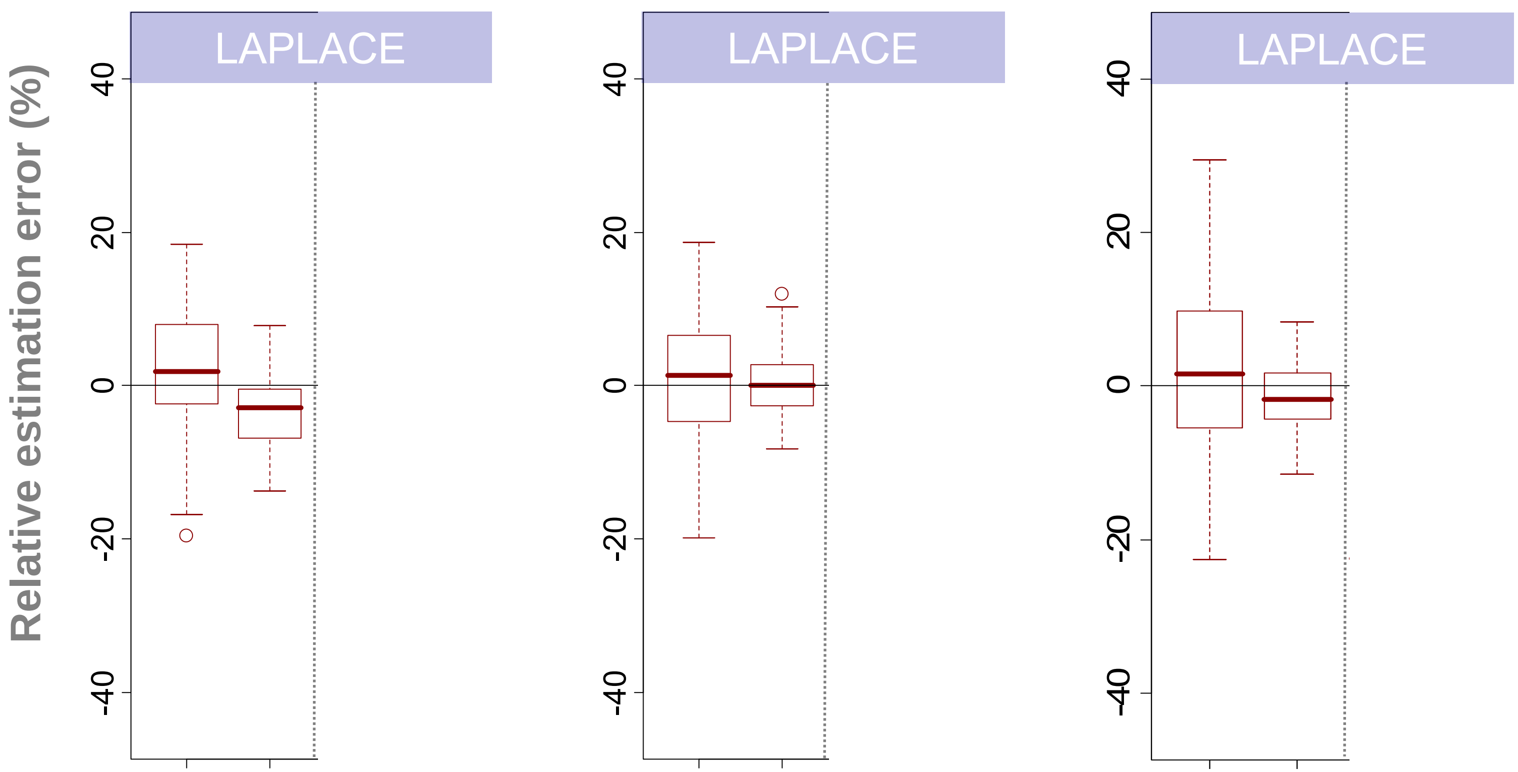


	PS model	PMAK model		PMIX model		
	λ	λ_1	λ_2	λ_1	λ_2	MP
R. Bias	-0.2 %	-0.3 %	0.3 %	0.4 %	0.8 %	-0.008 %

Results

Fixed effects

ZIP model	GP model	NB model

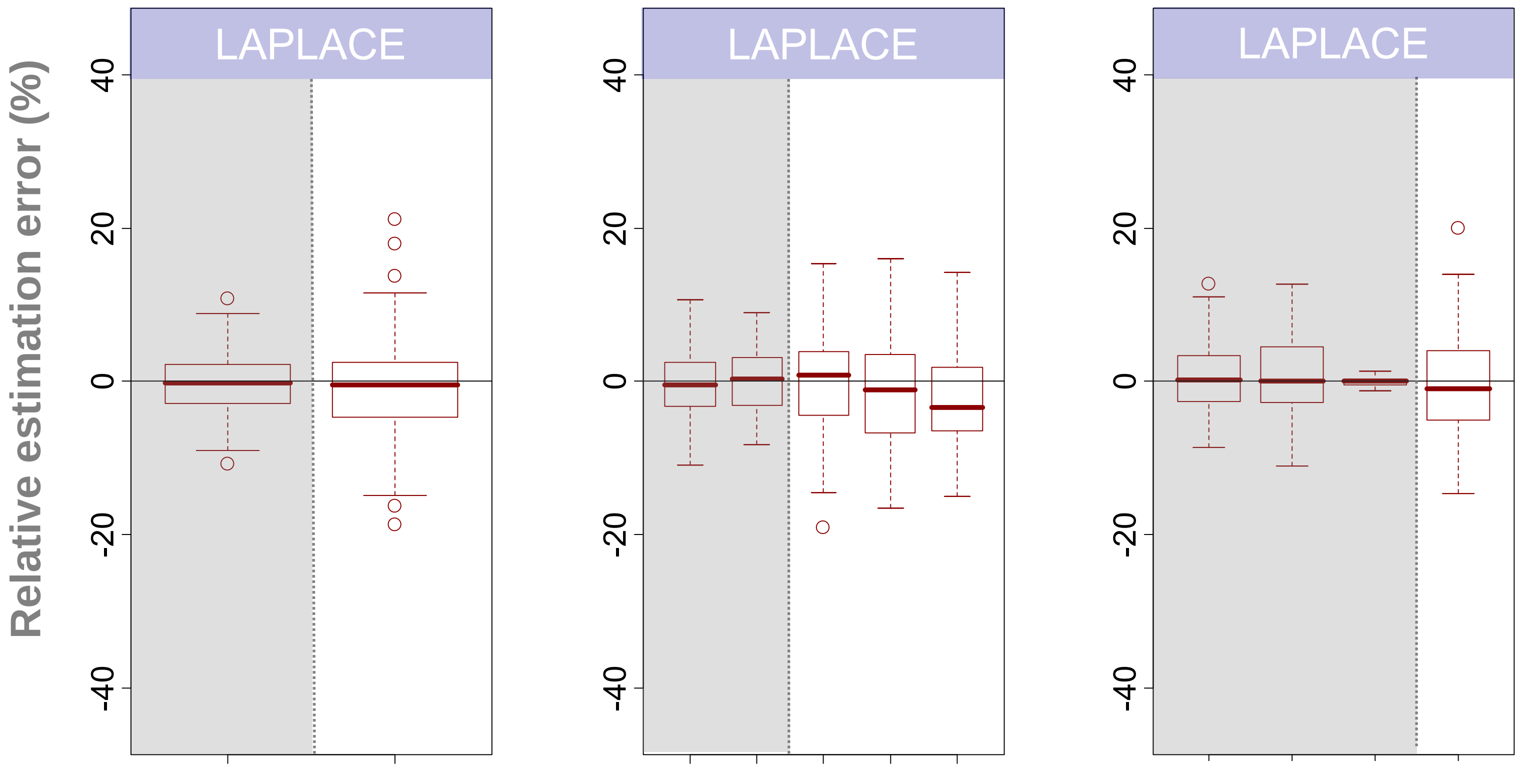


	ZIP model		GP model		NB model	
	P0	**λ**	**δ**	**λ**	**OVDP**	**λ**
R. Bias	**2.3 %**	**-3.4 %**	**0.7 %**	**0.1 %**	**1.8 %**	**-1.7 %**

Fixed and random effects

UPPSALA UNIVERSITET

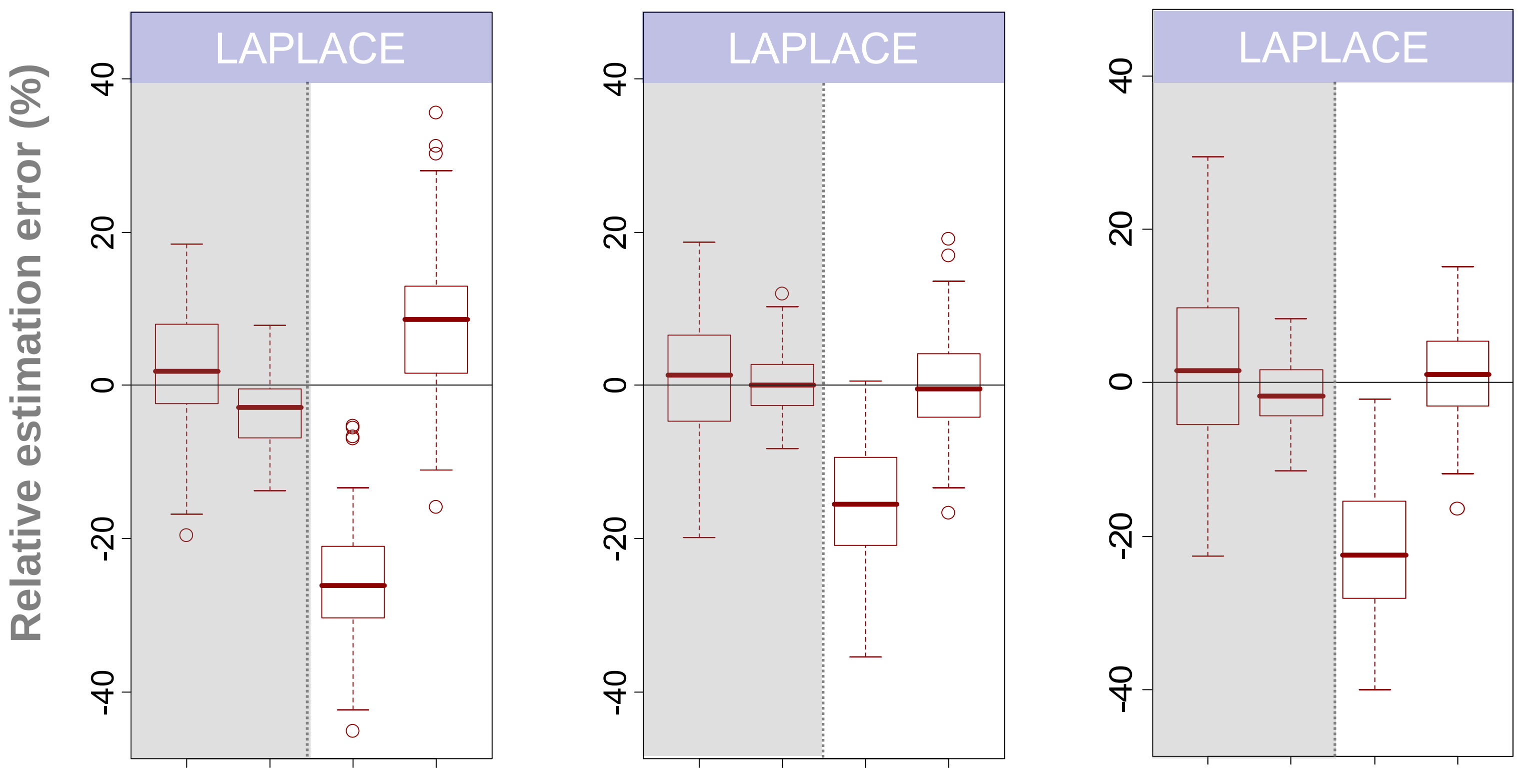
PS model | PMAK model | PMIX model



	PS model		PMAK model					PMIX model			
	λ	ω	λ_1	λ_2	ω_1	ω_2	ω_3	λ_1	λ_2	MP	ω
R. Bias		-0.7 %			-0.3 %	-1.5 %	-2.1 %				-0.3 %

Fixed and random effects

ZIP model | **GP model** | **NB model**

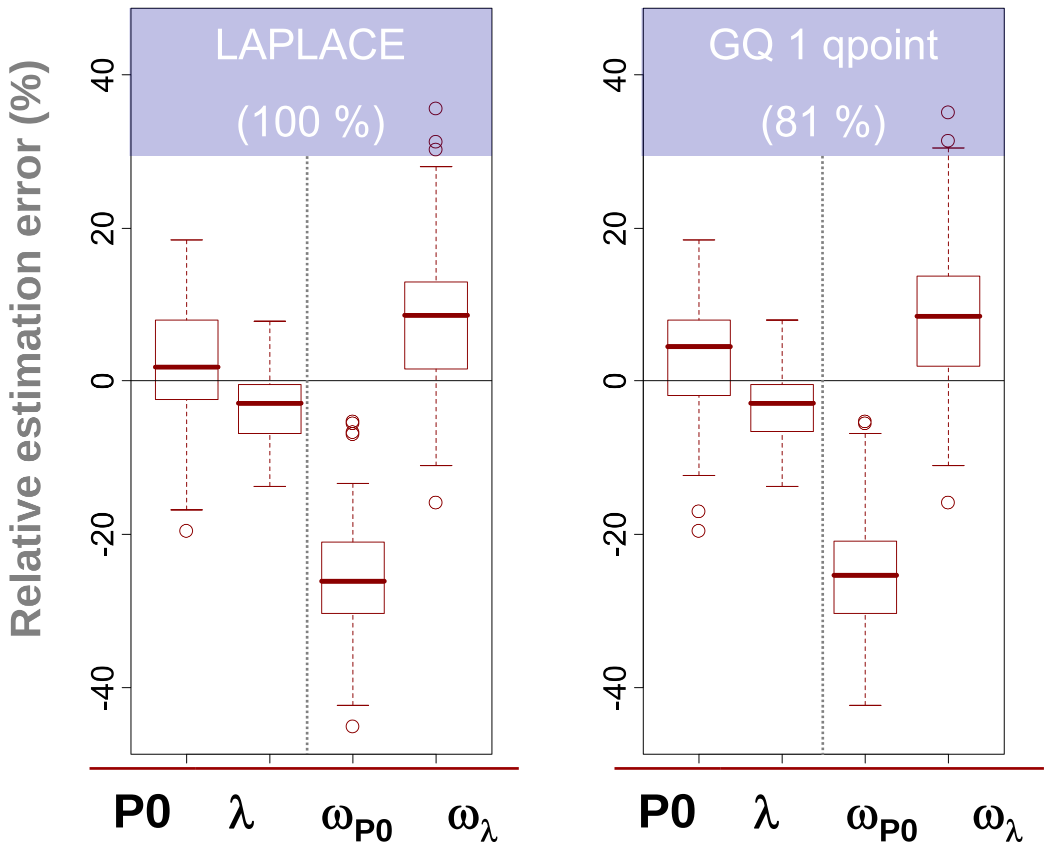


R. Bias	$P0$	λ	ω_{P0}	ω_{λ}	δ	λ	ω_{δ}	ω_{λ}	$OVDP$	λ	ω_{OVDP}	ω_{λ}
			-25.9 %	8.2 %			-15.7 %	0.1 %			-21.9 %	1.1 %

Zero-inflation parameter

- Background
- Aim
- Methodology
- **Results**
- Discussion
- Conclusion

ZIP model

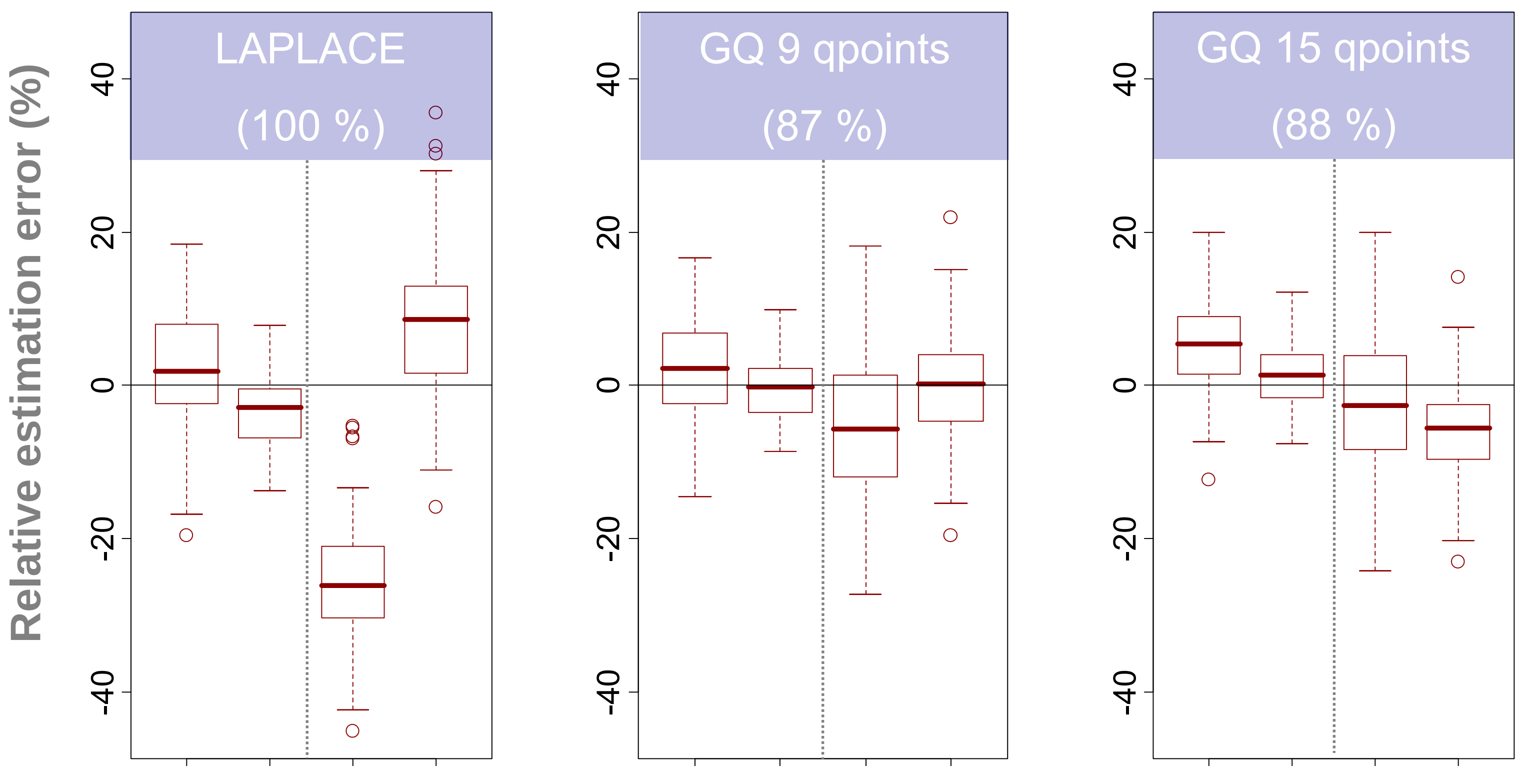


UPPSALA UNIVERSITET

Results

Zero-inflation parameter

ZIP model

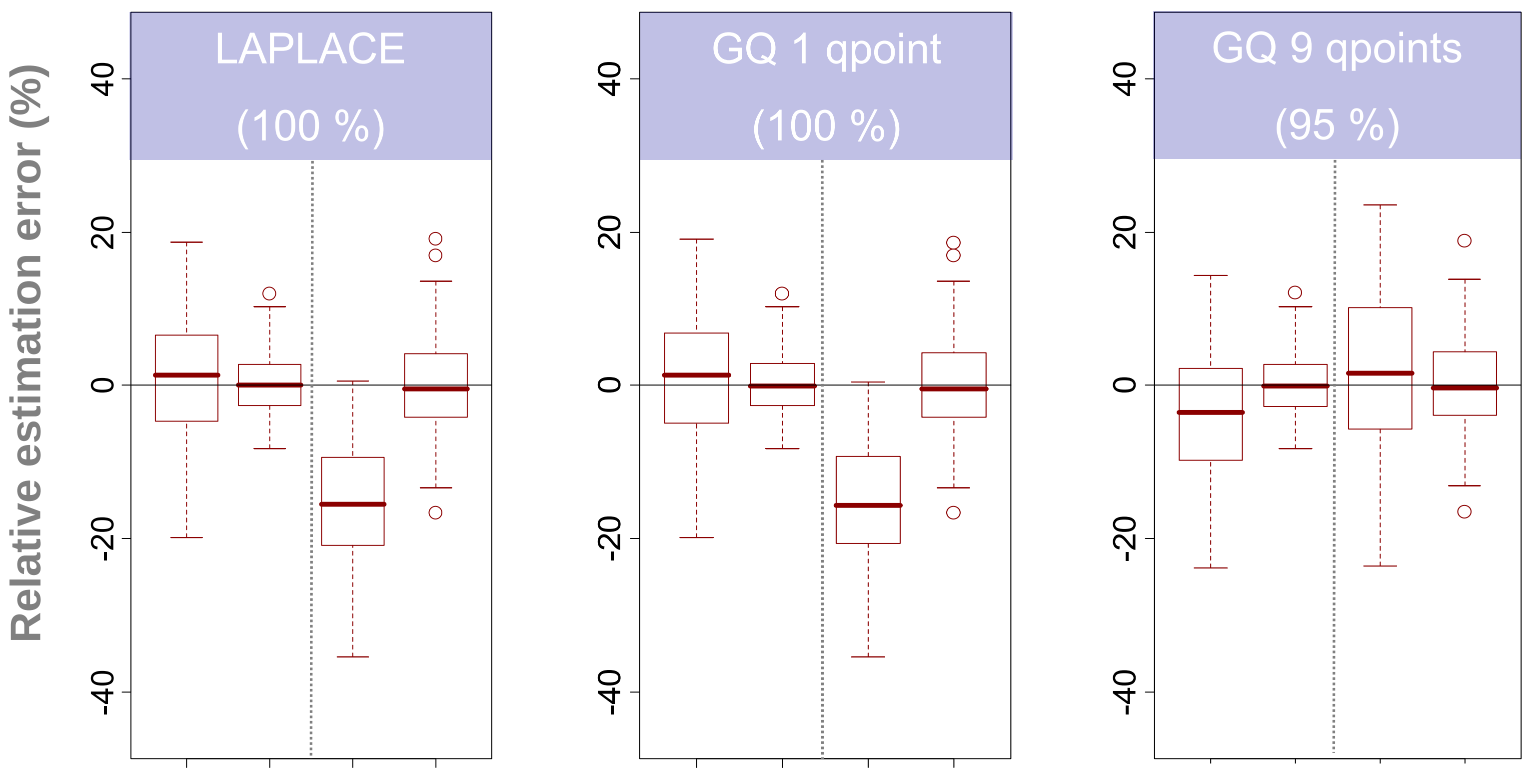


R. Bias	$P0$	λ	ω_{P0}	ω_{λ}
LAPLACE	2.3 %		-25.9 %	
GQ 9 qpoints	2.2 %		-5.5 %	
GQ 15 qpoints	5.2 %		-1.8 %	

- Background
- Aim
- Methodology
- **Results**
- Discussion
- Conclusion

Heterodispersion parameter

GP model



R. Bias

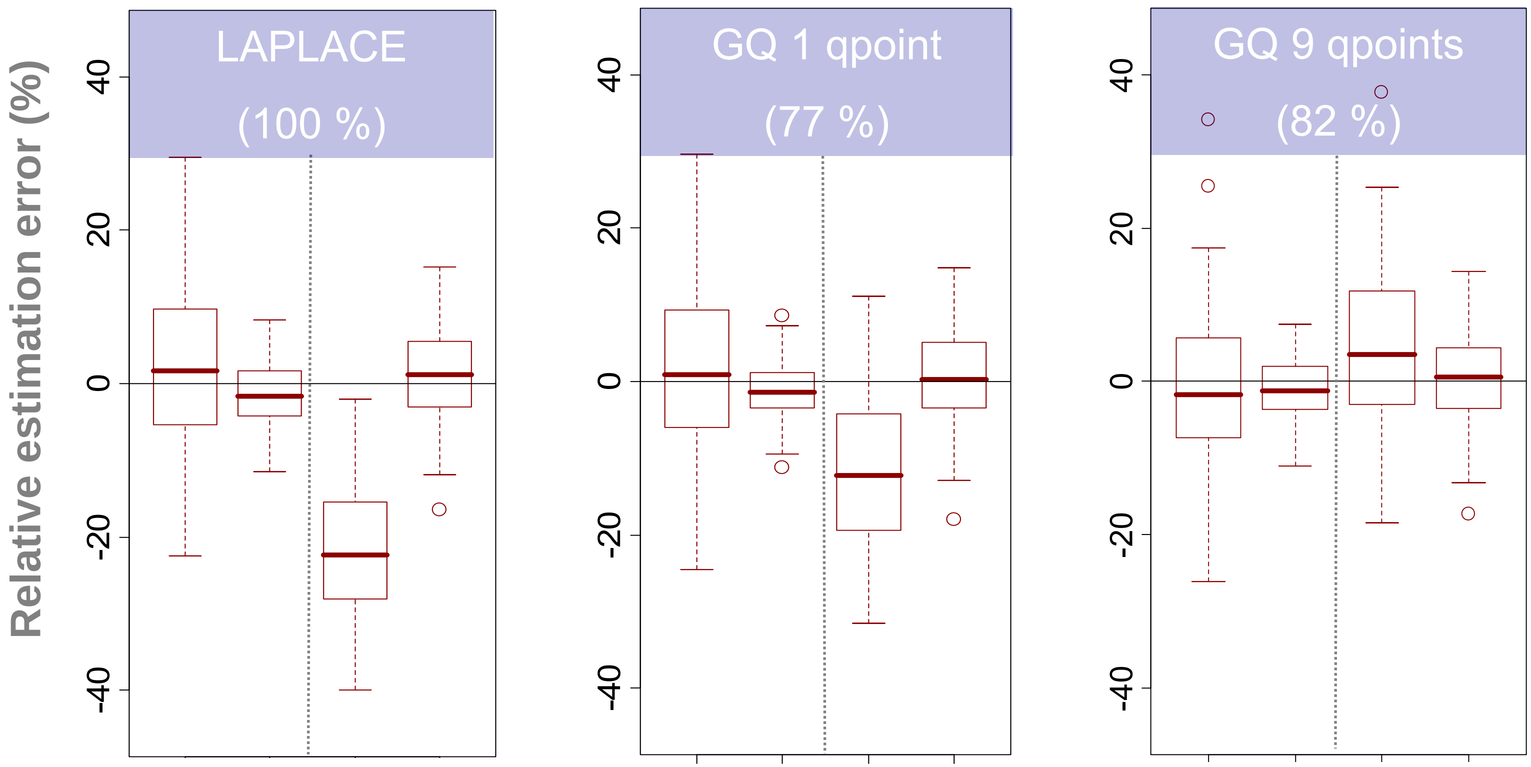
	δ	λ	ω_δ	ω_λ
LAPLACE	0.7 %		-15.7 %	
GQ 1 qpoint	0.7 %		-15.7 %	
GQ 9 qpoints	-4.1 %		1.7 %	

UPPSALA UNIVERSITET

- Background
- Aim
- Methodology
- **Results**
- Discussion
- Conclusion

Overdispersion parameter

NB model



	LAPLACE OVDP	LAPLACE λ	LAPLACE ω_{OVDP}	LAPLACE ω_{λ}	GQ 1 OVDP	GQ 1 λ	GQ 1 ω_{OVDP}	GQ 1 ω_{λ}	GQ 9 OVDP	GQ 9 λ	GQ 9 ω_{OVDP}	GQ 9 ω_{λ}
R. Bias	**1.8 %**		**-21.9 %**		**0.4 %**		**-10.3 %**		**-0.9 %**		**4.2 %**	

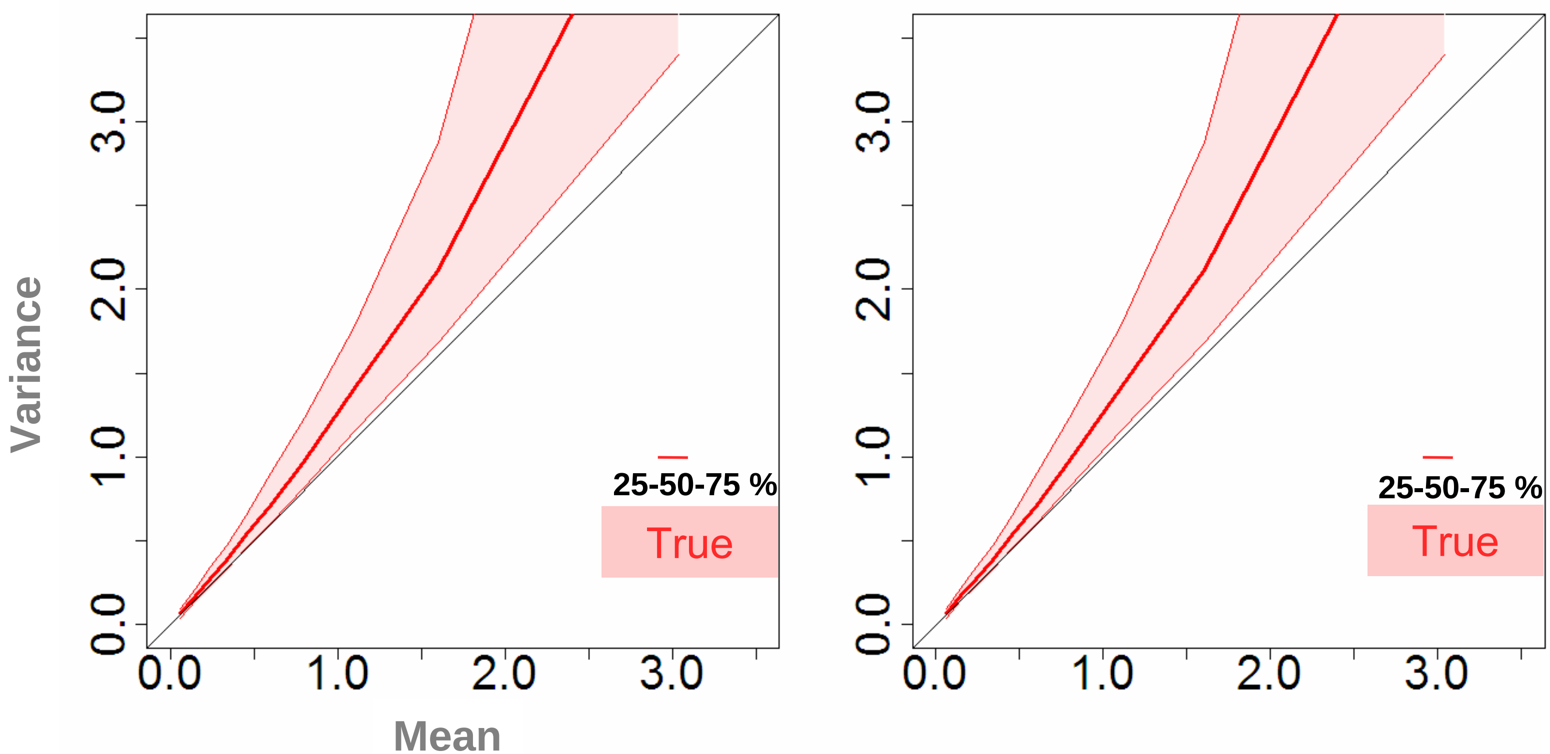
UPPSALA UNIVERSITET

- Background
- Aim
- Methodology
- **Results**
- Discussion
- Conclusion

Zero-inflation parameter

ZIP model

- Visual Predictive Check



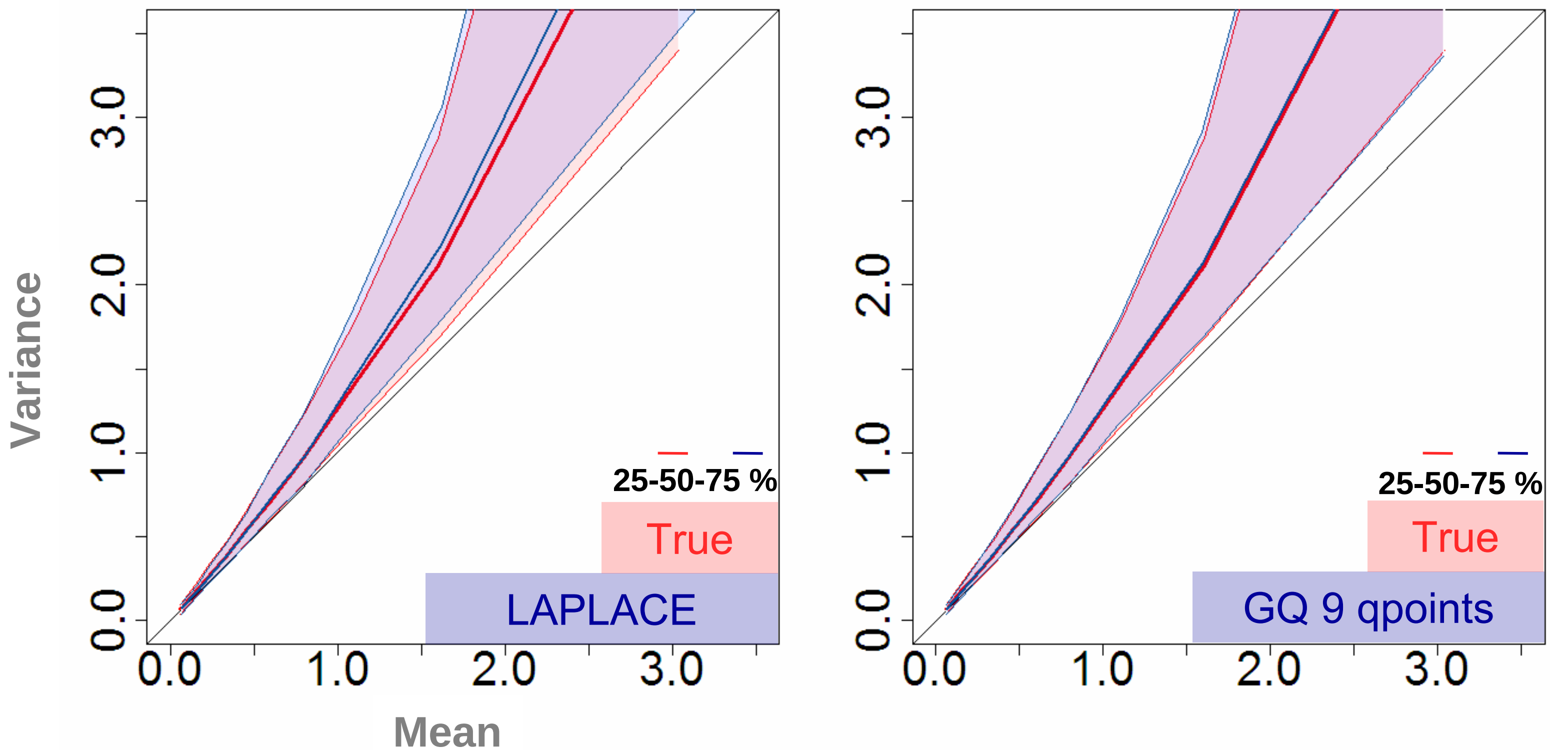
UPPSALA UNIVERSITET

Results

Zero-inflation parameter

ZIP model

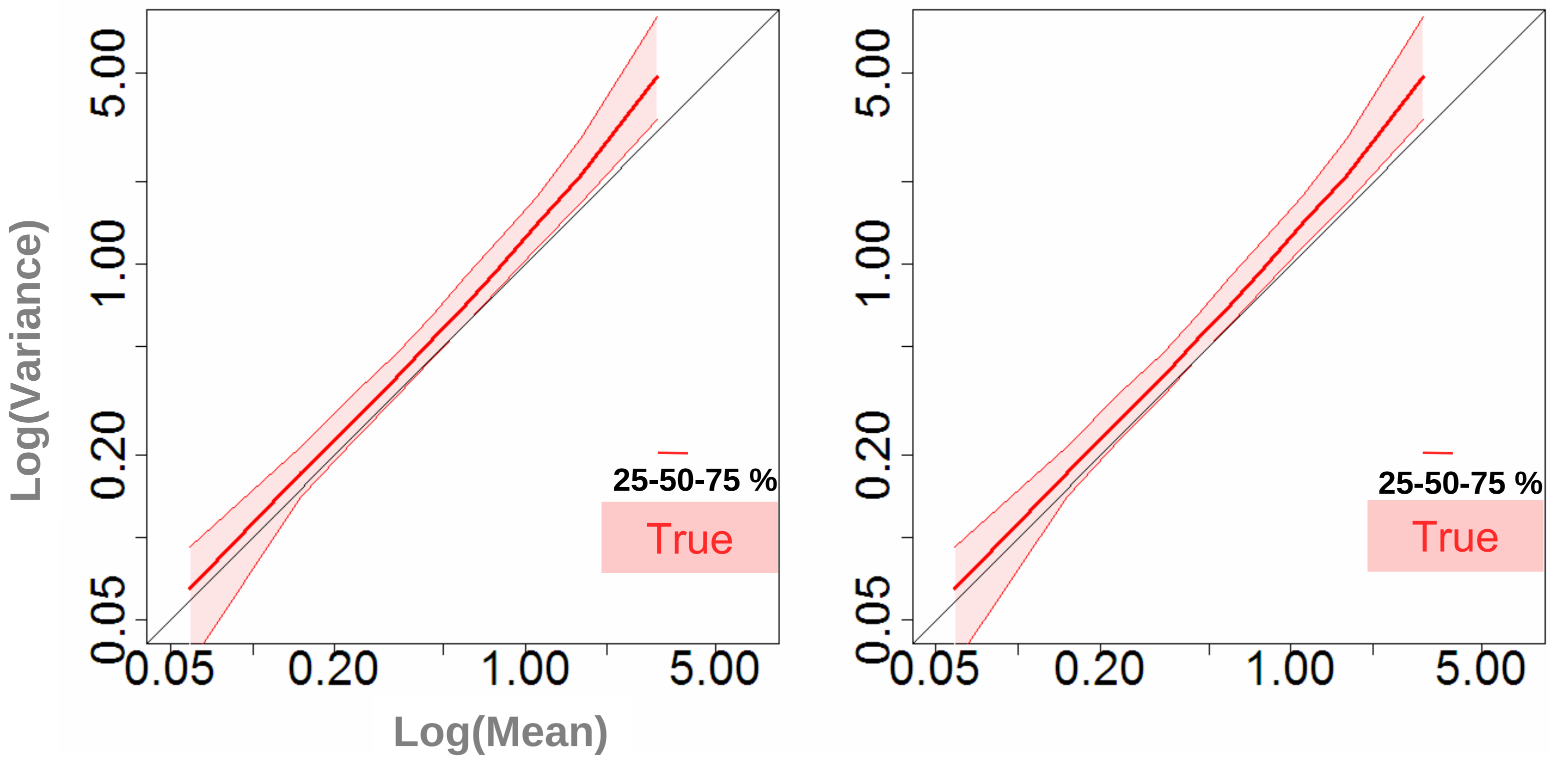
- Visual Predictive Check



Zero-inflation parameter

ZIP model

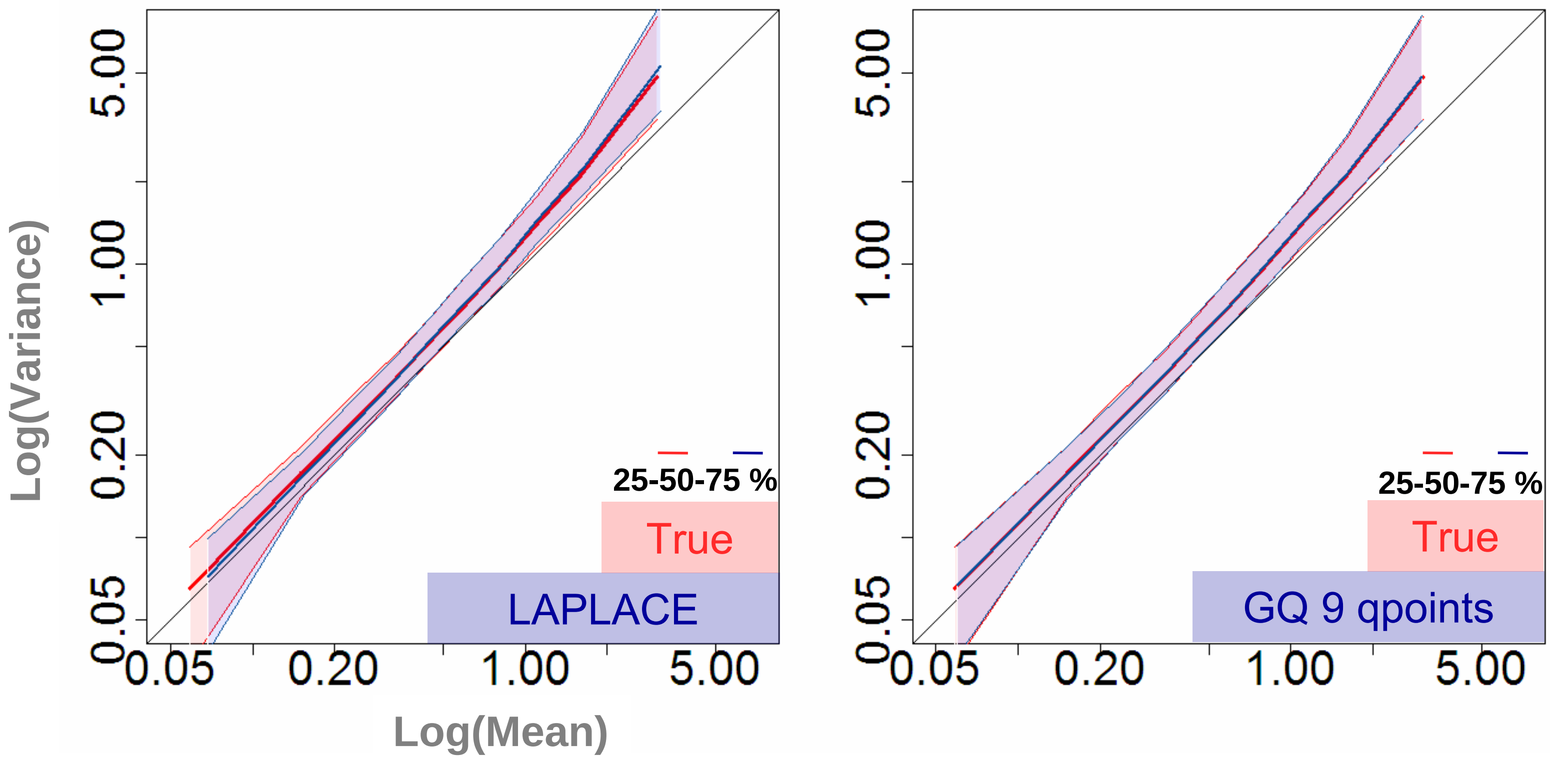
- Visual Predictive Check log-scale



Zero-inflation parameter

ZIP model

- Visual Predictive Check log-scale



UPPSALA UNIVERSITET

Discussion

- Investigation of an interesting range of models for count data

	Estimation properties	Drawback	Remark
LAPLACE	Good performance	Biased dispersion variability	Marginal consequence

UPPSALA UNIVERSITET

- Background
- Aim
- Methodology
- Results
- Discussion
- Conclusion

Discussion

- Investigation of an interesting range of models for count data

	Estimation properties	Drawback	Remark
LAPLACE	Good performance	Biased dispersion variability	Marginal consequence
GQ 9 qpoints	Better accuracy and precision	Longer run times	Lower stability if no “tweaking”

Conclusion

- Take home message

> Check estimation properties of LAPLACE
>
> for your model by performing SSE

UPPSALA
UNIVERSITET

Acknowledgments:

UCB Pharma

PAGE