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Modelling Techniques Handling Dynamic Pain Scores Characteristics

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Lewis Sheiner[1,2]

CLINICAL TRIALS AND THERAPEUTICS

A new approach to the analysis of analgesic drug trials, illustrated with bromfenac data

A clinical trial of an analgesic agent compares pain relief scores (ordered categorical responses) over time among groups of patients, each subject to a painful procedure and given various doses of active agent (including zero, i.e., placebo) on demand. Patients may elect to remedicate with an active agent if their pain relief is insufficient, so the sample of patients at any given time is biased toward those with better relief. Standard analyses usually (1) fill in the missing data but make no correction for so doing and (2) treat the ordered categorical variable as continuous. Both of these create problems in interpretation and inference, but the former is more serious than the latter. An alternative analysis has been recently proposed that deals with these problems. This article presents that method for a nonstatistical audience and illustrates its use on some data from the analgesic bromfenac. (Clin Pharmacol Ther 1994;56:309-22.)

Lewis B. Sheiner, MD *San Francisco, Calif.*

[1] Sheiner LB, CPT, v56 ,1994.
[2] Sheiner LB, JASA, v92, 1997.

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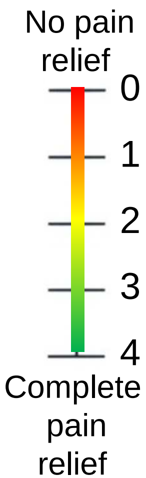
The data

Pain relief: 0-4 scale = 5-point scale

- 254 patients in acute pain after surgical procedure (molar extraction) in 6 dose arms
- ~8 observations within 6 hours recorded upon questioning



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The message

Showed increasing **interest for discrete data** & highlighted challenges linked to such data-type

Proposed **solutions** to model discrete data & implemented them for **non-linear mixed effects**

Pointed out that the different **characteristics of the data** should be **diagnosed** & addressed

The ordered categorical model

$$\operatorname{logit}\left(P\left(\mathrm{Y_{ij}} \geq \mathrm{m}\right)\right) = \sum_{\mathrm{k}=1}^{\mathrm{m}} \alpha_{\mathrm{k}} + \eta_{\alpha_{\mathrm{i}}}$$

$$P\left(\mathrm{Y_{ij}} \geq \mathrm{m}\right) = \frac{\mathrm{e}^{\operatorname{logit}\left(P\left(\mathrm{Y_{ij}} \geq \mathrm{m}\right)\right)}}{1 + \mathrm{e}^{\operatorname{logit}\left(P\left(\mathrm{Y_{ij}} \geq \mathrm{m}\right)\right)}}$$

$$\left.\begin{array}{c} P\left(\mathrm{Y_{ij}} = 0\right) = 1 - P\left(\mathrm{Y_{ij}} \geq 1\right) \\ P\left(\mathrm{Y_{ij}} = \mathrm{m}\right) = P\left(\mathrm{Y_{ij}} \geq \mathrm{m}\right) - P\left(\mathrm{Y_{ij}} \geq (\mathrm{m}+1)\right) \\ P\left(\mathrm{Y_{ij}} = \mathrm{M}\right) = P\left(\mathrm{Y_{ij}} \geq \mathrm{M}\right) \end{array}\right\}$$

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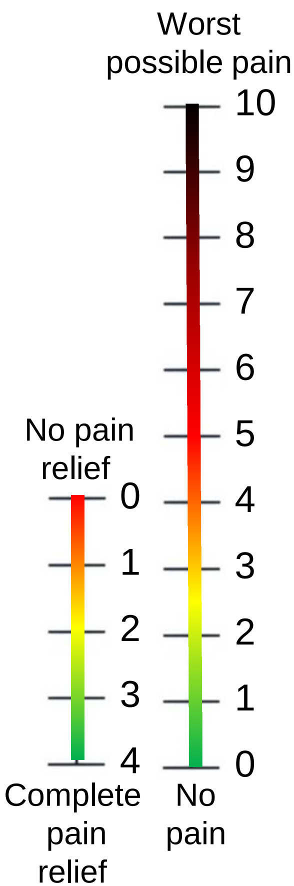
Our data



Pain relief: 0-4 scale = 5-point scale

- 254 patients in acute pain after surgical procedure (molar extraction) in 6 dose arms
- ~8 observations within 6 hours recorded upon questioning

Pain scores: 0-10 scale = 11-point scale[1,2]

- 231 patients in chronic pain from distal diabetic neuropathy in placebo arms
- ~100 daily observations during 18 weeks recorded in a diary

[1] McCaffery M, 1993.
[2] Preston CC, 2000.

Limitations due to number of points?

- **Number of parameters = M-1**
  - Because modeled: $P(\mathrm{Y_{ij}} \geq 1), \ldots, P(\mathrm{Y_{ij}} \geq \mathrm{M})$
  - And by definition: $P(\mathrm{Y_{ij}} \geq 0) = 1$

➔ Supporting information needed

- So: all categories must be represented in the population
- Otherwise: only a few categories can be described[1]

➔ Extra parameters limited

- So: only a few complex features can be considered[2]
- Otherwise: risk of overparameterization

[1] Kamal MA, JPharmSci, v99, 2010.
[2] Byon W, JClinPharm, v50, 2010.

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Assumptions linked to observations?

- **Statistical independence assumed**
  - Because: $P\left(\mathrm{Y_{ij}}|\mathrm{Y_{i(j-1)}}\right) = P\left(\mathrm{Y_{ij}}\right)$
  - Probabilities calculated disregarding previous predictions

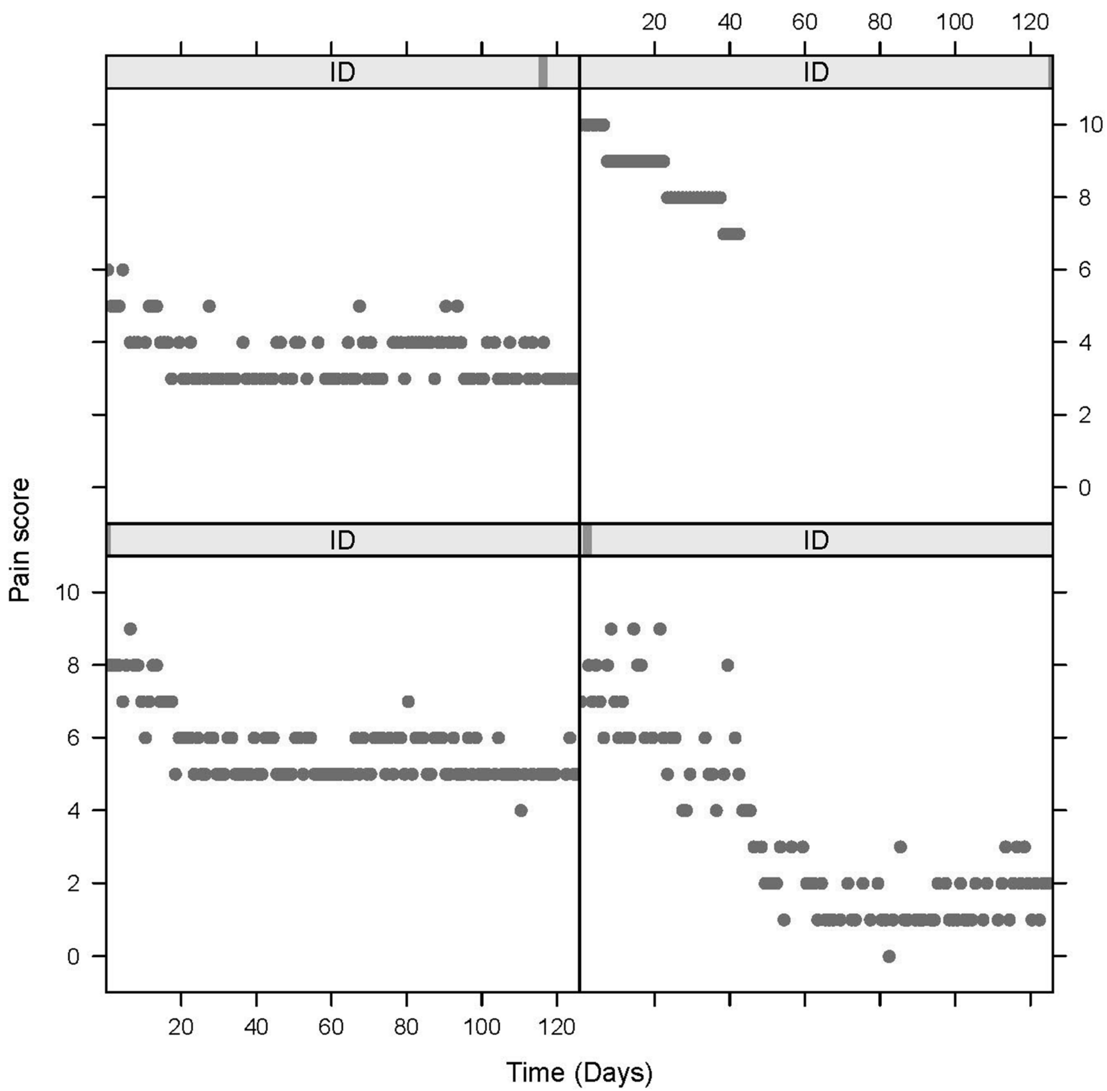
➔ Clustering, trends or patterns ignored

- i.e. serial correlation phenomenon
- Not often detected, nor easily addressed

➔ Model features addressing dependence needed

- e.g. Markov components, AR(1), etc. inclusion
- Otherwise: risk of model misspecification

Individual data



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General aim

- To explore and develop **platform models** and **modelling techniques** adapted to fit real pain scores, i.e. data presenting the characteristics:

Interval-constraints

Time-course

Serial correlation

Specific aims

- To investigate alternative approaches to the ordered categorical model through **simulations** (assuming as the true model the ordered categorical model)

- To develop and fit to the **real pain scores**:

1 count model	2 continuous models

- To propose **model diagnostics** adapted to pain scores data

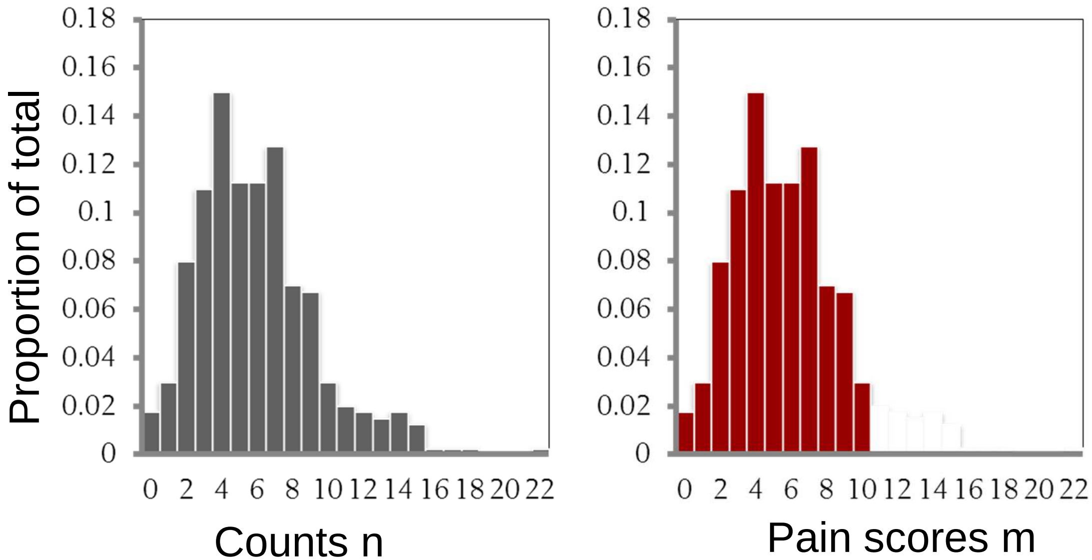
Outline

	1 count model	2 continuous models
Interval-constraints	Truncation	Logit-transformation
Time-course	Part II	
Serial correlation	Part III	

Count approach

- Probability distribution ➔ **Truncated distribution**

$$P(\mathrm{Y_{ij}} = \mathrm{m}) = \frac{P(\mathrm{Y_{ij}} = \mathrm{n})}{\sum_{\mathrm{n}=0}^{10} P(\mathrm{Y_{ij}} = \mathrm{n})}$$



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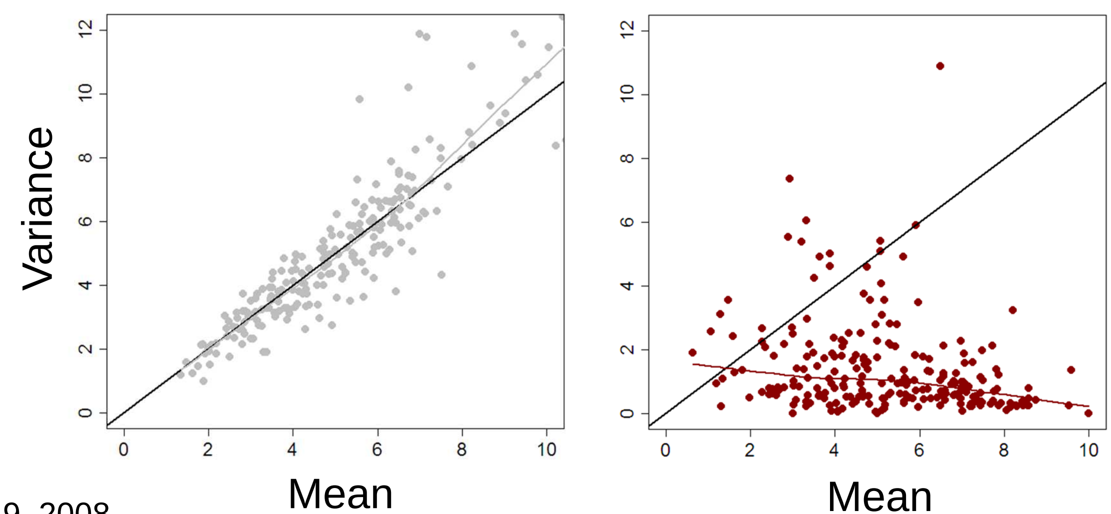
Count approach

- Probability distribution ➔ **Truncated distribution**

$$P\left(\mathrm{Y_{ij}}=\mathrm{m}\right)=\frac{P\left(\mathrm{Y_{ij}}=\mathrm{n}\right)}{\sum_{\mathrm{n}=0}^{10}P\left(\mathrm{Y_{ij}}=\mathrm{n}\right)}$$

- Poisson distribution ➔ **Generalized Poisson**[1,2]

$$P\left(\mathrm{Y_{ij}}=\mathrm{m}\right)=\frac{\lambda_{\mathrm{i}}(1-\delta_{\mathrm{i}})\cdot(\lambda_{\mathrm{i}}(1-\delta_{\mathrm{i}})+\mathrm{m}\cdot\delta_{\mathrm{i}})^{\mathrm{m}-1}\cdot e^{-(\lambda_{\mathrm{i}}(1-\delta_{\mathrm{i}})+\mathrm{m}\cdot\delta_{\mathrm{i}})}}{\mathrm{m}!}$$



[1] Consul P, 1989.
[2] Gschlossl S, StatPap, v49, 2008.

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Continuous approach

- Function transformation: **Logit-transformation [0,1]**

$$\mathrm{logit}(\lambda_i) = \ln\left(\frac{\lambda_i}{1-\lambda_i}\right)$$

- Rescaling: **Residual error on logit scale [-0.5,10.5]**

$$Y_{ij} = 11 \cdot \frac{e^{\mathrm{logit}(\lambda_i)+\varepsilon_{ij}}}{1+e^{\mathrm{logit}(\lambda_i)+\varepsilon_{ij}}} - 0.5 \qquad \varepsilon_{ij} \sim N(0,\sigma^2)$$

- **Rounding**

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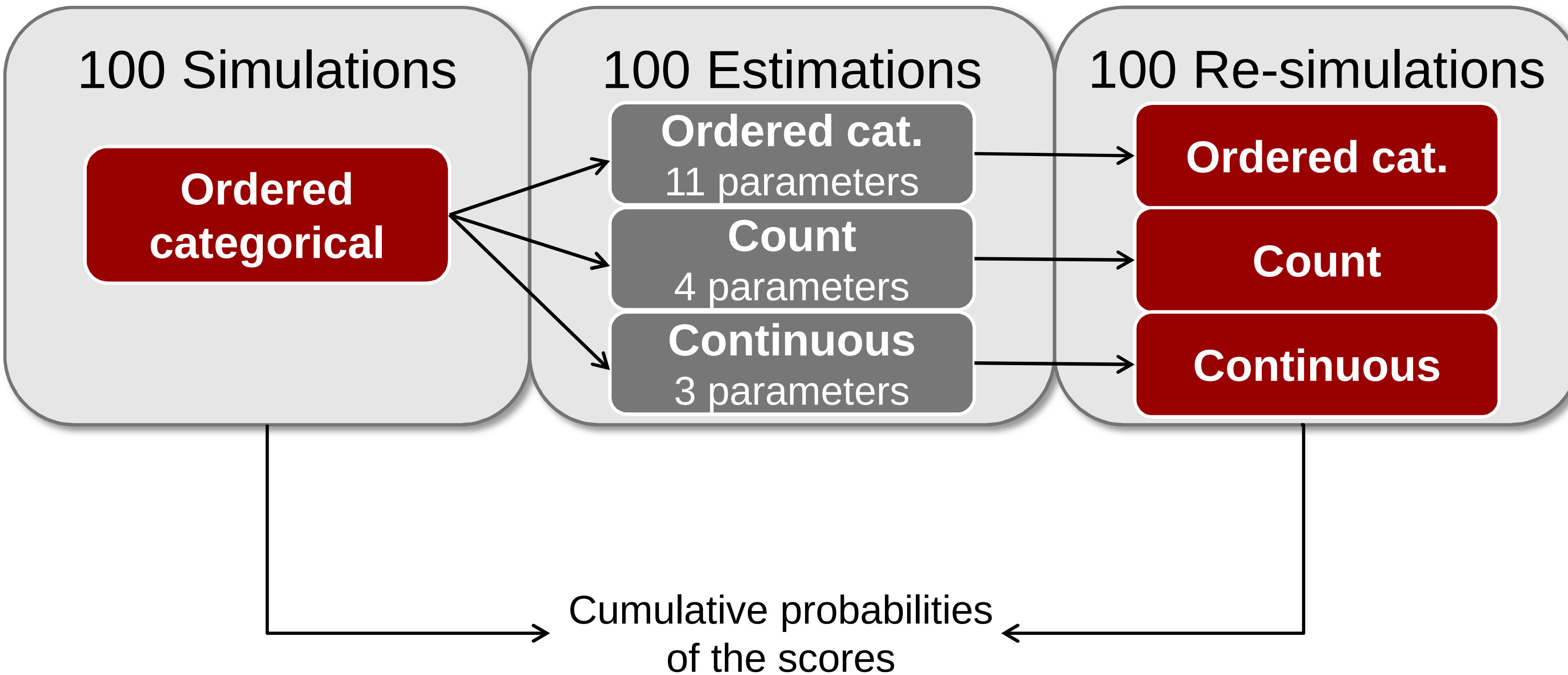
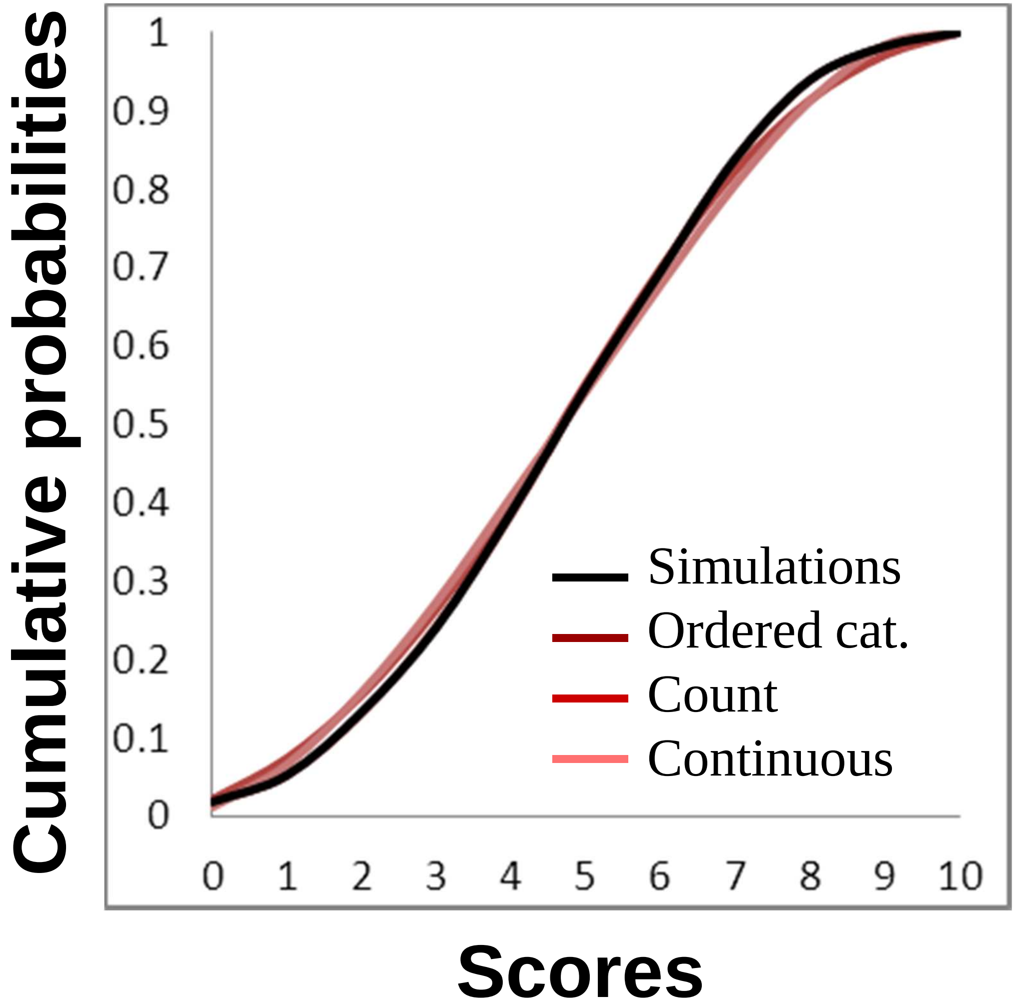
Simulation study

- Compare different approaches, alternatives to the ordered categorical model (taken as true model):



Simulation results



Outline

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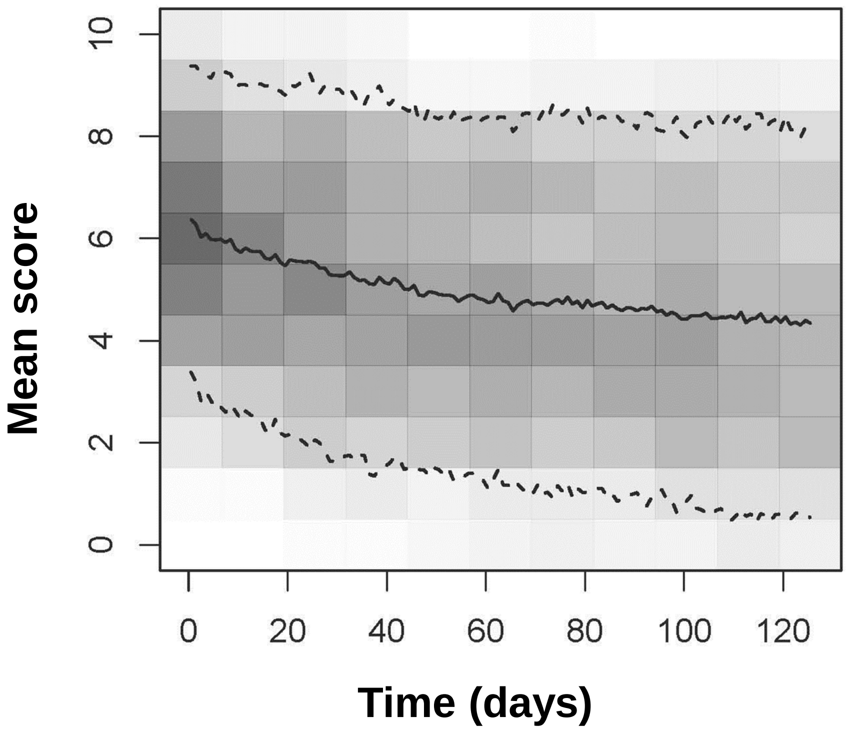
	1 count model	2 continuous models
Interval-constraints	Truncation	Logit-transformation
Time-course	Exponential decay	
Serial correlation	Part III	

Count and continuous models

- **Placebo effect: Exponential decay**

$$\lambda_{ij} = \mathrm{BASE}_i \cdot \left(1 - \mathrm{PE}_{\mathrm{max}_i} \cdot \left(1 - e^{\left(\frac{-\ln(2)}{\mathrm{PEt}_{1/2_i}} \cdot t_j\right)}\right)\right)$$



Raw data

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Estimation results

- **Placebo effect: Exponential decay**

$$\lambda_{ij} = \mathrm{BASE}_i \cdot \left(1 - \mathrm{PE}_{\mathrm{max}_i} \cdot \left(1 - e^{\left(\frac{-\ln(2)}{\mathrm{PEt}_{1/2_i}} \cdot t_j\right)}\right)\right)$$

	Count model		Continuous model	
	TV (RSE %)[1]	CV % [Sh$_\eta$ %] (RSE %)[1]	TV [Sh$_\varepsilon$ %] (RSE %)[2]	CV % [Sh$_\eta$ %] (RSE %)[2]
BASE (Score)	6.2 (17)	33 [11] (2)	6.2 (21)	32 [3] (14)
PE_{max} (%)	18.9 (8)	572 [21] (4)	19.8 (42)	761 [12] (20)
$PEt_{1/2}$ (days)	27.8 (9)	89 [49] (6)	32.3 (69)	129 [37] (27)
δ (dispersion)	-1.5 (0.8)	-100 [48] (3)	-	-
σ (SD of ε)	-	-	1.8 [16] (12)	-

[1], from bootstrapping; [2], from Monte Carlo importance sampling

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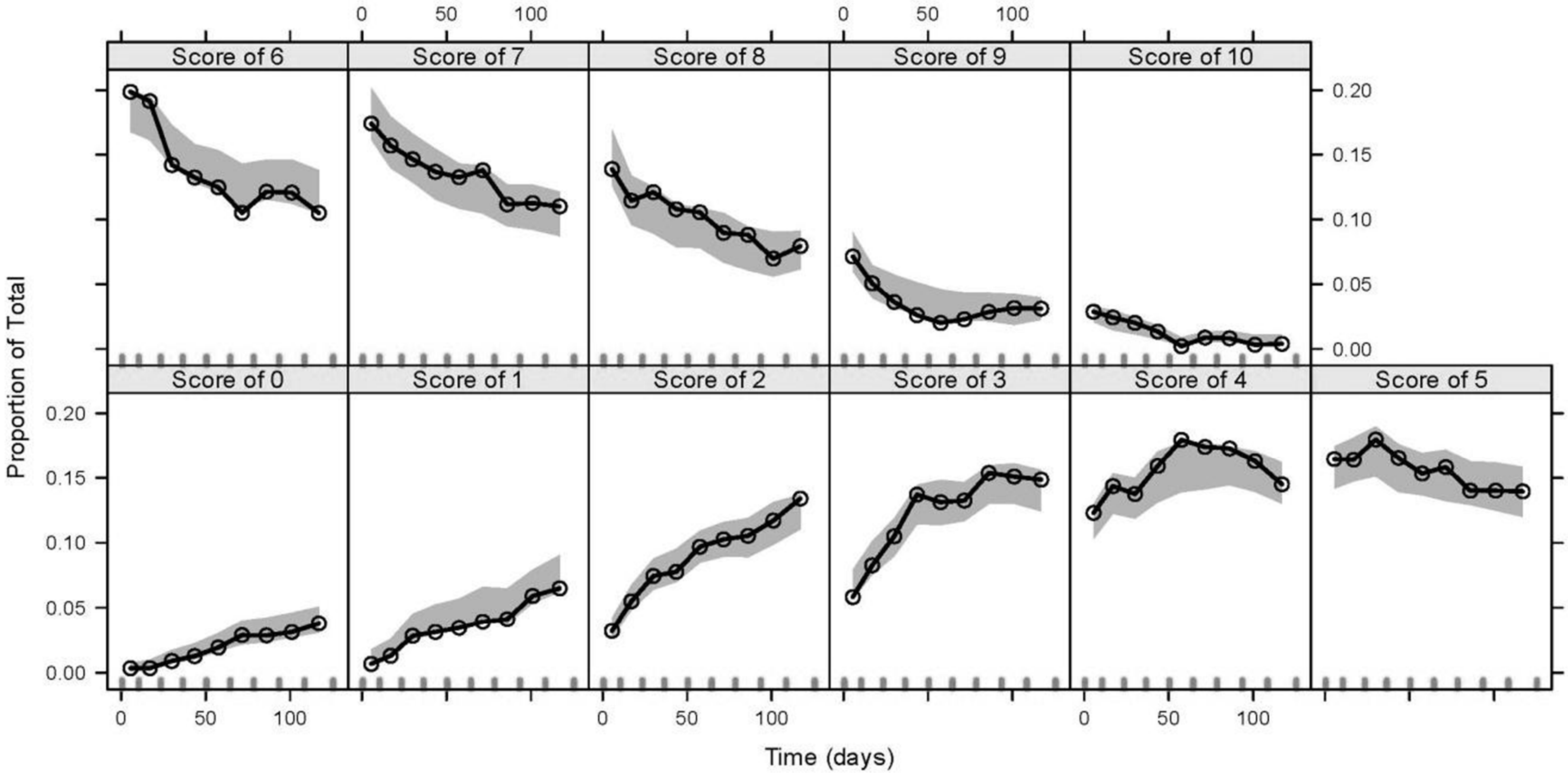
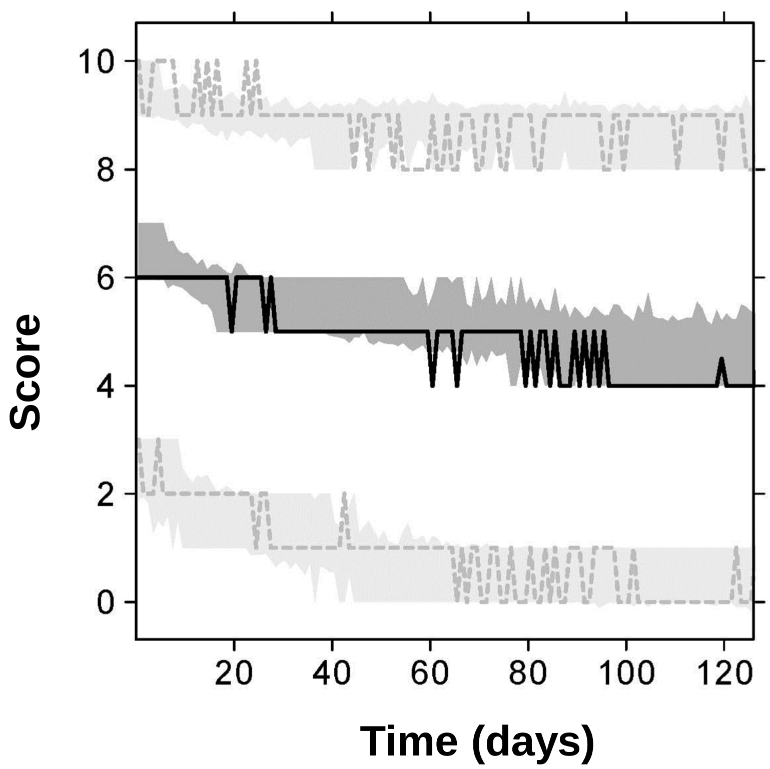
Model diagnostics

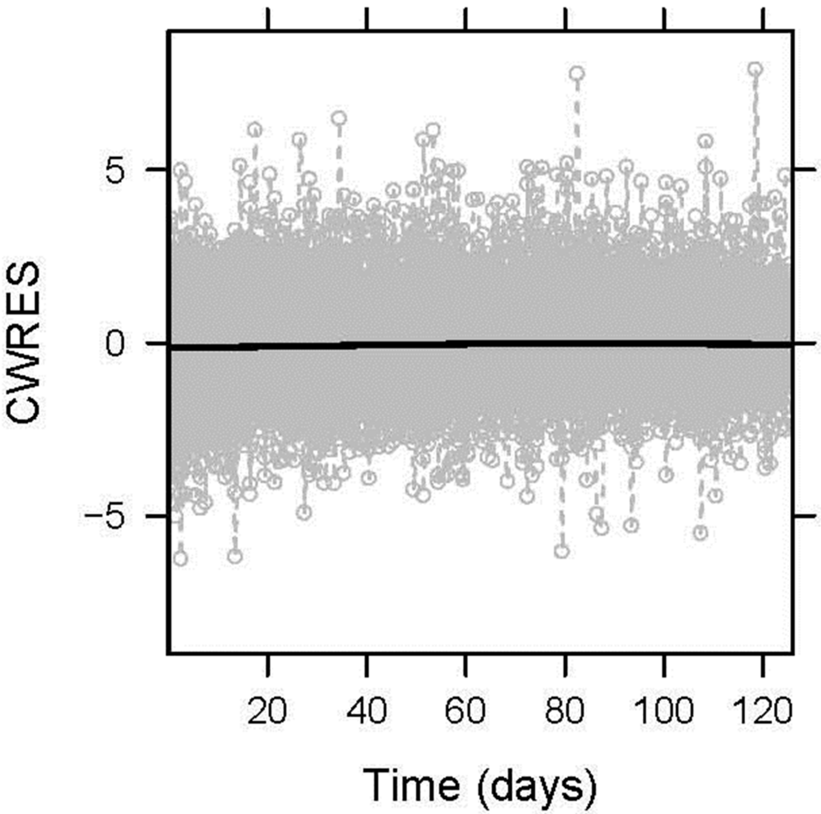
- **Count model**



Model diagnostics[1,2]

- **Continuous model**





[1] Karlsson MO, PAGE17, A1434, 2008.
[2] Hooker AC, Pharm Res, v24, 2007.

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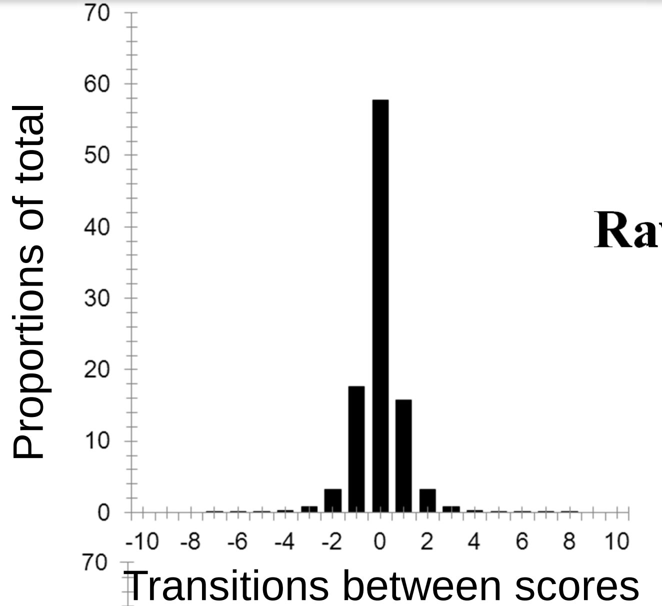
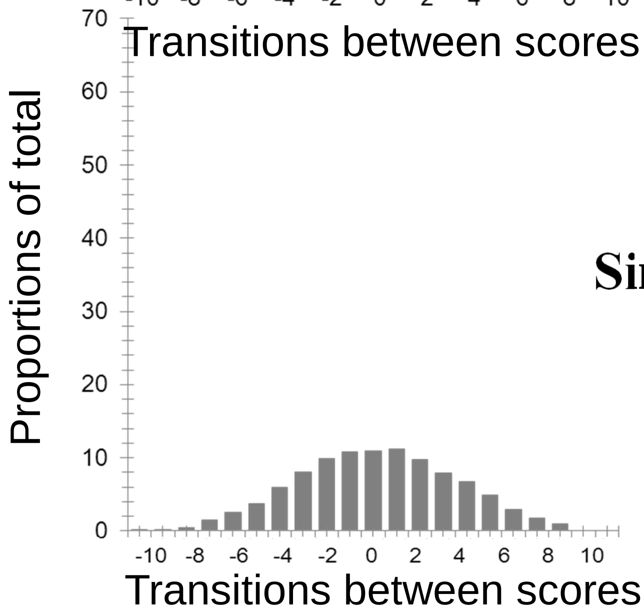
Outline

	1 count model	2 continuous models	
Interval-constraints	Truncation	Logit-transformation	
Time-course	Exponential decay		
Serial correlation	Markov	AR(1)	SDE

Count model



Raw data



Simulations

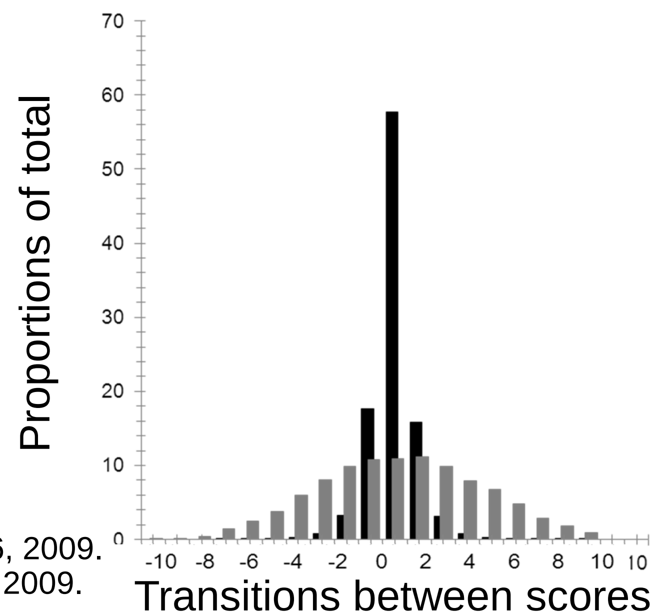
Count model

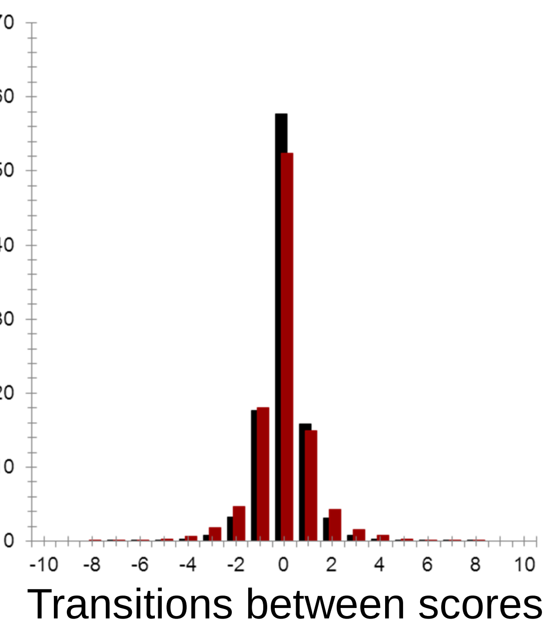
- **Markov components**[1,2] (1st-order)
  - **Transition inflation**

$$P\left(Y_{ij}=m \,\middle|\, \left|Y_{ij}-Y_{i(j-1)}\right|=z\right)=\ \pi_z+\left(1-\sum_{k=0}^{K}\pi_k\right)\cdot P\left(Y_{ij}=m\right)$$

$\pi_z=P\left(\left|Y_{ij}-Y_{i(j-1)}\right|=z\right)$, z=0, ± 1, ± 2, ± 3

$\pi_0=f\left(\pi_{0|0},\pi_{0|9},\pi_{0|10},\eta_i,\tau_0,t_j\right)$





[1] Troconiz IF, JPKPD, v36, 2009.
[2] Silber HE, JPKPD, v36, 2009.

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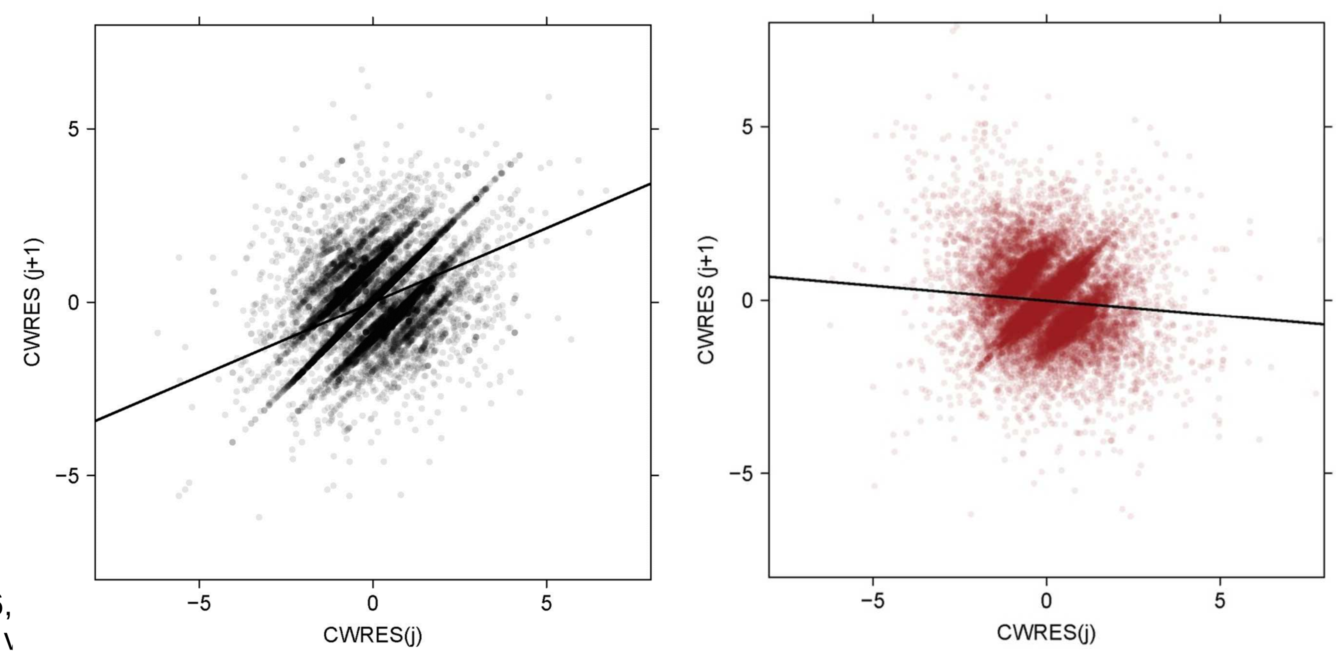
First continuous model

Autocorrelated errors[1,2]

- **Autoregressive time series AR(1)**

(Continuous-time correlation between residual errors)

$$\mathrm{Corr}(\varepsilon_{ij},\varepsilon_{ik}) = e^{\frac{-\ln(2)}{ARt_{1/2}}\cdot(t_k - t_j)}$$



[1] Silber HE, JPKPD, v36,
[2] Karlsson MO, JPKBio, v

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Second continuous model

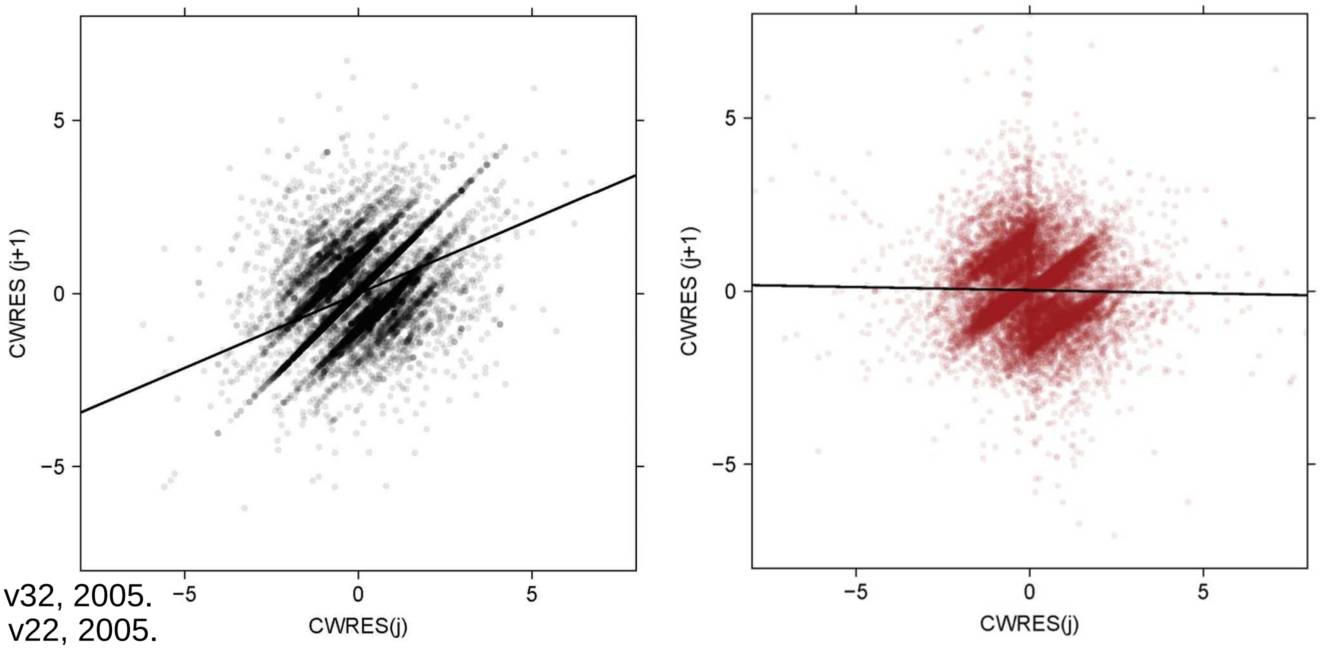
Stochastic process[1,2]

- **Stochastic Differential Equations (SDEs)**

(Drift incorporated as a standard Wiener process)

$$y = \hat{y} + \varepsilon_{ij} + A_1$$

$$\frac{dA_1}{dt} = \omega_w$$



[1] Overgaard RV, JPKPD, v32, 2005.
[2] Tornoe CW, PharmRes, v22, 2005.

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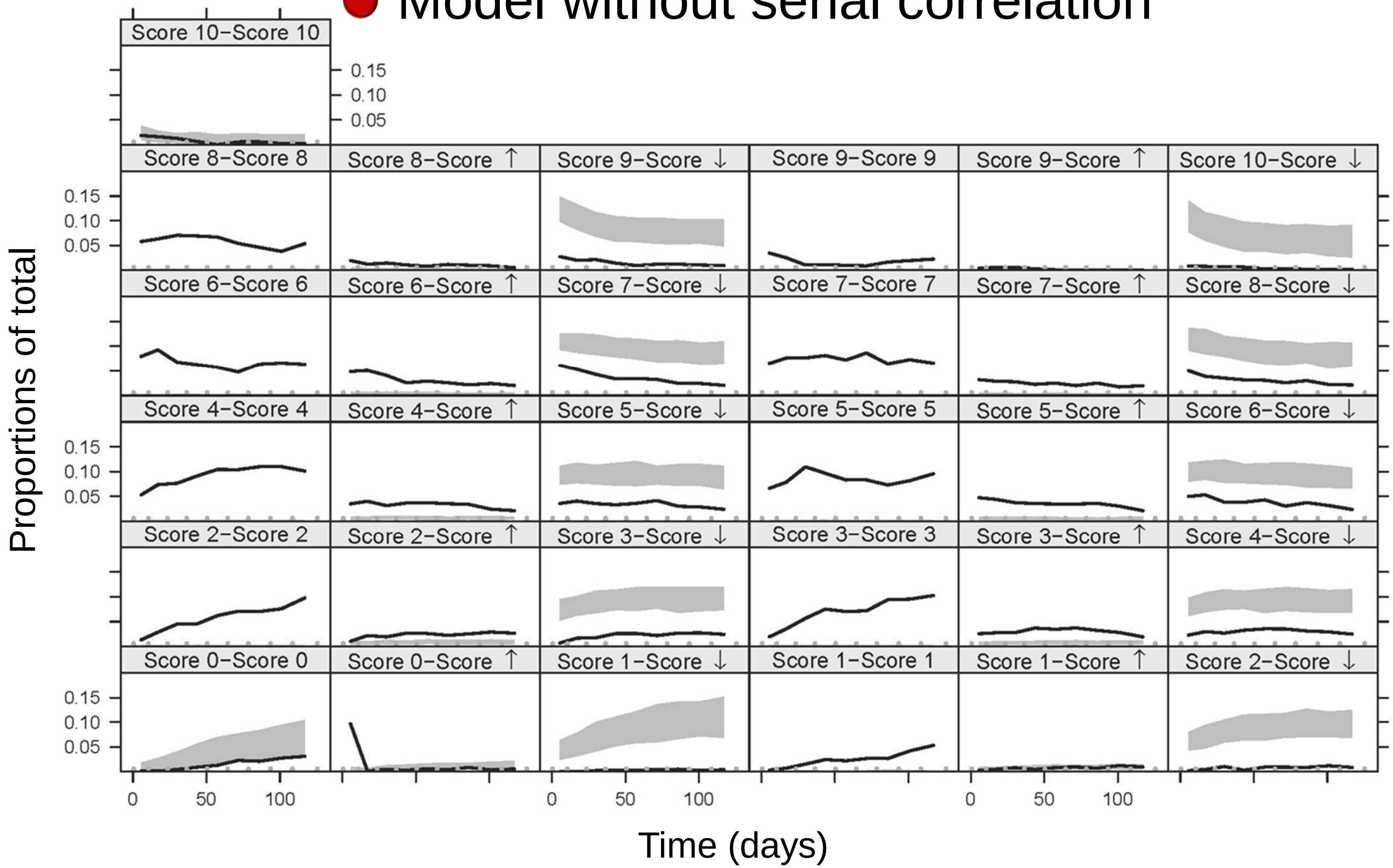
Serial correlation results

	Count model	Continuous models	
Serial correlation	Markov	AR(1)	SDE
ΔOFV	11,000	2,000	1,800
df	13	1	2
Measure	Probabilities of inflation	Autocorrelation half-life	Variance of the drift
Value	Up to 55%	0.93 day	0.038 score^2/day on logit scale

Model diagnostics

- Model without serial correlation



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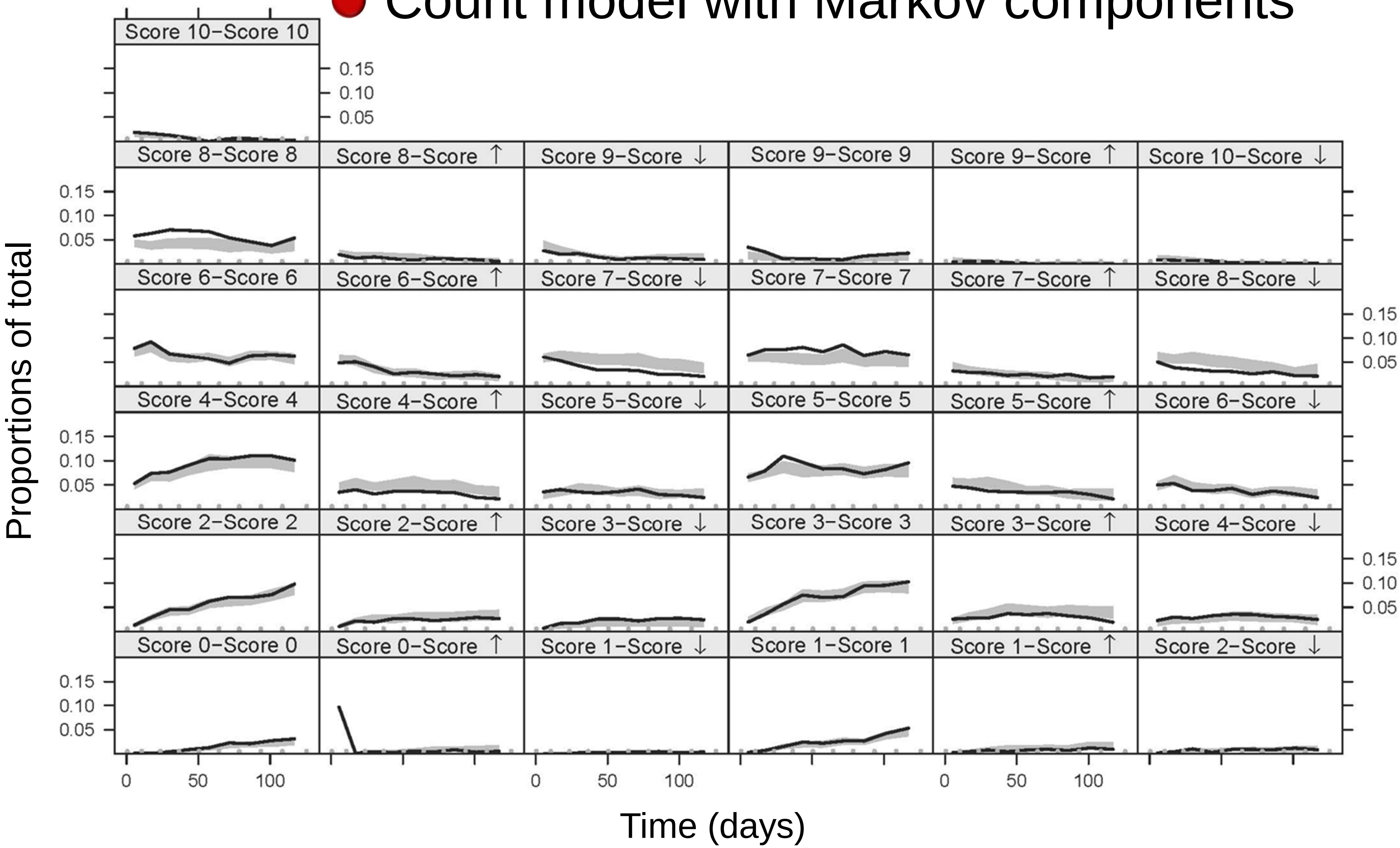
Model diagnostics

- Count model with Markov components



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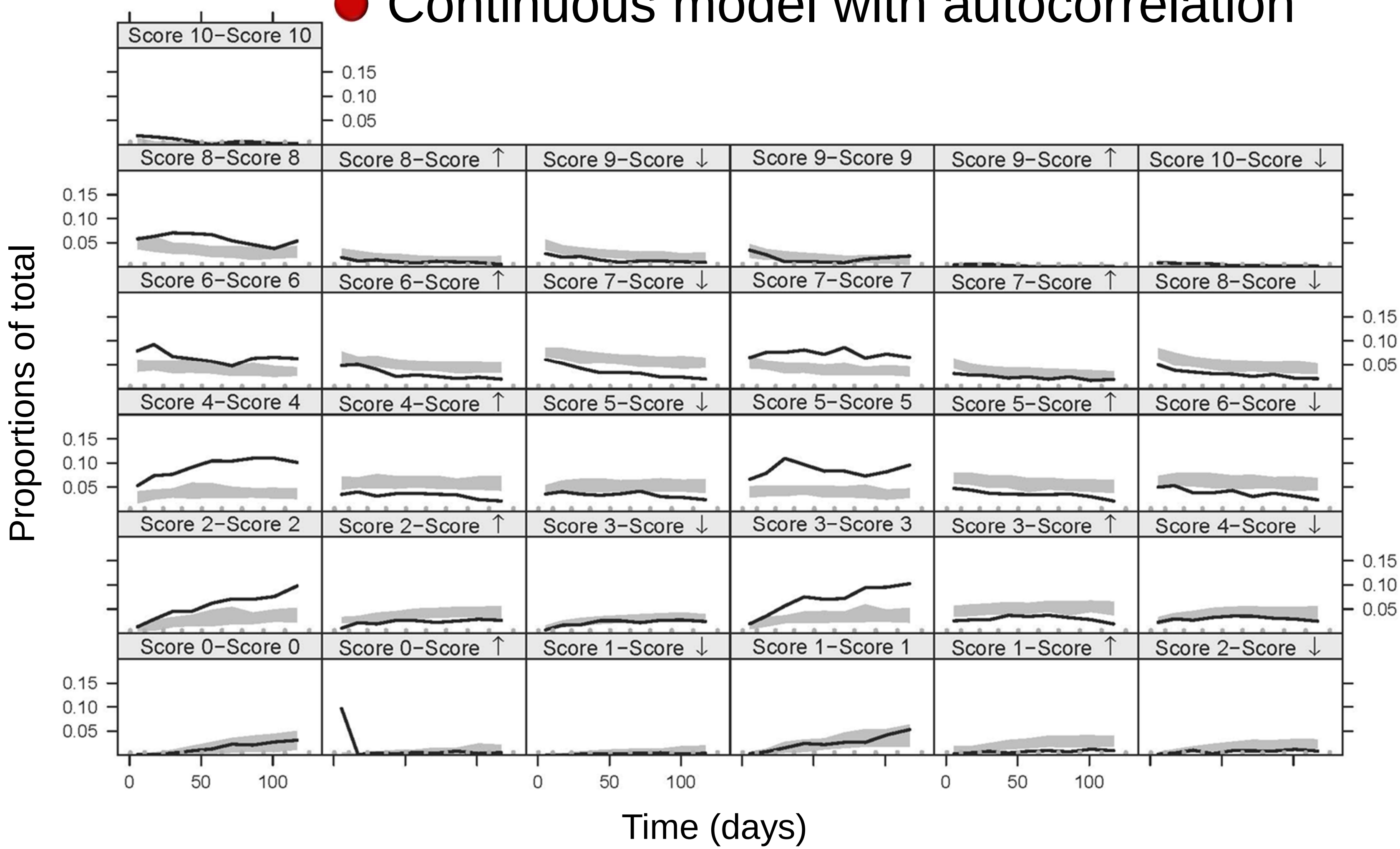
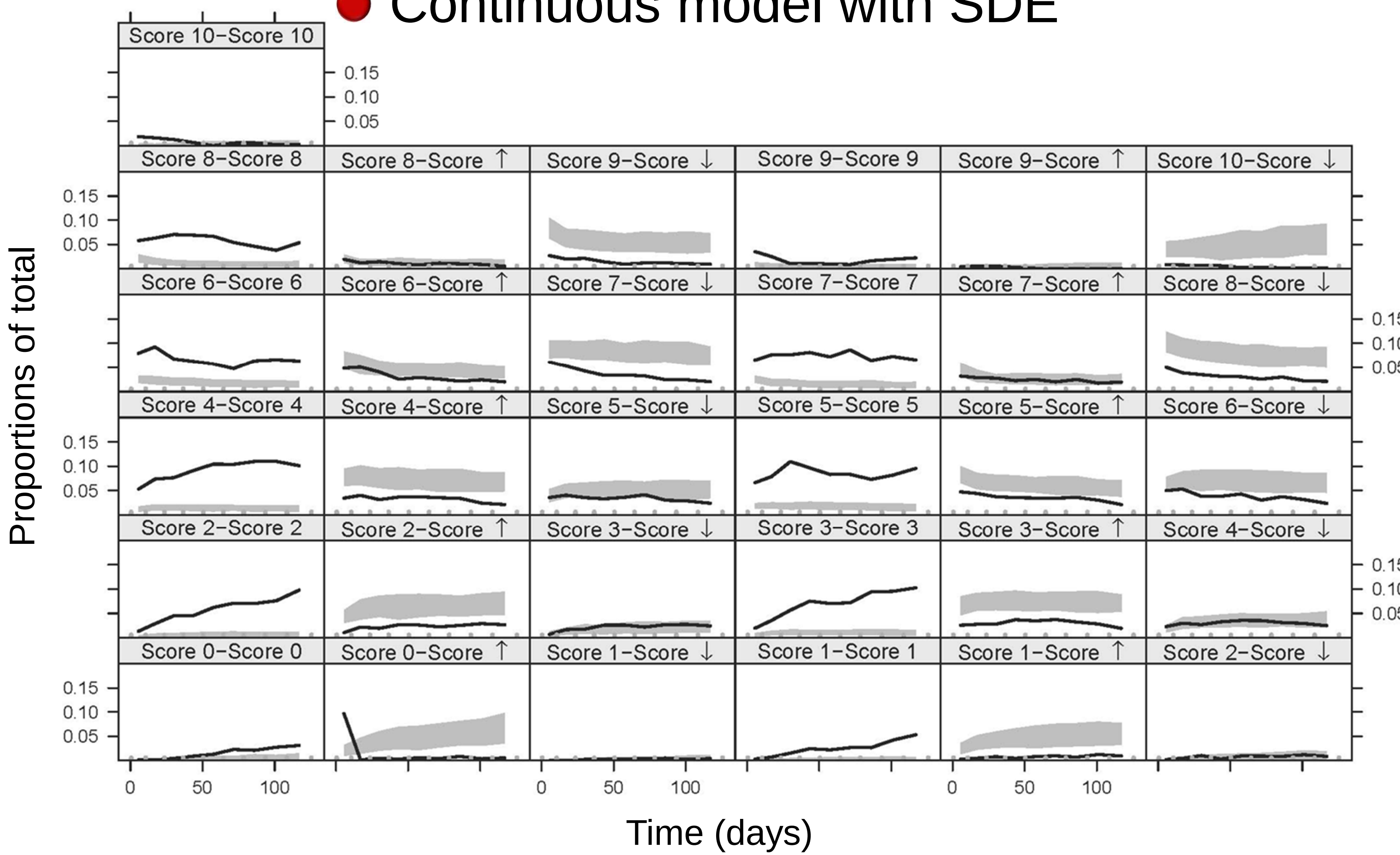
Model diagnostics

- Continuous model with autocorrelation



Model diagnostics

- Continuous model with SDE



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Outline

1 count model

2 continuous models

Interval-constraints

Truncation

Logit-transformation

Time-course

Exponential decay

Serial correlation

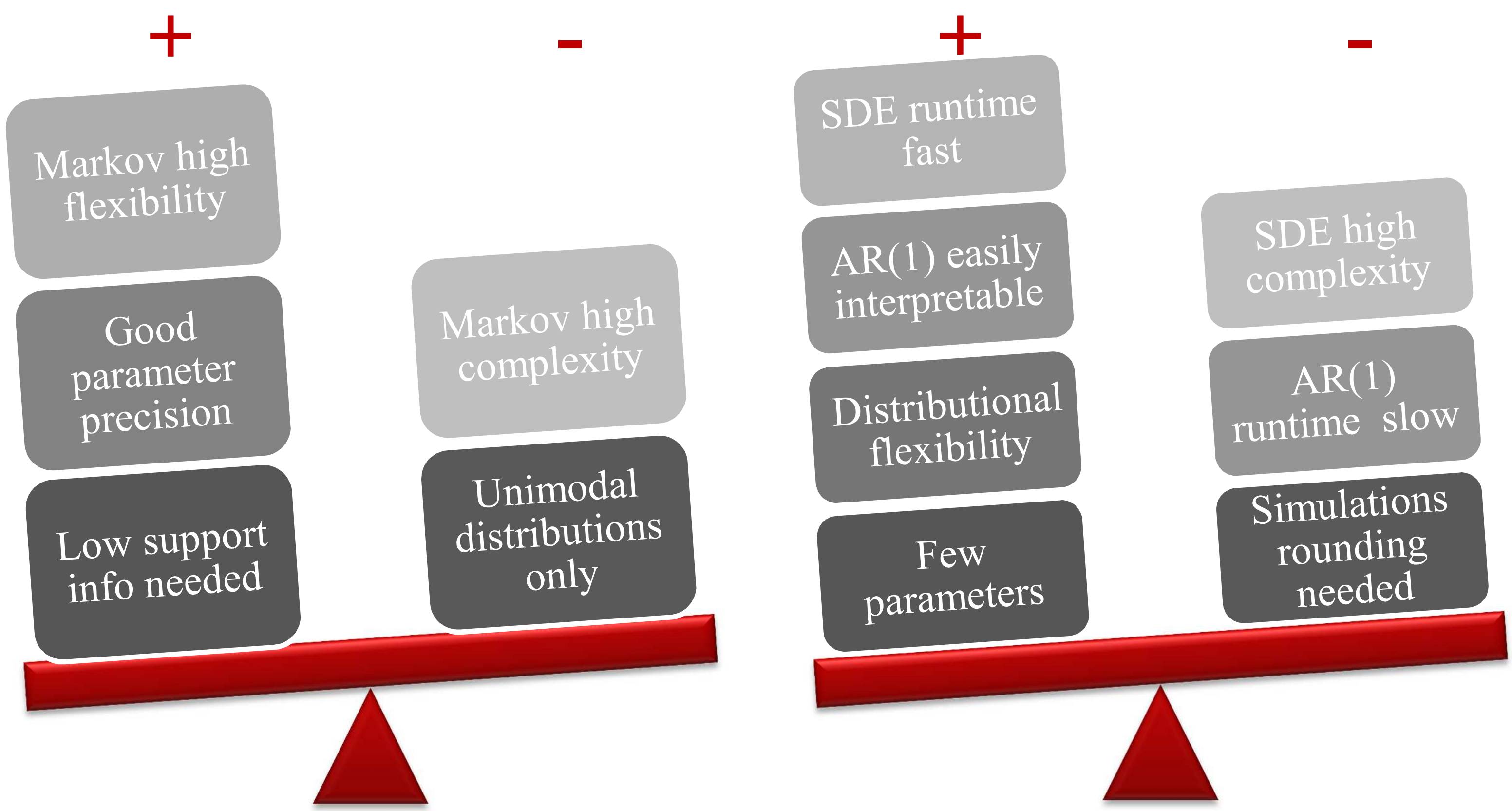
Markov

AR(1)

SDE

Discussion

Truncated count　　Logit-transf. continuous



Conclusions

- **Pain modelling = challenging, but:**
  - **11-point scales** accurately treated with a truncated count or a transformed continuous approach
  - **Real pain scores** satisfactorily handled with 3 novel models (all handling **serial correlation** detected in observed data)
  - All processes implemented in NONMEM

Integrated data characteristic inspection and **model diagnostics** are key steps in model development.

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PAGE committee

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