A bounded integer model for rating and composite scale data

2018-05-31

Gustaf Wellhagen, Maria Kjellsson and Mats Karlsson
Department of Pharmaceutical Biosciences
Upplasa University, Sweden
Aim

To develop a new method to handle rating and composite scale data in a parsimonious way, while respecting the nature of the data.
Rating and composite scales

• Good for assessing disease severity and therapeutic efficacy
• Rating scale: one question/item
  – Focus on scales with >10 categories
• Composite scale: several questions/items
• Commonly used in e.g. CNS disorders and autoimmune diseases
Rating scales
Likert rating scale: neuropathic pain
Likert rating scale: neuropathic pain

Score distribution

231 patients, 97 obs/patient

a. Ordered categorical (OC) model (Schindler & Karlsson AAPS J 2017)
Likert rating scale: neuropathic pain

Score distribution

Score time-course

231 patients, 97 obs/patient

a. Ordered categorical (OC) model (Schindler & Karlsson AAPS J 2017)
b. Continuous variable (CV) model (Plan et al. Clin Pharmacol Ther 2012)
Traditional approaches in NLME

• Ordered categorical (OC)
  – $n-1$ parameters to capture the baseline
  – Requires many observations
  – Cannot predict unobserved categories
• Continuous variable (CV)
  – Violates the categorical nature of the data
  – Problematic at the extremes of the scale
The bounded integer (BI) model
The bounded integer (BI) model

• Define two functions: \( f() \) and \( g() \):
  – Consist of fixed and random effects, time and covariates:
    • \( f(\theta, \eta, t, X) \) and \( g(\sigma, \eta, t, X) \)
    – Defines a distribution: \( N(f(), g()) \)
The bounded integer (BI) model

• Define two functions: \( f() \) and \( g() \):
  – Consist of fixed and random effects, time and covariates:
    • \( f(\theta, \eta, t, X) \) and \( g(\sigma, \eta, t, X) \)
  – Defines a distribution: \( N(f(), g()) \)
• Define n-1 cut-off values through the probit function:
  – \( Z_{1/n} \) to \( Z_{(n-1)/n} \)
  – Divides a standard normal curve into n equally sized areas
A scale with 5 categories

Given a standard normal distribution $N(0, 1)$:
- The probit is the quantile function
- $\Phi(x)$ is the cumulative distribution function
Given a standard normal distribution $N(0, 1)$:

- The probit is the quantile function
- $\Phi(x)$ is the cumulative distribution function

**probit(1/5)**

| Z-score | Percentile |
|---------|------------|
| -0.84   | 20%        |
| -0.25   | 40%        |
| 0.25    | 60%        |
| 0.84    | 80%        |

A scale with 5 categories
A scale with 5 categories

Given a standard normal distribution $N(0, 1)$:

- The probit is the quantile function
- $\Phi(x)$ is the cumulative distribution function

$\text{probit}(1/5)$

$\Phi(\text{probit}(1/5))$

Z-score: $-0.84$ (20%), $-0.25$ (40%), $0.25$ (60%), $0.84$ (80%)
A scale with 5 categories

probit(1/5)

Z-score

-0.84 -0.25 0.25 0.84

0 1 2 3 4

20% 20% 20% 20% 20%
A scale with 5 categories

$probit(1/5)$

Z-score $\rightarrow$ -0.84 $\rightarrow$ -0.25 $\rightarrow$ 0.25 $\rightarrow$ 0.84
The probability $P$ of each score is defined as:

$$P(0) = \Phi\left(\frac{\text{probit}(1/n) - f()}{g()}\right)$$

$$P(1) = \Phi\left(\frac{\text{probit}(2/n) - f()}{g()}ight) - \Phi\left(\frac{\text{probit}(1/n) - f()}{g()}\right)$$

... 

$$P(n-1) = \Phi\left(\frac{\text{probit}(n-1/n) - f()}{g()}ight) - \Phi\left(\frac{\text{probit}(n-2/n) - f()}{g()}\right)$$

$$P(n) = 1 - \Phi\left(\frac{\text{probit}(n-1/n) - f()}{g()}\right)$$
• The probability $P$ of each score is defined as:

\[
P(0) = \Phi(-0.84-f())/g())
\]

\[
P(1) = \Phi(-0.25-f())/g()) - \Phi(-0.84-f())/g())
\]

\[
P(2) = \Phi(0.25-f())/g()) - \Phi(-0.25-f())/g())
\]

\[
P(3) = \Phi(0.84-f())/g()) - \Phi(0.25-f())/g())
\]

\[
P(4) = 1 - \Phi(0.84-f())/g())
\]
An illustrating example

\( g() = 0.7 \)

\( f() = -0.545 \)
\[ P(0) = \Phi((-0.84 - 0.545)/0.7) = 0.34 \]
\[ P(I) = \Phi((-0.25 - 0.545)/0.7) - \Phi((-0.84 - 0.545)/0.7) = 0.33 \]
\[ P(2) = \Phi\left(\frac{0.25 - 0.545}{0.7}\right) - \Phi\left(\frac{-0.25 - 0.545}{0.7}\right) = 0.21 \]
\[ P(3) = \Phi((0.84 - 0.545)/0.7) - \Phi((0.25 - 0.545)/0.7) = 0.10 \]
\[ P(4) = 1 - \Phi \left( \frac{(0.84 - 0.545)}{0.7} \right) = 0.02 \]
## Comparison BI vs. OC – Likert example

| Model description                                      | ΔParameters OC-BI | ΔOFV OC-BI |
|--------------------------------------------------------|-------------------|------------|
| Base model                                             | 8                 | -372       |
| With random effects                                    | 7                 | 796        |
| With random effects and Markov components              | 4                 | 1365       |

OC model (Schindler & Karlsson AAPS J 2017)
Remarks on BI vs. OC models

- **BI advantages:**
  - Described the data better (OFV)
  - Needed fewer parameters
  - Runtimes were shorter
  - Allows interpolation and extrapolation
Composite scales
Alzheimer’s Disease Assessment Scale - Cognition (ADAS-Cog)

Tasks

Word-based

Rater assessed

Sum

Parkinson’s Disease

Movement Disorder Society - Unified Parkinson’s disease rating scale (MDS-UPDRS)

Non-motor experiences

Motor experiences

Motor examinations

Complications

Sum
Approaches for total score data from composite scales

• Ordered categorical (OC) model not used
• Commonly analysed as a continuous variable (CV):
  – Score_{obs,i,j} = Score_{predicted,i,j} + \varepsilon_{ij}
## Comparison BI vs. CV examples

| Disease               | Scale        | Categories | #Parameters CV = BI | ΔOFV CV-BI | ΔXV OFV CV-BI |
|-----------------------|--------------|------------|---------------------|------------|---------------|
| Parkinson’s disease   | UPDRS motor¹ | 109        | 16                  | 113        | 138           |

Data from: ¹Troconiz et al. CPT 1998
## Comparison BI vs. CV examples

| Disease                  | Scale          | Categories | #Parameters CV = BI | $\Delta$OFV CV-BI | $\Delta$XV OFV CV-BI |
|--------------------------|----------------|------------|---------------------|-------------------|---------------------|
| Parkinson's disease      | UPDRS motor$^1$ | 109        | 16                  | 113               | 138                 |
| Parkinson's disease      | MDS-UPDRS motor$^2$ | 133        | 14                  | 73                | 82                  |
| Alzheimer's disease      | ADAS-Cog$^3$   | 71         | 11                  | 730               | 793                 |
| Schizophrenia            | PANSS$^4$      | 181        | 17                  | 145               | 131                 |
| Schizophrenia            | PANSS$^5$      | 181        | 15                  | 126               | 170                 |

Data from: $^1$Troconiz et al. CPT 1998; $^2$Buatois et al. Pharm Res 2017; $^3$Ito et al. Alzheimers Dement 2011; $^4$Friberg et al. CPT 2009; $^5$Krekels et al. CPT PSP 2017
# Comparison BI vs. CV examples

| Disease          | Scale             | Categories | #Parameters CV = BI | ΔOFV CV-BI | ΔXV OFV CV-BI |
|------------------|-------------------|------------|---------------------|------------|---------------|
| Parkinson's disease | UPDRS motor\(^1\) | 109        | 16                  | 113        | 138           |
| Parkinson's disease | MDS-UPDRS motor\(^2\) | 133        | 14                  | 73         | 82            |
| Alzheimer's disease | ADAS-Cog\(^3\)   | 71         | 11                  | 730        | 793           |
| Schizophrenia    | PANSS\(^4\)      | 181        | 17                  | 145        | 131           |
| Schizophrenia    | PANSS\(^5\)      | 181        | 15                  | 126        | 170           |

Data from: \(^1\) Troconiz et al. CPT 1998; \(^2\) Buatois et al. Pharm Res 2017; \(^3\) Ito et al. Alzheimers Dement 2011; \(^4\) Friberg et al. CPT 2009; \(^5\) Krekels et al. CPT PSP 2017
Remarks on BI vs. CV

- **BI advantages:**
  - Described the data better (OFV and XV OFV)
  - Respects the scale boundaries
  - Allows simulation of real life-like data

- **BI disadvantages:**
  - Runtimes were longer
    - E.g. Troconiz data set average: 80 vs. 50 min
Model assumptions

Continuous: Linear

Continuous: Logit

Ordered categorical

Bounded integer
The bounded integer model:
  - Provides a good description of rating and composite scale data
  - Is parsimonious compared to ordered categorical models
  - Can interpolate and extrapolate well
  - Respects the integer nature of the data
  - Respects scale boundaries
  - Is a promising method to make use of total score data
Thank you for listening

• Thanks to colleagues in the Pharmacometrics Research Group at Uppsala University
## Comparison BI vs. CV examples

| Disease               | Scale         | #Patients | #Obs  | Scale range | Observed range | #Parameters CV = BI | ∆OFV CV-BI | ∆XV OFV CV-BI |
|-----------------------|---------------|-----------|-------|-------------|-----------------|-------------------|------------|---------------|
| Parkinson’s disease   | UPDRS motor¹ | 19        | 946   | 0-108       | 16-80           | 16                | 113        | 138           |
| Parkinson’s disease   | MDS-UPDRS motor² | 428     | 2720  | 0-132       | 1-77            | 14                | 73         | 82            |
| Alzheimer’s disease   | ADAS-Cog³     | 817       | 3594  | 0-70        | 0-70            | 11                | 730        | 793           |
| Schizophrenia         | PANSS⁴        | 1323      | 7728  | 30-210      | 30-176          | 17                | 145        | 131           |
| Schizophrenia         | PANSS⁵        | 1292      | 8520  | 30-210      | 30-167          | 15                | 126        | 170           |

Data from: ¹Troconiz et al. CPT 1998; ²Buatois et al. Pharm Res 2017; ³Ito et al. Alzheimers Dement 2011; ⁴Friberg et al. CPT 2009; ⁵Krekels et al. CPT PSP 2017
| Disease                | Scale                  | #Patients | #Obs  | Full range | Observed range | $\Delta$OFV Obs-Full |
|------------------------|------------------------|-----------|-------|------------|----------------|----------------------|
| Parkinson's disease    | UPDRS motor            | 19        | 946   | 0-108      | 16-80          | 16                   |
| Parkinson's disease    | MDS-UPDRS motor        | 428       | 2720  | 1-132      | 1-77           | 31                   |
| Alzheimer’s disease    | ADAS-Cog               | 817       | 3594  | 0-70       | 0-70           | 0                    |
| Schizophrenia          | PANSS                  | 1323      | 7728  | 30-210     | 30-176         | -58                  |
| Schizophrenia          | PANSS                  | 1292      | 8520  | 30-210     | 30-167         | 2                    |
• Scaling of Z-scores
• Larger variability at high absolute Z-score
• Translation between scales
• Markov elements
• T-distributed variability
• Residuals of rating/composite scales