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A bounded integer model for rating and composite scale data

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Aim

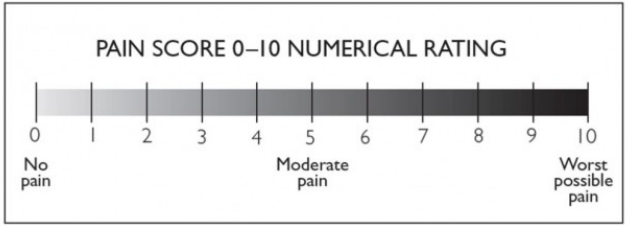
To develop a new method to handle rating and composite scale data in a parsimonious way, while respecting the nature of the data.

Rating and composite scales

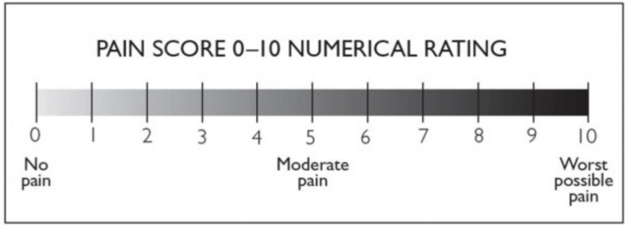
- Good for assessing disease severity and therapeutic efficacy
- Rating scale: one question/item
  - Focus on scales with >10 categories
- Composite scale: several questions/items
- Commonly used in e.g. CNS disorders and autoimmune diseases

Rating scales

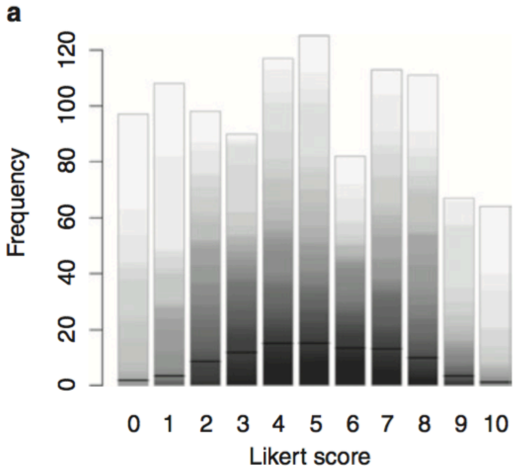
Likert rating scale: neuropathic pain



Likert rating scale: neuropathic pain



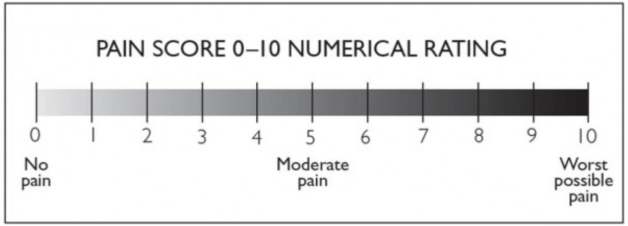
Score distribution



231 patients, 97 obs/patient

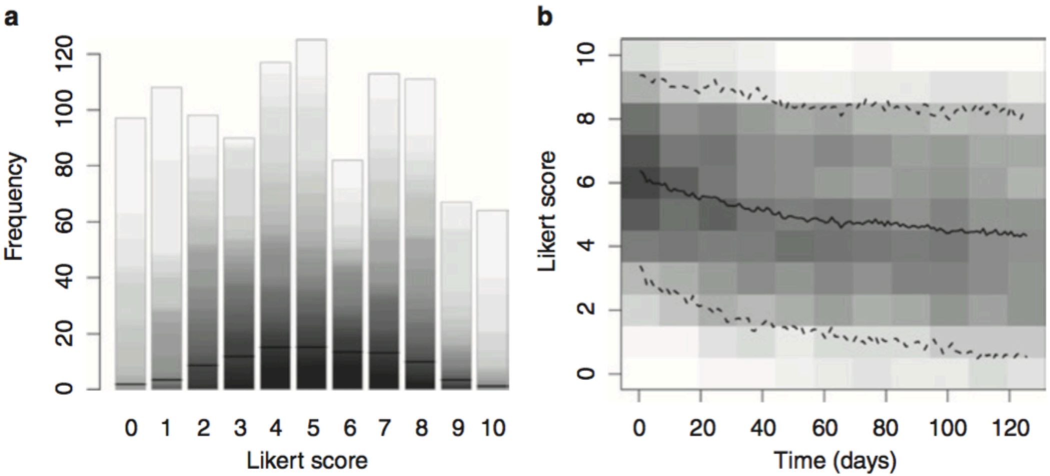
a. Ordered categorical (OC) model (Schindler & Karlsson AAPS J 2017)

Likert rating scale: neuropathic pain



Score distribution

Score time-course



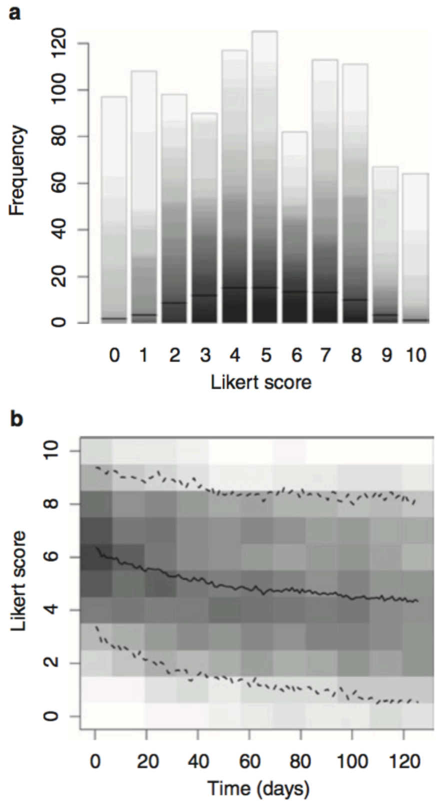
231 patients, 97 obs/patient

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



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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: $N(f(), g())$

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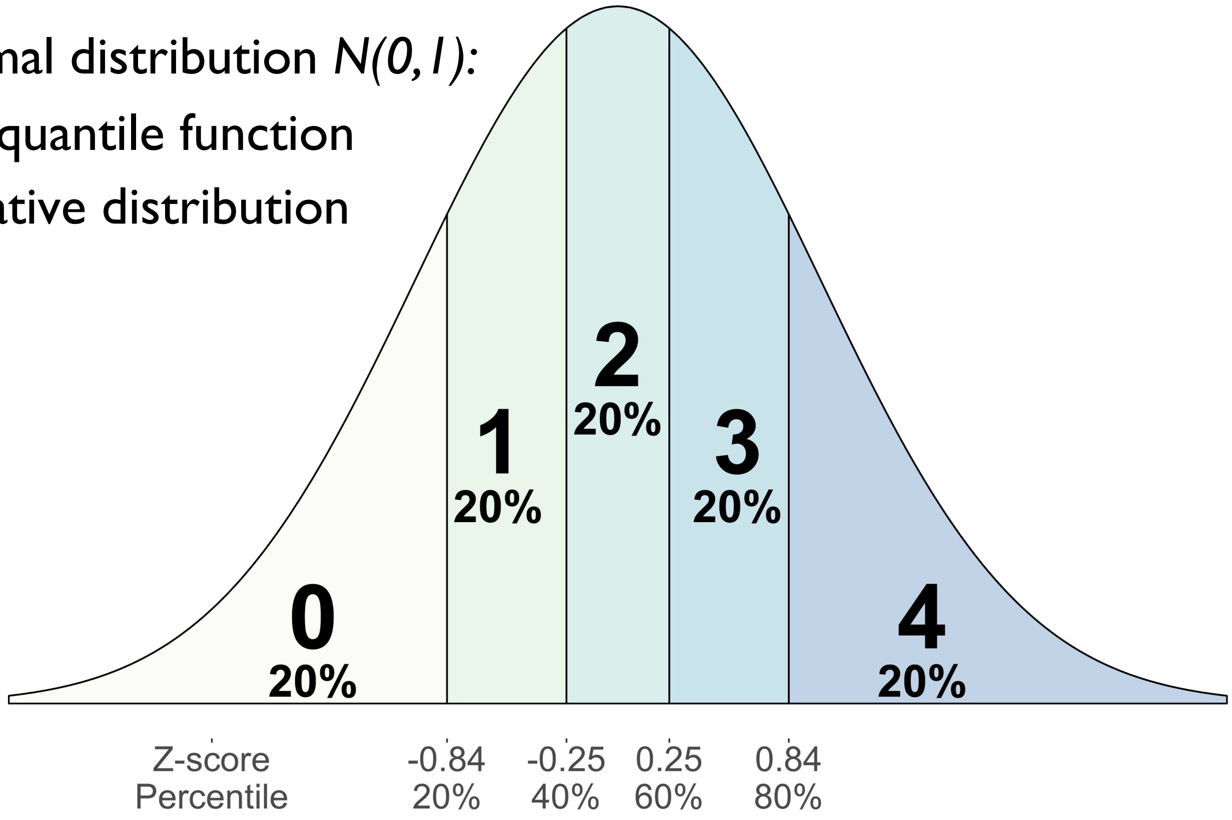
The bounded integer (BI) model

- 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
– *Φ(x)* is the cumulative distribution function



A scale with 5 categories

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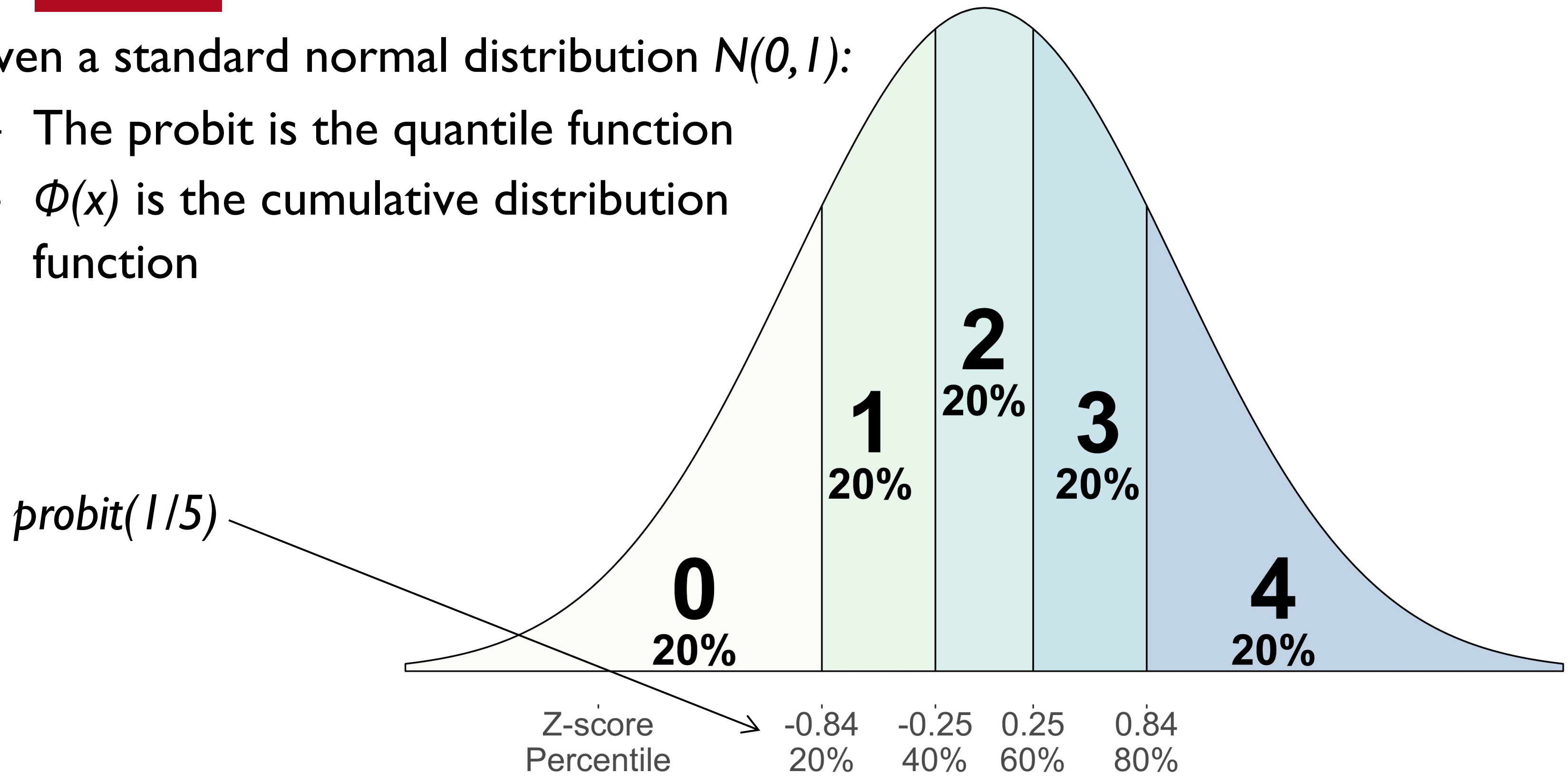

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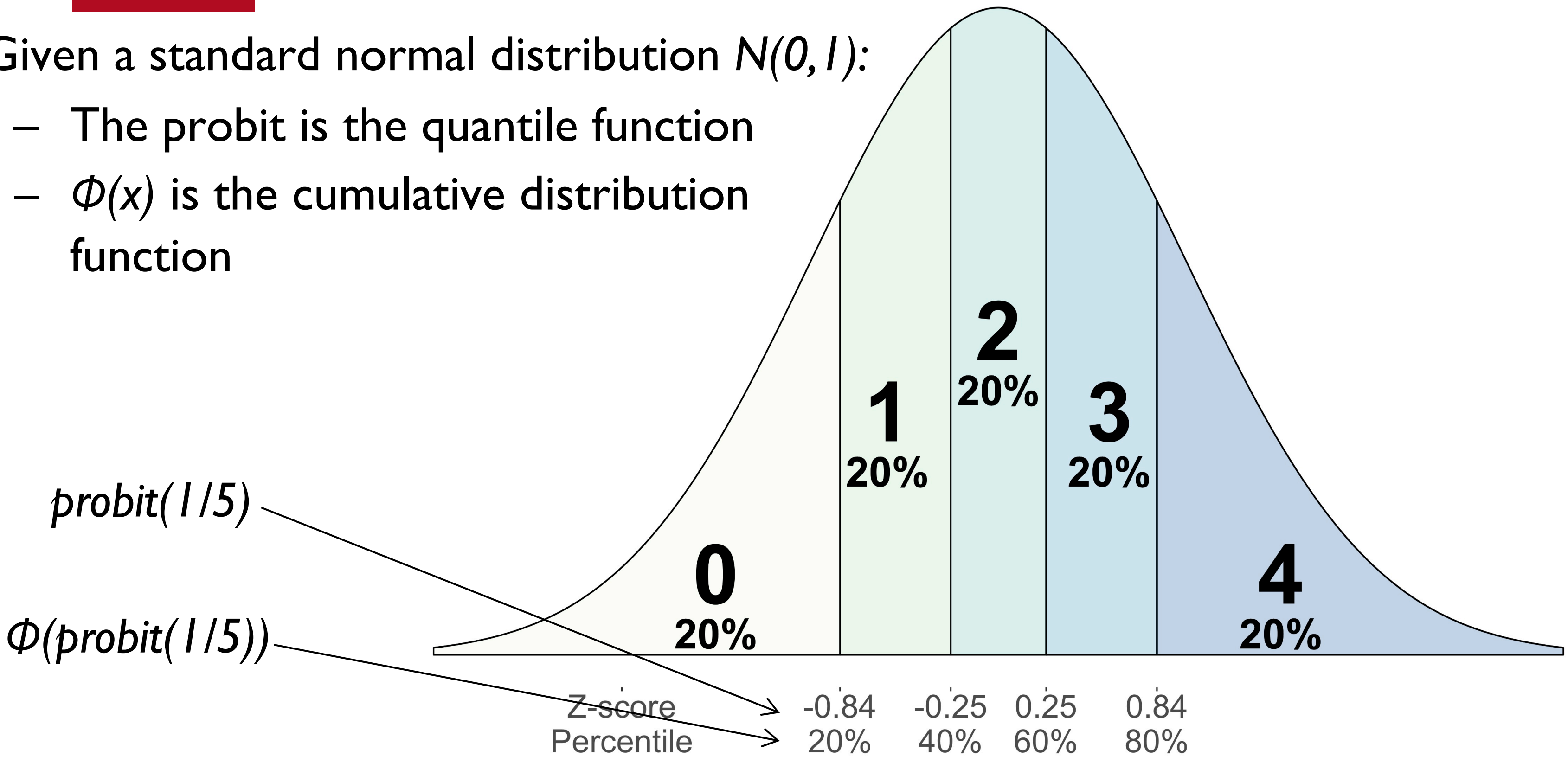

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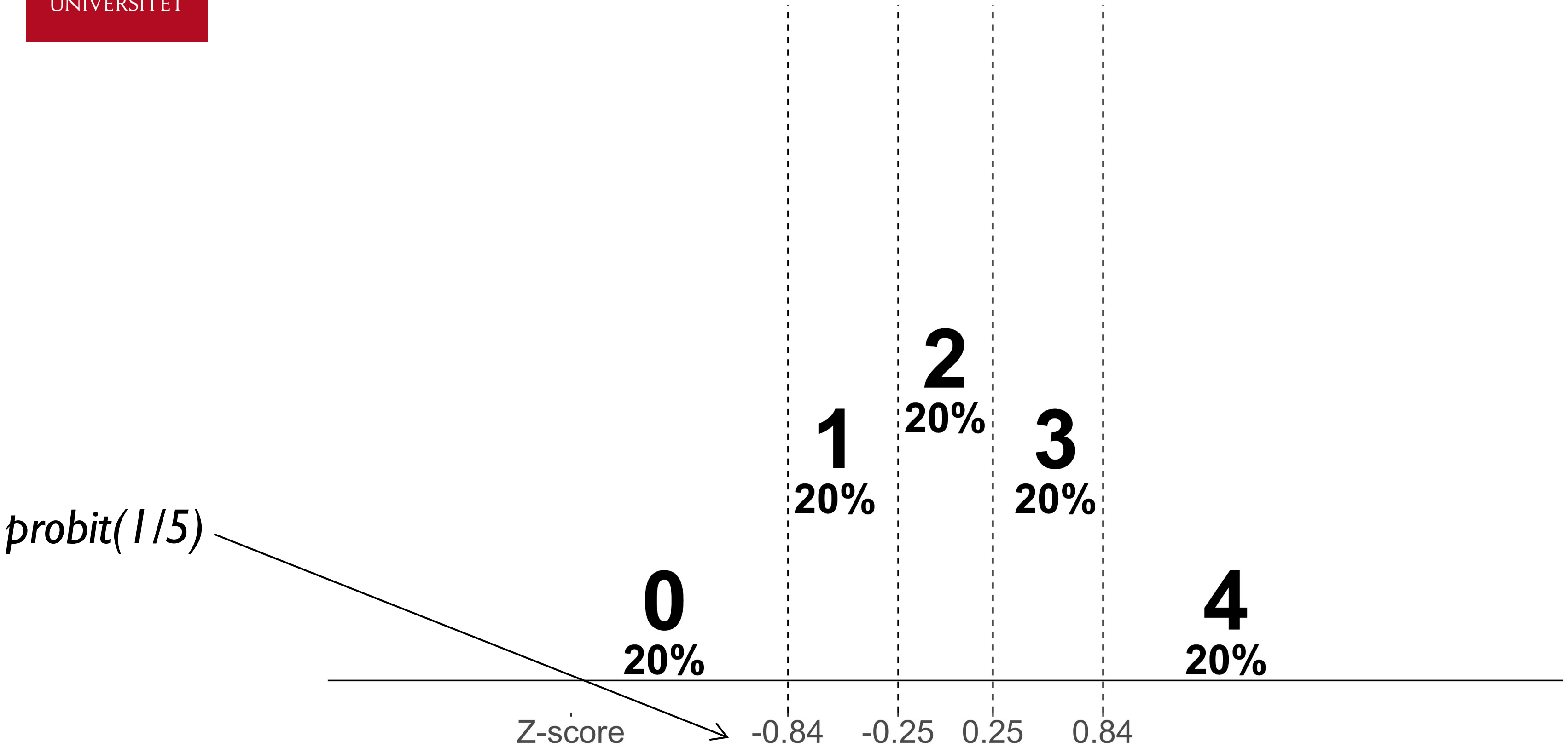
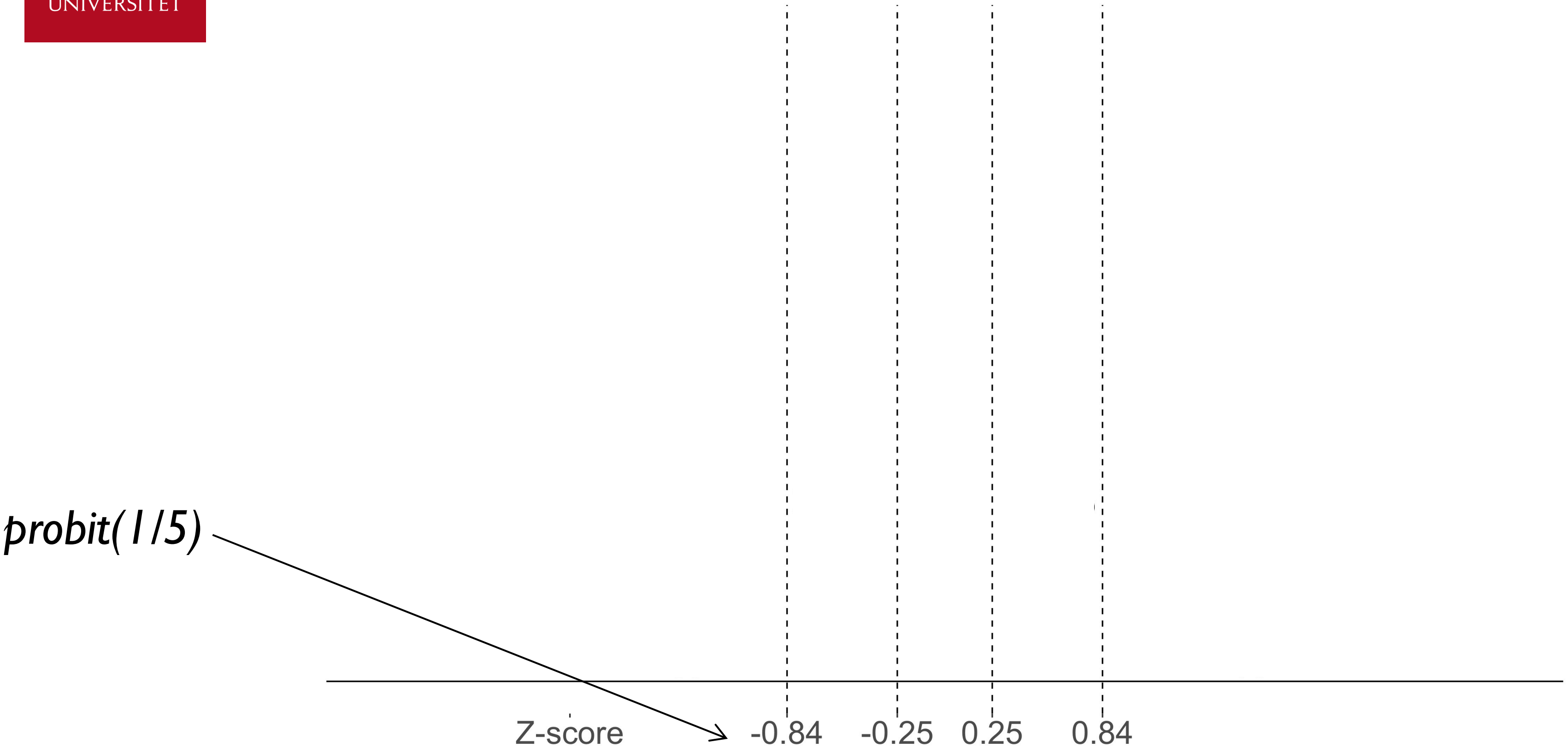


A scale with 5 categories



Probabilities

- The probability P of each score is defined as:

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

  $P(1) = \Phi((\text{probit}(2/n)-f())/g()) \quad – \Phi((\text{probit}(1/n)-f())/g())$

  …

  $P(n-1) = \Phi((\text{probit}(n-1/n)-f())/g()) – \Phi((\text{probit}(n-2/n)-f())/g())$

  $P(n) = 1 \quad – \Phi((\text{probit}(n-1/n)-f())/g())$

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Probabilities

- The probability P of each score is defined as:

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

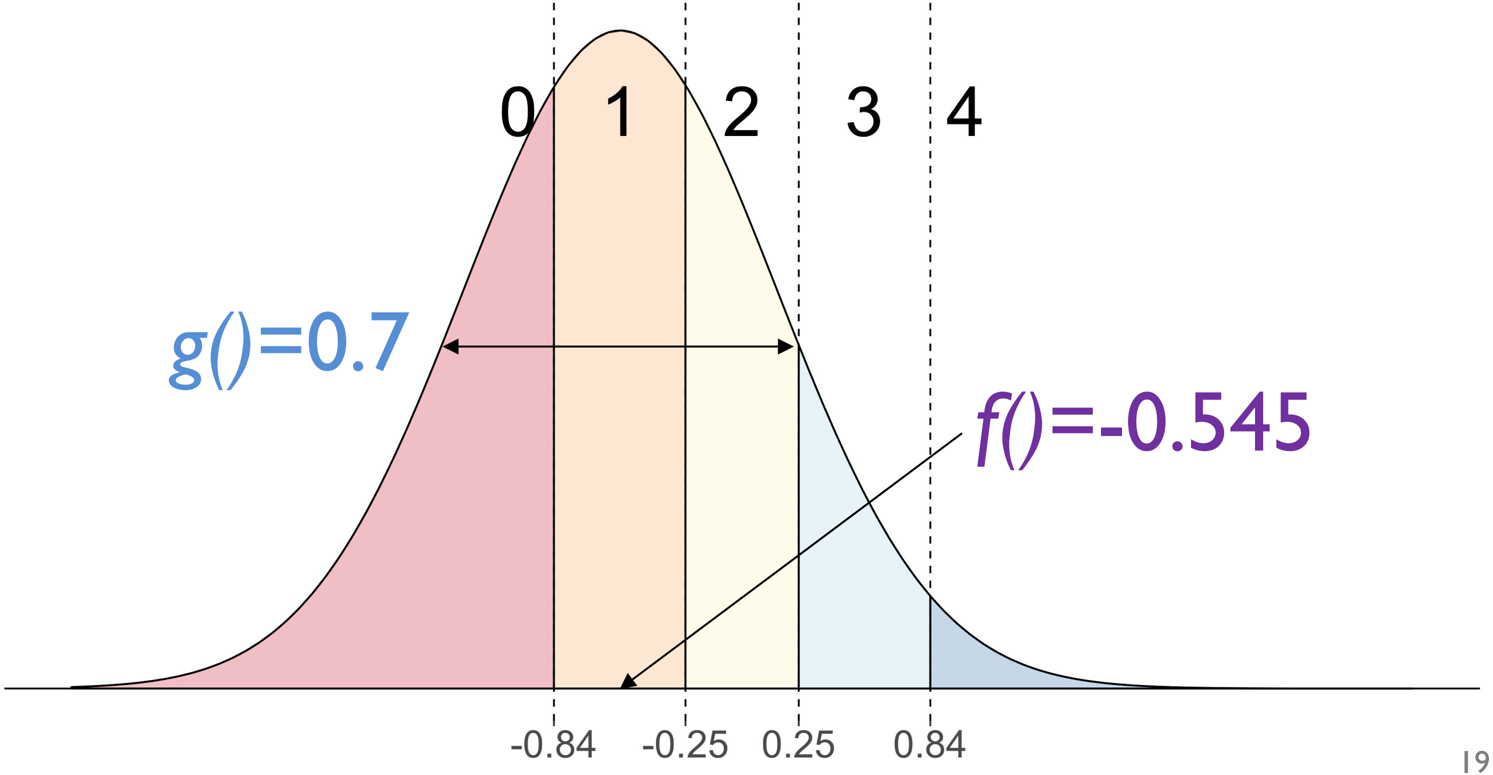
$$P(1) = \Phi(-0.25-f())/g()) - \Phi(-0.84-f())/g())$$

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

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

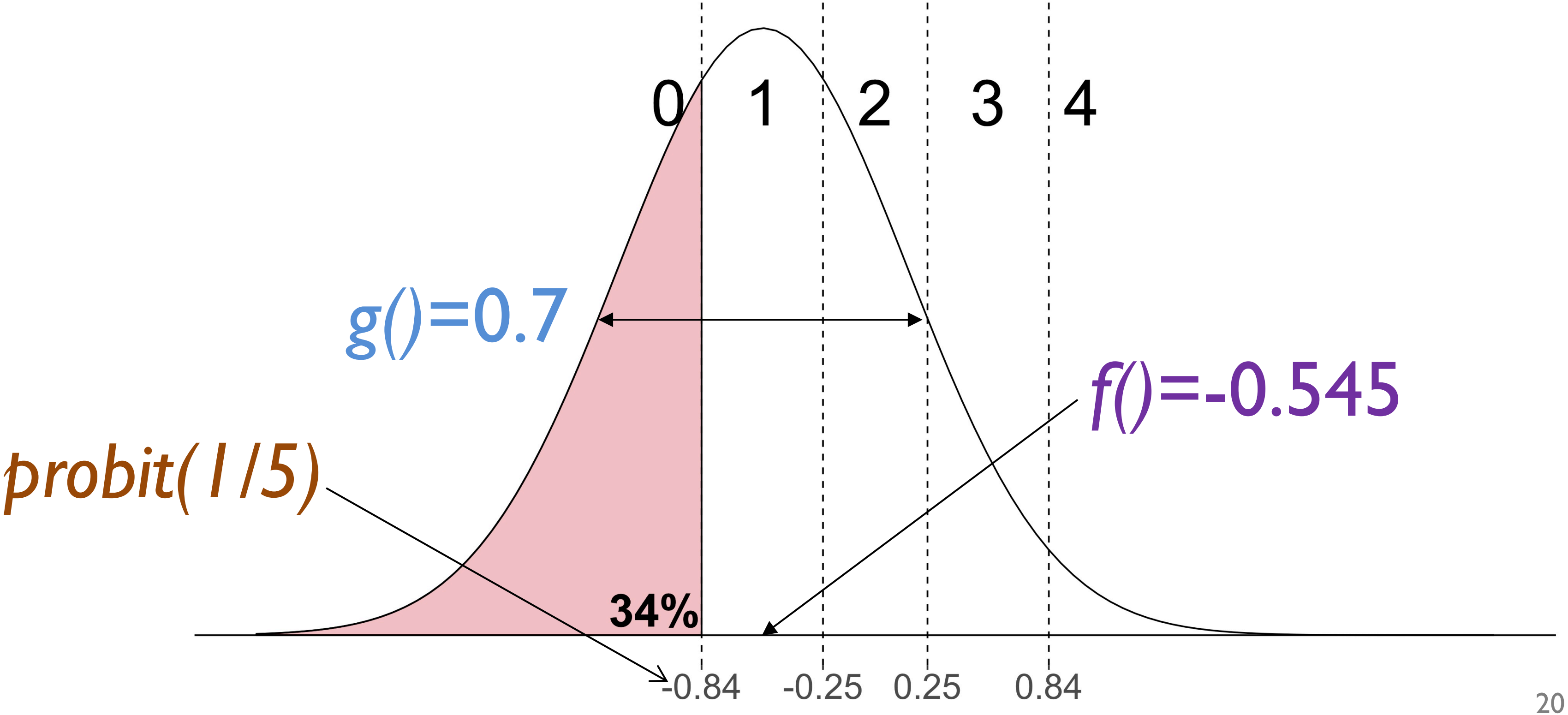
$$P(4) = 1 - \Phi(0.84-f())/g())$$

An illustrating example



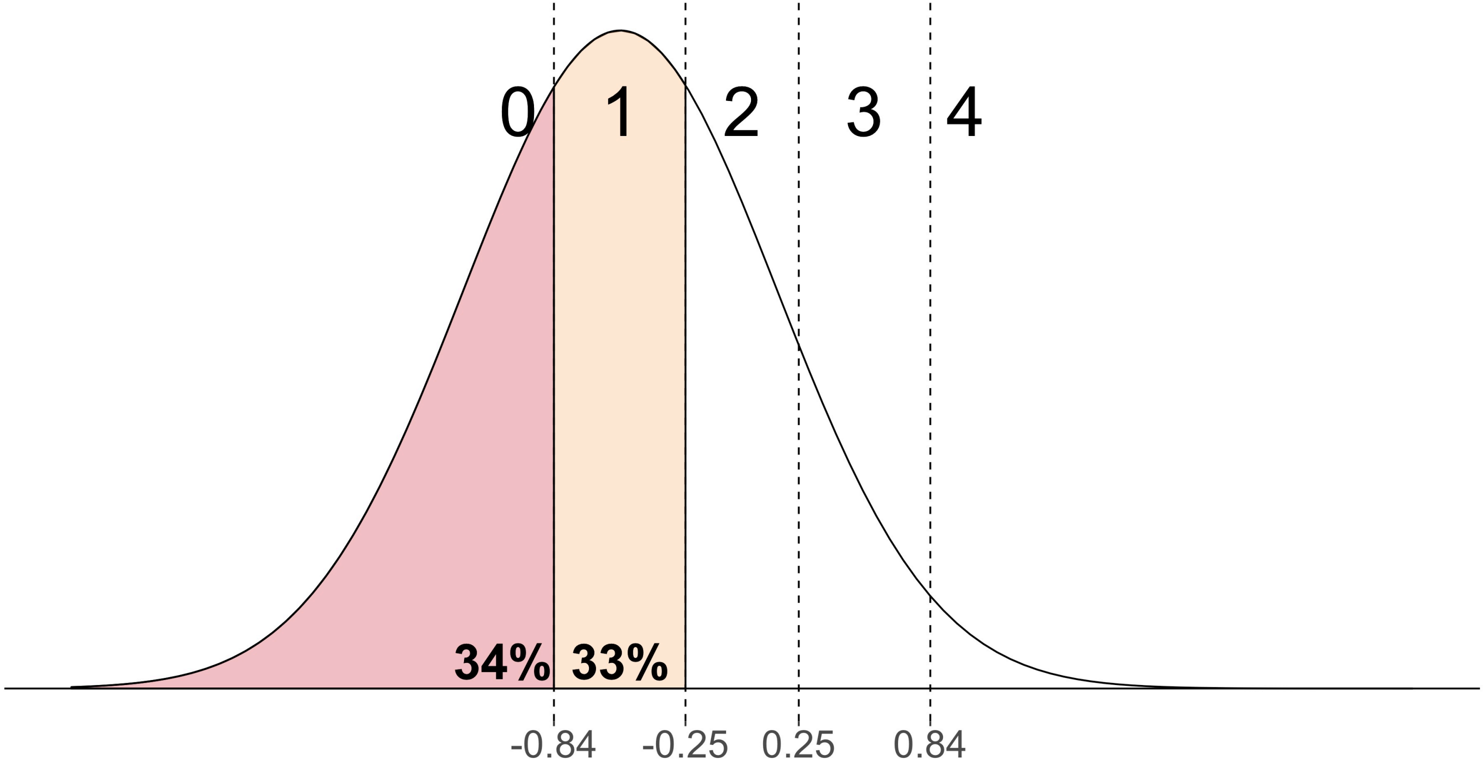
1st area

$$P(0) = \Phi((-0.84 - -0.545)/0.7) = 0.34$$



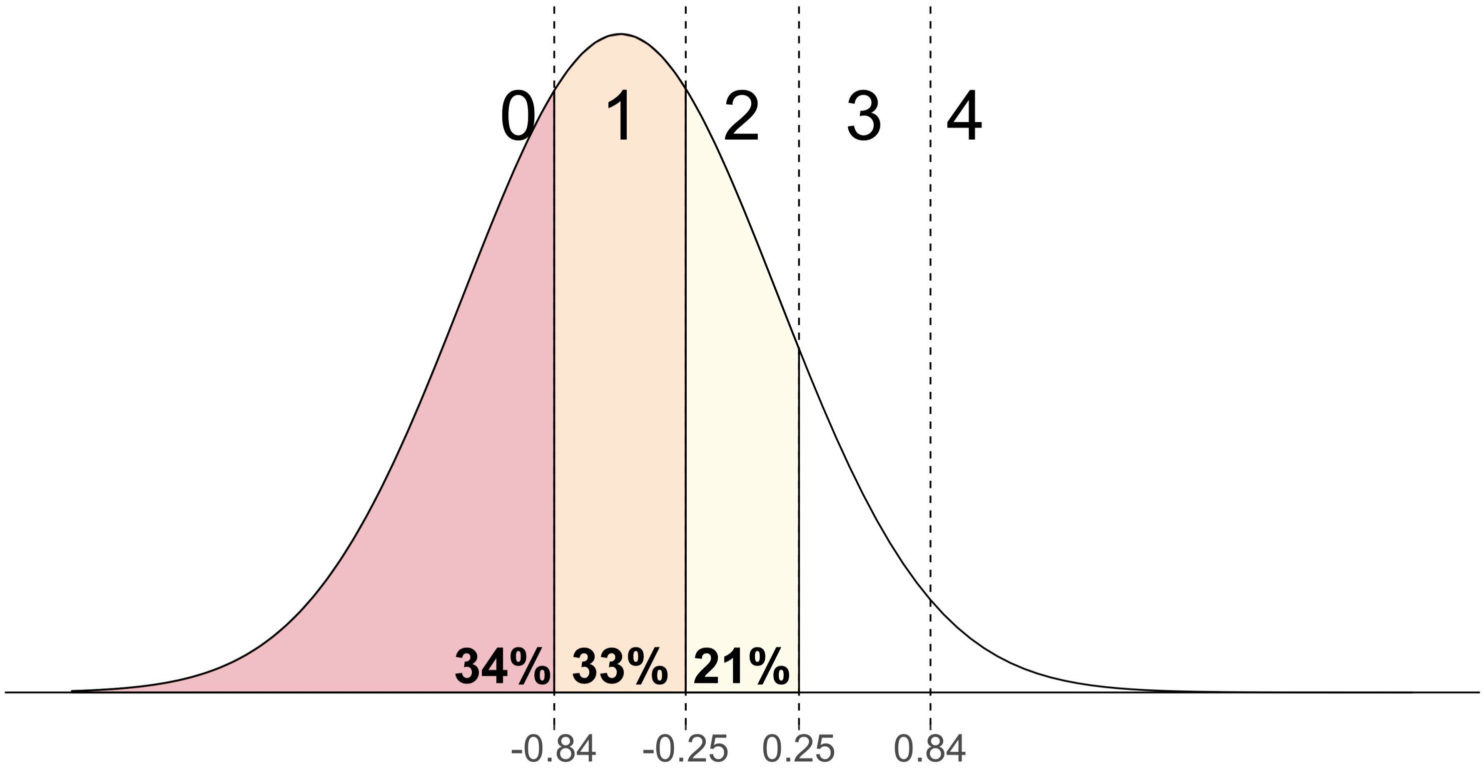
2^{nd} area

$P(1) = \Phi((-0.25 - -0.545)/0.7) - \Phi((-0.84 - -0.545)/0.7) = 0.33$



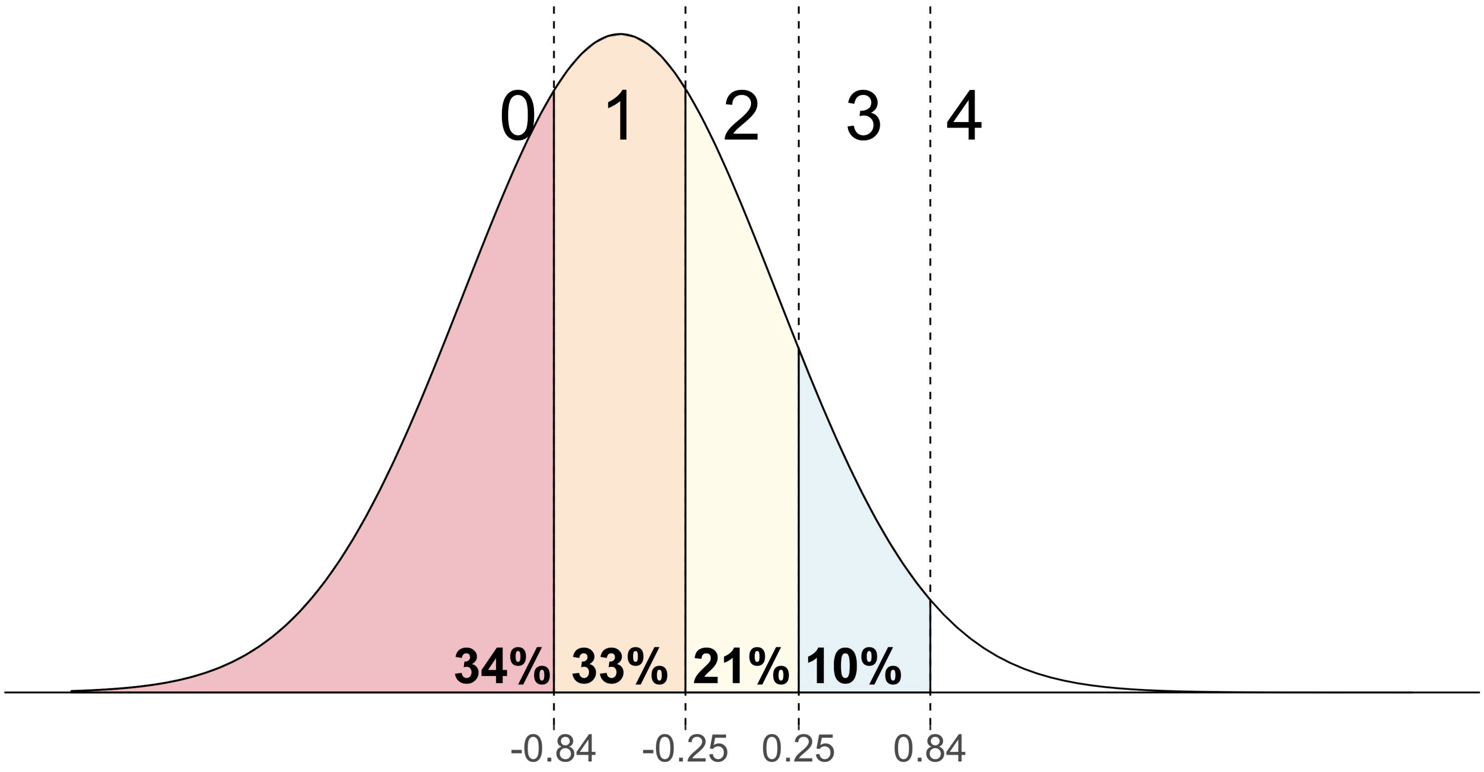
3rd area

$$P(2) = \Phi((0.25 - -0.545)/0.7) - \Phi((-0.25 - -0.545)/0.7) = 0.21$$



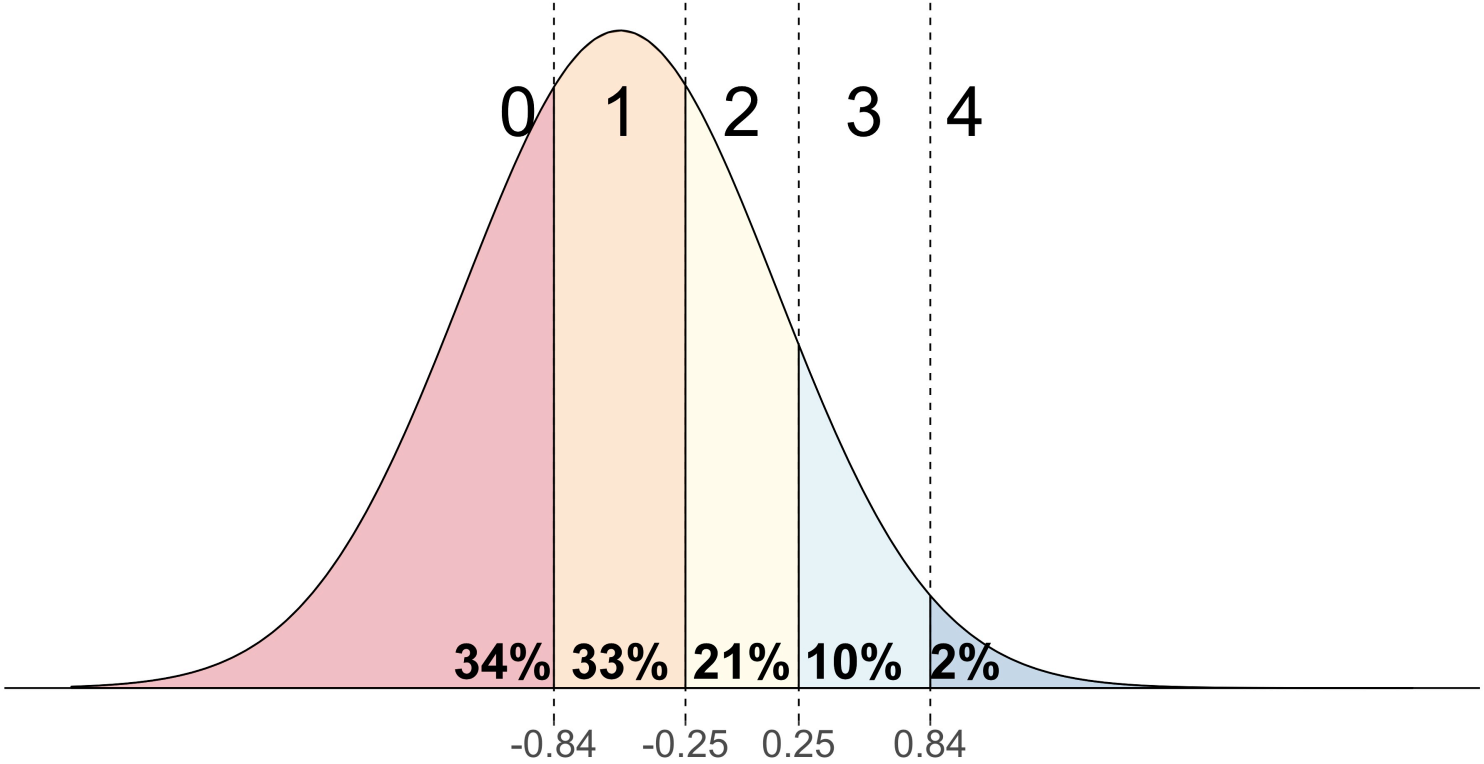
4th area

$$P(3) = \Phi((0.84 - -0.545)/0.7) - \Phi((0.25 - -0.545)/0.7) = 0.10$$



5th area

$P(4) = 1 - \Phi((0.84 - -0.545)/0.7) = 0.02$



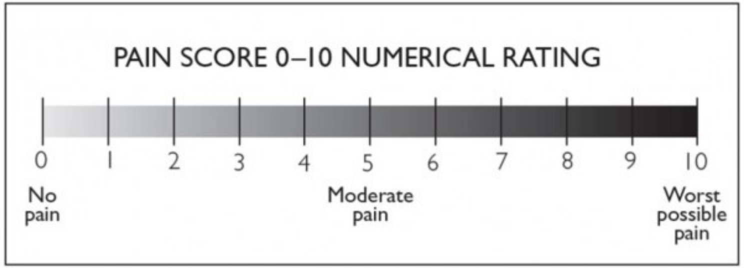
Comparison BI vs. OC – Likert example

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

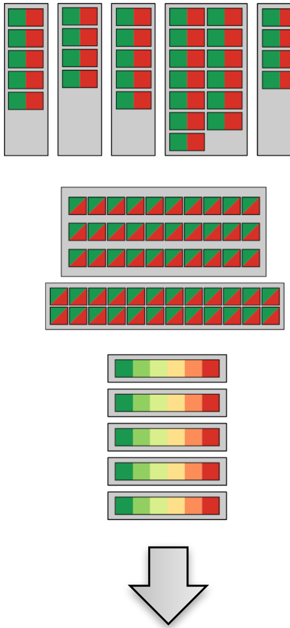
Alzheimer's Disease

Alzheimer's Disease Assessment Scale - Cognition
(ADAS-Cog)

Tasks

Word-based

Rater assessed



Sum

Parkinson's Disease

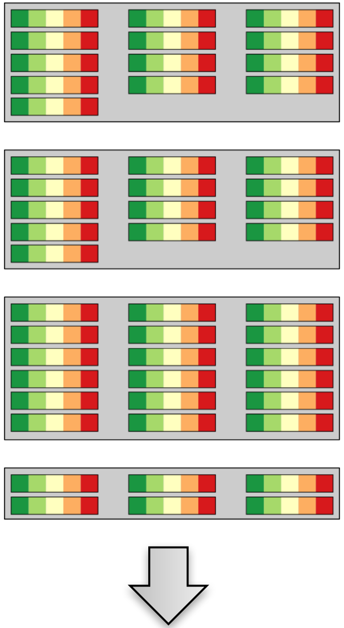
Movement Disorder Society - Unified Parkinson's disease rating scale
(MDS-UPDRS)

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):
  - $\text{Score}_{obs,i,j} = \text{Score}_{predicted,i,j} + \varepsilon_{ij}$

Comparison BI vs. CV examples

Disease	Scale	Categories	#Parameters CV = BI	ΔOFV CV-BI	ΔXV OFV CV-BI
Parkinson's disease	UPDRS motor[1]	109	16	113	138

Data from: [1]Troconiz et al. CPT 1998

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

Comparison BI vs. CV examples

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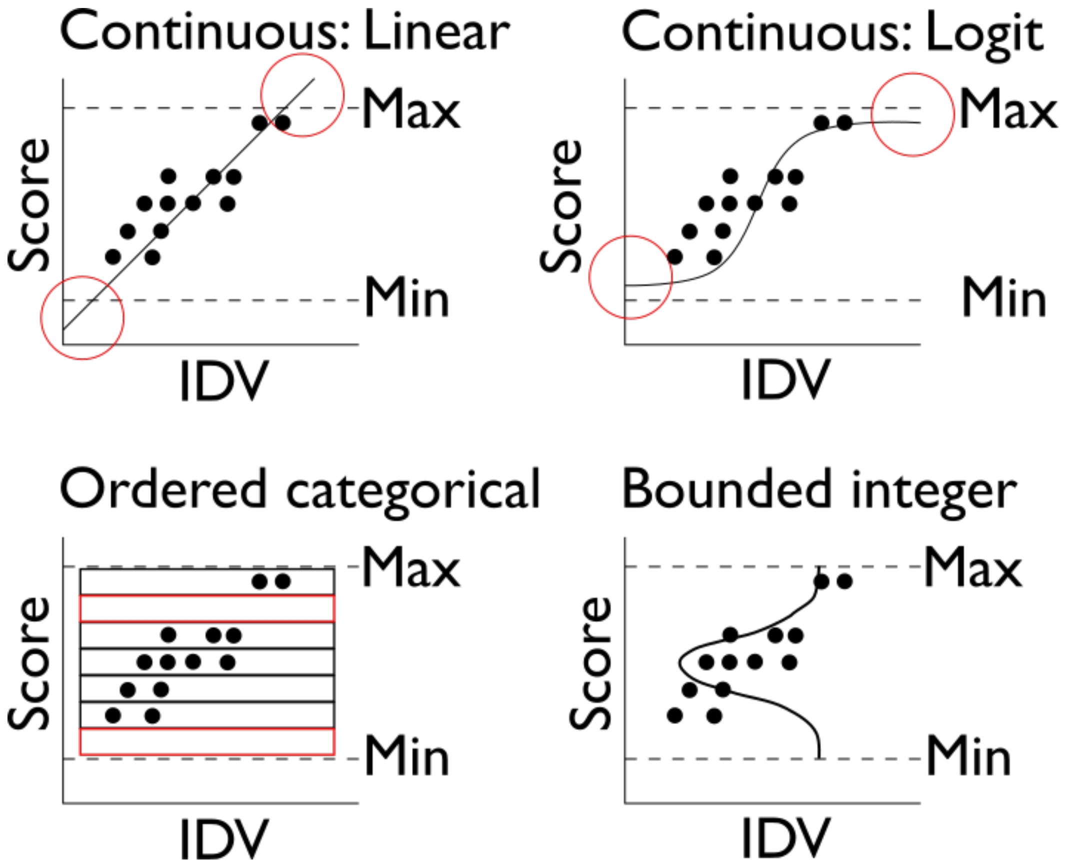
Remarks on BI vs. CV

- 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



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Concluding remarks

- 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

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Thank you for listening

- Thanks to colleagues in the Pharmacometrics Research Group at Uppsala University

Extra slides

Comparison BI vs. CV examples

Disease	Scale	#Patients	#Obs	Scale range	Observed range	#Parameters CV = BI	ΔOFV CV-BI	ΔXV OFV CV-BI
Parkinson's disease	UPDRS motor[1]	19	946	0-108	16-80	16	113	138
Parkinson's disease	MDS-UPDRS motor[2]	428	2720	0-132	1-77	14	73	82
Alzheimer's disease	ADAS-Cog[3]	817	3594	0-70	0-70	11	730	793
Schizophrenia	PANSS[4]	1323	7728	30-210	30-176	17	145	131
Schizophrenia	PANSS[5]	1292	8520	30-210	30-167	15	126	170

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Number of categories

Disease	Scale	#Patients	#Obs	Full range	Observed range	ΔOFV 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

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Under investigation

- Scaling of Z-scores
- Larger variability at high absolute Z-score
- Translation between scales
- Markov elements
- T-distributed variability
- Residuals of rating/composite scales