Pharmacometric approaches to categorical data analysis:

an example based on the relationship between remimazolam concentration and the modified observer's assessment of alertness and sedation scale

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21-10-2022
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Disclosures

Besides my research position at the UMCG, I am also a clinical pharmacokinetics assessor at the Dutch Medicines Evaluation Board (CBG-MEB).

Introduction
MOAAS scale

Introduction

- Observer's Assessment of Alertness and Sedation (OAAS) Scale was originally developed by Chernik *et al. (1990)*
  - To evaluate the ability of flumazenil (GABA-A antagonist) to reverse sedation induced by benzodiazepines (GABA-A agonists)

Table 1. Assessment categories of the observer's assessment of alertness/sedation scale (Chernik *et al. 1990*).

	Assessment categories			
Responsiveness	Speech	Facial expression	Eyes	Composite score level
Responds readily to name spoken in normal tone	Normal	Normal	Clear, no ptosis	5 (Alert)
Lethargic response to name spoken in normal tone	Mild slowing or thickening	Mild relaxation	Glazed or mild ptosis (less than half the eye)	4
Responds only after name is called loudly and/or repeatedly	Slurring or prominent slowing	Marked relaxation (slack jaw)	Glazed and marked ptosis (half the eye or more)	3
Responds only after mild prodding or shaking	Few recognizable words	—	—	2
Does not respond to mild prodding or shaking	—	—	—	1 (Deep sleep)

Introduction

- Modified OAAS Scale is Not standardised
  - Number of scores can be reduced to facilitate implementation (e.g. Peters *et al. 1999 → 4 categories*)
  - Number of scores can be increased to better characterise deep sedation (e.g. addition of a noxious stimuli or "truly" noxious stimuli [EOAA/S, Kim *et al. 2015*]) or agitation (e.g. Casati *et al. 1999, Drake et al. 2006)*
- Characteristics of ordinal data:
  - Finite number of scales (e.g. 4, 5, 6, 7 or even further reductions or extensions)
  - Order or ranking in scales (e.g. 5 [Awake] > 4 > … > 1 >0 [fully sedated])
  - Distance between categories cannot be defined or is meaningless (e.g. patient moving from 4 to 2 cannot be considered a doubling in sedation)

Introduction

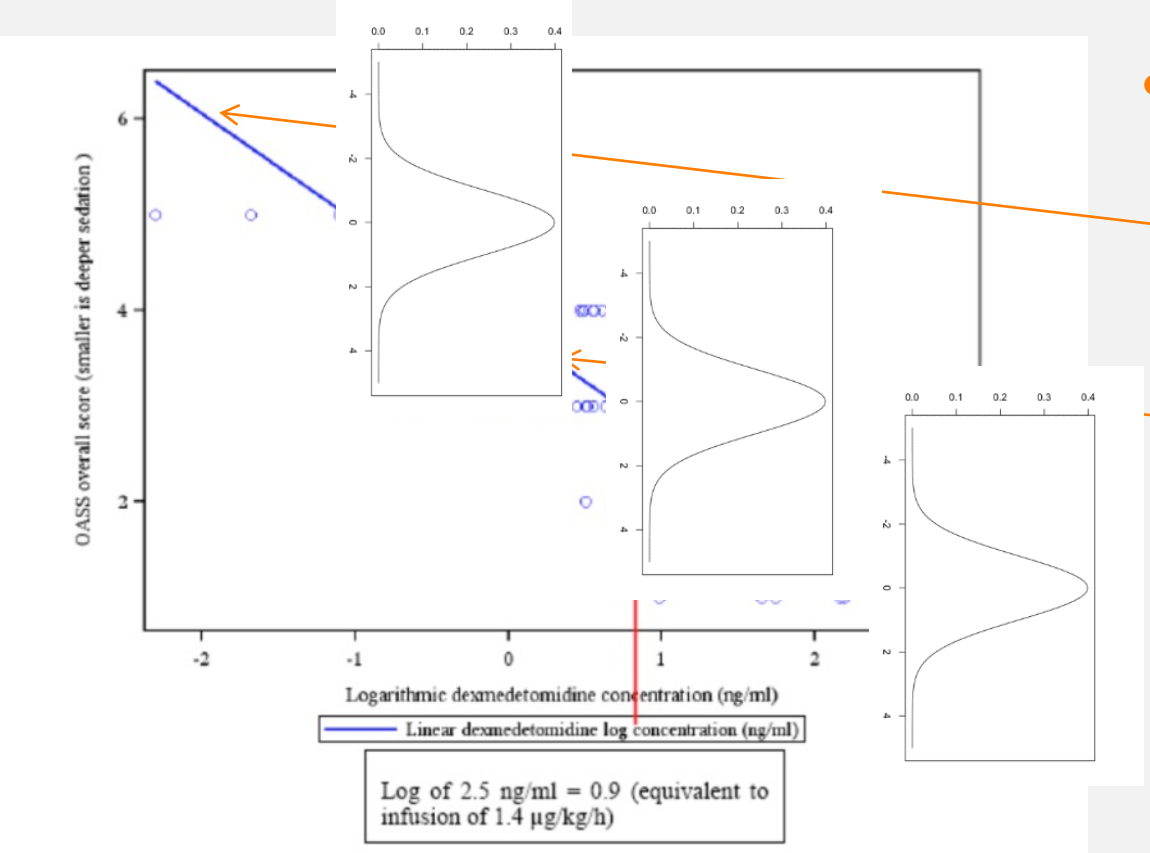


Figure 1. Exposure-response relationhip for dexmedetomidine and OAAS.
European Public Assessment Report, Dexdor, dexmedetomidine, EMEA/H/C/002268

- Data are sometimes treated as continuous data:
  - The model suggests an OAAS of 6 at exp(-2) = 0.14 ng/mL → violates finite number property
  - The model suggest an OAAS of 3.5 at exp(0.5) = 1.65 ng/mL → violates property of non-equal distances between scales.
  - Additionally, normality assumption of the model does not hold at the extremes

Introduction

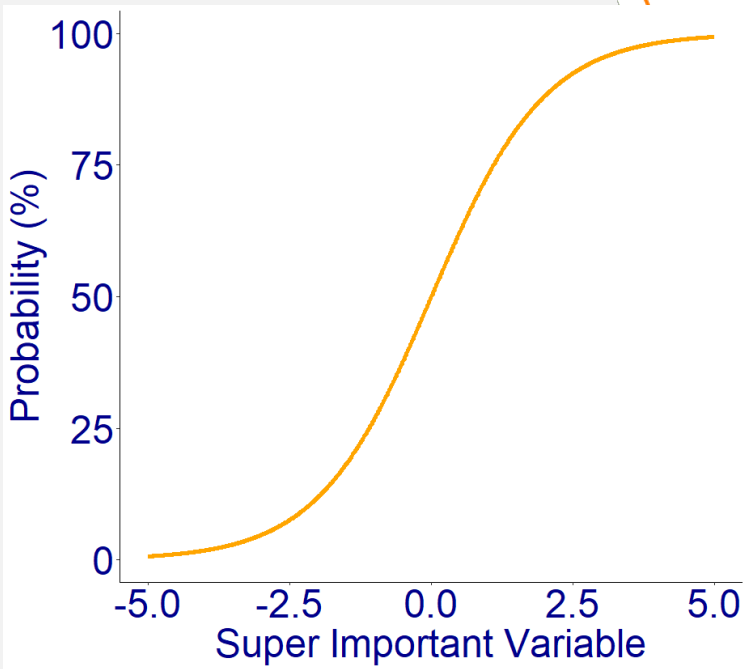
- To preserve the properties of ordinal data, we can model the probability of observing a certain MOAAS category

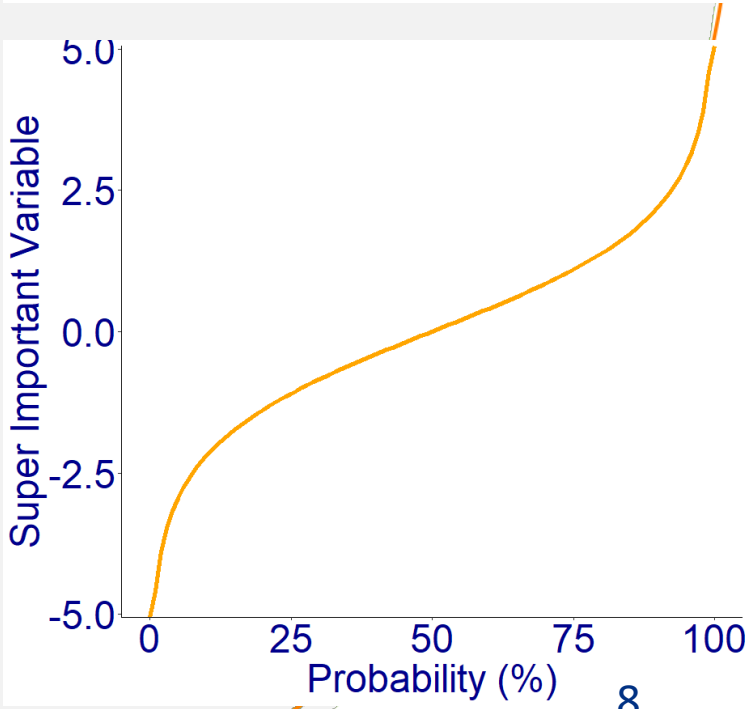
- Multiple approaches described:
  - Multinomial logistic model (Hedeker D. 2003, Agresti A. 2010)
  - Proportional odds model (Sheiner LB *et al. 1994*, Agresti A. 2010)
  - Adjacent categories model (Agresti A. 2010)
  - Differential odds model (Kjellsson MC *et al*. 2008)
  - Discrete-time markov model(s) (Karlsson MO *et al.* 2000)
  - (Minimal) continuous-time markov model (Schindler *et al.* 2017, Bergstrand *et al.* 2009)

Introduction Model Structures

Modelling Probability

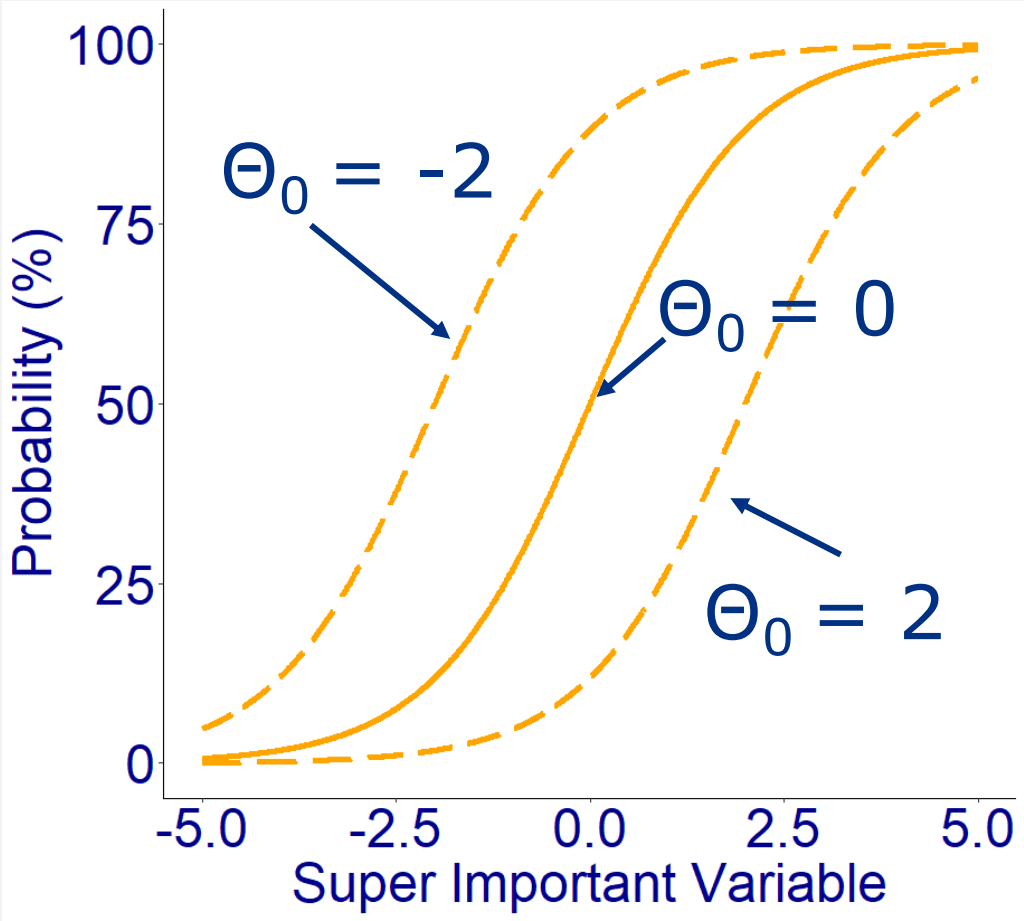
- Modelling Probabilities:
  - Probability is defined as the ratio of the number of events (of interest) to the total number of events.
  - Scale is limited to 0-1 (or 0 to 100%)
    - 0: no event
    - 1: event
  - Enforced by expit transform:
    - exp(x)/(1 + exp(x))
  - Reversed to infinite scale by logit transform:
    - ln(x/(1-x))





Logistic Model

- Model the probability of a single event
- Increasing the intercept (θ_0), shifts curve to the right



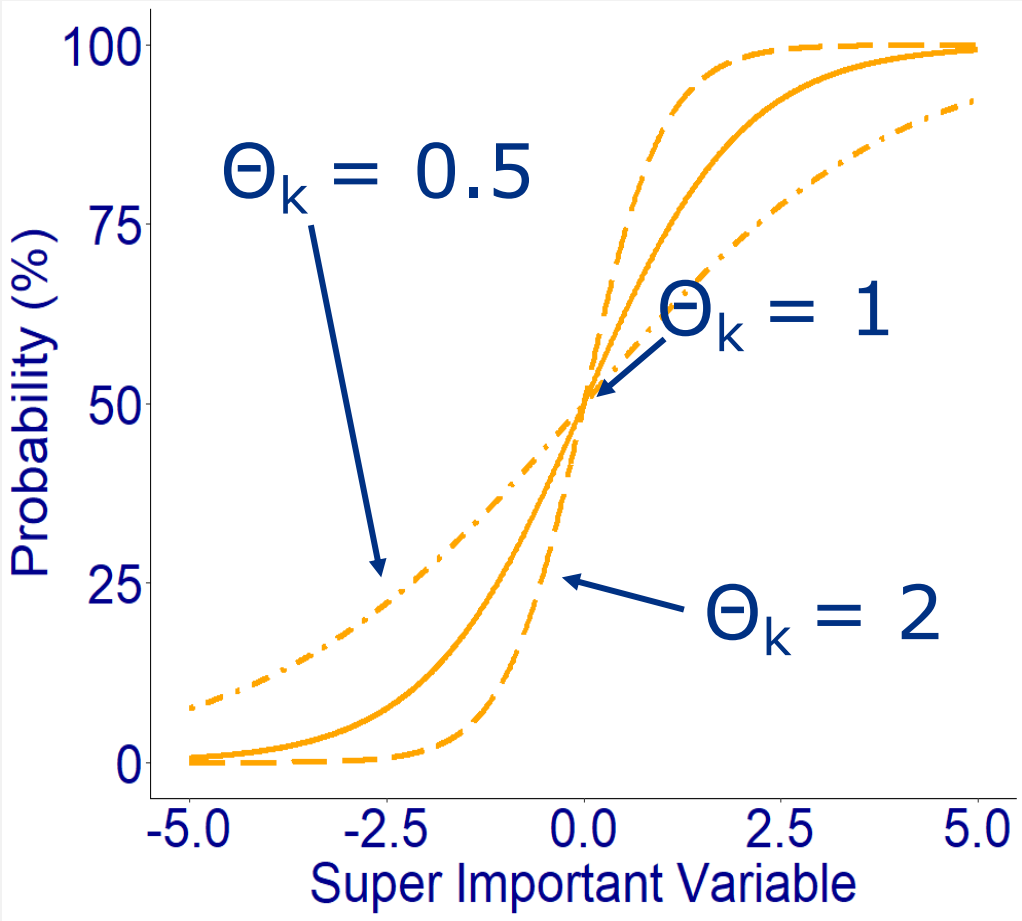
Model definition:

$$p(Y = j|x) = \frac{\exp(\theta_0 + \sum_{k=1} \theta_k x_k + \eta)}{1 + \exp(\theta_0 + \sum_{k=1} \theta_k x_k + \eta)}$$

j = category of interest
i = individual categories in summation
k = number of parameters/variables
θ = fixed effects
η = random effects

Logistic Model

- Increasing the slope (θ_k), shifts steepness of the curve



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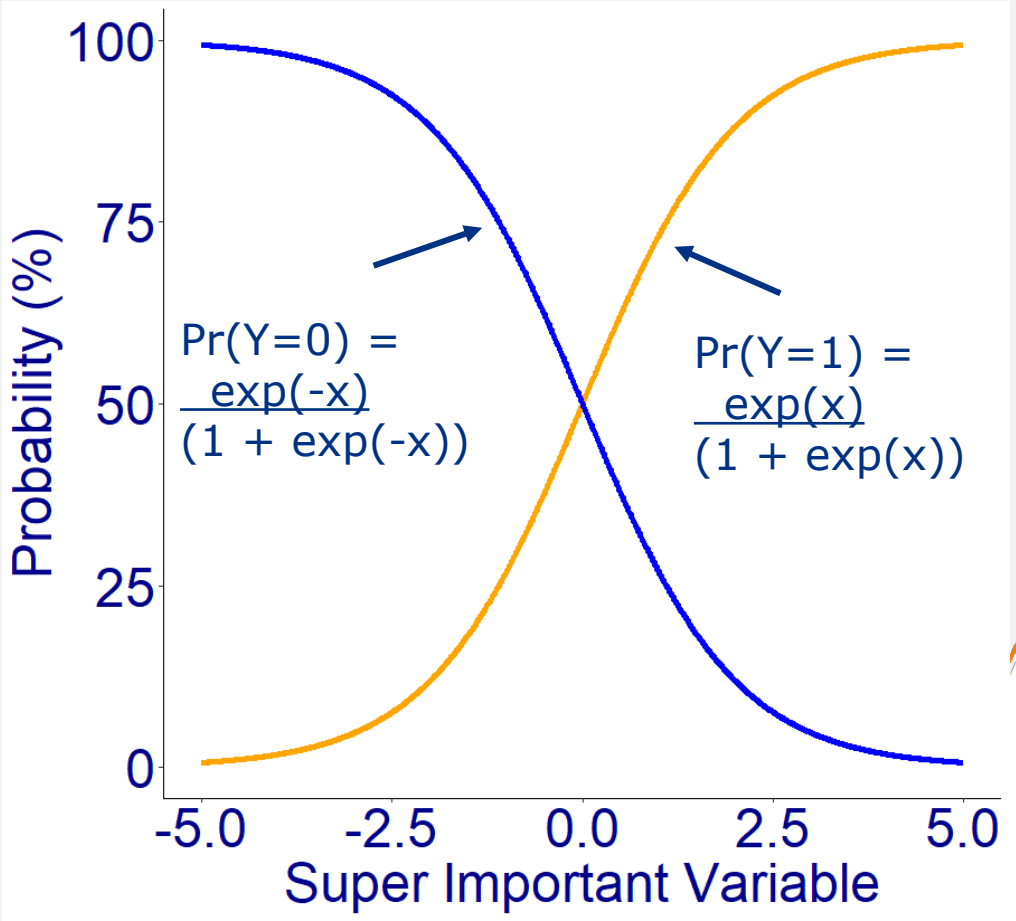
Logistic Model

- Inverse of the model is probability of other event



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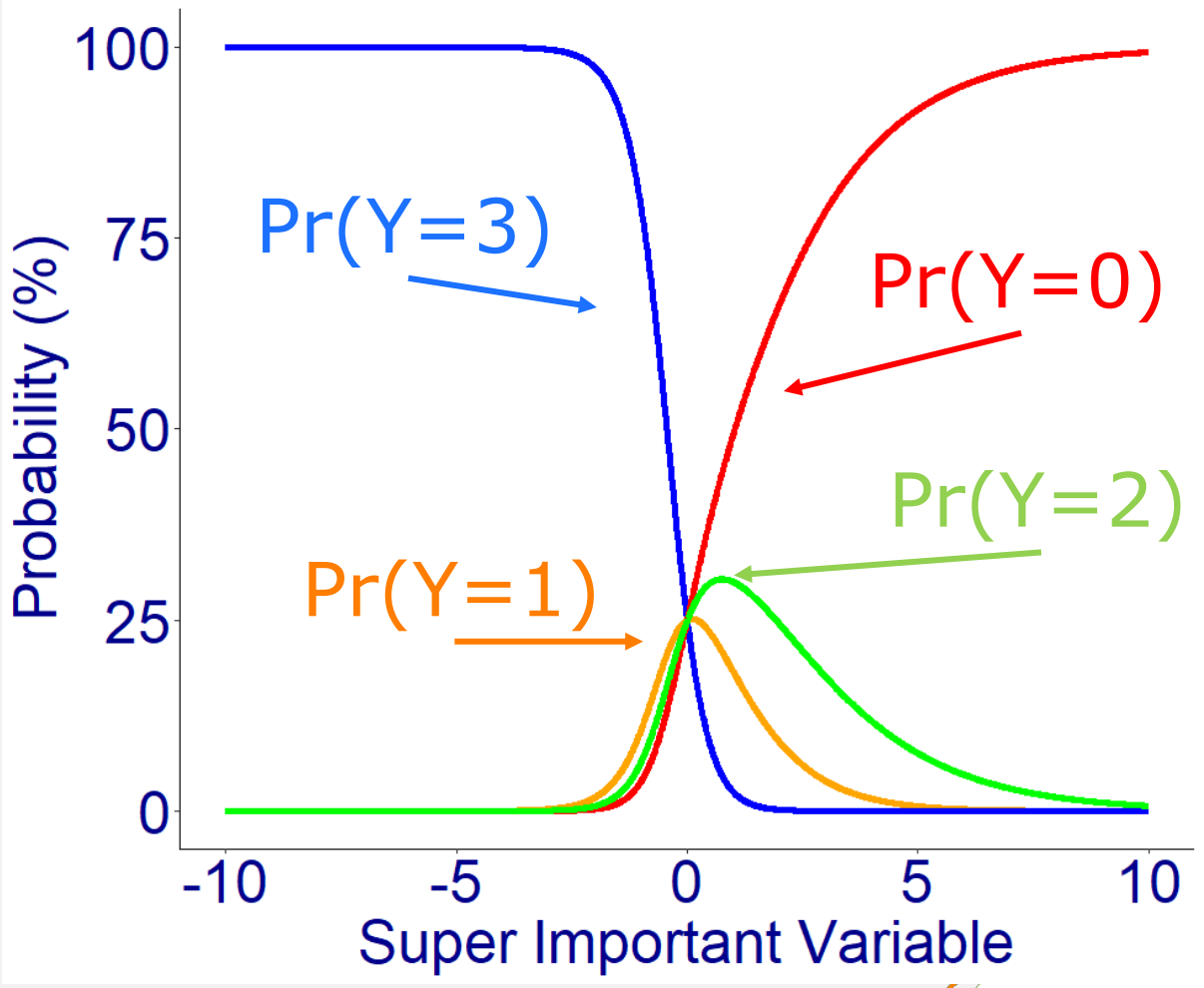
Multinomial logistic model

- Model structure ensures that sum of all probabilities is 1



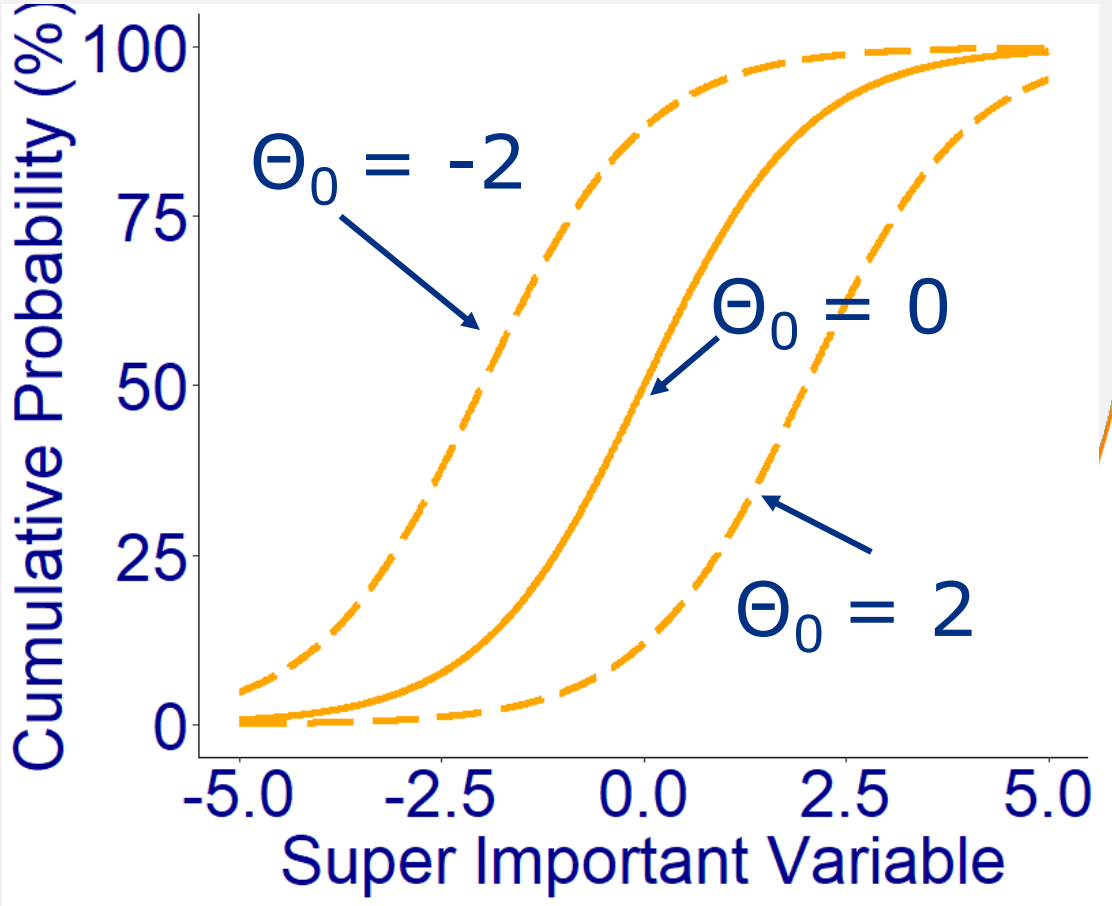
Model definition

$$p(Y = j|x) = \frac{\exp(\theta_{0j} + \sum_{k=1}^{p} \theta_{kj} x_{kj} + \eta_j)}{1 + \sum_{i=1}^{j-1} \exp(\theta_{0i} + \sum_{k=1}^{p} \theta_{ki} x_{ki} + \eta_i)}$$

j = category of interest
i = individual categories in summation
k = number of parameters/variables
θ = fixed effects
η = random effects

Proportional Odds Model

- Intercept (θ_0) parameter is used to force order, thus we can have $\Theta_{0,\ 1st\ category} > \Theta_{0,\ 2nd\ category} > \Theta_{0,\ 3rd\ category}$
- Proportional odds assumption: Predictor function is similar for all categories
- We are now modelling cumulative Pr(Y≤0), Pr(Y≤1), etc.



Model definition

$$p(Y \leq j|x) = \frac{\exp(\theta_{0j} + \sum_{k=1}^{p} \theta_k x_k + \eta\ )}{1 + \sum_{i=1}^{j-1} \exp(\theta_{0i} + \sum_{k=1}^{p} \theta_k x_k + \eta\ )}$$

j = category of interest
i = individual categories in summation
k = parameter number
p = number of parameters/variables
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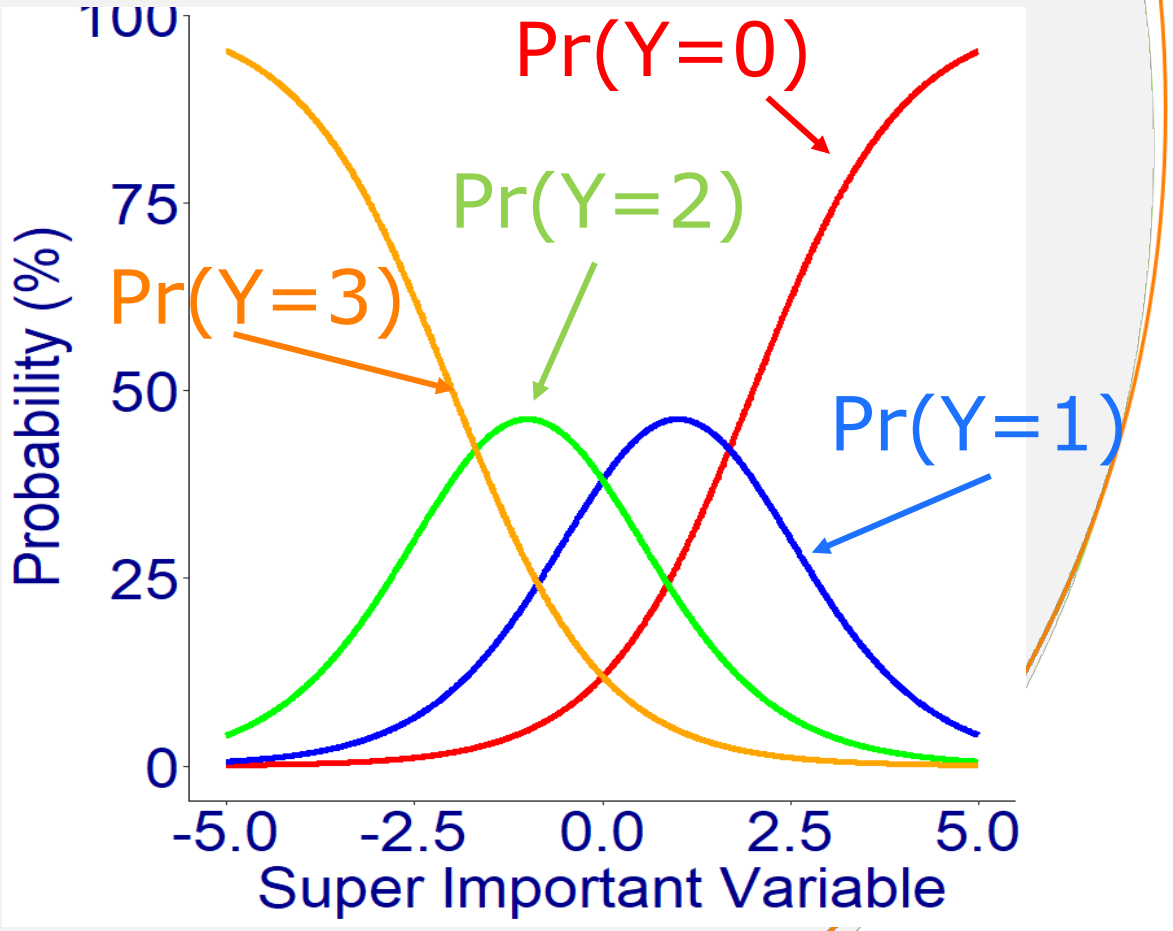
Proportional Odds Model

$p(\text{Y} = 0) = p(Y \leq 0|x)$
$p(\text{Y} = 1) = p(Y \leq 1|x) - p(Y \leq 0|x)$
…
$p(\text{Y} = \text{j}) = 1 - p(Y \leq j-1|x)$



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j = category of interest
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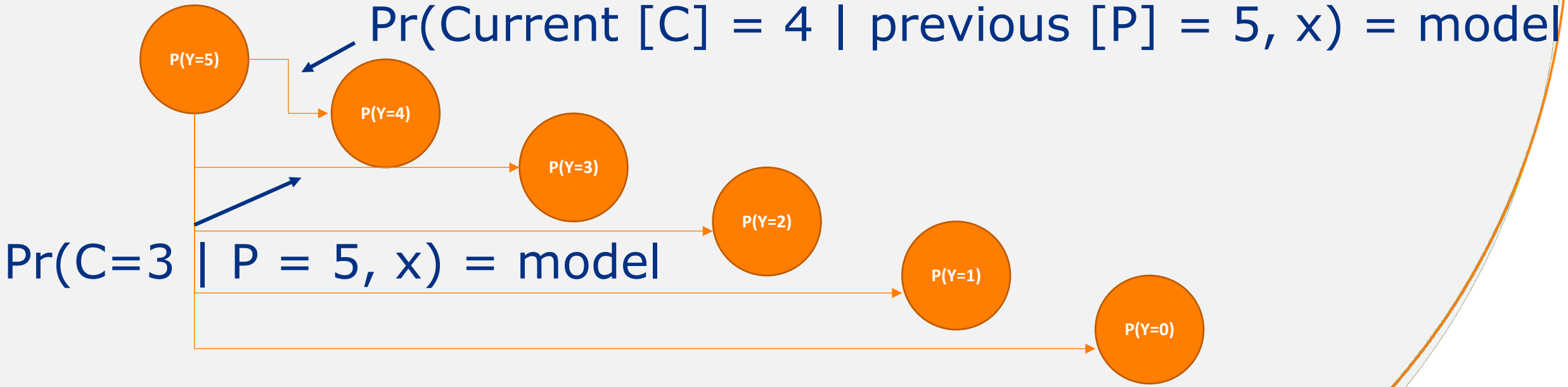
Alternative models

- Adjacent Categories Model
  - Probability of each MOAAS scale is compared to the next lower MOAAS scale
- Differential Odds Model
  - Extension of proportional odds model
  - Predictor function can vary per scale but only within boundaries of other scales
    - $\theta_{i5} > \theta_{i4} > \ldots > > \theta_{i0}$

Markov model

- In Markov Models, we model the probability of the current MOAAS score given that a certain MOAAS score was observed previously (i.e. transition probabilities)



Discrete-Time Markov Model

- All previous time-independent model structures can be extended to a Markov Model

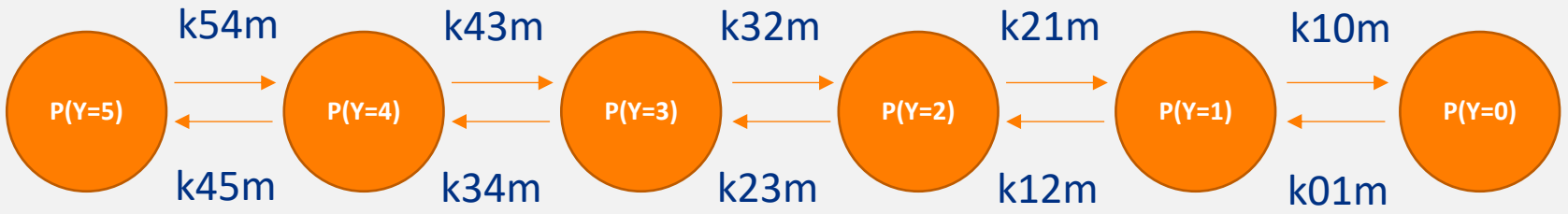
Example Model Definition (extension of Proportional Odds Model):
The probability of a MOAAS j at the current occasion (t) given that a MOAAS l was observed at the previous occasion (t- δ);

$$P(Y_t \geq j \mid Y_{t-\delta} = l, x) = \frac{\exp(\theta_{0jl} + \sum_{k=1}^{p} \theta_k x_k + \eta)}{1 + \sum_{i=1}^{j-1} \exp(\theta_{0j+i,l+i} + \sum_{k=1}^{p} \theta_k x_k + \eta)}$$

$$P(Y_t = j \mid Y_{t-\delta} = l) = P(Y_t \geq j+1 \mid Y_{t-\delta} = l) - P(Y_t \geq j \mid Y_{t-\delta} = l)$$

Continuous-Time Markov model

- Example structure (compartmental approach)



Example with remimazolam

Aim

- In this study, we evaluated which approach is most suitable to analyse the MOAA/S scale.
  - Emphasis on clinical implications between approaches described in literature (i.e. differences in exposure-response relationship)

Methods

- Remimazolam dataset
  - Four procedural sedation datasets of remimazolam

Table 2. Included studies

Clinical trial	*Number of subjects*	*Number of observations*
ONO-2745-01	35	1190
ONO-2745-02	8	296
CNS7056-001	54	1241
CNS7056-017	20	604

Methods

- **Step 1.** Obtain post-hoc Pharmacokinetic Empirical Bayes Estimates (EBEs) using the population pharmacokinetic model as described by Zhou *et al.* (Clin. Transl. Sci., 2021)

Methods

- **Step 2.** Develop MOAAS models using sequential approach
  - **Parameters estimation**
    - Maximum likelihood estimation
    - LaPlacian algorithm in NONMEM version 7.5
  - **Different structural models**
    - Drug effect models: Linear, emax or sigmoid drug effect
    - Delay PK and PD evaluated: with effect compartment
  - **Interindividual variability**
    - Explored on structural model parameters and drug effect parameters
  - **Model evaluation:**
    - Visual predictive checks (95% prediction interval, n = 100 simulations):
      - Proportion observations over concentration range and over time
      - Transitions over concentration range and over time
    - Numerically
      - Objective function value (improvement of 3.84, $p<0.05$, df=1)
      - Relative standard errors of model parameters (including variance estimates, <50%)

Results

Table 3. Overview of model results

Time-independent				
Models	**Multinomial Logistic Model**	**Proportional Odds Model**	**Adjacent Categories Model**	**Differential Odds Model**
OFV	5033.7	4774.0	4785.6	No improvement in OFV
RSE (%), mean [min-max]	9.1 [5.6 - 11.5]	15.6 [7.6 – 36.9]	23.2 [7.2– 36.3]	
Structural model parameters (n)	11	8	8	
Stochastic model parameters (n)	5	2	2	
Effect compartment	Yes	Yes	Yes	
Drug effect	Linear	Emax	Emax	
Time dependent: discrete time				
Models				
OFV				
RSE (%), mean [min-max]				
Structural model parameters (n)				
Stochastic model parameters (n)				
Effect compartment				
Drug effect				
Time dependent: continuous time				
Models				
OFV				
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Stochastic model parameters (n)	5	2	2	
Effect compartment	Yes	Yes	Yes	
Drug effect	Linear	Emax	Emax	
Time dependent: discrete time				
Models	**Markov Model (extension of Multinomial Logistic Model)**	**Markov Model (extension of Proportional Odds Model)**	**Markov Model (extension of Adjacent Categories Model)**	**Markov Model (extension of Differential Odds Model)**
OFV	4182.4	4016.3	3968.0	No improvement in OFV
RSE (%), mean [min-max]	26.7 [7.7 – 103.9]	18.6 [3.5 – 74.0]	24.0 [8.4 – 51.1]	
Structural model parameters (n)	33	32	32	
Stochastic model parameters (n)	1	1	1	
Effect compartment	Yes	Yes	Yes	
Drug effect	Sigmoid	Emax	Emax	
Time dependent: continuous time				
Models				
OFV				
RSE (%), mean [min-max]				
Structural model parameters (n)				
Stochastic model parameters (n)				
Effect compartment				
Drug effect				

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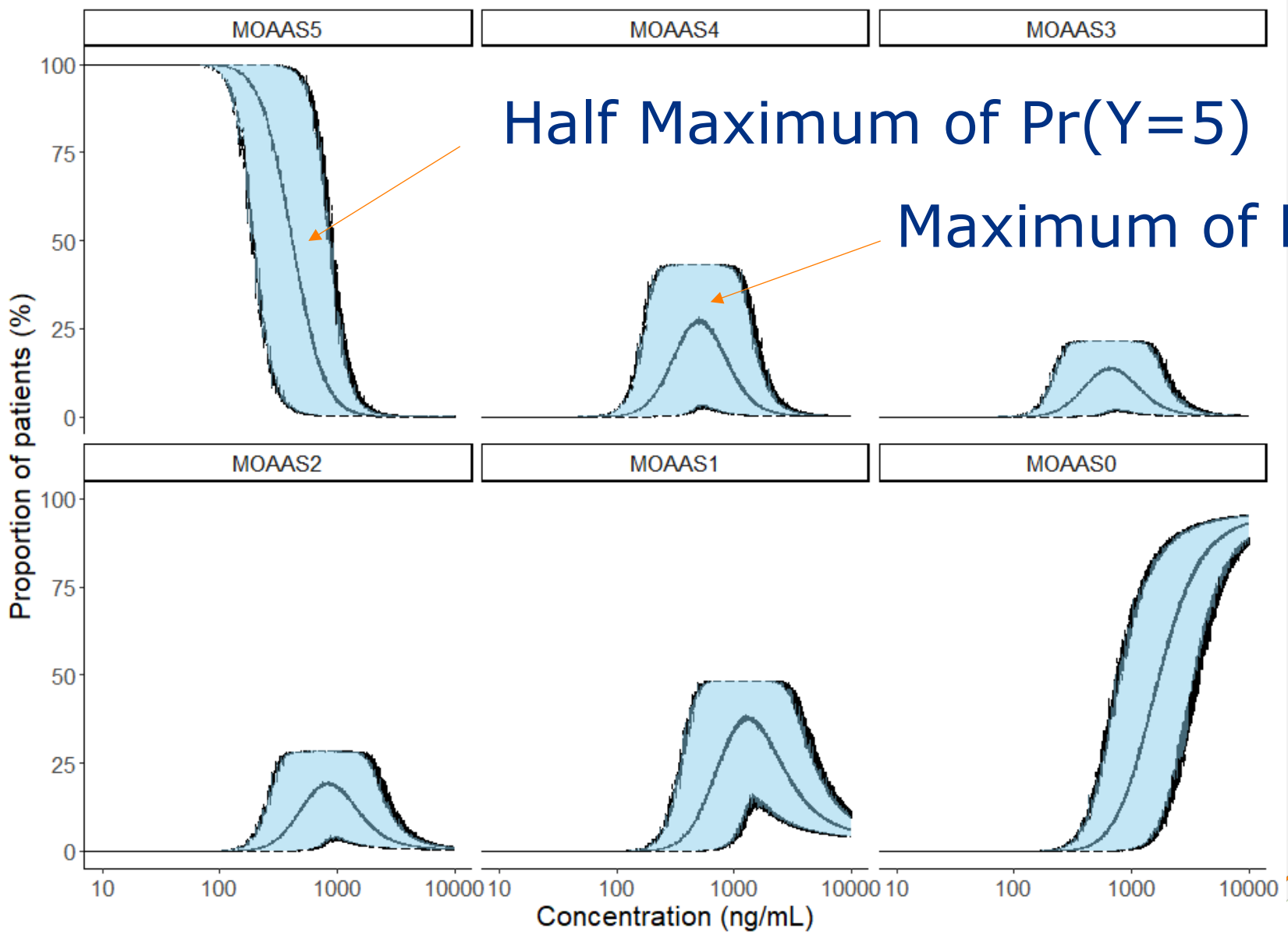
Structural model parameters (n)	33	32	32	
Stochastic model parameters (n)	1	1	1	
Effect compartment	Yes	Yes	Yes	
Drug effect	Sigmoid	Emax	Emax	
Time dependent: continuous time				
Models	**Minimal Markov Model**	**Markov Model**		
OFV	4616.2	4131.1		
RSE (%), mean [min-max]	8.9 [2.8 – 13.1]	15.7 [3.3 – 36.3]		
Structural model parameters (n)	8	14		
Stochastic model parameters (n)	1	1		
Effect compartment	No	No		
Drug effect	Emax	Emax/Sigmoid		

Figure 4. Example of simulation of exposure-response relationship

Solid line represents the median, shaded areas represent the 95% prediction interval.



Results

Table 4. Simulated concentration range (mean) at the (half-)maximum probability of observing a particular MOAAS category

Model	MOAAS5	MOAAS4	MOAAS3	MOAAS2	MOAAS1	MOAAS0
Multinomial Logistic Model	194	246	365	599	1712	2382
Proportional Odds Model	155	180	266	303	522	626
Adjacent Categories Model	168	214	317	442	682	850
Discrete-Time Markov Model (extension of multinomial)	180	260	380	593	1017	1136
Discrete-Time Markov Model (extension of proportional)	178	223	331	466	812	1049
Discrete-Time Markov Model (extension of adjacent)	186	248	330	508	921	1111
minimal Continuous-Time Markov Model	151	194	267	312	504	741
Continuous-Time Markov Model	216	228	293	400	748	961

Results

Figure 5. Comparison between simulation of typical patient after bolus administration (5 mg in 1 min) using the proportional odds (PO) model and continuous-time markov model (CTMM)

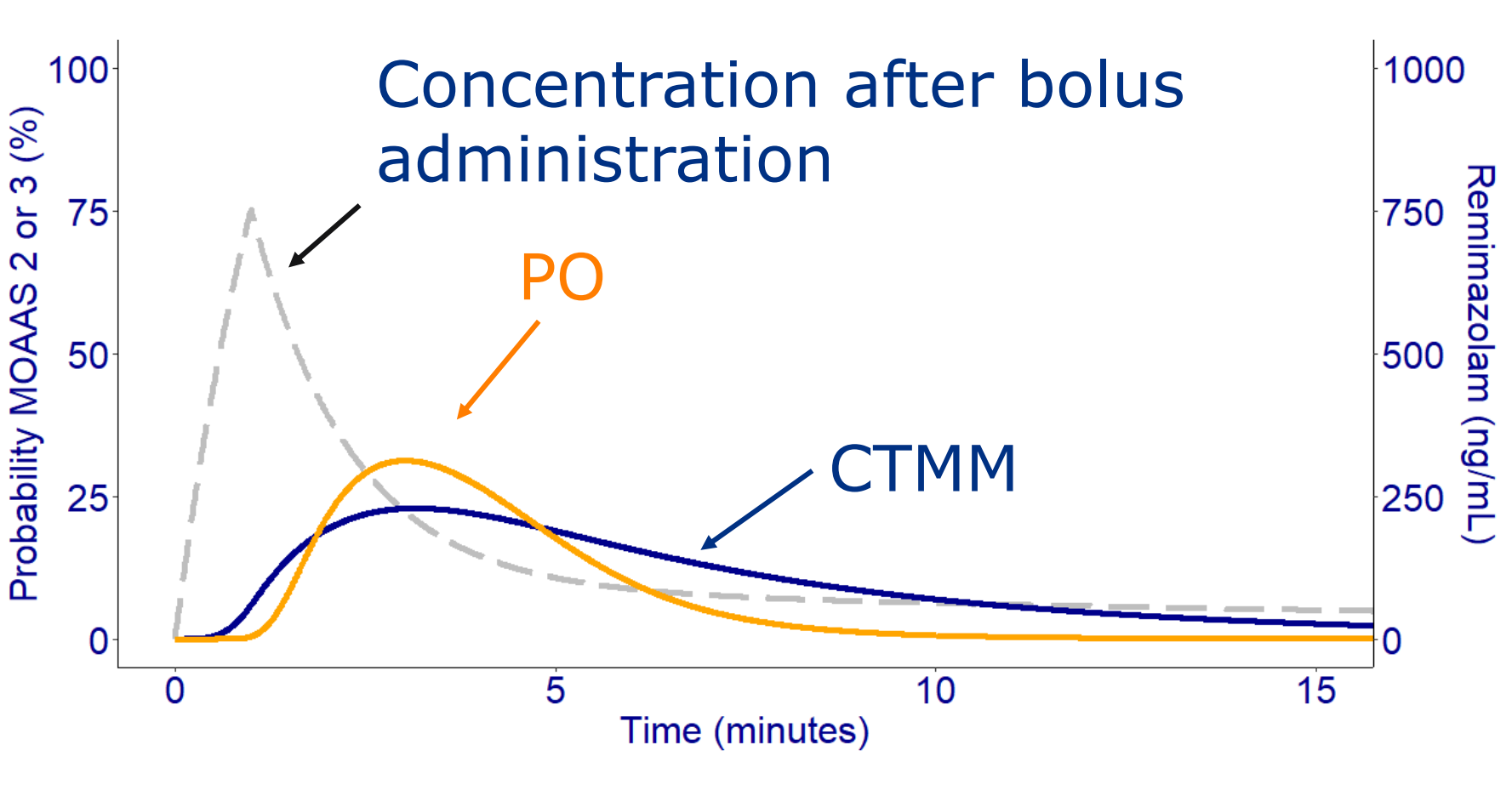
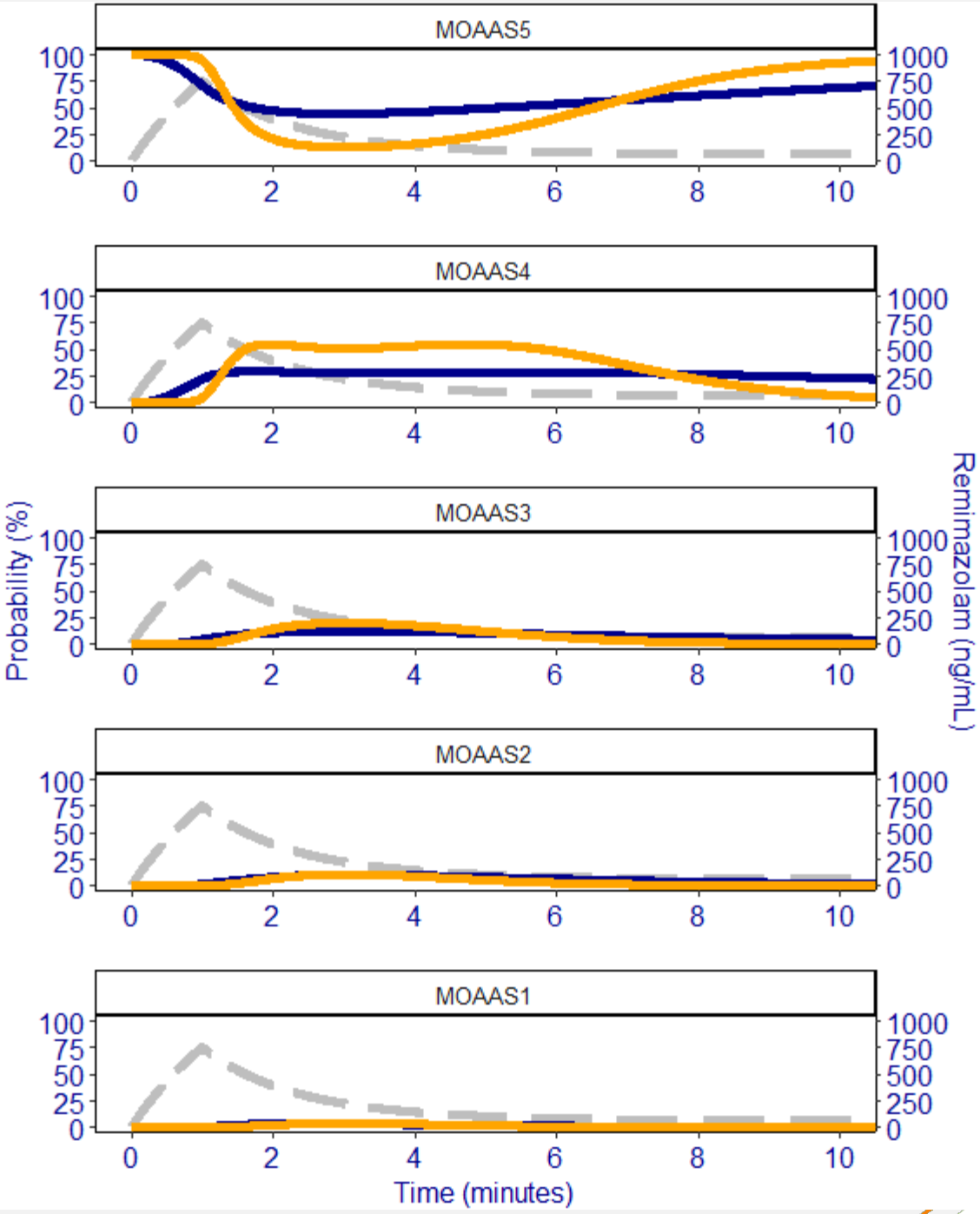


Figure 6. Comparison between simulation of typical patient after bolus administration (5 mg in 1 min) using the proportional odds (PO) model and continuous-time markov model (CTMM)



Discussion

Discussion - models

- Categorical models need fixes in case of missing categories
  - Especially, relevant for discrete-time Markov Models in case of sparse transitions
- Preserving ordering in the model structure improves overall model fit.
  - This is relevant for the time-independent models and discrete-time Markov Models.
- Discrete-time Markov models assume a discrete-time interval
  - Not very suitable in case of unequal sampling times
  - Not very suitable for extrapolations to different populations & trial designs
- Better to use continuous-time Markov models, in case of time dependencies
  - Comes at the cost of increasing computation times
  - Prevents use of targeting effect-site concentrations

Discussion – Exposure-Response

- Choice of structural model:
  - Changes the interpretation of the exposure-response relationship at steady-state, specifically for lower MOAAS categories
  - Changes the dynamic behaviour of the exposure-response relationship at non-steady-state
  - Changes the need for an effect compartment, but this could be a limitation of the study design.

Future studies

- Evaluation of different structural MOAAS models for other anaesthetic drugs.
  - Data available for ABP-700, Dexmedetomidine, Propofol and Sevoflurane

Back-Up

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Useful references

- Analysis of Ordinal Categorical Data. Agresti A. 2010. DOI:10.1002/9780470594001
- A mixed-effects multinomial logistic regression model. Hedeker D. Stat Med. 2003 May 15;22(9):1433-46.
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- Comparison of proportional and differential odds models for mixed-effects analysis of categorical data. Kjellsson MC, Zingmark PH, Jonsson EN, Karlsson MO. J Pharmacokinet Pharmacodyn. 2008 Oct;35(5):483-501.
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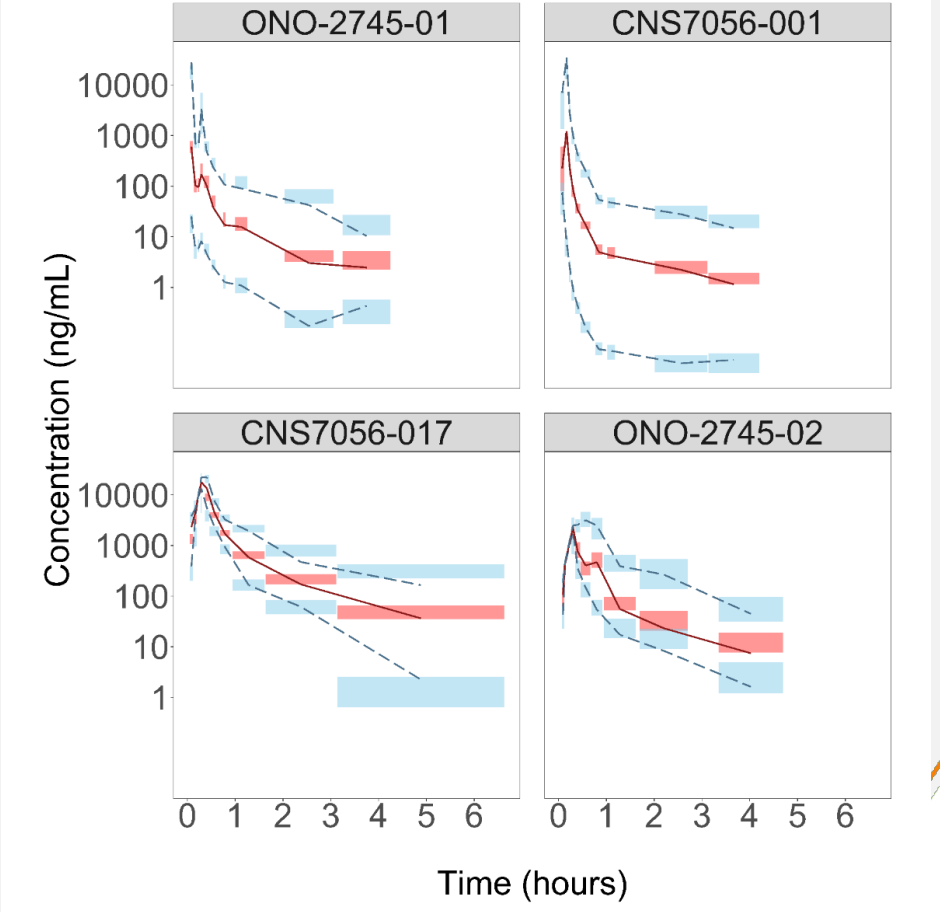
- Mechanistic modeling of a magnetic marker monitoring study linking gastrointestinal tablet transit, in vivo drug release, and pharmacokinetics. Bergstrand M, Söderlind E, Weitschies W, Karlsson MO. Clin Pharmacol Ther. 2009 Jul;86(1):77-83
- A Minimal Continuous-Time Markov Pharmacometric Model. Schindler E, Karlsson MO. AAPS J. 2017 Sep;19(5):1424-1435.

Results

- **Step 1.** Evaluate population pharmacokinetic model performance and obtain EBEs (i.e. individual PK parameters)

Figure 2. Prediction-corrected visual predictive check of the population pharmacokinetic model of remimazolam stratified by study.

Solid line represents the prediction-corrected median of the observations, dashed lines represent the 5th and 95th percentiles of the prediction-corrected observations. Shaded areas represent the 95% confidence interval of the prediction-corrected median (red) and 5th and 95th percentiles (blue).



Data fitting

- An example,
  - For a patient at time 0, an observation of MOAAS of 5 is made.
  - In a model where all probabilities are assumed to be equal
  - -2 Log-Likelihood is defined as:
    - Probability(MOAAS=5 | Model parameters, variables) = 1/6
    - -2 Log-Likelihood = -2 * natural log(1/6) = 3.58
  - In a better model, where probability of observing a MOAAS 5 is predicted to be higher:
    - -2 Log-Likelihood = -2 * natural log (2/6) = 2.19
- Parameter estimation minimizes the sum of -2 log-likelihood for all observed scores

Probabilities versus Odds

- Modelling Odds:
  - Ratio of the number of events to the number of non-events
  - Scale is limited to be higher than 0
  - Enforced by exponential transform: exp(x)

- Relationship between probabilities and odds:
  - Prob = Odds/(1+Odds),
    - e.g. Odds = 3, Prob = 3 / (1 + 3) = 0.75
  - Odds = Prob/(1–Prob),
    - e.g. Prob = 0.75, 0.75/(1–0.75) = 3

Differential Odds Model

- Example structure

$$p(Y \leq j|x) = \frac{\exp(\theta_{0j} + \sum_{i=1}^{p} \theta_{ij} x_j + \eta)}{1 + \exp(\theta_{0j} + \sum_{i=1}^{p} \theta_{ij} x_j + \eta)}$$

j = category of interest

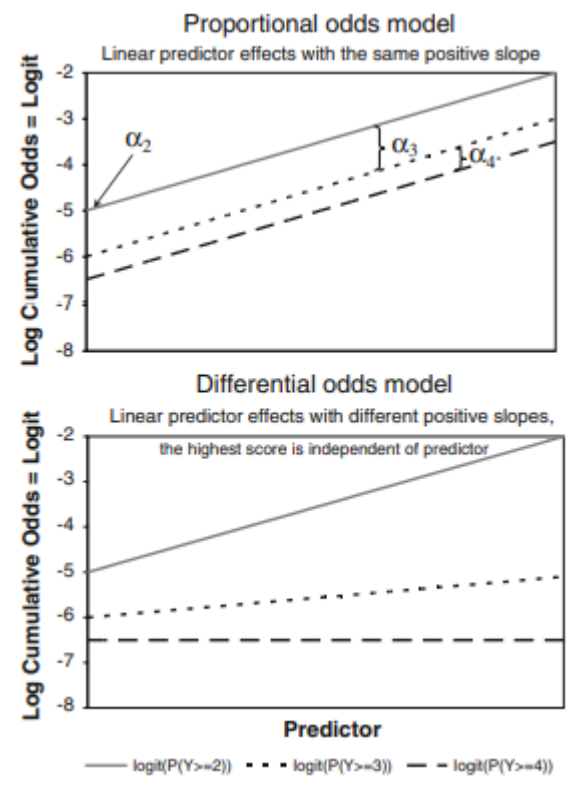
i = individual parameters in predictor function

Θ = fixed effects

η = random effects

- Predictor function is allowed to vary
  - In case of linear example above:
    - $\theta_{i5} > \theta_{i4} > \ldots. > > \theta_{i0}$

```
EMAX0 = EMAX
EMAX1 = EMAX * BETA1
EMAX2 = EMAX * BETA1 * BETA2
EMAX3 = EMAX * BETA1 * BETA2 * BETA3
EMAX4 = EMAX * BETA1 * BETA2 * BETA3 * BETA4
```



Results

Figure 3. Example Visual predictive check (continuous-time Markov Model)

Dots represent the observed datapoints, shaded areas represent the 95% prediction interval.