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Comparing the Proportional Odds Model to the Differential Drug Effect Model for Cumulative Logits

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Modelling Categorical Data

Ordered Categorical Data

- observations cannot be predicted directly, only the probability of making a particular observation
- the categories should be linked

- function of the parameters is related to ***Cumulative Probability***

$$P(Y \geq j) = g(\alpha_j, \beta, \mathbf{x}), \quad j = 1, ..., J$$

(with $P(Y \geq 1) = 1$ only need to model $j = 2, ..., J$.)

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Proportional Odds Model

$$g(\alpha_j, \beta, \mathbf{x}) = \frac{e^{f(\alpha_j,\beta,\mathbf{x})}}{1 + e^{f(\alpha_j,\beta,\mathbf{x})}}, \quad j = 2, ..., J$$

$$f(\alpha_j, \beta, \mathbf{x}) = \alpha_j + \beta\mathbf{x} + \eta_i$$

- Introduced by Lewis Sheiner (Sheiner CPT 1994)
- $g(\alpha_j,\beta,x)$ varies between 0 and 1
- x is the predictor vector
  - e.g. concentrations
- $\{\alpha_j\}$: the baseline probability for each category
- β: an effect that is the same for all categories
  - e.g. Emax and EC50

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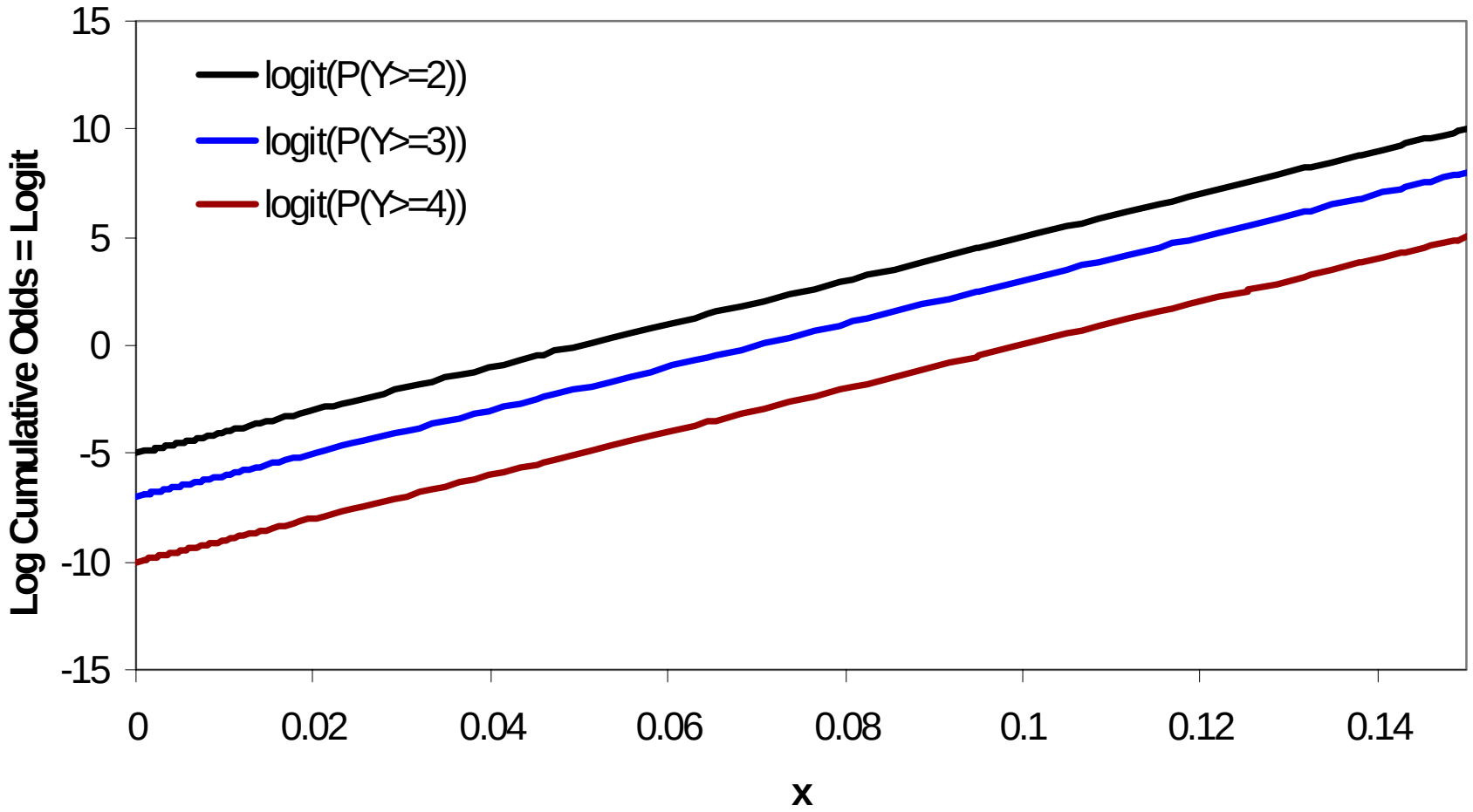
Proportional Odds Model



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Differential Drug Effect Model

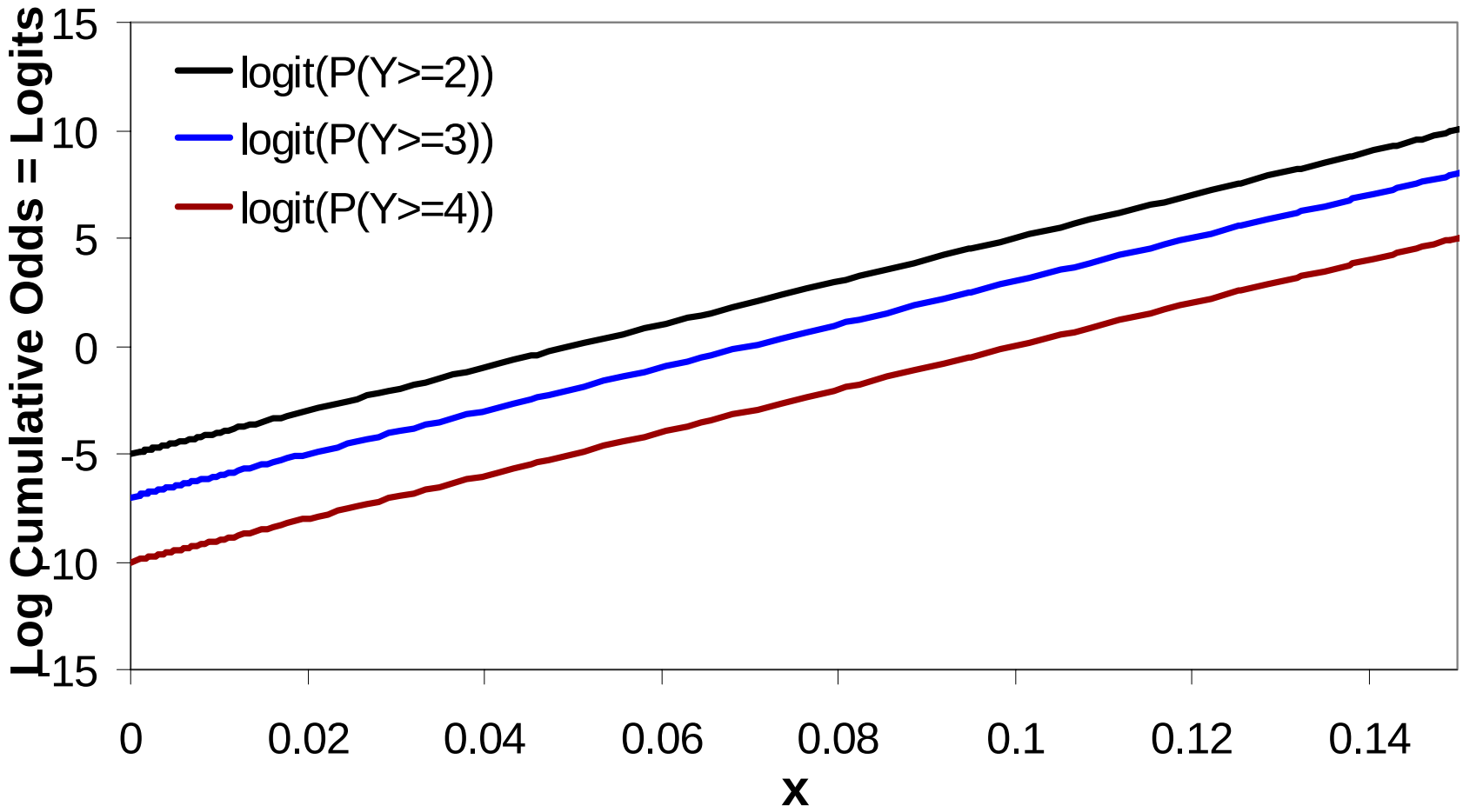
$$g(\alpha_j, \beta, \mathbf{x}) = \frac{e^{f(\alpha_j,\beta,\mathbf{x})}}{1 + e^{f(\alpha_j,\beta,\mathbf{x})}}, \quad j = 2, ..., J$$

$$f(\alpha_j, \beta, \mathbf{x}) = \alpha_j + \beta\mathbf{x} \cdot f_{diff}$$

$$f_{diff} = \prod_{n=3}^{j} \frac{e^{\phi_n}}{1 + e^{\phi_n}}$$

- Differential drug effect = f_{diff} varies between 0 and 1
- One parameter, ϕ is added per category, except for the 2 lowest categories
- Hierarchical with the proportional odds model

Proportional Odds Model



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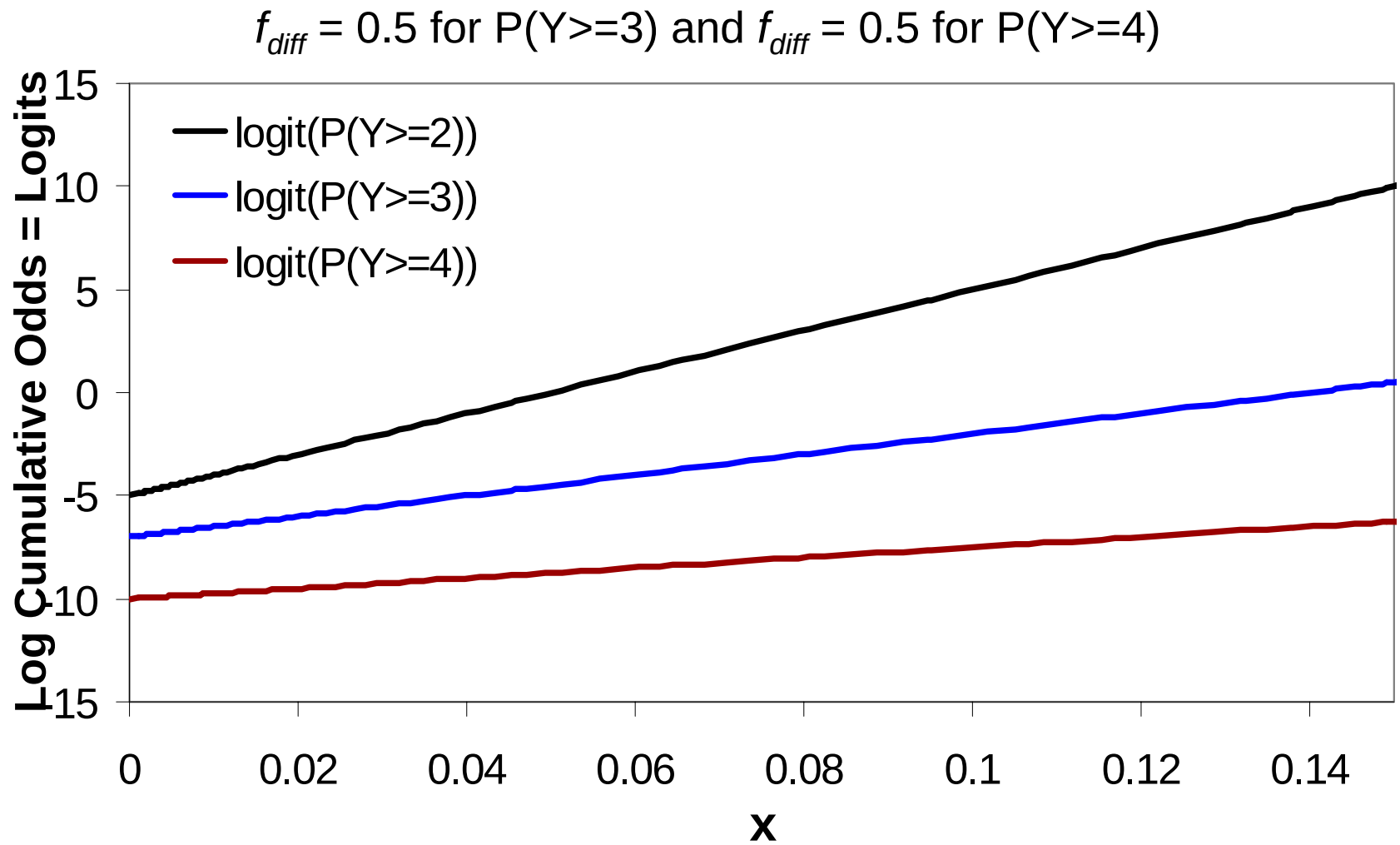
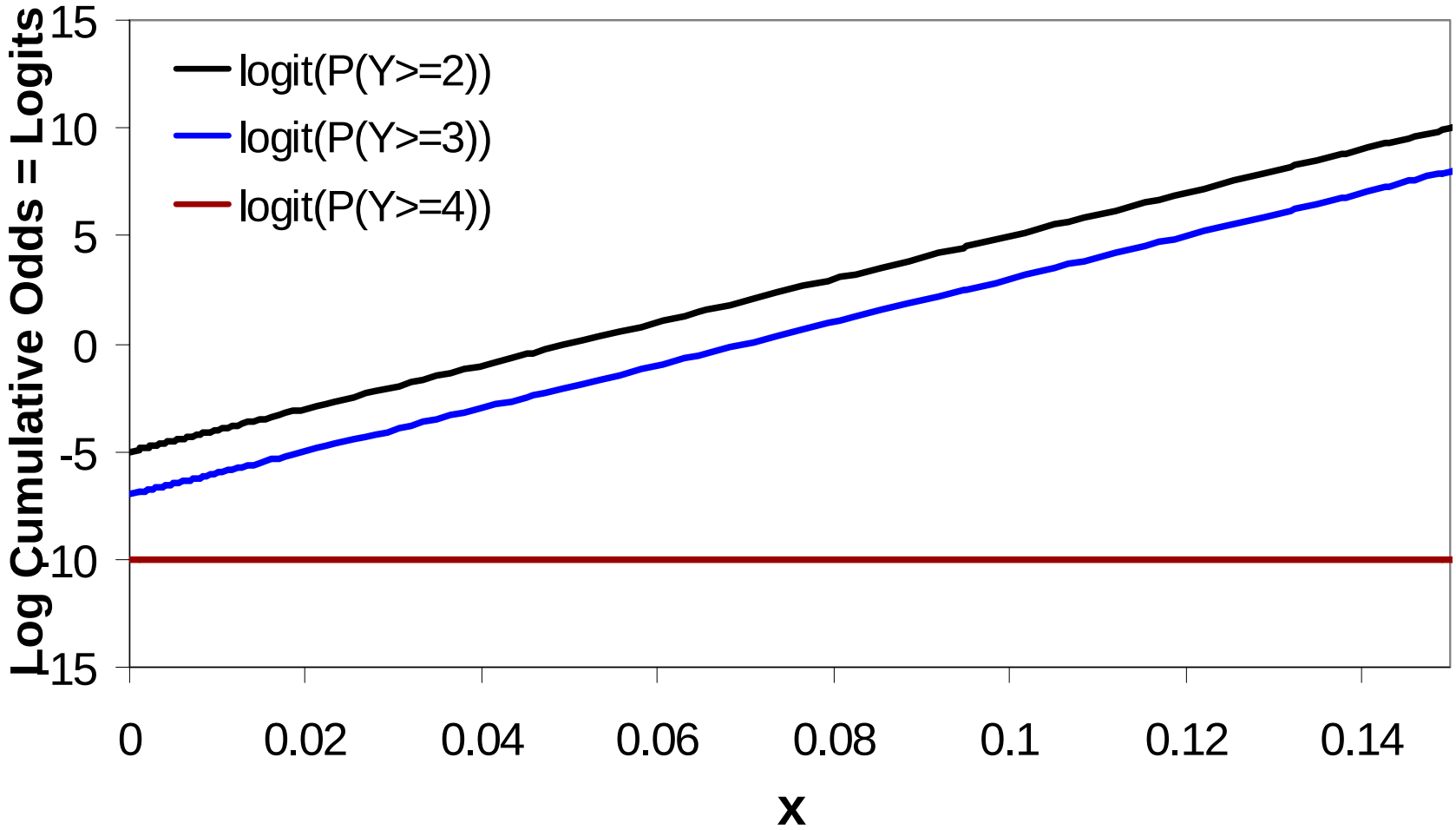
Differential Drug Effect Model



Differential Drug Effect Model

f_{diff} = 0 for P(Y>=4)



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Aim

To investigate the performance of the differential drug effect model relative to that of the proportional odds model by

- assessing the Type I error rate for the differential drug effect model and
- assessing possible improvements adding the differential drug effect to models for data previously analysed used the proportional odds model

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Data

Assessing Type I error rate

1. **4-Category simulated data**
   - Simulated using proportional odds model
   - Drug effect = Linear (dose)

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Data

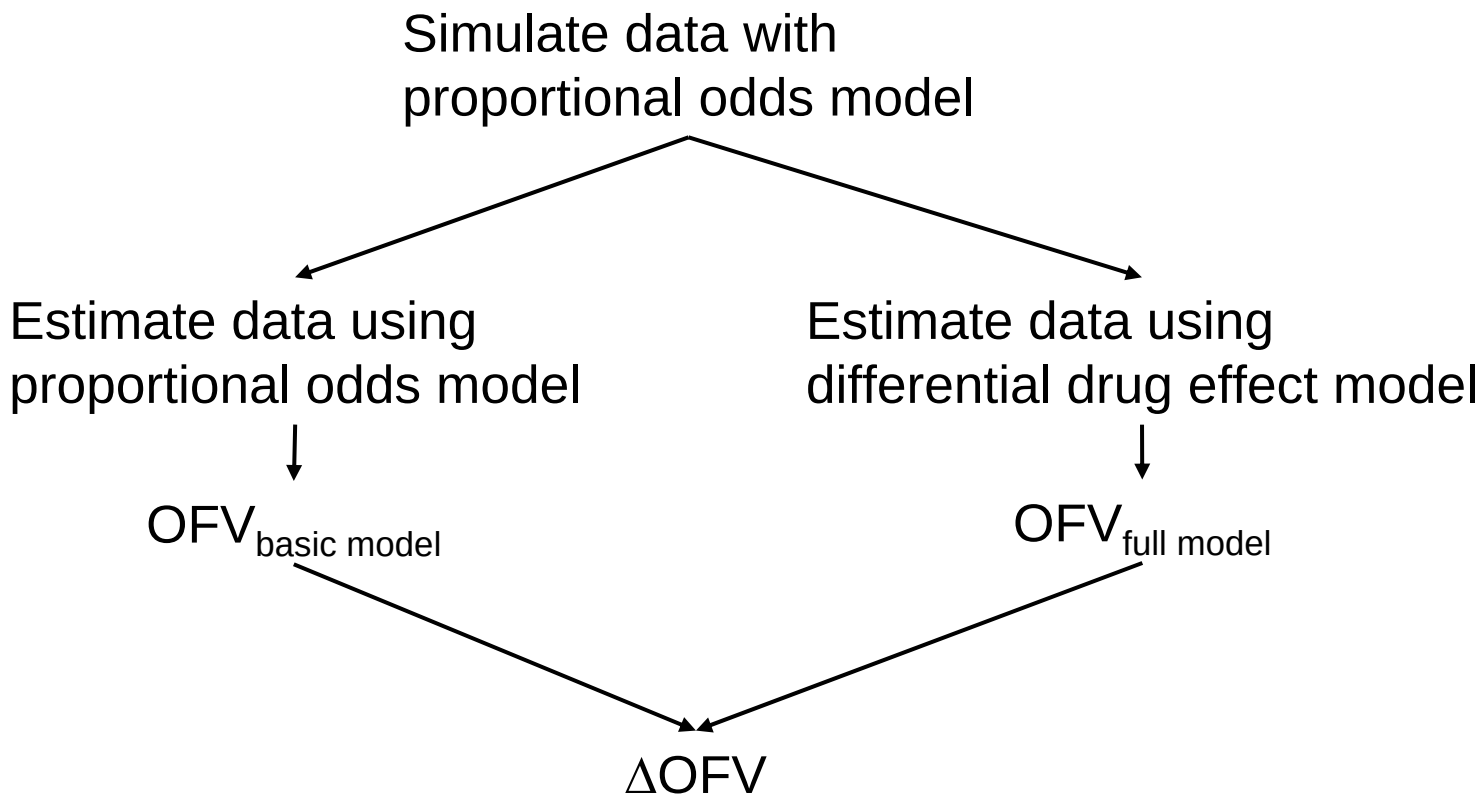
Assessing Possible Improvements adding the Differential Drug Effect Model

2. **3-Category T-cell data** (Zingmark *et al* BJCP 2004)
   - Drug effect = Emax (conc.)
   - Categorised continuous data
3. **5-Category diarrhoea data** (Xie *et al* CPT 2002)
   - Drug effect = Linear (AUC)
   - Parent drug + 2 metabolites
   - Point Scale (0-4)
4. **6-Category sedation data** (Zingmark *et al* BJCP 2002)
   - Drug effect = Step
   - 1. Fully awake
     2. Drowsy but answers when spoken to
     3. Answers slowly when spoken to
     4. Reacts when spoken to but does not answer
     5. Reacts only to pain
     6. Does not react to pain

Method

Assessing Type I error rate

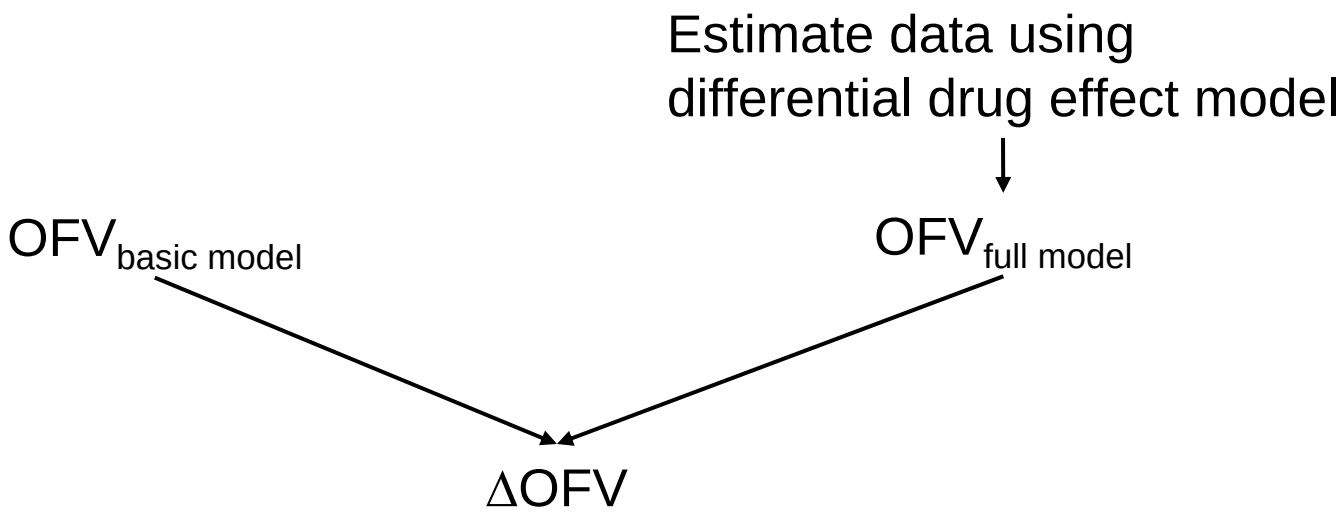
Using dataset 1
Repeat 1000 times



Method

Assessing Possible Improvements adding the Differential Drug Effect Model

Using datasets 2, 3 and 4



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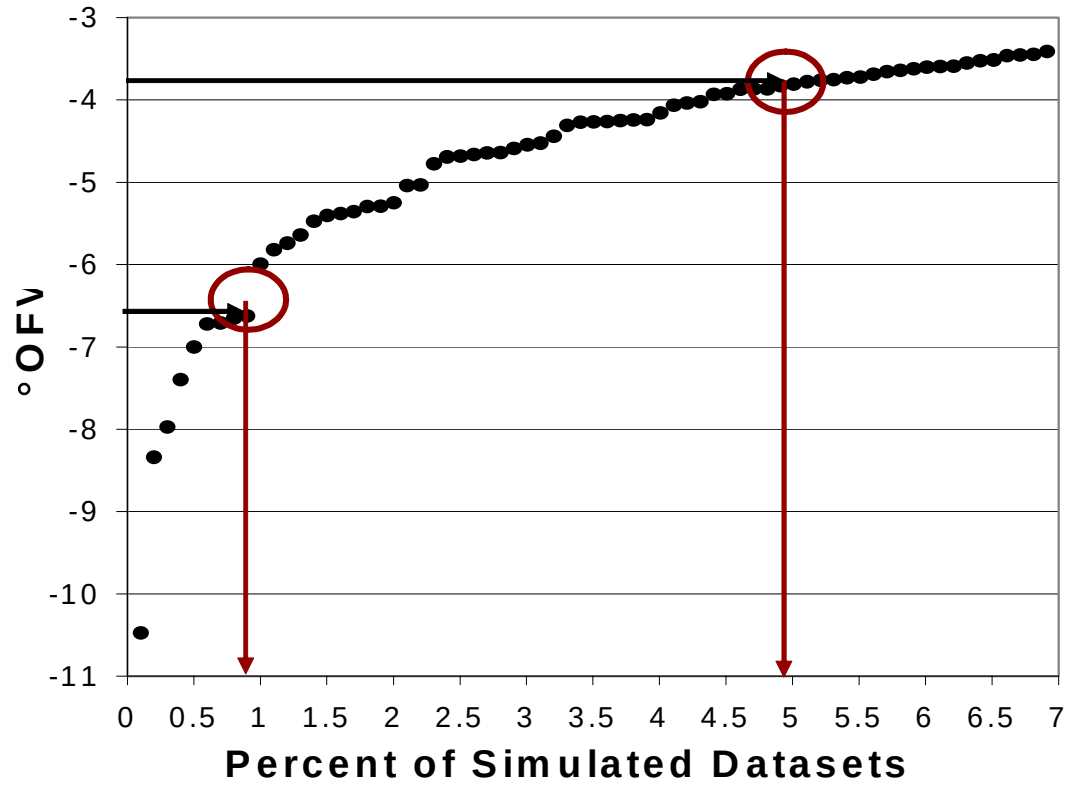
Results

Assessing Type I error rate



Nominal value	Corresponding drop in OFV	Type I error rate
5%	3.84	4.9%
1%	6.64	0.9%

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Results

Assessing Possible Improvements adding the Differential Drug Effect Model

Data		**df**	**Critical Values (5% sign. level, χ^2-distr.)**	**ΔOFV**
Data2 - T-cells		~1	3.84	3.0
	Parent drug	~1.5	4.92	1.8
Data 3 - Diarrhoea	Metab. 1	~1.5	4.92	0.5
	Metab. 2	~1.5	4.92	0.2
Data4 - Sedation		~2.5	6.90	74

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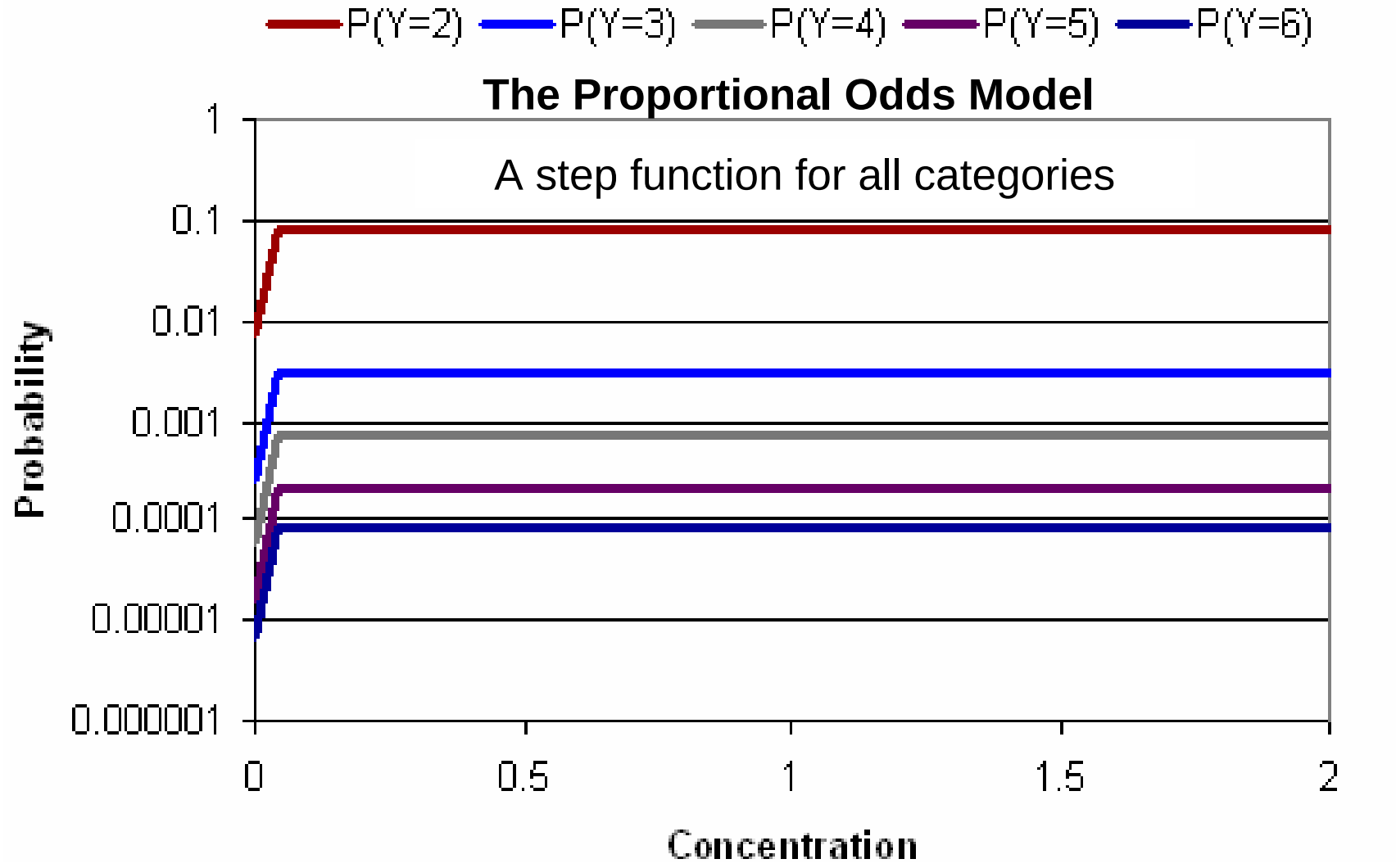
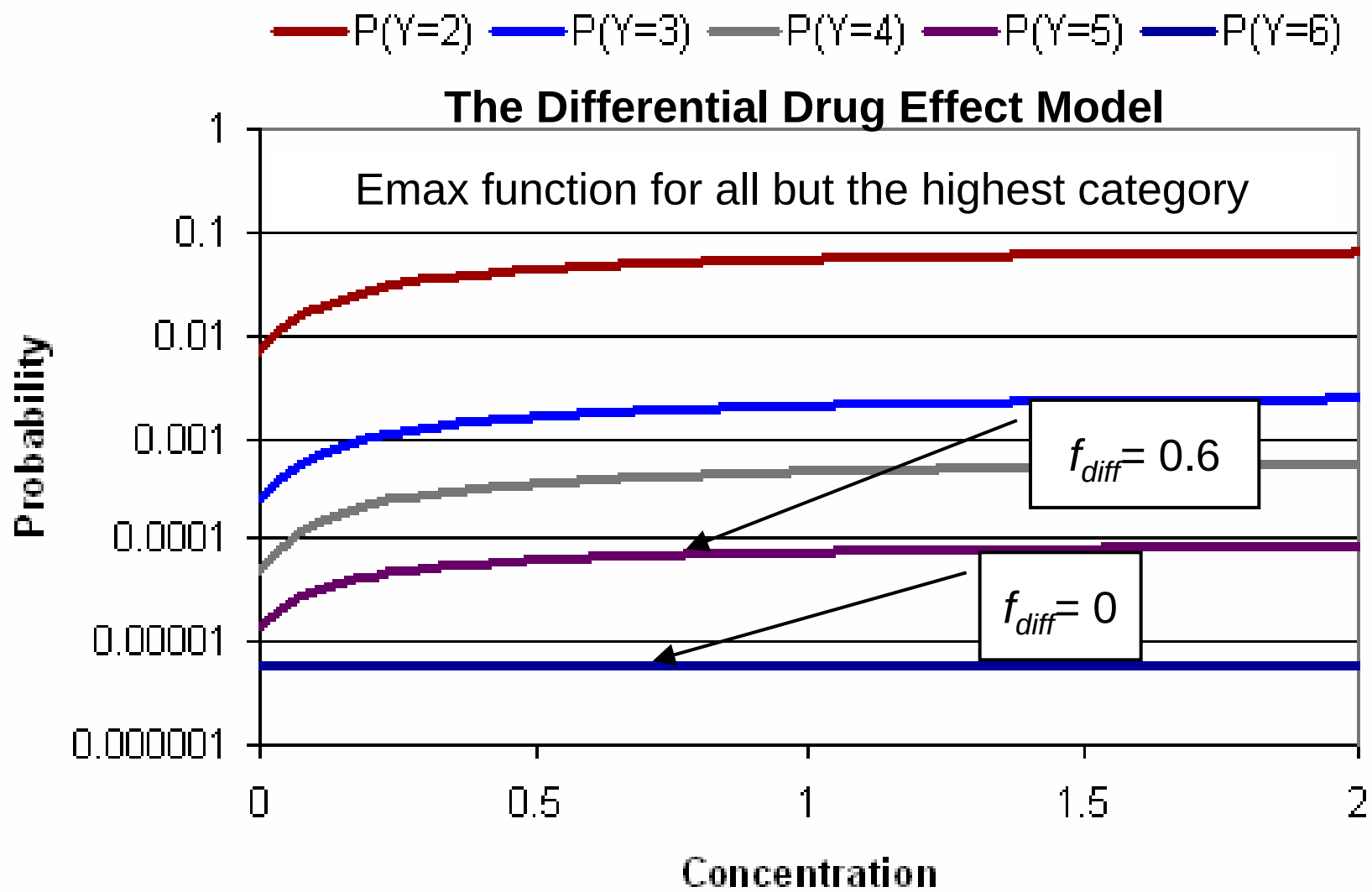
Results

Assessing Possible Improvements on Sedation Data



Results

Assessing Possible Improvements on Sedation Data



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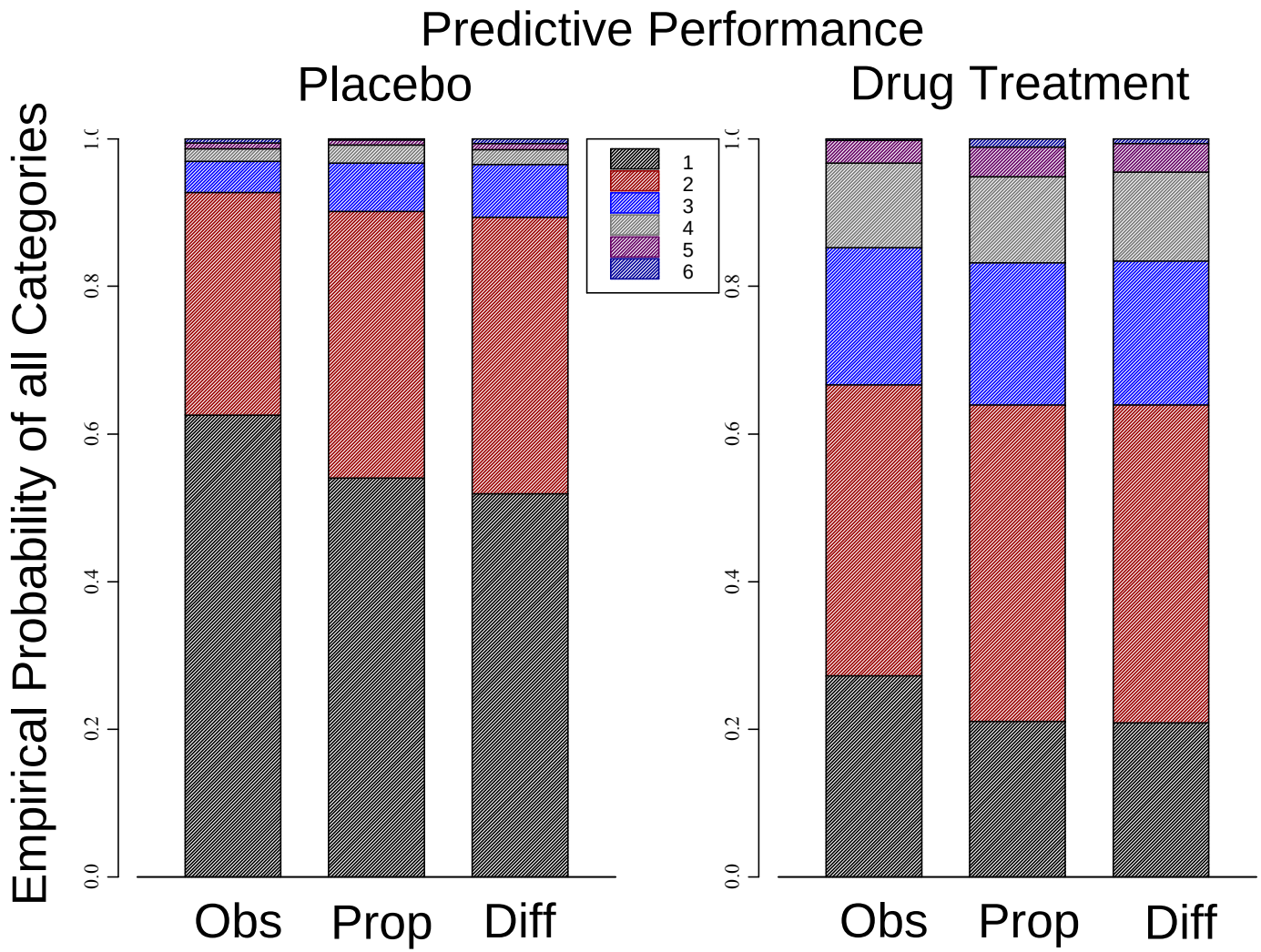
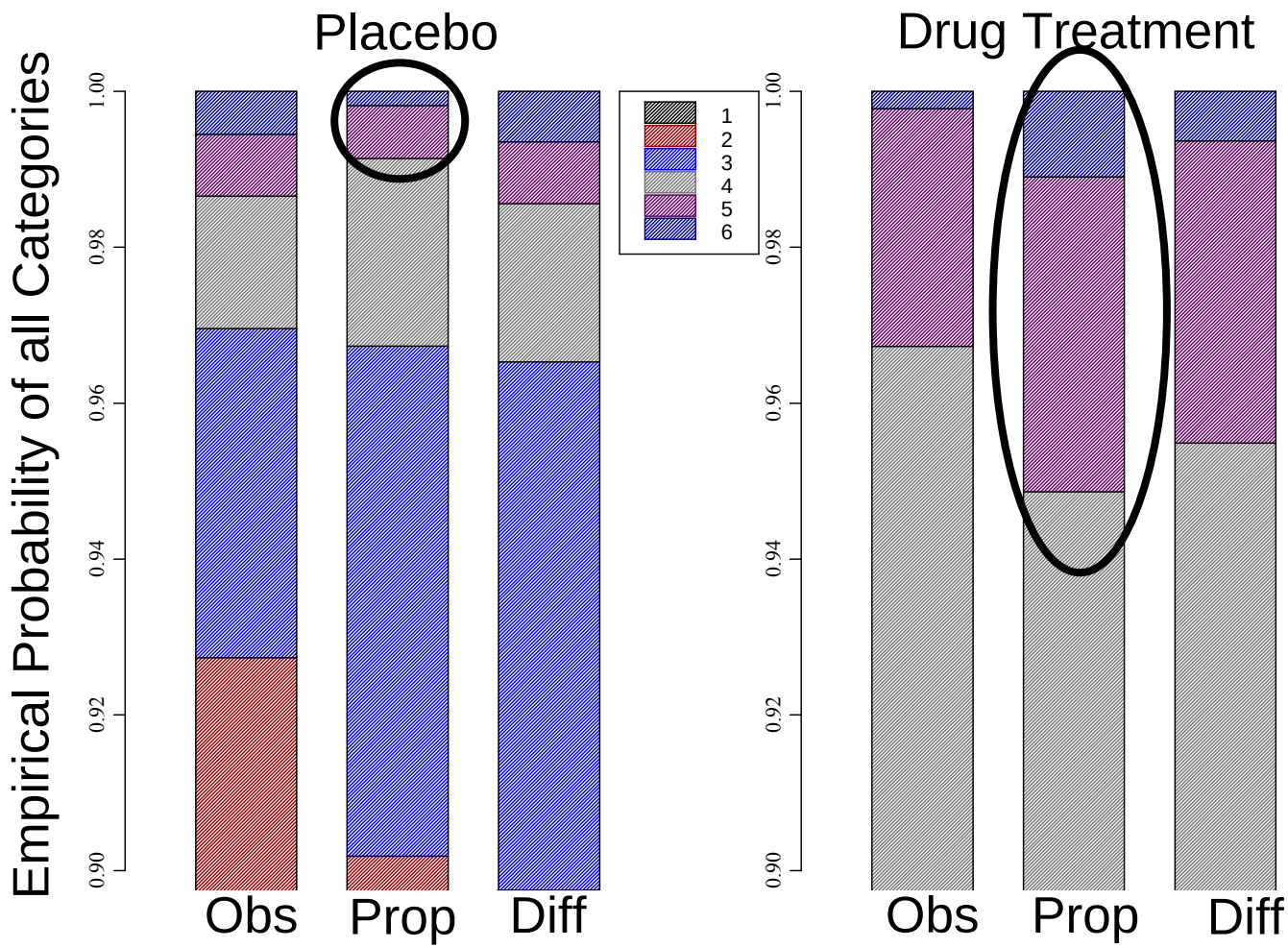
Results

Assessing Possible Improvements on Sedation Data



Results

Assessing Possible Improvements on Sedation Data



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Discussion

- The differential drug effect model offered no improvement over the proportional odds model for
  - Simulated data
  - Categorised continuous data
  - Diarrhoea data

- The differential drug effect model was adequate for describing
  - Sedation data

WHY?

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Discussion

- The proportional odds model is defined for ordered categorical data representing a categorisation of continuous scale (Agresti Categorical Data Analysis. 2002 Wiley)

- Simulated data
  - simulated using the proportional odds model
- T-cell data
  - categorised continuous data
- Diarrhoea data
  - scale appears homogeneous enough

Sedation?

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Discussion

- Sedation
  - Not representing a categorisation of a continuous scale
  - 1. Fully awake
    2. Drowsy but answers when spoken to
    3. Answers slowly when spoken to
    4. Reacts when spoken to but does not answer
    5. Reacts only to pain
    6. Does not react to pain

} Approx. Prop. Odds

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Discussion

Oncology

Toxicity	CD4 count	Atrioventricular heart block	Allergic reaction
0	WNL	None	None
1	< LLN – 500/mm^3	Asymptomatic, not requiring treatment	Transient rash, drug fever < 38^{o}C
2	200-<500/mm^3	Symptomatic, but not requiring treatment	Urticatia, drug fever ≥ 38^{o}C, asymptomatic bronchospasm
3	50-<200/mm^3	Symptomatic and requiring treatment	Symptomatic bronchspasm, requiring parental medication
4	<50/mm^3	Life-threatening	Anaphylaxis

Prop odds

Possibly Prop odds

Diff Drug

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Conclusion

- The differential drug effect model had the desired properties of not being indicated where it is not necessary and provide model improvement when the categorical data does not represent a categorisation of continuous data.

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