Meta-analysis of clinical dose response in a large drug development portfolio

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Introduction

Question 1

What do clinical dose response curves look like?

Question 2

How well were they determined by the studies conducted?

Question 3

Are there consistent quantitative trends in dose response across unrelated diseases and compounds?

Outline

1. Compounds/studies in the meta-analysis
2. Study characteristics and data
3. Examples of dose response curves
4. Summarizing E_{max} model fits
   - MLE estimation
   - Hierarchical models summarizing parameter distributions

Compound/study sampling frame

- Identified all phase 2 studies with reports completed between 1998-2009
- Repository represents approximately 10% of pharmaceutical R&D spending
- Repository represented 13 of 17 TAs in a CBO report [1]

Compound/study inclusion/exclusion criteria

Compound criteria

- Excluded oncology compounds
- Small molecules only
- To be included, a compound must differentiate from placebo based on review of study reports

Study criteria

Phase 2 studies. Phase 3 studies were included if they had $\geq$ 3 dose groups

Special situations

One drug, multiple uses

- One compound, two or more distinct subpopulations (e.g., treatment naive, treatment experienced). The less-studied sub-population is included in supplemental summaries, but not in cross-compound summaries.
- One compound, two diseases (e.g., RA and psoriasis) regarded as two compounds

Combination of drugs

Two combination compounds excluded, but mono-therapy data included with component compounds

Compound/study counts

- 33 compounds (29 distinct molecules)
- 76 studies

Endpoints, dosing, and masking

Endpoints/timepoints

Results for primary endpoint at primary visit. When multiple choices existed, the endpoint/time chosen to maximize availability across studies.

Dosing

- Dosing summarized by total daily dosing
  - This assumption was not always satisfactory as will be noted.

Masking/standardization

- Outcome data within compound standardized to an overall mean of 0 and SD of 1 (continuous endpoints).
- Dosing range standardized to $0 - 1$ for each compound.

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Study characteristics

Designs

All studies were parallel-group designs except for 2 cross-over studies.

Studies per compound

- 16 compounds had 1 study
- 9 compounds had two studies
- 8 compounds had 3 – 6 studies

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Dosing designs

Dose groups (including placebo) per compound

Number of Compounds	Number of Dose Groups
9	4
4	5
10	6
7	7
3	8 – 10

Ratio of the highest dose to the lowest (non-placebo) dose

- 25^{th} percentile is 8
- 50^{th} percentile is 16
- 75^{th} percentile is 30
- Maximum dosing ratio was 588

Data distributions

Data types

- 27 were continuous
- 6 were binary
- No time-to-event or (ordered) categorical outcomes

Distributions of continuous data

- Consistently bell-shaped
- Outliers were common, consistent with a t_7 distribution
- Heterogeneous variance was not common or severe

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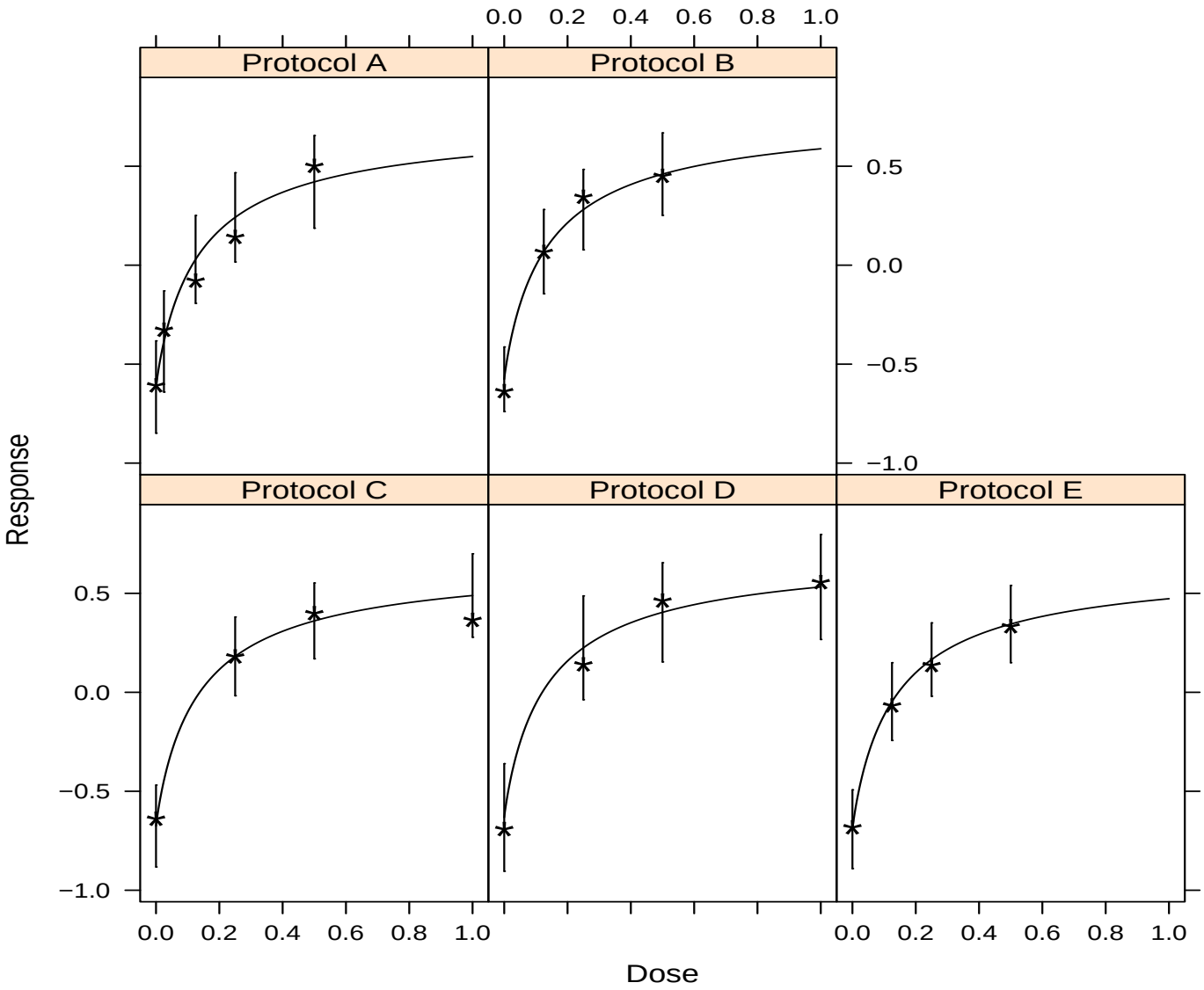
PDE5 inhibitor (ID 31)for erectile dysfunction



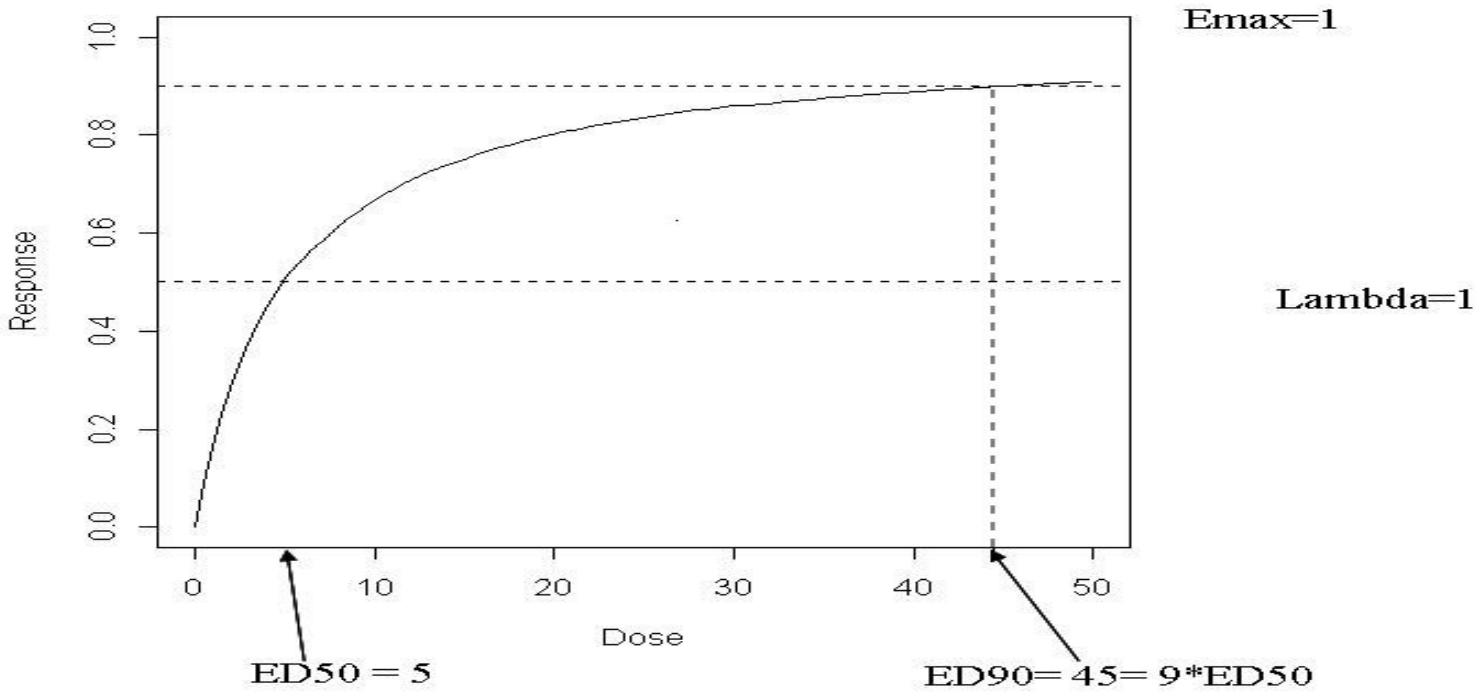
Emax Models

$$\mathrm{E}(Y \mid D) = \mathrm{E}_0 + \frac{\mathrm{E}_{\max} D^{\lambda}}{D^{\lambda} + \mathrm{ED}_{50}^{\lambda}}$$

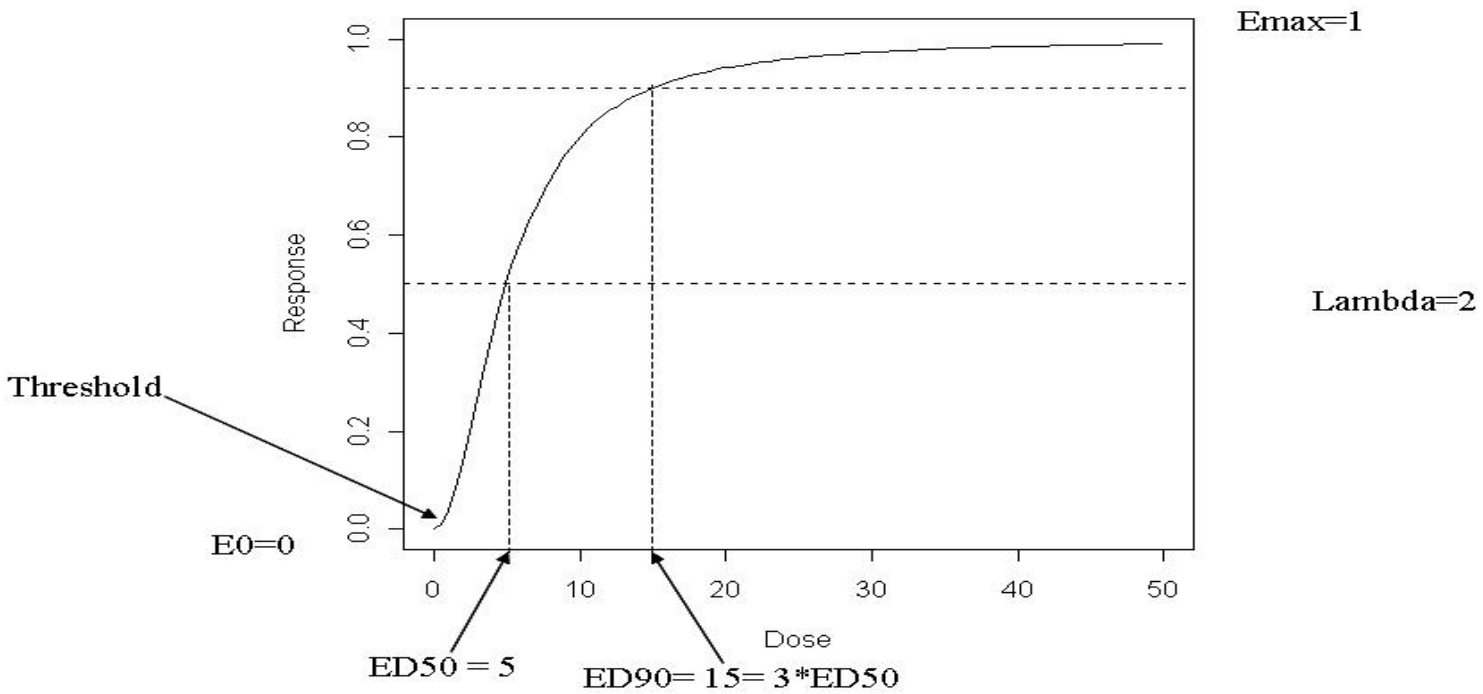
Pharmacological and Statistical origins

- Ubiquitous in pharmacology[2]
- Michaelis-Menten molecular binding
- Logistic (log-logistic) distribution function

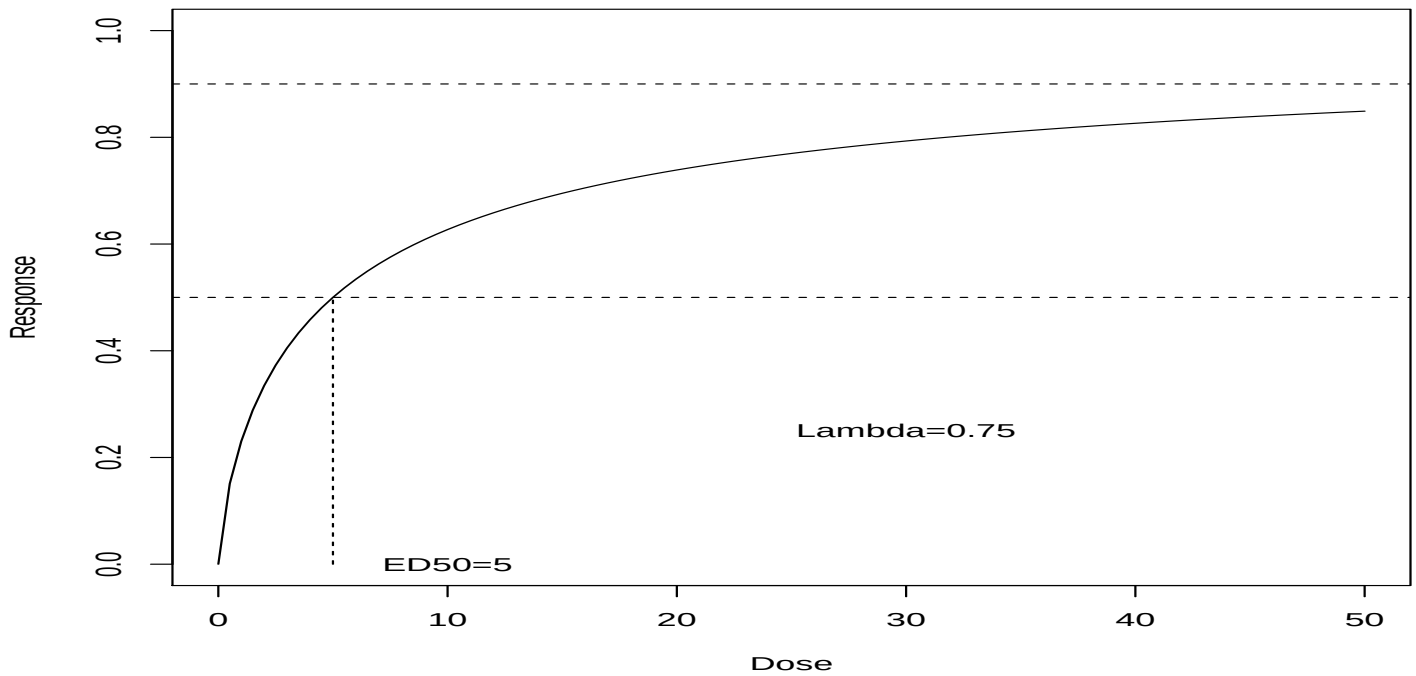
Hyperbolic (3-Parameter) Emax Model



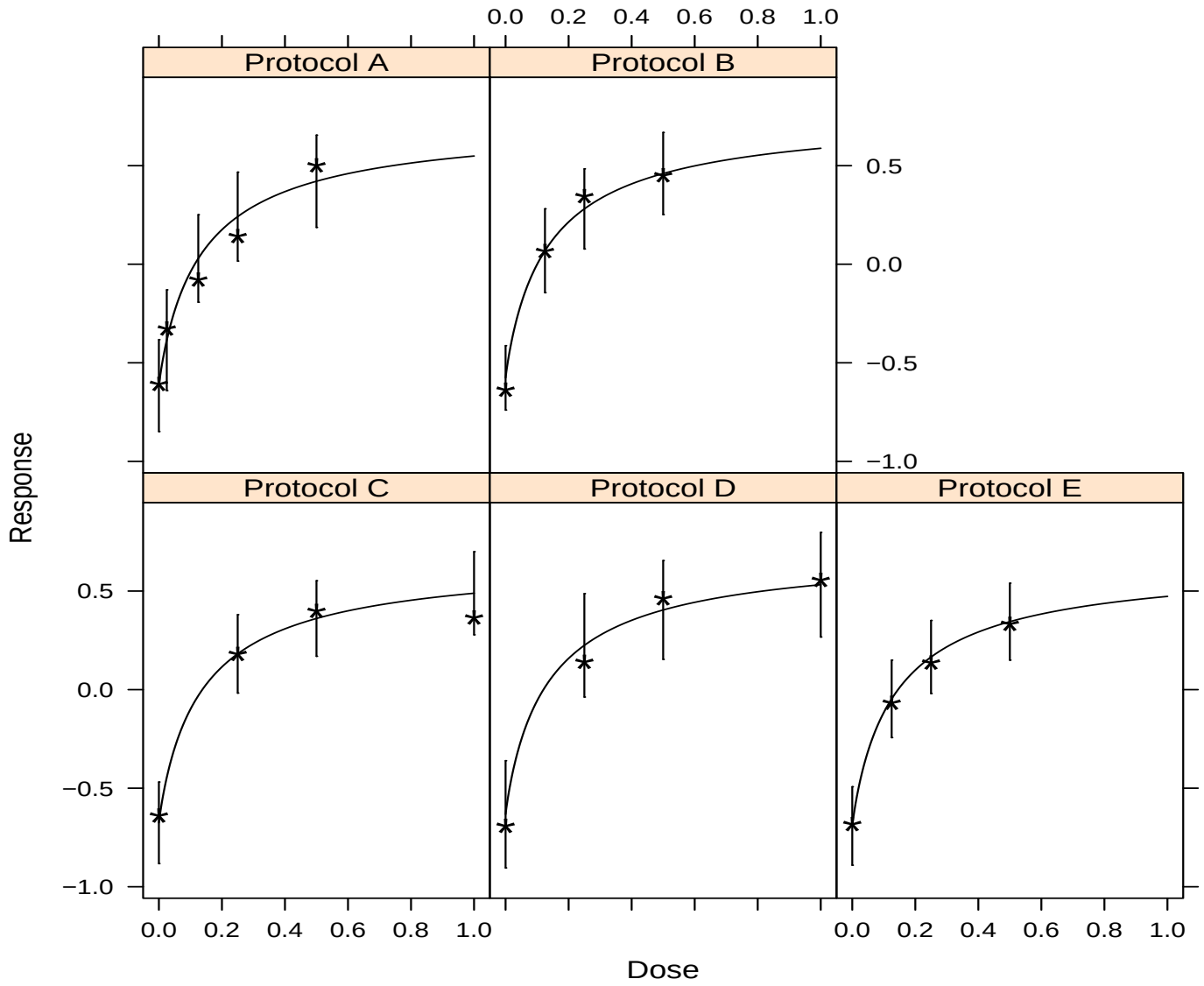
Sigmoid (4-Parameter) Emax Model



4-Parameter Emax Model



PDE5 inhibitor (ID 31)for erectile dysfunction



$\hat{\lambda} = 0.93$

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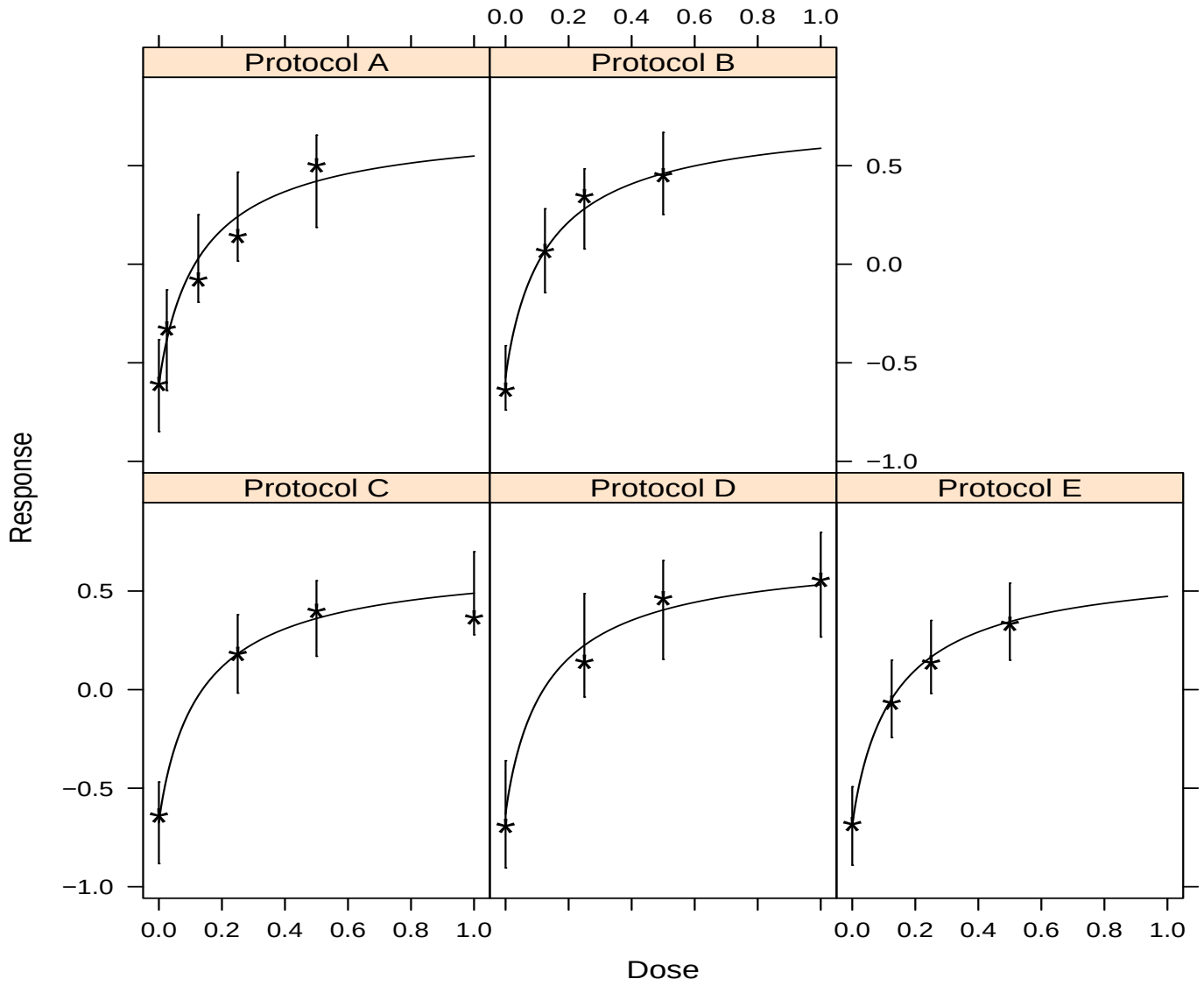

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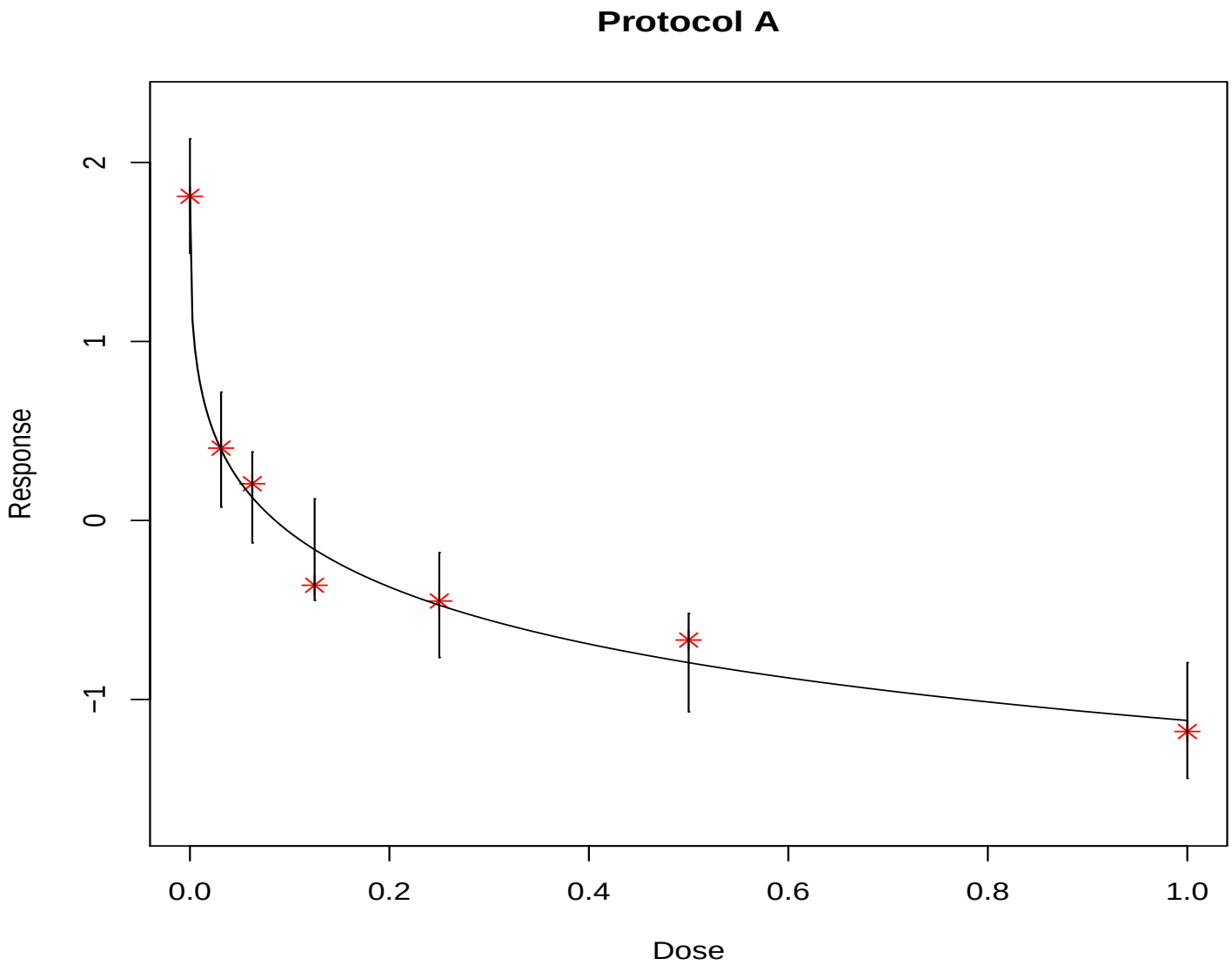
Statin (ID 6) for low density cholesterol



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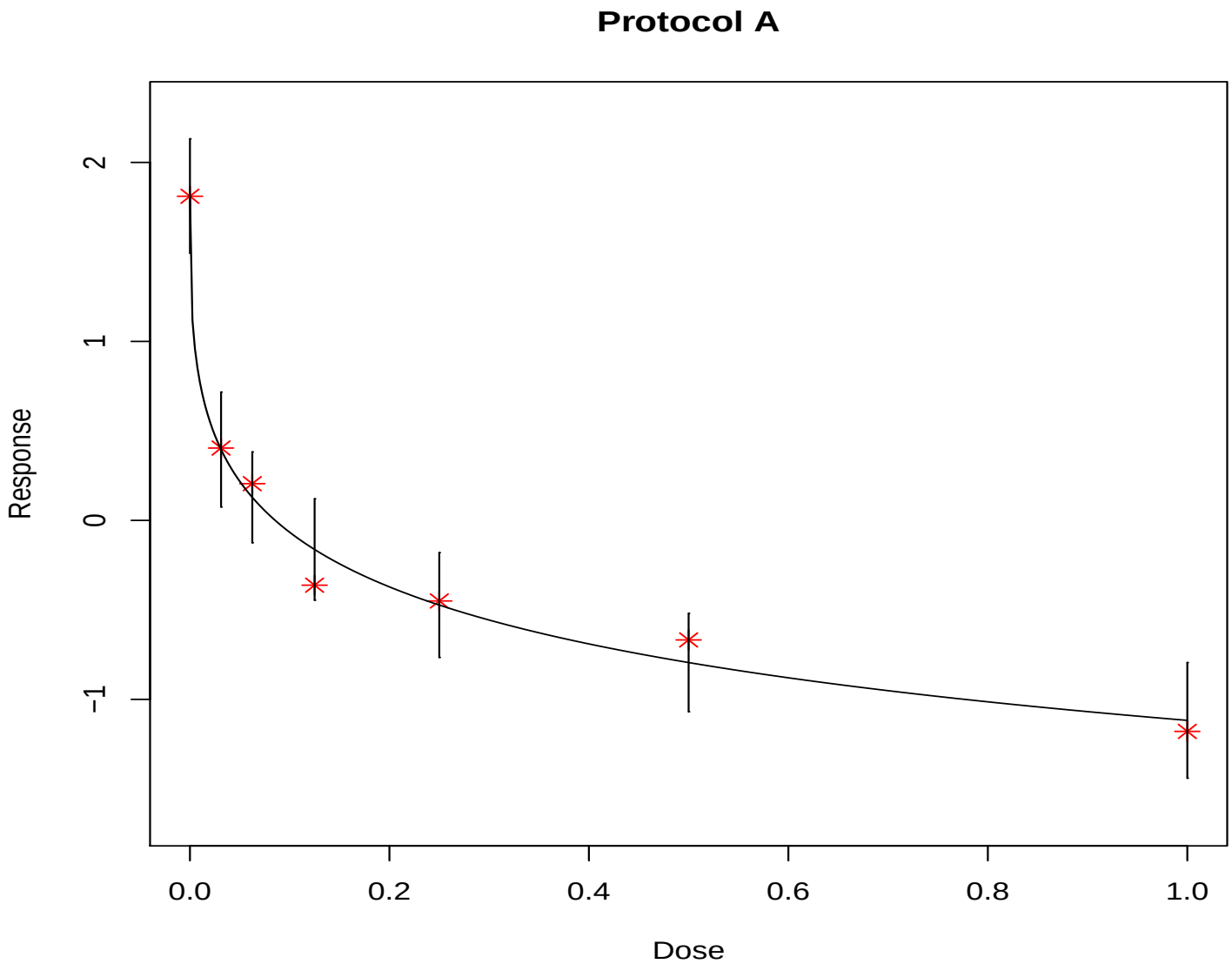

$$\hat{\lambda} = 0.35$$

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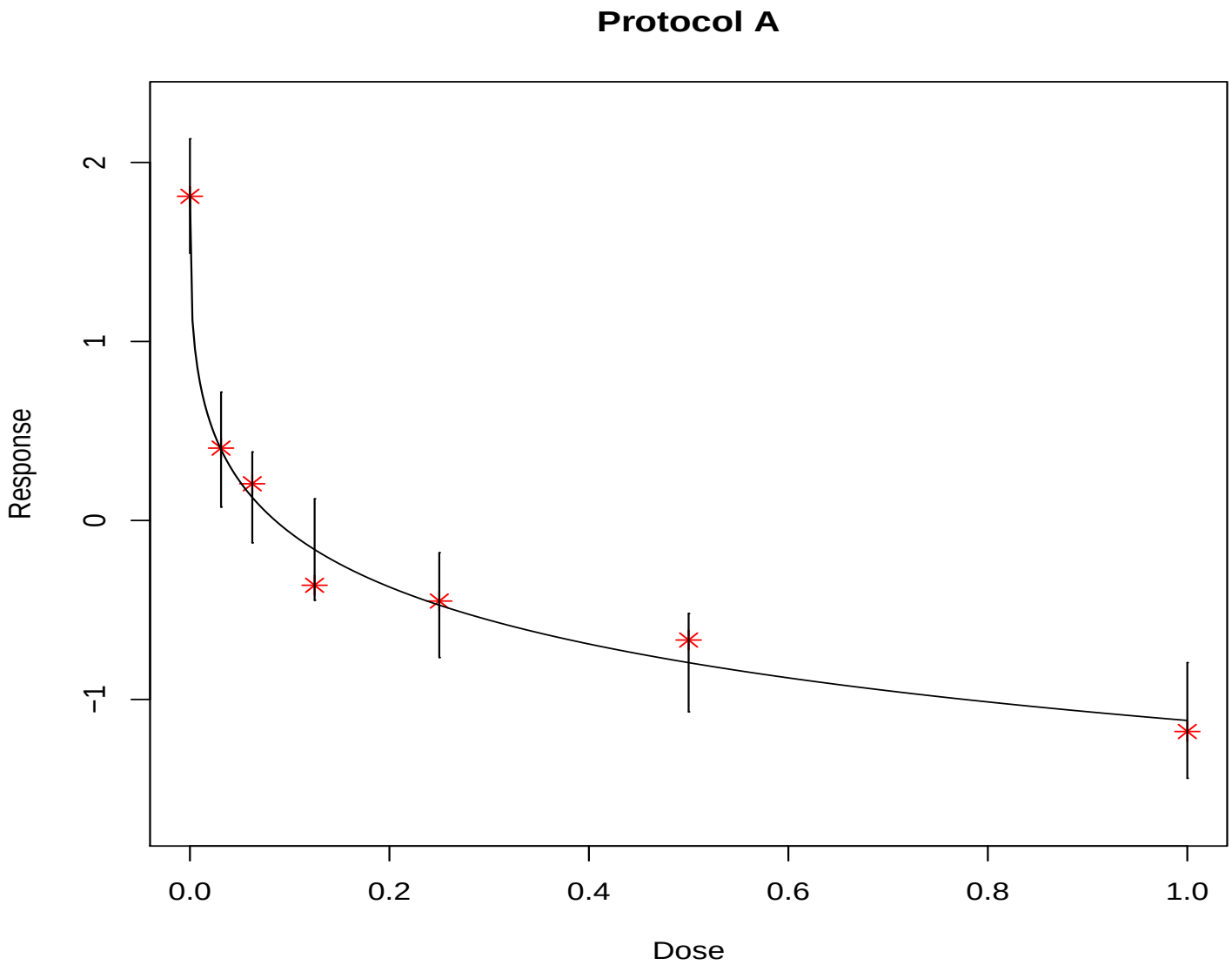
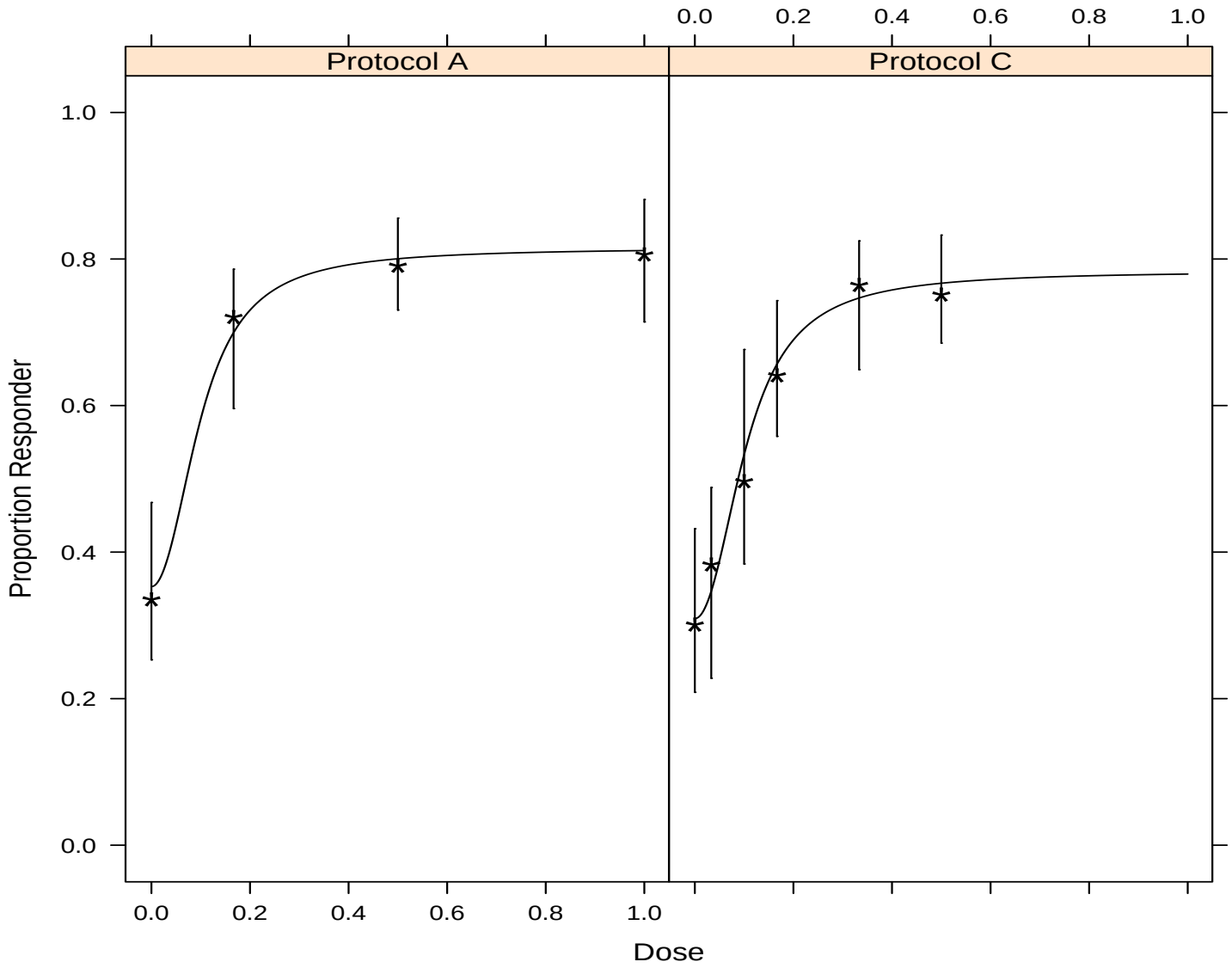


$\hat{\lambda} = 0.35$ Mandema et al[4]

JAK3 inhibitor (ID 25.1) for RA (binary endpoint)



$\hat{\lambda} = 2.02$

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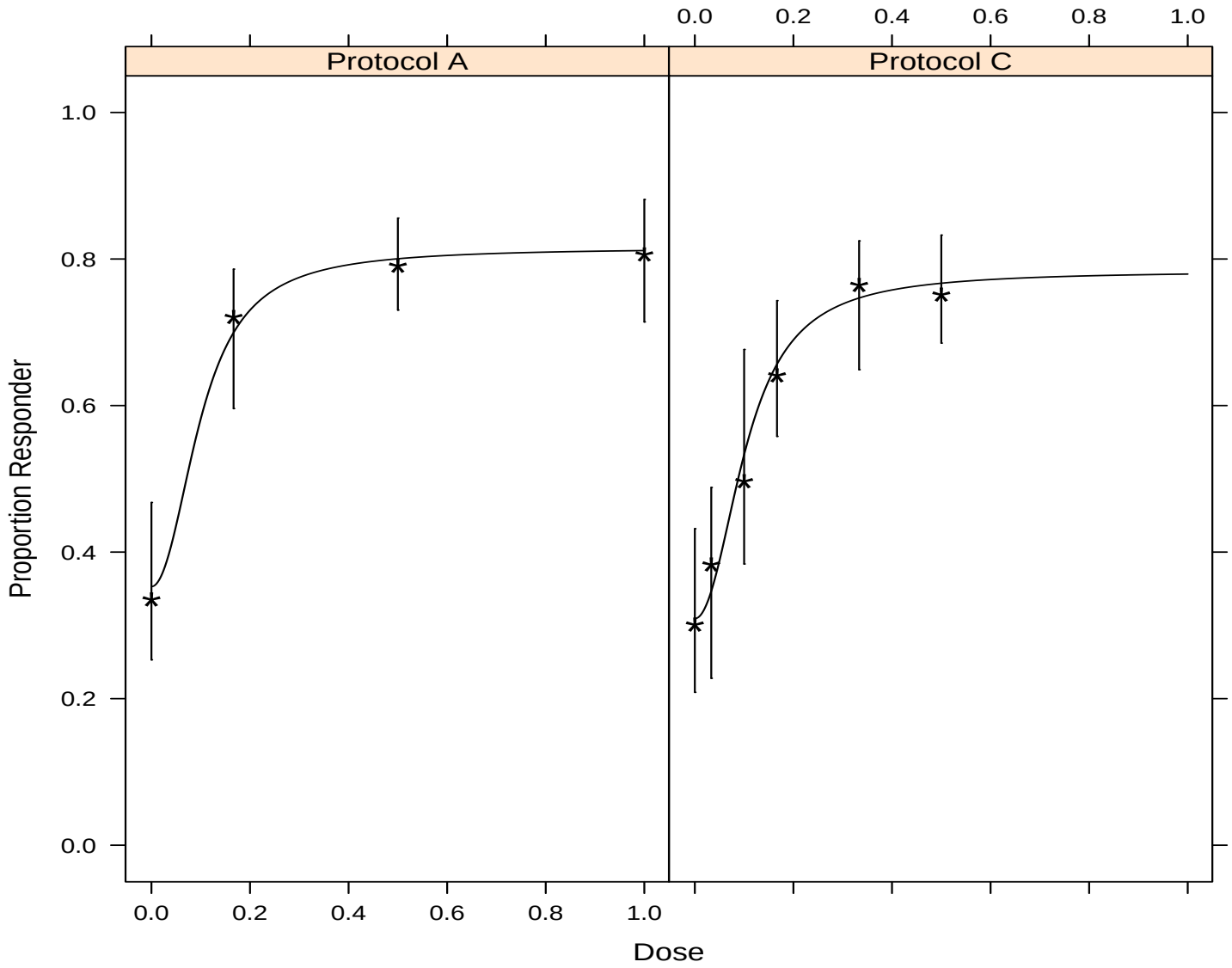
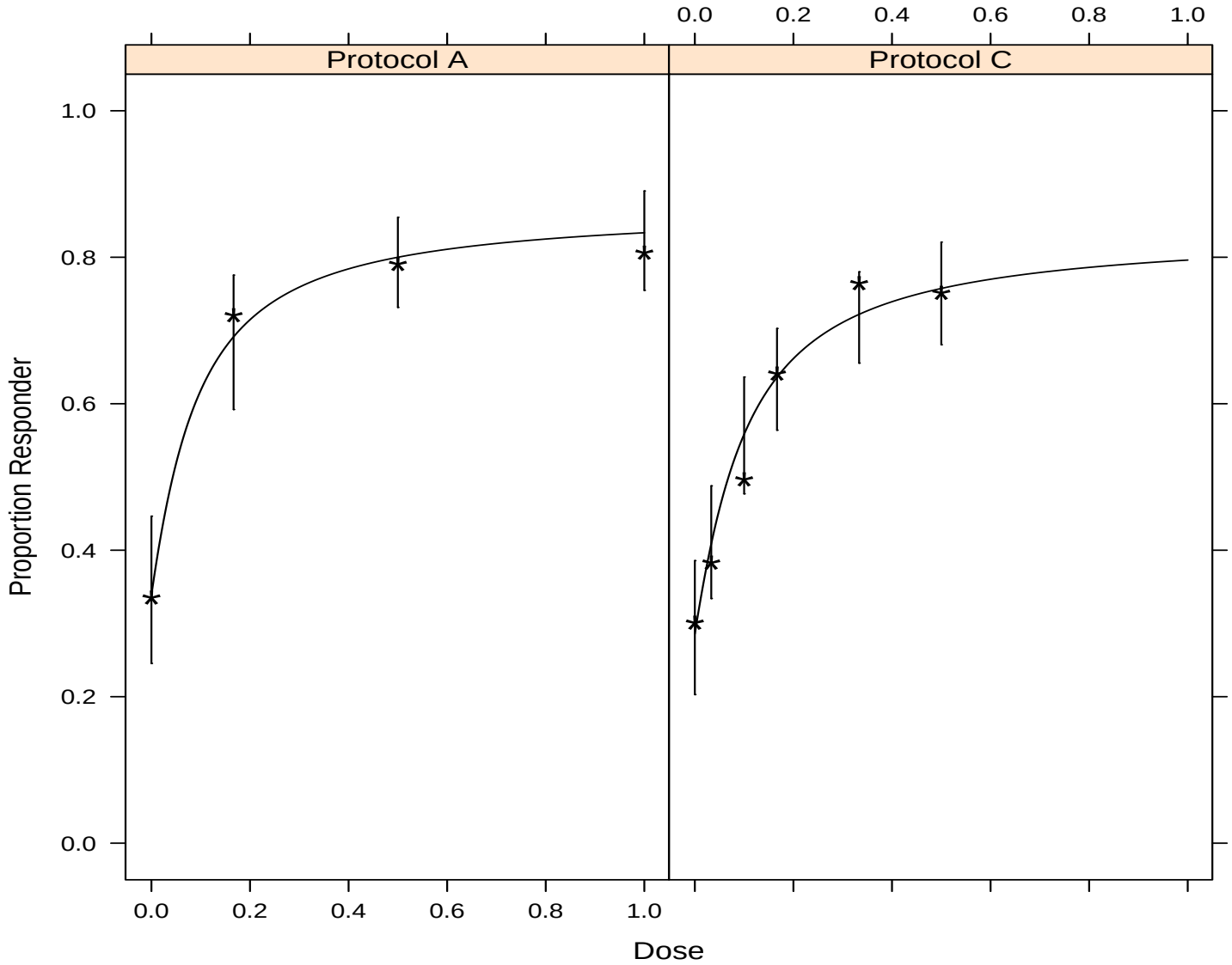
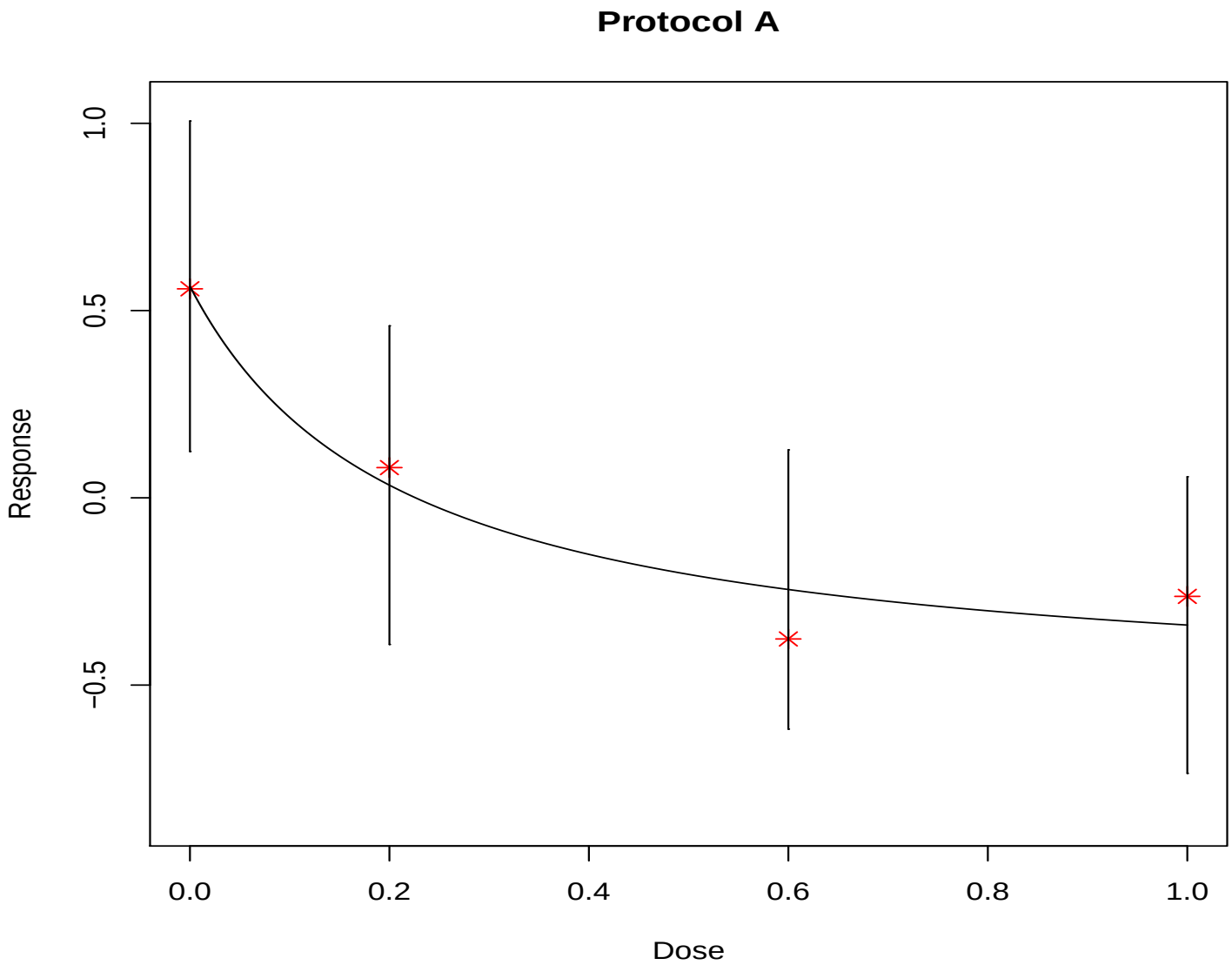


$$\hat{\lambda} = 2.02$$

JAK3 inhibitor (ID 25.1) with Hyperbolic model



CB1 inhibitor (ID 5) for weight loss load endpoint



$\lambda = 1$

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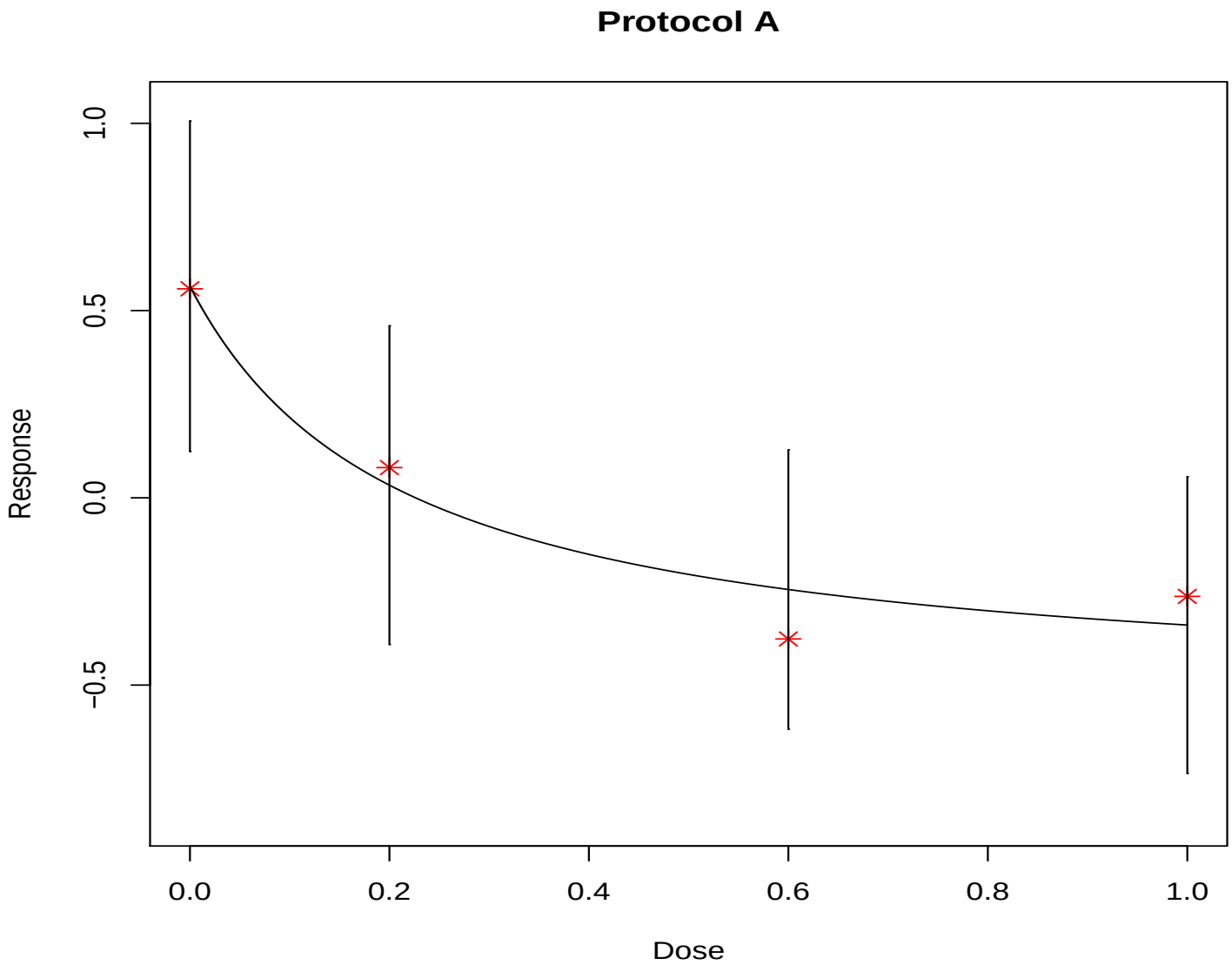
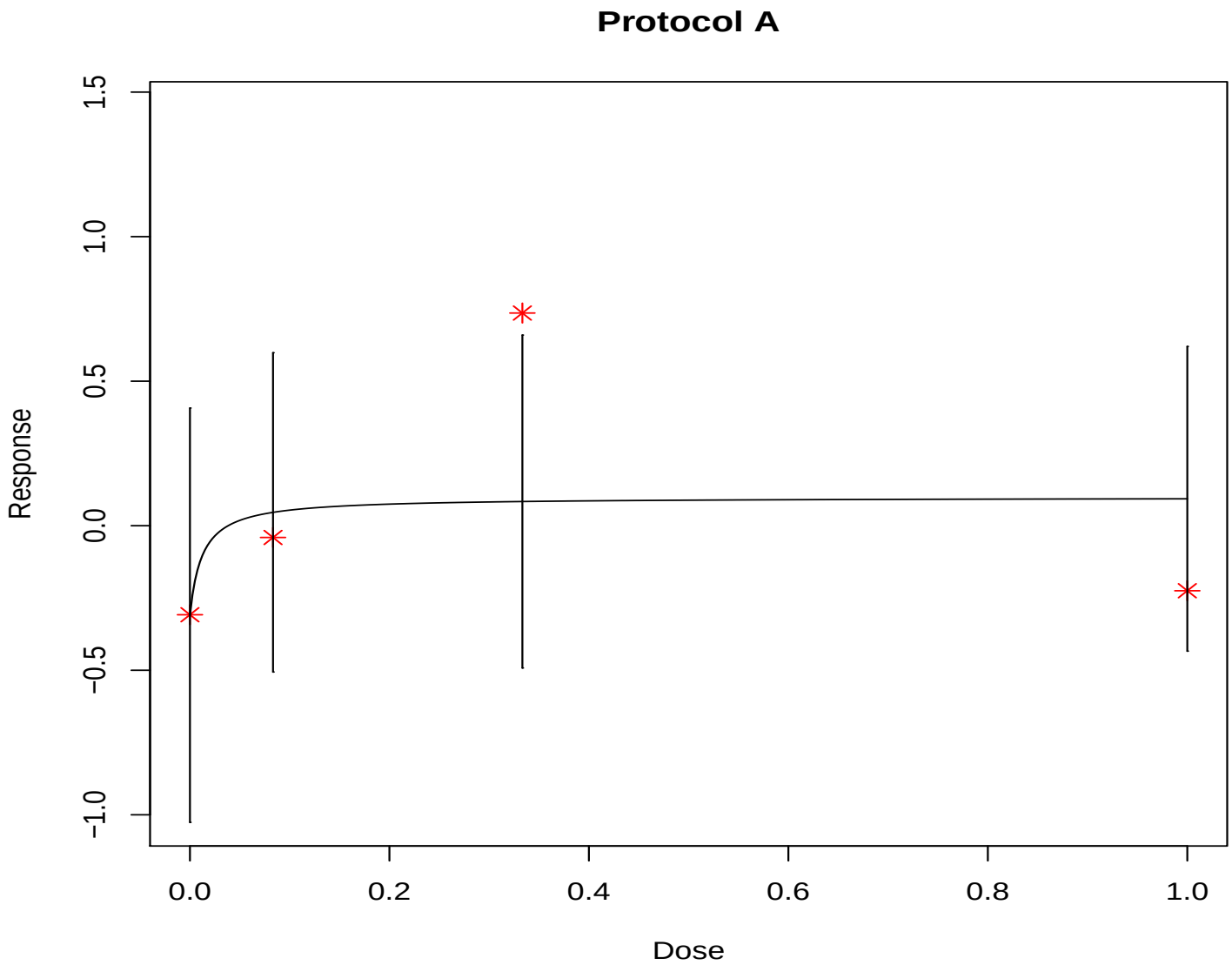


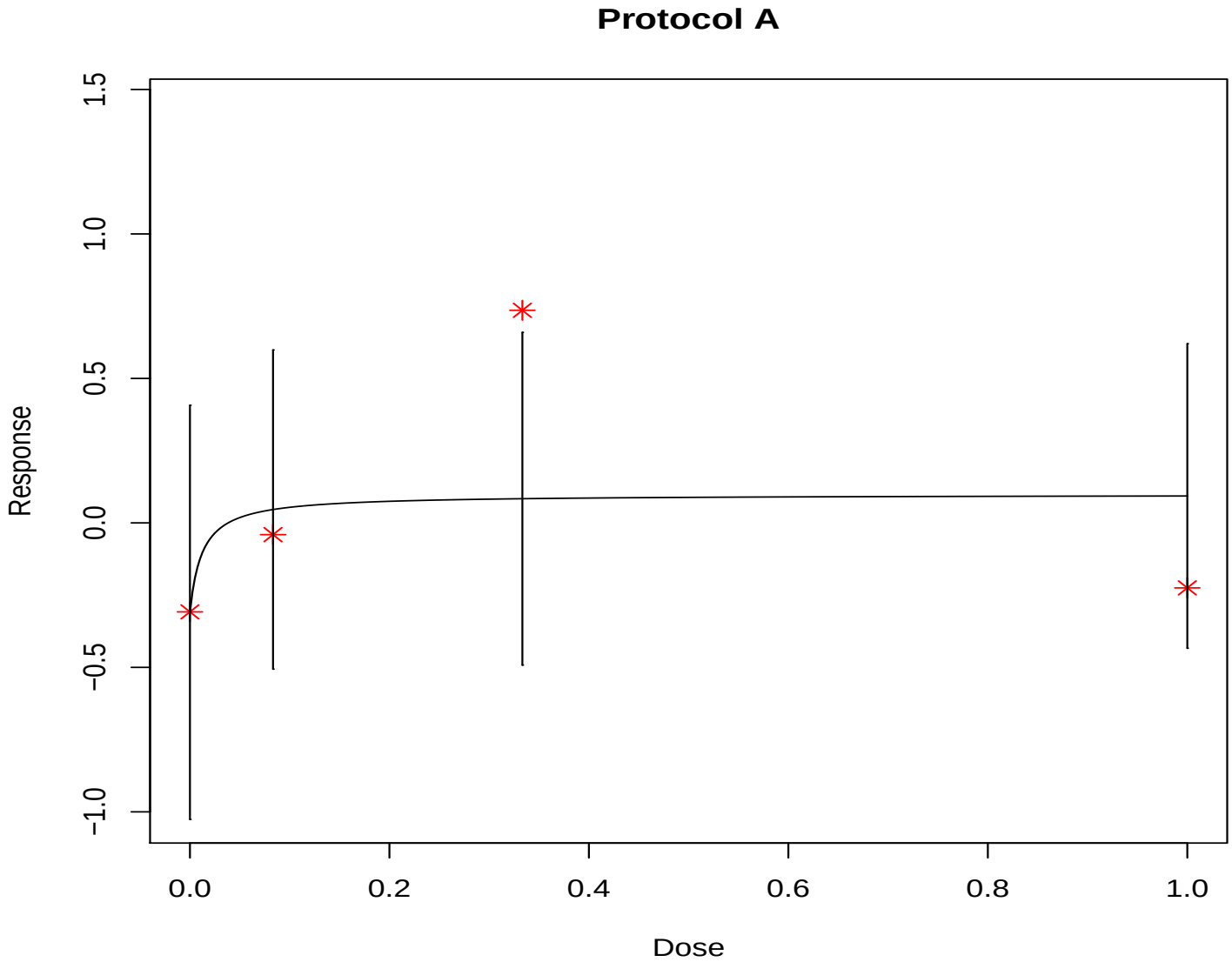
$\lambda = 1$

PPAR-α (ID 34) to increase high density cholesterol



Nissen, et al [5]

PPAR-α (ID 34) to increase high density cholesterol



Nissen, et al [5]

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Model adequacy

Placebo data

- Placebo response varied considerably between studies.
- Dose response relative to placebo was consistent between studies.

Goodness of fit testing

- Generally good goodness-of-fit tests

Summarizing the MLE of the Hill (λ)

Achieving convergence

- Automated algorithm trying different starting values and methods
- 30 of 32 hyperbolic models achieved nominal convergence
- 22 of 32 sigmoid models achieved nominal convergence

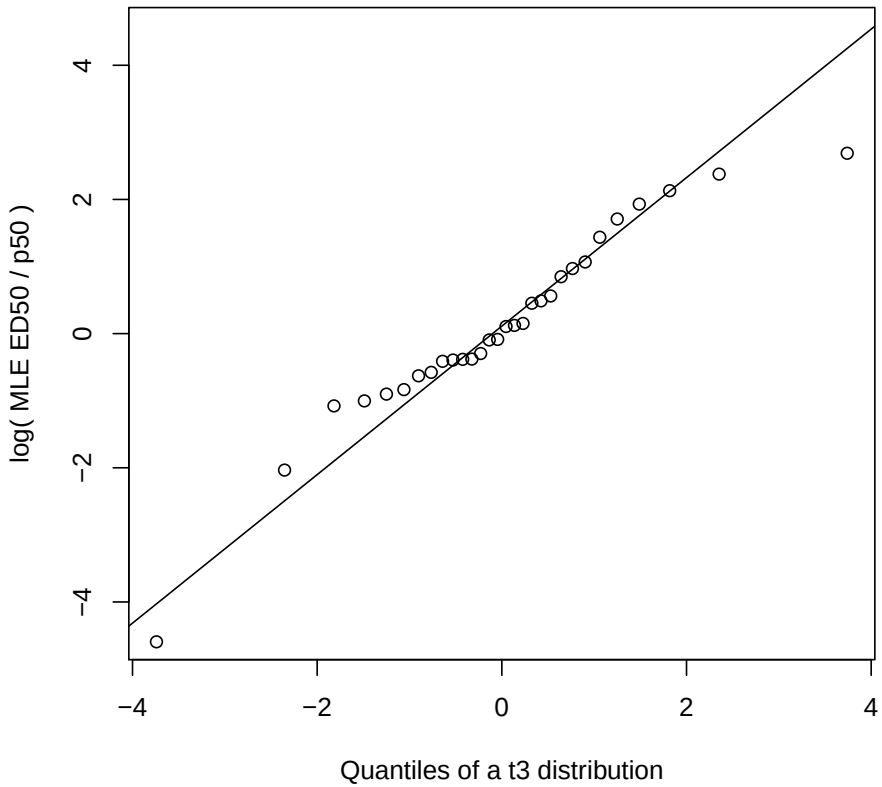
Distribution of Hill (λ) parameter estimates

- 25^{th} percentile is 0.85.
- 50^{th} percentile is 1.13.
- 75^{th} percentile is 1.61.

Summarizing the ED_{50} estimates

- Therapeutic doses range from micro-grams to grams, but much of the difference can be predicted from pre-clinical and early clinical data
- Dose response must be projected to select doses for first phase 2 study
- Many approaches and data sources

Quantile plot of $\log(\widehat{\mathrm{ED}}_{50}/\mathrm{P}_{50})$



90% of the compounds satisfied $(-2 < \log(\widehat{\mathrm{ED}}_{50}/\mathrm{P}_{50}) < 2)$ or equivalently, $(0.14\mathrm{P}_{50} < \widehat{\mathrm{ED}}_{50} < 7.4\mathrm{P}_{50})$.

Summarizing the magnitude of effects

Parameterization

- Summarize the estimated effect at the maximum dose tested divided by the within-group SD
  - Compounds with continuous endpoints

Other considerations

- Summarize absolute values of effects
- Only compounds with demonstrated efficacy are included in the summary

Summarizing the magnitude of effects

Standardized treatment estimates

Percentile	Standardized Effect
25	0.53
50	0.96
75	1.66

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Hierarchical model

Distributions for ED_{50} and λ across compounds

- Same model parameters for each compound
- Distributions specified for ED_{50} and λ across compounds
- Details are in a manuscript

	λ		$\mathrm{ED}_{50}/\mathrm{P}_{50}$	
Percentile	MLE	BAYES	MLE	BAYES
0.05	0.49	0.26	0.17	0.52
0.25	0.85	0.54	0.66	1.37
0.50	1.13	0.79	1.11	2.20
0.75	1.61	1.11	2.34	3.44
0.95	2.99	1.68	10	8.41

Primary conclusions of hierarchical modeling

Accounting for estimation errors in the λ and ED_{50}

- Compounds with $\lambda > 1.5$ are unusual.
- The spread of the $\mathrm{ED}_{50}/\mathrm{P}_{50}$ was reduced and $(\mathrm{P}_{50}/10, 10\mathrm{P}_{50})$ was confirmed as a crude 90% interval.

Why are the Bayes estimates of λ lower, and ED_{50} higher than the MLEs?

- There is near aliasing of models for λ in $(0.5, 1)$.
- Lower values of λ are compensated by larger values of the ED_{50} and $\mathrm{E}_{\mathrm{max}}$.

Conclusions

What do clinical dose response curves look like?

Most look like hyperbolic $\mathrm{E}_{\max}$ curves.

How well were they determined by the studies conducted?

- The answer varies between compounds due to reasons controllable and uncontrollable.
- Dosing ranges in the initial studies are too narrow.

Are there consistent quantitative trends in dose response across unrelated diseases and compounds?

- Yes
- Distributions of likely parameter values are potentially important in both design and analysis of dose response studies.

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