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Adaptive Designs: Current Status, Future Outlook

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Outline

- High Interest
  - What is an Adaptive Design?
- Available Designs – and their Infrequent Use
- Slowness of Translation into Practice
- Phase 2b Dose-Response/Finding/Selection Designs
  - Number of Doses and Dose-Interval
  - Adaptive strategies
- Models for Phase 2b Dose-Response/Finding/Selection Designs
  - Issues in fitting
  - Non-monotonic models
  - Smoothing approaches

Special Issues Covering Adaptive Designs
Current Interest - High

Journal of Biopharmaceutical Statistics, 16: 275–283, 2006

ISSN: 1054-3406 print/1520-5711 online
DOI: 10.1080/10543400600614742

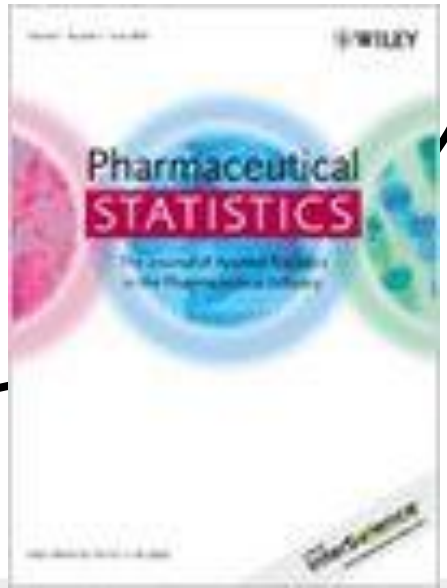
Drug Information Journal
OFFICIAL PUBLICATION OF THE DRUG INFORMATION ASSOCIATION

2006

of the International Biometric Society

Biometrical Journal

Methods · Applications · Case Studies · Regulatory Aspects · Reviews



Traditional Approach

- Most RCTs follow the formula exemplified in 1948 by Bradford-Hill and are “static”:
- Key elements driving the designs are specified in advance:
  - significance level
  - endpoint and hypothesis
  - type of test and test stastistic
  - Determine sample size under specified effect size and power
- Observe patients, estimate parameters (& CI), compute *p*-value for specified hypothesis,
- Make Decision

Traditional Design Framework

- "Static" design framework:
  - Results observed during trial are not used to guide it's course
  - Set-up provides solid inferential procedures
  - Different ways to improve efficiency : dynamic modification of trial's design during its course based on accumulating data
  - Lead to a broad group of methods known today as "adaptive designs"

Adaptive Designs

- Many of designs we call “data-depdendent” or “adaptive” today have been around for decades
  - e.g. group-sequential designs, response-adaptive randomization, flexible designs, sample size re-estimation
- These designs
  - Aim at improving some feature of a rigid traditional design (such as cost efficiency or addressing an ethical dilemma)
  - Share a common feature of mid-course adaptation(s)
- There has been considerable confusion as to what constitutes an adaptive design
- Need for a unified structured approach to terminology

Adaptive Designs
Definition - Executive Summary of PhRMA Working Group

- **Adaptive design** refers to a clinical study design that uses accumulating data to decide on how to modify aspects of the study as it continues, without undermining the *validity* and *integrity* of the trial
- Essential components:
  - changes are made by designs and not on an ad-hoc basis
  - adaptation is a design feature and not a remedy for poor planning
- ADAPTIVE BY DESIGN

- *Validity* means
  - providing correct statistical inference (such as adjusted p-values, unbiased estimates and adjusted confidence intervals, etc)
  - assuring consistency between different stages of the study
  - Minimising operational biases
- *Integrity* means
  - providing convincing results to a broader scientific community
  - preplanning, as much as possible, based on intended adaptations
  - maintaining confidentiality of data

Available Designs and Their Reported Use

- Up-and-Down: migraine, anesthesiology
- Play-the-winner: venous thrombo-embolism
- Randomised Play The Winner: ECMO, depression
- Group Sequential: increasing use
- Continual Reassessment Method: MTD, MED
- Sample size Reassessment (SSR): increasingly used
- Adaptive Interims for Confirmatory Studies: used in conjunction with (SSR)

- Phase 2b Dose-Response (modelling)
  - D-Optimal: no examples
  - Bayesian adaptive – a handful of examples
  - MCP-Mod: as yet nothing published
- Seamless Phase 2/3 – 2 examples
- Modern (yet old) Bayesian approaches – a handful of examples
- Adaptive Enrichment designs – a number currently running

The Slow Pace of Translation of Methodological Development into Practice

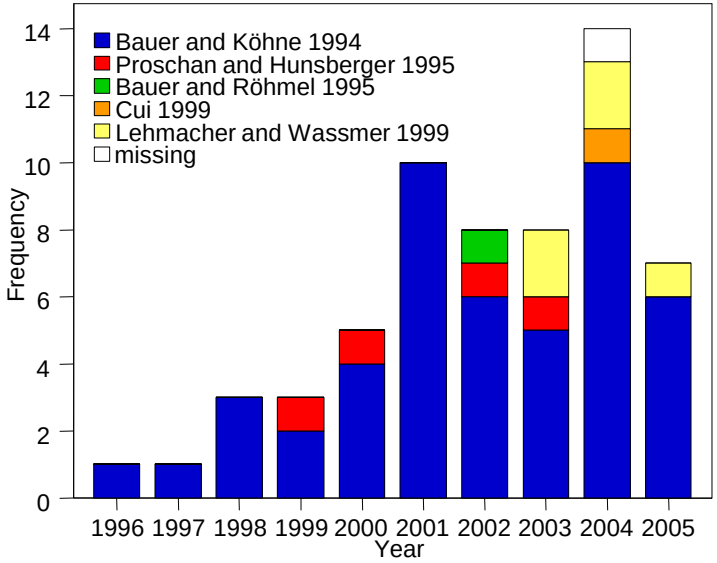
Sylvie Chevret (SIM, 2011)

- Bayesian clinical trials have been recommended for twenty years
  - Early phase trials -> phase III
  - BUT have been reported poorly used in practice
  - Possibly due to the usual time lag of the technical innovation spread - This was confirmed in this study with only 3% of biostatistical papers reaching 25 citations after publication, as compared to 15% of reviews and 32% of clinical trial reports
- Despite advantages and recommendations, Bayesian adaptive designs have not been widely adopted in practice
- Only 20 (1.6%) of 1,235 phase I cancer trials have been reported to follow a Bayesian design by Rogatko et al. (J Clin Oncol 2007)
- This could be in agreement with the previous report from Altman and Goodman (JAMA 1994)
  - « *Newer technical innovations still typically take 4 to 6 years before they achieve 25 citations in the medical literature.* »

The Slow Pace of Translation of Methodological Development into Practice

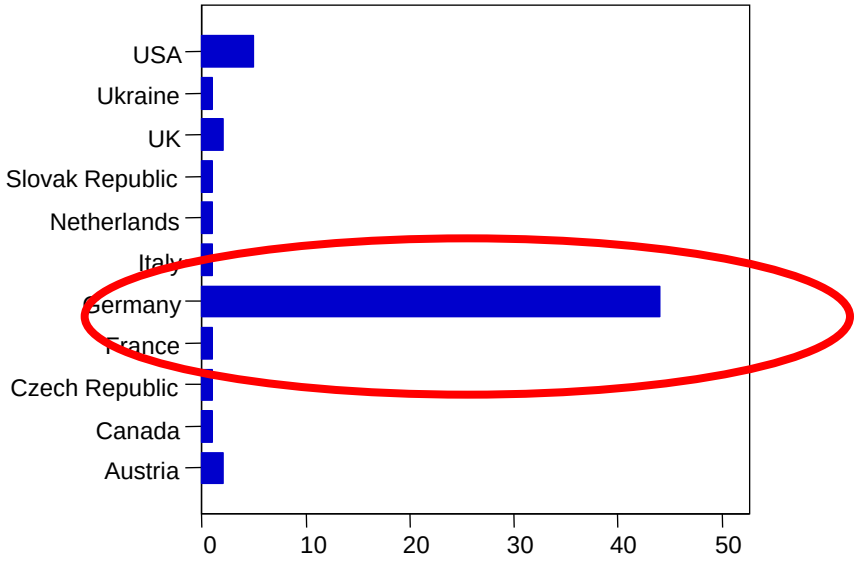
Bauer and Einfalt (Biometrical J, 2006)

- Identified 75 papers dealing with adaptive designs : 1989-2004
  - combination tests
  - conditional error function
  - did not consider Bayesian approaches



By: year and adaptive methodology

- Searched for “applied papers” in SCI, SSCI, IAHCI referring to at least one of the 75 papers
- Identified 60 applied medical papers



By: Country of corresponding author

The Slow Pace of Translation of Methodological Development into Practice

Altman & Goodman (JAMA, 1994)

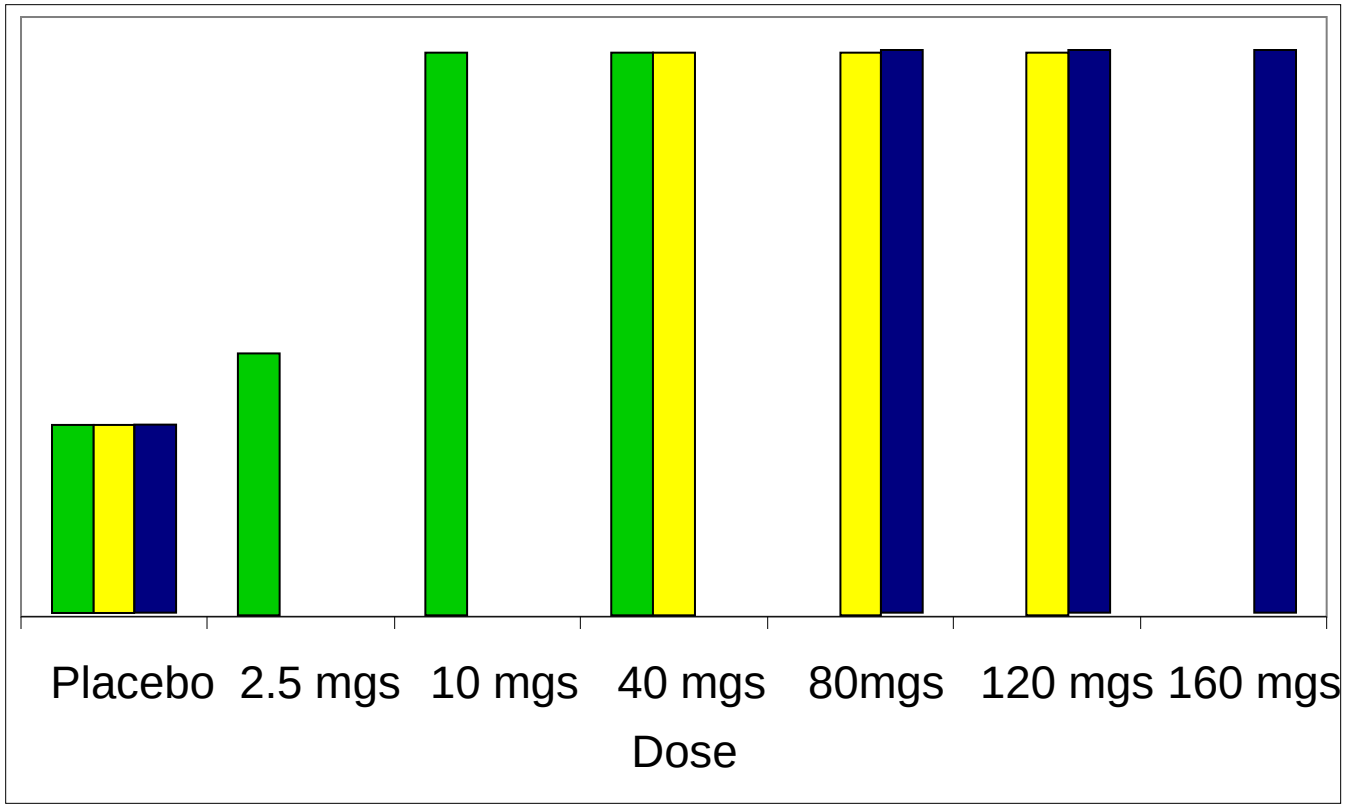
Table 3.—Newer Statistical Methods That May Be Seen More Often in the Coming Years

Method	Description	Purpose
Bootstrap (also called resampling; related to the jackknife)[17]	Multiple new data sets are generated by random sampling "with replacement" from the original data	To calculate SEs or assess the stability of a statistical model, often when standard assumptions are unreliable or the sampling distribution is unknown
Gibbs sampling[18,34]	Random sampling from conditional distributions within a complex structure	Bayesian estimation of complex models
Generalized additive models[35]	Nonparametric smoothing of explanatory variables in regression	To replace regression when assumptions are not tenable
Classification and regression trees[19,36] (also known as recursive partitioning)	Division of a set of subjects by combinations of characteristics, to minimize the differences within groups and to maximize the differences between groups	To find combinations of variables of predictive importance
Models for longitudinal data ("general estimating equations")[20]	Modeling repeated measurements of an outcome variable while allowing for covariates	Regression for multiple assessments of outcome
Models for hierarchical data (also called multilevel models)[37]	Fitting mixed linear models to hierarchical data using iterative generalized least squares	Modeling data with more than one level of variation (eg, within and between patients)
Neural networks[38]	Nonparametric modeling of complex data	To provide nonlinear approximations to multivariable functions or for classification

Phase 2b Dose Response/Finding/Selection Designs
1st Example

- Development in osteoarthritis
- 1st Cycle - pla, 80 mg, 120 mg, 160 mg (x2)
  - All 3 doses better than placebo, no differences between them
  - Doses based on pre-clinical data
- 2nd cycle - pla, 40mg, 80 mg, 120 mg (x4)
  - All 3 doses better than placebo, no differences between them
- 3rd Cycle – pla, 2.5 mg, 10mg, 40mg (x 64)
  - 2.5mg not different from placebo

Phase 2b Dose Selection Design Circa 1993

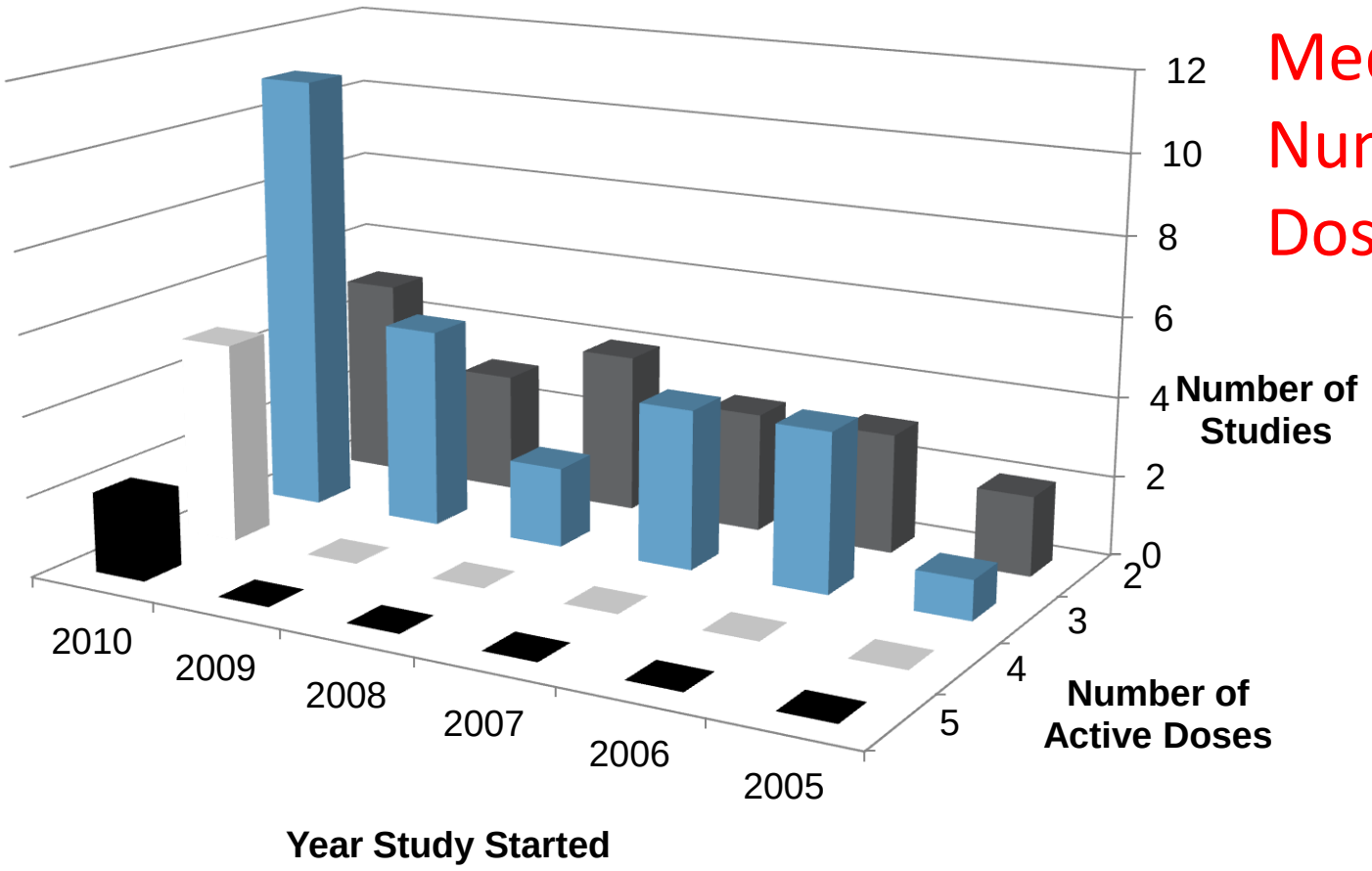


- More Efficient
  - wide range of doses, smaller numbers of patients per group
  - followed by one large parallel group study focusing on the doses showing promise in exploratory study.

Comparison Between Successful and Unsuccessful Phase II Programs

Initial Dose Finding Unsuccessful - More Studies Required			Initial Dose Finding Successful	
Study	Initial Dose Range	Total Dose Range Examined	Study	Dose Range Examined
1	4	64	1	40
2	1	4	2	8
3	6	16	3	4
4	4	8	4	10
			5	4
Median	4	12	Median	8

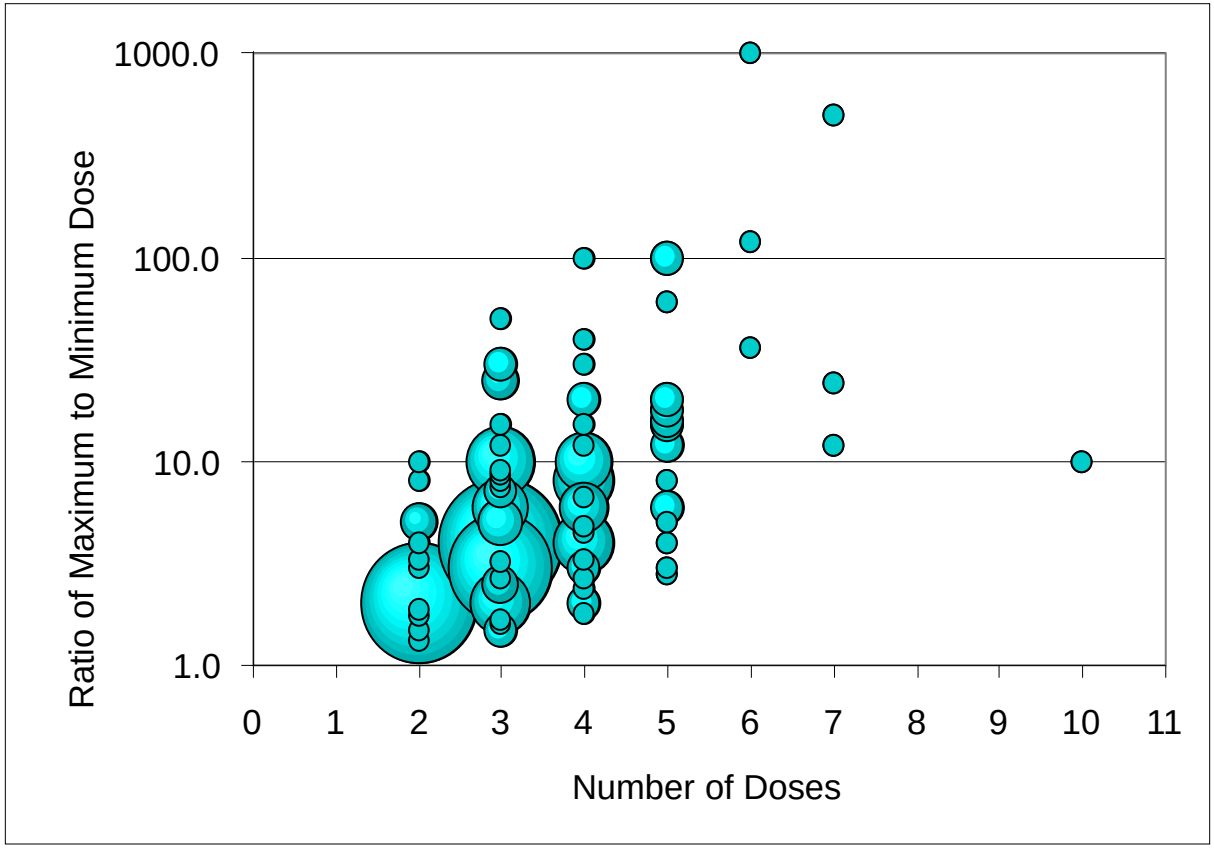
Phase 2b Dose Response/Finding/Selection Designs



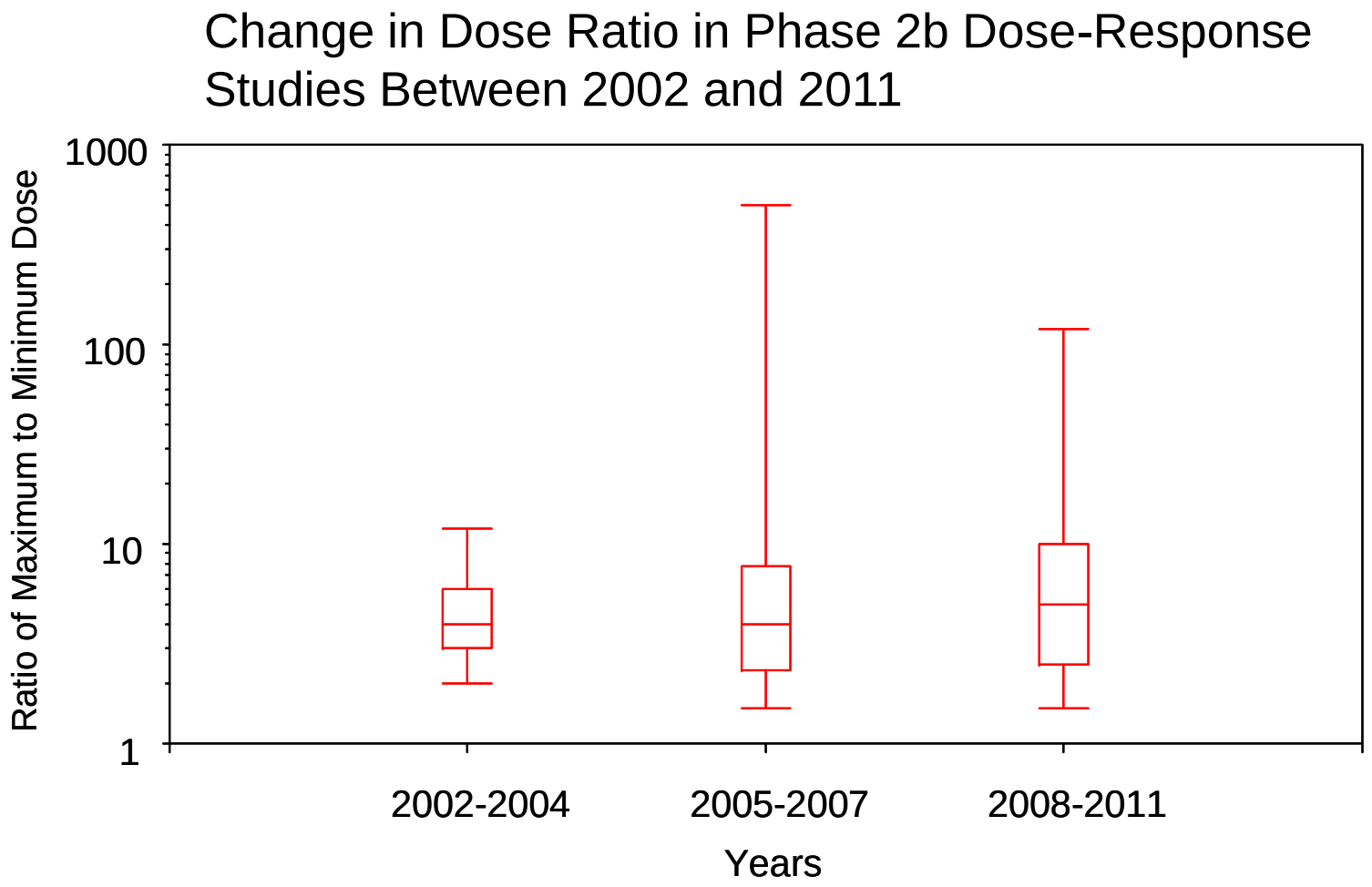
Median Number of Doses = 3

Phase 2 Adult Dose Response/Finding/Selection/Ranging Designs

Relationship Between Dose Ratio & Number of Doses

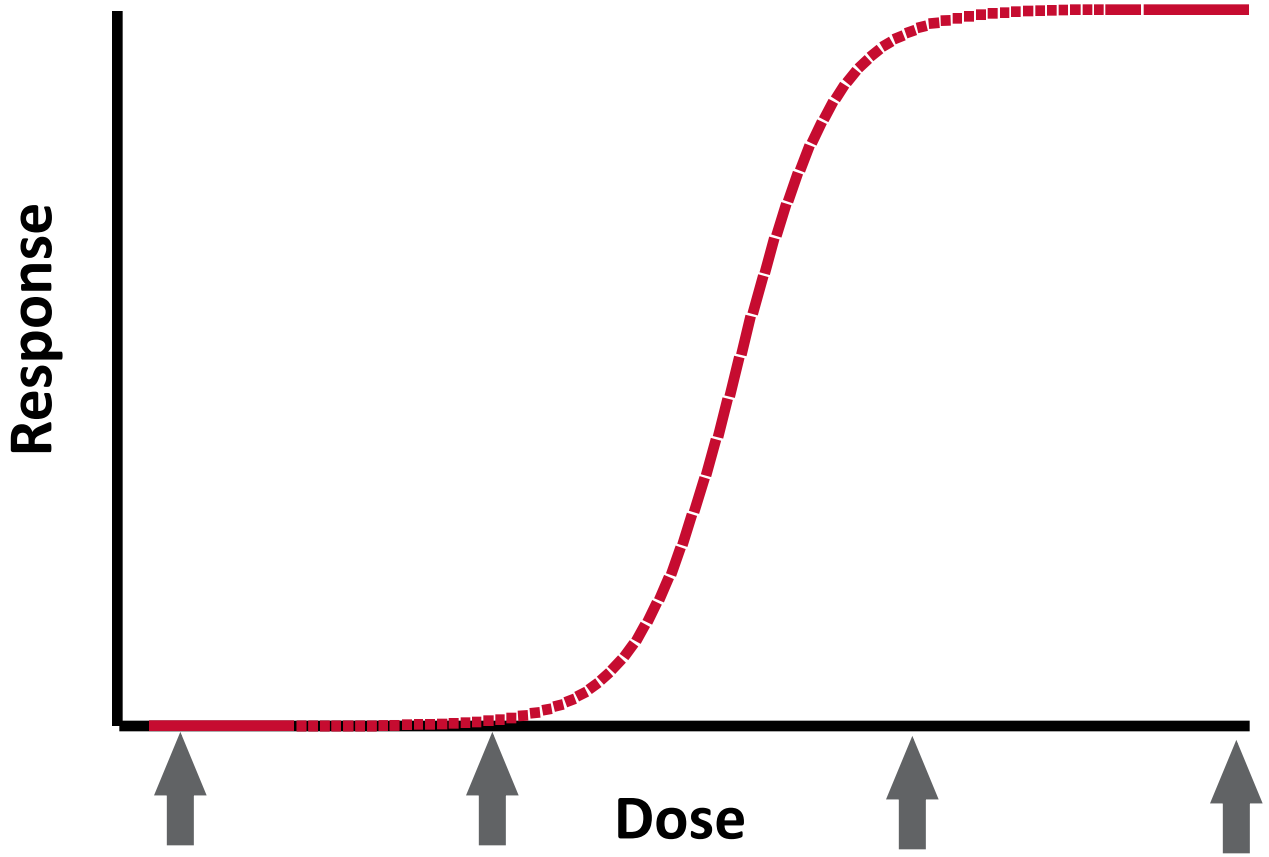


Phase 2 Adult Dose Response/Finding/Selection/Ranging Designs



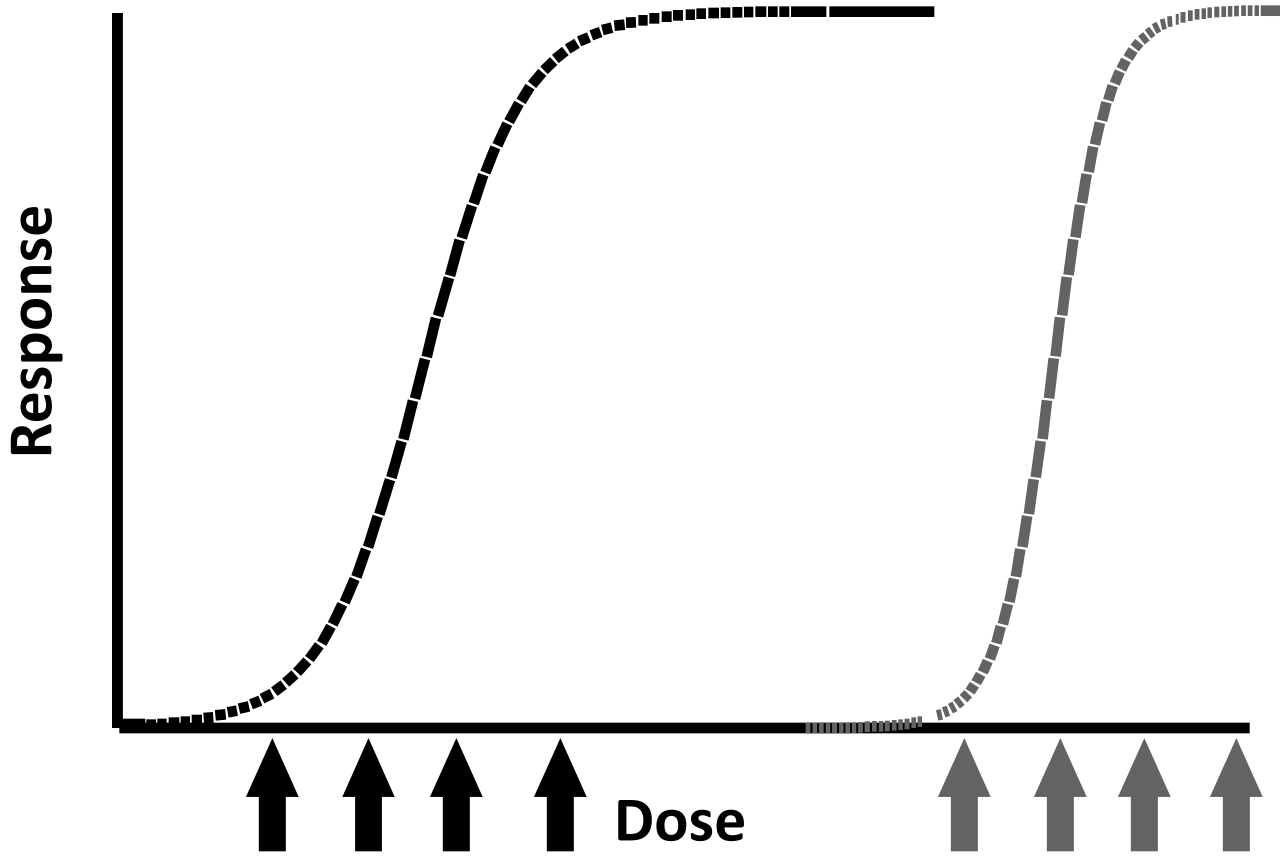
Phase 2b Dose Response/Finding/Selection Designs

Standard Design



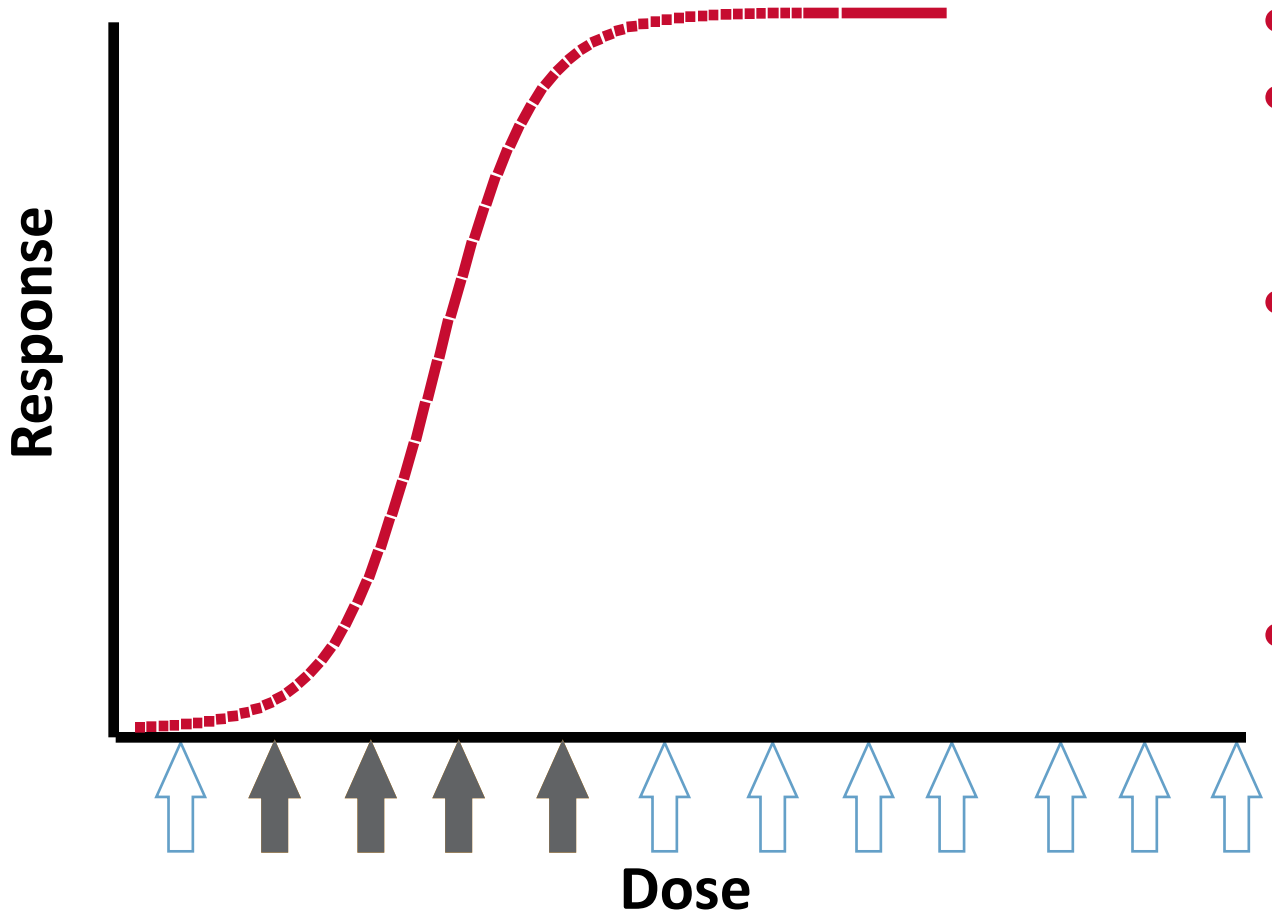
Phase 2b Dose Response/Finding/Selection Designs

Placebo + 4 doses available where to put them ?



Phase 2b Dose Response/Finding/Selection Designs

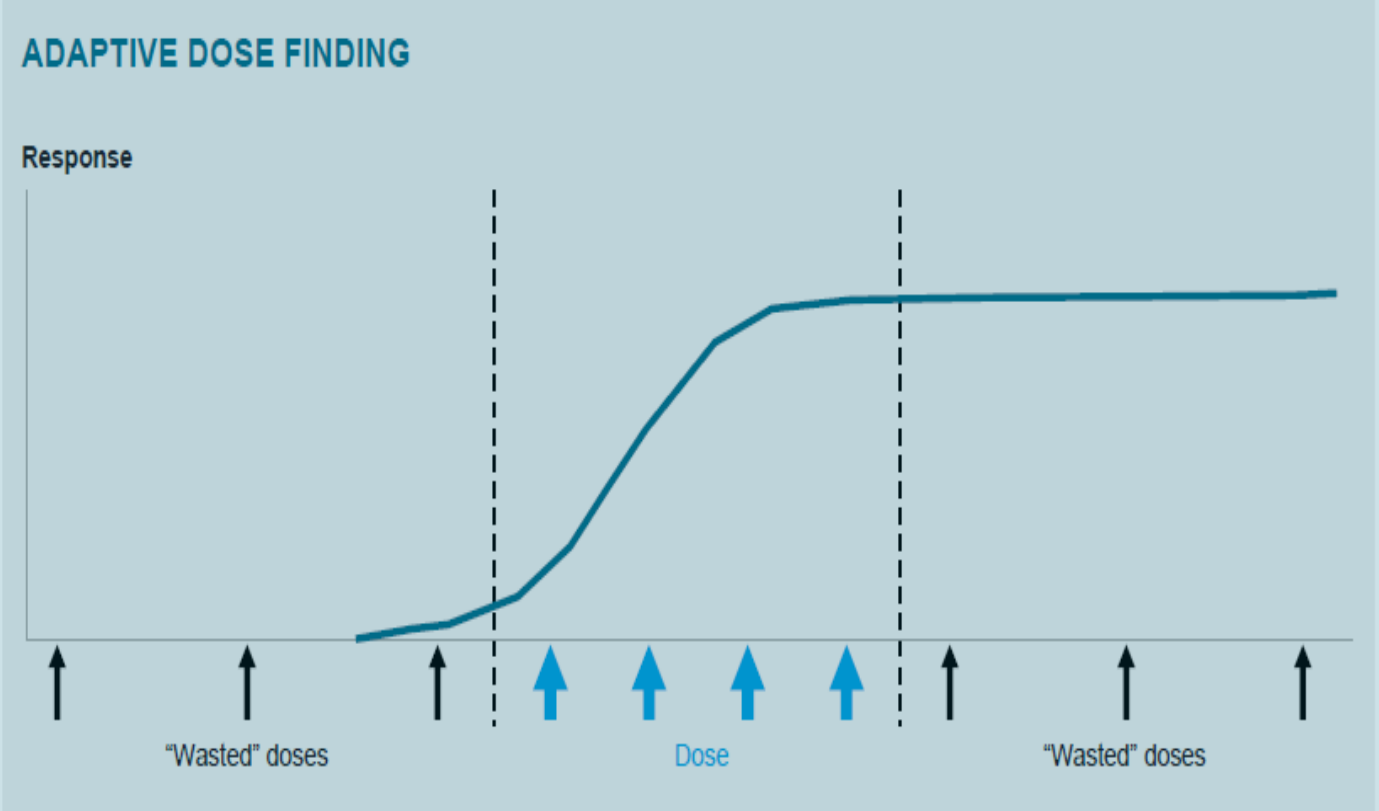
Choose Many Doses & Adapt



- Increase # of doses
- Adapt to steep part of dose response curve
- Concentrate on estimation rather than comparing individual doses to placebo
- Use of Bayesian Methods

Phase 2b Dose Response/Finding/Selection Designs

Choose Many Doses & Adapt

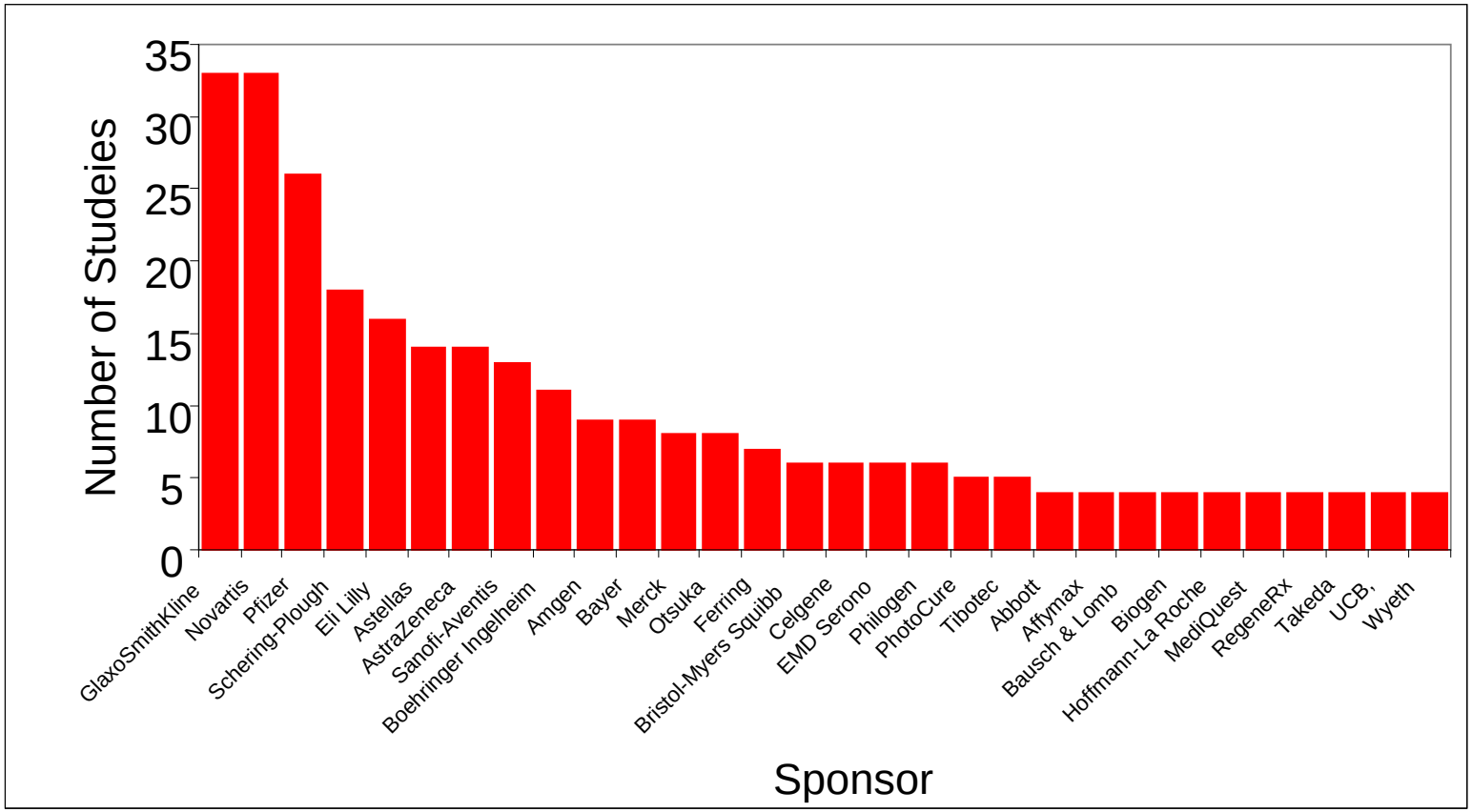


Invention Reinvented, McKinsey Perspectives on Pharmaceutical R&D 2010

What's the Model?

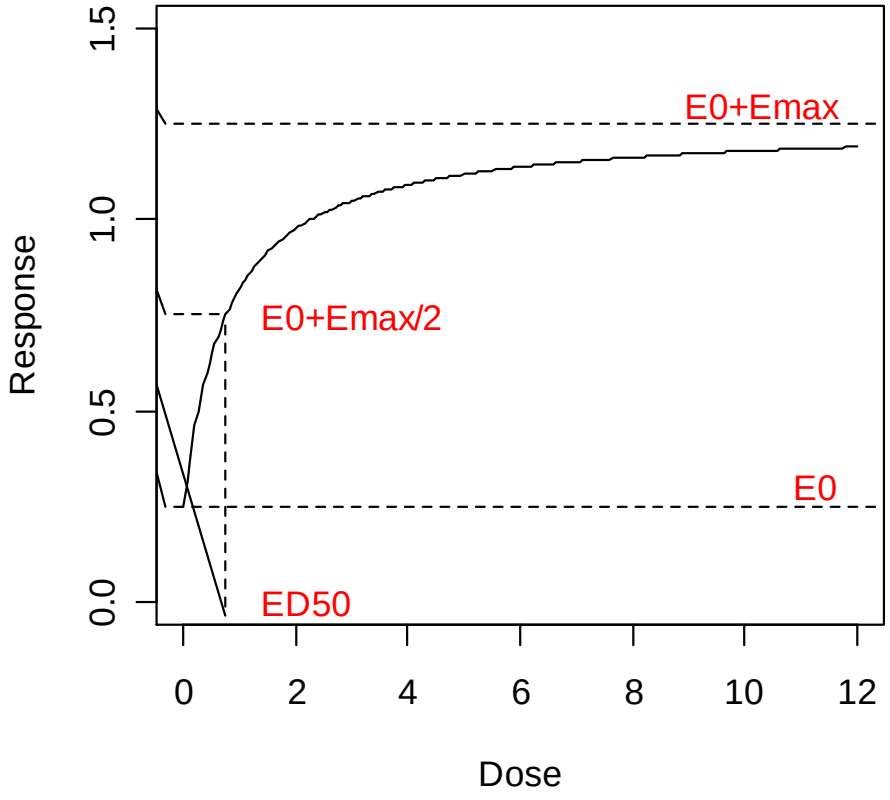
Dose-Response Studies 2002-2011

Numbers of Phase 2b Studies Sponsored by the Top 20 Sponsors Between 2002 and 2011

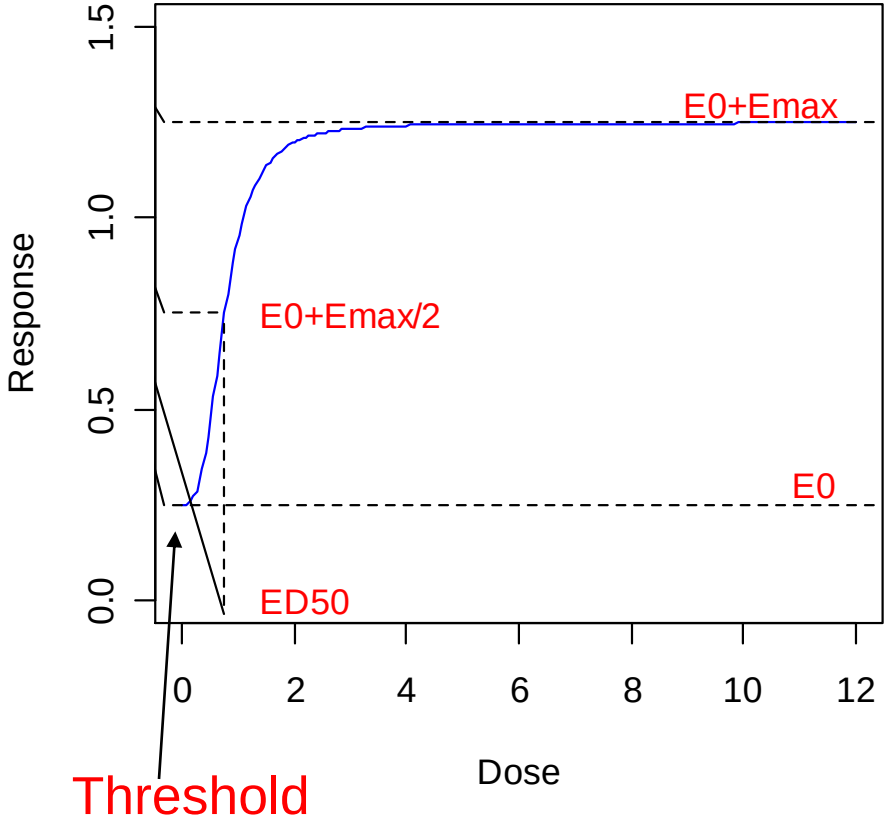


Emax Modela (3 & 4 Parameters)

$$E(Y|D) = E_0 + \frac{E_{max} D}{ED_{50} + D}$$



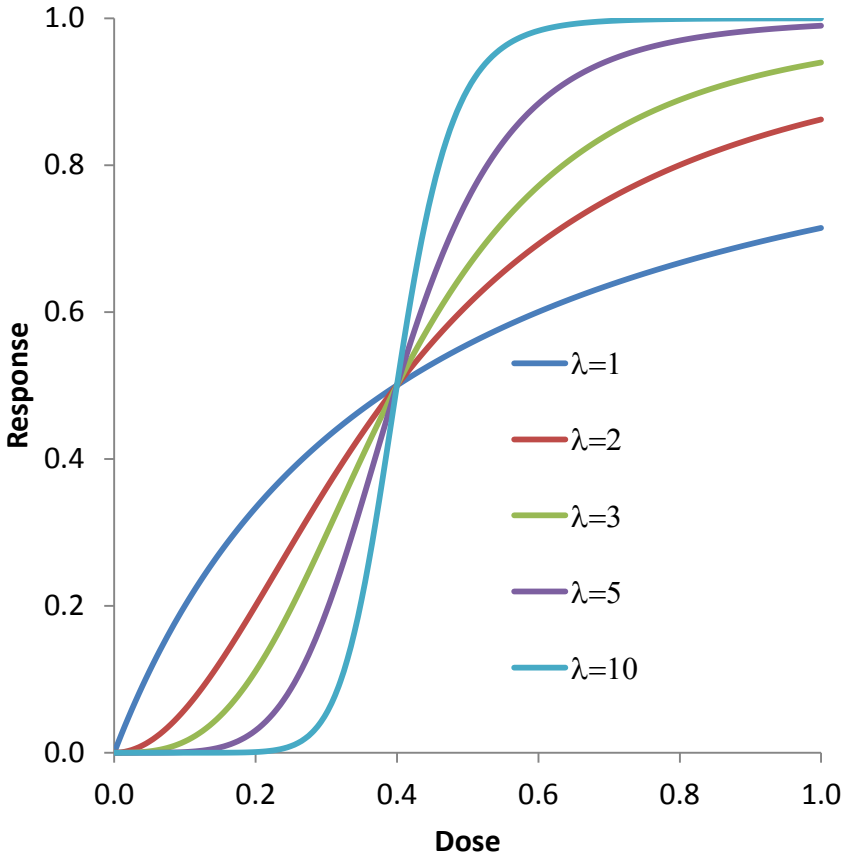
$$E(Y|D) = E_0 + \frac{E_{max} D^{\lambda}}{ED_{50}^{\lambda} + D^{\lambda}}$$



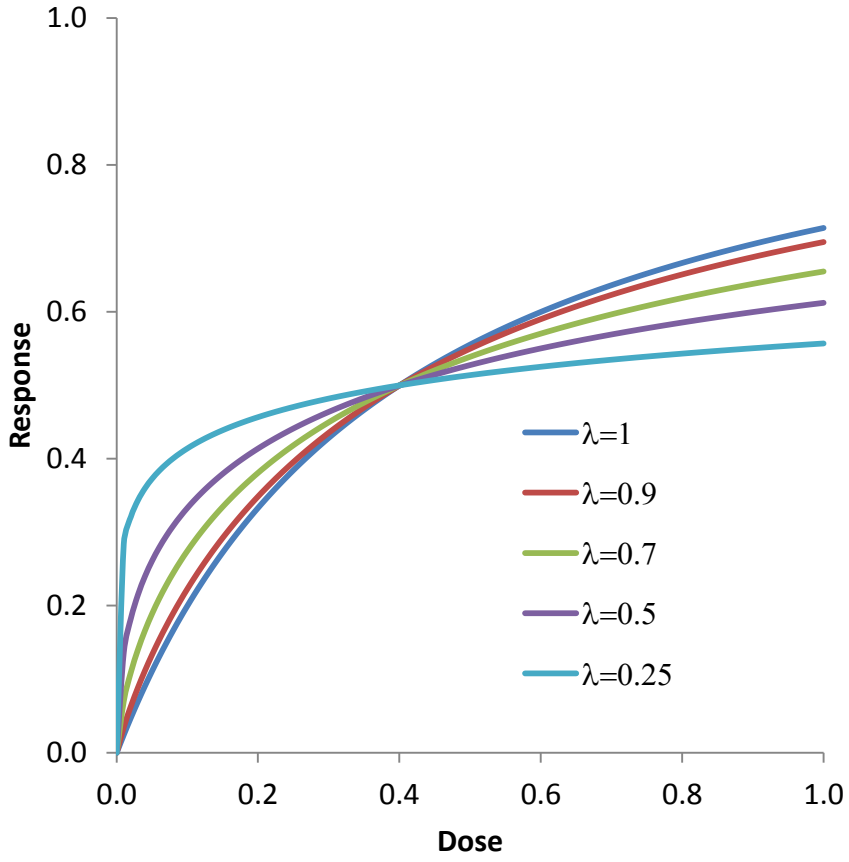
- Parameters E_0, E_{max}, ED_{50} and λ

Flexibility of the 4-parameter Emax Model

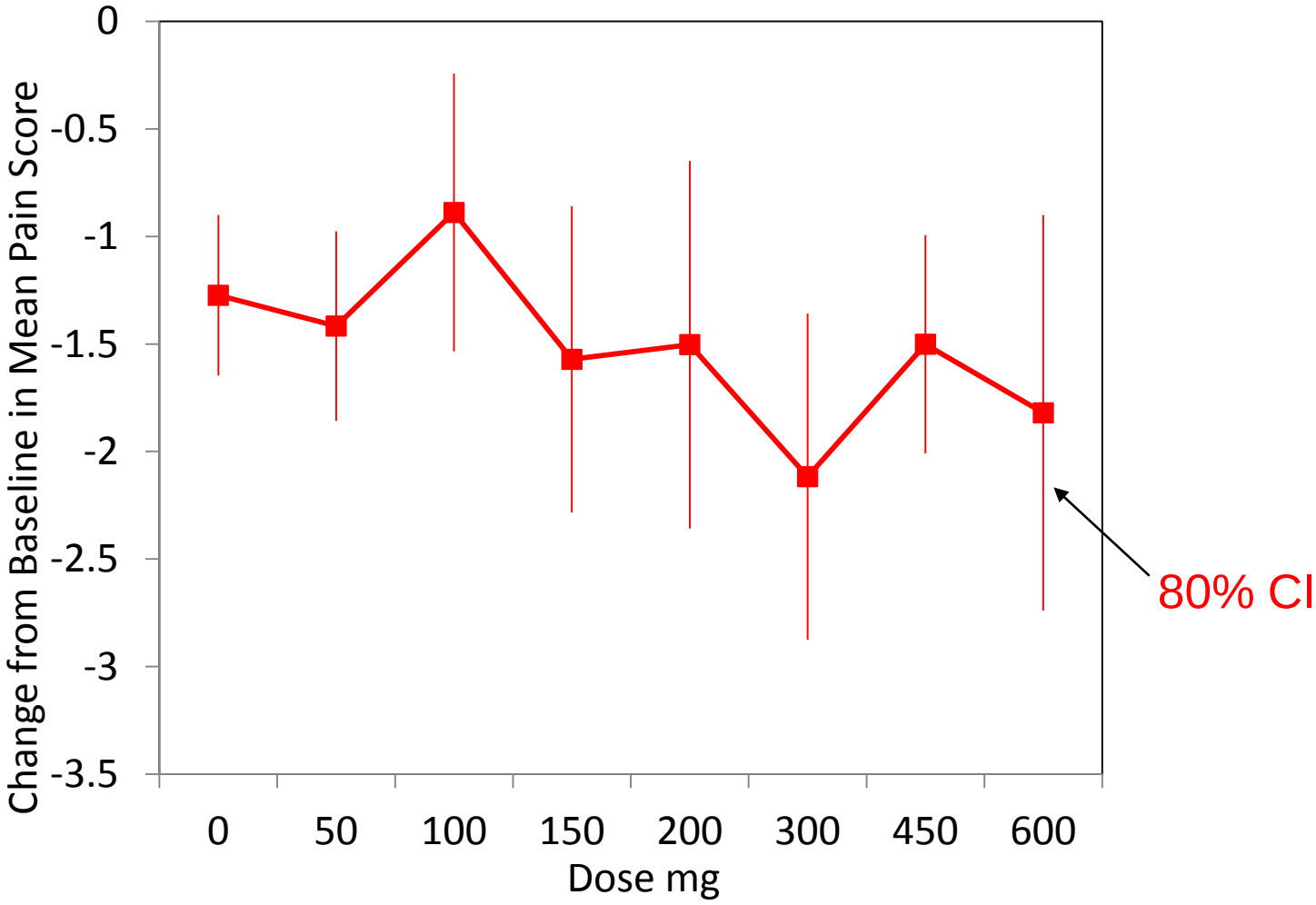
Lamda >1



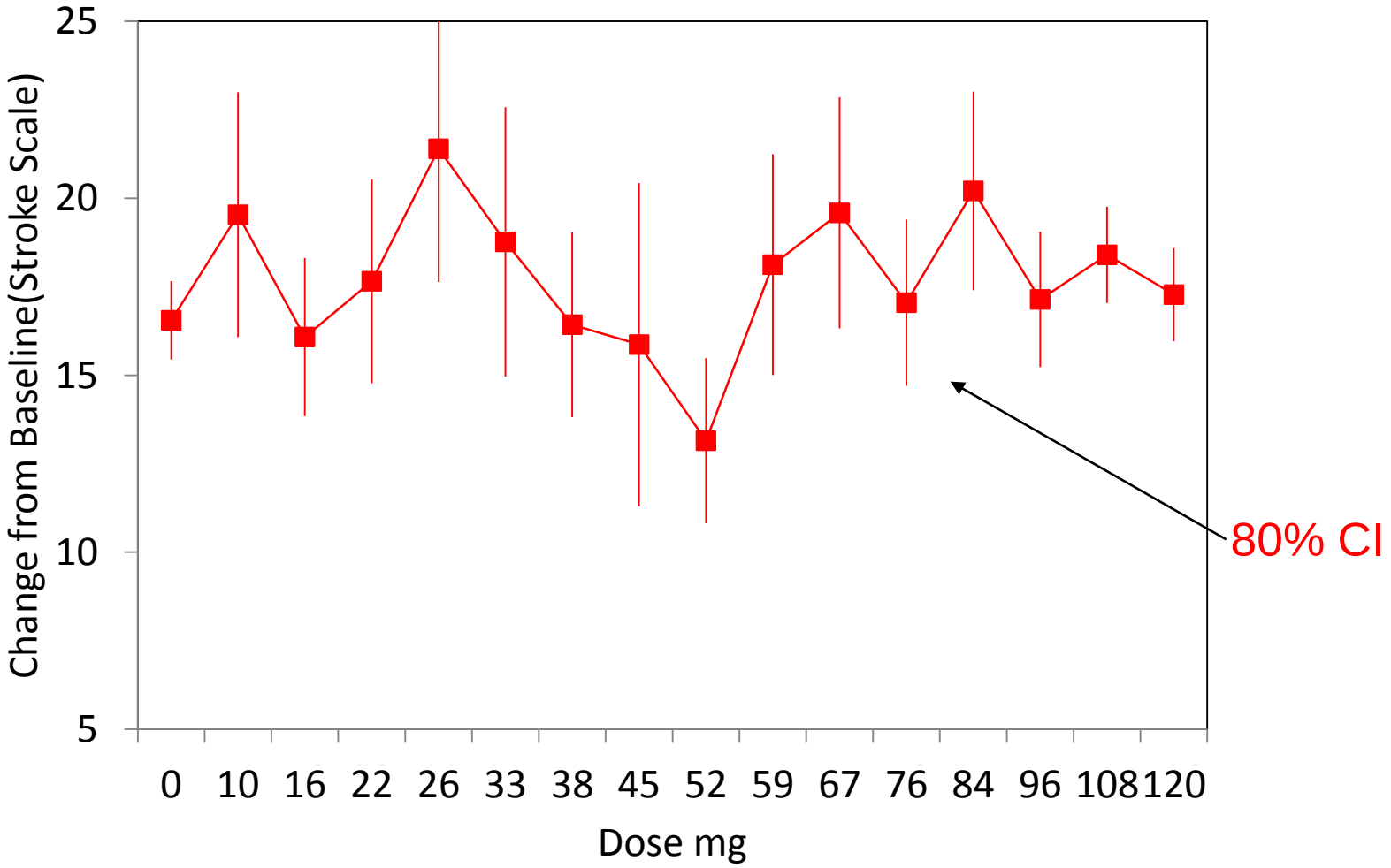
Lamda <1



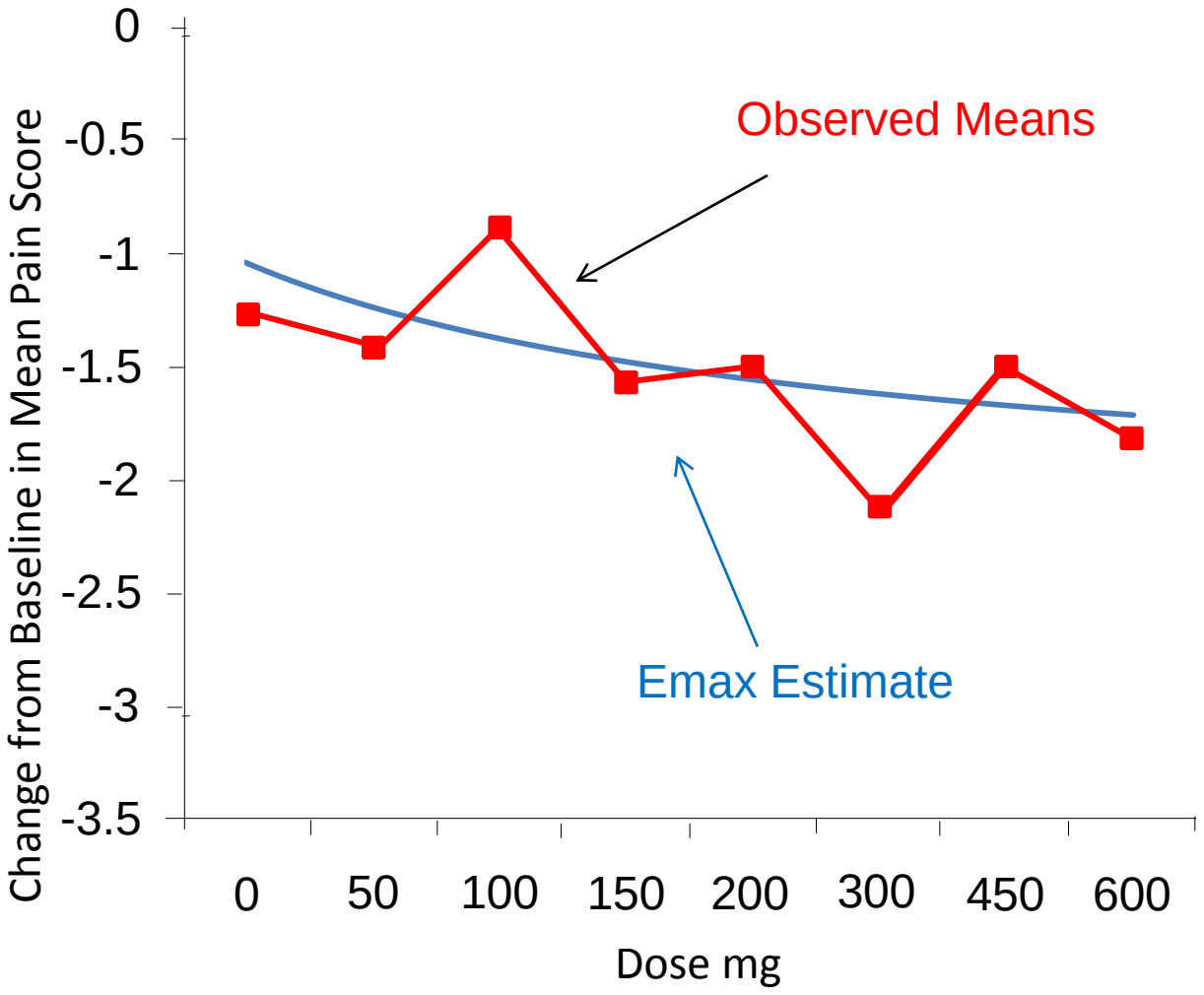
Results from 3 Dose Response Studies
Neuropathic Pain Study



Results from 3 Dose Response Studies Stroke Study



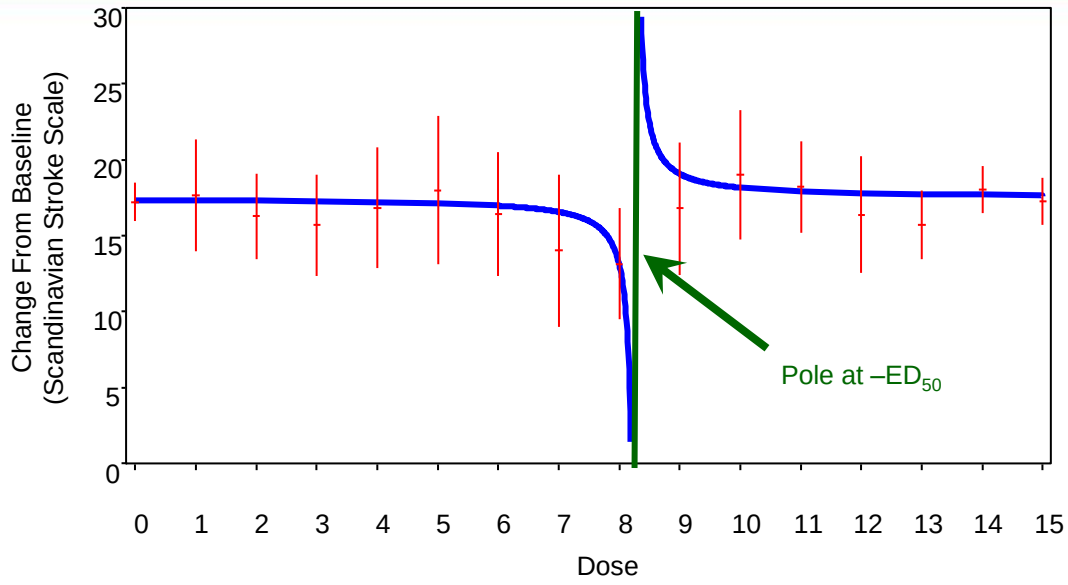
Pain Study
Fit of 3 Parameter Emax



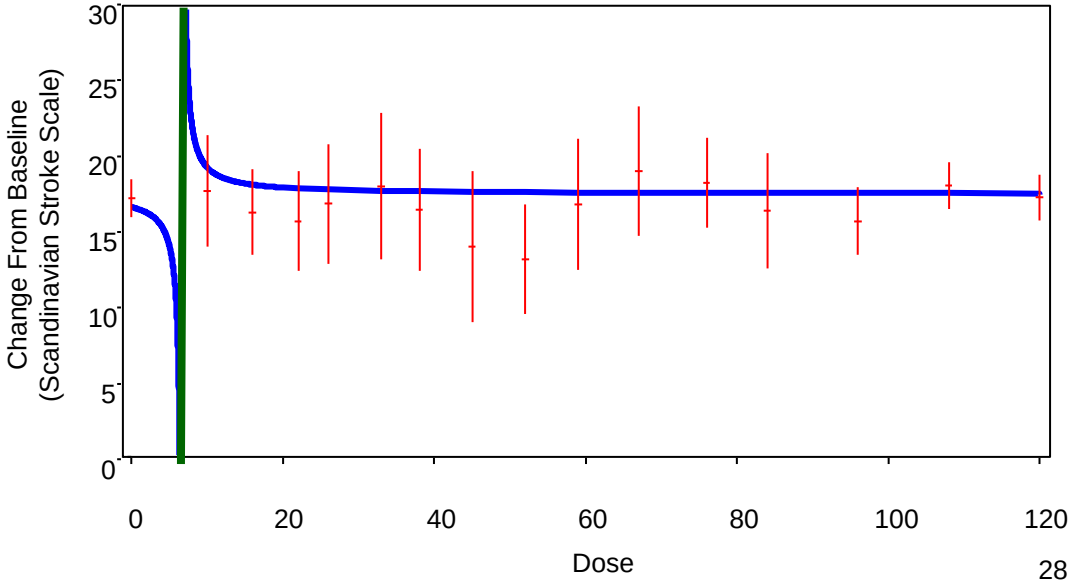
Fit of 3-parameter Emax Model Stroke Study

- For Stroke Study
  - 4-parameter Emax model failed to converge with numerical errors in derivatives
  - 3-parameter model converges, but the ED50 is negative
  - Unstable ML Estimation Is Common Under the Null Hypothesis

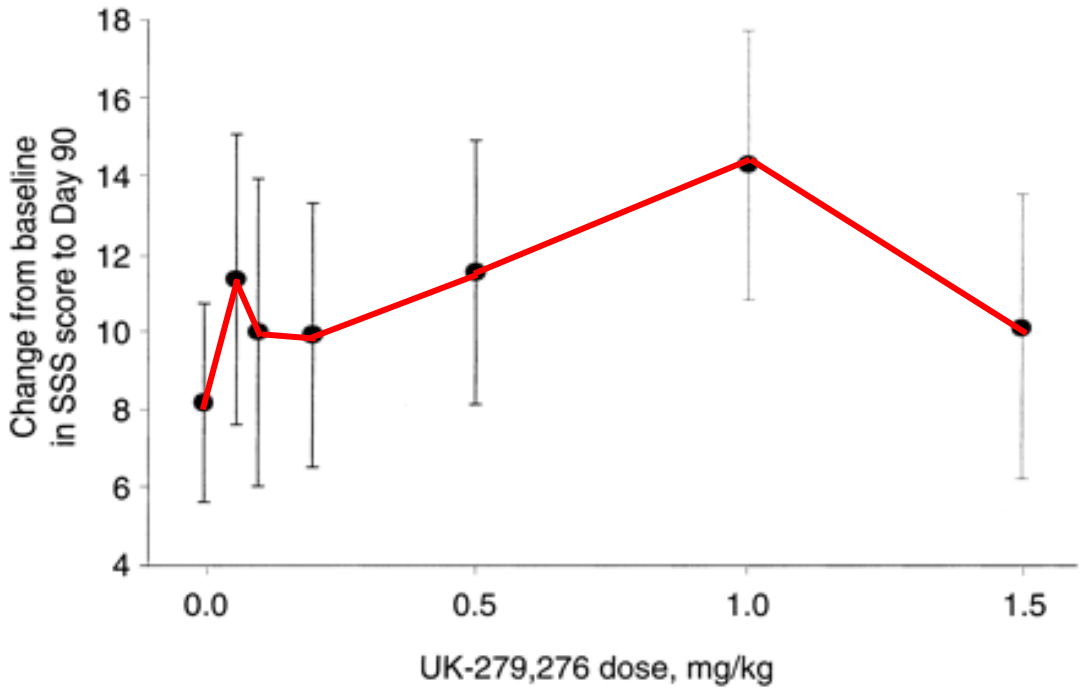
Nominal Doses



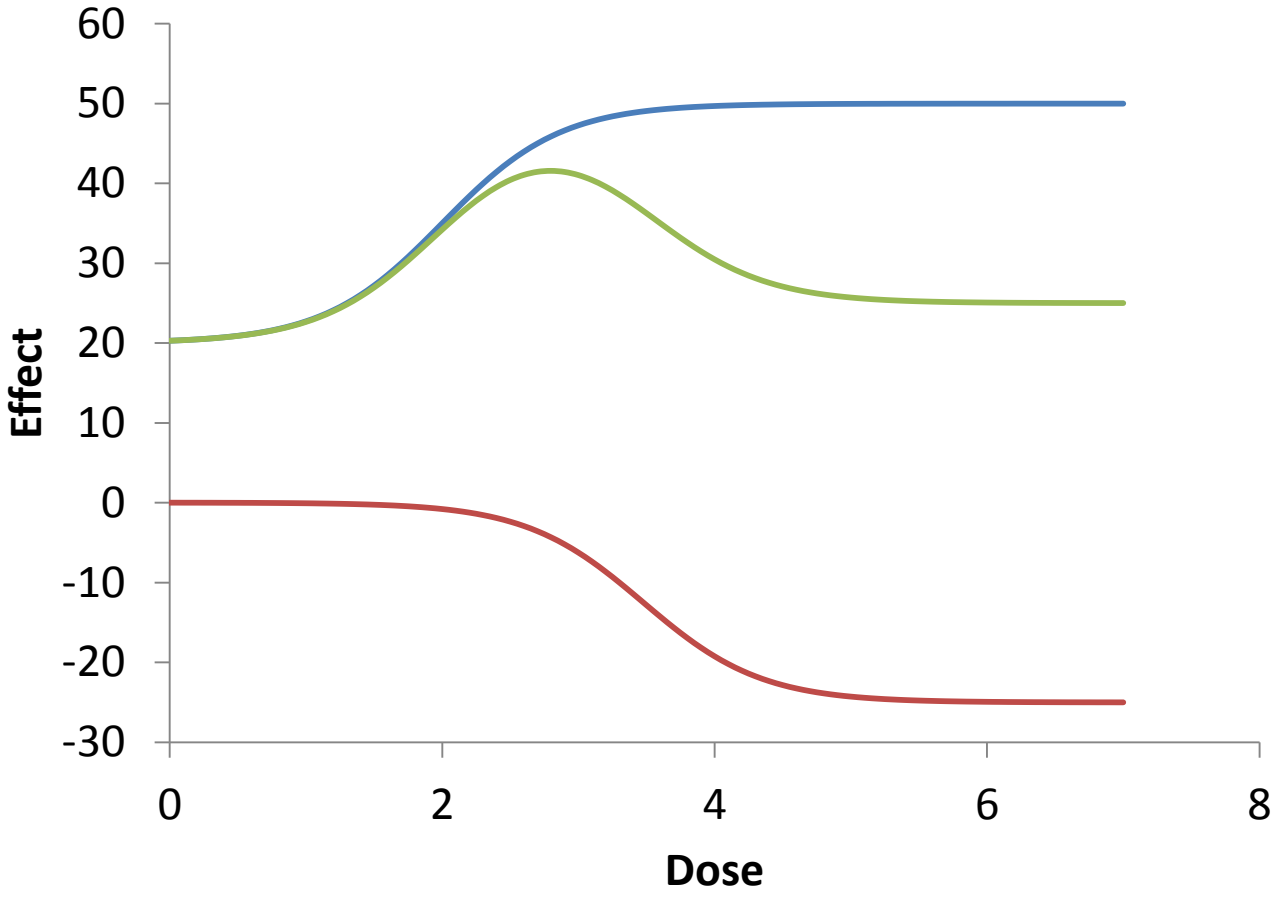
Actual Doses



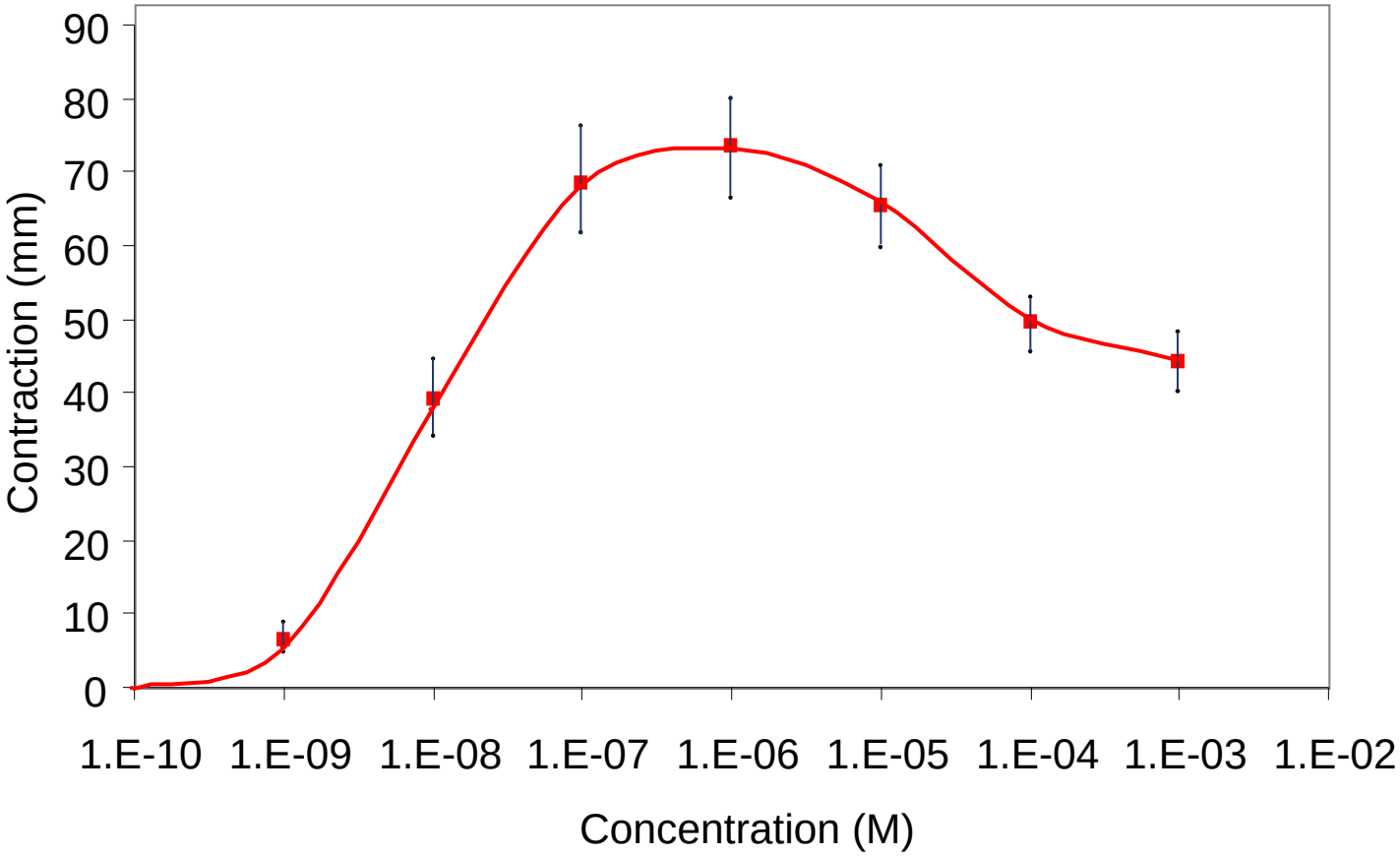
Stroke Clinical Trial Patient Safety Study



Superposition of Two Emax Curves



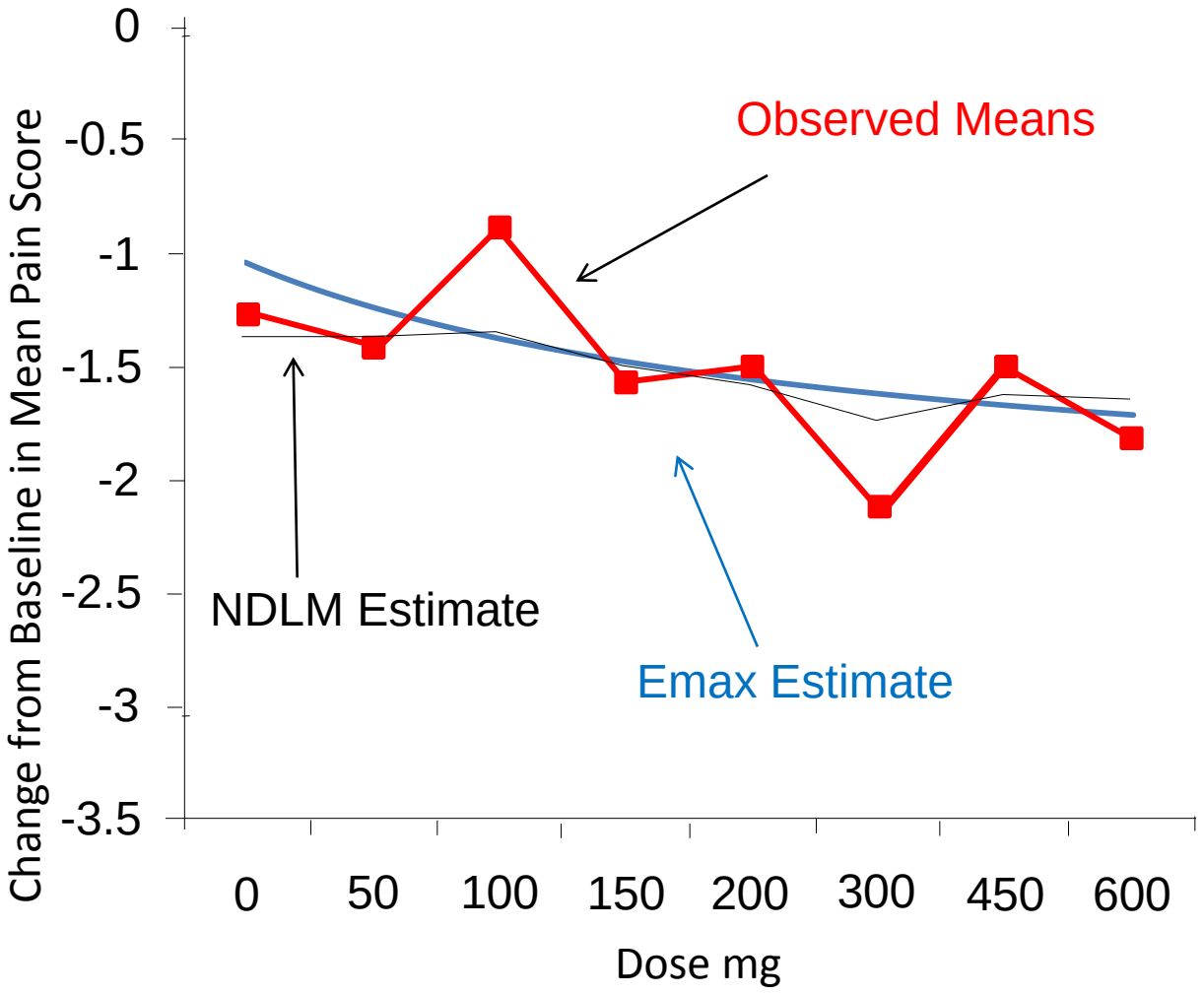
Effect of Acetycholine on Isoloated Guinea-Pig Ileum Fitted Using Superimposed Emax Models



Other approaches

- Smoothing
  - Normal Dynamic Linear Model (NDLM)
  - Splines
  - Gaussian Process Regression (GPR)
    - NDLM, Splines & GPR all impose a multivariate structure on the data
- Monotonicity
  - Restrict NDLM to monotone function
  - Isotonic regression
- Mixture of models
  - Bayesian model averaging

Pain Study
Fit of 3 Parameter Emax



Conclusions

- Innovation
  - Efforts should be taken to encourage a speedier translation of innovative methodology into practice
  - Needs support infrastructure
- Phase 2b Dose-Response
  - Choosing 2,3 or 4 doses is potentially wasteful and counter productive
  - Need to consider increasing the number of doses and the range of doses
  - Give serious thought to models for dose-response