Parametric Bayesian Dose Response Modeling

Neal Thomas
Statistics Research and Consulting Center
Pfizer
New London CT

Outline

- Brief review of Emax models
- Example from a Phase 2 trial
  - The analysis shows that the trial clinical data are not sufficient to estimate an feature of the dose response curve, which is typical of dose finding studies
  - Decision rules that can be computed from Bayesian analyses based on simulated values from the posterior distribution
  - Contrast Bayesian estimation with Maximum Likelihood estimation
- Simulations based on an example from a different Phase 2 trial
  - Demonstrates a different type of instability in ML estimation in a dose response setting and how the problem can be improved with a Bayesian analysis using weak prior information

Emax models

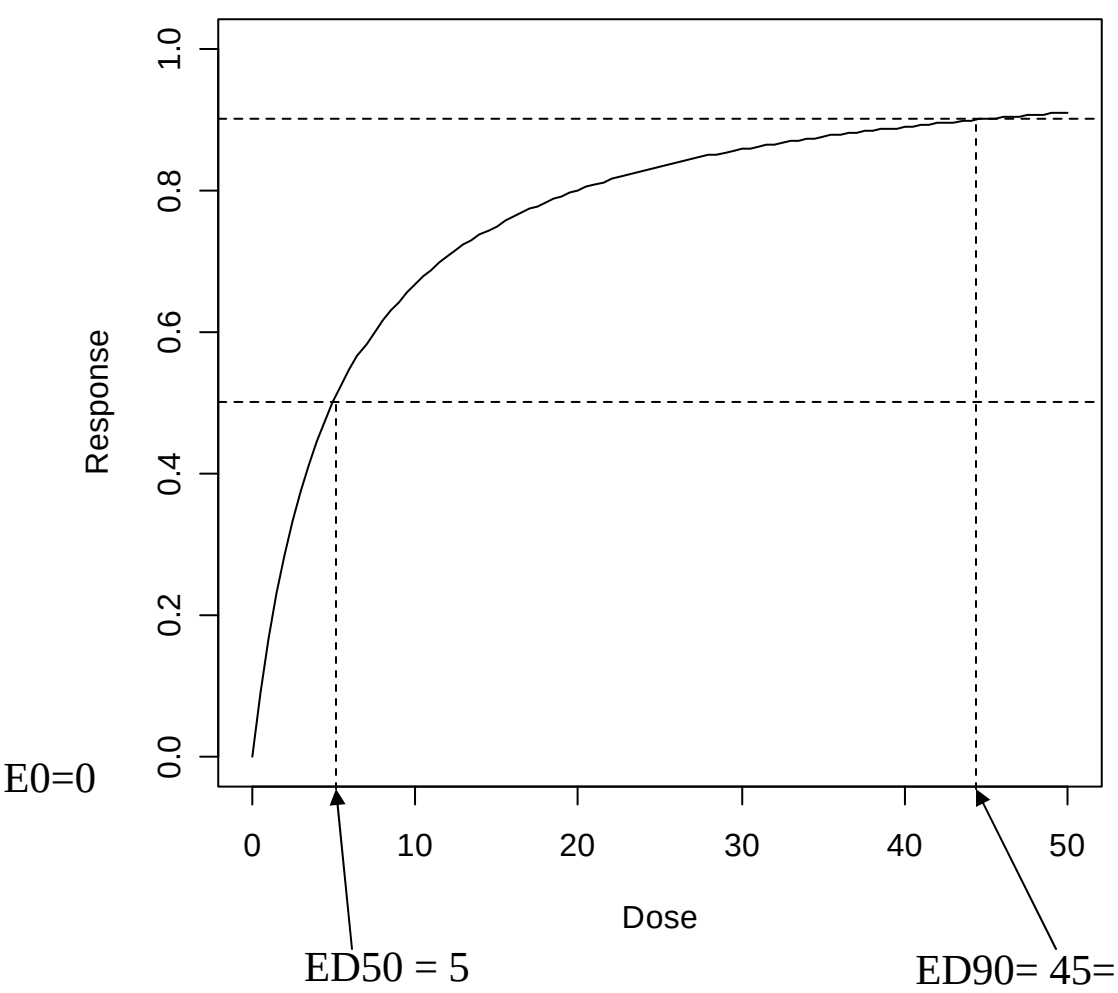
- 3-parameter Hyperbolic Emax model

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

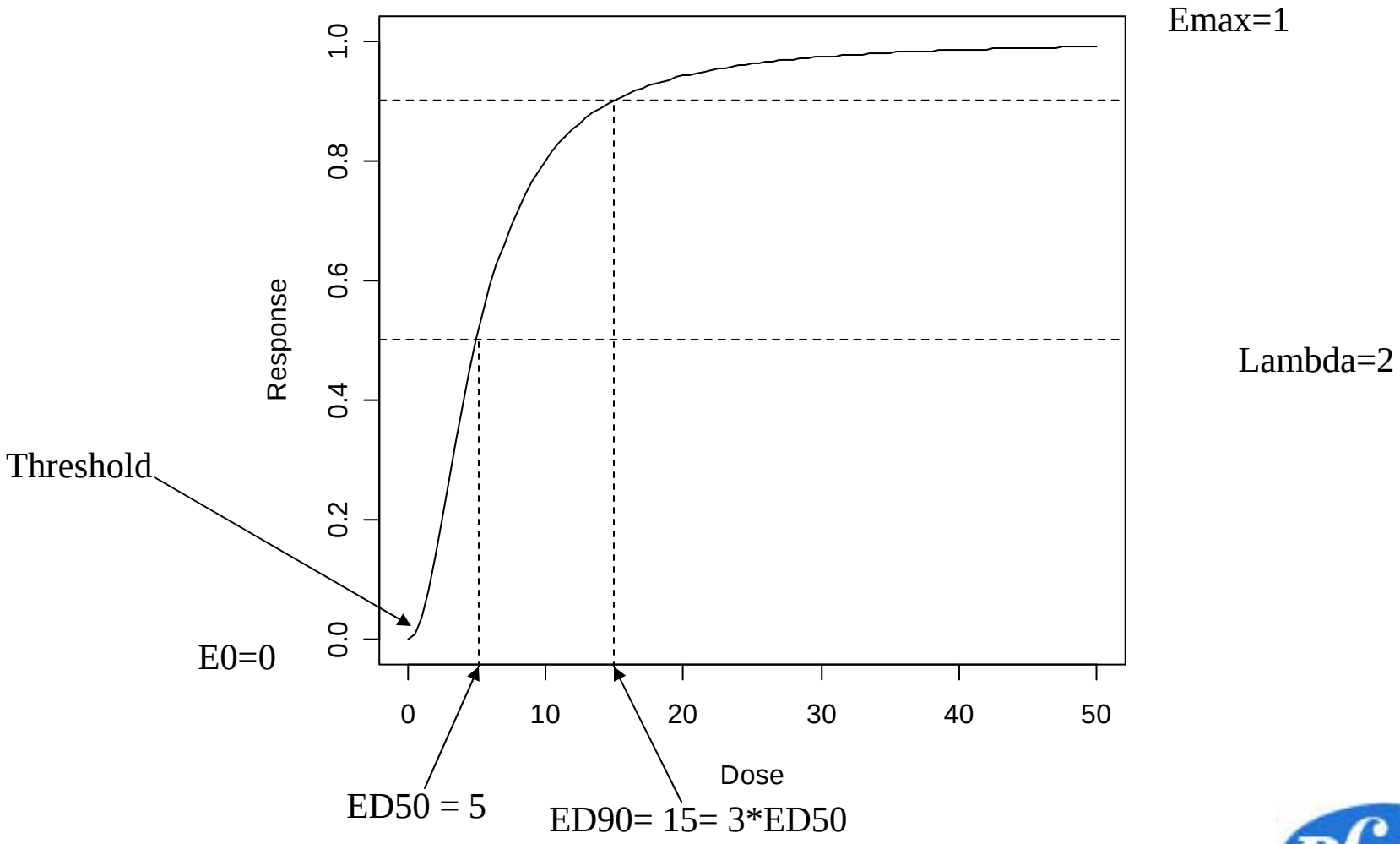
- 4-parameter Sigmoid Emax model

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

3 parameter Emax model



4-parameter Emax model



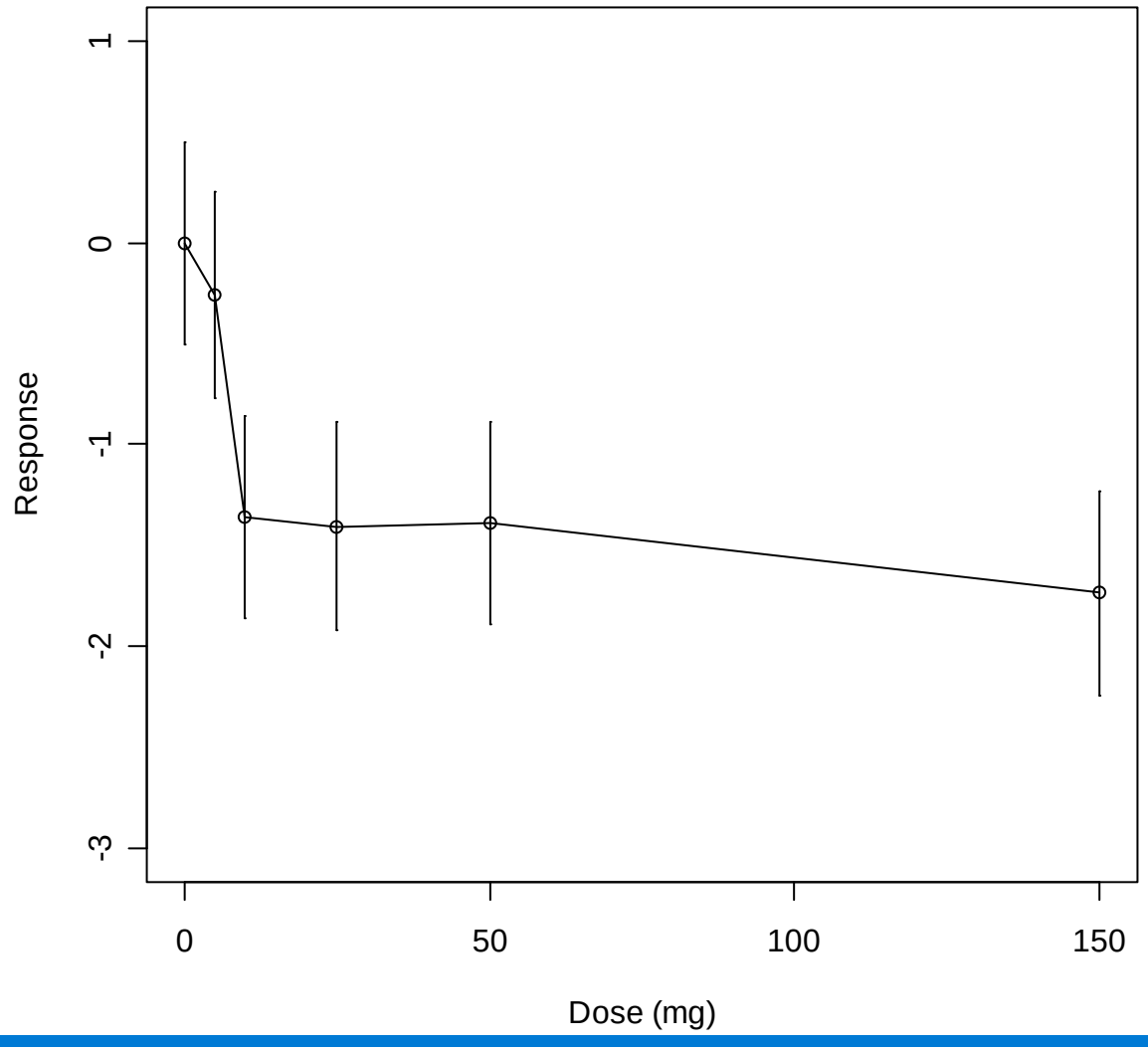
Why use Emax models?

- They can be derived from receptor occupancy models and are thus very popular in pharmacology
- They provide sufficiently accurate representations of most dose response curves.
  - Informal meta-analyses suggest the 4-parameter model is needed
    - Dutta et al (Journal of Pharmaceutical Sciences, 1995) meta-analysis of 42 studies found lambda near 2 most common
    - Danhof (Topics in Pharmaceutical Sciences, 1989)
  - Informal hierarchy of dose response shapes: therapeutic drugs generally, drugs within a therapeutic area, drugs with the same class
- The prevalence of use non-monotone dose response curves is a point of contention. Non-monotone dose response situations can sometimes be anticipated or at least understood using supplementary data.

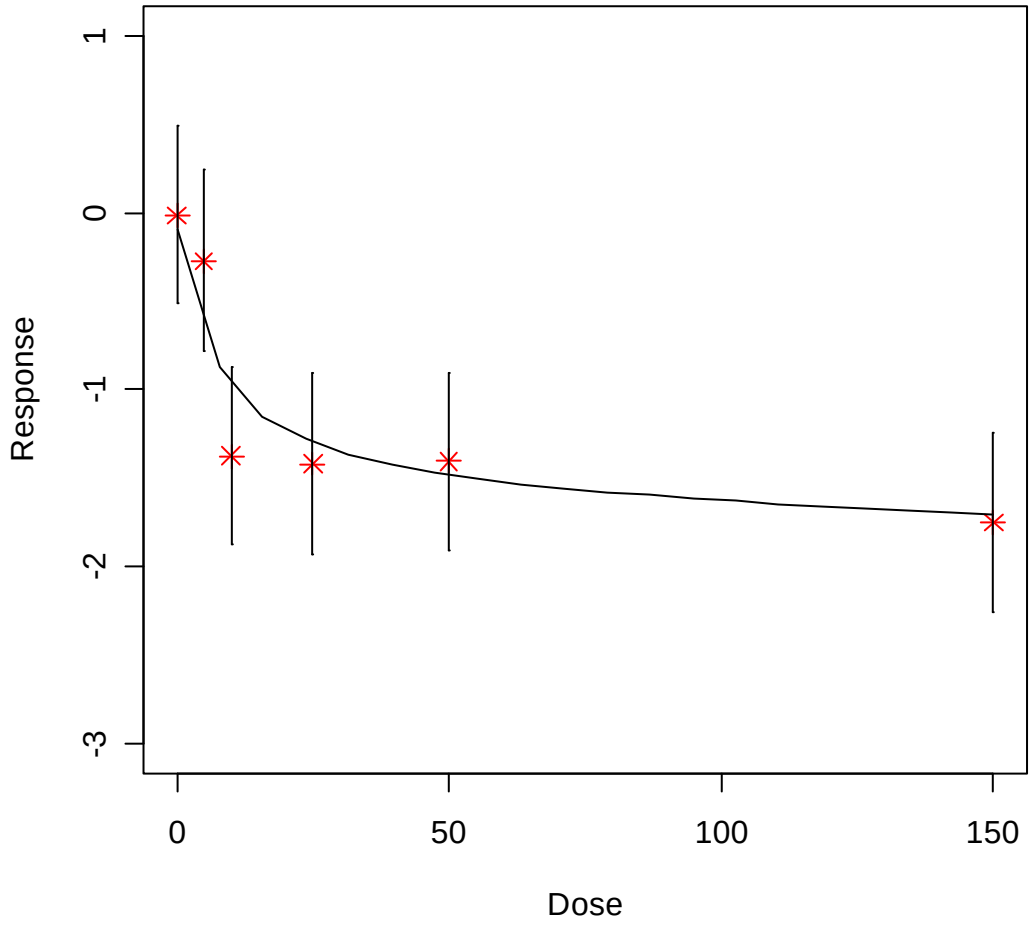
Recent anonymous example of dose finding/POC study

- Sources of information
  - Placebo response in other studies
  - Magnitude of response for other successful drugs in the therapeutic area
  - Animal testing (especially important for ED50)
  - Phase I biomarker data
  - Generic experience with dose response curves

Plot of dose group means



Bayes posterior fit



The curve is the posterior mean plotted over a dense grid of doses.

BUGS was used for the computations.

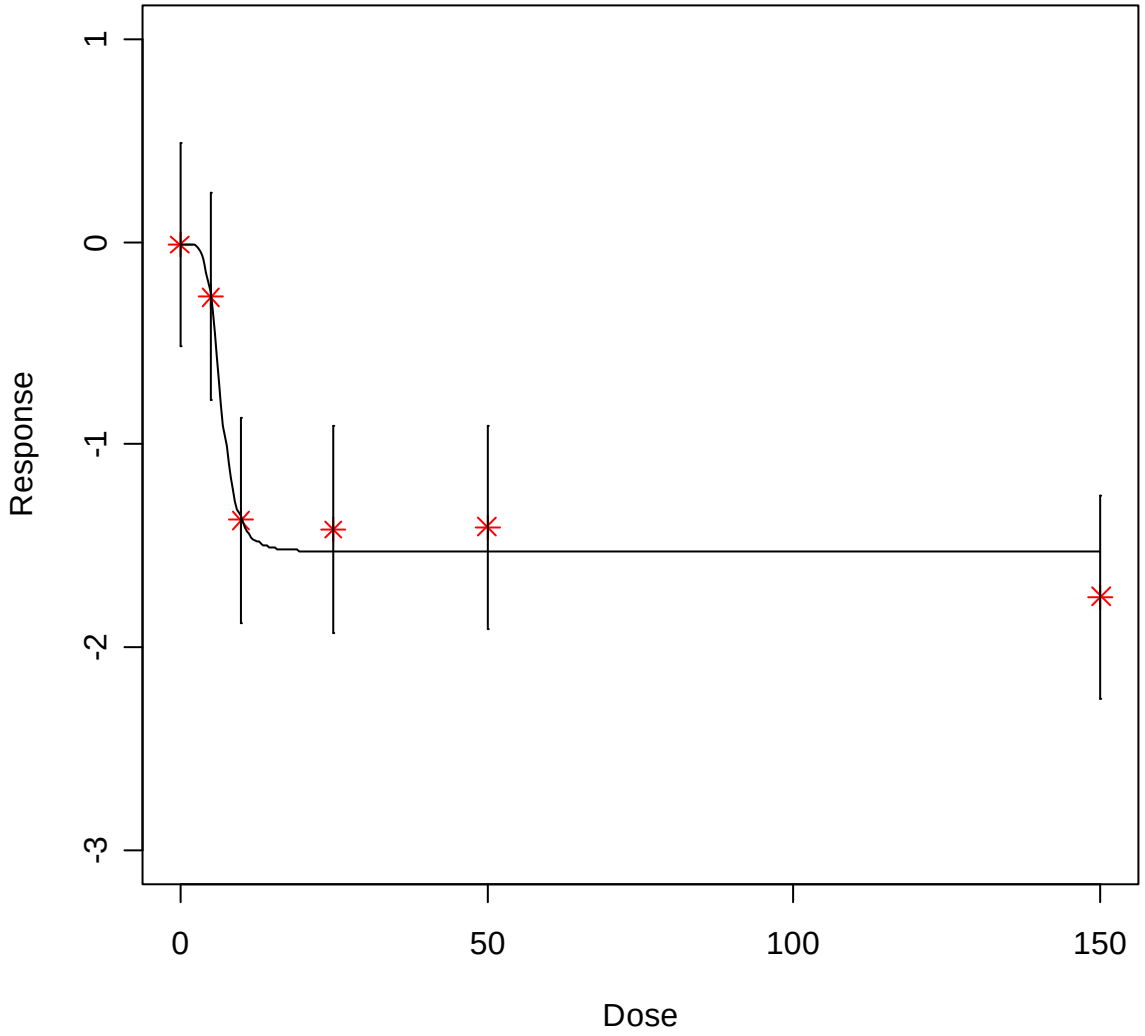
Distribution of lambda

Percentile	Prior Distribution (skewed transformed Beta)	Posterior Distribution
10%	0.53	0.41
50%	1.68	1.03
90%	3.89	3.30

Bayes decision criteria

	Pr(Estimate exceeds 1 and statistical significance)		Pr(Estimate exceeds 1 in two independent trials and statistical significance)	
Dose	Small n P3	Large n P3	Small n P3	Large n P3
25 mg	0.62	0.64	0.47	0.50
50 mg	0.71	0.74	0.58	0.63
75 mg	0.77	0.79	0.64	0.69

4-Parameter Maximum Likelihood Estimate (MLE)



MLE lambda=5.4

ED50=6.5 mg

Comparing dose recommendations from the MLE and Bayesian estimates

- The Bayesian dose response curve reaches a 1 point improvement at 14.5 mg, the MLE curve reaches 1 point at 7.6 mg (The Bayes estimation predicts a doubling of the dose.)

- The Bayesian analyses predicts additional improvement in efficacy between 25 and 75 mg, with higher confidence of achieving the targeted objectives at 75 mg

- The MLE analysis suggests it is futile to consider doses greater than 25 mg

Why should we prefer the Bayesian analyses?

- Both estimation methods produce well-fitting curves with nearly identical fit criteria (e.g., least squares)
  - MSE=2.868 (NLS, MLE) MSE=2.896 (Bayes posterior means)

- The MLE solution predicts:
  - A very sharp threshold with little spacing between ineffective and highly effective doses. Such dose response curves have not been observed often in practice, and they are hard to derive from more refined PK/PD models with realistic conditions.
  - An ED50 that is extremely low compared to the original projections. The low ED50 could be correct, but the Bayes model, with similar agreement with the current data, does not require us to fully discount the past data.

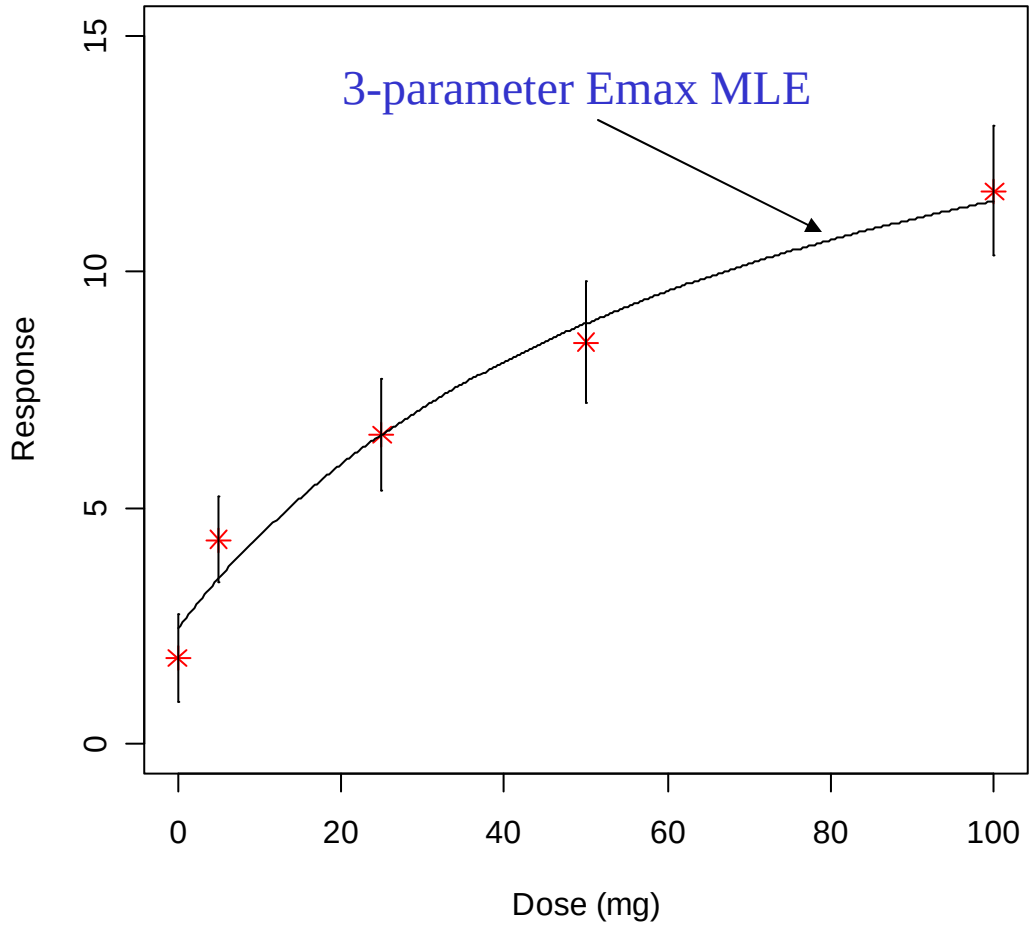
Bayes analysis (cont)

- The Bayesian analysis provides easily computed answers to the most important questions such as “How likely are we to achieve the objectives in Phase 3 studies?” and “Will the chances of success be appreciably higher if we use (add) a 75 mg dose in Phase 3?
  - The simulation-based (BUGS) Bayes estimation provides a simple and flexible approach to compute relevant probabilities without the need for new analytic approximations.

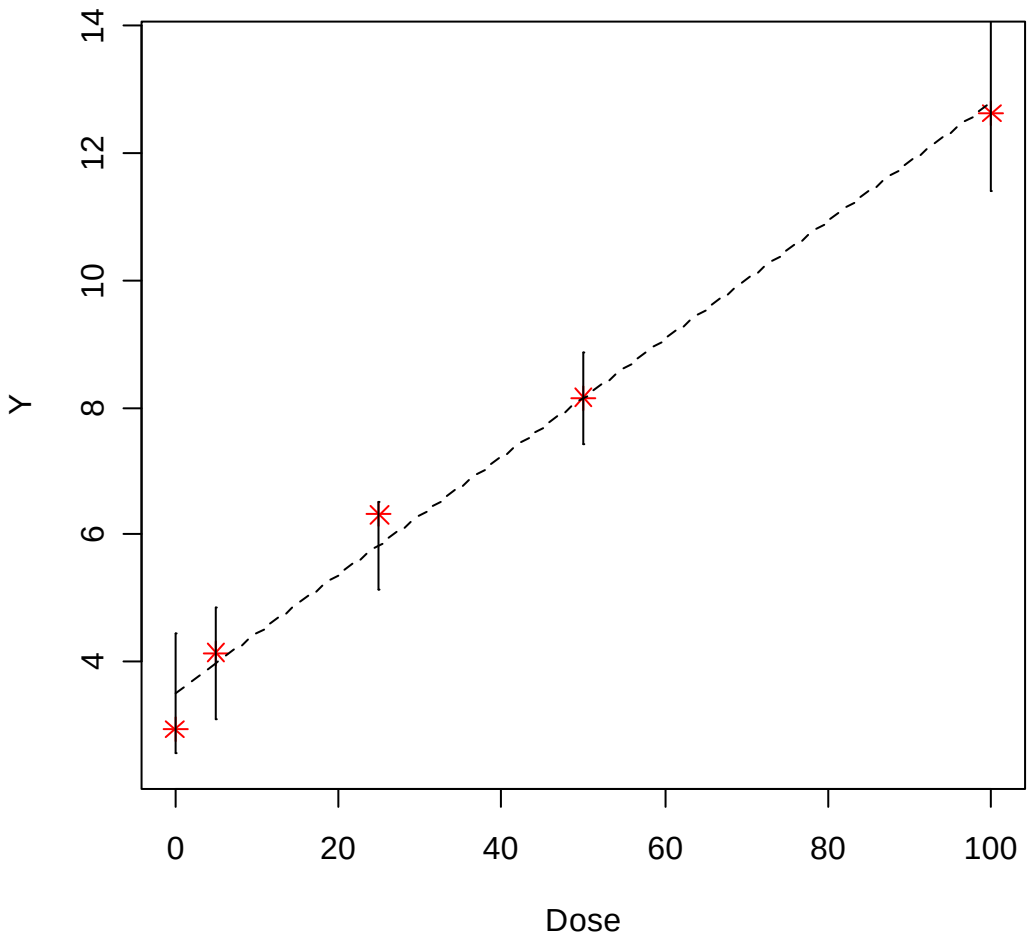
- The typical output of the MLE analyses and hypotheses testing approaches to dose selection, e.g., p-values and confidence intervals do not directly address these questions thus requiring implicit translation of the statistical reporting to these questions by clinicians.

- The asymptotic normal approximations underlying many of the common inferences are poor in the dose response setting.

An example well approximated by a 3-parameter Emax model



Example of simulated data set (first simulated data set where ML estimation failed)

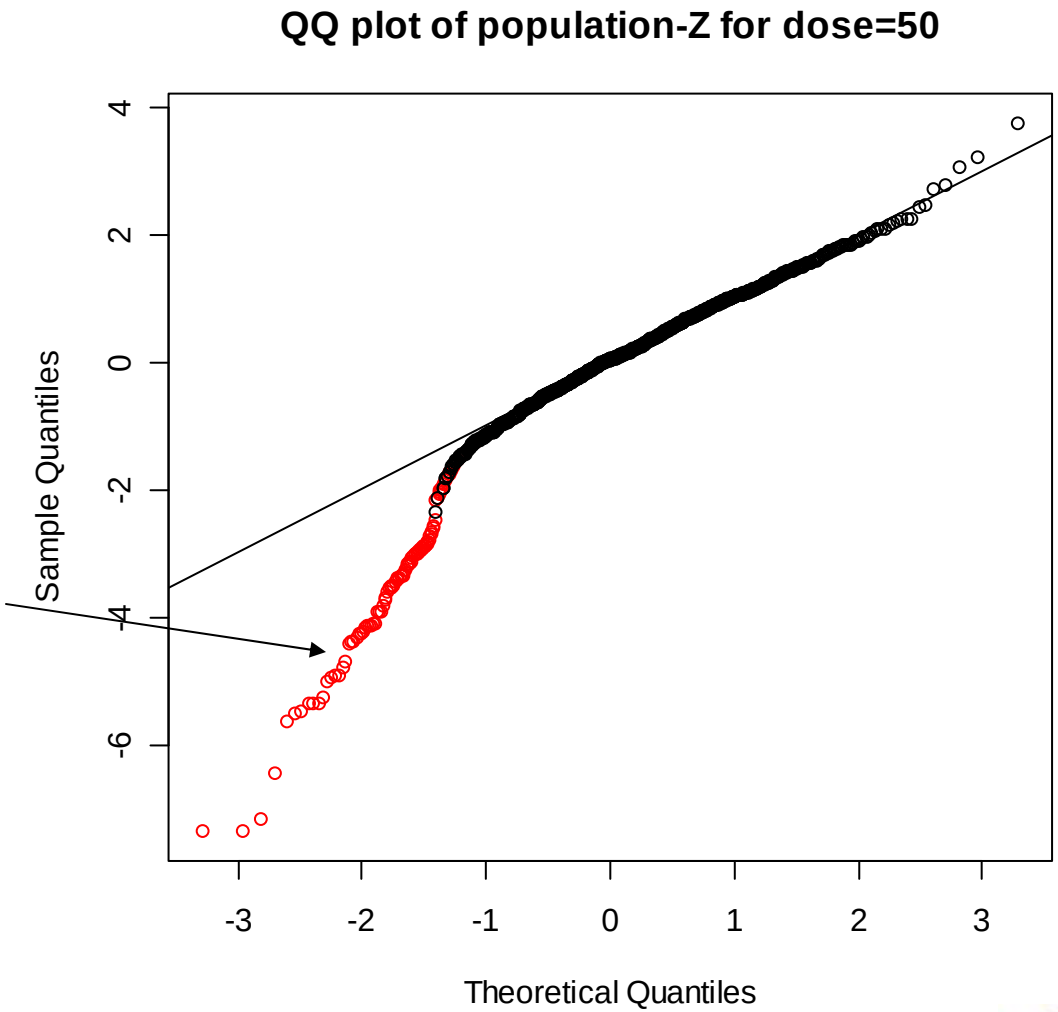


The 3 parameter Emax MLE diverged. Linear model substituted (good fit). The MLE from 10% of the simulated data sets diverged.

Population-Z for the 50 mg dose is -3.21.

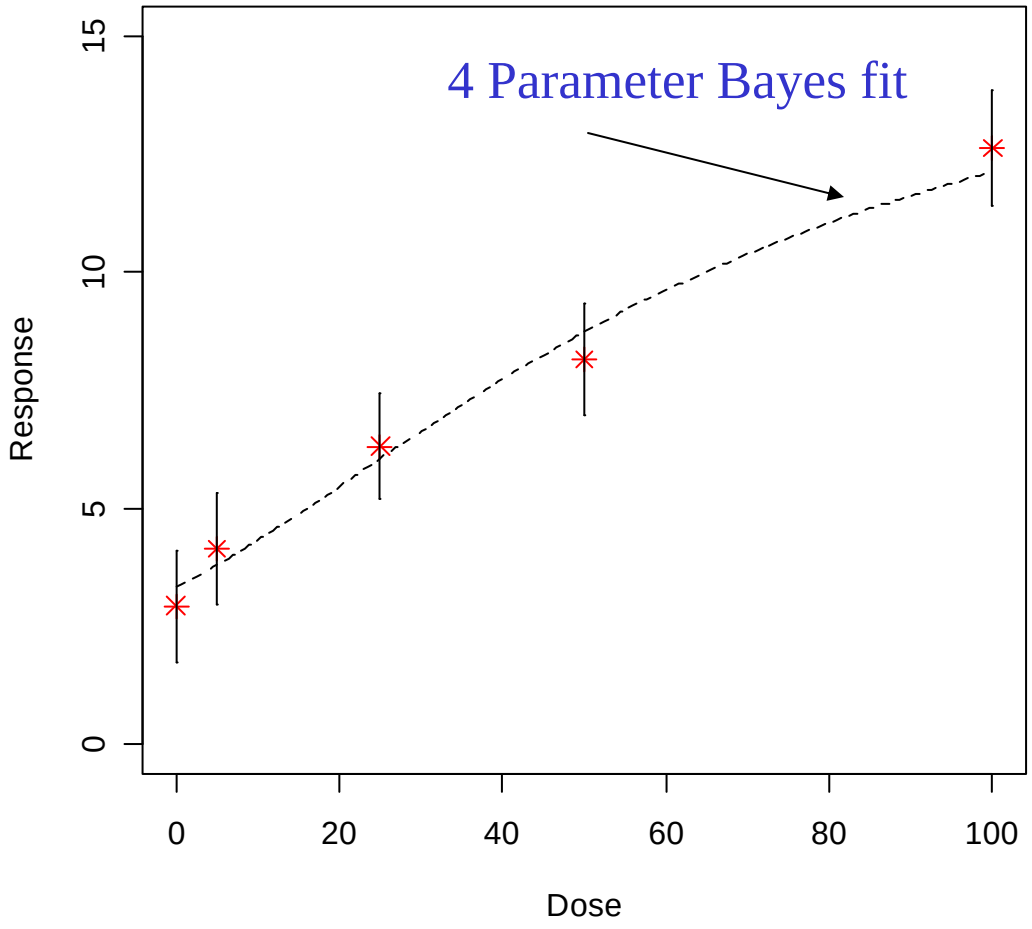
Comparison of 50 mg dose to placebo

More than (asymptotic) predicted difference due to bias when the linear model is substituted



Coverage of nominal 90% interval: 85.5%

Bayes fit to simulated data (near linear)



Population-Z for the 50 mg dose is -0.94.

The posterior SD for 50 mg minus placebo is 1.12. The corresponding SE for the linear fit is 0.57.

Conclusions

- Two situations displayed where the ML estimation is unstable. ML estimation is also unstable when all doses are on the 'plateau', or when the signal-to-noise ratio is low
  - Weak prior information can improve estimation in this settings
- Bayesian estimation of the 4-parameter Emax model (more) correctly accounts for model uncertainty
- Bayesian analyses can be pre-specified in an SAP
  - MLE analyses are difficult to pre-specify because of the need for alternative approaches if resulting estimation is unstable
- Even when the prior information is weak and comes from multiple hard-to-quantify sources, Bayes estimation can be useful for dose selection.