Bayesian Fitting of a Logistic Dose-Response Curve with Numerically Derived Priors

(Pharmaceutical Statistics 2009, 8(4): 279 – 286)

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Objectives

- Describe elicitation process and show example of expert opinion

- **Describe formation of prior distributions using the expert opinion:**
    - **(1) using the CDF/simulation method**
    - **(2) using bootstrapping**

- Summarize posterior estimates and fitted logistic curves

Setting

- Phase I study of new chemical entity – placebo and six ascending dose cohorts

- Potential to cause specific type of cardiovascular adverse event (AE)

- This class of drug/adverse event profile familiar to internal experts

- We wished to fit dose-response curve (relating dose to probability of AE) utilizing internal expert opinion

Logistic Curve

pr(AE) = exp(a + b*dose) / (1 + exp(a + b*dose))

For a Bayesian fitting, we require priors for the two parameters a and b (referred to below as “intercept” and “dose effect”)

(logistic not a necessary option – same process could be applied to other curves)

BUT experts cannot be expected to provide prior opinions directly about these parameters – instead we must focus on elicitation of “observable quantities”

We asked internal experts to provide opinion on probability of adverse event at each of the doses in the Ph I trial

Elicitation

Full of difficulties and potential pitfalls

Vast literature (mostly outside of statistical journals) on processes, methods, and difficulties

Good introductions in:

Meyer MA, Booker JM. Eliciting and Analyzing Expert Judgment: A Practical Guide. ASA-SIAM Series on Statistics and Applied Probability. Philadelphia,2001.

O'Hagan A, Buck CE, Daneshkhah A, Eiser R, Garthwaite P, Jenkinson D, Oakley J, Rakow T. Uncertain Judgements: Eliciting Experts' Probabilities. ISBN-10: 0-470-02999-4, 2006.

Elicitation

No consensus on what is “best” (nor on what “best” might mean) – many conflicting conclusions in literature

Some common problems and potential biases – “availability” “anchoring” “representativeness”

Kynn M (2007) The 'heuristics and biases' bias in expert elicitation. JRSS A 171 (1):239 - 264.

In practice – be thoughtful, careful and pragmatic

Elicitation

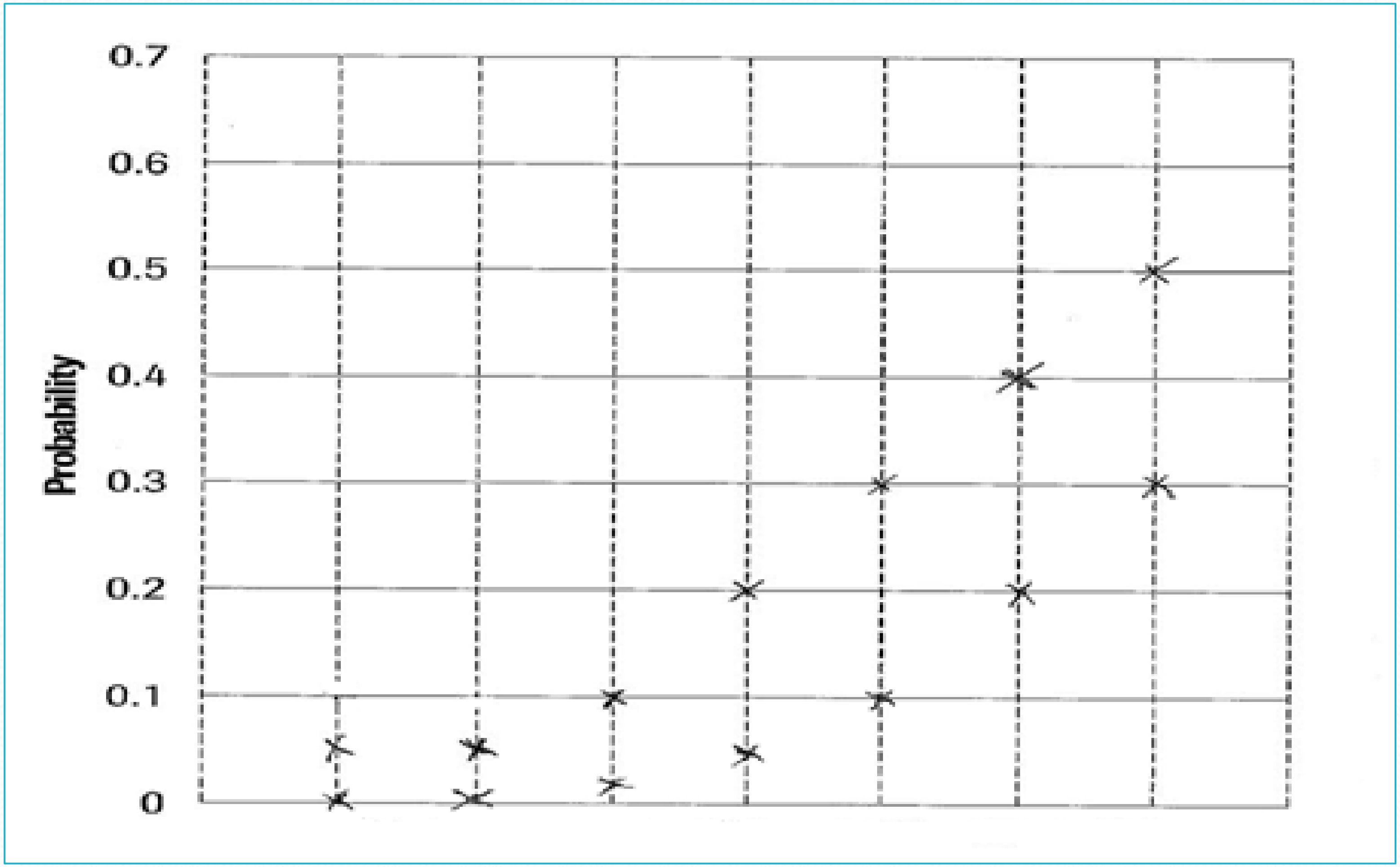
Our Process:

meet experts, describe Bayesian methods, explain the nature of the information we wish them to provide

provide tabular and graphical presentations, asking, for each dose, expert's best estimate of probability of AE at each dose, and estimate such that they are 90% confident that the probability is not greater

cross-check, compare, examine for consistency, re-visit with experts

Example of (graphical) expert prior opinion:



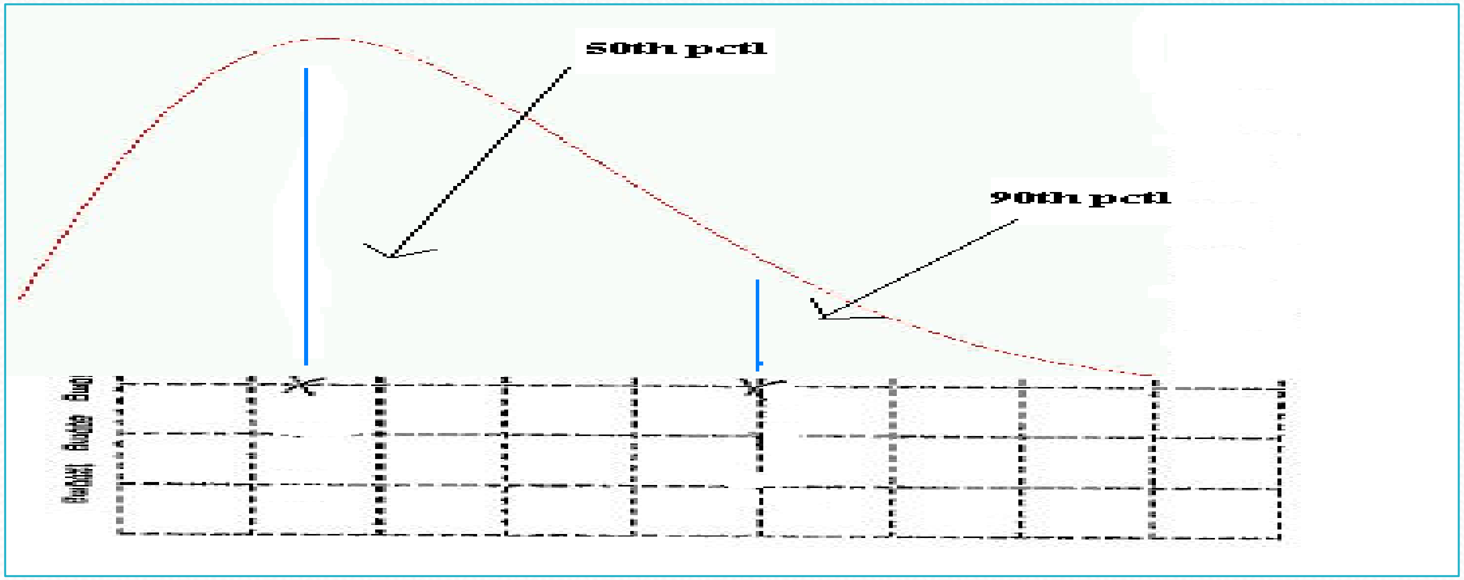
Priors for the logistic parameters

How did we convert this information into priors for the two parameters of the logistic curve?

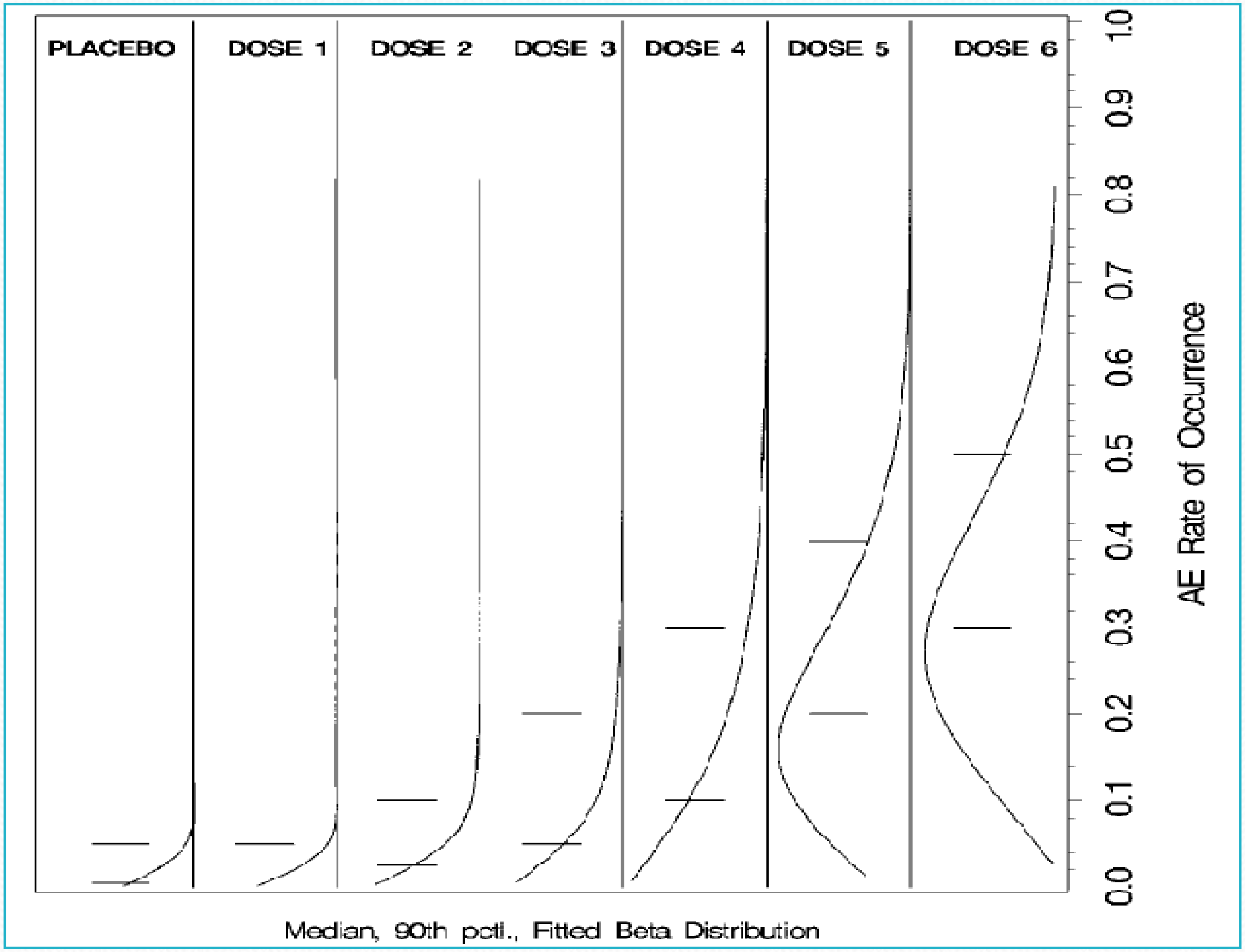
- Form priors using CDF technique + simulation
- Form priors using direct bootstrapping

Forming priors using CDF/simulation:

- Interpret each “best” and “90%” estimate as the median and 90th percentile for response probability at each dose
- Use these two pieces of information to fit a beta distribution for the response probability at each dose



Forming priors using CDF/simulation:



Forming priors using CDF/simulation:

- Using these beta-distributions, generate repeated samples of simulated data and fit logistic curves to each simulated dataset – thereby building up empirical distributions for two logistic parameters

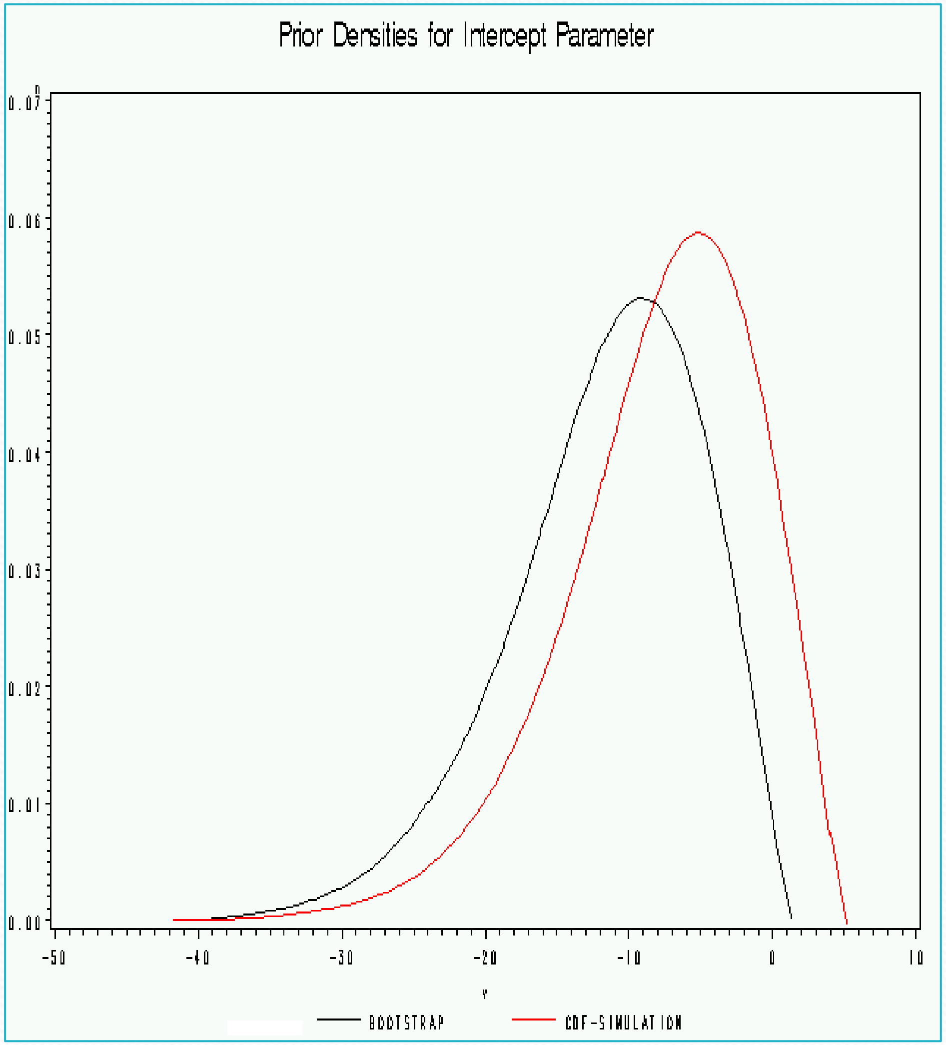
- Fit beta-distributions to these empirically-derived distributions for the logistic parameters

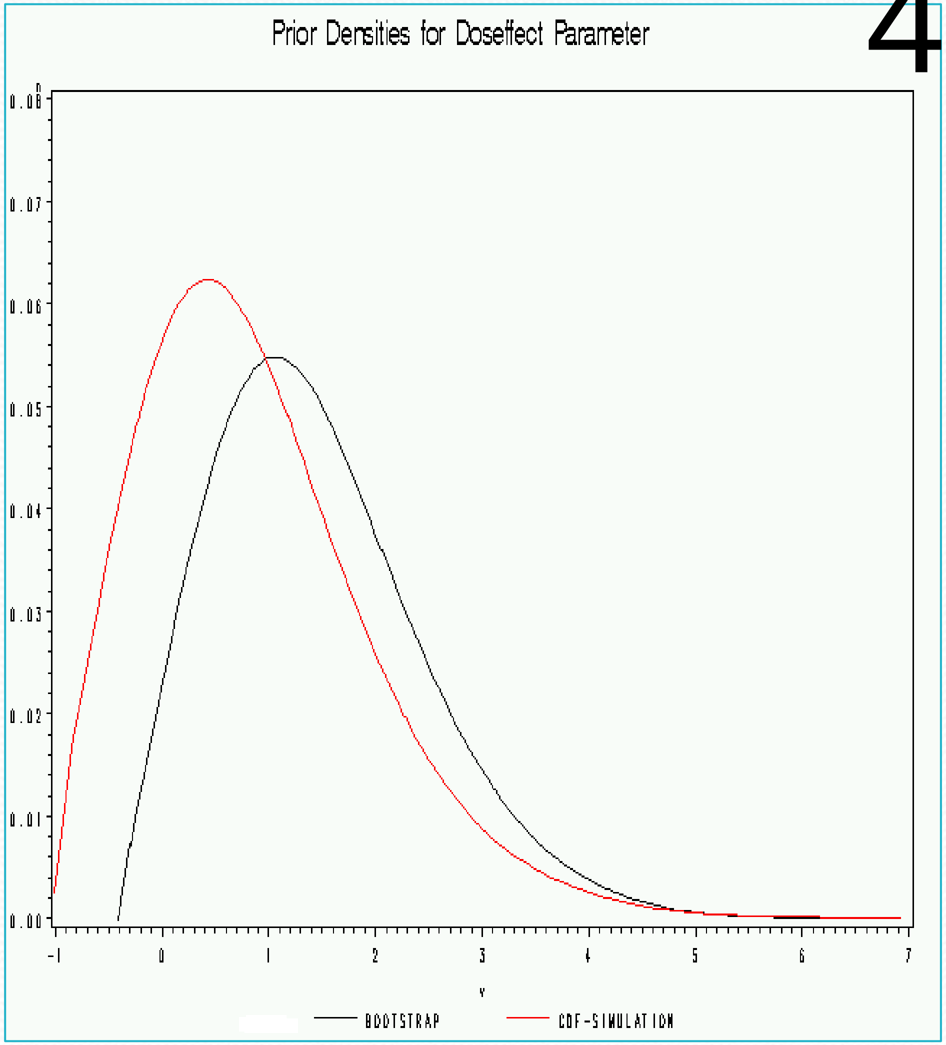
(beta not a necessary option – other pdfs could be chosen)

Forming priors by bootstrapping:

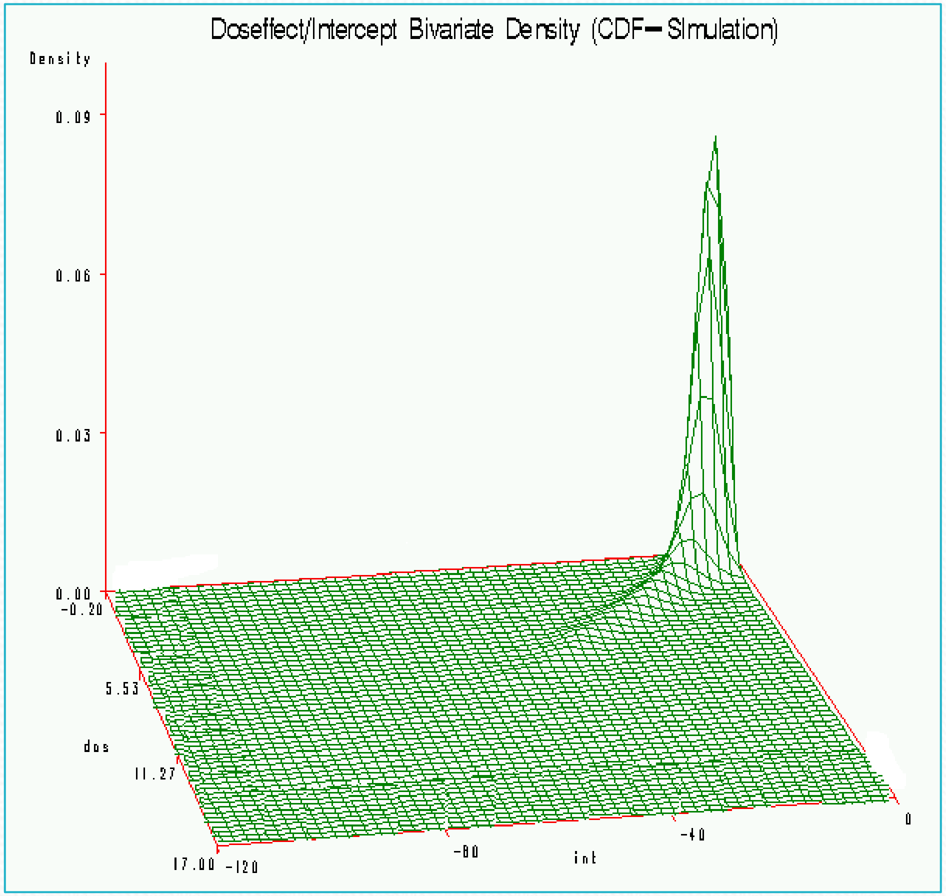
- draw repeated bootstrap samples directly from the expert "data" (weighting the "median" and "90th percentile)
- fit a logistic curve to each bootstrap sample, and accumulate empirical distributions for the logistic parameters
- Fit beta-distributions to the empirically derived distributions for the two logistic parameters **(beta not a necessary option)**
- Use these fitted beta-distributions as priors for the two logistic parameters

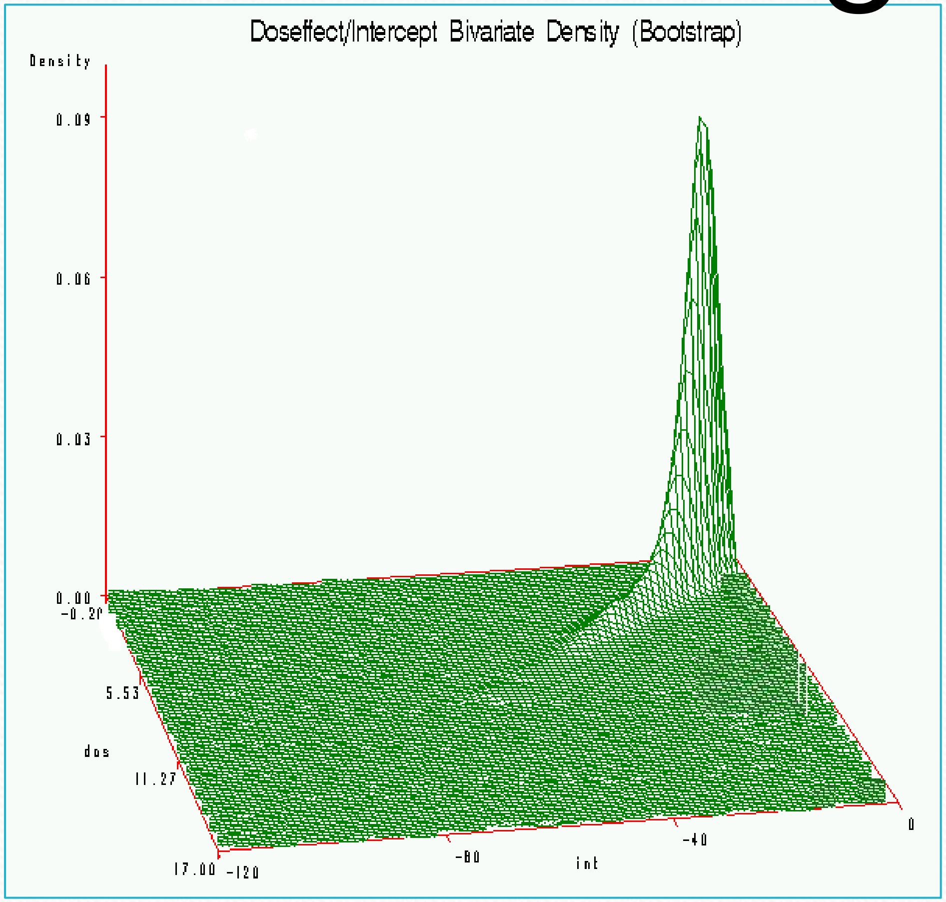
Comparison of priors from the two methods:



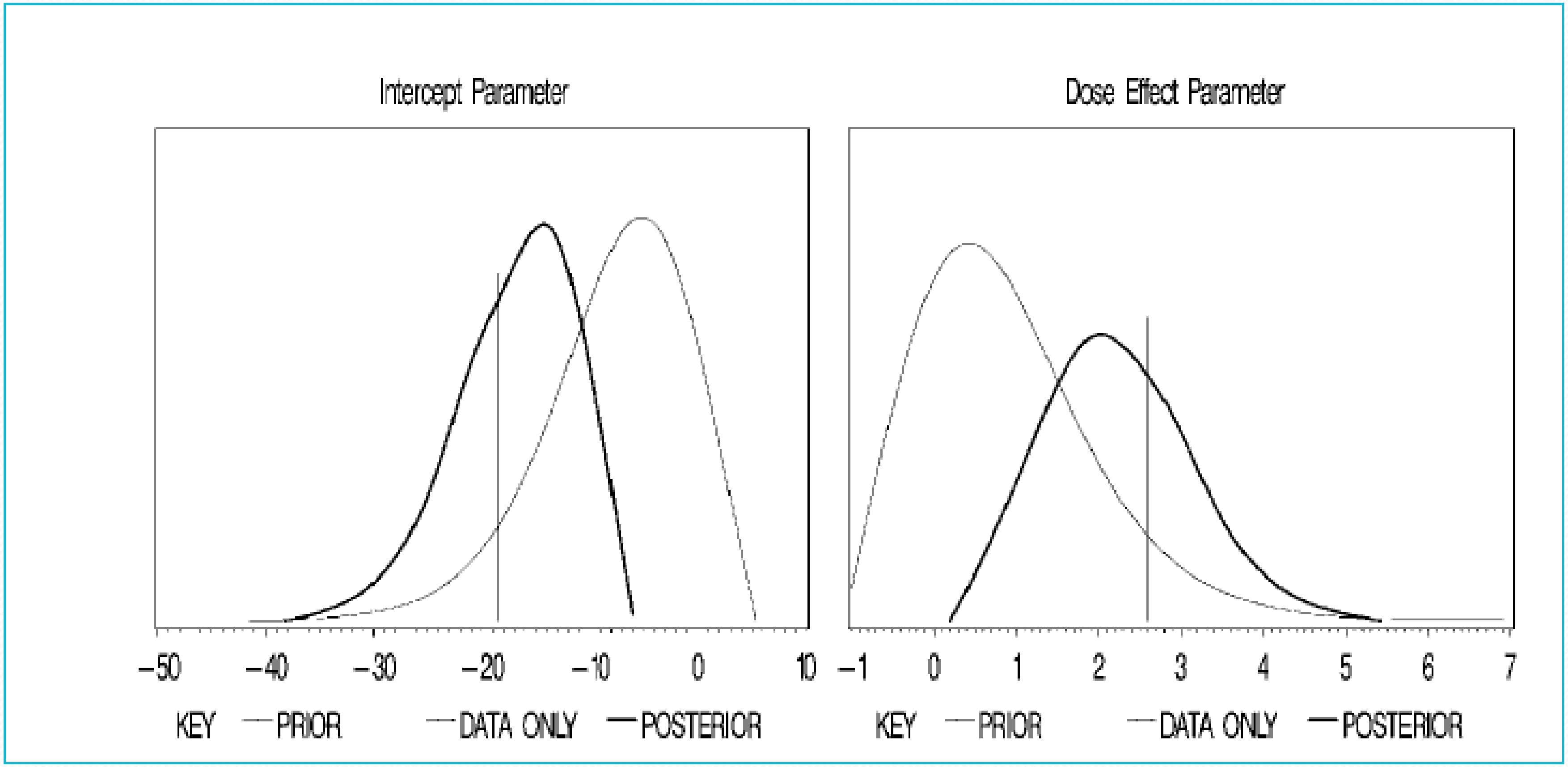


Priors are correlated:





Prior and posterior densities from the CDF-simulation method:



Summary of parameter estimates:

Table I. Posterior parameter estimates for logistic dose–response models using different priors.

Mean and SD of posterior distributions	Intercept	Dose effect
Bootstrap-beta priors	−15.43 (4.746)	2.12 (0.6846)
Tsutakawa prior	−13.71 (7.496)	1.00 (1.1260)
CDF/simulation beta priors	−15.29 (5.385)	2.11 (0.7955)
Bootstrap–independent beta priors	−14.21 (4.368)	1.95 (0.6502)
CDF/simulation–independent beta priors	−12.63 (4.376)	1.72 (0.6556)

Summary:

- Elicitation of graphical prior opinion on form of dose-response curve was well received and straightforward
- Two options for formation of priors for the actual parameters are simple to implement
- Implementation of Bayesian methodology in the context of a Phase I study, especially where conclusions will be used internally, is a valuable formal way of using expert opinion
- Nelson Kinnersley is developing and applying these methods in further work as part of a PhD thesis