NONPARAMETRIC BAYESIAN BIOASSAY

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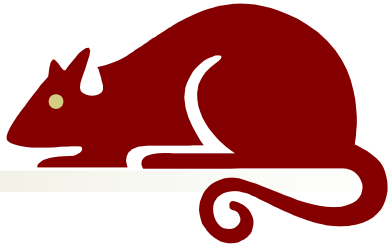
OUTLINE



1. Bioassay experiments
2. Nonparametric Bayesian approach
3. Results
4. Conclusions

BIOASSAY EXPERIMENT

- **Biological assay** – set of techniques relevant to the measurement of the potency of a stimulus; physical, chemical or biological, by means of the reactions that it produces in living matters.

- **Bioassay data**:
  - $x_1, \ldots, x_M$ - set of doses (signifying the level of applied stimulus e.g. drug, vitamin, hormone)
  - $n_1, \ldots, n_M$ - the number of subjects (rats, mice) which are administered dose *x*
  - $s_1, \ldots, s_M$ - the results of experiment are measured by quantal responses (died or not), the numbers of affected subjects at each dose

STATISTICAL INFERENCE

- Estimation of the **tolerance distribution** *P(x)* (potency of the stimulus) for any dose level *x* (also for nonobserational dose levels).

- Study of an **effective dose** $\hat{x}$, such that for a fixed *p*, $P(\hat{x}) = p$.

- **The design of the experiment** to accomplish in an optimal way the potency curve.

NONPARAMETRIC BAYESIAN

- BAYES RULE:

$$posterior = \frac{likelihood \times prior}{marginal \;\; distribution}$$

Combination of two sources of information:

prior information:
experiment:
(knowledge from experts

+

bioassay

(bioassay data)

NONPARAMETRIC BAYESIAN

- Likelihood:
  - The number of events at x_i follows the binomial distribution; the subjects respond independently.
  - The joint likelihood is a product :

$$L(s \mid p) = \prod_{i=1}^{M} \binom{n_i}{s_i} p_i^{s_i} (1 - p_i)^{n_i - s_i}$$

- Nonparametric prior:
  - Dirichlet process prior or Beta – product prior

DIRICHLET PROCESS PRIOR

- Random probability distribution *P* is generated by DP if for any partition $x_1, \ldots, x_M$ of the sample space the vector $(P(x_1), \ldots, P(x_M))$ follows a Dirichlet distribution:

$$(P(x_1), \ldots, P(x_M)) \sim D(\alpha P_0(x_1), \ldots, \alpha P_0(x_M))$$

- $E(P(x_i)) = P_0(x_i)$ and $\text{var}(P(x_i)) = \dfrac{P_0(x_i)(1 - P_0(x_i))}{\alpha + 1}$

- $P(x_i) \sim Beta(\alpha P_0(x_i), \alpha(1 - P_0(x_i)))$ and

$$P(x_i) \mid P(x_{i-1}), P(x_{i+1}) \sim Beta(\alpha(P_0(x_i) - P_0(x_{i-1})), \alpha(P_0(x_{i+1}) - P_0(x_i)))$$

- Dirichlet is a conjugate family for the multinomial.

PRIOR CONSTRAINT ON THE SHAPE OF POTENCY CURVE

- ***Convex prior :*** non-decreasing density function
- ***Concave prior :*** non-increasing density function
- ***Ogive prior*** : convex and then concave

All of these shapes are commonly employed in the field of bioassay as reasonable shape constraint on a dose – response relation.

POSTERIOR

- Form of the posterior:

$$f(p_1,\ldots,p_M \mid s) = C\{\prod_{i=1}^{M} p_i^{s_i}(1-p_i)^{n_i-s_i}\}\prod_{i=1}^{M+1}(p_i - p_{i-1})^{\alpha\xi_i - 1},$$

  - It is a mixture of Dirichlet
  - It becomes increasingly intractable as the number of dose levels increases, especially for obtaining the marginals

  There is need to find estimation methods

ESTIMATION METHODS

- **Ramsey (1972);** MLE method, the joint mode of the posterior is used to summarize the posterior distribution

- **Gelfand and Kuo (1991)**; one of the MCMC method - Gibbs sampler, generating samples from the conditional distributions instead from the marginals.

Gibbs sampler is used to obtain our results.

GIBBS SAMPLER PROCEDURE

- Specify the initial values $p^{(0)} = (p_1, \ldots, p_M)$,
- Generate draws $p^{(1)} = (p_1, \ldots, p_M)$ from the conditionals:

- $p_1^{(1)}$ from $\pi(p_1 \mid p_2^{(0)}, \ldots, p_M^{(0)})$,
  $\vdots$
- $p_i^{(1)}$ from $\pi(p_i \mid p_1^{(1)}, \ldots, p_{i-1}^{(1)}, p_{i+1}^{(0)}, \ldots, p_M^{(0)})$,
  $\vdots$
- $p_M^{(1)}$ from $\pi(p_M \mid p_1^{(1)}, \ldots, p_{M-1}^{(1)})$,

Single iteration represents a transition from
$p^{(0)} = (p_1, \ldots, p_M)$ to $p^{(1)} = (p_1, \ldots, p_M)$

- After *r* iterations the Gibbs sequence $p^{(0)}, p^{(1)}, \ldots, p^{(r)}$ is generated.

GIBBS SAMPLING

The conditional distributions needed to Gibbs sampler:

- Conditional multinomial

$$Z_i = (Z_{i1}, \ldots, Z_{i,M+1}) \sim Mult(n_i, \lambda) \quad , \quad \text{for} \quad i = 1, \ldots, M$$

where: $\lambda = (\lambda_1, \ldots, \lambda_{M+1})$ with $\lambda_j = p_j - p_{j-1}$, $p_0 \equiv 0$ and $p_{M+1} \equiv 1$

Observe: $Z_i = [Z_i(1), Z_i(2)] = [(Z_{i1}, \ldots, Z_{ii}), (Z_{ii+1}, \ldots, Z_{iM+1})]$

where: $Z_i(1) \sim Mult\{s_i, p_i^{-1}\lambda(1)\}$, $Z_i(2) \sim Mult\{n_i - s_i, (1-p_i)^{-1}\lambda(2)\}$

with: $\lambda(1) = (\lambda_1, \ldots, \lambda_i)$, $\lambda(2) = (\lambda_{i+1}, \ldots, \lambda_{M+1})$

GIBBS SAMPLING

The conditional distributions needed to Gibbs sampler:

- Conditional Beta

$$p_i \mid p_{i-1}, p_{i+1} \sim p_{i-1} + (p_{i+1} - p_{i-1}) Beta(\bar{\xi}_i, \bar{\xi}_{i+1})$$

where:

$$\bar{\xi}_i = \alpha\left(P_0(x_i) - P_0(x_{i-1})\right) + \sum_{j=1}^{M} Z_{ji}$$

$$\bar{\xi}_{i+1} = \alpha\left(P_0(x_{i+1}) - P_0(x_i)\right) + \sum_{j=1}^{M} Z_{ji+1}$$

GIBBS SAMPLING

Procedure:

- Specify the initial value $p^{(0)} = (p_1, \ldots, p_M)$,
  - for each $i = 1, \ldots, M$ sample from multinomials:
  - for each $i = 1, \ldots, M$ sample from conditional beta distributions (using the results from multinomial)

Single iteration (the last two steps) represents a transition from $p^{(0)}$ to $p^{(1)}$ - after *r* iterations: $p^{(r)} = \left(p_1^{(r)}, \ldots, p_M^{(r)}\right)$

After *v* replications of this procedure (starting from the same initial value) $p^{r1}, \ldots, p^{rv}$ is calculated.

EXPERIMENTS

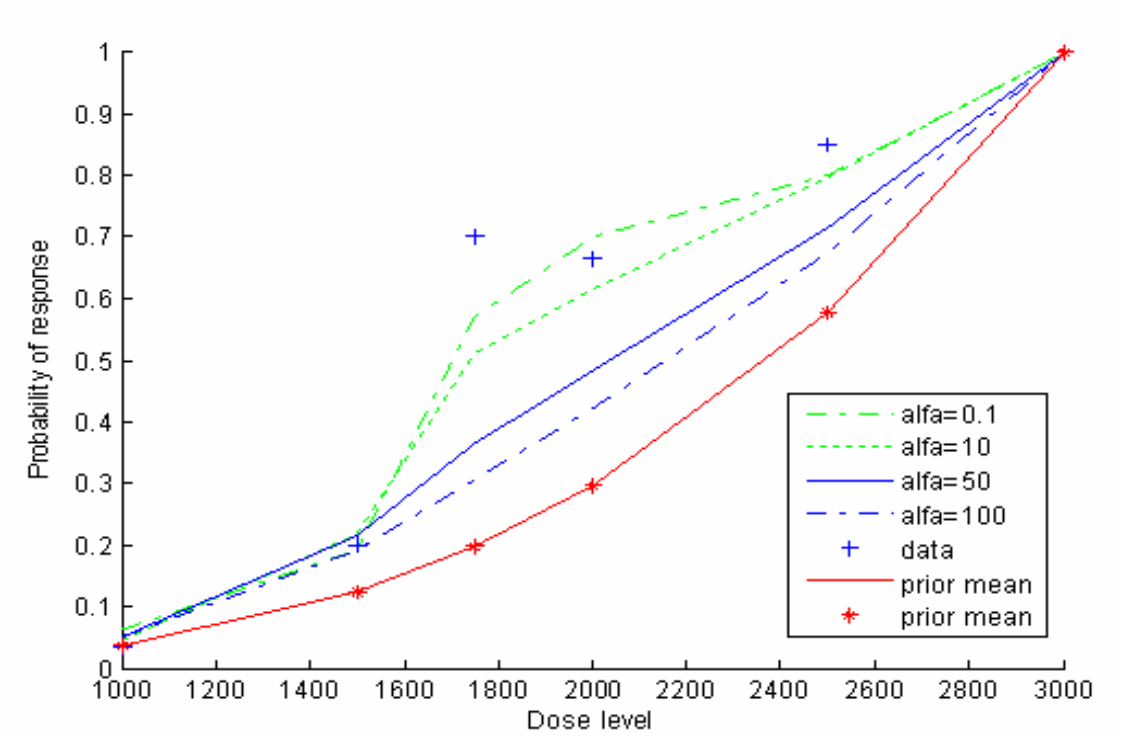
- Bioassay data:

Dose	Nr subjects	Nr responses
1000	30	1
1500	30	6
1750	10	7
2000	30	20
2500	20	17
3000	10	10

- Two base distributions: $P_o(x) = \frac{x^3}{3000^3}$, $P_o(x) = \frac{x}{3000}$
- 4 values of precision parameter α : 0.1, 10, 50, 100
- Gibbs sampler with 1500 replications and 80 iterations

RESULTS

- Prior mean and posterior mean with different values of α for $P_o(x) = \frac{x^3}{3000^3}$



RESULTS

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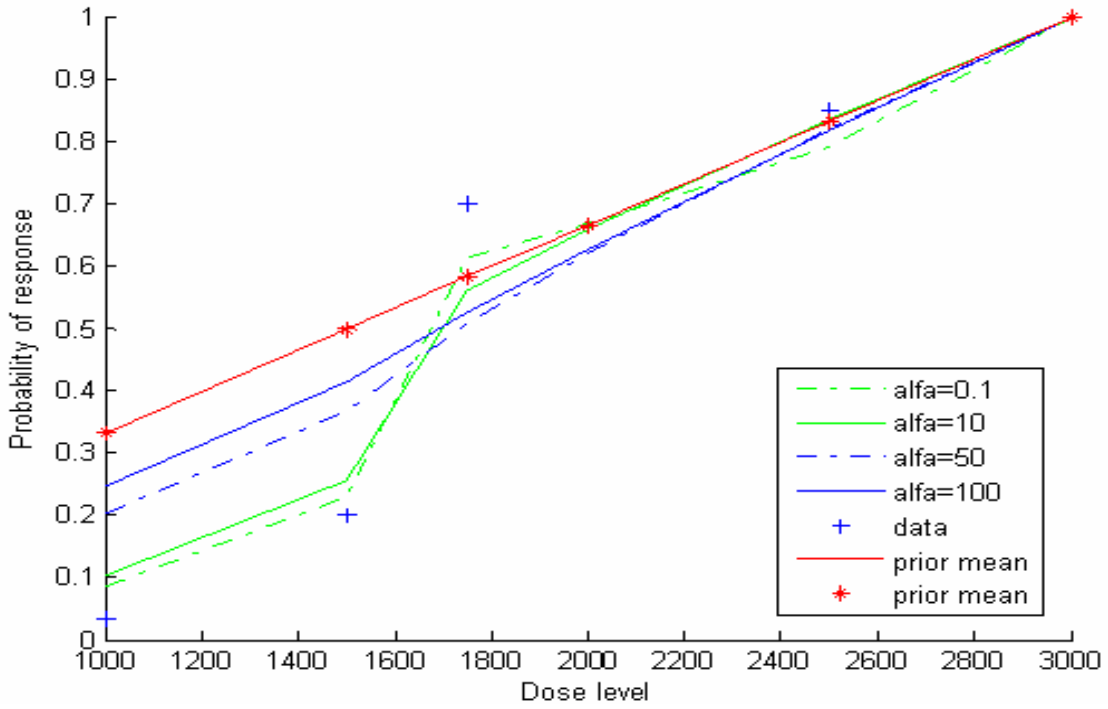
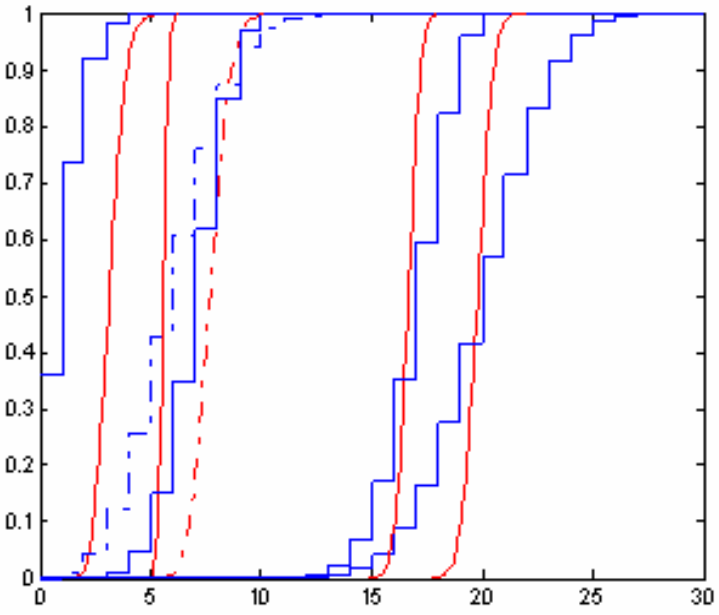
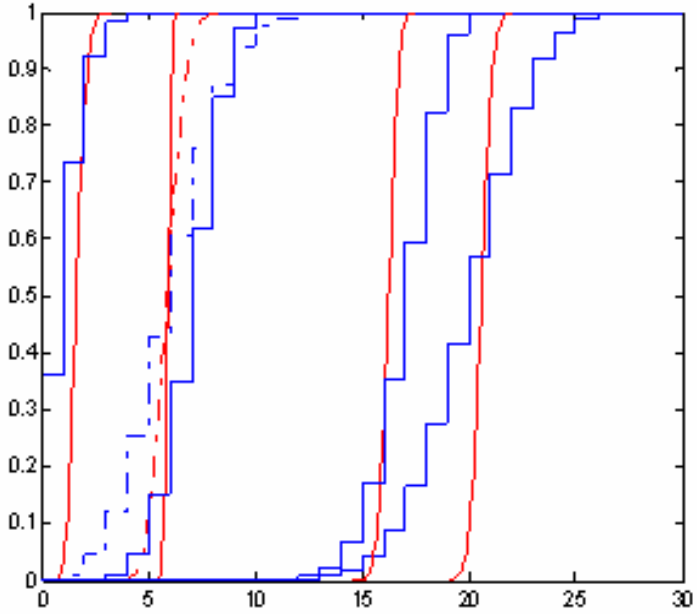


RESULTS

- Model suitability to recover the observational probabilities

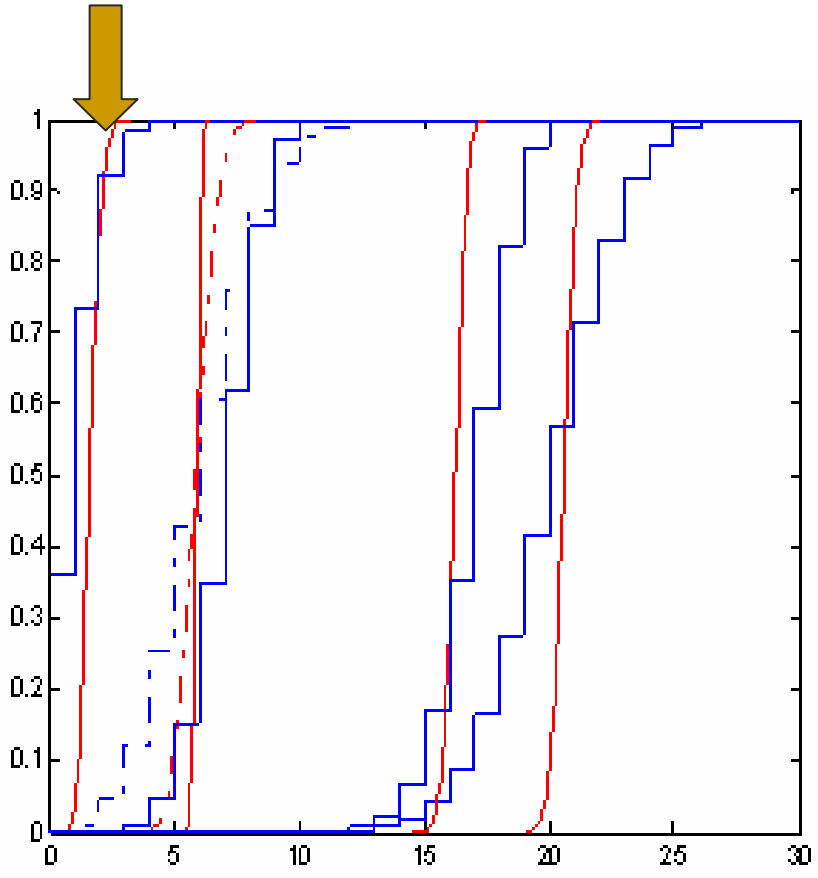
NPB for $P_o(x) = \frac{x^3}{3000^3}$ and with $\alpha = 10$ (LHS) *and* $\alpha = 1$ (RHS)



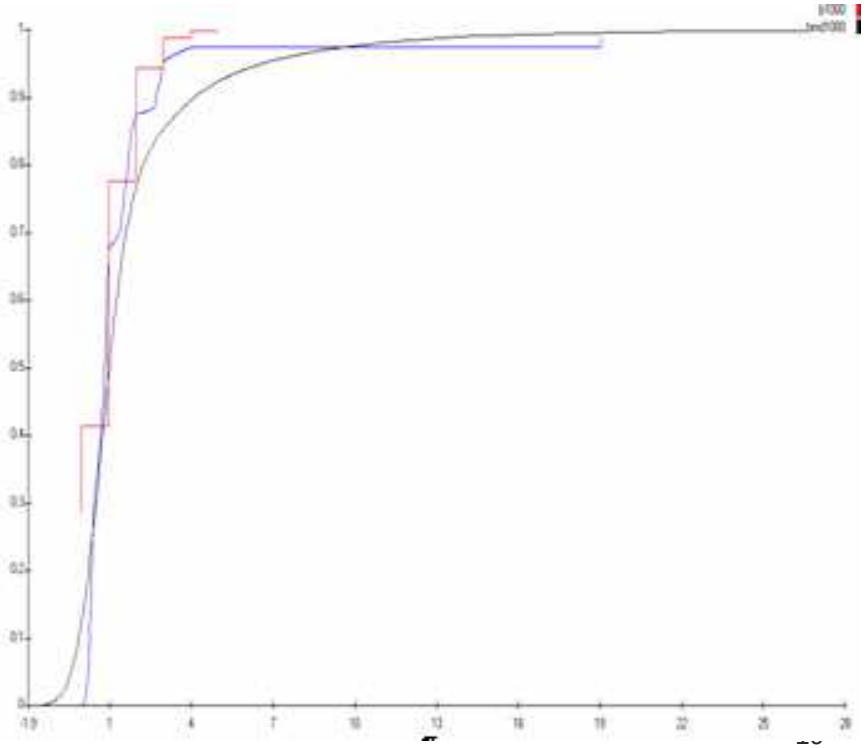


RESULTS

NPB approach

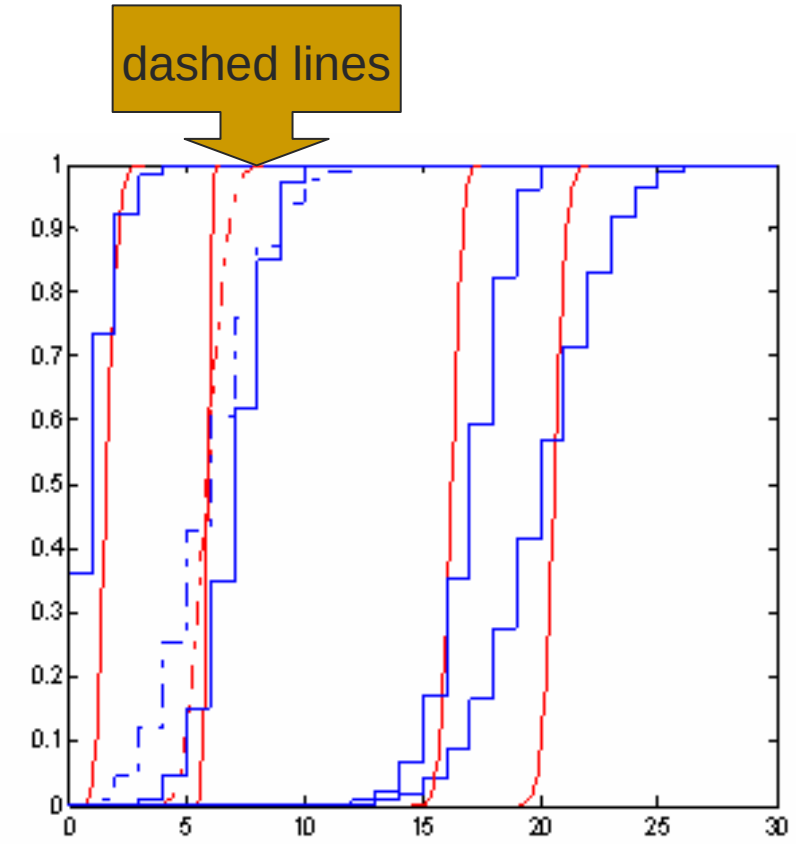


BMD software and PI- dose 1000

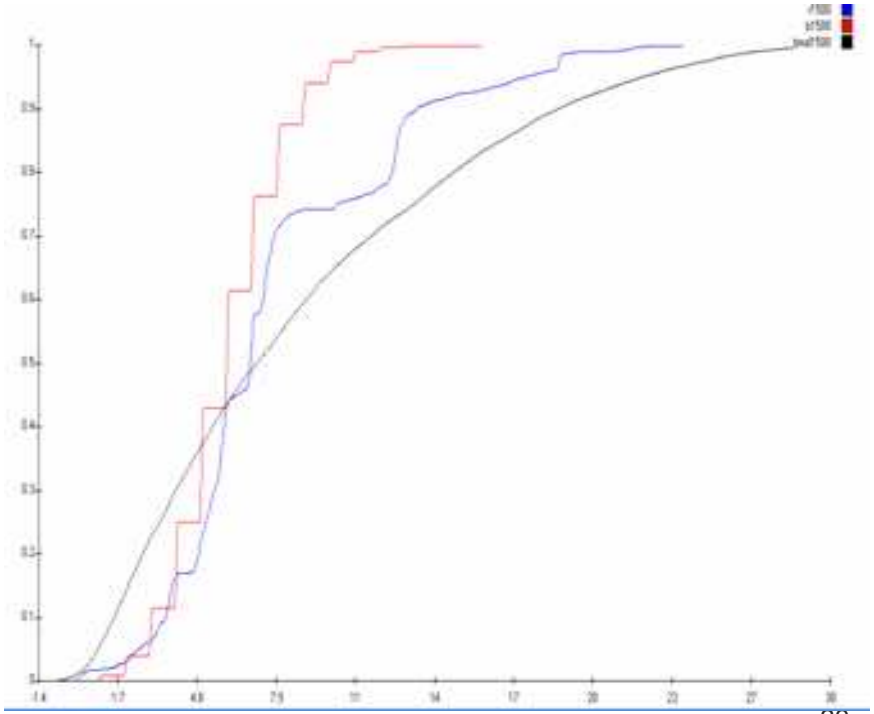


RESULTS

NPB approach

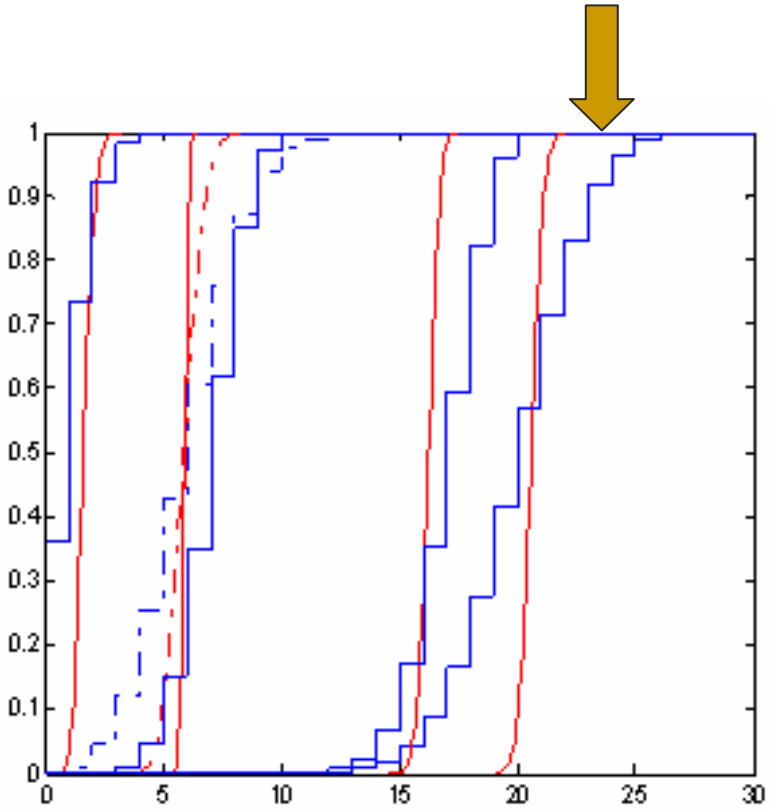


BMD software and PI–dose 1500

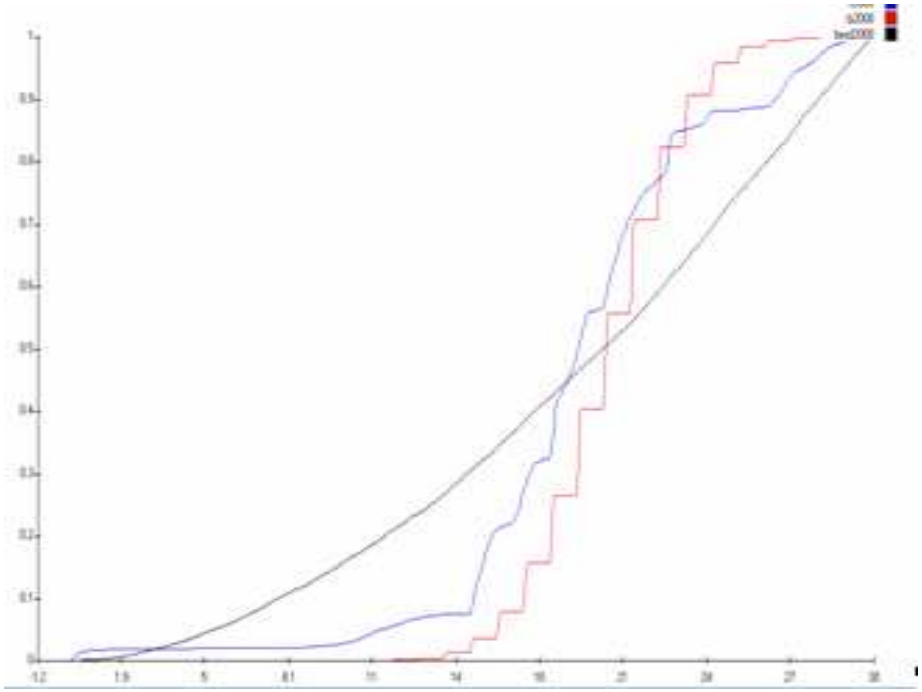


RESULTS

NPB approach

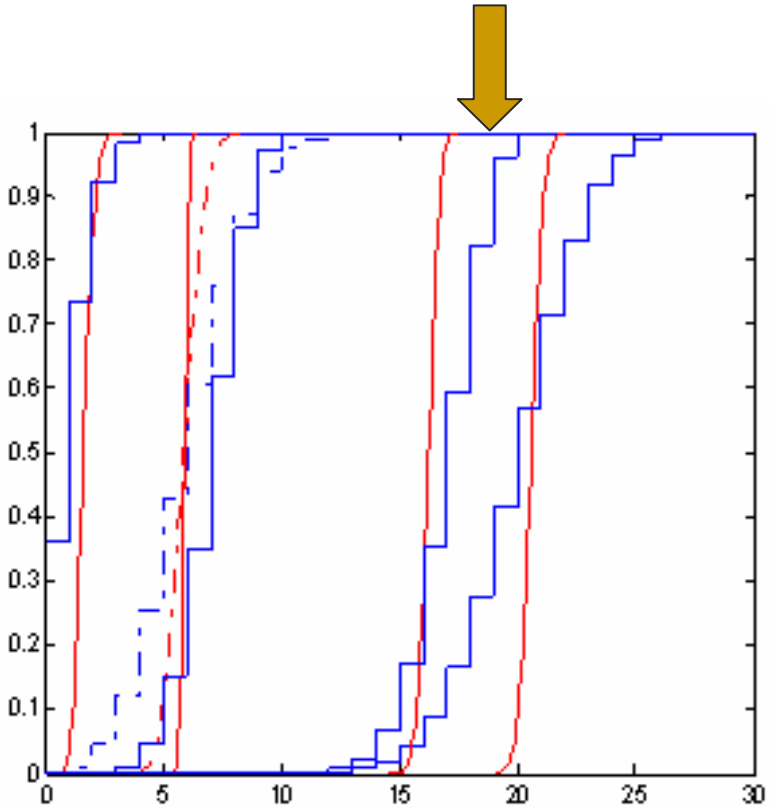


BMD software and PI–dose 2000

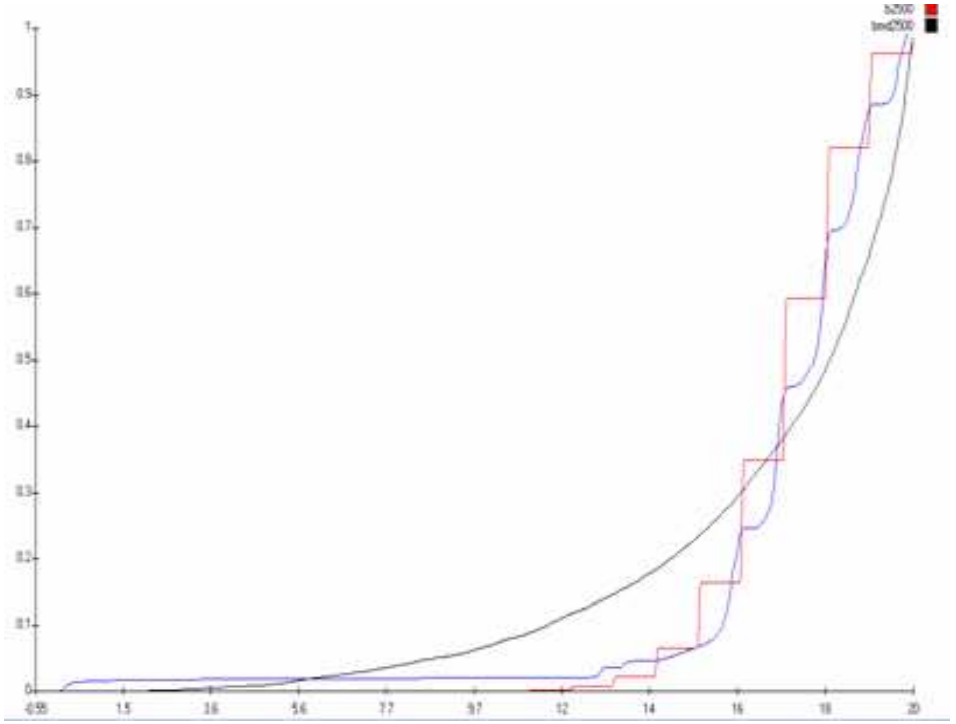


RESULTS

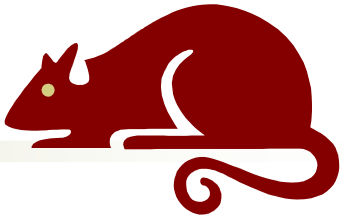
NPB approach



BMD software and PI–dose 2500



CONCLUSIONS



- Problems with specifying the precision parameter and base distribution for Dirichlet prior.
- If no prior information is available then the non informative prior can be used (e.g. Jeffreys prior).
- Model suits the data not so good at each of the dose levels.
- Useful extension in bioassay study is constraint on the shape of the potency curve.

QUESTIONS