The new BMD methodology
–
Insights and understandings

Marc Aerts

February 15, 2023

EUROPEAN FOOD SAFETY AUTHORITY

What's new?

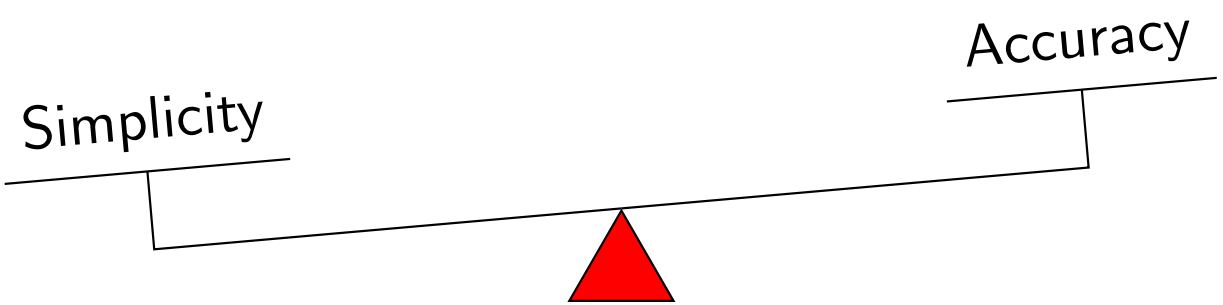
- extension of current PROAST implementation
  - ▷ more candidate models for continuous endpoints
  - ▷ unifying framework across types of endpoints
  - ▷ Bayesian implementation
  - ▷ informative priors
  - ▷ preliminary tests
  - ▷ computationally sufficiently fast
  - ▷ user R4EU interface
- all methodological and technical details

Outline

- Main statistical methodology
  - ▷ Components of the models
  - ▷ Bayesian inference
  - ▷ Model averaging
- Preliminary statistical tests
- Some further illustrations
- Summary simulation study

Components of dose response model

- distribution of the response at a specified dose level $y|x$
- effect of dose x on the median Med(x) of this distribution



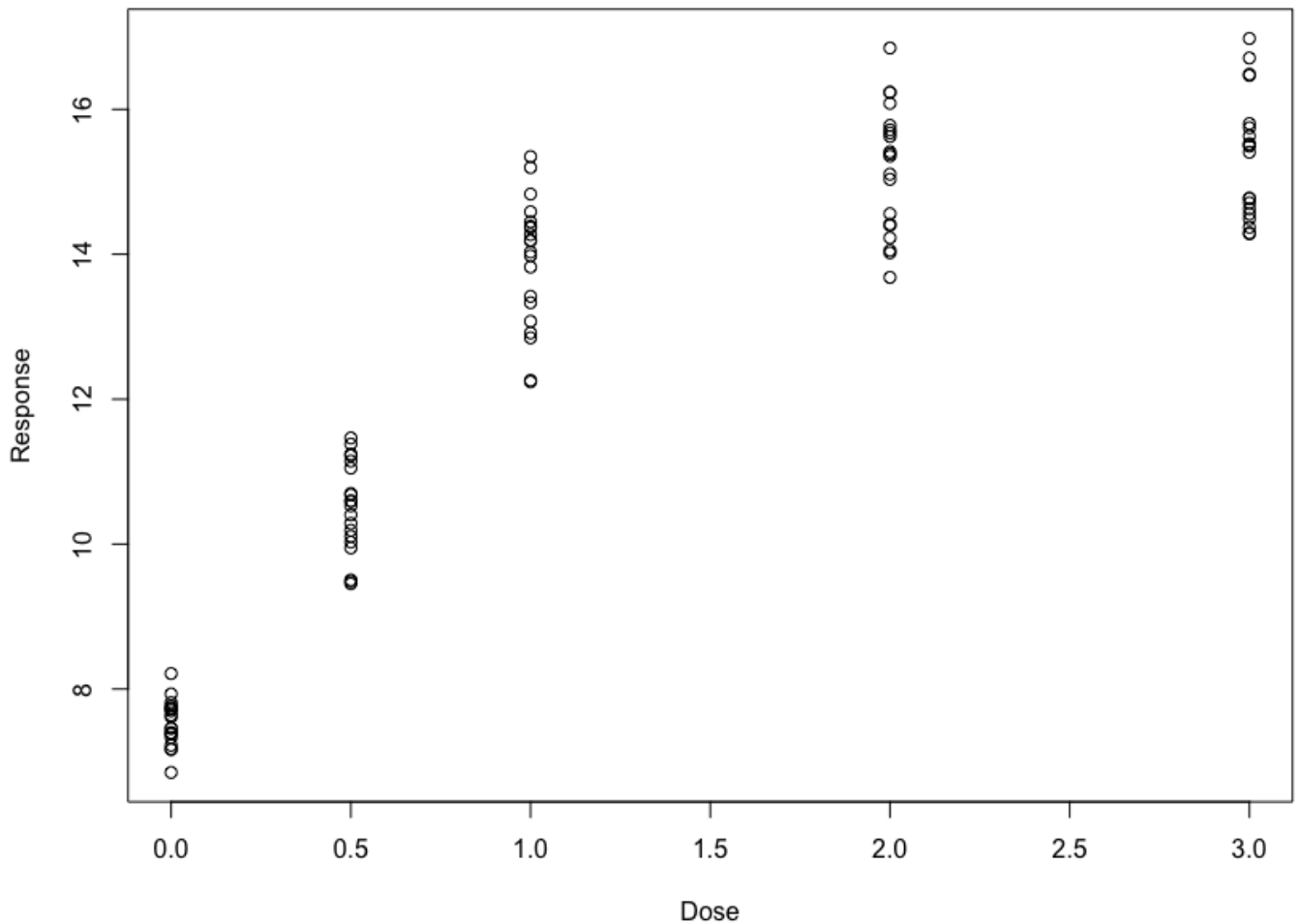
Model components

$$y|x$$

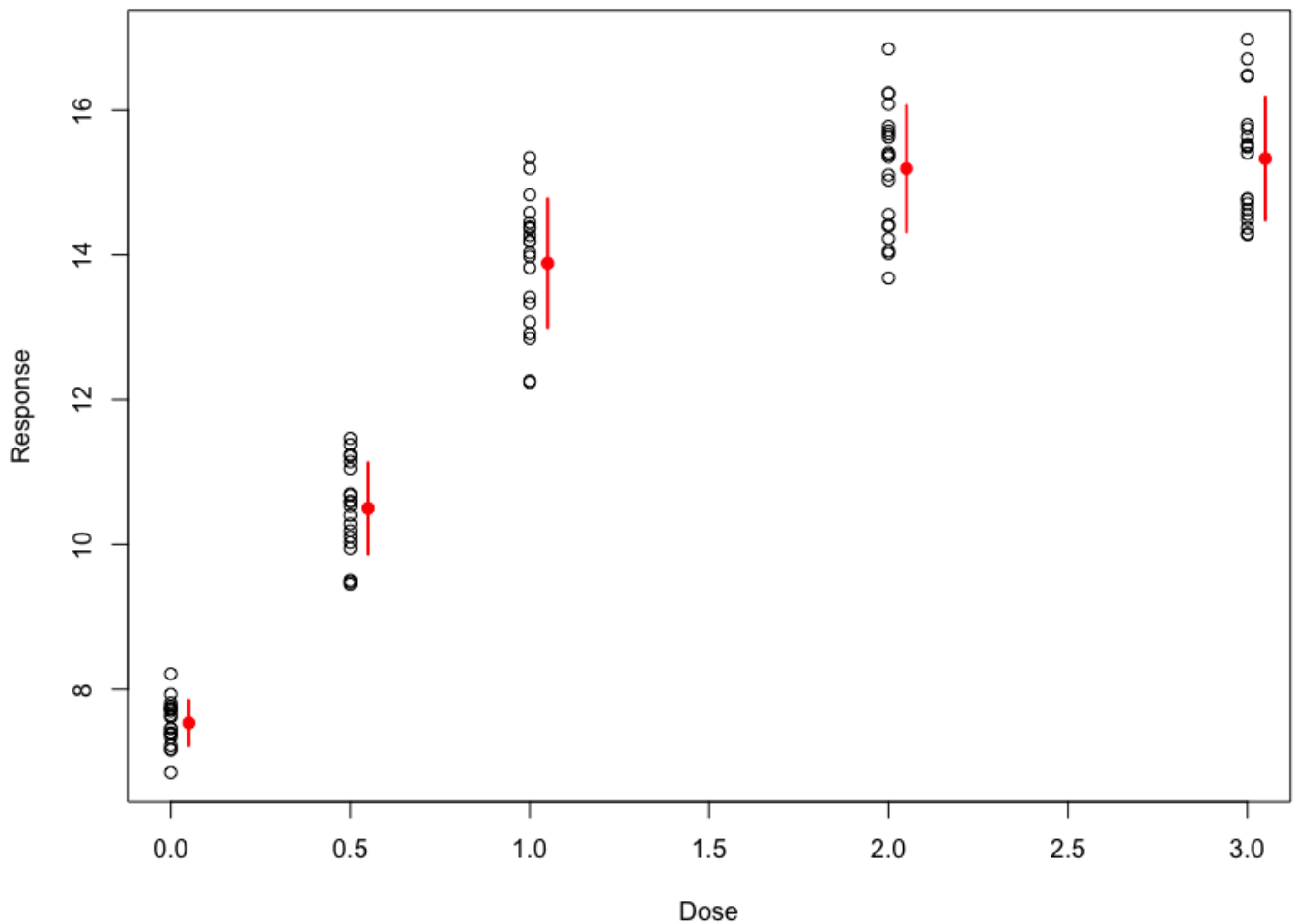
response | dose

?

Continuous response (Example 3.1, Figure C.3 in guidance)



Continuous response (Example 3.1, Figure C.3 in guidance)



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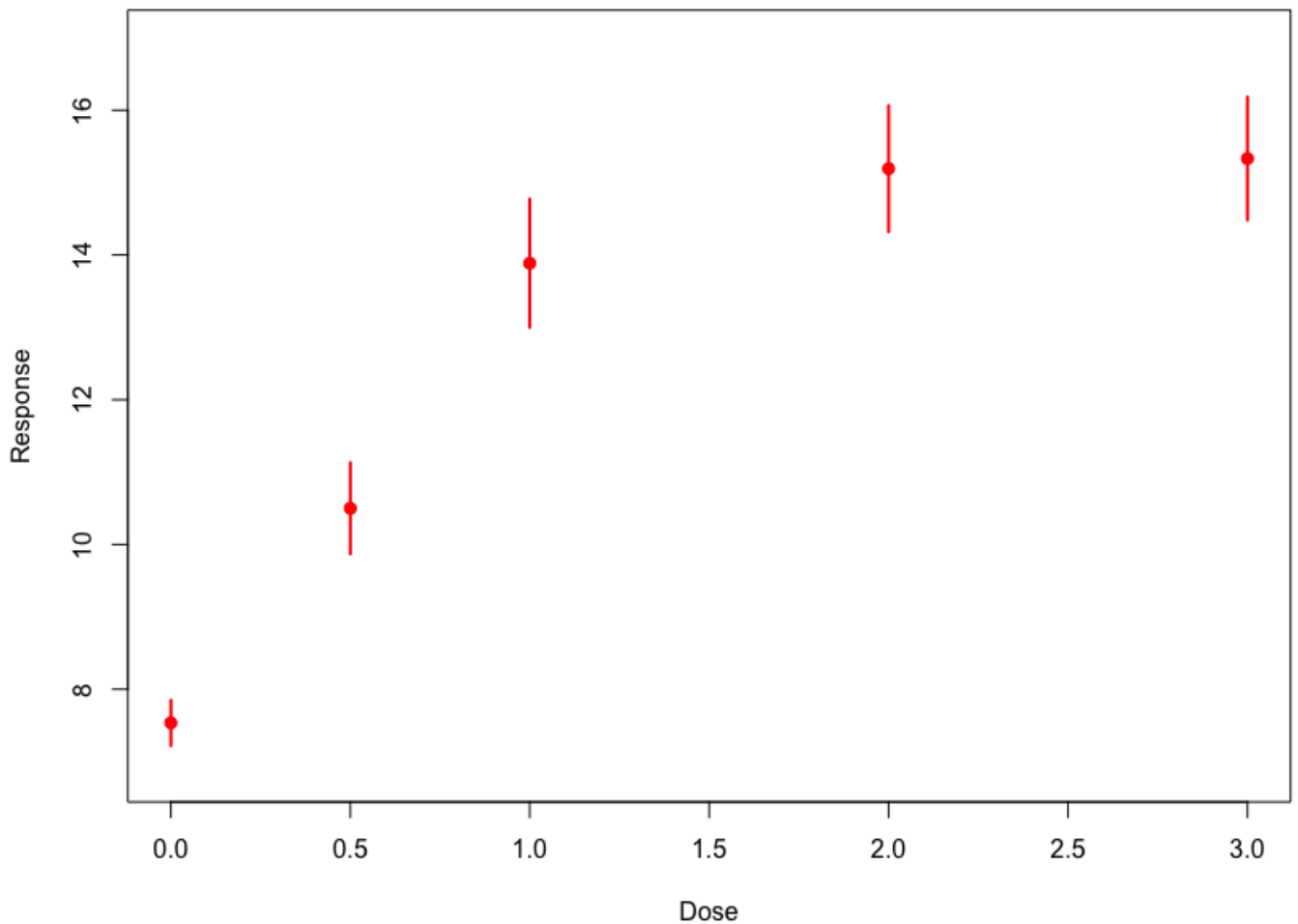
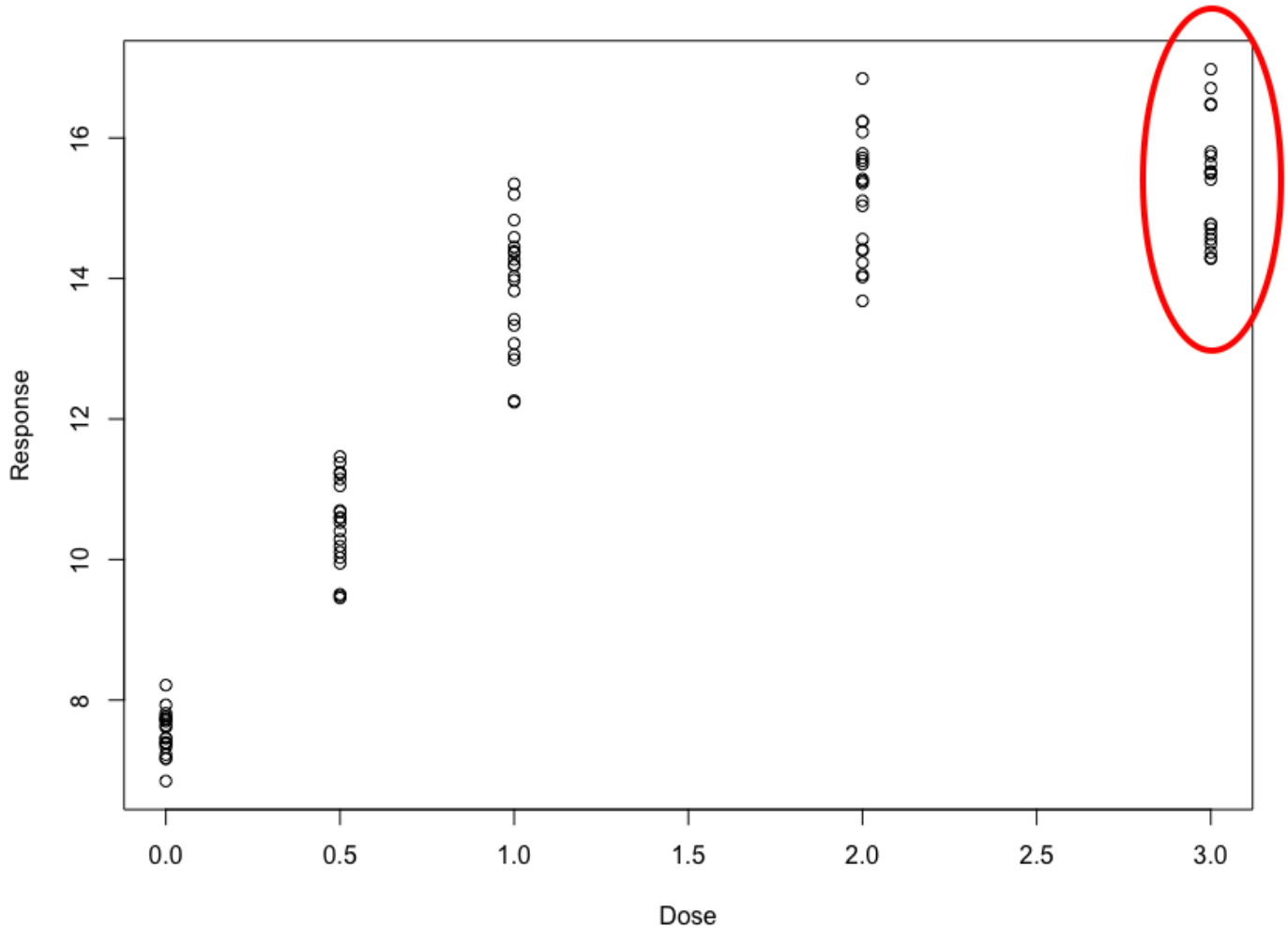


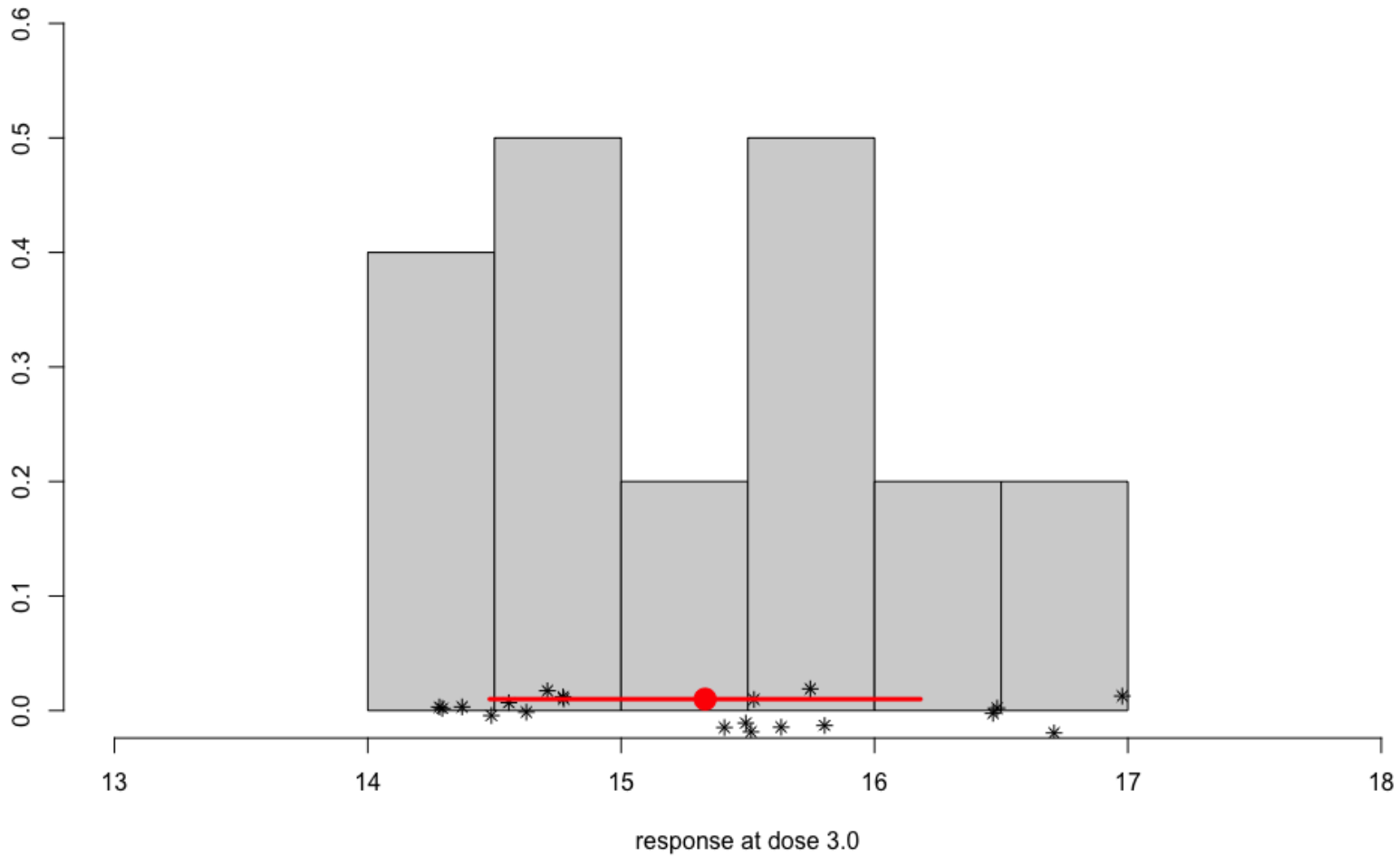
Model components

- **continuous**
  - ▷ normal
    $$y|x \sim \mathsf{N}(\mu(x), \sigma^2)$$
  - ▷ log-normal
    $$y|x \sim \mathsf{LOGN}(\mu(x), \sigma^2)$$
- **quantal**
  - ▷ Bernoulli
    $$y|x \sim \mathsf{Bernoulli}(\pi(x))$$
- Extension to **clustered** observations
- Extension to **covariates**

Continuous response (Example 3.1, Figure C.3 in guidance)



Data at highest dose



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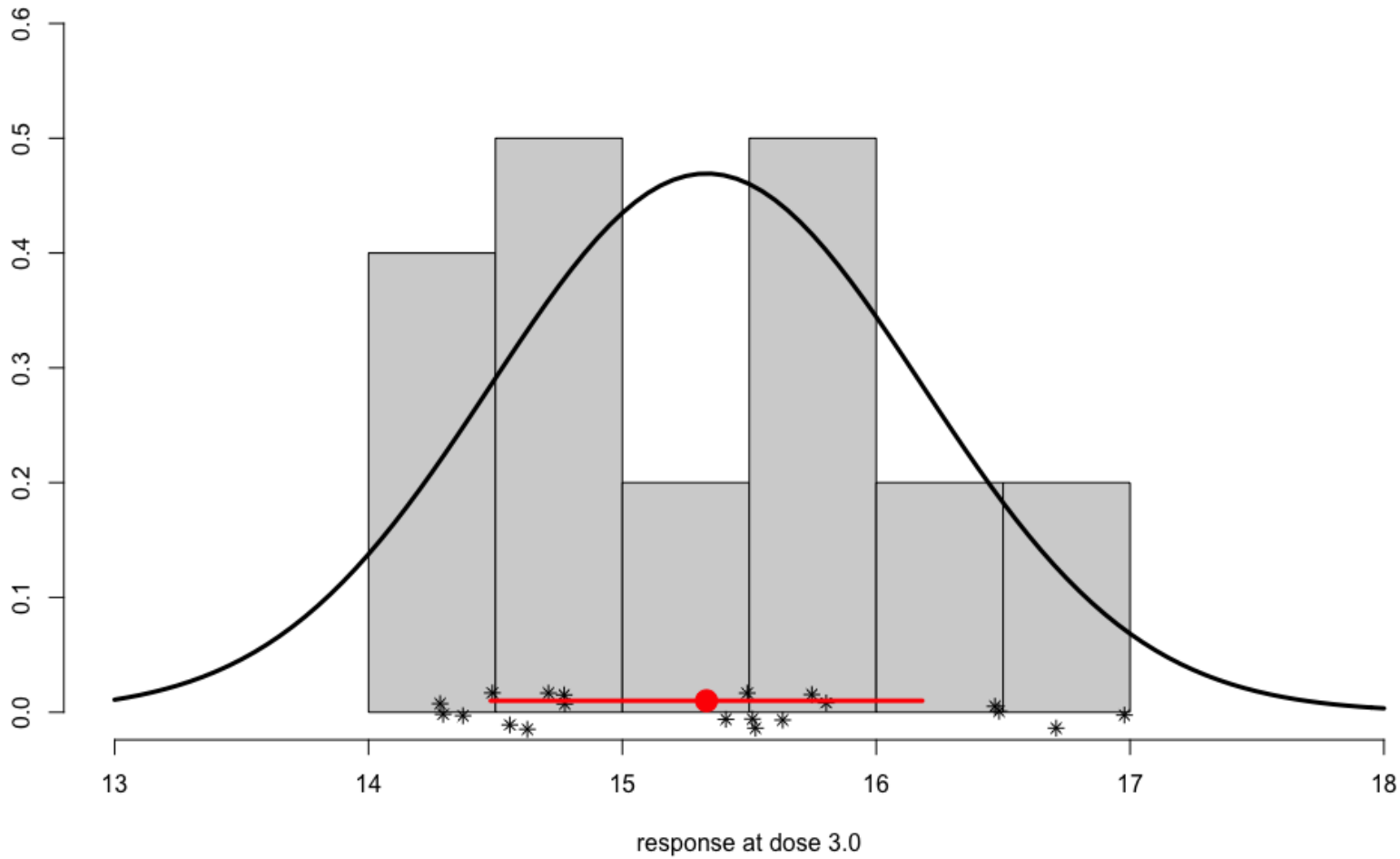

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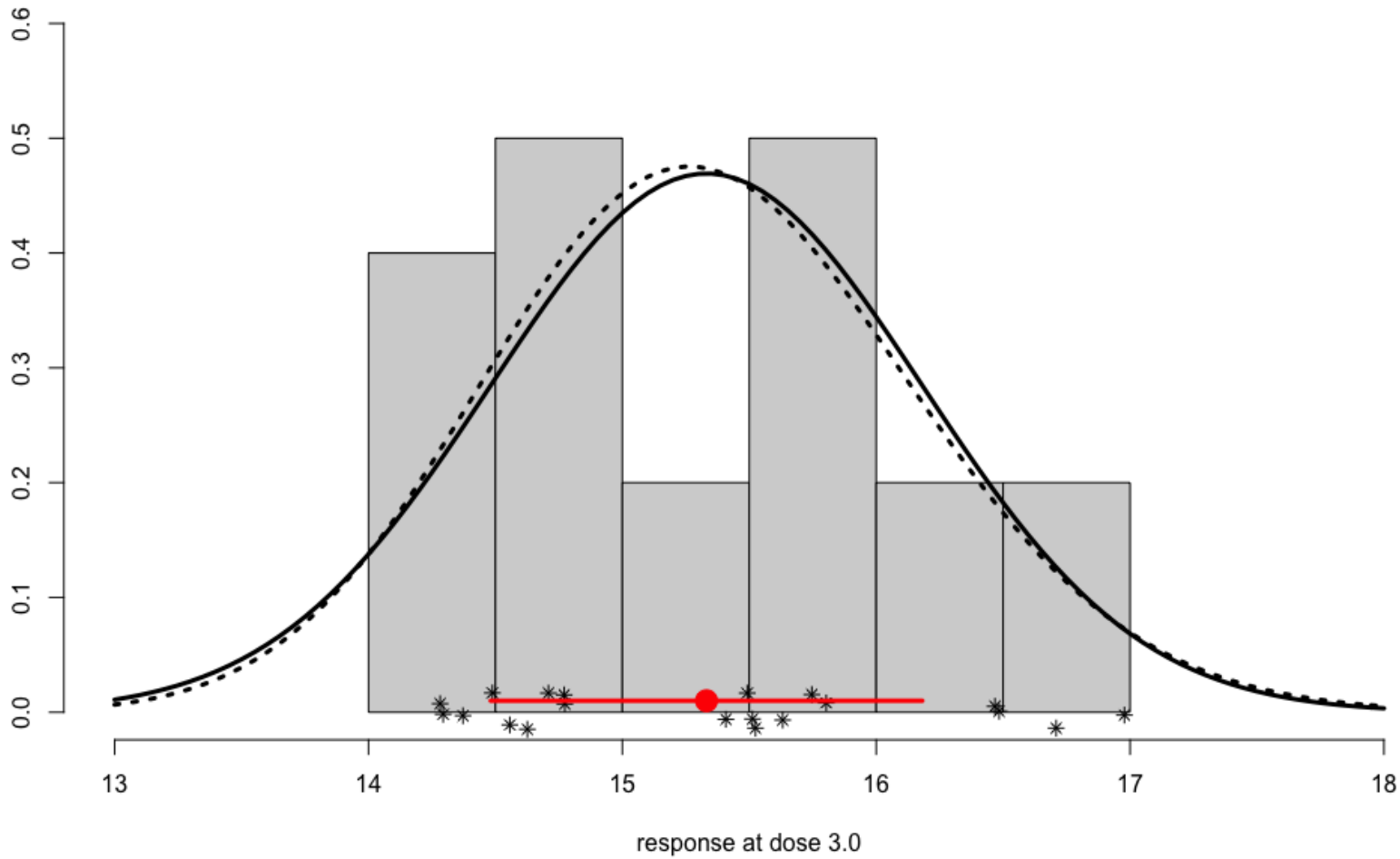

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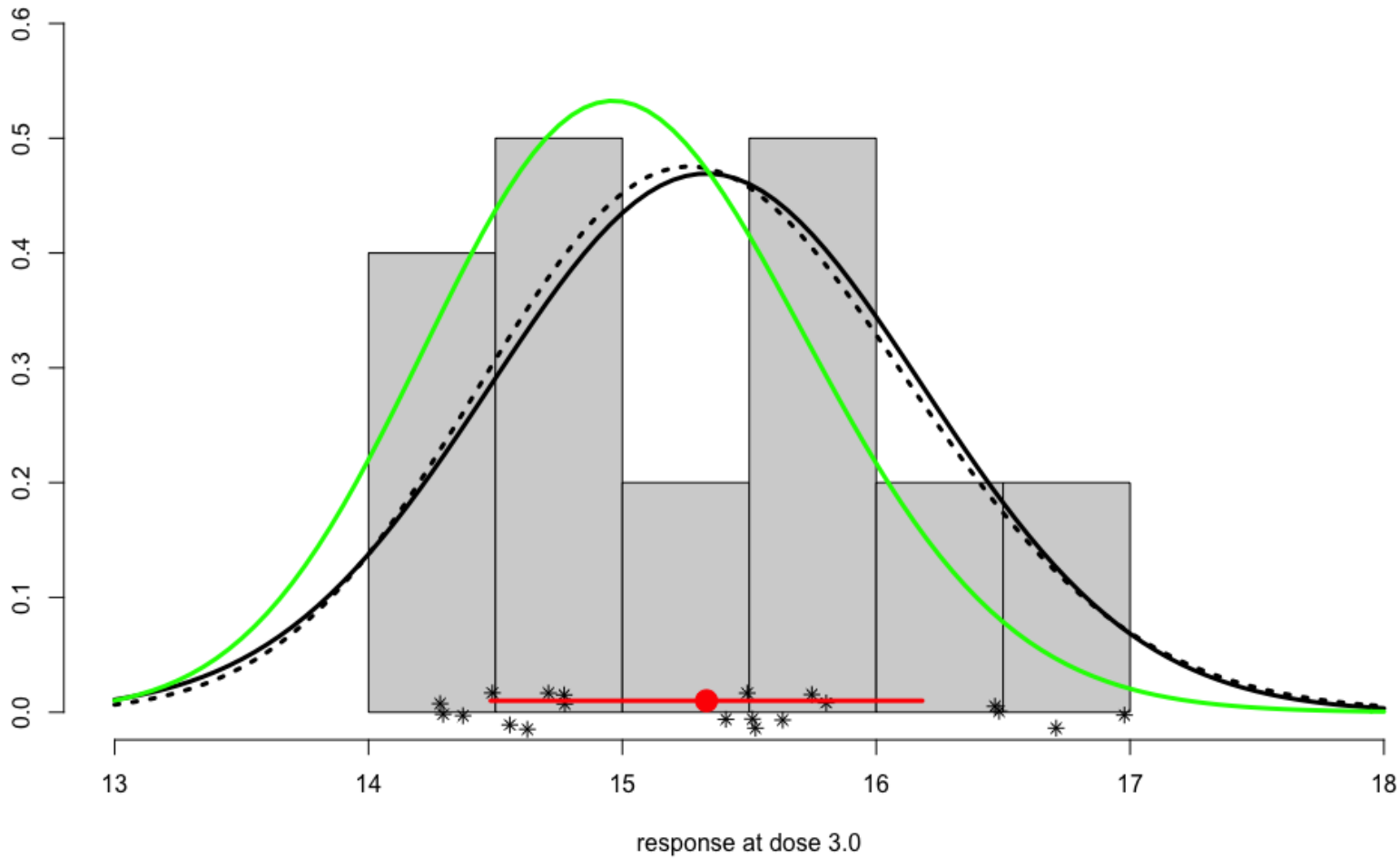
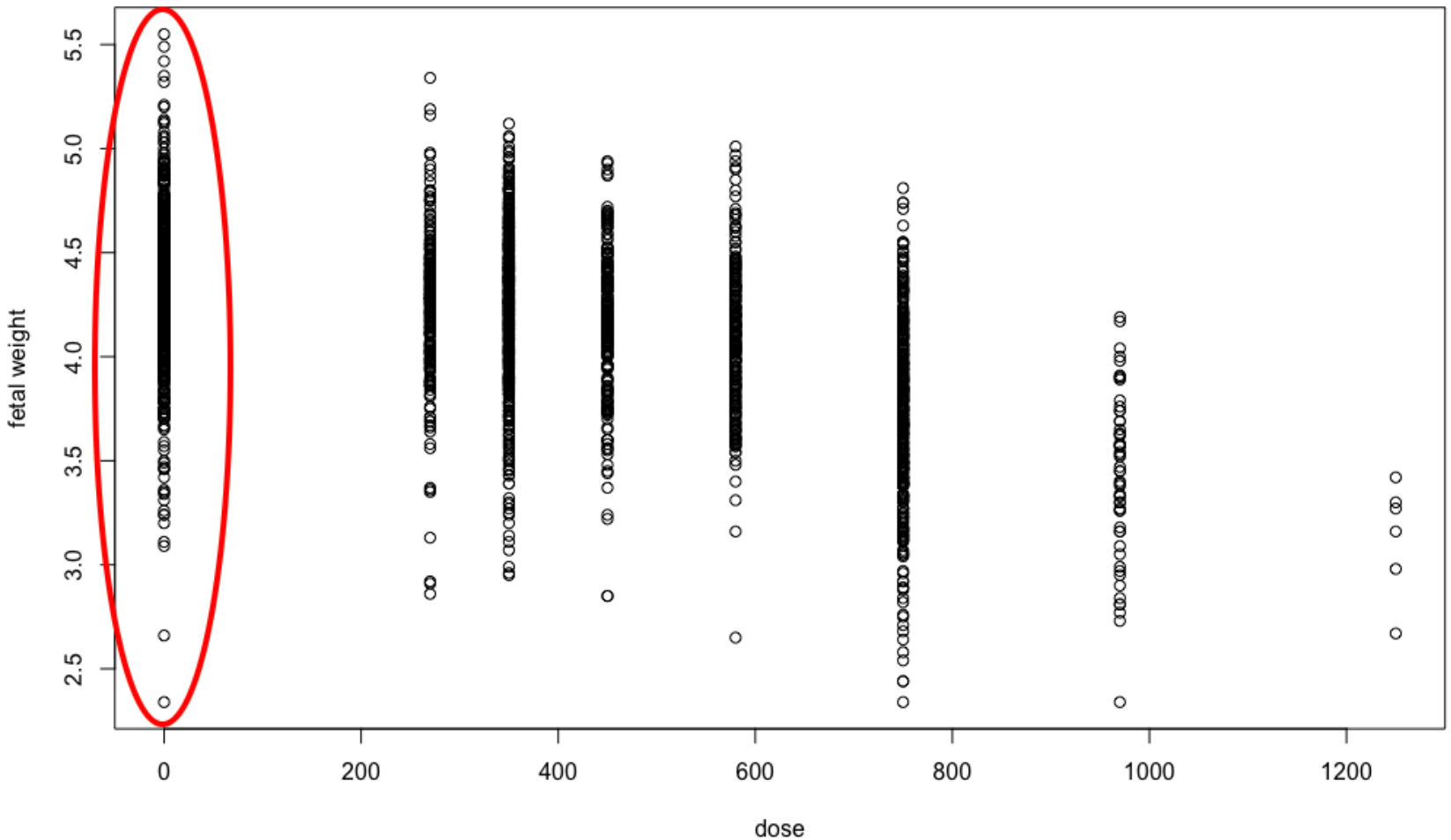


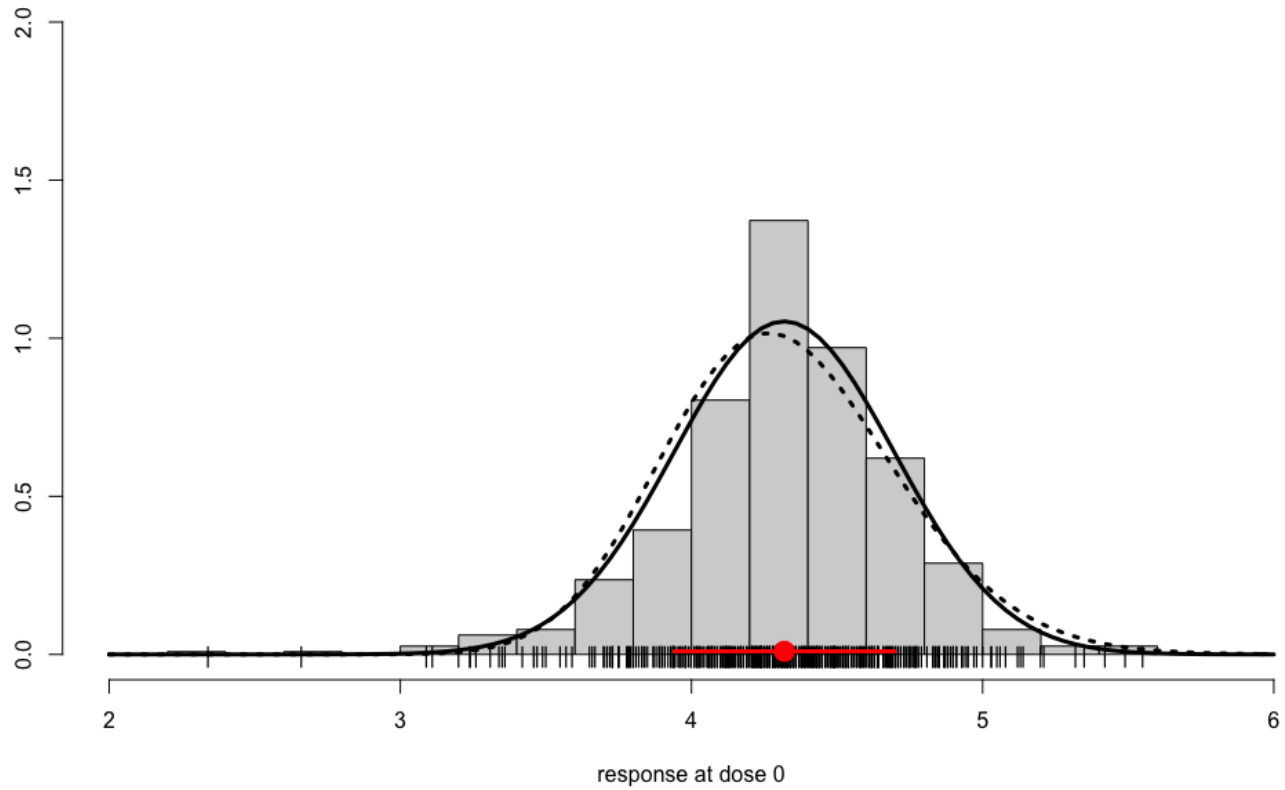
Normal and log-normal distribution

The fetal weight example (dataset `das5.rda` in PROAST)



Normal and log-normal distribution

Fetal weight control group



$$P(\text{weight} < 0) = 2.05 \times 10^{-30}$$

Normal and log-normal distribution

$$y \sim \mathsf{N}(\mu, \sigma^2) \quad \text{or} \quad y \sim \mathsf{LOGN}(\mu, \sigma^2)$$
$$\Updownarrow$$
$$\log(y) \sim \mathsf{N}(\mu, \sigma^2)$$

Mixing up notation: μ's refer to different parameters (σ's as well)

Normal and log-normal distribution

$$y \sim \mathsf{N}(\mu, \sigma^2) \quad \text{or} \quad y \sim \mathsf{LOGN}(\mu, \sigma^2)$$
$$\Updownarrow$$
$$\log(y) \sim \mathsf{N}(\mu, \sigma^2)$$

	$\mathsf{N}(\mu, \sigma^2)$	$\mathsf{LOGN}(\mu, \sigma^2)$
mean	μ	$e^{\mu+\sigma^2/2}$
median	μ	e^{μ}
variance	σ^2	$(e^{\sigma^2}-1)e^{2\mu+\sigma^2}$
coefficient of variation	σ/μ	$\sqrt{e^{\sigma^2}-1}$

Normal and log-normal distribution

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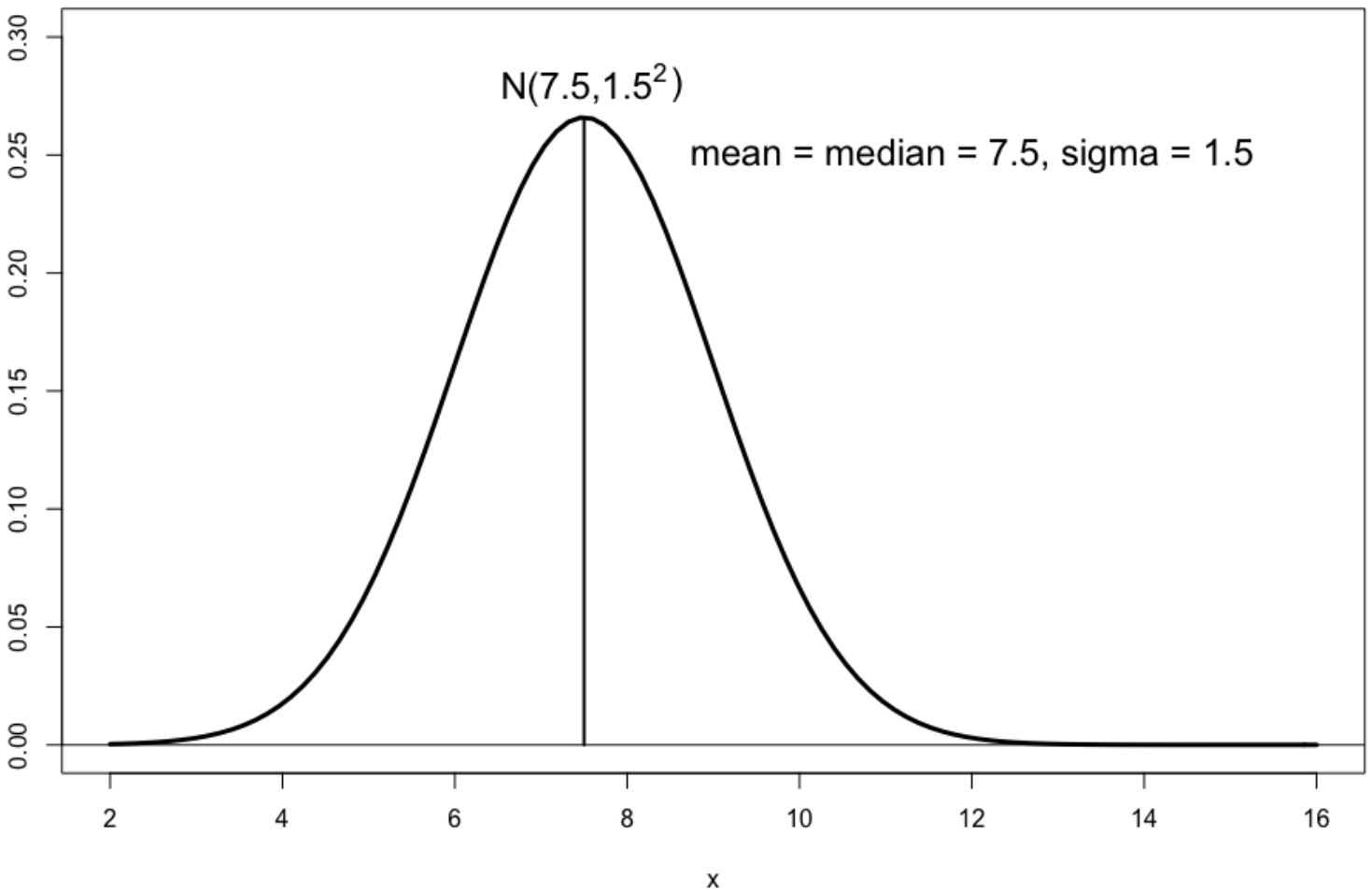

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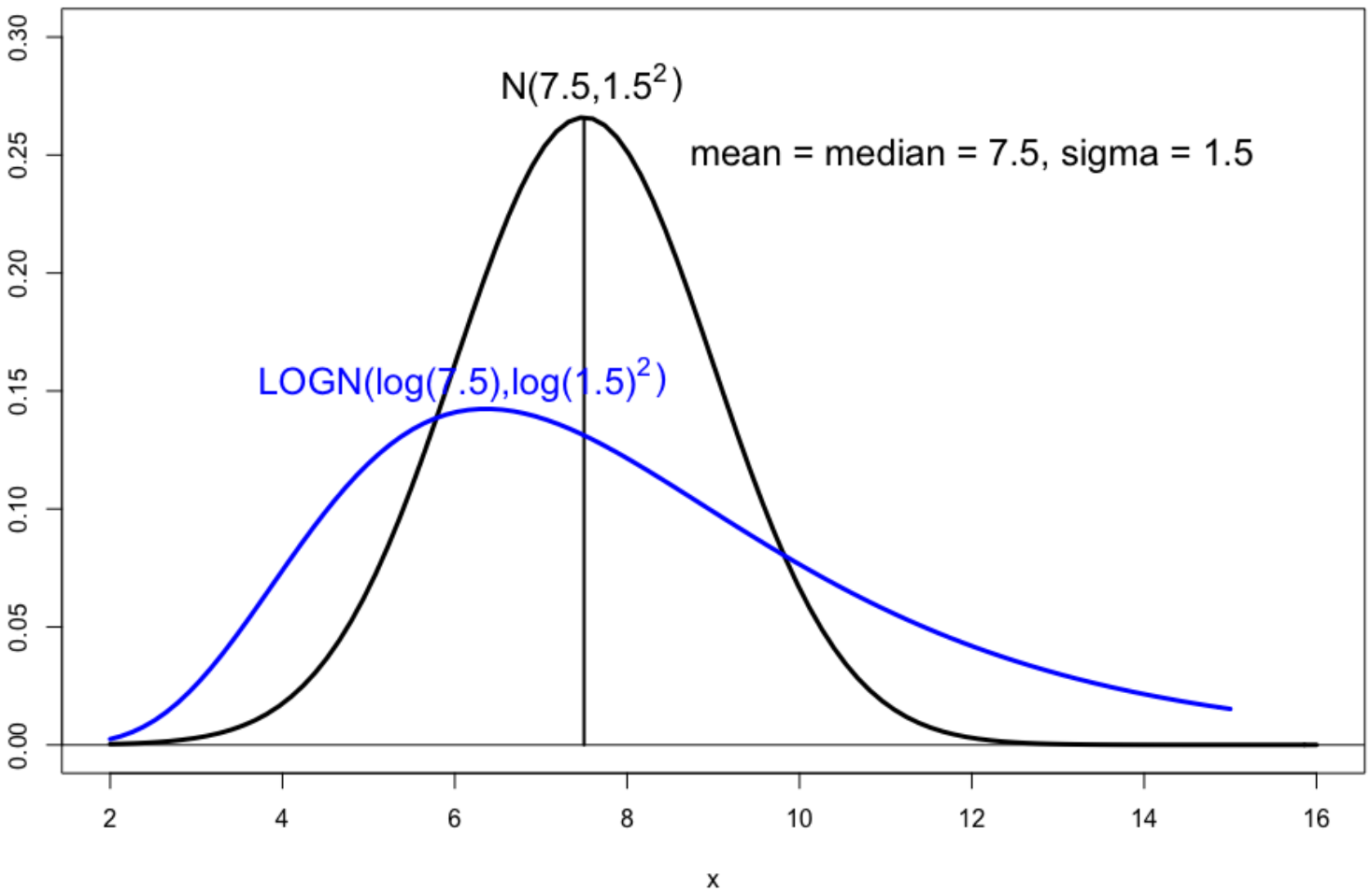

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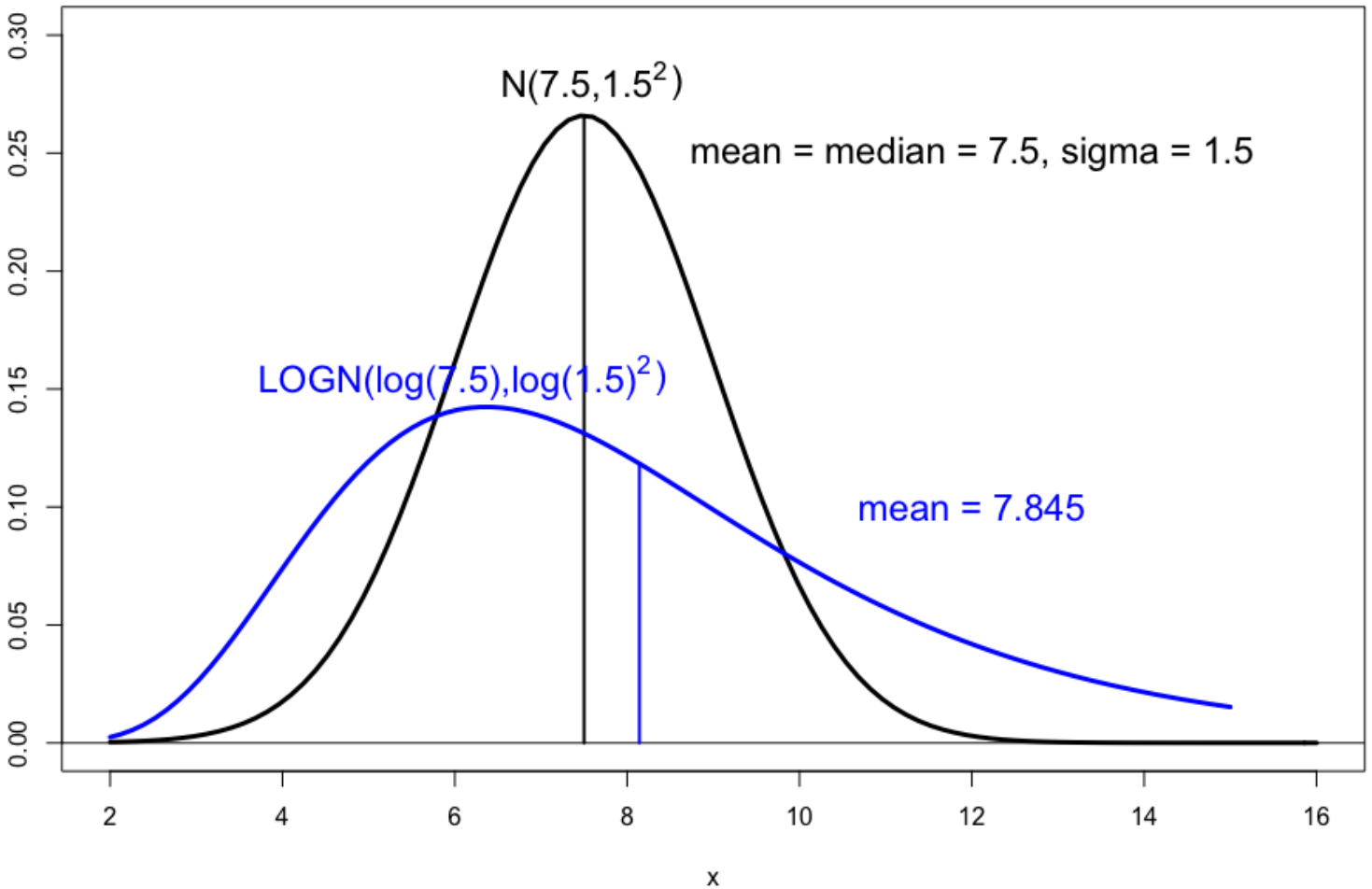

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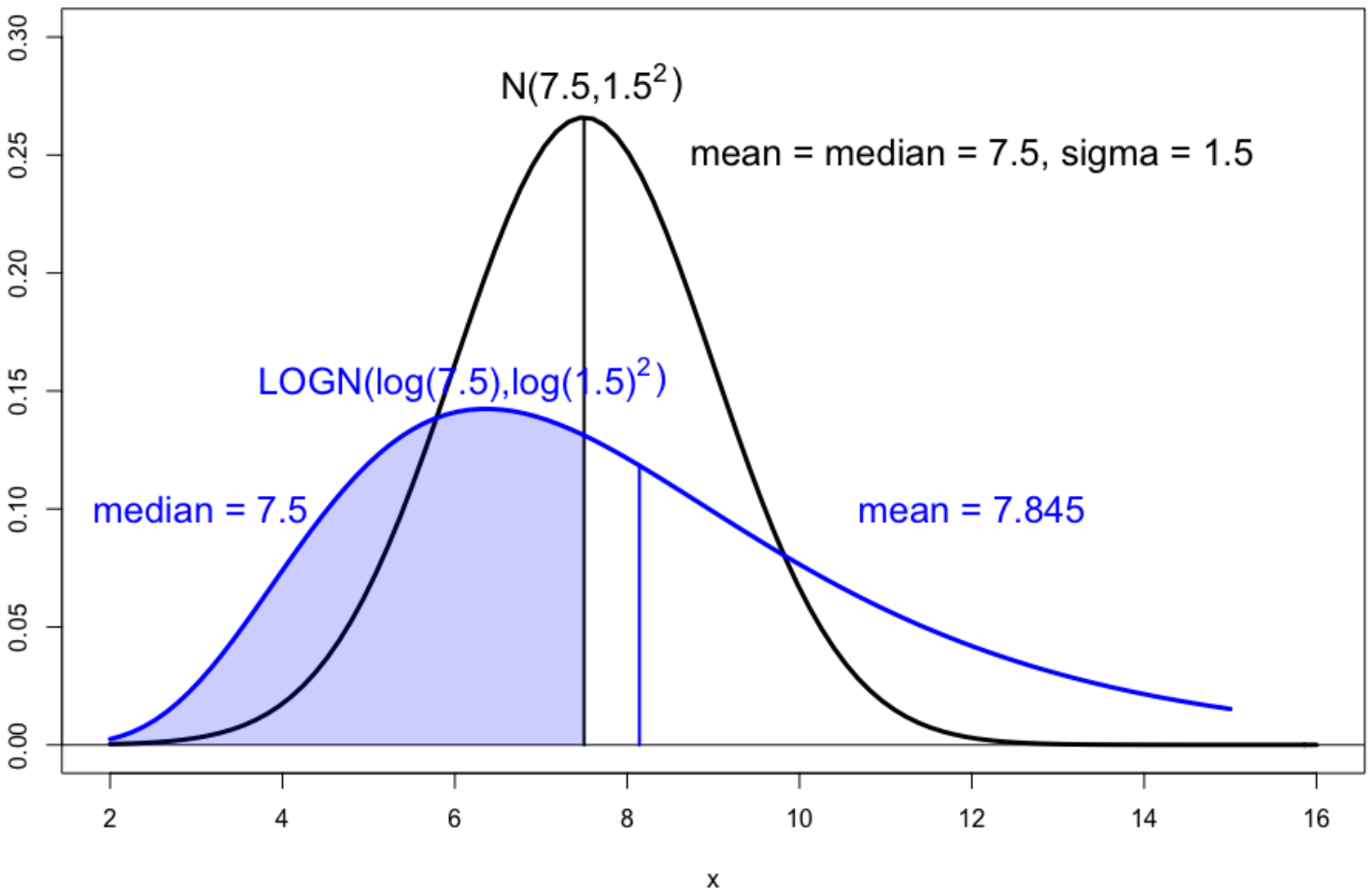


Model components

What do we mean by

median Med(x) of

response $\mid$ dose$=x$

?

Normal and log-normal distribution

	$\mathsf{N}(\mu, \sigma^2)$	$\mathsf{LOGN}(\mu, \sigma^2)$
mean	μ	$e^{\mu+\sigma^2/2}$
median	μ	e^{μ}
variance	σ^2	$(e^{\sigma^2}-1)e^{2\mu+\sigma^2}$
coefficient of variation	σ/μ	$\sqrt{e^{\sigma^2}-1}$

Normal and log-normal distribution

	$\mathsf{N}(\mu(x), \sigma^2)$	$\mathsf{LOGN}(\mu(x), \sigma^2)$
mean	$\mu(x)$	$e^{\mu(x)+\sigma^2/2}$
median $\mathsf{Med}(x)$	$\mu(x)$	$e^{\mu(x)}$
variance	σ^2	$(e^{\sigma^2}-1)e^{2\mu(x)+\sigma^2}$
coefficient of variation	$\sigma/\mu(x)$	$\sqrt{e^{\sigma^2}-1}$

Definition of BMD for a given BMR

- **Median** for continuous response
  - ▷ normal $\text{Med}(x) = \mu(x)$
  - ▷ log-normal $\text{Med}(x) = e^{\mu(x)}$

$$\text{BMR} = \frac{\text{Med}(\text{BMD}) - \text{Med}(0)}{\text{Med}(0)}$$

- **Adverse event probability** for quantal response $\pi(x)$

$$\text{BMR} = \frac{\pi(\text{BMD}) - \pi(0)}{1 - \pi(0)}$$

Dose response models for continuous response

Table 2: Candidate models for both distributional assumptions

Family	Model	$y\|x \sim N(\mu(x), \sigma^2)$	$y\|x \sim LOGN(\mu(x), \sigma^2)$
		Dose–response function $(\mu(x))$	**Dose–response function** $(e^{\mu(x)})$
1a	Exponential[(i)]	$a \cdot \left(1 + (c-1) \cdot \left(1 - e^{-b \cdot x^d}\right)\right)$	$e^{a \cdot \left(1 + (c-1) \cdot \left(1 - e^{-b \cdot x^d}\right)\right)}$
	Inverse Exponential	$a \cdot \left(1 + (c-1) \cdot e^{-b \cdot x^{-d}}\right)$	$e^{a \cdot \left(1 + (c-1) \cdot e^{-b \cdot x^{-d}}\right)}$
	Hill[(ii)]	$a \cdot \left(1 + (c-1) \cdot \left(1 - \frac{b}{b + x^d}\right)\right)$	$e^{a \cdot \left(1 + (c-1) \cdot \left(1 - \frac{b}{b + x^d}\right)\right)}$
	Log-Normal	$a \cdot (1 + (c-1) \cdot \Phi(\log(b) + d \cdot \log(x)))$	$e^{a \cdot (1 + (c-1) \cdot \Phi(\log(b) + d \cdot \log(x)))}$
1b	Gamma[(iii)]	$a \cdot \left(1 + (c-1) \cdot \frac{\gamma(d, b \cdot x)}{\Gamma(d)}\right)$	$e^{a \cdot \left(1 + (c-1) \cdot \frac{\gamma(d, b \cdot x)}{\Gamma(d)}\right)}$
	LMS-two stage	$a \cdot \left(1 + (c-1) \cdot \left(1 - e^{-b \cdot x - d \cdot x^2}\right)\right)$	$e^{a \cdot \left(1 + (c-1) \cdot \left(1 - e^{-b \cdot x - d \cdot x^2}\right)\right)}$
2	Probit increasing	$a \cdot \Phi\left(c + b \cdot x^d\right)$	$e^{a \cdot \Phi\left(c + b \cdot x^d\right)}$
	Probit decreasing	$a \cdot (1 + \Phi(c)) - a \cdot \Phi\left(c + b \cdot x^d\right)$	$e^{a \cdot (1 + \Phi(c)) - a \cdot \Phi\left(c + b \cdot x^d\right)}$
	Logistic increasing	$a \cdot \frac{e^{c + b \cdot x^d}}{1 + e^{c + b \cdot x^d}}$	$e^{a \cdot \frac{e^{c + b \cdot x^d}}{1 + e^{c + b \cdot x^d}}}$
	Logistic decreasing	$a \cdot \left(1 + \frac{e^c}{1 + e^c}\right) - a \cdot \frac{e^{c + b \cdot x^d}}{1 + e^{c + b \cdot x^d}}$	$e^{a \cdot \left(1 + \frac{e^c}{1 + e^c}\right) - a \cdot \frac{e^{c + b \cdot x^d}}{1 + e^{c + b \cdot x^d}}}$

Exponential model in previous guidance is defined as

$$a[c-(c-1)e^{-bx^d}]$$

which equals the expression in the new guidance

$$\begin{aligned} a[c-(c-1)e^{-bx^d}] &= a[c-(1-c)(-e^{-bx^d})] \\ &= a[c-(1-c)(-e^{-bx^d}+1-1)] \\ &= a[c-(1-c)(-e^{-bx^d}+1)+(1-c)] \\ &= a[1-(1-c)(-e^{-bx^d}+1)] \\ &= a[1+(c-1)(1-e^{-bx^d})] \end{aligned}$$

For all models

- a and c determine background and maximum response

  e.g. for family 1 with the normal distribution

  - ▷ background $= a$
  - ▷ maximum response $= ac$

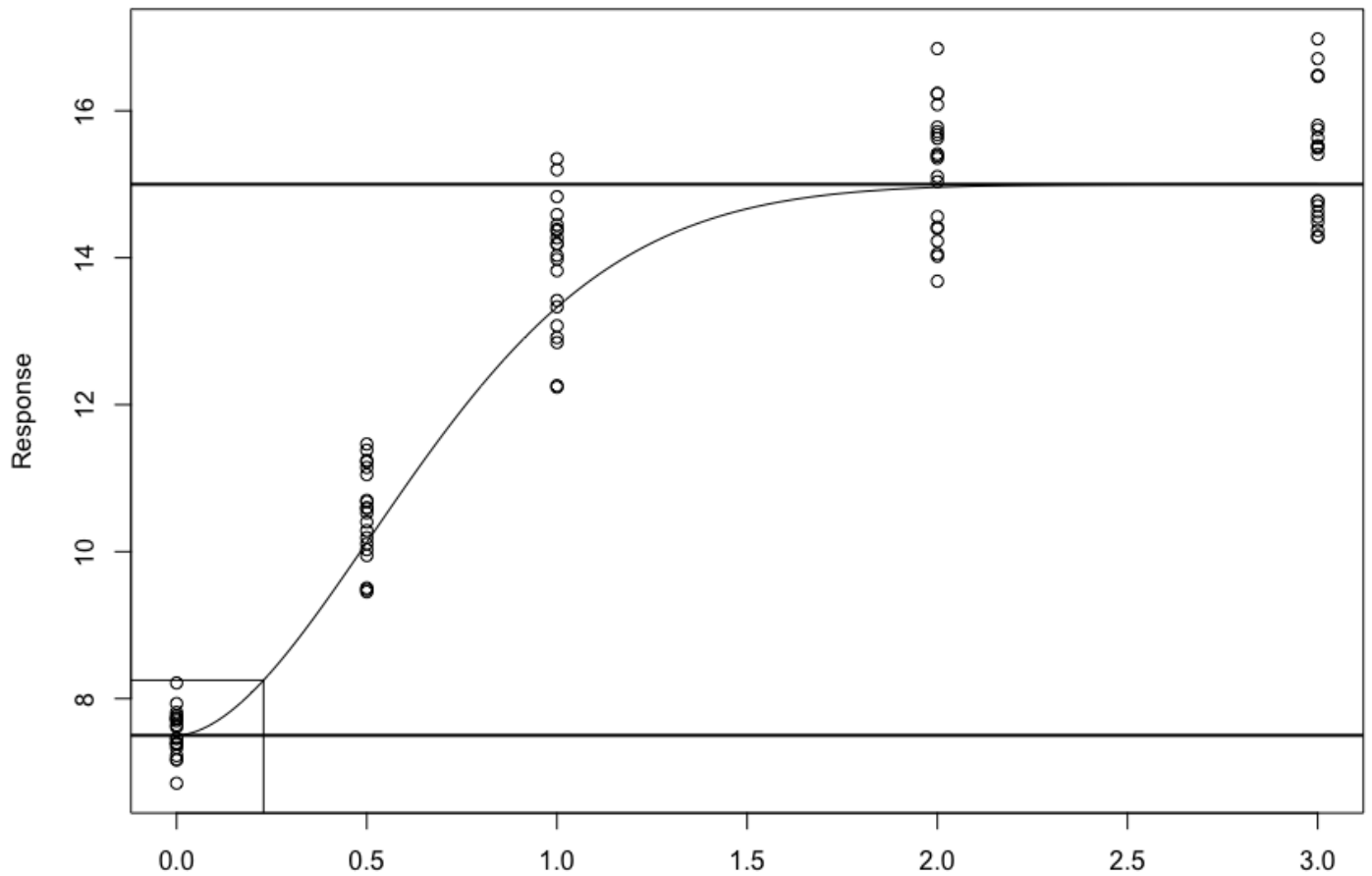
- b and d determine the monotone functional pattern of the model from background to maximum response

Reparameterisation

- **natural** parameters
  - ▷ background response
  - ▷ maximum response
  - ▷ BMD
- **technical** parameters
  - ▷ parameter d
  - ▷ σ for continuous responses

Back to the simulated example based on the exponential model

background $= 7.5$, maximum $= 15$, BMD $= 0.229$ (BMR $= 0.1$), $d = 1.8$

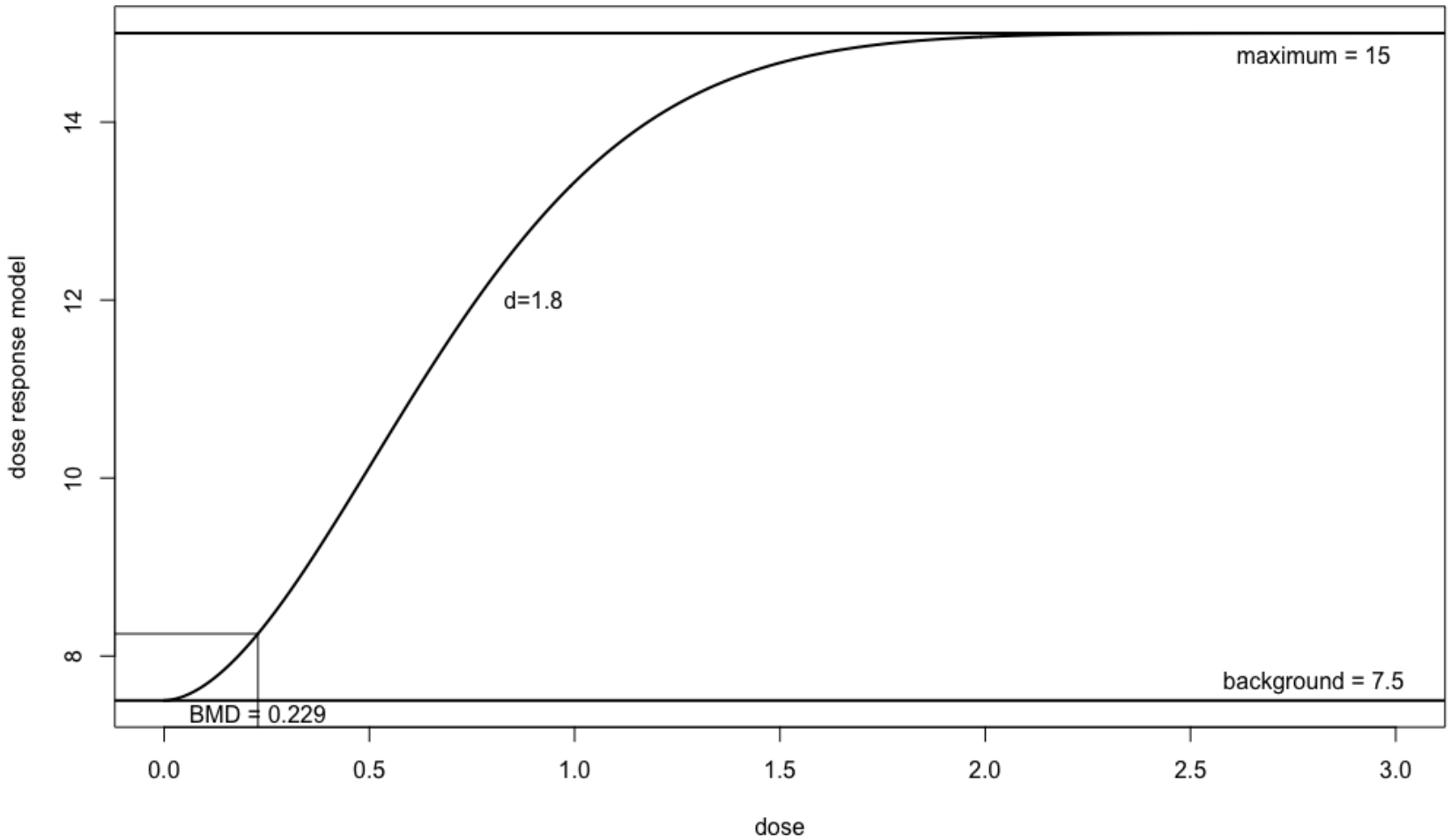


What is the effect of different values for the parameter d

on a particular model?

Dose response models for continuous response

Technical parameter d in the exponential model



Dose response models for continuous response

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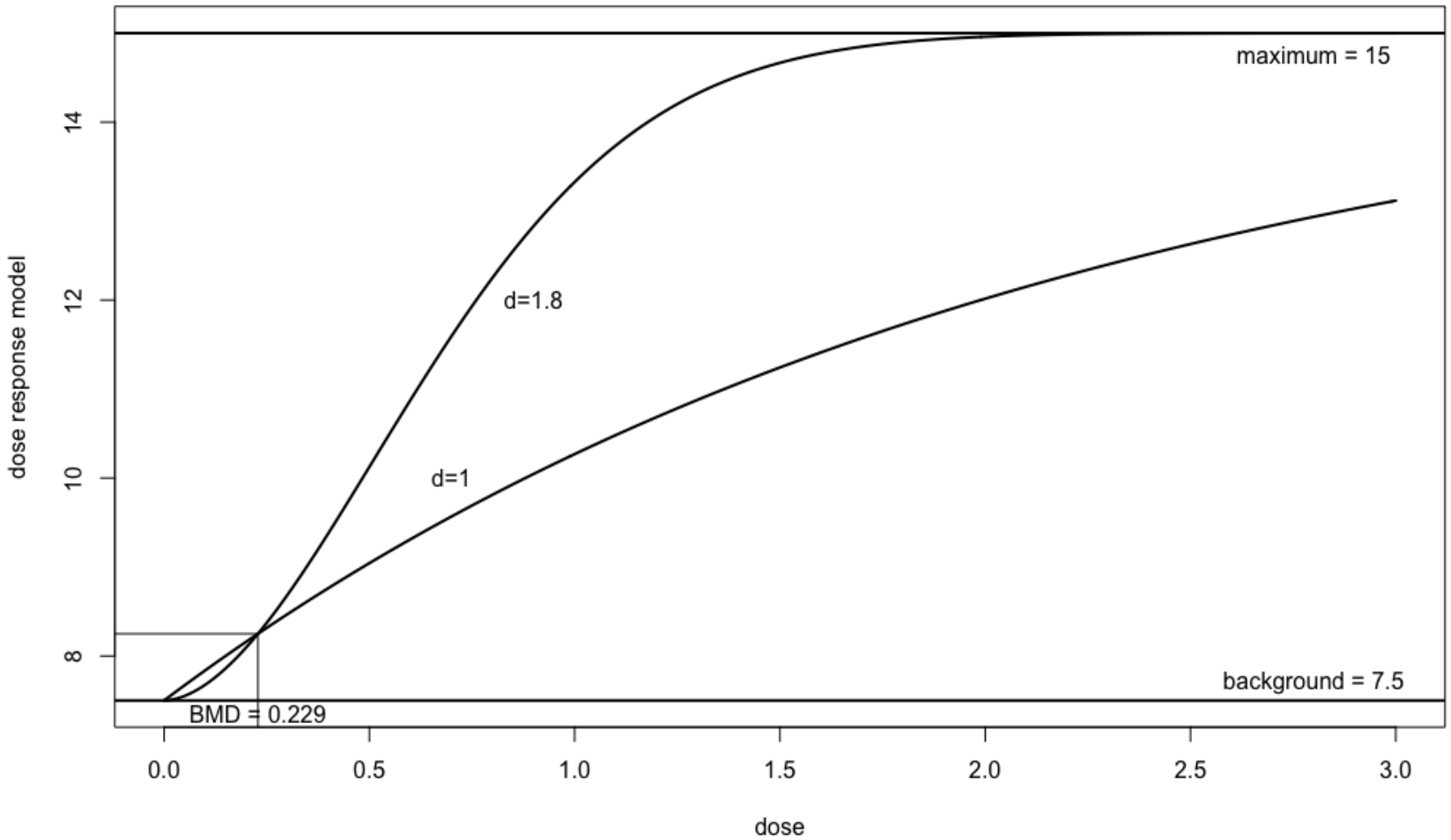
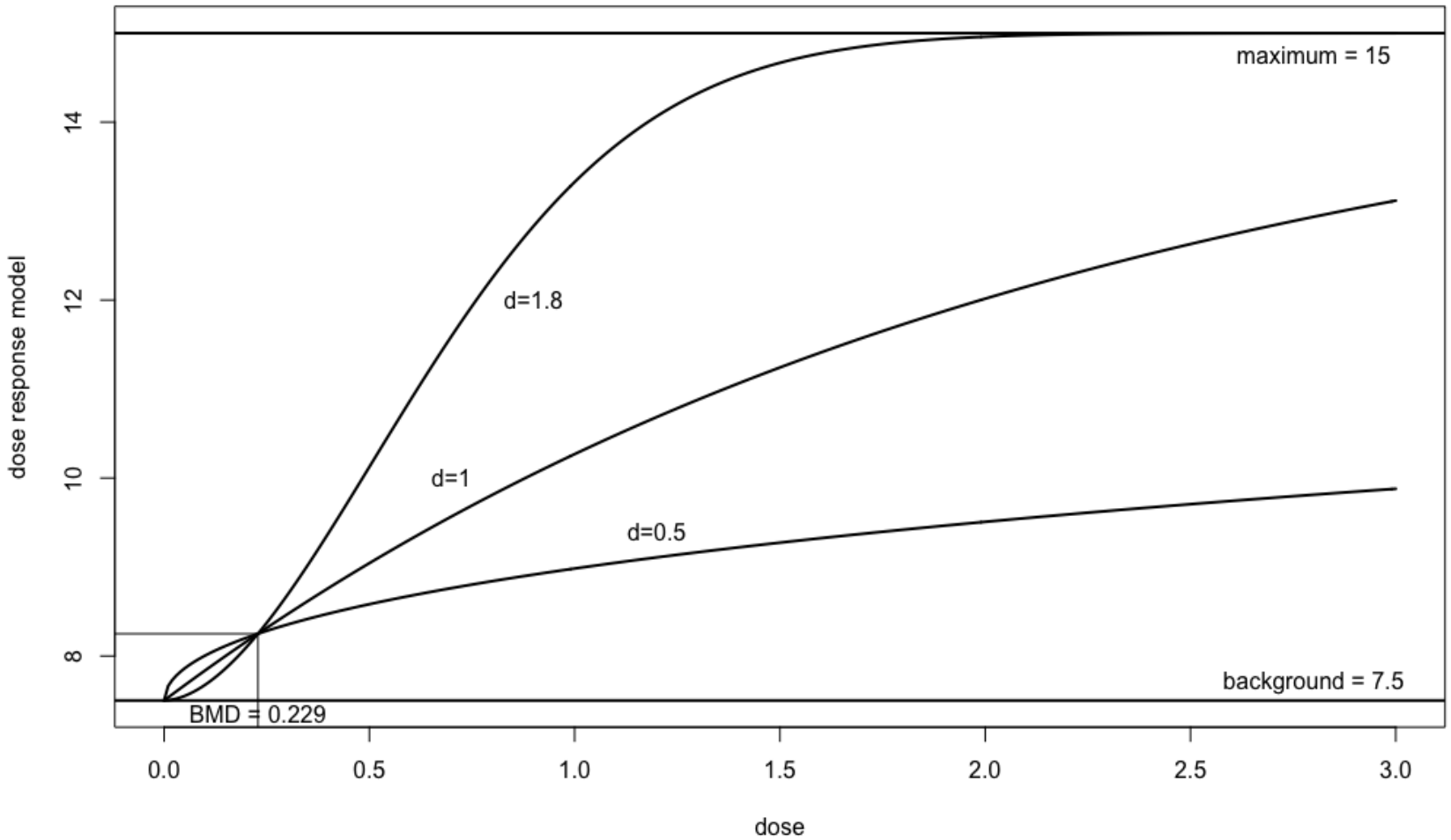


Dose response models for continuous response

Technical parameter d in the exponential model



Dose response models for continuous response

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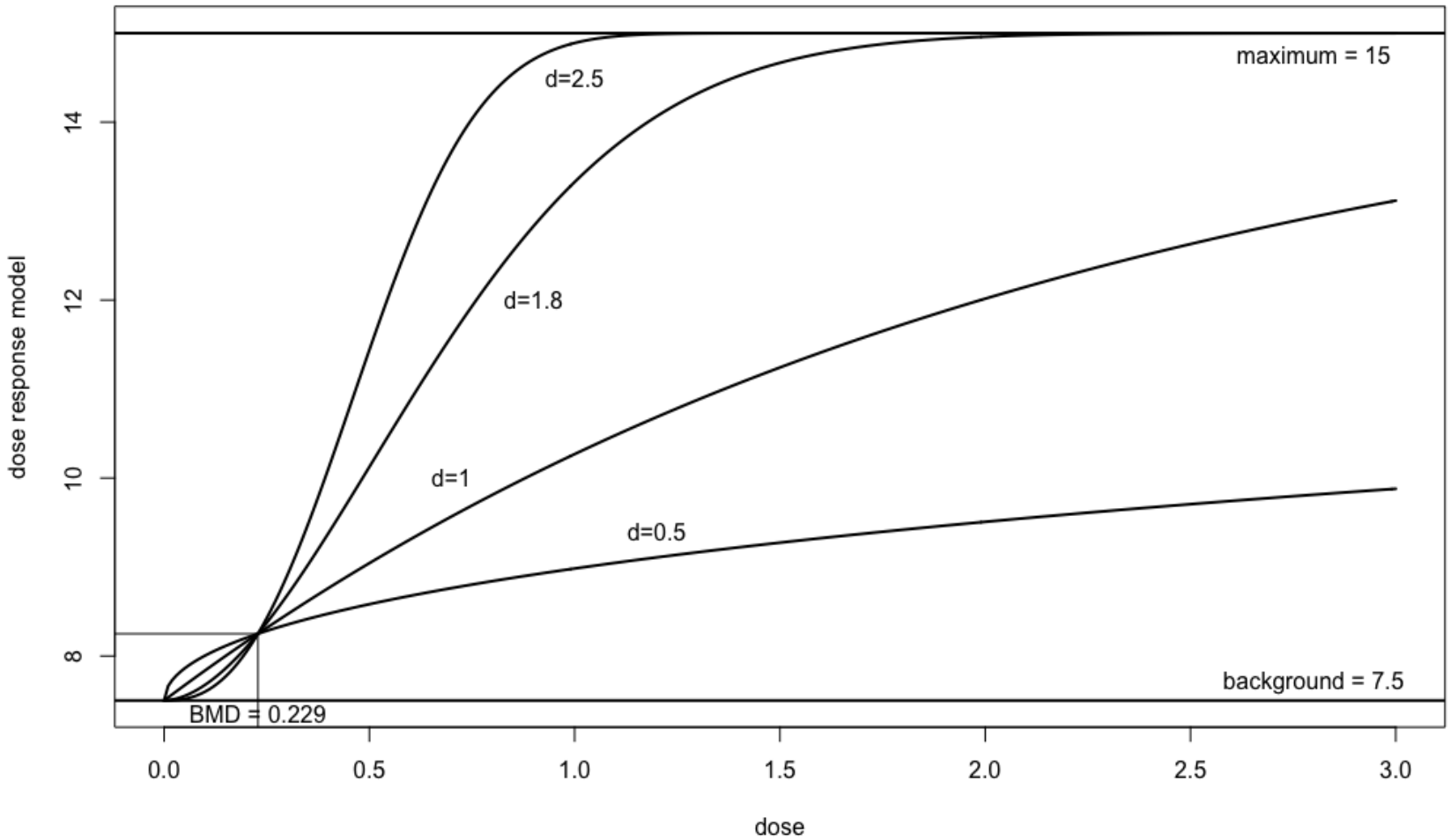

Dose response models for continuous response

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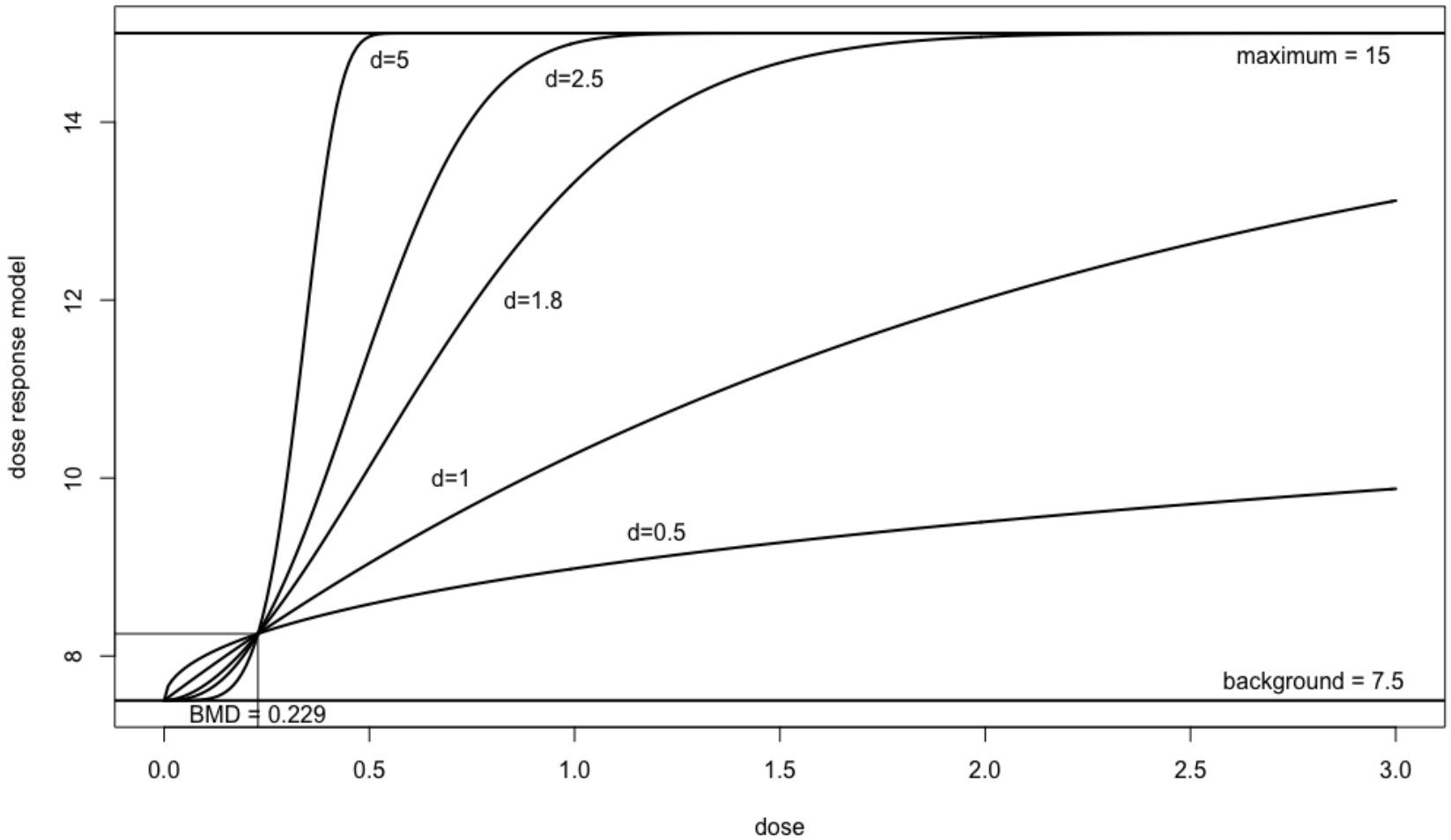
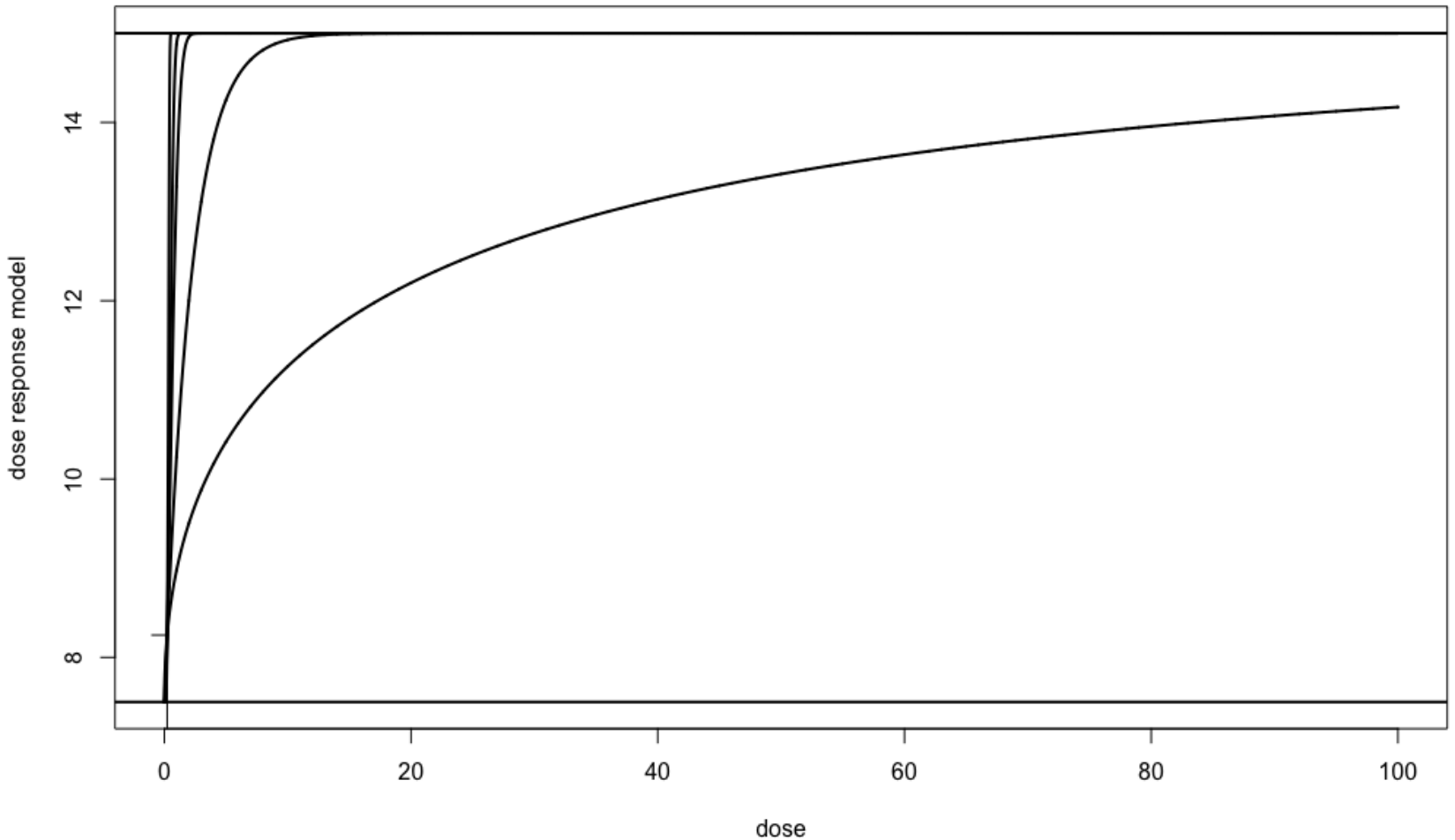


Dose response models for continuous response

Maximum response at very large dose (in limit to infinity)



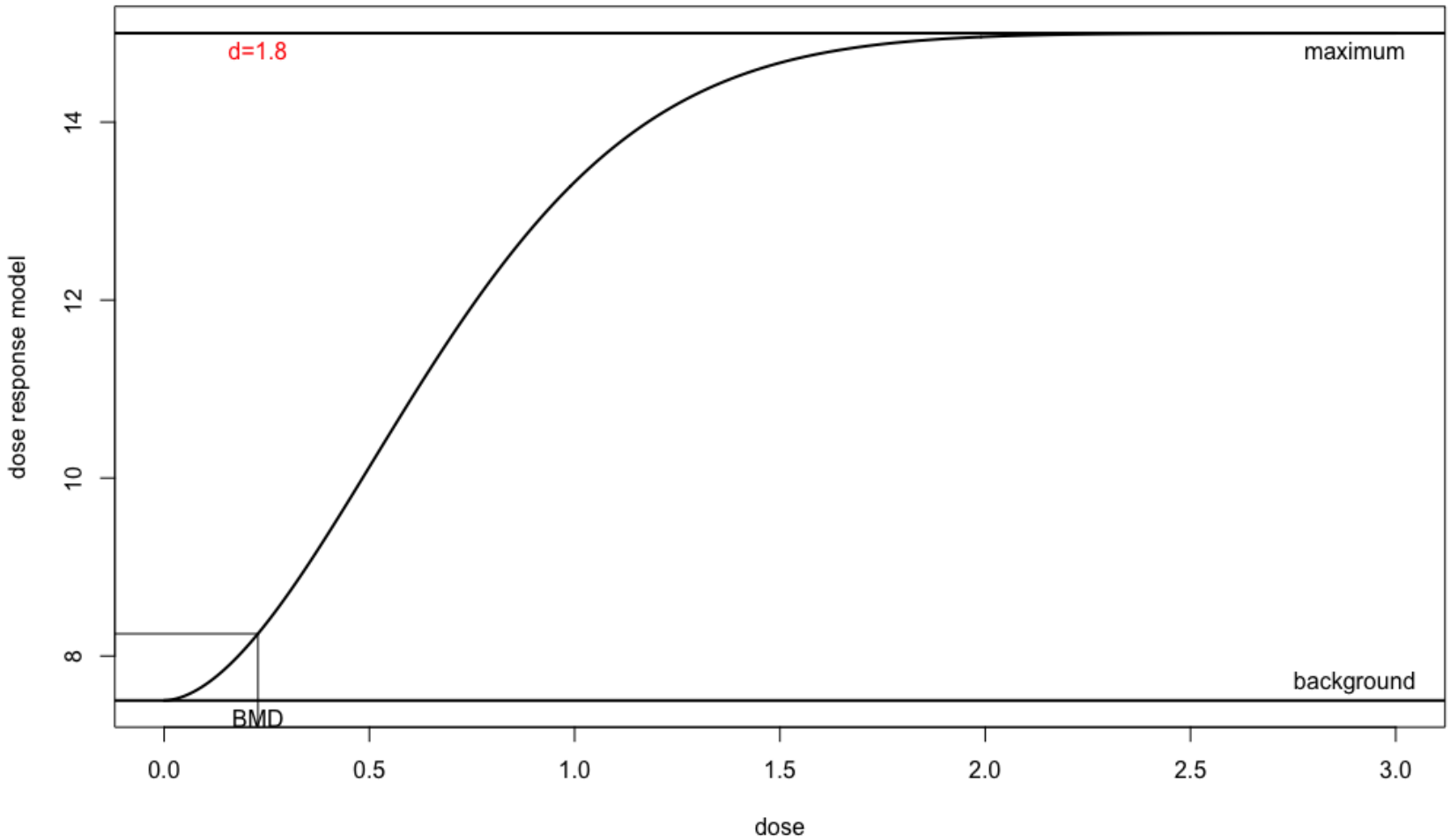
Dose response models for continuous response

How do models differ with all parameters fixed,

including parameter d?

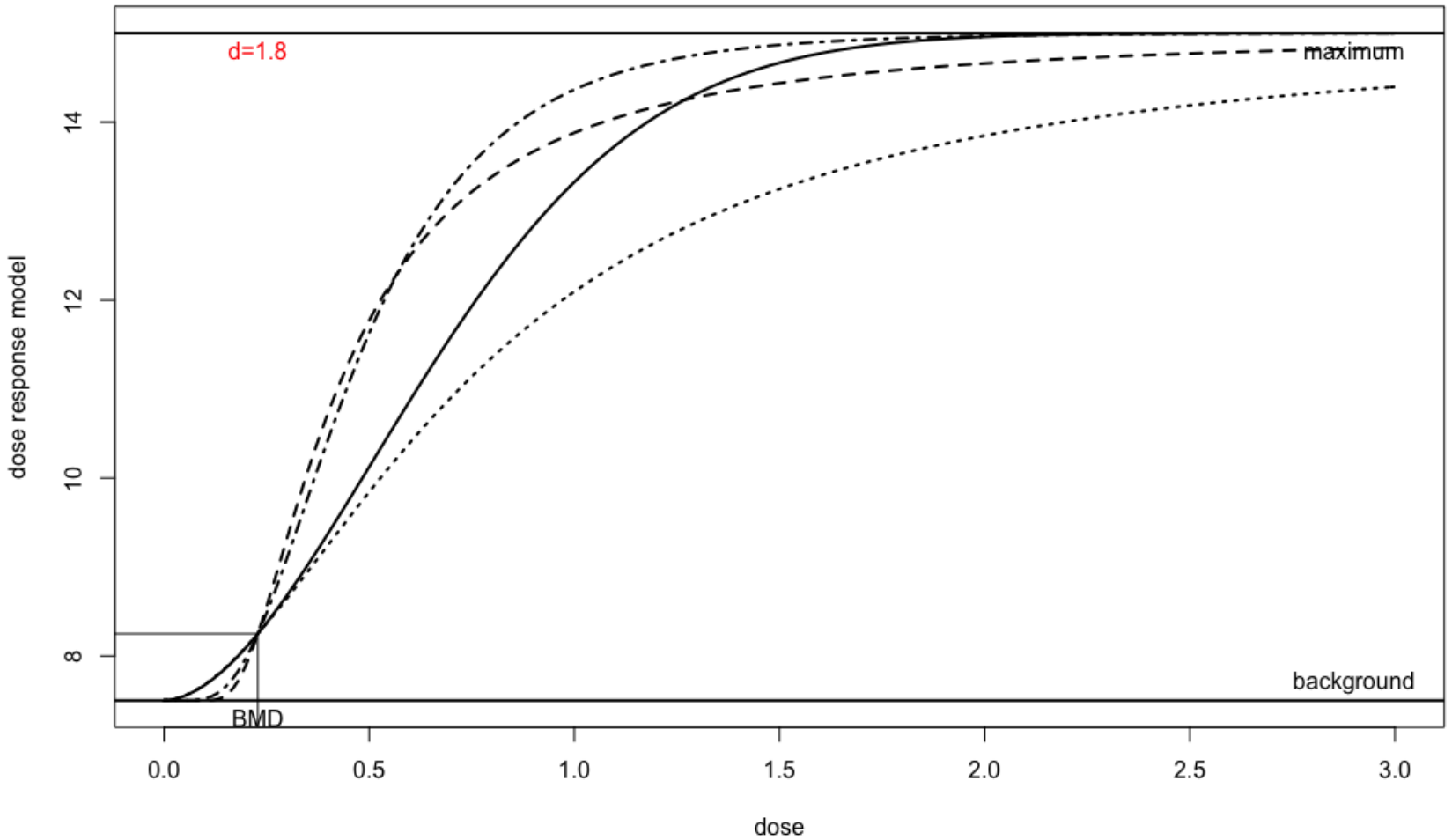
Dose response models for continuous response

Technical parameter $d = 1.8$ in the exponential model



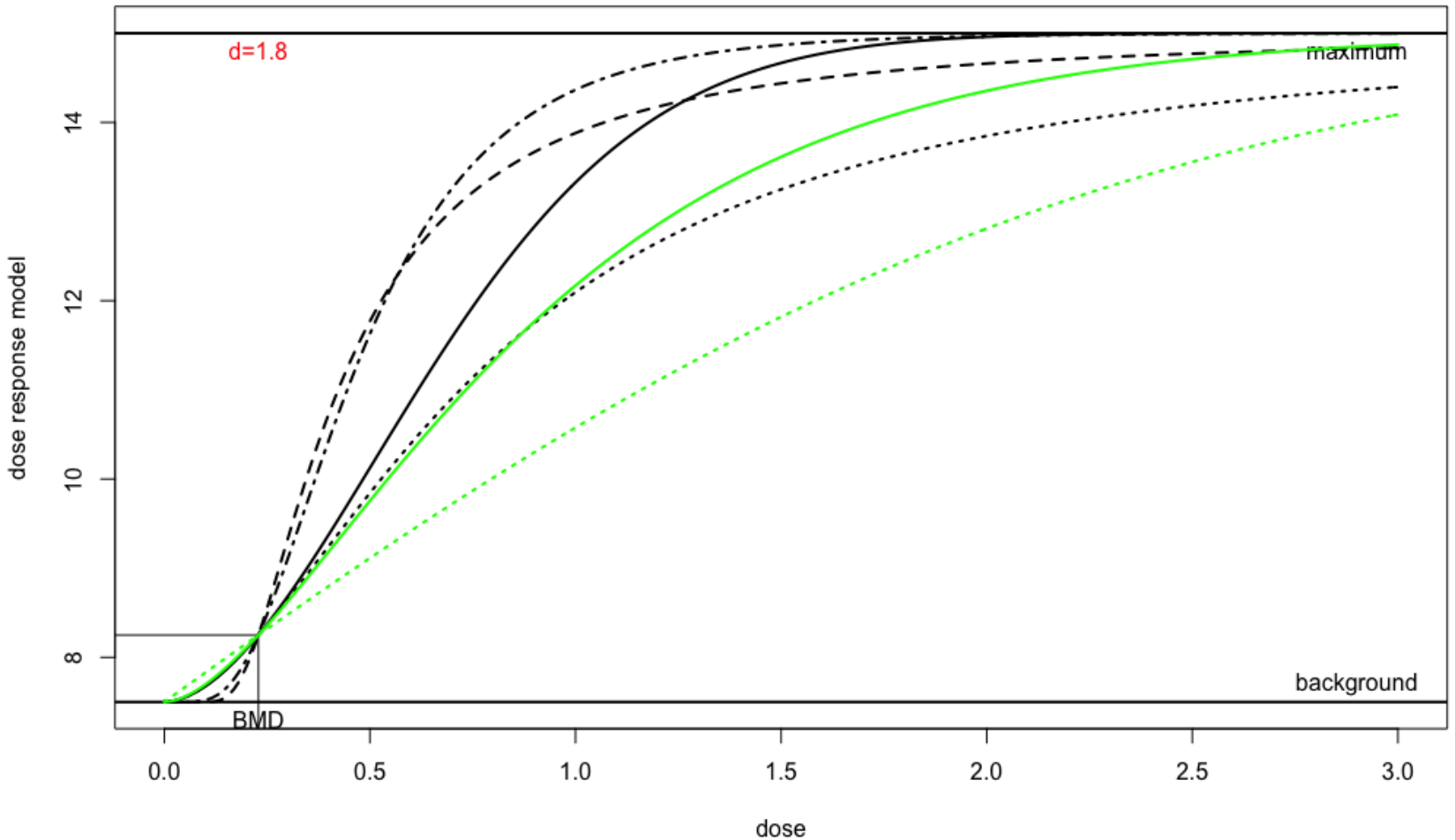
Dose response models for continuous response

Technical parameter $d = 1.8$ fixed for family 1a



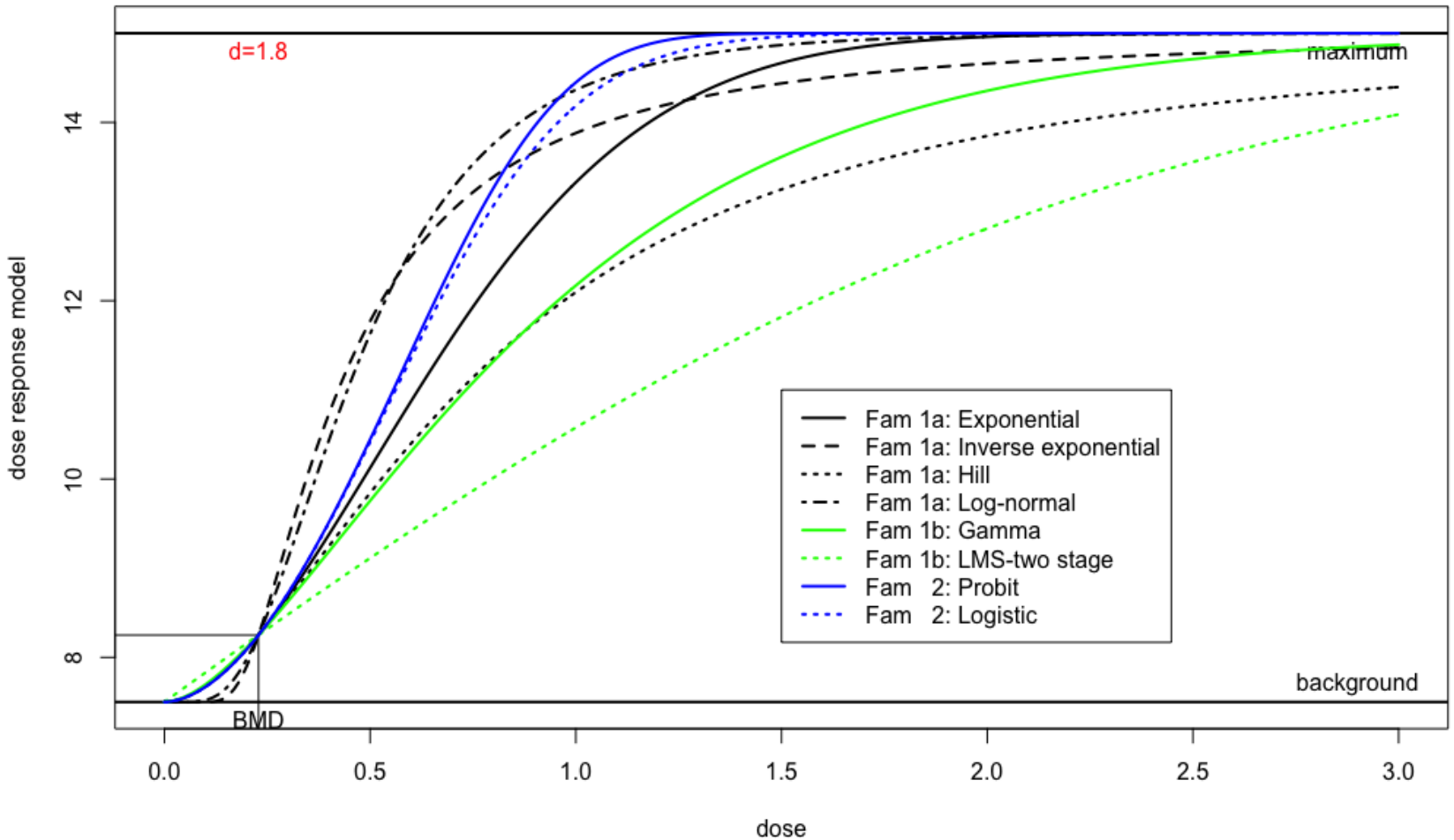
Dose response models for continuous response

Technical parameter $d = 1.8$ fixed for family 1a,b



Dose response models for continuous response

Technical parameter $d = 1.8$ fixed for family 1a,b and 2



Dose response models for quantal response

2 parameters less

- no variance parameter σ
- max response equals 1

Same 8 candidate models

- family 1 (a & b) $\qquad ac = 1 \Rightarrow c = 1/a$

$$a(1+(c-1)F(x;b,d)) = a(1+(\frac{1}{a}-1)F(x;b,d) = a+(1-a)F(x;b,d)$$

Dose response models for quantal response

Table 3: Candidate models for quantal endpoints

Family	**Model**	$\mathbf{y}\|\mathbf{x} \sim \textbf{Bernoulli}(\pi(\mathbf{x}))$ **Dose–response function** $(\mu(x))$
1a	Exponential	$a + (1-a) \cdot \left(1 - e^{-b \cdot x^d}\right)$
	Inverse Exponential	$a + (1-a) \cdot e^{-b \cdot x^{-d}}$
	Hill	$a + (1-a) \cdot \left(1 - \frac{b}{b + x^d}\right)$
	Log-Normal	$a + (1-a) \cdot \Phi(\log(b) + d \cdot \log(x))$
1b	Gamma	$a + (1-a) \cdot \frac{\gamma(d, b \cdot x)}{\Gamma(d)}$
	LMS-two stage	$a + (1-a) \cdot \left(1 - e^{-b \cdot x - d \cdot x^2}\right)$
2	Probit increasing	$\Phi\left(a + b \cdot x^d\right)$
	Logistic increasing	$\frac{e^{a+b \cdot x^d}}{1+e^{a+b \cdot x^d}}$

Questions ?

Outline

- Main statistical methodology
  - ▷ Components of the models
  - ▷ Bayesian inference
  - ▷ Model averaging
- Preliminary statistical tests
- Some further illustrations
- Summary simulation study

Bayesian inference

- extension of maximum likelihood (ML) inference
- parameters get distributions as well
- prior distribution $\xrightarrow{data}$ posterior distribution

Thyroid epithelial cell vacuolisation data

- 2-year study in rats
- 3 doses of a substance
- changes in thyroid epithelial cell vacuolisation
- in 2017 and 2022 guidance

Dose (mg/kg day)	No of animals with thyroid epithelial vacuolisation	No of animals in dose group
0	6	50
3	6	50
12	34	50
30	42	50

Thyroid epithelial cell vacuolisation data

Dose (mg/kg day)	No of animals with thyroid epithelial vacuolisation	No of animals in dose group
0	6	50
3	6	50
12	34	50
30	42	50

Consider the estimation of the **proportion** $\pi(0)$ **for control group**

- data: 6 out of 50
- frequency estimator

$$\hat{\pi}(0) = \frac{6}{50} = 0.12$$

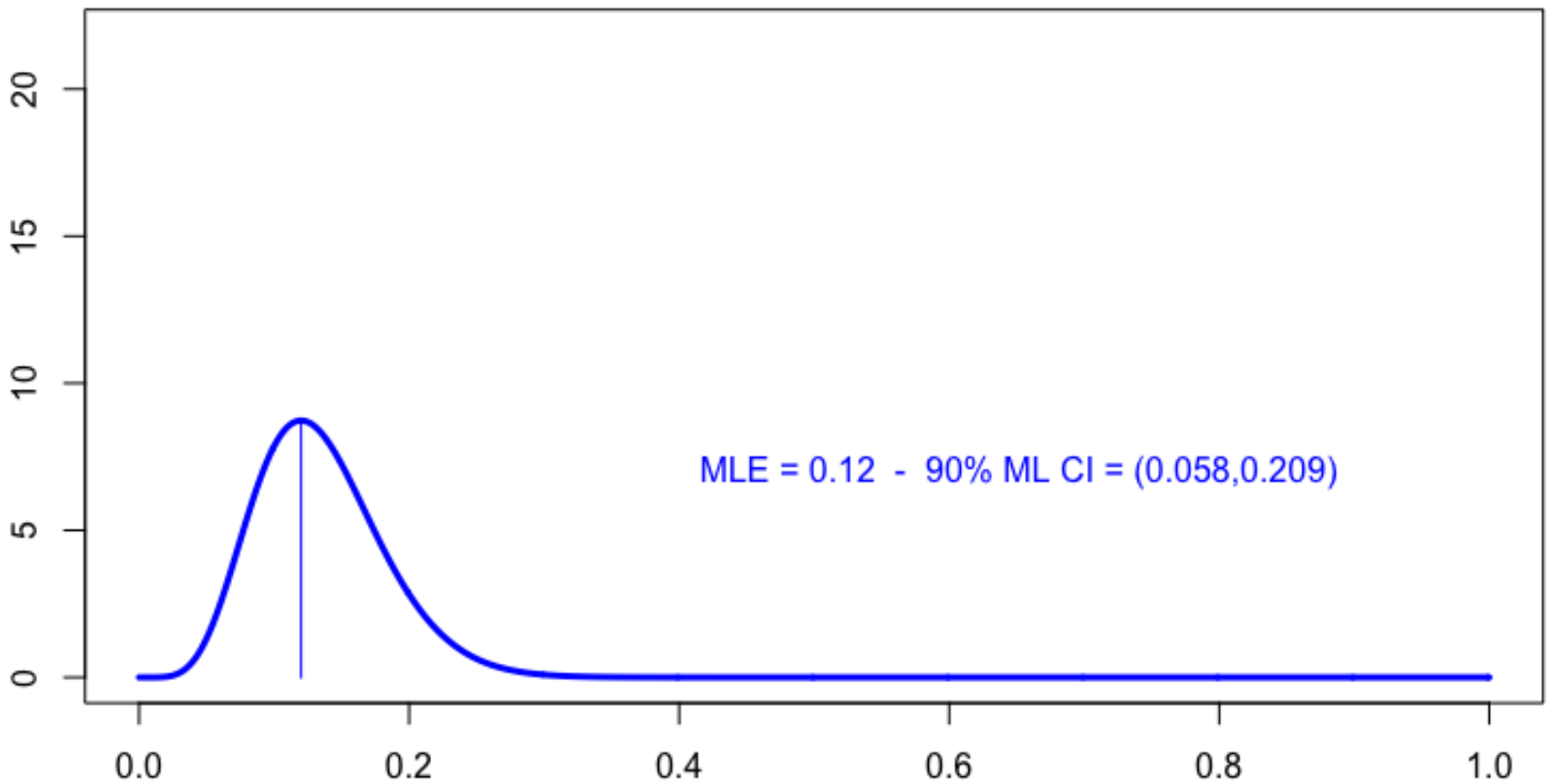
- ? maximum likelihood estimate (MLE)

Thyroid epithelial cell vacuolisation data

MLE for proportion at control level

- likelihood expresses the plausibility of the observed data as a function of proportion $\pi(0)$
- the ML estimate maximizes this plausibility or likelihood
- the likelihood function is determined by the distribution for the response
- all evidence, obtained from an experiment, about an unknown quantity is contained in the likelihood function
- for quantal data: the binomial distribution

Thyroid epithelial cell vacuolisation data



Central formula

$$P(B|A) = \frac{P(A|B)P(B)}{P(A)}$$

or

$$f(\text{parameters}|\text{data}) = \frac{f(\text{data}|\text{parameters})f(\text{parameters})}{f(\text{data})}$$

or

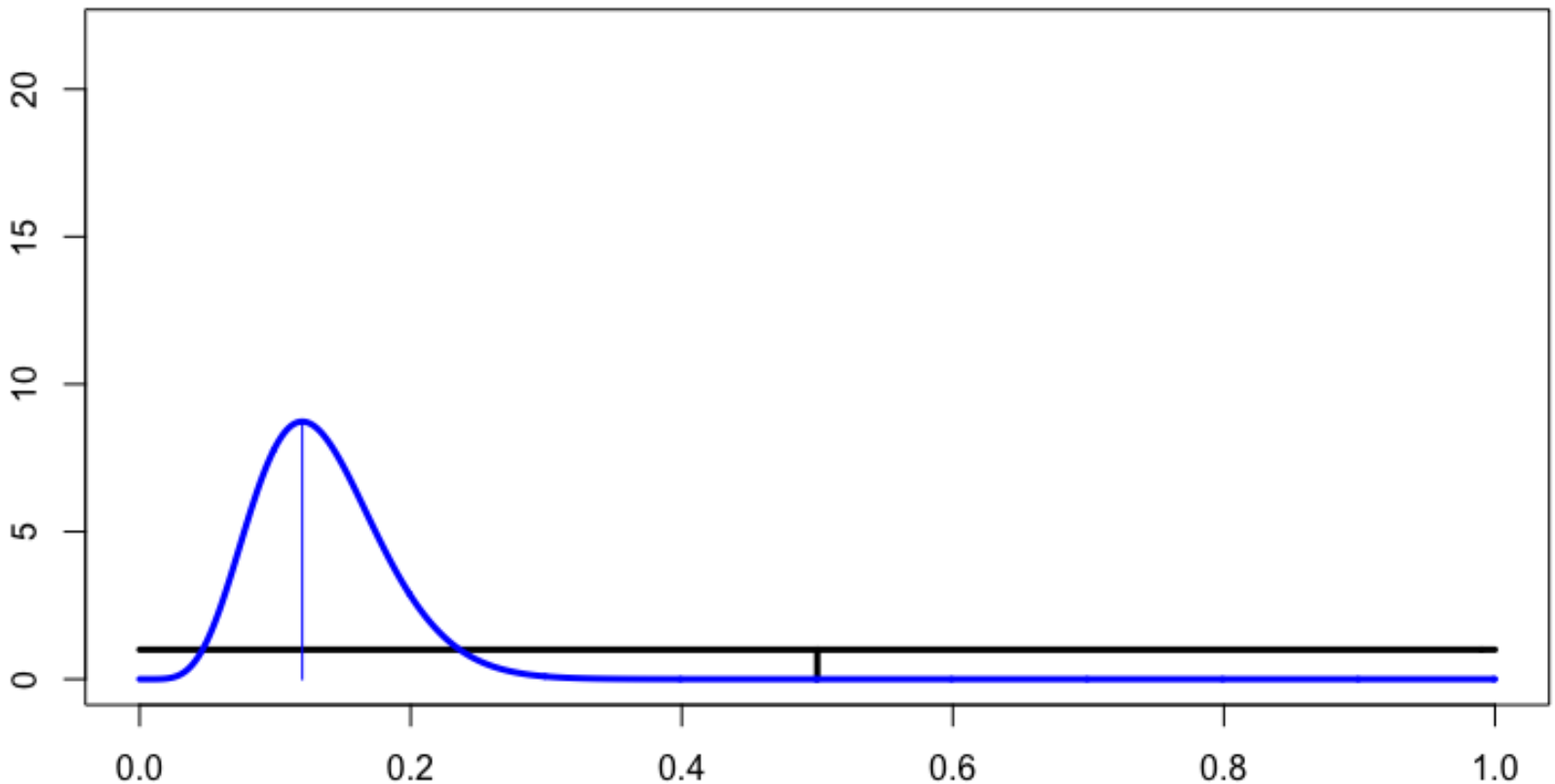
$$\text{posterior distribution} \propto \text{likelihood} \times \text{prior distribution}$$

or

$$\text{prior distribution} \xrightarrow{\text{data}} \text{posterior distribution}$$

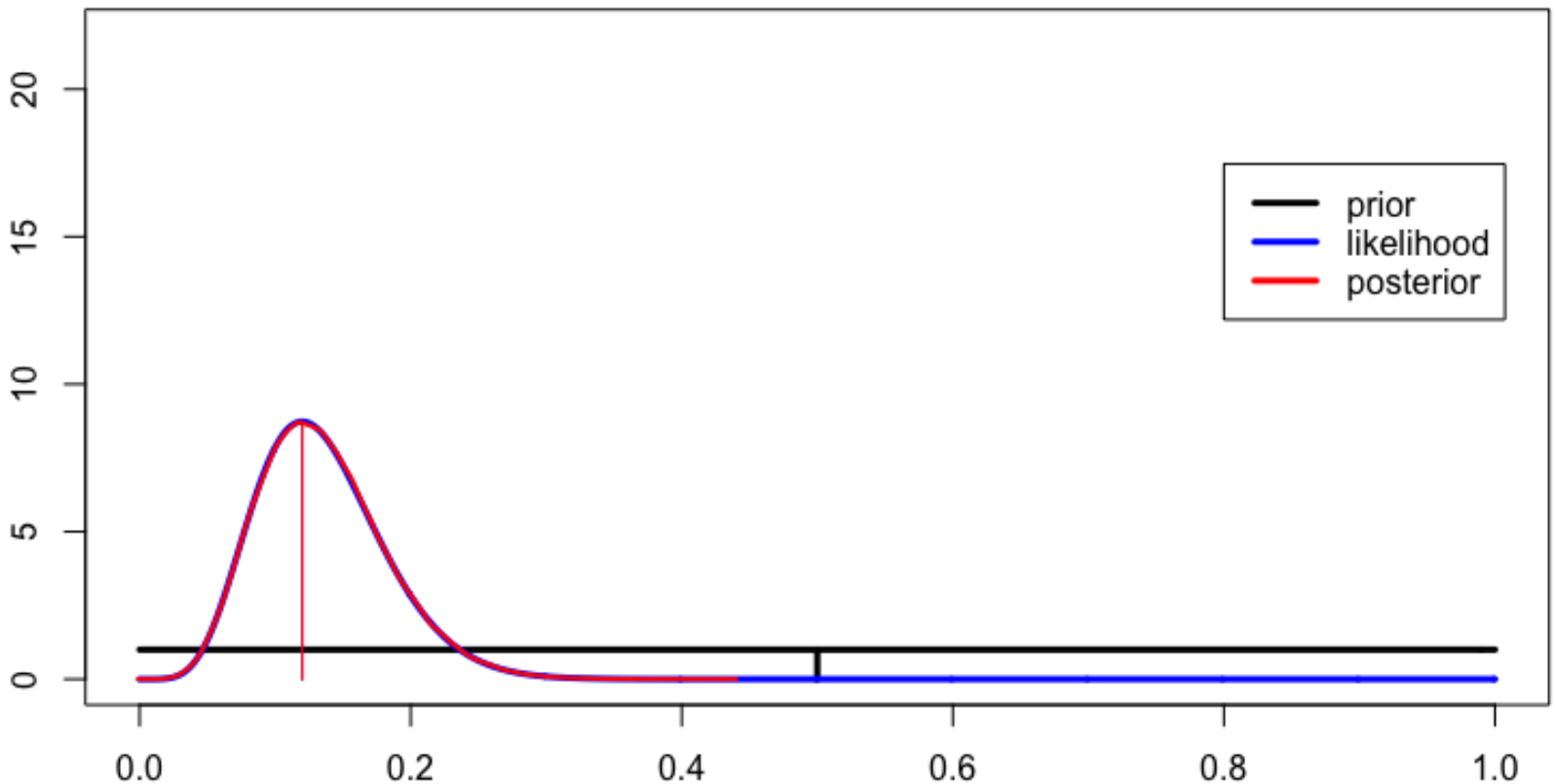
Thyroid epithelial cell vacuolisation data

uninformative U(0,1) prior for $\pi(0)$



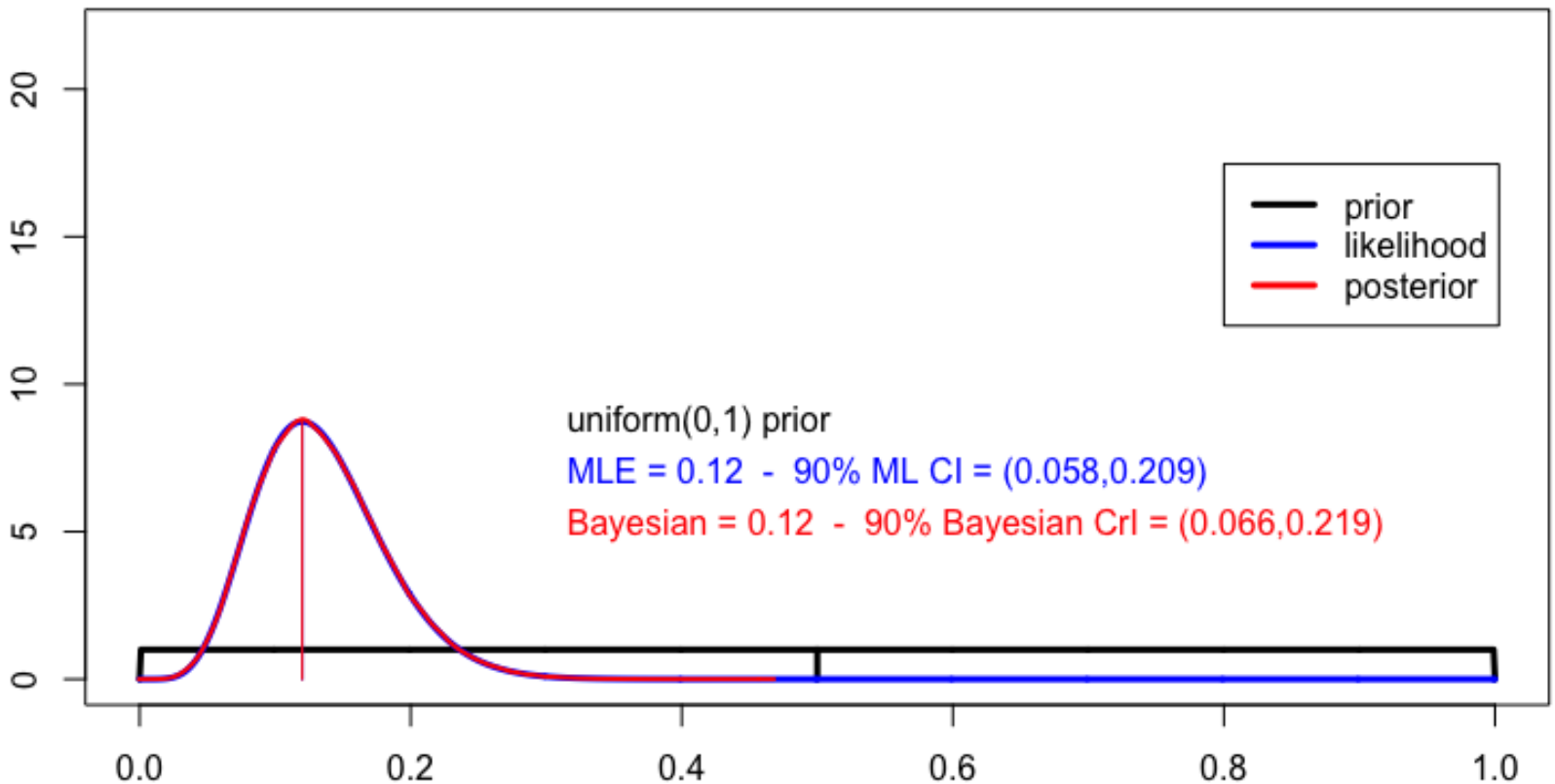
Thyroid epithelial cell vacuolisation data

uninformative U(0,1) prior for $\pi(0)$



Thyroid epithelial cell vacuolisation data

uninformative U(0,1) prior for $\pi(0)$



Central formula

$$\text{posterior distribution} \quad \propto \quad \text{likelihood} \times \text{prior distribution}$$

so

frequentist estimation

$$\cong \text{Bayesian estimation with uninformative prior}$$

and

$$\xrightarrow{\text{other info}} \text{prior distribution} \xrightarrow{\text{current data}} \text{posterior distribution}$$

Prior distribution

Use of **informative prior**

- determined before analysis
- informed decision to use (or not) prior information
- sensitivity analysis
- construction of informative prior based on
  - ▷ literature, e.g. reported estimates, confidence intervals
  - ▷ expert opinion
  - ▷ historical data

Informative prior distribution

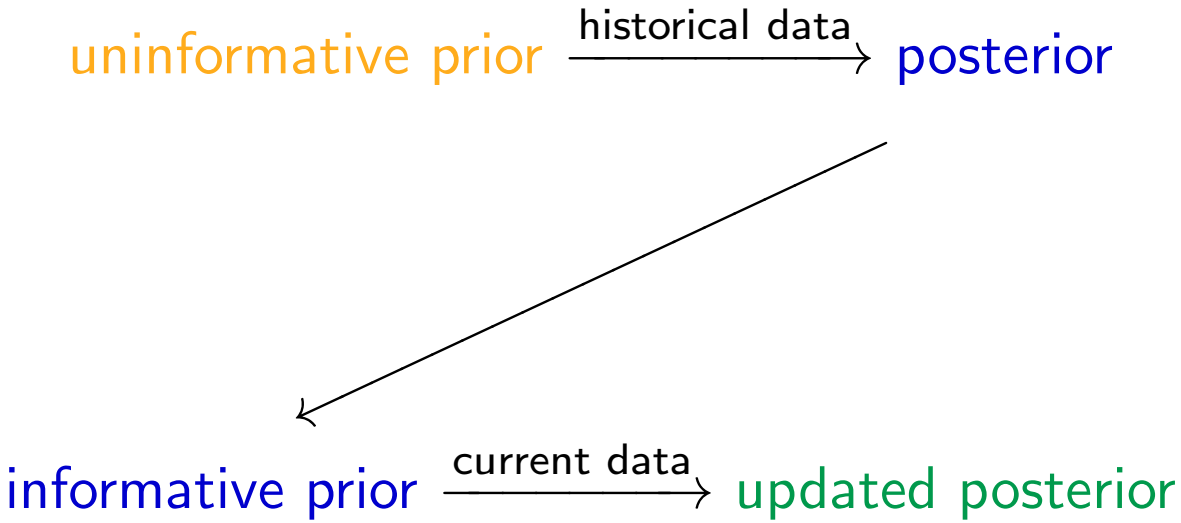
Information from **historical data** about $\pi(0)$

- 10 adverse events, out of 100
- similar experimental conditions

How to use these historical data?

Informative prior distribution

How to use these historical data?



How to construct the informative prior from posterior?

Informative prior distribution

Posterior distribution from historical data and uninformative prior

- point estimate 0.1: 10 out of 100 adverse events
- 99% Bayesian CrI: [0.044, 0.200]

Construction of informative prior using PERT distribution with

- ▷ mode =0.1
- ▷ min = 0.044, max = 0.200
- ▷ shape ?

PERT distribution

- widely used in risk analysis
- defined by the minimum, most likely and maximum value, and shape

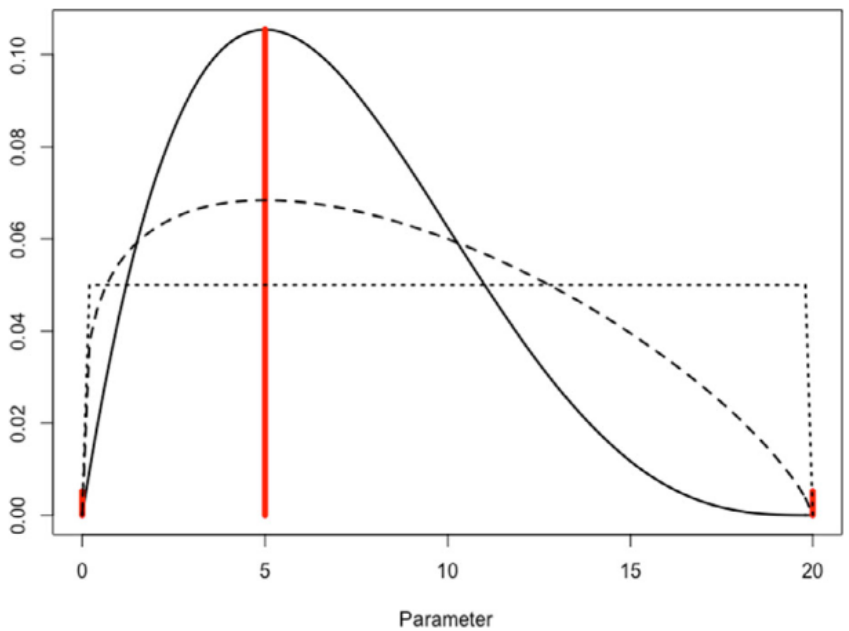
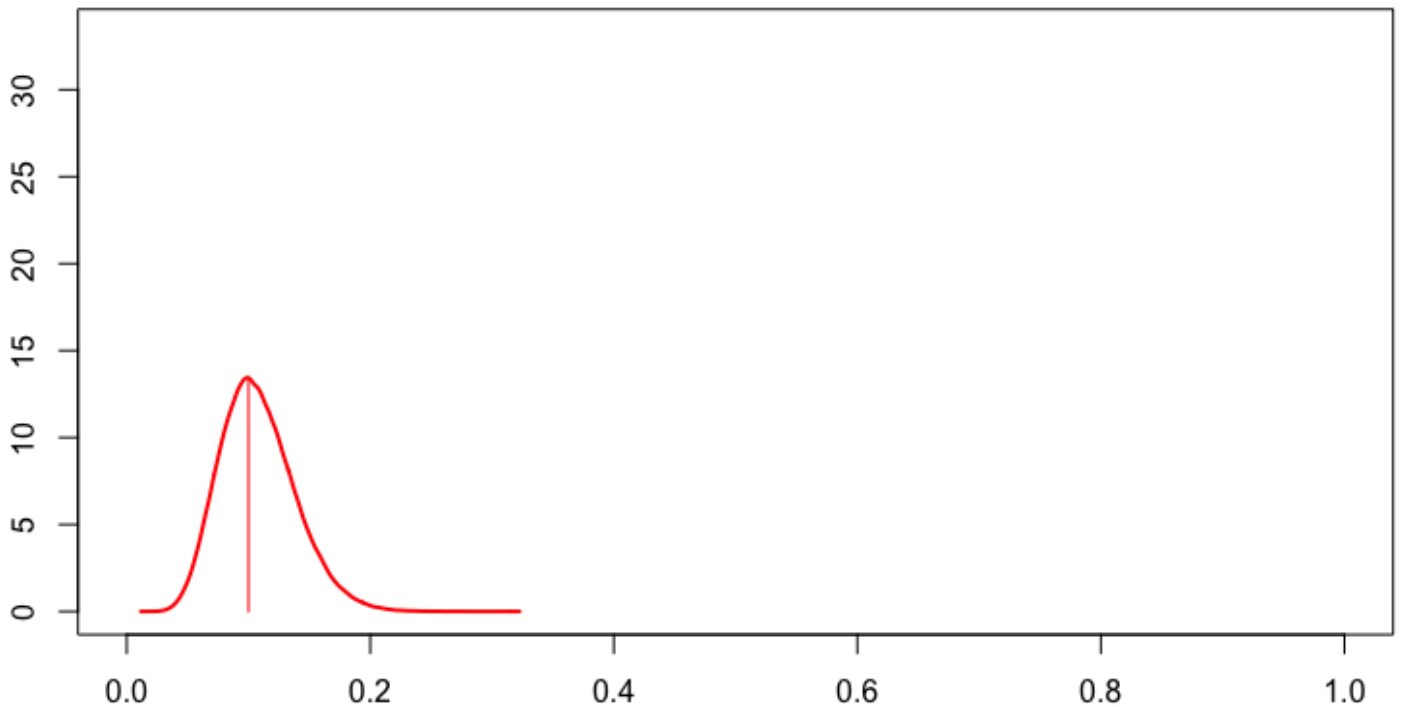


Figure 4: PERT densities with minimum = 0, mode = 5, maximum = 20 (vertical red lines) and shape.Varying from 0 (dotted line), 1 (dashed line) to 4 (solid line)

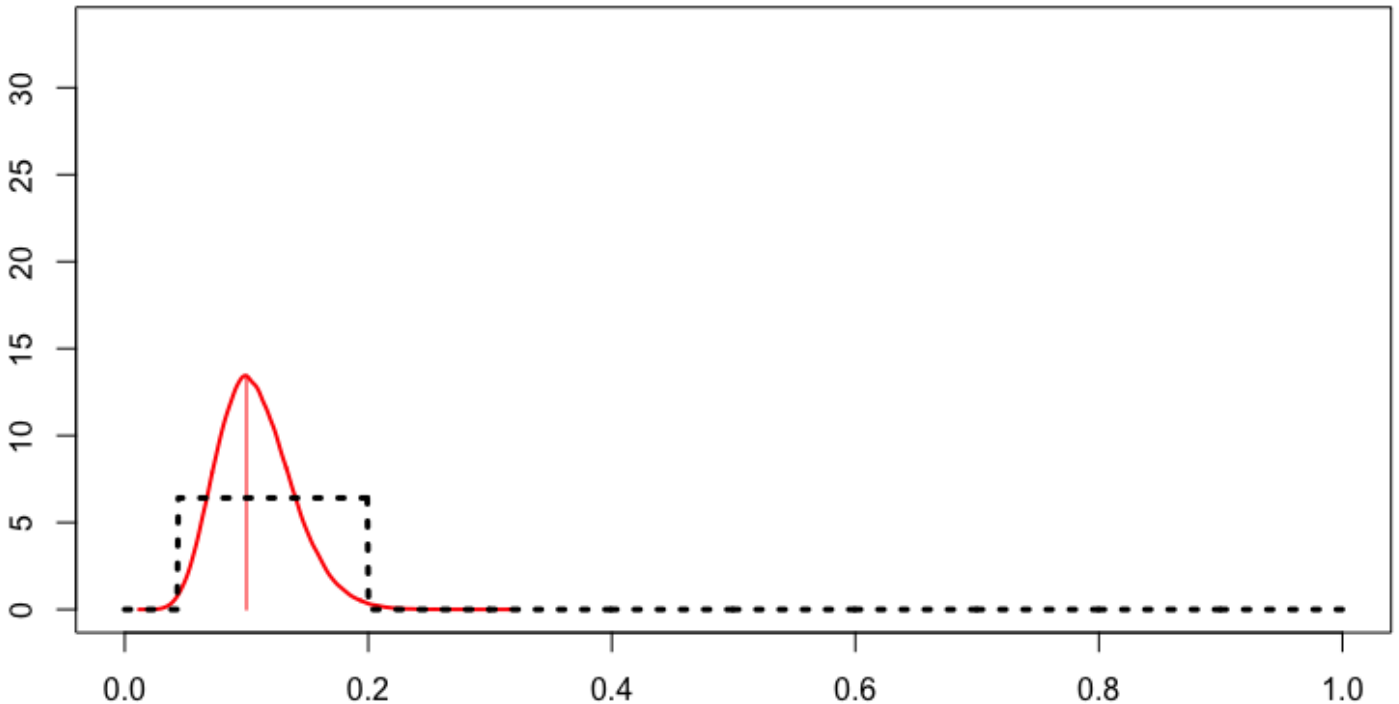
Construction of informative prior using PERT

Posterior distribution: 99% Bayesian CrI: [0.044, 0.200] around 0.1



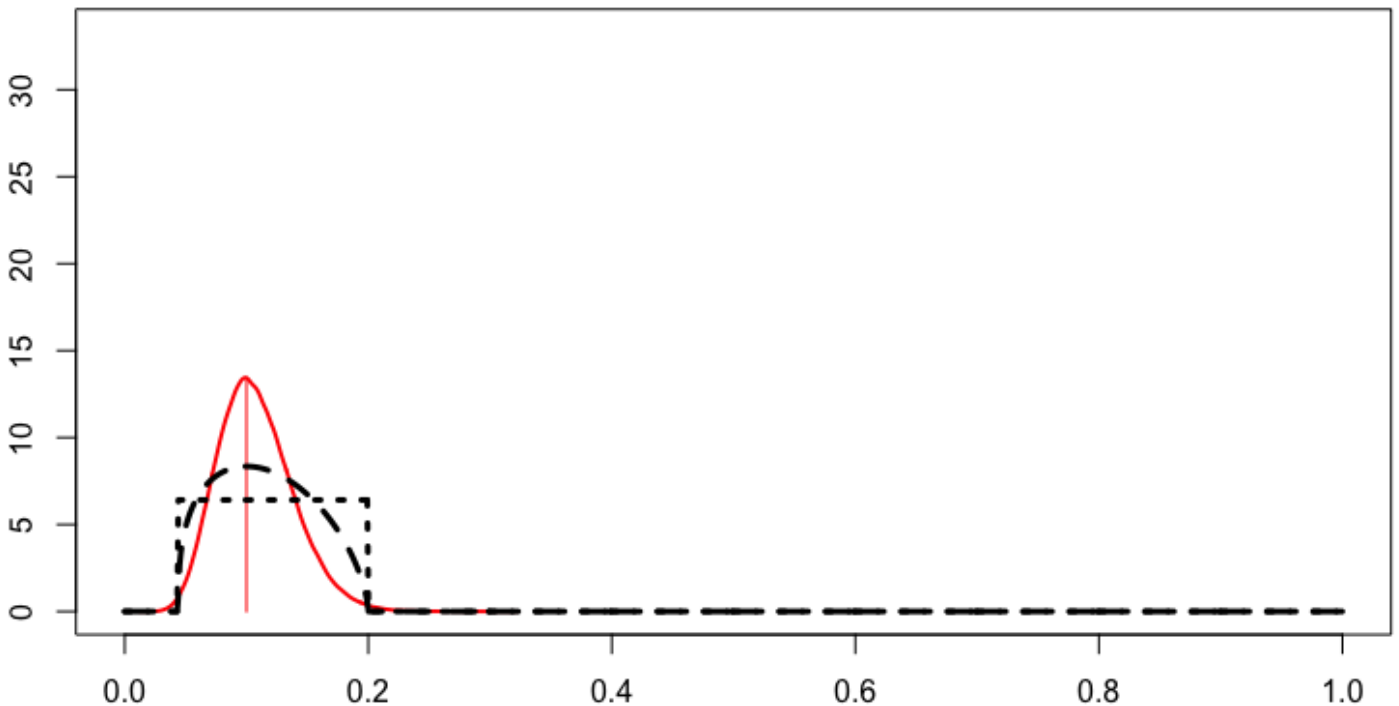
Construction of informative prior using PERT

PERT with mode =0.1, min = 0.044, max = 0.2, shape = 0



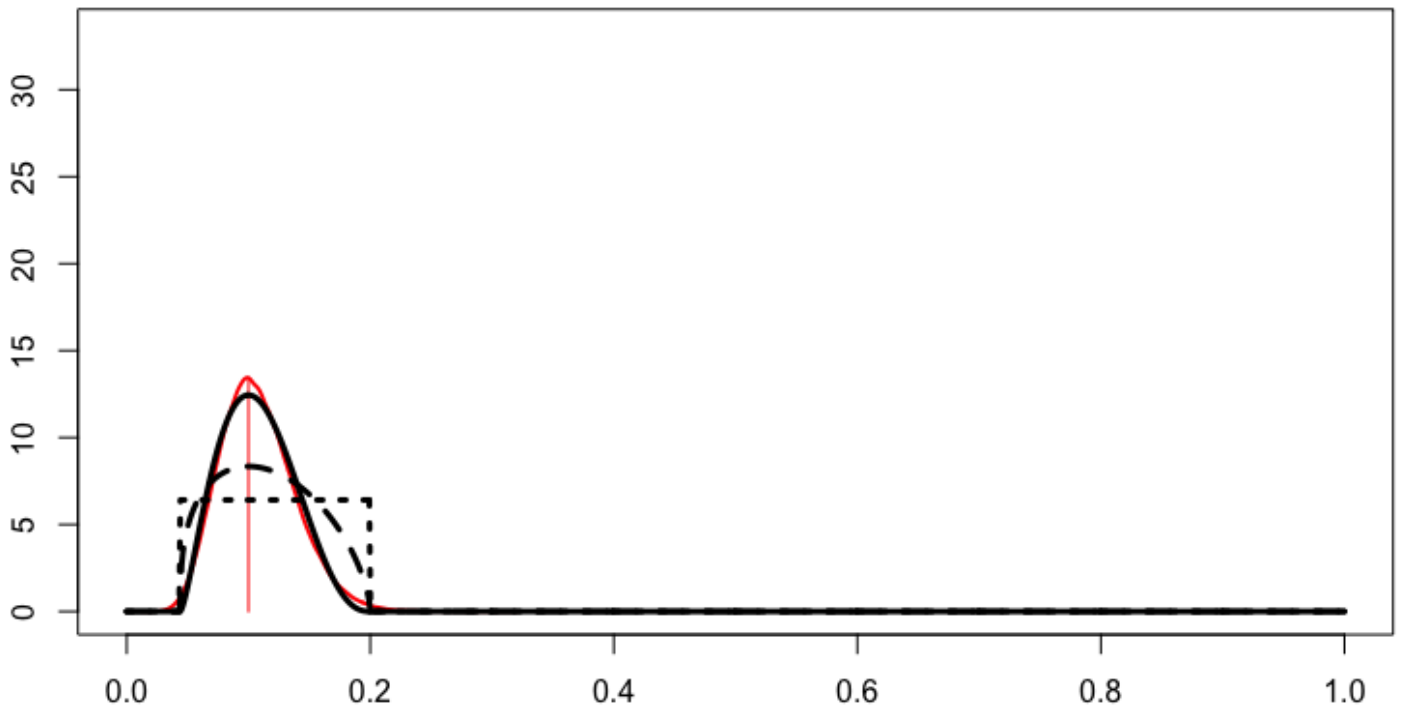
Construction of informative prior using PERT

PERT with mode =0.1, min = 0.044, max = 0.2, shape = 1



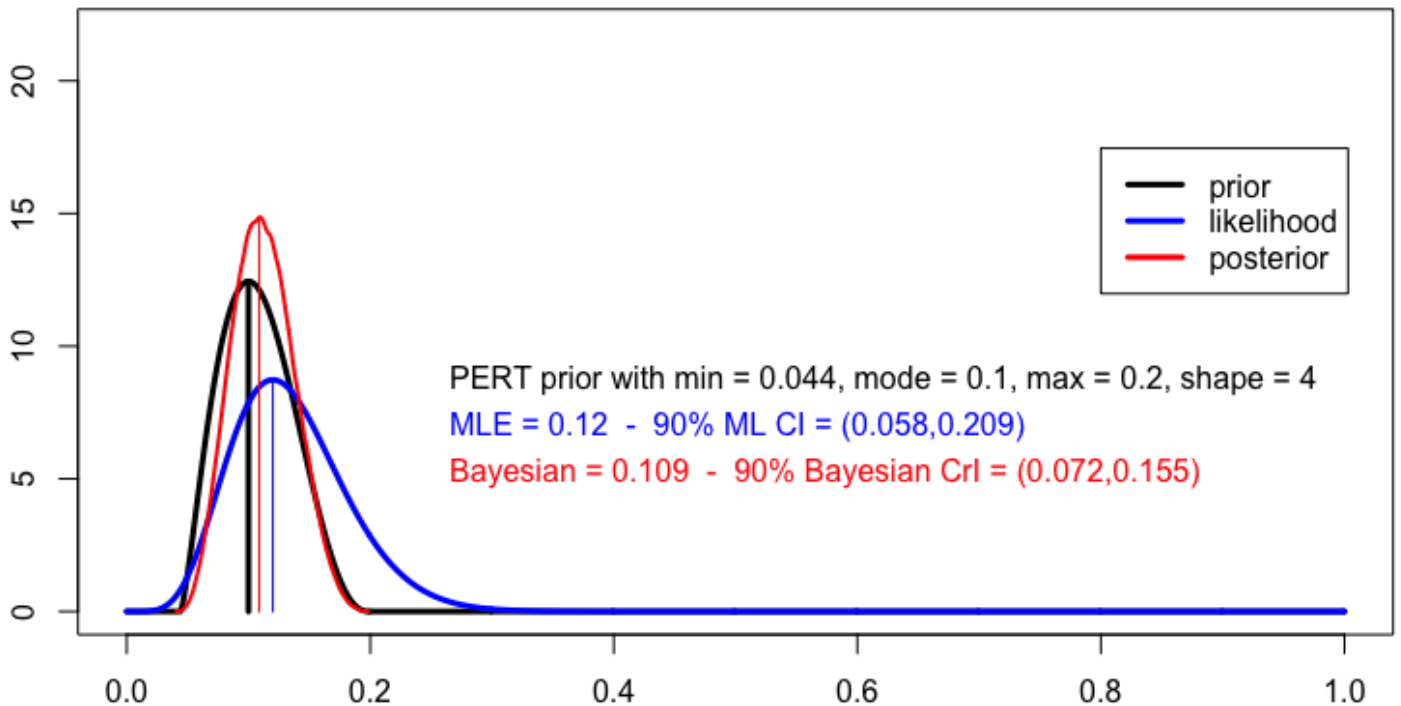
Construction of informative prior using PERT

PERT with mode =0.1, min = 0.044, max = 0.2, shape = 4



Informative prior distribution

Analysis with informative prior using PERT with shape = 4

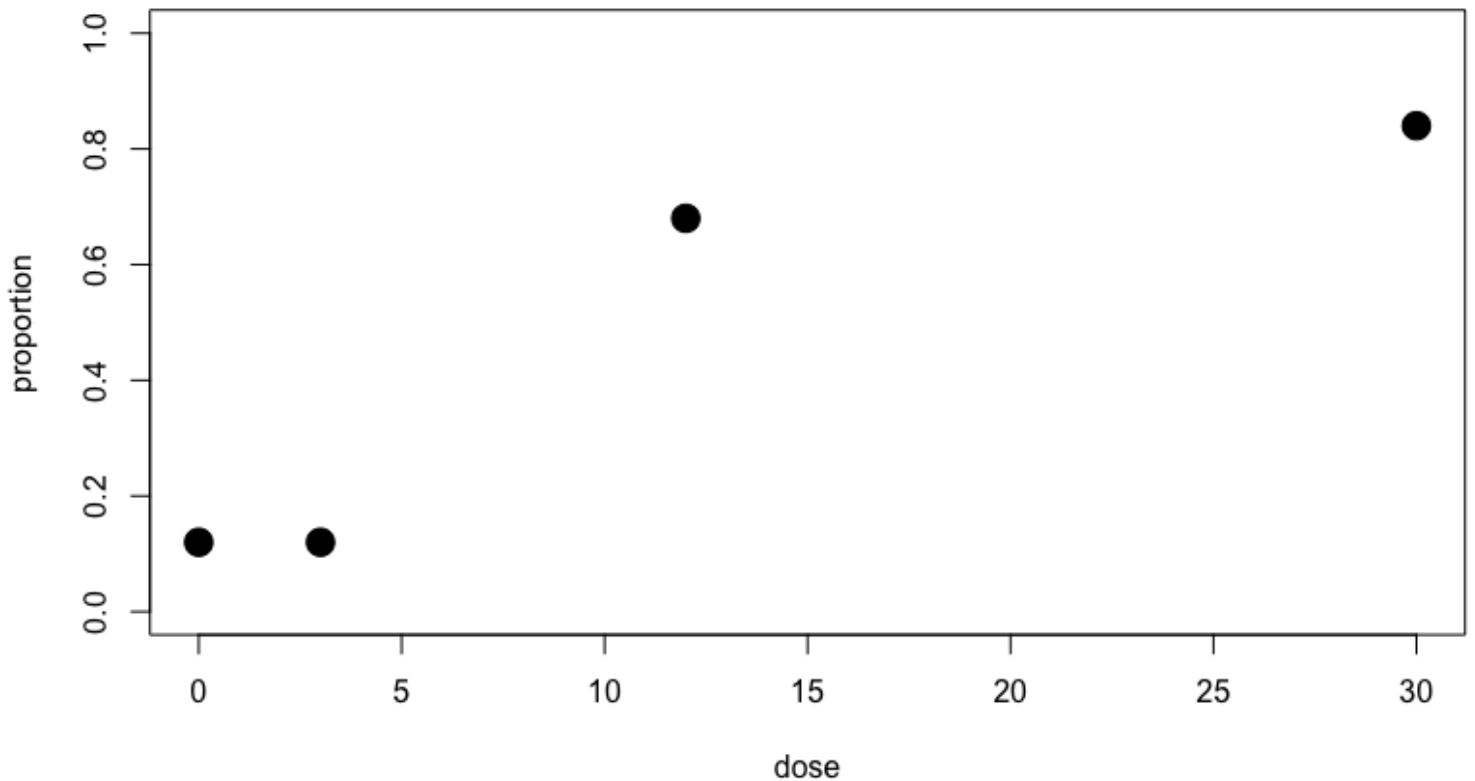


Sensitivity analysis

prior	$\hat{\pi}(0)$	CrIL	CrIU	CrIU/CrIL
uninformative	0.120	0.066	0.219	3.31
PERT shape=0	0.120	0.067	0.187	2.80
PERT shape=1	0.115	0.068	0.174	2.55
PERT shape=4	0.109	0.072	0.155	2.16

Thyroid epithelial cell vacuolisation data revisited

Dose (mg/kg day)	No of animals with thyroid epithelial vacuolisation	No of animals in dose group
0	6	50
3	6	50
12	34	50
30	42	50



Construction of priors

- a challenge in non-linear models
- PERT prior on natural parameters, based on
  - ▷ insights from simulations
  - ▷ practical considerations

  and normal priors on transformed technical parameters d and σ^2

Prior distributions on model parameters

Default priors for natural parameters

C,Q BMD: uniform (=PERT) on the full dose range

C,Q background: PERT with mode on observed average in control group and with wide range

C maximum: PERT with mode on observed average at max dose and with wide range

Default priors for technical parameters

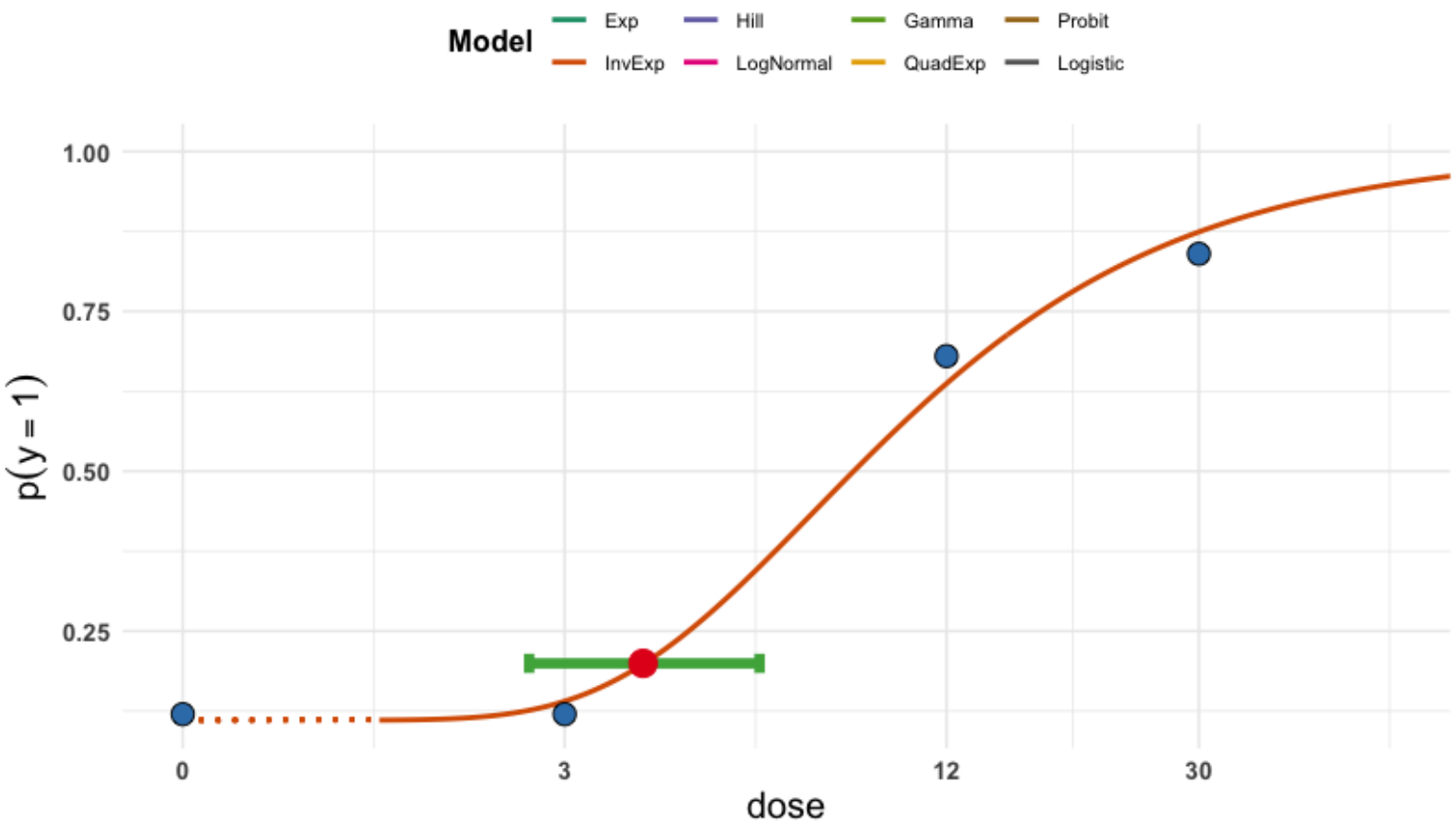
C,Q $\log(d)$: N(1,1) truncated at 5

C $\log(1/\sigma^2)$: normal, loosely based on the scale of the data

Thyroid epithelial cell vacuolisation data

Inverse exponential model using BMR=0.1, with **default priors**

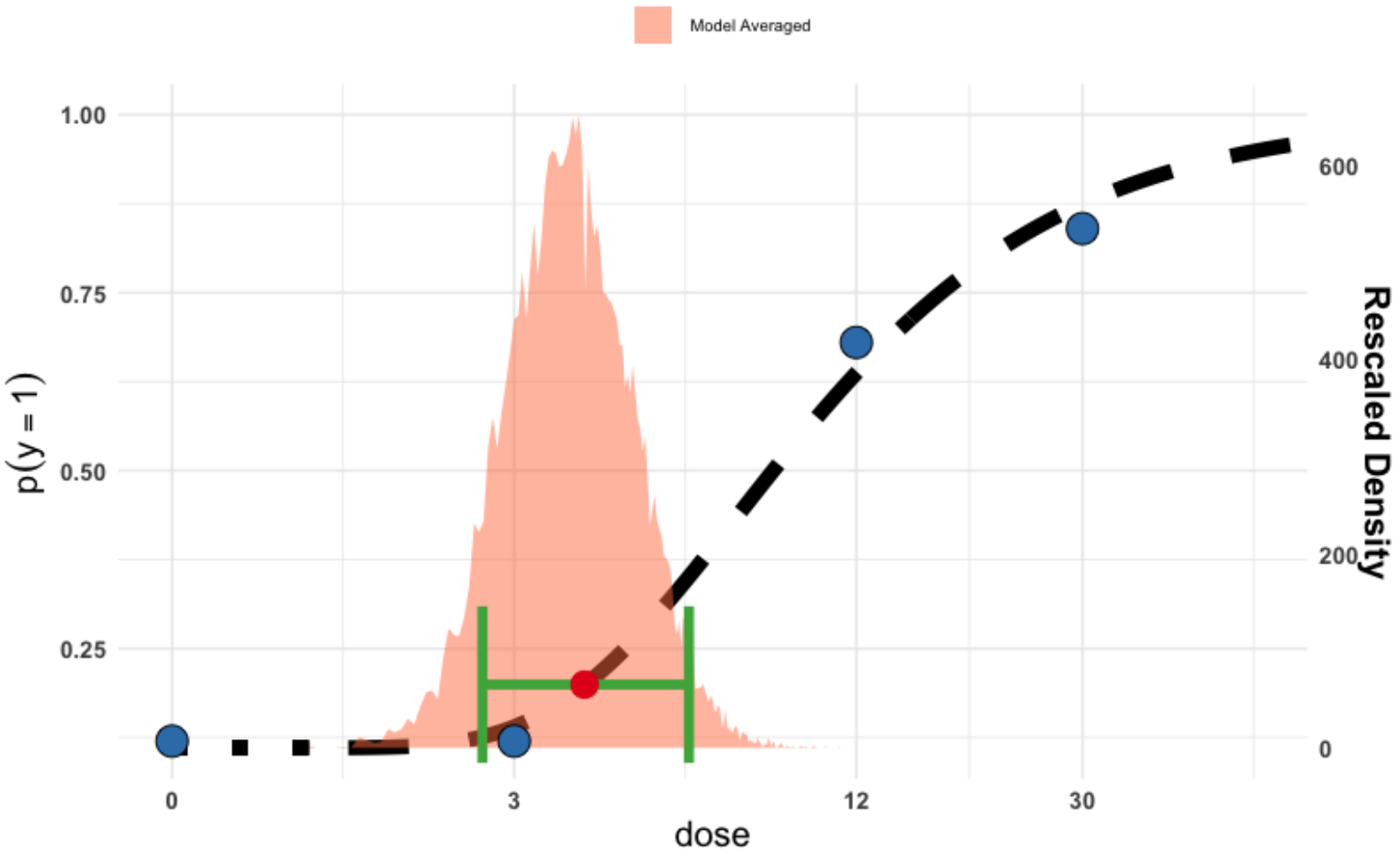
BMD=3.99 (BMDL=2.64,BMDU=6.09) BMDU/BMDL=2.31



Thyroid epithelial cell vacuolisation data

Inverse exponential model using BMR=0.1, with **default priors**

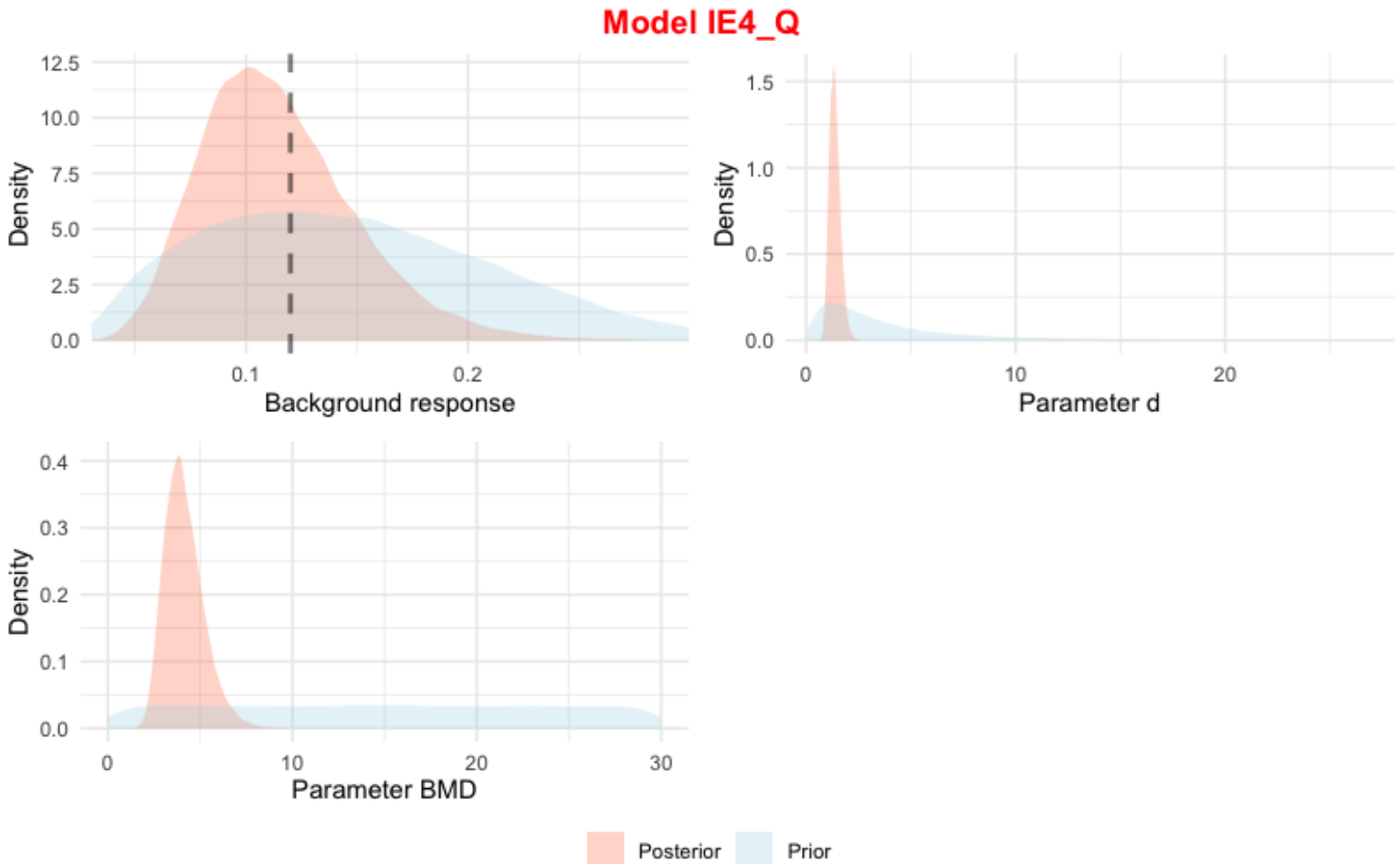
BMD=3.99 (BMDL=2.64,BMDU=6.09) BMDU/BMDL=2.31



Thyroid epithelial cell vacuolisation data

Inverse exponential (IE) using BMR=0.1, with **default priors**

BMD=3.99 (BMDL=2.64,BMDU=6.09) BMDU/BMDL=2.31



Thyroid epithelial cell vacuolisation data

Inverse exponential (IE) using BMR=0.1, with **default priors**

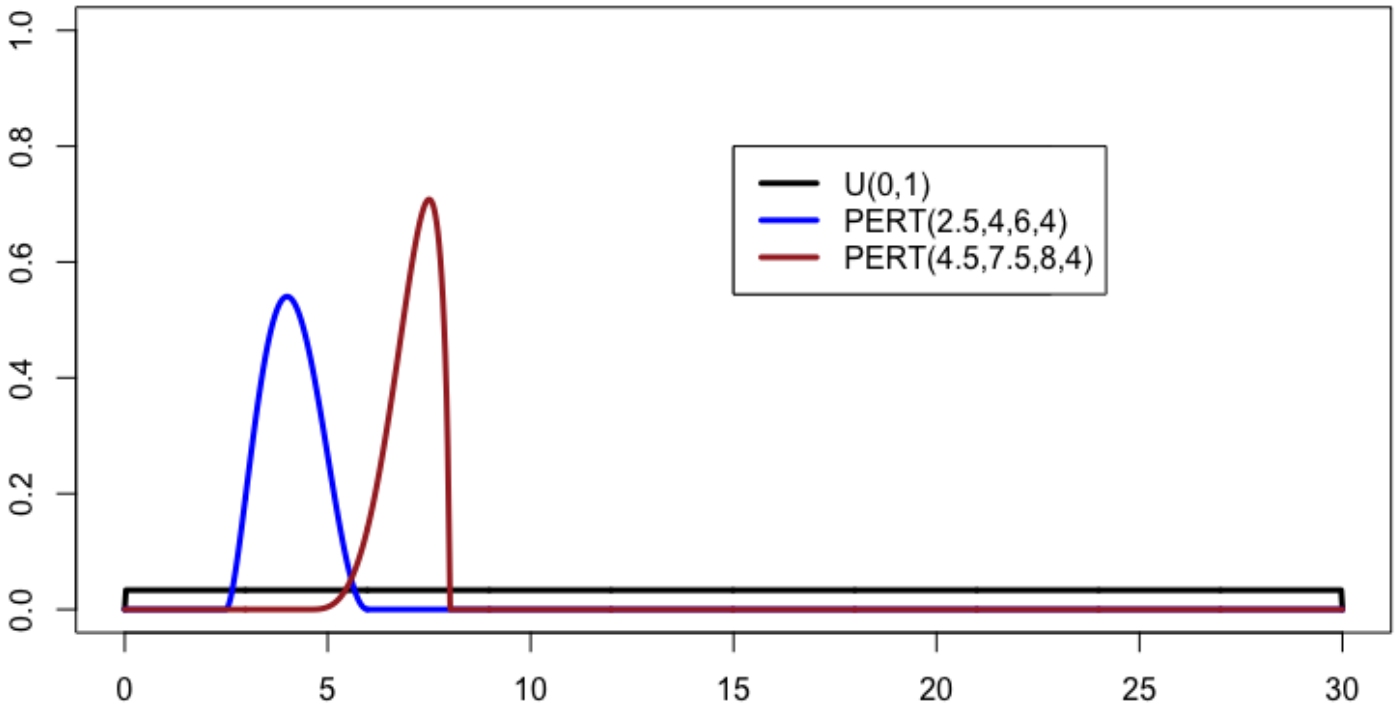
BMD=3.99 (BMDL=2.64,BMDU=6.09) BMDU/BMDL=2.31

Consider **informative** priors on BMD

- min=2.5, mode=4, max=6, shape=4
- min=4.5, mode=7.5, max=8, shape=4

Thyroid epithelial cell vacuolisation data

Priors on BMD

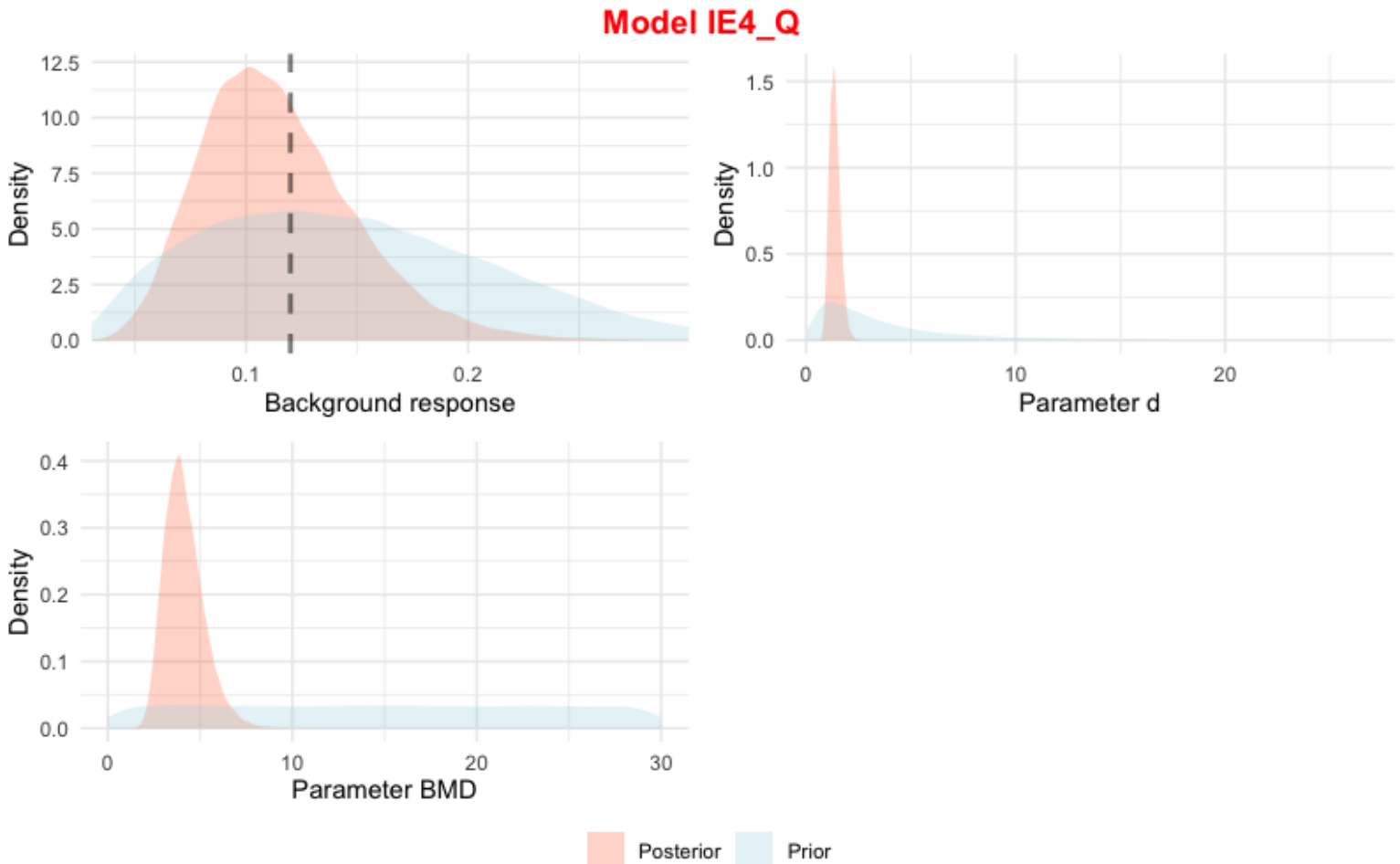


How do different priors affect the BMD estimation and the BMDL, BMDU?

Thyroid epithelial cell vacuolisation data

IE MODEL with **default priors**

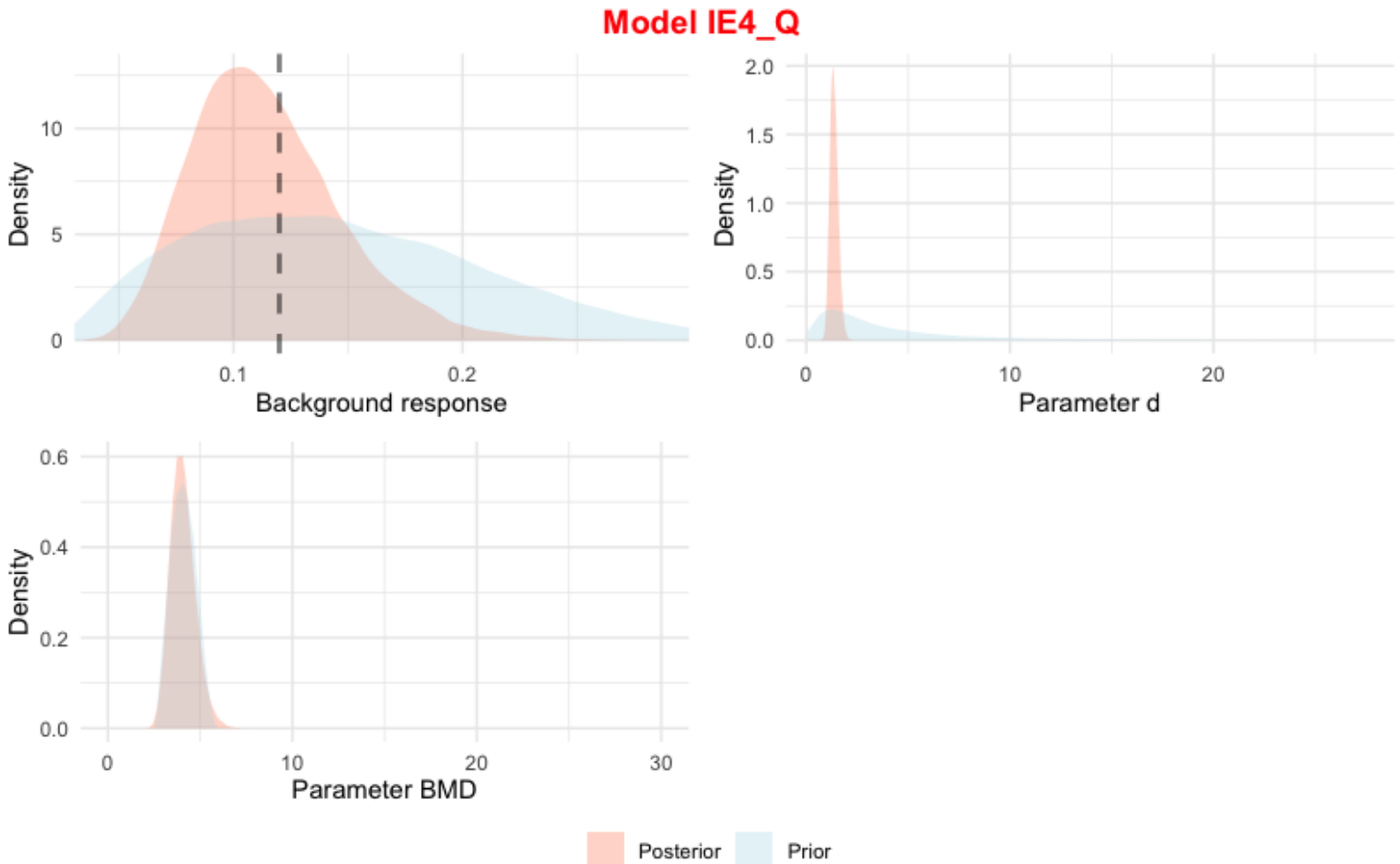
BMD=3.99 (BMDL=2.64,BMDU=6.09) BMDU/BMDL=2.31



Thyroid epithelial cell vacuolisation data

IE MODEL with BMD prior **PERT(2.5,4,6,sh=4)**

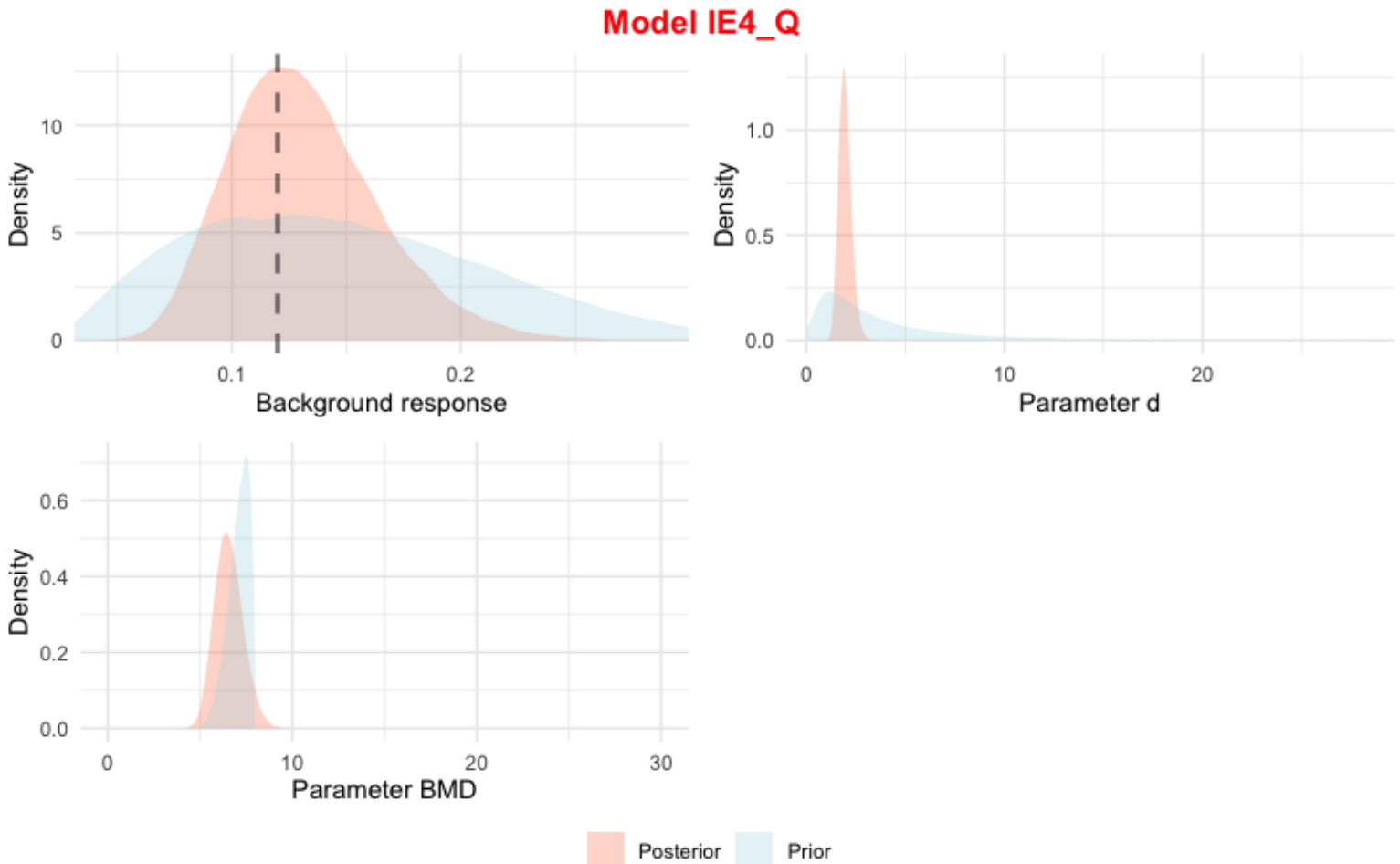
BMD=4.02 (BMDL=3.06, BMDU=5.28) BMDU/BMDL=1.73



Thyroid epithelial cell vacuolisation data

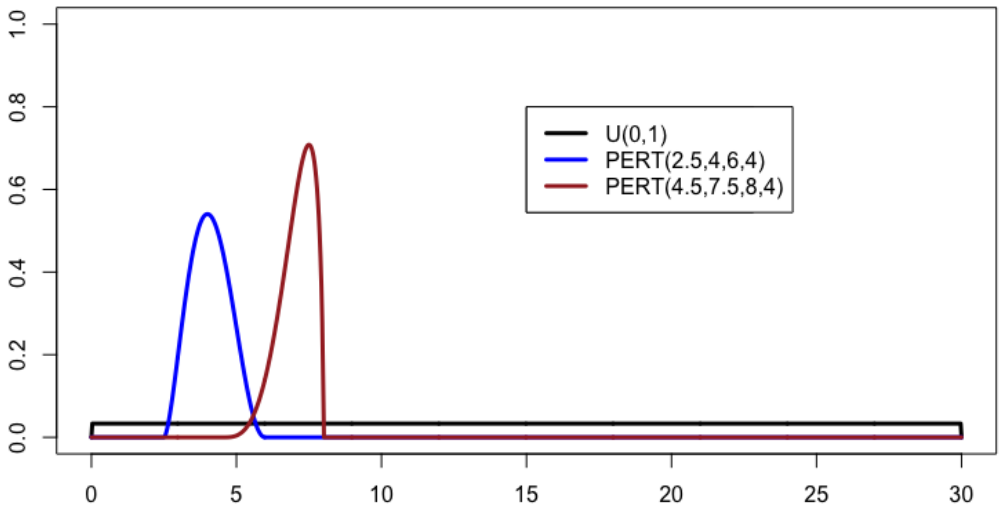
IE MODEL with BMD prior **PERT(4.5,7.5,8,sh=4)**

BMD=6.52 (BMDL=5.36, BMDU=7.91) BMDU/BMDL=1.47



Thyroid epithelial cell vacuolisation data

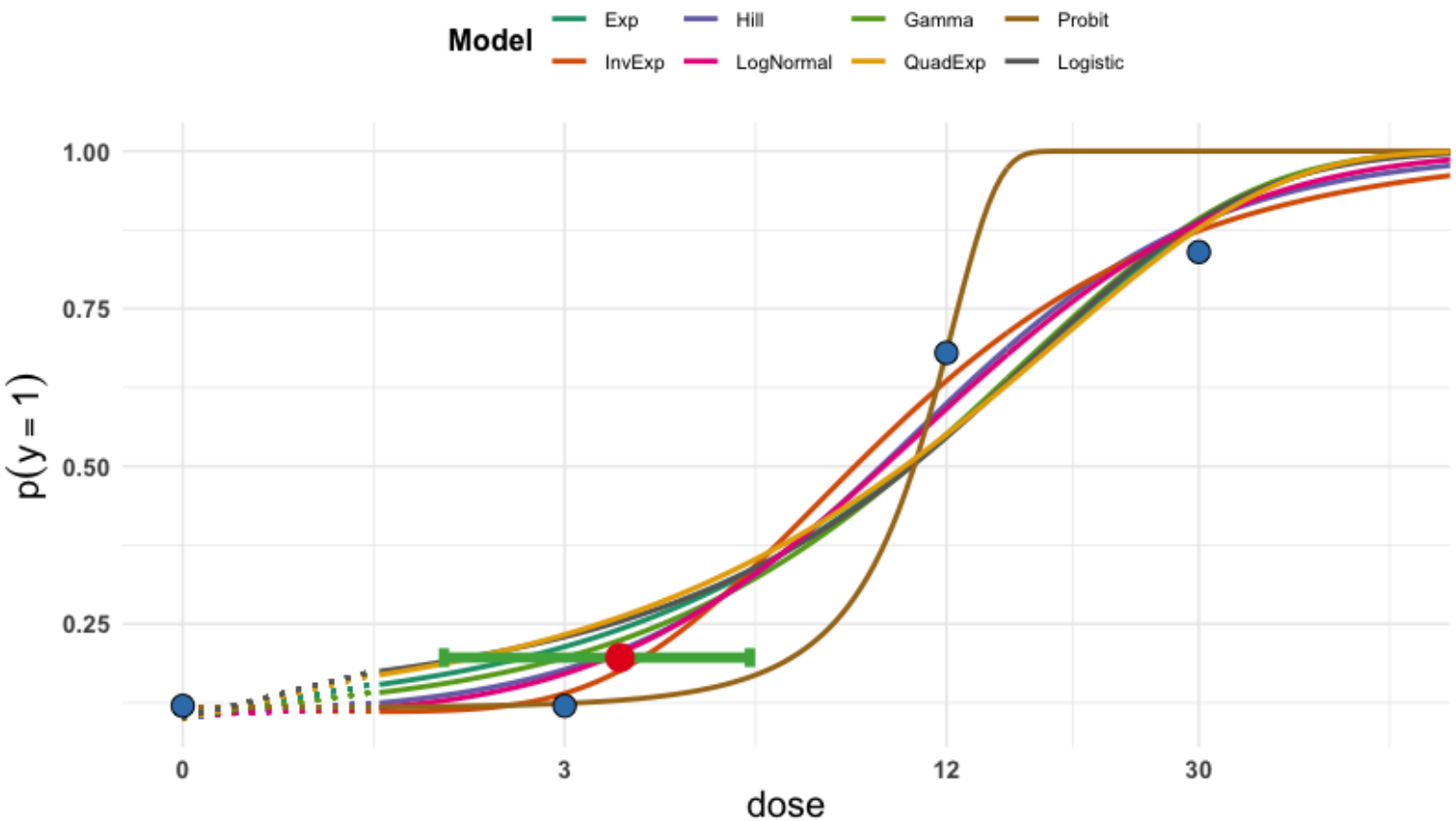
IE MODEL with BMD priors



prior	BMD	BMDL	BMDU	BMDU/BMDL
U(0,1)	3.99	2.64	6.09	2.31
PERT(2.5,4,6,sh=4)	4.02	3.06	5.28	1.73
PERT(4.5,7.5,8,sh=4)	6.52	5.36	7.91	1.47

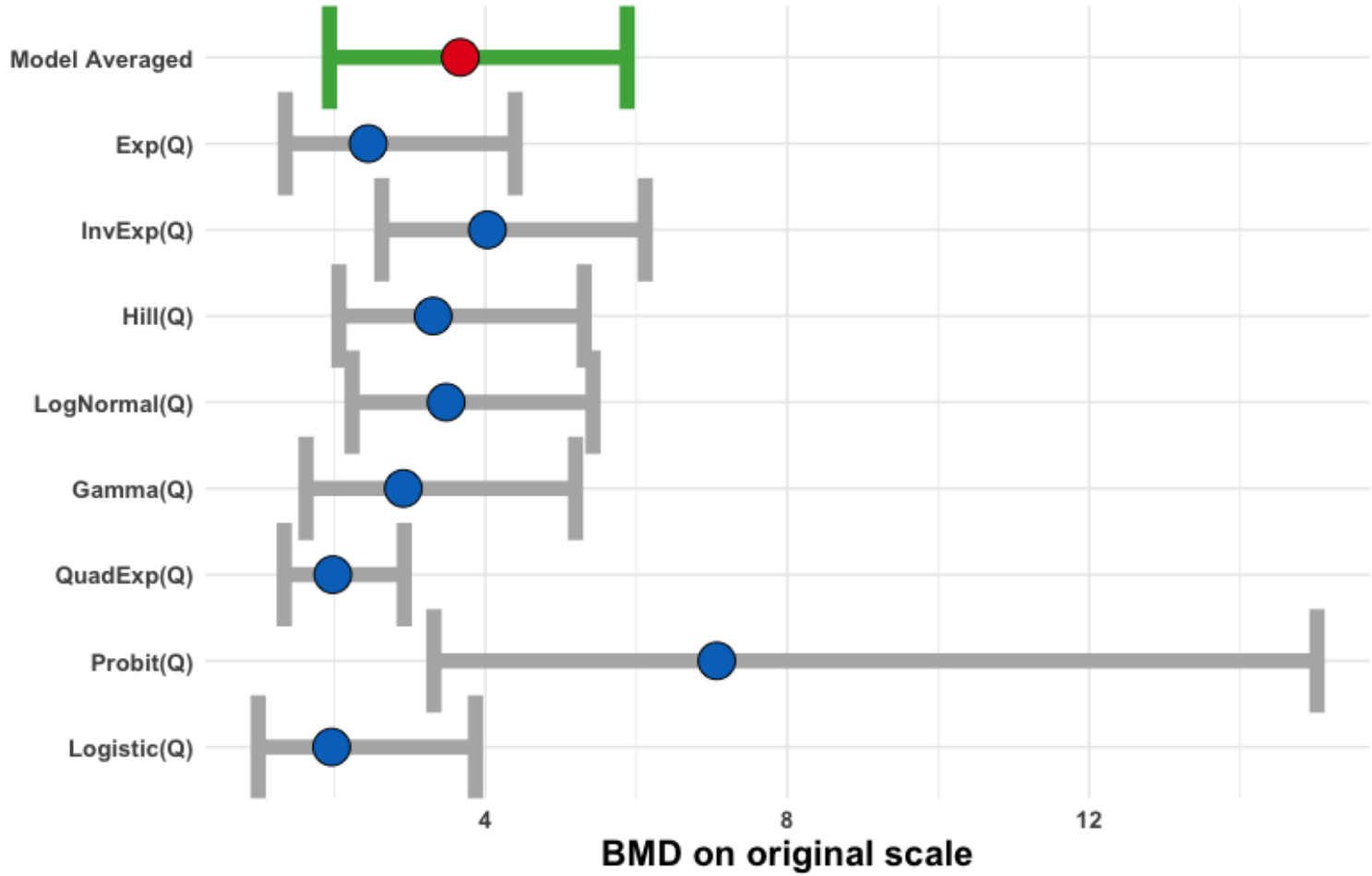
Thyroid epithelial cell vacuolisation data

all models with default priors



Thyroid epithelial cell vacuolisation data

all models with default priors



Questions ?

Outline

- Main statistical methodology
  - ▷ Components of the models
  - ▷ Bayesian inference
  - ▷ Model averaging
- Preliminary statistical tests
- Some further illustrations
- Summary simulation study

Model averaging

- multi-model inference
- suite of models should be rich enough
- frequentist model averaging

$$\text{averaged model fit} = \sum_{\text{model}} w_{\text{model}} \times \text{fitted model}$$

- model weight w_{model} based on goodness-of-fit criterion (AIC)
- use averaged model fit to determine BMD
- BMDL (and BMDU) based on bootstrap

Bayesian model averaging

- same rationale
- priors and posteriors on two levels
  - ▷ on the parameters of each specific model
  - ▷ on the models within the suite of candidate models
- different implementation

  averaged BMD posterior =
  weighted mixture of model specific BMD posteriors

  weights = posterior probabilities of the models
- BMDL (and BMDU) defined as quantiles of averaged posterior

Prior probabilities on candidate models

Default prior distribution on set of candidate models

C uniform distribution: probability 1/16 for each model

Q uniform distribution: probability 1/8 for each model

Bayesian model averaging

Technical issue:

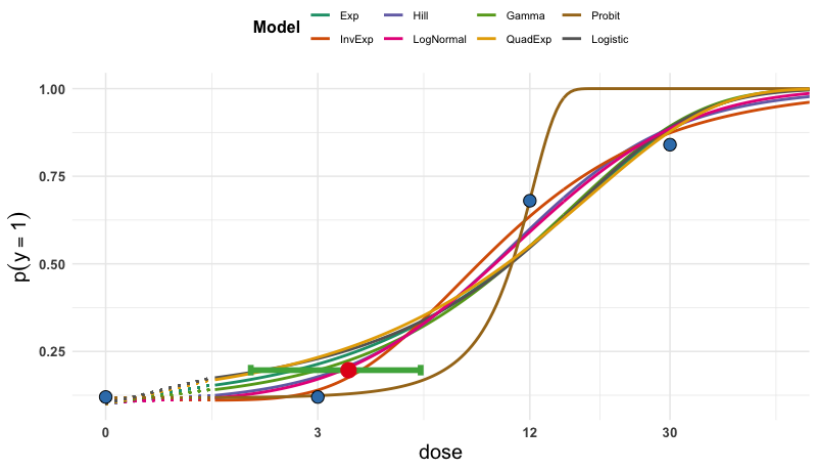
- for the posterior probabilities of the models
- not analytically tractable integrals

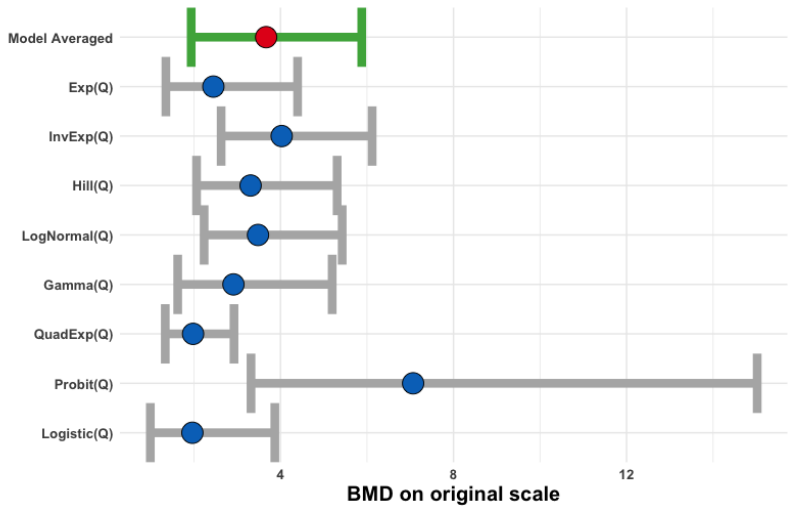
Solutions:

- approximation of integrand: Laplace approximation
- numerical methods to compute integrals: Bridge sampling

Thyroid epithelial cell vacuolisation data revisited

all models with default priors

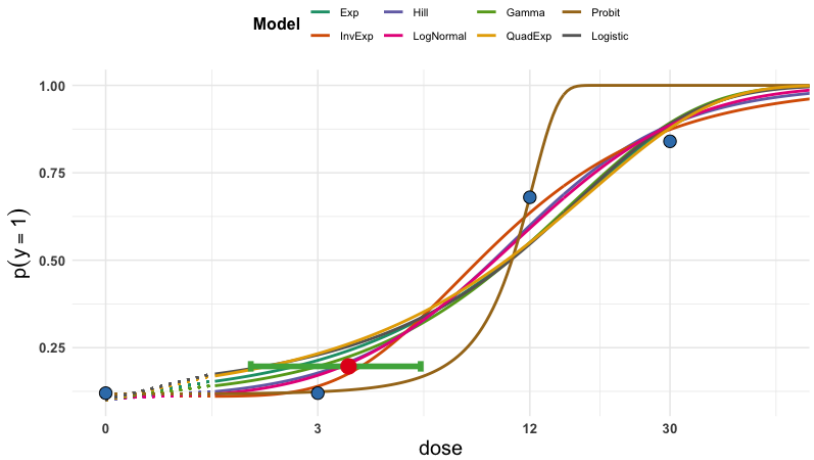


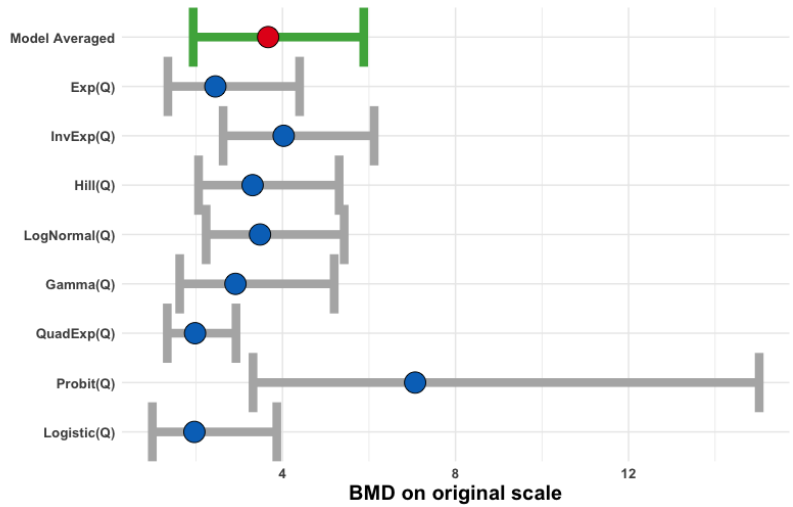


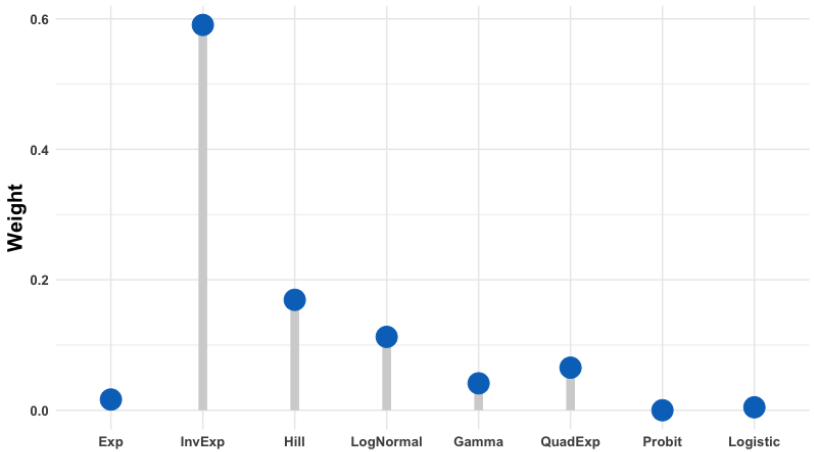
Thyroid epithelial cell vacuolisation data

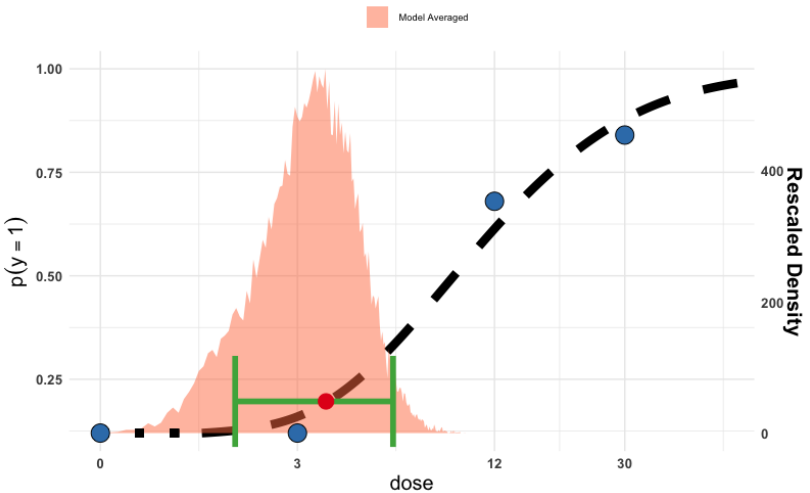
Laplace approximation

BMD=3.67 (BMDL=1.94, BMDU=5.88) BMDU/BMDL=3.04



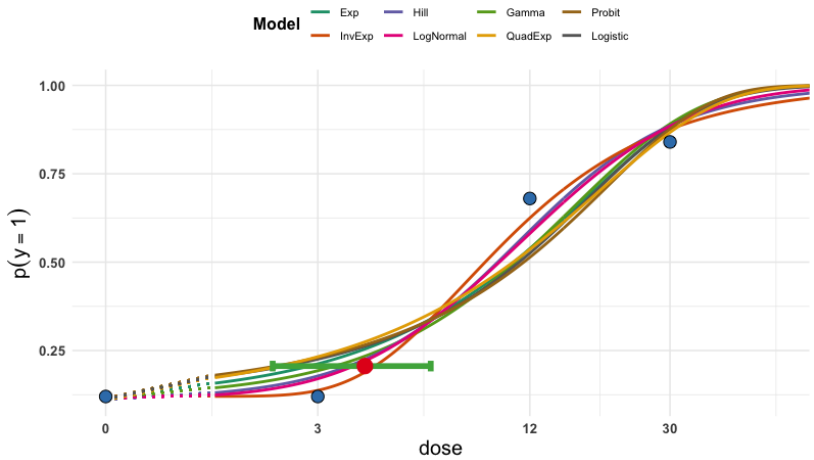


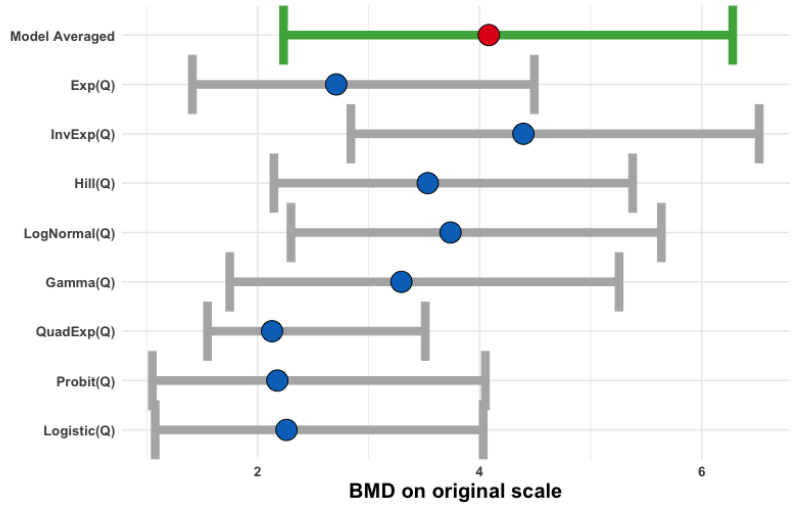


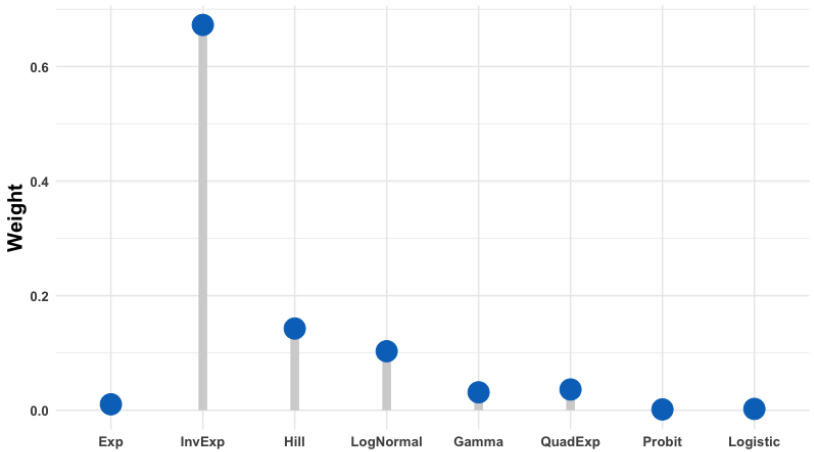


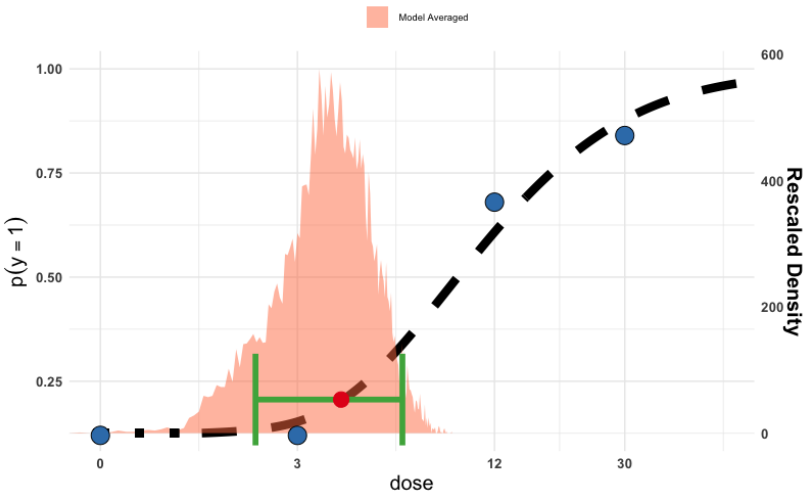
Bridge sampling

BMD=4.08 (BMDL=2.23, BMDU=6.28) BMDU/BMDL=2.81









Questions ?

Outline

- Main statistical methodology
  - ▷ Components of the models
  - ▷ Bayesian inference
  - ▷ Model averaging
- Preliminary statistical tests
- Some further illustrations
- Summary simulation study

Preliminary statistical tests

- For continuous response

$$y|x \sim \mathsf{N}(\mu(x), \sigma^2), \quad y|x \sim \mathsf{LOGN}(\mu(x), \sigma^2)$$

  - ▷ constant variance (normality) & constant coefficient of variation (log-normality)
  - ▷ constant variance & coefficient of variation for individual data
  - ▷ normality & log-normality for individual data
- Testing for no dose effect
- Testing best model fits sufficiently well
- Data suitable for estimating the BMD (next presentation)

Testing

- **Frequentist** hypothesis testing: based on **p-value**
- **Bayesian** hypothesis testing: based on **Bayes factor**

Frequentist For continuous response

$$y|x \sim \mathsf{N}(\mu(x), \sigma^2), \quad y|x \sim \mathsf{LOGN}(\mu(x), \sigma^2)$$

- ▷ constant variance (normality) & constant coefficient of variation (log-normality)
- ▷ constant variance & coefficient of variation for individual data
- ▷ normality & log-normality for individual data

Bayesian Testing for no dose effect

Bayesian Testing best model fits sufficiently well

Testing constant variance (normality)

Indirect test focusing on the **variability across dose levels**

Normality assumption

$$y|x \sim \mathsf{N}(\mu(x), \sigma^2)$$

implying **null hypothesis of homoscedasticity**

$$H_0 : \sigma_1^2 = ... = \sigma_N^2 = \sigma^2$$

Bartlett test for constant variance using only summary statistics

Log-normality assumption

$$y|x \sim \text{LOGN}(\mu(x), \sigma^2) \quad \Leftrightarrow \quad \log(y)|x \sim \text{N}(\mu(x), \sigma^2)$$

implying **null hypothesis of homoscedasticity**

$$H_0 : \sigma_1^2 = ... = \sigma_N^2 = \sigma^2 \text{ on log-scale}$$

$$\Updownarrow$$

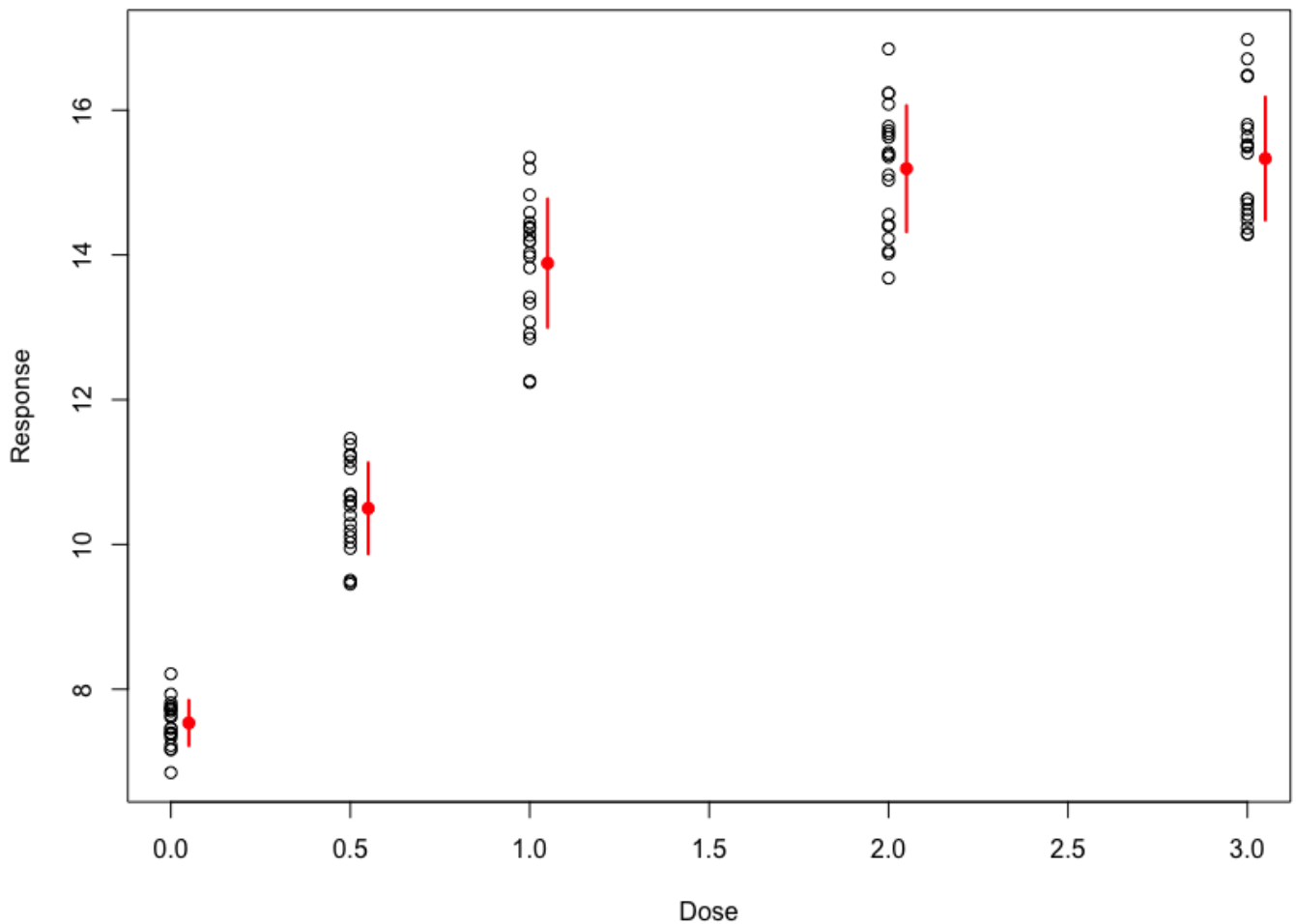
$$H_0 : \text{CV}_1 = ... = \text{CV}_N = \sqrt{e^{\sigma^2} - 1} \text{ on original scale}$$

with

$$\text{CV} = \text{coefficient of variation} = \frac{\sqrt{\text{Var}(y|x)}}{E(y|x)}$$

Bartlett test for constant coefficient of variation

Continuous response (Example 3.1, Figure C.3 in guidance)



Bartlett test for constant variance or CV

Continuous response (Example 3.1, Figure C.3 in guidance)

- Distributional assumption of constant variance for the normal distribution is not met, Bartlett test p-value is 3e-04
- Distributional assumption of constant coefficient of variation is met, Bartlett test p-value is 0.4295

Conclusion: evidence against the normal distribution

Testing constant variance or CV for individual data

Same hypotheses

- normal distribution

$$H_0 : \sigma_1^2 = ... = \sigma_N^2$$

- log-normal distribution

$$H_0 : \mathrm{CV}_1 = ... = \mathrm{CV}_N$$

Levene test using individual data

Testing constant variance or CV

Continuous response (Example 3.1, Figure C.3 in guidance)

SD Distributional assumption of constant variance for the normal distribution is not met, Bartlett test p-value is 0.0003

ID Distributional assumption of constant variance for the normal distribution is not met, Levene test p-value is 0.0046

SD Distributional assumption of constant coefficient of variation is met, Bartlett test p-value is 0.430

ID Distributional assumption of constant coefficient of variation is met, Levene test p-value is 0.550

Conclusion: evidence against the normal distribution

Frequentist For continuous response

$$y|x \sim \mathsf{N}(\mu(x), \sigma^2), \quad y|x \sim \mathsf{LOGN}(\mu(x), \sigma^2)$$

- ▷ constant variance (normality) & constant coefficient of variation (log-normality)
- ▷ constant variance & coefficient of variation for individual data
- ▷ normality & log-normality for individual data

Bayesian Testing for no dose effect

Bayesian Testing best model fits sufficiently well

Testing normality or log-normality for individual data

Individual data: **Shapiro-Wilk** frequentist test for normality

- normality assumption

$$H_0 : y|x \sim \text{normal distribution}$$

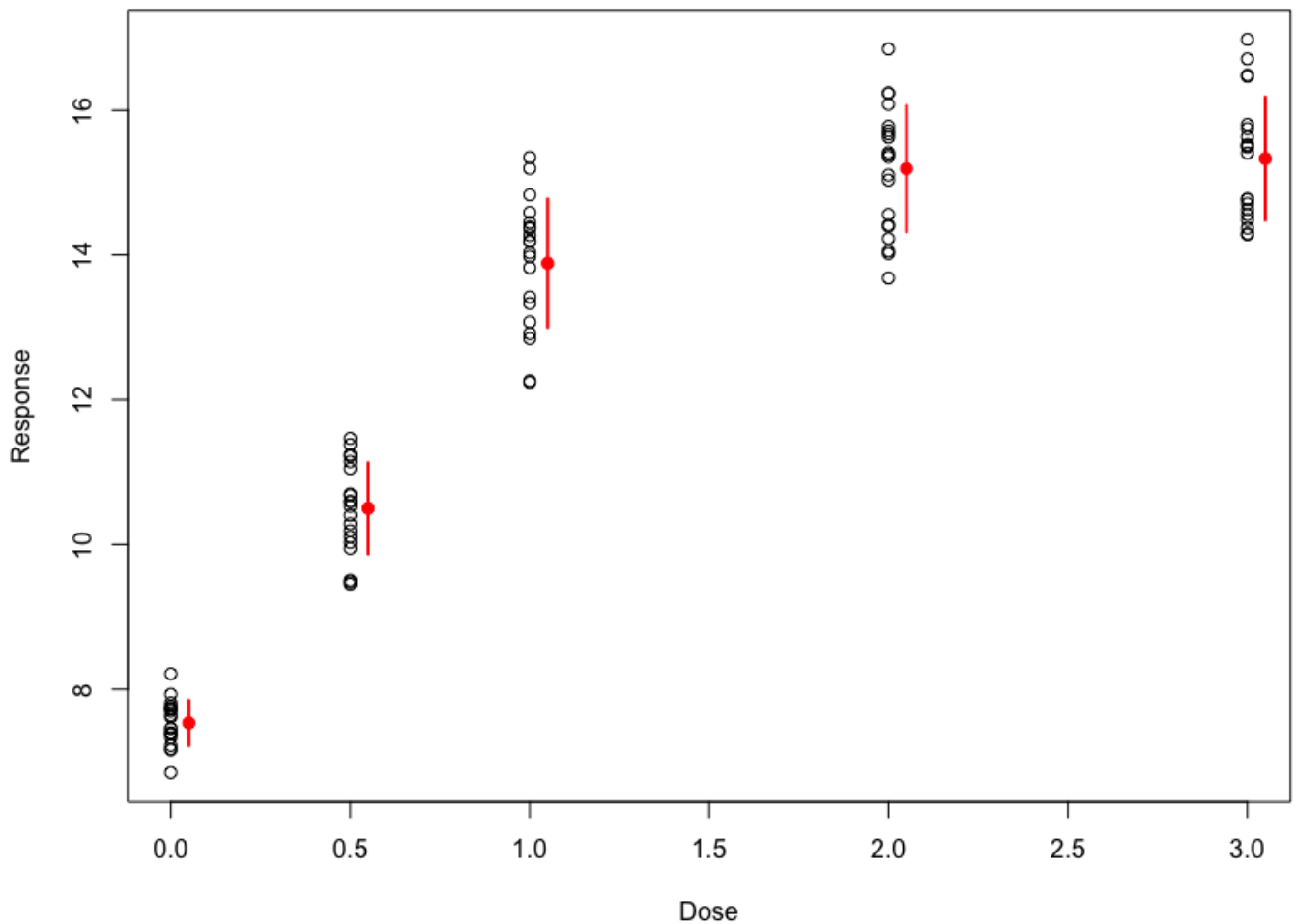
- log-normality assumption

$$H_0 : y|x \sim \text{log-normal distribution}$$

$$\Updownarrow$$

$$H_0 : \log(y)|x \sim \text{normal distribution}$$

Continuous response (Example 3.1, Figure C.3 in guidance)



Shapiro-Wilk testing for normality or log-normality

Continuous response (Example 3.1, Figure C.3 in guidance)

- at each dose level
- collapsing all dose levels (after centering)

Results

- there is no evidence against normality at level 5%
- there is evidence against normality at level 10% for dose 3
- there is no evidence against log-normality at level 5%
- there is evidence against log-normality at level 10% for dose 3

Frequentist For continuous response

$$y|x \sim \mathsf{N}(\mu(x), \sigma^2), \quad y|x \sim \mathsf{LOGN}(\mu(x), \sigma^2)$$

- ▷ constant variance (normality) & constant coefficient of variation (log-normality)
- ▷ constant variance & coefficient of variation for individual data
- ▷ normality & log-normality for individual data

Bayesian Testing for no dose effect

Bayesian Testing best model fits sufficiently well

Bayesian testing with Bayes factor

- measures change prior $\rightarrow$ posterior in favor of H_0
- central equation

$$\frac{P(H_0|\text{data})}{P(H_a|\text{data})} = \frac{P(\text{data}|H_0)}{P(\text{data}|H_a)} \times \frac{P(H_0)}{P(H_a)}$$

$$\frac{P(H_0|\text{data})}{1 - P(H_0|\text{data})} = \frac{P(\text{data}|H_0)}{P(\text{data}|H_a)} \times \frac{P(H_0)}{1 - P(H_0)}$$

$$\text{prior odds for } H_0 = \text{Bayes factor} \times \text{prior odds for } H_0$$

$$\text{prior odds for } H_0 \xrightarrow{\text{Bayes factor}} \text{posterior odds for } H_0$$

Bayesian testing with Bayes factor

$$\text{BF} = \frac{P(\text{data}|H_0)}{P(\text{data}|H_a)}$$

Bayes factor	interpretation
$\text{BF} > 10$	strong evidence favoring H_0 against H_a
$3 < \text{BF} \leq 10$	some evidence favoring H_0 against H_a
$1/3 \leq \text{BF} \leq 3$	insufficient evidence favoring any hypothesis
$1/10 \leq \text{BF} < 1/3$	some evidence favoring H_a against H_0
$\text{BF} < 1/10$	strong evidence favoring H_a against H_0

Testing for no dose effect

H_0 : no effect of dose & H_a : any effect of dose

$$\text{BF} = \frac{P(\text{data}|H_0)}{P(\text{data}|H_a)}$$

Bayes factor	interpretation
$\text{BF} > 10$	strong evidence favoring H_0 against H_a
$3 < \text{BF} \leq 10$	some evidence favoring H_0 against H_a
$1/3 \leq \text{BF} \leq 3$	insufficient evidence favoring any hypothesis
$1/10 \leq \text{BF} < 1/3$	some evidence favoring H_a against H_0
$\text{BF} < 1/10$	strong evidence favoring H_a against H_0

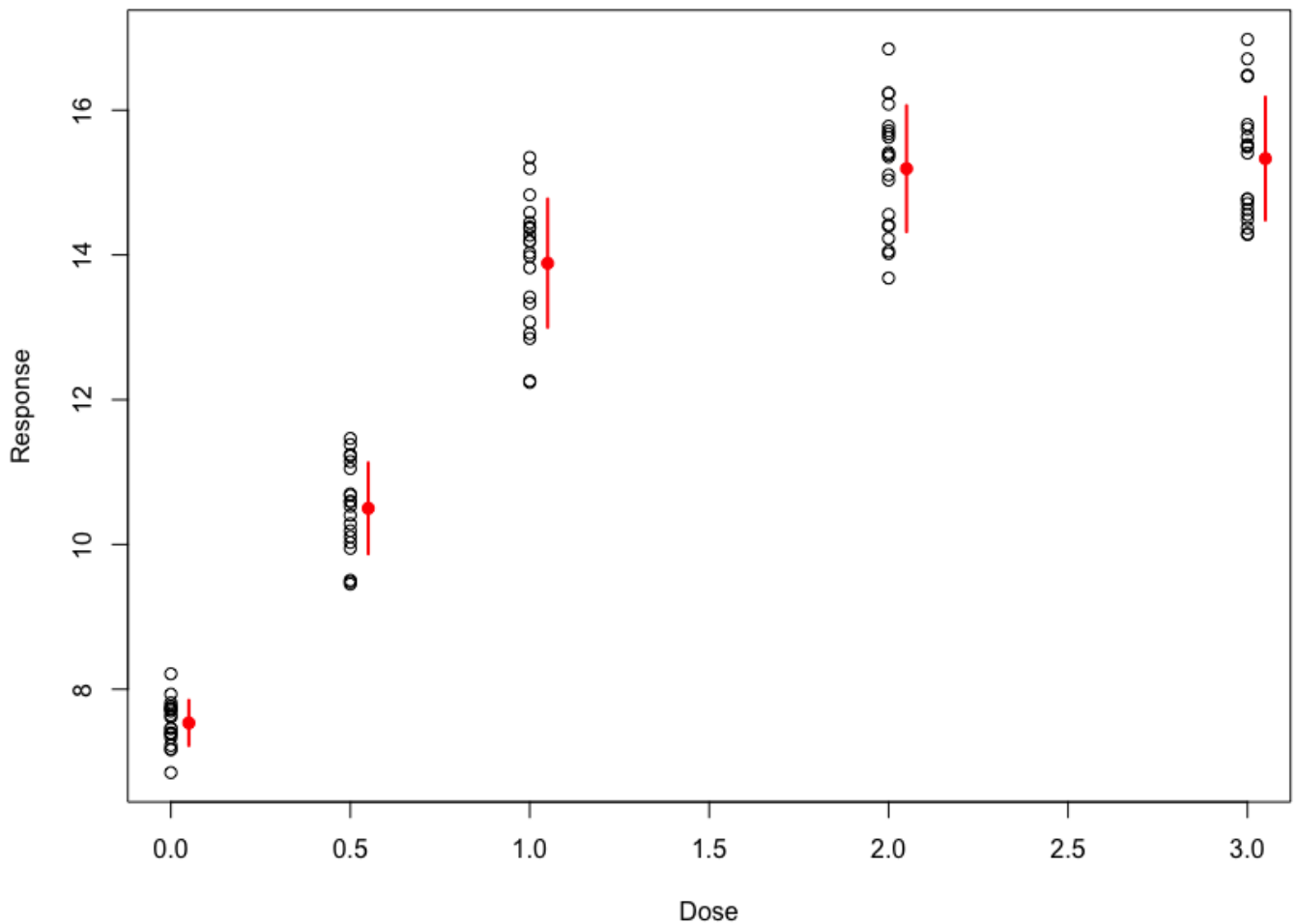
Testing for no dose effect

H_0 : no effect of dose & H_a : any effect of dose

$$\text{BF} = \frac{P(\text{data}|H_0)}{P(\text{data}|H_a)}$$

Bayes factor	interpretation
$\text{BF} > 10$	sufficient evidence that there is no dose-effect
$\text{BF} \leq 10$	insufficient evidence that there is no dose-effect

Continuous response (Example 3.1, Figure C.3 in guidance)



Output

- Bayes factor in favor of null model over SM:

$$\text{BF} = 0.000 \leq 10$$

- there is insufficient evidence that there is no dose effect

Testing best model fits sufficiently well

H_0 : best model & H_a : saturated model

$$\text{BF} = \frac{P(\text{data}|H_0)}{P(\text{data}|H_a)}$$

Bayes factor	interpretation
$\text{BF} > 10$	strong evidence favoring H_0 against H_a
$3 < \text{BF} \leq 10$	some evidence favoring H_0 against H_a
$1/3 \leq \text{BF} \leq 3$	insufficient evidence favoring any hypothesis
$1/10 \leq \text{BF} < 1/3$	some evidence favoring H_a against H_0
$\text{BF} < 1/10$	strong evidence favoring H_a against H_0

Testing best model fits sufficiently well

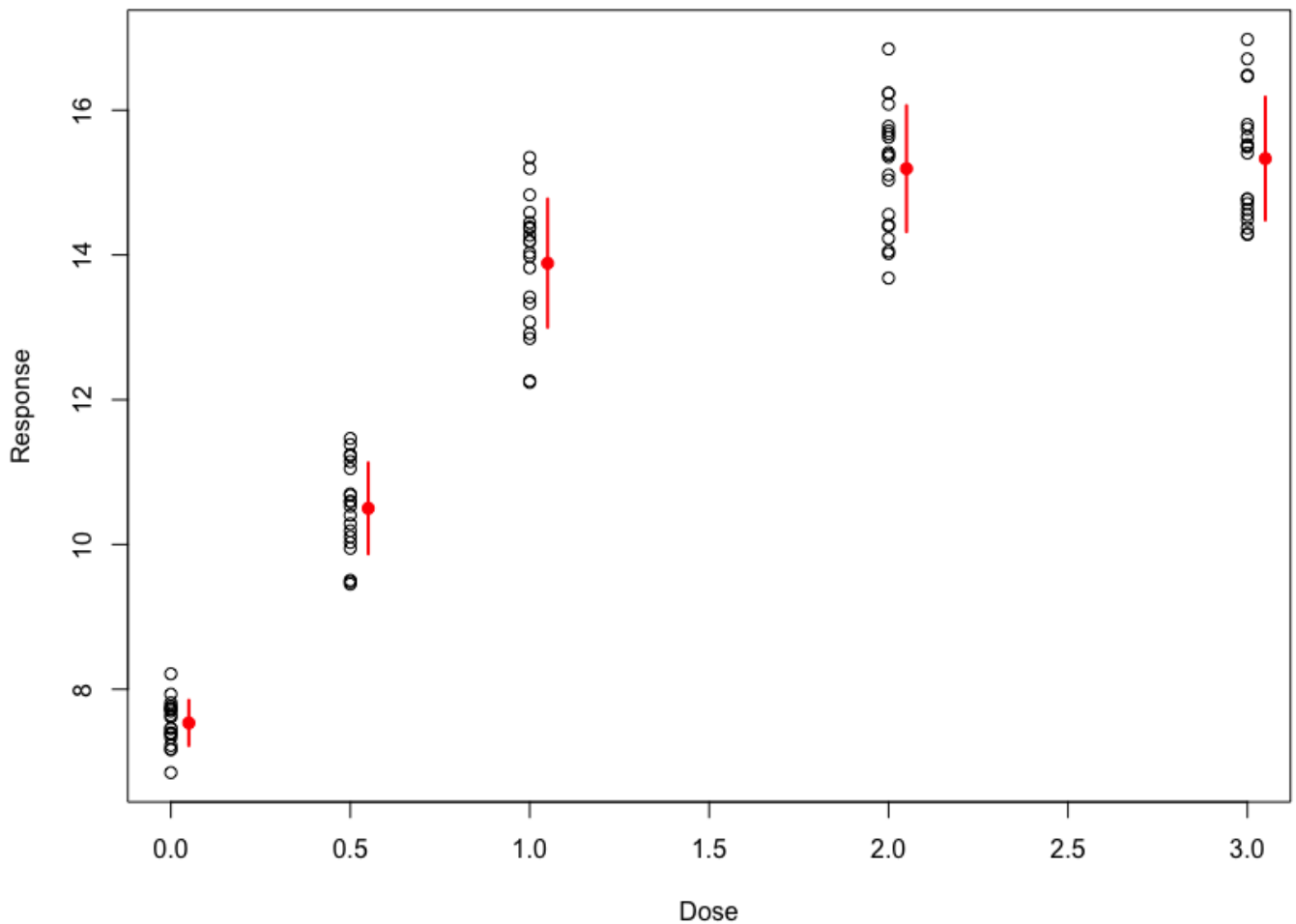
H_0 : best model & H_a : saturated model

$$\text{BF} = \frac{P(\text{data}|H_0)}{P(\text{data}|H_a)}$$

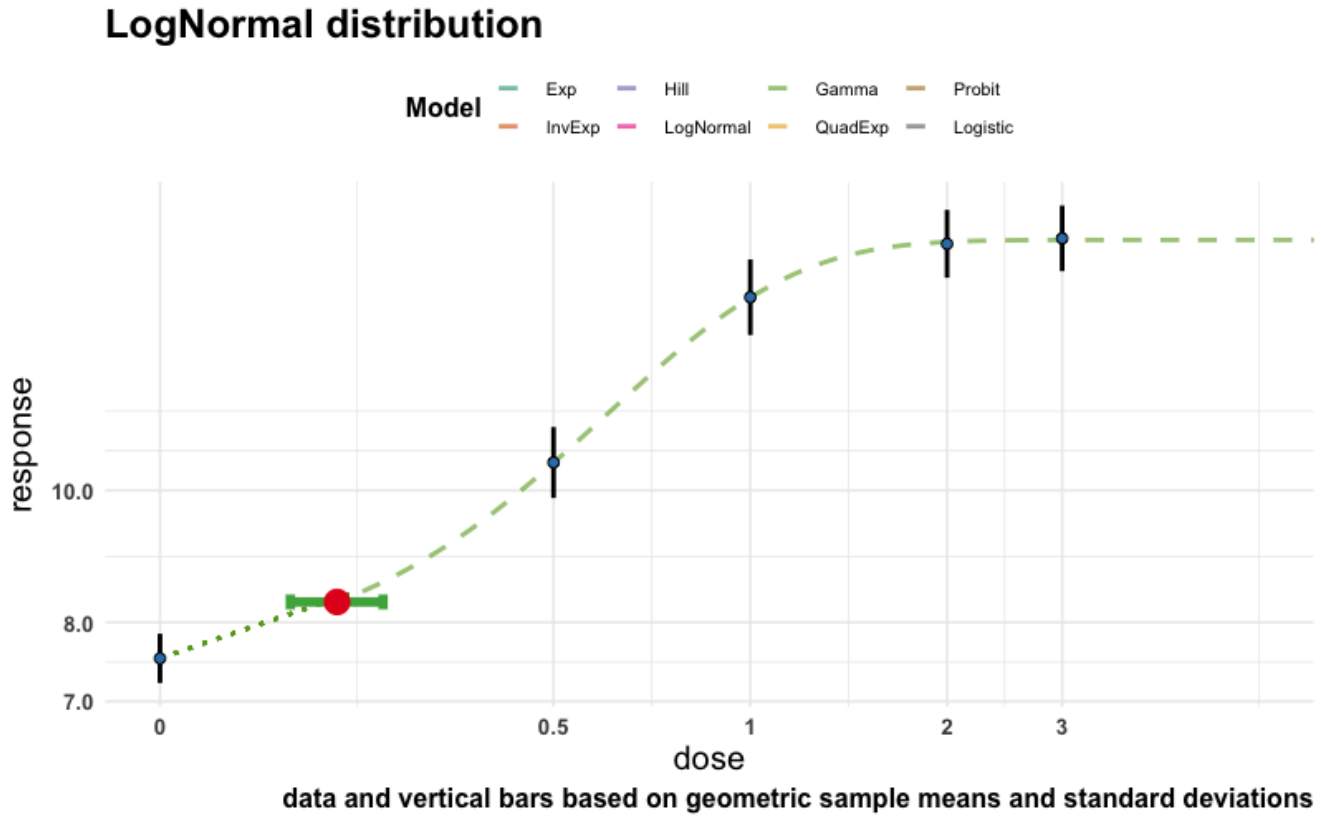
Bayes factor	interpretation
BF $\geq 1/10$	best fitting model fits sufficiently well
BF $< 1/10$	none of the models provide an adequate fit do the data

Testing best model fits sufficiently well

Continuous response (Example 3.1, Figure C.3 in guidance)



Testing best model fits sufficiently well



Output

- best fitting model fits sufficiently well

$$\text{BF} = 9.404 \geq 1/10$$

Questions ?

Outline

- Main statistical methodology
  - ▷ Components of the models
  - ▷ Bayesian inference
  - ▷ Model averaging
- Preliminary statistical tests
- Some further illustrations
- Summary simulation study

ILLUSTRATION 1

The simulated continuous response

Example 3.1, Figure C.3 in guidance

Continuous response (Example 3.1, Figure C.3 in guidance)

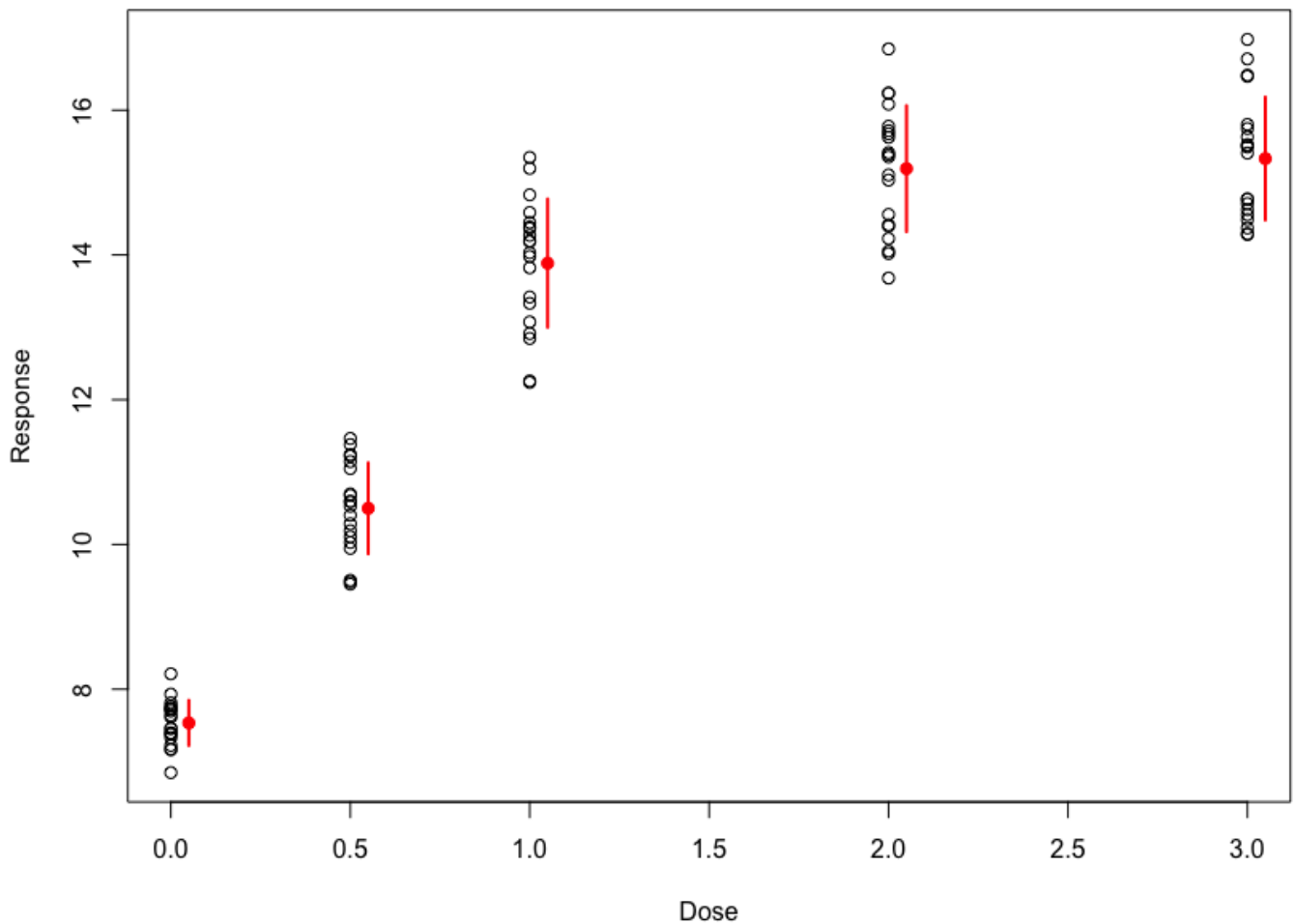


Illustration simulation example

- one dataset generated from a log-normal exponential model
- $a = 2.015, b = 1.5, c = 1.344, d = 1.8, \sigma = 0.05$
- natural parameters
  - ▷ median background response $= e^{2.015} = 7.501$
  - ▷ median maximum response $= e^{2.015 \times 1.344} = 15.002$
  - ▷ BMD $= 0.2287$, with BMR $= 0.10$
- dose levels 0, 0.5, 1, 2, 3
- constant group size of 20

Wrapping-up

- insufficient evidence that there is no dose-effect
- best model (gamma) fits sufficiently well
- evidence the homoscedastic normal distribution does not fit well
- no such evidence against the log-normal distribution

Illustration simulation example

Two analyses: individual data & summary data

differences?

Illustration simulation example

- Shapiro-Wilk tests only in case of individual data
- with individual data exact geometric summary statistics
  - ▷ for control group: exact (individual data)

    gmean = 7.528749, gsdev = 1.042578
  - ▷ for control group: approximate (summary data)

    gmean = 7.528454, gsdev = 1.042420

Illustration simulation example: weights

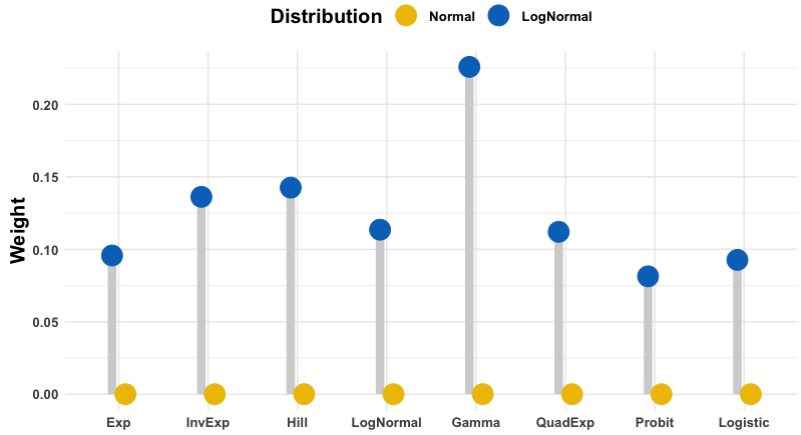
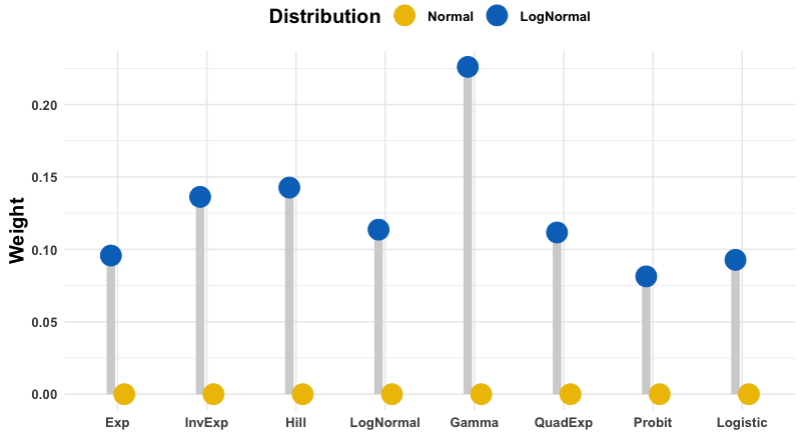
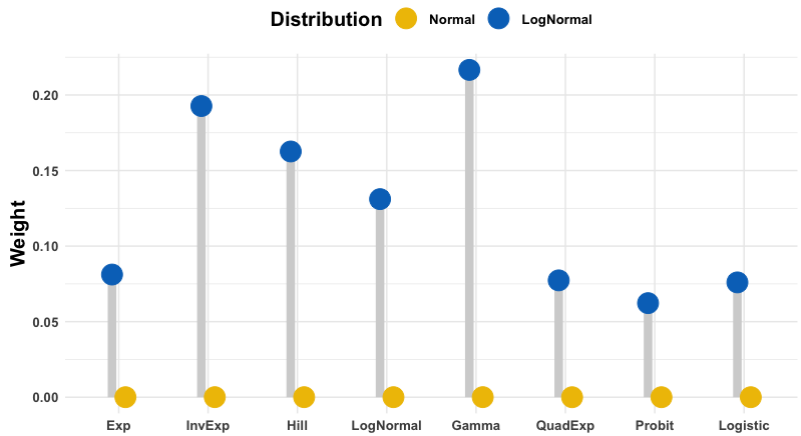
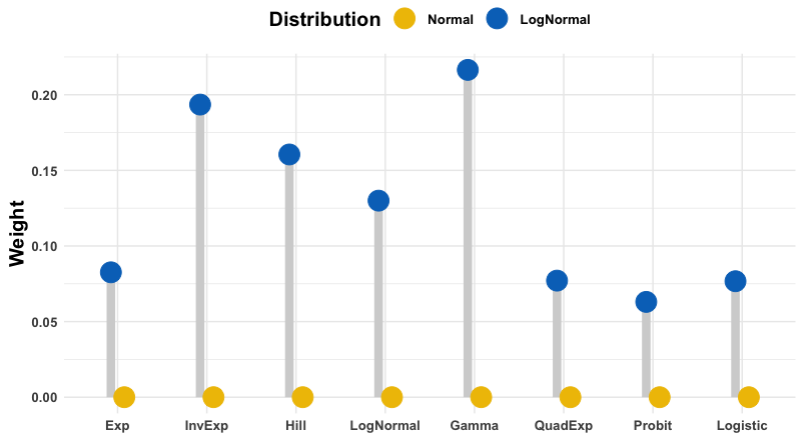
	individual data	summary data
Laplace		
Bridge		

Illustration simulation example: BMD estimates

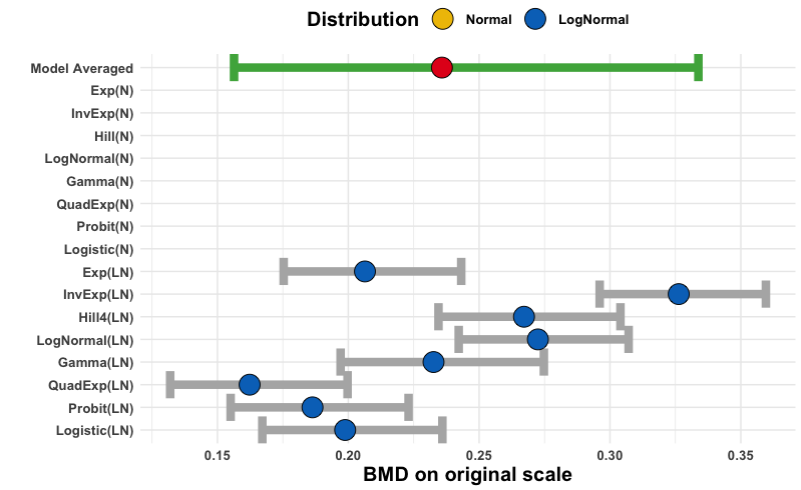
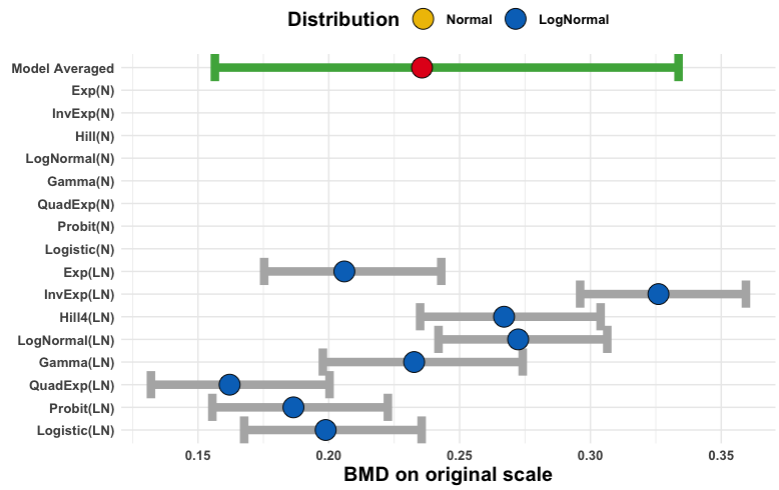
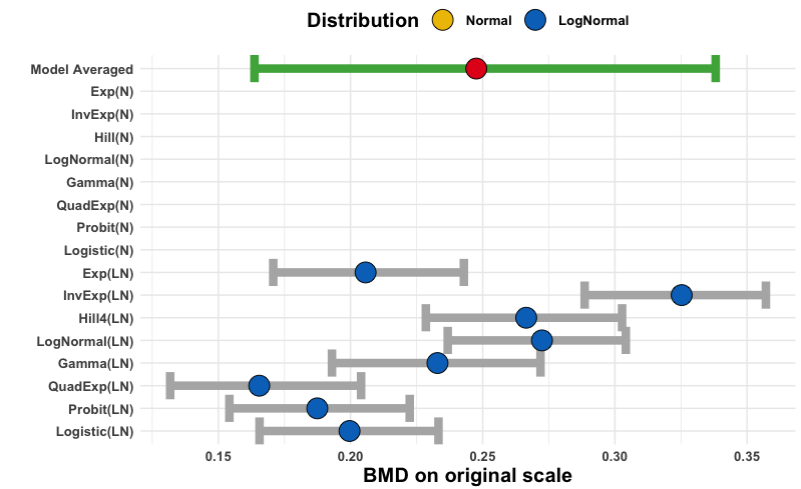
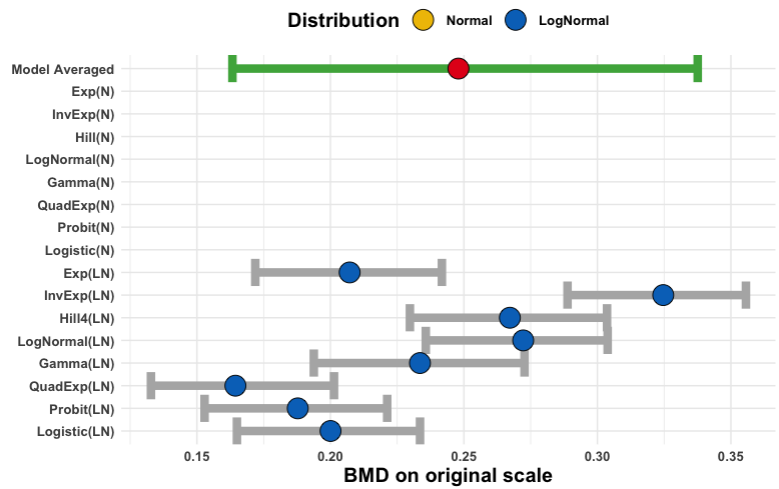
	individual data	summary data
Laplace		
Bridge		

Illustration simulation example: log-normal fits

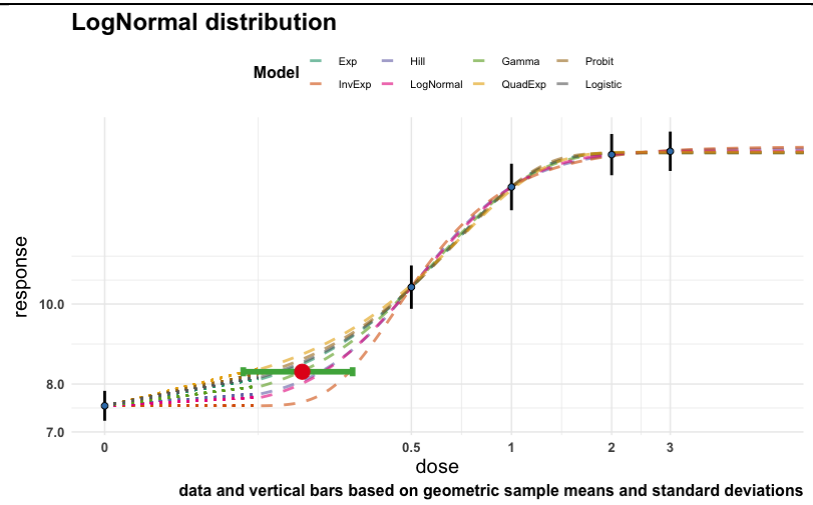
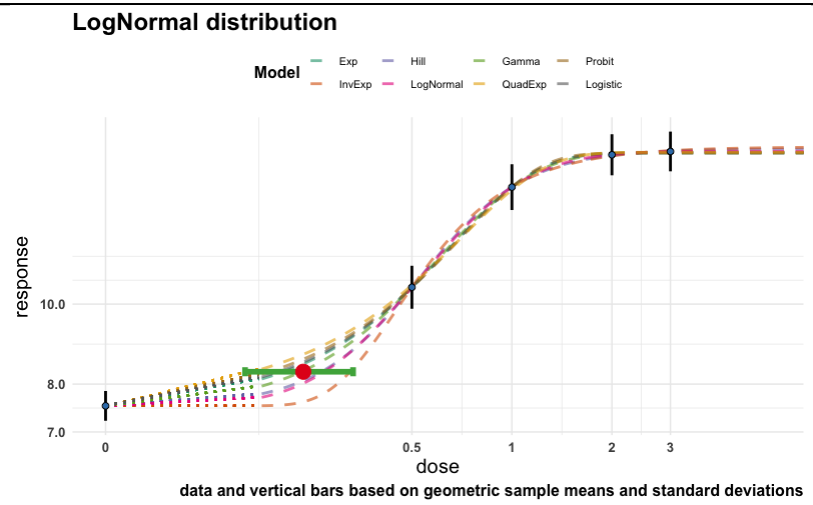
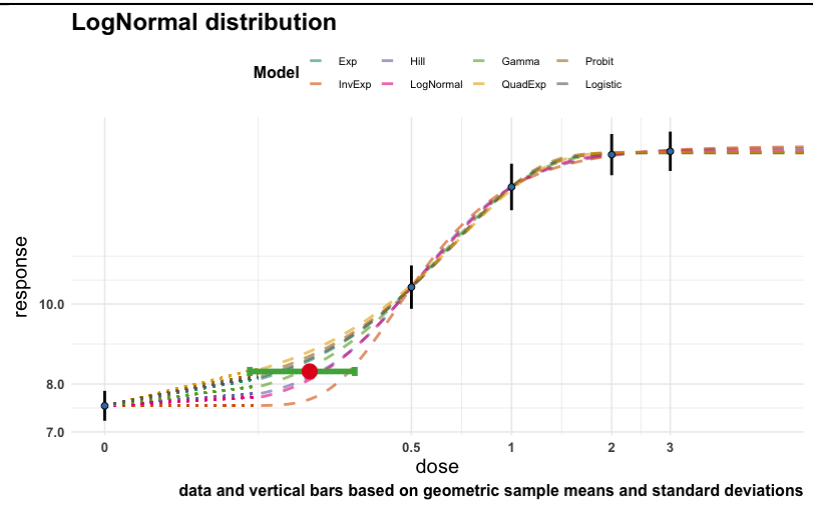
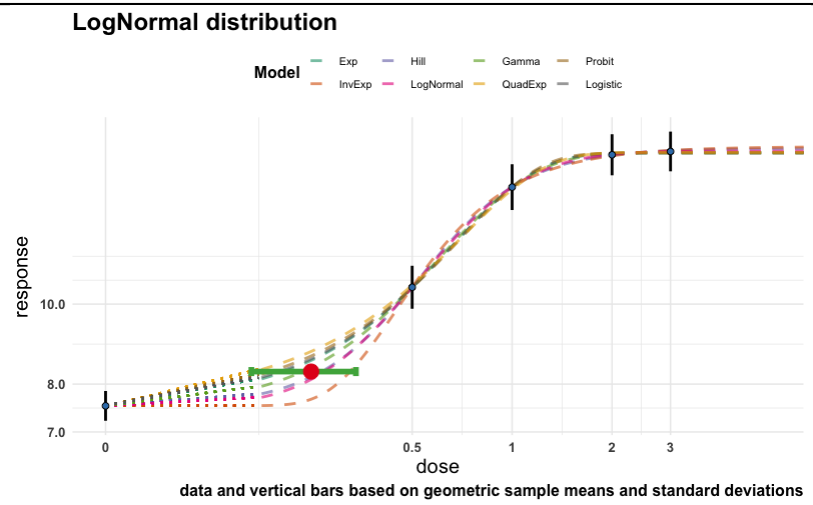
	individual data	summary data
Laplace		
Bridge		

Illustration simulation example: BMD posterior

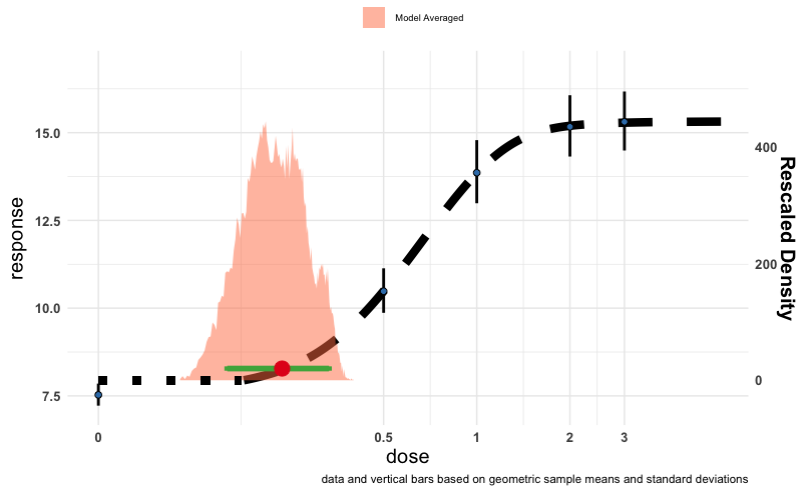
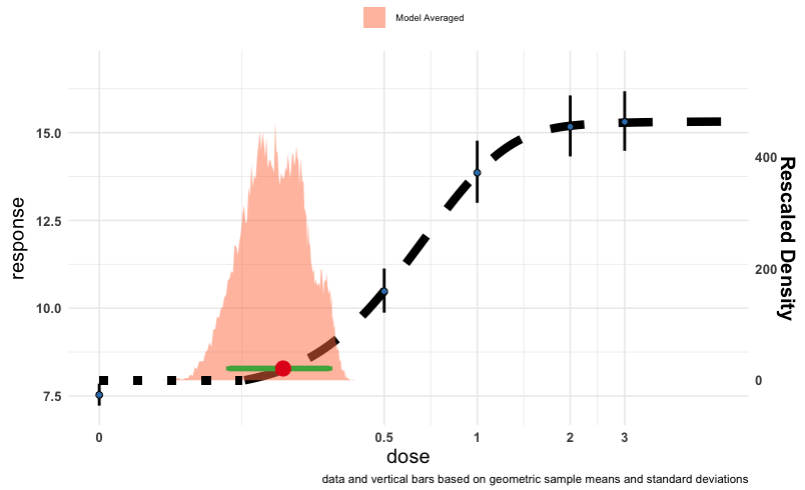
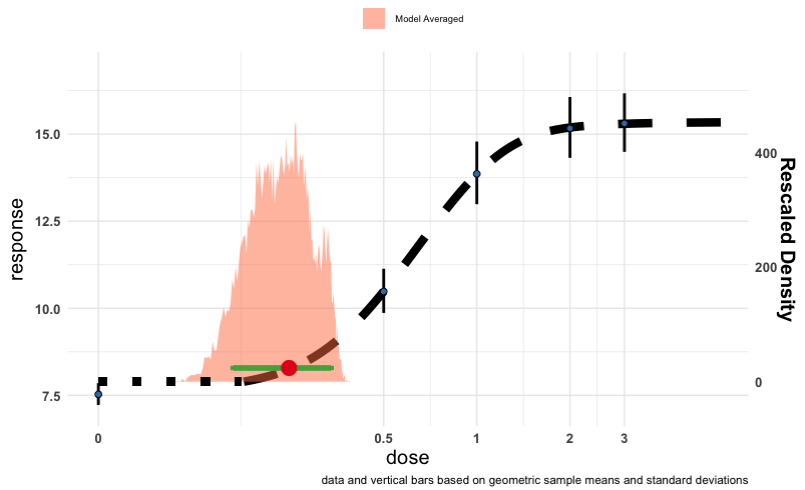
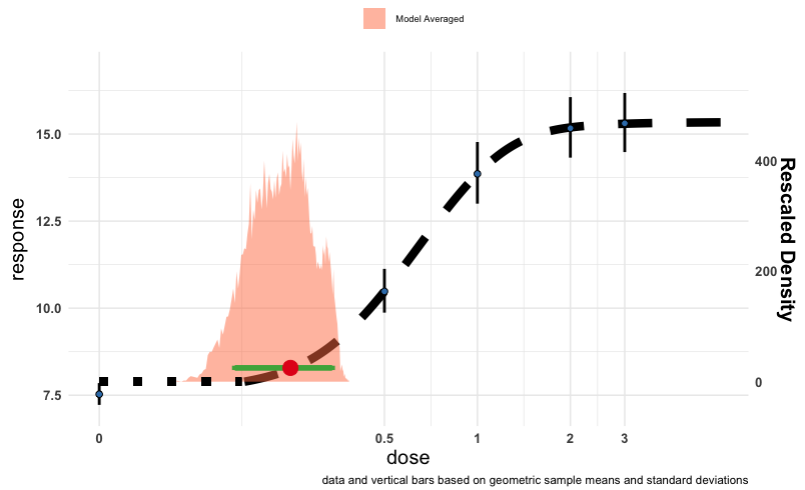
	individual data	summary data
Laplace		
Bayesian		

Illustration simulation example: BMD estimates

True BMD = 0.2287

	individual data			summary data		
	BMDL	BMD	BMDU	BMDL	BMD	BMDU
Laplace	0.1562	0.2350	0.3329	0.1574	0.2355	0.3326
Bridge	0.1633	0.2472	0.3378	0.1640	0.2481	0.3385

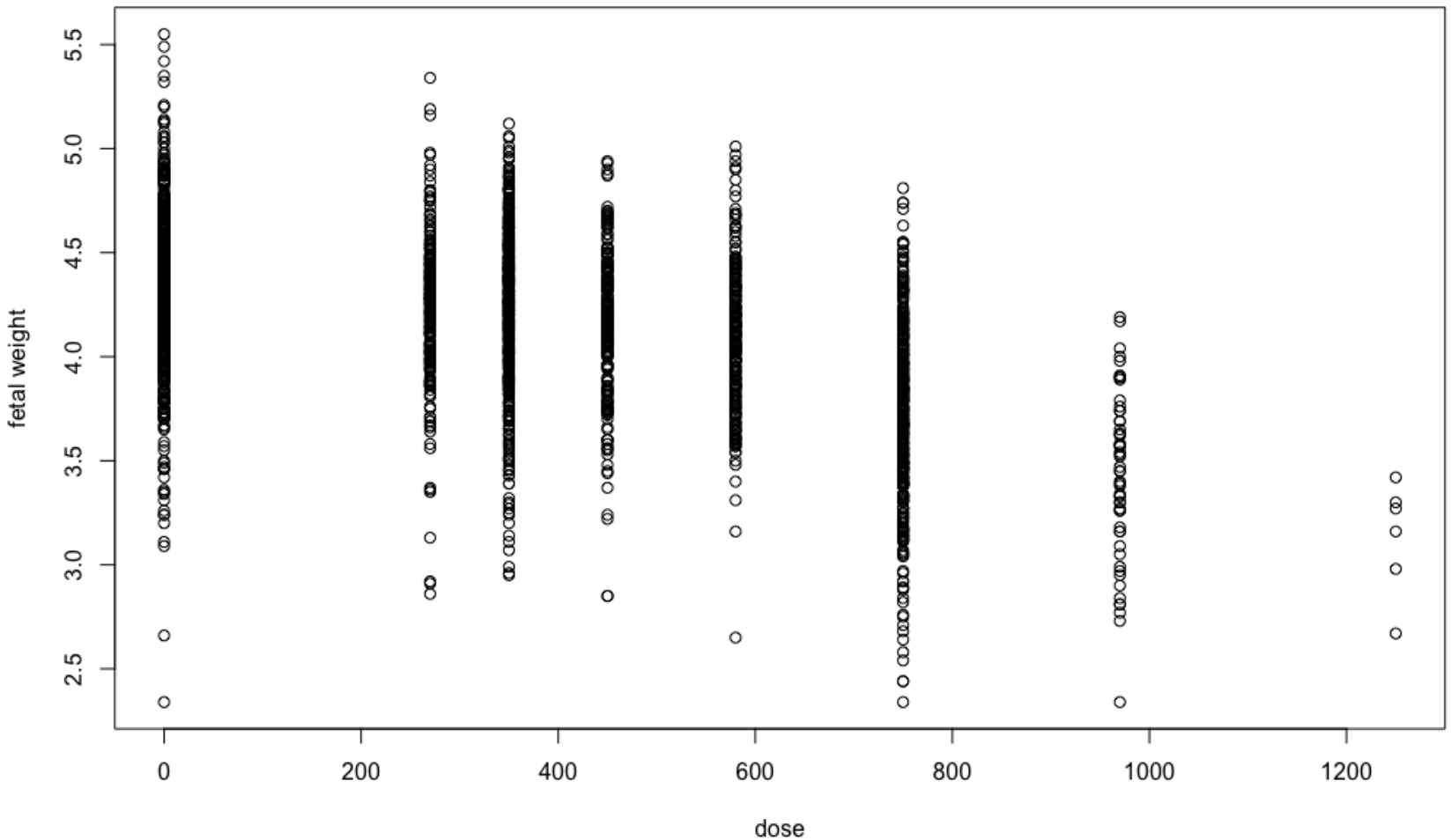
ILLUSTRATION 2

The fetal weight example

Dataset `das5.rda` in PROAST

Illustration 2

The fetal weight example (dataset `das5.rda` in PROAST)



BMR = 0.05

Preliminary statistical tests

Frequentist For continuous response

$$y|x \sim \mathsf{N}(\mu(x), \sigma^2), \quad y|x \sim \mathsf{LOGN}(\mu(x), \sigma^2)$$

- ▷ constant variance (normality) & constant coefficient of variation (log-normality):
  reject both, p-val 0.0000, 0.0000 resp.
- ▷ constant variance & coefficient of variation for individual data: reject both, p-val 0.0003, 0.0000 resp.
- ▷ normality & log-normality for individual data:
  reject both except at dose 970 and 1250

Bayesian Testing for no effect
insufficient evidence of no dose-effect (BF=0.0000)

Bayesian Testing best model fits sufficiently well
best fitting model fits sufficiently well (BF>2900)

Illustration fetal weight example

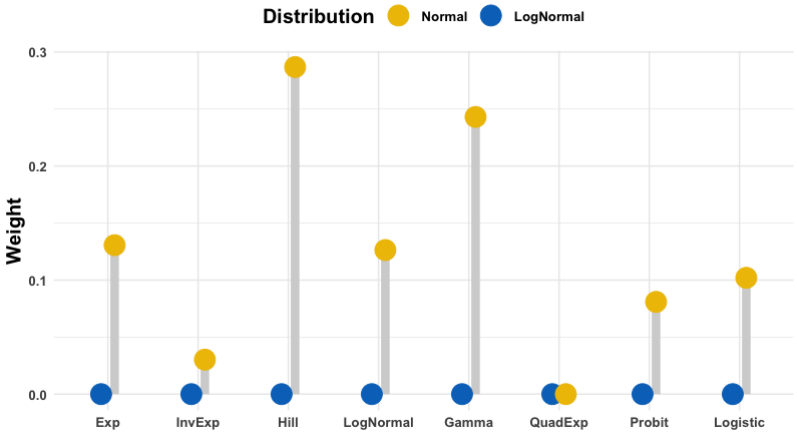
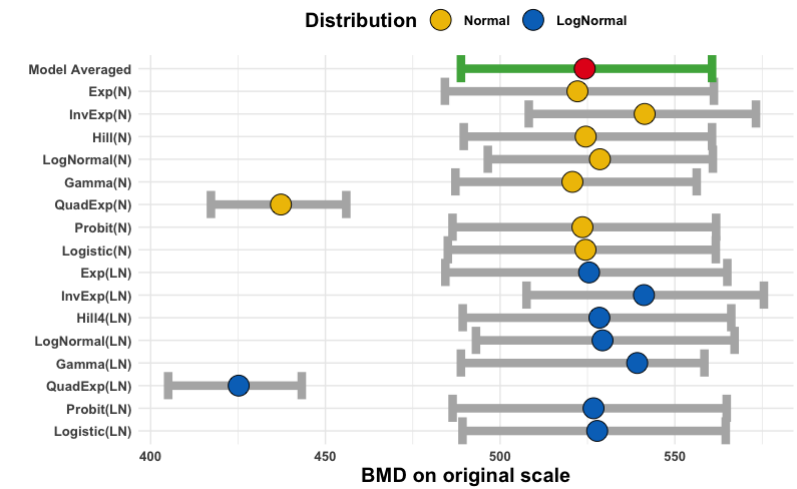
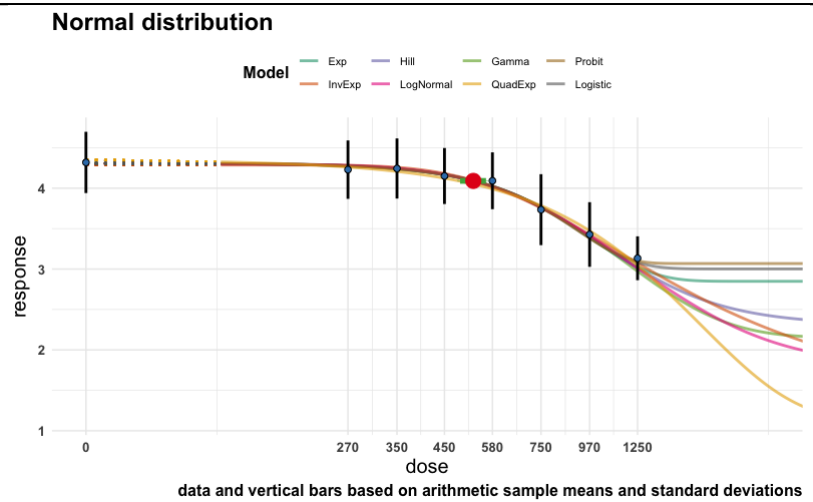
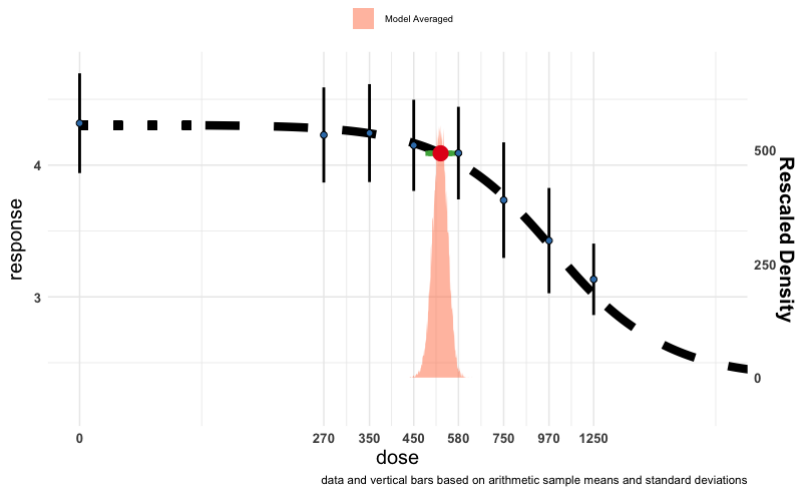
weights		
BMD		

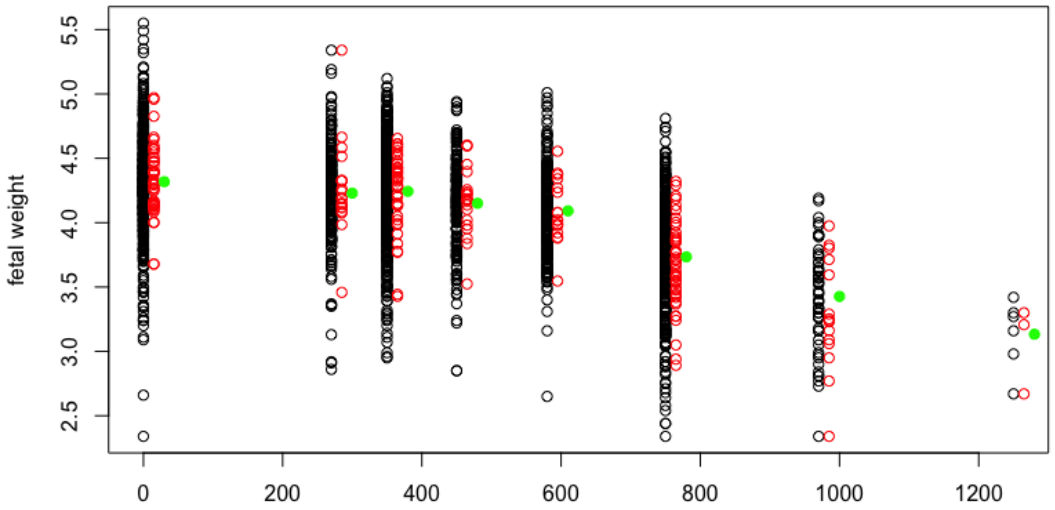
Illustration fetal weight example

N fits	
MA	

BMD estimates

	BMDL	BMD	BMDU	
Bridge	488.80	524.21	560.64	

Illustration fetal weight example



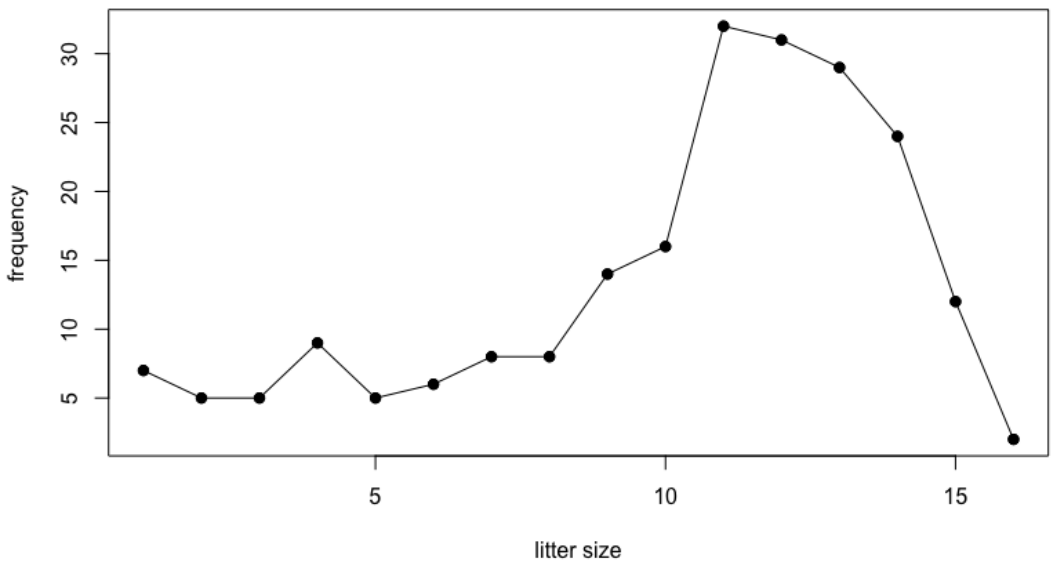


Illustration fetal weight example

Clustered or hierarchical data

- total of 2184 fetuses
- total of 213 litters
- within cluster/litter correlation ρ
  - ▷ $\rho = 0 \rightarrow$ 2184 independent units of information
  - ▷ $\rho = 1 \rightarrow$ 213 independent units of information
  - ▷ $0 < \rho < 1 \rightarrow 213 <$ effective sample size < 2184
- correlated data $\rightarrow$ implicit reduced sample size
- correlated data $\rightarrow$ wider CrI

Illustration fetal weight example

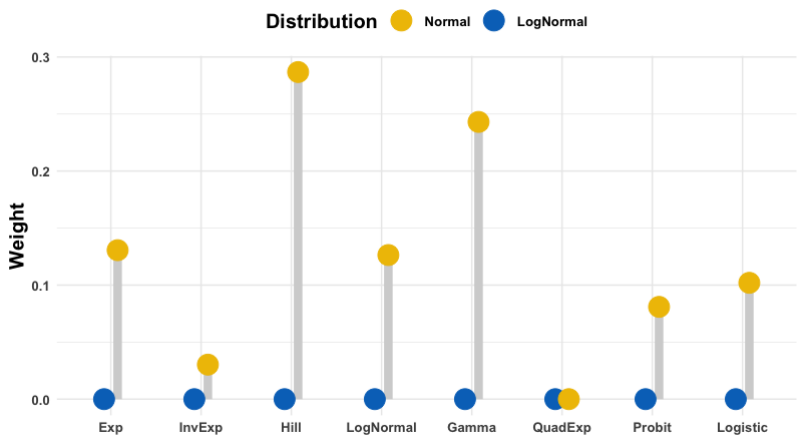
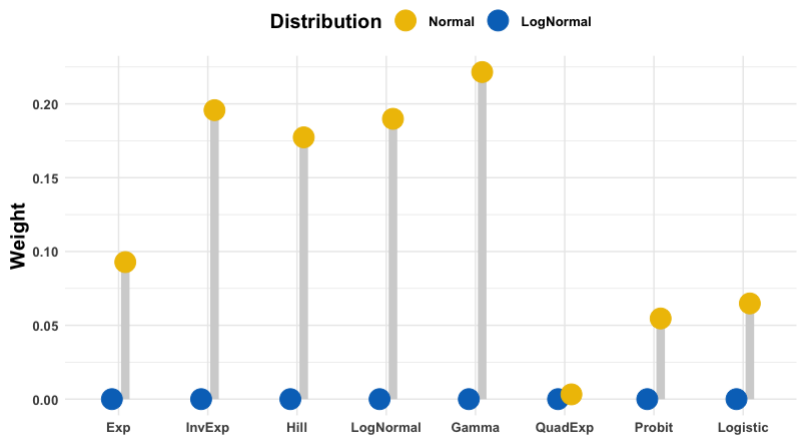
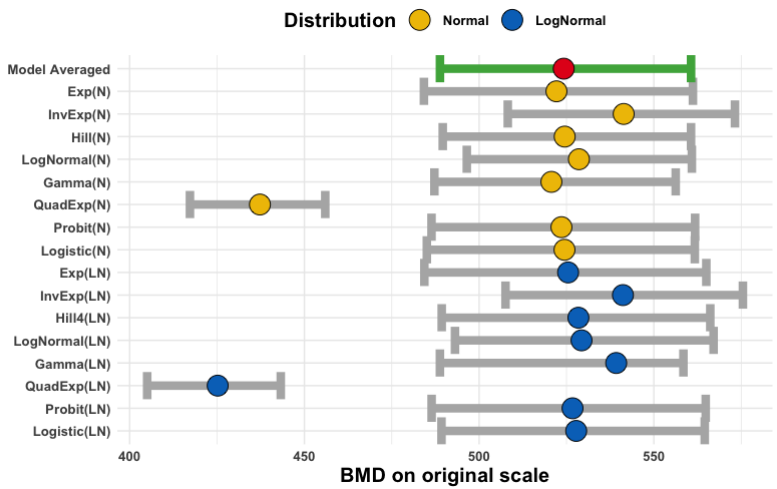
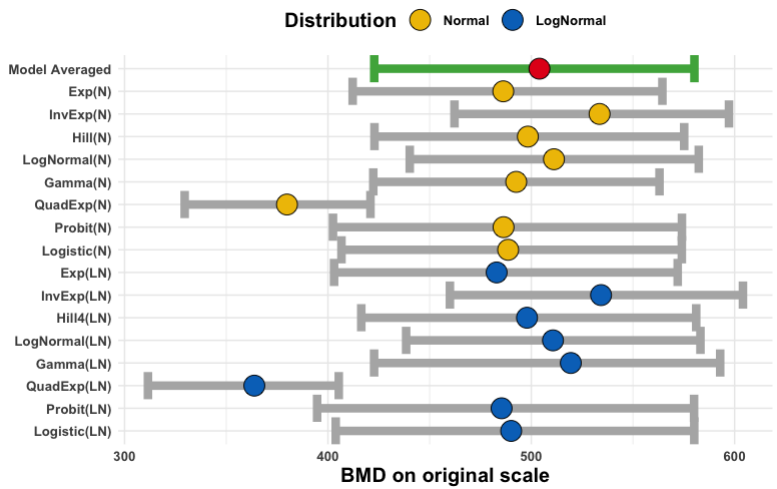
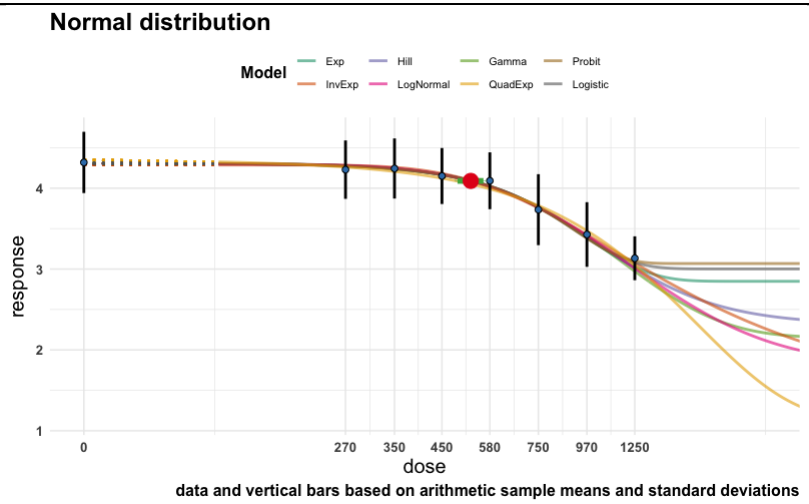
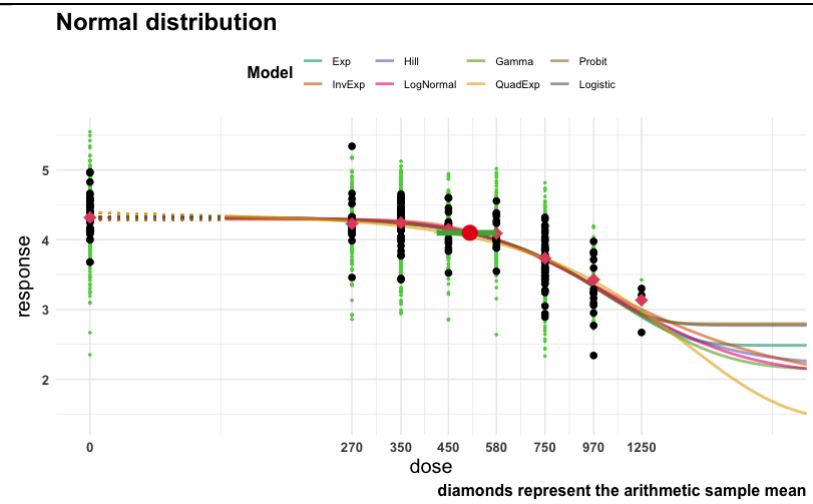
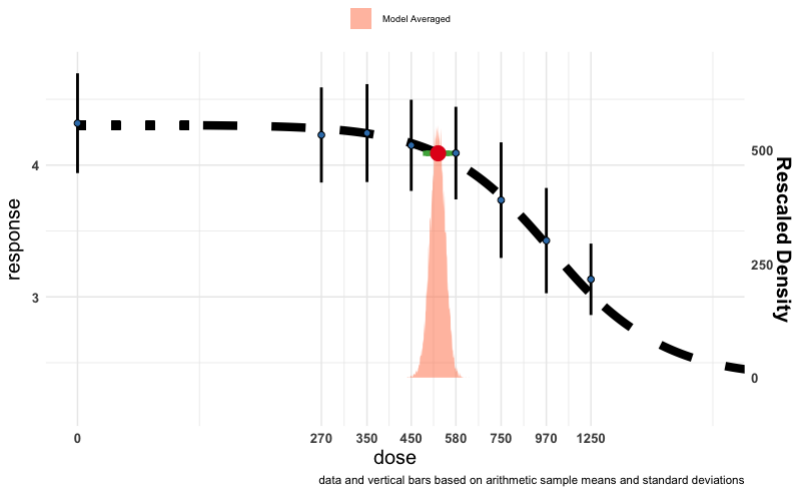
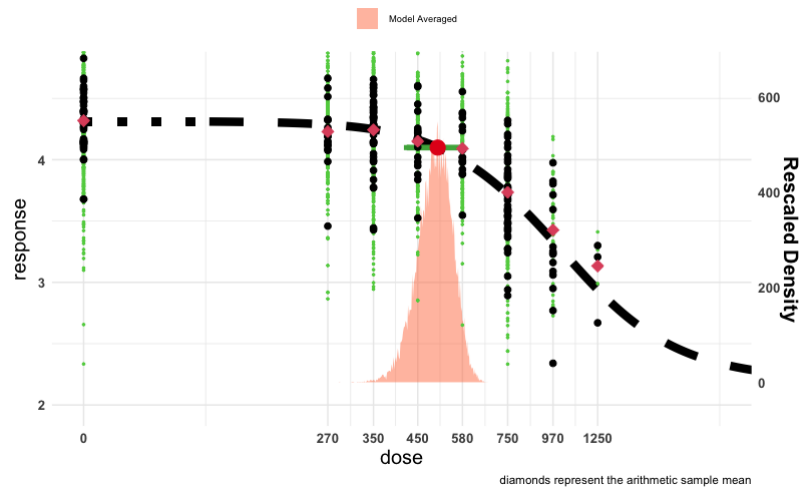
	independent	clustered
weights		
BMD		

Illustration fetal weight example

	independent	clustered
N fits		
MA		

BMD estimates

	independent			clustered		
	BMDL	BMD	BMDU	BMDL	BMD	BMDU
Bridge	488.80	524.21	560.64	422.77	504.01	580.22

Intra-litter correlation

ρ estimated as 0.49 with 95% CrI [0.44,0.55]

ILLUSTRATION 3

Effects of Th17 cells example

Luo *et al*, 2016

Illustration Th17 cells example

- Th17 cell frequency in the spleen in offspring mice (%)
- covariate: groups by sex and day of measurement
- no litter effect considered

Illustration Th17 cells example

Dose	Mean	SD	N	group
0	1.336	0.36	10	female PND21
0	1.348	0.31	10	female PND21
0.475	1.625	0.343	10	female PND21
4.75	2.2	0.663	10	female PND21
47.5	3.336	0.637	11	female PND21
0	1.222	0.233	10	female PND42
0	1.252	0.326	10	female PND42
0.475	1.541	0.325	10	female PND42
4.75	1.819	0.556	10	female PND42
47.5	2.477	0.477	11	female PND42
0	1.347	0.369	10	male PND21
0	1.327	0.282	10	male PND21
0.475	1.554	0.242	10	male PND21
4.75	1.774	0.501	10	male PND21
47.5	2.405	0.532	11	male PND21
0	1.194	0.235	10	male PND42
0	1.234	0.287	10	male PND42
0.475	1.426	0.278	10	male PND42
4.75	1.646	0.477	10	male PND42
47.5	2.226	0.526	11	male PND42

Covariate analysis

- no covariate effect on the distribution itself (normal or log-normal)
- each parameter may depend on covariate $\rightarrow 2^5 \times 16 = 512$ submodels !!!
- reduction to 4 submodels, for each model
  - ▷ background and variance σ^2, **both** depend on covariate, **or none**
  - ▷ BMD and parameter d, **both** depend on covariate, **or none**

Strategy

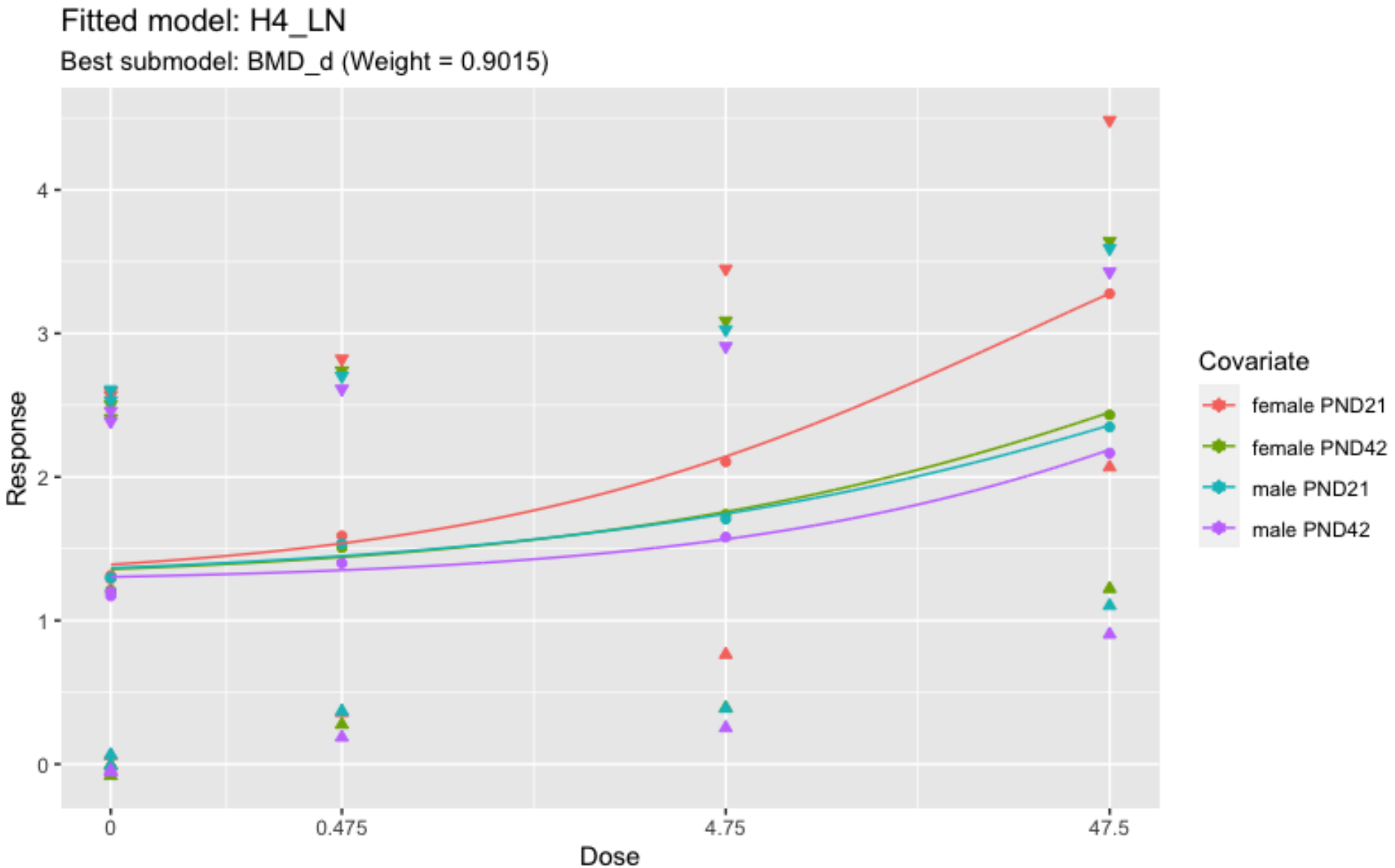
- for each model: select best submodel
- at least one best submodel with covariate-dependent BMD?
  - ▷ yes: group dependent model averaged BMD
  - ▷ no: a single model averaged BMD

Illustration Th17 cells example

Snapshot of submodels

	Model	Weight	Submodel	Submodel.weight	Covariate	BMDL	BMD	BMDU
41	H4_LN	0.9015	BMD_d	0.9910175	female PND21	0.1231119	0.4126029	1.396848
42	H4_LN	0.9015	BMD_d	0.9910175	female PND42	0.2674835	1.0315713	3.950697
43	H4_LN	0.9015	BMD_d	0.9910175	male PND21	0.2275329	0.9828678	4.250223
44	H4_LN	0.9015	BMD_d	0.9910175	male PND42	0.9651136	3.3858943	11.940734
45	LN4_LN	0.0000	all	1.0000000	female PND21	2.2337773	3.6123927	5.812152
46	LN4_LN	0.0000	all	1.0000000	female PND42	0.1668996	0.7215784	3.199886
47	LN4_LN	0.0000	all	1.0000000	male PND21	18.6858249	33.4590809	60.606824
48	LN4_LN	0.0000	all	1.0000000	male PND42	0.3438165	1.6891112	8.248429
49	G4_LN	0.0000	a_sigma2	0.9993374	female PND21	0.2115289	0.6003031	1.717347
50	G4_LN	0.0000	a_sigma2	0.9993374	female PND42	0.2115289	0.6003031	1.717347
51	G4_LN	0.0000	a_sigma2	0.9993374	male PND21	0.2115289	0.6003031	1.717347
52	G4_LN	0.0000	a_sigma2	0.9993374	male PND42	0.2115289	0.6003031	1.717347

Illustration Th17 cells example



Group dependent BMD estimates

	BMDL	BMD	BMDU
female PND21	0.123	0.419	1.420
female PND42	0.267	1.047	3.967
male PND21	0.231	1.001	4.412
male PND42	0.976	3.444	12.407

Questions ?

Outline

- Main statistical methodology
  - ▷ Components of the models
  - ▷ Bayesian inference
  - ▷ Model averaging
- Preliminary statistical tests
- Some further illustrations
- Summary simulation study

Simulation study

Strengths

- mimic real case
- true mechanisms known
- effect of single & multiple factors
- different performance measures
- insight in performance
- recommendations

Limitations

- limited to selected scenarios
- data of real case generated by more complex mechanisms

Simulation study for continuous response

General settings

- scenarios used by US-EPA
- mimic a typical rat bioassay (Piao et al. 2013)
- body weight loss and liver weight gain
- experimental designs based on FDA's Redbook 2000
- 120 scenarios for both endpoints
- 1000 datasets generated for each scenario

General recommendations

- background informative prior: less influential
- maximum response informative prior:
  - ▷ very useful when data do not contain information about asymptote
  - ▷ can affect the estimation beneficially
- BMD informative prior: highly influential
  - ▷ only use shape=4 if sufficient evidence about most likely value is available

General recommendations

- sensitivity analysis for impact of different weakly informative priors for d, especially if fits for the default choice seem less optimal
- if evidence is available that the BMD is to be expected within the experimental range
  - ▷ switch extended range off for default prior for BMD
  - ▷ consider sensitivity analysis

Thank you for your attention !

Questions ?