Bayesian Model Averaging for Dose-Response

Matthew W. Wheeler
National Institute of Environmental Health Sciences

Why Model Averaging?

What assumptions are in a Statistical Analysis?

A statistical analysis is an attempt to synthesize observed data for inference given some mathematical assumptions.

- In the simplest case of a mean, one assumes:
  - Normal approximation.
  - Mean and Finite variance
- For Linear Regression, one assumes:
  - The mean is related to observed covariates.
  - Symmetric Error.

If an assumption doesn't hold, inference increasingly comes into question.

Benchmark Dose Analysis

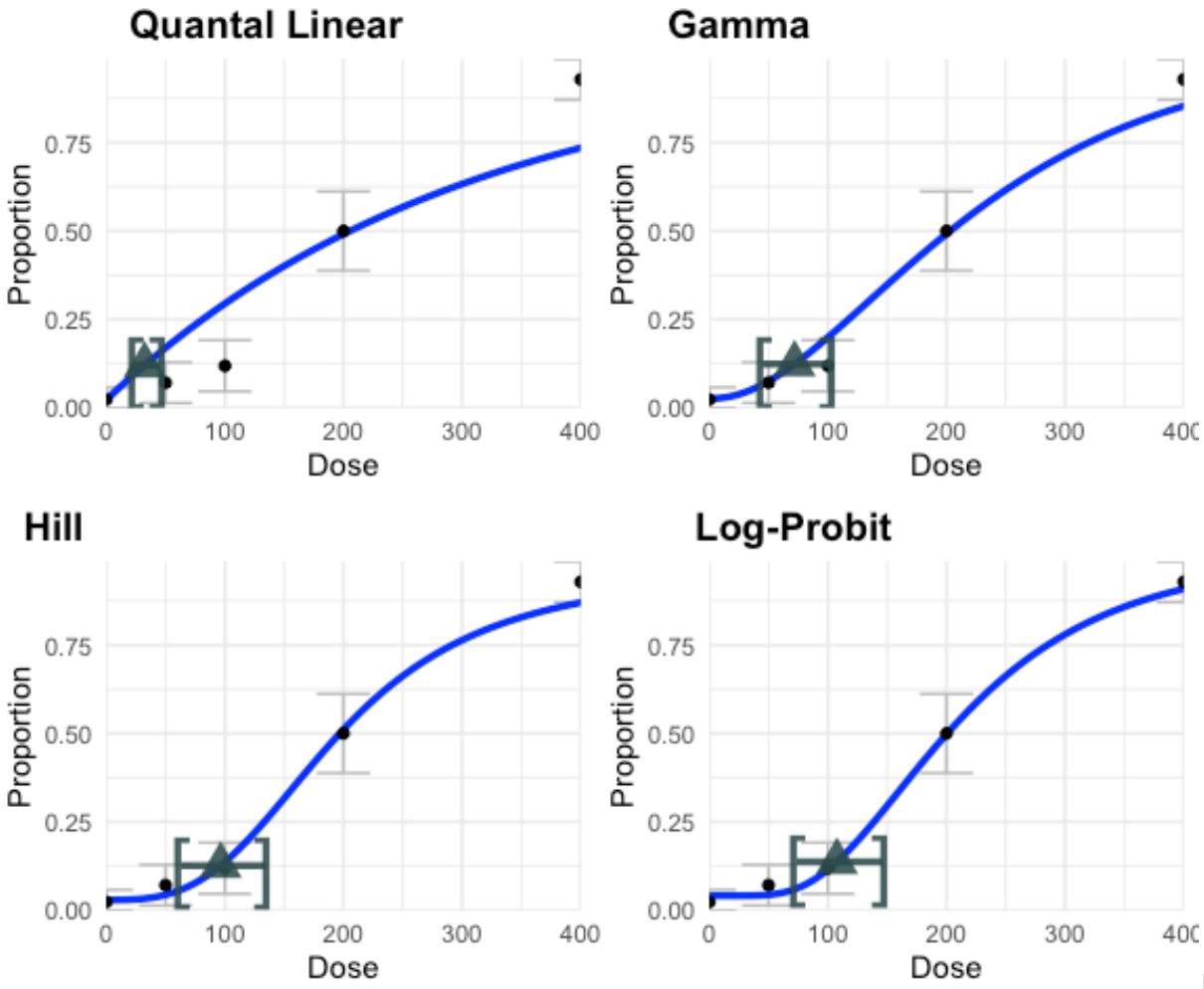
Historically has the following assumptions

- The expected response is a non-linear, monotonic, continuous function of dose.
- Distributional assumptions:
  - Binomial (Dichotomous Data)
  - Normal/Lognormal (Continuous Data)
- A handful of observations can reliably describe the dose-response.

If any one of these assumptions doesn't hold, inference may be compromised.

When the Expected dose-response is wrong

Inference Errors



Model Averaging

Model averaging is a statistical procedure that amalgamates the strength of evidence between models. Inference is then based upon this amalgam (Raftery et al., 1997)

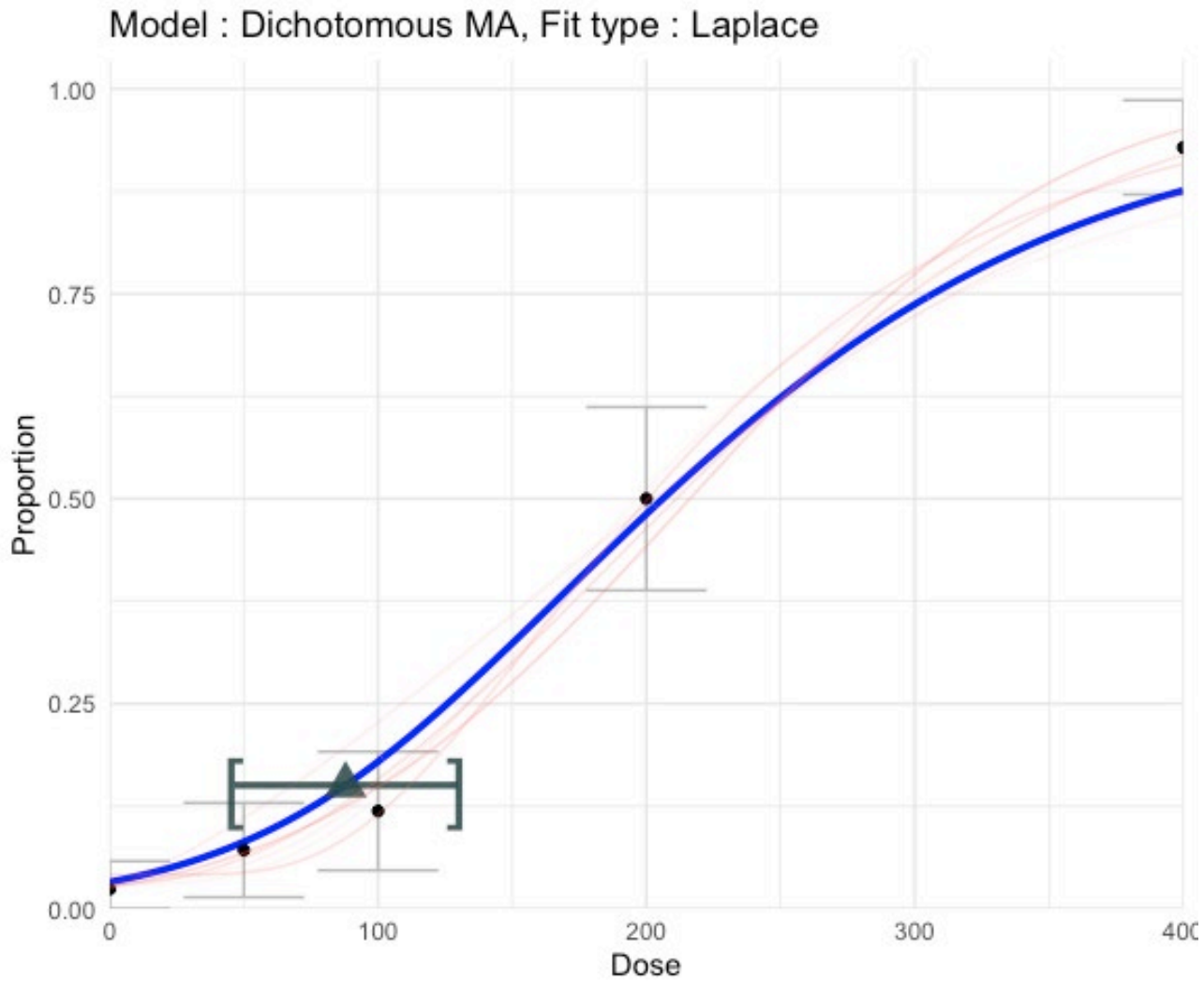
Given some statistic of interest, this is done by creating a weighted average:

$$\hat{\mu}_{ma} = \sum \hat{w}_i \hat{\mu}_i$$

$$\text{where } \sum \hat{w}_i = 1$$

Source: Raftery, Madigan, and Hoeting. ……..JASA, 1997year

Model Averaged Dose-Response



Superior Inference as described in:

EFSA Scientific Committee, More, S. J., Bampidis, V., Benford, D., Bragard, C., Halldorsson, T. I., ... & Schlatter, J. (2022). Guidance on the use of the benchmark dose approach in risk assessment. *EFSA Journal*, *20*(10), e07584.

Wheeler, Matthew W., and A. John Bailer. "Properties of model-averaged BMDLs: a study of model averaging in dichotomous response risk estimation." *Risk Analysis: An International Journal* 27.3 (2007): 659-670.

Wheeler, M. W., Blessinger, T., Shao, K., Allen, B. C., Olszyk, L., Davis, J. A., & Gift, J. S. (2020). Quantitative risk assessment: Developing a Bayesian approach to dichotomous dose–Response uncertainty. *Risk Analysis*, *40*(9), 1706-1722.

Wheeler, M. W., Cortiñas Abrahantes, J., Aerts, M., Gift, J. S., & Allen Davis, J. (2022). Continuous model averaging for benchmark dose analysis: Averaging over distributional forms. *Environmetrics*, *33*(5), e2728.

Why Bayesian Analysis

In science, we love to talk about "objectivity" in inference. People get scared of Bayesian analysis because it introduces "subjective" information. Based upon the above, the inference is based upon unknown assumptions.

This was noted 50 years ago by Good (1973)

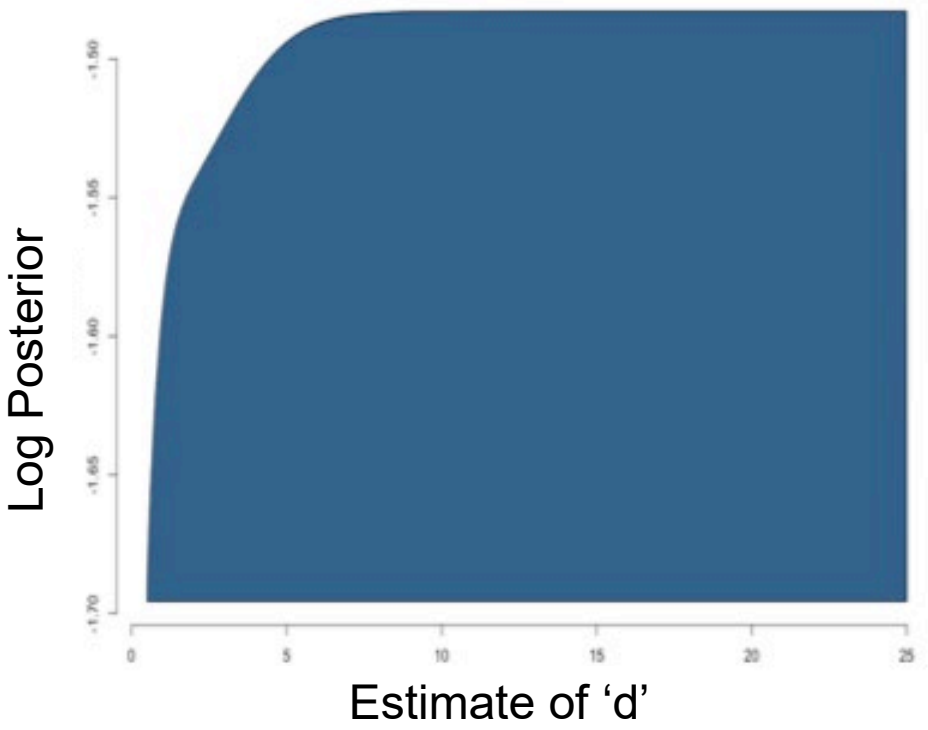
> *"The subjectivists states his judgements, whereas the objectivist sweeps them under the carpet by calling assumptions knowledge, and he basks in the glorious objectivity of science."*

Though I appreciate Good's bluntness, I also appreciate the need to be objective in science. Note: The prior probability distribution in Bayesian inference is necessary for a probabilistic interpretation of the fitted BMD model.

Problem:

Despite our best intentions the problem of dose-response estimation cannot be done reasonably without further assumptions. This problem comes from the non-linear nature of our dose-response functions.

The problem with maximum likelihood



The Hill Model

$$f(dose) = a + \frac{b \times dose^d}{c^d + dose^d}$$

…… you need a MAXIMUM, which we don't always have

Bayesian Analysis

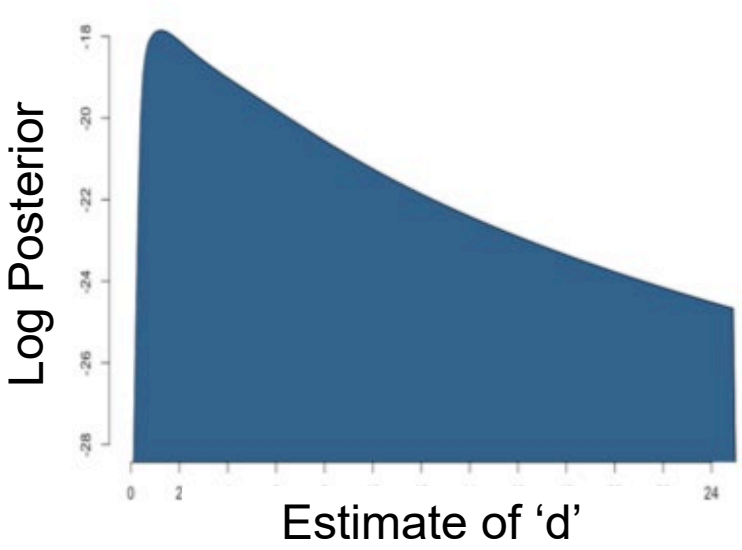
If you don't have a maximum, **ALL** traditional inference methods simply don't apply.

That is the core of our problem: We often don't have enough data to fit the dose-response using maximum likelihood estimation.

The Bayesian method allows us to "**add**" reasonable information to the analysis to perform statistical inference. The problem with this approach is that different people have different definitions of "**reasonable.**"

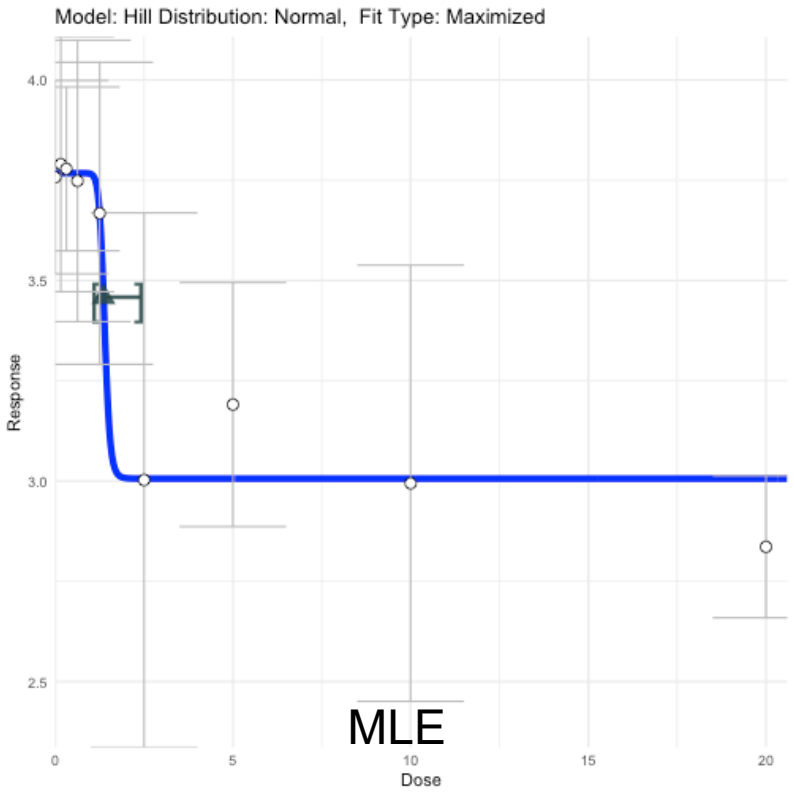
Non-informative Bayesian methods are in the same camp as maximum-likelihood – they produce unreliable results (Wheeler, 2023)

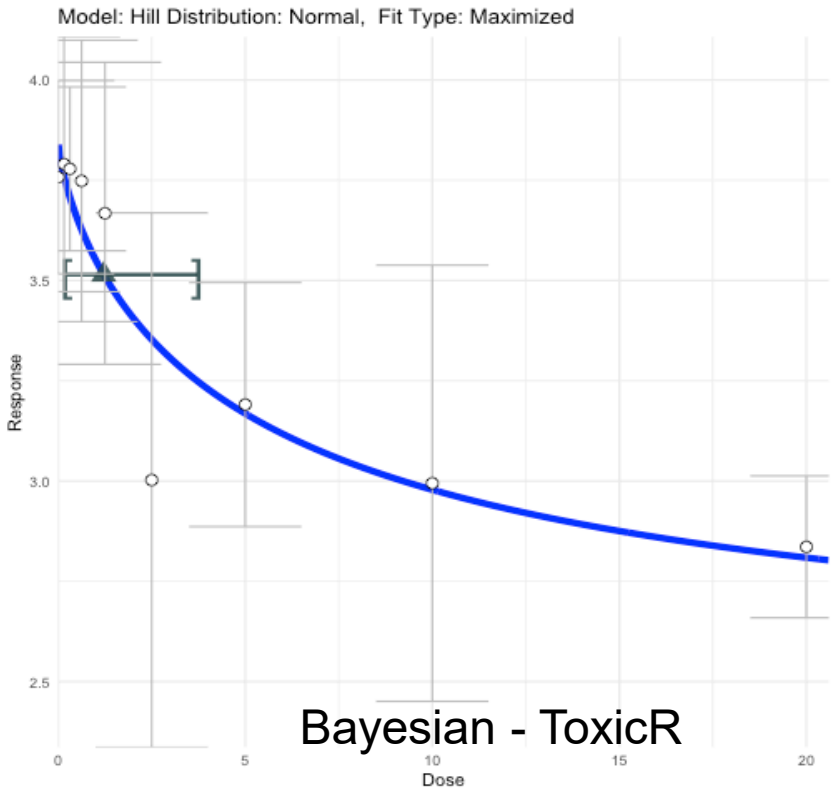
A little information goes a long way…



The parameter ‘d’ is given Cauchy prior, and everything ‘collapses’ and we can perform inference.

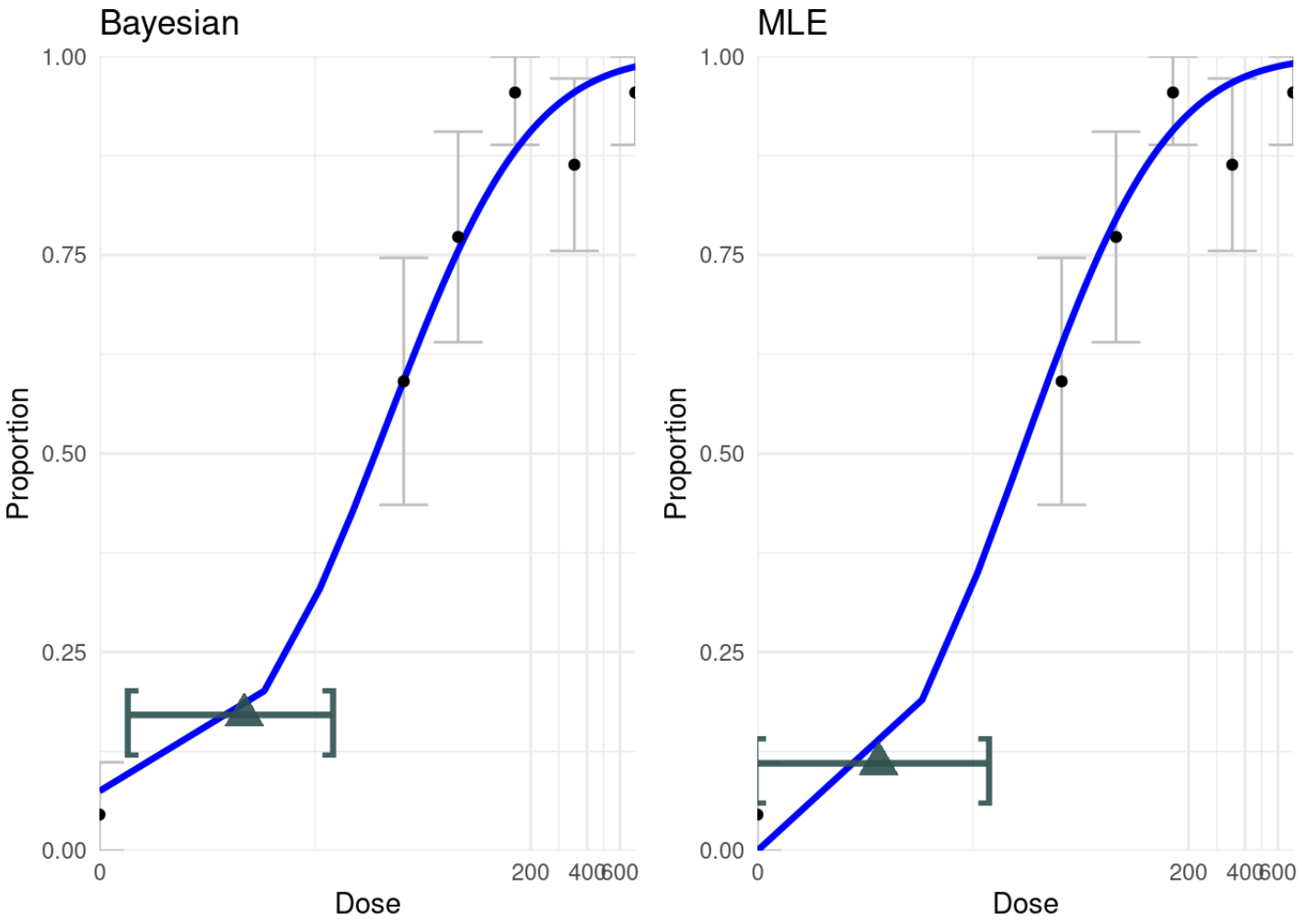
A little information goes a long way…



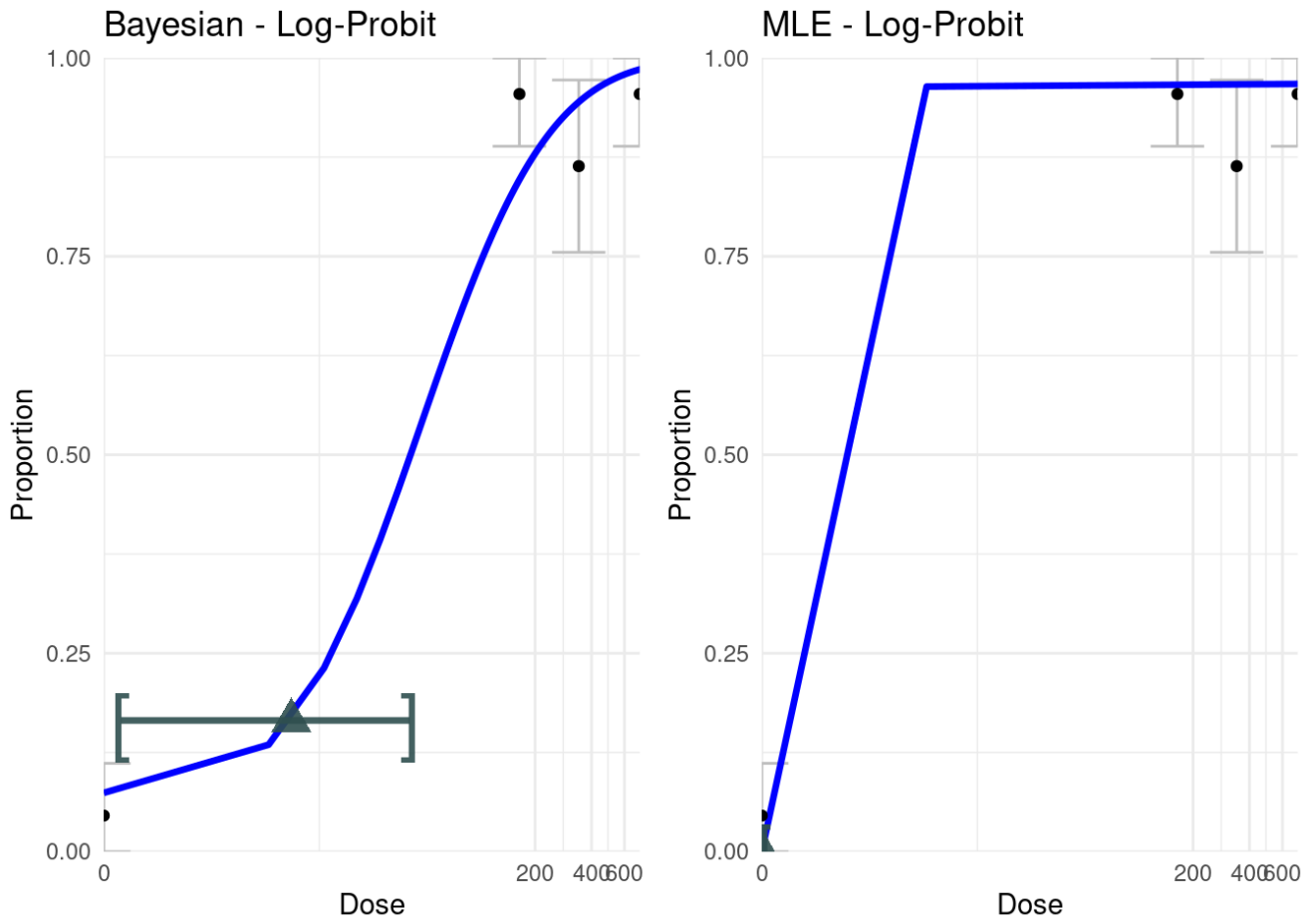


Notice how the Bayesian approach changes inference.

Analysis with FULL data



Analysis with removed data



EFSA's BMDs vs. ToxicR

Reference	EFSA, BMR 10%, Bridge	ToxicR, BMR 10%
3,3'-Dimethylbenzidine dihydrochloride (F, rats, combined adenoma or carcinoma)	(0.14, 1.6)	(0.17, 1.8)
8-Methoxypsoralen (M, rats, combined adenoma or adenocarcinoma)	(0.64, 12.3)	(0.66, 11.9)
Benzo[a]pyrene (F, rats, hepatocellular carcinoma)	(2.9, 4.8)	(2.4, 4.2)
C.I. Acid red 114 (M, rats, basal cell adenoma or carcinoma)	(1.5, 4.1)	(1.6, 5.1)
Cadmium chloride (M, rats, interstitial cell tumors)	(10.4, 199.4)	(7, 130.3)

When we add Bayesian and Model Averaging

Inference becomes “robustified.” This is not perfect, but in simulation studies, we find that we get much more statistically correct results.

In the case of priors, most “reasonable” approaches get qualitatively the same answers.

- A priors sensitivity analysis can quantitate just how different the answers are.

We note that there are some very unreasonable answers one can get if you don’t do MA and Bayesian inference with the above-mentioned data.

Thank You!