Innovative Pediatric Trials: A Statistical Examination of Design and Analysis Strategies

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Disclaimer

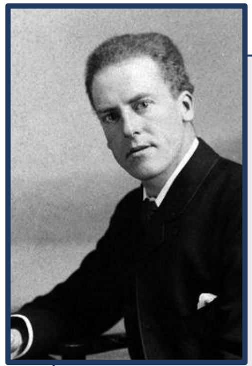
The views and opinions expressed in this presentation are solely my own and do not necessarily reflect the views of Eli Lilly & Company or Indiana University School of Health.

Outline

1. Bayesian methods – an introduction
2. Extrapolation using Bayesian methods
3. Design & operating characteristics for extrapolation
4. Simulation to fine-tune extrapolation

Two approaches to statistical thinking

Philosophical differences → Mathematical differences



Frequentists ask the question,

"Given my assumptions (null hypothesis), how likely is my data?"

Bayesians ask the question,

"Given my data (plus any prior knowledge), how probable is my hypothesis?"

- Neither approach is better, although for some questions one approach may be more useful or more powerful
- Need to apply the best tool for to answer the question
- The Bayesian approach is more natural to incorporate prior information
- Bayesian methods are more computationally intense, which has been the primary limiter in their use until recently.

Prior Distribution: What We Knew

The **prior distribution** is the probability distribution on our parameter of interest, for example rate, based on already attained information (e.g.: publications, internal data, expert opinion, meta-analyses, RWD, etc.).

Prior distribution
(previous knowledge about rate)

$\times$

Likelihood
(new data)

$\propto$

Posterior distribution
(updated knowledge about rate)

"The Prior *times* the Likelihood *is proportional to* the Posterior."

Posterior Distribution: What We Now Know

The **posterior distribution** is the probability distribution on our parameter of interest, for example rate, based on the cumulative information from what is known *a priori* (represented as the prior distribution) and what is observed in a new study (represented as the likelihood).

Prior distribution
(previous knowledge about rate)

$\times$

Likelihood
(new data)

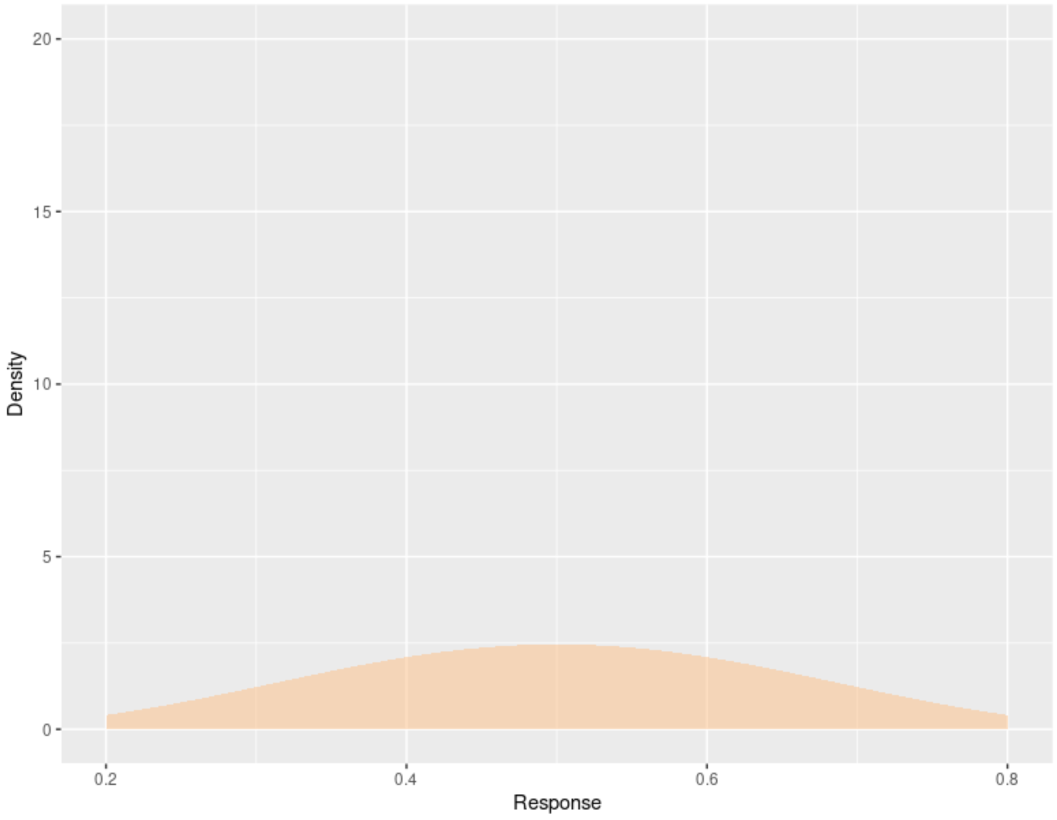
$\propto$

Posterior distribution
(updated knowledge about rate)

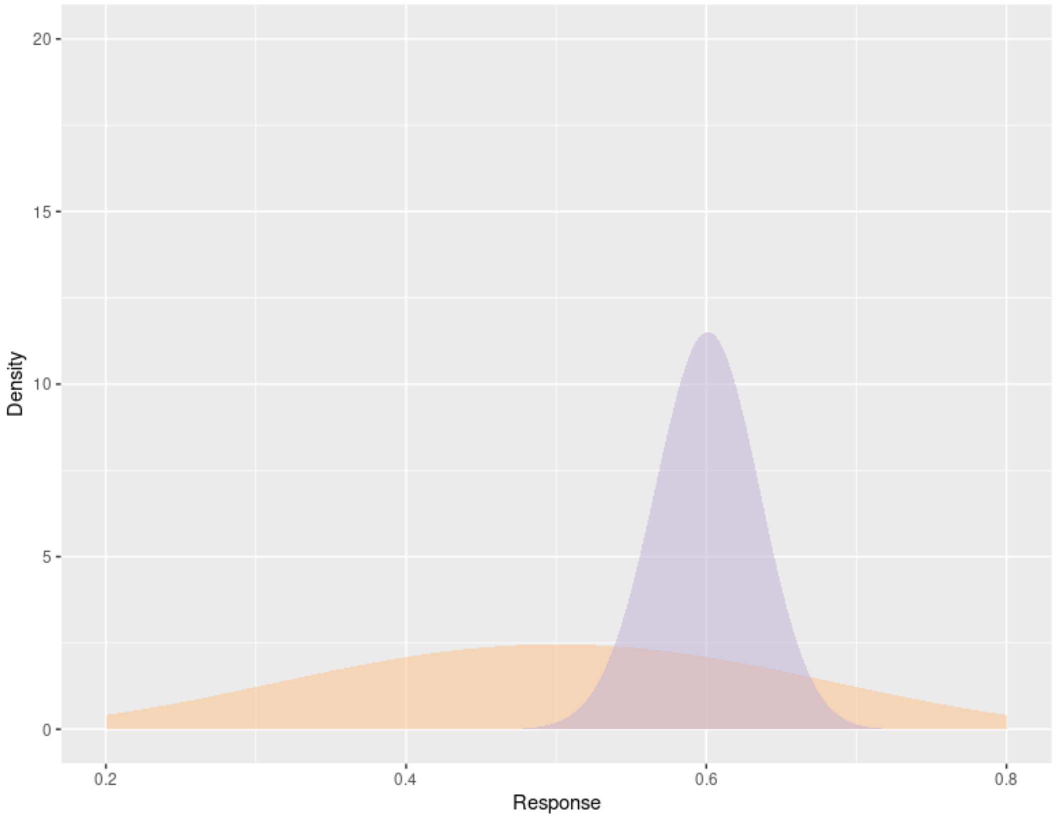
“The Prior *times* the Likelihood *is proportional to* the Posterior.”

Bayesian Methods: An Illustration

Prior

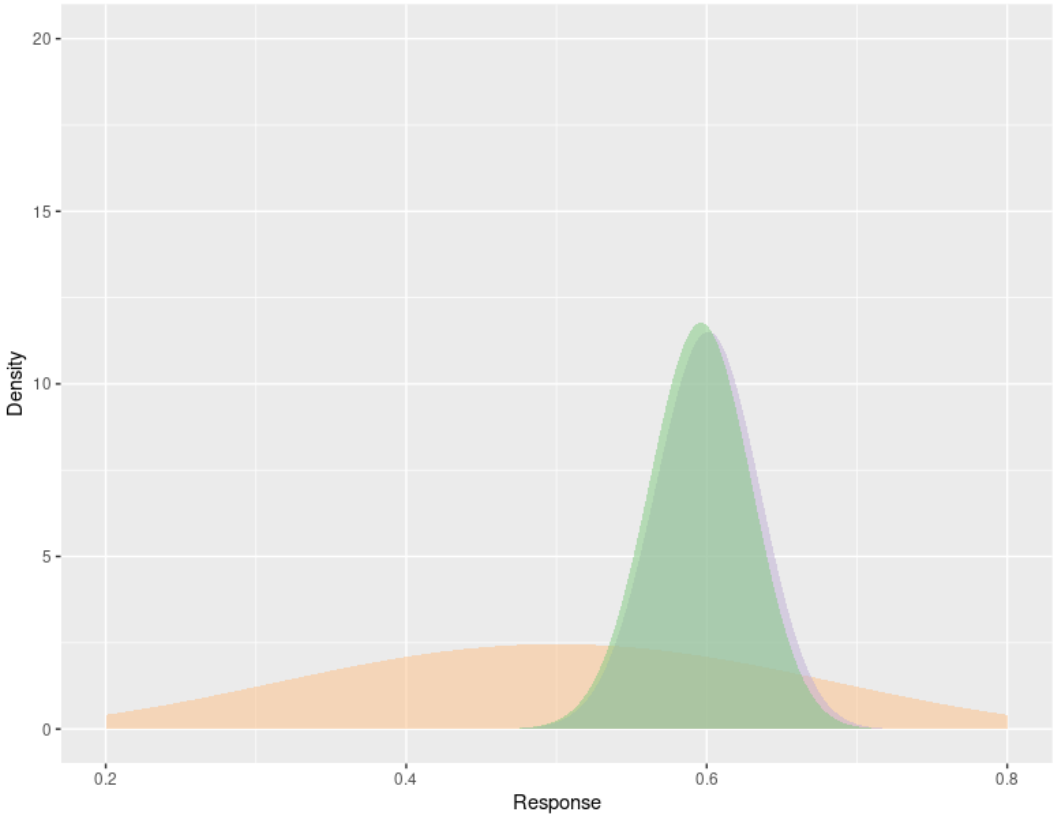


Prior & Likelihood



Bayesian Methods: An Illustration

Posterior ∝ Prior * Likelihood

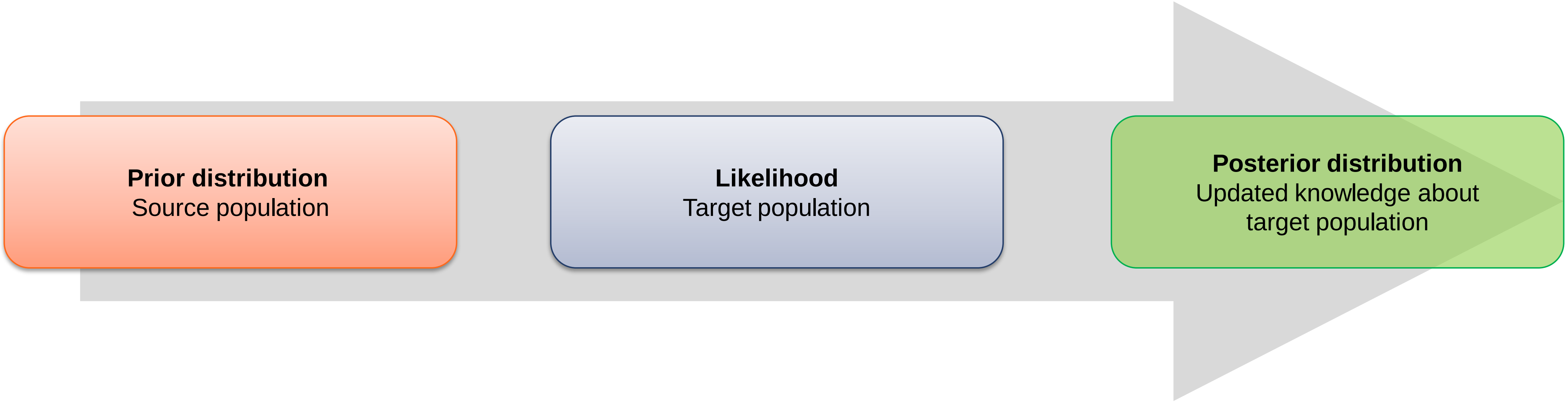


Posterior used for inference & decision-making

- Posterior mean response is estimated to be 0.595
- 95% probability the mean response is between (0.528,0.661)
- The probability that the mean response is greater than 0.60 is 44.8%.
- Decision-rules based on posterior probability thresholds

Bayesian methods are a natural fit for extrapolation when borrowing data in the analysis

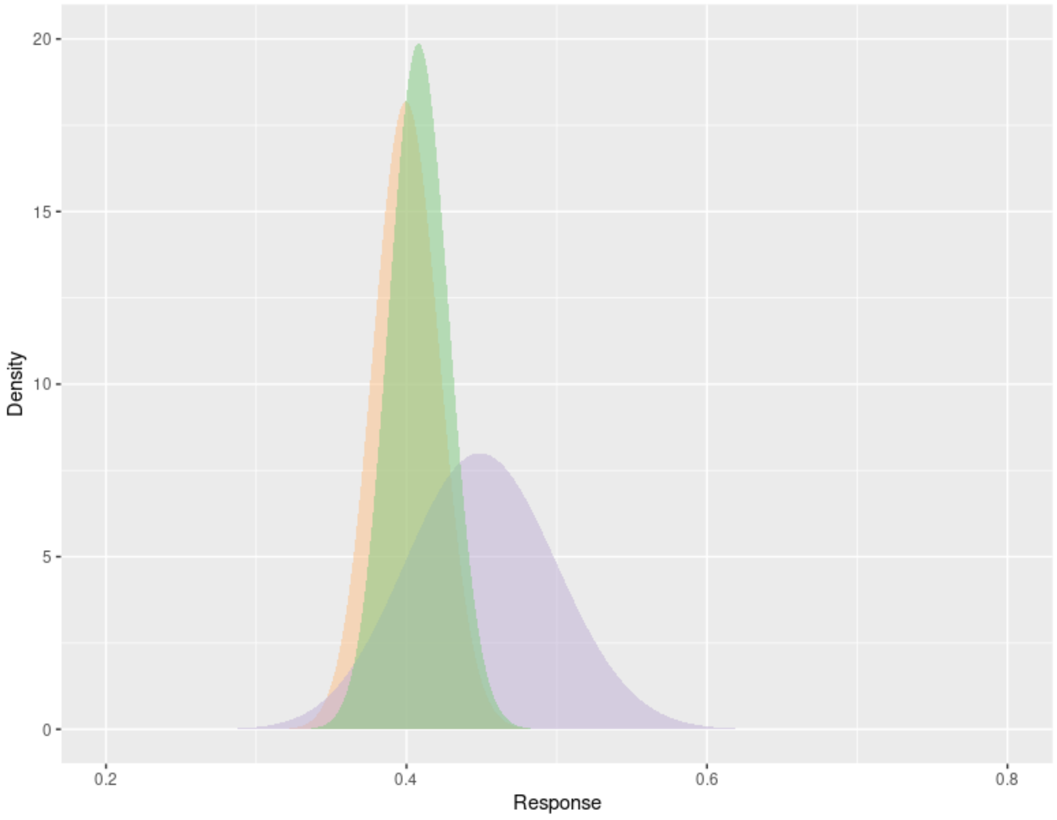
Bayesian analyses are perfectly structured to incorporate prior knowledge from the source population in the analyses of the target population via the prior distribution.



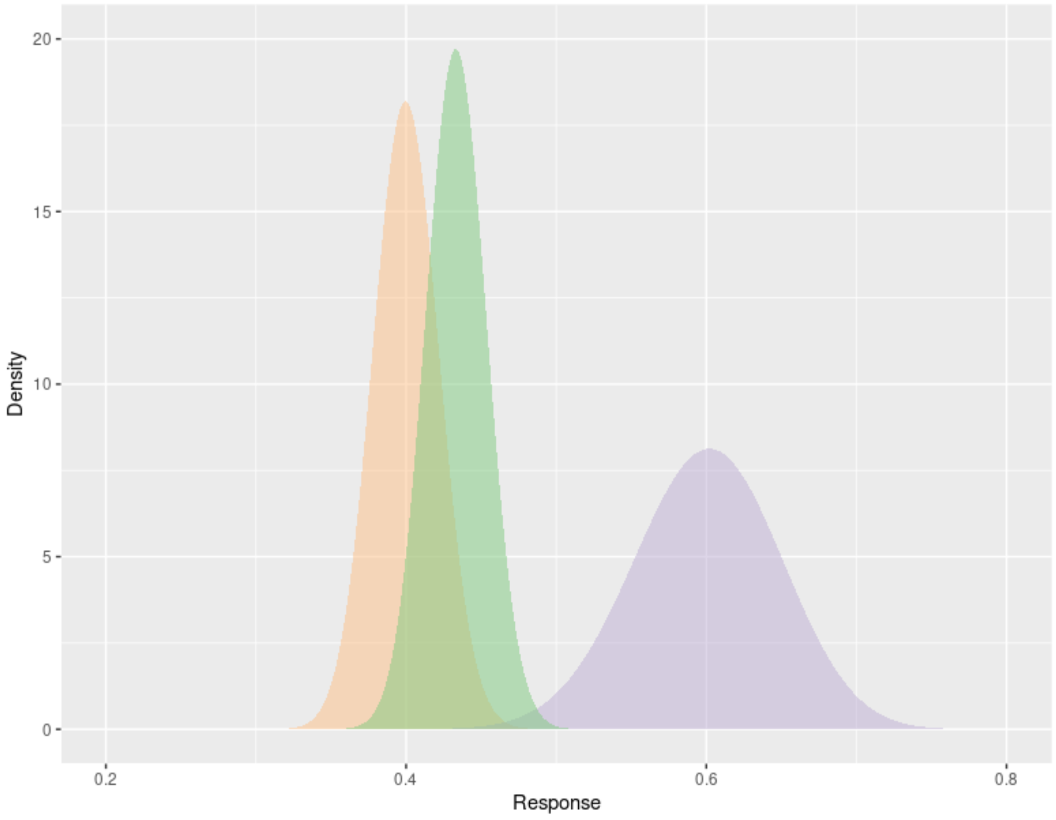
Leveraging prior information may improve the precision of estimates in the source population, and could provide an opportunity to make decisions with smaller sample sizes (leverage what is already known).

Challenge 1: Adult data may overwhelm the pediatric data

Prior & likelihood are similar



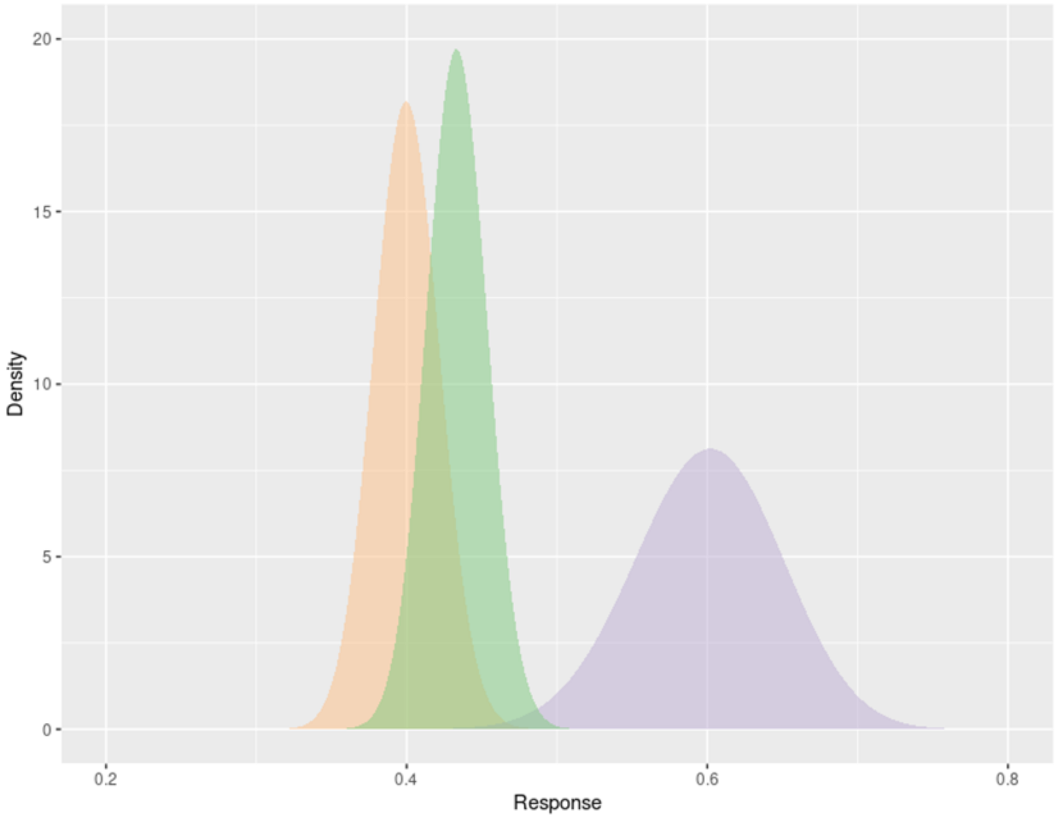
Prior-Likelihood Conflict



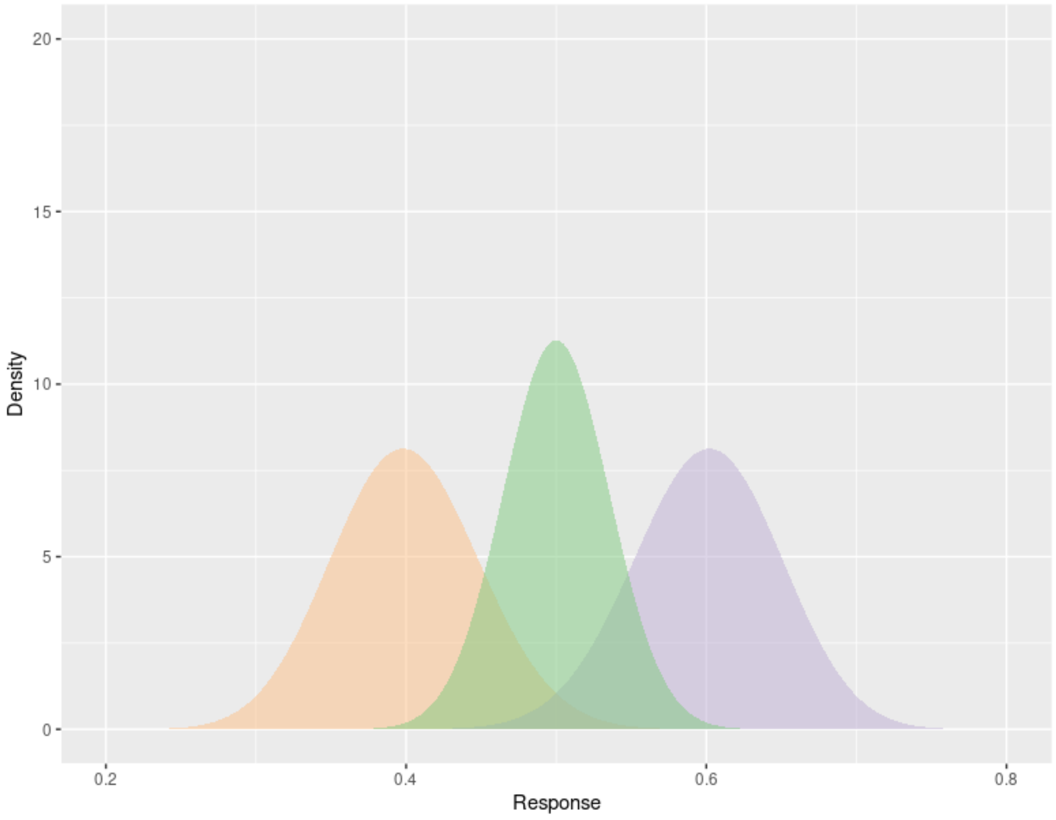
There is a risk that the posterior is more heavily influenced by the prior data, causing any results of the analysis to not rely on the new data (and thus unnecessary).

Discounting offers a way to reduce the impact of prior knowledge on the posterior (updated) result

Original Prior



Discounted Prior



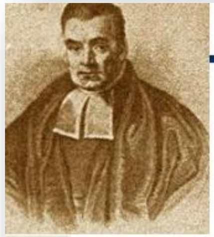
The posterior is less influenced by the discounted prior, but also contains less information (precision).

Challenge 2: Prior-Data Conflict

Being Stubborn and Wrong

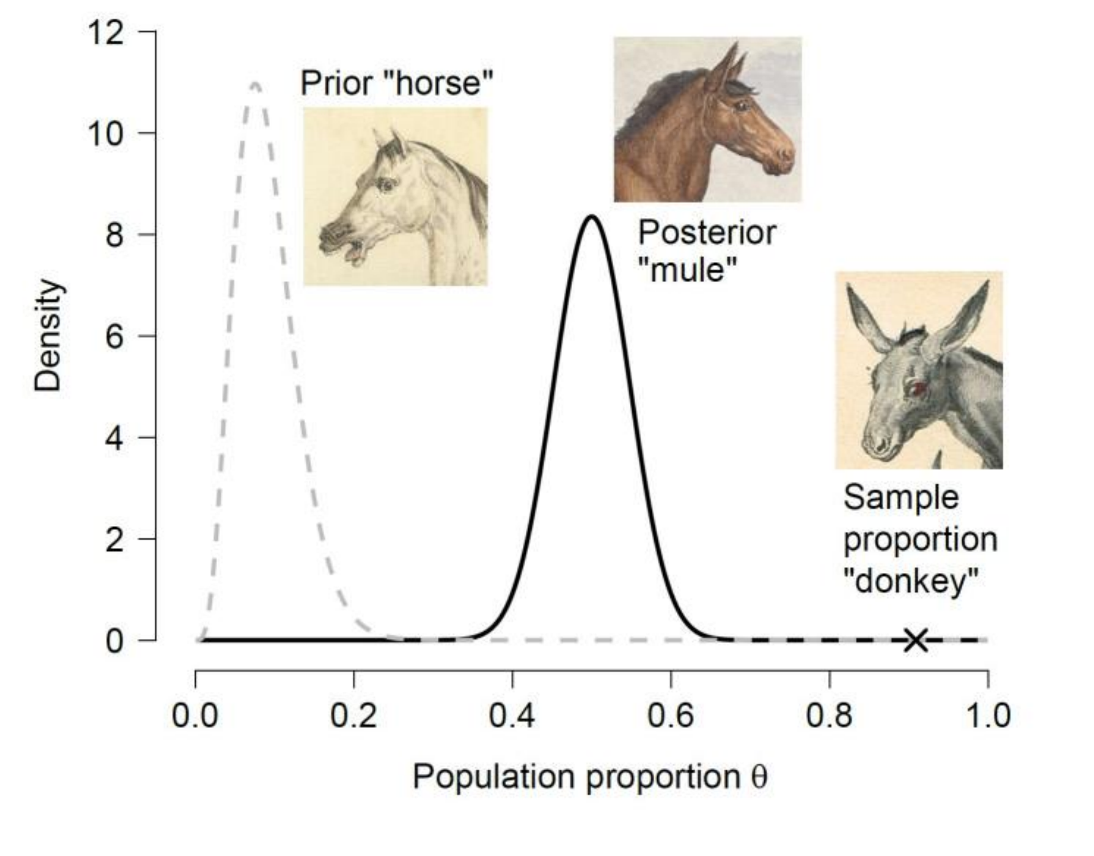
In a nutshell, a Bayesian will perform poorly if he/she is both misguided (with prior mean far from the true value of the parameter) and stubborn (placing a good deal of weight near the prior mean).

Samaniego, 2013



Definition of a Bayesian (Adjusted from Senn, 2007)

"One who, strongly expecting a horse and clearly viewing a donkey, confidently asserts having seen a mule."



Dynamic borrowing methods: discount influence of prior depending on similarity of prior & likelihood

Effects are the same

- Fixed borrowing model
- Pooling

Effects come from a common distribution

- Hierarchical Bayesian models
- Multi-level model
- Power prior model

Effects are in the same neighborhood

- Commensurate prior model
- Machine Learning model

Effects are similar, but provides "off-ramp" if wrong

- Mixture prior model

Effects are unrelated

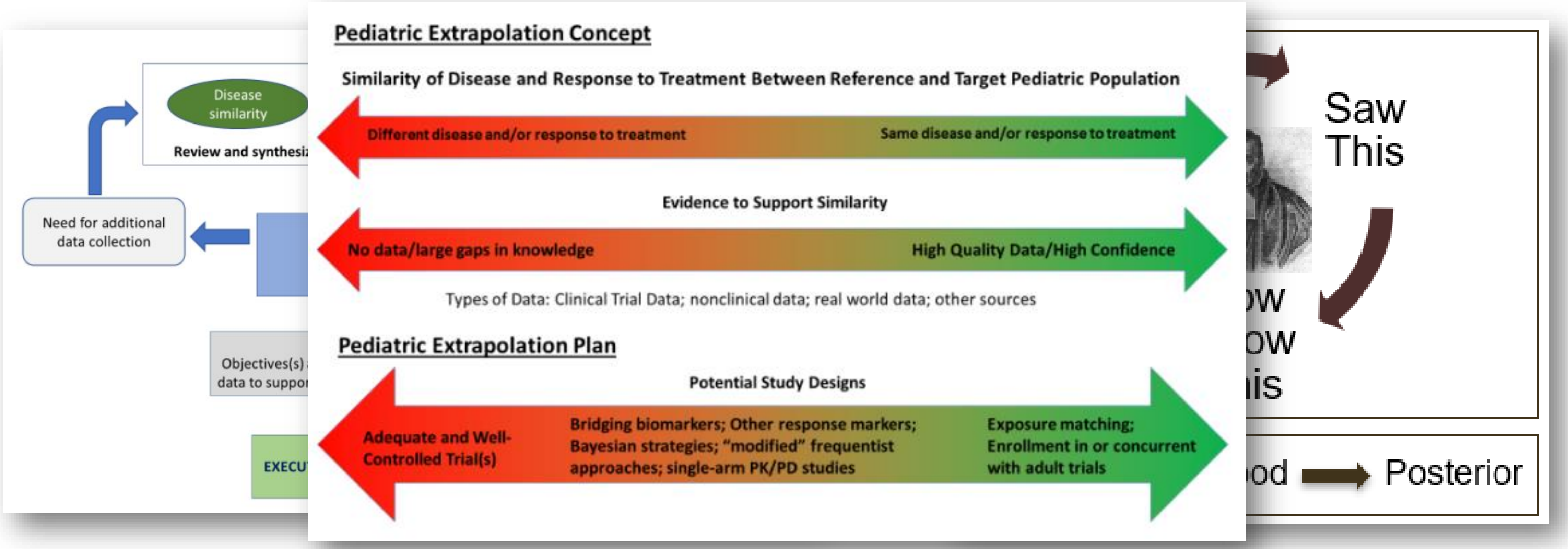
- Independent model

Selecting an appropriate prior

- Prior data generally should not carry more weight than the new trial results
- Which adult data is best to use in the prior?
  - Combine other approaches (such as propensity scores) to find the most similar adults as the basis of the a priori belief
- Consider prior structures that allow for dynamic borrowing, when the extrapolation assumption of similarity in response may not be true
- Perform sensitivity analyses using vague priors and other prior forms that could be of interest to determine the choice of prior on the posterior distribution and any conclusions

Bayesian methods are a powerful tool for extrapolation

The Bayesian framework of updating knowledge mirrors the Extrapolation Framework.



Extrapolation is a continuum, and Bayesian methods allow for borrowing along a continuum.

Examples of Bayesian Methods for Pediatric Extrapolation

- November 8, 2022 Meeting of the Pulmonary-Allergy Drugs Advisory Committee (fda.gov). Bayesian hierarchical model to borrow across age groups (adults, adolescents, children) and dose groups to improve estimation and reduce uncertainty particularly in the smaller subgroups (younger children).
- Bayesian robust mixture priors to borrow historical adult and pediatric data for a new pediatric MS clinical trial.
  - Schmidli et. al. (2020). Beyond Randomized Clinical Trials: Use of External Controls. Clin Pharmacol Ther. 107(4):806-816. doi: 10.1002/cpt.1723. Epub 2019 Dec 17. PMID: 31725899.
- Approval of belimumab for children with SLE, using a post-hoc Bayesian analysis with informative prior knowledge based on adult efficacy via a robust mixture prior. PowerPoint Presentation (fda.gov).
- Bayesian analysis of baricitinib for JIA-Uveitis, with a decision-rule based on historical data (historical data used in the decision rule, not in the estimation of the posterior).
  - Ramanan et al. (2021). Clinical effectiveness and safety of baricitinib for the treatment of juvenile idiopathic arthritis-associated uveitis or chronic anterior antinuclear antibody-positive uveitis: study protocol for an open-label, adalimumab active-controlled phase 3 clinical trial (JUVE-BRIGHT). Trials. 22. 689. 10.1186/s13063-021-05651-5.

True of False? Extrapolation increases error rates

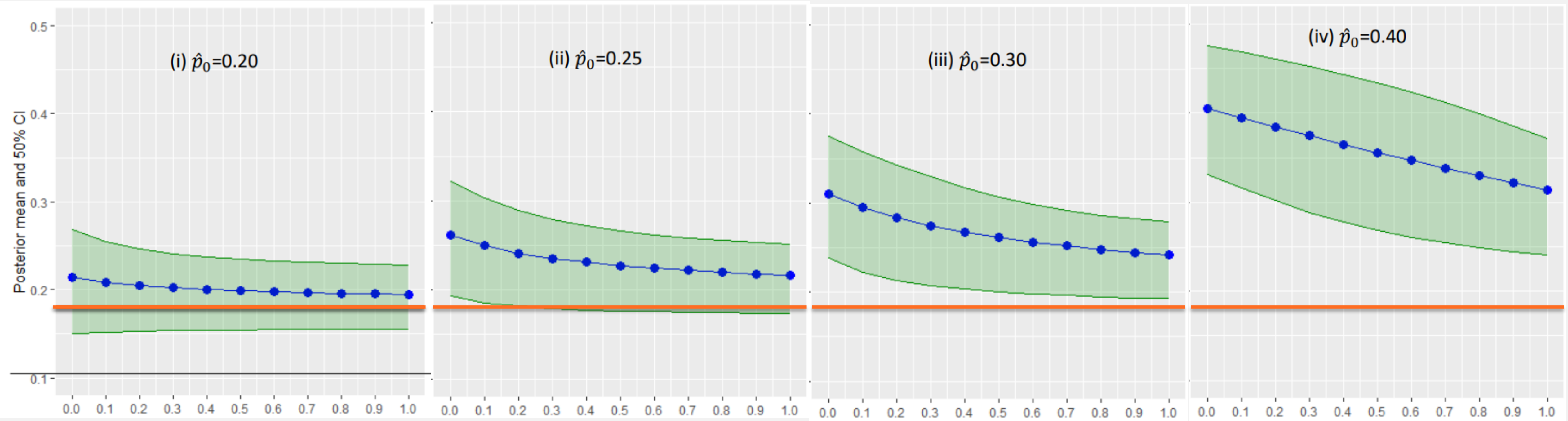
Any potential error in the source population is propagated to the target population when extrapolating.

- Type 1 error: If the conclusion in adults is that a drug is effective, then the error at risk is Type I (truth is that the drug is ineffective). By leveraging positive data in adults, the probability of deciding the drug is effective in children is more likely thus increasing the type I error probability in pediatrics.
- Type II error: also inflated, but not discussed! For example, if the adult data is negative and the program is terminated, also terminating any future or ongoing peds studies, then the probability of a type II error in pediatrics is 100%!

Borrowing shrinks new estimates towards historical estimates

Pediatric data similar to prior adult data

Pediatric data very dissimilar to prior adult data



Degree of borrowing impacts degree of shrinkage (potential bias)

Borrowing data may lead to increased precision, when data are consistent

Borrowing data may lead to increased variability, when data are inconsistent

- At the planning stage, how confident are we that borrowing is appropriate?
- How do we protect against risks of borrowing?

Operating characteristics of interest, assuming positive adult data

Drug not effective in pediatrics

Type I error or False Positive Rate

(inflated when extrapolating)

Bias: shrinkage towards a positive effect

Drug equally effective in pediatrics and adults

Power or True Positive Rate

(increased when extrapolating)

No bias, results in increased precision

Drug effective in pediatrics, but not equal to adults

Power

(increased or decreased, depending on direction of the inconsistency)

Bias: pediatric effect will be skewed in the direction of the adult data (may be positive or negative)

Bias and error rate inflation may be reduced by discounting the amount of adult data being borrowed, however discounting may also decrease the true positive rate and power if the responses are similar.

Program-level simulation

SCENARIO

Adults = Peds Null	Adults = Peds Efficacious	Adults Eff. Peds Null	Peds more efficacious than adults	Peds less efficacious than adults

Adult Study 1

Adult Study 2

Pediatric Study

- Power increases
- Precision increases
- No bias

Under this ideal scenario, extrapolation may allow for leaner pediatric programs (extrapolation can regain any power loss due to smaller sample size)

Program-level simulation

SCENARIO

Adults = Peds Null	Adults = Peds Efficacious	Adults Eff. Peds Null	Peds more efficacious than adults	Peds less efficacious than adults

Adult Study 1

Adult Study 2

→ Pediatric Study

Operating characteristics of interest for pediatric trial(s):

- Probability of type I error in peds (inflated when extrapolating)
- Bias: pediatric estimate pulled in the direction of adults (positive effect)

Often the most concerning scenario (type I error rate inflation in peds). Many novel approaches have been used specifically to address this scenario (e.g. dynamic borrowing)

Program-level simulation

SCENARIO

Adults = Peds Null	Adults = Peds Efficacious	Adults Eff. Peds Null	Peds more efficacious than adults	Peds less efficacious than adults

Adult Study 1

Adult Study 2

→ Pediatric Study

<u>Operating characteristics of interest for pediatric trial(s):</u>

- Power (increased, but incorrectly)
- Bias: pediatric effect being pulled in direction of a more efficacious effect

Type III error: making a correct decision incorrectly

Key Messages

Developing an extrapolation proposal requires a cross-functional team!

Bayesian methods can be a powerful tool to leverage prior data.

The characterization of the prior is critical in Bayesian methods.

Borrowing may have positive or negative impacts on operating characteristics.

The degree to which extrapolation can be relied upon to modify the design of a new trial will be dependent on the perceived level of risk by extrapolating (where on the continuum do you fall?).