Bayesian Re-Design of a Single Arm Pediatric Trial via Borrowing Information from the Concurrent Adult Trials and Historical Pediatric and Adult Trials from the Same Class of Drugs

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Disclosure

No relevant disclosures

Outline

- Introduction
- The Proposed Methodology
- Applications to Pediatric Trials and R Shiny App
- Summary and Discussion

Introduction

Challenges and Opportunities in Pediatric Drug Development

Challenges

Small patient population

Limited physiological data

Ethical complexity

Same evidentiary standards as adults

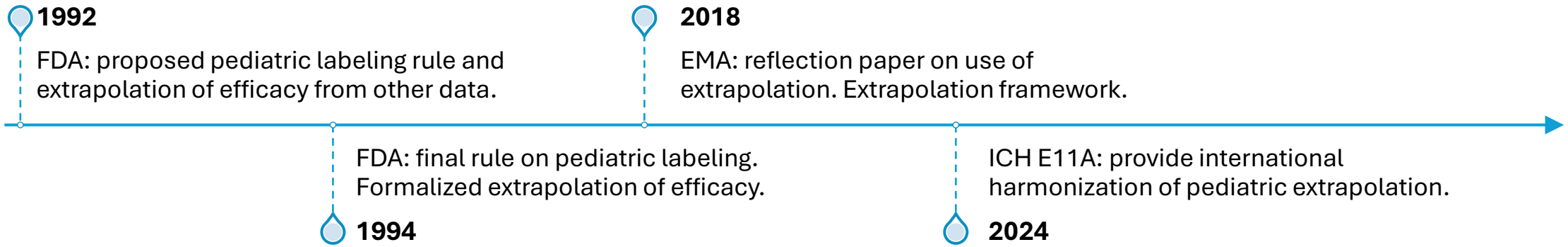
Pediatric drug development lags after adult development

Opportunities

BPCA & PREA legislation incentives

Extrapolation & innovative methods encouraged

Pediatric Extrapolation



- **Definition:** an approach to providing evidence in support of effective and safe use of drugs in the pediatric population when it can be assumed that the course of the disease and the expected response to a medicinal product would be sufficiently similar in the target (pediatric) and reference (adult or other pediatric) population. (ICH E11(R1))
- **Target population:** pediatric
- **Reference/Source population:** adult or other pediatric (e.g., age groups)
- Based on an assessment of the relevant **similarities of disease**, **drug pharmacology**, and **response to treatment** between the two populations
- Extrapolation based on drug's **mechanism-of-action (MOA)** a viable option in the same disease

MOA-Based Extrapolation

Table: Three Archetypes/Treatment Landscape Based on MOA

Archetypes	Adults	Pediatric
A: First in class or first in indication in adults	No approval yet; may be phase 2 in adult establishing POC	No approval and no studies
B: Established class with adult safety and efficacy achieving registration	Approvals in same class	No approvals
C: Established class with adult and pediatric trial conducted, achieving registration	Approvals in same class	Approvals in same class

From archetype C to B then to A, the level of uncertainties increase.

Pediatric Trial Re-design Work

- ASA BIOP section pediatric working group
  - Start with archetype C
  - Redesign pediatric drug program that is relatively recent
- Built on previous review work of recent use of pediatric extrapolation in pediatric drug development in US (Ye et al, 2023)
  - Therapeutic areas considered: antiviral, antiasthma and CNS that can fall under archetype C
- Indication and drug candidate selection criteria:
  - Well-understood MOA
  - Initial pediatric approval after 2019
  - Existing trial with relatively moderate/large sample size
- Sources:
  - FDA pediatric data spreadsheet
  - EMA website for PIP
  - Reference papers
- Hepatitis C virus (HCV) was selected

HCV Treatment and Available Data

DAA agents in HCV treatment regimens

- More effective than older treatments
- Well-understood MOA

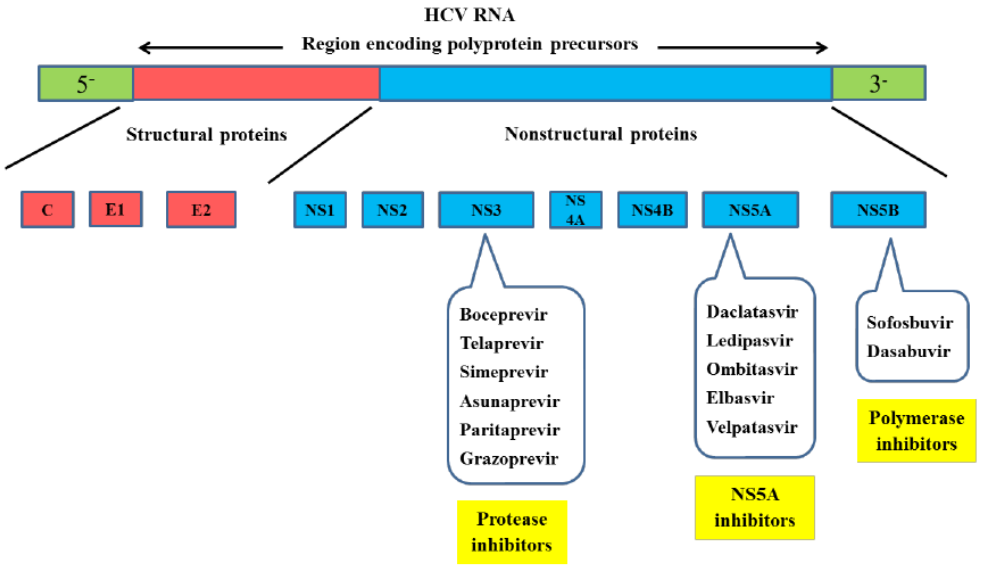


Figure: proteins encoded by the hepatitis C virus genome as targets for direct acting antivirus (DAA) agents.

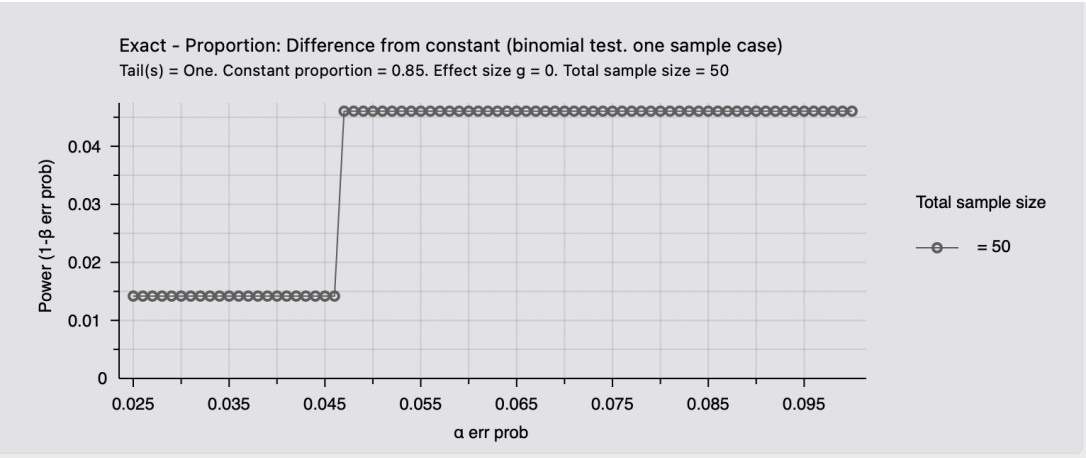
DAA Trade Name	Adult Indication Initial FDA Approval Time	Pediatric Indication Initial FDA Approval Time	Pediatric Age Group	NS3/4A Protease Inhibitor	NS5B Nucleotide Polymerase Inhibitor	NS5A Polymerase Inhibitor
Harvoni	2014	2017	3 years of age and older		✓	✓
Zepatier	2016	2021	12 years of age and older or weighing at least 30 kg	✓		✓
Epclusa	2016	2020	3 years of age and older		✓	✓
Vosevi	2017	NA	NA	✓	✓	✓
Mavyret	2017	2019	3 years of age and older	✓		✓

- Target population: Epclusa pediatric
- Reference population: Epclusa adult, Harvoni (same MOA) adult and pediatric, Mavyret (similar MOA) adult
- Data: 8 trials, 1494 patients

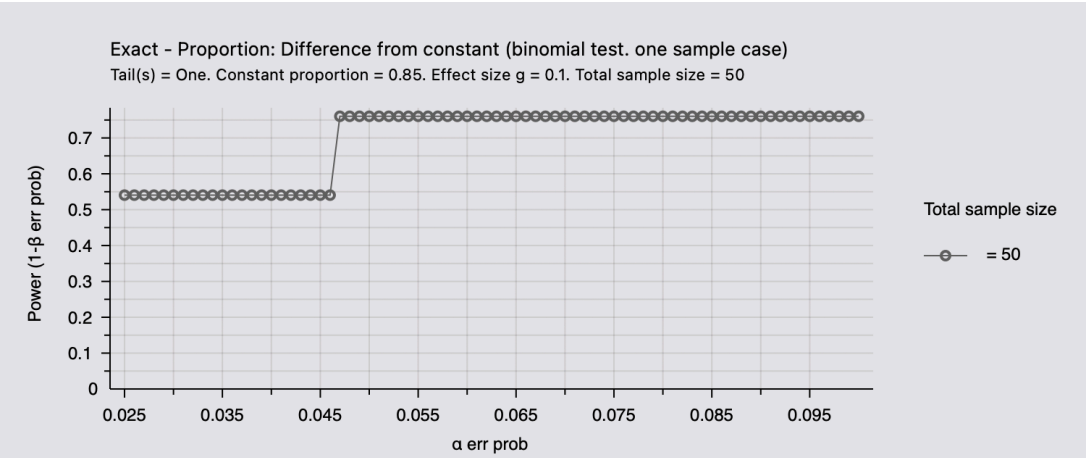
Single-Arm Trials with Binary Endpoint

Single-arm trials with binary endpoints are often considered as the simplest design. However, due to the discrete nature of the binomial distribution, the commonly used deterministic decision rule may not always achieve the intended type I error exactly (Liu et al., 2024).

With the currently available software, such as G*Power 3 and STATA, the actual type I error cannot be exactly controlled at the intended level.

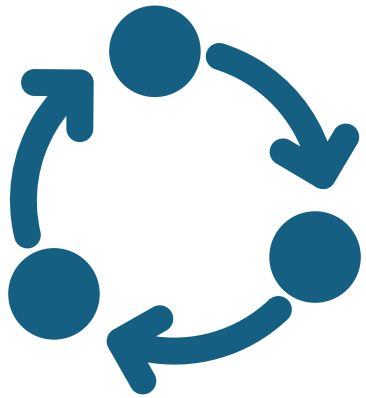


The actual type I error is always **lower** than the intended level.



The actual type I error is below the intended level causes the power to be **underestimated**.

The Proposed Methodology



Design Setting

- Consider to re-design a superiority pediatric one arm trial with a binary outcome variable in the HCV indication.
- The primary endpoint to support HCV efficacy: sustained virologic response at 12 weeks (SVR12) after the end of therapy.
- Let $y^{(n)} = (y, n)$ denote the binomial data with y outcome responders out of n subjects. Also, let θ denote the rate.
- The hypotheses for superiority testing can be formulated as follows.

$$H_0: \theta \leq \theta_0 \text{ versus } H_1: \theta > \theta_0 \qquad (1)$$

where $0 < \theta_0 < 1$ denotes a minimum SVR12 rate determined by a sponsor and/or a regulatory agency.

Decision Rule and Key Quantity

- **Decision Rule:** Let $T(y^{(n)})$ denote a test statistic. We define a deterministic decision rule based on $T(y^{(n)})$ to reject H_0 as

$$\psi(y) = \begin{cases} 1 & \text{if } T(y) \geq \gamma \\ 0 & \text{if } T(y) < \gamma \end{cases} \tag{2}$$

- **Key Quantity:** We define

$$\beta^{(n)}_{\pi^{(s)}} = \int_{\Theta_s} \sum_{y=0}^{n} \psi(y) f(y|n,\theta) \pi^{(s)}(\theta) d\theta \tag{3}$$

Bayesian Type I Error and Power

- **Parameter space**:
  - Let Θ_0 and Θ_1 denote the parameter spaces corresponding to H_0 and H_1.
- **Sampling prior:**
  - $\pi_0^{(s)}(\theta)$ denote a sampling prior with support Θ_0
  - $\pi_1^{(s)}(\theta)$ denote a sampling prior with support Θ_1
- **Type I error:** $\beta^{(n)}_{\pi_0^{(s)}}$
- **Power:** $\beta^{(n)}_{\pi_1^{(s)}}$

Size of a Bayesian Test

- As discussed in Liu et al. (2024), the **size of a Bayesian test** is defined as

$$\alpha^{(n)} = \sup\{\beta^{(n)}_{\pi_0^{(s)}} : \pi_0^{(s)} \text{with the support } \Theta_0\} \tag{4}$$

- For a binomial endpoint, to obtain an exactly intended size of the test, the deterministic decision rule in (2) needs to be extended to the **randomized decision rule** as follows

$$\psi(y) = \begin{cases} 1 & \text{if } T(y) > \gamma \\ \xi & \text{if } T(y) = \gamma \\ 0 & \text{if } T(y) < \gamma \end{cases} \tag{5}$$

where $0 \leq \xi \leq 1$.

Achieving Exact Type I Error

- We consider a point mass sampling prior as

$$\pi_0^{(s)}(\theta) = \Delta_{\{\theta=\theta_0\}} \tag{6}$$

- Under this special sampling prior, the type I error is given by

$$\beta^{(n)}_{\Delta_{\{\theta=\theta_0\}}} = \sum_{y=0}^{n} [1\{T(y) > \gamma\} + \xi 1\{T(y) = \gamma\}] f(y|n, \theta_0) \tag{7}$$

- Exact type I error search algorithm

The Posterior Probability (PP) Approach

- For the approach proposed by Chen *et al.* (2011), let

$$T(\mathrm{y}^{(n)}|\pi^{(f)}) = P(\theta > \theta_0|y, n, \pi^{(f)}) \quad (8)$$

  where the probability is computed with respect to the posterior distribution given the data $\mathrm{y}^{(n)}$ and the fitting prior $\pi^{(f)}(\theta)$.
- A beta prior, Beta(a_0, b_0), where $a_0 > 0$ and $b_0 > 0$, is assumed for $\pi^{(f)}$.
- The test statistic is reduced to

$$T(\mathrm{y}^{(n)}|\pi^{(f)}) = 1 - F_{Beta(y+a_0, n-y+b_0)}(\theta_0) \quad (9)$$

where $F_{Beta(y + a_0, n - y + b_0)}$ is the cumulative distribution function (cdf) of $Beta(y + a_0, n - y + b_0)$.

Power Calculation

- Consider another point mass sampling prior for calculating the power as

$$\pi_1^{(s)}(\theta) = \Delta_{\{\theta=\theta_1\}} \tag{10}$$

- From the randomized decision rule in (5), the key quantity is reduced to

$$\beta^{(n)}_{\Delta_{\{\theta=\theta_1\}}} = \sum_{y=0}^{n} [1\{T(y|\pi^{(f)}) > \gamma\} + \xi 1\{T(y|\pi^{(f)}) = \gamma\}] f(y|n, \theta_1) \tag{11}$$

- Under this setting, the power is independent of the choice of fitting prior.

Empirical Illustrations

- Provide an example illustrating how the proposed algorithm calculates the value of γ and ξ that ensure the key quantity attains the exact type I error in setting without borrowing.
  - ξ remained unaffected by the choice of the fitting prior
  - γ decreases as shape parameters of fitting prior increase
- Power is independent of the choice of fitting prior as well

		n = 50			n = 76			n = 100		
$(a_0, b_0)^*$	α	y_α	γ	ξ	y_α	γ	ξ	y_α	γ	ξ
$\theta_0 = 0.85$										
$(\frac{1}{10^3}, \frac{1}{10^3})$	0.025	47	0.9839	0.3394	70	0.9766	0.1343	92	0.9866	0.8383
	0.050	46	0.9487	0.0598	69	0.9456	0.0057	91	0.9700	0.8155
	0.100	46	0.9487	0.8168	69	0.9456	0.9982	89	0.8935	0.0086
	0.150	45	0.8772	0.3533	68	0.8918	0.6509	89	0.8935	0.7894
$(\frac{1}{3}, \frac{1}{3})$	0.025	47	0.9773	0.3394	70	0.9704	0.1343	92	0.9833	0.8383
	0.050	46	0.9341	0.0598	69	0.9344	0.0057	91	0.9639	0.8155
	0.100	46	0.9341	0.8168	69	0.9344	0.9982	89	0.8788	0.0086
	0.150	45	0.8525	0.3533	68	0.8743	0.6509	89	0.8788	0.7894
$(\frac{1}{2}, \frac{1}{2})$	0.025	47	0.9734	0.3394	70	0.9669	0.1343	92	0.9814	0.8383
	0.050	46	0.9259	0.0598	69	0.9282	0.0057	91	0.9605	0.8155
	0.100	46	0.9259	0.8168	69	0.9282	0.9982	89	0.8711	0.0086
	0.150	45	0.8394	0.3533	68	0.8650	0.6509	89	0.8711	0.7894
(1,1)	0.025	47	0.9587	0.3394	70	0.9546	0.1343	92	0.9748	0.8383
	0.050	46	0.8978	0.0598	69	0.9075	0.0057	91	0.9490	0.8155
	0.100	46	0.8978	0.8168	69	0.9075	0.9982	89	0.8461	0.0086
	0.150	45	0.7967	0.3533	68	0.8347	0.6509	89	0.8461	0.7894
$\theta_0 = 0.9$										
$(\frac{1}{10^3}, \frac{1}{10^3})$	0.025	49	0.9943	0.6931	73	0.9839	0.3157	95	0.9746	0.0381
	0.050	48	0.9631	0.2080	72	0.9496	0.0465	95	0.9746	0.7763
	0.100	48	0.9631	0.8495	72	0.9496	0.8144	94	0.9388	0.7121
	0.150	47	0.8799	0.2762	71	0.8811	0.3639	93	0.8766	0.3695
$(\frac{1}{3}, \frac{1}{3})$	0.025	49	0.9888	0.6931	73	0.9768	0.3157	95	0.9667	0.0381
	0.050	48	0.9453	0.2080	72	0.9340	0.0465	95	0.9667	0.7763
	0.100	48	0.9453	0.8495	72	0.9340	0.8144	94	0.9243	0.7121
	0.150	47	0.8451	0.2762	71	0.8548	0.3639	93	0.8541	0.3695
$(\frac{1}{2}, \frac{1}{2})$	0.025	49	0.9851	0.6931	73	0.9725	0.3157	95	0.9621	0.0381
	0.050	48	0.9347	0.2080	72	0.9252	0.0465	95	0.9621	0.7763
	0.100	48	0.9347	0.8495	72	0.9252	0.8144	94	0.9162	0.7121
	0.150	47	0.8261	0.2762	71	0.8406	0.3639	93	0.8420	0.3695
(1,1)	0.025	49	0.9691	0.6931	73	0.9562	0.3157	95	0.9458	0.0381
	0.050	48	0.8961	0.2080	72	0.8944	0.0465	95	0.9458	0.7763
	0.100	48	0.8961	0.8495	72	0.8944	0.8144	94	0.8888	0.7121
	0.150	47	0.7636	0.2762	71	0.7941	0.3639	93	0.8028	0.3695

* Shape parameters for fitting Beta priors.

		n = 50		n = 76		n = 100	
$\theta_0 = 0.85$							
$(a_0, b_0)^*$	α	0.9	0.95	0.9	0.95	0.9	0.95
$(\frac{1}{10^3}, \frac{1}{10^3})$	0.025	0.1588	0.6152	0.2347	0.8328	0.3023	0.9264
	0.050	0.2611	0.7685	0.3541	0.9147	0.4272	0.9654
	0.100	0.3980	0.8715	0.5052	0.9639	0.5842	0.9886
	0.150	0.4965	0.9196	0.6004	0.9787	0.6778	0.9942
$(\frac{1}{3}, \frac{1}{3})$	0.025	0.1588	0.6152	0.2347	0.8328	0.3023	0.9264
	0.050	0.2611	0.7685	0.3541	0.9147	0.4272	0.9654
	0.100	0.3980	0.8715	0.5052	0.9639	0.5842	0.9886
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$(\frac{1}{2}, \frac{1}{2})$	0.025	0.1588	0.6152	0.2347	0.8328	0.3023	0.9264
	0.050	0.2611	0.7685	0.3541	0.9147	0.4272	0.9654
	0.100	0.3980	0.8715	0.5052	0.9639	0.5842	0.9886
	0.150	0.4965	0.9196	0.6004	0.9787	0.6778	0.9942
(1,1)	0.025	0.1588	0.6152	0.2347	0.8328	0.3023	0.9264
	0.050	0.2611	0.7685	0.3541	0.9147	0.4272	0.9654
	0.100	0.3980	0.8715	0.5052	0.9639	0.5842	0.9886
	0.150	0.4965	0.9196	0.6004	0.9787	0.6778	0.9942
$\theta_0 = 0.9$							
$(a_0, b_0)^*$	α	0.93	0.96	0.93	0.96	0.93	0.96
$(\frac{1}{10^3}, \frac{1}{10^3})$	0.025	0.0958	0.3174	0.1301	0.4817	0.1680	0.6349
	0.050	0.1648	0.4579	0.2204	0.6462	0.2627	0.7527
	0.100	0.2831	0.6351	0.3476	0.7796	0.4003	0.8633
	0.150	0.3721	0.7276	0.4438	0.8498	0.5014	0.9154
$(\frac{1}{3}, \frac{1}{3})$	0.025	0.0958	0.3174	0.1301	0.4817	0.1680	0.6349
	0.050	0.1648	0.4579	0.2204	0.6462	0.2627	0.7527
	0.100	0.2831	0.6351	0.3476	0.7796	0.4003	0.8633
	0.150	0.3721	0.7276	0.4438	0.8498	0.5014	0.9154
$(\frac{1}{2}, \frac{1}{2})$	0.025	0.0958	0.3174	0.1301	0.4817	0.1680	0.6349
	0.050	0.1648	0.4579	0.2204	0.6462	0.2627	0.7527
	0.100	0.2831	0.6351	0.3476	0.7796	0.4003	0.8633
	0.150	0.3721	0.7276	0.4438	0.8498	0.5014	0.9154
(1,1)	0.025	0.0958	0.3174	0.1301	0.4817	0.1680	0.6349
	0.050	0.1648	0.4579	0.2204	0.6462	0.2627	0.7527
	0.100	0.2831	0.6351	0.3476	0.7796	0.4003	0.8633
	0.150	0.3721	0.7276	0.4438	0.8498	0.5014	0.9154

* Shape parameters for fitting Beta priors.

Prior Specification - Power Prior

- Let the data from the current study be denoted $D = (n, y)$, and denote the historical data by $D_0 = (n_0, y_0)$.
- Let $L(\theta|D)$ and $L(\theta|D_0)$ denote the likelihood function for current study D and historical data D_0, respectively.
- Given a_0, the power prior (Ibrahim and Chen, 2000; Ibrahim et al., 2015) of model parameter θ for the current study is defined as

$$\pi(\theta|D_0, a_0) \propto L(\theta|D_0)^{a_0}\pi_0(\theta) \quad (12)$$

  where $\pi_0(\theta)$ is the initial prior for θ.
- a_0 can be interpreted as a discounting parameter that control the degree of discounting for each historical dataset, and $0 \leq a_0 \leq 1$.
- The resulting posterior distribution is given by

$$\pi(\theta|D, D_0, a_0) \propto L(\theta|D)L(\theta|D_0)^{a_0}\pi_0(\theta) \quad (13)$$

Meta-Analytic Predictive Prior and Robust MAP Prior

- Neuenschwander et al. (2010) proposed a meta-analytic-predictive (MAP) approach to derive the prior for new trial from historical data using a hierarchical model.
- We suppose that K historical trials in the same population are available, and that the data y_{0k} in trial k with n_{0k} patients is modeled as

$$y_{0k} \sim Bin(n_{0k}, \theta_{0k}),\ k = 1, \ldots, K \tag{14}$$

- The exchangeable parameters ψ = logit(θ), and are distributed as

$$\psi_*, \psi_1, \ldots \psi_K \sim N(\mu, \tau^2) \tag{15}$$

- Schmidli et al. (2014) proposed an extension of MAP prior to handle the possibility of prior-data conflict by mixing a MAP prior with a vague prior, called Robust MAP prior (RMAP) and is given by

$$\pi_{RMAP}(\theta) = (1 - w_0)\pi_{MAP}(\theta) + w_0\pi_0(\theta), \tag{16}$$

where $\pi_{MAP}(\theta)$ is the approximated MAP prior, $\pi_0(\theta)$ is a vague conjugate prior, and w_0 is the prior probability that the new trial differs systematically from the historical trials.

Applications to Pediatric Trials and R Shiny App

Source Data Selected from the Reference Population

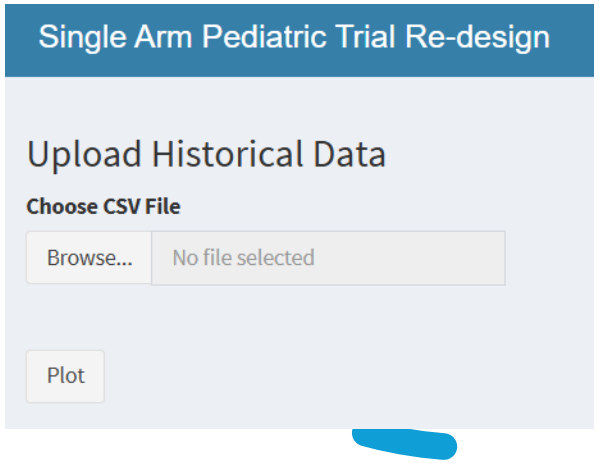
- Indication: HCV
- Target population: Epclusa pediatric
- Reference population: Epclusa adult, Harvoni (same MOA) adult and pediatric, Mavyret (similar MOA) adult
- Data: 8 trials, 1494 patients

Trial	Drug	% SVR12 rate (# of responders/nk)
ASTRAL-1a	Epclusa	98.5% (323/328)
ION-1	Harvoni	98.6% (211/214)
ION-2	Harvoni	93.6% (102/109)
ION-3	Harvoni	95.4% (206/216)
Study 1116*	Harvoni	98.0% (98/100)
ENDURANCE-1	Mavyret	99.7% (351/352)
EXPEDITION-1	Mavyret	98.9% (89/90)
VOYAGE-2	Mavyret	100% (85/85)

R Shiny App – Data Upload and Summary Statistics

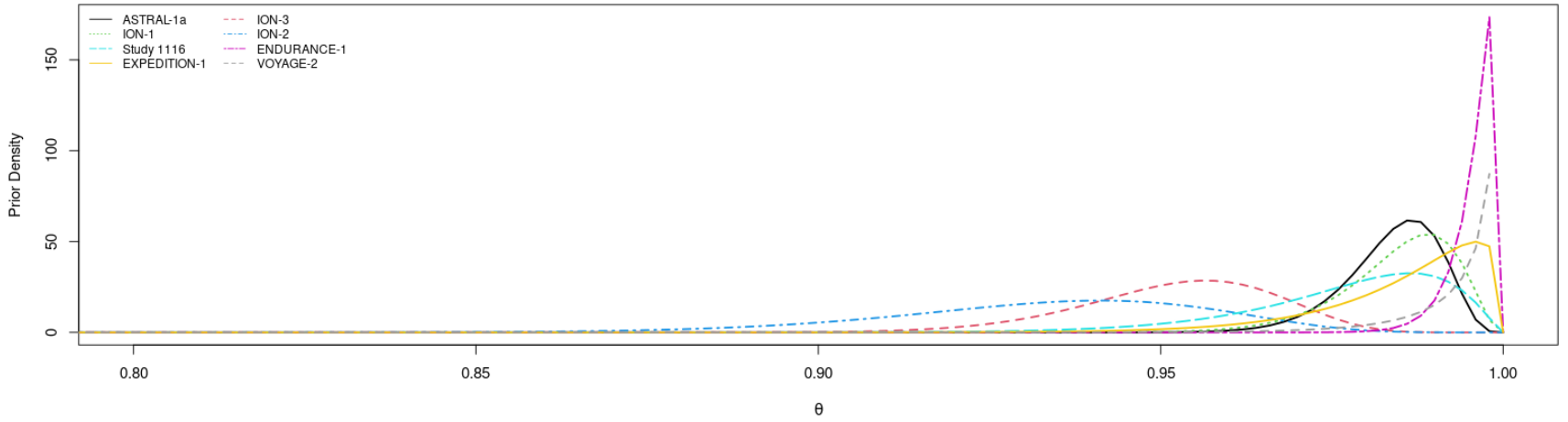
Data Upload

Trial	x	n
ASTRAL-1a	323	328
ION-3	206	216
ION-1	211	214
ION-2	102	109
Study 1116	98	100
ENDURANCE-1	351	352
EXPEDITION-1	89	90
VOYAGE-2	85	85



Summary Statistics and Plot of Priors

	Trial	Rate	Mean	SD	Median	Mode	HPD
1	ASTRAL-1a	0.985	0.984	0.126	0.985	0.987	(0.97, 0.996)
2	ION-3	0.954	0.952	0.213	0.954	0.957	(0.924, 0.979)
3	ION-1	0.986	0.984	0.123	0.986	0.989	(0.968, 0.998)
4	ION-2	0.936	0.933	0.249	0.936	0.941	(0.886, 0.976)
5	Study 1116	0.98	0.977	0.15	0.98	0.986	(0.948, 0.999)
6	ENDURANCE-1	0.997	0.996	0.061	0.997	0.999	(0.99, 1)
7	EXPEDITION-1	0.989	0.985	0.12	0.989	0.996	(0.96, 1)
8	VOYAGE-2	1	0.996	0.062	0.999	1	(0.983, 1)



R Shiny App – Power Prior

Historical Data

Show 10 entries Search: Reset Weights

	Trial	x	n	weight
1	ASTRAL-1a	323	328	0
2	ION-3	206	216	0
3	ION-1	211	214	0
4	ION-2	102	109	0
5	Study 1116	98	100	0
6	ENDURANCE-1	351	352	0
7	EXPEDITION-1	89	90	0
8	VOYAGE-2	85	85	0

Showing 1 to 8 of 8 entries Previous 1 Next

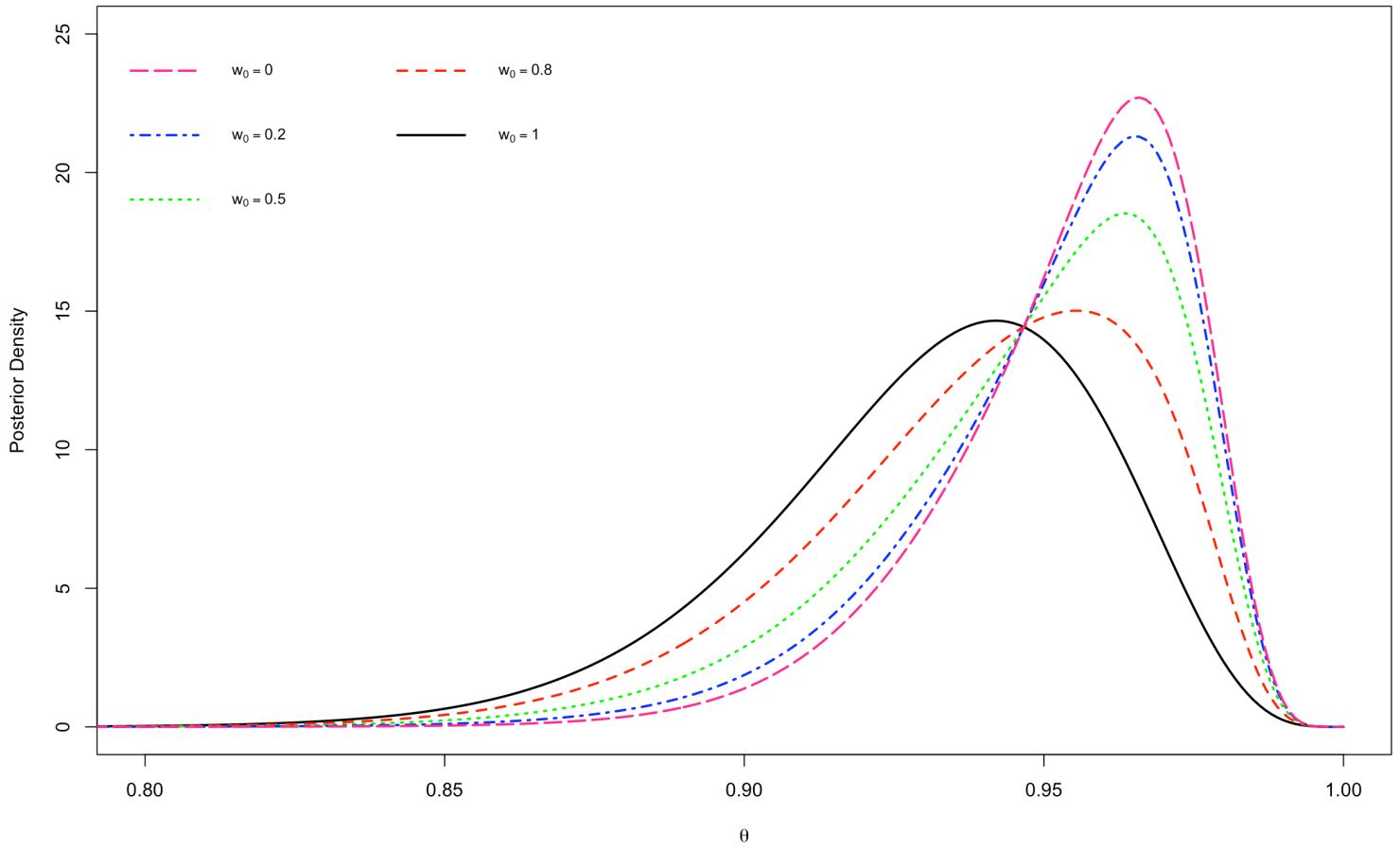
Design Setting

θ_0	θ_1	Intended level	n
0.9	0.96	0.1	76

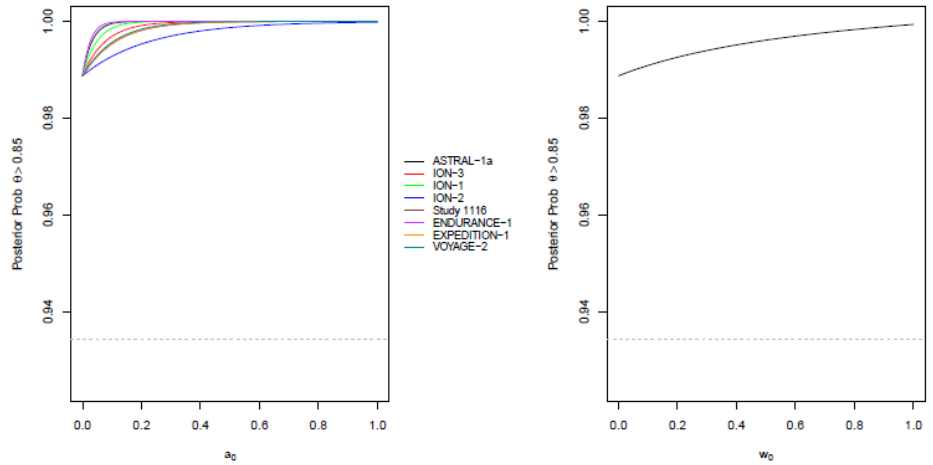
a	b		
0.333333333333333	0.333333333333333	Calculate T1E or Power	Plot

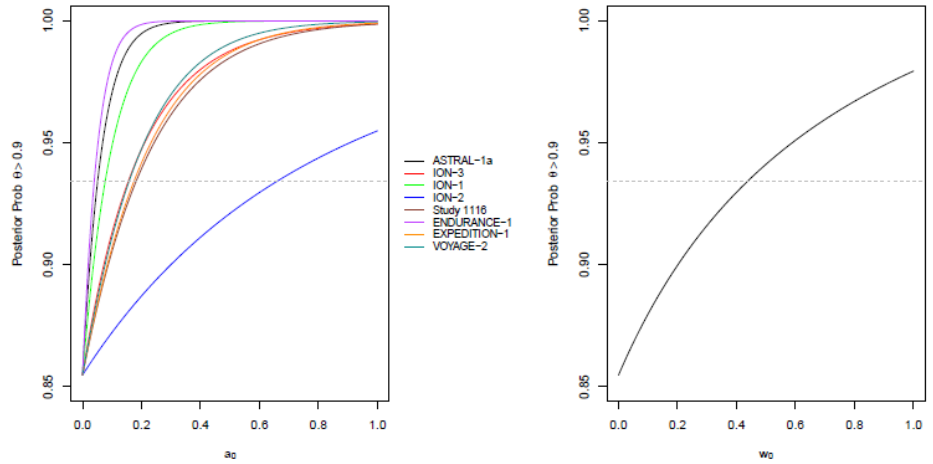
Target Trial Data and Posterior Distribution with RMAP

Trial	Drug	% SVR12 rate (# of responders/n)
1143C	Epclusa	93.4% (71/76)



Robustness of the Power Prior and RMAP Prior by Varying Weight of Borrowing Historical Data





- The posterior probability that the response rate in the current pediatric group exceeds θ_0 is a function of the weight assigned to borrowing historical data using power prior and the RMAP prior.
- From the design setting, the success criteria γ is 0.934 (dashed line).
- When $\theta_0 = 0.85$, strong evidence of efficacy in the pediatric group is observed even when no historical data is borrowed for both priors.
- Under the scenario of $\theta_0 = 0.9$, the success can be concluded for power prior if there are 66% of the information is borrowed from trial ION-2, while for RMAP prior, with 45% of all historical data being borrowed, the posterior probability will exceed the cut-off γ.

Summary and Discussion

- **MOA-based extrapolation:** aligns with recommendation from ICH E11A; accelerates pediatric drug development by integrating data from multiple drugs with the same or similar mechanisms of action, rather than relying solely on data from the same drug.

- **New methodology:**
  - **Randomized Bayesian test:** within a general Bayesian decision rule-based framework
  - **Achieve exact type I error**: maximize the power of the study with binary endpoint.
  - **Analytical form of the test statistics derived:** The type I error and the power are computed exactly without using Monte Carlo sampling.
  - **Application to a real trial example**

- **R Shiny App:** easy for application.

- **Future extension:** application to other setting (rare disease, etc); alternative data source (RWE, etc)

Thank you!

Back Up

U.S. Legislation and Pediatric Drug Development

PREA (Pediatric Research Equity Act)

- Drugs and biologics
- **Mandatory** studies
- Requires studies **only on indication**(s) **under review**
- **Orphan indications exempt** from studies
- Pediatric studies must be labeled

BPCA (Best Pharmaceuticals for Children Act)

- Drugs and biologics
- **Voluntary** studies with incentives
- Studies relate to entire moiety and **may expand indications**
- Studies may be requested for orphan indications
- Pediatric studies must be labeled

Exact Type I Error Search Algorithm

Algorithm Exact Type I Error Search Algorithm

1. Write $t_{y+1} = T(y)$ and $p_{y+1} = f(y|n, \theta_0)$ for $y = 0, 1, \ldots, n$.
2. Sort $t_1, \ldots, t_{n+1}$ in a descending order such that $t_{(1)} \geq t_{(2)} \geq \cdots \geq t_{(n+1)}$. Let $p_{(y)}$ denote the value of p_y corresponding to $t_{(y)}$.
3. For $0 < \alpha < 1$, find $i_\alpha \geq 1$ such that

$$\sum_{i=1}^{i_\alpha - 1} p_{(i)} < \alpha \leq \sum_{i=1}^{i_\alpha} p_{(i)}.$$

4. Set $\gamma = t_{(i_\alpha)}$.
5. Compute

$$\xi = \frac{\alpha - \sum_{i=1}^{i_\alpha - 1} p_{(i)}}{p_{(i_\alpha)}}. \tag{8}$$

Bayesian Extrapolation Design: Exposure-Response Curves Comparison between Pediatric and Adult Populations

Zhongheng Cai, PhD, Lian Ma (Greaterna), Jingjing Ye* (BeOne Medicines), Haitao Pan (St. Jude), *presenter

Society of Clinical Trials Annual Conference
Vancouver, Canada, May 20, 2025

Outline

1. Introduction
2. Bayesian Pediatric Extrapolation Design
3. Simulation and Results
4. Summary

Introduction

Challenges in Pediatric Drugs Development

- **Small Population Size**: meet the statistical needs difficult and recruitment typically slow
- **Ethical Complexity**: Children are a vulnerable patient population.
- **Economic barriers and limited data**: Small market for profitability; limited clinical/pharmacology data

Pediatric Extrapolation

- To encourage pediatric drug development, there are currently US legislatives

  (1) Pediatric Research Equity Act (PREA) (Congress 2003)
  (2) Best Pharmaceuticals for Children Act (BPCA) (Congress 2002).
  (3) Race for Children Act (Part of FDARA, Aug. 18, 2017)

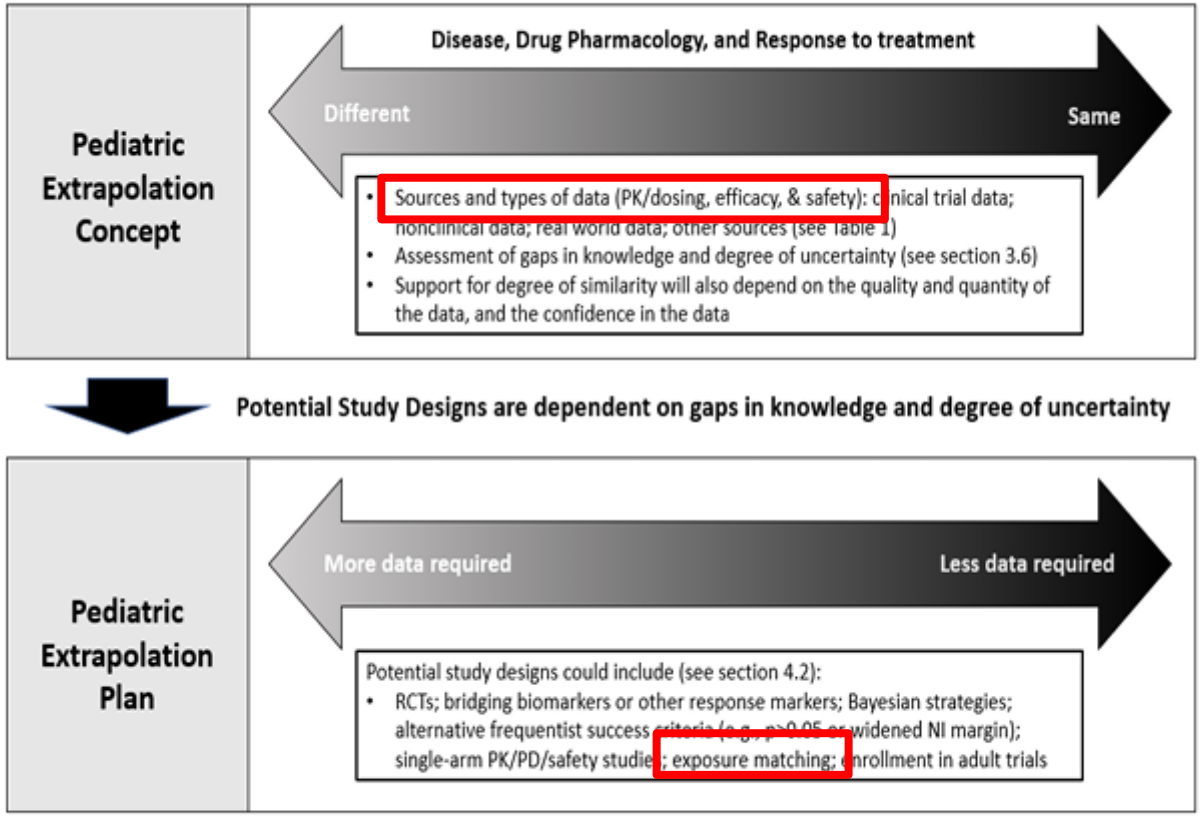
- International Harmonization ICH E11 A

Pediatric extrapolation can be used. It is the approach of **leveraging available data from adults or older age groups** to draw conclusions for the pediatric population.

FDARA: The FDA Reauthorization Act

When Do We Use Pediatric Extrapolation?

Figure 1: Pediatric Extrapolation as a Continuum



PK = pharmacokinetics/pharmacokinetic; RCTs = randomized controlled trials; NI = noninferiority; PD = pharmacodynamic.
Section 3.6 = section III.F; section 4.2 = section IV.B.

ICH E11A

Research Questions

- How to **measure the similarity of exposure-response curve** between adult and pediatrics?

- What is **the design to assess the exposure-response similarity**?

Literature

- Few literature has demonstrated how to quantify the similarity of curve between adult and pediatrics. Most of the similarity are checked by the visual inspection (subjective).

- Zhang et al., (2021) proposed the noninferiority (NI) testing paradigm to assess exposure-response similarity. They claimed that there is a need for the development of a method to directly compare pediatric with adult curve.

- Dette et al. (2018, 2024) considered the maximal deviation between the two curves as a measure of similarity.

Our Contribution

We propose an innovative Bayesian approach for the evaluation of E-R curve similarities between adult and pediatric populations:

1. Encompasses the entire curve rather than selected points;

2. Develop an algorithm to determine sample size and key design parameters;

3. Involve developing a method to simulate datasets under both null and alternative hypotheses, allowing for type I error and type II error control. R code is available at https://github.com/zhongheng-Biostatistics/Pediatric-Bayesian-Extrapolation-Design

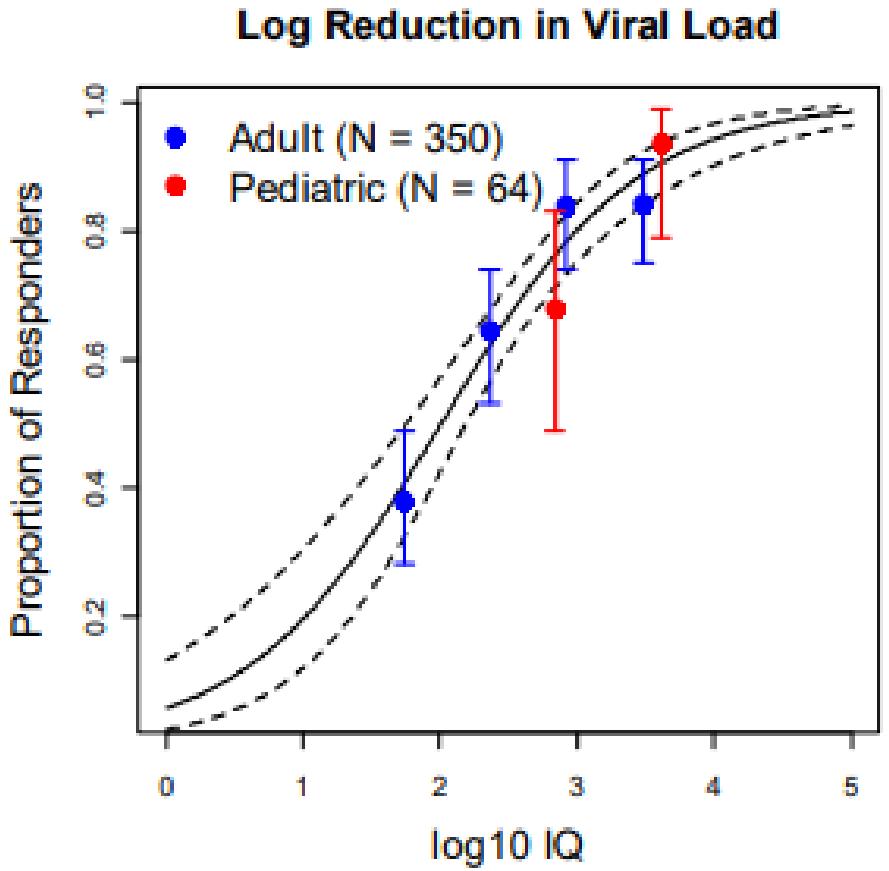
Bayesian Pediatric Extrapolation Design

Motivating Example

- Darunavir is a protease inhibitor (PI) that is employed in the therapeutic regimen and prophylaxis of HIV/AIDS. In December 2008, FDA approved the utilization of darunavir for pediatric patients.

- Binary Primary endpoint
  - Whether the plasma viral load decrease from baseline for at least 1.0 $\log_{10}$ at week 24.

- Pharmacokinetics parameter:
  - inhibitory quotient (IQ)



Research Question

- With the fitted adult curve, at design stage

  (1) Propose a design to identify the sample size to control desired type I/II error rates;

  (2) Check if the similarity between adult and pediatric population can be claimed.

Exposure-Response (E-R) Curve Similarity Assessment

- Assume the E-R curve is logistic regression fitting to each pediatric and adult curves:

$$f_j(x_{i,j}, \boldsymbol{\beta}_j) = P(Y_{i,j} = 1) = logit^{-1}(\beta_{0,j} + \beta_{1,j} x_{i,j}), \quad x_{ij} \in [A, B],$$

  - i is the patient indicator i= 1, . . . , k_j;
  - j is the group indicator:
    - j =1 - pediatric;
    - j =2 - adult.

- Define the measure of similarity as maximum deviation between the two curves:

$$d(f_1, f_2) = max_{x \in [a,b]}\{f_2(x, \boldsymbol{\beta}_2) - f_1(x, \boldsymbol{\beta}_1)\}$$

where $[a, b] \subseteq [A, B]$ denotes the interval we are interested in and $f_2(x, \boldsymbol{\beta}_2)$ is fitted adult E-R curve.

Bayesian Decision Criteria

- Hypothesis is defined as:

$$H_0: d(f_1, f_2) \geq \varepsilon_h; \quad H_1: d(f_1, f_2) < \varepsilon_h.$$

where ε_h is pre-specified margin to accept similarity.

In the Bayesian context, we accept the alternative hypothesis if

$$\text{Prob}(\, Reject\ H_0 \,|Data) > \varepsilon_{bayes}$$

where ε_{bayes} (tuning parameter) is the posterior probability threshold that we claim the alternative is true, e.g., 95%, 90%.

Design Parameters

- Maximum allowable deviation ε_h
- Decision probability to claim similarity ε_{bayes}
- Desirable type I/II error rates or Feasible Sample Size
- Weight to borrow adult information w
- Other possible considerations: PK parameter intervals, e.g. whole curve or partial curve?

Robust Elicited Points Prior (REPP) –Prior Elicitation

Recall need coefficients in logistic regression, and there are three conceptual steps to construct the REPP:

Step 1: *Model the difference of log odds ratio :* Select some points in the interval [a, b] such that the experts can speculate the distribution information of the difference of log odds ratio between the pediatric and the adult population. For example, 25th quantile, median, 95% CI, mean or variance. Approximate the difference by the normal distribution.

Step 2: *Derive the informative part of REPP:* Generate the synthetic data points at the chosen points, and obtain the posterior samples of the coefficients, which constitutes the informative part of the REPP.

Step 3: *Ensemble the REPP:* Mix the informative part with a normal distribution with large variance.

Considerations in Step 1 for REPP – Establish Maximum acceptable deviation

- We recommend three selected points by asking the following question

> *"Based on your knowledge, what are the maximum acceptable deviation at 25th percentile, median, and 75th percentile of log odds ratio between the pediatric and fitted adult curve?"*

Once these quantities are obtained, normal distributions can be fitted using a least squares, adjusting parameters to align the quantiles of the fitted normal distribution as closely as possible with expert judgments.

Considerations in Step 2 for REPP – Adult Information Relevance

- For each of the chosen points at $\boldsymbol{x} = (x_1, x_2, x_3)$, we generate a dataset comprising 1000 data points, and solve the following minimization problem:

$$min_{(\beta_{0,1},\, \beta_{1,1})} \sum_{i=1}^{3} \sum_{j=1}^{1000} (y_{ij} - f_1(x_i, \boldsymbol{\beta}_1))^2 .$$

- The informative part of REPP is derived by summarizing the posterior sample through a mixture of two normal distributions, denoted as $h_k(\beta_{k,1})$.

Considerations in Step 3 for REPP

Combining the informative part with noninformative part,

- REPP for the coefficients is

$$\pi(\beta_{k,1}) = \mathrm{w}h_k(\beta_{k,1}) + (1-\mathrm{w})\mathrm{N}(0,100^2)$$

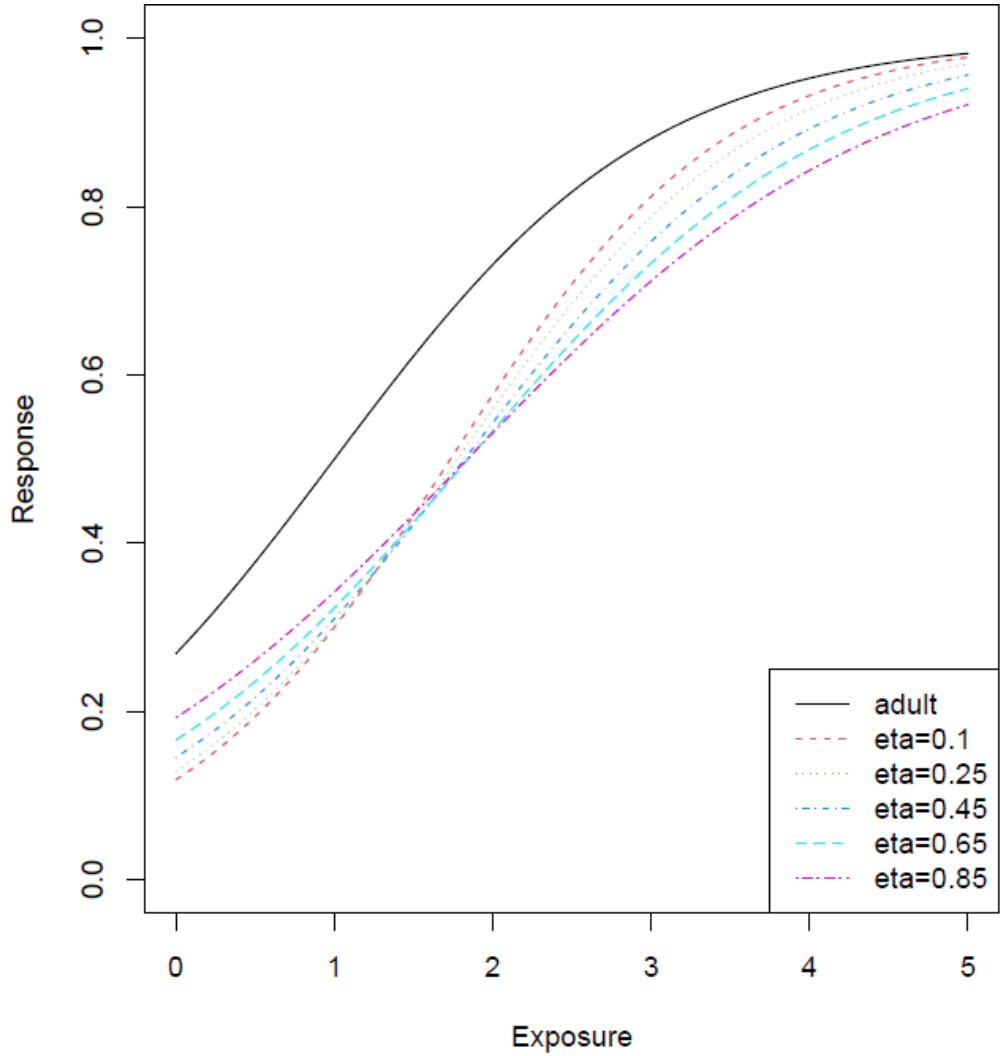
where $\mathrm{w} \in [0,1]$ (tuning parameter) is the weight of the adult information in the prior.

Possible Pediatric Curves are Infinite given Maximum Deviation

- Introduce $\eta \in [0,1]$

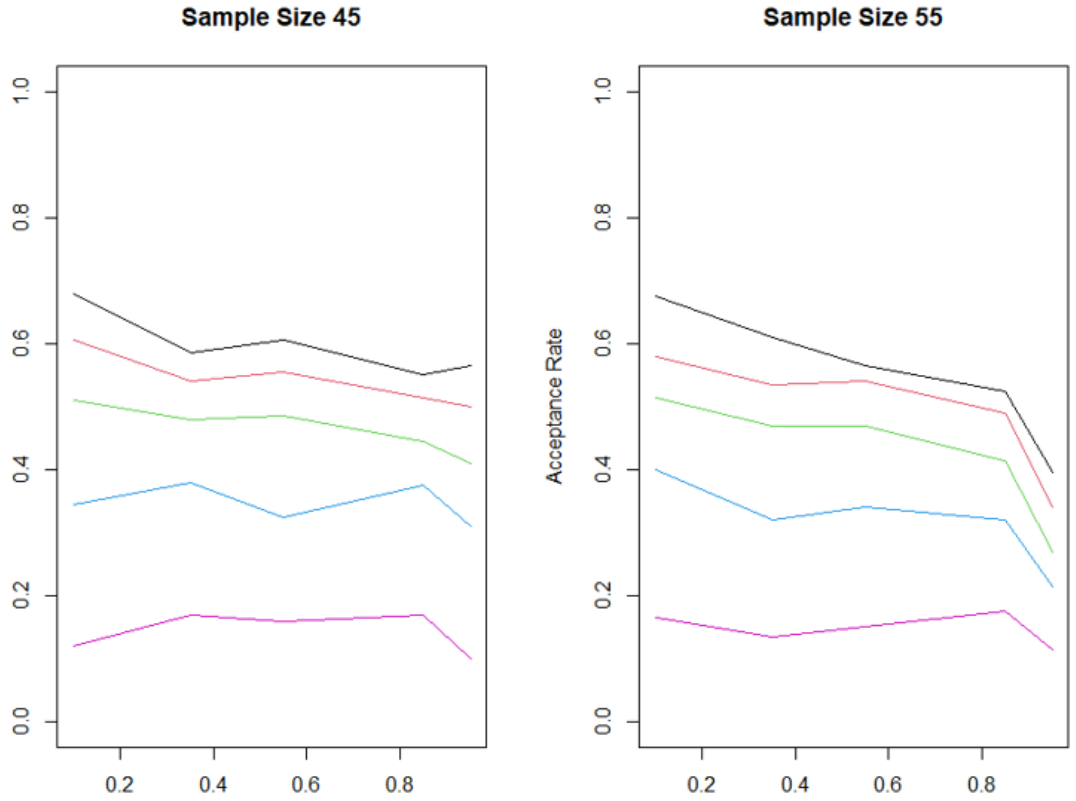
Measure difference of areas between pediatric and adult curves

Smaller difference, more similar



$\mathrm{Prob}(Reject\ H_0|Data)$ v.s η

- X axis is η. Y axis is $\mathrm{Prob}(Reject\ H_0|Data)$
- The figure in the right panel shows the trend of posterior probability changing with the η.
- Different colors means different ε_{bayes}. Black: 0.8; red: 0.85; green: 0.90; blue: 0.95; purple: 0.99.



Simulation and Results

Simulation setting

- Recall that we have two aims in the analysis of the real data:
  (1) **Design:** Use the above proposed method to design an extrapolation study for pediatric;
  (2) **Trial Data Analysis:** Check the similarity based on the published results.

- Simulation setting:

$$n \in \{40,45,50,55,60,64\}.$$
$$w \in \{0.1,0.2,0.3,0.4,0.5\}.$$
$$\varepsilon_{bayes} \in \{0.8,0.85,0.9,0.95,0.99\}$$

$\alpha = 0.2,\ 1-\beta = 0.7, [A,B] = [0,5], [a,b] = [2.5,5], \varepsilon_h = 0.2$ and $n_{sim} = 1000.$

Results

- First number in the bracket is type I error. Second number is the power.

- The red numbers are the pairs satisfying the type I and II error constraint.

- Blue ones are the *admissible* tuples. They are chosen by the following rules:

  (1) At least one number satisfies the constraint and the other one is at most 0.05 far from target value;
  (2) If there are two or more *admissible* tuples in one column given sample size, we choose the one with the least w.

sample size	w \ ϵ_{bayes}	0.8	0.85	0.9	0.95	0.99
$n = 40$	0.1	(0.40,0.850)	(0.305,0.815)	(0.240,0.750)	(0.135,0.650)	(0.025,0.375)
	0.2	(0.645,0.920)	(0.535,0.890)	(0.440,0.850)	(0.305,0.775)	(0.080,0.515)
	0.3	(0.665,0.950)	(0.610,0.930)	(0.500,0.875)	(0.340,0.790)	(0.155,0.585)
	0.4	(0.725,0.955)	(0.660,0.940)	(0.565,0.895)	(0.410,0.820)	(0.120,0.580)
	0.5	(0.740,0.965)	(0.665,0.940)	(0.560,0.935)	(0.365,0.855)	(0.100,0.610)
$n = 45$	0.1	(0.455,0.880)	(0.345,0.865)	(0.26,0.820)	(0.165,0.705)	(0.050,0.430)
	0.2	(0.570,0.935)	(0.470,0.910)	(0.36,0.825)	(0.245,0.760)	(0.090,0.525)
	0.3	(0.625,0.930)	(0.555,0.910)	(0.44,0.885)	(0.285,0.830)	(0.085,0.545)
	0.4	(0.710,0.920)	(0.615,0.900)	(0.49,0.875)	(0.335,0.835)	(0.100,0.630)
	0.5	(0.755,0.965)	(0.705,0.935)	(0.60,0.910)	(0.435,0.835)	(0.155,0.600)
$n = 50$	0.1	(0.425,0.900)	(0.340,0.860)	(0.265,0.795)	(0.150,0.705)	(0.040,0.475)
	0.2	(0.530,0.915)	(0.490,0.890)	(0.39,0.845)	(0.260,0.785)	(0.070,0.510)
	0.3	(0.645,0.930)	(0.560,0.915)	(0.47,0.890)	(0.290,0.835)	(0.105,0.630)
	0.4	(0.615,0.935)	(0.530,0.925)	(0.44,0.910)	(0.355,0.840)	(0.125,0.655)
	0.5	(0.760,0.970)	(0.655,0.960)	(0.520,0.925)	(0.360,0.890)	(0.1,0.640)
$n = 55$	0.1	(0.510,0.880)	(0.395,0.845)	(0.330,0.770)	(0.175,0.690)	(0.015,0.425)
	0.2	(0.540,0.900)	(0.505,0.880)	(0.430,0.845)	(0.245,0.755)	(0.065,0.535)
	0.3	(0.690,0.955)	(0.640,0.950)	(0.535,0.920)	(0.350,0.845)	(0.140,0.675)
	0.4	(0.615,0.945)	(0.550,0.935)	(0.450,0.910)	(0.345,0.830)	(0.110,0.605)
	0.5	(0.700,0.940)	(0.620,0.920)	(0.555,0.905)	(0.375,0.870)	(0.105,0.645)
$n = 60$	0.1	(0.455,0.875)	(0.415,0.845)	(0.335,0.795)	(0.20,0.72)	(0.040,0.490)
	0.2	(0.520,0.925)	(0.455,0.890)	(0.365,0.84)	(0.240,0.750)	(0.070,0.55)
	0.3	(0.585,0.910)	(0.485,0.885)	(0.400,0.87)	(0.255,0.800)	(0.09,0.620)
	0.4	(0.695,0.950)	(0.615,0.945)	(0.545,0.940)	(0.365,0.885)	(0.085,0.70)
	0.5	(0.685,0.950)	(0.610,0.925)	(0.530,0.89)	(0.325,0.850)	(0.10,0.65)
$n = 64$	0.1	(0.460,0.875)	(0.379,0.850)	(0.290,0.810)	(0.20,0.740)	(0.040,0.525)
	0.2	(0.465,0.930)	(0.400,0.925)	(0.320,0.895)	(0.195,0.805)	(0.050,0.575)
	0.3	(0.565,0.910)	(0.460,0.895)	(0.420,0.825)	(0.285,0.775)	(0.100,0.585)
	0.4	(0.740,0.935)	(0.675,0.925)	(0.515,0.895)	(0.340,0.840)	(0.055,0.640)
	0.5	(0.695,0.965)	(0.610,0.965)	(0.525,0.950)	(0.350,0.875)	(0.085,0.685)

Proposed Measurement

- Type I error and power associated with specific parameters may be interpreted as the "average" of the Type I error and power.

- For all the *admissible* tuples, we calculate the type I error and the power $\eta_i \in \{0.1, \ldots, 0.9\}$ under H_0 and H_1 , respectively. Calculate the proportions that type I error is no more than α and power is no less than $1 - \beta$.

- The larger proportion indicates more stable performance.

Proposed Measurement

- The first number in the bracket is the proportion with respect to type I error. The second number is with respect to power. The red pairs indicate both proportions are greater than or equal to 0.8.

sample size	$(w, \epsilon_{\text{bayes}})$				
	(0.1,0.95)	(0.2,0.95)	(0.3,0.99)	(0.4,0.99)	(0.5,0.99)
40	(0.8,0.36)				
45	(1,0.54)				
50	(0.9,1)			(0,1)	
55	(0.2,1)		(0.7,1)		
60	(0.7,1)			(0.6,1)	
64	(0.8,1)	(0.1,1)			(0.6,1)

- For the design, if we need the smallest sample size with stable performance, we can choose $n = 50$ and $(w, \varepsilon_{bayes}) = (0.1,0.95)$.

Trial Data Analysis

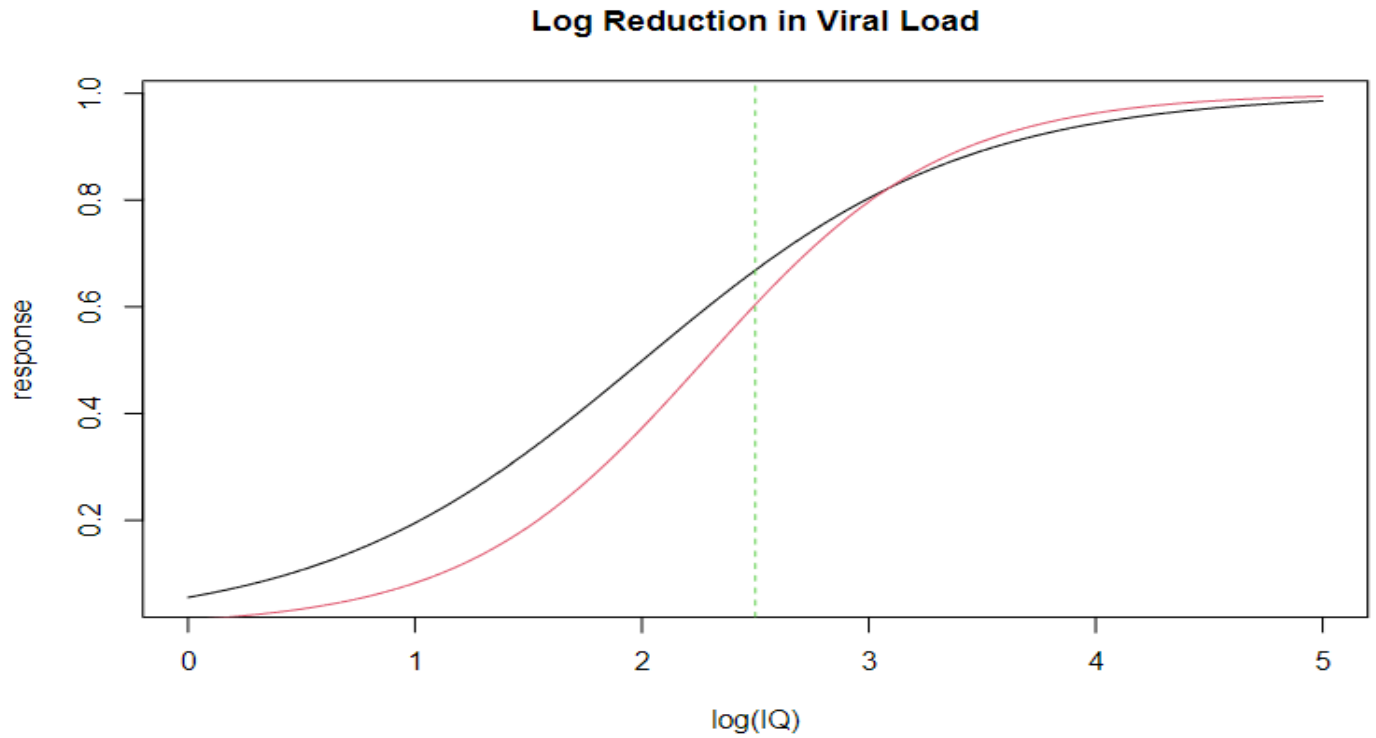
- From the table above, we may choose $(w, \varepsilon_{bayes}) = (0.1, 0.95)$.

- For trial data analysis, we reconstruct the pediatric curve (see the right panel). The maximum distance is 0.0643.

- Based on the published result, the event

$$1\{\text{Prob}(Reject\ H_0 | Data) > 0.95\}$$

holds. Hence, we accept the similarity of two exposure-response curve.



Summary

- We propose one new prior, REPP, to borrow the adult information.

- A new framework to generate coefficient from the infinite parameter space. It can be extended to more complicated cases: such as the Emax model for the continuous endpoint or L_2 distance comparison.

- Our design provides a more flexible result, which allows us to discuss with clinical team and regulatory bodies about the choice of the parameters.

Thank You

Exploring Similarity in the Context of Extrapolation and Its Impact on Analysis?

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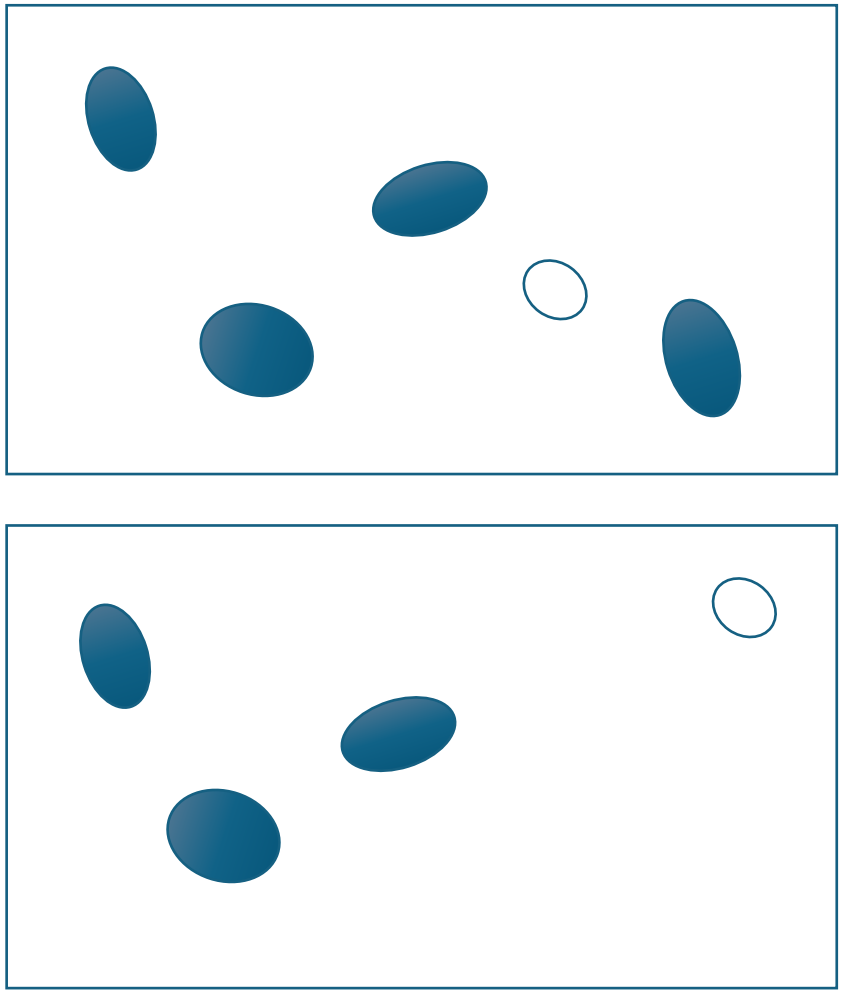
Pfizer Research and Development

Interpolation vs Extrapolation

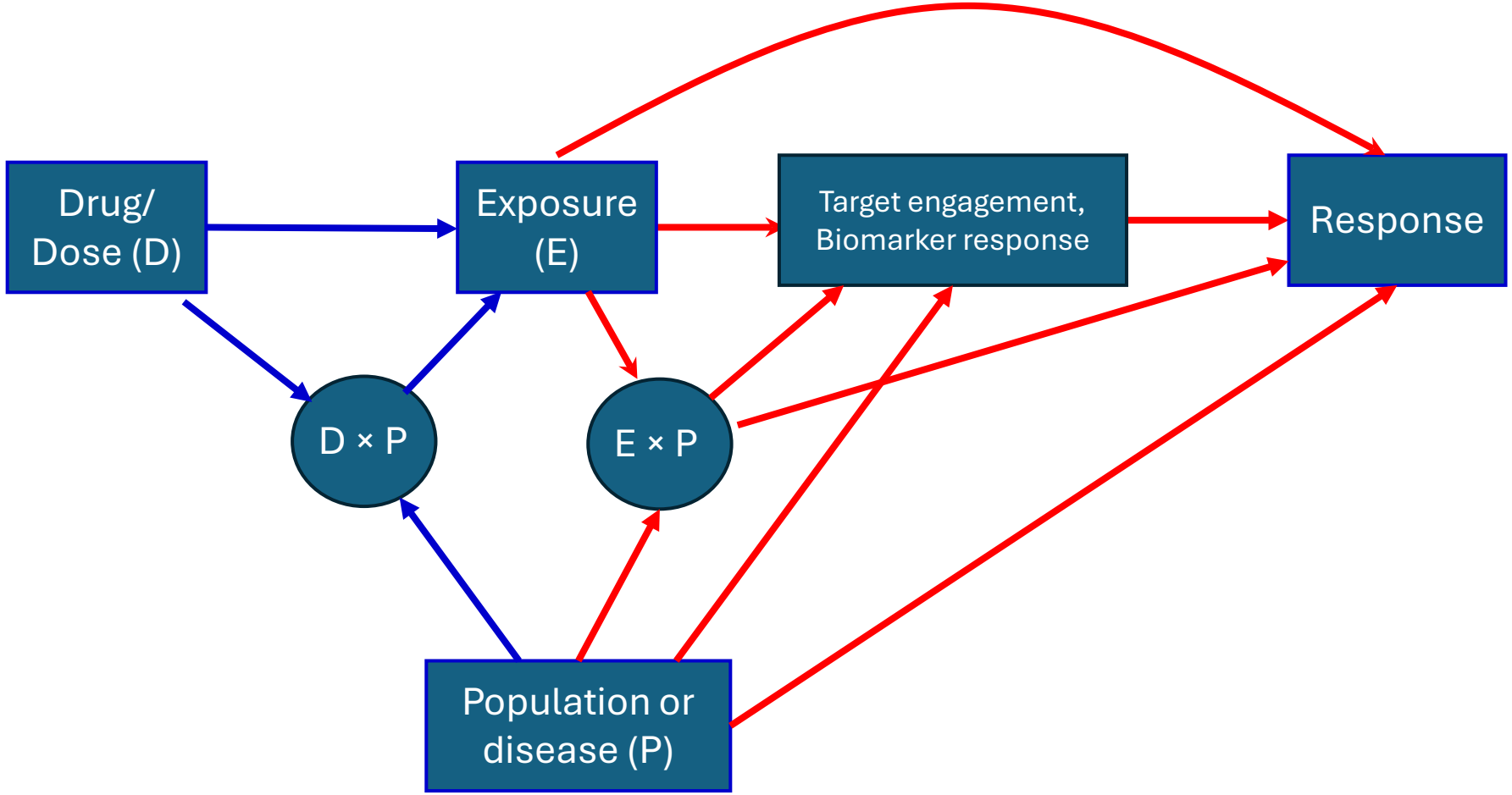
Interpolation: predicting outcomes within the range of observed data, under the assumption that no (**multi-dimensional**) intrinsic differences exist between the reference and target populations. Usually used in stratification of cohorts

Extrapolation: predicting outcomes beyond the range of observed data and relies on additional assumptions about the similarity of disease progression and treatment response across populations.

... in other words, extrapolation requires more assumptions to make inference valid



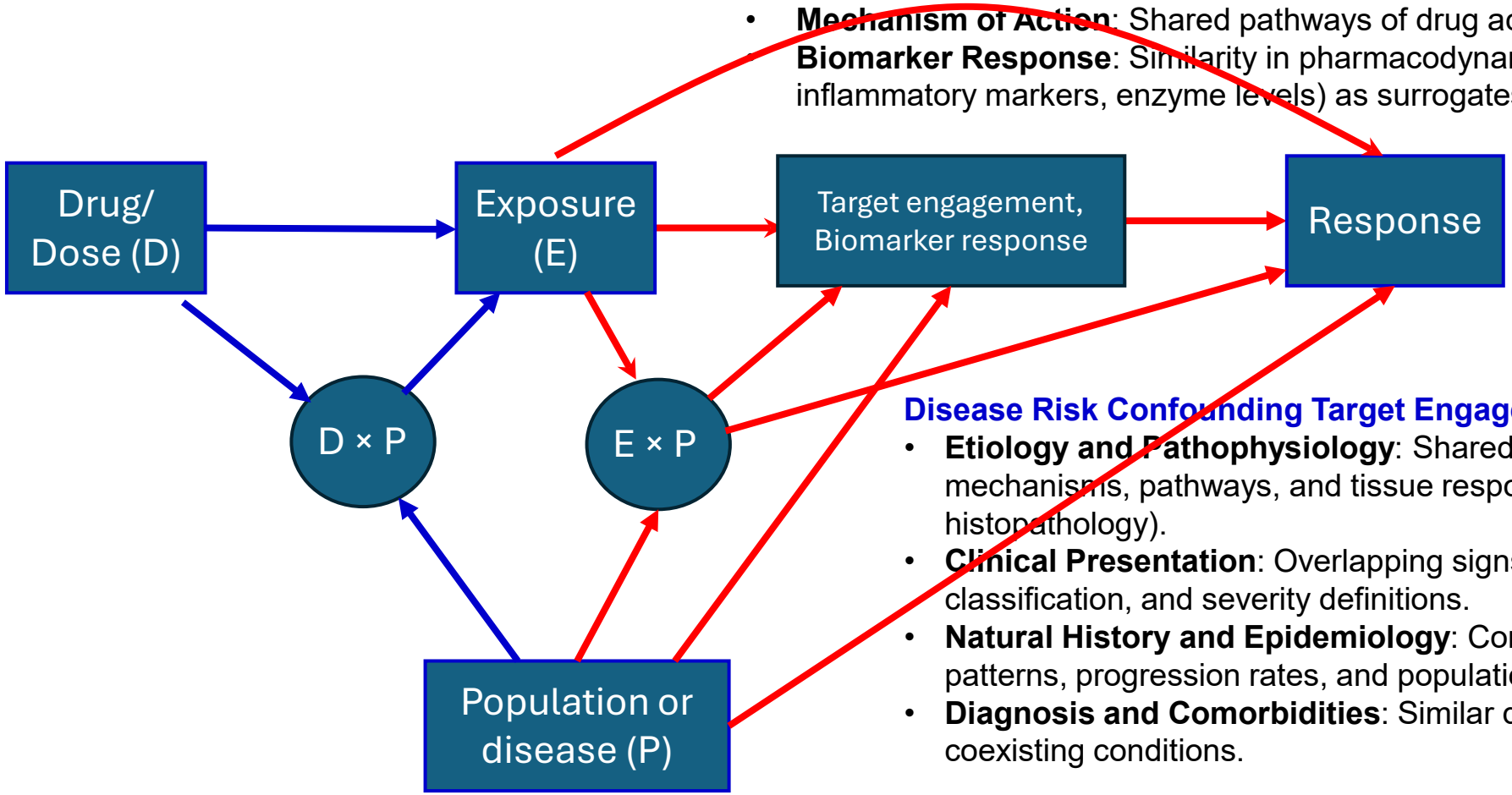
Population/Exposure Interaction and Confounding with Response



Population/Exposure Interaction and Confounding with Response

Target engagement, MOA, and PD Marker mediating Exposure and Response

- **Target Engagement**: Comparable drug-receptor interactions, target expression, and occupancy levels.
- **Mechanism of Action**: Shared pathways of drug action across age groups.
- **Biomarker Response**: Similarity in pharmacodynamic biomarkers (e.g., inflammatory markers, enzyme levels) as surrogates for effect



Disease Risk Confounding Target Engagement and Response

- **Etiology and Pathophysiology**: Shared underlying mechanisms, pathways, and tissue responses (e.g., histopathology).
- **Clinical Presentation**: Overlapping signs, symptoms, disease classification, and severity definitions.
- **Natural History and Epidemiology**: Comparable onset patterns, progression rates, and population-level characteristics.
- **Diagnosis and Comorbidities**: Similar diagnostic criteria and coexisting conditions.

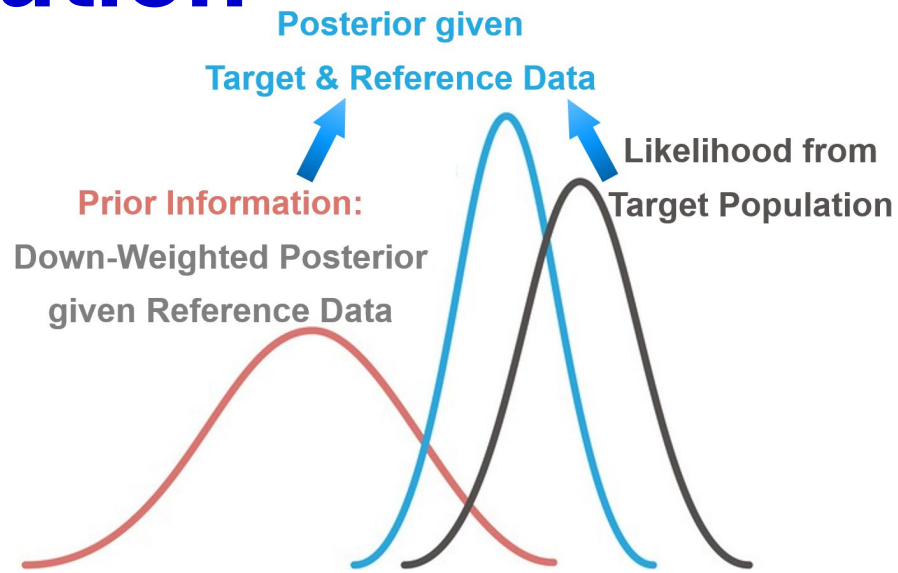
Impact on Bayesian analysis

- We can model the entire hierarchical causal interaction network between populations.
- Complexity of the high dimensional interaction network can be simplified by introducing an **maximum/minimum similarity** (or disimilarity) as a measure of how disease risk and exposure interact and confound response
- The maximum/minimum similarity is somewhat unrelated to precision of the endpoint measurement
- The use of one disease population as a reference to a target disease population can be guided by this maximum/minimum similarity measure
  - Discounting should not be all about difference in observed outcomes (precision) but by the average dissimilarity of the disease populations

Our Simple Proposal/Contribution

Existing Methodology: Data extrapolation using Bayesian framework

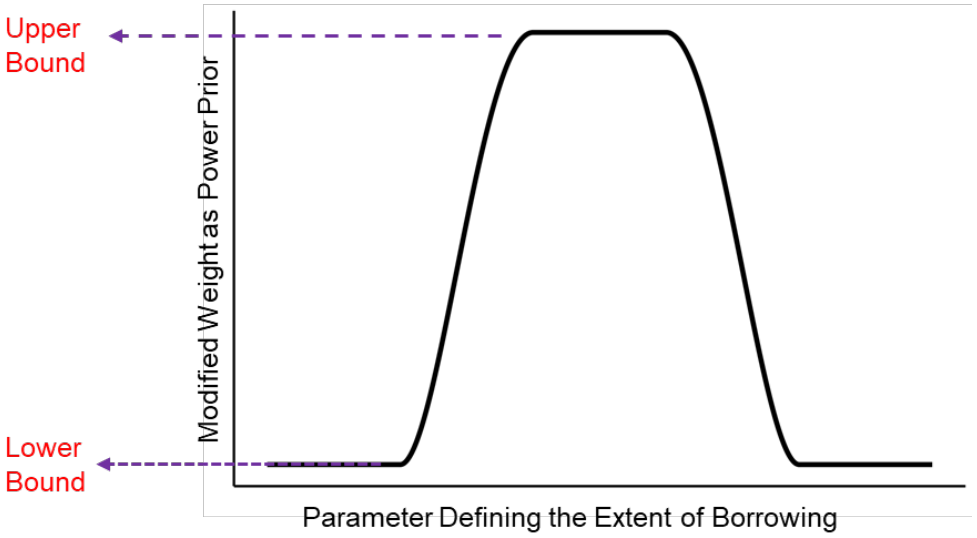
- Incorporate reference data as a part of prior information
- Down-weight reference information based on dissimilarity between two population



Contribution: Control the Extent of Borrowing

1. Difference in disease risk among subpopulations
   - Avoid full borrowing and use max similarity
2. Similarity of the disease and the expected response
   - Avoid no borrowing and use min similarity

Bound the extent of borrowing from above and below



Background Materials: Bayesian Extrapolation Models

(Normalized) Power Prior (Chen and Ibrahim, 2000 & Ye and Duan 2008)

- Initial prior on $\boldsymbol{\theta}$: $\pi(\boldsymbol{\theta})$
- Posterior of $\boldsymbol{\theta}$ give $\boldsymbol{D_0}$
  - ➢ Conventional approach: $\pi_C(\boldsymbol{\theta} \mid \boldsymbol{D_0}) \propto L(\boldsymbol{\theta} \mid \boldsymbol{D_0})\pi(\boldsymbol{\theta})$
    - Fully borrowing reference information
  - ➢ Modification: $\pi(\boldsymbol{\theta} \mid \boldsymbol{D_0}, a_0) \propto \frac{L(\boldsymbol{\theta}|\boldsymbol{D_0})^{a_0}\pi(\boldsymbol{\theta})}{\int L(\boldsymbol{\theta}|\boldsymbol{D_0})^{a_0}\pi(\boldsymbol{\theta})d\boldsymbol{\theta}}$

Down-weight the likelihood of reference observation by a_0

Normalizing constant

- Posterior of $\boldsymbol{\theta}$ and a_0 give $\boldsymbol{D_0}$ and $\boldsymbol{D}$

$$\pi(\boldsymbol{\theta}, a_0 \mid \boldsymbol{D_0}, \boldsymbol{D}) \propto (likelihood)\ (informative\ prior)$$
$$\propto L(\boldsymbol{\theta} \mid \boldsymbol{D}) \frac{L(\boldsymbol{\theta}|\boldsymbol{D_0})^{a_0}\pi(\boldsymbol{\theta})}{\int L(\boldsymbol{\theta}|\boldsymbol{D_0})^{a_0}\pi(\boldsymbol{\theta})d\boldsymbol{\theta}}\pi(a_0)$$

Notations

- Unknown parameters of interest: $\boldsymbol{\theta}$
- Observations from reference population: $\boldsymbol{D_0}$
- Observations from target population: $\boldsymbol{D}$

Background Materials: Bayesian Extrapolation Models

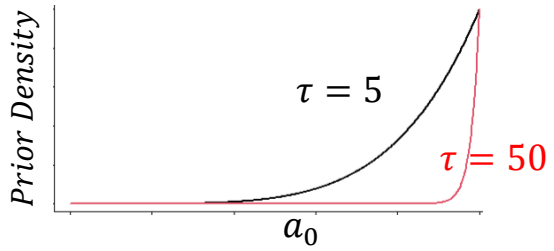
Commensurate Power Prior (Hobbs et al. 2011/2014)

- Assume different parameters for reference and target population
  - $\boldsymbol{\theta_0}$ for reference population
  - $\boldsymbol{\theta}$ for target population

- Measure commensurability between two populations
  - e.g., for one-dimensional location parameters $\theta \mid \theta_0 \sim N\left(\theta_0, \frac{1}{\tau}\right)$

  - Use to determine the amount of borrowing

$$a_0 \mid \tau \sim Beta\left(\max(\log(\tau), 1), 1\right)$$



- Commensurate power prior given reference observations

$$\pi(\theta, \theta_0, a_0, \tau \mid \boldsymbol{D_0}) \propto \frac{L(\theta_0 \mid \boldsymbol{D_0})^{\boldsymbol{a_0}} \pi(\theta_0)}{\int L(\theta_0 \mid \boldsymbol{D_0})^{\boldsymbol{a_0}} \pi(\theta_0) d\theta_0} \pi(\theta \mid \theta_0, \tau) \pi(a_0 \mid \tau) \pi(\tau)$$

Contribution: Controlling the Extent of Borrowing via Bounding Prior on a_0

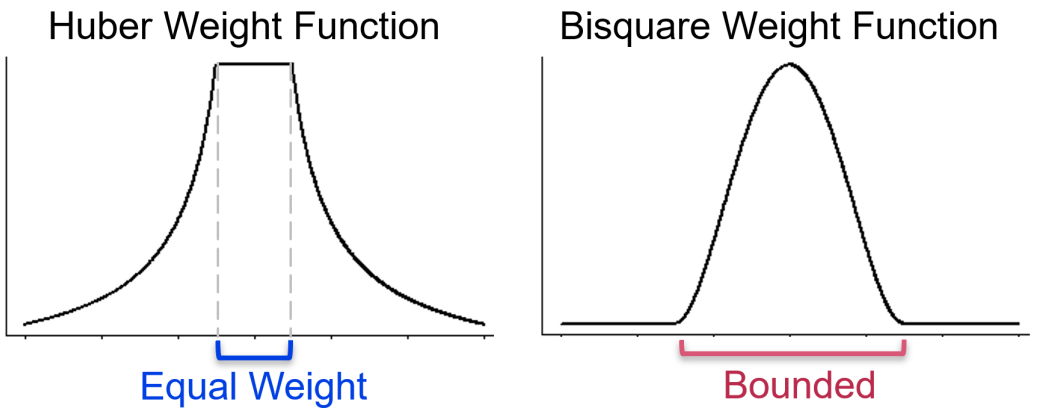
Bounded Beta Prior

- Generalized beta distribution that is bounded by $[a_{low}, a_{upp}]$.

Existing Weight Functions

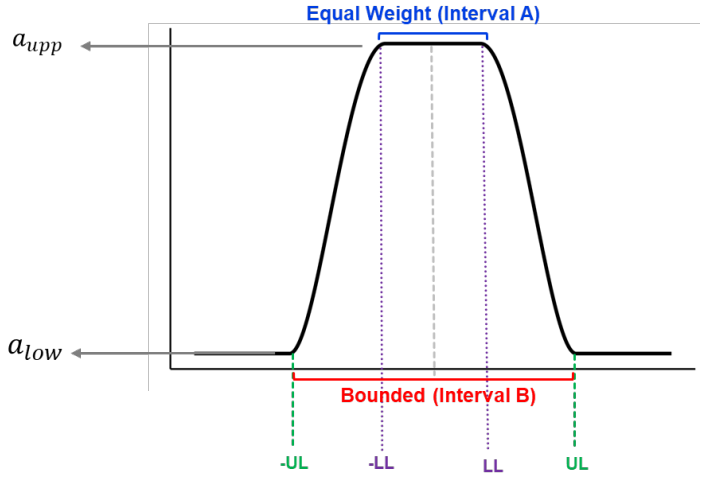
- Huber weight function:
  - ➢ Pro: Equal weight on a prespecified interval
  - ➢ Con: Not bounded

- Bisquare weight function:
  - ➢ Pro: Bounded and smoothness
  - ➢ Con: Informative prior



Modified Weight Function as Prior on a_0

- Combine Huber+Bisquare functions adopting their pros
  - ➢ Interval A: High prior belief
  - ➢ Beyond interval A: Smooth decrease in prior belief
  - ➢ Beyond interval B: Very low prior belief



Simulation Study: Binary Response Model for Single-arm Clinical Trials

Observation Model $Y_i \sim Bernoulli(p)$

- Initial prior on p : Uniform(0,1)
- Priors on a_0 :
  1. Unbounded prior on (0,1)
  2. Beta/Uniform distribution with $(\alpha = 1,\ \beta = 1)$ bounded on [0.05, 0.5]
  3. Modified weight prior with constant value within [0.1, 0.6] and bounded on [0.05, 0.5]

Simulation Setting

- 40 Target observations; 80 reference observations

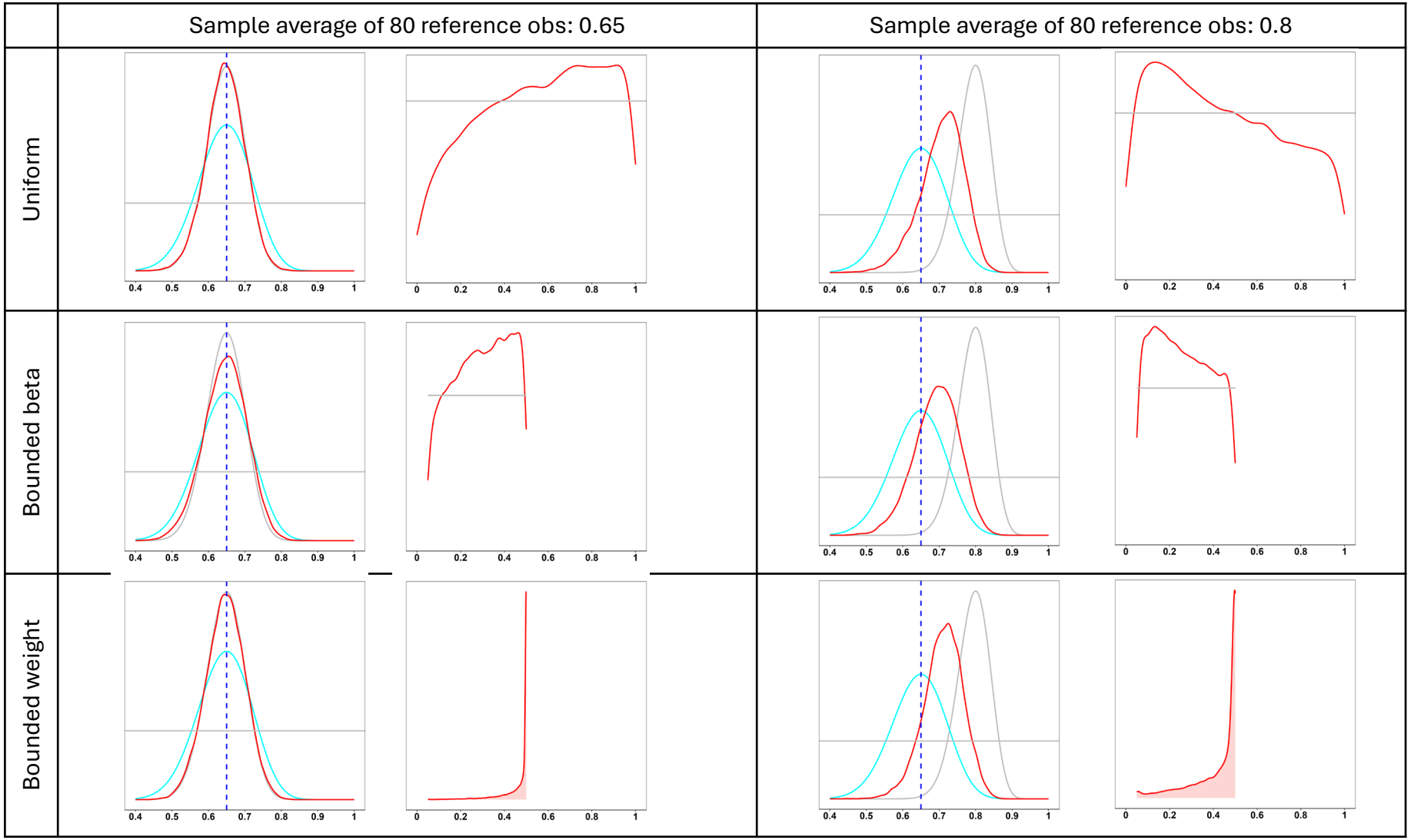
Simulation Results

- Posteriori distribution properties
- Root mean squared error
- Average number of borrowed reference observations (ESS)
- Operating characteristic curves, type one error and power.

$$\text{ESS} = n\left(\frac{var(p|\boldsymbol{D})}{var(p|\boldsymbol{D},\boldsymbol{D_0})} - 1\right)$$

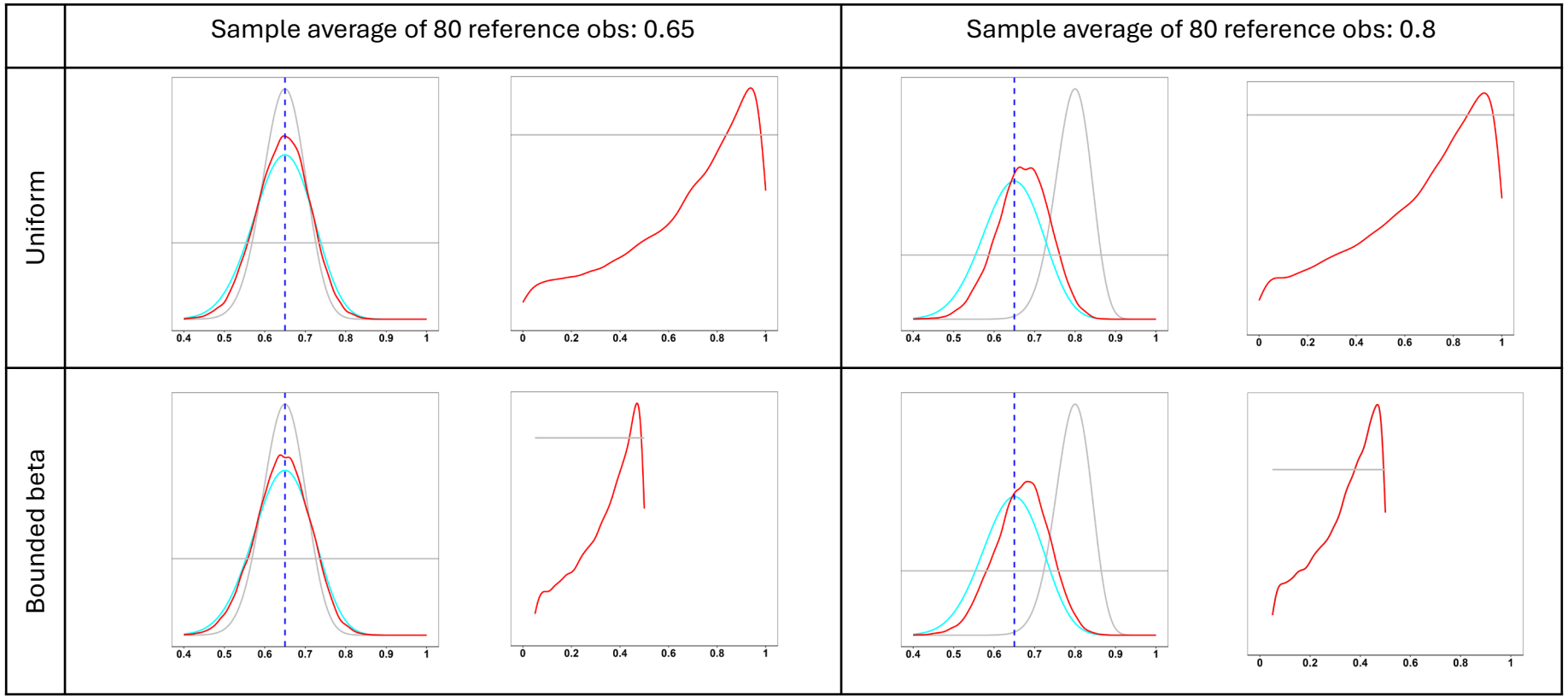
Marginal Posteriors using Normalized Power Prior

- 40 target observations with sample average 0.65



Marginal Posteriors using Commensurate Power Prior

- 40 target observations with sample average 0.65

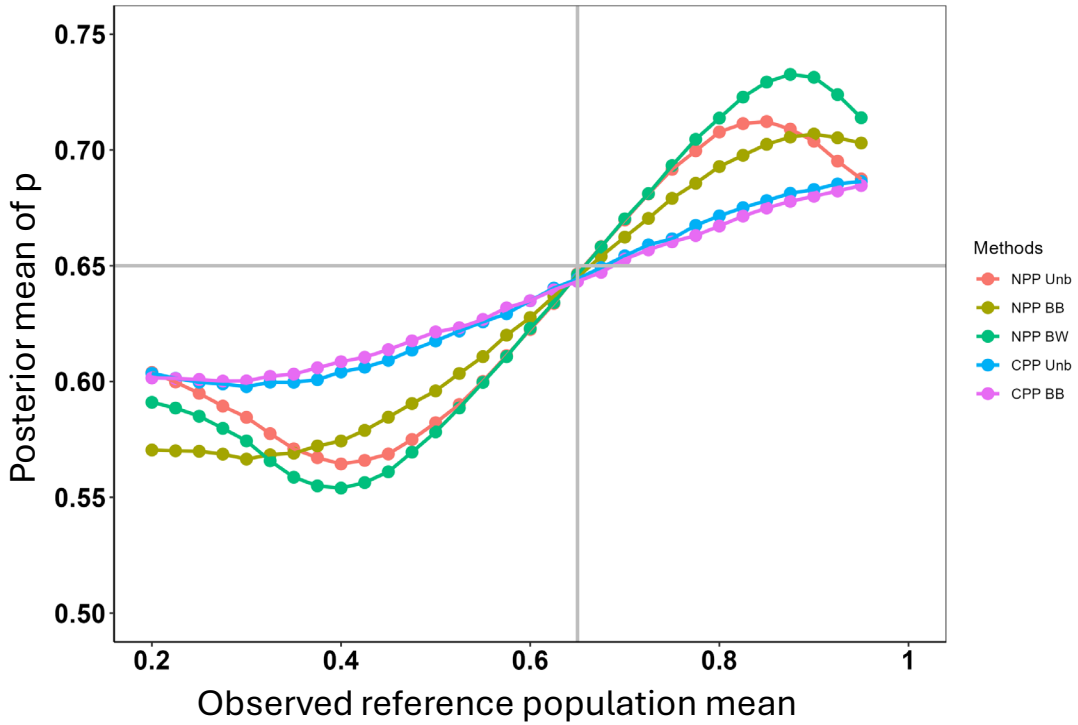


Posterior Mean Properties

40 target observations with sample average 0.65, 80 reference observations with varying observed mean

Dynamic borrowing

- **NPP**
  - "S-shape" curves are observed for NPP, with or without bounding. As the difference between the observed sample average in target (D) and reference population (D0) increase, the posterior mean of p is first getting closer to the parameter estimate based on D0 at the beginning, then going back to the parameter estimate based on D.
  - Bounded weight method is the most sensitive one to the difference between observed sample average of D0 and D
- **CPP**
  - The flat curves are observed for CPP methods.
  - The degree of adaptive borrowing is less than using NPP methods.



Simulation Study Details

Simulation Setting

- Mimic the setting after study read out for the reference (adult) population D0, with sample mean 0.65 for 80 samples.
- Planning for a study with target (adolescent) population D, with sample size 40.
- Assuming varying unknown true p for the target population

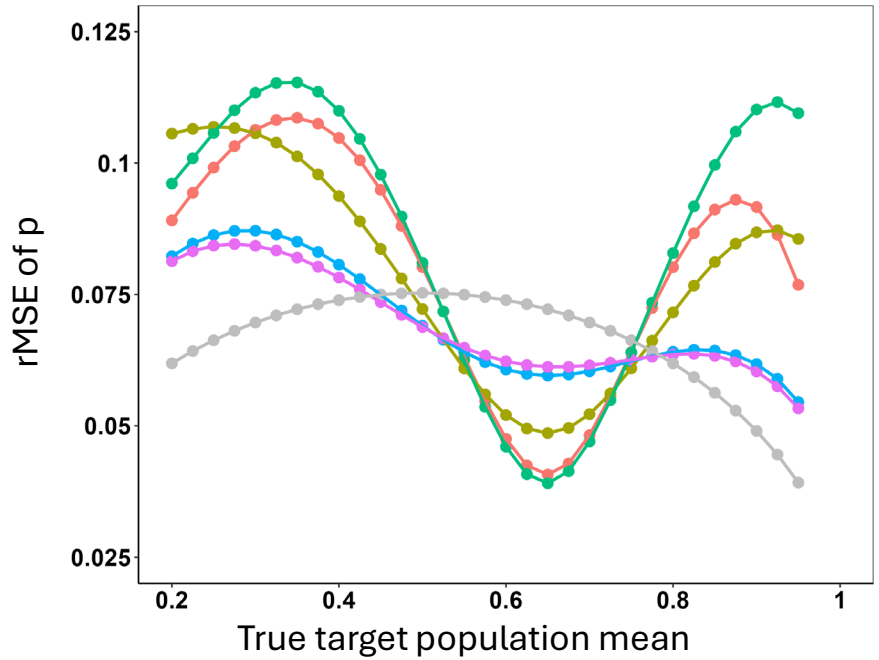
Hypothesis Testing

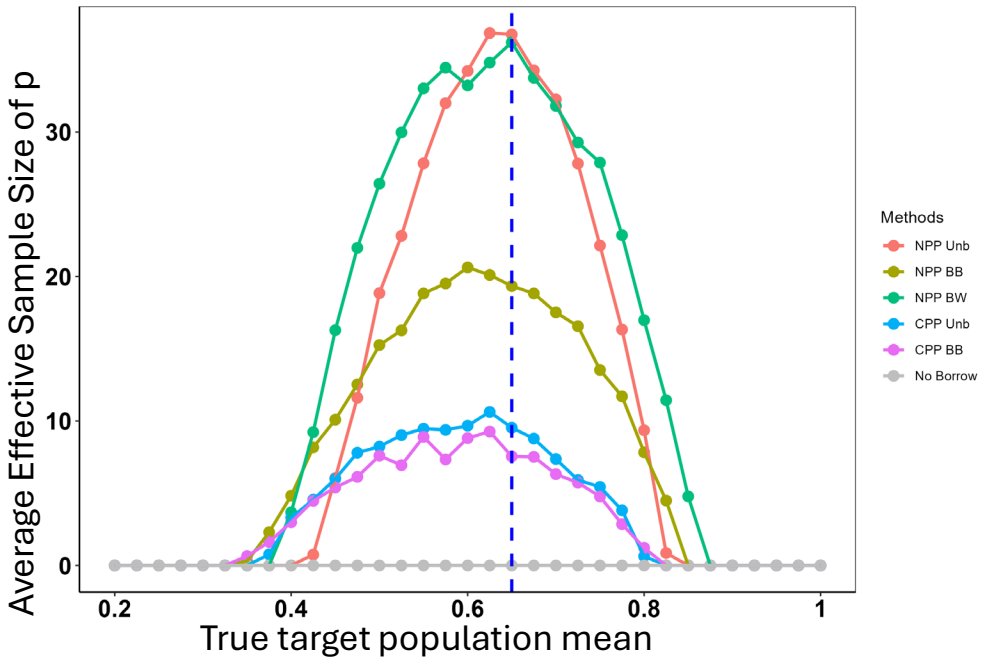
- H0: p <= 0.5 VS H1: p> 0.5
- Declare success if the posterior probability Pr(p > 0.5|Data) > 0.975.

Simulation Results Calculation

- Monte Carlo method
  - rMSE = $\sqrt{\frac{1}{m}\sum_{1}^{m}(\widehat{p_i} - p)^2}$, where $\widehat{p_i}$ is the estimate in the ith sample
- Based on all possible outcome of binomial outcome and the distribution function (currently used)
  - rMSE = $\sqrt{\sum_{j=0}^{j=40}\left(\widehat{p_j} - p\right)^2 * dbinom(p, x = j, n = 40)}$, where $\widehat{p_i}$ is the estimate when observing j responders out of the 40 patients from D.

Estimation Performance – rMSE and ESS





Dynamic borrowing

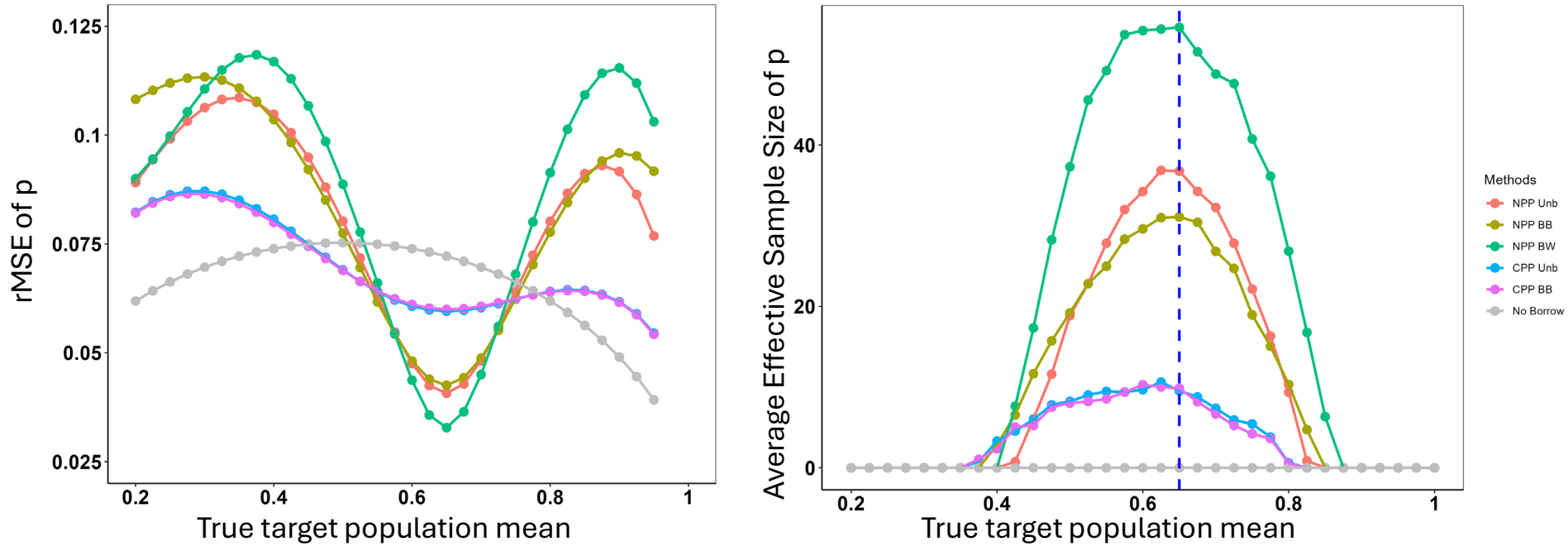
- borrowing is reduced when the true control rate is far from the observed reference data

'Sweet Spot' for improved rMSE

- When the true target population mean is close to observed reference data (.5 ~ .7), the borrowing method outperforms no borrowing
- NPP methods outperform CPP when true target population mean is around (.5 ~ .7)
- Bounded weight behave similarly to unbounded NPP

Estimation Performance with Larger Upper Bound for a_0 – rMSE and ESS

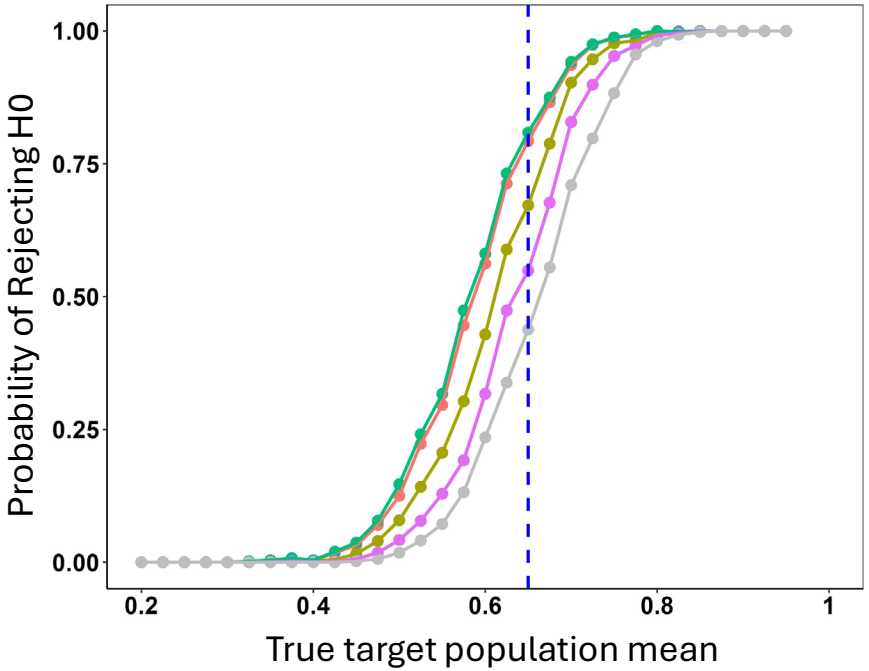
a_{upp}=0.8

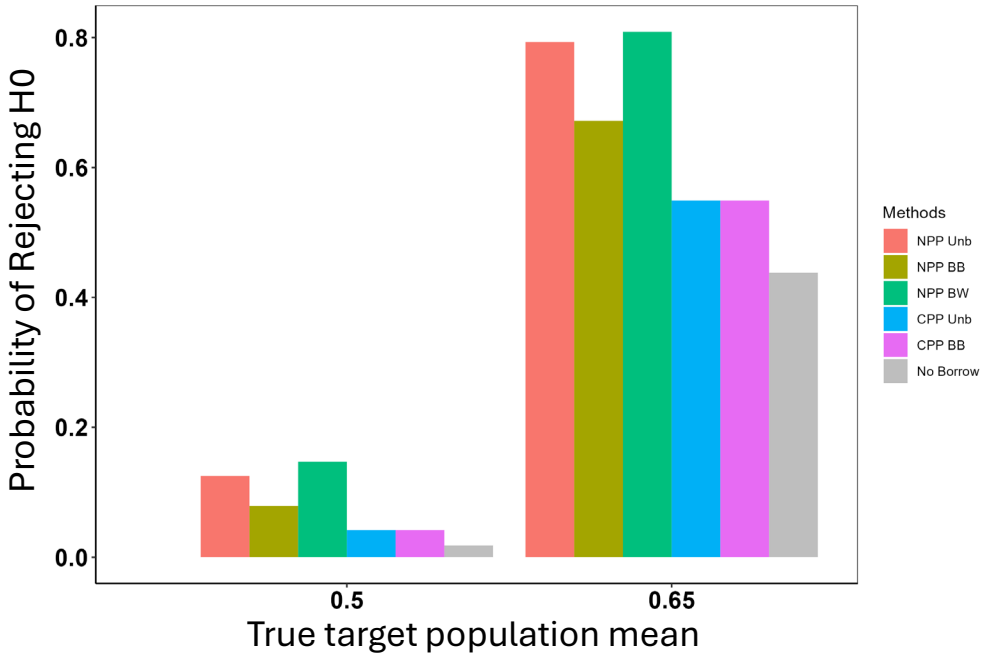


Effect of upper bound

- The upper bound forces a larger amount of borrowing
- NPP bounded weight and bounded beta methods perform better when true target population mean is close to the observed reference sample mean.

Operating Characteristic





Effect of borrowing

- The no borrowing method is the most conservative (lowest type one error and power), while the NPP bounded weight borrowing method is the most aggressive (increased type one error, and highest power).
- CPP borrowing methods, with or without bounded prior, have almost the identical type one error and power

Summary

- There is a complex hierarchical relationship between Population disease risk with Dose, Exposure, Response so that extrapolation and associated analysis requires scrutiny
  - Bayesian analysis and use of reference and target disease populations simplify this relationship through difference in observed outcomes
  - Instead, we propose a max/min similarity to summarize this complex relationship and implemented within established Bayesian methods
- Proposed an approach controlling the extent of borrowing via bounding weight prior on a_0
  - The degree of borrowing is dynamically adjusted through the bounded weight prior based on similarity between target data and reference data
  - It is flexible to incorporate various extent of prior belief with constant weight value and smooth decrease for prespecified interval for prior on a_0; avoid full borrowing and no borrowing as well.
  - Posterior mean of p using bounded weight approach is sensitive to the dissimilarity between target data and reference data
  - Bounded weight method is aggressive in borrowing, particularly when true target mean is close to observed reference mean
  - It has increased type one error, and highest power among all the approaches in this study