Meta-Analytic Approaches to Using Historical Data in Clinical Trials

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Outline

- Introduction with Examples
- Overview of Approaches
- Meta-Analytic Approaches
  - Meta-Combined and Meta-Analytic-Predictive Approach
  - Prior Effective Sample Size
  - Robustness
- More on Meta-Analytic-Predictive (MAP) Priors
- Conclusions

Introduction with Examples

1. Introduction and Examples

Informed Decision Making

- Informed decisions should be based on all relevant information
- In particular, when
  - information is sparse
  - new information is difficult to obtain
- Contextual or complementary data are often available

1. Introduction and Examples

Historical Data

- These data often referred too as «historical data»
  - But they may be come from a parallel experiment
  - Or, from data in the same experiment.
    E.g., in a clinical trial, from a similar subgroup
- Considering historical and current data is an example of evidence synthesis
- Various aspects to consider
  - methodological and practical issues and challenges
  - pros and cons

1. Introduction and Examples

Use of Historical Data: Pros & Cons

- Pros
  - **Design:** historical data are always used
    - This information puts the current experiment into perspective
    - For example: information about variability and expected effect sizsed drives sample size calculations
  - **Analysis:** historical data are rarely used.
    However, these data can improve the inference for key parameters
    - adjusted estimates (safeguard against extremes)
    - better precision

1. Introduction and Examples

Use of Historical Data: Pros & Cons

- Cons
  - What is relevant historical data?
    - Requires judgment about similarity of historical and current setting
    - Requires interaction between subject matter experts
  - How to incorporate historical data?
    - Requires a statistically principled approach
  - How much is the historical data worth?
  - What if historical data and actual data are in conflict?
    - Requires careful evaluation of the reasons
    - Problem can be mitigated by using a robust statistical approach

1. Introduction and Examples

Clinical Trials

- Use of historical data is attractive
  - Smaller sample sizes: e.g., smaller placebo group
  - More **ethical** (less placebo patients), or more **scientific** trials (learn more about new treatment)
  - Decreased costs and trial duration
- Historical data: various formats, e.g.
  - for control group only (our focus)
  - for effect parameter (mean difference, risk-ratio,...)
  - aggregate and/or individual data

1. Introduction and Examples

Novartis Experience

- Use of historical data
  - In all phase I oncology trials (to inform prior distributions)
  - In a substantial percentage of phase II trials
  - In special cases (e.g. non-inferiority trials)
- Experience overall positive
- However, there are challenges
  - Practical: drug development is highly regulated (company internal and external standards)
  - Practical: more time needed for study design
  - Methodological: innovative statistics

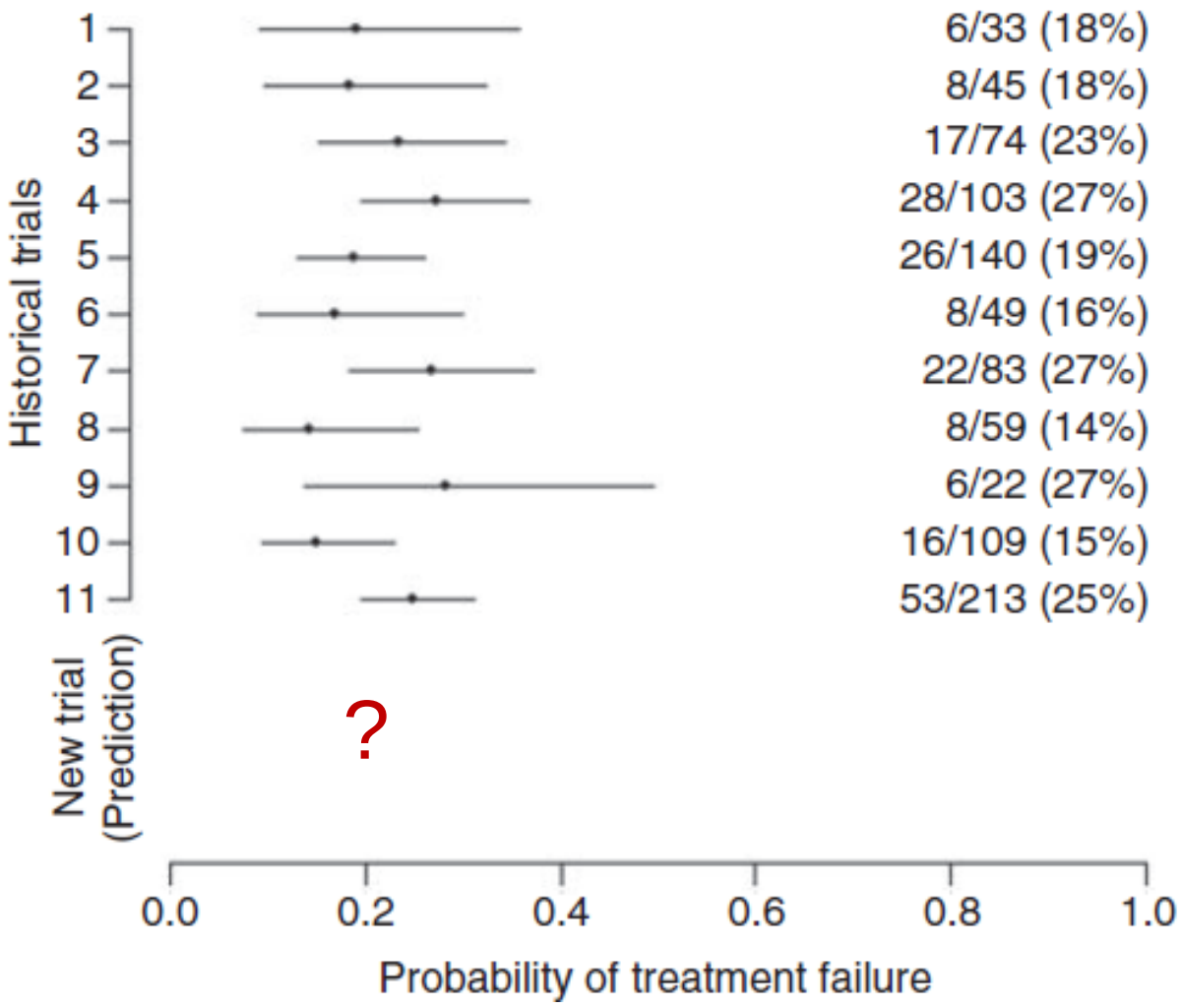
Example 1

Phase IV Trial

- Phase IV transplantation trial
- Binary outcome: treatment failure
- New treatment (T) vs. standard of care (C)
- Standard design: requires 450 patents per arm
- Historical data
  - 930 historical controls from 11 internal trials
  - Can these data be used to make control arm smaller?
  - See N et al. 2010

Example 1

Phase IV Trial: Control Data from 11 Historical Trials



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Example 2

Phase II Design

- Phase II Trial in Ulcerative Colitis
- Outcome: clinical remission at week 8
- Placebo data from 4 external trials (363 historical controls) of similar design

Source	r/n	%
VanAssche (2007)	6/56	10.7
Feagan (2005)	9/63	14.3
Rutgeerts *et al.* I (2005)	18/121	14.9
Rutgeerts *et al.* II (2005)	7/123	5.7
Total	40/363	11.0

Example 3

Design of a Phase I Oncology Trial in Japan

- **Western** (on-going) first-in-human study
  - Objective: determine the maximum tolerated dose **(MTD)**
  - Endpoint: frequency of dose-limiting toxicity **(DLT)**
- Phase I study in **Japan** to find Japanese MTD
  - Often, no ethnic differences
  - For Japanese trial, can we make use of Western data?

Dose	100	200	400	800	1500	3000	TOTAL
# Patients	5	6	5	9	8	4	37
# DLT	0	0	0	0	1	3	4

↑ Tentative Western MTD

Overview of Approaches

2. Overview of Approaches

Find Relevant Historical Data

- 1st step: idenfity relevant historical data
  - Systematic Reviews methodology
    - E.g. Cochrane Handbook (Higgins and Green 2011)
  - Pocock's (1976) criteria
    - Inclusion/exclusion criteria for patient population
    - Type of study design
    - Exact definition of the outcome
    - Quality of study execution and management;
    - Potential biases due to time trends
  - Requires cross-functional expertise
    - A psychological barrier for many statisticians
    - May not lead to a unique set of trials ($\rightarrow$ sensitivity analyses)

2. Overview of Approaches

Basic Notation

- Index for
  - Historical data from *H* trials: ***1,...H***
  - Current/new trial: *****
- Data
  - Historical: $Y_1,...Y_H$ Current: Y_*
- Parameters
  - Historical: $\theta_1 , ... , \theta_H$ Current: θ_*
  - Use of historical data requires an assumption of similarity: formally expressed by parameter model for

$$\theta_1,..., \theta_H, \theta_*$$

2. Overview of Approaches

Approaches

- Original work in pre-clinical applications (1970s)
- The main approaches are
  1. Pocock's approach (bias model)
  2. Ibrahim & Chen Power Priors
  3. Meta-Analytic approaches (hierarchical models)
  - Approaches 1-3
    - Are conceptually and mathematically similar
    - Discount the historical data; see Spiegelhalter et al. 2004

2. Overview of Approaches

Pocock (1976)

- Differences between new and historical trial

$$\delta_h = \theta_* - \theta_h \quad (h=1,...,H)$$

- Assumption: no systematic biases
  This requires careful selection of historical data

$$\delta_h \sim N(0,\tau_\delta^2)$$

- The above model can be extended, but this requires additional assumptions
  - Bias assumptions $\rightarrow$ δ_h not centered at 0
  - Historical trials of different quality $\rightarrow$ different τ_δ
    - e.g., larger for observational, smaller for randomized controlled trials

2. Overview of Approaches

Power Priors (Ibrahim and Chen 2000)

- Prior for θ_*
  - For one historical trial:

$$p(\theta_*|Y_1) \propto L(\theta_*|Y_1)^a \times \pi_0(\theta_*)$$

  - Accounts for historical data via discounted likelihood
  - $a \in [0,1]$ determines the amount of discounting
    - $a = 1$: pooling of historical and new data; $a = 0$: no borrowing
  - Notes:
    - $\pi_0(\theta_*)$, a default non-informative prior
    - No formal model for θ_1 (historical) and θ_* (but see slides 20-21)
    - Extension to more trials: power parameters $a_1,...,a_H$

2. Overview of Approaches

Power Priors: Two Versions

- Fixed *a*
  - Discounting does not depend on how similar historical and new data are
- What about unknown *a* *(=α)?*
  - Prior on α ?

$$p(\theta_*, \alpha \mid Y_1) \propto L(\theta_* | Y_1)^{\alpha} \times \pi(\alpha) \times \pi_0(\theta_*)$$

  - This is not correct:
    - $L(\theta_* | Y_1)^{\alpha}$, conditional prior of θ_* given α; $\pi(\alpha)$ marginal prior of α
    - Normalizing constant on right-hand side depends on unknown α
    - Derivation of normalizing constant can be difficult
    - See Duan et al. 2006, N et al. 2009

2. Overview of Approaches

Power Priors: Unknown Power Parameter

- Simple Example: one trial with binary data
  - Uniform prior for power parameter α
  - Historical data: x_0 responders, y_0 non-responders, $n_0=x_0+y_0$
  - New data: x responders, y non-responders, $n=x+y$
  - Power priors
    - Original: $\propto \theta^{\alpha x0} (1-\theta)^{\alpha y0}$
    - Normalized: $= \Gamma(\alpha n_0+2)\, \Gamma^{-1}(\alpha x_0+1)\, \Gamma^{-1}(\alpha y_0+1)\, \theta^{\alpha x0} (1-\theta)^{\alpha y0}$
  - Data: historical $x_0/n_0=20/100$, new $x/n=20/100$
    - α posterior from original prior: $0.02\ (0.00,0.07)_{95\%}$???
    - α posterior from normalized prior: $0.57\ (0.07,0.98)_{95\%}$

2. Overview of Approaches

Hierarchical Modeling Approaches

- Data (within trials) suggests a hierarchical model that allows for between-trial heterogeneity
  - $\theta_1,\ldots,\theta_C,\theta_* \sim N(\mu,\tau^2)$
    - For normal-normal hierarchical model (see later slides), there is a 1-1 mapping between τ and *a* (power parameter)
    - Historical data: n observations with standard deviation σ (known)

$$a = \frac{1}{1 + 2n\tau^2/\sigma^2}$$

  - $\theta_1=\ldots=\theta_C=\mu,\ \theta_* \sim N(\mu,\tau^2)$
    - Commensurate prior approach (Hobbs et al. 2011,2013)
  - Note:
    - for one historical trial, the above approaches are equivalent

2. Overview of Approaches

1-1 Relationship: Power Parameter a vs. Between-Trial sd τ

- Example
  - Normal data (known standard deviation σ)
  - Hierarchical model (between trial sd τ)
- Power parameter *a* (%) as a function of
  - historical sample size *n* (one trial)
  - between trial-heterogeneity (σ^2/τ^2, see N et al 2010)

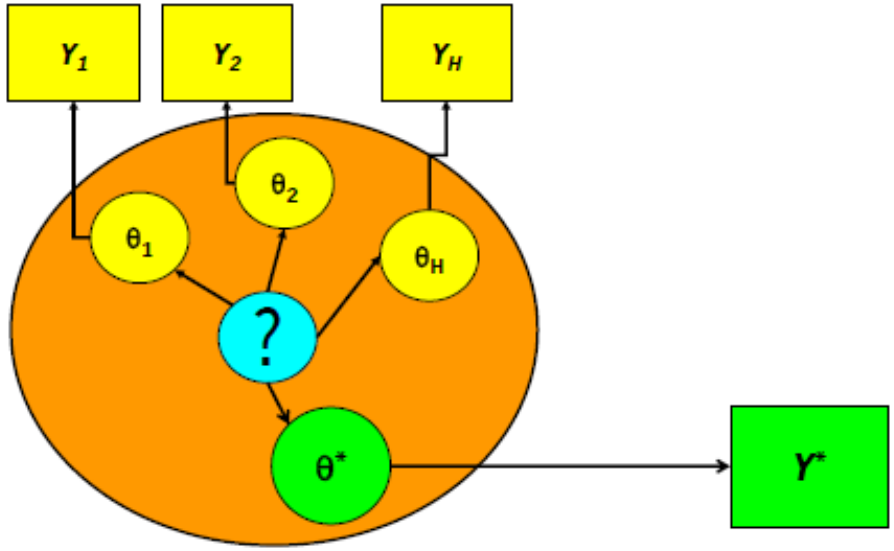
	large (4)	substantial (16)	moderate (64)	small (256)
n=25	7.0	20.0	60	80
n=50	4.0	10.0	40	70
n=100	2.0	7.0	20	60
n=250	0.8	3.0	10	30
n=500	0.4	2.0	6	20
n=1000	0.2	0.8	3	10

  - For moderate between-trial sd: historical data are worth
    - 20 subjects if n=100 (a=0.20),
    - 30 subjects if n=1000 (a=0.03)

Meta-Analytic Approaches

3. Meta-Analytic Approaches

Framework



- Meta-Analytic Approach
  - uses a data model $Y|\theta$, and a parameter model ?
  - infers the parameter of interest θ_*
    - at the end of the new trial (with Y_*),
    - or, at the design stage (without Y_*) $\rightarrow$ prior of θ_*

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3. Meta-Analytic Approaches

Retrospective or Prospective Use of Historical Data

- Two MA approaches
  - ***Meta-Analytic-Combined (MAC)*** is **retrospective**
    - Perform a meta-analysis of historical data and current trial data
    - Parameter of interest: the parameter in the actual trial

$$\theta_* \mid Y_1,\ldots Y_H, Y_*$$

  - ***Meta-Analytic-Predictive*** **(MAP)** is **prospective**

1) At design stage of current trial:
   Perform MA of historical data data and obtain distribution of θ_*

MAP Prior: $\theta_* \mid Y_1,\ldots Y_H$

2) Combine MAP prior with current trial data Y_* (Bayesian analysis)

3. Meta-Analytic Approaches

MAC or MAP?

- ***Meta-Analytic-Combined (MAC)***
  - No prior for θ^* required at design stage
  - Only one analysis required, can be (non-)Bayesian
- ***Meta-Analytic-Predictive (MAP)***
  - Historical information about θ^* is explicitely stated at design stage
  - Historical data can then be ignored
  - Fully Bayesian analysis required
- ***MAC*** or ***MAP*** ? Which one is better?

3. Meta-Analytic Approaches

MAC and MAP Are Equivalent

- For a hierarchical model, MAC and MAP are equivalent
  - HM $\rightarrow$ data conditionally independent given parameters
  - That is: $Y_h \mid \theta_1,...,\theta_h,...\theta_H, \theta_* = Y_h \mid \theta_h$
  - Proof:

$$
\begin{aligned}
p(\theta_\star|Y_\star, Y_\mathcal{J}) &\propto p(\theta_\star, \theta_\mathcal{J}|Y_\star, Y_\mathcal{J}) \\
&\propto p(Y_\star, Y_\mathcal{J}|\theta_\star, \theta_\mathcal{J}) \times p(\theta_\star, \theta_\mathcal{J}) \\
&= p(Y_\star|\theta_\star) \times p(Y_\mathcal{J}|\theta_\mathcal{J}) \times p(\theta_\star, \theta_\mathcal{J}) \\
&\propto p(Y_\star|\theta_\star) \times p(\theta_\star, \theta_\mathcal{J}|Y_\mathcal{J}) \\
&\propto p(Y_\star|\theta_\star) \times p(\theta_\star|Y_\mathcal{J})
\end{aligned}
$$

3. Meta-Analytic Approaches

Normal-Normal Hierarchical Model (NNHM)

NNHM, very popular model

- Sampling model

$$Y_h \mid \theta_h \sim N(\theta_h, s_h^2) \qquad h = 1,...,H, *$$

- Parameter model

$$\theta_h \mid \mu,\tau \sim N(\mu, \tau^2) \qquad h = 1,...,H, *$$

- Inference: for θ_*
  - Challenge: what is τ? (in particular if H is small)
  - Classical: various ways to estimate τ
  - Bayesian: priors on μ (often flat) and τ (contextual)

3. Meta-Analytic Approaches

*Inference for **known** τ (with improper prior for μ)*

Basic formulas for fixed τ: Classical and Bayesian results are the same

Meta-analytic weights

$$w_h = 1/(s_h^2 + \tau^2)$$

Inference for μ

$$\hat{\mu} = \sum_h w_h Y_h / \sum w_h, \quad Var(\hat{\mu}) = 1/\sum w_h$$

Shrinkage factors

$$B_h = s_h^2/(s_h^2 + \tau^2)$$

Inference for θ_h

$$\hat{\theta}_h = B_h\hat{\mu} + (1 - B_h)Y_h, \quad Var(\hat{\theta}_h) = B_h(\tau^2 + B_h Var(\hat{\mu}))$$

Inference for new parameter $\theta^\star$

$$\hat{\theta}^\star = \hat{\mu}, \quad Var(\hat{\theta}^\star) = \tau^2 + Var(\hat{\mu})$$

Special casel: 1 historical trial: $\hat{\theta}^\star = Y_1, \quad Var(\hat{\theta}^\star) = s_1^2 + 2\tau^2$

3. Meta-Analytic Approaches

Unknown τ

- Discounting of historical data depends on τ
- For small number of trials
  - Classical
    - The various estimates can differ substantially
    - It is unclear how to adjust for estimation uncertainty
    - Proposal: for θ_*, t distribution with H-2 df (Higgins et al. 2009)
  - Bayesian
    - Conclusions can be sensitive to the prior
    - Judgment required about plausible values for τ

3. Meta-Analytic Approaches

τ-Priors. Spiegelhalter et al. 2004, Gelman 2006

- Various priors for τ
  - Uniform, inverse-sqrt-gamma, Half-Normal, Half-Cauchy...
  - Recommendation: use prior that puts
    - most of its mass to values that represent plausible heterogeneity
    - remaining probability to unanticipated heterogeneity (e.g. large)
  - Example: binary data, parameter = logit(p)
    - τ = 2 (1) correspond to very large (large) heterogeneity
    - Half-Normal priors (Spiegelhalter et al. 2004)

$\tau \sim$ Half-Normal(scale=1.0) $\rightarrow$ Pr(τ<2) $\approx$ 0.95

$\tau \sim$ Half-Normal(scale=0.5) $\rightarrow$ Pr(τ<1) $\approx$ 0.95

3. Meta-Analytic Approaches

Prior Effective Sample Size (ESS)

- Idea:
  - express prior as an equivalent number of subjects
  - the ***prior effective sample size (ESS)***
- What we know from conjugate analyses:
  - Binomial(n,p) data, Beta(a,b) prior
    - **Prior ESS: $n_0 = a+b$**
    - Posterior mean is a weighted average of prior mean and sample mean (with weights n_0 and n)
  - Similar results for normal, Poisson, exponential data, ...

3. Meta-Analytic Approaches
Approximating ESS

- More generally: ESS for MAP prior $\theta^* | Y_1,...,Y_H$
  - Approximate prior effective sample size n_*
    - Idea: sample sizes are (approximately) proportional to precisions
    - Under completeley homogeneous trials, $\tau = 0$

      $\Rightarrow$ $n_* = N = \Sigma_h n_h$ = total # of historical subjects

      $\Rightarrow$ $\mathrm{Var}_{\tau=0}(\theta_* | Y_1,..., Y_H)$ is proportional to 1/N
    - If $\tau>0$ (reality!) $\Rightarrow$ $\mathrm{Var}_{\tau>0}(\theta_* | Y_1,..., Y_H)$ is proportional to $1/n_*$

$$n_* = \frac{\mathrm{Var}_{\tau=0}(\theta_* \mid Y_1,...,Y_H)}{\mathrm{Var}_{\tau>0}(\theta_* \mid Y_1,...,Y_H)} \times N$$

    - More general approach to ESS, see Morita et al. (2008, 2012)

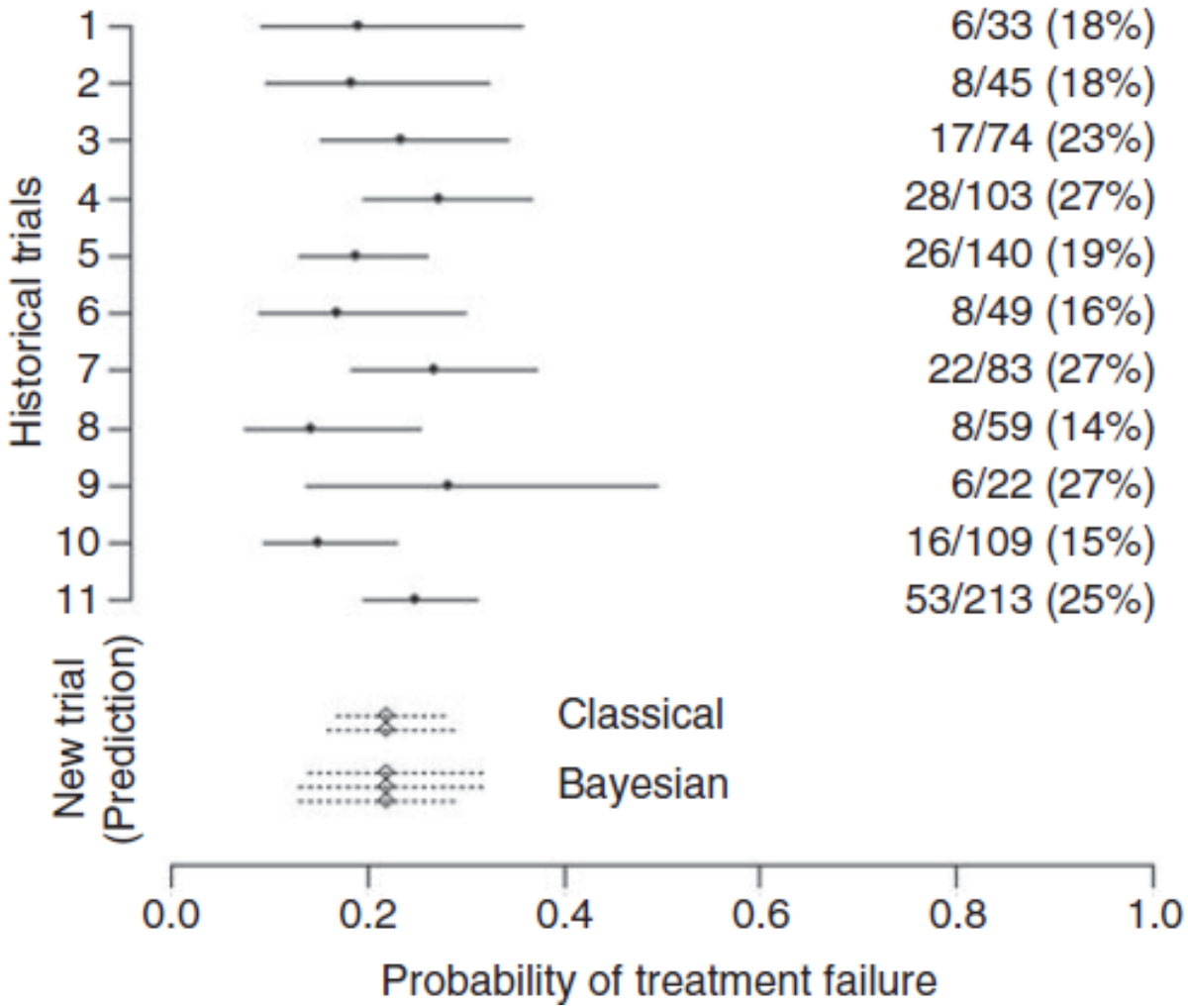
3. Meta-Analytic Approaches

Prior ESS for Example 1

- 11 historical trials with **N=930** patients
- Between-trial sd τ on log-odds scale **0.17 (0.01, 0.50)$_{95\%}$**
- 0.17: small/moderate

Results for log-odds θ_*

- Pooled: –1.27 (0.080)
- MAP: –1.29 (0.253)
- **Prior ESS**
  $n^* = 930 \times (0.08/0.253)^2$
  = 93



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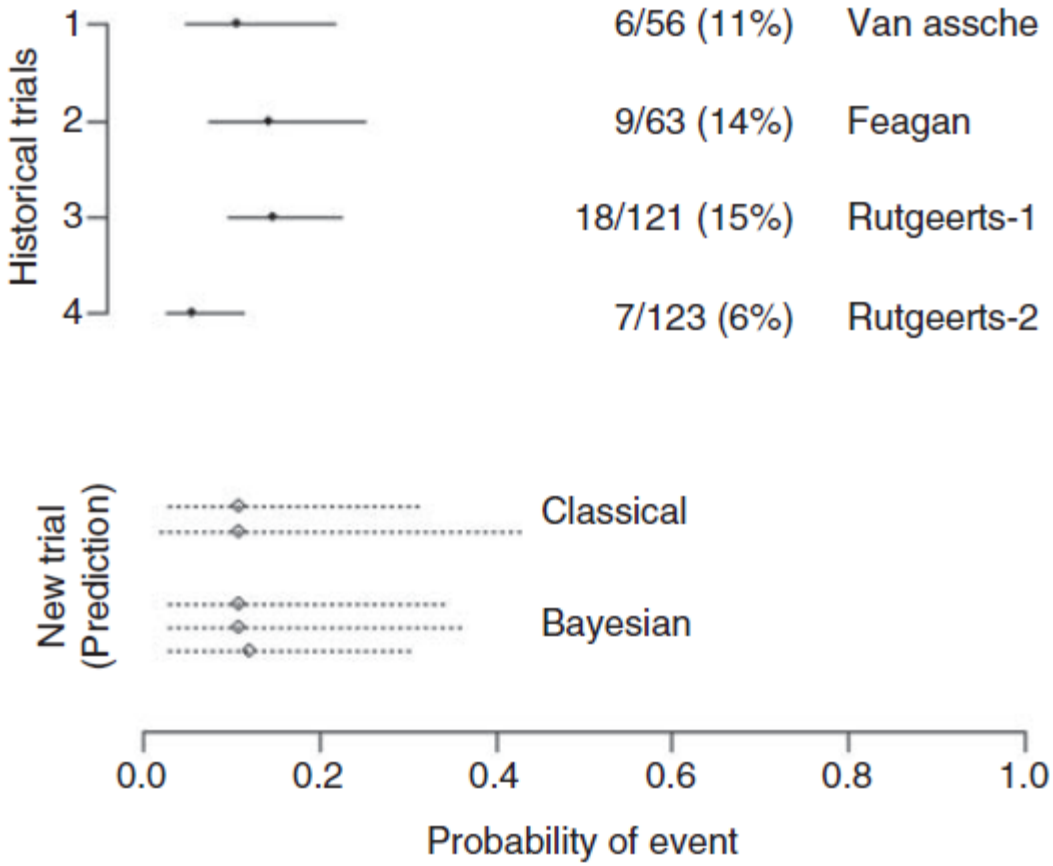
3. Meta-Analytic Approaches

Prior ESS for Example 2

- 4 historical trials with **N=363** patients
- Between-trial sd τ on log-odds scale **0.41 (0.03, 1.39)$_{95\%}$**
- 0.41: substantial

Results for log-odds θ_*

- Pooled: –2.01 (0.169)
- MAP: –2.08 (0.690)
- **Prior ESS**
  n* = 363×(0.169/0.690)^2
  = 22



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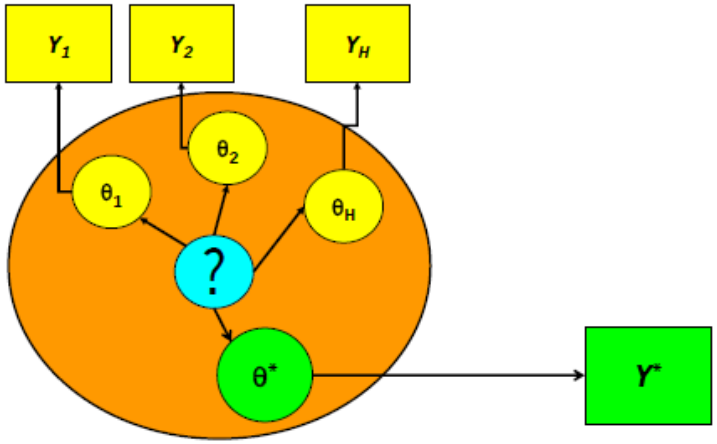
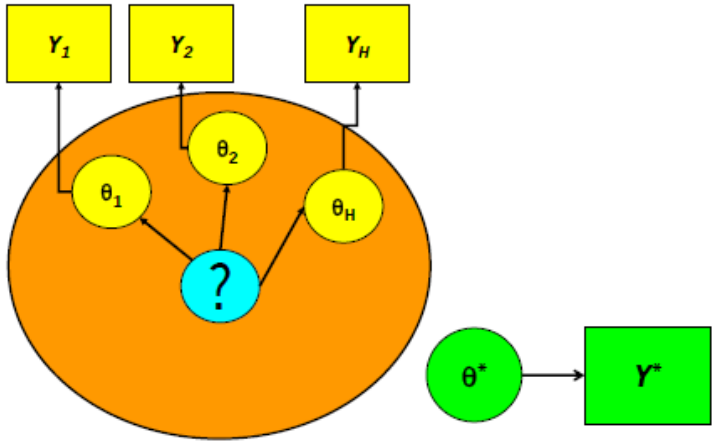
3. Meta-Analytic Approaches

Robust Meta-Analytic Priors

Similarity Scenario ($\rightarrow$ MAP prior)



Dissimilarity Scenario



- Conflict between historical data and actual data
  - Similarity of parameters is violated
  - Solution: robust priors (O'Hagan 1979); heavy-tailed (t or mixture)
- Robustifed MAP prior

  w $\times$ (MAP-prior) + (1-w) $\times$ (weakly-informative prior)

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3. Meta-Analytic Approaches

Example 3: Robust MAP Priors

- **Western** (on-going) first-in-human study
  - Objective: determine the maximum tolerated dose (MTD)
  - Endpoint: frequency of dose-limiting toxicity (DLT)
- Phase I study in **Japan** to find Japanese MTD
  - Often, no ethnic differences
  - For Japanese trial, can we use of Western data?

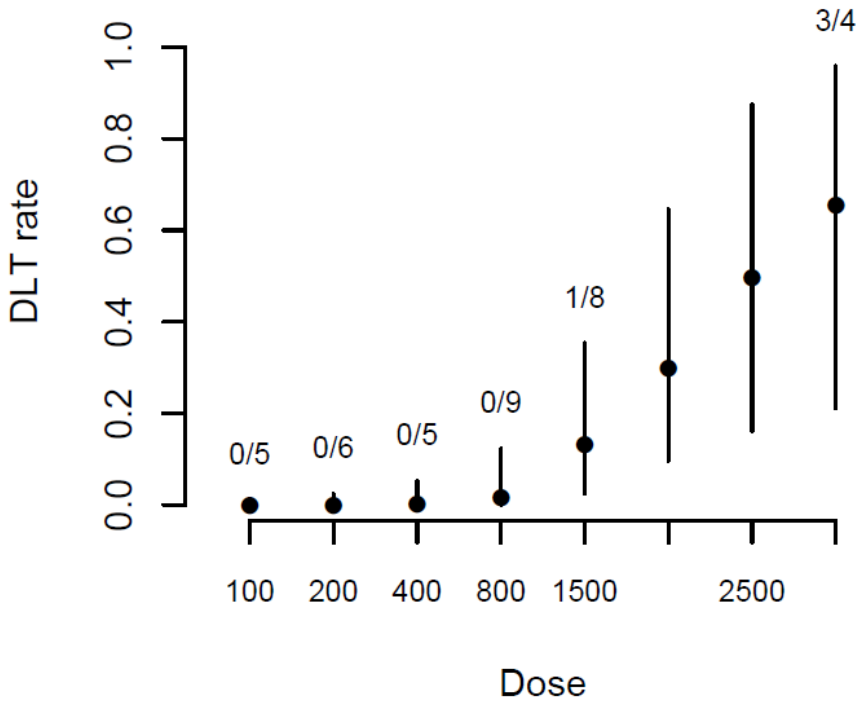
Dose	100	200	400	800	1500	3000	TOTAL
# Patients	5	6	5	9	8	4	37
# DLT	0	0	0	0	1	3	4

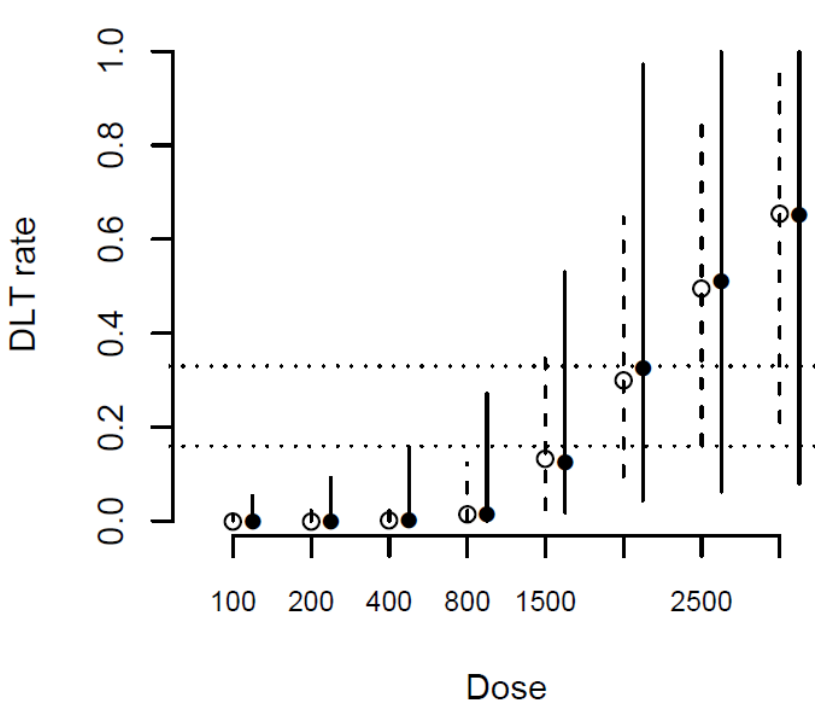
↑ Tentative MTD

3. Meta-Analytic Approaches

Example 3: MAP Prior for Similarity Scenario

- Model: logistic regression, with bivariate-normal prior for (α,β)
- Left: posterior from Western data
- Right: posterior from Western data (dotted line),
  MAP prior for Japan (solid line), under substantial heterogeneity





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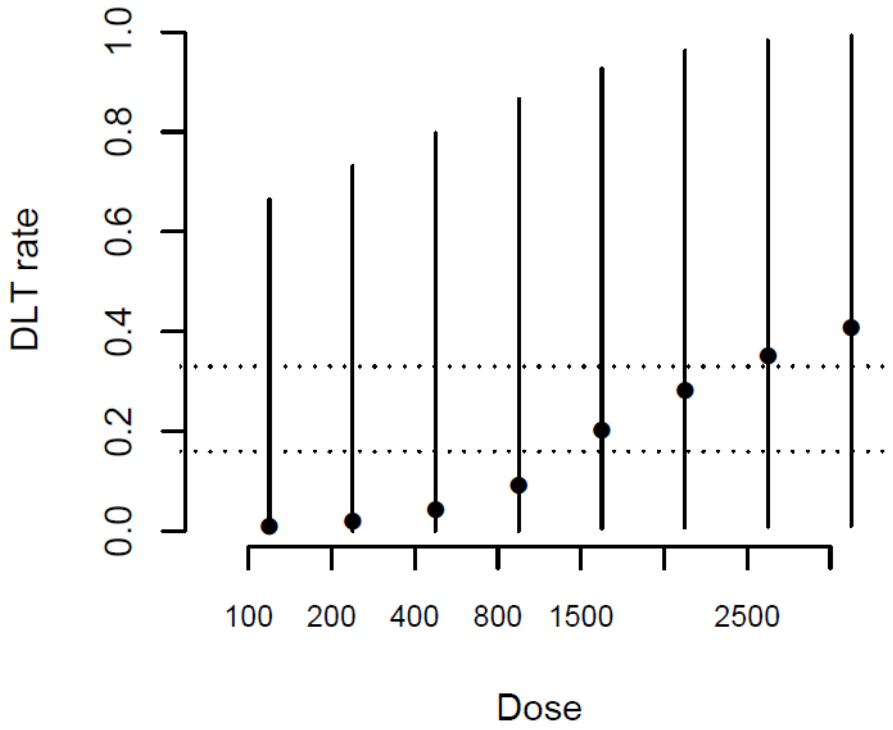
3. Meta-Analytic Approaches

Example 3: Weakly-Inf Prior for Dissimilarity Scenario

But what if ...

- There are relevant ethnic differences
- Better: to use weakly-informative prior (Figure)



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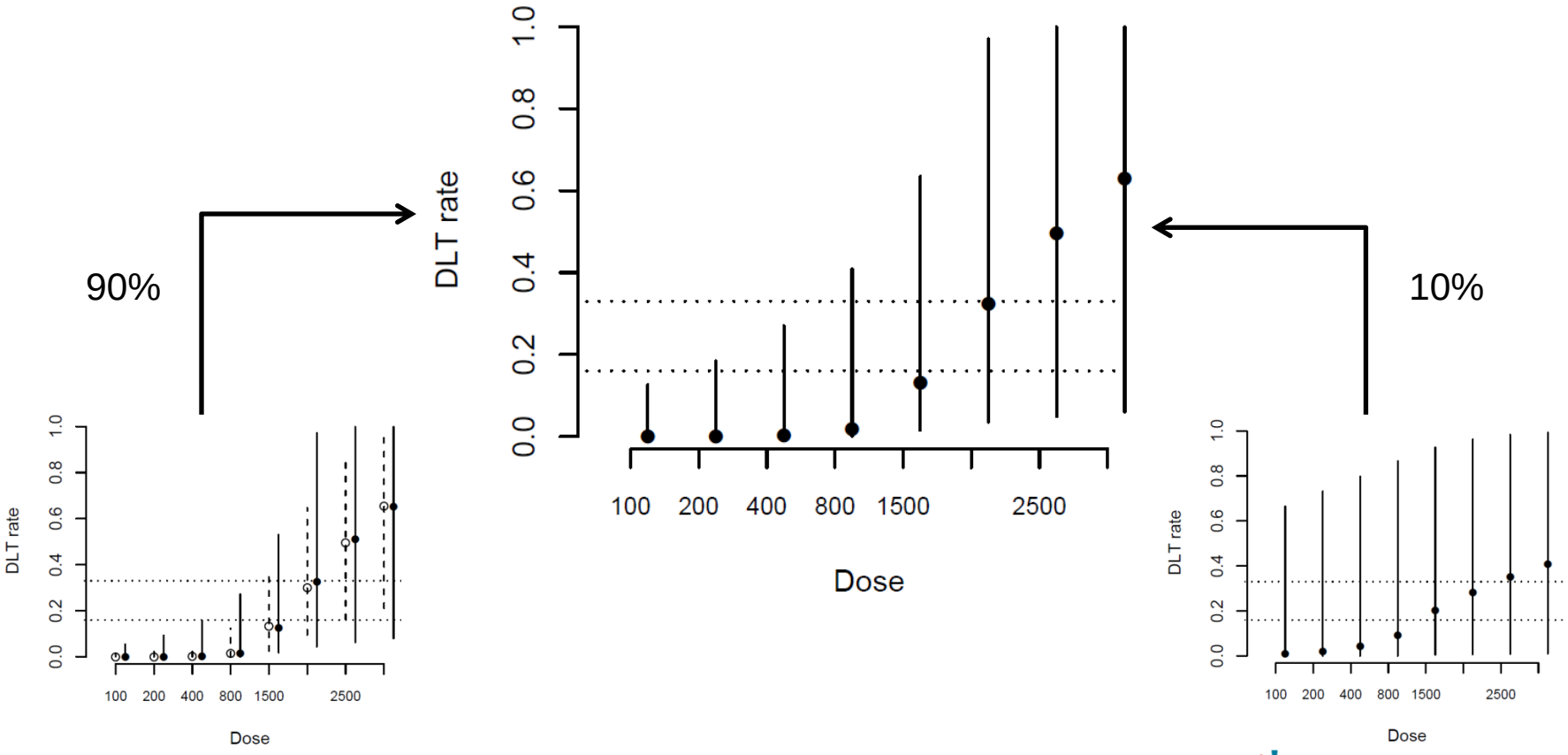
3. Meta-Analytic Approaches

Example 3: Robustification (Mixture Prior)

Mixture prior for the two scenarios, with the weights

- 90% for similarity scenario, 10% for dissimilarity scenario



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3. Meta-Analytic Approaches

Example 3: Two Data Scenarios

- Design properties
  - Assess operating characteristics
  - Assess data scenarios that may arise in the trial

Dose	100	200	400	800	1200	1500	3000
Western Data							
#DLT/#Pts	0 / 5	0 / 6	0 / 5	0 / 9		1 / 8	3 / 4
Japan: scenario 1 (similarity)							
			0 / 3	0 / 3	0 / 3	1 / 3	
Japan: scenario 2 (dissimilarity)							
			0 / 3	2 / 3			

3. Meta-Analytic Approaches

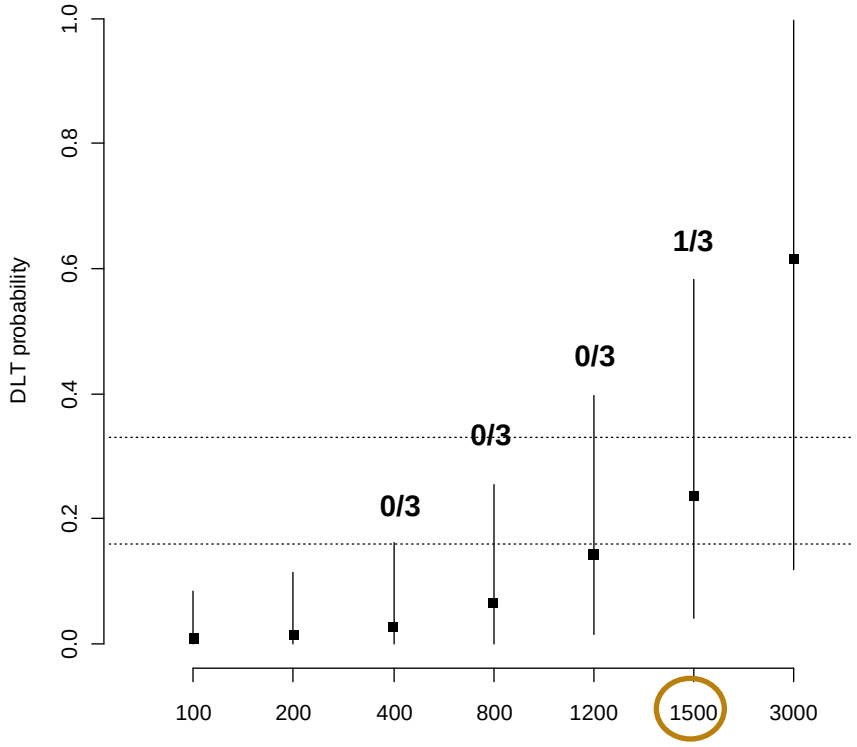
Example 3: Posteriors for Two Data Scenarios

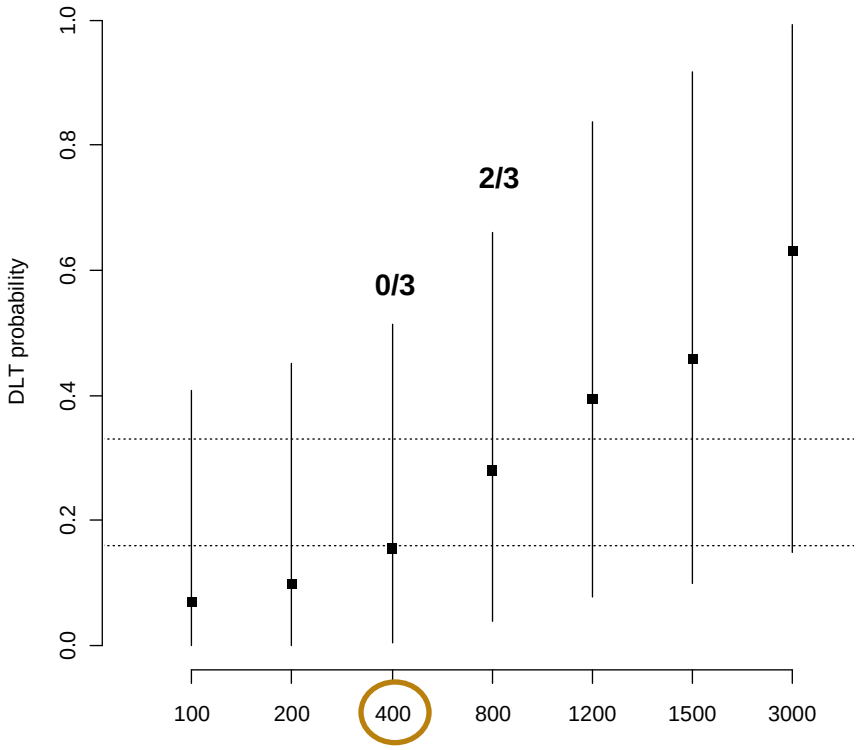
Similarity scenario

- Less uncertainty compared to prior
- Recommendation: **retest at 1500**
- Good borrowing from Western data

Dissimilarity scenario

- **More uncertainty** compared to prior
- Recommendation: **de-escalate to 400**
- Good robustness





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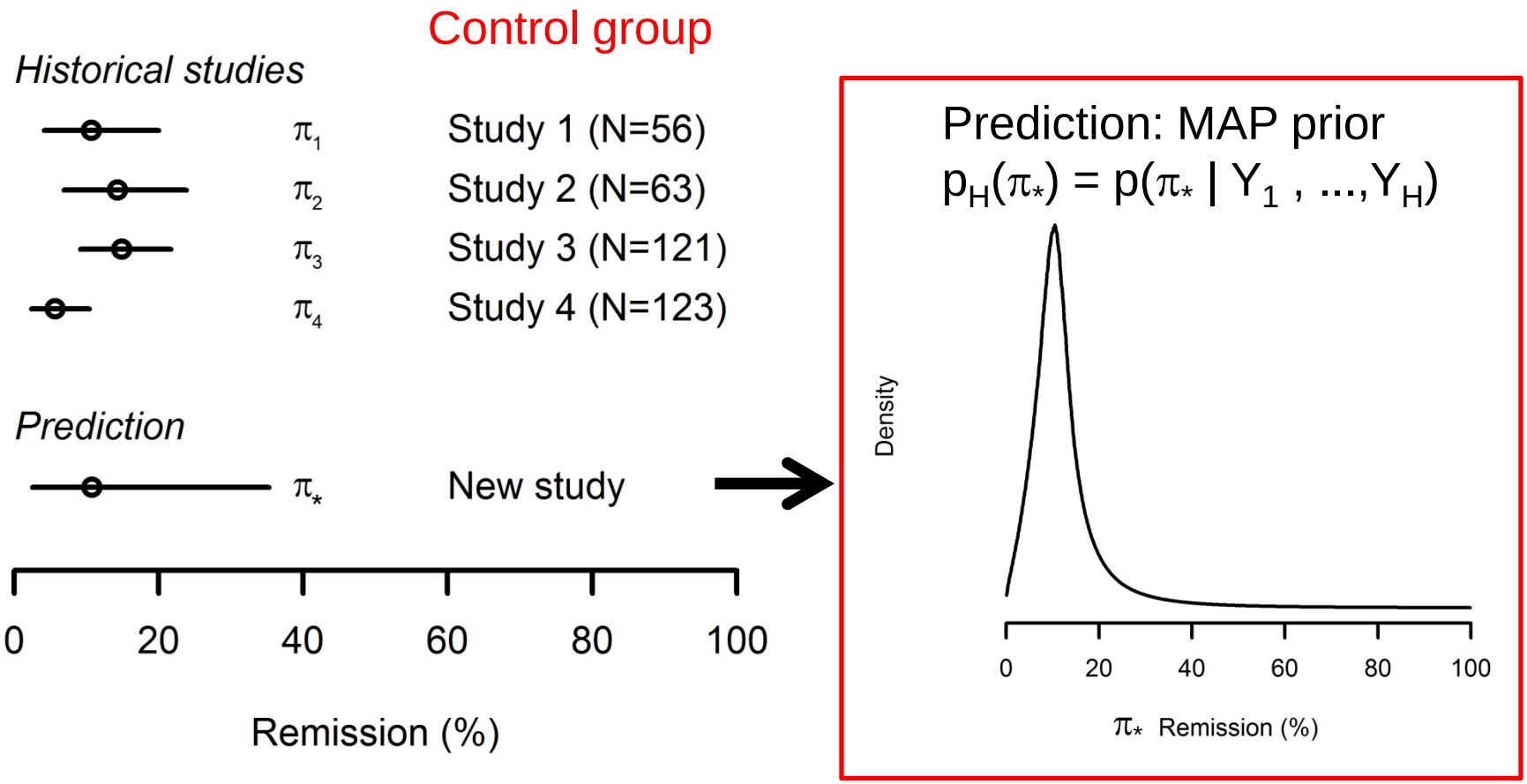
More on MAP Priors

4. More on MAP Priors

Example 2 Revisited



(density plot from MCMC sample)

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4. More on MAP Priors

Approximating the MAP Prior

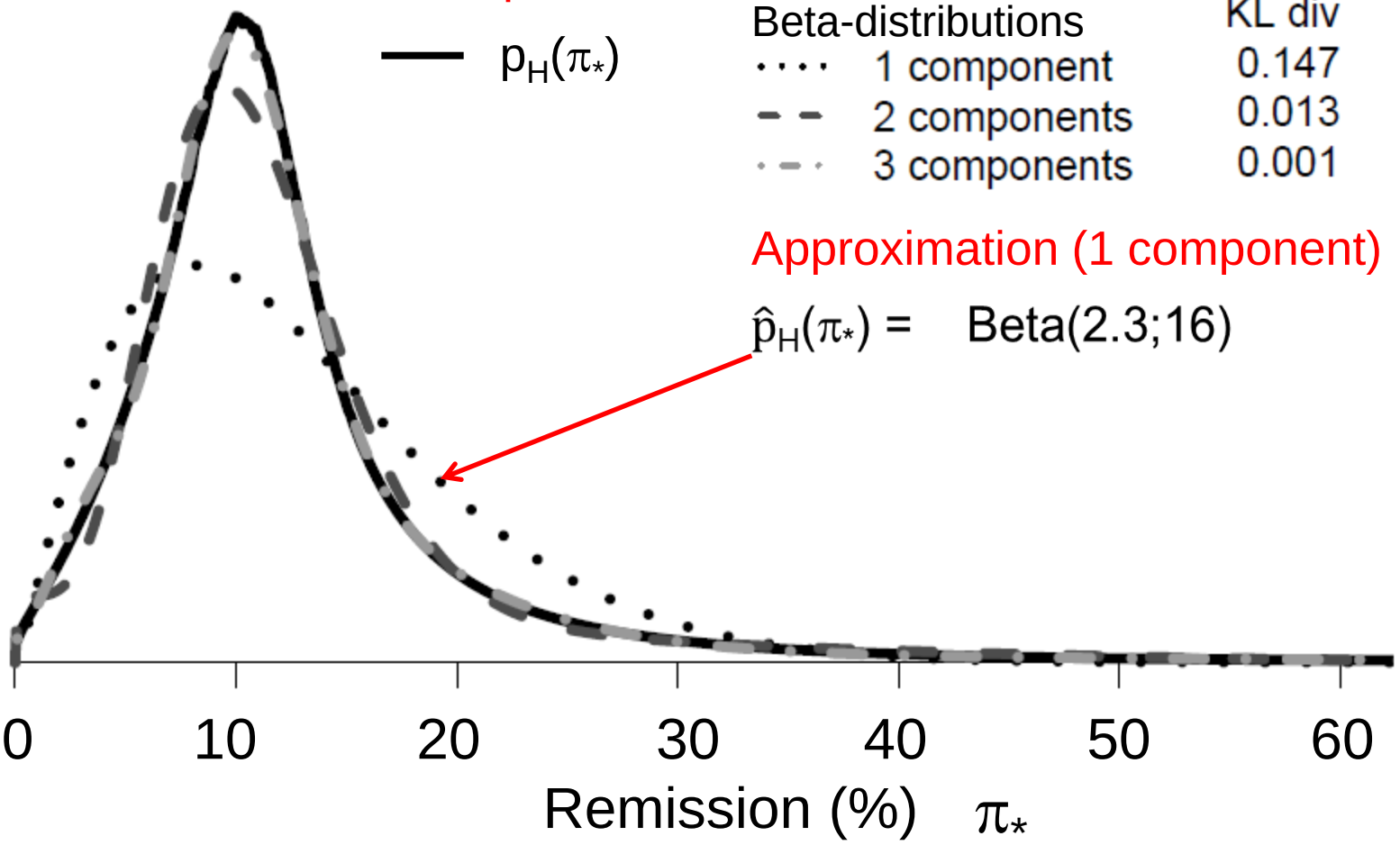
- MAP prior
  - Not available analytically (just MCMC sample), but can be well approximated by mixture of conjugate priors

    Dallal and Hall (1983), Diaconis and Ylvisaker (1985)

  - Mixture of conjugate priors. Advantages
    - *Easy communication*:
      discussions with clinical trial team, health authorities, ethics commitees, study protocols, publications
    - A*nalytical posterior calculation*
      $\rightarrow$ fast operating characteristics

4. More on MAP Priors

Example 2: MAP Prior approximated by single Beta



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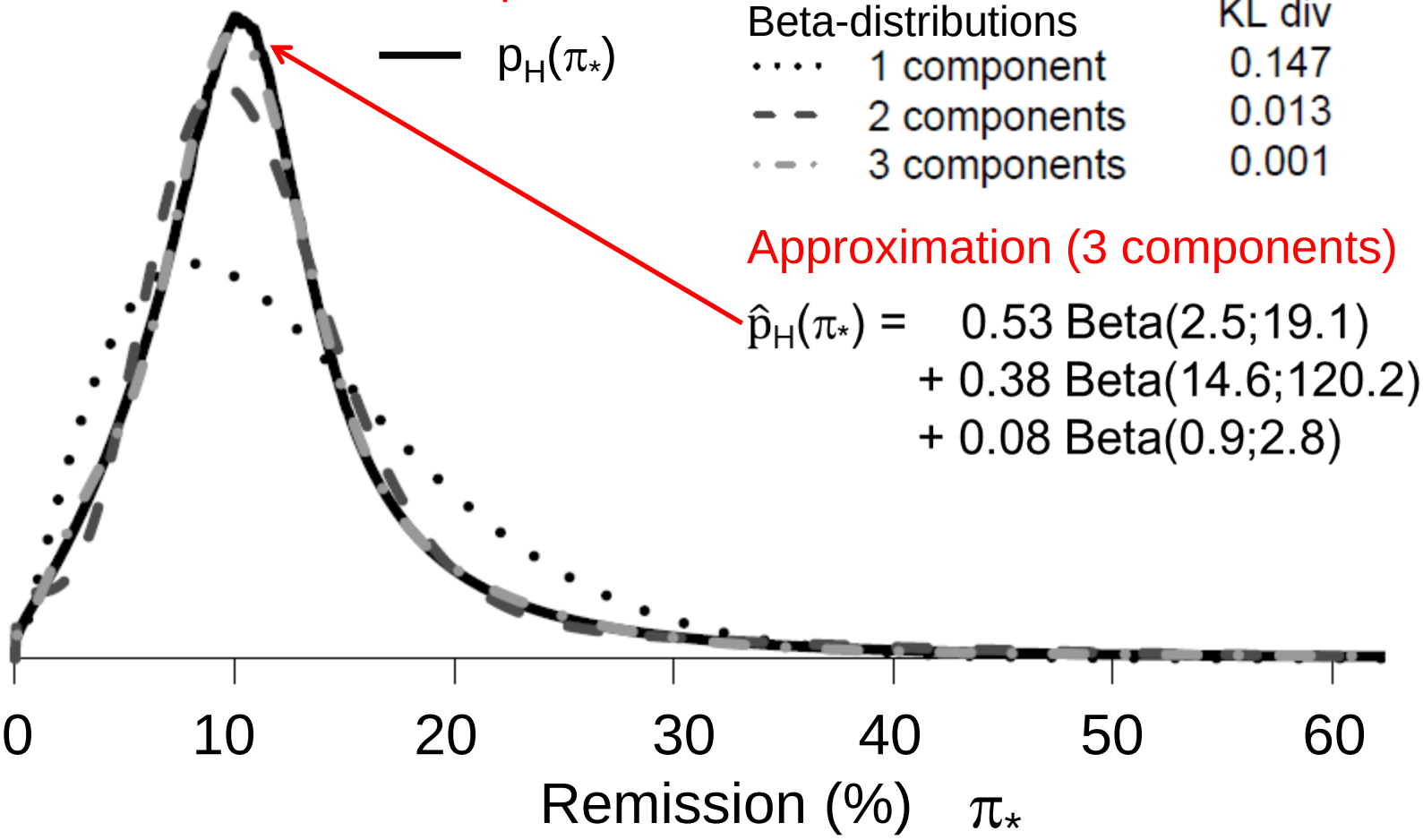
4. More on MAP Priors

Example 2: MAP Prior approximated by 3-comp Beta Mixture



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4. More on MAP Priors

Robustness

- Prior-data conflict
  - *Conjugate priors*: fixed prior-data compromise
  - *Heavy-tailed priors* : prior discarded under conflict

O'Hagan (1979), O'Hagan and Pericchi (2012)

- MAP priors
  - Typically heavy-tailed, hence naturally robust
  - Further robustness and more rapid adaptation to prior-data conflict by adding weakly-informative component:

$$w \times \text{MAP} + (1\text{-}w) \times \text{Uniform} \quad \text{e.g. } w = 0.9 \text{ or } 0.5$$

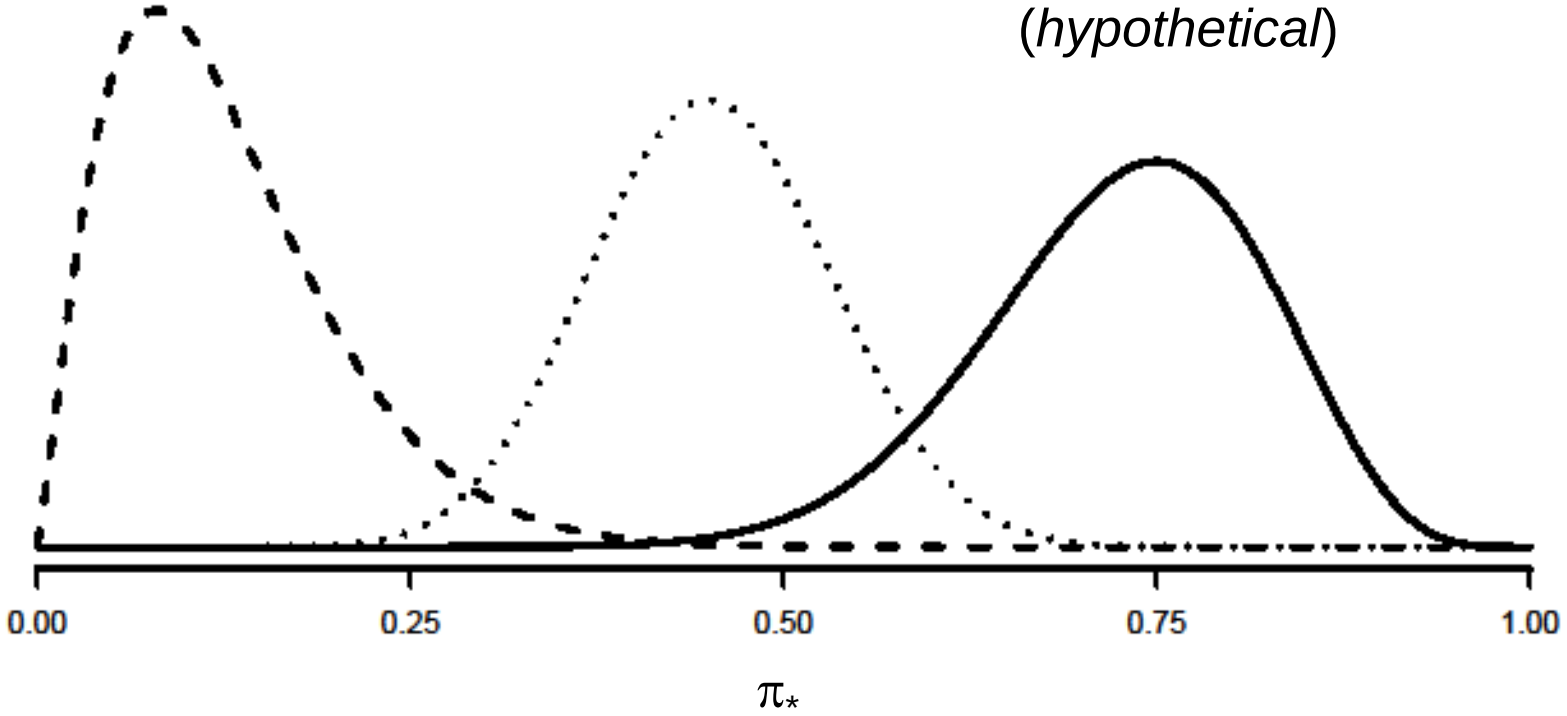
4. More on MAP Priors

Non-Robustness of Conjugate Prior

Conjugate prior
Beta(2.3,16)

Posterior
Beta(17.3,21)

Likelihood
15 / 20
(*hypothetical*)



"Bayesian - One who, vaguely expecting a horse and catching a glimpse of a donkey, strongly concludes he has seen a mule". Stephen Senn

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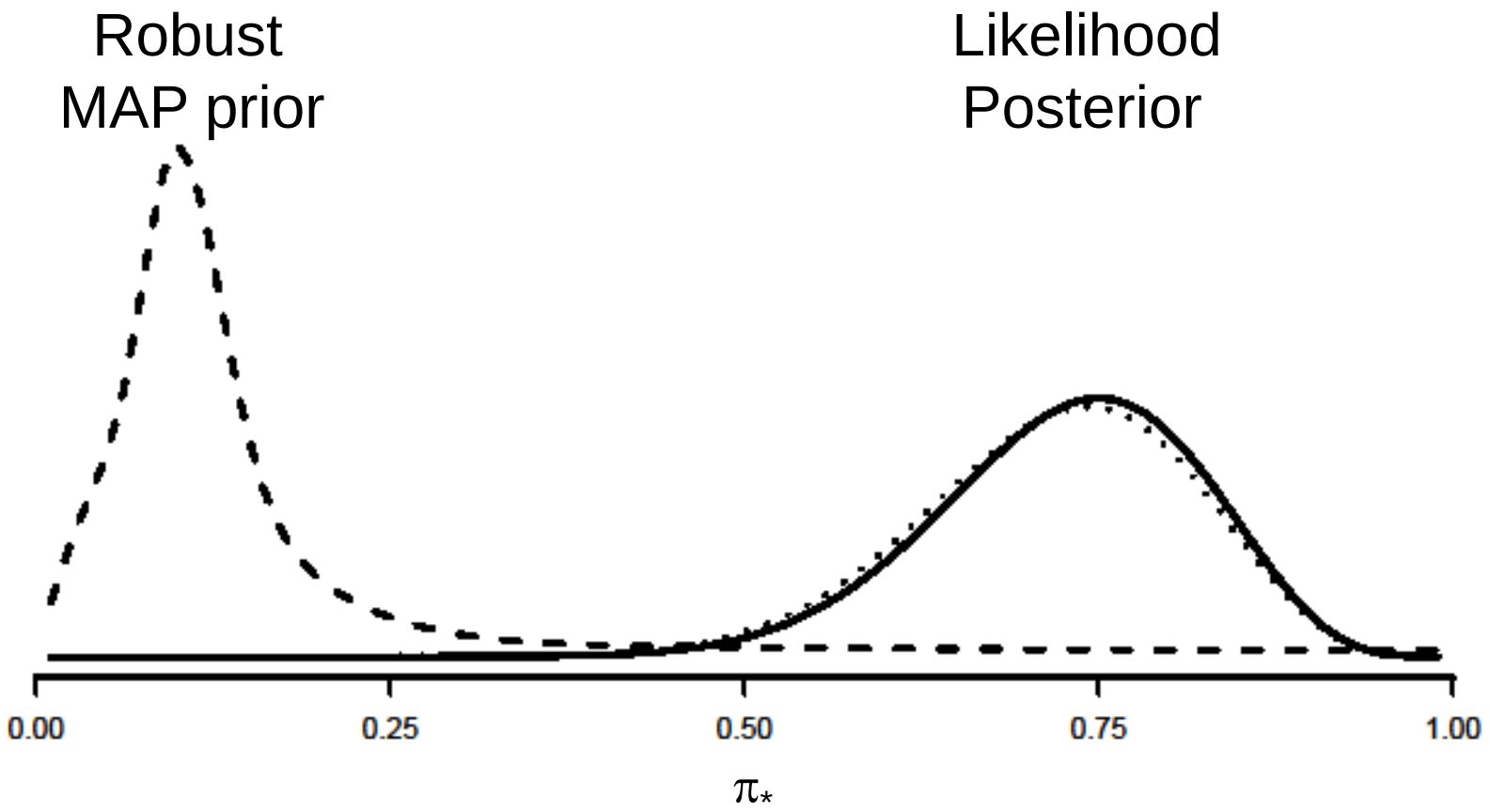
4. More on MAP Priors

Robustness of MAP Prior



- MAP = 0.53 Beta(2.5,19.1)+0.38 Beta(14.6,120.2)+0.08 Beta(0.9,2.8)
- Robust MAP = 0.9 x MAP + 0.1 x Beta(1,1)

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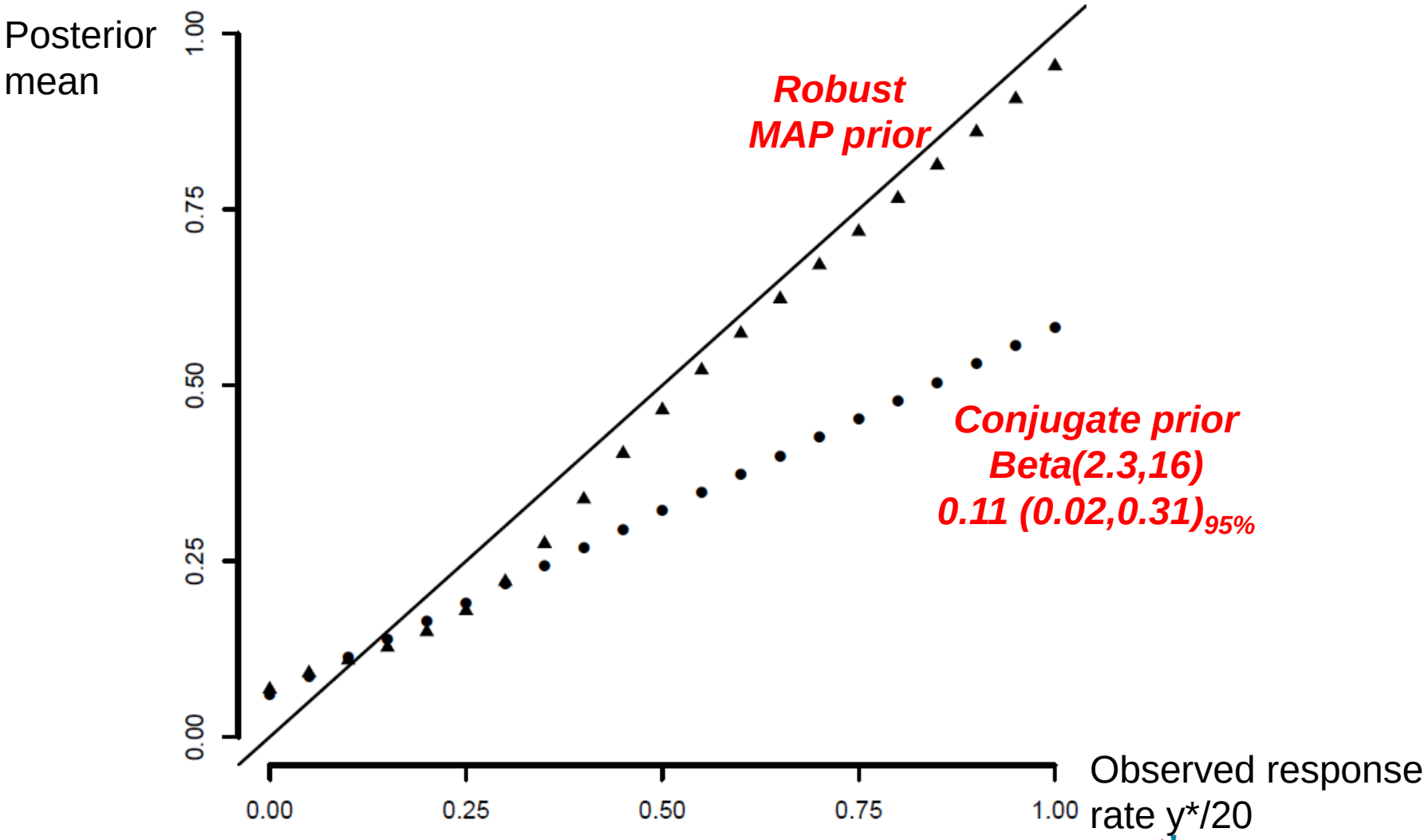
4. More on MAP Priors

Estimates for Simple Conjugate and Robust MAP Prior



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4. More on MAP Priors

Operating Characteristics (OC): Summary

- Frequentist properties (OC) for robust MAP priors
  - *Estimation*:
    - Bias well-controlled
    - MSE: better for MAP priors compared to weakly-informative priors if prior is well-specified
  - Testing
    - Success criterion = 1-α posterior probability for $\delta = \theta_T - \theta_* > 0$
    - Type-I error: some inflation (or deflation), but fairly well controlled
    - Power: gain in power compared to weakly-informative prior

4. More on MAP Priors

Operating Characteristics (Estimation): Two Designs

- Compare Control vs. Test
  - Control vs. treatment effect: $\delta = \theta_T - \theta_*$
  - Control prior worth n^* patients:

$$\theta_* \sim N(\theta_0, \sigma_0^2), \qquad \sigma_0^2 = \sigma^2 / n^*$$

  - Assume no information for test treatment (flat prior for θ_T)
  - Two Designs
    - Standard **B**alanced Design (B), with sample sizes *n*
    - **H**istorical Data Design (H): save n^* control patients

	C	C-prior	T
B: Balanced Design	*n*	-	*n*
H: Historical Data Design	*n*-n^*	n^*	*n*

4. More on MAP Priors

Operating Characteristics (Estimation): MSE

- Mean-squared error (MSE) for mean difference δ

$$\mathrm{MSE}_{(H)} > \mathrm{MSE}_{(B)} \quad \Leftrightarrow \quad |\theta - \theta_0|/\sigma_0 > 1$$

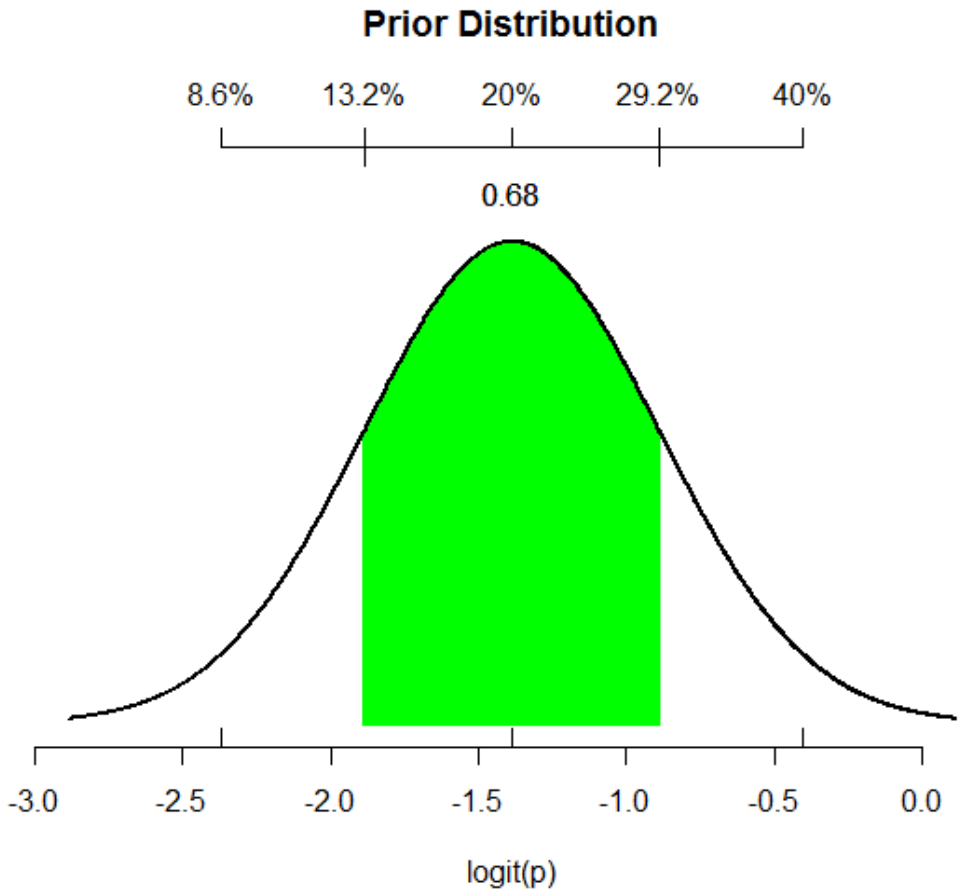
- **H**istorical data design better than **B**alanced design
  - if true parameter is less than one standard deviation away from the prior mean
  - i.e., if true parameter is in the 68% interval of the prior
- There is a benefit if prior is well-specified

4. More on MAP Priors

Operating Characteristics (Estimation): MSE - Example

Example: Binary data

- Control response rate
- Prior:
  - mean = 0.2, weight $n_* = 25$
- Normal approximation
  - logit(0.2) = –1.386
  - $(1/p+1/(1-p)) / n_* = 0.5^2$
- Prior:
  - logit(p) ~ $N(-1.386, 0.5^2)$
  - 95%-interval: ***0.086 to 0.4***



- For MSE, H-design better than B-design if $p \in (0.13, 0.29)$

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4. More on MAP Priors

Operating Characteristics (Testing): Comparison of Priors

- Test treatment vs. Control, binary endpoint
  - Vague prior for test treatment: Beta(1,1)
  - Informative prior for control, e.g.

    ESS

    i. Beta: simple conjugate Beta(4,16) prior: 0.19 $(0.06,0.40)_{95\%}$

    ii. Mix90: $0.9 \times$ Beta(4,6) $+ 0.1 \times$ Uniform

    iii. Mix50: $0.5 \times$ Beta(4,16) $+ 0.5 \times$ Uniform

    iv. Unif: Uniform prior
  - Robust prior on control discarded in case of prior-data conflict – may lead to inconclusive results
  - An adaptive design can reduce this risk (Hobbs et al. 2013)

4. More on MAP Priors

Operating Characteristics (Testing): Adaptive Design

- Two-stage adaptive design
  - Target sample size at end of trial:
    - n = 40 for control, m = 40 for test
  - Stage 1:
    - n_1 = 15 for control
    - m_1 = 20 for test
  - Interim analysis: for control, get interim ESS_C
  - Stage 2 of adaptive design:
    - 40 - ESS_C for control
    - 20 for test

4. More on MAP Priors

Operating Characteristics (Testing): Type-I Error, Power

Control Rate	Mix50	Mix90	Beta	Unif	Expected Sample Size (Control Group) Mix50	Mix90	Beta	Unif
Type-I Error (δ =0)								
0.1	0.6	0.1	0.0	1.8	28	20	20	40
0.2	2.5	1.5	1.6	2.3	26	20	20	40
0.3	3.9	5.5	6.1	2.4	29	21	20	40
0.5	**3.4**	**12.3**	**26.0**	**2.8**	**37**	**27**	**20**	**40**
Power (δ =0.3)								
0.1	92	81	82	90	28	20	20	40
0.2	88	86	88	82	26	20	20	40
0.3	83	88	93	80	29	21	20	40
0.5	**78**	**85**	**99**	**82**	**37**	**27**	**20**	**40**

Schmidli et al. (2014, submitted)

Conclusions

5. Conclusions

- Use of historical (trial-external) data is
  - attractive
  - ambitious
  - ambiguous
- *Attractive*
  - more information should lead to better inference, and, subsequently, to better decisions
  - various potential benefits: smaller control groups, more ethical trials, cost savings

5. Conclusions

- *Ambitious*
  - Requires upfront work: find relevant data
  - Statistically more challenging
  - MA approaches (various dialects) are useful
  - Robust approaches look promising
- *Ambiguous*
  - Compromise between acceptable frequentist and Bayesian metrics is needed
- Clinical trials: the topic is important, and its importance will most likely grow in the near future

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