Robust meta-analytic-predictive priors in clinical trials with historical control information

Heinz Schmidli

Statistical Methodology, Novartis, Basel, Switzerland

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heinz.schmidli@novartis.com

Outline

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- Meta-Analytic-Predictive (MAP) priors
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  - Prior effective sample size
  - Robustness
- Extensions
- Conclusions

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Sandro Gsteiger, Anthony O'Hagan, David Spiegelhalter

Motivating example

Traditional clinical trial design

- *Disease*
  Ankylosing spondylitis
- *Experimental treatment*
  Secukinumab (monoclonal antibody)
- *Endpoint*
  Binary: response at week 6
- *Traditional clinical trial design*
  - Secukinumab (n=24) vs. Placebo (n=24)
  - Fisher's exact test

However: 8 similar historical placebo-controlled clinical trials with different experimental treatments available

Could this historical placebo information be used?

Motivating example

Clinical trial design and analysis with historical controls

Historical placebo information

- Bayesian primary analysis
- *Prior Placebo* Derived from 8 historical trials (N=533), using a Meta-Analytic-Predictive (MAP) approach

  Beta(11,32) worth 43=11+32 patients
- *Prior Experimental* Weakly informative

  Beta(0.5,1) worth 1.5=0.5+1 patients
- Design:

  Secukinumab (n=24) vs. Placebo (n=6)
- Results:

  14/24 Secukinumab vs. 1/6 Placebo, $p(\delta > 0 \mid \text{data}) > 99.8\%$

  Baeten et al. (2013) Lancet 382(9906):1705-1713

Historical control information

Design and analysis of clinical trials

- Advantages – less patients on placebo

  Ethics, recruitment speed, trial costs, trial duration

- Methodology
  - Bias model (Pocock)
  - Power prior (Ibrahim, Chen)
  - Commensurate prior (Hobbs, Carlin, Sargent)
  - Meta-Analytic-Predictive (MAP) prior (Spiegelhalter,Neuenschwander)

- Common to all approaches: discounting of historical information due to between-trial heterogeneity

Meta-Analytic-Predictive (MAP) priors

Deriving prior for control in new study – binary data

Control group data – number of responders Y

- new study: $Y_* \sim \text{Binomial}(\pi_*, n_*)$ $\theta_* = \text{logit}(\pi_*)$
- historical studies: $Y_h \sim \text{Binomial}(\pi_h, n_h)$ $\theta_h = \text{logit}(\pi_h)$ $h=1,...,H$

Exchangeability assumption

$$\theta_*, \theta_1, \ldots, \theta_H \sim \text{Normal}(\mu, \tau^2)$$

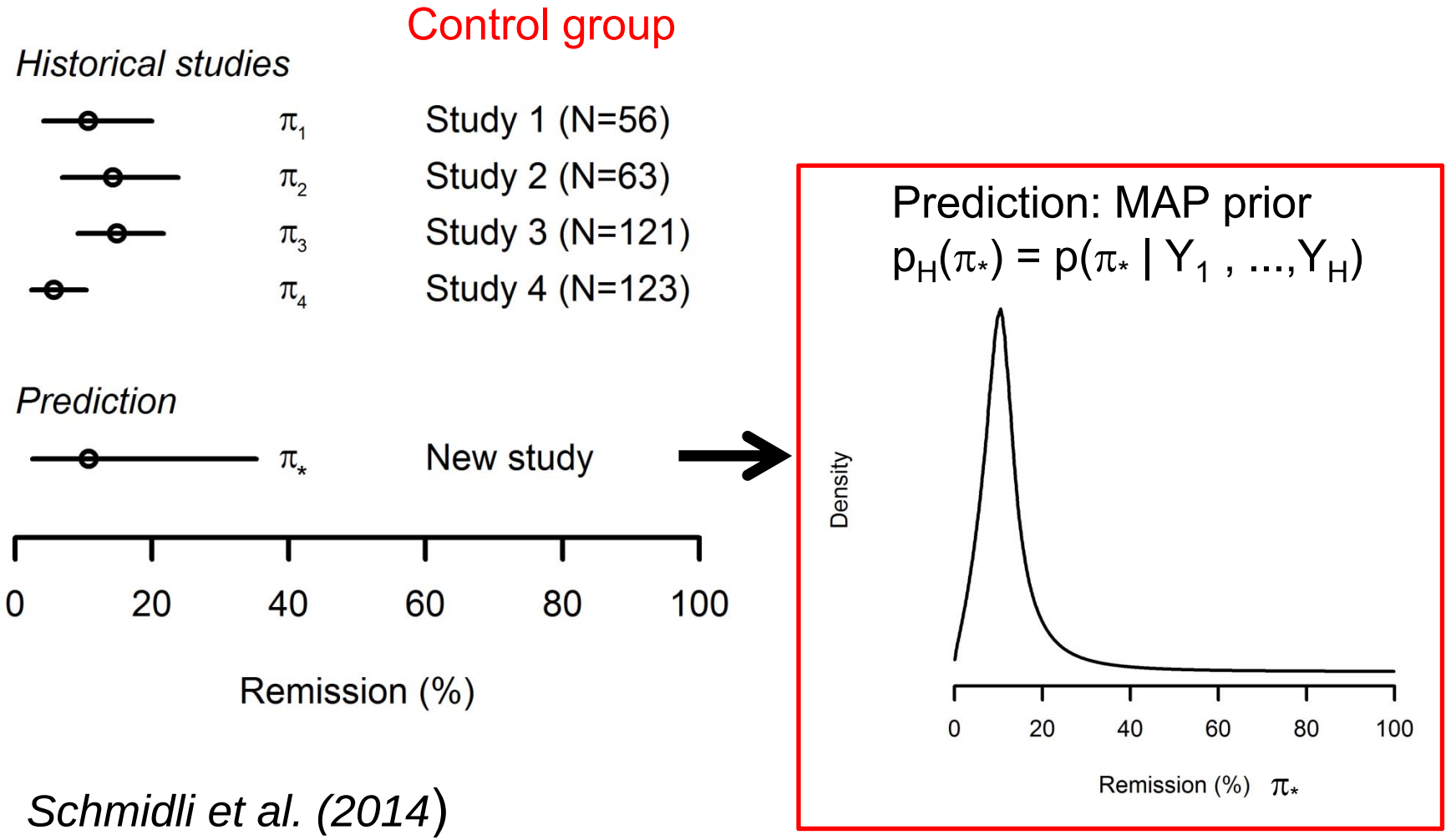
population mean μ, between-trial standard deviation τ

weakly informative priors for μ and τ

Spiegelhalter et al. (2004), Neuenschwander et al. (2010)

Meta-Analytic-Predictive (MAP) priors

Another example: Proof-of-Concept study in ulcerative colitis



Schmidli et al. (2014)

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Meta-Analytic-Predictive (MAP) priors

Biometric practice - approximating the MAP prior

- MAP prior $p_H(\pi_*)$

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

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

  ✓ *Easy communication*: discussions with clinical trial team, health authorities, ethics commitees; clinical trial protocols; publications

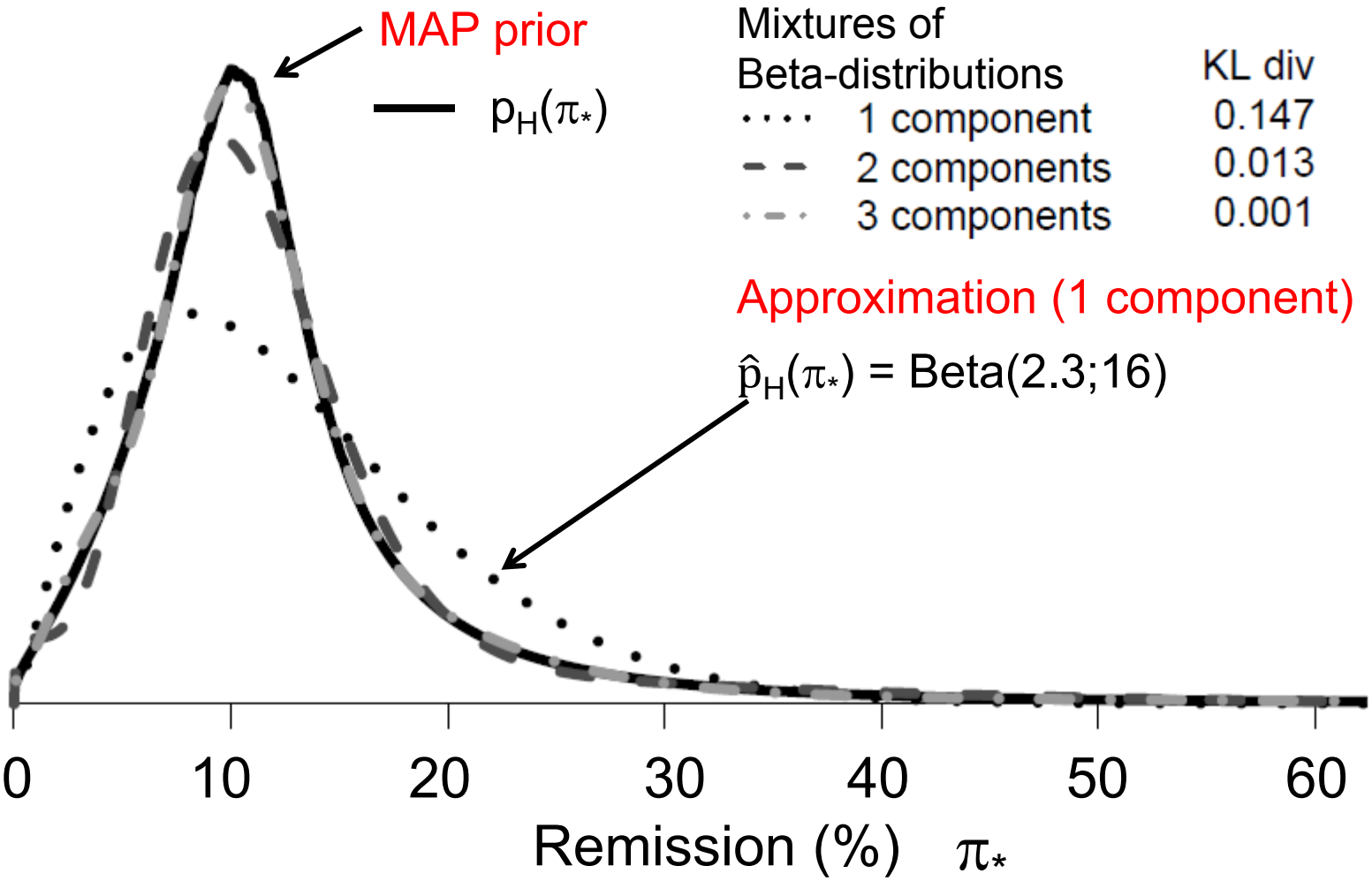
  ✓ *Analytical posterior calculation*: fast operating characteristics

- Kullback-Leibler divergence as measure of closeness between MAP prior and its approximation
  - Arguably most appropriate for inference problems

    Bernardo and Smith (1994), O'Hagan and Forster (2004)
  - Equivalent to ML estimation of mixture model using MCMC sample: standard software can be used (e.g. procedure FMM in SAS)

Meta-Analytic-Predictive (MAP) priors

Biometric practice - approximating the MAP prior



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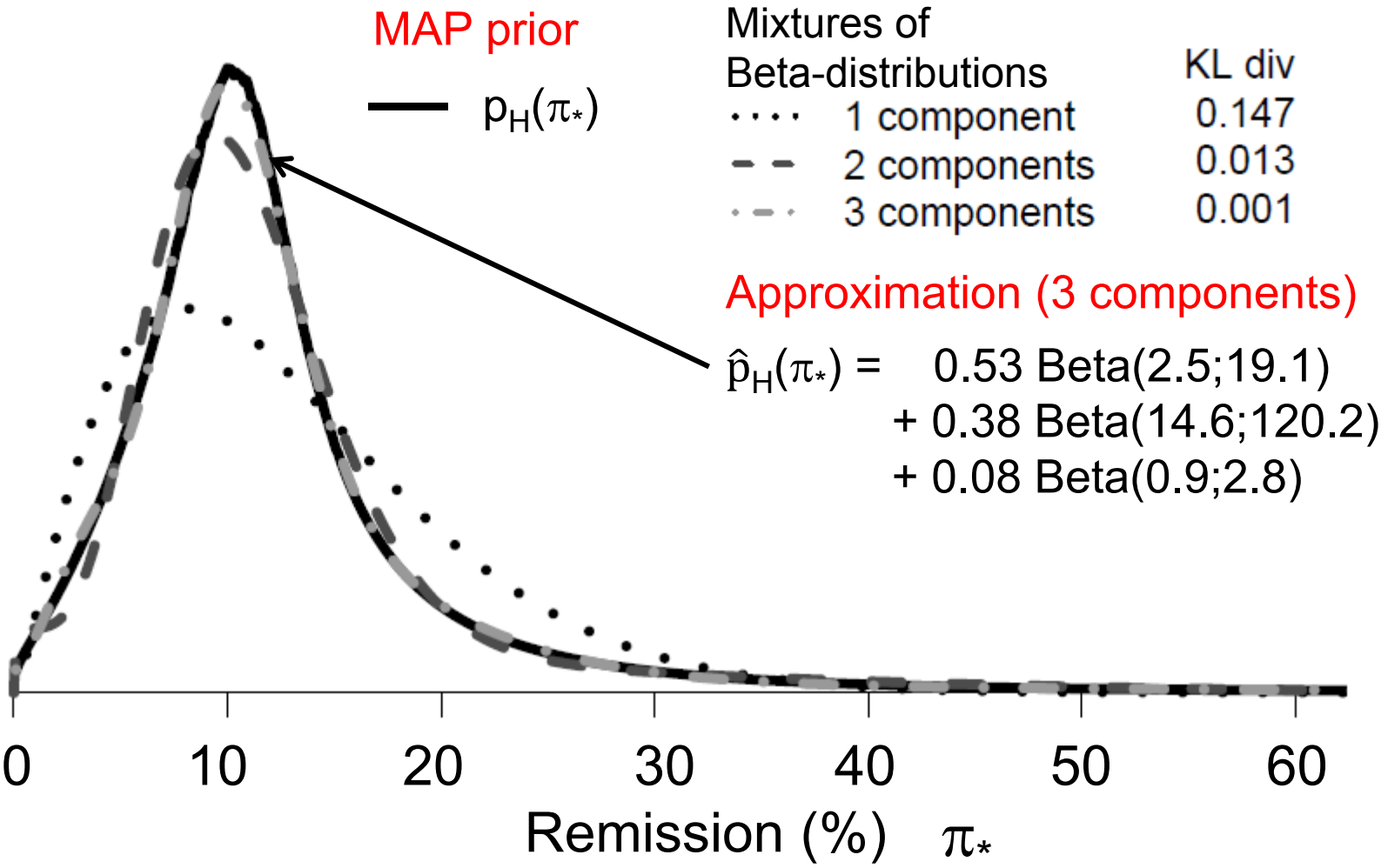
Meta-Analytic-Predictive (MAP) priors

Biometric practice - approximating the MAP prior



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Meta-Analytic-Predictive (MAP) priors

Prior effective sample size ESS

- *Conjugate prior*: Beta(a,b) => ESS = a+b
- *Mixture of conjugate priors*:

  ESS is sample size such that expected information of posterior under non-informative prior is same as information of informative prior

  Morita, Thall and Müller (2008, 2012)

Proof-of-Concept study in ulcerative colitis

Approximation to MAP prior $p_H(\pi_*)$

$\hat{p}_H(\pi_*)$=0.53 Beta(2.5;19.1)+0.38 Beta(14.6;120.2)+0.08 Beta(0.9;2.8)

ESS = 81

ESS=18 for single component approximation Beta(2.3;16)

Meta-Analytic-Predictive (MAP) priors

Robustness

- Prior-data conflict
  - *Conjugate priors*: compromise between prior and data

    Fuquene, Cook and Pericchi (2009)
  - *Priors with heavy tails*: prior information discarded with increasing conflict => appropriate in clinical trial setting

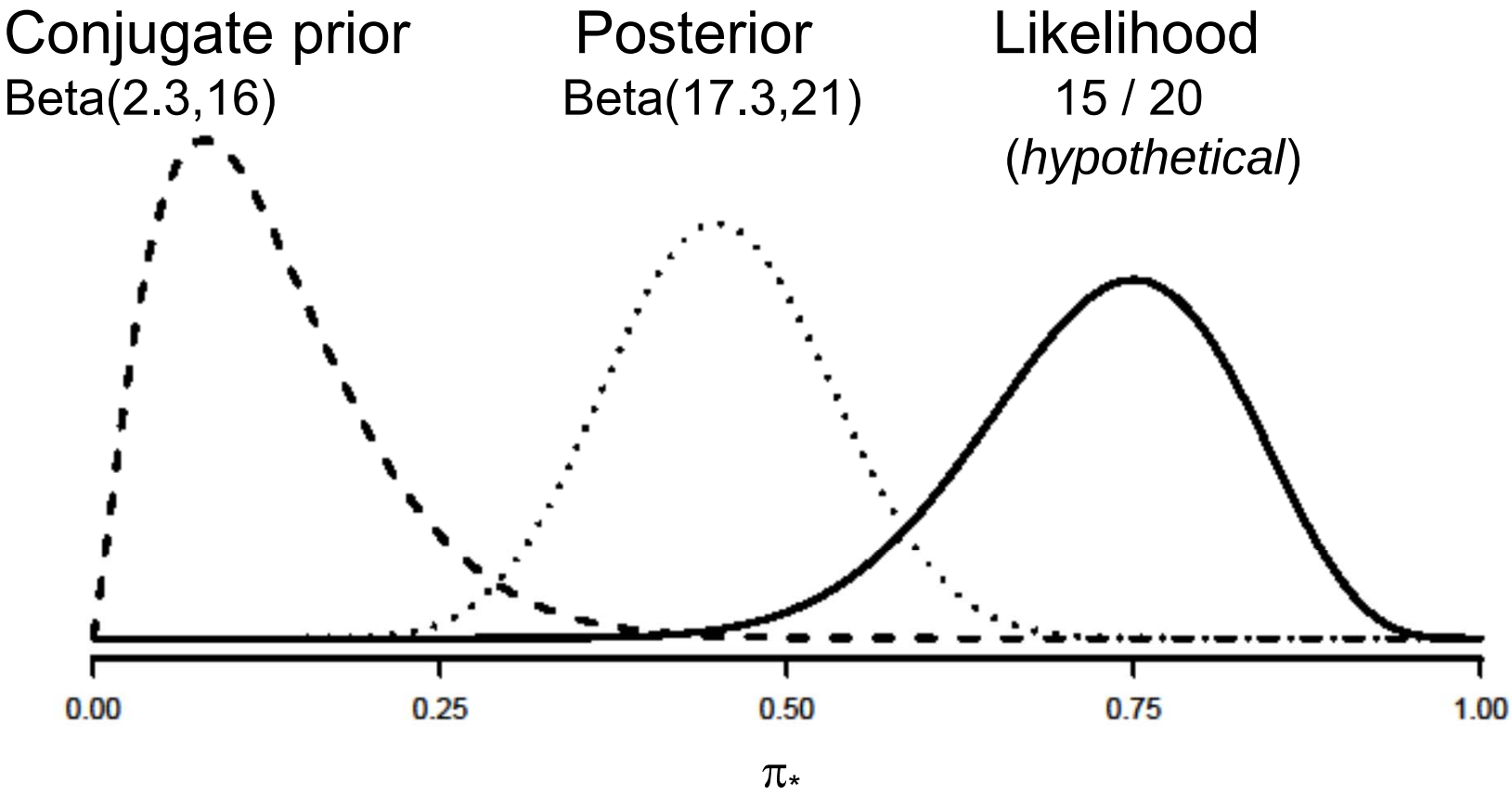
    O'Hagan and Pericchi (2012)
- MAP priors
  - Typically heavy-tailed, hence naturally robust
  - Further robustness and more rapid adaptation to prior-data conflicts by adding extra weakly-informative mixture component.

    e.g. $p_{HR}(\pi_*) = 0.9\, p_H(\pi_*) + 0.1\, \text{Beta}(1,1)$

De Groot always carried an ε of probability for surprises in his pocket!

Meta-Analytic-Predictive (MAP) priors

Robustness – conjugate prior – hypothetical example



"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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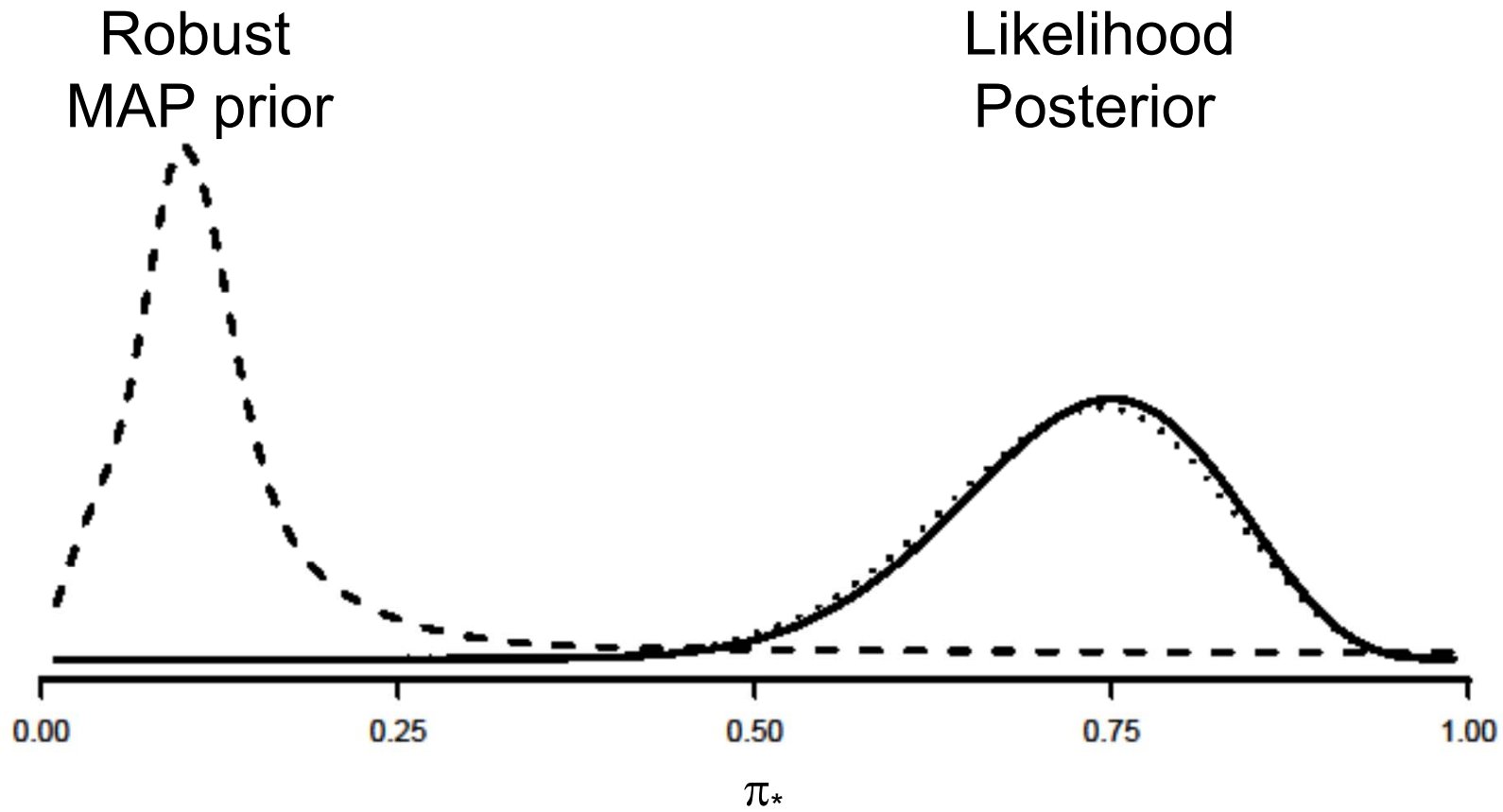
Meta-Analytic-Predictive (MAP) priors

Robustness – MAP prior



Robust MAP prior: $p_{HR}(\pi_*) = 0.9\, p_H(\pi_*) + 0.1\, \text{Beta}(1,1)$

$p_H(\pi_*)$=0.53 Beta(2.5;19.1)+0.38 Beta(14.6;120.2)+0.08 Beta(0.9;2.8)

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Extensions

Network meta-analysis and meta-regression

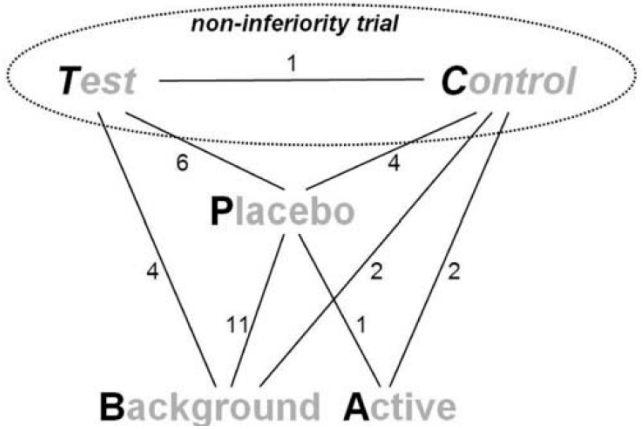
- Multiple treatments

  Network meta-analytic-predictive approach

  Example

  24 historical trials, 5 treatments

  Schmidli et al. (2013)



- Partial exchangeability

  Meta-regression

  Example

  51 historical trials, >17000 patients

  Different drug combinations

  Witte et al. (2013)

First Author	Year	Endpoint	Treatment combination	n	N	%
Andres	2008	M6 composite	CS+B+Tac(r)+MPS	22	151	14.6%
			CS+B+Tac(s)+MPS	16	141	11.3%
Chan	2008	M6 composite	CS+B+Tac(r)+EVR	7	49	14.3%
			CS+B+Tac(s)+EVR	7	43	16.3%
Vincenti	2008	M12 composite	B+CsA(s)+MPS	40	112	35.7%

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Conclusions

- Use of historical control information is attractive

  Ethics, recruitment speed, trial costs, trial duration

- Meta-Analytic-Predictive (MAP) prior can be approximated by mixture of conjugate priors
  - Easy communication
  - Analytical posterior calculation
  - Typically robust to prior-data conflict, however may want to add extra weakly-informative mixture component
- In rare case of prior-data conflict
  - Inference with robust prior still valid
  - May lead to inconclusive trial results $\Rightarrow$ adaptive design

"... think it possible that you may be mistaken." Cromwell

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