Borrowing information from historical data With applications in pharmaceutical research

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Hans van Houwelingen Award ceremony — June 15 2023

1
Bayes Theorem

▷ Bayes Theorem combines prior and data information:

$$p(\boldsymbol{\theta}|\mathcal{D}) = \frac{L(\boldsymbol{\theta}|\mathcal{D})p(\boldsymbol{\theta})}{p(\mathcal{D})} = \frac{L(\boldsymbol{\theta}|\mathcal{D})p(\boldsymbol{\theta})}{\int L(\boldsymbol{\theta}|\mathcal{D})p(\boldsymbol{\theta})d\boldsymbol{\theta}}$$

▷ with:

- Unknown parameters $\boldsymbol{\theta}$ & data: $\mathcal{D}$
- **Likelihood** $L(\boldsymbol{\theta} \mid \mathcal{D})$: plausibility of $\boldsymbol{\theta}$ given data $\mathcal{D}$
- **Prior** $p(\boldsymbol{\theta})$: prior density of $\boldsymbol{\theta}$ values (information on $\boldsymbol{\theta}$ independent of $\mathcal{D}$)
- **Posterior** $p(\boldsymbol{\theta} \mid \mathcal{D})$: posterior density of $\boldsymbol{\theta}$ values as a result of combining prior and data information

- **One of the major selling arguments of the Bayesian approach**
  - ▷ **Prior information can be incorporated in a Bayesian analysis!**
  - ▷ Bayes theorem works with any prior information, even quite subjective
  - ▷ For a scientific analysis, external information should have a sound basis .... using expert knowledge or studies done in the past
  - ▷ However, ... most Bayesian analyses just use vague priors!

- I have been teaching and preaching Bayesian methods since 1991:
  - ▷ promoting the Bayesian approach
  - ▷ highlighting its mathematical, statistical and logical elegance
  - ▷ highlighting its computational advantages
  - ▷ and ... **mentioning that external information can be incorporated**

- **But**:
  - ▷ In most of my examples I focus(sed) on the use of Bayesian methods/ software for **statistical modelling**
  - ▷ ... and used **vague/non-informative priors**

- **Obstacles to use informative priors**:

  ▷ No external information is available ... although

  Box & Tiao (1973): ... one can never be in a state of complete ignorance

  ▷ Statistical model is complex/novel and prior information on parameters is difficult to specify

  ▷ The data set is large and an informative prior would make no difference

  ▷ One is not willing to make use of external information (objective Bayesian)

  ▷ Too different or even conflicting external information is present

  ▷ ...

- **Bayesian approach in pharmaceutical research**

  ▷ For a long time Bayesian approach in pharmaceutical research is ignored, primarily because of regulatory issues

  ▷ But there is recently an increasing interest in the approach in drug/medical devices research because:

  - There is a variety of historical data available obtained in highly controlled settings
  - Often the same control treatment is used in subsequent trials
  - Drug development is done in stages: I, II, III, IV and information/data obtained in previous stage is valuable for next stage
  - For rare diseases and in pediatric studies, it may be difficult to recruit enough patients
  - Using prior information proves also to be useful for persomalized medicine
  - In medical device studies controlled studies may be hard to organize

  ... and so the Bayesian approach attracted interest with clinical trialists

- **Some publicity**

Bayes20XX Meetings

- **Expert knowledge?**
  - ▷ Realistic limits of parameters can easily be built-in:
    - ◦ Normal priors for log-odds ratios
    - ◦ Monotonic evolutions in time expressed by a positive/negative regression coefficient
  - ▷ Elicitation of prior knowledge?
    - ◦ Experts have difficulties expressing their knowledge into probabilistic language (see also book: Thinking, Fast and Slow of Daniel Kahneman).
    - ◦ Papers/books have been written to better extract knowledge
    - ◦ But none of the methods found their way in real clinical applications

2
Use of historical data

- Making use of historical data = **borrowing information from the past**
- **Borrowing information** is now a **hot topic** in pharmaceutical research
- Frequentist approaches are possible but Bayesian approach is more elegant
- **Key question**: **How to turn historical information into a prior?**
- Three main approaches:
  - Pooling
  - Power approach
  - Meta-analytic approach

- Focus in literature on borrowing information from **historical controls**
- But could also be applied to treatment estimate
- But wherever and whenever possible **concurrent (randomized) controls** are to be preferred

Motivating data set: HOVON AML trials

- **HOVON trials**: European RCTs on chemotherapy for AML patients since 1988, coordinated by Dept Hematology Erasmus MC (Rotterdam, NL)
- Binary outcome = complete remission or complete response (CR)
- RCTs considered: HOVON 4, HOVON 4A, HOVON 29, HOVON 42 and HOVON 42A
- All of these trials had essentially the same control treatment, see Banbeta et al (2019)

Trial	Group	Year	N	CR (%)
HOVON 4	Control	1988-1992	359	279 (77.7)
HOVON 4A	Control	1992-1993	252	208 (82.5)
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HOVON 42	Control	2002-2004	437	358 (81.9)
HOVON 42A	Control	2004-2006	259	214 (82.6)
HOVON 42A	Treatment	2004-2006	252	211 (83.7)

▷ Analysis HOVON 42A data (ψ = odds ratio $> 1 \Rightarrow$ experimental better):

- Without historical data: $\overline{\psi}_M = 1.08\ [0.68, 1.72]$

- Question of (at that time) the head of hematology at Erasmus MC:

Can we reduce the size of the control arm without sacrificing the power of the study?

2.1 Pooling

▷ Assume a **single historical** study:

- Current study: $\mathcal{D}$ sample of size n, with parameter θ with likelihood $L(\theta \mid \mathcal{D})$
- Historical study: $\mathcal{D}_0$ sample of size n_0 with parameter θ_0 with likelihood $L(\theta_0 \mid \mathcal{D}_0)$

▷ **Assume** $\theta_0 = \theta$

▷ (Initial) Prior of historical data: $p_0(\theta)$, then posterior from historical data:

$$p_P(\theta \mid \mathcal{D}_0) \propto L(\theta \mid \mathcal{D}_0)\, p_0(\theta)$$

▷ Naive approach to borrow information from historical study: use $p_P(\theta \mid \mathcal{D}_0)$ as prior for $L(\theta \mid \mathcal{D})$, then posterior for θ:

$$p_P(\theta \mid \mathcal{D}_0, \mathcal{D}) \propto L(\theta \mid \mathcal{D}_0)\, L(\theta \mid \mathcal{D})\, p_0(\theta) \equiv L(\theta \mid \mathcal{D}_0, \mathcal{D})\, p_0(\theta)$$

equivalent to **pooling**

- **Pooling**: assumes that the historical studies and current study measure **exactly the same effect** and **are treated equally**

- Wadsworth, Hampson & Jaki (2018): review of historical data in analysis of current data
  - Eight of 58 papers just pooled historical and current data

- However, pooling is too naive and **not recommended** in general

  Based on too strong assumption that past data and current data are exchangeable

- While control treatments in HOVON 4, HOVON 4A, HOVON 29, HOVON 42 and HOVON 42A were basically the same, the standard of care changed over the years

2.2 Power prior

Conditional power prior

- Same settings as before, so $\boldsymbol{\theta_0 = \theta}$!
- Now **discount the prior information**, i.e. we realize that historical data may differ from current data
- **Power prior** for a **fixed** λ (conditional power prior):

$$p_{CPP}(\theta \mid \mathcal{D}_0, \lambda) = \frac{L(\theta \mid \mathcal{D}_0)^\lambda \, p_0(\theta)}{\int_\Theta L(\theta \mid \mathcal{D}_0)^\lambda \, p_0(\theta) \, d\theta}$$

with 0 (= no borrowing) $\leq \lambda \leq 1$ (= pooling)

Conditional power prior for Gaussian case

- Suppose σ^2 is known, and:
  - Current data: $\boldsymbol{y} = \{y_1, \ldots, y_n\}$ i.i.d. $\sim \mathsf{N}(\mu, \sigma^2)$
  - Historical data: $\boldsymbol{y}_0 = \{y_{01}, \ldots, y_{0,n_0}\}$ i.i.d. $\sim \mathsf{N}(\mu, \sigma^2)$
  - Initial normal prior: $\mu \sim \mathsf{N}(\mu_0, \sigma_0^2)$ for the historical data

- Construction of power prior:

$$L(\mu \,|\, \boldsymbol{y}_0) = \frac{1}{\sqrt{2\pi\sigma^2}} \exp\left[-\frac{1}{2\sigma^2} \sum_{i=1}^{n_0} (y_{0i} - \mu)^2\right]$$

$$L(\mu \,|\, \boldsymbol{y}_0)^\lambda = \left(\frac{1}{\sqrt{2\pi\sigma^2}}\right)^\lambda \exp\left[-\frac{1}{2\sigma^2/\lambda} \sum_{i=1}^{n_0} (y_{0i} - \mu)^2\right]$$

- The likelihood$^\lambda$ $\propto$ Gaussian with variance $\sigma^2/\lambda \Rightarrow$ power prior for Gaussian case inflates prior variance

Gaussian conditional power prior:

- With initial Gaussian prior ($\mu \sim \mathsf{N}(\mu_0, \sigma_0^2)$), power prior for current data becomes $\mathsf{N}(\overline{\mu}_0, \overline{\sigma}_0^2)$, with

$$\overline{\mu}_0 = \frac{\mu_0/\sigma_0^2 + n_0\lambda\,\overline{y}_0/\sigma^2}{1/\sigma_0^2 + n_0\lambda/\sigma^2} \quad \& \quad 1/\overline{\sigma}_0^2 = 1/\sigma_0^2 + n_0\lambda/\sigma^2$$

Posterior based on Gaussian conditional power prior:

- Combined with current Gaussian data $\boldsymbol{y}$ gives posterior $\mathsf{N}(\overline{\mu}, \overline{\sigma}^2)$

$$\overline{\mu} = \frac{\overline{\mu}_0/\overline{\sigma}_0^2 + n\overline{y}/\sigma^2}{1/\overline{\sigma}^2 + n/\sigma^2} \quad \& \quad 1/\overline{\sigma}^2 = 1/\overline{\sigma}_0^2 + n/\sigma^2$$

Conditional power prior for binomial case

- Suppose:
  - Current data: $y \sim \text{Bin}(n, \theta)$
  - Historical data: $y_0 \sim \text{Bin}(n_0, \theta)$
  - Initial prior: $\theta \sim \text{Beta}(\alpha_0, \beta_0)$

- Binomial conditional power prior:

$$\text{Beta}(\theta \,|\, \lambda y_0 + \alpha_0, \lambda(n_0 - y_0) + \beta_0)$$

- Posterior based on binomial power prior:

$$\text{Beta}(\theta \,|\, \lambda y_0 + \alpha_0 + y, \lambda\,(n_0 - y_0) + \beta_0 + (n - y))$$

What λ to choose???

- **Interpretation of λ**
  - Proportion of historical data used in current study: $\lambda = r/n_0$, with r amount of historical sample used
- **How to choose λ?**
  1. **Fix** λ (static borrowing information): from substantive knowledge/regulatory input $\Rightarrow$ **conditional power prior**
  2. Give λ a prior and estimate from historical and current data (dynamic borrowing information) $\Rightarrow$ **joint power prior**
     - Estimated λ is inverse proportional to discrepancy between historical and current data

Estimate λ from joint posterior of historical and current data

Joint power prior p_{JPP}

- Give λ a prior $p(\lambda)$, then joint power prior:

$$p_{JPP}(\theta, \lambda \,|\, \mathcal{D}_0) = \frac{L(\theta \,|\, \mathcal{D}_0)^\lambda p_0(\theta) p(\lambda)}{\int_0^1 \int_\Theta L(\theta \,|\, \mathcal{D}_0)^\lambda p_0(\theta) p(\lambda)\, d\theta\, d\lambda}$$

  and estimate λ from joint posterior of historical and current data

- Proposed and examined by Ibrahim & Chen in a series of papers

- But, ... joint power prior **does not satisfy likelihood principle**, since

$$\frac{[c_1 L(\theta \,|\, \mathcal{D}_0)]^\lambda p_0(\theta) p(\lambda)}{\int_0^1 \int_\Theta [c_1 L(\theta \,|\, \mathcal{D}_0)]^\lambda p_0(\theta) p(\lambda)\, d\theta\, d\lambda} \neq \frac{[c_2 L(\theta \,|\, \mathcal{D}_0)]^\lambda p_0(\theta) p(\lambda)}{\int_0^1 \int_\Theta [c_2 L(\theta \,|\, \mathcal{D}_0)]^\lambda p_0(\theta) p(\lambda)\, d\theta\, d\lambda}$$

Estimate λ from joint posterior of historical and current data

Modified/Normalized power prior p_{MPP}

- First normalize the conditional power prior, then apply prior $p(\lambda)$

$$p_{MPP}(\theta, \lambda \mid \mathcal{D}_0) = p_{CPP}(\theta \mid \mathcal{D}_0, \lambda)\, p(\lambda)$$
$$= \frac{L(\theta \mid \mathcal{D}_0)^{\lambda} p_0(\theta)}{\int_{\Theta} L(\theta \mid \mathcal{D}_0)^{\lambda} p_0(\theta) d\theta}\, p(\lambda)$$

- Modified power prior p_{MPP} satisfies likelihood principle

- Marginal posteriors $p(\lambda \mid \mathcal{D}, \mathcal{D}_0)$ and $p(\theta \mid \mathcal{D}, \mathcal{D}_0)$ can then be determined

Modified power prior binomial case

▷ Modified power prior $\boldsymbol{p_{MPP}(\theta, \lambda \,|\, y_0, n_0)}$

$$p_{MPP}(\theta, \lambda \,|\, y_0, n_0) \propto \frac{\theta^{\lambda\, y_0 + \alpha_0 - 1}(1-\theta)^{\lambda\,(n_0 - y_0) + \beta_0 - 1}}{B(\lambda\, y_0 + \alpha_0, \lambda\,(n_0 - y_0) + \beta_0)}\, p(\lambda)$$
$$= \text{Beta}(\theta \mid \lambda\, y_0 + \alpha_0, \lambda\,(n_0 - y_0) + \beta_0)\, p(\lambda)$$

▷ Denominator in binomial case

$$C(\lambda) = \int L(\theta \,|\, y_0, n_0)^{\lambda}\, \text{Beta}(\theta \,|\, \alpha_0, \beta_0) d\theta$$
$$= \frac{\binom{n_0}{y_0}^{\lambda} B(\lambda\, y_0 + \alpha_0, \lambda\,(n_0 - y_0) + \beta_0)}{B(\alpha_0, \beta_0)}$$

▷ The normalizing constant is **often not easy to determine**, **more later**

Modified power prior applied to HOVON AML trials

- **HOVON trials**: European RCTs on chemotherapy for AML patients since 1988, coordinated by Dept Hematology Erasmus MC (Rotterdam, NL)
- Binary outcome = complete remission or complete response (CR)
- RCTs considered: HOVON 4, HOVON 4A, HOVON 29, HOVON 42 and HOVON 42A
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▷ Analysis HOVON 42A data (ψ = odds ratio $> 1 \Rightarrow$ experimental better):

- Without historical data: $\overline{\psi}_M = 1.08\ [0.68, 1.72]$
- With HOVON 42 historical control data: $\overline{\psi}_M = 1.12\ [0.74, 1.67]$, $\overline{\lambda}_M = 0.58\ [0.07, 0.98]$

Some findings on the estimated power λ

- Posterior median of λ:

  ≈ 0, when historical data differ a lot from current data

  ≈ 0.6 with Beta(1,1) and ≈ 0.7 with Beta(0.5,0.5), when historical data are similar to current data

  Estimate of θ didn't change much even for large data sets

- For extensions of the power prior to multiple historical data, **WAIT A BIT!**

2.3 Meta-analytic prediction prior

- Suppose there are $\boldsymbol{K}$ historical studies:
  - Current study: $\mathcal{D}$ sample of size n with parameter θ and likelihood $L(\theta \mid \mathcal{D})$
  - Historical studies: K samples $\mathcal{D}_k$ of size n_k with parameters θ_k and likelihood $L(\theta_k \mid \mathcal{D}_k)$

- Assume now that the historical trials and the current trial are exchangeable

$\Rightarrow$ Loosely speaking: θ and $\theta_1, \ldots, \theta_K$ are about the same, or

$$\theta_1, \ldots, \theta_K, \theta \sim G(\boldsymbol{\phi})$$

- Neuenschwander et al. (2010) suggested the meta-analytic predictive (MAP) prior

The meta-analytic predictive (MAP) prior

▷ With normality assumption

$$\theta_1, \ldots, \theta_K, \theta \mid \mu, \tau^2 \sim \mathsf{N}(\mu, \tau^2)$$

▷ The meta-analytic predictive prior (PPD):

$$\theta \mid \mathcal{D}_1, \ldots, \mathcal{D}_K$$

▷ If σ_k and τ^2 known + flat prior for μ:

$$\theta \mid \widehat{\theta}_1, \ldots, \widehat{\theta}_K, \tau \sim \mathsf{N}\left(\frac{\sum w_k \widehat{\theta}_k}{\sum w_k}, \frac{1}{\sum w_k} + \tau^2\right)$$

- $\mathcal{D}_k$ produce estimate $\widehat{\theta}_k \quad (k = 1, \ldots, K)$
- Weights $w_k = \frac{1}{\sigma_k^2 + \tau^2}$, with often σ_k^2 $(k = 1, \ldots, K)$ fixed
- Large value of τ implies that little is learned from past studies
- τ is given an informative and sensible prior

Two equivalent meta-analytic approaches (Schmidli et al, 2014)

- **MAP approach**: Two-step approach
  - Compute MAP prior for the unknown parameter θ
  - Use MAP prior in combination with current data
  - Example **pediatric study**: MAP prior based on adult data applied on pediatric data

- **MAC approach**: Simultaneous approach
  - Specify hierarchical model combining historical & current data
  - Example **pediatric study**: adult and pediatric data are obtained simultaneously

MAP prior applied to HOVON AML trials

- **HOVON trials**:
  - European RCTs on chemotherapy for AML patients since 1988, coordinated by Dept Hematology Erasmus MC (Rotterdam, NL)
  - Binary outcome = complete remission or complete response (CR)
  - RCTs considered: HOVON 4, HOVON 4A, HOVON 29, HOVON 42 and HOVON 42A
  - All of these trials had essentially the same control treatment, see Banbeta et al (2019)

- Now **HOVON 4, 4A, 29 and 42 control data** into the analysis of the HOVON 42A data:
  - Assume exchangeability of all control arms
  - Aim MAP approach: estimate ψ more precisely using historical information on $\theta = \text{logit(control rate)}$

Using the MAP prior to analyze data from HOVON 42A

- θ_k = logit(probability) CR in k^{th} historical control arm
- y_k = observed proportion CR in k^{th} historical control arm

▷ Two steps:

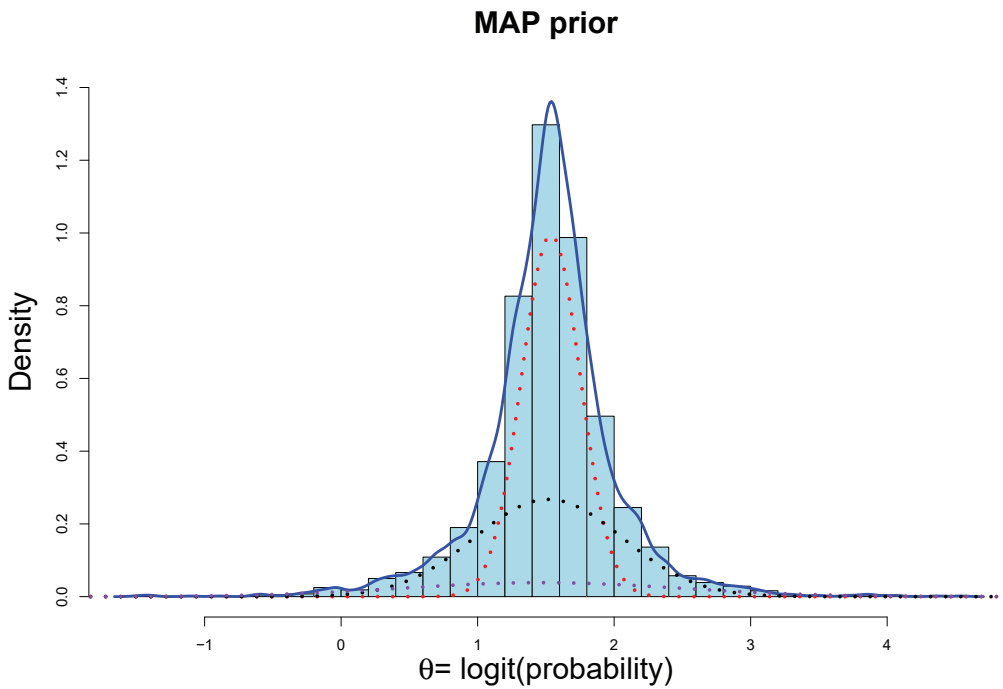
1. Estimate MAP prior based on CR in studies HOVON 4, 4A, 29 and 42
2. Use MAP prior to analyze the control & experimental data of HOVON 42A

▷ Estimation MAP prior is done via MCMC ⇒ no analytical expression

▷ Analysis using RBesT R package + Bayesian analysis

1. RBesT estimates the MAP prior for θ (logit scale) by MCMC sampling
2. Approximate the sampled MAP prior by mixture of normals
3. Feed the mixture of normals in OpenBUGS program

Results



Estimated MAP prior from MCMC calculations

Gaussian mixture with 3 components

- **Vague prior on** θ: $\overline{\psi}_M = 1.084$ [0.68, 1.72]
- **MAP prior on** θ: $\overline{\psi}_M = 1.088$ [0.71, 1.68]

3
Choice of historical studies

▷ How should we choose/select the historical studies?

▷ **Pocock's criteria** (Pocock, 1976) for historical controls:

> 1. Such a group must have received a precisely defined standard treatment which must be the same as the treatment for the randomized controls.
> 2. The group must have been part of a recent clinical study which contained the same requirements for patient eligibility.
> 3. The methods of treatment evaluation must be the same.
> 4. The distributions of important patient characteristics in the group should be comparable with those in the new trial.
> 5. The previous study must have been performed in the same organization with largely the same clinical investigators.
> 6. There must be no other indications leading one to expect differing results between the randomized and historical controls. For instance, more rapid accrual on the new study might lead one to suspect less enthusiastic participation of investigators in the previous study so that the process of patient selection may have been different.

⇒ Historical controls should be similar to current control

▷ But, **these criteria are quite strict**!

How can we relax Pocock's criteria?

- Pocock's criteria prevent using dynamic borrowing methods for e.g.
  - Pediatric studies: adult data are not obtained from the same kind of subjects
  - Rare diseases: historical controls are taken from the real world
  - Bridging studies: subjects from another geographical region cannot be taken from the same institution

⇒ **Extend dynamic borrowing methods**:

▷ Match historical and current data

▷ Covariate correction/propensity score analysis:

- **MAP prior/MAC approach**: conditional exchangeability
- **Power prior**: e.g. van Rosmalen et al. (2018), Banbeta, Lesaffre, van Rosmalen (2022)
- **Extension of Pocock's criteria**: Hatswell et al. (2020)

Possible problem(s) at design stage

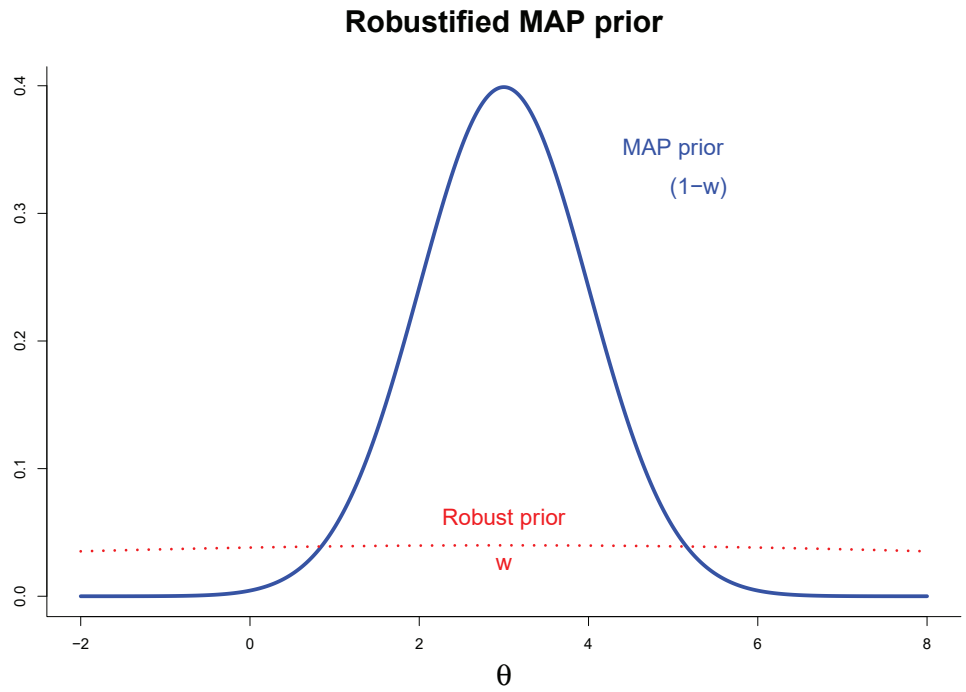
- At the **design stage** it is not clear whether (all) historical data will be compatible with future data (prior-data conflict)

- **We should only** borrow information **when current data are similar to historical data**

- Schmidli et al. (2014): **mixture prior** for historical control parameter
  - **MAP prior** for θ when current control is **similar** to historical controls
  - **Vague prior** for θ when current control is **quite different** from historical controls (prior-data conflict)

$=$ **robustified MAP prior**

Robustified MAP prior



$$\theta \sim (1-w) \times \mathsf{N}(\mu, \tau^2) + w \times p_{0R}$$

p_{0R} (robust) Gaussian distribution with same mean but large SD

w fixed usually taken small (0.1)

4
Extensions of the power prior approach

- Now K historical studies (Chen et al., 2000), but assume $\boldsymbol{\theta_1 = \ldots = \theta_K = \theta}$
- **Modified power prior** based on historical data:

$$p_{MPP}(\theta, \boldsymbol{\lambda} \,|\, \{\boldsymbol{y}_k, n_k\}) \propto \frac{\left[\prod_{k=1}^{K} L(\theta \,|\, \boldsymbol{y}_k)^{\lambda_k}\right] p_0(\theta)\, p(\lambda_1, \ldots, \lambda_k)}{\int \left[\prod_{k=1}^{K} L(\theta \,|\, \boldsymbol{y}_k)^{\lambda_k}\right] p_0(\theta)\, d\theta}$$

with

- $\lambda_k = 0 \Rightarrow$ no borrowing from k^{th} historical study
- $\lambda_k = 1 \Rightarrow$ pooling of k^{th} historical data with current data

Further extensions by our group

- Combination of the hierarchical approach in the MAP prior and power prior: hierarchical/dependent modified power prior (p_{DMPP})
- **Idea**: historical studies are similar $\Rightarrow$ also the powers
- Powers λ_k $(k = 1, \ldots, K)$ have a hierarchical distribution

$$\lambda_k \sim \text{Beta}(\alpha_\lambda, \beta_\lambda) \quad (k = 1, \ldots, K)$$
$$(\alpha_\lambda, \beta_\lambda) \sim p(\alpha_\lambda, \beta_\lambda)$$

  - For historical controls with binary endpoints, see Banbeta, van Rosmalen, Dejardin & Lesaffre (2019)
  - For linear regression, see Banbeta, Lesaffre & van Rosmalen (2022)
  - For analysis of counts, see Banbeta, Lesaffre, Martina & van Rosmalen (2022)

Modified power prior binomial case with multiple historical studies

- Assume
  - ▷ $p(\boldsymbol{\lambda}) = p(\lambda_1, \ldots, \lambda_K) = \prod_{k=1}^{K} p(\lambda_k)$
  - ▷ $p_0(\theta)$ is Beta(α_0, β_0) with α_0 and β_0 fixed and known

- Modified power prior:

$$p_{MPP}(\theta, \boldsymbol{\lambda} \,|\, \{y_k, n_k\}) \propto \frac{\theta^{\sum_{k=1}^{K} \lambda_k y_k + \alpha_0 - 1} (1-\theta)^{\sum_{k=1}^{K} \lambda_k (n_k - y_k) + \beta_0 - 1}}{B(\sum_{k=1}^{K} \lambda_k y_k + \alpha_0, \sum_{k=1}^{K} \lambda_k (n_k - y_k) + \beta_0)} \prod_{k=1}^{K} p(\lambda_k)$$
$$= \text{Beta}(\theta \,|\, \sum_{k=1}^{K} \lambda_k y_k + \alpha_0, \sum_{k=1}^{K} \lambda_k (n_k - y_k) + \beta_0) \prod_{k=1}^{K} p(\lambda_k)$$

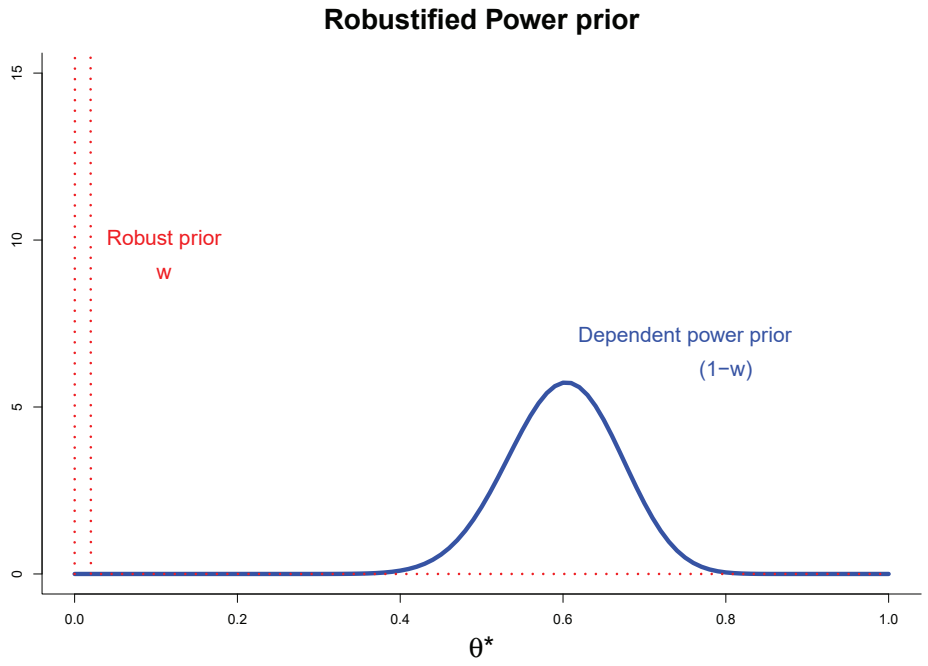
- Again the normalizing constant is easy to compute

- Up to 2 historical controls, path sampling can be used but computation is probably too demanding for ($\geq$) 3 historical data sets

Robustified dependent power prior

▷ Banbeta et al. (2019): **robustified** p_{DMPP}, i.e. p_{RDMPP}, in 2 ways:

- **Version 1**: $\lambda_k \sim (1-w) \times \text{Beta}(\lambda_k \,|\, \alpha_\lambda, \beta_\lambda) + w \times p_{0R}(\lambda_k)$ $(k = 1, \ldots, K)$ $\Rightarrow$ individual historical controls can be ignored
- **Version 2**: $\boldsymbol{\lambda} \sim (1-w) \times \text{Beta}(\boldsymbol{\lambda} \,|\, \alpha_\lambda, \beta_\lambda) + w \times p_{0R}(\boldsymbol{\lambda})$ $\Rightarrow$ either all or none historical controls are ignored



5
Design aspects

- What are the operating characteristics of the dynamic borrowing approaches?

$\Rightarrow$ Questions:

  - ▷ How much information is used with dynamic borrowing methods? $\rightarrow$ **effective sample size**
  - ▷ Do dynamic borrowing methods control Pr(Type I error)?
  - ▷ Is it worth borrowing historical information? $\rightarrow$ **power**

5.1 Effective sample size

▷ **How much information do we borrow from historical studies?**

⇒ **Effective sample size (ESS)**

▷ Several proposals have been made:

- Principle: What is the equivalent number of subjects implied by the prior?
- Developments were focussed on MAP prior e.g. Morita, Thall & Muüller (2008), Neuenschwander et al. (2020)
- But also possible for power prior (but no results available for MPP)

▷ **Problem**: Cannot take into account prior-data conflict!

⇒ simple proposal by Malec (2001) for use a posteriori

$$\text{ESS}_M = n\frac{\text{Var}(\theta \mid \mathcal{D}, \text{non-informative prior})}{\text{Var}(\theta \mid \mathcal{D}, \text{informative prior})} - n$$

5.2 Is Pr(Type I error) controlled?

- Dynamic borrowing methods are Bayesian ⇒ repeated sampling properties are unknown
- Regulatory authorities (FDA, EMA, ...) require the operating characteristics (Pr(Type I error), Pr(Type II error))
- How to compute the operating characteristics (OCs)?
  - **Classical**:
    - Compute $\Pr(\text{Type I error})$ and check if $\leq \alpha$
    - Determine $1 - \Pr(\text{Type II error}) = \text{power}$
  - **Dynamic borrowing methods**: classical computation +
    - combining possible settings of historical data

What can happen?

- ▷ Historical data can help or hurt, depending on how similar the historical data are to the current data
- ▷ If similar, then $\Pr(\text{Type I error})$ can be controlled and power increased
- ▷ If not similar, then $\Pr(\text{Type I error})$ may not be controlled and power may decrease
- ▷ Most often, extensive simulations will be needed to assess the properties
- ▷ There is also a discussion in the literature how the simulations should be done:
  - **Conditional approach**: given the historical data averaging over the current data
  - **Unconditional approach**: averaged over the historical and current data simultaneously
- ▷ In practice: we don't know in advance whether or not there will be a prior-data conflict. We can only protect ourselves using a robust prior

5.3 Is it worth borrowing historical information?

- Effect of dynamic borrowing methods on **future HOVON study**:
  - ▷ Results CR HOVON 42A: Experimental: 83.7% ⇔ Control: 82.6%
  - ▷ Design **new study HOVON 43**:
    - $\alpha = 0.05$
    - Experimental: 83% + 7% ⇔ Control: 83%
    - Bayesian power: $\int_{\mathcal{D}} \Pr\left(\pi_E - \pi_C > 0 \mid \mathcal{D}\right) > 0.95$
  - ▷ Power (based on RBesT, using pre-posterior calculations):
    - Uniform prior for experimental arm & control arm: 74%
    - Classical power: 74%
    - MAP power: 81%
    - Robustified MAP power: 80%
- Published literature and simulations: there is gain in power (⇒ smaller study size)

6
Other approaches

- **Pocock's approach**: $\theta = \theta_0 + \delta$, with $\delta \sim \mathsf{N}(0, \sigma_\delta^2)$ + prior on σ_δ, Pocock (1976)
- **Commensurate (power) prior**: version of Pocock's approach and related to MAP approach, Hobbs, Sargent & Carlin (2012)
- **Test-then-Pool approach**: first significance test for discrepancy between historical and current control(s), if not significant then pool, Viele et al. (2014)
- **Empirical Bayes approach**: estimates λ from marginal likelihood avoiding to compute the normalizing constant, Gravestock & Held (2017)
- Watch the talk of **Tim Friede**

7
Closing remarks

- Dynamic borrowing methods are subject to intensive research especially in the pharmaceutical industry, but also in many other application areas!
- Reason is clear: Recyling (patient) data = may save money and patients
- We will see increasingly more modern/non-classical clinical trial designs:
  - Adaptive designs, with interim analyses, stopping or adding new arms to the trial, re-estimation of the necessary sample size
  - Platform trials including basket trials, umbrella trials
  - Making use of extra available non-trial data, such as real-world data
  - Price and Scott (2022) describe the recent FDA initiative to discuss the feasibility and acceptance of complex innovative designs
- Note not covered: multiparameter case, partial pooling approach, ...

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