Bayesian methods in biomedical research

Part IV: Bayesian applications in medical research

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Introduction

Examples of Bayesian applications

3 different real-world use cases in biomedical sciences:

illustrations where the Bayesian approach can be particularly useful

⚠ **Disclaimer:** this course is NOT

- ~~a meta-analysis short-course~~
- ~~an adaptive design in clinical trials short-course~~

Post-mortem re-analysis of an under-powered randomized trial

Original analysis of EOLIA

EOLIA (Combes *et al.*, *NEJM*, 2018):

- randomized clinical trial
- evaluation of a new treatment for severe acute respiratory distress syndrome
- outcome: mortality rate after 60 days
- 249 patients:
  - 125 controls
    $\Rightarrow$ mechanical ventilation (conventional treatment)
  - 124 treated
    $\Rightarrow$ ECMO (extracorporeal membrane oxygenation – new(er) treatment)

Frequentist analysis:

$\Rightarrow$ Relative Risk of death at 60 days for ECMO compared to control: 0.76

$CI_{95\%} = [0.55, 1.04]$

p-value $= 0.09$

Bayesian re-analysis of EOLIA data

Goligher *et al.* (*JAMA*, 2018)

	Group	
	ECMO	**Control**
group size n	124	125
number of deaths at 60 days	44	57

Observed data in the EOLIA trial

Your turn !

Read EC Goligher *et al.* Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome and Posterior Probability of Mortality Benefit in a Post Hoc Bayesian Analysis of a Randomized Clinical Trial, *JAMA* 320(21): 2251, 2018. **[DOI:10.1001/jama.2018.14276]**

Practical: exercise 6

Bayesian meta-analysis

What is a meta-analysis

"An analysis of analyses"

$\Rightarrow$ a single quantitative summary of studies answering the *same research question*

Ex: medical therapies effects are often evaluated in multiple different studies.

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$\Rightarrow$ pool individual observations from multiple studies ?

- ⚠ potential differences in the pooled experiments
- ⚠ only aggregated summary statistics estimates ("effect sizes") available – alongside uncertainty (e.g. standard errors)

Study Heterogeneity

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Often, different studies used different populations
⇒ potential extra-variability

\+ different sample sizes ⇒ also impact the estimate and its variability

Meta-analysis random effects model

Common approach for meta-analysis:

$$y_i \sim \mathcal{N}(\theta_i, \sigma_i^2)$$

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$\Rightarrow$ between study variability: $y_i \sim \mathcal{N}(\mu, \sigma_i^2 + \tau^2)$

Hierarchical generalization of the fixed effect model:

$$y_i \sim \mathcal{N}(\mu, \sigma_i^2)$$

$\Rightarrow$ assume same average effect for each study

Bayesian meta-analysis in practice

Meta-analysis: a perfect usecase for Bayesian analysis ?

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Meta-analysis: a perfect usecase for Bayesian analysis ?

- few observations
- informative *prior*
- sequential

Going further

Scientific literature search

⚠ FIRST (!) exhaustive search of the scientific literature

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Meta-analysis $\in$ evidence synthesis

e.g. meta-regression, mechanistic modeling, ...

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- random effects model will down-weight studies with larger sample sizes – Serghiou & Goodman, *JAMA*, 2018

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  a bug or a feature ?

Your turn !

Read ND Crins *et al.* Interleukin-2 Receptor Antagonists for Pediatric Liver Transplant Recipients: A Systematic Review and Meta-Analysis of Controlled Studies, *Pediatric Transplantation* 18(8):839, 2014. **[DOI:10.1111/petr.12362]**

Practical: exercise 7

BONUS content: CRM dose-escalation

Continuous Reassessment method

CRM [O'Quigley *at al.*, 1990]

Objective: identify the optimal dose
(i.e. Minimum Efficient Dose or Maximum Tolerated Dose)

$\Rightarrow$ select iteratively the dose for the next (batch of) recruited patient(s)
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- 😁 treat each patient ethically (dose best supported by the current evidence)
- 😁 *prior* knowledge
- 😁 sequential Bayesian: online update of the posterior

Your turn !

Read F Kaguelidou *et al.* Dose-Finding Study of Omeprazole on Gastric pH in Neonates with Gastro-Esophageal Acid Reflux Using a Bayesian Sequential Approach, *PLOS ONE* 11(12):e0166207, 2016. **[DOI:10.1371/journal.pone.0166207]**

Practical: BONUS exercise 9