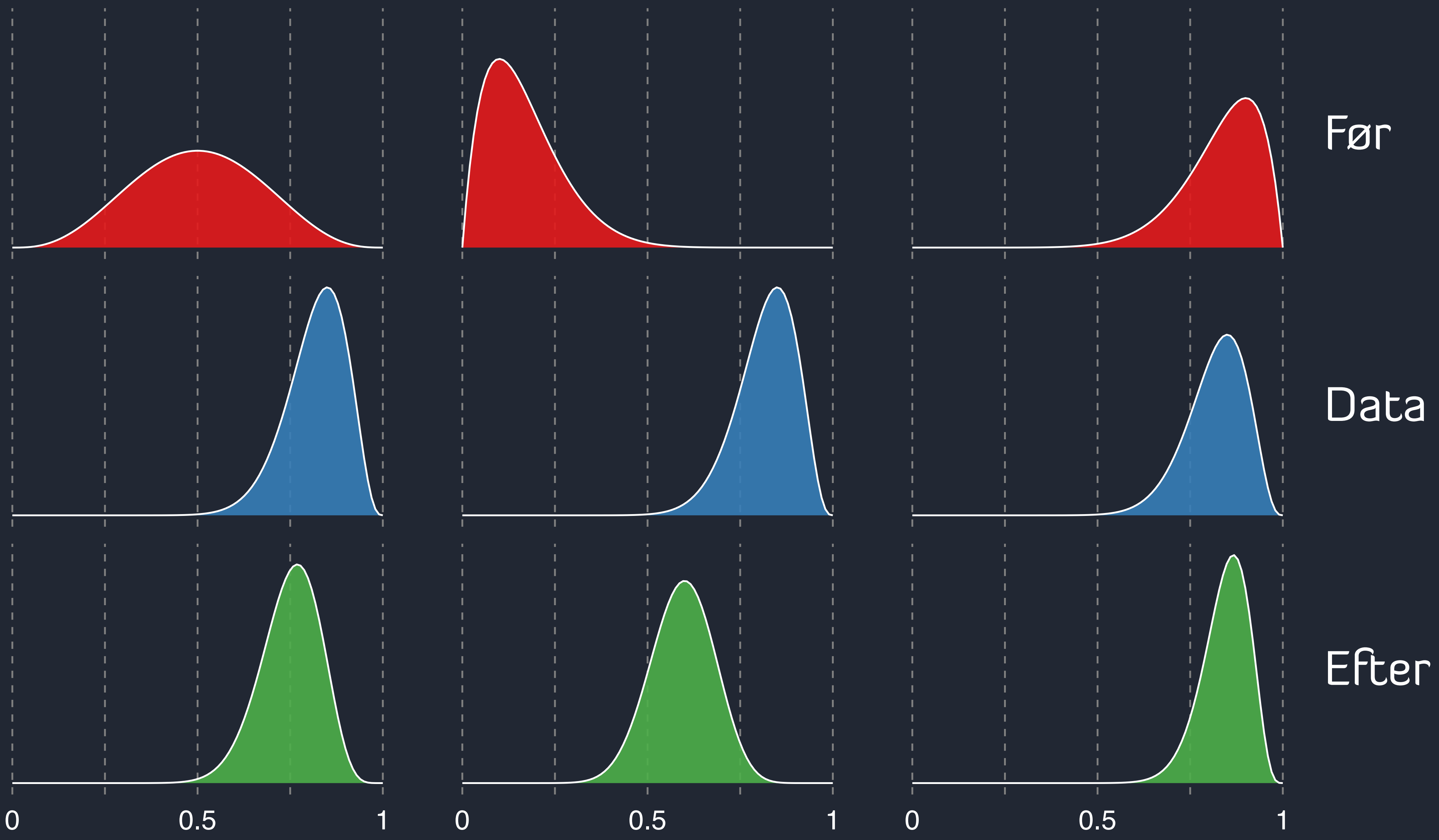
Bayesiansk analyse af RCT



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Bayesiansk analyse

Menneskelig intuition sat på formel

Formalisme for statistisk læring

Man starter ikke forfra hver gang

Beslutningsanalyser naturlige fortsættelser

Frekventist vs. Bayesian

Frekventist

Tillid til data, hvis parametre er korrekte

Bayesian

Tillid til parametre i lyset af nye data

Afledte parametre fås direkte

(f.eks. risk ratio, risk difference, odds ratio)

Bayes' theorem

$$p(\theta|\text{data}) \propto p(\text{data}|\theta) \cdot p(\theta)$$

posterior likelihood prior

θ = én eller flere parametre, f.eks. RR eller NNT

ARDS, ECMO og død

Lad os designe nyt RCT ("før EOLIA-studiet")

Effekt af ECMO på 60-dagesmortalitet ved ARDS

Effektmål: Risiko-ratio

2 arme: ECMO vs. ingen ECMO

10-100 patienter i hver arm

Hvor mange dør (og overlever) i hver arm?

Beta-prior

sandsynlighed for event

antal events

$$p \sim \text{beta}(\alpha, \beta)$$

antal ikke-events

= der er et afsnit i notebook-
filen med overskriften

>> "Crowd priors"

Observerede data (klassisk 2 x 2)

	Intervention	Kontrol
Event	z_i	z_k
Patienter	N_i	N_k
Risiko	$\frac{z_i}{N_i}$	$\frac{z_k}{N_k}$

	ECMO	Standard
Døde	**44**	**57**
Patienter	**124**	**125**
Risiko	**0,35**	**0,46**
Risk ratio	**0,78**	
Risk diff.	**0,10**	
NNT	**9,89**	

Coligher et al. 2018

Binomial likelihood

antal events antal patienter

$$z \sim \mathrm{binomial}(n, p)$$

sandsynlighed for event

>> "Likelihood"

Conjugacy

prior	beta(a, b)
+	
likelihood	binomial(z, n)
=	
posterior	beta(a + z, b + n− z)

Afledte parametre

Når man har posteriore samples af risici

$$\mathrm{RR} = \frac{\theta_{\mathrm{ECMO}}}{\theta_{\mathrm{kontrol}}}$$

$$\mathrm{ARR} = \theta_{\mathrm{kontrol}} - \theta_{\mathrm{ECMO}}$$

$$\mathrm{NNT} = \frac{1}{\mathrm{ARR}}$$

Bayes' barrierer

Opfattes som kompliceret og "mathy"

(Fejlagtig) ide om bayesiansk analyse som subjektiv og frekventistisk som objektiv

Det er mere besværligt end frekventist-metoder

Fornuftig prior-specifikation ofte svært

Man tvinger sig selv til at formalisere eksisterende viden eller mangel derpå

Frekventist-metoder velfunderede og miljøet

Bayesiansk model

Priors

Data

Datamodel

Antagelser
(f.eks. uafhængige priors)

Alle konklusioner er betingede af disse

5 trin i bayesiansk analyse

Designfase

1. Karakteriser data
2. Definer fornuftig datamodel
3. Specificer priors

Analysefase

4. Opdater parametre i lyset af nye data — fortolk resultater
5. Lav posterior predictive checking

DBDA, p. 25

1. Karakteriser data (outcome)

Numerisk (interval eller ratio)

Binært

Tid-til-event

Kategorisk eller ordinalt

Antal (evt. per personer/dage)

2. Fornuftig datamodel

Sandsynligheden θ for event i hver arm

Binomial-fordeling er en klassiker

z indbyrdes uafhængige events ud af n forsøg

— benyttes også i logistisk regression

Et bud på modellen brugt i Coligher 2018

Læses nedefra.

RR er asymmetrisk og kan i princippet være alt mellem 0 og uendelig => log-Normal prior

Risiko for død **skal** ligge mellem 0% og 100%

$$
\begin{aligned}
z_{\text{ECMO}} &\sim \text{binomial}(n_{\text{ECMO}}, \theta_{\text{ECMO}}) \\
\theta_{\text{ECMO}} &= \text{RR} \cdot \theta_{\text{kontrol}} \\
\text{RR} &\sim \text{log-Normal}(\mu, \tau) \quad \text{tabel 1, kolonne 2 og 3} \\
z_{\text{kontrol}} &\sim \text{binomial}(n_{\text{kontrol}}, \theta_{\text{kontrol}}) \\
\theta_{\text{kontrol}} &\sim \text{uniform}(0, 1)
\end{aligned}
$$

Data Prior-værdier Parametre

Coligher 2018, p. E4

3. Priors

Fra publicerede resultater/data
(både RCT og observationelle)

Fra domæneeksperter ("subjektive")

Logiske/regularisering af parameterestimater
(f.eks. er en reel RR > 10 meget usandsynlig)

4. Opdater parametre

Eksakt analyse

(simple modeller med conjugate priors)

Approksimationer ved samples fra posterior

(Markov Chain/Hamiltonian Monte Carlo)

Moderne software kæmpe hjælp

(BUGS, JAGS eller Stan)

DBDA , kap. 7 & 14 • DBA3, kap. 10–12 • BMBS, kap. 9

Hierarkiske modeller

Meta-analyser

Data-drevne priors

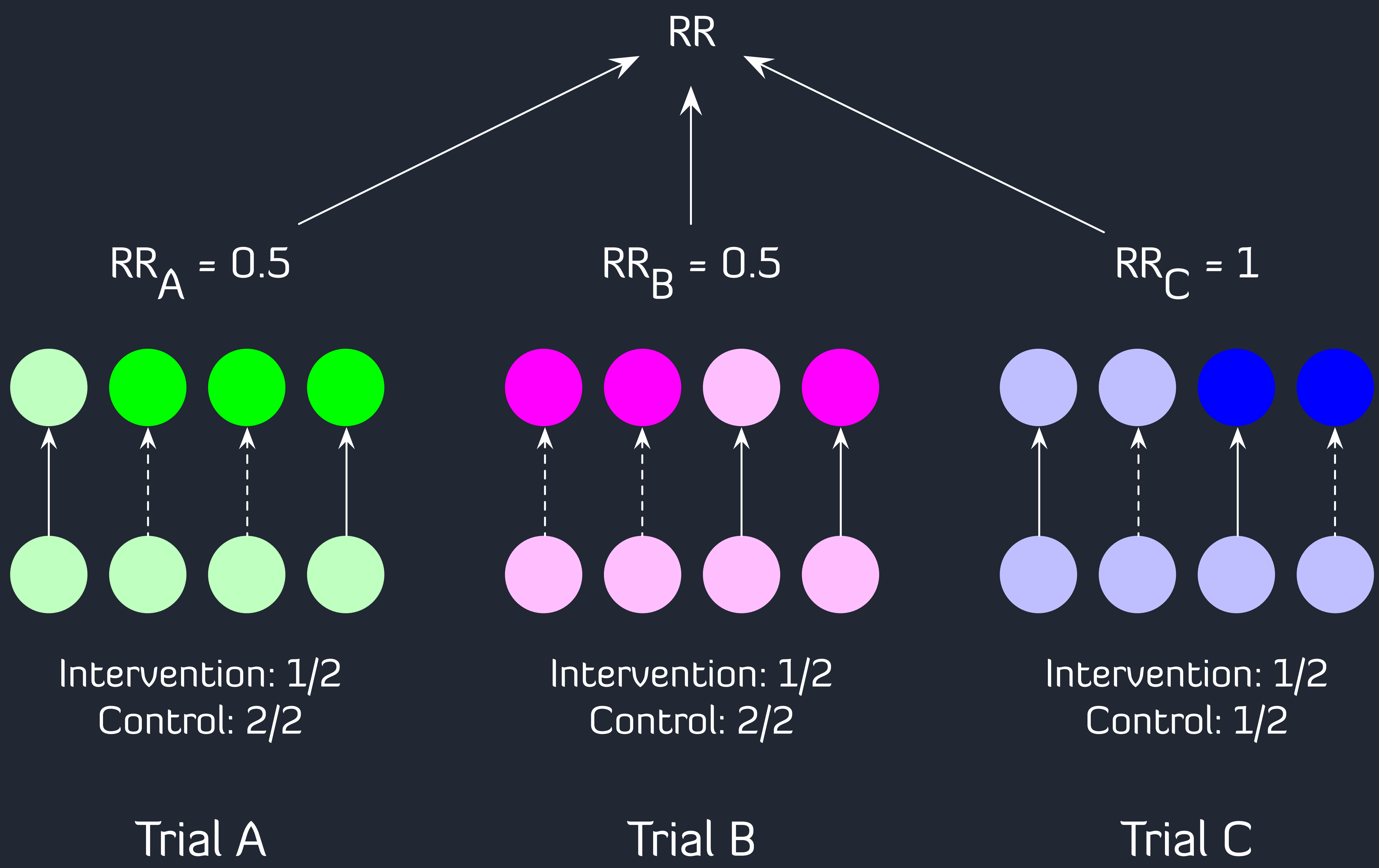
Interim-analyser

Parrede data eller gentagne målinger

TSA bygger (vist) på denne modeltype

Hierarkiske modeller

Mixed effects   Random effects   Multi-level   Partial pooling



5. Posterior predictive checking

Brug posteriore parametre til at prædiktere observerede data

Helt fundamentalt for at gå videre med modellen

Dejligt let i Stan!

Estimere posteriore fordelinger med Stan

>> "Model-fitting med Stan"

Stan's posteriors er tilnærmelser

Diagnostik nødvendig

(minimum chain mixing, divergent transitions)

Springer det over her

men afgørende at gøre og afrapportere

Afrapporting

Specify the priors

Explain how the priors were selected

Describe the statistical model used

Describe the techniques used in the analysis

Identify the statistical software program used in the analysis

Summarize the posterior distribution with a measure of central tendency
and a credibility interval

Assess the sensitivity of the analysis to different priors

"The Bayesian approach is tailored to decision making.

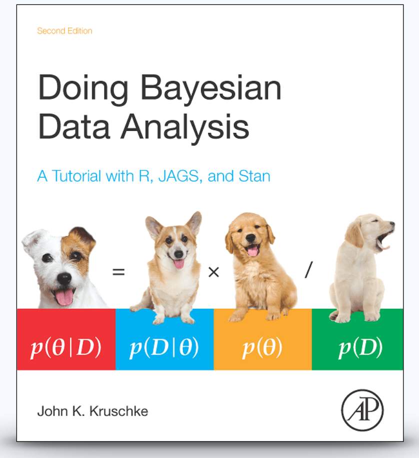
Designing a clinical trial is a decision problem.

Drawing a conclusion from a trial (...) is a decision problem.

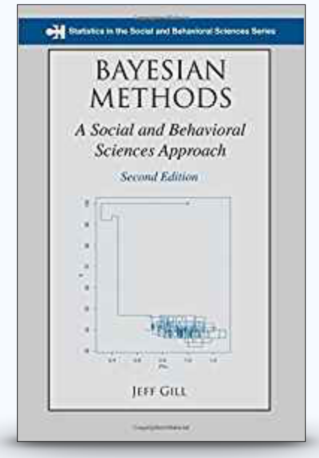
Allocating resources among various research projects is a decision problem.

Stopping drug development is a decision problem."

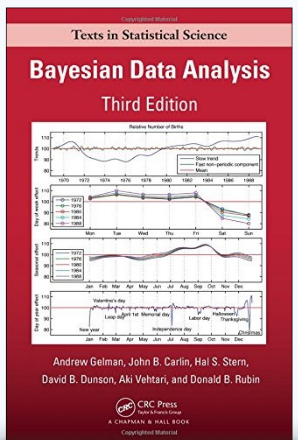
Berry 1993, p. 1378



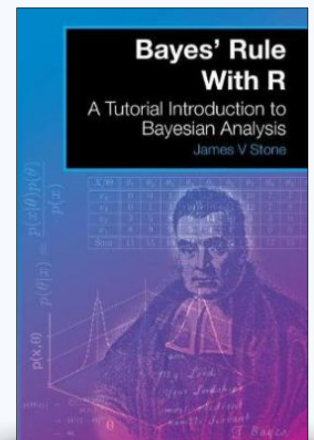
John K. Kruschke. *Doing Bayesian Data Analysis: a tutorial with R, JAGS, and Stan*. 2015. Academic Press. 2nd. ed. [DBDA] — SUPER INTRO



Jeff Gill. *Bayesian Methods: a Behavioural and Social Sciences approach*. 2007. Chapman and Hall/CRC. 2nd ed. [BMBS] — LIDT GAMMEL



Andres Gelman et al. *Bayesian Data Analysis*. 2013. Chapman and Hall/CRC. 3rd ed. [BDA3] — MEGET TEKNISK, "BIBLEN"



James V. Stone. *Bayes' Rule: a tutorial introduction to Bayesian analysis*. 2013. Septel Press. 1st ed. [BRTI] — FIN & PUDSIG

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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

Ewan C. Goligher, MD, PhD; George Tomlinson, MD, PhD; David Hajage, PhD; Duminda N. Wijeysundera, MD, PhD; Eddy Fan, MD, PhD; Peter Jüni, MD; Daniel Brodie, MD; Arthur S. Slutsky, MD; Alain Combes, MD, PhD

Time for Clinicians to Embrace Their Inner Bayesian?
Reanalysis of Results of a Clinical Trial of Extracorporeal Membrane Oxygenation

Roger J. Lewis, MD, PhD; Derek C. Angus, MD, MPH, FRCP

Extracorporeal Life Support for Acute Respiratory Failure
A Systematic Review and Metaanalysis

Laveena Munshi[1], Teagan Telesnicki[2], Allan Walkey[3], and Eddy Fan[1]

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Basic Statistical Reporting for Articles Published in Biomedical Journals: The "Statistical Analyses and Methods in the Published Literature" or The SAMPL Guidelines"

Thomas A. Lang[a] and **Douglas G. Altman**[b]
[a]Principal, Tom Lang Communications and Training International
[b]Director, Centre for Statistics in Medicine, Oxford University

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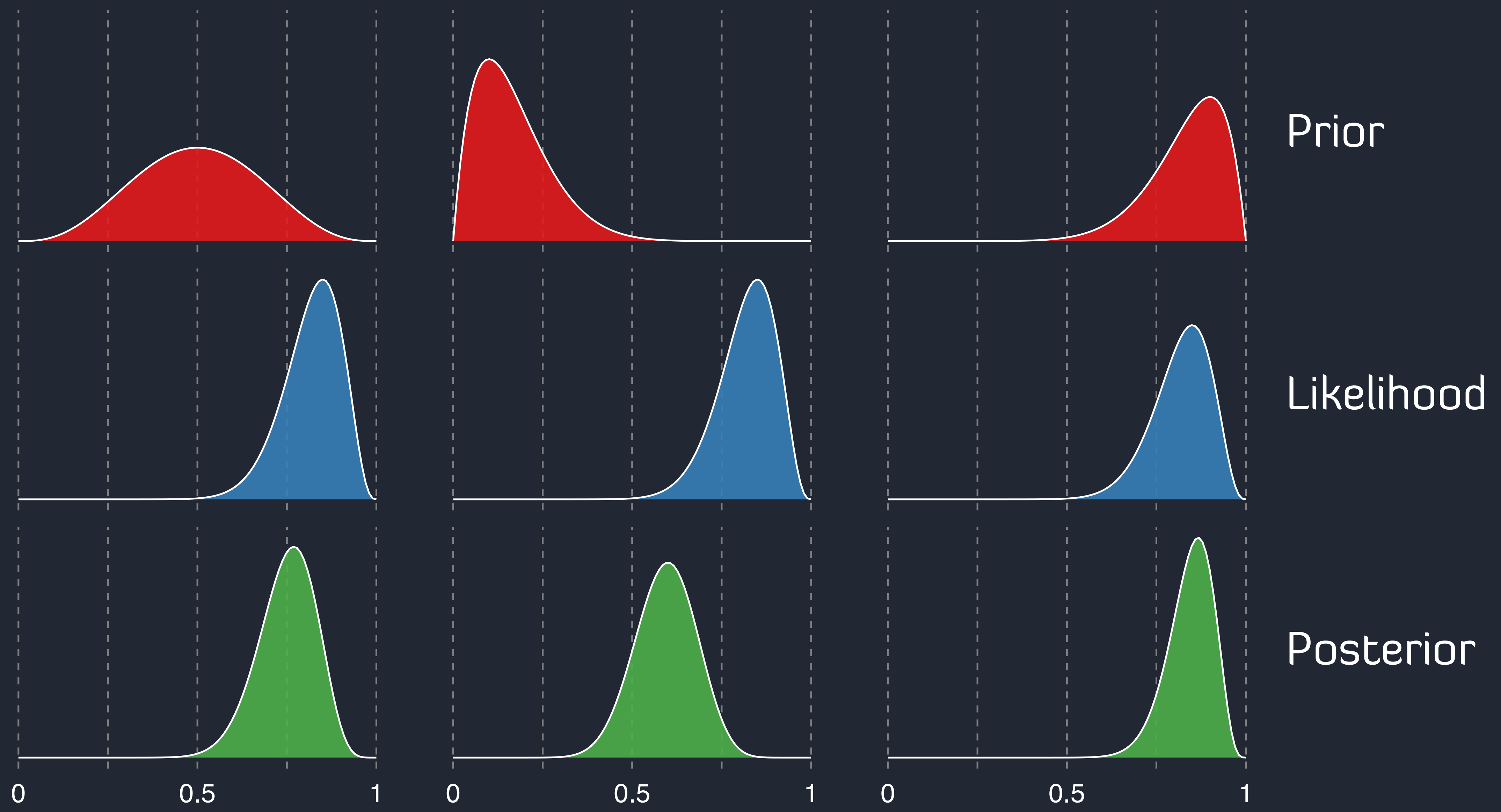
A CASE FOR BAYESIANISM IN CLINICAL TRIALS

DONALD A. BERRY



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