

# Worksheet 6

## Foundations of Bayesian Methodology

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### Exercise 3 (Bayesian meta-analysis with bayesmeta)

The aim of the exercise is to compute a Bayesian meta-analysis of  $\log(\text{OR})$  of treatment and placebo based on eight historical studies. The historical data of the responders in placebo and treatment can be found in Table 1. The data comes from the Baeten et al. study [1] and has been used for the prior elicitation.

#### Log odds ratio and its standard error

From the chapter *Comparison of proportions* on pages 137 and 138 in the book “Likelihood and Bayesian Inference” [2] we know that the log odds ratio  $y$  equals:

$$y = \log(\text{OR}) = \log\left(\frac{x_P}{n_P - x_P}\right) - \log\left(\frac{x_T}{n_T - x_T}\right)$$

And that the standard error equals

$$\sigma = \text{SE}(\log(\text{OR})) = \sqrt{\frac{1}{x_P} + \frac{1}{n_P - x_P} + \frac{1}{x_T} + \frac{1}{n_T - x_T}}$$

```
pl_total <- c(107, 44, 51, 39, 139, 20, 78, 35)
pl_case <- c(23, 12, 19, 9, 39, 6, 9, 10)
tr_total <- c(208, 38, 150, 45, 138, 20, 201, 34)
tr_case <- c(120, 18, 107, 26, 82, 16, 126, 23)
log_or <- log(pl_case/(pl_total-pl_case)) - log(tr_case/(tr_total-tr_case))
log_or_se <- sqrt(1/pl_case + 1/(pl_total-pl_case) + 1/tr_case + 1/(tr_total-tr_case))
labels <- 1:length(pl_total)
```

```
dat <- data.frame(labels, tr_case, tr_total, pl_case, pl_total, log_or, log_or_se)
knitr::kable(dat, align="c", digits=3, caption="Historical data for meta-analysis")
```

Table 1: Historical data for meta-analysis

labels	tr_case	tr_total	pl_case	pl_total	log_or	log_or_se
1	120	208	23	107	-1.605	0.274
2	18	38	12	44	-0.875	0.469
3	107	150	19	51	-1.433	0.341
4	26	45	9	39	-1.518	0.485
5	82	138	39	139	-1.323	0.256
6	16	20	6	20	-2.234	0.742
7	126	201	9	78	-2.556	0.383
8	23	34	10	35	-1.654	0.524

## Full bayesian meta-analysis - theory

We consider the full Bayesian meta-analysis expressed by the Bayesian normal-normal hierarchical model (NNHM) with three levels of hierarchy.

Likelihood:

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

for  $i = 1, \dots, k$

Random effects:

$$\theta_i \sim N(\mu, \tau^2)$$

Priors:

$$\mu \sim N(\nu, \gamma^2)$$

$$\tau \sim |N(0, A^2)| = \text{HN}(A)$$

where  $\nu = 0, \gamma = 4, A = 0.5$

$\sigma_i$  represents the within-study standard deviation of the  $i$ -th study. This value is assumed to be fixed (known). The heterogeneity of random effects is denoted by  $\tau$  which represents the between-study standard deviation.

The Bayes Theorem for the Bayesian NNHM reads:

$$f(\mu, \tau, \boldsymbol{\theta} \mid (y_1, \sigma_1), \dots, (y_k, \sigma_k)) = f((y_1, \sigma_1), \dots, (y_k, \sigma_k) \mid \boldsymbol{\theta}) \cdot f(\boldsymbol{\theta} \mid \mu, \tau) \cdot f(\mu) \cdot f(\tau) \cdot C^{-1}$$

where  $\boldsymbol{\theta} = \{\theta_1, \dots, \theta_k\}$  and  $C = f((y_1, \sigma_1), \dots, (y_k, \sigma_k))$  is a normalizing constant obtained by integrating out parameters  $\mu, \tau, \boldsymbol{\theta}$  in the numerator of the above printed equation.

The approximation of the log-posterior is then:

$$\log(\text{Posterior}) \approx \log(\text{Likelihood}) + \log(\text{Random-effects model}) + \log(\text{Prior})$$

Further details can be found in the script [3].

In the following a NNHM is applied to the data obtained in Table 1. The model is defined in the formulas for the Likelihood, Random effect and Prior above. We fit the model numerically with the help of the function `bayesmeta` from the package `bayesmeta` [4]. This function allows to derive the posterior distribution of the two parameters in a random-effects meta-analysis and provides functions to evaluate joint and marginal posterior probability distributions and more.

## Full bayesian meta-analysis - R implementation and visualization

```
full.bayes <- bayesmeta(y = dat[, "log_or"],
  sigma = dat[, "log_or_se"],
  labels = dat[, "labels"],
  mu.prior.mean = 0, mu.prior.sd = 4,
  tau.prior = function(t){dhalfnormal(t, scale = 0.5)},
  interval.type = "central",
  predict = T)
```

The summary of the function returns a matrix listing some summary statistics, namely marginal posterior mode, median, mean, standard deviation and a (shortest) 95% credible intervals, of the marginal posterior distributions of  $\tau$  and  $\mu$ , and of the posterior predictive distribution of  $\theta$ . See Table 2 for the condensed summary statistics.

```
summary(full.bayes)
```

```
## 'bayesmeta' object.
## data (8 estimates):
##      y      sigma
## 1 -1.6054775 0.2740073
## 2 -0.8754687 0.4691896
## 3 -1.4329256 0.3412963
## 4 -1.5176304 0.4853221
## 5 -1.3229761 0.2563070
## 6 -2.2335922 0.7420210
## 7 -2.5556757 0.3832411
## 8 -1.6538897 0.5238200
##
## tau prior (proper):
## function(t){dhalfnormal(t, scale = 0.5)}
## <bytecode: 0x0000000025dfbfa8>
##
## mu prior (proper):
## normal(mean=0, sd=4)
##
## ML and MAP estimates:
##      tau      mu
## ML joint    0.2094171 -1.592280
## ML marginal 0.2852879 -1.590235
## MAP joint    0.1614761 -1.585174
## MAP marginal 0.2334117 -1.587618
##
## marginal posterior summary:
##      tau      mu      theta
## mode    0.2334117 -1.5876182 -1.5805059
## median  0.2702386 -1.5919563 -1.5884808
## mean    0.2949284 -1.5946544 -1.5946544
## sd      0.1941244 0.1879906 0.4002409
## 95% lower 0.0153332 -1.9777397 -2.4509871
## 95% upper 0.7397310 -1.2281569 -0.7646060
##
## (quoted intervals are central, equal-tailed credible intervals.)
##
## Bayes factors:
##      tau=0      mu=0
## actual 1.0209152 3.11865e-05
## minimum 0.7030068 1.23805e-06
##
## relative heterogeneity I^2 (posterior median): 0.3343206
```

Table 2: Summary statistics for parameters (bayesmeta)

	mode	median	mean	sd	95% lower	95% upper
tau	0.2334	0.2702	0.2949	0.1941	0.0153	0.7397
mu	-1.5876	-1.5920	-1.5947	0.1880	-1.9777	-1.2282
theta	-1.5805	-1.5885	-1.5947	0.4002	-2.4510	-0.7646

Figure 1 illustrates the forest plot of the model printed with the function `forestplot`.

Figure 2 shows the four plots given by the `plot` function of `bayesmeta`. The first plot is another simple forest plot, showing the 8 estimates along with the combined estimate (diamond) and prediction interval (bar).

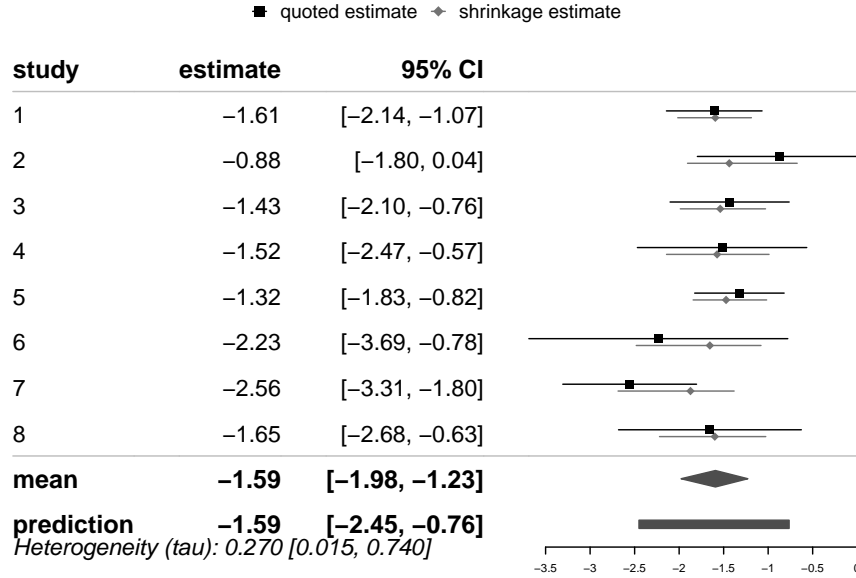


Figure 1: Forest Plot provided by ‘bayesmeta’ with the data from Table 1.

The second plot illustrates the joint posterior density of both parameters  $\mu$  and  $\tau$ ; a darker shading indicates higher posterior density values. The red contour lines show (approximate) 90%, 95% and 99% confidence regions for the joint distribution. The solid blue line traces the conditional posterior expectation value  $\mathbb{E}[\mu \mid \tau, y, \sigma]$ , and the dashed lines enclose the corresponding 95% interval as a function of  $\tau$ . The green lines indicate marginal posterior median and 95% intervals for both parameters.

The third and fourth plot show the marginal density functions of  $\mu$  and  $\tau$ , respectively. The posterior median and (highest posterior density) 95% interval are also indicated by a vertical line and a darker shading. The dashed line shows the prior density in comparison.

Figure 3 illustrates the marginal posteriors for all model parameters.

```
## Compare resulting marginal densities;

## The effect parameter (mu):
mu <- seq(-2.5, -.5, le=200)
plot(mu, full.bayes$dposterior(mu=mu), type="l", lty="solid",
     xlab=expression("effect " * mu),
     ylab="",
     main="",
     ylim=c(0,2.5))

## The heterogeneity parameter (tau):
tau <- seq(0, 1, le=200)
plot(tau, full.bayes$dposterior(tau=tau), type="l", lty="solid",
     xlab=expression("heterogeneity " * tau),
     ylab="",
     main="",
     ylim=c(0,2.5))

## Show the individual effects' posterior distributions:
theta <- seq(-3, -0.5, le=300)
plot(range(theta), c(0,2.5), type="n", xlab=expression(theta[i]), ylab="")
for (i in 1:full.bayes$k) {
```

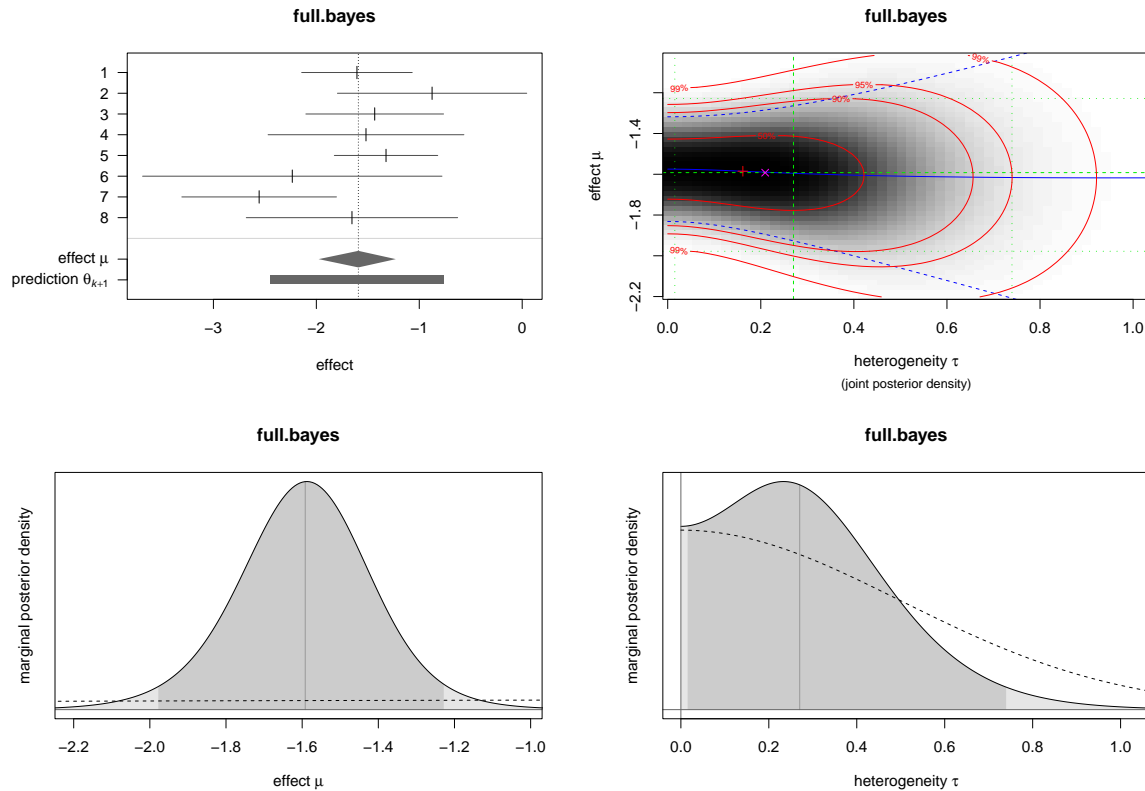


Figure 2: Plots provided by `extttbayesmeta` with the data from Table 1.

```
## Draw effect's posterior distribution:
lines(theta, full.bayes$dposterior(theta=theta, indiv=i),
      col="darkblue", lty="solid")
}
abline(h=0)

theta <- seq(-2.5, -0.5, le=200)

plot(theta, full.bayes$dposterior(theta=theta, predict=T), type="l", lty="dashed",
     xlab=expression("effect " * theta[new]),
     ylab=expression(""),
     main="", ylim=c(0, 2.5))
lines(theta, full.bayes$dposterior(theta=theta, predict=T), lty="solid")

pooledMean <- full.bayes$summary["mean", "mu"]
pooledCRI <- full.bayes$post.interval(mu.level=0.95, individual=F)

x <- 1:8
y <- full.bayes$theta["mean", ]
l <- full.bayes$theta["95% lower", ]
u <- full.bayes$theta["95% upper", ]

plotCI(x, y, li=l, ui=u, ylim=c(-4, 0), xlab="random effect", ylab="equi-tailed 95% CrI",
      pch=18, main="Posterior equi-tailed 95% CrI of the random effect")
points(x, rep(pooledMean, 8), col="red", pch=7)
abline(h=pooledMean, col="red")
abline(h=pooledCRI[1], col="red", lty=2)
```

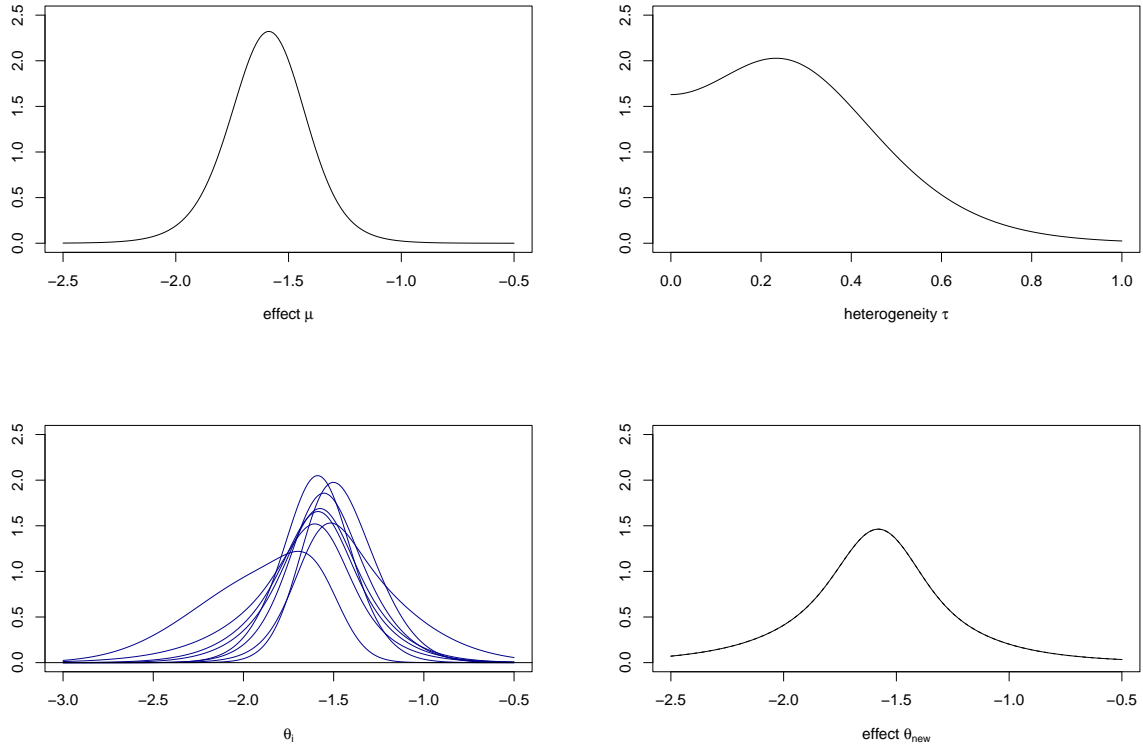
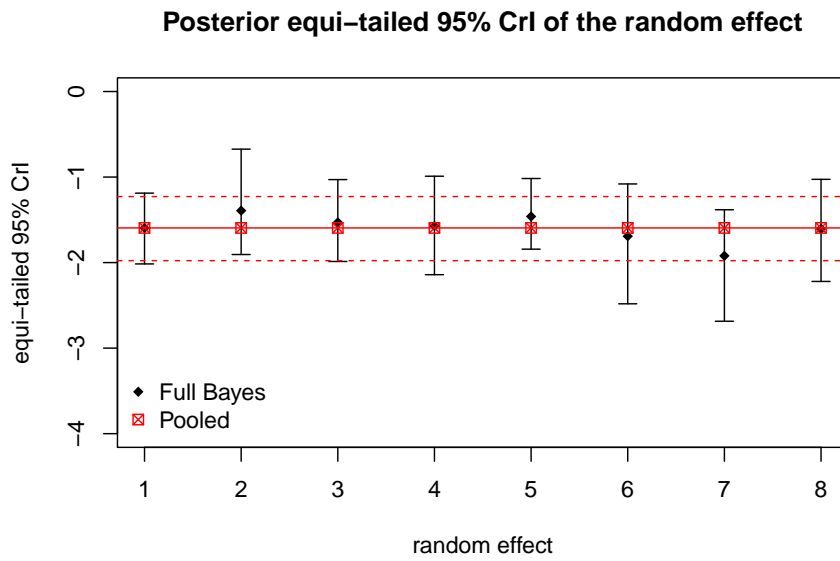


Figure 3: Marginal posterior distributions for all parameters in the model provided by ‘bayesmeta’ with the data from Table 1.

```
abline(h=pooledCRI[2], col="red", lty=2)
legend("bottomleft", legend=c("Full Bayes", "Pooled"),
      col=c("black", "red"), pch=c(18, 7), bty="n")
```



The full Bayesian meta-analysis expressed by NNHM provides inference on the random effects  $\theta_1, \dots, \theta_k$  that lies in between the inference provided by two models. It returns a pooled inference, see the red

confidence band in the figure above. The pooled model is based on the assumption that the true location of  $\theta$  is equivalent for all given studies, so  $\theta_1 = \dots = \theta_k$  which equals having a between-study variability  $\tau = 0$ . This assumption changes the NNHM model defined, due to the fact that random effects model collapses to  $\theta$ , a normal distribution with location  $\theta$  and variance  $\tau^2 = 0$ . The new model then reads:

Likelihood:

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

for  $i = 1, \dots, k$

Prior:

$$\theta \sim N(\nu, \gamma^2)$$

A sequential application fo the Bayes theorem leads to the posterior:

$$\theta \mid y_1, \dots, y_n \sim N\left(\frac{\sum_{i=1}^k \frac{y_i}{\sigma_i^2} + \frac{\nu}{\gamma^2}}{\sum_{i=1}^k \frac{1}{\sigma_i^2} + \frac{1}{\gamma^2}}, \left(\sum_{i=1}^k \frac{1}{\sigma_i^2} + \frac{1}{\gamma^2}\right)^{-1}\right)$$

The Figure above shows the results when the in between-study heterogeneity  $\tau = 0, \nu = 0$  and  $\gamma = 4$ . The pooled posterior mean is equal to -1.5946544 and the pooled standard deviation is equal to 0.1879906.

See pages 88 and 89 of the script [3] for the discussion of the change in the model definition as well as the plots of the credible intervals for empirical Bayes.

## Exercise 4 (Bayesian meta-analysis with JAGS)

The goal of this exercise is to provide an alternative meta-analysis of data based on the file `06worksheet_JAGSextension.R`.

### Meta-analysis based on `06worksheet_JAGSextension.R`

Likelihood:

$$y_j \sim \text{Bin}(n_j, p_j)$$

$$\eta_j \sim N(0, 1/\tau_{\text{prec}})$$

for  $i = 1, \dots, k$ , where  $\tau_{\text{prec}} = 1/\tau^2$

Priors:

$$\mu \sim U(-10, 10)$$

$$\beta \sim U(-10, 10)$$

$$\tau \sim U(0, 10)$$

```
pl1.data <- list(
  N = 16,
  y = c(23., 12., 19., 9., 39., 6., 9., 10., 120., 18., 107., 26., 82., 16., 126., 23.),
  n = c(107., 44., 51., 39., 139., 20., 78., 35., 208., 38., 150., 45., 138., 20., 201., 34.),
  C1 = c(0., 0., 0., 0., 0., 0., 0., 0., 1., 1., 1., 1., 1., 1., 1., 1.)
)

pl1.params <- c("mu", "beta", "tau", "p1.star", "p2.star")
```

```
pl1_modelString <- "model {
  # sampling model (likelihood)
  for (j in 1:N) {
    y[j] ~ dbin(p[j], n[j])
    logit(p[j]) <- mu + beta * C1[j] + eta[j]
    eta[j] ~ dnorm(0, tau.prec)
  }
}
```

```

# prediction for posterior predictive checks
y.pred[j] ~ dbin(p[j], n[j])
PPC[j] <- step(y[j] - y.pred[j]) - 0.5 * equals(y[j], y.pred[j])
}

# priors
mu ~ dunif(-10, 10)
beta ~ dunif(-10, 10)
tau ~ dunif(0, 10)
tau.prec <- 1/tau/tau

# population effect
p1 <- 1/(1+exp(-mu))
p2 <- 1/(1+exp(-mu-beta))

# predictive distribution for new study effect
eta.star ~ dnorm(0, tau.prec)
p1.star <- 1/(1+exp(-mu-eta.star))
p2.star <- 1/(1+exp(-mu-beta-eta.star))
}"

writeLines(pl1_modelString, con="./models/MetaAnalysis.txt")

```

```

# model initiation
rjags.pl1 <- jags.model(
  file = "./models/MetaAnalysis.txt",
  data = pl1.data,
  n.chains = 4,
  n.adapt = 4000
)

```

```

## Compiling model graph
##   Resolving undeclared variables
##   Allocating nodes
## Graph information:
##   Observed stochastic nodes: 16
##   Unobserved stochastic nodes: 36
##   Total graph size: 222
##
## Initializing model

```

```

# burn-in
update(rjags.pl1, n.iter = 4000)

# sampling/monitoring
fit.rjags.pl1.coda <- coda.samples(
  model = rjags.pl1,
  variable.names = pl1.params,
  n.iter = 50000,
  thin = 5
)

summary(fit.rjags.pl1.coda)

```

```

##
## Iterations = 8005:58000
## Thinning interval = 5

```



```
## Number of chains = 4
## Sample size per chain = 10000
##
## 1. Empirical mean and standard deviation for each variable,
##    plus standard error of the mean:
##
##          Mean      SD Naive SE Time-series SE
## beta      1.6226 0.21524 0.0010762      0.0024915
## mu       -1.1125 0.15957 0.0007978      0.0017587
## p1.star   0.2527 0.06746 0.0003373      0.0004365
## p2.star   0.6206 0.08077 0.0004038      0.0004692
## tau       0.2996 0.12980 0.0006490      0.0014453
##
## 2. Quantiles for each variable:
##
##          2.5%      25%      50%      75%      97.5%
## beta      1.19731  1.4871  1.6210  1.7562  2.0613
## mu       -1.43256 -1.2144 -1.1122 -1.0097 -0.7991
## p1.star   0.13396  0.2104  0.2469  0.2869  0.4065
## p2.star   0.44401  0.5763  0.6234  0.6690  0.7771
## tau       0.08057  0.2110  0.2873  0.3737  0.5929
```

```
m.fit.rjags.pl1.coda <- as.matrix(fit.rjags.pl1.coda)
d.chains <- data.frame(
  iterations = rep(8001:18000, times=4),
  chains = rep(c("chain1", "chain2", "chain3", "chain4"), each=10000),
  beta = m.fit.rjags.pl1.coda[, "beta"],
  mu = m.fit.rjags.pl1.coda[, "mu"],
  p1.star = m.fit.rjags.pl1.coda[, "p1.star"],
  p2.star = m.fit.rjags.pl1.coda[, "p2.star"],
  tau = m.fit.rjags.pl1.coda[, "tau"]
)

ggplot(d.chains, aes(x=iterations, y=beta, color=chains)) + geom_line(alpha=0.5) +
  labs(title="Trace of beta", x="Iterations") + theme_classic()

ggplot(d.chains, aes(x=beta, y=..density..)) +
  geom_density(color="darkblue", fill="lightblue", alpha=0.5) +
  labs(title="Density of beta", y="Density") + theme_classic()

ggplot(d.chains, aes(x=iterations, y=mu, color=chains)) + geom_line(alpha=0.5) +
  labs(title="Trace of mu", x="Iterations") + theme_classic()

ggplot(d.chains, aes(x=mu, y=..density..)) +
  geom_density(color="darkblue", fill="lightblue", alpha=0.5) +
  labs(title="Density of mu", y="Density") + theme_classic()

ggplot(d.chains, aes(x=iterations, y=p1.star, color=chains)) + geom_line(alpha=0.5) +
  labs(title="Trace of p1.star", x="Iterations") + theme_classic()

ggplot(d.chains, aes(x=p1.star, y=..density..)) +
  geom_density(color="darkblue", fill="lightblue", alpha=0.5) +
  labs(title="Density of p1.star", y="Density") + theme_classic()

ggplot(d.chains, aes(x=iterations, y=p2.star, color=chains)) + geom_line(alpha=0.5) +
  labs(title="Trace of p2.star", x="Iterations") + theme_classic()

ggplot(d.chains, aes(x=p2.star, y=..density..)) +
```

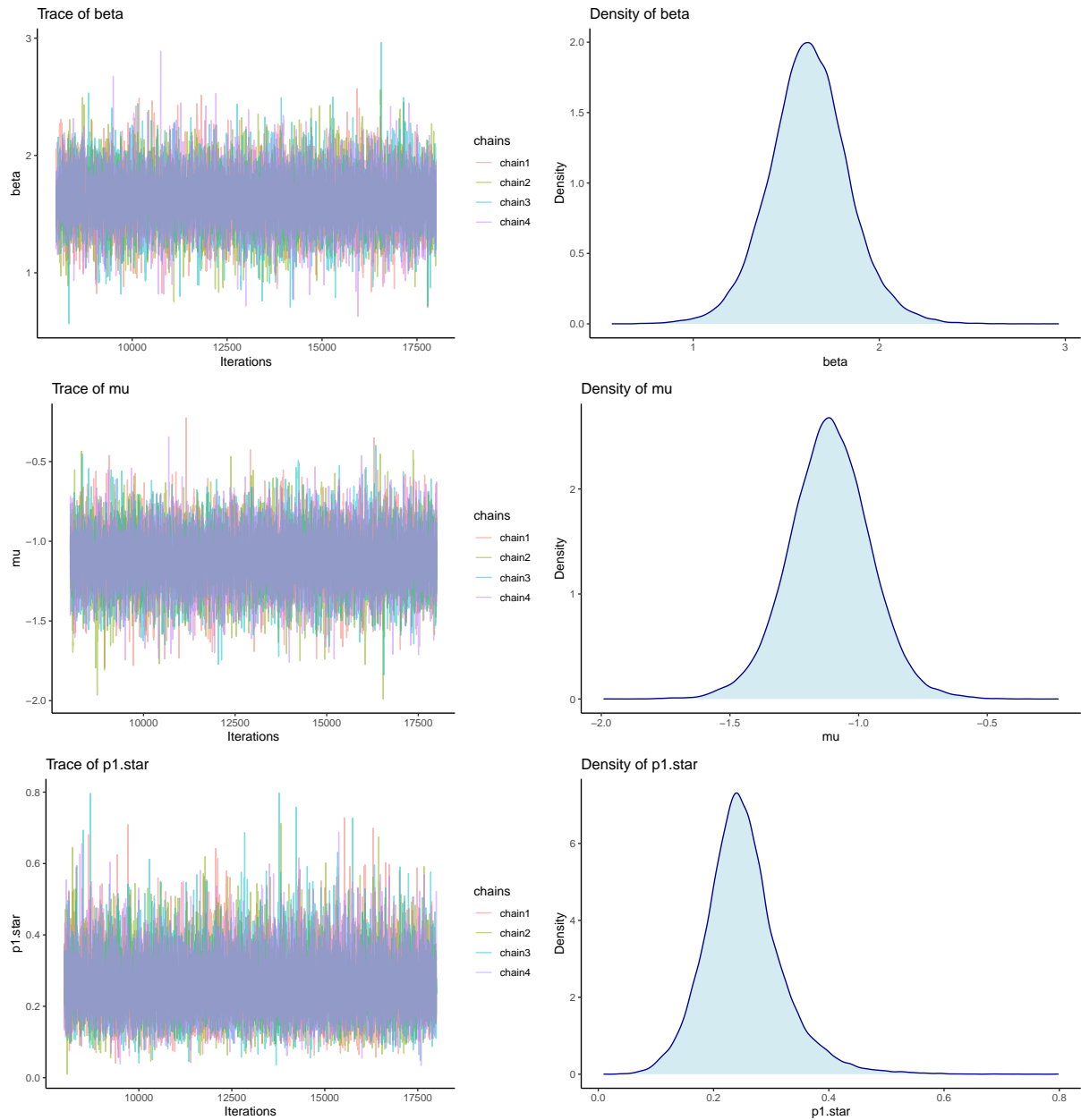
```

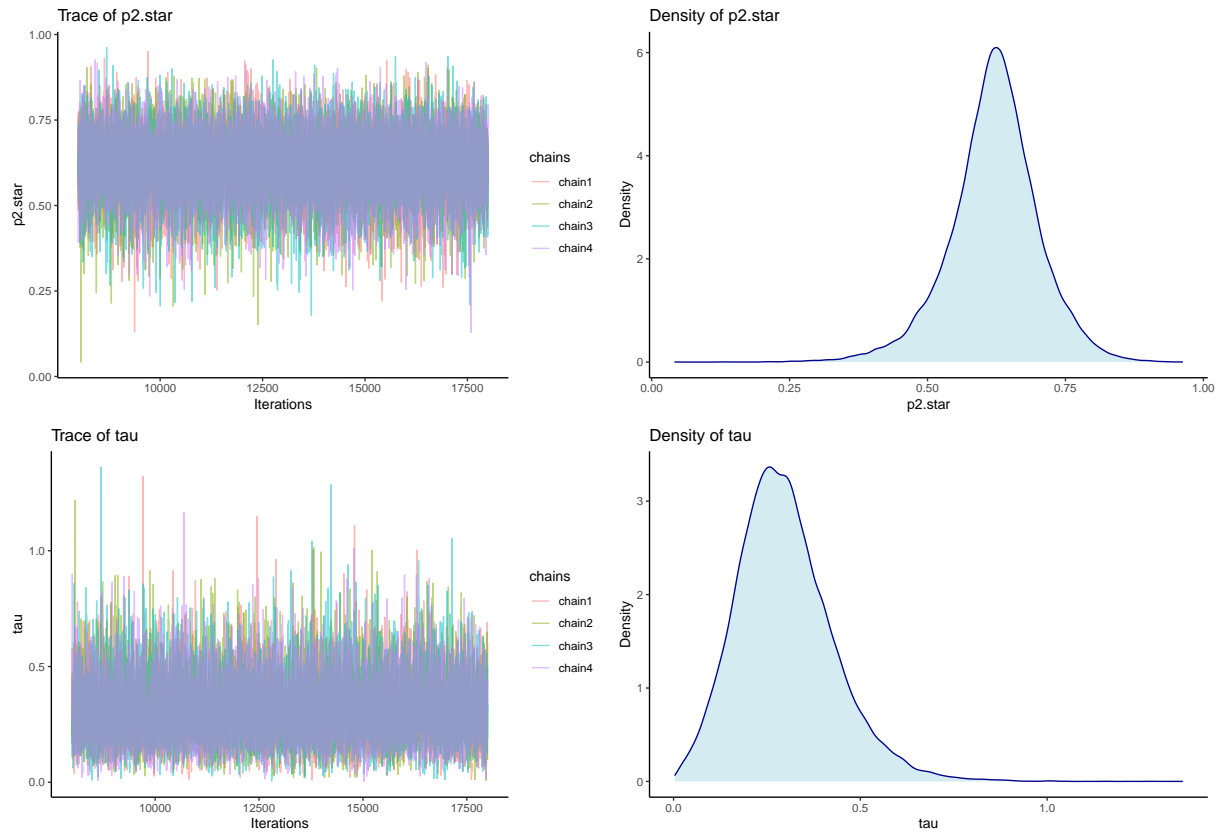
geom_density(color="darkblue", fill="lightblue", alpha=0.5) +
labs(title="Density of p2.star", y="Density") + theme_classic()

ggplot(d.chains, aes(x=iterations, y=tau, color=chains)) + geom_line(alpha=0.5) +
labs(title="Trace of tau", x="Iterations") + theme_classic()

ggplot(d.chains, aes(x=tau, y=..density..)) +
geom_density(color="darkblue", fill="lightblue", alpha=0.5) +
labs(title="Density of tau", y="Density") + theme_classic()

```





```
d.summary <- t(rbind(
  colMeans(m.fit.rjags.pl1.coda),
  apply(m.fit.rjags.pl1.coda, 2, function(x) sd(x)),
  apply(m.fit.rjags.pl1.coda, 2, function(x) quantile(x, probs=c(0.025, 0.5, 0.975)))
))

colnames(d.summary) <- c("Mean", "SD", "2.5%", "Median", "97.5%")
knitr::kable(d.summary, align="c", digits=4, caption="Summary statistics for parameters (JAGS)")
```

Table 3: Summary statistics for parameters (JAGS)

	Mean	SD	2.5%	Median	97.5%
beta	1.6226	0.2152	1.1973	1.6210	2.0613
mu	-1.1125	0.1596	-1.4326	-1.1122	-0.7991
p1.star	0.2527	0.0675	0.1340	0.2469	0.4065
p2.star	0.6206	0.0808	0.4440	0.6234	0.7771
tau	0.2996	0.1298	0.0806	0.2873	0.5929

## Comparison and discussion

### Model (Exercise 1 of Worksheet 5)

In this model, we first apply the logit-transformation to  $p_i = x_i/n_i$  to get an approximately normal distribution of logit-transformed rates. We then use the delta method to compute the standard of logit-transformed rates.

$$y_i = \text{logit}(p_i) = \log \frac{p_i}{1 - p_i} = \log \frac{x_i}{n_i - x_i}$$

$$\sqrt{\frac{1}{\tau_i^s}} = \text{SE}(y_i) = \sqrt{\frac{1}{x_i} + \frac{1}{n_i - x_i}}$$

The full Bayesian meta-analysis is conducted using the Bayesian normal-normal hierarchical model (NNHM) with three levels of hierarchy:

Likelihood:

$$y_i \sim N(\theta_i, 1/\tau_i^s)$$

for  $i = 1, \dots, N$

Random effects:

$$\theta_i \sim N(\mu, 1/\tau)$$

Priors:

$$\mu \sim N(0, 100^2)$$

$$\tau \sim G(0.001, 0.001)$$

### Model (Exercise 3 of Worksheet 6)

This model uses the same idea as for the model in Exercise 1 of Worksheet 5. The only difference is that in this model we consider the historical data for both placebo and treatment groups. We first compute the so-called log odds ratio, which is simply the difference between logit-transformed rates in the placebo group and logit-transformed rates in the treatment group. We then use the formula from [Held and Sabanes Bove, 2020, p. 137–138] to compute the standard error of the log odds ratio.

$$y = \log(\text{OR}) = \log \frac{x_P}{n_P - x_P} - \log \frac{x_T}{n_T - x_T}$$

$$\sigma = \text{SE}(\log(\text{OR})) = \sqrt{\frac{1}{x_P} + \frac{1}{n_P - x_P} + \frac{1}{x_T} + \frac{1}{n_T - x_T}}$$

The full Bayesian meta-analysis is conducted using the Bayesian normal-normal hierarchical model (NNHM) with three levels of hierarchy:

Likelihood:

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

for  $i = 1, \dots, k$

Random effects:

$$\theta_i \sim N(\mu, \tau^2)$$

Priors:

$$\mu \sim N(\nu, \gamma^2)$$

$$\tau \sim |N(0, A^2)| = \text{HN}(A)$$

where  $\nu = 0, \gamma = 4, A = 0.5$

### Model (Exercise 4 of Worksheet 6)

Unlike models stated before, this model uses a linear regression with a normal error ( $\eta_j$ ) to directly model the number of responders with only one predictor indicating whether in the treatment or not.

$$y_j = \mu + \beta \cdot \text{C1}_j + \eta_j$$

where  $\text{C1}_i$  is a binary variable which is equal to 0 if placebo and 1 otherwise.

Likelihood:

$$y_j \sim \text{Bin}(n_j, p_j)$$

$$\eta_j \sim N(0, 1/\tau_{\text{prec}})$$

for  $i = 1, \dots, k$ , where  $\tau_{\text{prec}} = 1/\tau^2$

Priors:

$$\mu \sim U(-10, 10)$$

$$\beta \sim U(-10, 10)$$

$$\tau \sim U(0, 10)$$

## Exercise 5 (Moments of the Poisson-gamma distribution)

Let  $Y|\lambda \sim P(\lambda)$  with  $\lambda \sim G(\alpha, \beta)$ . Use the expressions for iterated expectation

$$\mathbb{E}(Y) = \mathbb{E}_\lambda[\mathbb{E}_Y(Y | \lambda)]$$

and variance (Held and Sabanes Bove, 2020, Section A.3.4)

$$\text{Var}(Y) = \text{Var}_\lambda[\mathbb{E}_Y(Y | \lambda)] + \mathbb{E}_\lambda[\text{Var}_Y(Y | \lambda)]$$

To derive both, the expectation and the variance of the random variable  $Y$ .

Hints: Poisson distribution:  $X \sim \text{Po}(\lambda) : \mathbb{E}(X) = \lambda, \text{Var}(X) = \lambda$

Gamma distribution:  $X \sim G(\alpha, \beta) : \mathbb{E}(X) = \alpha/\beta, \text{Var}(X) = \alpha/\beta^2$

Solution:

$$\begin{aligned} \mathbb{E}(Y) &= \mathbb{E}_\lambda[\mathbb{E}_Y(Y | \lambda)] \quad \because Y | \lambda \sim \text{Po}(\lambda) \\ &= \mathbb{E}_\lambda(\lambda) \quad \because \lambda \sim G(\alpha, \beta) \\ &= \frac{\alpha}{\beta} \end{aligned}$$

$$\begin{aligned} \text{Var}(Y) &= \text{Var}_\lambda[\mathbb{E}_Y(Y | \lambda)] + \mathbb{E}_\lambda[\text{Var}_Y(Y | \lambda)] \quad \because Y | \lambda \sim \text{Po}(\lambda) \\ &= \text{Var}_\lambda(\lambda) + \mathbb{E}_\lambda(\lambda) \quad \because \lambda \sim G(\alpha, \beta) \\ &= \frac{\alpha}{\beta^2} + \frac{\alpha}{\beta} \\ &= \frac{\alpha(1 + \beta)}{\beta^2} \end{aligned}$$

## Exercise 6 (Empirical Bayes)

Consider observed numbers of lip cancer cases per district for each of 56 districts in Scotland:

```
y <- c(11, 5, 15, 9, 6, 9, 2, 3, 26, 39, 20, 31, 9, 16, 6, 16, 19, 17, 15, 11, 19,
7, 10, 0, 7, 7, 9, 2, 8, 8, 11, 6, 28, 4, 1, 1, 1, 8, 6, 3, 2, 1, 7, 10, 9, 11, 3,
11, 5, 8, 3, 7, 0, 8, 7, 13)
```

Assume that these observations are *i.i.d.* realizations of the model  $Y | \lambda \sim \text{Po}(\lambda)$  with  $\lambda \sim G(\alpha, \beta)$ . Apply and compare two different approaches to compute empirical Bayes estimates for each district:

### Numerical maximization of log-likelihood

- (a) Numerical maximization of the log-likelihood corresponding to the Poisson-gamma distribution as described by (Held and Sabanes Bove, 2020, p. 210) to obtain the marginal maximum likelihood estimator.

$$\underbrace{f(\lambda | y_{1:n})}_{\text{Posterior}} \propto \underbrace{f(y_{1:n} | \lambda)}_{\text{Likelihood}} \cdot \underbrace{f(\lambda)}_{\text{Prior}}$$

Likelihood:

$$f(y_{1:n} | \lambda) = \prod_{i=1}^n \frac{\lambda^{y_i} \exp(-\lambda)}{y_i!} \propto \lambda^{\sum_{i=1}^n y_i} \exp(-n\lambda)$$

Prior:

$$f(\lambda) = \frac{\beta^\alpha}{\Gamma(\alpha)} \lambda^{\alpha-1} \exp(-\beta\lambda) \propto \lambda^{\alpha-1} \exp(-\beta\lambda)$$

Posterior:

$$\begin{aligned} f(\lambda \mid y_{1:n}) &\propto f(y_{1:n} \mid \lambda) \cdot f(\lambda) \\ &\propto \lambda^{\sum_{i=1}^n y_i} \exp(-n\lambda) \cdot \lambda^{\alpha-1} \exp(-\beta\lambda) \\ &= \lambda^{\sum_{i=1}^n y_i + \alpha - 1} \exp(-(n + \beta)\lambda) \end{aligned}$$

$$f(\lambda \mid y_{1:n}) \propto \lambda^{(\alpha + \sum_{i=1}^n y_i) - 1} \exp(-(\beta + n)\lambda)$$

Hence

$$\lambda \mid y_{1:n} \sim G\left(\alpha + \sum_{i=1}^n y_i, \beta + n\right)$$

In the empirical Bayes setting, we define the estimates of the prior based on the maximum likelihood estimates of the prior predictive distribution. This is also called the marginal likelihood and in our context has the Poisson-gamma form  $y_i \sim \text{PoG}(\alpha, \beta, 1)$  with the log-likelihood

Likelihood:

$$y_i \mid \lambda \sim \text{Po}(\lambda)$$

Prior:

$$\lambda \sim G(\alpha, \beta)$$

Prior predictive distribution:

$$\begin{aligned} f(y_i) &= \int_0^\infty f(y_i \mid \lambda) \cdot f(\lambda) d\lambda \\ &= \int_0^\infty \frac{\lambda^{y_i} \exp(-\lambda)}{y_i!} \cdot \frac{\beta^\alpha}{\Gamma(\alpha)} \lambda^{\alpha-1} \exp(-\beta\lambda) d\lambda \\ &= \frac{\beta^\alpha}{\Gamma(\alpha)} \cdot \frac{1}{y_i!} \int_0^\infty \lambda^{y_i + \alpha - 1} \exp(-(1 + \beta)\lambda) d\lambda \\ &= \frac{\beta^\alpha}{(\beta + 1)^{\alpha + y_i}} \cdot \frac{\Gamma(\alpha + y_i)}{\Gamma(\alpha)} \cdot \frac{1}{y_i!} \underbrace{\int_0^\infty \frac{(\beta + 1)^{\alpha + y_i}}{\Gamma(\alpha + y_i)} \lambda^{(\alpha + y_i) - 1} \exp(-(\beta + 1)\lambda) d\lambda}_{\text{integrates to 1}} \\ &= \frac{\beta^\alpha}{(\beta + 1)^{\alpha + y_i}} \cdot \frac{\Gamma(\alpha + y_i)}{\Gamma(\alpha)} \cdot \frac{1}{y_i!} \end{aligned}$$

Log-likelihood:

$$\begin{aligned} l(\alpha, \beta) &= \log \prod_{i=1}^n f(y_i) \\ &= \sum_{i=1}^n \log f(y_i) \\ &= \sum_{i=1}^n \log \left( \frac{\beta^\alpha}{(\beta + 1)^{\alpha + y_i}} \cdot \frac{\Gamma(\alpha + y_i)}{\Gamma(\alpha)} \cdot \frac{1}{y_i!} \right) \\ &= \sum_{i=1}^n \left[ \alpha \log(\beta) - (\alpha + y_i) \log(\beta + 1) + \log \left( \frac{\Gamma(\alpha + y_i)}{\Gamma(\alpha)} \right) - \log(y_i!) \right] \\ &\propto \sum_{i=1}^n \left[ \alpha \log(\beta) + \log \left( \frac{\Gamma(\alpha + y_i)}{\Gamma(\alpha)} \right) - (\alpha + y_i) \log(\beta + 1) \right] \end{aligned}$$

```
## Log-likelihood function
ll <- function(x) {
  alpha <- x[1]
  beta <- x[2]
  ll <- sum(alpha * log(beta) + log( (gamma(alpha + y))/(gamma(alpha)) ) -
            (alpha + y) * log(beta + 1))
  return(ll)
}

## Maximize log-likelihood function
opt <- optim(par=c(0.1, 0.1), fn=ll, control = list(fnscale = -1))

## Print the maximum likelihood estimates
opt$par
```

```
## [1] 1.8321593 0.1914292
```

Thus, we have  $\hat{\alpha}_{\text{ML}}$  and  $\hat{\beta}_{\text{ML}}$  and can put them into the posterior formula calculated above.

## Machining of moments based on the Exercise 5

- (b) Matching of moments based on the Exercise 5 above, which provides the marginal moment estimator.

In the Exercise 5, we have derived:

$$\mathbb{E}(Y) = \frac{\alpha}{\beta}$$

$$\text{Var}(Y) = \frac{\alpha(1 + \beta)}{\beta^2}$$

Let us start with  $\text{Var}(Y)$ :

$$\text{Var}(Y) = \frac{\alpha(1 + \beta)}{\beta^2}$$

$$\text{Var}(Y) = \mathbb{E}(Y) \cdot \frac{1 + \beta}{\beta}$$

$$\frac{\text{Var}(Y)}{\mathbb{E}(Y)} = \frac{1}{\beta} + 1$$

$$\beta = \frac{1}{\frac{\text{Var}(Y)}{\mathbb{E}(Y)} - 1}$$

$$\mathbb{E}(Y) = \frac{\alpha}{\beta}$$

$$\alpha = \beta \mathbb{E}(Y)$$

$$= \frac{\mathbb{E}(Y)}{\frac{\text{Var}(Y)}{\mathbb{E}(Y)} - 1}$$

$$\begin{cases} \alpha &= \frac{\mathbb{E}(Y)}{\frac{\text{Var}(Y)}{\mathbb{E}(Y)} - 1} \\ \beta &= \frac{1}{\frac{\text{Var}(Y)}{\mathbb{E}(Y)} - 1} \end{cases}$$

```
## Moment-matching function
match.moments <- function(mean, var) {
  alpha <- mean / (var/mean - 1)
  beta <- 1 / (var/mean - 1)
  return(params = c(alpha=alpha, beta=beta))
}

params <- match.moments(mean = mean(y), var = var(y)); params
```

```
##      alpha      beta
## 1.7295501 0.1806993
```

```
alpha <- params[1]
beta <- params[2]
```

## Comparison and discussion

Compare means and the lengths of equi-tailed 95%CrI obtained by both approaches. Report your results

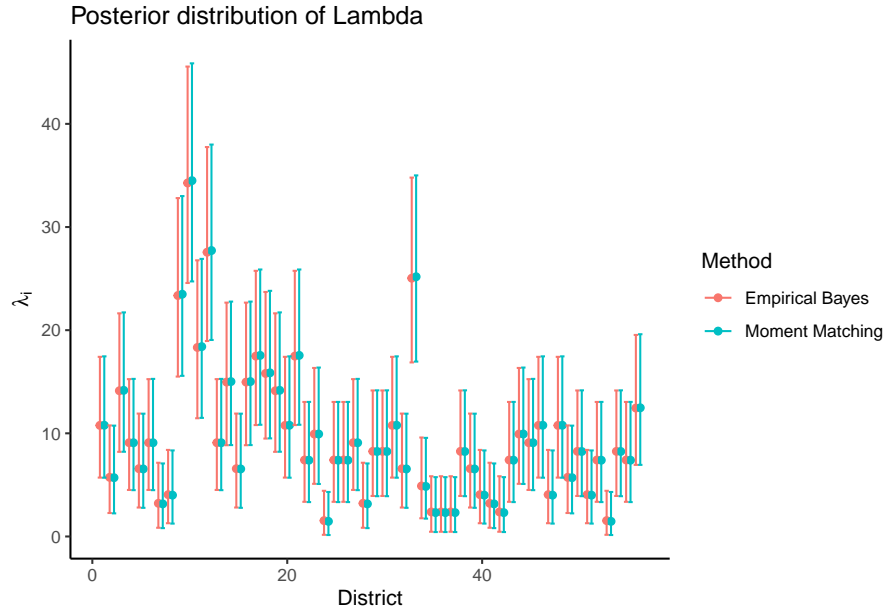
```
column.names <- c("District", "Mean", "Lower", "Median", "Upper", "Length", "Method")
df1 <- data.frame(matrix(nrow=length(y), ncol=7))
df2 <- data.frame(matrix(nrow=length(y), ncol=7))
colnames(df1) <- column.names
colnames(df2) <- column.names

for (i in 1:length(y)) {
  ## Empirical Bayes
  df1[i, 1] <- i
  df1[i, 2] <- (opt$par[1]+y[i]) / (opt$par[2]+1)
  df1[i, 3:5] <- qgamma(c(0.025, 0.5, 0.975), shape=opt$par[1]+y[i], rate=opt$par[2]+1)
  df1[i, 6] <- df1[i, 5] - df1[i, 3]
  df1[i, 7] <- "Empirical Bayes"

  ## Moment Matching
  df2[i, 1] <- i
  df2[i, 2] <- (alpha+y[i]) / (beta+1)
  df2[i, 3:5] <- qgamma(c(0.025, 0.5, 0.975), shape=alpha+y[i], rate=beta+1)
  df2[i, 6] <- df2[i, 5] - df2[i, 3]
  df2[i, 7] <- "Moment Matching"
}

d.plot <- rbind(df1, df2)
ggplot(data=d.plot, aes(x=District, y=Mean, color=Method)) +
  geom_point(position=position_dodge(.9)) +
  geom_errorbar(aes(ymin=Lower, ymax=Upper), width=.9, position=position_dodge(0.9)) +
  # scale_color_manual(values = c(3, 4)) +
  labs(title = "Posterior distribution of Lambda",
       y=expression(lambda[i]), x="District") + theme_classic()
```





```
mean.diff <- df1$Mean - df2$Mean
length.diff <- df1$Length - df2$Length

d.comparison <- rbind(
  c("Mean"=mean(mean.diff), quantile(mean.diff, probs=c(0.025,0.5,0.975))),
  c("Mean"=mean(length.diff), quantile(length.diff, probs=c(0.025,0.5,0.975)))
)

rownames(d.comparison) <- c("Mean difference", "Length difference")
knitr::kable(d.comparison, align="c", digits=4, caption="Comparison of the two methods")
```

Table 4: Comparison of the two methods

	Mean	2.5%	50%	97.5%
Mean difference	-0.0001	-0.1549	0.0119	0.0701
Length difference	-0.0337	-0.1375	-0.0380	0.0786

The Moment Matching method yields in general higher values and the width of the confidence intervals tends to be larger.

## References

- [1] Baeten, D., X. Baraliakos, J. Braun, J. Sieper, P. Emery, D. van der Heijde, I. McInnes, J. van Laar, R. Landewé, P. Wordsworth, J. Wollenhaupt, H. Kellner, J. Paramarta, J. Wei, A. Brachat, S. Bek, D. Laurent, Y. Li, Y. Wang, A. Bertolino, S. Gsteiger, A. Wright, and W. Hueber (2013). Antiinterleukin-17A monoclonal antibody secukinumab in treatment of ankylosing spondylitis: a randomised, double-blind, placebo-controlled trial. *The Lancet* 382, 1705–1713.
- [2] Held, L. and D. Sabanés Bové (2020). *Likelihood and Bayesian Inference: With Applications in Biology and Medicine*. Springer.
- [3] Roos, M. (2022). *Foundations of Bayesian Methodology: FS22*, Department of Biostatistics at Epidemiology, Biostatistics and Prevention Institute, University of Zurich
- [4] Röver, C. (2020). Bayesian random-effects meta-analysis using the bayesmeta R package. *Journal of Statistical Software* 93(6), 1–51.