Model-based meta-analysis using arm-based models

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Introduction

Model-based meta-analysis

- **Meta-analysis**: methods to combine multiple studies
- Potential **heterogeneity** between studies
- When dosing information available from different studies
- Dose-response models such as E_{max} are applied
- **Model-based meta-analysis (MBMA)** (Mandema et al., 2005)

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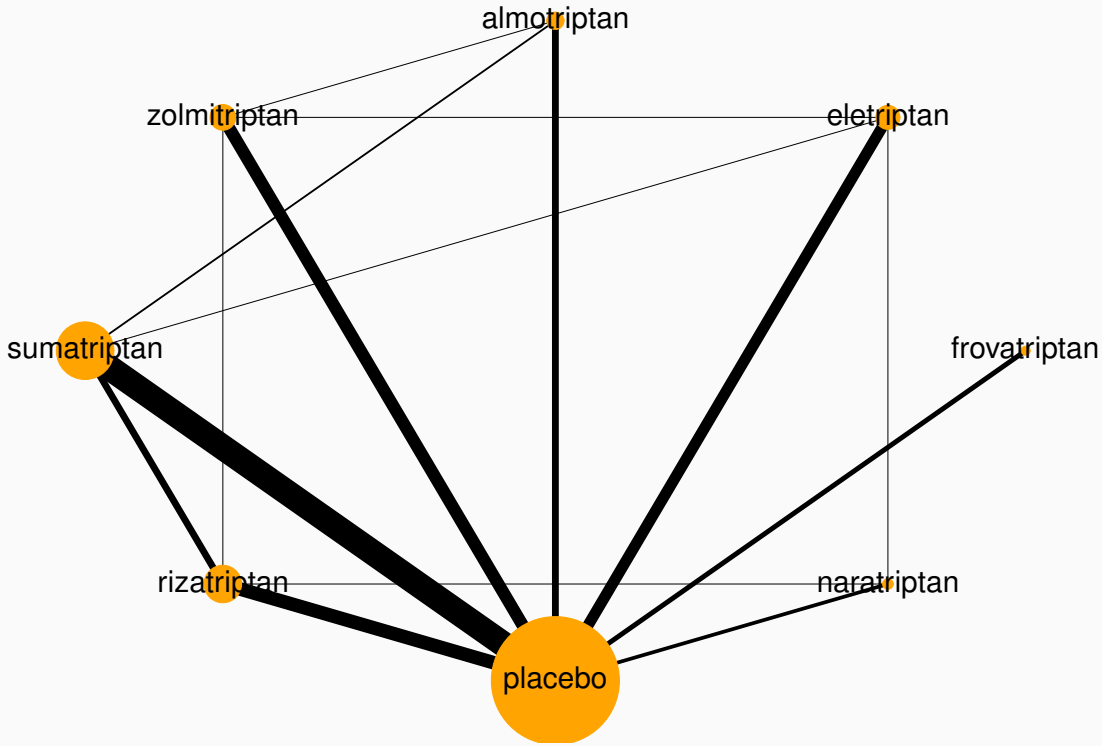
An illustrative example (Thorlund et al., 2014)

- The efficacy of 7 triptans in migraine pain relief
- Primary endpoint: Headache free at 2 hours (binary)
- Consists of 70 RCTs



An illustrative example (Thorlund et al., 2014)

- Considering only eletriptan vs placebo trials
- Consists of 12 RCTs

Trial	Dose (mg)	Number of patients	Number of responses
1	0	70	6
1	40	69	24
2	0	195	43
2	20	197	93
2	40	173	61
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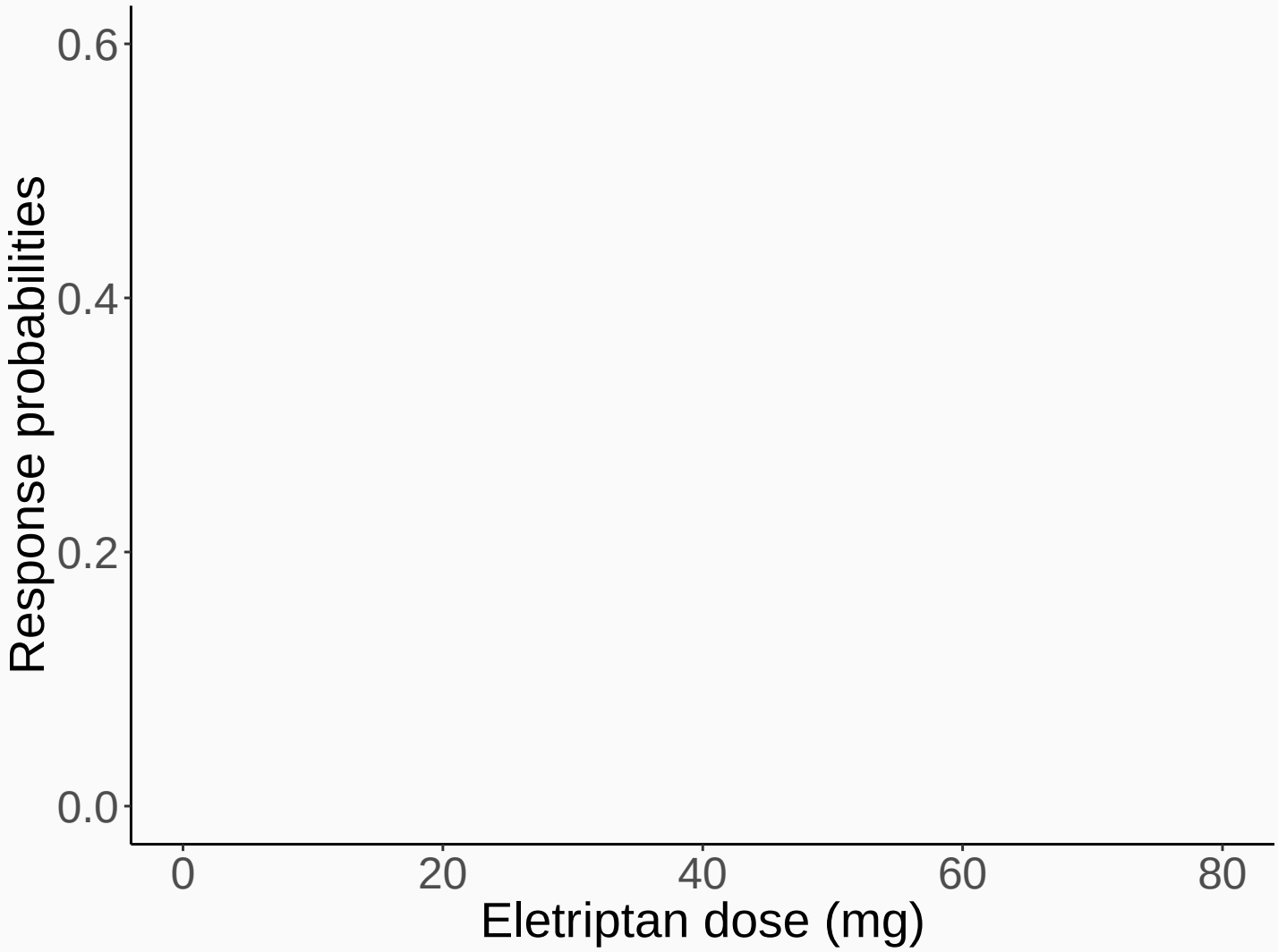
Probability of patients with headache-free response at 2 hours



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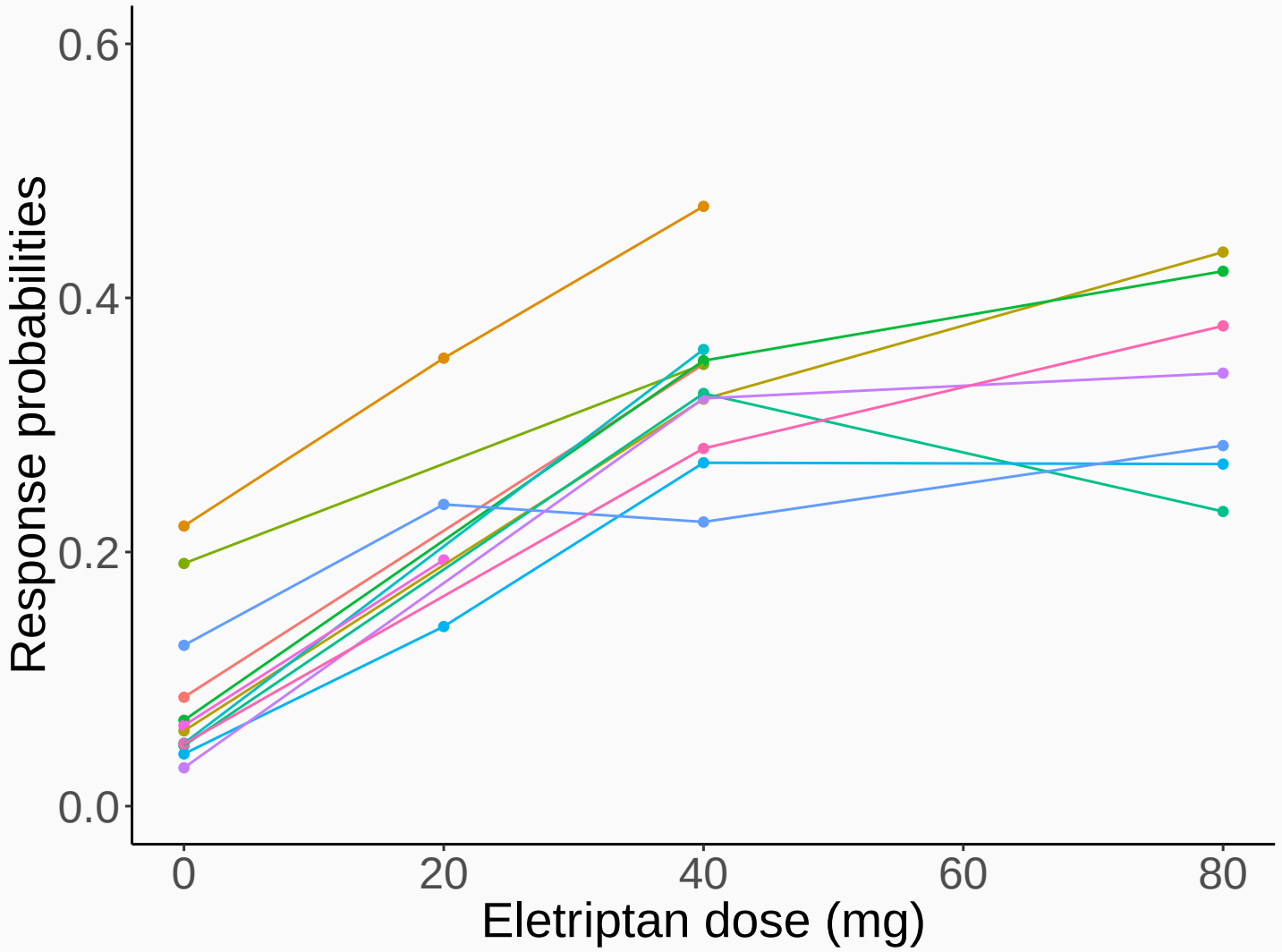

Methods

Four statistical models for MBMA

- Trial i and dose k, number of events $r_{i,k} \sim \text{Bin}(\pi_{i,k}, n_{i,k})$

$$\text{logit}(\pi_{i,k}) = \begin{cases} \mu_i, & \text{(control arm)} \\ \mu_i + \delta_{i,k}, & \text{(treatment arm)} \end{cases}$$

  - μ_i: the effect on control arm (baseline risk)
  - $\delta_{i,k}$: relative effect (arm with dose k vs control arm)

- Dose-response relationship e.g. E_{max}:

$$f(\text{dose}_{i,k}) = \frac{E_{max} \cdot \text{dose}_{i,k}}{ED_{50} + \text{dose}_{i,k}}$$

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Four statistical models for MBMA

1. Baseline model (Boucher and Bennetts, 2016)
   - $\mu_i \sim \mathcal{N}(\mu, \sigma^2)$
   - $\delta_{i,k} = f(\text{dose}_{i,k})$
2. Contrast-based (CB) model (Mawdsley et al., 2016)
   - Baseline risks μ_i as fixed effects
   - Two-arm trials: $\delta_{i,k} \sim \mathcal{N}(f(\text{dose}_{i,k}), \tau^2)$
   - Three-arm trials: $\delta_i = (\delta_{i,1,2}, \delta_{i,1,3})^T \sim \mathcal{N}(f(\text{dose}_i), \Sigma)$

     where $\Sigma = \begin{bmatrix} \tau^2 & \tau^2/2 \\ \tau^2/2 & \tau^2 \end{bmatrix}$

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Four statistical models for MBMA

3. Baseline + CB model (Dias and Ades, 2016)
   - $\mu_i \sim \mathcal{N}(\mu, \sigma^2)$ as in the Baseline model
   - $\delta_{i,k}$ is modelled as in the CB model

4. Arm-based (AB) model (Zhang et al., 2014)
   - $\text{logit}(\pi_{i,k}) = \delta_{i,k}$
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Remarks on the four models

1. Baseline model: Between-trial heterogeneity **only** in baseline risks μ_i

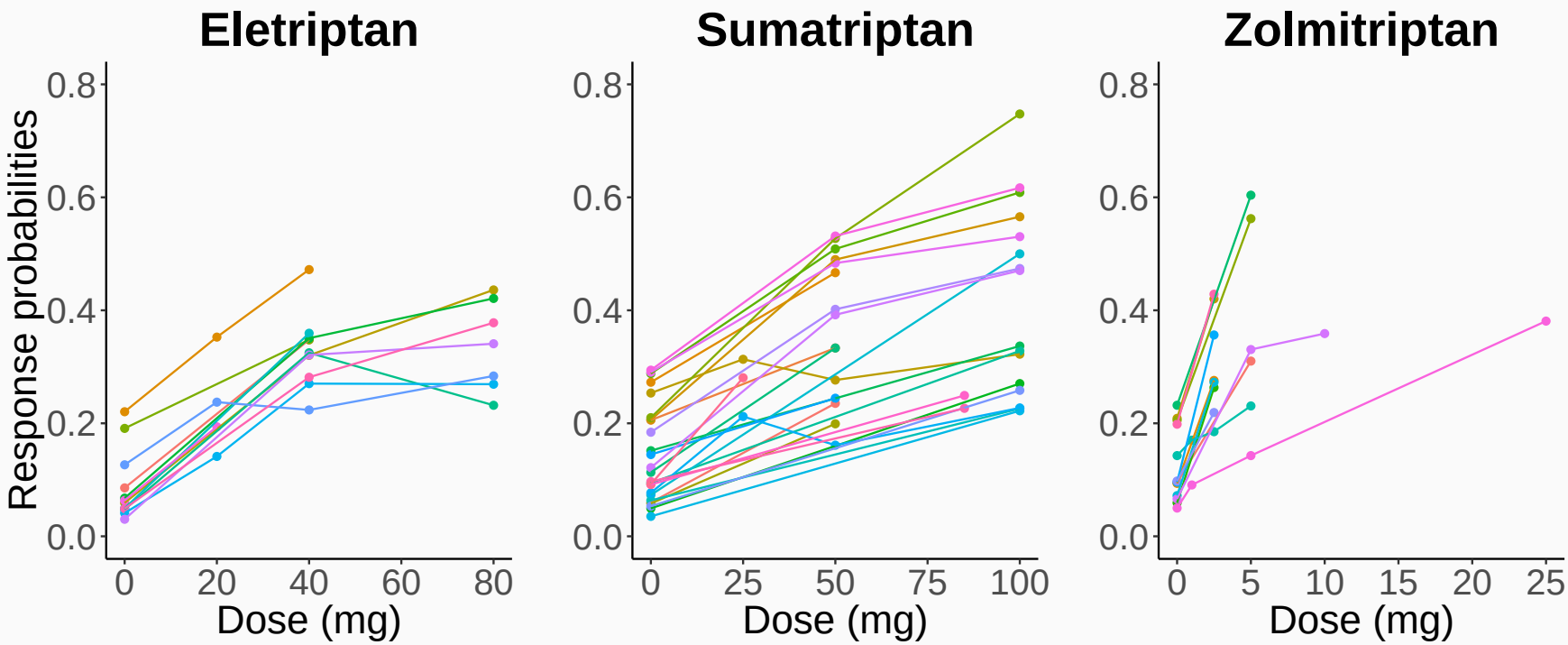
2. Contrast-based model: No **overall** baseline risk estimate

3. Baseline + CB model: Two **variance** parameters σ^2 and τ^2

4. Arm-based model: Modelling **absolute** effects (as opposed to relative effects)

Application

Considering 3 drugs for illustration



Priors and computations

- Same priors are used across 4 models
  - $\mathcal{N}(0, 10^2)$ for μ, E_{max} and ED_{50}
  - $\mathcal{HN}(2.5)$ for σ and τ.
- Computations are done using **Stan**.
- Using non-centered parametrization and Cholesky decomposition (Stan Development Team, 2019)

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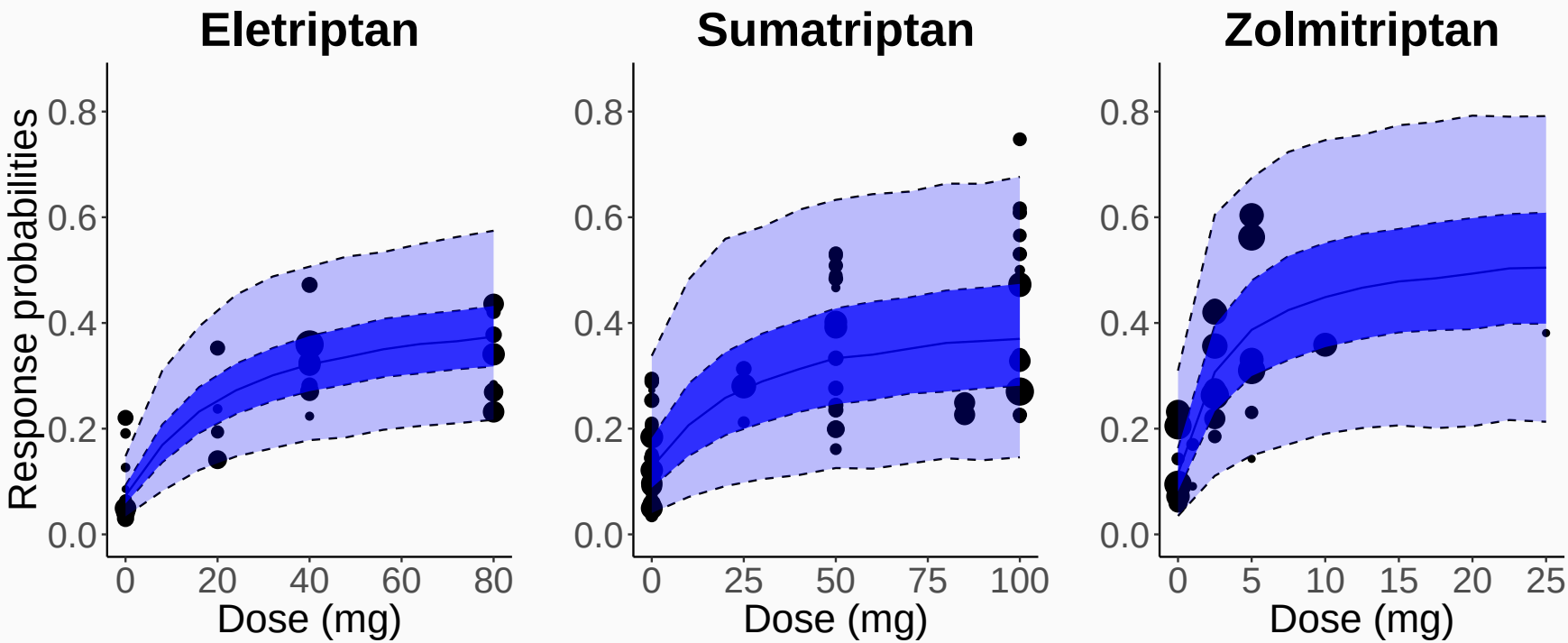
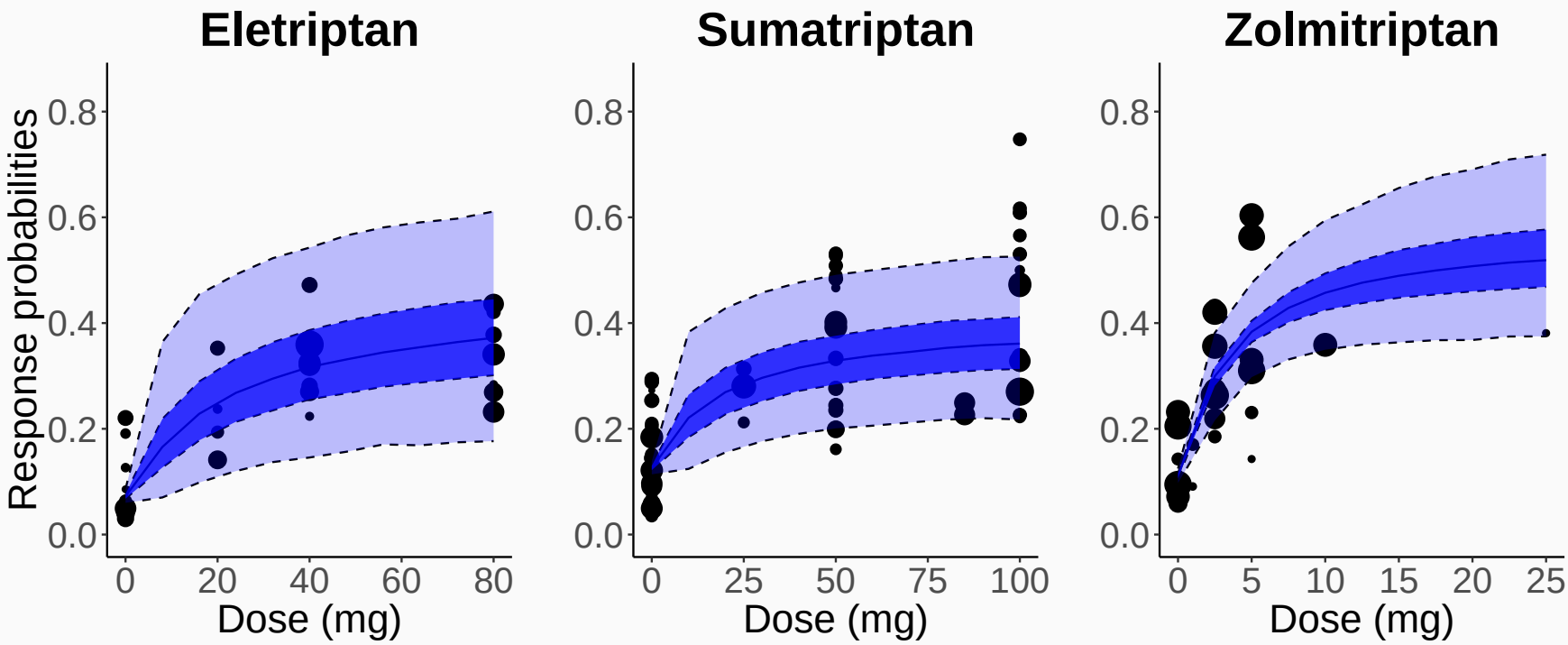
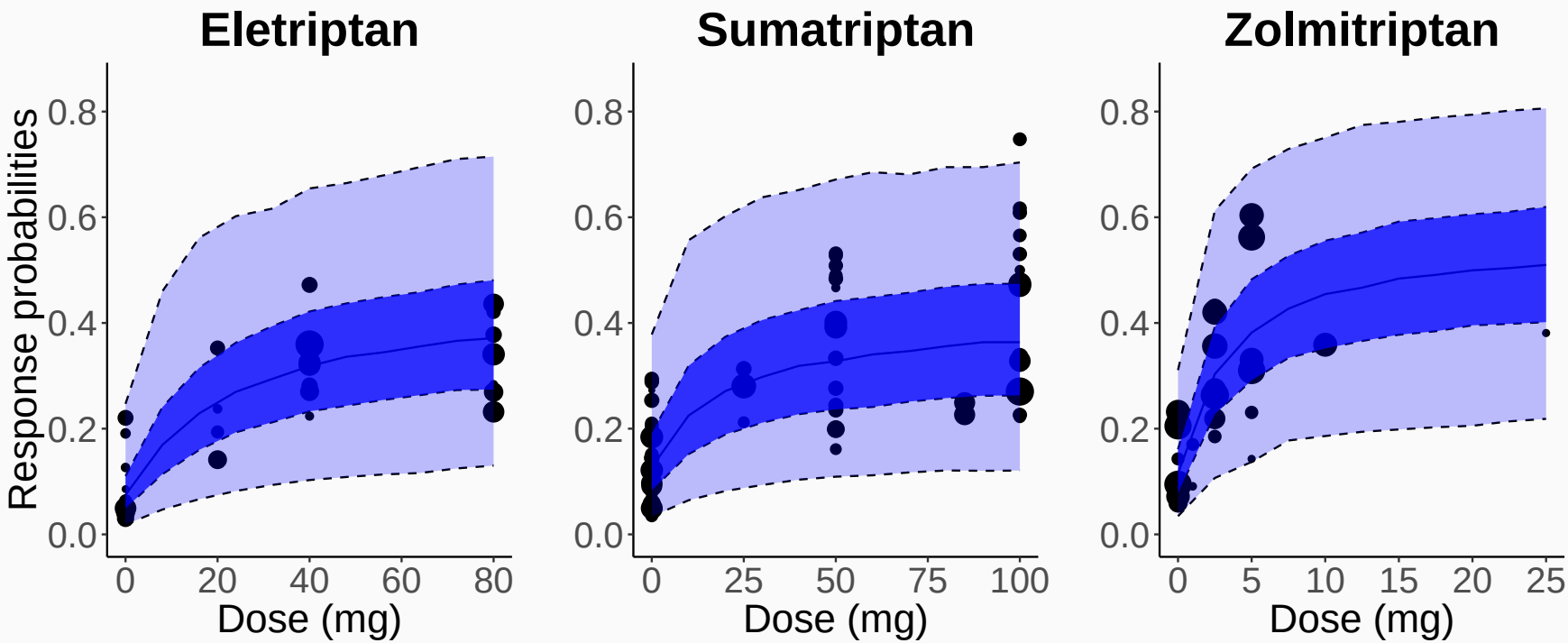
1) Baseline model



2) Contrast-based model



3) Baseline + Contrast-based model



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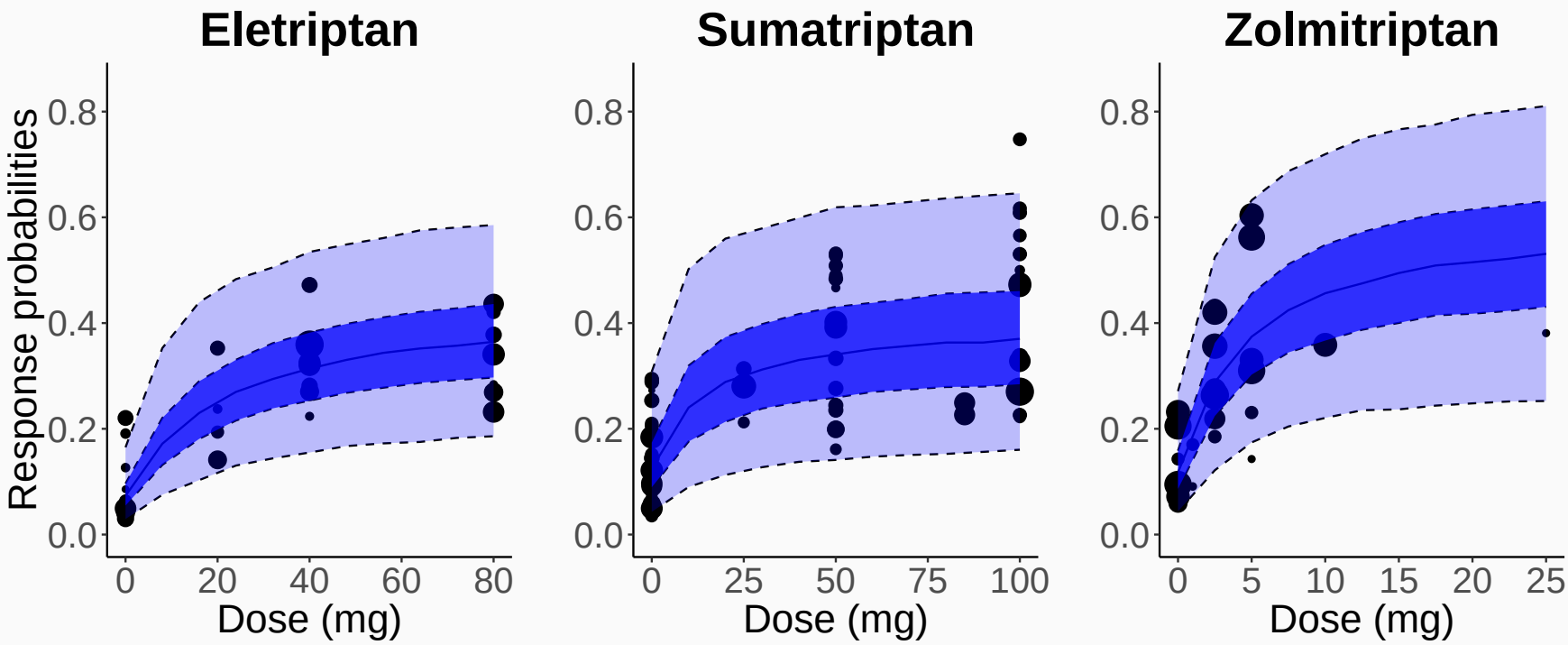

(Model-based) meta-analysis using Stan: MetaStan

Available on CRAN

Converting dataset to a one-arm-per-row format

```
create_MBMA_dat(data = data,
                armVars = c(dose = "d", responders = "r",
                            sampleSize = "n"),
                nArmsVar = "nd")
```

Fitting an arm-based model with E_{max} functional form

```
MBMA_stan(data = datMBMA,
          model = "AB_Emax",
          Emax_prior = c(0, 10),
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Conclusions

Discussion and conclusions

- Some parametrizations (e.g. AB and CB + Baseline models) might be more suitable for dose-response predictions in MBMA than others
- We also considered different functional forms $f(\text{dose}_{i,k})$ (e.g. log-linear and logistic) other than E_{max}.
    - 5 of 7 triptans: Bayesian model averaging puts all weights on E_{max} model
- Work in progress
    - Simulations to assess operating characteristics
    - Model-based **network** meta-analysis

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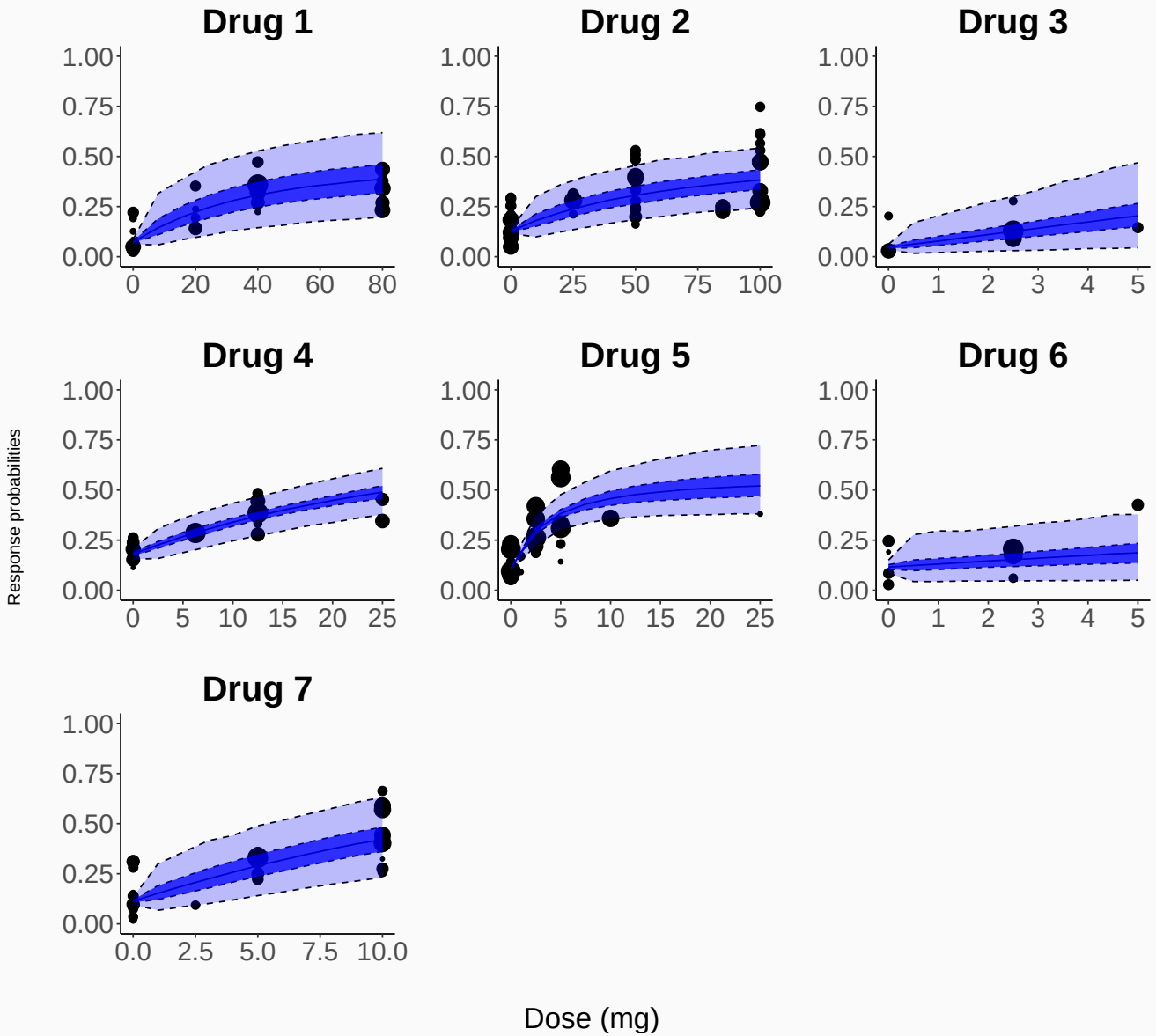

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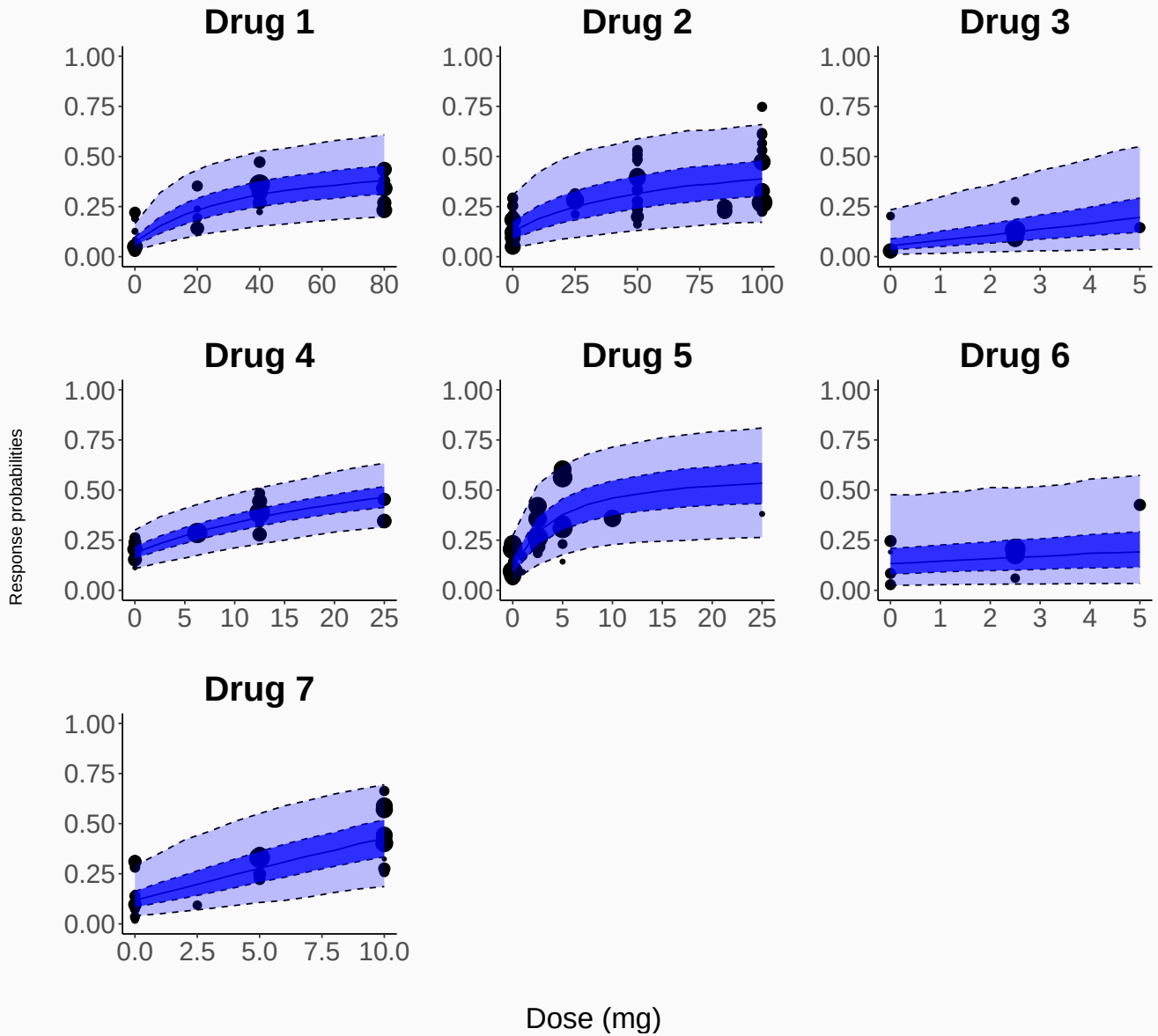

Parameter estimates (Zolmitriptan)

	μ	E_{max}	ED_{50}	σ	τ
Baseline	-2.05 (0.17)	2.24 (0.32)	2.07 (0.85)	0.54 (0.12)	-
CB	-2.08 (0.07)	2.43 (0.48)	2.54 (1.34)	-	0.12 (0.10)
Baseline + CB	-2.04 (0.17)	2.29 (0.39)	2.25 (1.06)	0.54 (0.12)	0.11 (0.08)
AB	-2.01 (0.16)	2.44 (0.60)	3.13 (1.92)	0.48 (0.08)	-

WAIC estimates

	Eletriptan	Sumatriptan	Zolmitriptan
Baseline	298.3 (30.5)	437.1 (23.7)	189.3 (8.2)
CB	229.1 (7.6)	402.3 (11.7)	190.4 (8.4)
Baseline + CB	238.3 (10.7)	407.7 (13.5)	189.7 (8.1)
AB	229.2 (8.3)	396.2 (8.4)	194.0 (7.9)

Bayesian model averaging

- Require the marginal likelihood
- The bridge sampling estimator (Gronau et al., 2018) using the **bridgesampling** R package
- Each model is weighted by its posterior probability