BRMS.MMRM: A MODERN R PACKAGE FOR BAYESIAN MMRMS

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Agenda

- Openstatsware team
- Bayesian MMRMs
- {brms.mmrm} package
- Future work

About

https://www.openstatsware.org/

ASA BIOP
European SIG in PSI
EFSPI

Formed in
August 2022

56 members from 35 organizations

(new ones welcome!)

Goals

Engineer selected R packages

Develop good software engineering practices

Collaborate with other R initiatives (e.g. R Consortium).

open stats ware

known for

mixed model for repeated measures

Frequentist MMRMs are ubiquitous.

Specifically tailored to pharma, strong agreement with SAS

Uses TMB for robustness and speed.

What about Bayesian MMRMs?

- Example: Chronic Pain Master Protocol ISA in chronic lower back pain:

What is the study measuring?

Primary Outcome Measures

Outcome Measure	Measure Description	Time Frame
Change From Baseline for Average Pain Intensity as Measured by the Numeric Rating Scale (NRS) at Week 4	The NRS was used to describe pain severity. Participants were asked to describe their average pain over the past 24 hours, on a scale of 0 to 10: 0 = no pain, and 10 = pain as bad as you can imagine. Posterior mean change from baseline, 95 percent (%) credible interval was derived using Bayesian mixed model repeated measures. Data presented are posterior mean with 95% credible interval.	Baseline, Week 4

From https://clinicaltrials.gov/study/NCT05086289

Applied Modelling in Drug Development

Applied Modelling in Drug Development

Flexible regression modelling in Stan via `brms`

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13.4.2 `brms` implementation

The code below shows how we specify a MMRM model in a very similar way to `SAS` and the `lme4` approach.

```
# Setup forward difference contrasts for changes between visits
contrasts(simulated_data$AVISIT) <- MASS::contr.sdif

mmrm_model1 <- bf(CHG ~ 1 + AVISIT + BASE + BASE:AVISIT + TRT01P +
                  autocor = ~unstr(time=AVISIT, gr=USUBJID),
                  sigma ~ 1 + AVISIT + TRT01P + AVISIT:TRT01P)
```

https://opensource.nibr.com/bamdd/src/02h_mmrm.html

Openstatsware Bayesian MMRM Subteam

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Goals

- ✓ Industry-wide standard implementation of Bayesian MMRMs.
- ✓ Modern backend tools.
- ✓ Easy to specify common types of MMRMs.
- ✓ Analyst-friendly workflow with easy post-processing.
- ❑ Historical borrowing through informative priors (ongoing).

New R package: {brms.mmrm}

{brms.mmrm}: friendly interface for MMRMs with {brms}

{brms}: Bayesian regression models with Stan

Stan: probabilistic programming language
for statistical modeling and computation.

Analyst-friendly workflow

1

Setup and pre-processing

brm_data()
brm_simulate_prior()

brm_archetype_cells()
brm_archetype_effects()
brm_archetype_average_cells()
brm_archetype_average_effects()
brm_archetype_successive_cells()
brm_archetype_successive_effects()

2

Modeling

brm_formula()
brm_formula_sigma()

brm_model()

3

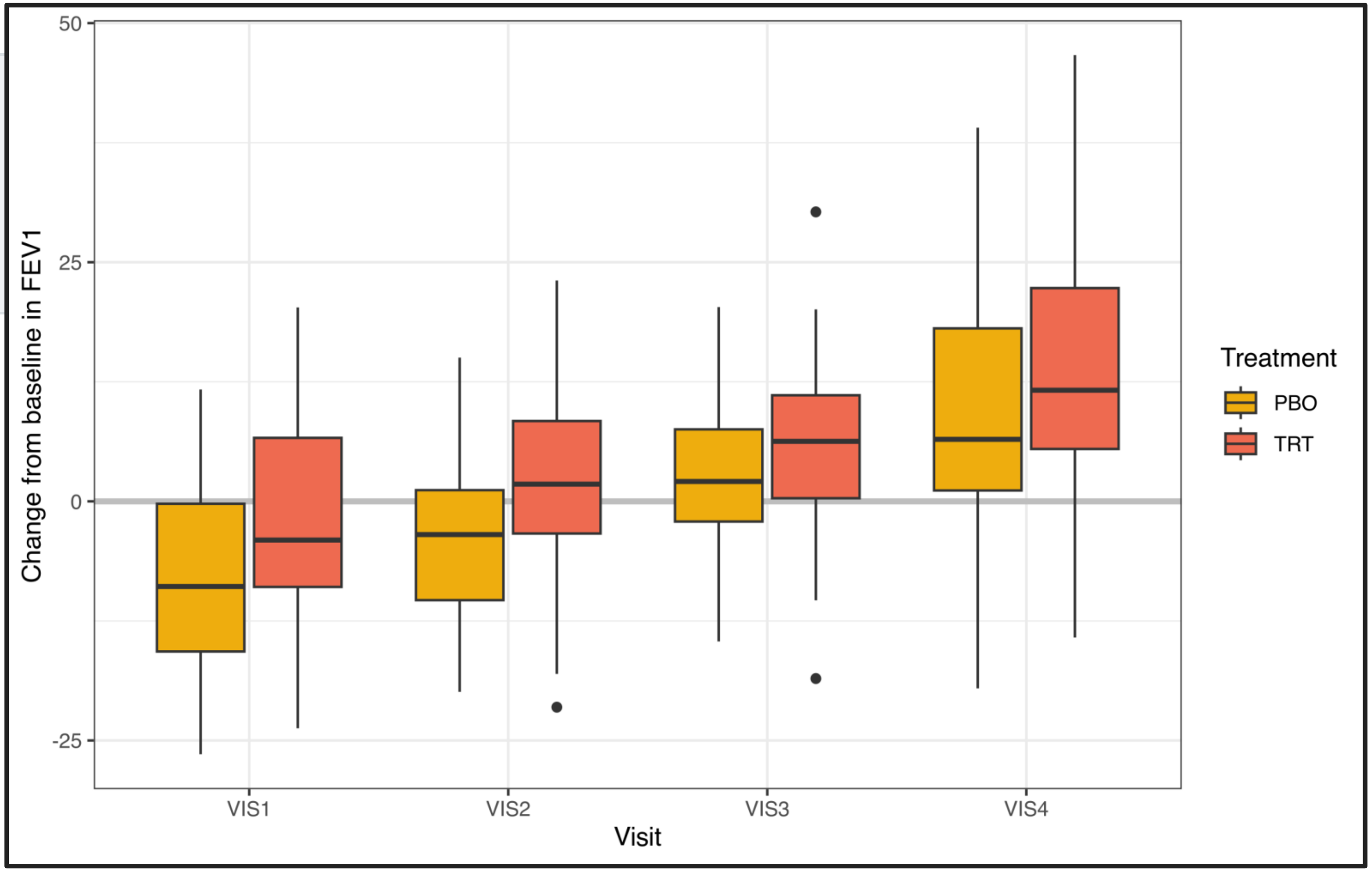
Post-processing, summaries, and visualization

brm_marginal_draws()
brm_marginal_summaries()
brm_marginal_probabilities()

brm_plot_compare()
brm_plot_draws()

Example pulmonology dataset

```r
data(fev_data, package = "mmrm")
raw_data <- fev_data %>%
  mutate(FEV1_CHG = FEV1 - FEV1_BL)
```



- Simulated clinical trial in chronic obstructive pulmonary disease (COPD).
- FEV1 = forced expired volume in one second.

Flexible model specification

```
brm_formula(data)
#> FEV1_CHG ~ FEV1_BL + FEV1_BL:AVISIT + ARMCD + ARMCD:AVISIT + AVISIT +
#>   RACE + WEIGHT + unstr(time = AVISIT, gr = USUBJID)
#> sigma ~ 0 + AVISIT

brm_formula(
  data,
  model_missing_outcomes = TRUE,
  group_time = FALSE,
  sigma = brm_formula_sigma(
    data,
    intercept = TRUE,
    group_time = TRUE
  )
)
#> FEV1_CHG | mi() ~ FEV1_BL + FEV1_BL:AVISIT + ARMCD + AVISIT +
#>   RACE + WEIGHT + unstr(time = AVISIT, gr = USUBJID)
#> sigma ~ ARMCD:AVISIT + AVISIT
```

Priors with {brms}

```r
library(brms)
prior <- c(
  set_prior("student_t(4, 0, 10)", class = "Intercept"),
  set_prior("cauchy(0, 5.2)", coef = "sigma")
)

prior[, c("prior", "class", "coef")]
#>                prior     class  coef    source
#>  student_t(4, 0, 10) Intercept        (unknown)
#>       cauchy(0, 5.2)         b sigma (unknown)
```

Fit the model

```r
fit <- brm_model(
  data = data,
  formula = formula,
  chains = 4,
  cores = 4,
  iter = 10000,
  warmup = 2000,
  refresh = 100
)
#> Compiling Stan program...
#> Start sampling
#> ...
```

***Stan automatically throws warnings when convergence diagnostics fail.

{brms} fitted model object

```
class(fit)
#> [1] "brms_mmrm_model" "brmsfit"

summary(fit)
#>  Family: gaussian
#>   Links: mu = identity; sigma = log
#> Formula: FEV1_CHG ~ FEV1_BL + FEV1_BL:AVISIT + ARMCD + ARMCD:AVISIT +
#>   AVISIT + RACE + WEIGHT + unstr(time = #> AVISIT, gr = USUBJID)
#>          sigma ~ 0 + AVISIT
#>    Data: modeled_data (Number of observations: 537)
#>   Draws: 4 chains, each with iter = 10000; warmup = 2000; thin = 1;
#>          total post-warmup draws = 32000
```

Inference on marginal means

```r
summaries_fit <- fit %>%
  brm_marginal_draws() %>%
  brm_marginal_summaries()

unique(summaries_fit$marginal)
#> [1] "difference_group" "effect"
#> [3] "response"         "sigma"
```

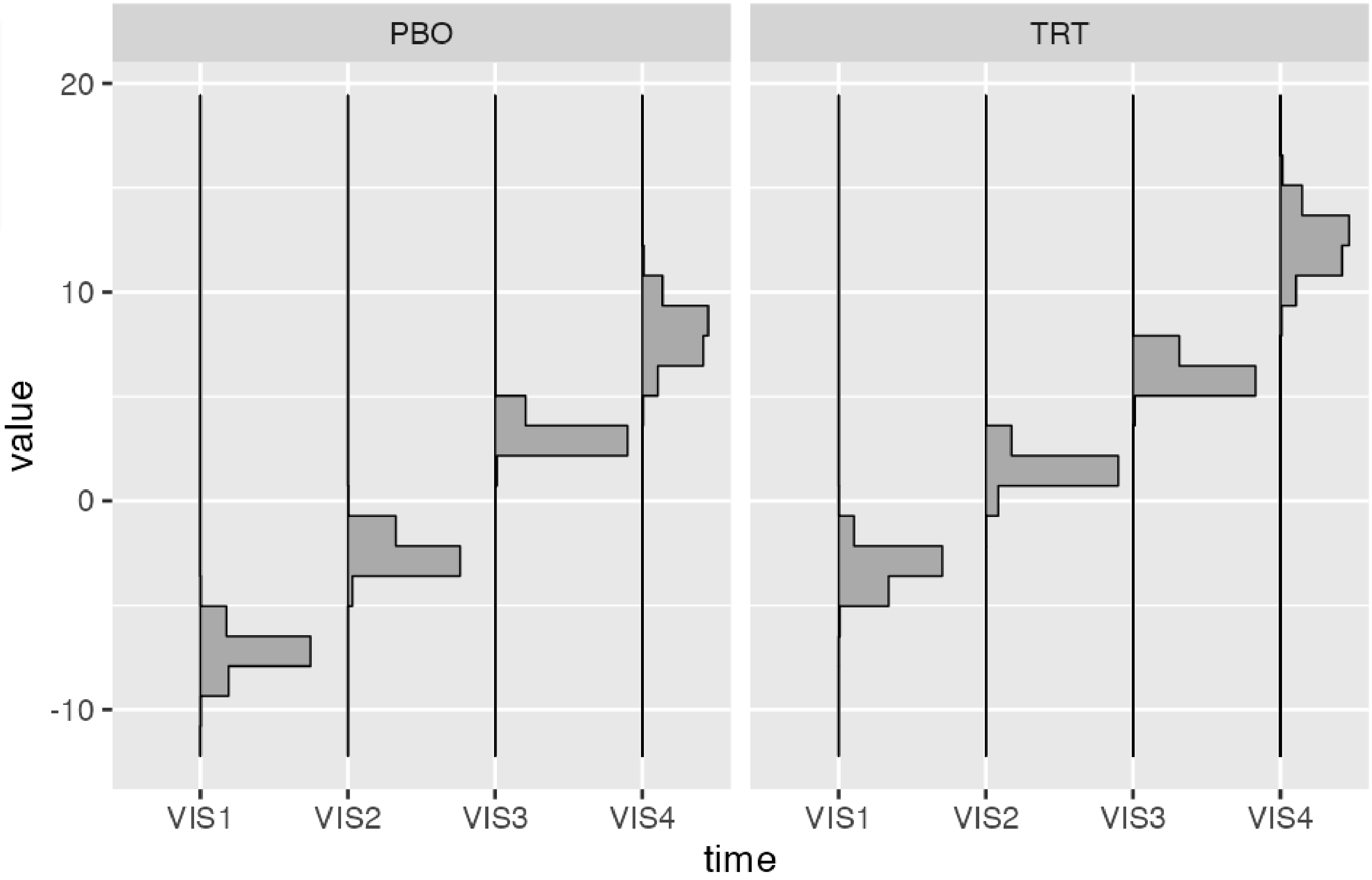
```r
summaries_fit
#> # A tibble: 120 × 6
#>    marginal         statistic group time  value    mcse
#>    <chr>            <chr>     <chr> <chr> <dbl>   <dbl>
#>  1 difference_group lower     TRT   VIS1   1.92 0.0202
#>  2 difference_group lower     TRT   VIS2   2.41 0.0136
#>  3 difference_group lower     TRT   VIS3   1.65 0.0105
#>  4 difference_group lower     TRT   VIS4   1.02 0.0260
#>  5 difference_group mean      TRT   VIS1   4.02 0.00734
#>  6 difference_group mean      TRT   VIS2   4.04 0.00397
#>  7 difference_group mean      TRT   VIS3   2.98 0.00342
#>  8 difference_group mean      TRT   VIS4   4.35 0.00778
#>  9 difference_group median    TRT   VIS1   4.02 0.00889
#> 10 difference_group median    TRT   VIS2   4.04 0.00508
```

See also
brm_marginal_probabilities():

$$P(\mathrm{TRT} - \mathrm{PBO} > x \mid \mathrm{data})$$

Visualize posterior samples

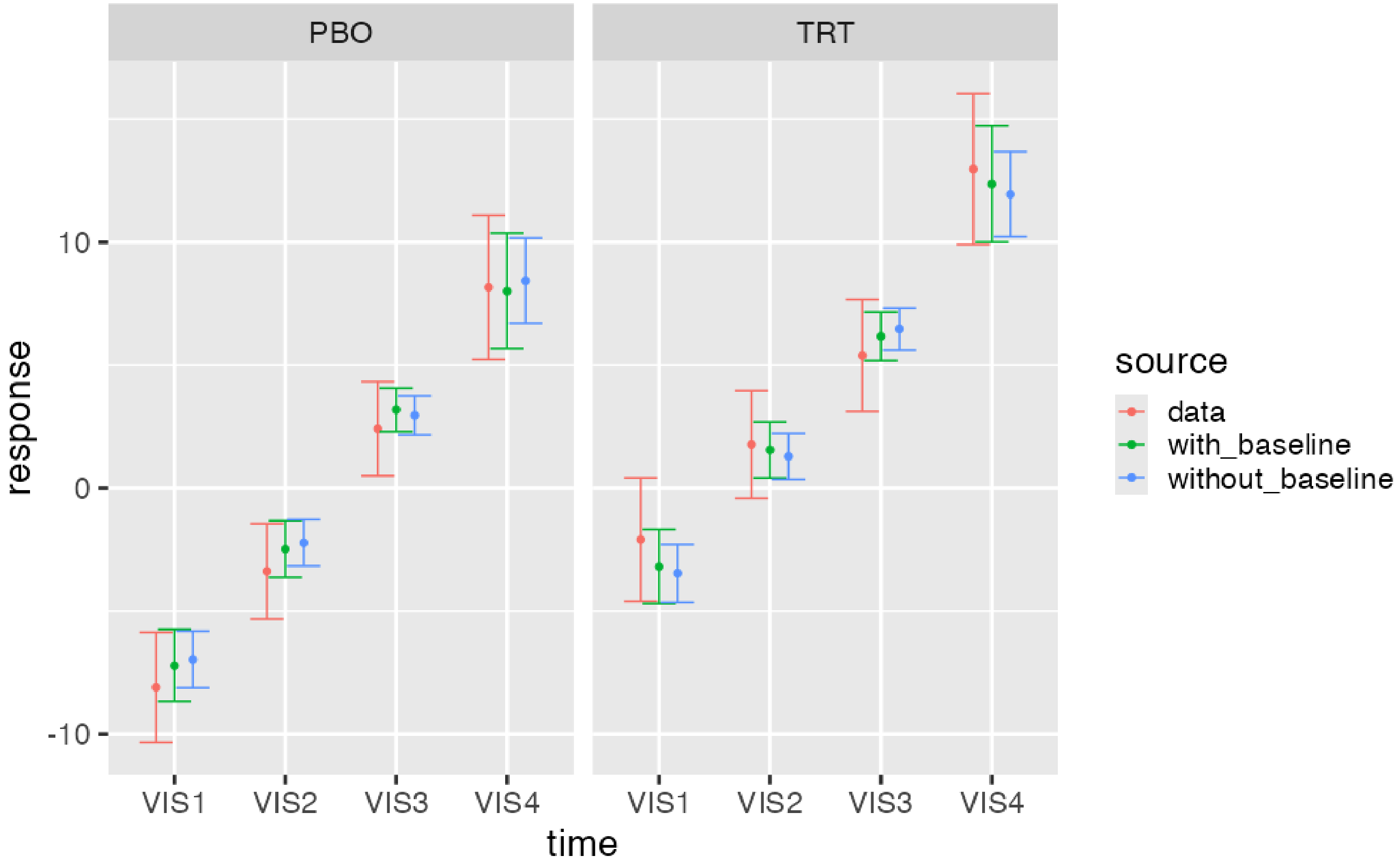
```r
library(ggplot2)
brm_plot_draws(draws$response) +
  theme_gray(20)
```



Lilly

Compare models and data

```r
brm_plot_compare(
  data = brm_marginal_data(data),
  with_baseline = summaries_fit,
  without_baseline = summaries_fit2
) +
  theme_gray(20)
```



Informative priors

Without {brms.mmrm} archetypes	**With {brms.mmrm} archetypes**
✗ Hard to interpret specific model coefficients.	✓ Transparent interpretation of fixed effects.
✗ Covariate adjustment risks implicitly conditioning on a strange reference level.	✓ Guardrails so priors have the intended effect on the model.
✗ Consistent interface for specifying priors.	✓ Consistent interface for specifying priors.

Informative priors

Without {brms.mmrm} archetypes

- ✗ Hard to interpret specific model coefficients.
- ✗ Covariate adjustment risks implicitly conditioning on a strange reference level.
- ✗ Consistent interface for specifying priors.

With {brms.mmrm} archetypes

- ✓ Transparent interpretation of fixed effects.
- ✓ Guardrails so priors have the intended effect on the model.
- ✓ Consistent interface for specifying priors.

Informative prior archetypes

```
archetype <- brm_archetype_successive_cells(data, baseline = FALSE)
```

```
archetype
#> # A tibble: 800 × 20
#>    x_PBO_VIS1 x_PBO_VIS2 x_PBO_VIS3 x_PBO_VIS4 x_TRT_VIS1
#>  *      <dbl>      <dbl>      <dbl>      <dbl>      <dbl>
#>  1          1          0          0          0          0
#>  2          1          1          0          0          0
#>  3          1          1          1          0          0
#>  4          1          1          1          1          0
#>  5          1          0          0          0          0
#>  6          1          1          0          0          0
```

... ...

Transparent interpretation

```
summary(archetype)
#> # This is the "successive cells" informative prior archetype in brms.mmrm.
#> # The following equations show the relationships between the
#> # marginal means (left-hand side) and fixed effect parameters
#> # (right-hand side).
#> #
#> #    PBO:VIS1 = x_PBO_VIS1
#> #    PBO:VIS2 = x_PBO_VIS1 + x_PBO_VIS2
#> #    PBO:VIS3 = x_PBO_VIS1 + x_PBO_VIS2 + x_PBO_VIS3
#> #    PBO:VIS4 = x_PBO_VIS1 + x_PBO_VIS2 + x_PBO_VIS3 + x_PBO_VIS4
#> #    TRT:VIS1 = x_TRT_VIS1
#> #    TRT:VIS2 = x_TRT_VIS1 + x_TRT_VIS2
#> #    TRT:VIS3 = x_TRT_VIS1 + x_TRT_VIS2 + x_TRT_VIS3
#> #    TRT:VIS4 = x_TRT_VIS1 + x_TRT_VIS2 + x_TRT_VIS3 + x_TRT_VIS4
```

Labels for specification

```
label
#> # A tibble: 8 × 3
#>   code                         group time
#>   <chr>                        <chr> <chr>
#> 1 student_t(4, -7.57, 4.96) PBO   VIS1
#> 2 student_t(4,  3.14, 7.86) PBO   VIS2
#> 3 student_t(4,  8.78, 8.18) PBO   VIS3
#> 4 student_t(4,  3.36, 8.10) PBO   VIS4
#> 5 student_t(4, -2.96, 4.78) TRT   VIS1
#> 6 student_t(4,  3.13, 7.64) TRT   VIS2
#> 7 student_t(4,  7.65, 8.24) TRT   VIS3
#> 8 student_t(4,  4.64, 8.21) TRT   VIS4
```

Returns a valid brms prior for the important fixed effects.

```
prior <- brm_prior_archetype(label = label, archetype = archetype)
```

Everything downstream is the same

```
formula <- brm_formula(archetype)
formula
#> FEV1 ~ 0 + x_PBO_VIS1 + x_PBO_VIS2 + x_PBO_VIS3 + x_PBO_VIS4 +
#>   x_TRT_VIS1 + x_TRT_VIS2 + x_TRT_VIS3 + x_TRT_VIS4 +
#>   nuisance_WEIGHT + nuisance_SEX_Male +
#>   unstr(time = AVISIT, gr = USUBJID)
#> sigma ~ 0 + AVISIT
```

```
model <- brm_model(
  data = archetype,
  formula = formula,
  prior = prior,
  refresh = 0
)
#> Compiling Stan program...
#> Start sampling
```

```
draws <- brm_marginal_draws(
  data = archetype,
  formula = formula,
  model = model
)
summaries_model <- brm_marginal_summaries(draws)
summaries_data <- brm_marginal_data(archetype)
brm_plot_compare(model = summaries_model, data = summaries_data)
```

Future and ongoing work

- Multiple historical data sources (e.g. computationally efficient meta-analytic predictive priors).
- Data sources with misaligned time points.
- Borrowing from a subset of time points.
- Quantification of prior effective sample size.

Thanks

- Openstatsware
- Bayesian MMRM Subteam
- BAYES 2024

Sources

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Appendix: Bayesian MMRM definition

Bayesian MMRM definition

Repeated measures of each patient y_n:

Legend

Data

Parameters

$$y_n = \begin{bmatrix} y_{n1} \\ \vdots \\ y_{nT} \end{bmatrix}$$

Bayesian MMRM definition

Legend

Data

Parameters

Independent multivariate normal patients n = 1, ..., N:

$$y_n \overset{\text{ind}}{\sim} \text{MVN}\left(X_n b,\ \Sigma_n\right)$$

Bayesian MMRM definition

Legend

Data

Parameters

Separately model variances and correlations:

$$\Sigma_n = \begin{bmatrix} \sigma_{n1} & & \\ & \ddots & \\ & & \sigma_{nT} \end{bmatrix} \cdot \Lambda \cdot \begin{bmatrix} \sigma_{n1} & & \\ & \ddots & \\ & & \sigma_{nT} \end{bmatrix}$$

Bayesian MMRM definition

Legend

Data

Parameters

Distributional regression for standard deviations:

$$\sigma_n = \exp\left(Z_n b_\sigma\right)$$

sigma ~ AVISIT*TRT01P + AGE + ...

Bayesian MMRM definition

Legend

Data

Parameters

Priors for parameters:

$$b \sim F()$$

$$b_\sigma \sim G()$$

Usually independent normals and Student t's

$$\Lambda \sim H()$$

Usually unstructured: $\mathrm{LKJ}\left(\mathrm{shape} = \eta\right)$