

Bayesian modeling workflow for pharmacometric applications using bbr.bayes with Stan/Torsten

Bill Gillespie
Stan Con 2023
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What “problems” are we trying to solve?

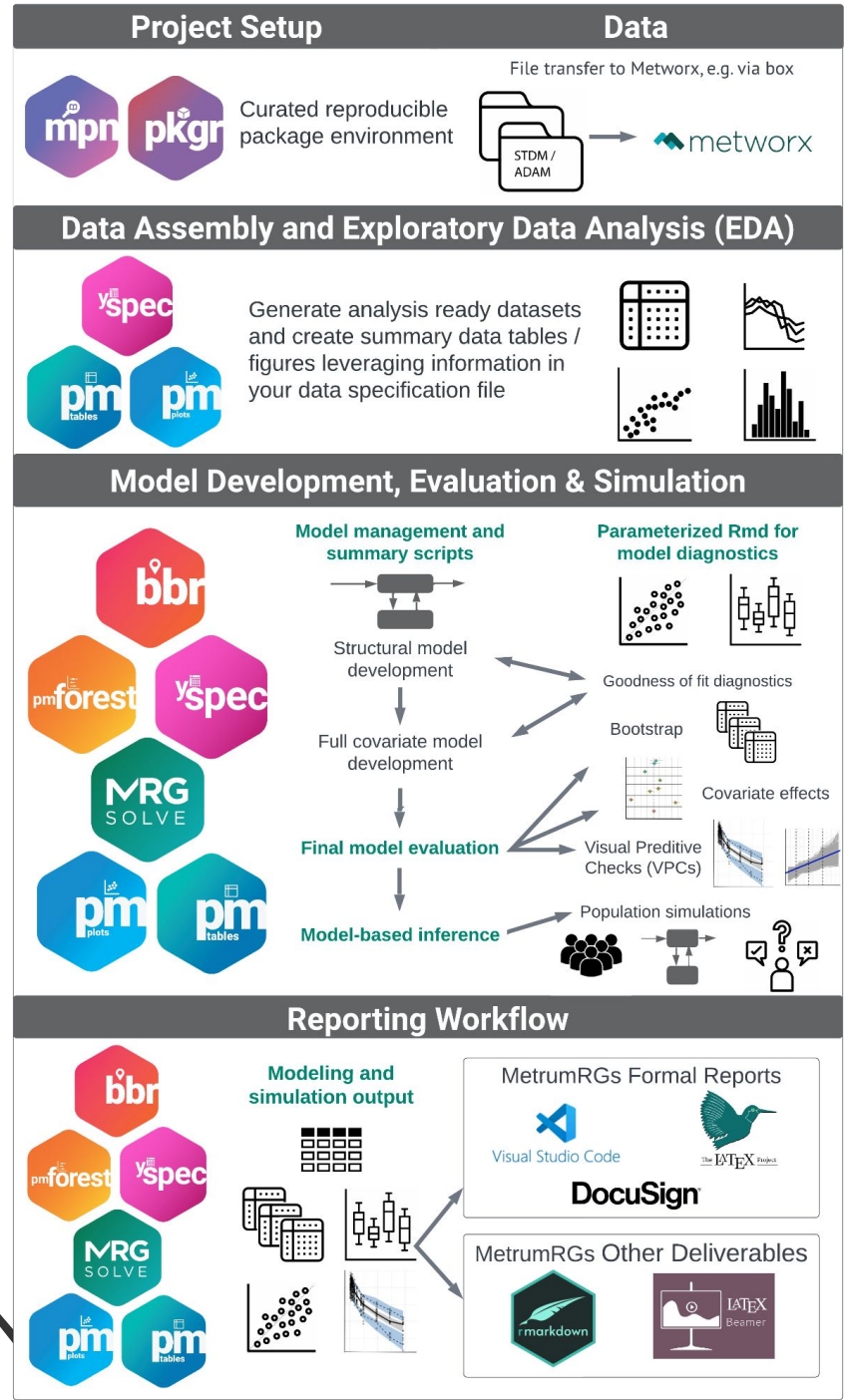
- Inconsistent implementation of Bayesian workflows or incomplete retention of key information may lead to non-reproducibility—a serious problem in a highly regulated industry.
- Heterogeneous workflows and coding practices make QC more difficult and time-consuming.
- Summarizing and comparing multiple models in a workflow is often a relatively slow manual process.

Our approach: the R package bbr.bayes

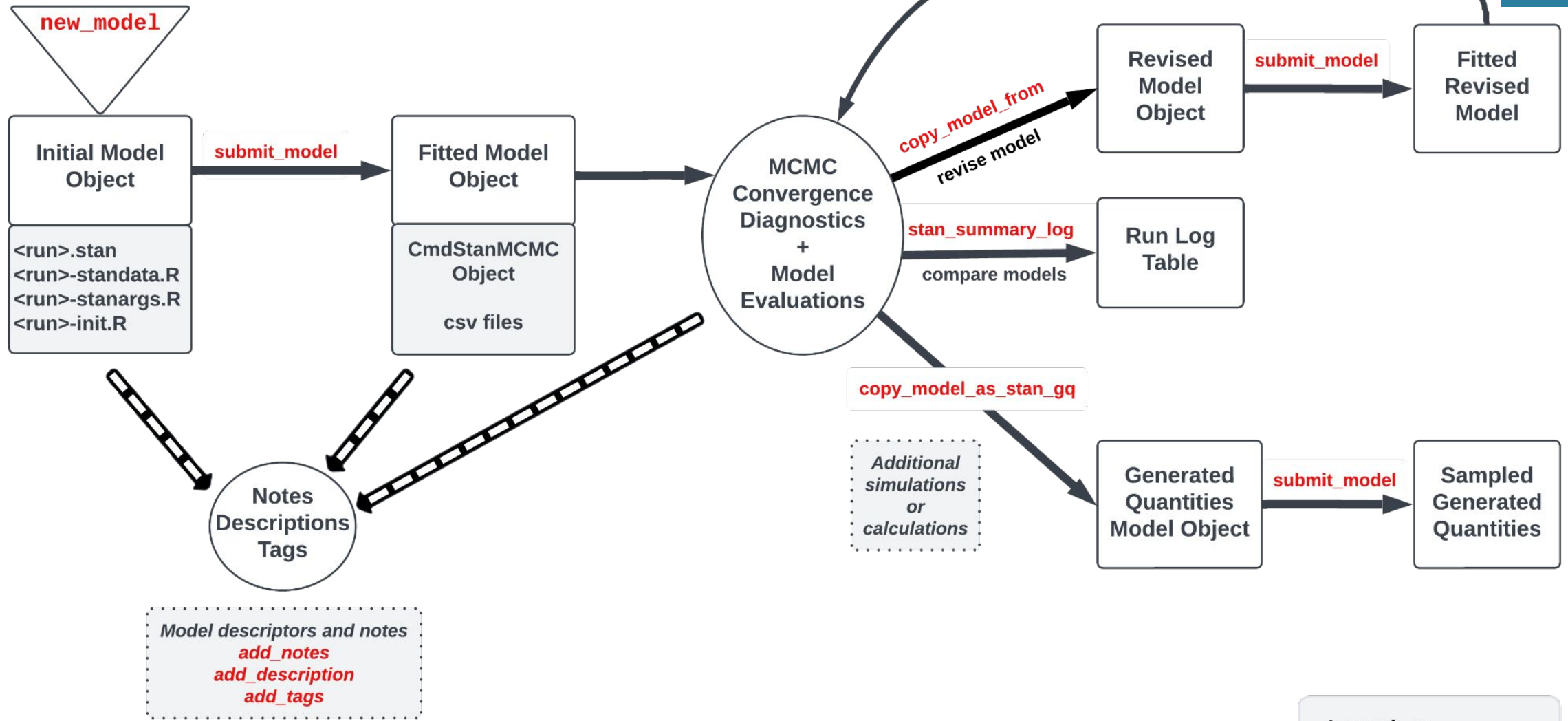
- <https://github.com/metrumresearchgroup/bbr.bayes>
- Integrates with bbr, a package for managing data analyses using NONMEM.
- All elements needed for tracing and reproducing a data analysis are retained in a consistent structure.
- Functions are provided for summarizing and comparing multiple models within a project.

bbr.bayes extends our collection of open source tools for pharmacometric applications, a.k.a., the MetrumRG Ecosystem (MeERGE)

Confidential

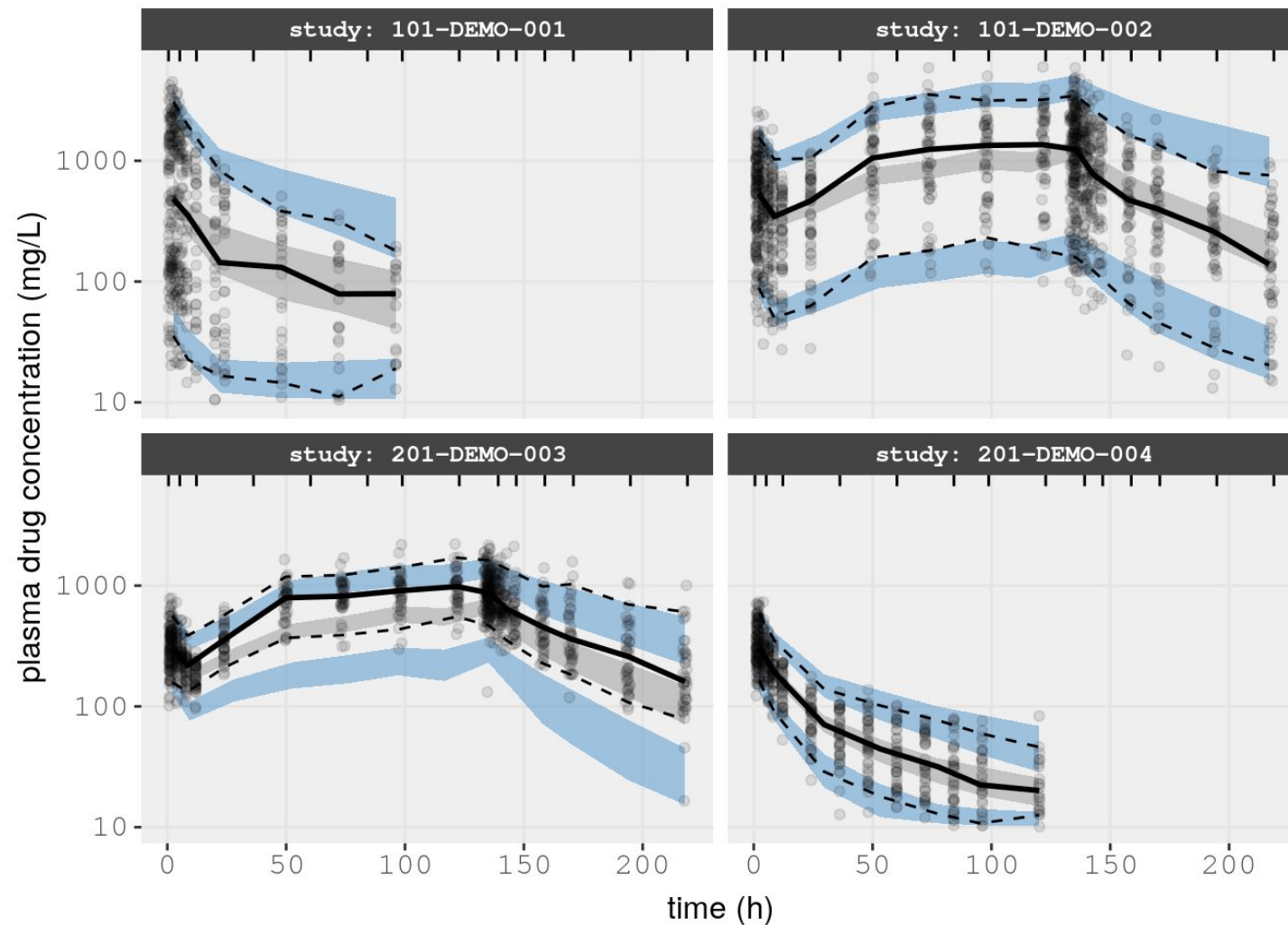


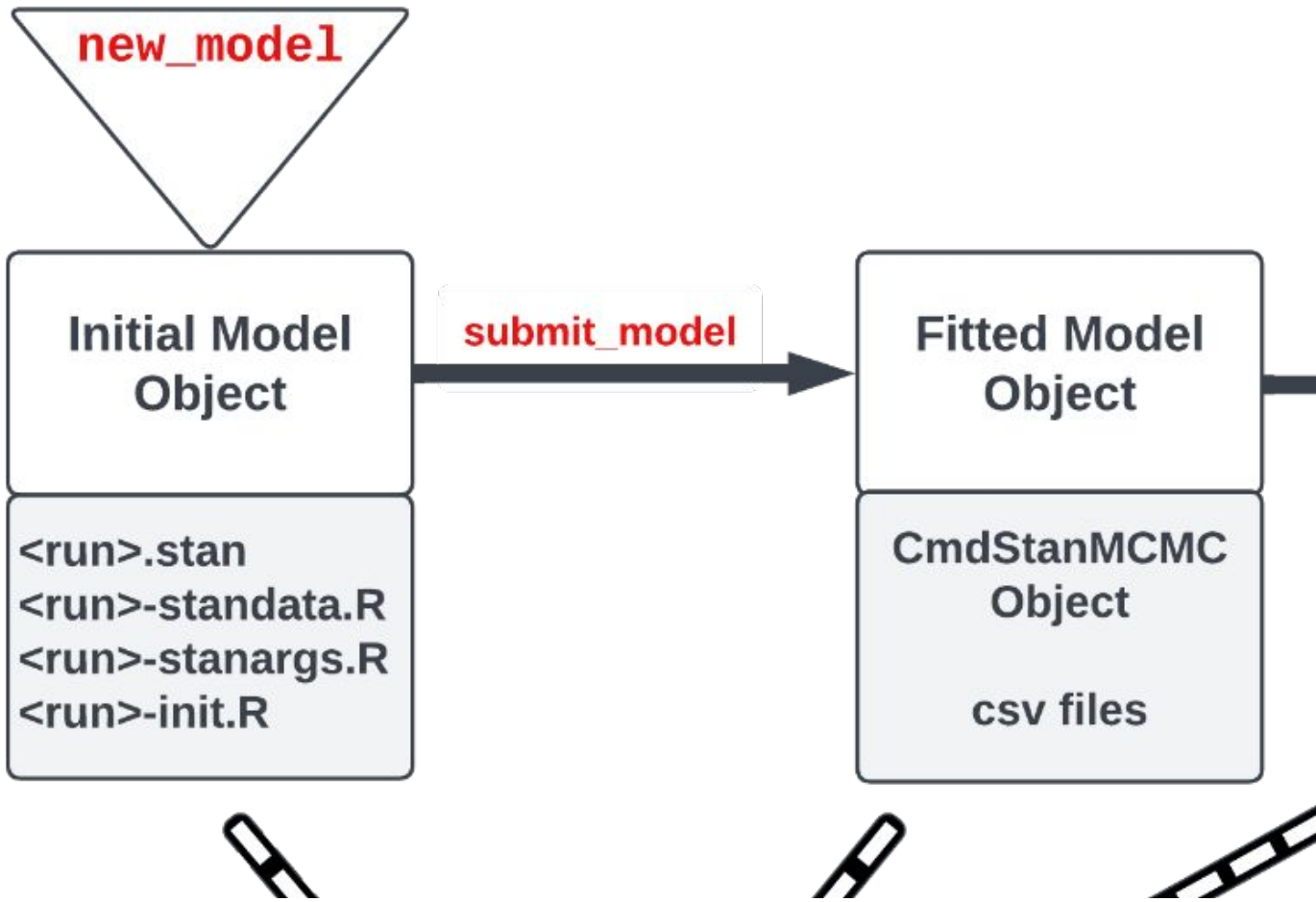
Bayesian workflow using bbr.bayes



A typical population pharmacokinetic analysis

- Longitudinal plasma drug concentration data from 4 studies
- 160 individuals
- Nonlinear hierarchical model with inter-individual variability in several parameters





● **new_model**

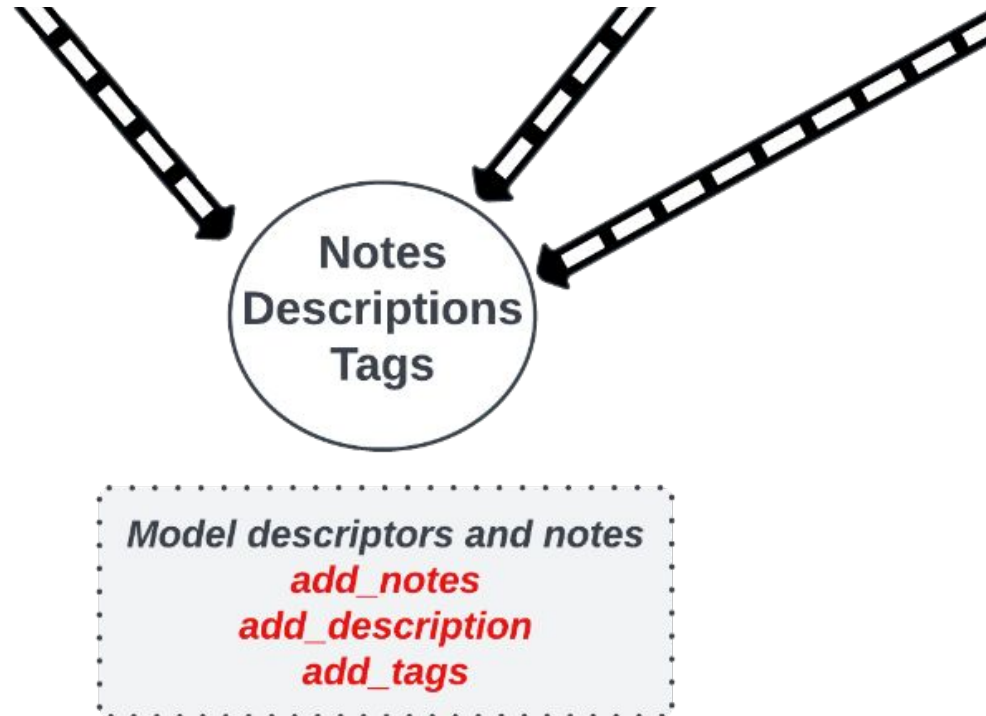
- Create a `bbr.bayes` model object
- Initialize a file structure containing a model, data, initial estimates & `cmdstanr` arguments

● **submit_model**

- Compile & run model
- Interface a `bbr.bayes` model object with `cmdstanr`

- Model objects may be annotated

- **add_description**
- **add_tags**
- **add_notes**




```
ppkexpo1 <- new_model(here(modelDir, "ppkexpo1"),  
  .model_type = "stan", .overwrite = TRUE) %>%  
  add_description("Base popPK model") %>%  
  add_tags(with(TAGS, c(two_cpt_abs,  
    CP,  
    logCL_normalIIV,  
    logQ_normalIIV,  
    logV2_normalIIV,  
    logV3_normalIIV,  
    logka_normalIIV,  
    lognormal_ruv)))
```

Files | Plots | Packages | Help | Viewer

New Folder | New Blank File | Upload | Delete | Rename | More

/ > data > bbr-stan > ex3-bbr2 > model > stan > ppkexpo1

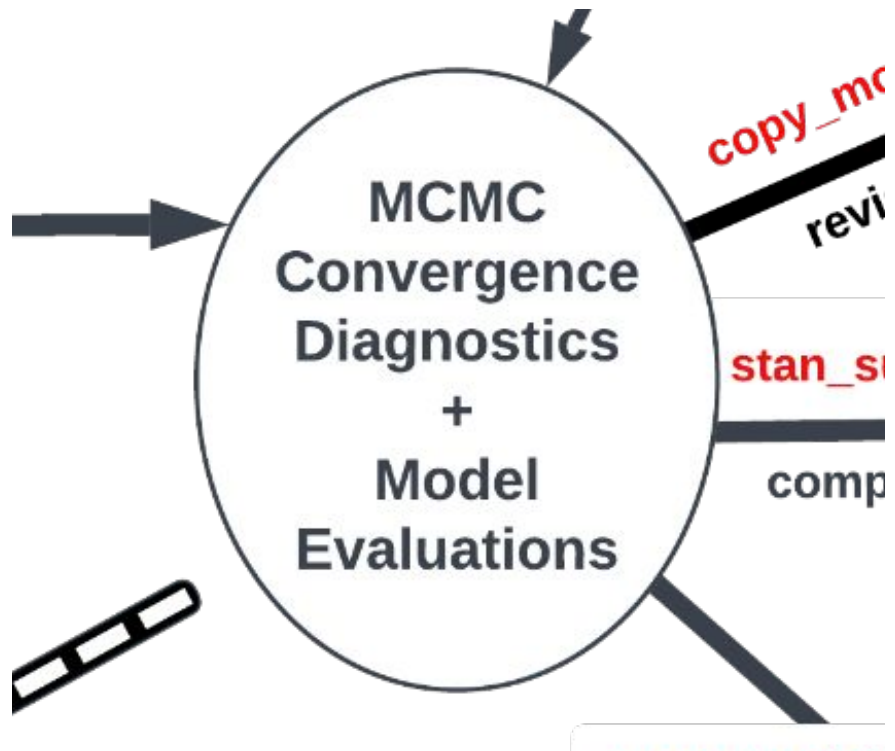
Name

- ..
- ppkexpo1-init.R
- ppkexpo1-stanargs.R
- ppkexpo1-standata.R
- ppkexpo1.stan

model-management-demo.Rmd | ppkexpo1.yaml | ppkexpo1.R

```
1 model_type: stan
2 description: Base popPK model
3 tags:
4 - linear two compartment + first-order absorption
5 - centered parameterization
6 - log(CL) ~ normal IIV
7 - log(Q) ~ normal IIV
8 - log(V2) ~ normal IIV
9 - log(V3) ~ normal IIV
10 - log(ka) ~ normal IIV
11 - lognormal RUV
12
```

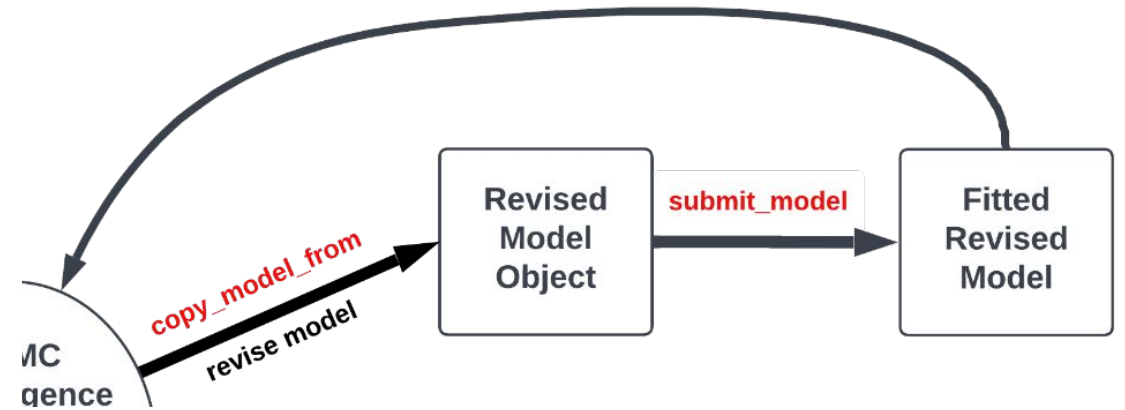
```
ppkexpol <- ppkexpol %>%  
  set_stanargs(list(iter_warmup = 250,  
                    iter_sampling = 250,  
                    thin = 1,  
                    chains = 4,  
                    parallel_chains = 4,  
                    seed = 1234,  
                    save_warmup = FALSE),  
              .clear = TRUE)  
ppkexpol_fit <- ppkexpol %>%  
  submit_model(.overwrite = TRUE)
```



- bbr.bayes does not currently have functions for MCMC & model fitting diagnostics.
- We rely on other tools, e.g., cmdstanr, posterior, bayesplot, tidybayes & tidyvpc.

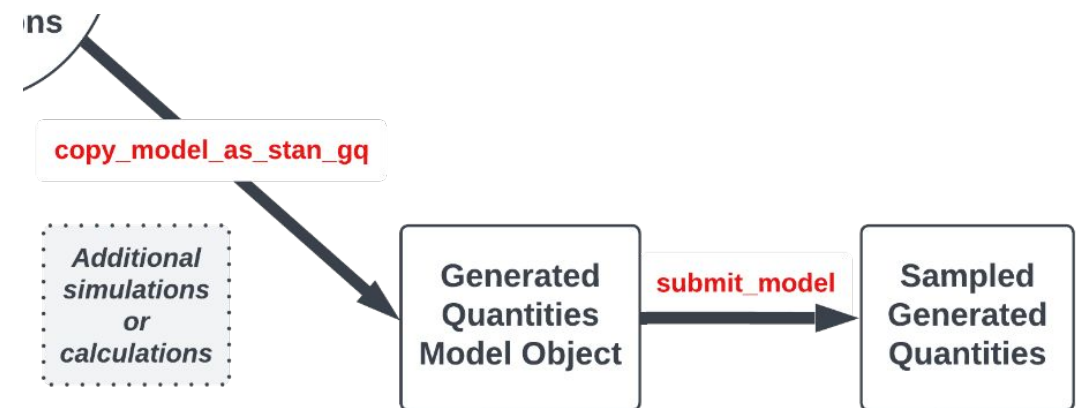
- **copy_model_from**

- Copy a previous model & metadata
- Facilitates iterative model development



- **copy_model_as_stan_gq**

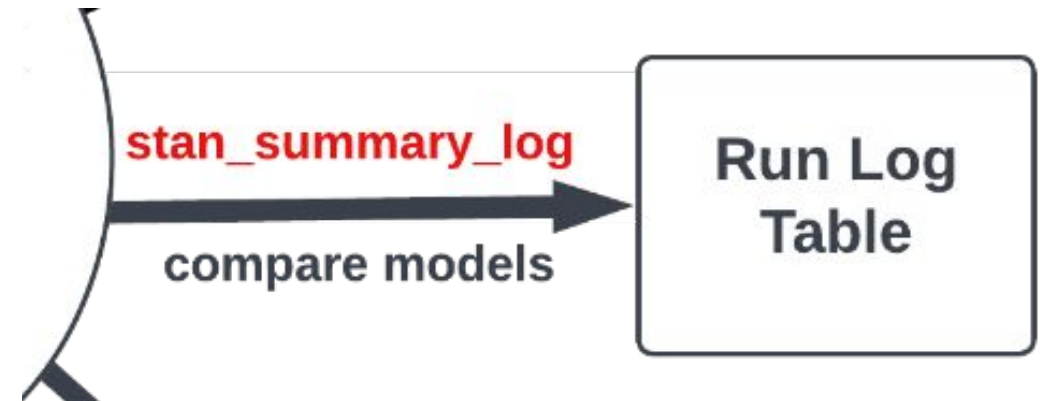
- Copy a previous model, metadata & sampled parameters
- For simulations using `cmdstanr` `$generate_quantities`



- **run_log**

- **stan_summary_log**

- Summarize & compare models
- May include:
 - description, tags, notes
 - model parameter summaries
 - MCMC diagnostics
 - Model fitting diagnostics, e.g., elpd



```
model_log <- run_log(modelDir) %>%  
  stan_add_summary(variables = "lp__",  
                   summary_fns = list("median")) %>%  
  add_tags_diff()  
model_log %>%  
  select(run, based_on, description, tags_added,  
         tags_removed, lp___median) %>%  
  mutate(lp___median = signif(lp___median, 4)) %>%  
  knitr::kable() %>%  
  kable_styling()
```


run	based_on	description	tags_added	tags_removed	lp__median
ppkexpo1	NULL	Base popPK model	linear two compartment + first-order absorption, centered parameterization , log(CL) ~ normal IIV , log(Q) ~ normal IIV , log(V2) ~ normal IIV , log(V3) ~ normal IIV , log(ka) ~ normal IIV , lognormal RUV		1206
ppkexpo2	ppkexpo1	Base popPK model with non-centered parameterization	non-centered parameterization	centered parameterization	-30.18
ppkexpo3	ppkexpo2	PopPK model: ppkexpo2 + allometric scaling	fixed allometric scaling		-32.19
ppkexpo4	ppkexpo3	PopPK model: ppkexpo3 + allometric scaling & effects of EGFR, age, and albumin in CL	EGFR on CL , age on CL , albumin on CL		-33.61

```
sum_log <- stan_summary_log(modelDir) %>%  
  filter(method == "sample") %>%  
  mutate(elpd = map(fit,  
    ~.$loo(variable='log_lik')$elpd))  
  
sum_log %>%  
  select(run, iter_warmup, iter_sampling,  
    num_divergent, bad_ebfmi, elpd) %>%  
  mutate(elpd = signif(elpd, 5)) %>%  
  knitr::kable() %>%  
  kable_styling()
```

run	iter_warmup	iter_sampling	num_divergent	bad_ebfmi	elpd
ppkexpo1	250	250	9	TRUE	-18217
ppkexpo2	250	250	0	FALSE	-18213
ppkexpo3	250	250	0	FALSE	-18193
ppkexpo4	250	250	0	FALSE	-18186

Preview of coming attractions

- Support for NONMEM Bayesian analysis
- Online “expos” illustrating workflows using `bbr.bayes`
 - Bayesian exposure-response modeling using Stan
 - Bayesian popPK using NONMEM
 - Bayesian popPK using Stan/Torsten
- Extend `copy_model_from()` to import models and metadata from external GitHub model libraries

About the MeRGE Expo

An example population exposure-response analysis using a MetrumRG Ecosystem (MeRGE) Bayesian workflow.

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[About the MeRGE Expo](#)

About >

About the Github Repo

About Metworx

Tools >

The Expo demonstrates example of using `bbr.bayes` in a typical Bayesian exposure-response modeling and simulation (M&S) workflow, including model fitting, model evaluation and model summarization, using the same process and suite of tools that we use at Metrum Research Group, to ensure traceable and reproducible pharmacometrics research. This Expo is not meant to be a complete vignette on using all of the features of `bbr.bayes` or the other tools used in the workflow. Links to additional information about each of the tools can be found in the Tools section of the Expo.



Credit where it is due

Design & implementation

- Seth Green
- Kyle Meyer

Design, advice & testing

- Jonathan French
- Tim Waterhouse