Democratizing Bayesian joint models in clinical drug development: From premise to daily practice in oncology

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Part I: Context

Motivation

- We want to inform the probability of success (PoS) in Phase 3 *via* extrapolation from Phase 1b/2 and historical or real-world data
- PoS is based on assurance of successful Phase 3
- To calculation the *assurance*, we need access to the assumed distribution of true effect *via* the posterior predictive distribution of the quantity of interest (e.g. HR)

Framework

Two-stage adaptive Phase 2 trial with interim analysis (I) testing monotherapy (A) vs. combination (A+B), leveraging data from an intermediate endpoint (M) and a clinical outcome (Y), from both current and historical/RWD.

		Interim (I)		Final (F)	
Source	Group	M	Y	M	Y
Current	A+B	$M_{I,A+B}$	$Y_{I,A+B}$	$M_{F,A+B}$	$Y_{F,A+B}$
	A	$M_{I,A}$	$Y_{I,A}$	$M_{F,A}$	$Y_{F,A}$
Historical/RWD	Ah	$M_{I,Ah}$	$Y_{I,Ah}$	$M_{F,Ah}$	$Y_{F,Ah}$
				Auxiliary	Quantity to predict

Joint model to leverage rich M data

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Joint model

Auxiliary

Quantity to predict

Borrowing to leverage rich historical/real-world data

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Borrowing

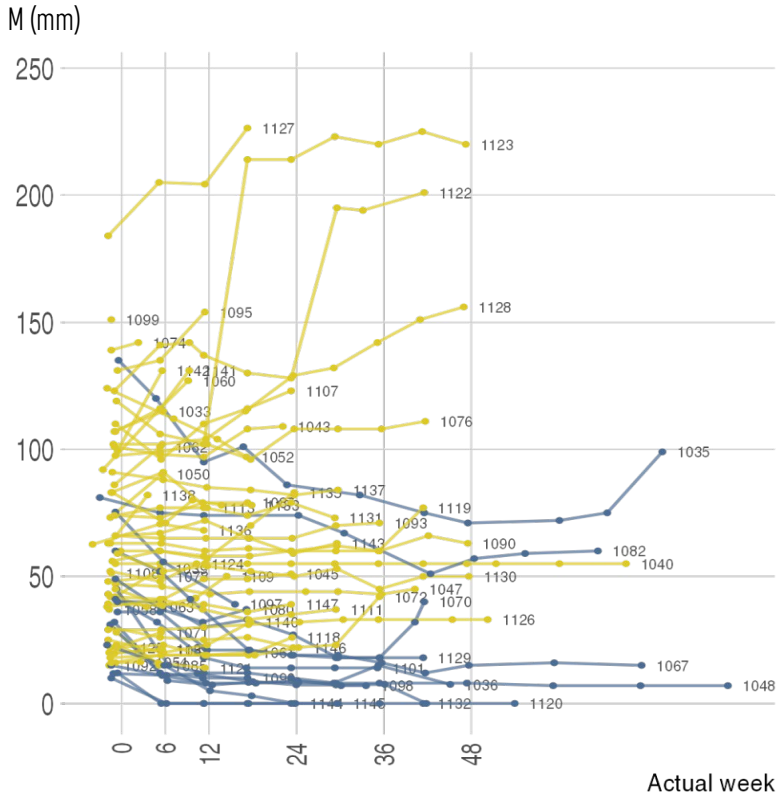
Auxiliary

Quantity to predict

Intermediate endpoint

M = Sum of Lesion Diameters

- Standardized in solid tumor indications (RECIST1.1)
- Measured repeatedly over time, at regular intervals
- Multiple advantages compared to BOR (longitudinal, continuous, etc)



Part II: Estimators

Tumor growth inhibition

1. Left untreated, a tumor is growing

2. Tumor shrinkage results from therapeutic interventions.

    ↪ Merino *et al.* 2023 *JCO* (FDA CDER and OCE): "ORR is unique because it can be directly attributed to treatment, since tumors generally do not regress spontaneously."

Overall, SLD(t) informs both disease's dynamic and drug effect.

JM sub-models

M_{ijk} : j^{th} measurement in patient *i* belonging to arm (or study) *k*

Tumor size sub-model:

$$M_{ijk} = g(t, \psi_{ik}) + \varepsilon_{ijk}$$

$$\varepsilon_{ijk} \sim \mathbb{N}(0, \sigma_e^2)$$

$$\boldsymbol{\psi}_{ik} = \{log(M_{0,ik}), logit(\phi_{ik}), log(k_{s,ik}), log(k_{g,ik})\}$$

$$\psi_{ik} = \mu_k \cdot exp(\eta_i) \qquad \boldsymbol{\eta}_i^T \sim \mathbb{N}(0, \Omega)$$

$$\mu_k = \mu + \xi_k \qquad \xi_k \sim \mathbb{N}(0, \tau)$$

$$g\left(t, \boldsymbol{\psi}_{ik}\right) = M_{0,i} \cdot \left((\phi_{ik}) \cdot \underbrace{exp\left(-k_{s,ik} \cdot t\right)}_{\text{Drug induced shrinkage}} + (1 - \phi_{ik}) \cdot \underbrace{exp\left(k_{g,ik} \cdot t\right)}_{\text{Drug independent (re)growth}}\right)$$

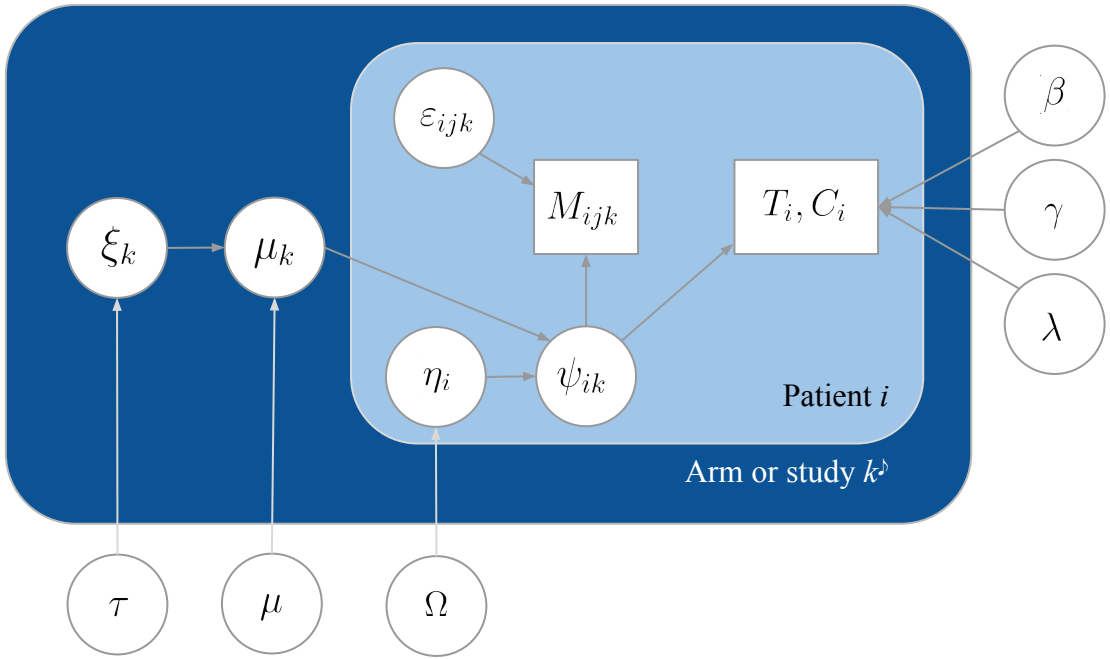
Survival sub-model:

$$h(t, \psi_{ik}) = h_0(t) \cdot exp(\beta \cdot f(t, \boldsymbol{\psi}_{ik})) \quad \text{with e.g.} \quad h_0(t) = \frac{\gamma}{\lambda}\left(\frac{t}{\lambda}\right)^{\gamma - 1} \quad \text{Weibull baseline hazard function}$$

Different link functions f considered e.g.

- Predicted value or predicted slope (1st deriv) of M at time t
- Clinically relevant parameter of the tumor size model

Graphical model



♪(A, A+B, Ah)

Bayesian inference

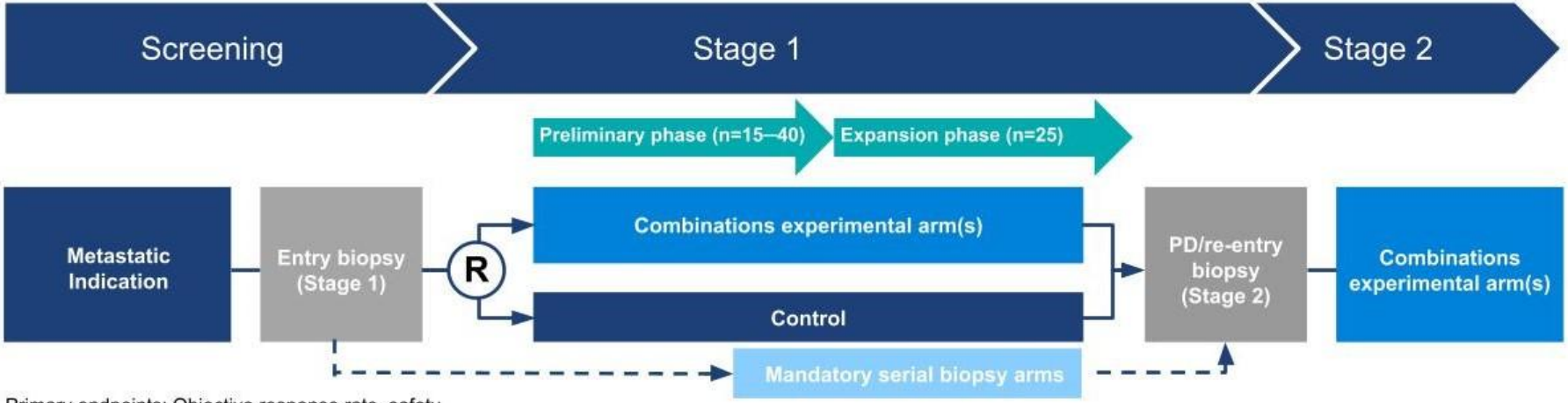
- Using Stan which implements a self-tuning HMC algorithm
- Tumor size model:
  (1) Hierarchical normal model with hyper-priors for the pop-level parms
- Survival model:
  (2) Treatment is not a covariate: Treatment effect is assumed to be 100% mediated by tumor size (next talk)
  (3) Complete pooling (consequence of (2))

```
model{
  real ypred_ij;
  real yobs_ij;

  // Hyper priors definition.
  mean_mu_ks ~ lognormal(1,0.5); // log(3)
  mean_mu_kg ~ lognormal(-0.36,1); // log(0.7)
  mean_mu_phi ~ beta(5,5);
  sd_mu_ks ~ lognormal(0,0.5);
  sd_mu_kg ~ lognormal(0,0.5);
  sd_mu_phi ~ lognormal(0,0.5);

  // Priors definition.
  mu_bsld ~ lognormal(55,5);

  mu_ks[sld_par_shared] ~ lognormal(mean_mu_ks, sd_mu_ks);
  mu_kg[sld_par_shared] ~ lognormal(mean_mu_kg, sd_mu_kg);
  logit(mu_phi[sld_par_shared]) ~ normal(logit(mean_mu_phi), sd_mu_phi);

  mu_ks[sld_par_separate] ~ lognormal(1,0.5);
  mu_kg[sld_par_separate] ~ lognormal(-0.36,1);
  mu_phi[sld_par_separate] ~ beta(5,5);

  omega_bsld ~ lognormal(0,1);
  omega_ks ~ lognormal(0,1);
  omega_kg ~ lognormal(0,1);
  omega_phi ~ lognormal(0,1);

  sigma ~ lognormal(-1.6,0.8);

  eta_tilde_bsld ~ normal(0,5);
  eta_tilde_ks ~ normal(0,5);
  eta_tilde_kg ~ normal(0,5);
  eta_tilde_phi ~ normal(0,5);

  p ~ gamma(2, 0.5);
  1 / lambda ~ lognormal(0, 5);
  beta ~ normal(0,5);
  gamma ~ normal(0,5);
  beta_os_cov ~ normal(0, 5);

  target += sum(log_lik);
}
```

Part III: Example

Motivating example (1/2)

Question:
In an indication XYZ and with a backbone A, should we prioritize to initiate Ph3 activities to test A+B vs. A?



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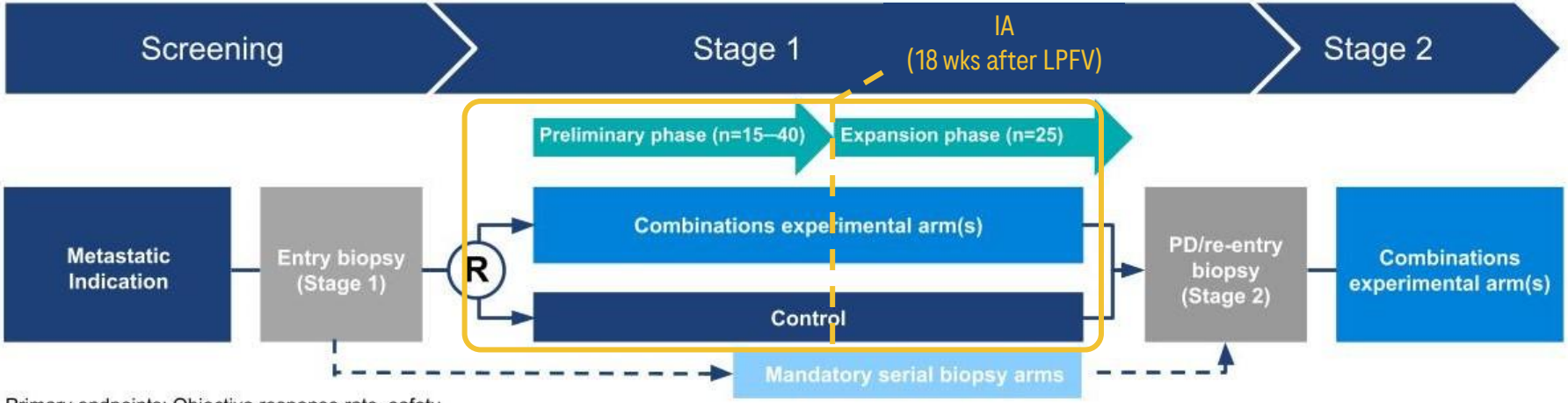


Primary endpoints: Objective response rate, safety
Secondary endpoints: Progression free survival (PFS), Overall survival (OS), Duration of response (DOR), Disease control

Motivating example (2/2)

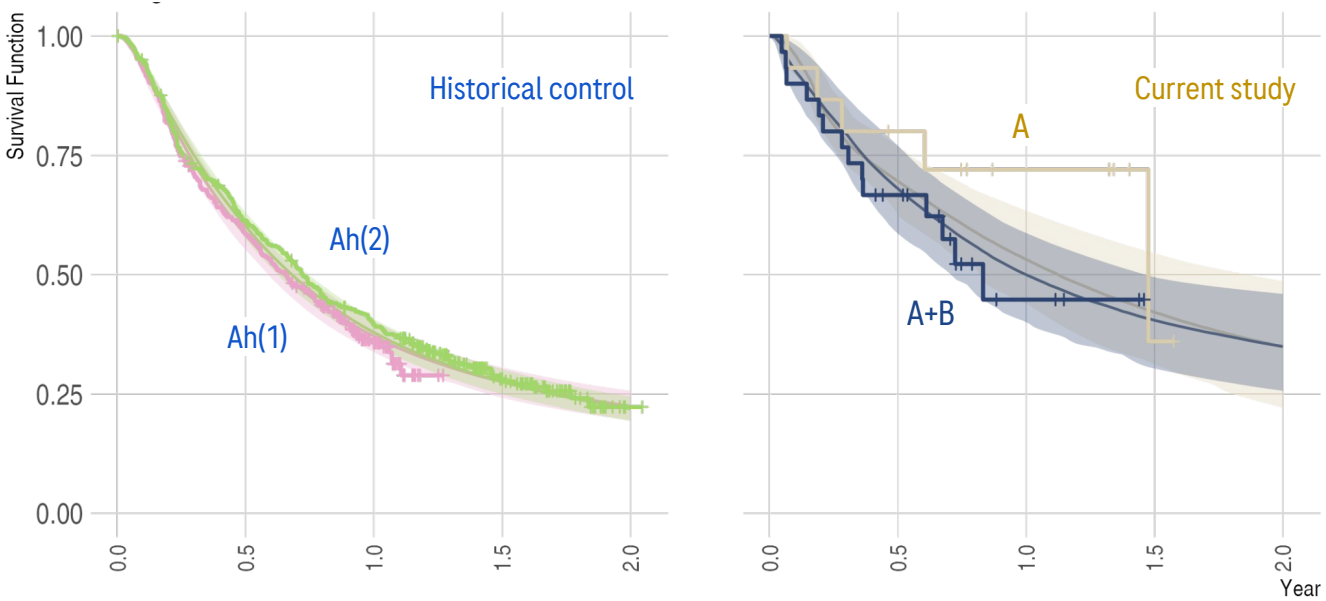
Current study | Historical control

	A (N= 29)	A+B (N= 30)	Ah(1) (N= 315)	Ah(2) (N= 467)
N w/ baseline SLD	29	30	314	465
N OS eval.	29	30	309	457
Baseline SLD (mm)	69.9 (46.9)	50.8 (28.5)	74.8 (50.7)	66.6 (44.4)
Liver Met. (Yes)	0 (0%)	0 (0%)	99 (31%)	138 (30%)
ECOG (1+)	16 (55%)	22 (73%)	196 (62%)	249 (53%)
Albumin (g/L)	41.0 (3.7)	40.5 (4.3)	38.3 (4.9)	39.1 (5.2)
LDH (U/L)	212 (83.8)	230 (96.2)	284.8 (205.2)	284.8 (188.2)
CRP (mg/L)	25.6 (36.9)	16.5 (21.4)	33.3 (41.4)	31.9 (41.5)
NLR	5.23 (5.18)	4.33 (5.2)	5.4 (5.1)	4.8 (4.4)

Note: Continuous Variables: Mean (SD); Categorical: N (%)

Predicted OS

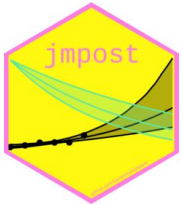
Predictions based on IA data + historical data borrowing



- This JM describes OS using log-logistic baseline hazard + slope as link function
- Predicted survival curves on 0-2 year interval are precise and largely overlapping
- No evidence of A+B>A so far (assurance close to 0)
- Only 15 data points for survival in group A (vs. 30 in A+B) ⟶ too sparse

Jmpost

Filling a gap



https://genentech.github.io/jmpost/

	{JM}	{JMbayes2}	{INLAjoint}	{rstanarm}	{jmpost}
Nonlinear mixed-effect model	No	No	No	No	**Yes**
Bayesian inference	No	Yes	Yes	Yes	Yes
Algorithm	Adaptive Gauss-Hermite	Custom MCMC	INLA	self-tuning HMC (Stan)	self-tuning HMC (Stan)

Note: {brms} does not support the fitting of Joint Models.

Disclaimer: Under active development; not a stable API yet.

Concluding remarks

Presentation to clinical team members

- Cross-functional team
- 5-min to convince
- Build trust; MDs trust *data* primarily
- Align beforehand, in particular:
  Assumptions ⟶ which bias to concede ? e.g. time-varying HR, NPH, link function, ...

- Commitment to make this happen.

Thank you for your attention

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BACK-UP

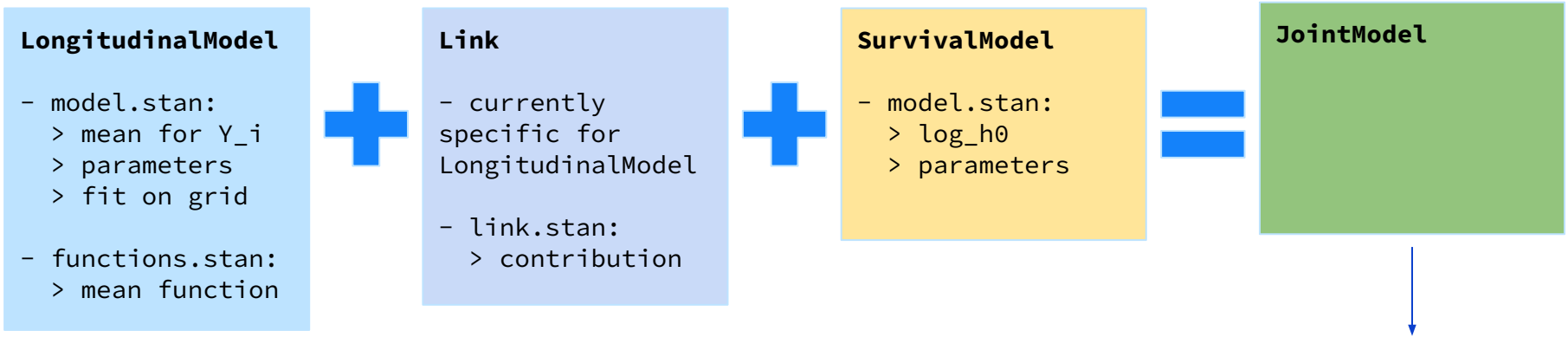
Joint TGI-OS models' selected history

circa	TGI-OS	JM	Other
2020		Kerioui *et al. Stat in Med* (Bayesian TGI-OS) Tardivon *et al. CPT* (TGI-OS)	
	Bruno *et al. CPT* (TGI-OS for prediction)		Carpenter *et al. JSS* (Stan)
2010	Claret *et al. JCO* (TGI-OS 2stgM) Stein *et al.* TheOnco (TGI-OS 2stgM)		Eisenhauer *et al. EJC* (RECIST)
2000		Law *et al. Biostatistics* (NLME sub-model; PSA-OS)	
		Hu *et al. Biometrics* (Bayesian) Tsiatis *et al. JASA*	
1990	Kaplan *et al. Cancer* (Decay and growth expM; PSA)		
	Norton *Cancer Res* (TGI expM in clin dev)		

Company sponsored

Introducing jmpost

Model Specification



LongitudinalGSF
LongitudinalRandomSlope

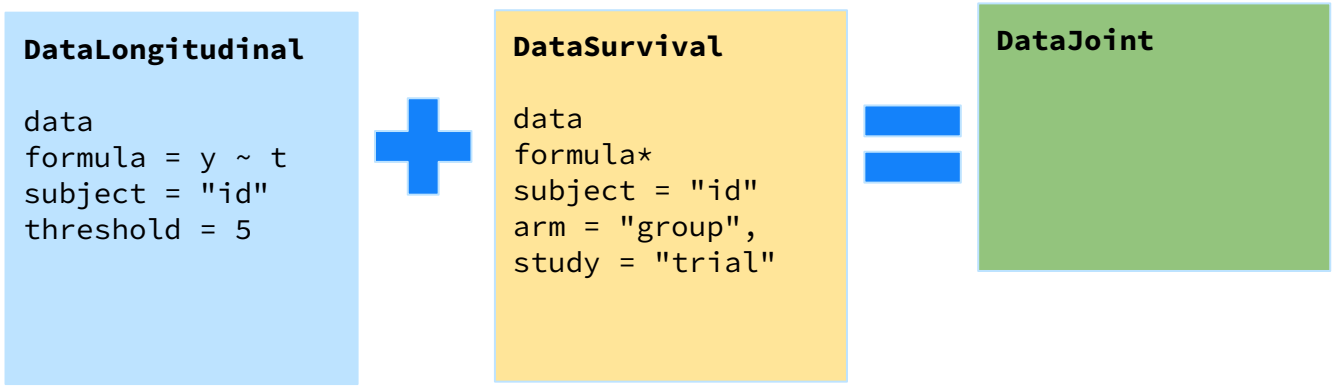
LinkNone
LinkGSF (TTG, dSLD)
LinkRandomSlope

SurvivalExponential
SurvivalLogLogistic
SurvivalWeibullPH

Disclaimer: Under active development; not a stable API yet.

Introducing jmpost (cont'd)

Data Specification

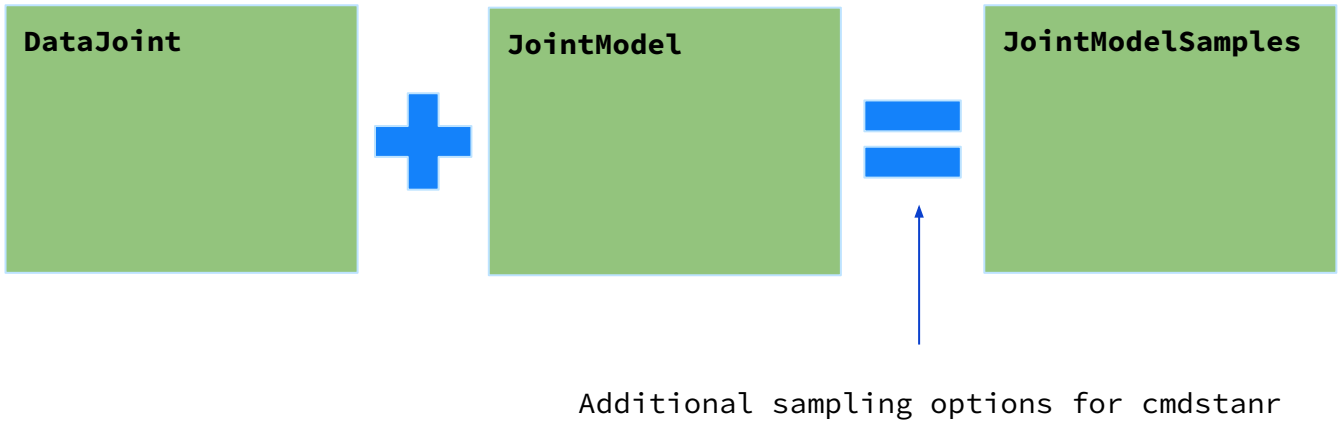


*formula = Surv(t, event) ~ cov1 + cov2 + …

Disclaimer: Under active development; not a stable API yet.

Introducing jmpost (cont'd)

MCMC sampling



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Training program (for statisticians)

1. Introduction to the statistical methodology
    a. Joint Models
    b. Bayes 101
    c. Decision making
2. Previous case studies
    a. Kerioui paper example
    b. Clinical trial example
3. Implementation
    a. Stan high-level overview
    b. jmpost structure
    c. Rerunning a case study with jmpost

Doing now what patients need next