Practical ***Bayesian inference in trials*** is ***easier*** and more ***efficient*** when using the approximation method ***INLA.***

Background & Aim

Bayesian inference has the capability to *address various levels of uncertainty* and naturally *adapt to the data and to all relevant information at hand*. However, the typical simulation methods used for Bayesian inference are hard to implement due to **software complexity** and **high computational costs.**

The **approximation method INLA** is a **fast alternative** to simulation-based **MCMC** methods. This has been proven in numerous simulation studies. However, the accuracy and efficiency of INLA method in real world clinical trial have not been investigated. Our study aimed to compare INLA with two MCMC methods (implemented in STAN and JAGS) on **1)** posterior distribution estimation accuracy **2)** ease of implementation of the software/package and **3)** computation time **using real Bayesian adaptive trial data.**

Methods

○ Simulation-based Methods(MCMC): **JAGS STAN** ○ Approximation-based Method: **INLA**

○ Ordinal Logistic Regression(Proportional Odds Model)

○ $\log\left(\frac{P(Y_i \le j|X_i = x)}{P(Y_i \ge j|X_i = x)}\right) = \alpha_j + \beta_1 gender_i + \beta_2 treatment_i + U_{site,i} + V_{age,i} + W_{time,i}$

○ Binary Logistic Regression

○ $\log\left(\frac{P(Y_i = 1|X_i = x)}{P(Y_i = 0|X_i = x)}\right) = \alpha + \beta_1 gender_i + \beta_2 treatment_i + U_{site,i} + V_{age,i} + W_{time,i}$

○ Cox Survival Model

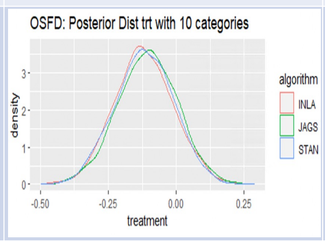
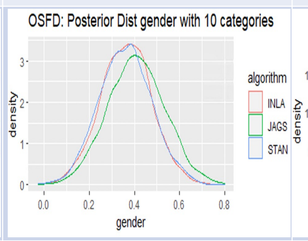
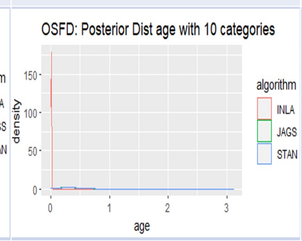
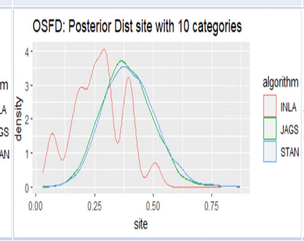
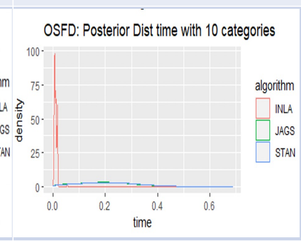
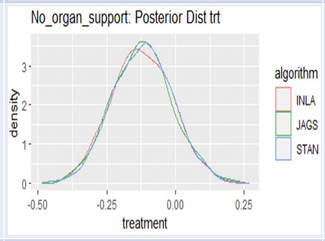
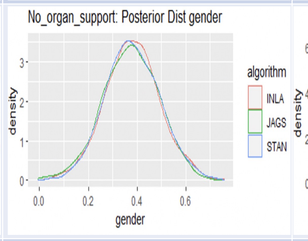
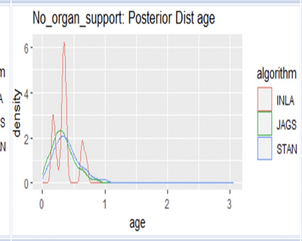
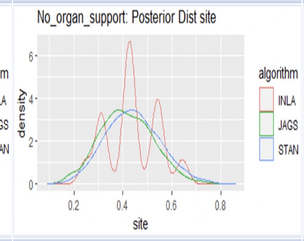
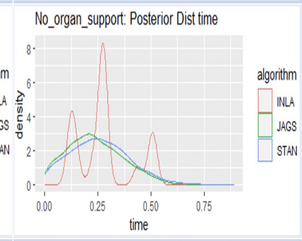
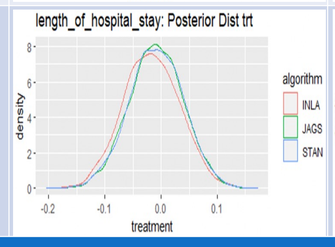
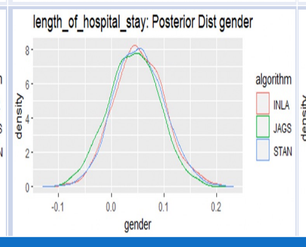
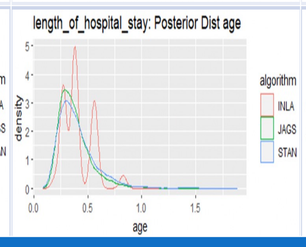
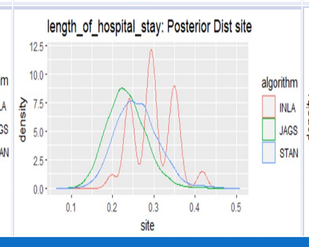
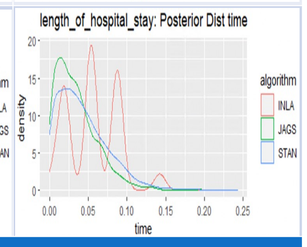
○ $\lambda_i(t) = \lambda_{0i}(t)\exp(\beta_1 gender_i + \beta_2 treatment_i + U_{site,i} + V_{age,i} + W_{time,i})$

- Since response-adaptive randomization in the trial may lead to imbalances in baseline covariates between treatment groups over time, the models were adjusted for age, gender, site and enrollment period.

- In order to investigate the variation at different age, site and time-period level, we put a hierarchical structure on these effects.

Results

Posterior Distributions

Model	Fixed Effects		Random Effects		
	Treatment	Gender	Age	Site	Time
Ordinal Logistic Regression ***Organ Support Free Days(1)***					
Binary Logistic *Regression* ***Survival without Organ Support(2)***					
Cox Regression ***Length of Hospital Stay(3)***					

Runtime

Model	*INLA*	JAGS	STAN
(1)	***31.28 seconds***	1.5 hours	30.5 minutes
(2)	***4.74 seconds***	7.2 minutes	7.35 minutes
(3)	***13.22 seconds***	6.8 hours	59.23 minutes

Discussions

○ Posterior density curves for the treatment and gender estimated with the INLA almost overlapped with the simulation methods.

○ INLA does not estimate posterior of the hierarchical model variance well.

○ INLA requires noticeably less computational time compared to STAN and JAGS (seconds compared to hours)

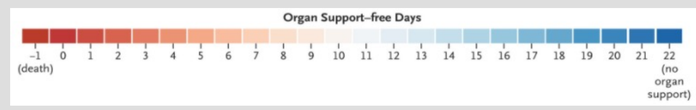
○ STAN and INLA have higher feasibility of implementation in statistical software R as there are well-established R packages.

Trial Information

International adaptive randomized controlled multiplatform trial to investigate the treatment effect of therapeutic anticoagulation with heparin in non-critically ill patients with covid-19 compared to usual care.

Key Outcomes of the Study

- ***Primary Outcome:***
  - ***Ordinal Outcome***
    - Organ Support Free Days



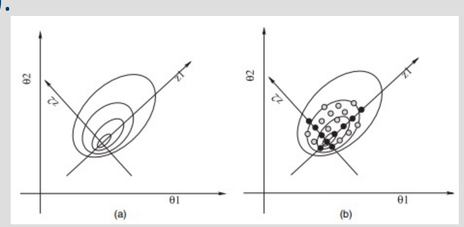
- ***Secondary Outcomes:***
  - ***Binary Outcomes:***
    - Survival until hospital discharge
    - Survival without receipt of organ support
    - Survival without receipt of invasive mechanical ventilation(IMV)
    - Survival without mechanical respiratory support
    - A major thrombotic event or death
  - ***Time to Event Outcome:***
    - Length of hospital stay

Priors

- ***Regression model coefficients***
  - Intercept: Normal($\mu = 0, \tau = 0.1$)
  - Gender: Normal($\mu = 0, \tau = 0.1$)
  - Treatment: Normal($\mu = 0, \tau = 0.1$)
- ***Hierarchical model variance: (Age, site , enrolment time-period)***
  - Normal($\mu = 0, \sigma^2$)
  - σ^2 ~ Half t distribution with df = 3, scale = 2.5

INLA:

Starting at the mode of the joint posterior of the hyperparameters, INLA explores the probability space by performing a grid search after finding the search direction mathematically. The search stops when the search point is too far away from the mode, based on a pre-set threshold. The approximation can be improved by exploring the parameter space in finer search steps (smaller step lengths).



Reference

○ Stan Version 2.29 User Manual

○ JAGS Version 4.3.0 User Manual

○ Julian F, James W, Yue, Bayesian Regression Modeling with INLA

○ Andrew Gelman. "Prior distributions for variance parameters in hierarchical" Bayesian Analysis, 1(3) 515-534 September 2006.

○ ATTACC Investigators, ACTIV-4a Investigators, REMAP-CAP Investigators (2021). Therapeutic Anticoagulation with Heparin in Noncritically Ill Patients with Covid-19. *The New England journal of medicine*, *385*(9), 790–802.

A Comparison of Methods in Bayesian Inference in Clinical Trials

Ziming Chen, Jeffrey Berger, Lana Castellucci, Michael Farkouh, Ewan Goligher, Beverley Hunt, Lucy Kornblith, Patrick Lawler, Eric Leifer, Matthew Neal, Ryan Zarychanski, Anna Heath

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