



Statistical Sciences
UNIVERSITY OF TORONTO

Point-by-point review response and revision summary of Manuscript BA2012-009
“Bayesian inference for Cox Proportional Hazard Models with Partial likelihoods, Semi-parametric Covariate Effects, and Correlated Observations”

Dear Dr Guindani (Editor-in-Chief) and Editors,

We wish to thank you for giving us this opportunity to revise our manuscript, and thank the associate editor and the referee for their detailed and helpful comments. We have read through the reviewer’s comments in details, and worked hard to address and incorporate all the suggestions in our revised manuscript, as detailed in the point-by-point responses in the following pages. The main revisions we made can be summarized as the followings:

- We have improved our posterior approximation method by removing the Gaussian noise in the additive linear predictors. The size of the latent parameter vector in the new posterior approximation method will no longer grow with the sample size, and hence makes the proposed method more computationally efficient and scalable.
- To address the AE’s comments, we expanded the two real data analysis examples in our revised manuscript. In the revised version, we not only implemented our proposed Laplace-approximation based method for the inference, but also the MCMC method for the same model based on partial likelihood. It turns out that our proposed approach gave similar result with MCMC method, but took significantly shorter time. This suggests that when computational efficiency is of primary concern, our proposed Laplace-approximation based method can be an appealing alternative to the practitioners who wish to conduct survival analysis based on partial likelihood.
- To address the referee’s comments, we expanded our simulation section to illustrate the accuracy of our proposed method. We considered two simulation settings where our approach tends to be more accurate than existing full-likelihood method, one with frailties of different sparsity, and another with semi-parametric smoothing with baseline hazards of different smoothness. As suggested in the referee’s comment, we measured accuracies in terms of Mean Square Errors (MSE) and posterior coverage probability with nominal level of 95 percent, through 300 independent replications. This provides guideline for practitioners who wish to conduct similar analysis, on how to choose the appropriate inference method depending on the setting of their problems.

We believe this revision is a significant improvement compared to our original manuscript, and we hope it is now suitable for publication in *Bayesian Analysis*. Thanks again for the consideration of our work.

Sincerely,

Ziang Zhang
PhD student

Alex Stringer
PhD Candidate

Jamie Stafford
Professor

Patrick Brown
Professor

Point-by-point review response

Comments from the Associate Editor:

1. *I recommend expanding your paper so as to include appropriate conceptual and numerical comparisons between MCMC based inference for the Cox model and the proposed methodology, to better inform applied statisticians.*

Response: We would like to thank the associate editor for this very constructive suggestion. In our revised manuscript, we have included comparisons between MCMC based inference and inference from the proposed method in the two real data analysis examples. These comparisons both show the accuracy of our proposed way of approximate Bayesian inference, and demonstrate the significant computational advantages of the proposed method over MCMC based method.

Comments from the Referee:

1. *The model specification presented in Equation 1 is general as it accounts for predictors whose association with the log-hazard is modelled as linear or semi-parametrically, and for a frailty term. It is not immediately clear though if the computational challenges provided by the use of the Cox PH model with partial likelihood have anything to do with the specific model that was considered or the same would arise regardless of the model adopted for the effect of the predictors. If this is the case, in my opinion, the presentation of the method might be more effective if introduced, at first, for the simplest model, for example the one only counting only the covariates x_{ij} . The more complex model could be introduced at a later stage as the one implemented in the examples of Section 4.*

Response: (to do: explain why the choice of model specification will be important for INLA, but won't be important for the proposed method, due to the C matrix that is already dense)

2. *The starting point of the paper is that existing approaches based on INLA cannot be applied to Cox PH models with partial likelihood. It should be clarified in the introduction if other Bayesian methods, either exact or approximate, have been used in the literature. This aspect should be clarified. In addition, I think it might be worth mentioning another class of nonparametric models for the baseline hazard function, such as the one of Dykstra & Laud, (1981), where the baseline hazard function is modelled by means of a gamma process.*

Response: (to do: added the discussion of this alternative class of models mentioned by the referee, in the introduction section)

3. I find the simulation study of Section 4 not very compelling as, in my opinion, it fails at satisfactorily address two questions that I think are relevant when adopting a new and approximate method for posterior computation. Namely, 1) how good is the approximation? 2) How is the method compared with alternative strategies for posterior computations, both in terms of accuracy and computational efficiency?

I will list some points which I believe would help making the simulation study more compelling. These suggestions are nothing but a possible option, other ideas might be equally valid. As for point 1, it would be interesting -for example- to explore the coverage of the approximate posterior estimates on a set of several replicates. Another option could be to compare posterior estimates of the proposed approximate method with those obtained with standard MCMC (when the parametric form of the baseline hazard which generated the data is known). As for point 2, right now the only comparisons are rather qualitative and made only on the analysis of the real data sets of Sections 4.2 and 4.3. A comparison could be carried out also in the case of simulated data: one option that seems in line with how the material is presented would be to compare posterior inference obtained with the proposed method, with the one produced by the approach of Martino et al., (2011). Such comparison could be done under various settings, e.g. settings where the smoothness assumptions required by Martino and co-authors are met by the data generating process, and settings where the same requirements are not met.

Response: We agree that the original simulation study in our manuscript is not very compelling, and we have expanded the simulation section based on the precious suggestion of the referee. The simulation section now contains two specific examples on which the proposed approximate inference method performs significantly better than the existing approximate inference method based on full likelihood, namely when the frailties are sparse, and when the true baseline hazard function is complicated. According to the suggestion from the referee, we have explored the coverage rates of approximate posterior credible intervals on a set of independent replicates for each method in each simulation example, and we have computed and compared the empirical MSE of each method. Also, as the referee has mentioned, we have now provided the simulation results under various settings (e.g. settings where the smoothness of baseline hazard is at different levels, settings where the sparsity of frailties is at different levels).

Furthermore, we have expanded two data analysis examples to include the inferential result from MCMC method on partial likelihood. The revised examples both compared the posterior estimates of the proposed approximate method with MCMC, and demonstrated the computational efficiency of the proposed approach over MCMC.

With these expansions in the simulation and example section, we believe the two questions mentioned by the referee are now satisfactorily answered in our revised manuscript.